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Design, synthesis and biological evaluation of 6-substituted quinolines derived from cabozantinib as c-Met inhibitors

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Abstract

Based on the cabozantinib scaffold, novel c-Met inhibitors were rationalized from the limited knowledge of structure–activity relationships for the quinoline 6-position. Emphasis was given to modifications capable of engaging in additional polar interactions with the c-Met active site. In addition, *ortho*-fluorinations of the terminal benzene ring were explored. Fifteen new molecules were synthesized and evaluated in a c-Met enzymatic binding assay. A wide range of substituents were tolerated in the quinoline 6-position, while the *ortho*-fluorinations performed were shown to give considerable reductions in the c-Met binding affinity. The antiproliferative effects of the compounds were evaluated in the NCI60 cancer cell line panel. Most notably, compounds **15b** and **18b** were able to inhibit cell proliferation more efficiently than cabozantinib in leukemia, CNS, and breast cancer cell lines. The in vitro data agreed well with the in silico docking results, where additional hydrogen bonding was identified in the enzymatic pocket for the *para*-amino substituted **15b** and **18b**.

KEYWORDS
cabozantinib, c-Met, kinases, NCI60, quinolones

1 | INTRODUCTION

Despite a surge in the available cancer treatments over the last decades, drug resistance and tumor relapse remain as prominent challenges.[1] Therefore, finding new ways of inhibiting molecular pathways responsible for tumor cell proliferation, migration, and invasion is a main focus in cancer research.[2,3] The tyrosine kinase c-Met (hepatocyte growth factor receptor) plays a central role in many cancer diseases, and abnormal activation leads to tumor growth and proliferation, dissociation of cells from its primary site and distant colonization. Because of this, dysregulation of c-Met has been proposed as one of the primary drivers for cancer development and metastatic processes.[4,5] Considerable efforts have been made in developing inhibitors of c-Met,[6–8] and some examples of small-molecule inhibitors are shown in Figure 1, including the regulatory approved cabozantinib (**1**) and crizotinib (**2**).

Cabozantinib (**1**) is a multikinase inhibitor, which inhibits, among others, the kinases c-Met and vascular endothelial growth factor receptor (VEGFR).[9] Cabozantinib is approved for medullary thyroid cancer and advanced renal cell carcinoma, and several clinical studies are currently performed for other cancer indications such as prostate and colorectal cancer.[10] Crizotinib (**2**) is approved for lung cancer, and inhibits the kinases ALK and ROS1 in addition to c-Met. Capmatinib (**3**) and AMG 337 (**4**) are examples of inhibitors that are exquisitely selective for the c-Met kinase, both currently in clinical trials for lung cancer and metastatic solid tumors.

Extensive research has been conducted to explore the structure–activity relationships (SARs) for c-Met inhibitors similar to

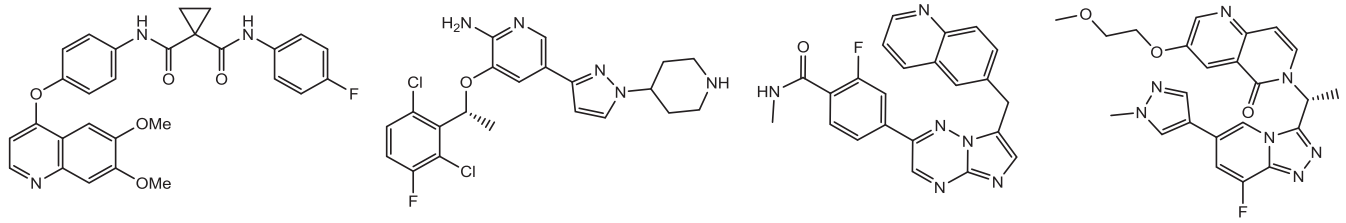


FIGURE 1 Examples of known inhibitors of c-Met, including the regulatory approved inhibitors cabozantinib (**1**) and crizotinib (**2**)

cabozantinib.[11–13] For the hinge-binding quinoline moiety, modifications have primarily been made at the 7-position, these frequently being groups intended to increase solubility.[14] With other heterocycles as hinge-binders, substituents known to participate in more direct interactions with the enzyme have been explored, exemplified with amines, anilines, and nitrogen containing heterocycles in Figure 2.[15–18] Molecules containing such variations have been shown to have strong interactions with the c-Met active site, made possible by the formation of additional hydrogen bonds. Substitutions at the quinoline 6-position have been less studied, and we, therefore, sought to explore this position and whether the introduction of functional groups capable of engaging in polar interactions could improve the c-Met binding affinity. This was rationalized with the introduction of additional heteroatoms, fluorinated groups, and hydrogen bond donors or acceptors as depicted in Figure 2, and this strategy resulted in the target scaffold **5**. In addition to the modifications at the quinoline 6-position, the bioisosteric replacement of hydrogen with fluorine in *ortho*-positions of the terminal benzene ring was of interest since this would block one of the main metabolic pathways for this compound class.[19,20] In this study, we present the synthesis and in vitro evaluation of these novel kinase inhibitors.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The two fluorinated analogs of the terminal aromatic ring, **6a** and **6b**, were prepared starting from cyclopropane-1,1-dicarboxylic acid by reaction with the corresponding aniline, as shown in Scheme 1.

The 6-hydroxy-7-methoxyquinoline scaffold in **5** was synthesized in a similar manner to earlier reported work,[21] although starting from 3-hydroxy-4-methoxy acetophenone, which was first benzylated to **7**, then nitrated to **8**, and further reduced to the aniline **9**. Cyclization into the 4-hydroxy quinoline **10** was achieved using ethyl formate and further reacted with 1-fluoro-4-nitrobenzene to give diaryl ether **11**, which was reduced to the aniline **12**. The acids **6** were then coupled with aniline **12** into the main scaffold **13**, which could then be

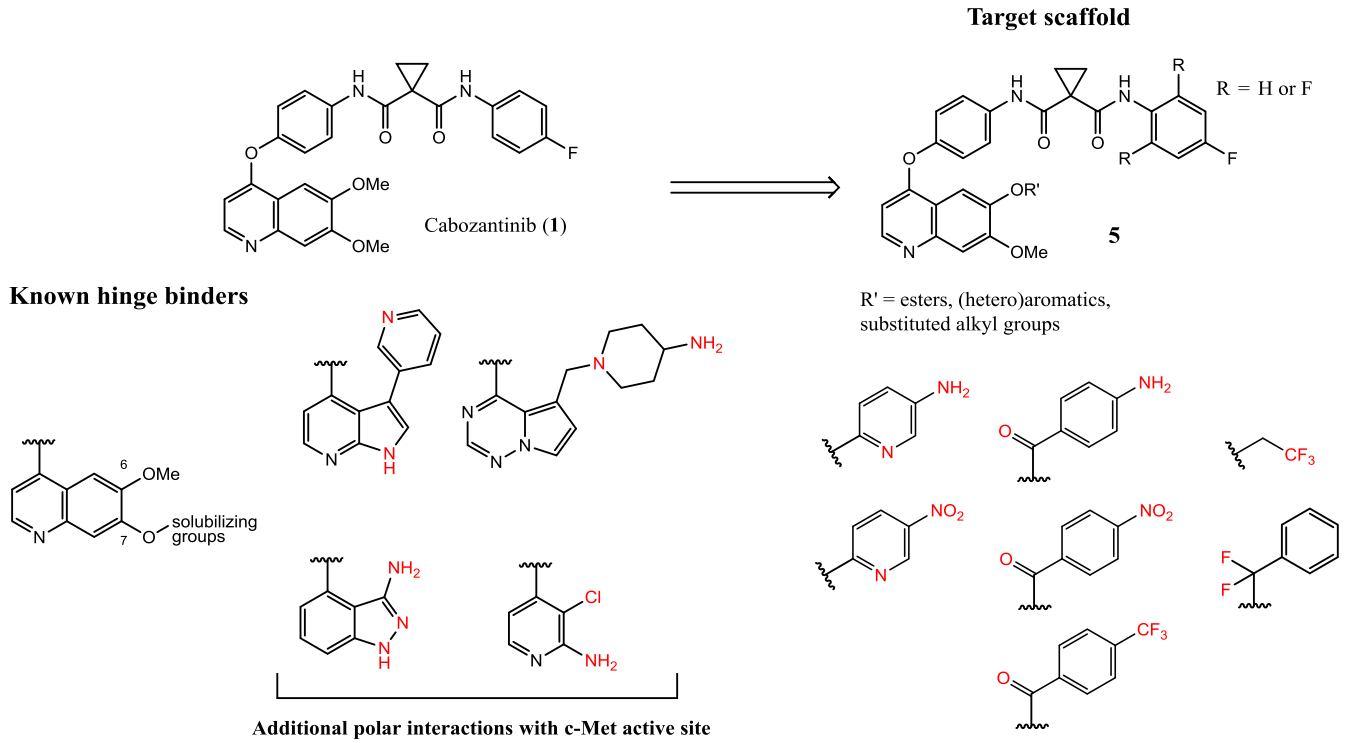
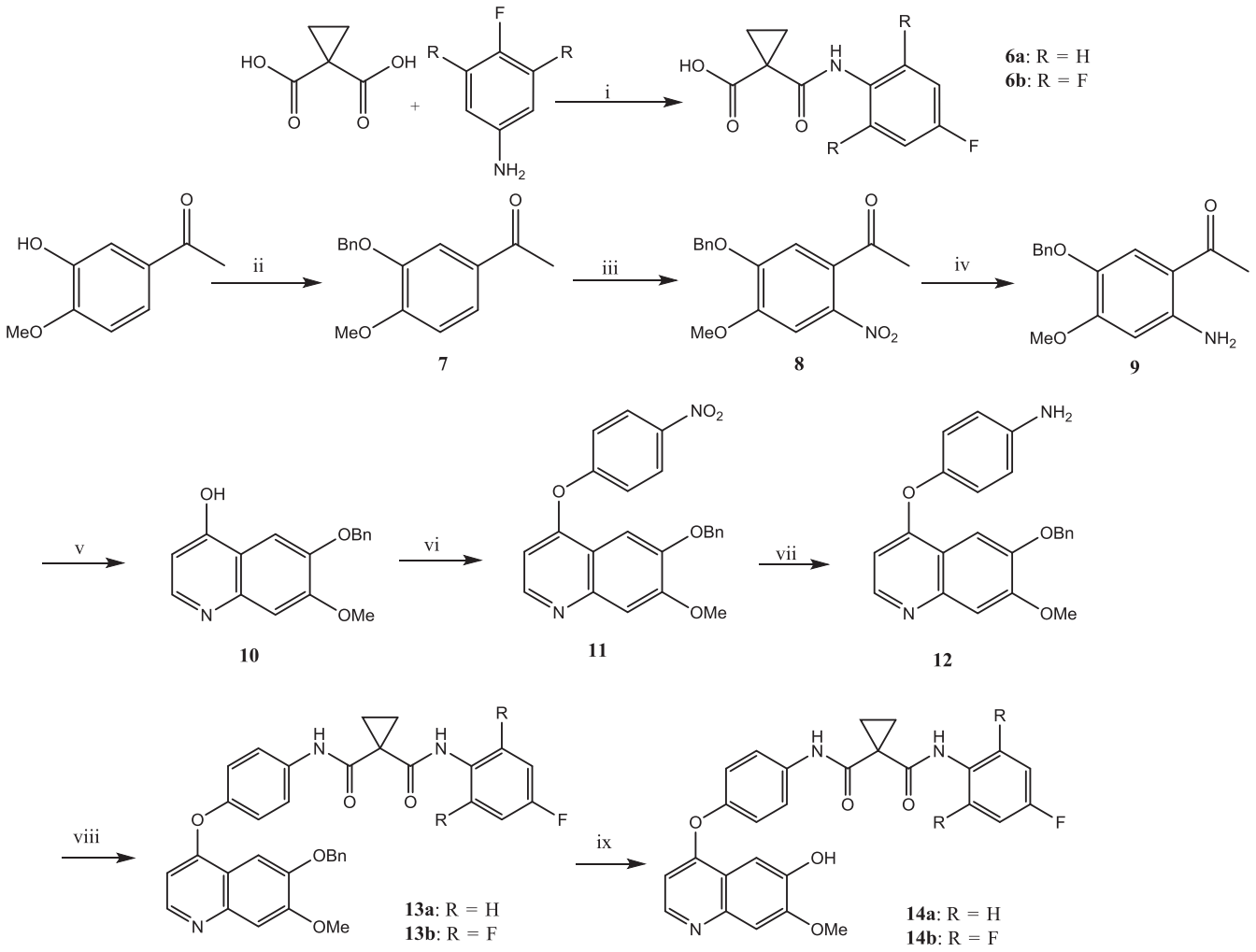


FIGURE 2 Examples of known variations around the hinge binding heterocycles and our proposed target scaffold **5**. Atoms with the capability of engaging in polar interactions are displayed in red



SCHEME 1 Synthesis of compounds **13a,b** and **14a,b**. Reagents and conditions: (a) NEt_3, $SOCl_2$, THF, rt, 20 hr (**6a** in 30%, **6b** in 41%); (b) BnBr, K_2CO_3, 40°C, 18 hr, 91%; (c) HNO_3, H_2SO_4, DCM, rt, 0.5 hr, 92%; (d) Fe, NH_4Cl, EtOH, H_2O, 70°C, 3 hr, 89%; (e) NaOEt, ethyl formate, DME, rt, 24 hr, 99%; (f) 1-fluoro-4-nitrobenzene, Cs_2CO_3, DMF, MeCN, 55°C, 24 hr, 21%; (g) Fe, NH_4Cl, EtOH, H_2O, 70°C, 84%; (h) **6a** or **6b**, HATU, DIPEA, DMF, rt, 20 hr (**13a** in 61%, **13b** in 62%); (i) Pd/C, 1,4-cyclohexadiene, EtOH, 70°C, 6 hr (**14a** in 78%, **14b** in 79%)

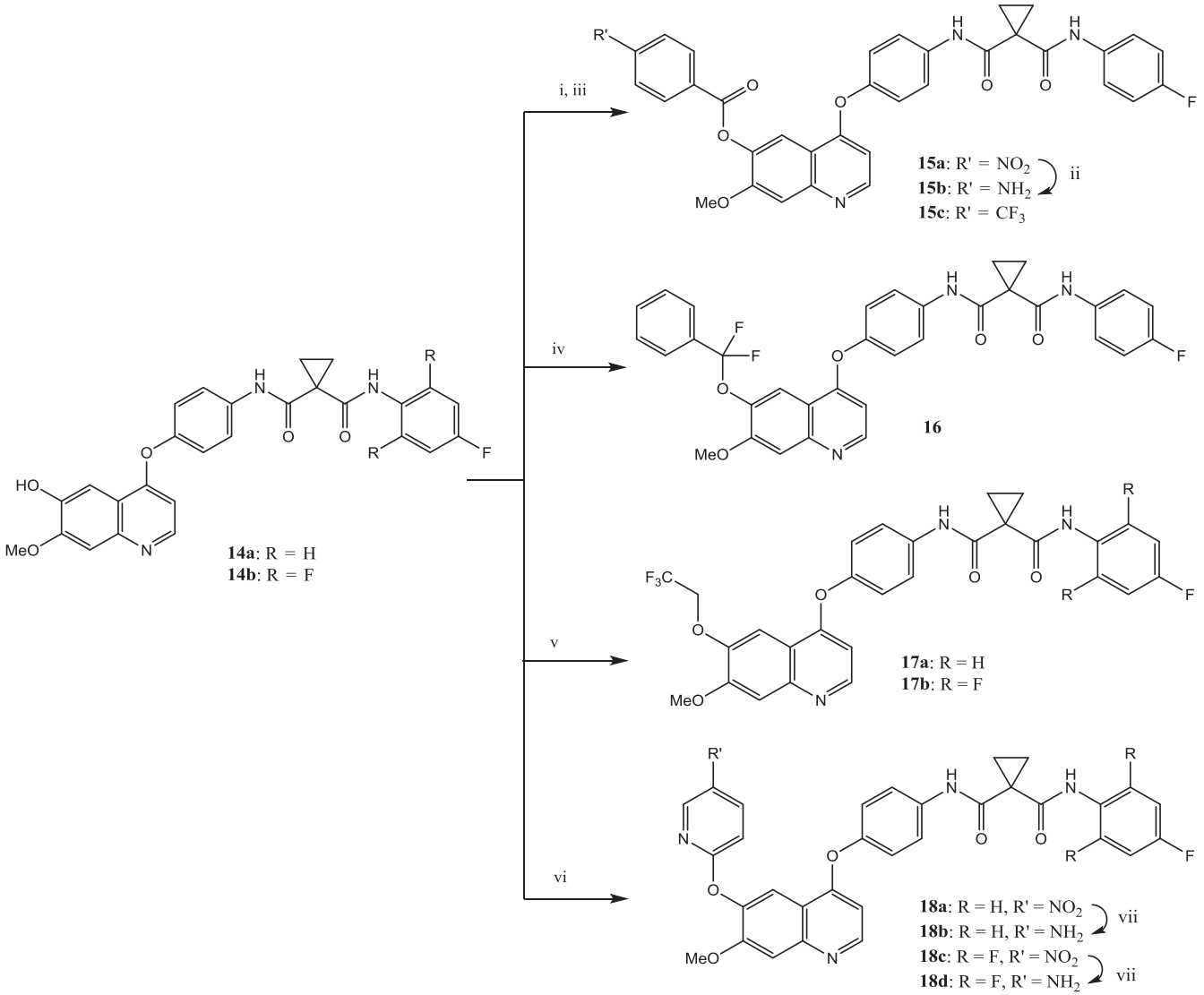
deprotected to the phenols **14**. Cleavage of amide bonds was observed using hydrogen gas, and 1,4-cyclohexadiene was therefore applied as a milder hydrogen source. Synthesis of **19** was performed in a similar manner, using steps f–h, starting from 6,7-dimethoxyquinolin-4-ol.

Further functionalization to compounds **15–18** could be achieved as shown in Scheme 2. The phenol **14a** was esterified into the *para*-substituted nitro, amino, and trifluoromethyl esters **15**. The highly fluorinated analogs **16** and **17** were synthesized using chloro difluoromethylbenzene or 1,1,1-trifluoro-2-iodoethane, respectively. These reagents were prone to produce several side-products, so the yields were correspondingly low. Using 2-chloro-5-nitro-pyridine, the nitropyridyls **18a** and **18c** were achieved, which then were reduced to the corresponding aminopyridyls **18b** and **18d**.

2.2 | Biology

The novel compounds were evaluated for enzymatic c-Met binding affinity, and the results are reported in Table 1.

The introduction of two additional fluorine atoms on the terminal aromatic ring reduced the inhibition of c-Met, and this is observed for all six pairs of compounds shown in Table 1. The increase in IC_{50} values resulting from this *ortho*-fluorination ranges from a factor of about two for the amino pyridinyl derivatives (**18b**/**18d**), to a factor of 30 for the benzyl ethers (**13a**/**13b**). The *ortho*-fluorinated analog of cabozantinib as such, compound **19**, was shown to be 27 times less potent than cabocantinib. For the quinoline 6-position, a range of both alkyl and aromatic substituents are well tolerated. By comparing the benzyl esters **15** and the pyridyls **18**, it is evident that the nature of the *para*-substituent is important, with the observed affinity trend NH_2>NO_2>CF_3. The aniline ester **15b** is the most potent inhibitor of c-Met in the series with an IC_{50} of 19 nM. Moreover, the difluorinated benzyl ether **16** was twice as potent compared to the unfluorinated benzyl ether **13a**, while the trifluoroethyl analog **17a** exhibited 50% reduced potency compared to cabozantinib. The 6-*O*-demethylated analog **14a** was equipotent to cabozantinib.



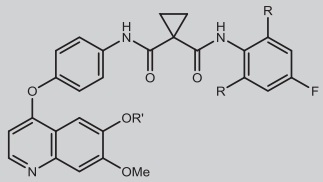
SCHEME 2 Synthesis of compounds **15–18**. Reagents and conditions: (a) 4-nitrobenzoyl chloride, Cs_2CO_3, DMF, rt, 5 hr, 37%; (b) Fe, NH_4Cl, EtOH, H_2O, 70°C, 3 hr, 60%; (c) 4-(trifluoromethyl)benzoic acid, HATU, DMAP, DMA, rt, 16 hr, 53%; (d) chlorodifluoromethylbenzene, Cs_2CO_3, DMF, 100°C, 20 hr, 6%; (e) 1,1,1-trifluoro-2-iodoethane, Cs_2CO_3, DMF, 110°C, 5 hr (**17a** in 33%, **17b** in 4%); (f) 2-chloro-5-nitro-pyridine, Cs_2CO_3, DMF, rt, 1.5 hr (**18a** in 75%, **18c** in 93%); (g) Fe, NH_4Cl, EtOH, H_2O, 70°C, 3 hr (**18b** in 54%, **18d** in 59%)

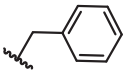
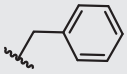
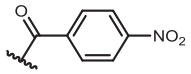
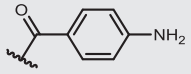
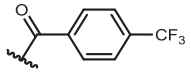
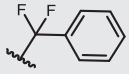
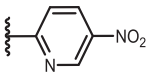
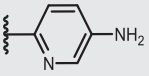
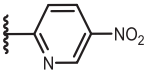
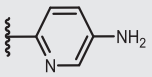
In summary, substituents in the quinoline 6-position capable of engaging in polar interactions seem to augment c-Met affinity.

The analogs **14a**, **15a**, **15b**, **18b**, and **18d** were progressed for further evaluation in a cancer cell proliferation inhibition assay. This selection was based on low IC_{50} values for c-Met, while simultaneously maintaining a structural diversity to further explore the efficacy in cell-based assays. These studies were performed using the NCI60 program at the National Cancer Institute (NCI).[22,23] Here, the compounds were tested at 10-μM concentration in a broad range of cell lines from nine different tumor types. The results are presented in Table 2 as observed growth percent.

From Table 2, it can be deduced that the tested compounds were able to inhibit growth in a wide range of tumor cell lines. The most potent compounds were **15b** and **18b**, which is consistent with the observed trend in Table 1. The compound **14a**, the 6-*O*-demethylated analog of cabozantinib, is seen to have a markedly reduced ability for the inhibition of cell proliferation, even though c-Met affinity is comparable with cabozantinib. The importance of the *para*-amino group in **15b** and **18b** is evident from the notably reduced capability of the *para*-nitro analog **15a** to influence the growth rates, despite comparable c-Met IC_{50} values. These observations indicate that the 6-position on the quinoline ring is important for the interaction with other kinases in addition to c-Met, as can be expected for this class of multikinase inhibitors. The same trend is also seen with the trifluorinated compound **18d** performing overall better in the cell-based assay than compounds **14a** and **15a**, despite its lower c-Met affinity. This observation is in compliance with known SAR on related structures that have shown that c-Met affinity is more sensitive to modifications on the terminal benzene ring than is VEGFR.[24] Compared with cabozantinib, higher growth suppressive effects are

TABLE 1 Inhibition of c-Met enzymatic activity for the synthesized compounds **13**–**19**



Compound	R	R′	IC_{50} (nM)[b]
13a	H		135
13b	F		4,074
14a	H	H	32
14b	F	H	201
15a	H		47
15b	H		19
15c	H		394
16	H		75
17a	H		70
17b	F		1,558
18a	H		324
18b	H		64
18c	F		6,000
18d	F		113
19	F	Me	1,078
Cabozantinib (**1**)[a]	H	Me	40

[a]Reference compound in the assay.
[b]n ≥ 2. Average values are given.

seen with **15b** and **18b** in several of the cell lines, particularly in cells derived from leukemia, CNS, and breast cancer. **15b** and **18b** were progressed for 5-dose testing, and the results for selected cancer cell lines are reported in Table 3.

The results from the 5-dose assay corroborate compounds **15b** and **18b** as potent inhibitors of cancer cell proliferation. All mean GI_{50}, TGI, and LC_{50} values for **15b** and **18b** are lower than for cabozantinib, except for the TGI value for **15b**. The lowest GI_{50} values observed were 50 and 40 nM with **18b** in the HOP-92 and KM-12 cell lines, respectively. The reported means in Table 3 are for all NCI60 cancer cell lines, and the complete data are given in the Supporting Information.

To examine whether the structural modifications affected the kinase selectivity profile, a screen was performed on six kinases in addition to c-Met. Kinase selectivity was assessed for the analogs **15b**, **18b**, and **18d**, and is presented in Table 4.

As can be seen in Table 4, the novel analogs have a similar kinase selectivity profile as cabozantinib, albeit with a lower affinity toward c-Kit. Interestingly, **18b** exhibits a stronger inhibition of ALK. In light of the different cell proliferation results among the compounds in Table 2, additional modes of action cannot be ruled out.

2.3 | In silico evaluation

Introduction of various functionalities to the 6-position of the quinoline could potentially influence the binding mode of the ligands to the active site of c-Met. The most potent synthesized ligands, were, therefore, further evaluated by molecular docking using AutoDock Vina[25] via the PyRx[26] interface. The experimental crystal structure with the c-Met inhibitor foretinib (PDB: 3LQ8) was employed.

By overlaying the docked structures of cabozantinib, **15b** and **18b**, it is seen in Figure 3a that the three ligands are well aligned within the receptor site. The introduced 4-amino phenyl ester in **15b** and 4-amino pyridinyl in **18b** were shown to overlap, and instead of pointing out in the solvent-accessible area, as is the case, for example, the morpholine in foretinib, these groups engage in an additional hydrogen bonding to Ala-1226. To accommodate this hydrogen bonding, the docked structure of **18b** is shifted rightward in Figure 3a, which may emphasize the importance of this interaction. The interactions with the specific parts of the active site are exemplified with **18b** in Figure 3b. The nitrogen in the quinoline ring forms a hydrogen bond with Met-1160, while the amide linker interacts with Lys-1110 and Phe-1223.

3 | CONCLUSION

Rationalized from the limited knowledge of SAR around the quinoline 6-position, novel c-Met inhibitors were designed based on the cabozantinib scaffold. In particular, the introduction of functional groups capable of engaging in direct interactions with the enzyme were emphasized. Several of the compounds displayed similar or increased potency compared to cabozantinib in a c-Met enzymatic assay. Compounds **14a**, **15a**, **15b**, **18b**, and **18d** evaluated in the NCI60 program displayed high antiproliferative activity, with **15b** and **18b** being the most potent, especially in leukemia, CNS, and breast cancer cell lines. Additional hydrogen bonds to the c-Met active site were observed by molecular docking for the *para*-amino substituted **15b** and **18b**. Further on, it was shown that c-Met affinity

TABLE 2 The effect on cell proliferation for the compounds **14a**, **15a**, **15b**, **18b**, and **18d** at 10 μM on the NCI60 cell lines

	Growth percent (%)					
Cell line	**14a**	**15a**	**15b**	**18b**	**18d**	**Cabozantinib[a]**
Leukemia						
CCRF-CEM	29.03	86.47	27.84	61.18	70.87	15
HL-60(TB)	54.53	92.86	**−43.90**	22.95	38.25	15
K-562	9.30	57.69	**−20.88**	3.07	7.69	−10
MOLT-4	44.86	72.20	**3.73**	29.51	38.53	22
RPMI-8226	52.76	88.82	**10.37**	48.51	50.14	22
SR	41.31	99.25	9.85	11.92	58.46	8
Non-small-cell lung cancer						
A549/ATCC	56.45	99.66	33.57	22.65	48.02	15
EKVX	71.05	81.32	**25.74**	**15.93**	45.20	40
HOP-62	57.65	88.90	**11.72**	51.19	67.73	30
HOP-92	33.42	32.64	−13.34	−11.47	2.04	−35
NCI-H226	67.06	83.06	55.73	36.46	37.70	−25
NCI-H23	57.42	71.44	37.78	49.31	53.55	30
NCI-H322M	87.72	100.58	43.02	49.41	74.83	25
NCI-H460	48.11	95.06	24.72	30.99	65.43	10
NCI-H522	68.01	87.82	**21.45**	51.26	54.96	25
Colon cancer						
COLO 205	91.01	103.66	−36.55	8.91	44.26	−50
HCC-2998	79.26	108.76	**25.79**	72.05	81.52	38
HCT-116	52.01	94.60	23.12	40.70	56.58	13
HCT-15	61.83	94.27	25.87	27.86	45.50	20
HT29	95.14	96.93	1.03	9.65	34.84	0
KM12	22.48	18.82	12.35	**3.70**	15.53	10
SW-620	34.36	76.61	33.48	36.75	40.32	2
CNS cancer						
SF-268	65.76	79.34	29.43	36.82	55.46	30
SF-295	35.17	64.41	**−74.56**	0.16	30.58	−15
SF-539	24.48	39.12	**−1.20**	5.06	21.15	3
SNB-19	82.03	96.77	**37.63**	54.50	78.74	40
SNB-75	33.97	44.96	**−34.57**	**−12.47**	21.75	−5
U251	66.05	79.71	**7.81**	33.56	67.30	30
Melanoma						
LOX IMVI	39.75	89.12	**−51.42**	**10.67**	49.35	13
MALME-3M	64.02	82.24	25.98	43.11	58.96	−5
M14	49.46	94.34	10.84	39.85	56.88	0
MDA-MB-435	52.60	84.00	33.16	**3.34**	**3.80**	15
SK-MEL-2	88.13	97.53	**31.31**	54.29	81.50	35
SK-MEL-5	66.38	89.42	33.98	39.16	**29.00**	35
UACC-257	71.49	107.25	33.55	33.95	53.78	35
UACC-62	34.78	80.12	40.09	**5.29**	24.38	10
Ovarian cancer						
IGROV1	52.10	72.65	60.70	**−24.06**	28.14	0
OVCAR-3	78.71	100.65	47.48	49.88	75.28	35

(Continues)

TABLE 2 (Continued)

Cell line	Growth percent (%)					
	14a	15a	15b	18b	18d	Cabozantinib[a]
OVCAR-4	37.08	75.47	51.72	29.88	28.41	25
OVCAR-5	80.78	101.37	30.98	40.01	70.03	13
OVCAR-8	73.73	88.98	51.86	47.12	69.69	38
NCI/ADR-RES	71.74	85.76	35.52	73.79	82.31	20
SK-OV-3	86.52	108.17	69.65	61.33	81.28	25
Renal cancer						
786-0	96.20	106.39	**−17.36**	39.15	96.45	25
A498	59.38	89.70	64.04	−20.88	−6.52	−35
ACHN	67.80	87.50	39.53	18.58	50.87	20
CAKI-1	78.05	93.52	20.86	43.54	65.58	10
RXF 393	58.46	83.78	−10.38	11.48	65.77	−15
SN12C	30.54	53.95	27.61	14.83	30.60	12
TK-10	76.75	104.78	72.19	36.33	84.53	12
UO-31	54.41	71.15	9.18	19.76	45.26	0
Prostate cancer						
PC-3	57.10	79.70	25.44	24.46	51.54	20
DU-145	77.70	97.70	45.34	49.53	80.74	30
Breast cancer						
MCF7	51.21	82.13	23.78	**9.52**	31.74	25
MDA-MB-231/ATCC	71.02	96.91	**−1.25**	42.69	65.87	15
HS 578T	42.71	52.64	**−16.93**	7.33	25.79	0
BT-549	79.90	90.40	**36.09**	61.89	74.18	40
T-47D	55.32	88.82	**19.45**	**5.99**	29.00	25
MDA-MB-468	86.40	111.19	59.28	31.72	33.34	27
Mean[c]	59.53	84.46	19.99	28.71	49.57	13.7

Note: Data are presented as growth percent; 100 is no change (as for the control), 0 is no growth (same number of cells), and below 0 is lethality (reduction in number of cells).
[a]Values extracted from the NCI60 database and included for comparison.
[b]Bold values indicate better-observed effect than with cabozantinib.
[c]Mean growth observed.
[d]NCI database #: 807002 (**14a**), 806999 (**15a**), 807003 (**15b**), 807000 (**18b**), 807001 (**18d**).

was more negatively affected than the antiproliferative properties by *ortho*-fluorinations performed on the terminal benzene ring. A similar kinase selectivity profile as for cabozantinib was observed for **15b**, **18b**, and **18d**. In conclusion, new SAR knowledge for the 6-position of the quinoline ring has been obtained, indicating that such modifications are generally well tolerated. Further evaluation of **15b** and **18b** as new anticancer agents are warranted.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

All chemicals were purchased from Sigma-Aldrich or Fluorochem and used without further purification. Air and/or moisture sensitive reactions were performed under argon atmosphere with dried solvents and reagents. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} plates, and visualized using UV light at 312 or 365 nm, a phosphomolybdic acid solution (12 g phosphomolybdic acid in 250 ml EtOH) or a potassium permanganate (1.5 g $KMnO_4$, 10 g K_2CO_3, 2.5 ml 5 M NaOH/H_2O, 200 ml H_2O) solution for detection. Column chromatography was performed with silica gel (pore size 60 Å, 230–400 mesh particle size) purchased from Fluka. ^1H and ^{13}C NMR spectra were obtained on a Bruker AVIII HD 400 instrument (400/101 MHz). Chemical shifts (δ) are reported in parts per million, and coupling constants are reported in Hertz (Hz). The residual proton solvent resonance in ^1H NMR ($CDCl_3$ at δ 7.27, DMSO-d_6 at δ 2.50) and the residual carbon solvent resonance in ^{13}C NMR ($CDCl_3$ at δ 77.16 ppm and DMSO-d_6 at δ 39.52) are used as reference (please see the Supporting Information for the original spectra). Accurate mass determination (HRMS) in positive or

TABLE 3 GI_{50}, TGI, and LC_{50} values for the compounds **15b** and **18b** in the NCI60 panel

	15b			18b			Cabozantinib		
Cell line	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}	GI_{50}	TGI	LC_{50}
Leukemia									
K-562	1.10	4.90	>100	0.89	>100	>100	0.25	3.16	>100
SR	0.63	>100	>100	3.24	>100	>100	2.00	25.12	>100
CNS cancer									
SF-539	0.25	2.04	>100	0.85	4.79	56.23	1.58	12.59	>100
U251	0.59	>100	>100	2.82	16.60	>100	3.98	>100	>100
Melanoma									
LOX IMVI	1.91	5.37	>100	1.74	3.47	6.92	2.51	15.85	>100
SK-MEL-2	2.40	14.45	>100	2.51	6.46	45.71	7.94	25.12	>100
Breast cancer									
MDA-MB-231/ATCC	2.00	6.46	60.26	2.45	8.51	>100	3.16	39.81	>100
HS 578T	0.29	2.09	>100	1.66	7.41	>100	0.79	10.00	>100
Mean (all 60 cell lines)	1.91	38.02	91.20	2.09	23.99	87.10	2.58	35.40	97.80

Note: Values are in μM.

[a]GI_{50}, TGI, and LC_{50}; concentrations where 50% growth inhibition, total growth inhibition, and 50% cell lethality are observed.

negative mode was performed on a Waters Prospec Q instrument, ionized by electrospray (ESI). Liquid chromatography-mass spectrometry was performed on a Thermo Finnigan LCQ Deca XP Plus using a gradient from 10 to 90% acetonitrile in water over 10 min and preparative high-performance liquid chromatography (HPLC) was performed on a Waters Delta Prep 4000, using a gradient from 20 to 80% acetonitrile in water, collecting fractions of 10 ml/min. Chemical purity was >95% for the biologically tested structures.

The InChI codes of the investigated compounds together with some biological activity data are provided as Supporting Information.

4.1.2 | Synthesis of 1-((4-fluorophenyl)carbamoyl)-cyclopropanecarboxylic acid (6a)

Triethylamine (0.68 ml, 4.88 mmol) was added via syringe to a solution of cyclopropane-1,1-dicarboxylic acid (579 mg, 4.45 mmol) in THF (10 ml) at 0°C. The solution was stirred for 15 min at 0°C before $SOCl_2$ (0.33 ml, 4.54 mmol) was added via syringe. After another 15 min of stirring, 4-fluoroaniline (0.574 mg, 5.17 mmol) in THF (5 ml) was added via cannula at 0°C, and the solution was then stirred at ambient temperature for 20 hr. The reaction mixture was quenched with NaOH (30 ml, 1 M) and diluted with EtOAc (10 ml). The phases were separated, and the organic phase was extracted with NaOH (2 × 10 ml, 1 M). The combined basic extracts were then acidified to pH 1–2 with HCl (1 M), and the title compound was achieved by suction filtration as a white solid (0.41 g, 41%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.71 (s, 1H), 7.60–7.57 (m, 2H), 7.15–7.10 (m, 2H), 1.39 (s, 4H).[24]

4.1.3 | Synthesis of 1-((2,4,6-trifluorophenyl)-carbamoyl)cyclopropanecarboxylic acid (6b)

The title compound was achieved in a similar manner as **6a** using cyclopropane-1,1-dicarboxylic acid (363 mg, 2.79 mmol) and 2,4,6-trifluoroaniline (476 mg, 3.24 mmol) and obtained as a white solid (0.217 g, 30%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.25 (s, 1H), 7.22–7.17 (m, 2H), 1.50–1.46 (m, 2H), 1.44–1.40 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.64, 167.83, 159.09, 156.60, 111.52, 100.77, 27.15, 18.22. HRMS (ESI–) *m/z* calcd. for $C_{11}H_7F_3NO_3$ $[M–H]^-$: 258.0384, found 258.0382.

TABLE 4 Percent inhibition of the kinases at 1 μM of **15b**, **18b**, and **18d**

	Percent inhibition at 1 μM						
Compound	RET	ALK	ROS	c-Met	VEGFR2	EGFR	c-Kit
15b	97	39	90	95	97	22	61
18b	99	80	97	99	100	28	75
18d	92	28	96	97	98	18	71
Cabozantinib, **1**	99	38	91	99	93	19	94

Note: Cabozantinib was included as a reference.

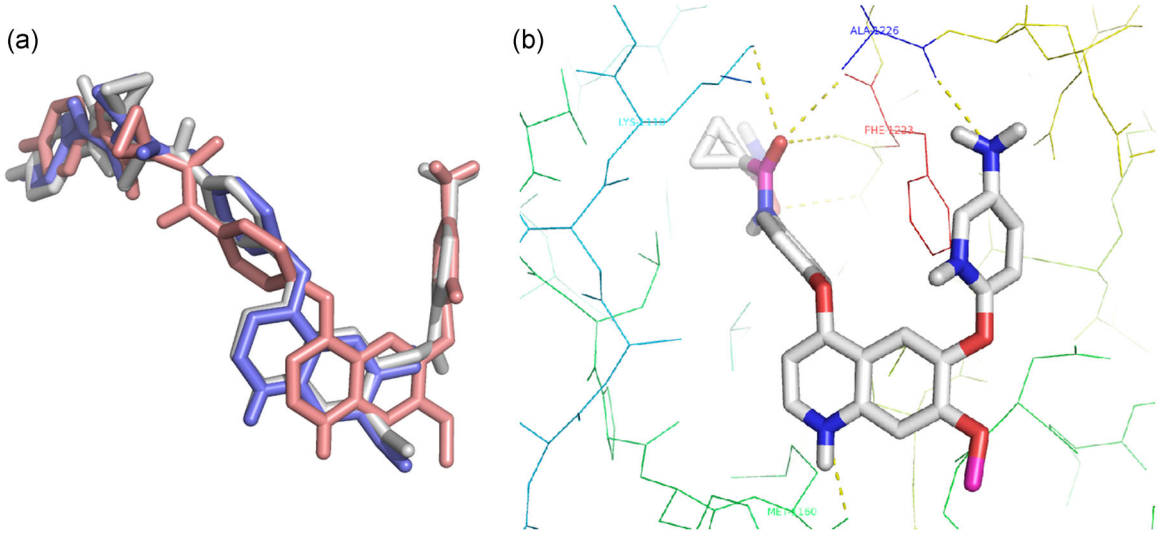


FIGURE 3 (a) Overlaid structures of cabozantinib (blue), **15b** (white), and **18b** (pink) in the active site of c-Met. (b) Main polar interactions with the enzyme active site exemplified with **18b**. Some protein residues are removed for clarity

4.1.4 | Synthesis of 1-(3-(benzyloxy)-4-methoxyphenyl)ethanone (7)

Benzyl bromide (10.7 ml, 90.1 mmol) was added to a stirred solution of 3-hydroxy-4-methoxy acetophenone, **6** (13.5 g, 81.4 mmol) and K_2CO_3 (18.6 g, 134.6 mmol) in DMF (100 ml). The solution was stirred at 40°C for 18 hr, and then diluted with EtOAc (80 ml) and water (80 ml). The crude mixture was extracted with EtOAc (2 × 50 ml), washed with water (4 × 50 ml) and brine (50 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The title compound was achieved as a white solid (18.9 g, 91%) and used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.56 (m, 2H), 7.46 (d, 2H, *J* = 7.2 Hz), 7.38 (t, 2H, *J* = 7.6 Hz), 7.3 (t, 1H, *J* = 7.3 Hz), 6.91 (d, 1H, *J* = 9.2 Hz), 5.19 (s, 2H), 3.94 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.82, 154.05, 148.16, 136.69, 130.48, 128.73, 128.17, 127.66, 123.66, 112.85, 110.54, 71.08, 56.22, 26.34.[27]

4.1.5 | Synthesis of 1-(5-(benzyloxy)-4-methoxy-2-nitrophenyl)ethanone (8)

7 (18.9 g, 73.8 mmol) was dissolved in DCM (250 ml) and cooled to 0°C on an ice bath. HNO_3 (10 ml, 223.8 mmol) was slowly added over 10 min, before H_2SO_4 (8 ml, 150.1 mmol) was added over 10 min. The solution was then stirred at ambient temperature for 15 min before it was washed with water (100 ml) and saturated $NaHCO_3$ solution (100 ml) until neutral. The organic phase was dried over $MgSO_4$ and concentrated on a rotary evaporator. The title compound was achieved as a light yellow solid (20.4 g, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.47–7.34 (m, 5H), 6.81 (s, 1H), 5.22 (s, 2H), 3.98 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0, 153.2, 150.3, 138.9, 135.2, 132.6, 129.0, 128.7, 127.6, 110.7, 107.3, 71.7, 56.7, 30.4. HRMS (ESI+) *m/z* calcd. for $C_{16}H_{15}NNaO_5$ $[M+Na]^+$: 324.0842, found 324.0843.

4.1.6 | Synthesis of 1-(2-amino-5-(benzyloxy)-4-methoxyphenyl)ethanone (9)

Iron (17 g, 304.4 mmol), NH_4Cl (19 g, 312.5 mmol), and **8** (20.4 g, 67.6 mmol) were weighed out in a round-bottom flask and water (150 ml) and EtOH (200 ml) were added. The reaction mixture was stirred for 3 hr at 70°C and then cooled and filtered through Celite, which was then washed with EtOAc (150 ml). The filtrate was then washed with water (150 ml) and brine (100 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The crude mixture was purified by column chromatography (heptane/EtOAc, 2:1). The title compound was achieved as an off-white solid (16.4 g, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.43 (m, 5H), 7,16 (s, 1H), 6.17 (s, 1H), 5.07 (s, 2H), 3.90 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.66, 156.57, 147.53, 138.97, 137.40, 128.67, 128.13, 127.87, 119.19, 111.08, 99.65, 73.12, 55.95, 27.81. HRMS (ESI+) *m/z* calcd. for $C_{16}H_{17}NNaO_3$ $[M+Na]^+$: 294.1101, found 294.1102.

4.1.7 | Synthesis of 6-(benzyloxy)-7-methoxyquinolin-4-ol (10)

9 (16.4 g, 60.3 mmol) and sodium ethoxide (17 g, 250 mmol) were weighed out in a round-bottom flask, put under argon, dissolved in DME (200 ml) and stirred for 30 min. Ethyl formate was added via syringe, and the mixture was stirred for 24 hr at room temperature. The solution was then made neutral using 1 M HCl, and the solids formed were filtered off and washed with water (100 ml). The filtrate was extracted with EtOAc (2 × 80 ml), washed with water (100 ml) and brine (100 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The crude product was purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2), and the product was achieved as a light brown solid (16.9 g, 99%). ^{1}H NMR (400 MHz, methanol-d_4): δ 7.90 (d, 1H, *J* = 7.2 Hz), 7.70 (s, 1H), 7.49 (d, 2H, *J* = 7.6 Hz), 7.38 (t, 2H, *J* = 7.6 Hz), 7.32 (d, 1H, *J* = 7.2 Hz), 7.04

(s, 1H), 6.33 (d, 1H, *J* = 6.8 Hz), 5.18 (s, 2H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, methanol-d_4): δ 175.2, 157.2, 149.6, 140.9, 138.2, 137.7, 129.6, 129.2, 128.9, 119.1, 107.4, 105.7, 100.0, 72.0, 56.9. HRMS (ESI+) *m/z* calcd. for $C_{17}H_{15}NNaO_3$ $[M+Na]^+$: 304.0944, found 304.0944.

4.1.8 | Synthesis of 6-(benzyloxy)-7-methoxy-4-(4-nitrophenoxy)quinoline (11)

10 (16.9 g, 60.2 mmol) and Cs_2CO_3 (39.1 g, 120 mmol) were weighed out in a round-bottom flask, dissolved in DMF (200 ml) and acetonitrile (150 ml), and stirred for 20 min. 1-Fluoro-4-nitrobenzene (21.67 g, 153.6 mmol) was then added over 5 min via syringe. The mixture was stirred at 55°C for 24 hr, then diluted with EtOAc (200 ml) and washed with water (4 × 150 ml) and brine (100 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The crude mixture was purified by column chromatography (heptane/EtOAc, 4:1, heptane/EtOAc/MeOH, 5:5:2), and the title compound was achieved as an yellow solid (5 g, 21%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, 1H, *J* = 4.8 Hz), 8.28 (d, 2H, *J* = 9.2 Hz), 7.55 (s, 1H), 7.42 (d, 2H, *J* = 5.6 Hz), 7.37 (s, 1H), 7.35–7.28 (m, 3H), 7.18 (d, 2H, *J* = 9.2 Hz), 6.72 (d, 1H, *J* = 5.6 Hz), 5.25 (s, 2H), 4.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.6, 158.7, 154.4, 149.7, 148.0, 144.5, 136.0, 128.8, 128.3, 127.5, 126.4, 119.6, 116.7, 107.6, 106.5, 101.2, 71.1, 56.5. HRMS (ESI+) *m/z* calcd. for $C_{23}H_{19}N_2O_5$ $[M+H]^+$: 403.1288, found 403.1287.

4.1.9 | Synthesis of 4-((6-(benzyloxy)-7-methoxyquinolin-4-yl)oxy)aniline (12)

Iron (6.6 g, 118.2 mmol), NH_4Cl (6.5 g, 107.7 mmol), and **11** (5 g, 12.5 mmol) were weighed out in a round-bottom flask, and water (80 ml) and EtOH (100 ml) were added. The reaction mixture was stirred for 3 hr at 70°C, and then cooled and filtered through Celite, which was then washed with EtOAc (150 ml). The organic filtrate was then washed with water (150 ml) and brine (100 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The title compound was achieved as a light brown solid (3.89 g, 84%), and used without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, 1H, *J* = 5.2 Hz), 7.67 (s, 1H), 7.52 (d, 2H, *J* = 7.2), 7.43 (s, 1H), 7.40 (t, 2H, *J* = 7.6 Hz), 7.35–7.31 (m, 1H), 6.97 (d, 2H, *J* = 8.4 Hz), 6.75 (d, 2H, *J* = 8.8 Hz), 6.42 (d, 1H, *J* = 5.2 Hz), 5.29 (s, 2H), 4.04 (s, 3H), 3.71 (bs, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 153.5, 148.8, 148.7, 146.6, 146.2, 144.3, 136.5, 128.7, 128.2, 127.8, 122.3, 116.4, 116.0, 107.8, 102.8, 101.6, 71.0, 56.3. HRMS (ESI+) *m/z* calcd. for $C_{23}H_{21}N_2O_3$ $[M+H]^+$: 373.1547, found 373.1546.

4.1.10 | Synthesis of *N*-(4-((6-(benzyloxy)-7-methoxyquinolin-4-yl)oxy)phenyl)-*N*-(4-fluorophenyl)-cyclopropane-1,1-dicarboxamide (13a)

6a (0.560 g, 2.51 mmol), HATU (1.28, 3.37 mmol), and DMF (40 ml) were placed in a round-bottom flask, and then DIPEA (0.87 ml, 4.99 mmol) was added. Aniline **12** (0.814 g, 2.19 mmol) dissolved in DMF (40 ml) was added after 10 min. The mixture was stirred for 20 hr at ambient temperature, and then diluted with EtOAc (60 ml), washed with water (4 × 30 ml) and brine (2 × 30 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The solid was further purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2), and the title compound was achieved as a white solid (0.767 g, 61%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.17 (s, 1H), 10.04 (s, 1H), 8.49 (d, 1H, *J* = 5.2 Hz), 7.76 (d, 2H, *J* = 8.8 Hz), 7.66 (s, 1H), 7.65–7.62 (m, 2H), 7.52, d, 2H, *J* = 6.8 Hz), 7.42 (s, 1H), 7.42 (t, 2H, *J* = 7.6 Hz), 7.38–7.33 (m, 1H), 7.22, (d, 2H, *J* = 9.2 Hz), 7.15 (t, 2H, *J* = 8.8 Hz), 6.45 (d, 1H, *J* = 5.6 Hz), 5.26 (s, 2H), 3.96 (s, 3H), 1.48 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.2, 168.1, 160.1, 157.1, 152.8, 149.5, 148.8, 148.4, 136.5, 136.6, 135.1, 128.4, 128.0, 122.4, 122.4, 122.2, 121.1, 115.1, 115.1, 114.9, 107.8, 103.2, 100.6, 70.0, 55.8, 31.5, 15.9. HRMS (ESI+) *m/z* calcd. for $C_{34}H_{29}FN_3O_5$ $[M+H]^+$: 578.2086, found 578.2086.

4.1.11 | Synthesis of *N*-(4-((6-(benzyloxy)-7-methoxyquinolin-4-yl)oxy)phenyl)-*N*-(2,4,6-trifluorophenyl)cyclopropane-1,1-dicarboxamide (13b)

6b (0.616 g, 2.38 mmol), HATU (1.8 g, 4.73 mmol), and DMF (40 ml) were placed in a round-bottom flask, and then DIPEA (0.87 ml, 4.99 mmol) was added. Aniline **12** (0.811 g, 2.18 mmol) dissolved in DMF (40 ml) was added after 10 min. The mixture was stirred for 20 hr at room temperature. The mixture was then diluted with EtOAc (60 ml), washed with water (4 × 30 ml) and brine (2 × 30 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The solid was further purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2). The title compound was achieved as a white solid (0.827 g, 62%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.39 (s, 1H), 9.64 (s, 1H), 8.48 (d, 1H, *J* = 5.2 Hz), 7.78 (d, 2H, *J* = 8.8 Hz), 7.66 (s, 1H), 7.51 (d, 2H, *J* = 6.8 Hz), 7.42 (s, 1H), 7.42 (t, 2H, *J* = 7.6 Hz), 7.37–7.33 (m, 1H), 7.28 (t, 2H, *J* = 8.4 Hz), 7.22 (d, 2H, *J* = 9.0 Hz), 6.44 (d, 1H, *J* = 5.2 Hz), 5.26 (s, 2H), 3.95 (s, 3H), 1.59–1.50 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.9, 167.7, 159.9, 156.9, 152.7, 149.6, 148.9, 148.3, 146.5, 136.5, 136.1, 128.4, 128.0, 122.0, 121.1, 115.1, 111.3, 108.0, 103.1, 101.1, 100.8, 100.6, 100.5, 70.0, 55.8, 30.3, 16.2. HRMS (ESI+) *m/z* calcd. for $C_{34}H_{27}F_3N_3O_5$ $[M+H]^+$: 614.1897, found 614.1896.

4.1.12 | Synthesis of *N*-(4-fluorophenyl)-*N*-(4-((6-hydroxy-7-methoxyquinolin-4-yl)oxy)phenyl)-cyclopropane-1,1-dicarboxamide (14a)

13a (0.174 g, 0.301 mmol) was placed under argon in a round-bottom flask and dissolved in dry ethanol (6 ml). Pd/C (50% water content, 10% loading, 67 mg, 0.0315 mmol Pd) was added under an argon atmosphere, before 1,4-cyclohexadiene (0.28 ml, 3.01 mmol) was added via syringe. The reaction mixture was heated for 6 hr at 80°C and then filtered through Celite, which was then washed with EtOAc

(20 ml). The organic filtrate was washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The crude was further purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2), and the title compound was achieved as a white solid (0.114 g, 78%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.08 (s, 1H), 10.32 (s, 1H), 10.05 (s, 1H), 8.72 (d, 1H, *J* = 6 Hz), 7.84 (d, 2H, *J* = 8 Hz), 7.71 (s, 1H), 7.67–7.61 (m, 2H), 7.62 (s, 1H), 7.34 (d, 2H, *J* = 8.4 Hz), 7.15 (t, 2H, *J* = 8 Hz), 6.74 (d, 1H, *J* = 6 Hz), 4.03 (s, 3H), 1.49 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.24, 168.16, 164.87, 155.79, 149.68, 148.02, 142.41, 137.66, 135.19, 122.48, 122.41, 122.30, 121.30, 115.75, 115.16, 114.94, 103.27, 102.79, 100.32, 56.43, 31.72, 15.41. HRMS (ESI+) *m/z* calcd. for $C_{27}H_{23}FN_3O_5$ $[M+H]^+$: 488.1616, found 488.1615.

4.1.13 | Synthesis of *N*-(4-((6-hydroxy-7-methoxyquinolin-4-yl)oxy)phenyl)-*N*-(2,4,6-trifluorophenyl)cyclopropane-1,1-dicarboxamide (14b)

13b (0.186 g, 0.303 mmol) was placed under argon in a round-bottom flask and dissolved in dry ethanol (15 ml). Pd/C (50% water content, 10% loading, 60 mg, 0.028 mmol Pd) was added under an argon atmosphere, before 1,4-cyclohexadiene (0.28 ml, 3.01 mmol) was added via syringe. The mixture was heated for 6 hr at 80°C and then filtered through Celite, which was then washed with EtOAc (30 ml). The organic filtrate was washed with water (15 ml) and brine (15 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The crude was further purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2), and the title compound was achieved as a white solid (0.125 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.36 (s, 1H), 9.94 (s, 1H), 9.64 (s, 1H), 8.43 (d, 1H, *J* = 5.2 Hz), 7.74 (d, 2H, *J* = 8.8 Hz), 7.45 (s, 1H), 7.37 (s, 1H), 7.28 (t, 2H, *J* = 8.4 Hz), 7.19 (d, 2H, *J* = 8.8 Hz), 6.42 (d, 1H, *J* = 5.2 Hz), 3.95 (s, 3H), 1.58–1.49 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.8, 167.6, 159.5, 159.3, 152.3, 149.9, 147.9, 147.4, 145.9, 135.9, 122.1, 120.7, 115.8, 107.8, 103.2, 102.4, 101.1, 100.8, 100.5, 55.6, 30.3, 16.2. HRMS (ESI+) *m/z* calcd. for $C_{27}H_{21}F_3N_3O_5$ $[M+H]^+$: 524.1428, found 524.1428.

4.1.14 | Synthesis of 4-(4-(1-((4-fluorophenyl)-carbamoyl)cyclopropane-1-carboxamido)phenoxy)-7-methoxyquinolin-6-yl 4-nitrobenzoate (15a)

14a (51 mg, 0.105 mmol) and Cs_2CO_3 (85 mg, 0.261 mmol) were weighed out in a round-bottom flask, dissolved in DMF (3 ml) and stirred for 10 min. 4-Nitrobenzoyl chloride was then added, and the resulting mixture was stirred for 5 hr at ambient temperature. The solution was diluted with EtOAc (10 ml) and water (10 ml), extracted with EtOAc (2 × 10 ml), washed with NaOH (3 × 10 ml, 1 M), water (4 × 10 ml), and brine (10 ml), and then dried over $MgSO_4$ and concentrated on a rotary evaporator. No further purification was needed, and the title compound was achieved as a white solid (25 mg, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.48 (s, 1H), 8.76 (s, 1H), 8.63 (d, 1H, *J* = 5.6 Hz), 8.42 (d, 2H, *J* = 8.8 Hz), 8.37 (d, 2H, *J* = 8.8 Hz), 8.15 (s, 1H), 7.63 (d, 2H, *J* = 8.8 Hz), 7.62 (s, 1H), 7.48–7.44 (m, 2H), 7.15 (d, 2H, *J* = 9.2 Hz), 7.04 (t, 2H, *J* = 8.8 Hz), 6.50 (d, 1H, *J* = 5.2 Hz), 3.98 (s, 3H), 1.74–1.62 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.41, 168.87, 163.19, 162.11, 159.95 (d, *J* = 245 Hz), 153.94, 151.28, 151.16, 150.54, 149.45, 140.35, 135.31, 134.58, 133.19 (d, *J* = 3 Hz), 131.63, 123.90, 122.90, (d, *J* = 8 Hz), 122.64, 121.75, 116.03, 115.81, 114.88, 108.87, 103.27, 56.42, 29.34, 17.72. HRMS (ESI+) *m/z* calcd. for $C_{34}H_{25}FN_4O_8$ $[M+H]^+$: 637.1729, found 637.1726.

4.1.15 | Synthesis of 4-(4-(1-((4-fluorophenyl)-carbamoyl)cyclopropane-1-carboxamido)phenoxy)-7-methoxyquinolin-6-yl 4-aminobenzoate (15b)

Iron (21 mg, 0.286 mmol), NH_4Cl (26 mg, 0.486 mmol), and **15a** (21 mg, 0.033 mmol) were weighed out in a round-bottom flask, and water (1 ml) and EtOH (2 ml) were added. The reaction mixture was stirred for 3 hr at 70°C, and then cooled and filtered through Celite, which was then washed with EtOAc (10 ml). The organic filtrate was then washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The crude was further purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2), and the title compound was achieved as a white solid (12 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (s, 1H), 9.02 (s, 1H), 8.56 (d, 1H, *J* = 5.6 Hz), 8.09 (s, 1H), 8.04 (d, 2H, *J* = 8.8 Hz), 7.59 (d, 2H, *J* = 9.2 Hz), 7.55 (s, 1H), 7.49–7.45 (m, 2H), 7.12 (d, 2H, *J* = 9.2 Hz), 7.03 (t, 2H, *J* = 8.8 Hz), 6.71 (d, 2H, *J* = 8.8 Hz), 6.45 (d, 1H, *J* = 5.2 Hz), 4.20 (bs, 2H) 3.96 (s, 3H), 1.72–1.64 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.19, 169.13, 165.13, 162.06, 159.85 (d, *J* = 245 Hz), 158.63, 154.78, 151.80, 150.64, 141.22, 135.11, 133.32 (d, *J* = 3 Hz), 132.76, 122.80 (d, *J* = 7 Hz), 122.67, 121.73, 118.21, 115.99, 115.83, 115.76, 115.02, 114.03, 108.40, 103.05, 56.35, 29.24, 17.80. HRMS (ESI+) *m/z* calcd. for $C_{34}H_{27}FN_4O_6$ $[M+H]^+$: 607.1987, found 607.1984.

4.1.16 | Synthesis of 4-(4-(1-((4-fluorophenyl)-carbamoyl)cyclopropane-1-carboxamido)phenoxy)-7-methoxyquinolin-6-yl 4-(trifluoromethyl)benzoate (15c)

14a (36 mg, 0.0738 mmol), HATU (50 mg, 0.131 mmol), DMAP (10 mg, 0.0819 mmol), and 4-(trifluoromethyl)benzoic acid (36 mg, 0.189 mmol) were weighed out in a round-bottom flask and dissolved in THF (2 ml) and DMA (1 ml), and the reaction mixture was stirred overnight at ambient temperature. The mixture was then diluted with water (5 ml) and EtOAc (5 ml), extracted with EtOAc (2 × 5 ml), washed with water (4 × 5 ml) and brine (5 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The crude was further purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2), and the title compound was achieved as a white solid (26 mg, 53%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.19 (s, 1H), 10.05 (s, 1H), 8.65 (d, 1H, *J* = 5.2 Hz), 8.37 (d, 2H, *J* = 8 Hz), 8.29 (s, 1H), 8.01 (d, 2H, *J* = 8.4 Hz), 7.76 (d, 2H, *J* = 8.8 Hz), 7.63 (s, 1H), 7.66–7.62

(m, 2H), 7.25 (d, 2H, J = 8.8 Hz), 7.15 (t, 2H, J = 9.2 Hz), 6.51 (d, 1H, J = 5.2 Hz), 3.95 (s, 3H), 1.47 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.12 (merged C=O), 163.20, 160.94, 158.26 (d, J = 241 Hz), 153.30, 151.80, 149.29, 149.13, 139.79, 136.60, 135.16 (d, J = 2 Hz), 132.25, 130.80, 126.09, 126.05, 122.45, 122.37, 122.21, 121.08, 115.12, 114.90, 114.60 (d, J = 20 Hz), 109.14, 103.03, 56.38, 31.55, 15.38. HRMS (ESI+) m/z calcd. for $C_{35}H_{26}F_4N_3O_6$ $[M+H]^+$: 660.1752, found 660.1750.

4.1.17 | Synthesis of *N*-(4-((6-(difluoro(phenyl)-methoxy)-7-methoxyquinolin-4-yl)oxy)phenyl)-*N*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (16)

14a (50 mg, 0.103 mmol) and Cs_2CO_3 (50 mg, 0.150 mmol) were weighed out in a round-bottom flask, dissolved in DMF (2 ml) and stirred for 10 min. Chloro difluoromethylbenzene (0.02 ml, 0.152 mmol) was then added via syringe, and the mixture was stirred for 20 hr at 100°C. The mixture was then diluted with water (5 ml) and EtOAc (5 ml), extracted with EtOAc (2 × 5 ml), washed with water (4 × 5 ml) and brine (5 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The crude was further purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2), and the title compound was achieved as a white solid (4 mg, 6%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.51 (s, 1H), 8.65 (s, 1H), 8.57 (d, 1H, J = 5.6 Hz), 8.3 (s, 1H), 7.83 (d, 2H, J = 6.8 Hz), 7.67 (d, 3H, J = 8.8 Hz), 7.55–7.45 (m, 5H), 7.19 (d, 2H, J = 8.8 Hz), 7.06 (t, 2H, J = 8.8 Hz), 6.52 (d, 1H, J = 5.6 Hz), 4.05 (s, 3H), 1.87–1.65 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 170.10, 168.69, 167.56, 160.89, 159.27, 158.94, 148.34, 143.27, 142.41, 137.34, 132.93, 131.57, 128.79, 125.82, 123.27, 123.22, 122.87, 121.67, 116.06, 115.91, 115.15, 114.96, 102.44, 101.90, 57.56, 29.83, 18.33. HRMS (ESI+) m/z calcd. for $C_{34}H_{27}F_3N_3O_5$ $[M+H]^+$: 614.1897, found 614.1896.

4.1.18 | Synthesis of *N*-(4-fluorophenyl)-*N*-(4-((7-methoxy-6-(2,2,2-trifluoroethoxy)quinolin-4-yl)oxy)-phenyl)cyclopropane-1,1-dicarboxamide (17a)

14a (50 mg, 0.103 mmol) and Cs_2CO_3 (69 mg, 0.212 mmol) were weighed out in a round-bottom flask, dissolved in DMF (1 ml), and stirred for 10 min. 1,1,1-Trifluoro-2-iodoethane (82.5 mg, 0.393 mmol) in DMF (1 ml) was then added via syringe, and the mixture was stirred for 5 hr at 110°C. The mixture was then diluted with water (5 ml) and EtOAc (5 ml) and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 5 ml), and the combined organic phases were washed with water (4 × 5 ml) and brine (5 ml), dried over $MgSO_4$ and concentrated on a rotary evaporator. The crude product was further purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2), and the title compound was achieved as a white solid (19 mg, 33%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.58 (s, 1H), 8.76 (s, 1H), 8.51 (s, 1H), 7.67 (s, 1H), 7.66 (d, 2H, J = 8.8 Hz), 7.55 (s, 1H), 7.49–7.46 (m, 2H), 7.16 (d, 2H, J = 8.8 Hz), 7.04 (t, 2H, J = 8.8 Hz), 6.49 (d, 1H, J = 5.1 Hz), 4.55 (q, 2H, J = 8.1 Hz), 4.04 (s, 3H), 1.78–1.72 (m, 2H), 1.70–1.65 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ 169.53, 168.86, 161.86, 161.18, 158.75, 153.90, 150.49, 147.75, 135.46, 133.18, 128.86, 127.80, 123.00, 122.92, 122.64, 121.77, 116.04, 115.82, 104.18, 67.18 (d, J = 35 Hz), 56.47, 31.06, 29.30, 17.86. HRMS (ESI+) m/z calcd. for $C_{29}H_{24}F_4N_3O_5$ $[M+H]^+$: 570.1647, found 570.1646.

4.1.19 | Synthesis of *N*-(4-((7-methoxy-6-(2,2,2-trifluoroethoxy)quinolin-4-yl)oxy)phenyl)-*N*-(2,4,6-trifluorophenyl)cyclopropane-1,1-dicarboxamide (17b)

14b (75 mg, 0.144 mmol) and Cs_2CO_3 (94 mg, 0.289 mmol) were weighed out in a round-bottom flask, dissolved in DMF (1 ml), and stirred for 10 min. 1,1,1-Trifluoro-2-iodoethane (0.03 ml, 0.304 mmol) in DMF (1 ml) was then added via syringe, and the mixture was stirred for 5 hr at 110°C. The mixture was then diluted with water (5 ml) and EtOAc (5 ml) and the phases were separated. The aqueous phase was extracted with EtOAc (2 × 5 ml), and the combined organic phases were washed with water (4 × 5 ml) and brine (5 ml), dried over $MgSO_4$ and concentrated on a rotary evaporator. The crude product was further purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2), and the title compound was achieved as a white solid (4 mg, 5%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.51 (d, 1H, J = 5.3 Hz), 7.77 (s, 1H), 7.66 (d, 2H, J = 8.9 Hz), 7.56 (s, 1H), 7.15 (d, 2H, J = 8.9 Hz), 6.78 (t, 2H, J = 7.5 Hz), 6.49 (d, 1H, J = 5.5 Hz), 4.55 (t, 2H, J = 8.1 Hz), 4.05 (s, 3H), 1.89–1.86 (m, 2H), 1.71–1.68 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 171.36, 168.01, 162.24, 160.51, 159.33, 157.55, 149.75, 148.36, 136.23, 127.76, 124.17, 122.88, 122.59, 122.11, 121.72, 121.28, 115.62, 109.86, 107.29, 103.89, 103.06, 100.96, 66.94, 56.88, 28.52, 19.07. HRMS (ESI+) m/z calcd. for $C_{29}H_{22}F_6N_3O_5$ $[M+H]^+$: 606.1458, found 606.1457.

4.1.20 | Synthesis of *N*-(4-fluorophenyl)-*N*-(4-((7-methoxy-6-((5-nitropyridin-2-yl)oxy)quinolin-4-yl)oxy)-phenyl)cyclopropane-1,1-dicarboxamide (18a)

2-Chloro-5-nitropyridine (35 mg, 0.221 mmol) was added to a solution of **14a** (45 mg, 0.0922 mmol) and Cs_2CO_3 (91 mg, 0.279 mmol) in DMF (3 ml). The mixture was stirred for 1.5 hr at ambient temperature, and the mixture was then diluted with water (5 ml) and EtOAc (5 ml), extracted with EtOAc (2 × 5 ml), washed with water (4 × 5 ml) and brine (5 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The crude was further purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2), and the title compound was achieved as a light yellow solid (44 mg, 79%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 10.05 (s, 1H), 8.98 (d, 1H, J = 2.8 Hz), 8.67–8.64 (m, 1H), 8.62 (d, 1H, J = 2.8 Hz), 8.08 (s, 1H), 7.76 (d, 2H, J = 8.8 Hz), 7.66–7.62 (m, 2H), 7.62 (s, 1H), 7.37 (d, 1H, J = 8.8 Hz), 7.24 (d, 2H, J = 8.8 Hz), 7.14 (t, 2H, J = 8.8 Hz), 6.52 (d, 1H, J = 5.2 Hz), 3.87 (s, 3H), 1.48 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.12, 168.11, 166.04, 161.13, 158.24 (d, J = 240 Hz), 153.99, 151.21, 149.03, 148.56, 144.48, 141.84, 140.63, 136.62, 135.79, 135.13 (d, J = 2 Hz), 122.38 (d, J = 8 Hz), 122.16, 121.06,

115.09, 114.87, 114.04, 111.12, 108.91, 102.99, 56.25, 31.51, 15.39. HRMS (ESI+) *m/z* calcd. for $C_{32}H_{25}FN_5O_7$ $[M+H]^+$: 610.1730, found 610.1729.

4.1.21 | Synthesis of *N*-(4-((6-((5-aminopyridin-2-yl)-oxy)-7-methoxyquinolin-4-yl)oxy)phenyl)-*N*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (18b)

Iron (58 mg, 1.03 mmol), NH_4Cl (44 mg, 0.823 mmol), and **18a** (29 mg, 0.048 mmol) were weighed out in a round-bottom flask, and water (2 ml) and EtOH (3 ml) were added. The reaction mixture was stirred for 3 hr at 70°C, and then cooled and filtered through Celite, which was then washed with EtOAc (10 ml). The organic filtrate was then washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The crude was further purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2), and the title compound was achieved as a white solid (15 mg, 54%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.18 (s, 1H), 10.05 (s, 1H), 8.57, (d, 1H, *J* = 5.6 Hz), 7.74 (d, 2H, *J* = 8.8 Hz), 7.65 (s, 1H), 7.65–7.62 (m, 2H), 7.53 (s, 1H), 7.48 (d, 1H), 7.20 (d, 2H, *J* = 8.8 Hz), 7.14 (t, 2H, *J* = 8.8 Hz), 7.13–7.10 (m, 1H), 6.85 (d, 1H, *J* = 8.4 Hz), 6.46 (d, 1H, *J* = 5.2 Hz), 3.90 (s, 3H), 1.48 (s, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.15 (merged C=O), 160.75, 158.27 (d, *J* = 241 Hz), 154.39, 153.87, 149.93, 149.16, 147.33, 146.07, 141.63, 136.56, 135.16 (d, *J* = 2 Hz), 132.00, 125.72, 122.42 (d, *J* = 8 Hz), 122.17, 121.07, 115.12, 114.90, 111.80, 110.46, 108.26, 102.89, 55.99, 31.56, 15.41. HRMS (ESI+) *m/z* calcd. for $C_{32}H_{27}FN_5O_5$ $[M+H]^+$: 580.1991, found 580.1988.

4.1.22 | Synthesis of *N*-(4-((7-methoxy-6-((5-nitropyridin-2-yl)oxy)quinolin-4-yl)oxy)phenyl)-*N*-(2,4,6-trifluorophenyl)cyclopropane-1,1-dicarboxamide (18c)

2-Chloro-5-nitropyridine (29 mg, 0.183 mmol) was added to a solution of **14b** (46 mg, 0.0879 mmol) and Cs_2CO_3 (77 mg, 0.236 mmol) in DMF (3 ml). The mixture was stirred for 1.5 hr at ambient temperature, and the mixture was then diluted with water (5 ml) and EtOAc (5 ml), extracted with EtOAc (2 × 5 ml), washed with water (4 × 5 ml) and brine (5 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The crude was further purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2), and the title compound was achieved as a light yellow solid (53 mg, 93%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.42 (s, 1H), 9.65 (s, 1H), 8.98 (d, 1H, *J* = 2.8 Hz), 8.66–8.64 (m, 1H), 8.62 (d, 1H, *J* = 2.8 Hz), 8.06 (s, 1H), 7.76 (d, 2 H, *J* = 8.8 Hz), 7.62 (s, 1H), 7.36 (d, 1H, *J* = 8.8 Hz), 7.30–7.23 (m, 4H), 6.51 (d, 1H, *J* = 5.6 Hz), 3.87 (s, 3H), 1.56–1.51 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.84, 167.68, 166.08, 160.93, 160.1 (dt, J = 245, 15 Hz), 158.1 (ddd, J = 249, 7 Hz), 153.89, 151.41, 149.19, 148.88, 144.50, 141.80, 140.64, 136.38, 135.79, 122.03, 121.14, 114.93, 113.99, 111.4 (dd, J = 17.0, 4.9 Hz), 111.13, 109.18, 103.00, 100.8 (dt, J = 26.4, 2.5), 56.24, 30.34, 16.24. HRMS (ESI+) *m/z* calcd. for $C_{32}H_{23}F_3N_5O_7$ $[M+H]^+$: 646.1544, found 646.1540.

4.1.23 | Synthesis of *N*-(4-((6-((5-aminopyridin-2-yl)-oxy)-7-methoxyquinolin-4-yl)oxy)phenyl)-*N*-(2,4,6-trifluorophenyl)cyclopropane-1,1-dicarboxamide (18d)

Iron (27 mg, 0.483 mmol), NH_4Cl (31 mg, 0.58 mmol), and **18c** (32 mg, 0.050 mmol) were weighed out in a round-bottom flask, and water (2 ml) and EtOH (3 ml) were added. The reaction mixture was stirred for 3 hr at 70°C, and then cooled, filtered through Celite, which was then washed with EtOAc (10 ml). The organic filtrate was then washed with water (10 ml) and brine (10 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. The crude was further purified by column chromatography (heptane/EtOAc, 1:1, heptane/EtOAc/MeOH, 5:5:2), and the title compound was achieved as a white solid (18 mg, 59%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.39 (s, 1H), 9.64 (s, 1H), 8.55 (d, 1H, *J* = 5.4 Hz), 7.74 (d, 2H, *J* = 9 Hz), 7.63 (s, 1H), 7.51 (s, 1H), 7.46 (d, 1H, *J* = 3 Hz), 7.28 (t, 2H, *J* = 7.8 Hz), 7.20 (d, 2H, *J* = 8.4 Hz), 7.10 (dd, 1H, *J* = 3, 9 Hz), 6.84 (d, 1H, *J* = 9 Hz), 6.43 (d, 1H, *J* = 5.4 Hz), 3.89 (s, 3H), 1.55–1.50 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 169.87, 167.75, 160.28, 159.17, 157.39, 154.31, 153.93, 150.45, 149.51, 148.02, 144.98, 141.70, 136.32, 131.89, 125.74, 122.09, 121.12, 114.97, 111.82, 110.46, 108.92, 102.97, 100.90, 56.06, 30.53, 16.45. HRMS (ESI+) *m/z* calcd. for $C_{32}H_{25}F_3N_5O_5$ $[M+H]^+$: 616.1802, found 616.1800.

4.1.24 | Synthesis of *N*-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-*N*-(2,4,6-trifluorophenyl)-cyclopropane-1,1-dicarboxamide (19)

6b (0.167 g, 0.64 mmol), HATU (0.424 g, 1.12 mmol), and DMF (5 ml) were placed in a round-bottom flask, and then DIPEA (0.26 ml, 1.49 mmol) was added. 4-((6,7-Dimethoxyquinolin-4-yl)oxy)aniline[28] (0.156 g, 0.53 mmol) dissolved in DMF (5 ml) was added after 10 min. The mixture was stirred for 20 hr at room temperature. The mixture was then diluted with EtOAc (20 ml), washed with water (4 × 10 ml) and brine (2 × 10 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. This solid was further purified on a preparative HPLC, and the title compound was achieved as a white solid (0.128 g, 45%). ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.55 (s, 1H), 9.64 (s, 1H), 8.79 (d, 1H, *J* = 6.4 Hz), 7.86 (d, 2H, *J* = 8.9 Hz), 7.73 (s, 1H), 7.62 (s, 1H), 7.38 (d, 2H, *J* = 8.8 Hz), 7.29 (t, 2H, *J* = 8.5 Hz), 6.79 (d, 1H, *J* = 6.5 Hz), 4.03 (s, 3H), 4.03 (s, 3H), 1.59–1.53 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 169.99, 167.83, 165.19, 160.2 (ddd, *J* = 249.16, 8 Hz), 158.2 (dt, *J* = 246, 15 Hz), 155.82, 150.99, 148.12, 143.56, 137.88, 137.45, 122.16, 121.48, 115.35, 111.4 (t, *J* = 27 Hz), 103.20, 100.9 (td, *J* = 17, 5 Hz), 100.57, 100.26, 56.56, 56.42, 30.48, 16.32. HRMS (ESI+) *m/z* calcd. for $C_{28}H_{23}F_3N_3O_5$ $[M+H]^+$: 538.1584, found 538.1585.

4.1.25 | Synthesis of *N*-(4-((6,7-dimethoxyquinolin-4-yl)oxy)phenyl)-*N*-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide (1, cabozantinib)

6a (0.146 g, 0.654 mmol), HATU (0.415 g, 1.09 mmol), and DMF (5 ml) were placed in a round-bottom flask, and then DIPEA (0.26 ml, 1.49 mmol) was added. 4-((6,7-Dimethoxyquinolin-4-yl)oxy)aniline (0.157 g, 0.53 mmol) dissolved in DMF (5 ml) was added after 10 min. The mixture was stirred for 20 hr at room temperature. The mixture was then diluted with EtOAc (20 ml), washed with water (4 × 10 ml) and brine (2 × 10 ml), dried over $MgSO_4$, and concentrated on a rotary evaporator. This solid was further purified using preparative HPLC. The title compound was achieved as a white solid (0.112 g, 42%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.20 (s, 1H), 8.74 (s, 1H), 8.46 (d, 1H, *J* = 6.4 Hz), 7.99 (s, 1H), 7.79 (d, 2H, *J* = 8.8 Hz), 7.63 (s, 1H), 7.50–7.47 (m, 2 H), 7.18 (d, 2H, *J* = 8.8 Hz), 7.02 (t, 2H, *J* = 8.8 Hz), 6.68 (d, 1H, *J* = 6.4 Hz), 4.13 (s, 3H), 4.09 (s, 3H), 1.83–1.81 (m, 2H), 1.69–1.67 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 170.08, 169.04, 165.83, 159.99 (d, *J* = 246 Hz), 156.86, 151.90, 148.70, 141.46, 138.70, 137.12, 133.15 (d, *J* = 3 Hz), 123.24 (d, *J* = 8 Hz), 122.95, 121.65, 116.20, 115.87 (d, *J* = 23 Hz), 102.67, 101.13, 100.05, 57.37, 56.74, 29.21, 18.23. MS (ESI+) *m/z* calcd. for $C_{28}H_{24}FN_3O_5$ $[M+H]^+$: 502.2, found 502.3.

4.2 | Biological assays

4.2.1 | Enzymatic c-Met assay

The enzymatic c-Met assay was purchased from Cyclex and used following the manufacturer's instructions. Briefly, while placed on ice, recombinant c-Met was added to wells precoated with a substrate, and the reaction was started by adding buffer containing the inhibitors in appropriate dilutions. The plate was incubated at 30°C for 60 minutes. After washing with buffer, a horseradish peroxidase-conjugated detection antibody PY-39 was added to each well, and then incubated at ambient temperature for 60 min. The TMB substrate was added after another round of washing and then incubated at ambient temperature for 10 min. Stop solution was then added, and absorbance was measured using a spectrophotometric plate reader (Perkin Elmer VICTOR™ X3). The results were analyzed using GraphPad Prism 7.04.

4.2.2 | Cell proliferation

Testing was performed by the Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute. The studies were performed using the NCI60 panel and performed according to their internal procedures.[29]

4.3 | Molecular docking

Dockings were performed using AutoDock Vina[25] via the PyRX[26] interface. The experimental crystal structure of foretinib in the enzymatic site of c-Met was downloaded from the Protein Data Bank (PDB: 3LQ8). This was prepared for docking using AutoDock Tools (ligand and water removed and polar hydrogens added). The ligands were build using Avogadro,[30] and initial geometrical optimization was done using the same software. After docking, visualization of the conformations and binding interactions were done in PyMol.[31] Initially, the performance of the docking method was validated by the redocking of the experimental ligand.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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