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FULL PAPER

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Development of a multigram synthesis of the bradykinin receptor 2 agonist FR-190997 and analogs thereof

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Abstract

Using Fujisawa's B2R agonist FR-190997, we recently demonstrated for the first time that agonism at the bradykinin receptor type 2 (B2R) produces substantial antiproliferative effects. FR-190997 elicited an EC_{50} of 80 nM in the triple-negative breast cancer cell line MDA-MB-231, a much superior performance to that exhibited by most approved breast cancer drugs. Consequently, we initiated a program aiming primarily at synthesizing adequate quantities of FR-190997 to support further in vitro and in vivo studies toward its repurposing for various cancers and, in parallel, enable the generation of novel FR-190997 analogs for an SAR study. Prerequisite for this endeavor was to address the synthetic challenges associated with the FR-190997 scaffold, which the Fujisawa chemists had constructed in 20 steps, 13 of which required chromatographic purification. We succeeded in developing a 17-step synthesis amenable to late-stage diversification that eliminated all chromatography and enabled access to multigram quantities of FR-190997 and novel derivatives thereof, supporting further anticancer research based on B2R agonists.

KEYWORDS

B2R agonists, cancer, FR-190997, late-stage diversification, quinolines

1 | INTRODUCTION

Bradykinin (BK) is an endogenous peptidic hormone (a nonapeptide), and a key member of the kallikrein-kinin system exerting potent and diverse biological activities through two receptors, B1R and B2R.[1–3] The former is the inducible form whose expression is triggered by inflammation and stress whereas the latter is constitutively expressed in almost every cell type and tissue. BK action has been shown to be implicated in inflammation, nociception, autoimmunity, vasculopathy, viral infections, diabetes, CNS disorders, and many cancers.[3–16] In the context of cancer, biochemical research had established that long-term stimulation of B1R and B2R induce growth and invasion of cancer cells which led to an intense interest in developing initially peptidic and more recently nonpeptidic B2R (and B1R) antagonists as antiproliferative agents.[17–23] Intrigued by seemingly contradictory reports supporting that peptidic B1R agonists also provide antiproliferative benefits,[24–26] we decided to test a B2R agonist anticipating that

Authors would like to dedicate this article to the memory of Professor Donald Bethell.

the more widespread expression of the B2 receptor could precipitate a more profound antiproliferative effect. Cognizant of the pharmacokinetic issues of peptidic molecules, we sought a nonpeptidic B2R agonist to test our hypothesis. In contrast to the impetus in B2R antagonist research, B2R agonists remained overlooked and limited to peptidic analogs of bradykinin. The first and only examples of nonpeptidic B2R agonists have been reported by Fujisawa[27,28] (legacy company of Astellas) and were discovered during Fujisawa's research in understanding the structural features of novel nonpeptidic scaffolds that impart potent and selective B2R antagonism.[29–33] From this effort emerged FR-190997 (Figure 1), a highly selective and potent (IC_{50} 3 nm), nonpeptidic partial agonist of B2 receptor of bradykinin (B2R), that was investigated initially for cardiovascular indications and later for the treatment of glaucoma/ocular hypertension in animal studies.[34–36]

Consequently, we synthesized and tested FR-190997 in the triple-negative breast cancer (TNBC) cell line MDA-MB-231 and found it possessed remarkable antiproliferative potential (EC_{50} 80 nM), much superior to that of established peptidic and nonpeptidic B2R antagonists and to most approved breast cancer drugs.[37] In addition, we reported several prototype analogs of FR-190997 possessing similar antiproliferative properties with the aza analog of FR-190997, where the oxygen atom at the eight-position of the quinoline system is replaced by NH, being the best in that set. This work essentially introduced a new indication for B2R partial agonists and sparked a new research program in our laboratory concerning the synthesis of novel FR-190997 analogs for an SAR study aiming to explore the repurposing potential of B2R partial agonists as anticancer agents. This initiative faced a significant synthetic challenge as FR-190997 is a relatively large and complex molecule possessing multiple functional groups and substituents across several interlinked aromatic systems. The original Fujisawa synthesis of FR-190997 that we also employed for supplying our initial studies, comprises of 20 synthetic steps, 13 of which involve chromatographic purifications (Scheme 1) delivering the desired active pharmaceutical ingredient (API), FR-190997, in 0.32% yield. In this report, we communicate our process research efforts culminating in a synthesis for FR-190997 that does not require any chromatographic purification and which we have demonstrated at multigram scale. In addition, by using our new process, we prepared several novel analogs of FR-190997 to support an SAR with respect to antiproliferative potential.

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

2.1.1 | Fujisawa medicinal chemistry route

In a series of articles, Fujisawa described an extensive medicinal chemistry initiative in developing B2R antagonists.[29–33] Once the key scaffold emerged, dozens of variations in the key three domains (Figure 1) were generated and hybridized. One of the key findings in this work was that the substituent at the four-position of the quinoline moiety could switch the functional activity of the whole scaffold from antagonist to agonist with the 2-picolyloxy derivative being one of the most prominent advocates in imparting B2R agonism.[27,28]

The Fujisawa synthesis of this specific quinoline warhead (**2**, Scheme 1 in purple) involved five steps starting from *o*-anisidine, however, all steps, bar the first one, required chromatography. In executing this synthesis, we found that the high-temperature cyclisation rarely proceeded with a yield exceeding 30%. In addition, isolation of the highly polar intermediate **2** from the alkylation step was particularly troublesome, partly due to the difficulty in removing the 1,3-dimethyl-2-imidazolidinone (DMI) used as the solvent which also complicated the subsequent chromatography. These issues rendered the development of an alternative route to **2** a priority in our work. Fujisawa accomplished the synthesis of the dichloroanilide domain (**7**, Scheme 1 in green) in eight straightforward steps although the scale-up of this subsequence was also hampered by the chromatographic purifications required in four out of the eight steps. The same issues manifested in the synthesis of the substituted cinnamic acid derivative **9** due to the Wittig reaction involved (Scheme 1 in blue) including its condensation with **7** to form **10** and in the subsequent deprotection of the TBDPS group. The end game in

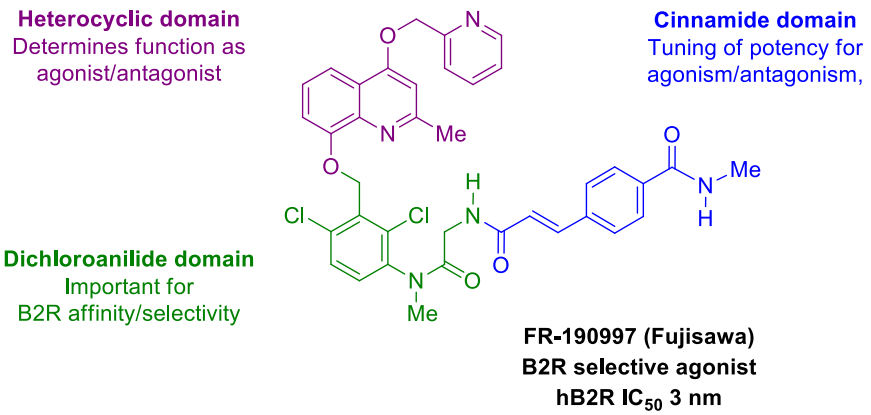
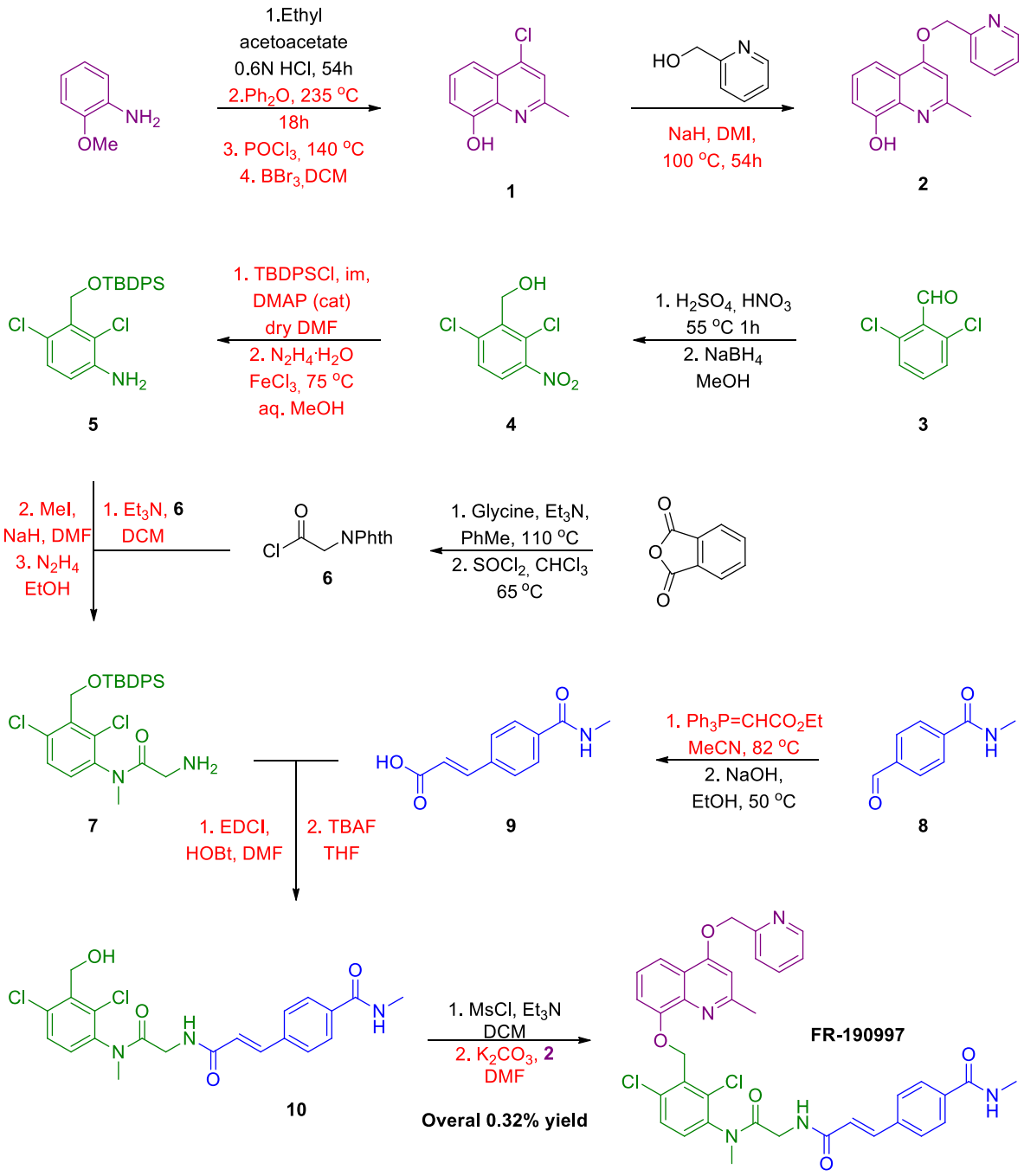


FIGURE 1 Structure of FR-190997.



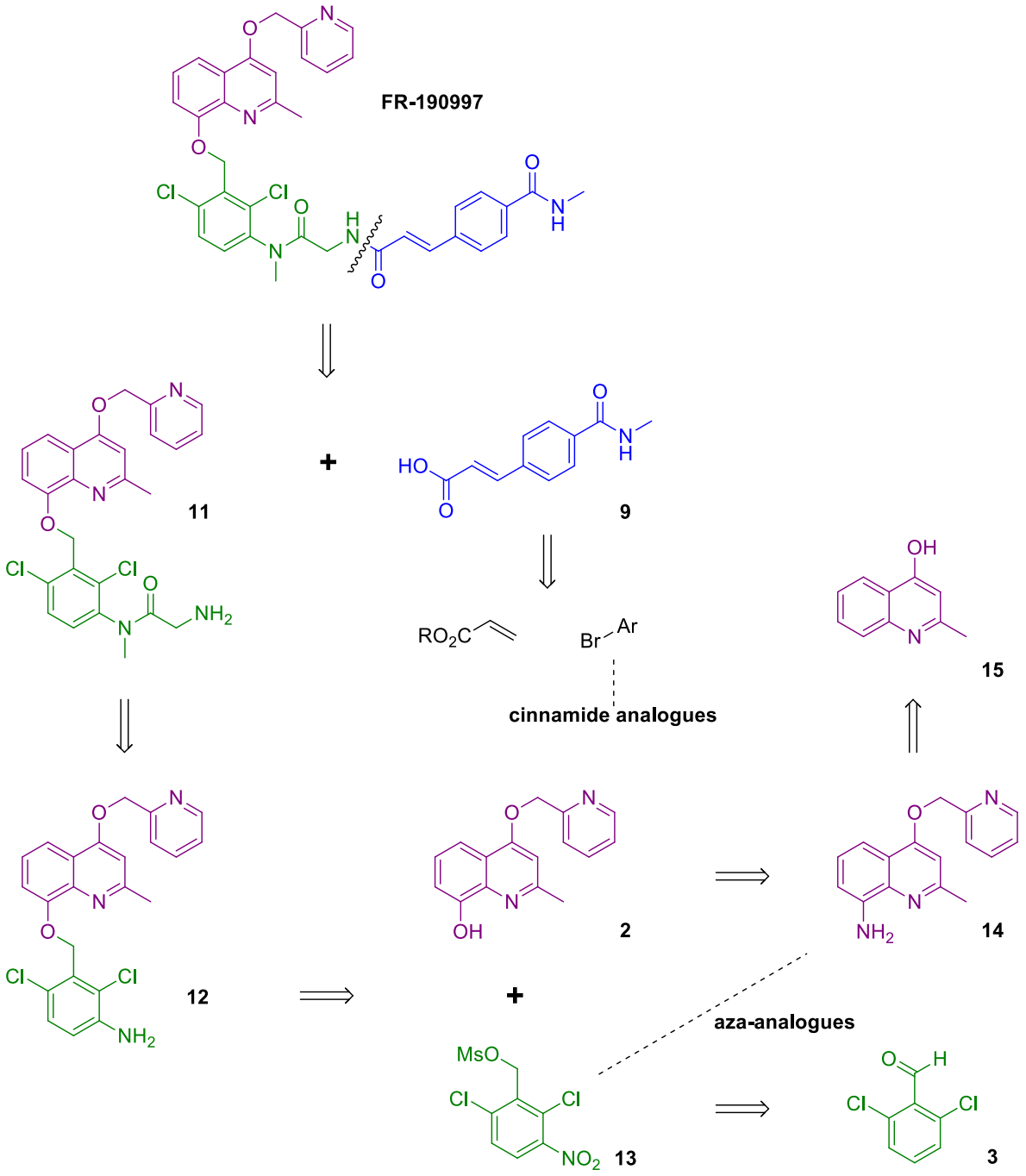
SCHEME 1 Medicinal chemistry route to FR-190997 as reported by Fujisawa. The steps with conditions in red color indicate requirement for chromatography.

Fujisawa's synthesis of FR-190997 concerned the attachment of the 8-hydroxyquinoline domain **2** to the advanced intermediate **10** via an S_N2 reaction with the mesylate derivative of the latter. Isolation of FR-190997 also required chromatography. In addition to the 13 chromatographic purifications, we also identified several cost contributors whose replacement or omission presented additional challenges for developing a viable synthesis. Aldehyde **8**, involved in the preparation of the cinnamic acid derivative **9**, costs more than 350 €/g and TBDPS-Cl although not expensive itself, it carries shipment restrictions that render its overall cost far from reasonable considering that it ultimately ends up entirely as waste. Furthermore, from a process development perspective, it was deemed desirable to dial out reactions at extreme temperatures such as the second step in the formation of **1** and obnoxious reagents such as the BBr_3 used in the subsequent demethylation step. Ideally, this demethylation, including the O-TBDPS and N-Phth protection-deprotection steps should be removed or drastically reduced to gain on atom economy, waste streams, cost, length of synthesis and batch cycle time.

2.1.2 | Development of an alternative route

It must be pointed out that the Fujisawa synthetic efforts aimed at variations in each of the three key domains to support an SAR study and were not specific to FR-190997. In addition, Fujisawa's work established that the precise quinoline and dichloroanilide domains present in FR-190997 are essentially indispensable for potent B2R agonism and some, yet limited, chemical space for generating potent analogs existed in the aromatic ring of the cinnamide domain. Our objective was, therefore, to develop a synthesis efficient enough to provide gram quantities of FR-190997 and flexible enough to accommodate generation of analogs in the cinnamide domain, including the respective aza analogs at the eight-position of the quinoline ring, as we have shown this atom switch preserves the B2R partial agonism/antiproliferative properties of the scaffold.

Accordingly, our approach pivoted on installing the cinnamide domain last so that the ultimate glycine intermediate **11** could be used as a late-stage diversification point in the synthesis of novel FR-190997 analogs (Scheme 2). The cinnamic acid derivatives required

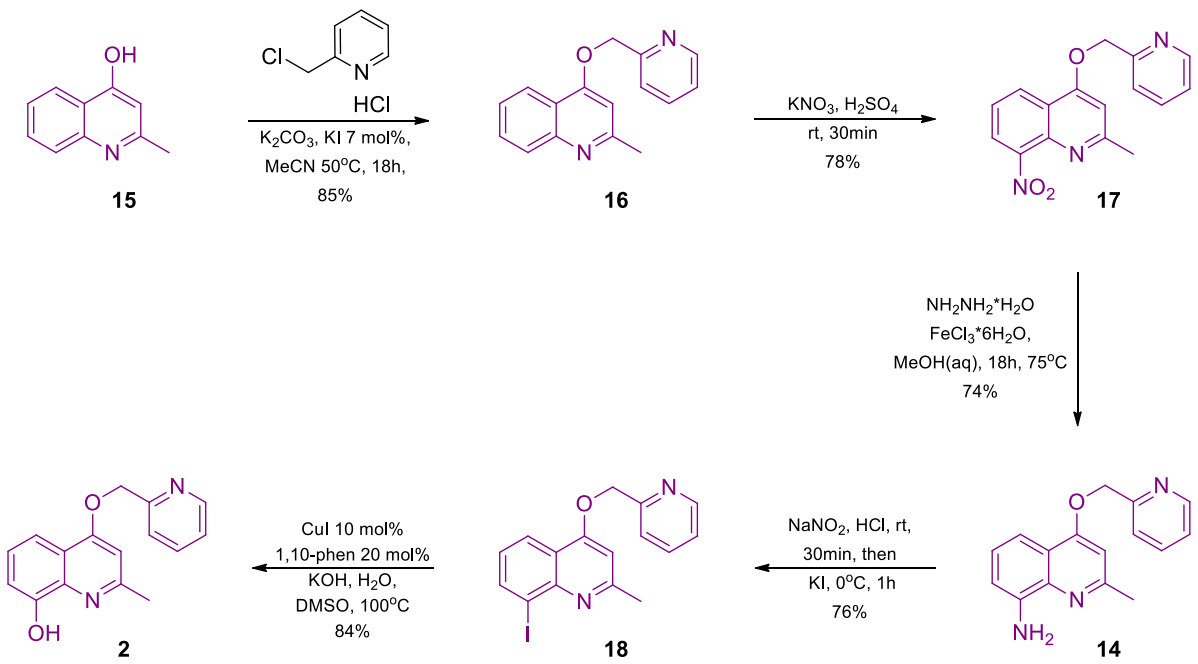


SCHEME 2 Retrosynthetic analysis of a new route to FR-190997 and analogs thereof.

for diversification in this end, including **9** for FR109997, may be accessed by a Heck reaction between appropriate acrylate esters and aryl bromides. Intermediate **11** may be derived from 12 via amide formation with an appropriate N-protected glycine, N-methylation of the anilide and deprotection of the glycine amine. In turn, 12 should be easily accessed by an S_N2 reaction between **2** and **13** followed by reduction of the nitro group, with the latter intermediate being available from **3** following nitration, aldehyde reduction and mesylation of the corresponding benzylic alcohol. For intermediate **2**, we considered several options, including commercially available 4-functionalised 2-methyl-8 hydroxy-(or protected hydroxy)-quinolines but their cost is prohibitive. Instead, we envisaged accessing **2** from the 8-amino analog **14** (via diazotization) because we also wanted to utilize the latter in the generation of aza analogs of both FR-190997 and its related cinnamide variants. Finally, intermediate **14** should be prepared selectively from the relatively inexpensive **15** after alkylation with 2-(chloromethyl)-pyridine followed by nitration (diverted to the eight-position by the 4-picolyloxy ether sterically shielding position 5).

2.1.3 | Synthesis of quinoline intermediates **2** and **14**

Rewardingly, the *O*-alkylation of **15** with 2-(chloromethyl)pyridine (Scheme 3) performed exceptionally well in comparison with the topologically reverse reaction, namely the *O*-arylation of 2-(hydroxymethyl)pyridine employed by Fujisawa. This S_N2 reaction progressed smoothly in either warm acetone or MeCN or DMF in the presence of carbonate bases and worked equally well with the more convenient to use and stable hydrochloride salt of 2-(chloromethyl)pyridine. Using 1.3 eq of the latter and a catalytic amount of KI, allowed the reaction to be completed over 18 h. Aqueous work up removed the excess of the alkylating agent and intermediate **16** was isolated as a red solid in 85% yield and good quality. After testing several nitration conditions, we found that with the use of KNO_3 and conc H_2SO_4, the formation of **17** could be accomplished within 30 min in a regioselective manner as anticipated. Reduction of the nitro group with hydrazine and catalytic $FeCl_3$ provided the key 8-aminoquinolino intermediate **14** which would serve both for the generation of analogs of FR-190997 and as precursor for the quinolin-8-ol intermediate **2**. Nevertheless, the desired NH_2-to-OH transformation proved much more challenging than initially anticipated. Diazotization of **14** followed by several protocols for converting aryldiazonium salts to phenols/hydroxy aromatics,[38–40] led to extensive decomposition of the substrate. Converting the diazonium intermediate of **14** to the iodo analog **18**, provided additional options. Initially, we attempted the direct displacement of the iodide by benzylic alcohol 4 using Pd catalyzed hydroxylation[41–44] or modified alkoxylation[45,46] protocols, but these gave almost invariably the corresponding aldehyde of **4** presumably resulting from β-hydride elimination of the intermediate $ArCH_2O$-Pd(II) complex.[45,46] Modifications of Cu-catalyzed alkoxylation reactions[47,48] were also unsuccessful regardless of the copper salt and ligand. Next, we briefly considered the prospect of the stepwise conversion of **18** to **2** via the corresponding boronic acid or boronate ester intermediate,[49] however, this would add an extra step and cost to the synthesis of **2** and FR-190997. We therefore chose to first investigate the direct Ar-I to Ar-OH transformation according to a protocol reported by the group of



SCHEME 3 New route to intermediate **2** performed at 5-g scale.

You.[50] Indeed, in the presence of KOH in DMSO at 100°C, the CuI/1,10-phenanthroline system worked very well in catalyzing the conversion of 8-iodoquinoline **18** to the key quinolin-8-ol intermediate **2** in 84% yield without the need for chromatography. We commend highly this catalytic reaction not only for enabling such a challenging transformation to be brought about in a single step but also for performing equally well at gram scale. Finally, our new 5-step synthesis of intermediate **2** (Scheme 3) was scaled up to 5 g and delivered the desired intermediate in excellent quality and 31% yield overall (ca 80% per step on average). An additional merit of the route we developed for **2** is that it proceeds via amino intermediate **14** which, as will be discussed below, enables the synthesis of aza analogs of FR-190997.

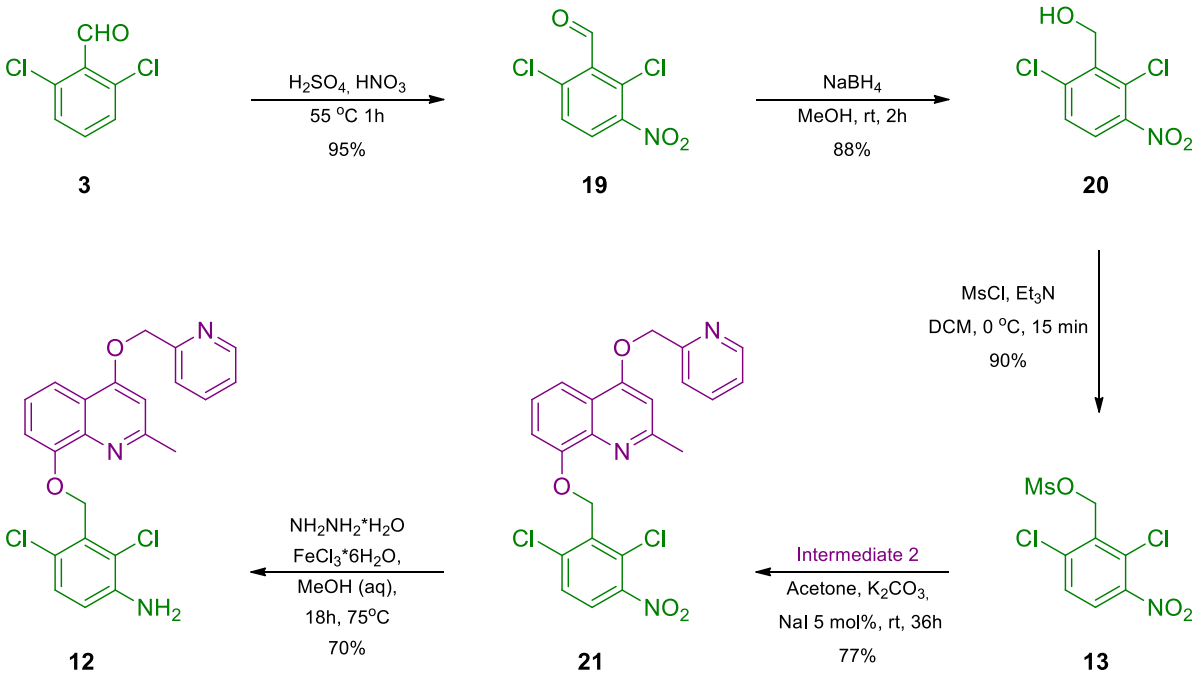
2.1.4 | Synthesis of intermediate **12**

According to our retrosynthetic analysis in Scheme 2, intermediate **12** requires joining intermediates **2** and **13** followed by reduction of the nitro group. The first step toward 13 was the regioselective nitration of **3**, and this was performed as per the Fujisawa protocol described in the original route. We found this to work very well even at multigram scale, affording aldehyde **19** as a pale yellow solid in 95% yield. Reduction of aldehyde **19** to alcohol **20** and formation of its corresponding mesylate **13** proved straight forward, requiring little optimization (88% and 90% yield respectively). For the alkylation of intermediate **2** with mesylate **13**, we tested several sets of conditions regarding solvent, base, additive and temperature before arriving at the optimum set which limits substantially formation of impurities. These were found to arise mainly from decomposition of the mesylate, particularly when attempting to force the reaction to complete faster at high temperatures. Allowing the reaction to progress slower at ambient temperature in acetone with potassium carbonate as base and in the presence of a catalytic amount of sodium iodide, afforded ether **21** as a pale yellow solid in 77% yield and excellent quality.

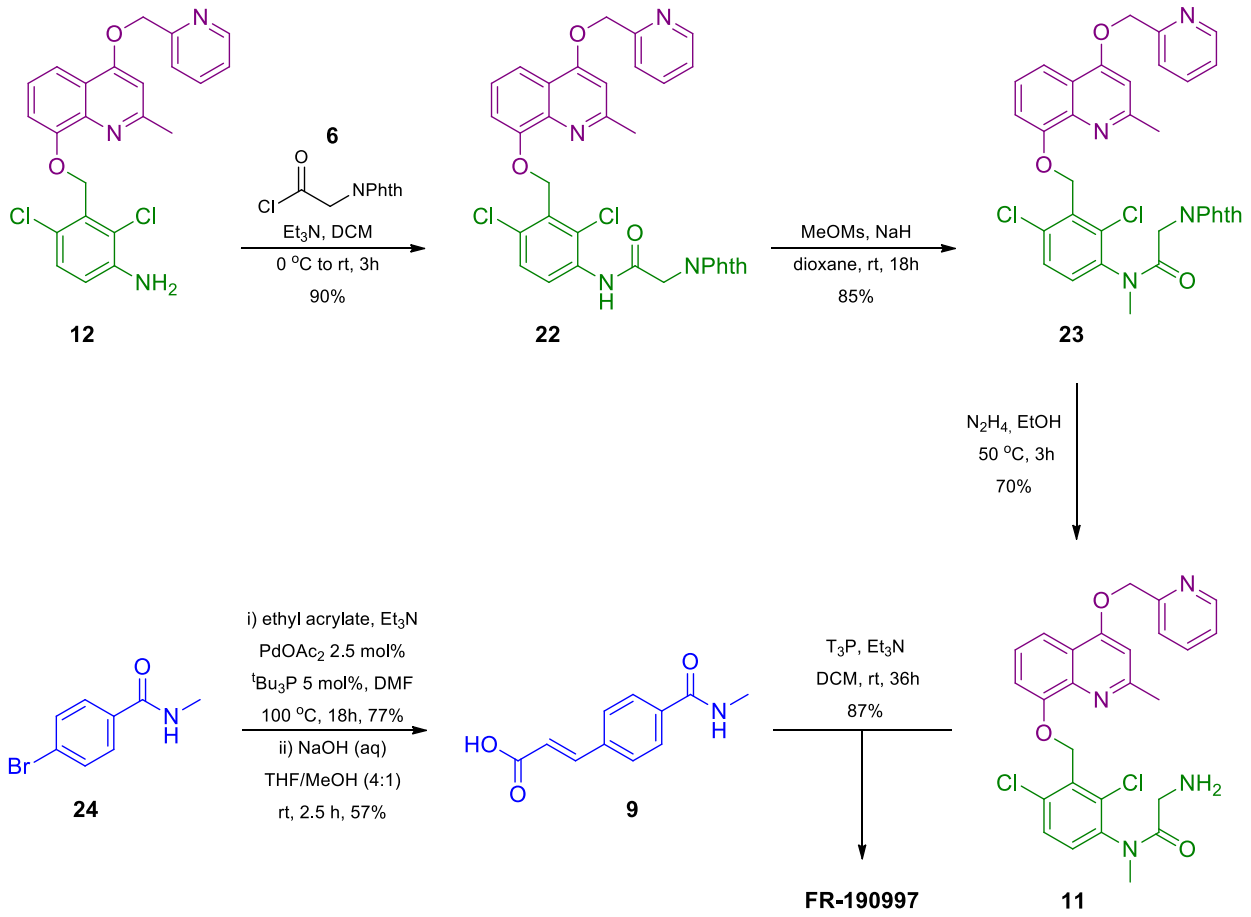
This reaction was of key importance in establishing an alternative convergent route to FR-190997 including the option for a late-stage diversification into other cinnamide analogs. Finally, reduction of the nitro group using the Fujisawa conditions that we also employed for **17**, gave aniline intermediate **12** as a yellow solid in 70% yield. More importantly, starting from **3**, the synthesis of **12**, which encompasses two of the key domains and >60% of FR-190997's structure, was executed successfully at 4-g scale affording the desired intermediate in ca 41% yield over the five steps (83% yield per step on average) (Scheme 4).

2.1.5 | Synthesis of intermediates **11**, **9** and the target molecule FR-190997

Aniline **12** proved uncharacteristically unreactive in forming an amide with N-protected (Boc or Phth) glycine derivatives under a variety of coupling conditions. Corroborating Fujisawa's approach, we also found that the *N*-phthalyl-glycinoyl chloride **6** (Scheme 5) was the only glycine equivalent that enabled useful conversions. In this way, intermediate **22** was generated in 90% provided that 6 was used within 2 weeks from its formation and stored in the fridge, otherwise reactions stalled (despite no visual signs of decomposition after longer periods at cold storage). We also improved the process for the



SCHEME 4 Synthesis of intermediate **12** performed at 4-g scale.



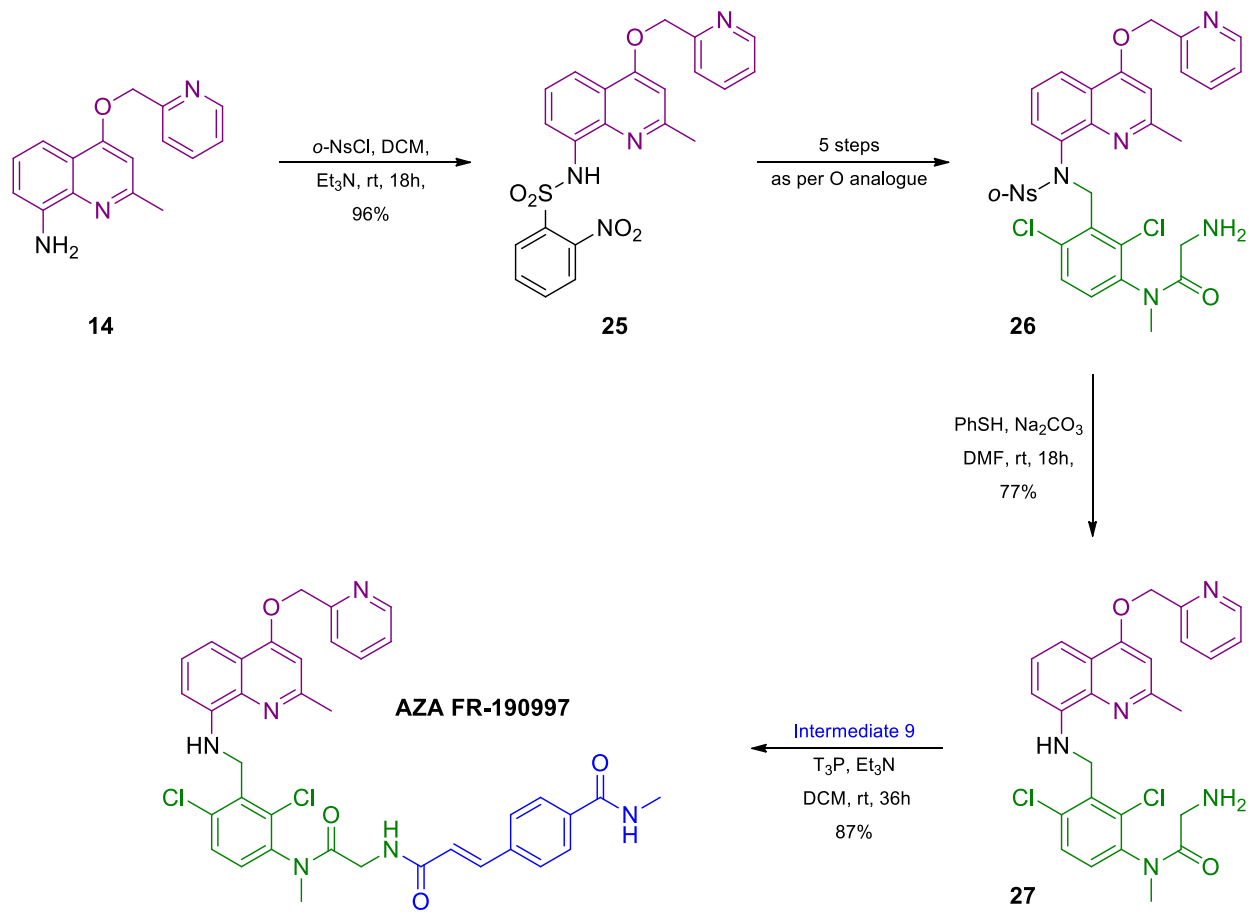
SCHEME 5 End game of the new route to FR-190997.

preparation of **6** by replacing chloroform with toluene without affecting the yield or the quality of the product. The N-installation of the methyl group in anilide **22** was also a challenging task. In our initial execution of the Fujisawa synthesis we successfully replaced the NaH/MeI/DMF protocol with a Mitsunobu reaction using MeOH as the methyl source which increased the yield of **23** from 65% to 70% however the necessity for chromatography was not abolished. We also tried to install the methyl group in aniline **12** before amide formation, but this aniline once again proved inert toward both MeI and Me_2SO_4. In another iteration, we prepared the corresponding formamide and formamidine derivatives of **12**, however, invariable to reducing agent and conditions employed, these were cleaved reforming **12**. In the end, we revisited the methylation of anilide **22** and obtained increased conversions after 24 h at ambient temperature using methyl mesylate and sodium hydride in either DMAc or DMF or dioxane. Attempts to accelerate the reaction and drive it to completion by applying higher temperatures resulted in significant byproduct formation which rendered chromatography a necessity. Nevertheless, allowing more concentrated reactions in DMF or dioxane to be completed at ambient temperature over 18 h, provided for the first time pure **23** in 85% yield. It must be noted that Fujisawa had established that introduction of this methyl group forces the amide bond to attain the *cis* conformation (Scheme 5) and twist out of the plane defined by the dichlorobenzene ring. This conformational preference appears to be essential for the B2R affinity of the scaffold, consequently it cannot not be dispensed from any of the novel analogs that we intend to synthesize. Hydrazinolysis of the phthalimide group in **23** unveiled the glycine derivative **11** in 70% yield, and this was performed with equal success at >1-g scale thus generating stock of this key intermediate for the synthesis of both FR-190997 and novel cinnamide analogs. The substituted cinnamic acid **9** to partner **11** in the final step toward FR-190997, was prepared in two steps from a Heck reaction between ethyl acrylate and *p*-bromo-(*N*-methyl)-benzamide **24** (conveniently prepared from *p*-bromo-benzoyl chloride and excess aqueous methylamine under Schotten-Baumann conditions) followed by hydrolysis of the ethyl ester. After a brief screen of several ligands, palladium pre-catalysts, bases and solvents for the Heck reaction, we quickly established that the conditions shown in Scheme 5, afford 77% yield of the Heck cinnamate ester product. This was subsequently hydrolyzed to generate substituted cinnamic acid **9** in 44% yield overall without the need for chromatography. For the final step in the synthesis of FR-190997 we screened several activators for **9** to promote its condensation with **11**. We found that T3P (50 w/w% solution in EtOAc) in the presence of triethylamine in DCM was provided, after appropriate work up, FR-190997 in 87% yield and excellent quality

without need for chromatography. This amide coupling required 36 h to complete at ambient temperature however we resisted the idea to accelerate the reaction with more forceful conditions as this strategy generated more impurities in previous occasions. The four steps from **12** to FR-190997, comprising the longest linear arm of this last part of the synthesis, operate at ca 46% yield (>82% yield per step on average). Overall, our new synthesis toward FR-190997 involves 17 steps with the longest linear arm being 11 steps (from starting material **15** via intermediate **21**) delivering the API in ca 8% yield. This route has the added advantage of a last stage diversification option into installing other substituted cinnamides thus enabling a SAR on this domain which is currently in progress.

2.1.6 | Synthesis of AZA-FR190997

As mentioned in the beginning of the discussion, we are also interested in generating the aza analog of FR-190997 at the linker joining the quinoline and the dichlorobenzyl domains. The design strategy behind this decision was to investigate the influence of the atom linking these domains in terms of B2R binding and selectivity over B1R as this had not been adequately addressed in Fujisawa's SARs. Replacing the oxygen atom by NH provides a hydrogen bond donor in a region which is critical in imparting agonist or antagonist activity to the molecule and, in addition, lowers the logP of the molecule from 5.61 to 5.24 (values from ChemBioOffice). Toward this end, we used amino intermediate **14** instead of quinolin-8-ol intermediate **2** in the S_N2 reaction with mesylate **13**. In contrast to the *O*-alkylation with **2**, the related *N*-alkylation with **14** did not perform well, producing a significant number of side products under a variety of conditions. In our earlier work, we had constructed both benzylic amine and ether linkages using a Mitsunobu reaction between benzylic alcohol **10** and **25**, the *o*-nosylamide of **14**, or quinolin-8-ol **2** respectively. In those Mitsunobu reactions *o*-nosylamide **25** outperformed **2** (42% and 8% yield respectively) therefore we decided to employ **25**, as its anion, directly in an S_N2 reaction with mesylate **13** (Scheme 6). Indeed, this strategy worked well and the revised S_N2 reaction afforded **25** in 96% yield. By applying the same transformations as per the *O*-analog, **25** was converted to **26** in 5 steps before the *o*-nosyl group was removed by treatment with thiophenolate anion furnishing **27** in 77% yield. Our T3P protocol for the final amide forming step also proved transferable in the condensation of **27** with **9** and generated the AZA FR-190997 in excellent yield and purity. We also established that it was possible to perform the amide coupling of **9** with **26** and remove the *o*-nosyl group in the last step with equal success and



SCHEME 6 Diversion of the new route to FR-1909997 to accommodate the preparation of the aza analog.

overall yields. The synthesis of the aza analog is one step shorter than FR1909997's as the diazotization, iodination and hydroxylation steps in the latter are offset by the attachment and removal of the *o*-nosyl group in the former. More importantly, this synthesis provided AZA FR1909997 was executed on a similar scale and provided a similar yield to our novel analog without the need for chromatography.

2.2 | Pharmacology/biology

As a final quality test, we compared the hB2R binding and antiproliferative effect of FR-190997 samples prepared in our earlier work by the Fujisawa route, which involved chromatographic purifications of several intermediates including FR-190997, against a sample from our new route described herein (no chromatography throughout). We found their performances to be essentially identical (hB2R IC_{50} 3 nM, MDA-MB-231 EC_{50} 80 ± 10 nM and hB2R IC_{50} 3 nM, MDA-MB-231 EC_{50} 70 ± 2 nM respectively). Biochemical assessment of AZA FR1909997 confirmed for the first time that the aza analog is also a selective B2R agonist (hB2R IC_{50} 150 nM, hB1R IC_{50} > 10 μM) possessing a lower logP than FR-190997 (5.24 vs. 5.61) and increased metabolic stability (unpublished data). Furthermore, AZA-FR1909997 also demonstrated significant cellular activity in the triple negative cancer cell line MDA-MB-231 (EC_{50} 170 ± 2 nM) thus corroborating our previous findings regarding its antiproliferative potential (Table 1). We also profiled FR-1909997 and AZA FR-190997 in an MDA-MB-231 growth inhibition assay and demonstrated sustained antiproliferative action over 72 h (Figure 2) devoid of apparent cytostatic or cytotoxicity events, considering that innate metabolic activity was also monitored.

TABLE 1 hB2R selectivity and MDA-MB-231 antiproliferative performance of FR-190997 and AZA FR-190997.

Compound	IC_{50} hB2R (nM)	IC_{50} hB1R (μM)	IC_{50} MDA-MB-231 (nM)
FR-190997	3 ± 0.2	>10	70 ± 2
AZA-FR190997	158 ± 2	>10	170 ± 2

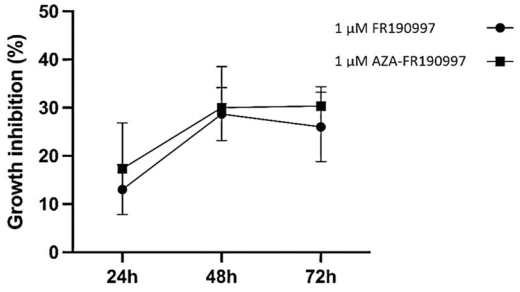


FIGURE 2 MDA-MB-231 growth Inhibition profiles of FR-190997 and AZA FR-190997.

In our previous report, we postulated potential mechanisms of action consistent with FR-190997 antiproliferative responses including B2Rsignalling cascade inhibition through receptor internalization and/or direct permeation of FR-190997 into the cell and engagement of intracellular B2R and related effectors (≠ membrane effectors)[19,37] although action through B2R homo- and heterodimers cannot be dismissed. Work on deciphering the mechanism by which FR-190997 exerts its antiproliferative effects is in progress.

3 | CONCLUSION

We developed a new synthesis for FR-190997 encompassing 17 steps and two points of convergence, with the longest linear arm being 11 steps. The entire synthesis proceeds through crystalline intermediates whose quality may be upgraded by crystallization although this was not necessary in this effort. In addition to being chromatography-free, the reactions involved are safe, efficient, operationally simple and utilize inexpensive materials. More importantly, our synthesis is robust, reproducible at multigram scale, may be completed within 10 laboratory days and delivers excellent quality FR190998 in ca 8% yield (longest linear part; ca 80% yield per step on average). Adjustments to this synthesis allowed for the preparation of novel analog AZA-FR190997 which was also obtained without the use of any chromatography and isolated in similar yield and appropriate quality.

Points for further improvement include reducing the amounts of $Pd/^tBu_3P{\cdot}HBF_4$ and Cu/1,10-phen in the Heck and hydroxylation reaction respectively and improving the overall yield to **9**. In this context, some modifications have already been implemented in the preparation of a novel series of 2-aryl acrylic acids as surrogates of **9** and the respective FR-190997 and AZA-FR190997 derivatives are currently being evaluated for cellular efficacy against various cancers. A report on this work will follow in due course.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

All reagents and solvents were obtained from commercial sources and used without further purification unless otherwise stated. 1H and 13 C NMR spectra were recorded on Bruker spectrometers at 400 or 600 MHz and 100 or 125 MHz, respectively (see the Supporting Information). Chemical shifts were reported on δ scale in ppm with solvent indicated as the internal reference. Coupling constants were reported in Hertz (Hz) and the standard abbreviations indicating multiplicity were used as follows: s = singlet, s(br) = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. High-resolution mass spectrometry (HRMS) experiments were recorded with electrospray ionization (ESI) on Synapt G2-Si mass spectrometer. The purity

of all the final compounds was confirmed to be ≥95% by NMR and/or HPLC using Agilent 1100 with the UV detector set at 220 nm, equipped with a Phenomenex Luna column (50 × 3.0 mm, 2.6 µm) at 40°C, flow of 1.0 mL/min with a solvent gradient of 7% to 95% B over 5.5 min, followed by 0.5 min at 95% B, followed by gradient change to 7% B over 2 min: solvent A = 0.05% TFA in water; solvent B = 0.05% TFA in acetonitrile.

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

4.1.2 | General procedure for the synthesis of FR-190997 and AZA-FR190997

*2-Methyl-4-(pyridin-2-ylmethoxy)quinoline (**16**)*

A round bottom flask (250 mL) was charged with 6.0 g of 4-hydroxy-2-methyl quinoline (**15**) (37.72 mmol, 1eq), 8.0 g of 2-(chloromethyl) pyridine hydrochloride (49.04 mmol, 1.3 eq), 15.64 g K_2CO_3 (113.16 mmol, 3 eq), KI (0.438 g, 2.64 mmol, 7 mol% and 5 vol DMF (0.3 M). The reaction mixture was stirred at 50°C for 18 h and monitored by HPLC. Upon completion, the solvent was removed in vacuo and the mixture was diluted with 90 mL of EtOAc. The organic phase was washed with an aqueous $NaHCO_3$ 5 w/w% (60 mL), water (60 mL), and brine (30 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed to afford 8.0 g (85% yield) of 16 as a red solid; ^{1}H-NMR (600 MHz, $CDCl_3$): δ ppm 8.63 (d, *J* = 4.8 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.29–7.25 (m, 1H), 6.69 (s, 1H), 5.41 (s, 2H), 2.66 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ ppm 160.9, 160.1, 156.1, 149.4, 148.9, 137.0, 129.9, 128.2, 124.9, 123.0, 121.6, 121.2, 119.8, 101.9, 70.7, 25.9. HRMS (*m/z*) $[M+H]^+$ calcd for $C_{16}H_{15}N_2O$ = 251.1184, found = 251.1188.

*2-Methyl-8-nitro-4-(pyridin-2-ylmethoxy)quinoline (**17**)*

A round bottom flask (100 mL) was charged with 6.0 g of compound **16** (24 mmol, 1eq), 19.0 mL of conc. H_2SO_4 and 2.42 g KNO_3 (24 mmol, 1 eq). The reaction mixture was stirred for 30 min at ambient temperature and monitored by HPLC. Upon completion, the mixture was neutralized (pH = 7) with NaOH 1 M and extracted with EtOAc (90 mL, 15 vol). The organic phase was washed with brine (60 mL, 10 vol), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to afford 5.52 g (78%) of 17 as a yellow solid; ^{1}H-NMR (600 MHz, $CDCl_3$): δ ppm 8.65 (d, *J* = 4.3 Hz, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.76 (t, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.30 (dd, *J* = 7.8 and 4.3 Hz, 1H), 6.80 (s, 1H), 5.43 (s, 2H), 2.67 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ ppm 163.4, 160.6, 155.4, 149.6, 147.9, 140.3, 137.1, 125.8, 123.7, 123.4, 123.3, 121.4, 121.2, 103.4, 71.2, 26.4. HRMS (*m/z*) $[M+H]^+$ calcd for $C_{16}H_{14}N_3O_3$ = 296.1035, found = 296.1031.

*2-Methyl-4-(pyridin-2-ylmethoxy)quinolin-8-amine (**14**)*

A round bottom flask (100 mL) was charged with 5.0 g of compound **17** (16.92 mmol, 1 eq), 70 mL of an aqueous MeOH (80% MeOH) (14 vol, 0.25 M solution), 205.04 mg $FeCl_3$*$6H_2O$ (0.76 mmol, 0.045 eq) and 205.04 mg of charcoal. Then, the mixture was heated at 75°C and 2.6 mL N_2H_4*H_2O (84.6 mmol, 5 eq) was added. The reaction mixture was stirred at the same temperature for 18 h and monitored by HPLC. Upon completion, the solvent was removed in vacuo and EtOAc (76 mL, 15.2 vol) was added. The organic phase was washed with aqueous $NaHCO_3$ 5 w/w% (24 mL) and brine (24 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to afford red oil. Addition of Et_2O induced precipitation of solid that was collected by vacuum filtration and washed on the filter with ice-cold Et_2O to afford 3.3 g (74%); of 14 as a yellow solid; ^{1}H-NMR (600 MHz, $CDCl_3$): δ ppm 8.63 (d, *J* = 4.8 Hz, 1H), 7.74 (td, *J* = 8.4 and 1.2 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.57 (dd, *J* = 8.4 and 1.2 Hz, 1H), 7.28–7.22 (m, 2H), 6.91 (dd, *J* = 8.4 and 1.2 Hz, 1H), 6.66 (s, 1H) 5.39 (s, 2H), 4.93 (br.s, 2H), 2.63 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ ppm 157.2, 156.4, 149.3, 143.2, 137.0, 129.0, 128.2, 125.6, 122.9, 121.1, 120.2, 110.9, 109.9, 102.0, 70.6, 25.8. HRMS (*m/z*) $[M+H]^+$ calcd for $C_{16}H_{16}N_3O$ = 266.1293, found = 266.1289.

*8-Iodo-2-methyl-4-(pyridin-2-ylmethoxy)quinoline (**18**)*

A round bottom flask (100 mL) was charged with 24.2 mL H_2O, 3.2 mL of conc. HCl (12 vol in total) and 2.1 g of compound **14** (7.9 mmol, 1 eq) was added under stirring. The resulting mixture was cooled at 0°C and a solution of 0.6 g $NaNO_2$ (8.7 mmol, 1.1 eq) in 5.45 mL (2.7 vol) of water was added, dropwise, and the resulting solution was stirred at the same temperature for 30 min. Then, a solution of 2.77 g of KI (16.6 mmol, 2.1 eq.) in 10.5 mL of water (5 vol), was added, dropwise, giving a red solution. The reaction mixture was stirred at rt for 1 h and monitored by HPLC. Upon completion, the aqueous phase was adjusted to the pH 9 with aqueous $NaHCO_3$ (5 w/w%) and extracted with EtOAc (32 mL, 15.2 vol). The organic phase was washed with aqueous NaS_2O_3 5 w/w% (21 mL, 10 vol) and brine (21 mL, 10 vol), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to afford 2.26 g (76%) of 18 as an orange solid; ^{1}H-NMR: δ ppm 8.64 (ddd, *J* = 4.8, 1.8, and 1.2 Hz, 1H), 8.29 (dd, *J* = 7.5 and 1.2 Hz, 1H), 8.26 (dd, *J* = 7.5 and 1.2 Hz, 1H), 7.75 (td, *J* = 7.8 and 1.8 Hz, 1H), 7.55 (dt, *J* = 7.8 Hz, 1H), 7.28 (ddt, *J* = 7.8, 5.4, and 0.6 Hz, 1H), 7.17 (dd, *J* = 8.4 and 7.8 Hz, 1H), 6.74 (s, 1H), 5.41 (s, 2H), 2.72 (s, 3H); ^{13}C-NMR: δ ppm 161.4, 160.9, 155.9, 149.4, 147.6, 140.4, 137.1, 126.0, 123.1, 122.5, 121.3, 120.3, 102.5,102.4,71.0, 26.2. HRMS (*m/z*) $[M+H]^+$ calcd for $C_{16}H_{14}IN_2O$ = 377.0151, found = 377.0155.

*2-Methyl-4-(pyridin-2-ylmethoxy)quinolin-8-ol (**2**)*

A reaction tube was charged with 10 mL DMSO (5 vol) and 10 mL H_2O. (5 vol) and was degassed by applying successive vacuum and nitrogen purge cycles under stirring. Next, 101.4 mg of CuI (0.532 mmol, 10 mol%), 192 mg of 1.10 phenanthroline (1.064 mol, 20 mol%), 0.90 g of KOH (16 mmol, 3eq) and 2.0 g of 18 (5.32 mmol, 1 eq) were added and the resulting solution was degassed again. The reaction mixture was heated to 100°C, stirred at the same temperature for 18 h and monitored by HPLC. Upon completion, the mixture was diluted with water (100 mL, 50 vol) and the aqueous phase was adjusted to pH 10–11 with aqueous NaOH 1M and

extracted with TMBE (30 mL, 15 vol). The organic phase was discarded, and the aqueous phase was adjusted to pH 6–7 with aqueous HCl 0.1 M. The aqueous phase was extracted with EtOAc (30 mL, 15 vol), washed with H_2O (15.0 mL, 7.5 vol) and brine (10 mL, 5 vol), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo, to afford 1.2 g (84%) of 2 as a beige solid; ^{1}H-NMR (600 MHz, $CDCl_3$): δ ppm 8.64 (d, *J* = 4.8, 1H) 7.75 (td, *J* = 7.8 and 1.2 Hz, 1H), 7.69 (dd, *J* = 8.4 and 1.2 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 8.4 Hz, 1H), 7.27 (dd, *J* = 7.8 and 4.8 Hz, 1H), 7.14 (dd, *J* = 8.4 and 1.2 Hz, 1H), 6.70 (s, 1H), 5.41 (s, 2H), 2.63 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ ppm 161.3, 158.1, 156.1, 151.6, 149.4, 138.9, 137.0, 125.7, 123.0, 121.2, 119.8, 111.9, 110.3, 102.6, 70.8, 25.5. HRMS (*m/z*) $[M+H]^+$ calcd for $C_{16}H_{15}N_2O_2$ = 267.1134, found = 267.1130.

*2,6-Dichloro-3-nitrobenzaldehyde (**19**)*

A round bottom flask (100 mL) was charged with 24 mL of conc.H_2SO_4 and 11.94 mL aqueous HNO_3 65 w/w% (123.4 mmol, 2.7 eq) and the solution was heated to 40°C. Then, 8.0 g of 2.6 dichlorobenzaldehyde 3 (45.6 mmol, 1 eq) were added. The mixture was stirred at the same temperature, strictly for 30 min and was monitored by HPLC. Upon completion, the reaction mixture was cooled to 0°C and 10 mL of water (1.25 vol) were added, producing a slurry. The solid was collected by vacuum filtration, washed on the filter with cold water and dried under vacuum to afford 9.34 g (95%) of 19 as a pale yellow solid; ^{1}H-NMR (600 MHz, $CDCl_3$): δ ppm 10.4 (s, 1H), 7.88 (d, *J* = 6 Hz, 1H), 7.55 (d, *J* = 6 Hz, 1H), 2.16 (s, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ ppm 207.1, 187.1, 139.6, 133.0, 130.1, 128.1, 30.9. HRMS (*m/z*) $[M+H]^+$ calcd for $C_7H_4Cl_2NO_3$ = 219.9568, found = 219.9574.

*(2,6-Dichloro-3-nitrophenyl)methanol (**20**)*

A round bottom flask (100 mL) was charged with 9.28 g of **19** (42.4 mmol, 1 eq) and dissolved in 80 mL of MeOH (17.2 vol). To this solution was added 0.78 g $NaBH_4$, (21 mmol, 0.5 eq), stirred for 2 h at ambient and monitored by HPLC. Upon completion, the solvent was removed in vacuo and DCM (92.8 mL, 10 vol) was added. The organic phase was washed with aqueous $NaHCO_3$ 5 w/w% (46 mL, 5 vol) and water (92 mL, 10 vol), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo, to afford 8.26 g (88%) of 20 as a yellow solid; ^{1}H-NMR (600 MHz, $CDCl_3$): δ ppm 7.71 (d, *J* = 8.7 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 5.05 (s, 2H), 2.16 (s, 1H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ ppm 147.9, 139.8, 138.4, 128.8, 128.6, 125.2, 60.1. HRMS (*m/z*) $[M+H]^+$ calcd for $C_7H_6Cl_2NO_3$ = 221.9725, found = 221.9721.

*2,6-Dichloro-3-nitrobenzyl methanesulfonate (**13**)*

A round bottom flask (25 mL) was charged with 2 g of compound **20** (9.06 mmol, 1 eq). Then, 20 mL DCM (10 vol, 0.45 M solution) and 4.0 mL Et_3N (27.2 mmol, 3 eq) were added, giving a white suspension. The mixture was cooled at 0°C and 1.14 mL MsCl (9.96 mmol, 1.1 eq) was added. The reaction mixture was stirred for 15 min at rt and monitored by HPLC. Upon completion the mixture was diluted with 30 mL DCM, washed with HCl 0.1 M (14 mL), an aqueous mixture of $NaHCO_3$ 5% (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to afford 2.44 g (90% yield) of compound 13 as a pale yellow solid which was used without further purification in the next step.

*8-[(2,6-Dichloro-3-nitrobenzyl)oxy]-2-methyl-4-(pyridin-2-ylmethoxy)quinoline (**21**)*

A round bottom flask (100 mL) was charged with a solution of 2.70 g of **2** (9.04 mmol, 1.2 eq) in 20 mL of acetone (7.4 vol). Next, 2.08 g of K_2CO_3 (15.04 mmol, 2 eq), a catalytic amount of NaI (56.36 mg, 0.376 mmol, 5 mol%) and 2.0 g of 13 (7.52 mmol, 1 eq), were added, giving a green suspension. The reaction mixture was stirred at ambient for 36 h and monitored by HPLC. Upon completion, the solvent was removed in vacuo and to the mixture was added DCM (30 mL, 11 vol). The organic phase was washed successively with aqueous HCl 0.1 M (20 mL, 7.4 vol), water (20 mL, 7.4 vol) and brine (20 mL, 7.4 vol), dried over Na_2SO_4, filtered and the solvent was removed in vacuo to afford 2.72 g (77%) of 21 as a pale yellow solid; ^{1}H-NMR (600 MHz, $CDCl_3$): δ ppm 8.66 (d, *J* = 4.2 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.74–7.80 (m, 2H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 8.66 (t, *J* = 7.8 Hz, 1H), 7.27–7.32 (m, 2H), 6.74 (s, 1H), 5.70 (s, 2H), 5.43 (s, 2H), 2.68 (s, 3H). ^{13}C-NMR (600 MHz, $CDCl_3$): δ ppm 159.3, 156.0, 154.0, 149.3 (2C), 140.1, 137.0 (2C), 130.0, 128.7, 128.6 (2C), 125.5, 124.6, 122.9, 121.2, 121.1, 115.9, 114.7, 102.4, 70.1, 67.5, 29.5. HRMS (*m/z*) $[M+H]^+$ calcd for $C_{23}H_{18}Cl_2N_3O_4$ = 470.0674, found = 470.0682.

*2,4-Dichloro-3-({[2-methyl-4-(pyridin-2-ylmethoxy)quinolin-8-yl]oxy}methyl)aniline (**12**)*

A round bottom flask (100 mL) was charged with 2.16 g of compound **21** (4.6 mmol, 1 eq) and 30.4 mL of aqueous MeOH 80%, giving a suspension. Then, 60 mg $FeCl_3$ * $6H_2O$ (0.228 mmol, 0.05 eq) και 60 mg charcoal were added, and the resulting mixture was heated to 75°C (reflux). N_2H_4*H_2O, 0.6 mL (18.4 mmol, 4 eq), was added and the mixture was stirred at the same temperature for 4 h and monitored by HPLC. Upon completion, the solvent was removed in vacuo and 32.8 mL EtOAc were added. The organic phase was washed with an aqueous mixture of $NaHCO_3$ 5% (20 mL) and brine (32 mL), dried over anhydrous Na_2SO_4, filtered through diatomaceous earth, and the solvent was removed in vacuo to afford 1.41 g (70%) of pure compound 12 as a yellow solid; ^{1}H-NMR (600 MHz, DMSO-d_6): δ ppm 8.66 (d, *J* = 4.2 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.74–7.80 (m, 2H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 8.66 (t, *J* = 7.8 Hz, 1H), 7.27–7.32 (m, 2H), 6.74 (s, 1H), 5.70 (s, 2H), 5.43 (s, 2H), 2.68 (s, 3H); ^{13}C-NMR (600 MHz, DMSO-d_6): δ ppm 158.9, 156.2, 149.8, 148.9, 145.1, 137.7, 137.0, 128.5, 126.0, 123.8, 122.3, 122.2, 121.7, 120.9, 120.6, 120.1, 116.8, 114.2, 111.4, 103.6, 71.2, 64.7, 31.7. HRMS (*m/z*) $[M+H]^+$ calcd for $C_{23}H_{20}Cl_2N_3O_2$ = 440.0933, found = 440.0939.

2-(1,3-Dioxoisoindolin-2-yl)acetyl chloride (N-*phthalyl-glycinoyl chloride) (**6**)*

A round bottom flask (250 mL), equipped with a Dean-Stark apparatus, was charged with 3.0 g glycine (40 mmol, 1 eq), 5.92 g

phthalic anhydride (40 mmol, 1 eq), 0.56 mL Et_3N (4 mmol, 0.1 eq) and 40 mL toluene (1 M), giving a suspension. The reaction mixture was stirred at reflux for 18 h. After the solvent was removed in vacuo, 64 mL water and 6.4 mL of conc. HCl, were added producing a white slurry. The solid was collected by vacuum filtration, washed on the filter with cold water and dried under vacuum to afford 7.2 g (88%) of *N*-phthalyl-glycine as a white solid; ^{1}H-NMR (600 MHz, DMSO-d_6): δ ppm 13.2 (br.s, 1H), 7.94–7.89 (m, 2H), 7.89–7.84 (m, 2H), 4.30 (s, 2H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ ppm 169.3, 167.7 (2C), 135.3 (2C), 131.9 (2C), 123.9 (2C), 39.4. HRMS (*m/z*) $[M-H]^-$ calcd for $C_{10}H_6NO_4$ = 204.0302, found = 204.0308.

A round bottom flask (250 mL) was charged with 7.2 g of *N*-phthalyl-glycine (25.09 mmol, 1 eq) and 43.2 mL of toluene (6 vol), giving a suspension. Then, 6.13 mL $SOCl_2$ (84.21 mmol, 2.4 eq) were added, dropwise. The reaction mixture was stirred at for 18 h at reflux. The resulting solution was cooled at ambient temperature and the solvent was removed in vacuo, giving a yellow solid. Residual thionyl chloride was removed by toluene put and take distillations (2 × 20 mL), to afford 7.39 g (94%) of 6 as a pale yellow solid; ^{1}H-NMR (600 MHz, $CDCl_3$): δ ppm 7.94–7.90 (m, 2H), 7.81–7.76 (m, 2H), 4.82 (s, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ ppm 169.1, 166.6 (2C), 134.7 (2C), 131.6 (2C), 124.0 (2C), 47.6 HRMS (*m/z*) $[M+H]^+$ calcd for $C_{10}H_7ClNO_3$ = 224.0109, found = 224.0101.

*N-[2,4-Dichloro-3-({[2-methyl-4-(pyridin-2-ylmethoxy)quinolin-8-yl]oxy}methyl)phenyl]-2-(1,3-dioxoisoindolin-2-yl)acetamide (**22**)*

A round bottom flask (50 mL), was charged with a solution of 1.0 g of **12** (2.29 mmol, 1 eq) in 11 mL dry DCM (0.2 M) and cooled to 0°C. Then 0.3 mL Et_3N (2.29 mmol, 1 eq) and 664 mg of 22 (2.98 mmol, 1.3 eq) were added. The reaction mixture was stirred at ambient for 3 h and monitored by HPLC. Upon completion, the mixture was diluted with 15 mL of DCM, washed with aqueous $NaHCO_3$ 5 w/w% (7.9 mL) and brine (7.9 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to afford 1.25 g (88%) of 22, as a beige solid.

*N-[2,4-Dichloro-3-({[2-methyl-4-(pyridin-2-ylmethoxy)quinolin-8-yl]oxy}methyl)phenyl]-2-(1,3-dioxoisoindolin-2-yl)-N-methylacetamide (**23**)*

A round bottom flask (50 mL), was charged with 192.5 mg NaH (50%) (8 mmol, 5 eq) and an argon atmosphere was established. Then, 1.0 g of compound **22** (1.6 mmol, 1 eq) and 9.5 mL of dry dioxane were added. The resulting mixture was cooled at 0°C and 447.5 mg of methyl mesylate (2.4 mmol, 1.5 eq) were added. The reaction mixture was stirred at rt for 18 h and monitored by HPLC. Upon completion, 15 mL DCM were added. The organic phase was washed with aqueous $NaHCO_3$ 5 w/w% (8 mL), water (8 mL) and brine (8 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to afford 875 mg (85%) of 23 as a beige solid; ^{1}H-NMR (600 MHz, $CDCl_3$): δ ppm 8.66 (d, *J* = 4.5 Hz, 1H), 8.66 (d, *J* = 4.5 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.89–7.83 (m, 3H), 7.77 (t, *J* = 7.7 Hz, 1H), 7.72–7.69 (m, 3H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.46–7.42 (m, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 5.7 Hz, 1H), 6.78 (s, 1H), 5.71 (dd, *J* = 24.7, 10.5 Hz, 2H), 5.44 (s, 2H), 3.25 (s, 4H), 2.19 (s, 2H).; ^{13}C-NMR (150 MHz, $CDCl_3$): δ ppm 153.0, 150.0, 149.4, 138,7, 138.1, 137.1, 137.0, 136.9, 134.8 134.1, 134.0 (2C), 132.2, 130.5, 130.0, 129.9, 123.5, 123.4 (3C), 123.1, 123.0, 121.3, 121.2, 68.2, 39.6, 36.2 (2C), 31.0, 30.0. HRMS (*m/z*) $[M+H]^+$ calcd for $C_{26}H_{23}Cl_2N_3O_3$ = 495.1116, found = 495.1110.

*2-Amino-N-[2,4-dichloro-3-({[2-methyl-4-(pyridin-2-ylmethoxy)quinolin-8-yl]oxy}methyl)phenyl]-N-methylacetamide (**11**)*

A round bottom flask (10 mL) was charged with 1.3 g of compound **24** (2 mmol, 1 eq), 15.6 mL EtOH (12 vol), heated to 50°C and 0.57 mL of $N_2H_4{}^*H_2O$ (12 mmol, 6 eq), was added. The reaction mixture was stirred at the same temperature for 3.5 h and monitored by HPLC. Upon completion, the solvent was removed in vacuo and 13 mL of aqueous HCl 0.5 M were added, giving a brown suspension that was extracted with 13 mL of TBME. The organic phase was discarded, and the aqueous phase was adjusted to pH 12 with aqueous NaOH 2 M and extracted with 13 mL of DCM. The organic phase was washed with brine (9 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to afford 0.72 g (70%) of 11 as a red solid; ^{1}H-NMR (600 MHz, $CDCl_3$): δ ppm 8.64 (m, 1H), 7.95 (dd, *J* = 8.4 and 0.6 Hz, 1H), 7.75 (td, *J* = 7.8 and 1.8 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.29–7.26 (m, 1H), 7.25–7.22 (m, 2H), 6.71 (s, 1H), 5.64 (s, 2H), 5.40 (s, 2H), 3.20 (s, 3H), 3.09 (d, *J* = 17.4 Hz, 1H), 2.97 (d, *J* = 17.4 Hz, 1H), 2.66 (s, 3H), 1.93 (br.s, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ ppm 173.1, 161.3, 159.8, 156.5, 154.3, 149.8, 142.4, 139.4, 138.1, 137.4, 137.0, 135.4, 130.7, 129.9, 125.1, 123.4, 121.7, 121.6, 116.2, 115.2, 102.8, 71.2, 68.7, 44.2, 36.3, 26.7. HRMS (*m/z*) $[M+H]^+$ calcd for $C_{26}H_{25}Cl_2N_4O_3$ = 511.1304, found = 511.1309.

*(E)-3-[4-(Methylcarbamoyl)phenyl]acrylic acid (**9**)*

Three hundred milligram of 4-bromo-*N*-methylbenzamide **25** (1.41 mmol, 1 eq), 0.3 mL of ethyl acrylate (2.82 mmol, 2 eq), 0.87 mL Et_3N (4.23 mmol, 3 eq), 8.1 mg of palladium(II) acetate (0.036 mmol, 2.5 mol%), 21 mg of tri-*tert*-butyl phosphonium tetrafluoroborate (0.072 mmol, 5 mol%) and 2.4 mL of DMF were charged in an oven-dried reaction tube equipped with a stirring bar and argon atmosphere was established. The reaction mixture was degassed by applying successive vacuum and nitrogen purge cycles under stirring, heated directly to 100°C for 18 h and monitored by HPLC. Upon completion, 3 mL H_2O was added, and the aqueous phase was extracted with 9 mL of EtOAc. The organic phase was washed with aqueous HCl 0.1 M (2.4 mL) and brine (1.5 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to afford 230 mg (70%) of ethyl (*E*)-3-(4-(methylcarbamoyl)phenyl)acrylate as a brown oil.

A round bottom flask (50 mL) was charged with 220 mg of ethyl (*E*)-3-(4-(methylcarbamoyl)phenyl)acrylate (0.94 mmol, 1 eq), 0.78 mL of THF and 3.08 mL of MeOH, giving an orange solution. Next, 0.84 mL of aqueous NaOH 5.5 M (188 mg, 4.7 mmol, 5 eq) was

added, dropwise. The reaction mixture was stirred at ambient for 2.5 h and monitored by HPLC. Upon completion, the solvents were removed in vacuo, and the residue was diluted with H_2O. The aqueous phase was extracted with 20 mL of TBME and adjusted to pH 2–3 with aqueous HCl 1 M. Next, the aqueous phase was extracted with 40 mL of EtOAc. The organic phase was washed with aqueous HCl 0.1 M and brine (20 mL), dried over Na_2SO_4, filtered and the solvent was removed in vacuo to afford 106 mg (55%) of 9 as a pale yellow solid; ^{1}H-NMR (600 MHz, DMSO-d_6): δ ppm 8.50 (d, J = 4.4 Hz, 1H), 7.86 (d, J = 8.3 Hz, 2H), 7.77 (d, J = 8.3 Hz, 2H), 7.62 (d, J = 16.0 Hz, 1H), 6.62 (d, J = 16.0 Hz, 1H), 2.51 (br. s, 3H); ^{13}C-NMR (150 MHz, DMSO-d_6): δ ppm 167.8, 166.4, 143.3, 137.1, 136.0, 128.5, 128.0, 121.2, 31.1, 26.5, 22.5. HRMS (m/z) $[M+H]^+$ calcd for $C_{11}H_{10}NO_3$ = 204.0666, found = 206.0672.

(E)-4-{3-[(2-{[2,4-Dichloro-3-({[2-methyl-4-(pyridin-2-ylmethoxy) quinolin-8-yl]oxy}methyl)phenyl](methyl)amino}-2-oxoethyl)amino]-3-oxoprop-1-en-1-yl}-N-methylbenzamide (FR-190997)

A round bottom flask (10 mL) was charged with 70 mg of compound **29** (0.14 mmol, 1 eq), 1.12 mL of DCM (0.13 M), 0.15 mL of Et_3N (1.1 mmol, 7.5 eq) and 29 mg of compound **9** (0.14 mmol, 1 eq). The resulting mixture was cooled to −5°C for 15 min under an argon atmosphere, and 98.6 mg of T_3P solution in EtOAc 50w/w%, (1.97 g of 0.31 mmol, 2.2 eq) were added, producing a red solution that was stirred at the same temperature for 15 min before allowed to attain ambient temperature and stirred for 36 h. The reaction was monitored by HPLC and upon completion, the mixture was diluted with 2 mL of DCM, washed with aqueous HCl 0.1 M (1.5 mL) and brine (1.5 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo, to afford 85 mg (87%) of FR-190997 as a white solid; ^{1}H-NMR (600 MHz, $CDCl_3$): δ ppm 8.64 (d, J = 4.2 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.72–7.76 (m, 3H), 7.85 (d, J = 7.8 Hz,1H), 7.55 (d, J = 15.6 Hz, 2H), 7.48 (d, J = 8.4 Hz, 1H), 7.36–7.45 (m, 2H), 7.26–7.30 (m, 2H), 6.79 (br.s, 1H) 6.72 (s, 1H), 6.45–6.55 (m, 2H), 5.63 (d, J = 3.6 Hz, 2H), 5.40 (s, 2H), 3.90 (dd, J = 18.0 and 4.8 Hz, 1H), 3.63 (dd, J = 18.0 and 3.6 Hz, 1H), 3.23 (s, 3H), 2.95 (d, J = 4.8 Hz, 3H), 2.61 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$): δ ppm 168.4, 167.4, 165.4, 161.1, 159.5, 156.0, 154.0, 149.4 (2C), 139.9, 138.3, 137.6, 137.0 (2C), 136.5, 135.3, 130.3, 129.7, 127.9 (2C), 127.4 (2C), 124.9, 123.0, 122.0, 121.3, 121.1, 115.5, 114.0, 102.5, 70.8, 68.9, 42.2, 36.1, 26.8, 26.0. HRMS (m/z) $[M+H]^+$ calcd for $C_{37}H_{34}Cl_2N_5O_5$ = 698.1937, found = 698.1931.

*N-[2-Methyl-4-(pyridin-2-ylmethoxy)quinolin-8-yl]-2-nitrobenzenesulfonamide (**25**)*

To a round bottom flask (100 mL), containing an ice-cold solution of 2 g of compound **14** (7.56 mmol, 1 eq) in 32 mL dry DCM (16 vol), was added 3.02 mL of Et_3N (22.68 mmol, 3 eq) and then 1.84 g of *o*-NsCl (8.32 mmol, 1.1 eq) portion-wise over 50 min. The mixture was stirred at 0°C for 30 min and at rt for 1 h. Next, the reaction mixture was re-cooled to 0°C and an additional 1 mL of Et_3N (7.56 mmol, 1 eq) and 1.17 g of *o*-NsCl (5.29 mmol, 0.7 eq) were added in the same manner as above. The reaction mixture was stirred at ambient temperature overnight and HPLC monitoring confirmed complete consumption of **14**. The reaction mixture was diluted with 20 mL of DCM and was washed once with an aq solution of 5% $NaHCO_3$ (10 mL), twice with water (10 mL), once with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to afford 3.27 g (96%) of **14**-*o*-nosylamide as an orange solid. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 10.15 (br.s, 1H),8.62 (d, J = 4.2 Hz, 1H), 8.09 (dd, J = 7.8 and 1.2 Hz, 1H), 7.94 (dd, J = 7.8 and 1.2 Hz, 1H), 7.91 (dd, J = 8.4 and 1.2 Hz, 1H), 7.81 (dd, J = 7.8 and 1.2 Hz, 1H), 7.73 (td, J = 7.8 and 1.2 Hz, 1H) 7.59 (td, J = 7.8 and 1.2 Hz, 1H), 7.56 (td, J = 7.8 and 1.2 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.32 (t, J = 8.4 Hz, 1H), 7.27 (m, 1H), 6.68 (s, 1H), 5.36 (s, 2H), 2.61 (s, 3H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$): δ 161.1, 159.4, 155.8, 149.4, 148.1, 139.5, 137.1, 133.6, 133.2, 132.4, 132.3, 131.3, 125.4, 124.8, 123.1, 121.3, 119.8, 117.1, 116.4, 102.8, 71.0, 25.6 ppm; HRMS (m/z) $[M+H]^+$ calcd for $C_{22}H_{18}N_4O_5S$ = 451.1076, found = 451.1074.

*2-Amino-N-[2,4-dichloro-3-({N-[2-methyl-4-(pyridin-2-ylmethoxy) quinolin-8-yl]-2-nitrophenylsulfonamido}methyl)phenyl]-N-methylacetamide (**26**)*

Prepared from compound **25** in five steps (namely reaction with compound **13**, reduction of the nitro group, amide formation with acyl chloride **6**, *N*-methylation and removal of the phthalidoyl group) performed in identical manner as described for the corresponding O-analogs (see preparation of compounds **21**, **12**, **22**, **23**, and **11**, respectively). Compound **26** is somewhat unstable in storage, therefore it was used directly in the next step (removal of the o-nosyl group or amide coupling with substituted cinnamic acids)

*2-Amino-N-[2,4-dichloro-3-({[2-methyl-4-(pyridin-2-ylmethoxy) quinolin-8-yl]amino}methyl)phenyl]-N-methylacetamide (**27**)*

To a round bottom flask (50 mL) containing a solution of 1 g of crude **26** (1.48 mmol, 1 eq) in 5 mL of DMF (5 vol) were added 1.10 g of Na_2CO_3 (10.36 mmol, 7 eq) and 0.755 mL of PhSH (7.4 mmol, 5 eq) and the reaction mixture was stirred vigorously at ambient temperature for 2 h before it was heated to 40–50°C and stirred for 1 h. Next, the reaction mixture was allowed to attain ambient temperature and an additional 157 mg of Na_2CO_3 (1.48 mmol, 1 eq) and 75.5 µL of PhSH (0.74 mmol, 0.5 eq) were added and the reaction mixture was further stirred at ambient temperaure for 18 h. HPLC monitoring confirmed complete consumption of **26** thus the reaction was diluted with water (50 mL, 10 vol) and extracted with DCM (3 × 20 mL). The organic phase was washed with water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. The resulting oil was dissolved in Et_2O (5 mL, 5 vol) and refrigerated overnight. The precipitate was collected by vacuum filtration, washed on the filter with ice-cold Et_2O and dried under vacuum to afford 730 mg (77%) of **27** as a yellow solid. Compound 27 is somewhat unstable on storage therefore it was used directly in the next step (amide coupling with substituted cinnamic acids). ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.62 (unresolv. dt, J = 4.8 Hz, 1H), 7.73 (td, J = 7.8 and 1.2 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.53 (dd, J = 7.8 and 0.6 Hz, 1H),7.43 (d, J = 8.4 Hz, 1H), 7.35 (t, J = 7.8 Hz, 1H), 7.26

(t, J = 7.8 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 7.2, 1H), 6.66 (s, 1H), 6.61 (unresolv. t, 1H), 5.39 (s, 2H), 4.82 (d, J = 1.8 Hz, 2H), 3.22 (s, 3H), 3.08 (d, J = 17.1 Hz, 1H), 2.99 (d, J = 17.1 Hz, 1H), 2.59 (s, 3H), 1.71 (br.s, 2H) ppm; ^{13}C-NMR (150 MHz, $CDCl_3$): δ 172.8, 161.1, 157.1, 156.4, 149.3, 143.3, 139.2, 138.8, 137.3, 137.0, 136.5, 135.6, 129.6, 129.3, 125.7, 122.9, 121.1, 119.8, 108.9, 106.4, 102.3, 70.6, 44.0, 43.9, 36.0, 25.8 ppm. HRMS (m/z) $[M+H]^+$ calcd for $C_{26}H_{25}Cl_2N_5O_2$ = 510.1464, found = 510.1466;

(E)-4-{3-[(2-{[2,4-Dichloro-3-({[2-methyl-4-(pyridin-2-ylmethoxy) quinolin-8-yl]amino}methyl)phenyl](methyl)amino}-2-oxoethyl) amino]-3-oxoprop-1-en-1-yl}-N-methylbenzamide (AZA FR-190997)

Prepared from compounds **27** and **9** in identical manner as described above for FR-190997.

^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.61 (unresolv. dt, J = 4.8 Hz, 1H), 7.75–7.70 (m, 3H), 7.58 (d, J = 7.8 Hz, 1H), 7.55–7.48 (m, 4H), 7.47 (d, J = 8.4 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.28–7.23 (m, 2H), 6.97 (d, J = 7.2 Hz, 1H), 6.73 (unresolv. t, 1H), 6.65 (s, 1H), 6.56 (unresolv. q, 1H), 6.50 (d, J = 15.6 Hz, 1H), 6.26 (unresolv. t, 1H), 5.38 (s, 2H), 4.81 (unresolv. d, 2H), 3.95(dd, J = 17.4 and 4.8 Hz, 1H), 3.63 (dd, J = 17.4 and 2.4 Hz,1H), 3.25 (s, 3H), 3.00 (d, J = 4.8 Hz, 3H), 2.59 (s, 3H) ppm. ^{13}C-NMR (150 MHz, $CDCl_3$): δ 168.3, 167.5 (2C), 165.2, 161.1, 157.0, 156.4, 149.3 (2C), 143.3, 140.0, 138.3, 137.6, 137.2, 137.0, 135.4, 129.9, 129.3, 127.9 (2C), 127.4 (2C), 125.7, 122.9, 122.0, 121.1, 119.8, 108.9 (2C), 106.4, 102.3, 70.6, 44.1, 42.1, 36.1, 26.8, 25.7 ppm. HRMS (m/z) $[M+H]^+$ calcd for $C_{37}H_{34}Cl_2N_6O_4$ = 697.2097, found = 697.2091.

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CONFLICTS OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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