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Discovery of *N*-[4-[6-*tert*-Butyl-5-methoxy-8-(6-methoxy-2-oxo-1*H*-pyridin-3-yl)-3-quinolyl]phenyl]methanesulfonamide (RG7109), a Potent Inhibitor of the Hepatitis C Virus NS5B Polymerase

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Abstract

In the last few years, there have been many advances in the efforts to cure patients with hepatitis C virus (HCV). The ultimate goal of these efforts is to develop a combination therapy consisting of only direct-antiviral agents (DAA). In this paper, we discuss our efforts that led to the identification of a bicyclic template with potent activity against the NS5B polymerase, a critical enzyme on the life cycle of HCV. Continuing our exploration to improve the stilbene series, the 3,5,6,8-tetrasubstituted quinoline core was identified as replacement of the stilbene moiety. 6-Methoxy-2(1*H*)-pyridone was identified among several heterocyclic head groups to have the best potency. Solubility of the template was improved by replacing a planar aryl linker with a saturated pyrrolidine. Profiling of the most promising compounds led to the identification of quinoline **41** (RG7109) which was selected for advancement to clinical development.

INTRODUCTION

Hepatitis C virus (HCV), a positive-strand RNA virus member of the Flaviviridae family, chronically infects 150 million people worldwide with an estimated incidence of new cases of 3–4 million each year.[1] HCV infection results in mild and acute liver disease, but chronic infections are common and may eventually develop into liver cirrhosis or hepatocellular carcinoma.[2]

Until 2011, the standard of care (SOC) for treating HCV had been a combination therapy of pegylated interferon-α (Peg-IFN) plus ribavirin (RBV). Response rates for HCV patients

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Accession Codes
Protein crystal structure coordinates and structure factor files have been deposited in the Protein Data Bank under the accession codes 4MIA (**41**) and 4MIB (**48**).

The authors declare no competing financial interest.

Supporting Information
Experimental procedure and spectroscopic data for compounds **34**, **40**, **43**–**47**, and **49**, and their corresponding synthetic intermediates. Data collection and refinement statistics for cocrystals of NS5B with **41** and **48**. This material is available free of charge via the Internet at http://pubs.acs.org.

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having genotypes 2 or 3 on a 24–48 week treatment show a sustained virological response (SVR, defined as the absence of detectable HCV RNA in blood serum for 24 weeks after treatment withdrawal) approaching 80%. Patients infected with HCV genotype 1 (GT-1) do not respond as well to this combination therapy demonstrating SVR rates of < 50% even after treatment therapies of 48 weeks in duration.[3]

With the recent approval of two HCV protease inhibitors (Telaprevir and Boceprevir) by the FDA, the standard of care for treatment of GT-1 infection is now Peg-IFN/RBV and a protease inhibitor. This triple combination improves the SVR rates up to 75% (Telaprevir) and 68% (Boceprevir) with genotype-1 naive patients,[4] and reduces treatment duration. Other protease inhibitors in clinical development are showing improved SVR rates of > 90% in some patients and with a more convenient once daily dosing (q.d.) regimen than the first two compounds approved with three times daily (t.i.d.) and twice daily (b.i.d.) dosing regimens, respectively.[5] The use of other direct-acting antivirals with different mechanisms of action (polymerase nucleoside inhibitor (NI) and non-nucleoside inhibitor (NNI) as well as nonstructural 5A (NS5A) inhibitors) have shown SVR > 80% in combination with Peg-IFN/RBV in phase II clinical studies.[4]

Interferon-associated side effects limit treatment success in a large number of patients.[6] Therefore, one of the primary future goals is to develop direct-acting antiviral (DAA) therapy that can achieve high SVR without the use of Peg-IFN. For this objective, there are currently several clinical trials ongoing with combinations of DAAs (protease inhibitor, polymerase NI, polymerase NNI, and NS5A inhibitor) to determine which will deliver the best results with respect to SVR and safety for different patient populations and against the most common genotypes (GT-1,2,3, and 4).[6] The development of potent and safe inhibitors of the different viral proteins is crucial to be able to achieve the goal of DAA therapy. The discovery of polymerase inhibitors and the development of a combination therapy that would eventually replace interferon-based treatment has been of interest to us for some time.[7,8]

The HCV nonstructural 5B (NS5B) protein contains the RNA-dependent RNA polymerase, the catalytic component of the HCV RNA replication machinery. This virus-specific enzyme plays an important role in the viral life cycle and thus represents an attractive therapeutic target. Several classes of inhibitors have been reported for the NS5B polymerase: NIs that bind in the active site, and NNIs that bind in at least 4 different allosteric sites identified so far (palm I, palm II, thumb I and thumb II).[9]

Different chemotypes have been reported to bind in the palm I allosteric site. From those chemical classes, at least five compounds have entered clinical trials and some of them have shown efficacy. Those are the *N*-acylpyrrolidine GSK625433 (**1**),[10] benzothiadiazine ANA598 (**2**),[11] benzodiazaphosphinine IDX375 (**3**),[12] and the uracil derivatives ABT-072 (**4**),[13] and ABT-333 (**5**)[14] (Figure 1).

We have been interested in the design of inhibitors that bind to the palm I allosteric site. Recently, we reported the *de novo* design of fragment **6**[15] with sub-μM potency against the HCV NS5B polymerase and the development of that fragment to stilbene **7**, a potent inhibitor of NS5B with single digit nM activity in the HCV subgenomic replicon assay.[16] From the start of our efforts, the objective was to find highly potent inhibitors of the replication of HCV with similar activity against both GT-1a and GT-1b. Even though **7** had an excellent biological profile, we continued exploring different scaffolds. It was important to keep the key functionalities (heterocyclic head and the sulfonamide group) in the right position to interact with the critical amino acids in the binding site. Among the different possibilities to achieve this, the option to have a bicyclic core that held both critical groups

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seemed to fit well based on modeling. Structure **8** was designed by analyzing the cocrystal structure of an analog of stilbene **7** with NS5B[16] where it was observed that the vinyl carbon linked to the phenylsulfonamide could be bridged to C-6 of the central core. Several advantages were foreseen by having a bicyclic aromatic core, e.g. restricted rotation into bound conformation for potency, opportunity to explore different linker groups to the sulfonamide, and use of heteroaromatic systems to modulate its drug-like properties. Based on this rationale, it was decided to explore bicyclic aromatic cores.

In this article, we describe our efforts on the exploration of the bicyclic core that led to the discovery of RG7109 (**41**), a potent inhibitor of the HCV NS5B polymerase that was selected for clinical development.

CHEMISTRY

To determine if a bicyclic core would either maintain similar or improved potency with respect to the stilbene series, four different ring systems were synthesized. Of the four bicyclic cores reported in Table 1, the 3,5,6,8-tetrasubstituted quinoline system was prepared using two similar routes as shown on Schemes 1 and 2.

In Scheme 1, the use of 4-*tert*-butyl-3-methoxybenzoic acid (**9**) as starting material allowed us to have two of the four desired substitutions already in place. This starting material was very useful since we planned to maintain these two groups in most of the initial set of bicyclic compounds. The first step of the synthesis was to convert the carboxylic acid **9** to the primary aniline **11** by a Curtius rearrangement *via* the corresponding carbamate **10**. Formation of the desired quinoline ring, using the amine group in **11** as a handle, had the disadvantage of producing two possible regioisomers. To avoid this, selective bromination of **11** *para* to the methoxy group to afford bromoaniline **12** was carried out prior to the cyclization reaction. Treatment of compound **12** with 2,2,3-tribromopropanal (prepared *in situ* from 2-bromo acrolein and bromine) achieved the formation of the desired 3,8-dibromoquinoline **13** ring system in moderate yield.[17] At this point, compound **13** possessed the two handles needed to add the required substitution on the template to complete the synthesis. Coupling of compound **13** with the corresponding boronic acid using $Pd(PPh_3)_4$ occurred in a regioselective manner at the least hindered bromine, affording 3-substituted quinoline **14**. Under similar reaction conditions, the heterocycles were attached onto C-8 of the quinoline system to give the desired final compounds. The second route utilized to synthesize derivatives of the quinoline with this specific substitution pattern is depicted in Scheme 2. For this alternative route, attachment of the heterocyclic group was done before the formation of the quinoline system. Scheme 1, being more versatile by virtue of introducing one of the variable elements (heterocyclic head group) after the modest-yielding quinoline-forming cyclization step, was used for most of the examples.

The naphthalene core with the appropriate substitution pattern was built starting from 7-bromotetralin-1-one (**18**), which was transformed to the corresponding trimethylsilane (TMS) enolate followed by alkylation to yield compound **19** (Scheme 3). Bromination at the α position of the ketone group afforded tetralin-1-one **20**, which was subsequently aromatized and the resulting phenol O-alkylated to obtain trisubstituted naphthalene **21**. Introduction of the second bromine *para* to the methoxy group was carried out as described above to obtain compound **22**. With the required substitution on the naphthalene core in place, the 4-(methanesulfonamido)phenyl and heterocycle groups were introduced to obtain the final product **24**.

Synthesis of the 2,5,7,8-tetrasubstituted quinoline was achieved by using a three component imino Diels-Alder reaction as reported by Kouznetsov.[18] Treatment of aniline **25** with 4-

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nitrobenzaldehyde followed by addition of the dienophile and Lewis acid gave a mixture of tetrahydroquinolines and desired quinoline **26**. The mixture of tetrahydroquinolines was oxidized with ceric ammonium nitrate (CAN) to afford quinoline **26** in 22% overall yield. Compound **26** was converted to the final product by reduction of its nitro group followed by methanesulfonylation of the resultant aniline and addition of the heterocycle head group at the C-5 position via cross coupling (Scheme 4).

The last bicyclic template synthesized was the 2,4,7-trisubstituted quinazoline as described in Scheme 5. 2-Amino-4-bromo-benzamide (**29**) was reacted with pivaloyl chloride followed by thermal ring closure under alkaline conditions to give corresponding quinazolin-4-one **30**. Coupling of compound **30** with 4-**(**methylsulfonamido)phenylboronic acid followed by reaction with phosphorous oxychloride afforded the chloroquinazoline **31** in good yield. The desired final product **32** was obtained following standard cross coupling conditions for the addition of the heterocycle on the C-4 position.

RESULTS AND DISCUSSION

Compound **33**, prepared according to Scheme 1, was made first to determine if the bicyclic core could replace the stilbene moiety in our previous series and still maintain potency. Compound **33** has the same 2(1*H*)-pyridone head as our lead stilbene **7** to allow us to make a close comparison. For 5-fluoropyridone **33**, the nitrogen of the quinoline system was expected to face the vicinity of the backbone of Tyr448 and Gly449, where a conserved molecule of water is normally observed in the crystal structures. It was thought that a hydrogen bond acceptor facing that area would be beneficial.[7] Compound **33** displayed single-digit nM activity and equipotency against both GT-1a and GT-1b strains in the replicon assay (Table 1). An attractive advantage of 5-fluoropyridone **33** was that it had a slightly better activity against GT-1a than stilbene **7**. With this encouraging result, we explored the possibility of removing the methoxy group from the core to determine its effect on potency. A 4-to 6-fold drop in activity was observed with the desmethoxy analog **34** indicating that the bicyclic core required methoxy group for good potency.

After these initial results, we continued exploring different bicyclic cores to determine which would give us the best potency and overall profile. For this exploration, 5-fluoro pyridone head was replaced with the uracil heterocycle while maintaining the methoxy, *tert*-butyl, and *N*-phenylmethanesulfonamide substituents. Uracil **35** displayed a decrease in activity against GT-1a, but maintained the same potency against GT-1b with respect to 5-fluoropyridone **33** in the replicon assay. For compounds **36**–**38,** the uracil head group was held constant so the activity of different bicyclic cores could be compared with quinoline **35**. Naphthalene **36** showed a 2- to 3- fold increase in potency against both genotypes with respect to quinoline **35**. Moving the quinoline nitrogen of **35** to the opposite position (**37**) caused the potency to decrease significantly. This drop in activity could be partially explained by the expected almost planar orientation of the *N*-phenylmethanesulfonamide group with respect to the quinoline ring due to the introduction of the quinoline nitrogen adjacent to the phenyl ring. Finally, quinazoline **38** was screened only against GT-1a and also displayed lower activity than quinoline **35**.

This initial exploration showed that the naphthalene core (**36**) had the best potency profile among the four bicyclic cores. Even though the naphthalene core presented the best activity, the 3,5,6,8-tetrasubstituted quinoline core was selected to continue exploring modifications on other parts of the template due to its ease of synthesis, flexibility to make modifications, and excellent potency in the replicon assay.

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With these initial results, we started our optimization efforts of the 3,5,6,8-tetrasubstituted quinoline core by exploring different heterocyclic head groups. Table 2 shows the compounds made along with their activity in the replicon assay. The first three compounds after compound **35** have a 2(1*H*)-pyridone as a head group. Of the three, compound **41** stood out because of its excellent potency and equipotency against both GT-1a and GT-1b. The dihydrouracil **42** displayed good potency and selectivity comparable to uracil **35**. When the dihydrouracil head of **42** was replaced by a cyclic urea moiety, the potency of the compound (**43**) decreased by 14-fold against GT-1a and 6-fold against GT-1b. A possible explanation for the decrease in potency is the difference in p*K*a of the *NH* of the dihydrouracil with respect to that of the cyclic urea (calculated[19] p*K*a for dihydrouracil **42** 8.7 and cyclic urea **43** 13.7). The increase in p*K*a could decrease the strength of the interaction of the *NH* with the backbone carbonyl of Gln446 resulting in a decrease on potency. C-linked uracil **44** displayed improved potency (~ 2-fold) against both genotypes with respect to N-linked uracil **35**.

The design of the bicyclic cores and head replacements was based on our understanding of the binding mode of the stilbene series in the palm I site.[16] The expected binding mode of the bicyclic series was confirmed from the crystal structure of compound **41** bound to NS5B (Figure 3). A careful analysis of the data shows that the 2(1*H*)-pyridone head is within hydrogen bond distance to the backbone carbonyl of Gln446 and the *NH* of Tyr448 (2.9 A in both cases). The lower ring of the quinoline template makes edge-to-face interactions with the side chain of Try448, and the *tert*-butyl group fills up the lower lipophilic pocket. These interactions are the same as those observed previously with the original fragment **6**.[15] The nitrogen of the quinoline core is within bonding distance to a conserved molecule of water (not shown on Figure 3). The main role for this ring, as replacement of the vinyl group, is to hold the linker of the methanesulfonamide in the right position. The phenyl ring that links the quinoline with the methanesulfonamide makes an edge-to-face interaction with Phe193 and the sulfonamide group is within hydrogen bond distance from the residues: Asp318, Asn 291, and Ser288 (2.7, 2.8, and 3.2 A, respectively). The sulfonamide functional group was essential for the high potency of the template, indicative of the importance of these interactions. The oxygen of the methoxy group on C-6 of the 2(1*H*)-pyridone is in close proximity (3.3 A) to the carbon of the backbone carbonyl Gly410.

At this point in our efforts to improve activity, the quinoline series had shown excellent potency in the HCV replicon assay against both GT-1a and GT-1b. Also, most of the physicochemical and ADME in vitro properties were within the desirable range (e.g. microsomal stability, CYP inhibition, permeability) except for solubility. Some of the compounds with the best biological activity exhibited low aqueous solubility (< 5 μg/mL). One approach to improve this property was by reducing the planarity of the compounds. With this in mind, we explored different replacements of the phenyl linker between the quinoline and the methanesulfonamide (Table 3). The four carbon alkyl or alkyne linkers (**45** and **46**, respectively) exhibited activity in the enzyme assay but it was not transferred to the replicon assay. The weak activity observed for these two compounds could be attributed to the different possible conformations of the linker which would prevent the methanesulfonamide group from making favorable interactions with Asp318, Asn 291, and Ser288. In order to minimize the number of possible conformations, we explored saturated ring systems as linkers. Azetidine (**47**) and piperidine (**49**) linkers gave similar results as the alkyl chains. To the contrary, the pyrrolidine ring linker (**48**) displayed the same potency as the corresponding phenyl linker (**39**). These results were expected since the conformationally-restricted ring systems of **47**–**49** would place the methanesulfonamide group in slightly different positions resulting in different activities. Compound **48** was cocrystallized with the NS5B polymerase and it demonstrates in the palm I site the same interactions as described for quinoline **41**. The pyrrolidine ring is within van der Waals

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radius contact distance of Phe193 (3.9–4.2 A) and places the methanesulfonamide in the right position to make the same network interactions in the catalytic site as quinoline **41** (Figure 4).

As anticipated, the replacement of the phenyl ring with a saturated linker (in this case the pyrrolidine ring) led to an increase in aqueous solubility (Table 3). The combination of good potency and improved solubility made the pyrrolidine linker an attractive option for further exploration. The phenyl linker of the best compounds described on Tables 1 and 2 was replaced with the pyrrolidine linker. The replacements also led to an increase in aqueous solubility, but potency was not always maintained in comparison to the corresponding phenyl linker compounds (data not shown). From this set of compounds, pyridone **50**, the pyrrolidine analog of compound **41**, had the best combination of overall properties (Figure 5). Although the potency of pyrrolidine **50** in the replicon assay was weaker than compound **41**, it still maintained almost equal potency against both GT-1a and GT-1b and good aqueous solubility.

It was desired to select a compound with long half-life in vivo to be able to dose the compound with a q.d. or b.i.d. dosing regimen in the clinic. Even though the majority of the compounds screened in our in vitro hepatocyte assay had medium to high stability (data not shown), a focused effort was carried out to determine if this parameter could be improved. As we showed in the stilbene template,[16] oxidation of the *tert*-butyl group in the bicyclic template was one of the major routes of metabolism (data not shown). Based on this observation, replacements of the *tert*-butyl were made on the uracil **35** template to determine if it was possible to improve the stability. Replacement of the methyl groups on the *tert*-butyl by fluorines (trifluoromethyl **51**) led to improved stability in human and rat hepatocytes, but a large drop in activity was observed against both GT-1a and GT-1b (Table 4). These results supported our assumption that the metabolism of *tert*-butyl group was responsible for most of the clearance observed. Two additional modifications were made to determine if cellular activity could be maintained while improving metabolic stability. Extension of the trifluoromethyl group by one carbon (1,1,1,-trifuoroethyl **52**) had a similar outcome as with trifluoromethyl **51**. The loss of potency seen in compounds **51** and **52** could be due to the less than optimal filling of the lower lipophilic pocket in the palm I site. To address this observation, compound **53** was prepared which contains a cyclopropyl group instead of two of the methyl groups of the *tert*-butyl and a difluoromethyl in replacement for the third methyl. These two changes maintain similar filling of the pocket as the *tert*-butyl but with metabolically stable substitutions. Cyclopropyl **53** displayed the expected high metabolic stability with an improvement in potency of 3- to 9-fold with respect to compounds **51** and **52** but still weaker than uracil **35**. Similar *tert*-butyl replacements have been recently reported with similar improvements in in vitro stability.[21] Unfortunately, the overall profile of these *tert*-butyl replacements did not meet our objective and were not pursued further.

After exploring the four different substitutions of the bicyclic template and understanding their role, five compounds were selected for further profiling in the replicon assay (Table 5). All the compounds selected showed potent inhibition against both GT-1a and GT-1b with almost equipotency against both genotypes (ratio 1a/1b = 1.1–2.2). The compounds were screened in the replicon assay in the presence of 40% human serum (HuS), a more relevant measurement of activity in terms of prediction of clinical efficacy. All the compounds maintained potency at or below 10 nM under the conditions of this assay. The plasma shift observed was relatively small (0.6- to 3.5-fold) for all the compounds except for pyridone **41** (3.8- to 9.4-fold). The EC_{90} in the presence of 40% HuS was used to determine the plasma trough concentration (C_{min}) needed to obtain efficacy in the clinic. We targeted potency at 5-fold coverage above the measured EC_{90}. Since this series generally had a weaker potency

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against GT-1a in the presence of 40% HuS, we decided to use this value to predict efficacy in human.

From this set of compounds, **41** and **50** were selected for further biological profiling against a panel of GT-1a and GT-1b NS5B clinical isolates from untreated patients in a transient replicon assay.[22] Both compounds showed similar or improved potency against the clinical isolates (transient replicon, Table 6) compared to the potencies observed using the stable HCV replicons (Table 5). Differences between the two HCV replicon systems have been previously reported[23] and could be due to a better inhibition of the HCV replicase complex in the transient replicon by the non-nucleoside inhibitors than in the stable replicon system. The major loss in potency in comparison with the rest of the GT-1a panel was seen with clinical isolate RO-38. The sequence of this NS5B isolate contains mutation S556G which is located close to the catalytic site where both of our compounds bind. The mean EC_{50} for compounds **41** and **50** in this set of clinical isolates was shown to be very similar. Against the panel of GT-1b clinical isolates, compound **41** displayed consistent values against the isolates and a mean EC_{50} similar to the one observed with the stable line. Compound **50** displayed a slight range of activities across the panel, but still with a low single-digit nM mean EC_{50} value.

The pharmacokinetic properties of compounds **41** and **50** were determined in rat and dog. Due to the low solubility of **41** (aqueous solubility < 1 μg/mL), this compound was dosed as a microprecipitated bulk powder (MBP) for oral dosing as described by Shah et al.[24,25] Compound **41** showed low clearance in both rat and dog with a $t_{1/2}$ of 4.3 h, which met our criteria to enable b.i.d. dosing in humans (Table 6). Bioavailability was moderate in both species achieving good levels at C_{max}. In addition, concentrations of 0.62 μg/mL (1.22 μM) and 0.99 μg/mL (1.95 μM), in rat and dog respectively, were observed at 8 h after oral dosing. These concentrations cover over 19-fold the EC_{90} observed for **41** in the GT-1a replicon assay in the presence of 40% human serum. This pharmacokinetic data together with the biological profile described above, lent additional confidence that suppression of the virus in humans could be achieved with compound **41** based on our prediction model.[26] It was estimated that **41** will show a viral load reduction of > 1.5 in a 3-days monotherapy with a dose of 49–120 mg b.i.d.

Compound **50** displayed a good profile in both species. When dosed to rats, it showed low clearance and a slightly better $t_{1/2}$ than **41** with an excellent bioavailability. These characteristics allowed compound **50** to reach a concentration of 1.79 μg/mL (3.5 μM) at 8 h after oral dosing. This concentration covers over 50-fold the EC_{90} observed for **50** in the GT-1a replicon assay in the presence of 40% human serum. The pharmacokinetic parameters in dog for **50** were similar to those observed in rat.

Compounds **41** and **50** both possess overall characteristics desirable for a clinical candidate. Compound **41** (a.k.a. RO5471354) was ultimately selected for advancement to clinical development.

CONCLUSION

In summary, exploration of a diverse set of bicyclic cores to replace our previous stilbene core led us to the identification of the 3,5,6,8-tetrasubstituted quinolines. This series displayed excellent potency in the HCV replicon assay and a minimal separation in activity between GT-1a and GT-1b. Optimization of the head group steered us to the identification of the 6-methoxypyridone as one of the most promising heads due to its potency and equal activity against both GT-1a and GT-1b. Replacement of the phenyl linker for saturated alkyl and cycloalkyl groups identified 3-substituted pyrrolidine as a promising linker. This linker

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maintained the potency and improved the solubility of the template. Efforts to replace the *tert*-butyl for a more metabolically stable group were successful in improving the stability of the template, but the replacements did not maintain the desired potency in the replicon assay. Overall, the optimization efforts led us to select five compounds for further biological profiling. Compounds **41** and **50** were then selected for pharmacokinetic studies in rat and dog to determine their potential as clinical candidates. Both compounds met or exceeded our criteria for clinical advancement based on the results described above. Ultimately, compound **41** was chosen for clinical development.

Our efforts to explore different scaffolds to improve the profile of our lead compound **7** yielded a compound with better biological activity. Compound **41** is equipotent against the two GT and has a 6 fold improvement in the 40% HS replicon assay (Table 5).

The development of fragment **6** to a compound that was selected for clinical development is another successful case where the use of fragments[15] together with structure-based design[16] led to the selection of a clinical candidate.

EXPERIMENTAL

General information

All reactions were performed in round-bottom flasks. The flasks were fitted with rubber septa and reactions were conducted under inert atmosphere. Plastic syringes and stainless steel needles were used to transfer air- and moisture-sensitive liquids. Most commercial reagents were purchased from Sigma Aldrich, Alfa Aesar, Strem, Lancaster, AstaTech, or TCI, and used as received. Solvents were purchased from Mallinckrodt and anhydrous dimethylformamide (DMF) and tetrahydrofuran (THF) from Sigma-Aldrich in a Sure/Seal system. Purification of crude material was performed using AnaLogix IntelliFlashTM 280 or Teledyne Isco CombiFlash® Companion® systems using silica gel columns RediSep Rf (particle size 40–63 μpowder). Deuterated solvents were purchased from Sigma-Aldrich. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker Avance 300 MHz, 400 MHz, or 500 MHz spectrometers at 25 °C. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$ δ 7.27, DMSO δ 2.50). Data is represented as follows: chemical shift, multiplicity (br. = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in Hertz (Hz), and integration. High resolution mass spectrometry (HRMS) data were obtained on a Thermo Finnigan LTQ Orbitrap XL spectrometer operated in ESI mode at a resolution of 30,000. Liquid chromatography-mass spectrometry (LC/MS) analyses were carried out using an Agilent 6140 single quadrupole in ES/APCI dual mode, and Agilent LC with a Zorbax SB-C18 2.1x30mm, 3.5μm column using a 0.02% TFA/water-acetonitrile solvent system. Microwave reactions were carried out in a Biotage Initiator reactor. Purity of tested compounds was ≥ 95% as confirmed by LC/MS.

Ethyl *N*-(4-*tert*-butyl-3-methoxy-phenyl)carbamate (10)—To a solution of 4-*tert*-butyl-3-methoxy-benzoic acid (**9**) (10.4 g, 50.0 mmol) in THF (200 mL) was added diphenylphosphoryl azide (11.3 mL, 52.4 mmol), Et_3N (8.4 mL, 60.3 mmol), and EtOH (29 mL) at rt. The reaction was heated at reflux for 23 h, cooled to rt and concentrated. The residue was dissolved in EtOAc (300 mL), washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and evaporated. The crude material was purified over SiO_2 (gradient: 0 to 25% EtOAc in hexane) to give ethyl carbamate **10** (10.12 g, 81%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.6 Hz, 1 H), 6.68 (dd, *J* = 8.2, 2.9 Hz, 1 H), 6.52 (br s, 1 H), 4.22 (q, *J* = 7.0 Hz, 2 H), 3.84 (s, 3H), 1.35 (s, 9 H), 1.31 (t, *J* = 7.3 Hz, 3 H). LC/MS (ES/APCI): 252.1 $(M + H)^+$.

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4-*tert*-Butyl-3-methoxy-aniline (11)—To a solution of ethyl carbamate **10** (11.88 g, 47.3 mmol) in EtOH (86 mL) was added a solution of KOH (29.17 g, 520 mmol) in EtOH (172 mL) at rt. The reaction mixture was heated at reflux for 15 h then cooled to rt and concentrated. The residue was partitioned with EtOAc (400 mL) and brine (400 mL). The organic layer was separated, dried over $MgSO_4$, and concentrated to dryness. The residue was purified over SiO_2 (gradient: 0 to 35% EtOAc in hexane) to give aniline **11** (8.16 g, 96%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 7.2, 2.2 Hz, 1 H), 6.42-6.33 (m, 2 H), 3.82 (s, 3H), 1.35 (s, 9 H). LC/MS (ES/APCI): 180.17 $(M + H)^+$.

2-Bromo-4-*tert*-butyl-5-methoxy-phenylamine (12)—NBS (8.1 g, 45.5 mmol) was added to a solution of aniline **11** (8.16 g, 45.5 mmol) in DMF (150 mL) at rt. The reaction mixture was stirred for 5 h at rt, diluted with EtOAc/hexane (1:1, 300 mL), washed with 1N NaOH (100 mL), brine (300 mL), dried over $MgSO_4$, filtered, and concentrated to afford crude bromoaniline **12** (11.75 g, quantitative) as brownish oil after drying under high vacuum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1 H), 6.40 (br s, 1 H), 3.78 (s, 3H), 1.31 (s, 9 H). LC/MS (ES): 258.04 $(M + H)^+$.

3,8-Dibromo-6-*tert*-butyl-5-methoxy-quinoline (13)—A solution of Br_2 (168 mg, 1.05 mmol) in AcOH (1.3 mL) was added to 2-bromoprop-2-enal (148 mg, 1.1 mmol) in AcOH (1.5 mL) at rt. After stirring for 15 min, a solution of bromoaniline **12** (260 mg, 1.01 mmol) in AcOH (5 mL) was added to the reaction. The reaction mixture was heated at 100 °C for 4 h. The reaction mixture was carefully poured into a cold saturated aqueous $NaHCO_3$ then extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified over SiO_2 (gradient: 0 to 10% EtOAc in hexane) to afford dibromide **13** (170 mg, 45%) as a brownish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, *J* = 2.6 Hz, 1 H), 8.53 (d, *J* = 1.9 Hz, 1 H), 8.08 (s, 1 H), 3.95 (s, 3 H), 1.49 (s, 9 H). LC/MS (ES/APCI): 374.0 $(M + H)^+$.

***N*-[4-(8-Bromo-6-*tert*-butyl-5-methoxy-3-quinolyl)-phenyl]methanesulfonamide (14)—**A sealed vial containing dibromide **13** (850 mg, 2.27 mmol), 4-(methanesulfonamido)phenylboronic acid (539 mg, 2.5 mmol), $Pd(PPh_3)_4$ (263 mg, 0.227 mmol), and Na_2CO_3 (725 mg, 6.83 mmol) in a mixture of MeOH (8 mL) and toluene (5 mL) was irradiated in a microwave reactor at 120 °C for 1 h. The reaction mixture was cooled to rt and diluted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude residue was purified over SiO_2 (gradient: 0 to 70% EtOAc in hexane) to afford 8-bromoquinoline **14** (600 mg, 57%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (d, *J* = 2.0 Hz, 1 H), 8.50 (d, *J* = 2.0 Hz, 1 H), 8.08 (s, 1 H), 7.73 (d, *J* = 8.1 Hz, 2 H), 7.40 (d, *J* = 7.7 Hz, 2 H), 6.50 (br s, 1 H), 4.00 (s, 3 H), 3.11 (s, 3H), 1.52 (s, 9 H). LC/MS (ES): 462.99 $(M + H)^+$.

4-*tert*-Butyl-5-methoxy-2-(2-methoxy-3-pyridyl)aniline (16)—A sealed vial containing bromoaniline **12** (700 mg, 2.71 mmol), (2-methoxy-3-pyridyl)boronic acid (612 mg, 4.4 mmol), $Pd(PPh_3)_4$ (231 mg, 0.2 mmol), and Na_2CO_3 (636 mg, 6 mmol) in a mixture of MeOH (1 mL) and CH_2Cl_2 (9 mL) was irradiated in a microwave reactor at 115 °C for 1 h. The reaction mixture was cooled to rt and diluted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified over SiO_2 (gradient: 0 to 50% EtOAc in hexane) to afford aniline **16** (420 mg, 54%) as a brownish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 4.7, 1.4 Hz, 1 H), 7.57 (dd, *J* = 6.8, 1.6 Hz, 1 H), 6.98 (dd, *J* = 7.1, 4.6 Hz, 1 H), 6.96 (s, 1 H), 6.32 (s, 1 H), 3.99 (s, 3 H), 3.83 (s, 3 H), 3.72-3.64 (br s, 2 H), 1.34 (s, 9 H). LC/MS (ES): 287.13 $(M + H)^+$.

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3-(3-Bromo-6-*tert*-butyl-5-methoxy-8-quinolyl)-1*H*-pyridin-2-one (17)—A solution of Br_2 (191 mg, 1.2 mmol) in AcOH (5 mL) was added to 2-bromoprop-2-enal (230 mg, 1.7 mmol) in AcOH (5 mL) at rt. The solution was titrated to the appearance of a faint reddish color. After stirring at rt for 15 min, a solution of aniline **16** (420 mg, 1.47 mmol) in AcOH (5 mL) was added. The reaction mixture was heated at 100 °C for 2 h. The reaction mixture was carefully poured into a cold saturated aqueous $NaHCO_3$ and then extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified over SiO_2 (1:1, EtOAc/hexane) to afford the corresponding 3-bromoquinoline **17** (155 mg, 27%) as a brownish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 2.3 Hz, 1 H), 8.55 (d, *J* = 1.7 Hz, 1 H), 7.88 (s, 1 H), 7.62 (dd, *J* = 6.6, 1.5 Hz, 1 H), 7.35 (dd, *J* = 6.4, 1.8 Hz, 1 H), 6.38 (t, *J* = 6.9 Hz, 1 H), 3.99 (s, 3 H), 1.52 (s, 9 H). LC/MS (ES): 388.94 $(M + H)^+$.

7-Bromo-2-*tert*-butyl-tetralin-1-one (19)—To a suspension of 7-bromotetralin-1-one (**18)** (10.0 g, 44.4 mmol) in CH_3CN (10 mL) was added Et_3N (7.43 mL, 53.3 mmol) followed by chloro(trimethyl)silane (6.81 mL, 53.6 mmol) at rt under argon. A solution of NaI (7.99 g, 53.3 mmol) in CH_3CN (72 mL) was added dropwise to the white suspension via cannula and stirred at rt for 30 min. The reaction mixture was diluted with ice-cold pentane (200 mL) then poured over ice water. The three different layers were separated and the top layer (pentane) dried over $MgSO_4$, filtered, and concentrated to give a yellow oil. The residue was purified over SiO_2 (hexane) to give pure (7-bromo-3,4-dihydronaphthalen-1-yl)oxy-trimethyl-silane (9.1 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (d, *J* = 1.9 Hz, 1 H), 7.26 (dd, *J* = 7.9, 2.3 Hz, 1 H), 6.97 (d, *J* = 7.9 Hz, 1 H), 5.21 (t, *J* = 4.9 Hz, 1 H), 2.70 (t, *J* = 7.9 Hz, 2 H), 2.31 (ddd, *J* = 12.8, 8.7, 4.9 Hz, 2 H), 0.26 (s, 9H).

A solution of (7-bromo-3,4-dihydronaphthalen-1-yl)oxy-trimethyl-silane (6.85 g, 23.0 mmol) in CH_2Cl_2 (23 mL) was cooled to −40 °C and 2-chloro-2-methyl-propane (1.32 mL, 12.0 mmol) was added under N_2. A solution of $TiCl_4$ (1.27 mL, 11.6 mmol) in CH_2Cl_2 (6 mL) at −40 °C was added to the above solution dropwise while the reaction mixture stirred vigorously to a dark brown/purple suspension. The reaction was allowed to reach rt and stirred over 3 days. The reaction mixture was poured over ice, diluted with EtOAc and water, neutralized with saturated aqueous $NaHCO_3$, and filtered over a plug of Celite® to remove chunky white precipitate. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified over SiO_2 (5/95, EtOAc/hexane) to yield *tert*-butyltetralin-1-one **19** (3.26 g, 50%) as yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.1 Hz, 1 H), 7.51 (dd, *J* = 8.2, 2.1 Hz, 1 H), 7.09 (d, *J* = 8.6 Hz, 1 H), 3.03–2.81 (m, 2 H), 2.34–2.23 (m, 2 H), 2.0–1.83 (m, 1 H), 1.09 (s, 9 H). LC/MS (ES/APCI): 281.1 $(M + H)^+$.

2,7-Dibromo-2-*tert*-butyl-tetralin-1-one (20)—To a solution of *tert*-butyltetralin-1-one **19** (3.0 g, 10.7 mmol) in AcOH (40 mL) was added a solution of Br_2 (0.6 mL, 11.6 mmol) in AcOH (20 mL) dropwise over 20 min via cannula to give a dark orange suspension. The reaction was stirred at rt for 1 h then warmed to 50 °C and stirred for 1 h. An extra quantity of neat Br_2 (0.1 mL, 1.9 mmol) was added and continued heating at 50 °C for another 1.5 h. The reaction was poured over ice, diluted with EtOAc and water, and neutralized with saturated aqueous $NaHCO_3$. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified over SiO_2 (hexane) to obtain compound **20** (3.8 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, *J* = 2.1 Hz, 1 H), 7.58 (dd, *J* = 8.5, 2.1 Hz, 1 H), 7.13 (d, *J* = 8.1 Hz, 1 H), 3.24 (ddd, *J* = 17.8, 12.7, 5.1 Hz, 1 H), 2.85 (ddd, *J* = 17.4, 5.1, 2.5 Hz, 1 H), 2.55 (ddd, *J* = 14.9, 4.7, 3.0 Hz, 1 H), 2.29 (ddd, *J* = 17.0, 11.5, 4.7 Hz, 1 H), 1.31 (s, 9 H).

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7-Bromo-2-*tert*-butyl-1-methoxy-naphthalene (21)—A white suspension of compound **20** (3.8 g, 10.6 mmol), LiBr (275 mg, 3.17 mmol), and Li_2CO_3 (780 mg, 10.6 mmol) in DMF (44.0 mL) was bubbled with argon for 10 min. The mixture was heated at 100 °C under N_2 for 1 h then cooled to rt. The reaction was diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, filtered, and concentrated to obtain 7-bromo-2-*tert*-butyl-naphthalen-1-ol (3.0 g) as a light brown viscous oil in pure form and used in the next reaction without purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (br s, 1 H), 7.64 (d, *J* = 9.4 Hz, 1 H), 7.49 (dd, *J* = 8.6, 2.4 Hz, 1 H), 7.23 (d, *J* = 8.2 Hz, 1 H), 7.37 (d, *J* = 9.0 Hz, 1 H), 1.52 (s, 9H).

To a suspension of 7-bromo-2-*tert*-butylnaphthalen-1-ol (2.9 g, 10.4 mmol) and K_2CO_3 (3.59 g, 26.0 mmol) in DMF (29.7 mL) was added MeI (0.78 mL, 12.5 mmol) and the mixture stirred at 25 °C for 18 h. The mixture was diluted with EtOAc and water and neutralized with 1N HCl. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated to obtain methoxynaphthalene **21** (3.0 g, 96% two steps) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 1.7 Hz, 1 H), 7.67 (d, *J* = 8.6 Hz, 1 H), 7.53–7.45 (m, 3 H), 3.95 (s, 3 H), 1.49 (s, 9 H).

4,7-Dibromo-2-*tert*-butyl-1-methoxy-naphthalene (22)—To a solution of methoxynaphthalene **21** (1.6 g, 5.46 mmol) in AcOH (30 mL) was added a solution of Br_2 (0.28 mL, 5.46 mmol) in AcOH (20 mL) dropwise via addition funnel under N_2. The reaction mixture was stirred at rt for 18 h then diluted with EtOAc and water, and neutralized with saturated aqueous $NaHCO_3$. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated to obtain compound **22** (2.0 g, 98%) in pure form as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 1.8 Hz, 1 H), 8.02 (d, *J* = 9.1 Hz, 1 H), 7.79 (s, 1 H), 7.59 (dd, *J* = 8.7, 1.8 Hz, 1 H), 3.94 (s, 3 H), 1.47 (s, 9 H).

***N*-[4-(5-Bromo-7-*tert*-butyl-8-methoxy-2-naphthyl)phenyl]methanesulfonamide (23)—**A sealed vial containing compound **22** (1.0 g, 2.69 mmol), 4-(methanesulfonamido)phenyl boronic acid (578 mg, 2.69 mmol), $Pd(PPh_3)_4$ (155 mg, 0.134 mmol), and Na_2CO_3 (855 mg, 8.06 mmol) in MeOH (7.14 mL), toluene (3.57 mL), and water (1.79 mL) was irradiated in a microwave reactor at 115 °C for 1.5 h. The reaction mixture was diluted with EtOAc and water and was neutralized with 1N HCl. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified over SiO_2 (gradient: 20 to 50% EtOAc in hexane) to obtain methanesulfonamide **23** (0.67 g, 54%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25–8.19 (m, 2H), 7.80 (s, 1 H), 7.78–7.70 (m, 3 H), 7.35 (d, *J* = 8.5 Hz, 2 H), 6.42 (br s, 1 H), 3.99 (s, 3 H), 3.09 (s, 3 H), 1.50 (s, 9 H).

5-Bromo-7-*tert*-butyl-8-methoxy-2-(4-nitrophenyl)quinoline (26)—A mixture of 5-bromo-3-*tert*-butyl-2-methoxy-aniline **25** (2.0 g, 7.75 mmol) and 4-nitrobenzaldehyde (1.4 g, 11.62 mmol) in CH_3CN (10 mL) was stirred at rt for 45 min. $BiCl_3$ (0.49 g, 1.55 mmol) was added to this mixture followed by a solution of *N*-vinylpyrrolidin-2-one (1.72 g, 15.5 mmol) in CH_3CN (10 mL) dropwise. The resulting mixture was stirred for 16 h then diluted with EtOAc and water (20 mL). A white solid precipitated and was filtered. The organic layer in the filtrate was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified over SiO_2 (gradient: 15 to 75% EtOAc in hexane) to afford a mixture of tetrahydroquinolines (978 mg) and compound **26** (312 mg).

To a solution of the mixture of tetrahydroquinolines (705 mg, 1.4 mmol) in CH_3CN (10 mL) at 0 °C was added dropwise a solution of CAN (1.92 g, 3.51 mmol) in CH_3CN (10 mL). The reaction mixture was stirred at 0 °C until all of the starting material was consumed. The

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reaction was diluted with EtOAc and water. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified over SiO_2 (gradient: 1 to 15% EtOAc in hexane) to afford quinoline **26** (302 mg, 622 mg total, 22% overall yield) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.9 Hz, 1 H), 8.46 – 8.35 (m, 4 H), 8.0 (d, *J* = 8.9 Hz, 1 H), 7.88 (s, 1 H), 4.36 (s, 3 H), 1.56 (s, 9 H). LC/MS (ES/APCI): 416.0 $[M + H]^+$.

***N*-[4-(5-Bromo-7-*tert*-butyl-8-methoxy-2-quinolyl)phenyl]methanesulfonamide (27)—**A solution of quinoline **26** (300 mg, 0.72 mmol), iron powder (121 mg, 2.17 mmol) and NH_4Cl (116 mg, 2.17 mmol) in a mixture of MeOH (30 mL) and water (10 mL) was heated at reflux for 1.5 h. The reaction mixture was cooled to rt and filtered through a pad of Celite®. The filtrate was concentrated and the residue was partitioned between EtOAc and water. The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 4-(5-bromo-7-*tert*-butyl-8-methoxy-2-quinolyl)aniline (204 mg, 73%) which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.8 Hz, 1 H), 8.11 (d, *J* = 8.4 Hz, 2 H), 7.86 (d, *J* = 8.8 Hz, 1 H), 7.73 (s, 1 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 4.34 (s, 3 H), 3.93 (br s, 1 H), 1.55 (s, 9 H).

To a solution of 4-(5-bromo-7-*tert*-butyl-8-methoxy-2-quinolyl)aniline (200 mg, 0.52 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added pyridine (92 μL, 1.14 mmol) followed by MsCl (42 μL, 0.55 mmol). The reaction mixture was stirred at 0 °C for 45 min before it was quenched with water and diluted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude was purified over SiO_2 (gradient: 20 to 70% EtOAc in hexane) to afford methanesulfonamide **27** (208 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 9.2 Hz, 1 H), 8.26 (d, *J* = 8.5 Hz, 2 H), 7.91 (d, *J* = 9.1 Hz, 1 H), 7.81 (s, 1 H), 7.37 (d, *J* = 8.8 Hz, 2 H), 6.53 (br s, 1 H), 4.35 (s, 3 H), 3.09 (s, 3 H), 1.51 (s, 9 H).

7-Bromo-2-*tert*-butyl-3*H*-quinazolin-4-one (30)—To a solution of 2-amino-4-bromo-benzamide **29**, (3.0 g, 14.0 mmol) and Et_3N (1.84 g, 18.2 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added dropwise pivaloyl chloride (1.68 g, 14.0 mmol). The resulting solution was allowed to reach rt and stirred for 18 h. Another portion of pivaloyl chloride (0.44 g) was added to the reaction at 0 °C and the solution stirred for 2 h at the same temperature then allowed to reach rt and stirred for additional 2 h. The mixture was concentrated under vacuum and the crude material was used in the next reaction without purification. To a suspension of the crude material in EtOH (28 mL) was added a solution of 10 M NaOH (2.8 mL, 28 mmol) and the resulting mixture refluxed under N_2 for 1.5 h. The reaction was poured onto ice, neutralized with 1 N HCl, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to quinazolinone **30** (2.07 g, 53% two steps) as a light yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.21 (br s, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H), 7.92 (d, *J* = 1.7 Hz, 1 H), 7.56 (dd, *J* = 8.4, 1.5 Hz, 1 H), 1.45 (s, 9 H). LC/MS (ES/APCI): 281.0 $[M + H]^+$.

***N*-[4-(2-*tert*-Butyl-4-chloro-quinazolin-7-yl)phenyl]methanesulfonamide (31)—**A microwave vial was charged with quinazolinone **30** (500 mg, 1.78 mmol), 4-(methanesulfonamidophenyl)boronic acid (421 mg, 1.96 mmol), $Pd(PPh_3)_4$ (206 mg, 0.178 mmol), Na_2CO_3 (566 mg, 5.34 mmol), MeOH (3 mL), and toluene (1.5 mL). The mixture was purged with argon for 5 min and the vial was sealed. The reaction was heated in a microwave reactor at 115 °C for 30 min. The mixture was concentrated in vacuum and the residue triturated with Et_2O to give the crude quinazoline as a brown solid. To a suspension of the crude quinazolinone (445 mg, 1.2 mmol) and DIPEA (358 mg, 0.38 mL, 1.83 mmol) in benzene (3 mL) was added $POCl_3$ (88 μL, 0.97 mmol) and the mixture heated at reflux

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for 6.5 h. The reaction mixture was cooled to rt and concentrated to dryness. The residue was diluted with EtOAc, washed with water, 1 N HCl, water, brine, dried over $MgSO_4$, and concentrated to give the crude chloroquinazoline **31** (406 mg, 87%) as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.3 Hz, 1 H), 8.18 (d, *J* = 1.3 Hz, 1 H), 7.85 (dd, *J* = 8.8, 1.3 Hz, 1 H), 7.76 (d, *J* = 8.5 Hz, 2 H), 7.39 (d, *J* = 8.5 Hz, 2 H), 7.12 (br s, 1 H), 3.11 (s, 3 H), 1.51 (s, 9 H). LC/MS (ES/APCI): 388.0 $[M - H]^-$.

***N*-{4-[6-*tert*-Butyl-8-(5-fluoro-2-oxo-1,2-dihydro-pyridin-3-yl)-5-methoxy-quinolin-3-yl]-phenyl}-methanesulfonamide (33) hydrobromide—**A mixture of the 8-bromoquinoline **14** (150 mg, 0.324 mmol), (5-fluoro-2-methoxy-3-pyridyl)boronic acid (112 mg, 0.657 mmol), $Pd(PPh_3)_4$ (40 mg, 0.035 mmol), and Na_2CO_3 (179 mg, 1.68 mmol) was suspended in MeOH (1.6 mL) and CH_2Cl_2 (0.4 mL). The reaction mixture was heated in a microwave reactor at 115 °C for 1 h. After cooling the mixture to rt, was poured into saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was separated and washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The product was purified over SiO_2 (gradient: 27 to 50% EtOAc in hexane) to yield *N*-[4-[6-*tert*-butyl-8-(5-fluoro-2-methoxy-3-pyridyl)-5-methoxy-3-quinolyl]phenyl]methanesulfonamide (121 mg, 73%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (d, *J* = 2.3 Hz, 1 H), 8.53 (d, *J* = 2.3 Hz, 1 H), 8.08 (d, *J* = 3.0 Hz, 1 H), 7.78 (s, 1H), 7.72 (d, *J* = 8.7 Hz, 2 H), 7.75 (dd, *J* = 8.3, 3.0 Hz, 1 H), 7.38 (d, *J* = 8.3 Hz, 2 H), 6.60 (s, 1 H), 4.05 (s, 3 H), 3.89 (s, 3 H), 3.1 (s, 3 H), 1.54 (s, 9 H).

To a solution of *N*-[4-[6-*tert*-butyl-8-(5-fluoro-2-methoxy-3-pyridyl)-5-methoxy-3-quinolyl]phenyl]methanesulfonamide (110 mg, 0.26 mmol) in acetic acid (2.5 mL) was added an aqueous solution of 48% HBr (0.06 mL, 1.1 mmol). The reaction vessel was sealed and heated at 60 °C for 18 h. The reaction was cooled to rt and a yellow powder precipitated. The solid was filtered, washed with Et_2O, and dried in the oven under vacuum to give pyridone **33** (71 mg, 55%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.0 (s, 1 H), 9.19 (d, *J* = 2.0 Hz, 1 H), 8.67 (d, *J* = 2.0 Hz, 1 H), 7.93 (d, *J* = 8.1 Hz, 2 H), 7.84 (s, 1 H), 7.77 (dd, *J* = 8.1, 3.0 Hz, 1 H), 7.71 (br t, *J* = 3.1 Hz, 1 H), 7.40 (d, *J* = 8.6 Hz, 2 H), 4.03 (s, 3 H), 3.07 (s, 3 H), 1.50 (s, 9 H). LC/MS (ES): 496.07 $(M + H)^+$.

***N*-[4-[6-*tert*-Butyl-8-(2,4-dioxopyrimidin-1-yl)-5-methoxy-3-quinolyl]phenyl] methanesulfonamide (35)—**The introduction of the uracil group was done following the procedure reported by Wagner et al.[27] A microwave vial was charged with 8-bromoquinoline **14** (200 mg, 0.431 mmol), uracil (72 mg, 0.642 mmol), *N*-(2-cyanophenyl)pyridine-2-carboxamide (19 mg, 0.085 mmol), CuI (8 mg, 0.042 mmol), K_3PO_4 (183 mg, 0.86 mmol), CH_2Cl_2, and MeOH. The suspension was degassed with argon followed by the addition of DMSO (1.5 mL). The vial was sealed and irradiated in a microwave reactor at 150 °C for 5 h. The reaction mixture was cooled to rt and diluted with EtOAc. The organic layer was washed with 1N $NaHSO_4$, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified over SiO_2 (EtOAc) to afford uracil **35** (17 mg, 8%) as a semi solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (br s, 1 H), 8.97 (d, *J* = 1.7 Hz, 1 H), 8.35 (d, *J* = 1.7 Hz, 1 H), 7.84 (s, 1 H), 7.63 (br s, 1 H), 7.44 (d, *J* = 8.7 Hz, 2 H), 7.38 (d, *J* = 7.9 Hz, 1 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 5.92 (d, *J* = 7.9 Hz, 1 H), 4.01 (s, 3 H), 2.95 (s, 3 H), 1.55 (s, 9 H). HRMS (ESI): calcd. for $C_{25}H_{27}O_5N_4S$, 495.16967; found, 495.16763 $[M + H]^+$.

***N*-[4-[7-*tert*-Butyl-5-(2,4-dioxopyrimidin-1-yl)-8-methoxy-2-naphthyl]phenyl] methanesulfonamide (36)—**A flask was charged with *N*-[4-(5-bromo-7-*tert*-butyl-8-methoxynaphthyl)phenyl]methanesulfonamide **23** (350 mg, 0.76 mmol), *tert*-butyl carbamate (124 mg, 1.06 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (104 mg, 0.1 mmol), 2-di-*tert*-

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butylphosphino-2′,4′,6′-triisopropylbiphenyl (145 mg, 0.34 mmol), sodium *tert*-butoxide (107 mg, 1.11 mmol), and toluene (10 mL) to give a white suspension. The mixture was flushed with argon for 10 min and stirred at rt over three days. The mixture was diluted with EtOAc and water and was neutralized with 1N HCl. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified over SiO_2 (gradient: 20 to 60% EtOAc in hexane) to give *tert*-butyl *N*-[3-*tert*-butyl-6-[4-(methanesulfonamido)phenyl]-4-methoxy-1-naphthyl]carbamate (196 mg) and used in the next reaction.

A solution of *tert*-butyl *N*-[3-*tert*-butyl-6-[4-(methanesulfonamido)phenyl]-4-methoxy-1-naphthyl]carbamate (0.196 g, 0.2 mmol), 4 M HCl in dioxane (0.49 mL, 1.97 mmol) in CH_2Cl_2 (1.5 mL) was stirred at rt for 3 h. The reaction was diluted with EtOAc, poured over ice, neutralized with saturated aqueous $NaHCO_3$, washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by over SiO_2 (gradient: 20 to 50% EtOAc in hexane) to yield *N*-[4-(5-amino-7-*tert*-butyl-8-methoxy-2-naphthyl)phenyl]methanesulfonamide (73 mg) as a light brown solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (br s, 1 H), 7.85 (d, *J* = 8.6 Hz, 1 H), 7.73 (d, *J* = 8.6 Hz, 2 H), 7.63 (d, *J* = 9.2 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 6.84 (br s, 1 H), 6.74 (br s, 1 H), 3.93 (s, 3 H), 3.07 (s, 3 H), 1.49 (s, 9 H).

In a flask covered with foil, silver cyanate (135 mg, 0.9 mmol) was heated under high vacuum at 50 °C for 18 h. To this dried material was added (*E*)-3-methoxyacryloyl chloride (65 mg, 0.54 mmol) and dry toluene (1.3 mL) and the slurry heated at 120 °C under N_2 for 30 min. The mixture was cooled to rt and the precipitate was allowed to settle in an ice bath. In a separate dry flask, *N*-[4-(5-amino-7-*tert*-butyl-8-methoxy-2-naphthyl)phenyl]methanesulfonamide (0.072 g, 0.18 mmol) was taken up in DMF (1 mL) and cooled to 0 °C. To the DMF solution was added dropwise the supernatant from the silver cyanate flask over 10 min. The light brown heterogeneous mixture formed was allowed to stir in an ice bath for 30 min. The mixture was diluted with EtOAc, washed with water, brine, and concentrated. The crude product was taken up in EtOH (1 mL) and added an 11% H_2SO_4 solution in water (1 mL). The mixture was heated at 120 °C for 1.5 h until all solid was in solution. The mixture was cooled to rt and poured over ice, diluted with EtOAc, washed with water, brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified over SiO_2 (gradient: 50 to 100% EtOAc in hexane) to give naphthalene **36** (60 mg, 67%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.53 (br s, 1 H), 9.94 (br s, 1 H), 8.27 (br s, 1 H), 7.87 (br d, *J* = 8.7 Hz, 1 H), 7.82 (d, *J* = 8.7 Hz, 2 H), 7.72 (d, *J* = 7.9 Hz, 1 H), 7.67 (d, *J* = 8.7 Hz, 1 H), 7.60 (s, 1 H), 7.37 (d, *J* = 8.6 Hz, 2 H), 5.72 (d, *J* = 7.7 Hz, 1 H), 4.02 (s, 3 H), 3.06 (s, 3 H), 1.48 (s, 9 H). LC/MS (ES/APCI): 491.9 $(M - H)^-$.

***N*-[4-[7-*tert*-Butyl-5-(2,4-dioxopyrimidin-1-yl)-8-methoxy-2-quinolyl]phenyl] methanesulfonamide (37)—**A microwave vial was charged with bromoquinoline **27** (60 mg, 0.13 mmol), uracil (73 mg, 0.65 mmol), *N*-(2-cyanophenyl)pyridine-2-carboxamide (14 mg, 0.063 mmol), CuI (6 mg, 0.03 mmol), K_3PO_4 (137 mg, 0.64 mmol), and DMSO (5 mL). The mixture was irradiated in a microwave reactor at 150 °C for 5 h. The reaction mixture was cooled to rt and the pH adjusted to *ca.* 2 with 2 N HCl. The mixture was extracted with EtOAc and the organic extract was washed sequentially with water, brine, dried over $MgSO_4$, and concentrated. The crude residue was purified over SiO_2 (5/95, MeOH/CH_2Cl_2) to afford quinoline **37** (9.3 mg, 14%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.49 (br s, 1 H), 10.09 (br s, 1 H), 8.29 (d, *J* = 8.8 Hz, 2 H), 8.12 (s, 2 H), 7.72 (d, *J* = 7.8 Hz, 1 H), 7.58 (s, 1 H), 7.38 (d, *J* = 8.9 Hz, 2 H), 5.71 (d, *J* = 7.8 Hz, 1 H), 4.33 (s, 3 H), 3.08 (s, 3 H), 1.47 (s, 9 H). LC/MS (ES/APCI): 495.0 $[M + H]^+$.

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***N*-[4-[2-*tert*-Butyl-4-(2,4-dioxopyrimidin-1-yl)quinazolin-7-yl]phenyl] methanesulfonamide (38)—**A mixture of chloroquinazoline **31** (100 mg, 0.256 mmol), uracil (88 mg, 0.78 mmol), and Cs_2CO_3 (168 mg, 0.516 mmol) in DMSO (2 mL) was heated in a sealed vial at 125 °C for 2.5 h. The crude reaction was diluted with EtOAc and washed with water, brine, dried over $MgSO_4$, and concentrated. The crude product was purified over SiO_2 (gradient: 30 to 50% EtOAc in hexane) to give the desired product quinazoline **38** (54 mg, 45%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (br s, 1 H), 10.06 (br s, 1 H), 8.28 (s, 1 H), 8.11–8.01 (m, 2 H), 8.01–7.91 (m, 3 H), 7.37 (d, *J* = 8.6 Hz, 2 H), 5.92 (d, *J* = 7.9 Hz, 1 H), 3.08 (s, 3 H), 1.47 (s, 9 H). LC/MS (ES/APCI): 464.0 $[M - H]^-$.

***N*-[4-[6-*tert*-Butyl-5-methoxy-8-(2-oxo-1*H*-pyridin-3-yl)-3-quinolyl]phenyl] methanesulfonamide (39)—**A microwave vial was charged with 3-bromoquinoline **17** (150 mg, 0.387 mmol), 4-(methanesulfonamido)phenylboronic acid (125 mg, 0.581 mmol), $Pd(PPh_3)_4$ (45 mg, 0.038 mmol), Na_2CO_3 (123 mg, 1.16 mmol), MeOH (1.5 mL), and CH_2Cl_2 (0.2 mL). The vial was sealed and irradiated in a microwave reactor at 115 °C for 1 h. The reaction mixture was cooled to rt and diluted with EtOAc. The organic layer was washed with water, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified over SiO_2 (5/95, MeOH/CH_2Cl_2) to afford pyridone **39** (40 mg, 21%) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 1.7 Hz, 1 H), 8.44 (d, *J* = 1.7 Hz, 1 H), 7.73 (s, 1 H), 7.67 (dd, *J* = 6.7, 1.7 Hz, 1 H), 7.50–7.42 (m, 3 H), 7.20 (d, *J* = 8.8 Hz, 2 H), 6.49 (t, *J* = 6.7 Hz, 1 H), 4.01 (s, 3 H), 3.0 (s, 3 H), 1.54 (s, 9 H). HRMS (ESI): calcd. for $C_{26}H_{28}O_4N_3S$, 478.17950; found, 478.17770 $[M + H]^+$.

***N*-[4-[6-*tert*-Butyl-5-methoxy-8-(6-methoxy-2-oxo-1*H*-pyridin-3-yl)-3-quinolyl]phenyl] methanesulfonamide (41) hydrobromide—**Using the two steps procedure for the preparation of **33** from **14** but using (2,6-dimethoxy-3-pyridyl)boronic acid, pyridone **41** (56 mg, 42% two steps) was obtained as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.01 (br s, 1 H), 9.18 (d, *J* = 1.7 Hz, 1 H), 8.79 (br s, 1 H), 7.94 (d, *J* = 8.3 Hz, 2 H), 7.76 (s, 1 H), 7.67 (d, *J* = 8.1 Hz, 1 H), 7.40 (d, *J* = 8.3 Hz, 2 H), 6.29 (d, *J* = 7.5 Hz, 1 H), 4.04 (s, 3 H), 3.89 (s, 3 H), 3.07 (s, 3 H), 1.50 (s, 9 H). HRMS (ESI): calcd. for $C_{27}H_{30}O_5N_3S$, 508.19007; found, 508.18848 $[M + H]^+$.

***N*-[4-[6-*tert*-Butyl-8-(2,4-dioxohexahydropyrimidin-1-yl)-5-methoxy-3-quinolyl]phenyl] methanesulfonamide (42)—**Acrylic acid (0.09 mL, 1.3 mmol) was added in 3 portions (0.02, 0.02, 0.05 mL) to a solution of *N*-[4-(8-amino-6-*tert*-butyl-5-methoxy-3-quinolyl)phenyl] methanesulfonamide (prepared with the same procedure as reported for *N*-[4-(5-amino-7-*tert*-butyl-8-methoxy-2-naphthyl)phenyl]methanesulfonamide in experimental for **36**) (252 mg, 0.631 mmol) in toluene (2.5 mL) at rt. After the first addition, the reaction mixture was stirred at 120 °C for 2 h. After the second addition, the reaction mixture was stirred at 120 °C for 1 h and after the third addition, the reaction mixture was stirred at 120 °C overnight. The reaction mixture was cooled to rt and concentrated. The residue was taken in glacial AcOH (2 mL) and urea (95 mg, 1.58 mmol) was added. The reaction mixture was stirred at 120 °C for 6 h then cooled to rt and the solvent evaporated. The dark brown residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was back extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and evaporated. The residue was purified over SiO_2 (gradient: 50 to 80% EtOAc in CH_2Cl_2) to give impure **42** (70 mg) as greenish gray powder. The powder was taken into a minimal amount of CH_2Cl_2 and the insoluble material was filtered and rinsed with a small amount of CH_2Cl_2 to give pure dihydrouracil **42** (40 mg, 13%) as a light gray powder. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.33 (br s, 1 H), 9.20 (d, *J* = 1.9 Hz, 1 H), 8.53 (d, *J* = 2.0 Hz, 1 H), 7.84 (d, *J* = 8.6 Hz, 2 H), 7.70 (s, 1 H), 7.31 (d, *J* = 8.5 Hz, 2 H), 4.00 (s, 3 H), 3.81 (br t, *J* = 6.5 Hz, 2 H), 2.98 (s, 3 H), 2.80 (t,

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J = 6.8 Hz, 2 H), 1.47 (s, 9 H). HRMS (ESI): calcd. for $C_{25}H_{29}O_5N_4S$, 497.18532; found, 497.18372 $[M + H]^+$.

***N*-[[(3*S*)-1-[6-*tert*-Butyl-5-methoxy-8-(2-oxo-1*H*-pyridin-3-yl)-3-quinolyl]pyrrolidin-3-yl]methyl]methanesulfonamide (48)—**A screw-capped vial was charged with bromoquinoline **17** (301 mg, 0.77 mmol), *N*-(*S*)-1-pyrrolidin-3-ylmethyl-methanesulfonamide (200 mg, 0.779 mmol), $Pd(OAc)_2$ (18 mg, 0.08 mmol), P(*tert*-Bu)$_3$ (24 μL, 0.079 mmol), *tert*-BuONa (298 mg, 3.1 mmol), and toluene (3 mL). The mixture was heated at 100 °C for 18 h. The reaction mixture was cooled to rt and diluted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified over SiO_2 (gradient: 0 to 10% MeOH in CH_2Cl_2) to obtain product **48** (60 mg, 15%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J* = 2.4 Hz, 1 H), 7.57 (dd, *J* = 6.8, 1.7 Hz, 1 H), 7.41 (s, 1 H), 7.36 (br d, *J* = 5.5 Hz, 1 H), 7.08 (d, *J* = 2.2 Hz, 1 H), 6.88 (br s, 1 H), 6.38 (t, *J* = 6.6 Hz, 1 H), 3.94 (s, 3 H), 3.47–3.34 (m, 2 H), 3.28 (q, *J* = 8.2 Hz, 1 H), 3.00–2.91 (m, 2 H), 2.89 (s, 3 H), 2.43 (quintuplet, *J* = 7.1 Hz, 1 H), 2.17–2.07 (m, 1 H), 1.89–1.77 (br s, 1 H), 1.68–1.58 (m, 1 H), 1.50 (s, 9 H). LC/MS (ES/APCI): 483.1 $(M - H)^-$.

***N*-[[(3*S*)-1-[6-*tert*-butyl-5-methoxy-8-(6-methoxy-2-oxo-1*H*-pyridin-3-yl)-3-quinolyl]pyrrolidin-3-yl]methyl]methanesulfonamide (50)—**A mixture of 3,8-dibromoquinoline **13** (1.876 g, 5.03 mmol), *tert*-butyl *N*-[[(3*S*)-pyrrolidin-3-yl]methyl]carbamate (1.52 g, 7.6 mmol), sodium *tert*-butoxide (728 mg, 7.49 mmol), (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphine) (582 mg, 1.01 mmol), and $Pd_2(dba)_3$ (460 mg, 0.5 mmol) in degassed toluene (10 mL) was warmed slowly to 100 °C and kept at this temperature for 22 h. The reaction mixture was cooled to rt and partitioned between EtOAc and saturated aqueous NH_4Cl. The aqueous layer was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified over SiO_2 (gradient: 10 to 50% EtOAc in hexane) to afford *tert*-butyl *N*-[[(3*R*)-1-(8-bromo-6-*tert*-butyl-5-methoxy-3-quinolyl)pyrrolidin-3-yl]methyl]carbamate (1.77 g, 71%) as a light green foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 2.8 Hz, 1 H), 7.66 (s, 1 H), 7.07 (d, *J* = 2.5 Hz, 1 H), 4.66 (br s, 1 H), 3.85 (s, 3 H), 3.56–3.48 (m, 2 H), 3.46–3.38 (m, 1 H), 3.26–3.11 (m, 3 H), 2.63–2.50 (m, 1 H), 2.21–2.10 (m, 1 H), 1.86–1.74 (m, 1 H), 1.40 (s, 9 H), 1.39 (s, 9 H). LC/MS (ES): 492 $(M + H)^+$.

A solution of *tert*-butyl *N*-[[(3*R*)-1-(8-bromo-6-*tert*-butyl-5-methoxy-3-quinolyl)pyrrolidin-3-yl]methyl]carbamate (1.76 g, 3.6 mmol) and 4 M HCl in dioxane (9 mL, 36 mmol) in CH_2Cl_2 (11 mL) was stirred at rt for 16 h. The reaction was concentrated and the residual orange oil was treated with of dry Et_2O (150 mL) and stirred at rt for 30 min. The supernatant was removed carefully and residual solid was dried under high vacuum to give [(3*R*)-1-(8-bromo-6-*tert*-butyl-5-methoxy-3-quinolyl)pyrrolidin-3-yl]methanamine (1.7 g) as an orange solid. This product was used in the next reaction without purification. To a solution of the primary amine (1.7 g, 3.4 mmol) and Et_3N (2.36 mL, 16.9 mmol) in CH_2Cl_2 (34 mL) was added methanesulfonyl chloride (0.29 mL, 3.8 mmol) at 0 °C. The reaction mixture was stirred at rt for 1 h. The reaction was quenched with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give *N*-[[(3*S*)-1-(8-bromo-6-*tert*-butyl-5-methoxy-3-quinolyl)pyrrolidin-3-yl]methyl]methanesulfonamide (1.44 g, 89%) as an oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, *J* = 2.5 Hz, 1 H), 7.61 (s, 1 H), 7.23 (t, *J* = 6.2 Hz, 1 H), 7.04 (d, *J* = 2.7 Hz, 1 H), 3.90 (s, 3 H), 3.64–3.53 (m, 2 H), 3.52–3.43 (m, 1 H), 3.28–3.21 (m, 1 H), 3.07 (t, *J* = 6.8 Hz, 2 H), 2.93 (s, 3 H), 2.60–2.44 (m, 1 H), 2.24–2.12 (m, 1 H), 1.90–1.78 (m, 1 H), 1.44 (s, 9 H).

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A solution of *N*-[[(3*S*)-1-(8-bromo-6-*tert*-butyl-5-methoxy-3-quinolyl)pyrrolidin-3-yl]methyl]methanesulfonamide (6.13 g, 13 mmol), (2,6-dimethoxy-3-pyridyl)boronic acid (2.86 g, 15.6 mmol), [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) chloride 1:1 complex with dichloromethane (412 mg, 0.5 mmol), Cs_2CO_3 (12.76 g, 39.1 mmol in 13 mL of water) in dioxane (50 mL) was purged with N_2 for 10 min and stirred at 80 °C for 1 h. The reaction was quenched with water (200 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified over SiO_2 (EtOAc) to obtain *N*-[[(3*S*)-1-[6-*tert*-butyl-8-(2,6-dimethoxy-3-pyridyl)-5-methoxy-3-quinolyl]pyrrolidin-3-yl]methyl]methanesulfonamide (6.26 g, 91%) as a yellow foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.42 (d, *J* = 2.7 Hz, 1 H), 7.58 (d, *J* = 7.9 Hz, 1 H), 7.25 (s, 1 H), 7.27–7.19 (m, 1 H), 7.06 (d, *J* = 2.7 Hz, 1 H), 6.44 (d, *J* = 7.9 Hz, 1 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.76 (s, 3 H), 3.61–3.36 (m, 3 H), 3.21 (dd, *J* = 9.7, 6.6 Hz, 1 H), 3.06 (t, *J* = 6.4 Hz, 2 H), 2.93 (s, 3 H), 2.60–2.47 (m, 1 H), 2.23–2.09 (m, 1 H), 1.90–1.75 (m, 1 H), 1.45 (s, 9 H). LC/MS (ES/APCI): 529.2 $(M + H)^+$.

To a solution of *N*-[[(3*S*)-1-[6-*tert*-butyl-8-(2,6-dimethoxy-3-pyridyl)-5-methoxy-3-quinolyl]pyrrolidin-3-yl]methyl]methanesulfonamide (120 mg, 0.227 mmol) in AcOH (2 mL) was added aqueous 48% HBr solution (0.13 mL) at rt. The reaction was stirred at 60 °C for 18 h. The reaction mixture was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated. The crude product was purified over SiO_2 (gradient: 0 to 5% MeOH in CH_2Cl_2) to give pyrrolidine **50** (47 mg, 40%) as a yellow foam. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (d, *J* = 2.7 Hz, 1 H), 7.56 (d, *J* = 8.1 Hz, 1 H), 7.32 (s, 1 H), 7.23 (t, *J* = 5.9 Hz, 1 H), 7.09 (d, *J* = 2.6 Hz, 1 H), 6.26 (br s, 1 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.63–3.50 (m, 2 H), 3.49–3.41 (m, 1 H), 3.23 (dd, *J* = 9.6, 6.3 Hz, 1 H), 3.08 (t, *J* = 6.3 Hz, 2 H), 2.94 (s, 3 H), 2.62–2.51 (m, 1 H), 2.13–2.12 (m, 1 H), 1.90–1.79 (m, 1 H), 1.46 (s, 9 H). HRMS (ESI): calcd. for $C_{26}H_{35}O_5N_4S$, 515.23227; found, 515.23059 $[M + H]^+$.

***N*-[4-[8-(2,4-dioxopyrimidin-1-yl)-5-methoxy-6-(trifluoromethyl)-3-quinolyl]phenyl]methanesulfonamide (51)—**A mixture of Cu(I) (10.03 g, 52.6 mmol) and CsF (21.40 g, 140.8 mmol) was finely ground in a mortar while in a glove bag under nitrogen atmosphere to afford a free-flowing powder and transferred to a flask. The flask was then charged with 2-iodo-5-nitroanisole (15.17 g, 54.3 mmol) and sulfolane (30 mL) and stirred rapidly at 45 °C. To this mixture was added trimethyl(trifluoromethyl)silane (19.2 g, 20 mL, 135 mmol) dropwise over 4 h using a syringe pump and the resulting mixture stirred at rt for 18 h. The reaction was diluted with EtOAc (500 mL) and stirred with Celite® for 5 min. The reaction mixture was filtered through a pad of Celite®, diluted with EtOAc (1 L) and washed with 10% NH_4OH, 1.0 N HCl, brine, dried over $MgSO_4$, filtered and concentrated. The amber residue was purified over SiO_2 (gradient: 0 to 40% CH_2Cl_2 in hexane) to afford 2-methoxy-4-nitro-1-(trifluoromethyl)benzene (8.61 g, 72%) as a yellow crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95–7.83 (m, 2 H), 7.77 (d, *J* = 8.2 Hz, 1 H), 4.03 (s, 3 H). LC/MS (ES/APCI): 220.9 $(M - H)^-$.

A Parr hydrogenation flask was charged with 2-methoxy-4-nitro-1-(trifluoromethyl)benzene (8.60 g, 38.9 mmol), 10% Pd/C (1.75 g), and EtOH (150 mL). The flask was placed under 57 psi of hydrogen pressure at 55 °C for 18 h. The reaction mixture was cooled and the catalyst filtered and washed with *iso*-propanol. The solvent was removed and the crude product was purified over SiO_2 (gradient: 0 to 40% EtOAc in hexane) to afford 3-methoxy-4-(trifluoromethyl)aniline (7.18 g, 96%) as a waxy off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.17 (d, *J* = 8.2 Hz, 1 H), 6.30 (br s, 1 H), 6.16 (dd, *J* = 8.2, 1.3 Hz, 1 H), 5.77 (s, 2 H), 3.75 (s, 3 H). LC/MS (ES/APCI): 192.1 $(M + H)^+$.

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To a solution of 3-methoxy-4-(trifluoromethyl)aniline (3.01, 15.7 mmol), AcOH (7.5 mL) and anhydrous dioxane (25 mL) was added a solution of Br_2 (2.7 g, 16.9 mmol in 20 mL dioxane) dropwise using a syringe pump over 30 min at 0 °C. The reaction mixture stirred at rt for 1 h, poured into a mixture of 1.0 M NaOH (150 mL) and 2.0 M Na_2CO_3 (150 mL) and extracted with CH_2Cl_2. The combined extracts were washed sequentially with 0.5 M Na_2CO_3, brine, dried over Na_2SO_4, filtered, and concentrated to afford 2-bromo-5-methoxy-4-(trifluoromethyl)aniline (4.10 g, 97%) as a black crystalline solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.44 (s, 1 H), 6.57 (s, 1 H), 3.77 (s, 3 H).

To a solution of 2-bromoprop-2-enal (1.91 g) in AcOH (50 mL) was added dropwise Br_2 (0.72 mL, 13.9 mmol). To this solution was added 2-bromo-5-methoxy-4-(trifluoromethyl)aniline (3.48 g, 12.9 mmol) and stirred at 100 °C for 1 h. The reaction was cooled to rt and poured into a stirred ice cold solution of 2.0 M NaOH (550 mL). To the mixture was slowly added 2.0 M Na_2CO_3 [vigorous foaming] until the solution reached pH 8. The resulting solution extracted with CH_2Cl_2 and the organic extracts washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified over SiO_2 (gradient: 0 to 100% CH_2Cl_2 in hexane) and re-chromatographed (gradient: 0 to 100% EtOAc in hexane) to afford 3,8-dibromo-5-methoxy-6-(trifluoromethyl)quinoline (938 mg, 19%) as an off-white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.26 (d, J = 2.2 Hz, 1 H), 8.91 (d, J = 2.2 Hz, 1 H), 8.33 (s, 1 H), 4.06 (s, 3 H).

A vial was charged with 3,8-dibromo-5-methoxy-6-(trifluoromethyl)quinoline (850 mg, 2.2 mmol), *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanesulfonamide (661 mg, 2.22 mmol), an aqueous solution of Cs_2CO_3 (2.2 g, 6.7 mmol in 2.3 mL of water) and dioxane (10 mL) and the mixture was sparged with N_2 for 10 min. Pd(dppf)Cl_2·CH_2Cl_2 (74 mg, 0.09 mmol) was added to the mixture and stirred at 65 °C for 110 min. The reaction was cooled and poured into CH_2Cl_2 and 0.5 M Na_2CO_3. The phases were separated and washed sequentially with water, brine, dried over $MgSO_4$, filtered, and concentrated. The product was purified over SiO_2 (gradient: 0 to 100% EtOAc in CH_2Cl_2) to afford *N*-[4-[8-bromo-5-methoxy-6-(trifluoromethyl)-3-quinolyl]phenyl]methanesulfonamide (538 mg, 51%) as a light amber solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.07 (br s, 1 H), 9.53 (d, J = 2.2 Hz, 1 H), 8.73 (d, J = 2.1 Hz, 1 H), 8.27 (s, 1 H), 8.0 (d, J = 8.6 Hz, 2 H), 7.42 (d, J = 8.6 Hz, 2 H), 4.11 (s, 3 H), 3.09 (s, 3 H).

A vial was charged with *N*-[4-[8-bromo-5-methoxy-6-(trifluoromethyl)-3-quinolyl]phenyl]methanesulfonamide (370 mg, 0.78 mmol), *tert*-butyl carbamate (110 mg, 0.94 mmol), $Pd_2(dba)_3$·$CHCl_3$ (120 mg, 0.116 mmol), 2-di-*tert*-butylphosphino-2′,4′,6′-tri-*iso*-propyl-1′,1′-biphenyl (150 mg, 0.353 mmol), sodium *tert*-butoxide (110 mg, 1.14 mmol), and toluene (3.5 mL) and the resulting mixture was degassed by bubbling argon for 10 min. The reaction mixture was stirred at rt for two days then diluted with EtOAc and washed with saturated aqueous NH_4Cl. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified over SiO_2 (gradient: 0 to 10% EtOAc in CH_2Cl_2) to obtain *tert*-butyl *N*-[3-[4-(methanesulfonamido)phenyl]-5-methoxy-6-(trifluoromethyl)-8-quinolyl]carbamate (398 mg, 78%) as a light brown foam.

A mixture of *tert*-butyl *N*-[3-[4-(methanesulfonamido)phenyl]-5-methoxy-6-(trifluoromethyl)-8-quinolyl]carbamate (390 mg, 0.16 mmol), 4 M HCl in dioxane (4 mL), and CH_2Cl_2 (4 mL) was stirred at rt for 4 h then concentrated. The residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated to give *N*-[4-[8-amino-5-methoxy-6-(trifluoromethyl)-3-quinolyl]phenyl]methanesulfonamide (300 mg, 73%) as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.21 (d, J = 2.1 Hz, 1 H), 8.53 (d, J = 2.3 Hz, 1 H), 7.93 (d, J

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= 8.6 Hz, 2 H), 7.41 (d, *J* = 8.5 Hz, 2 H), 6.97 (s, 1 H), 6.17 (br s, 2 H), 3.93 (s, 3 H), 3.08 (s, 3H).

(*E*)-3-Methoxy-acryloyl chloride (90 mg, 1.12 mmol) was added at rt to a suspension of a previously dried silver cyanate (180 mg, 1.2 mmol) in toluene (2 mL). The resulting slurry was stirred at reflux for 30 min. before being cooled to 0 °C. After the solid had settled, the supernatant was added dropwise to a solution of *N*-[4-[8-amino-5-methoxy-6-(trifluoromethyl)-3-quinolyl]phenyl]methanesulfonamide (100 mg, 0.243 mmol) in DMF (1.5 mL) at 0 °C and the resulting light orange mixture was stirred for 30 min. The reaction was partitioned between EtOAc and water, the organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was taken into EtOH (1.5 mL) and water (1.5 mL) and concentrated H_2SO_4 (0.2 mL) was added. The resulting sticky slurry was stirred at 110 °C for 1 h. DMF was added and stirred at 110 °C for 2 h before cooling to rt. The clear solution was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The residue was purified over SiO_2 (gradient: 0 to 40% EtOAc in CH_2Cl_2) to yield trifluoromethylquinoline **51** (20 mg, 16%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.11 (d, *J* = 2.3 Hz, 1 H), 8.89 (br s, 1 H), 8.59 (br s, 1 H), 8.56 (d, *J* = 2.3 Hz, 1 H), 7.72 (d, *J* = 8.7 Hz, 2 H), 7.43 (d, *J* = 8.6 Hz, 2 H), 6.79 (br s, 1 H), 4.04 (s, 3 H), 3.11 (s, 3 H).

***N*-[4-[8-(2,4-dioxopyrimidin-1-yl)-5-methoxy-6-(2,2,2-trifluoroethyl)-3-quinolyl]phenyl]methanesulfonamide (52)—**In a flask was dissolved 2-methoxy-4-nitro-benzaldehye (9.93 g, 54.8 mmol) in anhydrous DME (100 mL) and stirred to obtain a clear yellow solution. To this solution was added sequentially CF_3SiMe_3 (9.0 mL, 8.66 g, 60.9 mmol) and CsF (792 mg, 5.2 mmol), sonicated for 20 min, then stirred at rt for 40 min. A 2.0 M HCl solution (100 mL) was added and the resulting mixture stirred at rt for 1 h. EtOAc was added to the mixture, the two layers separated, and the organic phase washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified over SiO_2 (gradient: 0 to 100% CH_2Cl_2 in hexane) to give 2,2,2-trifluoro-1-(2-methoxy-4-nitro-phenyl) ethanol (13.1 g, 95%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.93 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.84 (d, *J* = 2.0 Hz, 1 H), 7.77 (d, *J* = 8.6 Hz, 1 H), 7.08 (d, *J* = 5.8 Hz, 1 H), 5.49 (quintuplet, *J* = 6.5 Hz, 1 H), 3.97 (s, 3 H).

To a solution of 2,2,2-trifluoro-1-(2-methoxy-4-nitro-phenyl)ethanol (13.01 g, 51.8 mmol) in THF (300 mL) was added NaH (2.25 g, 56.2 mmol, 60% wt dispersion in mineral oil) at rt. The mixture was sonicated for 20 min, then stirred at rt for 10 min. A solution of p-toluenesulfonyl chloride (11.86 g, 62.2 mmol) dissolved in THF (100 mL) was added at rt and the reaction stirred at 50 °C for 1.5 h. The solution was cooled and poured into 0.5 M $NaHCO_3$, diluted with EtOAc, the organic phase separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified over SiO_2 (gradient: 0 to 100% CH_2Cl_2 in hexane) to afford [2,2,2-trifluoro-1-(2-methoxy-4-nitro-phenyl)ethyl] 4-methylbenzenesulfonate (20.36 g, 97%) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.81–7.73 (m, 2 H), 7.69 (d, *J* = 8.4 Hz, 2 H), 7.60 (d, *J* = 8.5 Hz, 1 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 6.24 (q, *J* = 6.4 Hz, 1 H), 3.95 (s, 3 H), 2.33 (s, 3 H).

A Parr hydrogenation flask was charged with [2,2,2-trifluoro-1-(2-methoxy-4-nitro-phenyl) ethyl] 4-methylbenzenesulfonate (20.35 g, 50.2 mmol) and dissolved in EtOH (250 mL). To the solution was added 10% Pd/C (4.02 g) and hydrogenated under 55 psi of hydrogen at 50 °C for 1.5 h. The catalyst was filtered through a plug of glass wool and washed with hot EtOH. The filtrate was concentrated and the tosylate salt precipitated as a white solid. The residue was partitioned between 1.0 M NaOH and Et_2O. The organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified over SiO_2 (CH_2Cl_2) to obtain 3-methoxy-4-(2,2,2-trifluoroethyl)aniline (9.04 g, 88%) as an off-

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white solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.87 (d, J = 8.1 Hz, 1 H), 6.24 (d, J = 2.0 Hz, 1 H), 6.13 (dd, J = 8.0, 2.0 Hz, 1 H), 5.19 (br s, 2 H), 3.70 (s, 3 H), 3.32 (q, J = 11.7 Hz, 2 H). LC/MS (ES/APCI): 206.1 $(M + H)^+$.

To a solution of 3-methoxy-4-(2,2,2-trifluoroethyl)aniline (8.16 g, 39.8 mmol), AcOH (23 mL), and dioxane (100 mL) was added a solution of Br_2 (2.26 mL, 44 mmol) in dioxane (45 mL) dropwise over 30 min at 5 °C. The solution was warmed to rt and stirred for 1 h. The reaction was poured into 1.0 M NaOH and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to afford crude 2-bromo-5-methoxy-4-(2,2,2-trifluoroethyl)aniline (11.42 g) as a pale olive solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.21 (br s, 1 H), 6.48 (s, 1 H), 5.41 (br s, 2 H), 3.71 (s, 3 H), 3.38 (q, J = 11.6 Hz, 2 H). LC/MS (ES/APCI): 284.0 $(M + H)^+$.

To a solution of 2-bromoprop-2-enal (2.71 g, 20.1 mmol) in AcOH (25 mL) was added Br_2 (3.2 g, 1.0 mL, 20 mmol) at 0 °C. This solution was poured into a stirred solution of 2-bromo-5-methoxy-4-(2,2,2-trifluoroethyl)aniline (5.67 g, 19.9 mmol) and AcOH (25 mL) and the resulting mixture stirred at 100 °C for 2 h. The solution was cooled, diluted with water, and extracted with EtOAc. The extract was washed with 2.0 M NaOH, brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified over SiO_2 (CH_2Cl_2) to obtain 3,8-dibromo-5-methoxy-6-(2,2,2-trifluoroethyl)quinoline (2.69 g, 34%) as a light orange solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.13 (d, J = 2.3 Hz, 1 H), 8.76 (d, J = 2.3 Hz, 1 H), 8.19 (s, 1 H), 3.95 (s, 3 H), 3.90 (q, J = 11.2 Hz, 2 H). LC/MS (ES/APCI): 399.9 $(M + H)^+$.

A vial was charged with 3,8-dibromo-5-methoxy-6-(2,2,2-trifluoroethyl)quinoline (2.62 g, 6.5 mmol), *N*-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]methanesulfonamide (1.92 g, 6.5 mmol), an aqueous solution of Cs_2CO_3 (6.46 g, 19.8 mmol, 6 mL of water) and dioxane (25 mL) and the mixture was sparged with N_2 for 10 min. Pd(dppf)Cl_2·CH_2Cl_2 (161 mg, 0.19 mmol) was added to the mixture and stirred at 50 °C for 2 h. The reaction was cooled and poured into CH_2Cl_2 and 0.5 M Na_2CO_3. The phases were separated and the organic phase was washed sequentially with water, brine, dried over $MgSO_4$, filtered, and concentrated. The product was purified over SiO_2 (gradient: 0 to 60% EtOAc in CH_2Cl_2) to afford *N*-[4-[8-bromo-5-methoxy-6-(2,2,2-trifluoroethyl)-3-quinolyl]phenyl]methanesulfonamide (368 mg, 11%) as a solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.04 (s, 1 H), 9.40 (d, J = 2.2 Hz, 1 H), 8.62 (d, J = 2.2 Hz, 1 H), 8.13 (s, 1 H), 7.96 (d, J = 8.6 Hz, 2 H), 7.41 (d, J = 8.6 Hz, 2 H), 3.99 (s, 3 H), 3.90 (q, J = 11.2 Hz, 2 H), 3.09 (s, 3 H). LC/MS (ES/APCI): 489.0 $(M + H)^+$.

A flask was charged with *N*-[4-[8-bromo-5-methoxy-6-(2,2,2-trifluoroethyl)-3-quinolyl]phenyl]methanesulfonamide (1.0 g, 2.04 mmol), *tert*-butyl carbamate (290 mg, 2.48 mmol), $Pd_2(dba)_3$·$CHCl_3$ (106 mg, 0.1 mmol), 2-di-*tert*-butylphosphino-2′,4′6′-tri-*iso*-propyl-1′,1′-biphenyl (150 mg, 0.353 mmol), sodium *tert*-butoxide (287 mg, 3.0 mmol), and toluene (10 mL) and the resulting mixture was degassed by bubbling argon for 10 min. The reaction mixture was stirred at rt for 1.5 h then diluted with EtOAc and washed with saturated aqueous NH_4Cl. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified over SiO_2 (gradient: 0 to 25% EtOAc in CH_2Cl_2) to obtain *tert*-butyl *N*-[3-[4-(methanesulfonamido)phenyl]-5-methoxy-6-(2,2,2-trifluoroethyl)-8-quinolyl]carbamate (926 mg, 86%) as a foam. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.02 (s, 1 H), 9.24 (d, J = 2.1 Hz, 1 H), 8.88 (s, 1 H), 8.58 (d, J = 2.1 Hz, 1 H), 8.24 (s, 1 H), 7.93 (d, J = 8.7 Hz, 2 H), 7.41 (d, J = 8.7 Hz, 2 H), 3.96–3.79 (m, 2 H), 3.93 (s, 3 H), 3.08 (s, 3 H) 1.54 (s, 9 H). LC/MS (ES/APCI): 526.1 $(M + H)^+$.

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A mixture of *tert*-butyl *N*-[3-[4-(methanesulfonamido)phenyl]-5-methoxy-6-(2,2,2-trifluoroethyl)-8-quinolyl]carbamate (908 mg, 1.73 mmol), 4 M HCl in dioxane (8 mL), and CH_2Cl_2 (4 mL) was stirred at rt for 2 h then concentrated. The reaction was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified over SiO_2 (gradient: 0 to 50% EtOAc in CH_2Cl_2) to give *N*-[4-[8-amino-5-methoxy-6-(2,2,2-trifluoroethyl)-3-quinolyl]phenyl]methanesulfonamide (554 mg, 75%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.98 (s, 1 H), 9.08 (d, *J* = 2.2 Hz, 1 H), 8.42 (d, *J* = 2.1 Hz, 1 H), 7.89 (d, *J* = 8.7 Hz, 2 H), 7.39 (d, *J* = 8.5 Hz, 2 H), 6.80 (s, 1 H), 5.87 (s, 2 H), 3.84 (s, 3 H), 3.72 (q, *J* = 11.4 Hz, 2 H), 3.07 (s, 3 H). LC/MS (ES/APCI): 426.0 $(M + H)^+$.

A suspension of dried silver cyanate (529 mg, 3.5 mmol) and anhydrous toluene (3 mL) was stirred at 90 °C for 20 min. A solution of (*E*)-3-methoxyprop-2-enoyl chloride (216 mg, 1.8 mmol) in anhydrous toluene (2 mL) was added dropwise to the suspension and stirred at 90 °C for 30 min. The suspension was allowed to stand at rt for 10 min and the supernatant transfer by syringe to a solution of *N*-[4-[8-amino-5-methoxy-6-(2,2,2-trifluoroethyl)-3-quinolyl]phenyl]methanesulfonamide (249 mg, 0.58 mmol) in DMF (3 mL) at −20 °C. The reaction was allowed to reach rt and stirred for 18 h. The reaction was concentrated and the residue purified over SiO_2 (gradient: 0 to 70% EtOAc in CH_2Cl_2) to obtain a mixture of geometric isomers used in the next reaction (204 mg).

A suspension of the product from previous reaction (178 mg) and H_2SO_4 (0.5 mL) with EtOH (2 mL) and water (2 mL) was stirred at 110 °C for 2 h. The reaction was cooled to room temperature and let stand overnight. A yellow solid crystallized from the yellow supernatant. The solid was collected by filtration and washed with EtOH/water (1/1). The solid was dissolved in hot EtOH (10 mL) and water (10 mL) added. The resulting solution was allowed to cool to room temperature and a fluffy white crystals formed. The solid was collected by filtration, washed with 1:1 EtOH/water (1/1), and dried under vacuum to obtain the trifluoroethylquinoline **52** (107 mg, 6%) as white crystals. ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.51 (d, *J* = 1.8 Hz, 1 H), 10.03 (s, 1 H), 9.34 (d, *J* = 2.2 Hz, 1 H), 8.66 (d, *J* = 2.0 Hz, 1 H), 7.94 (d, *J* = 8.7 Hz, 2 H), 7.90 (s, 1 H), 7.72 (d, *J* = 7.9 Hz, 1 H), 7.40 (d, *J* = 8.7 Hz, 2 H), 5.71 (dd, *J* = 7.9, 1.9 Hz, 1 H), 4.04 (s, 3 H), 3.96 (d, *J* = 11.1 Hz, 1 H), 3.88 (d, *J* = 11.1 Hz, 1 H), 3.08 (s, 3 H). LC/MS (ES/APCI): 521.0 $(M + H)^+$.

***N*-[4-[6-[1-(Difluoromethyl)cyclopropyl]-8-(2,4-dioxopyrimidin-1-yl)-5-methoxy-3-quinolyl]phenyl]methanesulfonamide (53)—**Br_2 (4.48 mL, 86.9 mmol) in AcOH (50 mL) was added to a solution of 2-bromoprop-2-enal (11.7 g, 86.7 mmol) in AcOH (100 mL) at rt until the solution showed faint Br_2 color. To this solution was added methyl 4-amino-5-bromo-2-methoxy-benzoate (22.6 g, 86.9 mmol) and the resulting solution was gradually heated to 100 °C and stirring continued for 15 min. The reaction was cooled to rt and concentrated. The residue was neutralized with saturated aqueous $NaHCO_3$ and a precipitate formed. The resulting solid was filtered and washed with water and Et_2O to afford methyl 3,8-dibromo-5-methoxyquinoline-6-carboxylate (11.04 g, 34%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.08 (d, *J* = 2.3 Hz, 1 H), 8.76 (d, *J* = 2.4 Hz, 1 H), 8.46 (s, 1 H), 4.08 (s, 3 H), 4.01 (s, 3 H).

To a solution of methyl 3,8-dibromo-5-methoxy-quinoline-6-carboxylate (11.04 g, 29.5 mmol) in CH_2Cl_2 (550 mL) at 0 °C was added dropwise DIBAL (64.4 mL, 64.4 mmol, 1 M in CH_2Cl_2). The reaction was quenched with aqueous Rochelle salt and partitioned between water and CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified over SiO_2 (gradient: 0 to 10% MeOH in CH_2Cl_2) to afford (3,8-dibromo-5-methoxy-6-quinolyl)methanol (9.5 g, 93%). ^{1}H NMR

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(300 MHz, $CDCl_3$) δ 9.01 (d, *J* = 2.2 Hz, 1 H), 8.59 (d, *J* = 2.2 Hz, 1 H), 8.18 (s, 1 H), 4.93 (d, *J* = 5.7 Hz, 2 H), 3.98 (s, 3 H), 1.98 (t, *J* = 5.8 Hz, 1 H).

A solution of (3,8-dibromo-5-methoxy-6-quinolyl)methanol (7.82 g, 22.5 mmol), CBr_4 (8.97 g, 27.0 mmol), PPh_3 (7.09 g, 27.0 mmol) and CH_2Cl_2 (250 mL) was stirred at rt for 18 h. Additional CBr_4 (3.73, 11.2 mmol) and PPh_3 (2.95 g, 11.2 mmol) were added to the reaction and stirred for 1 h. The crude reaction mixture was concentrated and the residue purified over SiO_2 (gradient: 0 to 100% CH_2Cl_2 in hexane) to afford 3,8-dibromo-6-(bromomethyl)-5-methoxy-quinoline (7.62 g, 83%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (d, *J* = 2.3 Hz, 1 H), 8.58 (d, *J* = 2.2 Hz, 1 H), 8.07 (s, 1 H), 4.67 (s, 2 H), 4.06 (s, 3 H).

A mixture of 3,8-dibromo-6-(bromomethyl)-5-methoxy-quinoline (8.0 g, 19.5 mmol), KCN (12.4 g, 191 mmol), CH_2Cl_2 (156 mL), and water (140 mL) was heated at reflux for 15 min. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified over SiO_2 (gradient: 0 to 5% MeOH in CH_2Cl_2) to afford 2-(3,8-dibromo-5-methoxy-6-quinolyl)acetonitrile (4.53 g, 65%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (d, *J* = 2.2 Hz, 1 H), 8.57 (d, *J* = 2.3 Hz, 1 H), 8.09 (s, 1 H), 4.01 (s, 3 H), 3.93 (s, 2 H).

A mixture of 2-(3,8-dibromo-5-methoxy-6-quinolyl)acetonitrile (5.02 g, 14.1 mmol), 1,2-dibromoethane (1.46 mL, 16.9 mmol), and DMF (60 mL) was cooled to 0 °C and NaH (1.69 g, 42.3 mmol, 60% mineral oil dispersion) was added. The mixture was warmed to rt and stirred for 1 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified over SiO_2 (gradient: 0 to 100% CH_2Cl_2 in hexane) to afford 1-(3,8-dibromo-5-methoxy-6-quinolyl)cyclopropanecarbonitrile (1.91 g, 35%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, *J* = 2.0 Hz, 1 H), 8.61 (d, *J* = 2.1 Hz, 1 H), 8.00 (s, 1 H), 4.18 (s, 3 H), 1.83 (dd, *J* = 7.9, 5.3 Hz, 2 H), 1.49 (dd, *J* = 7.5, 4.9 Hz, 2 H).

To a solution of 1-(3,8-dibromo-5-methoxy-6-quinolyl)cyclopropanecarbonitrile (280 mg, 0.733 mmol) in CH_2Cl_2 (14 mL) was added DIBAL (0.87 mL, 0.87 mmol, 1 M in CH_2Cl_2) dropwise at −78 °C. The reaction mixture was stirred at the same temperature for 1 h. The reaction was quenched with aqueous Rochelle salt and extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified over SiO_2 (gradient: 0 to 100% CH_2Cl_2 in hexane) to afford 1-(3,8-dibromo-5-methoxy-6-quinolyl)cyclopropanecarbaldehyde (220 mg, 78%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1 H), 9.01 (d, *J* = 2.2 Hz, 1 H), 8.60 (d, *J* = 2.1 Hz, 1 H), 7.89 (s, 1 H), 3.92 (s, 3 H), 1.77 (dd, *J* = 7.6, 4.9 Hz, 2 H), 1.56 (dd, *J* = 7.0, 4.4 Hz, 2 H).

To a solution of 1-(3,8-dibromo-5-methoxy-6-quinolyl)cyclopropanecarbaldehyde (630 mg, 1.64 mmol) in CH_2Cl_2 (14 mL) was added diethylaminosulfur trifluoride (DAST) (1.05 g, 6.54 mmol) and the resulting solution was stirred at rt for 72 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified over SiO_2 (gradient: 50 to 100% CH_2Cl_2 in hexane) to afford 3,8-dibromo-6-[1-(difluoromethyl)cyclopropyl]-5-methoxyquinoline (600 mg, 90%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.0 (d, *J* = 2.0 Hz, 1 H), 8.57 (d, *J* = 2.1 Hz, 1 H), 8.07 (s, 1 H), 5.89 (t, *J* = 57.6 Hz, 1 H), 4.05 (s, 3 H), 1.35 (br t, *J* = 6.1 Hz, 2 H), 1.18–1.12 (br s, 2 H).

To a microwave vial was added 3,8-dibromo-6-[1-(difluoromethyl)cyclopropyl]-5-methoxyquinoline (600 mg, 1.47 mmol), 4-(methanesulfonamido)phenylboronic acid (317

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mg, 1.47 mmol), $Pd(PPh_3)_4$ (162 mg, 0.14 mmol), Na_2CO_3 (469 mg, 4.42 mmol), MeOH (9 mL), and toluene(3 mL). The vial was capped and heated in the microwave reactor at 120 °C for 1 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was diluted with CH_2Cl_2, washed with water, dried over Na_2SO_4, and concentrated. The crude material was purified over SiO_2 (gradient: 30 to 80% EtOAc in hexanes) to obtain *N*-[4-[8-bromo-6-[1-(difluoromethyl)cyclopropyl]-5-methoxy-3-quinolyl]phenyl]methanesulfonamide (670 mg, 91%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (d, *J* = 2.0 Hz, 1 H), 8.53 (d, *J* = 2.1 Hz, 1 H), 8.06 (s, 1 H), 7.73 (d, *J* = 8.4 Hz, 2 H), 7.41 (d, *J* = 8.5 Hz, 2 H), 6.69 (s, 1 H), 5.94 (t, *J* = 57.7 Hz, 1 H), 4.09 (s, 3 H), 3.11 (s, 3 H), 1.40–1.34 (br m, 2 H), 1.21–1.13 (br m, 2 H).

To a flask was added *N*-[4-[8-bromo-6-[1-(difluoromethyl)cyclopropyl]-5-methoxy-3-quinolyl]phenyl]methanesulfonamide (520 mg, 1.05 mmol), *tert*-butyl carbamate (147 mg, 1.25 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (123 mg, 0.12 mmol), 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (172 mg, 0.4 mmol), sodium *tert*-butoxide (301 mg, 3.14 mmol), and toluene (8 mL). The mixture was purged with argon for 20 min and stirred at rt for 72 h. The mixture was quenched with NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified over SiO_2 (gradient: 30 to 80% EtOAc in hexane) to give *tert*-butyl *N*-[6-[1-(difluoromethyl)cyclopropyl]-3-[4-(methanesulfonamido)phenyl]-5-methoxy-8-quinolyl]carbamate (150 mg, 27%) as a solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.01 (d, *J* = 2.2 Hz, 1 H), 8.82 (br s, 1 H), 8.49 (d, *J* = 2.3 Hz, 1 H), 8.39 (br s, 1 H), 7.72 (d, *J* = 8.5 Hz, 2 H), 7.40 (d, *J* = 8.5 Hz, 2 H), 6.53 (s, 1 H), 6.13 (t, *J* = 58.4 Hz, 1 H), 4.02 (s, 3 H), 3.10 (s, 3 H), 1.56 (s, 9 H), 1.36 (dd, *J* = 6.2, 5.0 Hz, 2 H), 1.22–1.14 (br m, 2 H).

To a solution of *tert*-butyl *N*-[6-[1-(difluoromethyl)cyclopropyl]-3-[4-(methanesulfonamido)phenyl]-5-methoxy-8-quinolyl]carbamate (150 mg, 0.28 mmol) in CH_2Cl_2 was added 4 M HCl in dioxane (1.55 mL, 6.2 mmol). The reaction was stirred at rt for 1h then neutralized with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude material was purified over SiO_2 (gradient: 30 to 80% EtOAc in hexane) to afford *N*-[4-[8-amino-6-[1-(difluoromethyl)cyclopropyl]-5-methoxy-3-quinolyl]phenyl]methanesulfonamide (110 mg, 90%) as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, *J* = 2.2 Hz, 1 H), 8.43 (d, *J* = 2.2 Hz, 1 H), 7.72 (d, *J* = 8.4 Hz, 2 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 6.90 (s, 1 H), 6.49 (br s, 1 H), 6.05 (t, *J* = 58.4 Hz, 1 H), 4.83 (br s, 2 H), 3.98 (s, 3 H), 3.10 (s, 3 H), 1.31 (dd, *J* = 6.7, 5.0 Hz, 2 H), 1.14–1.08 (br m, 2 H).

In a flask, (*E*)-3-methoxyacryloyl chloride (91.8 mg, 0.761 mmol) and dried silver cyanate (190 mg, 1.27 mmol) were combined with toluene (2 mL) and the mixture was heated to 130 °C and stirred for 30 min. The reaction was cooled down to 0 °C and allowed to settle. The supernatant was added dropwise to *N*-[4-[8-amino-6-[1-(difluoromethyl)cyclopropyl]-5-methoxy-3-quinolyl]phenyl]methanesulfonamide (110 mg, 0.25 mmol) in DMF (1 mL) at 0 °C. The reaction was stirred at 0 °C for 45min then diluted with EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude reaction mixture was purified over SiO_2 (gradient: 50 to 100% EtOAc in hexane) to obtain a mixture of geometric isomers used in the next reaction (160 mg) as a light yellow solid.

A slurry of the product from previous reaction (160 mg) and concentrated H_2SO_4 (0.35 mL) with EtOH (4 mL) and water (3 mL) was heated at 110 °C for 1.5 h. Most of EtOH was evaporated and the residue was neutralized with saturated aqueous $NaHCO_3$. The mixture was extracted with EtOAc, the organic layer was dried over Na_2SO_4, and concentrated. The crude product was concentrated and triturated with Et_2O and dried to yield the

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cyclopropylquinoline **53** (123 mg, 93%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (d, J = 1.5 Hz, 1 H), 10.0 (s, 1 H), 9.31 (d, J = 2.3 Hz, 1 H), 8.65 (d, J = 2.0 Hz, 1 H), 7.93 (d, J = 8.6 Hz, 2 H), 7.87 (s, 1 H), 7.69 (d, J = 8.0 Hz, 1 H), 7.39 (d, J = 8.6 Hz, 2 H), 6.15 (t, J = 57.0 Hz, 1 H), 5.69 (dd, J = 7.8, 1.8 Hz, 1 H), 4.12 (s, 3 H), 3.07 (s, 3 H), 1.32 (br s, 2 H), 1.21–1.15 (m, 2 H). LC/MS (ES/APCI): 529.0 $(M + H)^+$.

HCV NS5B polymerase biochemical assay protocol

The enzymatic activity of HCV polymerase (NS5B570n-Con1) was measured as described previously[15] with only two changes as follow: concentration of RNA template was 3 nM and concentration of NS5B570n-Con1 enzyme was 3 nM.

Stable HCV replicon assay

The stable GT-1a H77 and GT-1b Con1 subgenomic replicon cell lines expressing the renilla luciferase as a reporter gene (cell lines 2209-23 and pRLucH771b75S/I, respectively) were used as described by Le Pogam.[28]

Transient HCV replicon assay using a panel of GT-1 NS5B clinical isolates

The GT-1b Con1 and GT-1a H77 transient replicons in which the wild type NS5B gene has been replaced by NS5B isolates obtained from untreated patients were used as described by Le Pogam.[22]

HCV NS5B polymerase protein crystallography

HCV NS5B GT1b (BK 1-570) was expressed and purified as previously described.[29] Crystals of compound-bound polymerase were grown by sitting drop vapor diffusion set using 7 mg/ml protein plus 5 mM of each respective compound over a reservoir containing 50 mM sodium citrate (pH 4.9), 24% polyethylene glycol 4000, and 7.5% glycerol. Crystals were transferred to a solution of mother liquor plus 20% glycerol for cryoprotection and flash frozen in liquid nitrogen. Data were collected at the Advanced Light Source beamline 5.0.2 and Stanford Synchrotron Radiation Laboratories beam line 7-1. Data were reduced with HKL2000,[30] a molecular replacement solution determined with Phaser[31] and refined using cycles of Buster[32,33] with manual rebuilding using Coot.[34]

Hepatocyte metabolic stability assay

The compounds were incubated with approximately 1.0×10^6 cells/mL in suspension with Williams' medium E (supplemented with glutamine, antibiotics, insulin, dexamethasone, and 10% FCS) at 37 °C in an atmosphere of 5% CO_2. Hepatocyte incubations were done at different concentrations (0.1, 0.3, 1.0, 3.0, and 10.0 μM) of compounds on a Teleshake 1 Variomag at speed of 900 rpm. Incubations were terminated by the addition of 200 μL of methanol plus internal standard after 2, 10, 30, 60, 120, and 180 min of incubation. Samples were transferred to analytical plates and sealed. The supernatants were analyzed by LC/MS/MS. All incubations were conducted in duplicate, and the percentage of compounds remaining at the end of the incubation was determined from the LC/MS/MS peak area ratio.

Pharmacokinetics

Male Wistar/Han (CRL:WI) rats (Charles River Laboratories, Hollister, CA or Raleigh, NC) used in these studies weighed between 180 and 300 g and were surgically implanted with cannulas in the jugular and/or femoral veins. Male beagle dogs used in these studies. All studies were conducted under IACUC approved protocols, and animals were allowed free access to food and water. Single intravenous bolus doses were administered into the tail vein or into the jugular cannula of dual-cannulated animals using a dosing formulation consisting

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of 2% dimethyl acetamide/20% PEG400/23.4% HPBCD; the remaining cannulas were used for blood collection. Single oral doses were administered by gavage using a dosing formulation consisting of 2% Klucel LF in water. Blood was collected into tubes containing EDTA at typically 0.08 (*iv* only), 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h after dosing. Plasma concentrations were determined by a liquid chromatography/tandem mass spectrometry method (LC/MS/MS) following protein precipitation with acetonitrile.

Preparation of 41 microprecipitated bulk product

Amorphous form of the compound was manufactured by Solvent Controlled Precipitation (SCP) method. The drug and Eudragit L100-55 polymer (copolymers of acrylic and methacrylic acid) were dissolved in the dimethyl acetamide (DMA) by stirring at room temperature. The solution was then added to the temperature controlled anti solvent aqueous media (at dilute HCl, pH 3.0, temperature 2–8 °C) that allows rapid co-precipitation of drug and API. The residual DMA was extracted with frequent washing, followed by filtration and drying. The formulation showed amorphous X-ray diffraction pattern. The yield from SCP process was over 90%. Only Eudragit L100-55 polymer provided stable amorphous formulation which stayed amorphous for more than 60 days in the aqueous media as well as under extreme stress conditions of 40°C/100% RH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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ABBREVIATIONS USED

DAA	direct-antiviral agents
HCV	hepatitis C virus
MBP	microprecipitated bulk powder
NI	nucleoside inhibitor
NNI	non-nucleoside inhibitor
NS5B	nonstructural 5B
GT	genotype
SVR	sustained virological response

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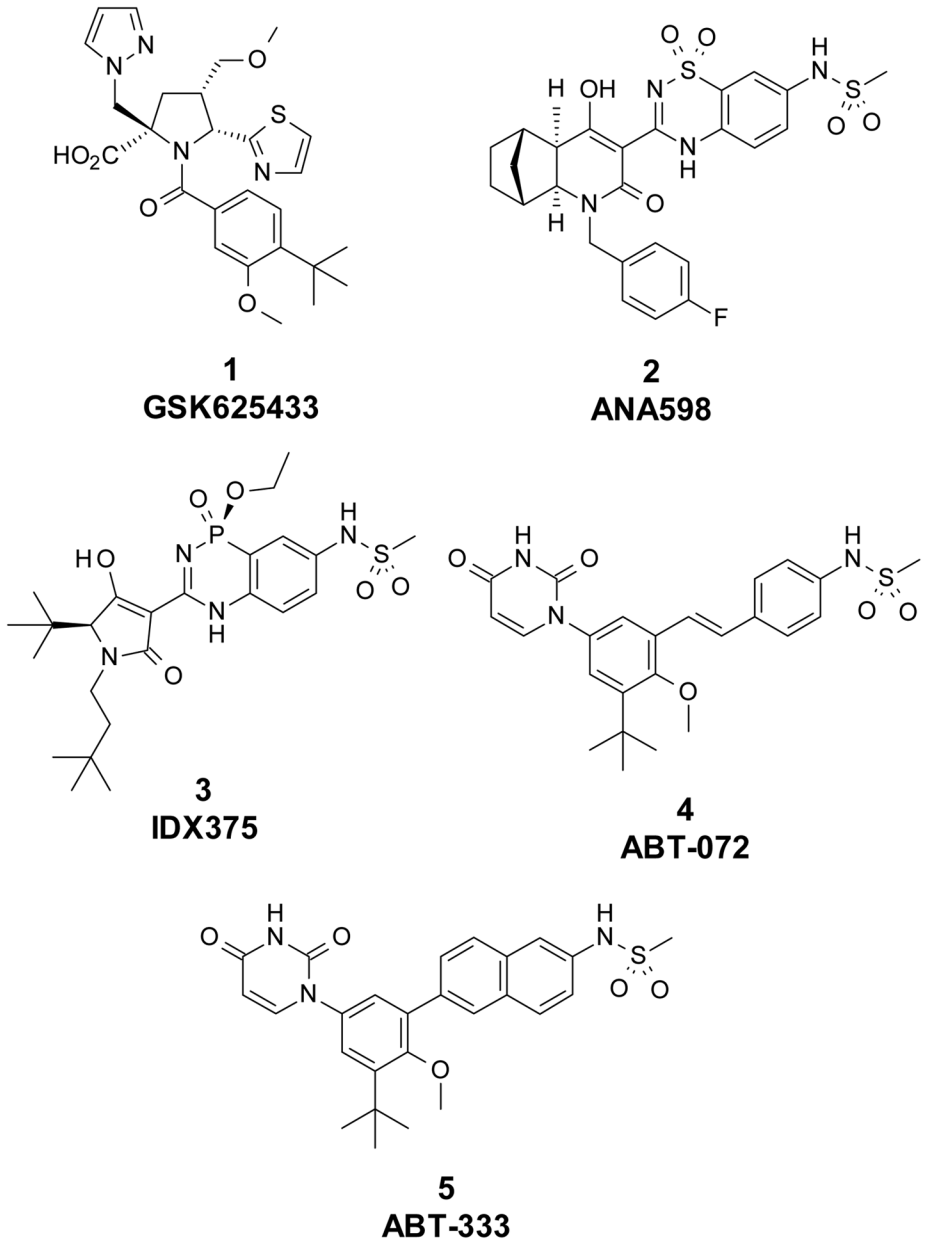

Figure 1.
Known HCV polymerase inhibitors that bind in the palm I allosteric site.

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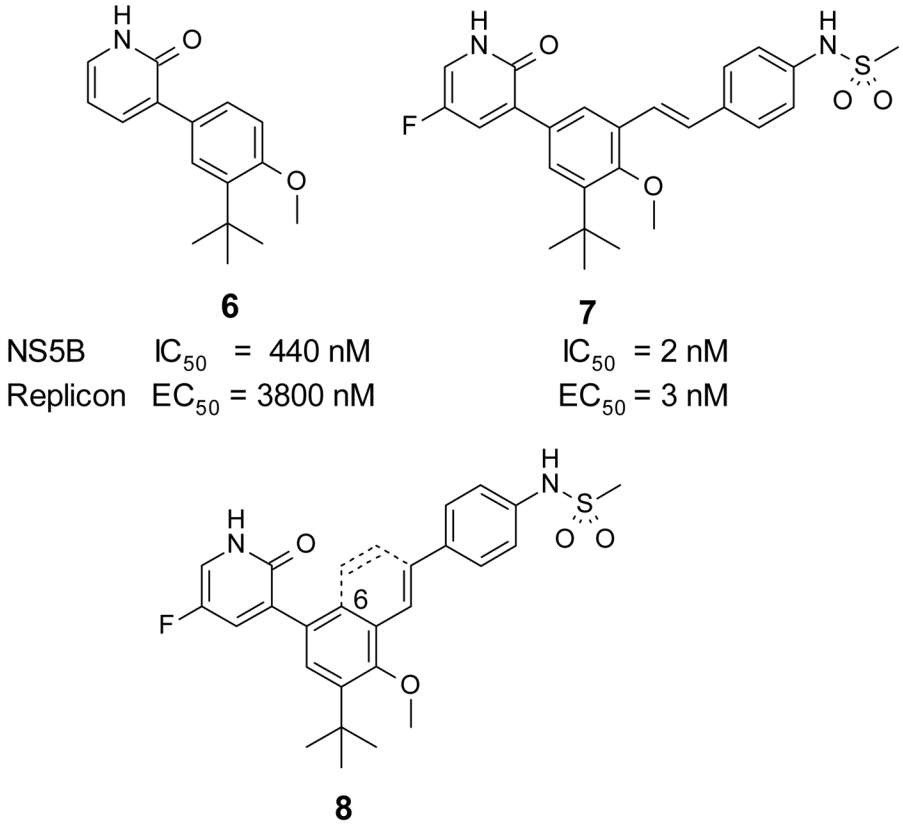

Figure 2.
3-Aryl pyridones. Biological data generated with HCV GT-1b strain.

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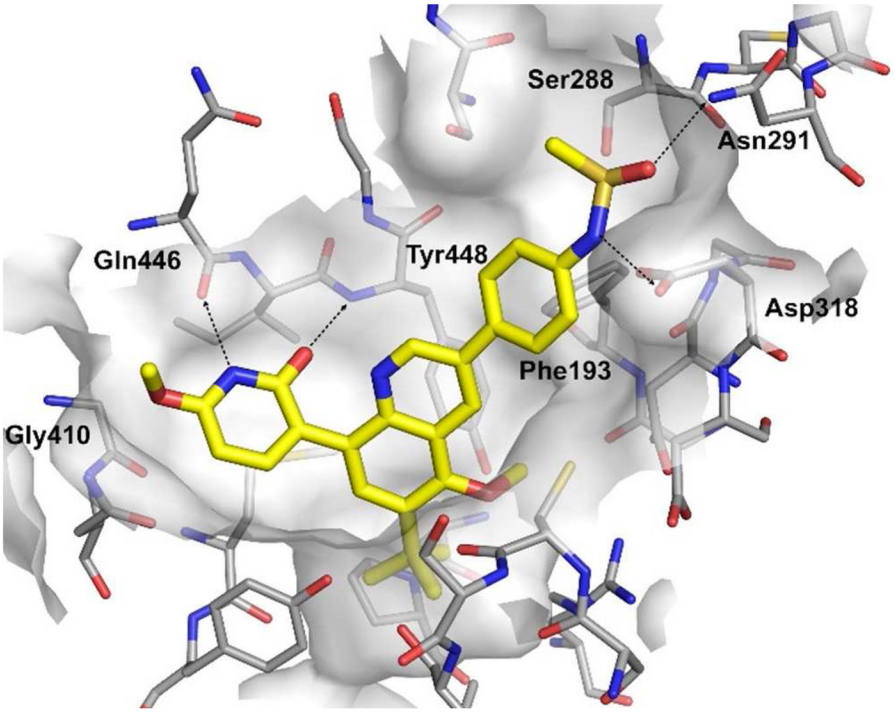

Figure 3.
Cocrystal structure of compound **41** with NS5B polymerase (GT-1b BK) in palm I allosteric site. Crystal structure figures were drawn with PyMOL.[20]

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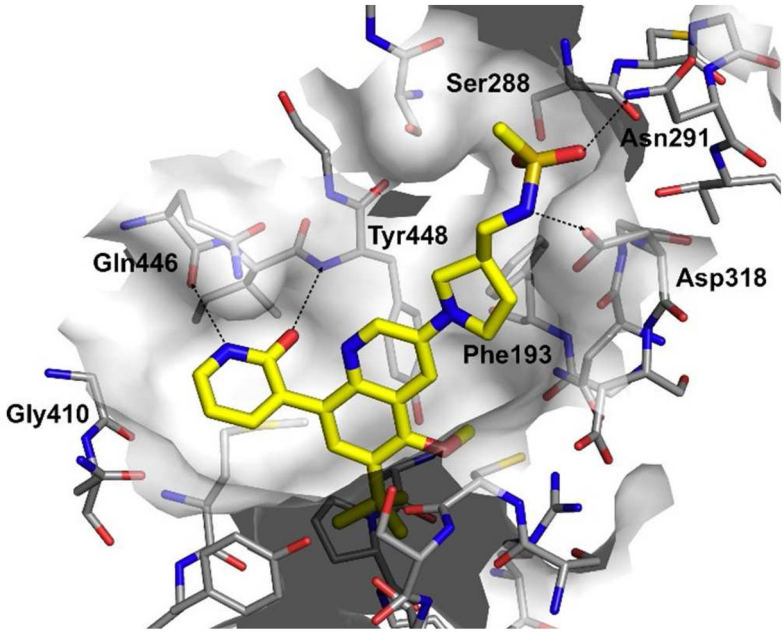

Figure 4.
Cocrystal structure of compound **48** with NS5B (GT-1b BK) polymerase in palm I allosteric site.

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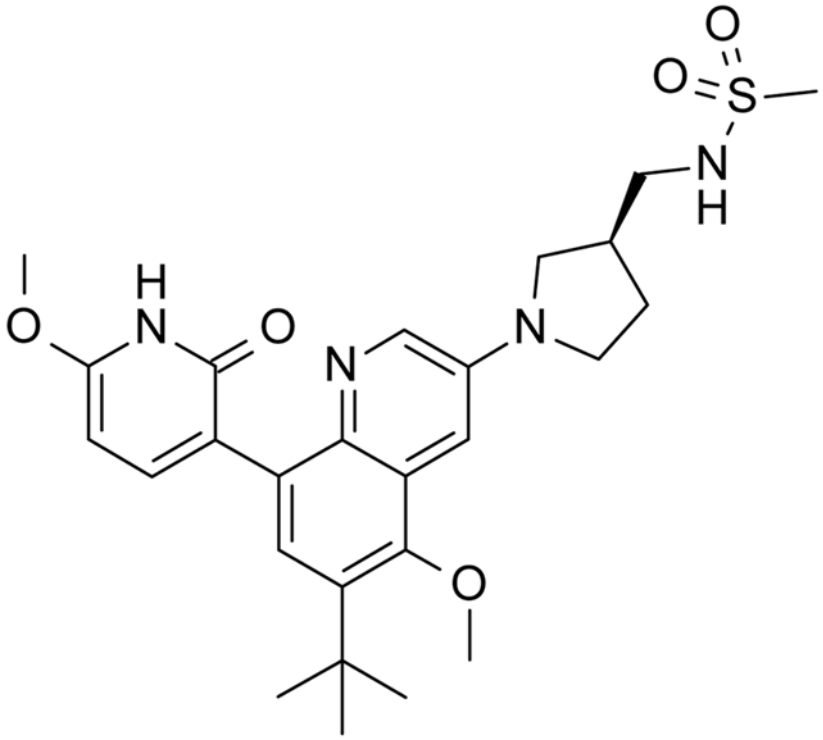


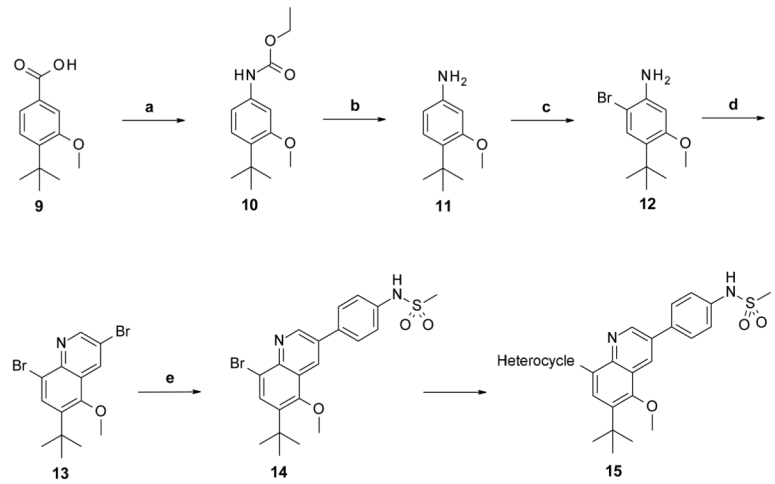
50

GT-1a Replicon EC_{50} = 17 nM

GT-1b Replicon EC_{50} = 12 nM

Aq. Solubility 39 μg/mL

Figure 5.
Best pyrrolidine derivative from the bicyclic series.



Scheme 1. Synthesis of 3,5,6,8-tetrasubstituted quinoline core

Reagents and conditions: (a) Ph_2PON_3, Et_3N, EtOH, THF, reflux, 81%; (b) aq. KOH, EtOH, reflux, 96%; (c) NBS, DMF, quantitative; (d) Br_2, 2-bromoprop-2-enal, AcOH, 100 °C, 45%; (e) 4-(methanesulfonamido)phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, MeOH, toluene, 120 °C, 57%.

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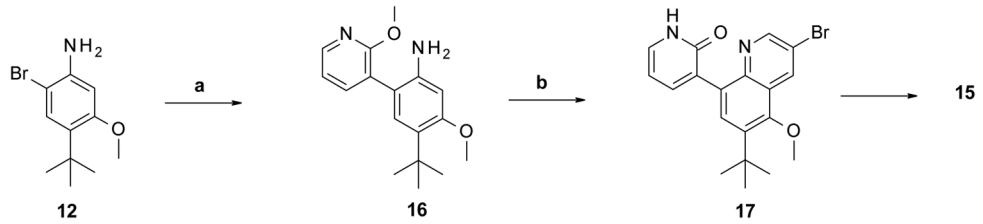

Scheme 2. Alternative synthesis of 3,5,6,8-tetrasubstituted quinoline core

Reagents and conditions: (a) (2-methoxy-3-pyridyl)boronic acid, $Pd(PPh_3)_4$, Na_2CO_3, MeOH, CH_2Cl_2, 115 °C, 54%; (b) Br_2, 2-bromoprop-2-enal, AcOH, 100 °C, 27%.

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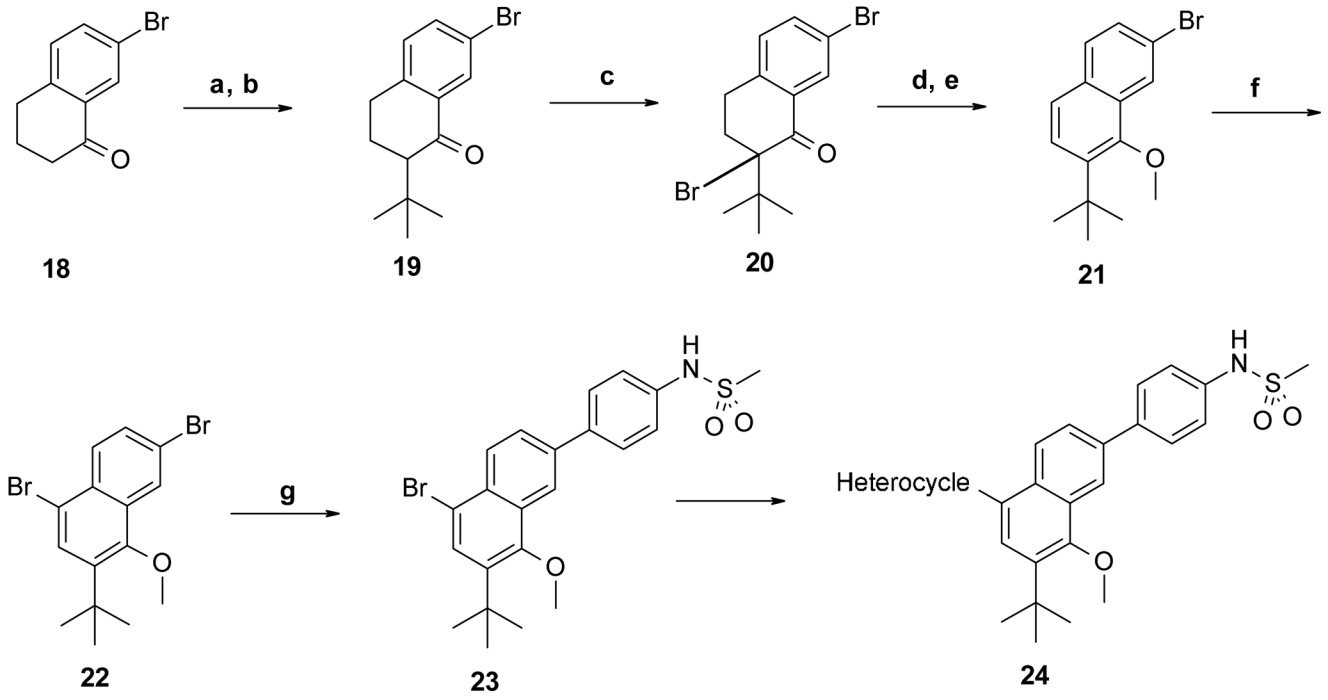
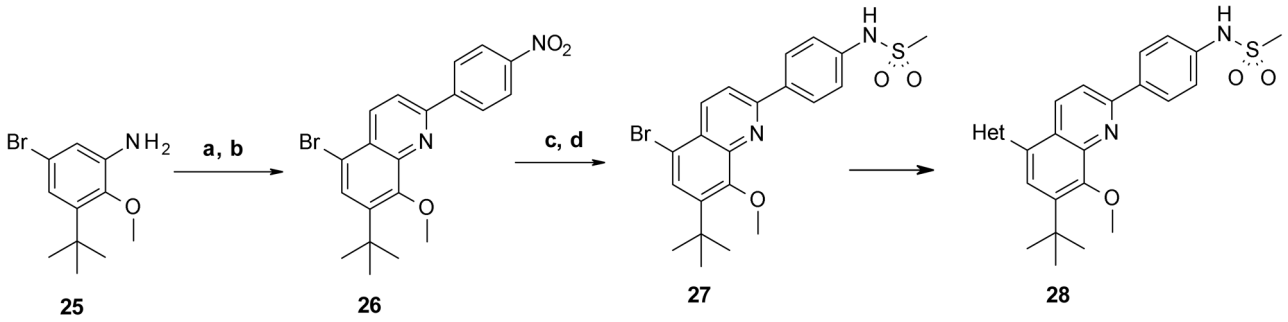


Scheme 3. Synthesis of 2,5,7,8-tetrasubstituted naphthalene core

Reagents and conditions: (a) TMSCl, NaI, Et_3N, CH_3CN, 69%; (b) 2-chloro-2-methyl-propane, $TiCl_4$, CH_2Cl_2, −40 °C, 50%; (c) Br_2, AcOH, 50 °C, 98%; (d) LiBr, Li_2CO_3, DMF, 100 °C; (e) MeI, K_2CO_3, DMF, 96% two steps; (f) Br_2, AcOH, 98%; (g) 4-(methanesulfonamido)phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, MeOH, toluene, 115 °C, 54%.



Scheme 4. Synthesis of 2,5,7,8-tetrasubstituted quinoline core

Reagents and conditions: (a) 4-nitrobenzaldehyde, *N*-vinylpyrrolidin-2-one, $BiCl_3$, CH_3CN; (b) CAN, CH_3CN, 0 °C, 22% two steps; (c) Fe, NH_4Cl, MeOH, water, reflux, 73%; (d) MsCl, pyridine, CH_2Cl_2, 0 °C, 86%.

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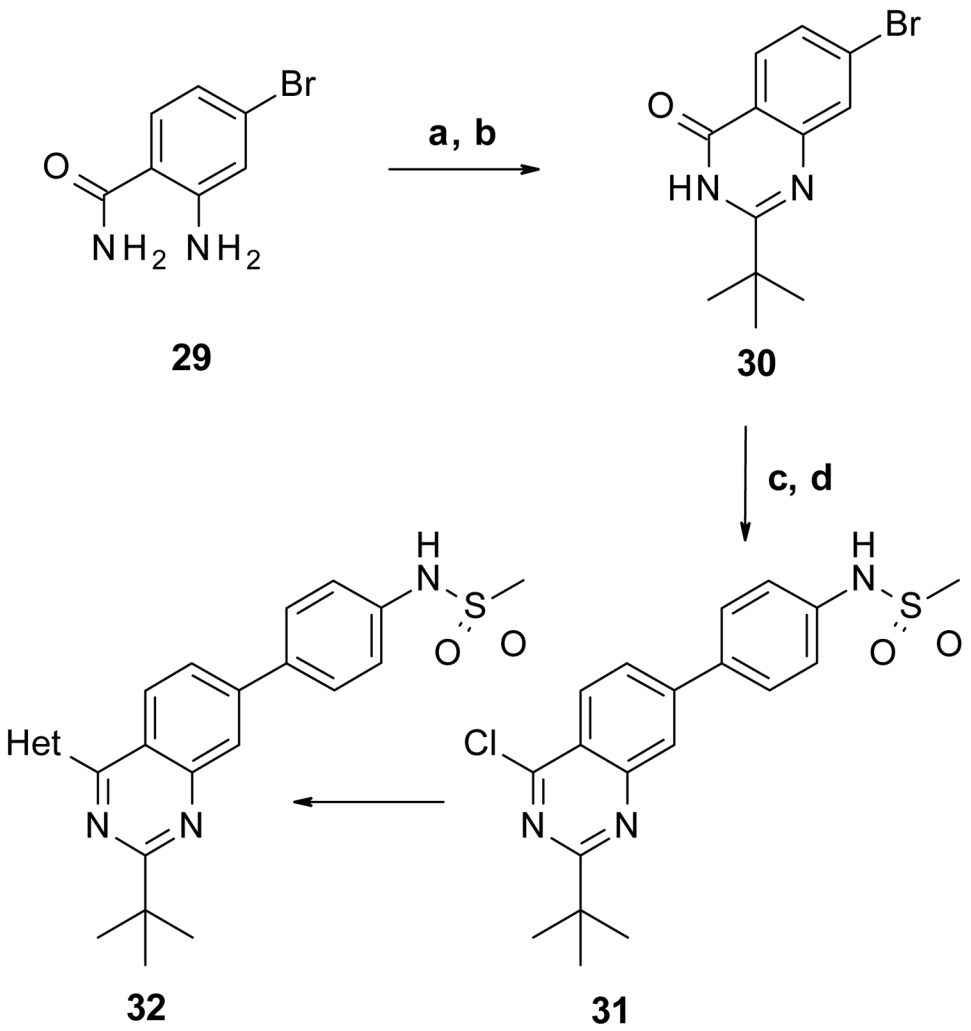

Scheme 5. Synthesis of 2,4,7-trisubstituted quinazoline core

Reagents and conditions: (a) Pivaloyl chloride, Et_3N, CH_2Cl_2; (b) aq. NaOH, EtOH, reflux, 52% two steps; (c) 4-(methanesulfonamido)phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, MeOH, toluene, 115 °C, 84%; (d) $POCl_3$, DIPEA, benzene, reflux, 87%.

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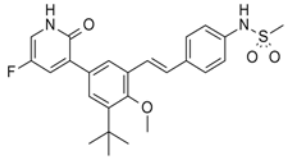
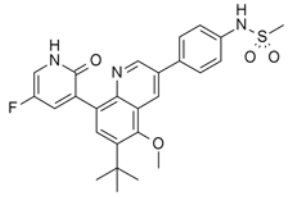
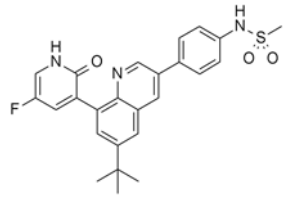
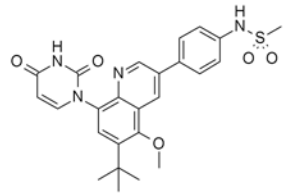
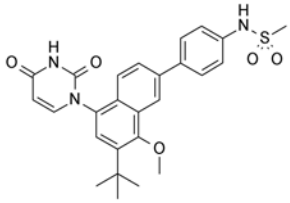
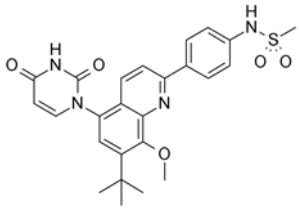
Table 1

Bicyclic Core Templates with Replicon (GT-1a and GT-1b) Data.

compd	Structure	GT-1a EC_{50} (nM)[a]	GT-1b EC_{50} (nM)[a]
7		8.0	3.0
33		3.8	3.5
34		25	16
35		7.2	3.2
36		4	1
37		83	12

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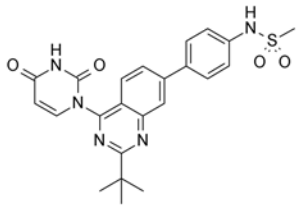
compd	Structure	GT-1a EC_{50} (nM)[a]	GT-1b EC_{50} (nM)[a]
38		17	NA

[a] EC_{50} measured using stable HCV (GT-1a H77, GT-1b Con1) subgenomic replicon assay ($n \geq 2$).

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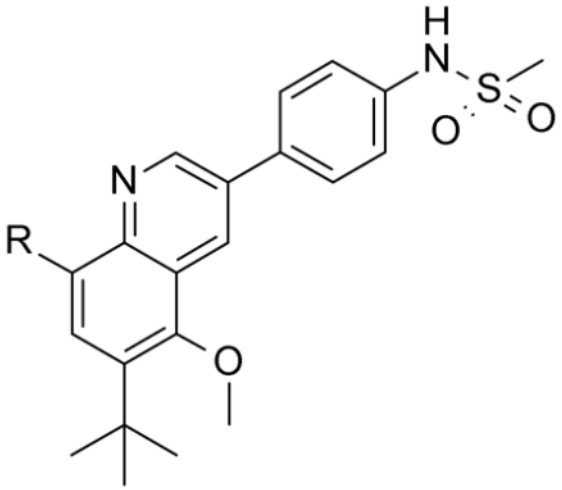
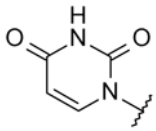
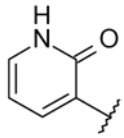
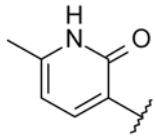
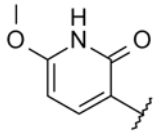
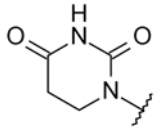
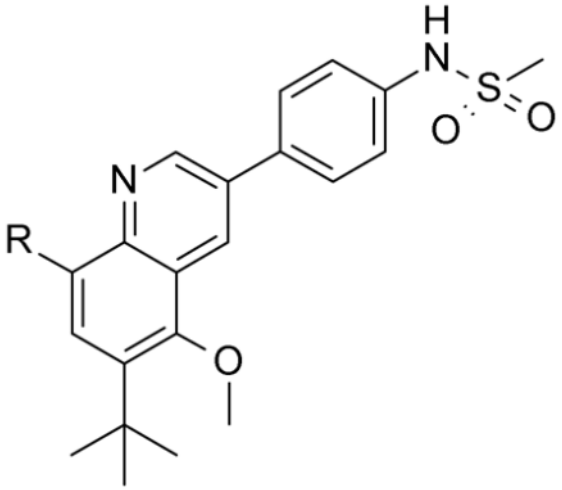
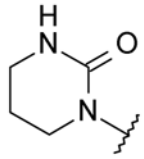
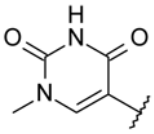
Table 2

Different Head Groups on the 3,5,6,8-Tetrasubstituted Quinoline Core with Replicon (GT-1a and GT-1b) Data.



compd	R	GT-1a EC_{50} (nM)[a]	GT-1b EC_{50} (nM)[a]
35		7.2	3.2
39		5.2	3.1
40		4.2	2.0
41		1.1	1.0
42		4.6	3.2



compd	R	GT-1a EC_{50} (nM)[a]	GT-1b EC_{50} (nM)[a]
43		64	20
44		3.0	1.5

[a] EC_{50} measured using stable HCV (GT-1a H77, GT-1b Con1) subgenomic replicon assay ($n \geq 2$).

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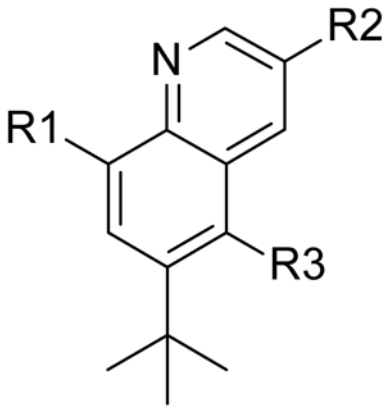
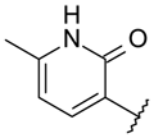
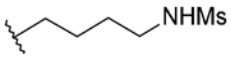
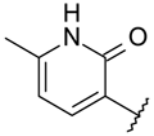
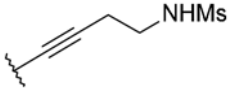
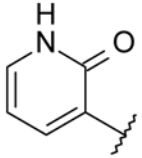
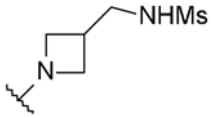
Table 3

Replacements of the Phenyl Linker with NS5B (GT-1b) and Replicon (GT-1a) data.



compd	R^1	R^2	R^3	GT-1b IC_{50} (nM)[a]	GT-1a EC_{50} (nM)[b]	Aqueous Solubility (μg/mL)[c]
45			OMe	12	> 1000	168
46			OMe	5	341	< 1
47			OMe	3.5	532	NA

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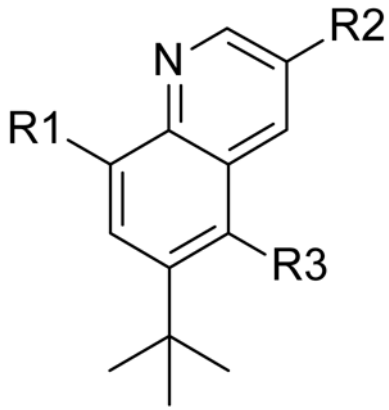
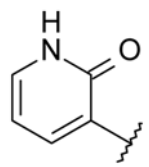
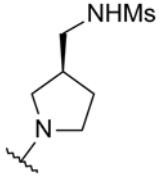
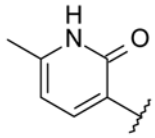
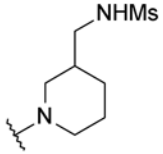


compd	R^1	R^2	R^3	GT-1b IC_{50} (nM)[a]	GT-1a EC_{50} (nM)[b]	Aqueous Solubility (μg/mL)[c]
48			OMe	0.2	7.9	11
49			H	625	> 1000	66

[a] IC_{50} against NS5B enzyme were measured using GT-1b Con1 strain and reported as nM.

[b] EC_{50} measured using stable HCV GT-1a H77 subgenomic replicon assay ($n \geq 2$).

[c] Aqueous solubility was measured using a thermodynamic solubility assay.

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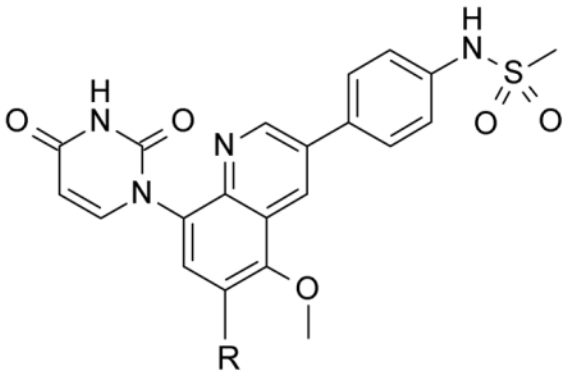
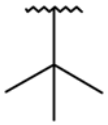
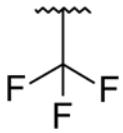
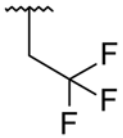
Table 4

Replacements of *tert*-Butyl Group with Replicon (GT-1a and GT-1b) and in vitro Hepatocytes Data.



compd	R	GT-1a EC_{50} (nM)[a]	GT-1b EC_{50} (nM)[a]	HH[b]	RH[b]
35		7.2	3.2	7.9	20
51		821	57	1.5	1.8
52		839	119	0.8	3.7

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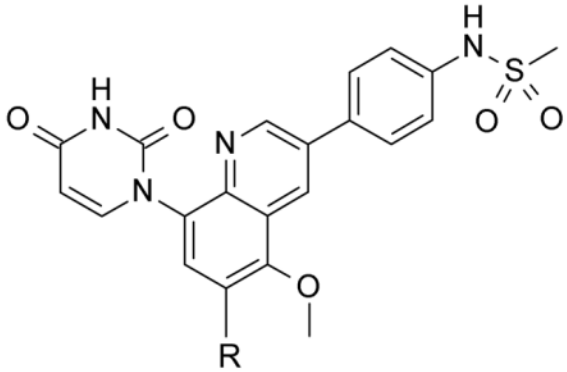
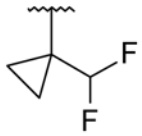


compd	R	GT-1a EC_{50} (nM)[a]	GT-1b EC_{50} (nM)[a]	HH[b]	RH[b]
53		95	16	0.1	1.7

[a] EC_{50} measured using stable HCV (GT-1a H77 and GT-1b Con1) subgenomic replicon assay ($n \geq 2$).

[b] Human hepatocytes (HH) and rat hepatocytes (RH) intrinsic clearance is reported in μL/min/10^6 cells. Human hepatocyte category ranking: high stability < 2.8, low stability > 15; rat hepatocyte category ranking: high stability < 5.4, low stability > 29.

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Table 5

Activity in the Replicon Assay for a Selected Set of Compounds in the Bicyclic Series

compd	GT-1a EC_{50} (nM)[a]	GT-1b EC_{50} (nM)[a]	Ratio 1a/1b	GT-1a 40% HuS[b] EC_{50} (nM)[a]	GT-1b 40% HuS EC_{50} (nM)[a]	Plasma Shift fold	GT-1a 40% HuS EC_{90} (nM)[a]	GT-1b 40% HuS EC_{90} (nM)[a]
7	8.0	3.0	2.7	66	22	7.3–8.2	531	128
35	7.2	3.2	2.2	16	5.6	1.7–2.2	123	29
39	5.2	3.1	1.7	4.0	11	0.8–3.5	25	47
41	1.1	1.0	1.1	10	3.8	3.8–9.4	63	19
42	4.6	3.2	1.4	10	3.5	1.7–2.1	48	20
50	17	12	1.4	10	7.5	0.6	61	44

[a] EC_{50} and EC_{90} measured using stable HCV (GT-1a H77, GT-1b Con1) subgenomic replicon assay ($n \geq 2$).

[b] Human serum (HS).

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Table 6

Activity of 41 and 50 Against GT-1a and GT-1b Clinical Isolates.

GT	Clinical Isolate	compd 41 EC_{50} ± SEM (nM)	compd 50 EC_{50} ± SEM (nM)
1a	H77	0.3 ± 0.03	0.65 ± 0.12
	RO-18	0.4 ± 0.05	0.5 ± 0.26
	RO-24	1.1 ± 0.23	2.5 ± 0.41
	RO-28	0.9 ± 0.05	0.2 ± 0.08
	RO-33	0.6 ± 0.09	0.7 ± 0.03
	RO-34	0.5 ± 0.02	0.4 ± 0.08
	RO-35	0.3 ± 0.09	0.5 ± 0.08
	RO-38	4.3 ± 0.07	9.5 ± 0.41
	RO-41	0.6 ± 0.17	0.27 ± 0.07
	mean	0.72	0.8
1b	Con1	0.32 ± 0.08	1.20 ± 0.27
	RO-1	0.11 ± 0.01	0.30 ± 0.06
	RO-2	0.19 ± 0.003	4.00 ± 1.63
	RO-3	0.43 ± 0.02	6.1 ± 0.12
	RO-4	0.11 ± 0.003	0.80 ± 0.16
	RO-7	0.22 ± 0.02	3.05 ± 0.37
	RO-8	0.33 ± 0.10	0.33 ± 0.10
	RO-9	0.34 ± 0.04	3.50 ± 0.41
	RO-10	0.34 ± 0.03	1.67 ± 0.33
	mean	0.26	1.6

EC_{50} measured using transient HCV subgenomic replicon assay ($n \geq 2$). SEM, Standard Error Mean * Geometric mean was calculated.

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Table 7

Pharmacokinetic parameters for 41 in rat and dog.

	iv				*po*				
species	**dose**[a]	**Cl (mL/min/kg)**	**V_{dss} (L/kg)**	**$t_{1/2}$ (h)**	**dose**[a,b]	**C_{max} (μg/mL)**	***C* at 8 h (μg/mL)**	**AUC(inf) (μg•h/mL)**	***F*%**
rat	2.6	11.4	2.2	4.3	30	2.1	0.62	13.8	26
dog	0.86	7.5	2.8	4.3	30	1.5	0.99	23.7	31

[a] Dose in mg/kg, 20% PEG400, n = 3.

[b] Amorphous MBP, n = 3.

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Table 8

Pharmacokinetic parameters for 50 in rat[a] and dog.[b]

	iv				*po*				
species	**dose**[a]	**Cl (mL/min/kg)**	**V_{dss} (L/kg)**	**$t_{1/2}$ (h)**	**dose**[a,b]	**C_{max} (μg/mL)**	***C* at 8 h (μg/mL)**	**AUC(inf) (μg•h/mL)**	***F*%**
rat	3.0	13.8	2.3	5.6	30	3.8	1.79	37.0	100
dog	1.0	4.4	1.5	5.1	3	0.36	0.21	4.2	36

[a] Dose in mg/kg, 20% PEG400, n = 3.

[b] Aqueous suspension, n = 3.