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Discovery and optimization of 2*H*-1λ²-pyridin-2-one inhibitors of mutant isocitrate dehydrogenase 1 for the treatment of cancer

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Abstract

Neomorphic mutations in isocitrate dehydrogenase 1 (IDH1) are oncogenic for a number of malignancies, primarily low-grade gliomas and acute myeloid leukemia (AML). We report a medicinal chemistry campaign around a 7,7-dimethyl-7,8-dihydro-2*H*-1λ^2-quinoline-2,5(6*H*)-dione screening hit against the R132H and R132C mutant forms of isocitrate dehydrogenase (IDH1). Systematic SAR efforts produced a series of potent pyrid-2-one mIDH1 inhibitors, including the atropisomer **(+)-119 (NCATS-SM5637, NSC 791985**). In an engineered mIDH1-

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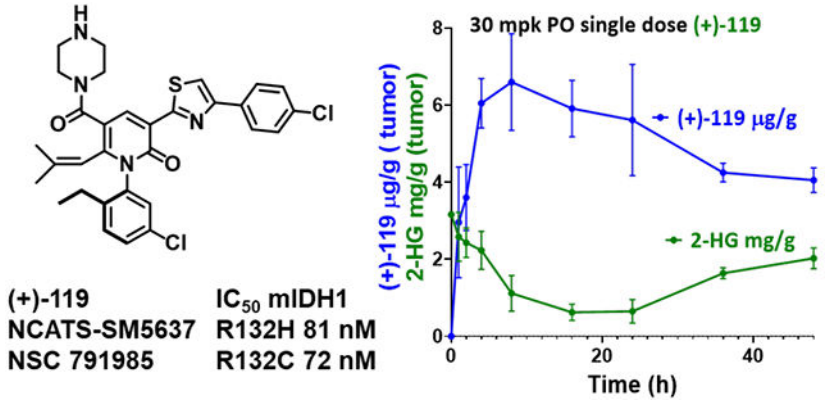
Supporting Information

1) Spectroscopic data (^{1}H NMR, LC/MS) for representative compounds.

2) Molecular formula strings of all compounds

U87-xenograft mouse model; after a single oral dose of 30 mg/kg, 16 h post dose, between 16-48 h, **(+)-119** showed higher tumoral concentrations that corresponded to lower 2-HG concentrations, when compared with the approved drug AG-120 (ivosidenib).

Graphical Abstract



Keywords

mIDH1; inhibitor; 2-hydroxyglutarate

Introduction

Over the past decade, mutant isocitrate dehydrogenases 1 (mIDH1) and 2 (mIDH2) have emerged as important targets for treating a range of malignancies.[1, 2] Normal (wild type, WT) IDH1 or IDH2 protein catalyzes the conversion of isocitrate to α-ketoglutarate (α-KG, also called 2-oxoglutarate, 2-OG), using $NADP^+$ as a co-factor.[3] Critical work has demonstrated that some acute myelogenous leukemias (AML) and gliomas possess heterozygous somatic mutations of IDH1 at position R132 and IDH2 at R140 or R172.[4–6] Analysis of clinical samples has shown that the majority of low-grade gliomas as well as ~20% of AML have IDH1 or IDH2 mutations, and a range of other solid tumors such as chondrosarcoma, cholangiocarcinoma, colon, pancreatic, and prostate cancer have also been found to carry IDH1/2 mutations, although to a lesser degree.[1, 7]

The canonical mutations to IDH1 and IDH2 confer a neomorphic (gain-of-function) activity. While WT IDH1 produces α-KG, α-KG is the substrate of mIDH1, which in a pseudo-reverse reaction using NADPH, produces *R*-2-hydroxyglutarate (2-HG).[8, 9] An analysis of serum 2HG levels in AML patients bearing IDH1 or IDH2 mutants showed a clear elevation (median 2HG of 3004 ng/mL) compared to patients with wild-type IDH (median 2HG of 61 ng/mL).[10] This 2-HG 'oncometabolite' has been shown to play a role in modifying cellular behavior.[11–13] For example, 2-HG inhibits α-KG-dependent enzymes,[14, 15] and direct evidence exists for inhibition of α-KG-dependent histone and DNA demethylases by 2-HG leading to elevated histone methylation, with consequent impact on gene expression and cell differentiation.[16]

Both mIDH1 and mIDH2 are attractive therapeutic targets due to their genetic gain-of-function, which confers an oncogenic role that is amenable to detection *via* both tumor gene sequencing and metabolite (2-HG) measurement.[17] Moreover, specific inhibition of mIDH1/2 should not produce target-related clinical side-effects as WT IDH's function would be unaffected. In 2017, only after ten years since the first reports of the role of IDH1/2 mutations in cancer, the FDA approved the mIDH2 inhibitor enasidenib from Agios/Celgene for treatment of relapsed or refractory AML (R/R AML).[18] In 2018, the FDA granted priority approval to Agios' mIDH1 inhibitor AG-120 (ivosidenib) for patients with R/R AML harboring IDH1 mutations as measured by the Abbott RealTime IDH1 Assay.[19] In May 2019 ivosidenib was approved as first-line treatment for AML with IDH1 mutation in patients who are at least 75 years old or who have comorbidities that preclude the use of intensive induction chemotherapy.[19] Agios continues to take ivosidenib through multiple clinical trials, notably, towards AML in combination with the chemotherapeutic drug azacytidine, and towards glioma and cholangiocarcinoma in patients harboring mIDH1.[20] Agios is also advancing its pan mIDH oral inhibitor AG-881 (vorasidenib) in trials with patients with advanced solid tumors (including gliomas) and low-grade glioma.[20, 21] In addition to this, Novartis and Bayer have also advanced IDH inhibitors IDH305 and BAY1436032 mIDH1 to clinical trials.[22, 23] In 2019 an updated succinct review of all reported classes of preclinical and clinical small molecule mIDH inhibitors was published.[24] It included Agios' tool mIDH1 inhibitor AG-5198,[25] probe molecules from Sanofi and GlaxoSmithKline,[26, 27] and CNS penetrant FT-2102 from Forma Therapeutics, Inc.[28]

We had been involved in an early assay development and screening program that produced the phenyl-glycine analog ML309 as a potent inhibitor of R132H mIDH1.[29, 30] We also developed a panel of biochemical and cell-based assays to enable inhibitor discovery campaigns and aid comparison to known mIDH1 probe and experimental therapeutic inhibitors.[31] Here we fully describe the hit-to-lead medical chemistry campaign based on a 7,7-dimethyl-7,8-dihydro-2*H*-1λ^2-quinoline-2,5(6*H*)-dione mIDH1 inhibitor chemical series that also emerged as a screening hit besides the chemotype that was optimized to ML309. Optimization led to the discovery, separation, and biological characterization of stable atropisomers from a 1-arylpyridin-2(*1H*)-one sub series. Exemplary analog **(+)-119** is used to demonstrate 2-HG reduction in a pharmacokinetic/pharmacodynamic (PK/PD) model with ivosidenib as a comparator molecule.

Our project was supported by the National Cancer Institute's (NCI) Experimental Therapeutics (NExT) Program facilitated within the NCI Chemical Biology Consortium (CBC). The goal of CBC's NExT Program is to bring together government, industry, and academic groups to enable a team-science approach towards the discovery and development of novel therapeutics (https://next.cancer.gov).

Results and Discussion

A diaphorase/resazurin-coupled assay for the IDH1 R132H mutation was developed and utilized to screen our in-house collection of nearly 390,000 small molecules (Figure 1A). In this quantitative high-throughput screen (qHTS), the assay was performed at 6 concentrations ranging from 76 μM to 2 nM. The inhibition associated with each well was

computed from the endpoint and normalized against control wells (no enzyme as positive control, DMSO as negative control). The percent inhibition at each of the concentrations of inhibitor tested was plotted and modeled by a four-parameter logistic fit using in-house software to determine the compound IC_{50} values. There were nearly 600 1536-well plates in the primary qHTS, which included library plate sets and a couple of DMSO plates inserted in the beginning and end of the screening for data correction purposes. The assay performed well with an average Z'-factor of 0.60 and S:B ratio around 3.2 (Figure 1B). Analysis of these dose-response curves resulted in 2,155 compounds that showed inhibition over 30% at the highest testing concentration. Among these 2,155 inhibitors, 769 were identified as high-quality inhibitors with single or dual asymptote curves and greater than 50% inhibition (Figure 1C), representing 0.2% of the chemical library.

The 2,155 hit compounds identified from the screen were thoroughly evaluated for both potency and percent inhibition; the autofluorescent compounds and promiscuous inhibitors (compounds that show activity in more than 20% of assays within historical screening data at NCATS) were eliminated from follow-up examination. A total of 761 prioritized hits were retested and screened in 12-pt dose-response in the primary screening assay to reconfirm activity. The compounds were further tested in a readout interference assay and IDH1-WT selectivity assay to refine and triage initial screening hits (assay hit triage workflow shown in Figure 1C). After structural clustering analysis and assessment of synthetic tractability to eliminate compounds that did not offer good starting points for hit-to-lead optimization, a 7,7-dimethyl-7,8-dihydro-2*H*-1λ^2-quinoline-2,5(6*H*)-dione chemotype (representative hit **1**, Figure 1) with good starting potency and selectivity over WT IDH1 was identified. As shown in Figure 1D, compound **1** displayed inhibition with an IC_{50} of 1.6 μM against R132H mIDH1, with no readout interference and off-target activity against WT IDH1. In addition to the R132H mutant,[32, 33] we also developed the analogous assay for the R132C mIDH1, a frequent mutation in AML and intracranial chondrosarcoma,[34, 35] and we sought to develop a class of inhibitors capable of targeting both mutations (**1** had an IC_{50} of 1.0 μM against R132C mIDH1).

Despite the moderate structural complexity of hit **1**, it was readily accessible via an efficient one-pot, multicomponent coupling (Scheme 1). Combining dione **I** and acetal **II** neat, resulted in quick conversion to reactive vinylogous amide **III**. Addition of a base (piperidine or KO*t*Bu) to nitrile **IV** generated an anion that, when added to intermediate **III** afforded intermediate **V** by a Michael addition-elimination sequence. Finally, incorporation of aniline Ar_2NH_2 **VI** provided the pyridinone ring system through cyclodehydration. This last two-step sequence was sufficiently tolerant of diverse substitution on both nitrile **IV** and aniline **VI** and was conducted in one pot, requiring only a single solvent exchange from isopropanol to acetic acid.

We initiated optimization of the 7,8-dihydroquinoline-2,5(1*H*,6*H*)-dione ring system by first establishing the essential components necessary for activity in this region. The cyclohexanone ring proved necessary as monocyclic analogs **2** and **3** were completely inactive. The carbonyl functionality appeared to play a lesser role though as des-carbonyl analogs **4** and **5** were only slightly less potent and/or efficacious against the R132H and the R132C IDH1 mutant enzymes (Table 1). The removal of the methyl groups (**6**), contraction

of the ring (**7**) and aromatization (**8**) all resulted in significant losses in activity. We also incorporated a heteroatom into this ring system with analogs **9** and **10**, and while amine **9** was less potent, lactam **10** displayed comparable activity to the hit, showing the amide functional group was well tolerated. In addition to focusing primarily on target potency, we closely monitored the activity of our molecules against wild type IDH1. Fortunately, none of the molecules in this series showed activity against WT IDH1 (IC_{50} >57 μM), nor did most of the compounds in the remainder of the hit-to-lead campaign described below. This brief survey of the core structure activity relationships (SAR) highlighted the importance of the geminal methyl groups, and the 6-membered ring as requirements for biochemical potency.

The next structural element investigated was the thiazole ring (Table 2). Given its proximity to the carbon center that acts as a nucleophile during the conversion of **III** to **V**, as shown above in Scheme 1, many of the modifications to the thiazole ring required developing new synthetic sequences which resulted in synthetic challenges and poor throughput; as a result, Table 2 has analogs that lack the *para*-chloro substituent present in the hit. The des-chloro compound **11** was essentially equipotent to **1** against R132H mIDH1 but lost efficacy towards the R132C mutant. Substitution at the 4-position of the thiazole in the form of a biaryl linkage seemed optimal in contrast to either substitution at the 5-position or modification to a fused ring system, with analogs **12-14** displaying significant losses in activity. Replacement of the thiazole with a variety of diazoles **15-22** had a dichotomic effect on mIDH1 potency with imidazoles **17** and **18**, pyrazoles **19** and **20**, maintaining activity, and the remainder of the analogs (**15**, **16**, **21-26**) experiencing significant losses in biochemical potency. This SAR led us to believe that maintaining a nitrogen positioned akin to the thiazole nitrogen (3-position highlighted in **1**, Table 2) was important, while a nitrogen at the 2-position abrogated activity (**16**, **20**, and **21**). Further supporting this observation, expansion of the ring to a benzene (**23-24**; *meta*- and *para*-substitution) proved unfavorable with complete loss in mIDH1 inhibitory activity, while substitution with a 2,6-disubstituted pyridine retained some activity (**25**). In an attempt to open the thiazole ring, we synthesized amide **26**, but this proved to be a detrimental variation of the thiazole. Thus, the thiazole segment, much like the cyclohexanone moiety, was not amenable to significant modification.

Tables 3 and 4 showcase the SAR exploration of the aryl group attached to the pyridone nitrogen (**R^1**). Synthetically this region was readily modifiable since it was made from the last step in Scheme 1; thus, it was extensively investigated. Given the steric congestion about the pyridinone aryl linkage, we posited that orientation of the pyridinone *ortho*gonal or perpendicular to the arene may be optimal, especially given the 2-methoxy substituent present in the hit molecule. Along these lines, removal of the two methoxy groups in the form of analog **27** resulted in a loss of activity against both mutant forms of IDH1 (Table 3). Installation of a variety of *ortho*-substituents regained target potency in the instance of small alkoxy substituents (**28-30**) and an ethyl substituent (**32**). The *ortho*-methyl substituted compound **31** was active but did not show inhibition beyond 75% at the highest concentration. Analogs with larger R^1 groups, like 2-*i*Pr (**33**), 2-Ph (**34**), or with free hydroxyl (**35**), larger alkoxy groups (**36**, **37**), or nitrogen containing substituents (**38-40**) provided only partial inhibition of the mutant enzymes even at the top concentration tested (38 μM). Interestingly, the only polar substituent to maintain activity was the 2-carboxylic

acid analog **41**. With 2-halo substitutions, a smaller 2-F (**42**) lost activity against both IDH1 mutants, but a 2-Cl (**43**) was equipotent to **1** for R132H, emphasizing the need of an *ortho*-substitution large enough to force the pyridone ring to be *ortho*gonal to the central bicyclic core and restrict rotation. Notably, both 2-trifluoromethyl (**44**) and 2-trifluoromethoxy (**45**) analogs exhibited improved mIDH1 activity over **1**, reiterating that varying electronic character was tolerated at the 2-position. Further modifications by extension with a carbon spacer (**48**) or conversion to alkyl groups (**49**, **50**) were not tolerated. A handful of heterocyclic replacements like a 2-pyridyl ring (**46**) were also evaluated; most heterocycles (analogs not shown) showed diminished activities, whereas 2,3-disubstituted thiophenes, such as compounds **51** and **52**, served as viable replacements.

Probing further substitution of the pyridinone arene, we aimed to develop a more complete understanding of this region of the pharmacophore (Table 4). By keeping the 2-OMe group constant and walking the second methoxy group around the remaining positions of the ring (**53-55**), the importance of the relative 2,5- and 2,6-substituent arrangements became apparent. A similar scan was conducted with a polar carboxylic acid group (**56-59**). The 2-OMe,6-CO_2H disubstituted compound **59** showed potent inhibition of both R132H and R132C mutant isoforms. Within this subset (**1**, **53-59**) we also noticed that the placement of a substituent at the 4-position led to a profound reduction of activity (**54, 57**). A 2-OMe,6-Me compound (**60**) was also potent indicating that an alkyl group could also be tolerated at the 6-position. Despite the synthetic challenges associated with substituting the phenyl for a pyridine given the diminished nucleophilic reactivity of amino pyridines in the conversion of **V** to **VII** (Scheme 1), we synthesized analogs **61** and **62**. These analogs demonstrated that this change was only tolerated if the pyridine nitrogen was in the 3-position, next to the 2-OMe substituent (**61**). We then moved on to change the 2-methoxy substituent to a 2-ethoxy substituent and evaluated the 2,5- and 2,6-diOEt compounds **63** and **64**. Both compounds showed submicromolar IC_{50}s. This remarkable breakthrough in IC_{50} <1.0 μM was also observed with a 2-ethyl group when it was combined with a 6-methyl or ethyl in **65** and **66** respectively.

Our earlier structure-activity relationship (SAR) study of the bicyclic dihydroquinoline-dione core in hit molecule **1** had revealed that most changes reduced potency, but lactam **10** maintained similar activity against the R132H IDH1 mutant (Table 1). This observation provided an attractive opportunity to both substitute the amide and open the ring to reveal new opportunities for SAR exploration in the northwestern region of the chemotype. To that end, we evaluated the ring-opened variants of the lactam as shown in Table 5; this was done with the symmetrical 2,6-diethylphenyl substituent at the R^1 position from lead **66**. This was a strategic decision as we realized the possibility of restricted rotation around N-R^1 could lead to atropisomers (*vide infra*) adding one more variable to our SAR analysis. Compared to ketone **66**, ester (**67**, **69**) and acid (**68**) variants lost much if not all mIDH1 target potency. However, amide **70** only experienced a small drop in R132H activity and did not show >75% inhibition at 38μM against R132C (Table 5). This analog proved pivotal in providing an additional SAR handle for a new amide-substituted pyridone series.

With only moderate variations to our initial multicomponent coupling, we were able to develop a modular synthesis tolerant of significant modification to both the amide and the pyridinone substituents (Scheme 2). The initial condensation between keto ester **Ia** and *N*,*N*-dimethylformamide dimethyl acetal **II** was carried out by heating the two components without any solvent to provide intermediate **III** which was then condensed with functionalized nitrile **IVa** under basic conditions. After addition of aniline **VIa** to ketonitrile **Va** and stirring with acetic acid, we discovered that further heating was required to efficiently drive pyridinone formation in **VIIa**. Lastly, ester hydrolysis and HATU-mediated amide couplings were utilized to efficiently access a diversity of ring-opened amide analogs (**VIII**).

Based on this synthetic route, we surveyed a structurally diverse set of amides as depicted in Table 6. The secondary dimethylamide **71** displayed similar activity to compound **70**, but larger alkyl substituents at the R^4 position provided analogs (**72-74**) with decreased mIDH1 activity. Incorporation of either a nitrogen or oxygen atom at or near the termini of an alkyl chain at the R^4 position (**75-81**) either maintained or even provided a boost in potency. Most noteworthy among these were ethanaloamide **75** and 2-aminoethyl carboxamide **78**, which exhibited 3-fold improvements in potency compared to analog **70**. Primary amides such as **82**, **83** and **84** with large ring substituents such as phenyl, benzyl and cyclohexyl respectively lost activity. We also evaluated cyclic secondary amides (**85-88**) and found that piperidine analog **85**'s activity was attenuated with ~50-65% inhibition at the highest concentration tested. The placement of distal heteroatoms (N,O) in morpholine **86** and *N*-Me-piperazine **88** maintained good potency, while *NH*-piperazine **87** was 7-fold more potent in mIDH1 R132H inhibition compared to analog **70**. Importantly, piperazine **87** also was more stable in a single point rat liver microsomal stability assay (**70**: $t_{1/2}$ = 1.5 min; **87**: $t_{1/2}$ > 30 min).[36] Additionally, **87** had better aqueous kinetic solubility than methyl amide **70** (**70**: [M] < 1 μM **87**: [M] = 6.7 μM). These results led us to maintain this substitution while we examined the SAR of the pyridinone 6-substituent.

Our evaluation of the pyridinone 6-substituent R^3 is presented in Table 7. The *n*-propyl analog **89** was ~3 fold more potent towards R132H mIDH1 but with a marked 15-fold improvement towards mR132C. While this trend did not carry to the α-branched isopropyl **90**, it emerged again with analogs **91-93** with β-branching. Indeed isobutylene **92** and cyclopropylmethyl **93** had benchmark potencies with IC_{50} < 100 nM for both IDH1 mutants. The replacement of the methyl group on the *n*-propyl side chain in **89** with an electron-donating methoxy (**94**) or electron-withdrawing trifluoromethyl group (**95**) led to a comparative reduction in potency. Within cyclic ethers, the racemic tetrahydrofuran **96** was more potent than the larger tetrahydropyran **97**. Analogous pyrrolidine **98** (racemic) proved to be much less potent with IC_{50} ~ 10 μM.

We postulated that perhaps steric congestion to this region of the pharmacophore helps position the piperazine away from R^3 (as suggestively drawn in Table 7); we suspect that the amide is also not coplanar to the pyridine pi-system. It could be that such a conformation is more desirable towards R132C activity, and results in the >10-fold increase in potency observed in analogs **89**, **91-93**, **96** compared to the methyl analog **87**. We assessed *in vitro*

drug-like properties in this set (Table 8); isobutylene **92** had a desirable balance between potency, rat liver microsome stability, and permeability. Thus, it was held at the R^3 position for further SAR studies. We also noticed that all compounds had low aqueous kinetic solubility. Table 7. Pyridinone 6-position SAR.

Upon optimizing the R^3 substituent, the NR^4R^5 site (see **VIII** in Scheme 2) was further explored (Table 9). A subset of analogs with diverse groups at the piperazine 3-position such as methyl **99**, ethyl **101**, propyl **102**, cyclopropyl **103**, hydroxymethyl **104**, ketone **105**, trifluoromethyl **106**, cyano **107**, acid **108** and amide **109** maintained their potency against both IDH mutants, showcasing that electron donating and withdrawing groups were tolerated at this position. The 2-methyl piperazine **100** was also potent. Furthermore, hetero-bicyclic systems also produced analogs **110-112** with nanomolar activity. Though these substitutions were tolerated for enzymatic inhibition, these additions typically did not provide additional benefits with respect to their *in vitro* drug-like properties (PAMPA, rat and mouse microsome stability, solubility) nor *in vivo* pharmacokinetic profiles (data not shown). Another noteworthy observation was that the analogs described in Tables 7–10 were at least 1000-fold selective for mIDH1s over wild-type IDH1.

Lastly, our SAR studies shifted back to the pyridinone 1-arene (Table 10). Analogous to our earlier studies, an *ortho* substituent proved essential. The complete removal of all substituents in **113** led to a 7.5-fold drop in R132H potency and a more significant 55-fold drop in R132C potency. The presence of one *ortho* ethyl in **114** was 1-3-fold less potent compared to its diethyl counterpart **92**. While the combination of ethyl,methyl-di-*ortho* substitutions in **115** led to a potency drop, especially towards the R132C mutant, the ethyl-chloro combination in **116** was equipotent to **92**. Keeping the *ortho*-ethyl group constant we shifted to the *meta* position (R^8) and found that methyl **117**, methoxy **118**, and chloro **119** maintained their potency across both mutants. While it was apparent that steric congestion around the pyridone seemed critical for activity, we anticipated that hindered rotation around the pyridone *N*-aryl bond likely led to the existence of atropisomers that could have dissimilar activities. As two representative examples, we separated the atropisomers in **118** and **119** and discovered they had a ~3- and 3-8-fold difference in the R132H and R132C biochemical potencies, respectively.

Having developed several biochemically potent mIDH1 inhibitors, for a representative set of compounds, we next assessed cellular activity in U87 cells, a cell line of glioblastoma origin engineered to express the IDH1 R132H mutation. Inhibition of 2-HG production, secreted from cells into media, was measured by mass spectrometry 48 hr after addition of compounds at 100 and 500 nM (Table 11). Analog **(+)-119** lowered 2-HG levels by more than 94% at 100 nM. Dose-response curves for atropisomer **(+)-119**, the corresponding unseparated mixture of atropisomers **119**, and the approved drug AG-120 are shown in Figure 2. **(+)-119** was more potent at reducing 2-HG levels than **119**, even though their biochemical IC_{50}s towards R132H mIDH1 were similar (114 and 81 nM). Notably, in this cellular assay **(+)-119** appears 100 times more potent (< 0.7 nM) than in the biochemical enzyme inhibition assay and more potent than AG-120 which had a comparable biochemical potency.

For the compounds in Table 11, an analysis of drug-like properties using our in-house high throughput assays showed that analogs **111**, **118**, **(−)-119** and **(+)-119** had promising stability in rat liver microsomes with $\mathbf{t_{1/2}}$ >30 min, high passive permeability, and low aqueous kinetic solubility. From this subset, based on its potent cellular activity, we chose **(+)-119** to showcase the chemical series in PK/PD studies.

To directly assess target engagement in cells, we used a high-throughput CETSA platform that uses a split NanoLuciferase (SplitLuc) reporter to detect soluble protein in cells.[37] After tagging the 15-amino acid sequence to the C-terminus of R132H mIDH1 (termed IDH1(R132H)-86b) and transient expression in HEK293T cells, soluble protein was measured by complementation of the larger 11S fragment which reconstitutes NanoLuciferase activity and allows its quantification using the substrate furimazine. Dose-response testing measured the ability of compounds to increase the thermal stability of IDH1(R132H)-86b when cells were heated to 56 °C for 3.5 min. **(+)-119** and AG-120 were equipotent in this assay, whereas the corresponding mixture **119** had a 10-fold greater EC_{50} (Figure 3).

We devised a scalable route to **(+)-119** and related analogs to enable *in vivo* testing (Scheme 3). Commencing with a similar multicomponent coupling with dicarbonyl 6,6-dimethyldihydro-2*H*-pyran-2,4(3*H*)-dione **Ic**, a multicomponent coupling reaction efficiently assembled **VIIb** which upon lactone hydrolysis and *in situ* elimination of the tertiary alcohol provided the sensitive intermediate **VIIc**. We observed proximity promoted deleterious cyclization back to lactone **VIIb** under a variety of neutralization conditions as well during the subsequent amide coupling. Careful neutralization with acetic acid to neutral pH and subsequent removal via wash steps was necessary following lactone hydrolysis. The amide bond formation also had to adhere to a strict order of addition of HATU, *i*Pr_2NEt, and then the Boc-protected piperazine to furnish **VIIIa** in 95% yield. Subsequently, separation of atropisomers proved optimal at the stage of the protected piperazine **VIIIa** with the use of a CHIRAL® OD-H column. Final deprotection, which necessitated short reaction times with a significant excess (35 equivalents) of trifluoroacetic acid in order to minimize re-lactonization, followed by neutralization of the TFA salt by aqueous sodium bicarbonate provided the pure atropisomer **(+)-119**. The stereochemical configuration of the atropisomer was proved by X-ray analysis of a single crystal of the intermediate **VIIb** (Supporting Information) that was formed during attempts to form a HCl salt of **(+)-119** (**NCATS-SM5637**, **NSC 791985**).

A single dose of 30 mg/kg **(+)-119** administered orally to CD1 mice lead to good exposure in the plasma with a C_{max}~3.34 μM and AUC_{last} of 24371 h*ng/g. It also crossed the blood brain barrier with an AUC of 6996 h*ng/g and a brain/plasma ratio of 28% (Figure 4).

We compared the activities of **(+)-119** and AG-120 *in vivo*, using the U87 mIDH1 (R132H) xenograft to assess PK/PD responses (Figure 5). After a single 30 mg/kg p.o. dose, AG-120 reached a higher plasma C_{max} than **(+)-119** but after 8 h **(+)-119** displayed higher plasma concentrations. Similarly, 4 h after dosing, concentrations of **(+)-119** in tumor were higher than AG-120. **(+)-119** had very slow clearance from tumor with sustained average concentrations of 9.5, 7.2, 6.8 μM at 24, 36, 48 h respectively compared to 1.6, 1.4, 0.77

μM for AG-120. These higher sustained tumoral concentrations of **(+)-119** appear to be responsible for the greater reduction in tumor 2-HG, as compared to AG-120, from the 16 h time point onwards. If this promising activity translates to the clinical setting, it could provide a therapeutic advantage over AG-120 (see Supporting Information for profiling data on **(+)-119**).

Conclusion

An extended medicinal chemistry campaign starting with a 7,8-dihydro-2*H*-1λ^2-quinoline-2,5(6*H*)-dione chemotype led to the discovery of new amide-substituted pyridones as potent R132H and R132C mIDH1 inhibitors. The lead compound **119** had nanomolar activities against both IDH1 mutants and lowered the mIDH1-catalyzed product 2-HG in cells. The single atropisomer **(+)-119 (NCATS-SM5637**, **NSC 791985)** was shown to engage mIDH1 in cells and reduce 2-HG production more potently that **119** (13-fold in HEK293 engagement assay and 30-fold in U87 2-HG assay). In a PK/PD model, after a single oral dose at 30 mg/kg, **(+)-119** showed sustained tumor concentrations (7 μM after 48 hr) and greater reduction in 2-HG levels at later time points (16-48 h) than the approved mIDH1 drug AG-120. Further head-to-head comparative animal studies in various mIDH1 driven cancer models with key compounds from this chemical series, such **NCATS-SM5637 (NSC 791985)**, and AG-120 are ongoing and will be reported in due course.

Experimental Section

Materials and Methods: Biology

mIDH1-R132H and mIDH-R132C enzyme assay—Pubchem AID 624002. Enzyme buffer was dispensed into black, solid 1536-well plates at 3 μL/well in 20 mM Tris buffer, pH 7.5, containing final concentrations of 10 mM $MgCl_2$, 20 mM NaCl, 0.001% Tween 20, 0.05% BSA, 2 mM β-ME and 5.2 nM IDH1 R132H. Then, 23 nL of compounds or DMSO were delivered to each well using a pin tool. *The inherent compound fluorescence was measured at this point at 590 nm on a ViewLux plate reader (Ex 525, Em 598, bodipy filter); this is test for assay interference as we measure resorufin (em 590 nm in the end).* The substrate buffer (3 μL; 20 mM Tris buffer, pH 7.5, containing final concentrations of 10 mM $MgCl_2$, 20 mM NaCl, 0.001% Tween20, 0.05% BSA, 0.008 mM NADPH, and 1 mM α-ketoglutarate) was added to start the enzymatic reaction, and the plate was briefly spun at 270xg. After the reaction was allowed to progress for 80 minutes at room temperature, the remaining NADPH was detected with the diaphorase/resazurin-coupled system. 3 μL of detection buffer (20 mM Tris buffer, pH 7.5, containing final concentrations of 10 mM $MgCl_2$, 20 mM NaCl, 0.001% Tween20, 0.05% BSA, 0.53 μM diaphorase and 0.012 mM resazurin) was added, and after 5 minutes the fluorescence at 590 nm was measured on an Envision plate reader (Ex 544, Em 590, bodipy filter, 10 flashes). The % activity was determined from the corrected fluorescence values. The activity was normalized with 5.2 nM R132H IDH1 (no inhibitor) as 0% inhibition and the activity with no enzyme as 100% inhibition.

We also measured for assay interference by measuring dose dependent activity against the diaphorase/resazurin-coupled system by repeating the assay above in the

absence of mIDH1. This will flag false positives that may inhibit the NADPH to NADP+ conversion.

Concentration-response curves were fitted to the signals arising from the resulting fluorescence. The concentration-response curves were then classified based on curve quality (r2), response magnitude and degree of measured activity, and compounds were subsequently categorized based on their curve class. Active inhibitors showed concentration-dependent increases in fluorescence, concordant with a decrease in IDH1 R132H activity and less substrate NADPH utilization. Inactive compounds showed no effect on fluorescence signal relative to the DMSO control.

Cellular 2-HG production assay—2-HG secreted from cells was quantified as previously described with modifications. U87-R132H cells were cultured in DMEM high glucose with glutamine supplemented with 10% FBS, 100 units/mL Penicillin, 100 ug/mL Streptomycin. 8000 cells/well/100 μL were seeded into clear, tissue culture-treated 96-well plates (Corning) in 100 μL culture medium excluding wells along the edge (which instead were filled with culture medium only) and incubated overnight at 37°C, 5% CO_2, 90% RH. Culture medium was aspirated and replaced with 100 μL of culture medium containing either vehicle (DMSO) or mIDH1 inhibitor. Assays were established with inhibitor tested at two concentrations 500 nM and 100 nM or as 7-point dose response. After 48 hr, 75 μL of the culture medium was collected and snap frozen on dry ice. Samples were analyzed by LC-MS for 2-HG concentrations using Rapidfire / Mass Spectrometry (Quintara). Remaining cells were assessed for viability by adding 100 μL of fresh media and 50 μL of CellTiter-Glo reagent (Promega). Luminescence was read using a ViewLux High-throughput CCD imager (PerkinElmer).

SplitLuc CETSA—The mIDH1(R132H) open reading frame was cloned into a pcDNA3.1(+) backbone using the NheI and EcoRI restriction sites. A 15 amino acid tag (86b, Gly-Ser-HiBiT-Gly-Ser) was fused in-frame to the carboxy terminus. HEK293T cells (obtained from ATCC; CRL-1573) were cultured in DMEM (4.5 g/L glucose) with 10% fetal bovine serum, 6 mM L-glutamine, 1 mM sodium pyruvate, 50U/mL penicillin, and 50 μg/mL streptomycin. Cells were grown at 37 °C in a humidified incubator maintained at 5% CO2. Cells were transfected in T75 flasks using a reverse transfection procedure, where 9 mL of complexes (45 μL Lipofectamine 2000 and 22.5 μg DNA) was combined with 10 mL of HEK293T cell suspension (1×10^6 cells/mL, 10 million cells total). After 24 h, cells were harvested by trypsinization, resuspended at 1×10^6 cells/mL (DPBS with $CaCl_2$ and $MgCl_2$ plus 1 g/L glucose) and dispensed (15 μL cells/well) into 384-well PCR plates (Roche) using a Multidrop Combi (ThermoFisher). Compounds (63 nL) or DMSO vehicle control (63 nL) were subsequently pinned using a pin tool (GNF) and incubated for 1 h at 37 °C. Plates were sealed and heated at 56 °C for 3.5 min and cooled to 25 °C using AB qPCR machine (Roche) with a ramp speed of 1.5 °C/sec for the heating phase and max ramp rate for the cooling phase. Three μL of 6% NP40 was added per well and incubated for 30 min to allow cell lysis followed by addition of 11S (purified from *E. coli*) and furimazine (Promega) substrate (at final concentrations of 100 nM and 0.5X, respectively). Samples were analyzed for luminescence intensity using a ViewLux reader.

Kinetic Solubility Assay—Pion's patented μSOL assay was used for kinetic solubility determination. In this assay, the classical saturation shake-flask solubility method was adapted as previously described.[38] Test compounds were prepared in 10 mM DMSO stock and diluted to a final drug concentration of 150 μM in the aqueous solution (pH 7.4, 100 mM Phosphate buffer). Samples were incubated at room temperature for 6 hours and vacuum-filtered using Tecan Te-Vac to remove any precipitates. The concentration of the compound in the filtrate was measured via UV absorbance (λ: 250-498 nm). The unknown drug concentration was determined by comparing the fully solubilized reference plate which contained 17 μM of compound dissolved in spectroscopically pure n-propanol. All compounds were tested in duplicates. The kinetic solubility (μg/mL) of compounds was calculated using the μSOL Evolution software. The three controls used were albendazole (low solubility), phenazolpyridine (moderate solubility) and furosemide (high solubility).[39]

Rat Liver Microsome Stability Assay—Single time point microsomal stability was determined in a 96-well HTS format. Sample preparation was automated using Tecan EVO 200 robot. High Resolution LC/MS (Thermo Q Exactive™) instrument was used to measure the percentage of compound remaining after incubation using a previously described method.[40] Six standard controls were tested in each run: buspirone and propranolol (for short half-life), loperamide and diclofenac (for short to medium half-life), and carbamazepine and antipyrine (for long half-life). 10 mM DMSO stock solutions of the drugs were first diluted to 10 μM in 1:2 MeCN:DI H_2O and then further diluted to 1 μM in assay buffer. Briefly, the incubation consisted of 0.5 mg/mL microsomal protein, 1.0 μM drug concentration, and NADPH regeneration system (containing 0.650 mM NADP+, 1.65 mM glucose 6-phosphate, 1.65 mM $MgCl_2$, and 0.2 unit/mL G6PDH) in 100 mM phosphate buffer at pH 7.4. The incubation was carried out at 37 °C for 15 min.[36] The reaction was quenched by adding 555 μL of acetonitrile (~1:2 ratio) containing 0.28 μM albendazole (internal standard). Sample acquisition and data analysis was done using a previously described method.[40]

Parallel Artificial Membrane Permeability Assay (PAMPA)—Stirring double-sink PAMPA method (patented by pION Inc.) was employed to determine the permeability of compounds via PAMPA as published before.[41] The PAMPA lipid membrane consisted of an artificial membrane of a proprietary lipid mixture and dodecane (Pion Inc.), optimized to predict gastrointestinal tract (GIT) passive permeability. The lipid was immobilized on a plastic matrix of a 96-well "donor" filter plate placed below a 96-well "acceptor" plate. pH 7.4 solution was used in both donor and acceptor wells. The test articles, stocked in 10 mM DMSO solutions, were diluted to 0.05 mM in aqueous buffer (pH 7.4), and the concentration of DMSO was 0.5% in the final solution. During the 30-minute permeation period at room temperature, the test samples in the donor compartment were stirred using the Gutbox technology (Pion Inc.) to reduce the aqueous boundary layer. The test article concentrations in the donor and acceptor compartments were measured using a UV plate reader (Nano Quant, Infinite® 200 PRO, Tecan Inc., Männedorf, Switzerland). Permeability calculations were performed using Pion Inc. software and were expressed in units of 10-6cm/s. Compounds with low or weak UV signal we analyzed using high resolution

LC/MS (Thermo QExactive). The three controls used were ranitidine (low permeability), dexamethasone (moderate permeability) and verapamil (high permeability).

Mouse Pharmacokinetic Studies.: Studies were conducted by Pharmaron. Fed male CD1 mice (sourced from Si Bei Fu LaboratoryAnimal Technology Co. Ltd.), approximately 6–8 weeks of age and weight of approximately 25–30 g, were dosed with **(+)-119** at 30 mpk dose PO. The formulation was a solution at 3 mg/mL in 20% PEG300, 40% of Solutol® solution (30% w/w in water), and 40% DI water. This was prepared prior to dosing a cohort of N=24 mice. Plasma and whole brain were collected from N=3 mice at 15 min, 30 min, 1 h, 2 h, 4 h, 6 h, 84 and 24h postdose. Approximately 0.200 mL of blood was collected via the heart puncture at each time point. Blood samples were then transferred into plastic microcentrifuge tubes containing heparin–Na as anticoagulant. Samples were then centrifuged at 4000g for 5 min at 4°C to obtain plasma. Plasma samples were then stored in polypropylene tubes, quickly frozen, and kept at −75°C until analyzed by LC/MS/MS. The following pharmacokinetic parameters were calculated for plasma and brain: T_{max}, C_{max}, AUC_{24h}. Animals were also monitored during the in-life phase by once daily cageside observations; no adverse clinical signs were noted as part of the PK report.

PK/PD—A PK-PD study was performed in 6-week old female athymic nude mice (nu/nu NCr). Mice were housed in microisolator cages with food and water provided ad libitum. All work was performed on an approved Institutional Animal Care and Use Committee protocol in AAALACi accredited facilities with automated 12 on – 12 off light cycles. Mice were implanted subcutaneously with the U87MG human glioblastoma cell line (1 x 107 cells/mouse) containing the IDH1 R132H mutation. On the day of tumor staging (~200 mg), mice were randomized into 3 groups of 32 mice each. These groups were treated with a single oral dose of either vehicle (10% NMP, 40% PEG300, 25% [30% Solutol® in Water], 25% Deionized Water), compound **(+)-119** at 30 mg/kg, or AG120 at 30 mg/kg. Mice were anesthetized with isoflurane by inhalation and the tumors and K2EDTA anticoagulated blood were collected from cohorts of 4 mice per group at 1, 2, 4, 8, 16, 24, 36, and 48 hr post dose. Plasma was obtained by centrifugation and all samples were flash frozen until analysis. **(+)-119** and AG120 in plasma and tumor tissue and 2-HG in tumor were quantified using validated LC-MS/MS methods.

Use of Animal Subjects.: All animal studies included as part of this manuscript were performed in accordance with institutional guidelines as defined by Institutional Animal Care and Use Committee (IACUC).

Experimental Section Chemistry

General Methods for Chemistry.—All air- or moisture-sensitive reactions were performed under positive pressure of nitrogen with oven-dried glassware. Anhydrous solvents or reagents such as dichloromethane, *N*,*N*-dimethylformamide (DMF), acetonitrile, methanol, and triethylamine were purchased from Sigma-Aldrich. To follow most chemical reactions LC/MS of reaction aliquots were analyzed using a gradient of 4% to 100% acetonitrile (containing 0.025% trifluoroacetic acid) and water (containing 0.05% trifluoroacetic acid) with a 4.5-minute run time at a flow rate of 1 mL/min in an Agilent

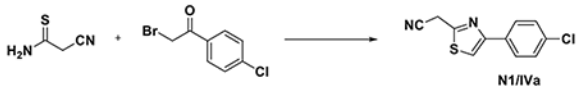
Extend-C18 column (3.5 micron, 4.6 x 100 mm) at a temperature of 50 °C using an Agilent Diode Array Detector. Confirmation of molecular formulae was accomplished using electrospray ionization in the positive mode with the Agilent Masshunter software (version B.02). **Preparative purification** was performed on a Waters semi-preparative HPLC system. The column used was a Phenomenex Luna C18 (5 micron, 30 x 75 mm) at a flow rate of 45 mL/min. The mobile phase consisted of acetonitrile and water (each containing 0.1% trifluoroacetic acid). A gradient of 10% to 50% acetonitrile over 8 minutes was used during the purification. Fraction collection was triggered by UV detection (220 nM). This purification method is referred to as **Standard Acidic Gradient Method**.

Purity of all final compounds was ≥95% as determined on an Agilent LC/MS (Agilent Technologies, Santa Clara, CA) using a 7-minute gradient of 4% to 100% acetonitrile (containing 0.025% trifluoroacetic acid) and water (containing 0.05% trifluoroacetic acid) with an 8-minute run time at a flow rate of 1 mL/min. A Phenomenex Luna C18 column (3 micron, 3 x 75 mm) was used at a temperature of 50 °C using an Agilent Diode Array Detector. Mass determination was performed using an Agilent 6130 mass spectrometer with electrospray ionization in the positive mode.

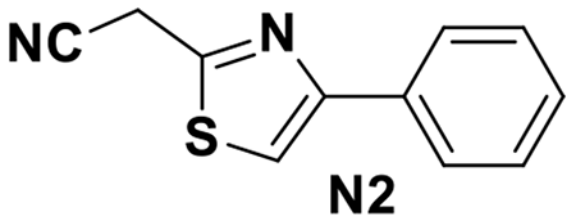
^{1}H NMR spectra were recorded on Varian 400 MHz spectrometers. Chemical shifts are reported in ppm with non-deuterated solvent (DMSO-h_6 at 2.50 ppm) as internal standard for DMSO-d_6 solutions. High resolution mass spectrometry was recorded on Agilent 6210 Time-of-Flight LC/MS system.

Synthetic Procedures

Synthesis of Nitrile Intermediates (Scheme 1, Intermediate IV)—

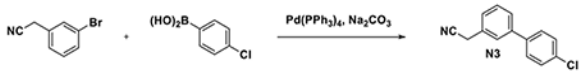


Method 1: 2-(4-(4-chlorophenyl)thiazol-2-yl)acetonitrile (N1 or IVa in Scheme 2, 3**):** To a solution of 2-bromo-1-(4-chlorophenyl)ethanone (2.33 g, 10 mmol) in ethanol (25 mL) was added 2-cyanoethanethioamide (1 g, 10 mmol). The reaction mixture was heated at reflux for 15.5 h. The reaction mixture was cooled to 0 °C. A precipitate formed and was removed by filtration washing with hexanes and subsequently drying under vacuum. The product, 2-(4-(4-chlorophenyl)thiazol-2-yl)acetonitrile is a brown powder; LCMS: *m/z* $(M+H)^+$ = 235.0; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.77 (m, 2H), 7.48 (s, 1H), 7.44 – 7.35 (m, 2H), 4.17 (s, 2H).

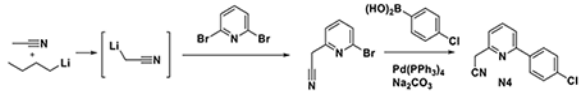


N2

2-(4-Phenylthiazol-2-yl)acetonitrile (N2, intermediate for compound **11)**: Synthesized by method **1** substituting 2-bromo-1-phenylethanone as a starting material. Following the reaction, the mixture was concentrated and purified via silica gel chromatography (0 to 30% EtOAc/hexanes). Product is a red-orange solid (1.53 g, 77%); LCMS: *m/z* $(M+H)^+$ = 201.1.

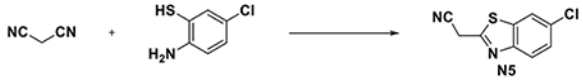


Method 2: 2-(4′-chloro-[1,1′-biphenyl]-3-yl)acetonitrile (N3, intermediate for compound **23)**: In a microwave vial, combined 2-(3-bromophenyl)acetonitrile (300 mg, 1.53 mmol), (4-chlorophenyl)boronic acid (287 mg, 1.84 mmol), tetrakis(triphenylphosphine)palladium(0) (88 mg, 0.077 mmol), 2M aqueous sodium carbonate solution (2.3 mL), and dimethoxyethane (10 mL). The reaction mixture was heated in a microwave with stirring at 140 °C for 1 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (2x10 mL), the organic layers were combined, dried with magnesium sulfate, concentrated and purified via silica gel chromatography (0 to 25% EtOAc/hexanes) to afford 2-(4′-chloro-[1,1′-biphenyl]-3-yl)acetonitrile (298 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.38 (m, 7H), 7.37 – 7.28 (m, 1H), 3.82 (t, *J* = 0.7 Hz, 2H).

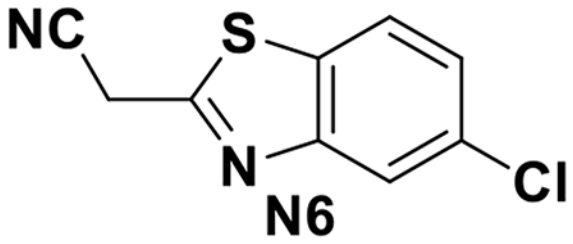


2-(6-(4-Chlorophenyl)pyridin-2-yl)acetonitrile (N4, intermediate for compound **25)**

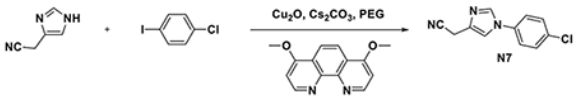
Method 3: 2-(6-Bromopyridin-2-yl)acetonitrile: A solution of n-butyllithium in hexanes (1.6M, 17.4 mL, 27.9 mmol) was added slowly to a solution of acetonitrile (1.5 mL, 28.7 mmol) in THF (40 mL) at −78 °C. A precipitate formed. The slurry stirred at this temperature for 30 min. A solution of 2,6-dibromopyridine (2 g, 8.4 mmol) in THF (10 mL) was added slowly to the slurry. The reaction mixture stirred at −78 °C for 45 min. The mixture was allowed to warm slowly to rt over 30 min. The reaction mixture was diluted with water and extracted with EtOAc (2x 10 mL), the organic layers were combined, dried with magnesium sulfate, concentrated, and purified via silica gel chromatography (0 to 40% EtOAc/hexanes) to afford 2-(6-bromopyridin-2-yl)acetonitrile (1.65 g, 99%) as a yellow oil that solidified upon cooling; LCMS: *m/z* $(M+H)^+$ = 197.0. **Method 2** was used to afford 2-(6-(4-chlorophenyl)pyridin-2-yl)acetonitrile **N4**; LCMS: *m/z* $(M+H)^+$ = 229.1



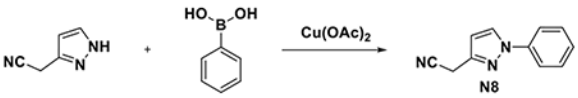
Method 4: 2-(6-chlorobenzo[d]thiazol-2-yl)acetonitrile (N5, intermediate for compound **13)**: Malononitrile (65 mg, 0.98 mmol) and 2-amino-5-chlorobenzenethiol (157 mg, 0.98 mmol) were heated at 50 °C for 4 h and at reflux for 1 h in a mixture of EtOH and AcOH. The reaction mixture was concentrated under a stream of air and 2-(6-chlorobenzo[d]thiazol-2-yl)acetonitrile was used without further purification.



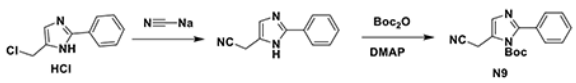
2-(5-chlorobenzo[d]thiazol-2-yl)acetonitrile (N6, intermediate for compound **14**): was prepared according to method **4**, however refluxing was conducted overnight followed by heating in a microwave at 120 °C for 1h and at 150 °C for 1 h. The reaction mixture was concentrated under a stream of air and 2-(5-chlorobenzo[d]thiazol-2-yl)acetonitrile was used without further purification; LCMS: *m/z* $(M+H)^+$ = 209.0.



Method 5: 2-(1-(4-chlorophenyl)-1H-imidazol-4-yl)acetonitrile (**N7**, intermediate for compound **15**): A mixture of 2-(1H-imidazol-4-yl)acetonitrile (150 mg, 1.4 mmol), 1-chloro-4-iodobenzene (467 mg, 1.96 mmol), 4,7-dimethoxy-1,10-phenanthroline (101 mg, 0.42 mmol), copper (I) oxide (20 mg, 0.14 mmol), cesium carbonate (776 mg, 2.38 mmol), PEG (250 mg) and DMSO (1.5 mL) was heated with stirring at 110 °C for 24 h. The reaction mixture was diluted with water, 0.1N HCl, and EtOAc, extracted (2x). The organic layers were combined, dried with magnesium sulfate, concentrated, and purified via reverse phase chromatography (C18) (5 to 100% acetonitrile/water [0.1% TFA]) to afford 2-(1-(4-chlorophenyl)-1H-imidazol-4-yl)acetonitrile (35 mg, 12%) as a yellow oil; LCMS: *m/z* $(M+H)^+$ = 218.0.



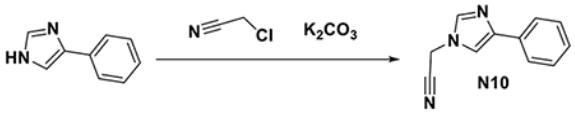
Method 6: 2-(1-phenyl-1H)-pyrazol-3-yl)acetonitrile (**N8**, intermediate for compound **19**): A mixture of copper (II) acetate 382 mg, 2.1 mmol), 2-(1H-pyrazol-3-yl)acetonitrile (150 mg, 1.4 mmol), phenylboronic acid (341 mg, 2.8 mmol), triethylamine (0.390 mL, 2.8 mmol), pyridine (0.227 mL, 2.8 mmol), 4 Angstrom molecular sieves (500 mg), and dichloromethane (10 mL) was heated at 55 °C overnight. The reaction mixture was filtered, extracted (DCM/1 N HCl), dried with magnesium sulfate, concentrated and 2-(1-phenyl-1H)-pyrazol-3-yl)acetonitrile was used without further purification; LCMS: *m/z* $(M+H)^+$ = 184.1.



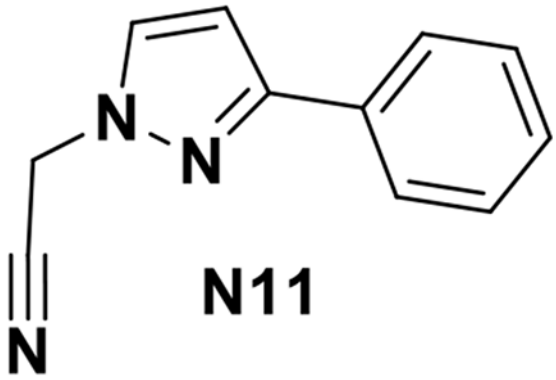
Method 7: 2-(2-phenyl-1H-imidazol-5-yl)acetonitrile: A mixture of 5-(chloromethyl)-2-phenyl-1H-imidazole hydrochloride (197 mg, 0.86 mmol) and sodium cyanide (127 mg,

2.58 mmol) in DMSO (3 mL) was stirred at rt overnight. The reaction mixture was diluted with water and saturated aqueous sodium bicarbonate solution, extracted (EtOAc x 2), dried with magnesium sulfate, concentrated and 2-(2-phenyl-1H-imidazol-5-yl)acetonitrile was used without further purification.

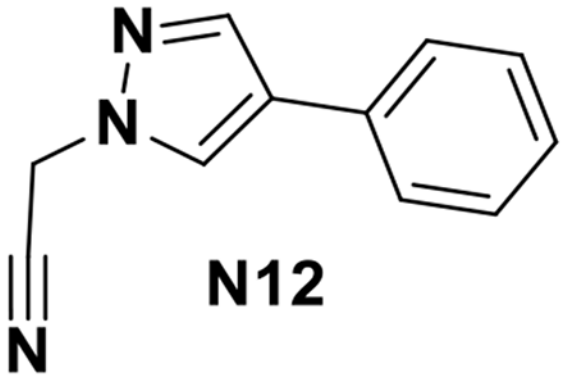
Method 8: ***tert*-Butyl 5-(cyanomethyl)-2-phenyl-1H-imidazole-1-carboxylate** (**N9**, intermediate for compound **17**): A mixture of 2-(2-phenyl-1H-imidazol-5-yl)acetonitrile (50 mg, 0.27 mmol), Boc_2O (0.070 mL, 0.3 mmol), and DMAP (trace) in acetonitrile (3 mL) and sodium cyanide (127 mg, 2.58 mmol) in DMSO (3 mL) was stirred at rt for 40 min and concentrated under a stream of air. *tert*-butyl 5-(cyanomethyl)-2-phenyl-1H-imidazole-1-carboxylate was used without further purification; LCMS: *m/z* $(M+H)^+$ = 284.1 (weak).



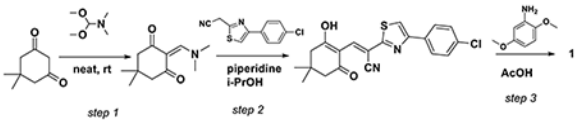
Method 9: 2-(4-phenyl-1H-imidazol-1-yl)acetonitrile (**N10**, intermediate for compound **16**): A mixture of 4-phenyl-1H-imidazole (250 mg, 1.7 mmol), chloroacetonitrile (0.22 mL, 3.5 mmol), and potassium carbonate (1.2 g, 8.7 mmol) in DMF (8 mL) was stirred at rt for 22 h. The reaction mixture was diluted with water, extracted (EtOAc x 2), dried with magnesium sulfate, concentrated to afford 2-(4-phenyl-1H-imidazol-1-yl)acetonitrile as a brown solid which was used without further purification; LCMS: *m/z* $(M+H)^+$ = 184.1.



2-(3-phenyl-1H-pyrazol-1-yl)acetonitrile (**N11**, intermediate for compound **20**) was synthesized by method **9**; LCMS: *m/z* $(M+H)^+$ = 184.1 (weak).



2-(4-Phenyl-1H-pyrazol-1-yl)acetonitrile (**N12**, intermediate for compound **21**) was synthesized by method **9**; LCMS: *m/z* $(M+H)^+$ = 184.1 (weak).

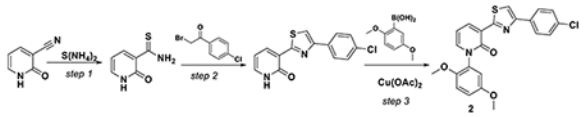


Method 10:

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (1): *Step 1:* In a vial, 5,5-dimethylcyclohexane-1,3-dione (0.100 g, 0.713 mmol) and DMF-DMA (0.096 mL,0.713 mmol) were mixed and stirred neat for 5 min. The reaction mixture became a yellow oil.

Step 2: To the mixture was added *i*-PrOH (2.55 mL), 2-(4-(4-chlorophenyl)thiazol-2-yl)acetonitrile (167 mg, 0.713 mmol), and piperidine (0.071 mL, 0.713 mmol). The reaction was allowed to stir at rt for 3 h. The solid went into solution. After 3 h, a precipitate formed at which point the solvent was removed by blowing down under a stream of air with mild heating at 30 °C.

Step 3: To the resulting residue were added acetic acid (1 mL) and 2,5-dimethoxyaniline (109 mg, 0.713 mmol). The reaction stirred for 15 min at rt, a precipitate formed almost immediately. The solvent was removed by blowing down under a stream of air with mild heating at 30 °C. The crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford as a TFA salt, 3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione LCMS: *m/z* $(M+H)^+$ = 521.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.22 (s, 1H), 8.12 – 8.05 (m, 2H), 7.58 – 7.50 (m, 2H), 7.23 (d, *J* = 9.2 Hz, 1H), 7.13 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.05 (d, *J* = 3.0 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 2.62 (d, *J* = 17.7 Hz, 1H), 2.46 (d, *J* = 2.9 Hz, 2H), 2.22 (d, *J* = 17.7 Hz, 1H), 0.99 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z $(M+H)^+$ calcd. for $C_{28}H_{26}ClN_2O_4S$; 521.1296 found 521.1321. Retention Time = 3.858 min.

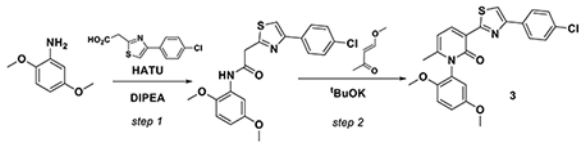


3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)pyridin-2(1*H*)-one (2): *Step 1*: **2-Oxo-1,2-dihydropyridine-3-carbothioamide:** Ammonium sulfide (0.509 mL, 2.99 mmol) was added to a solution of 2-oxo-1,2-dihydropyridine-3-carbonitrile (211 mg, 1.757 mmol) in methanol (14 mL). The reaction was heated in a microwave at 130 °C for 2 h. The mixture stood overnight at rt and crystals formed. The mixture was further cooled to 0 °C for 4 h. The methanol was poured off and the solid was triturated with methanol and used as is in the following step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 11.31 (s, 1H), 9.98 (s, 1H), 8.93 (dd, J = 7.4, 2.2 Hz, 1H), 7.77 (dd, J = 6.2, 2.3 Hz, 1H), 6.52 (dd, J = 7.4, 6.2 Hz, 1H).

Step 2: **3-(4-(4-Chlorophenyl)thiazol-2-yl)pyridin-2(1*H*)-one:** To 2-oxo-1,2-dihydropyridine-3-carbothioamide (124 mg, 0.804 mmol) in ethanol (2 mL) was added 2-bromo-1-(4-chlorophenyl)ethanone (188 mg, 0.804 mmol). The reaction mixture was heated at reflux for 17.5 h. The reaction mixture was cooled to rt and diluted with hexanes. The solid was removed by filtration washing with hexanes. Dry on high vacuum. The product (213 mg, 65%) is a red-brown powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.10 (s, 1H), 8.28 (dd, J = 7.2, 2.1 Hz, 1H), 7.80 (s, 1H), 7.76 – 7.68 (m, 2H), 7.30 (s, 1H), 7.20 – 7.11 (m, 2H), 6.15 (dd, J = 7.2, 6.3 Hz, 1H).

Step 3: **3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)pyridin-2(1*H*)-one (**Table 1**; Compound 2):** To a mixture of 3-(4-(4-chlorophenyl)thiazol-2-yl)pyridin-2(1H)-one (60 mg, 0.208 mmol), copper (II) acetate (56.6 mg, 0.312 mmol), and 2,5-dimethoxyphenylboronic acid (76 mg, 0.416 mmol) were added 1,4-Dioxane (2 mL) and pyridine (0.2 mL). The reaction mixture was sealed and heated at 80 °C for 60 hr. Filter thiol resin washing with EtOAc and concentrated. The crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford as a TFA salt, 3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5 (1H,6H)-dione. LCMS: *m/z* $(M+H)^+$ = 425.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (dd, J = 7.3, 2.0 Hz, 1H), 8.16 (s, 1H), 8.07 (d, J = 8.6 Hz, 2H), 7.78 (dd, J = 6.6, 2.0 Hz, 1H), 7.51 (d, J = 8.6 Hz, 2H), 7.17 (dd, J = 8.5, 1.3 Hz, 1H), 7.10 – 7.02 (m, 2H), 6.59 (t, J = 6.9 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H); HRMS (ESI) m/z $(M+H)^+$ calcd. for $C_{22}H_{18}ClN_2O_3S$; 425.0721 found 425.0723. Retention Time = 3.787 min.

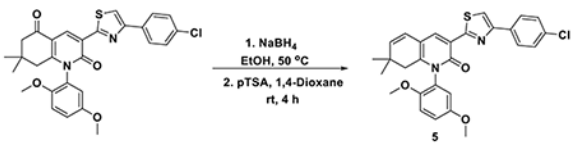
3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-6-methylpyridin-2(1H)-one (3):



Step 1: **2-(4-(4-chlorophenyl)thiazol-2-yl)-N-(2,5-dimethoxyphenyl)acetamide:** To a mixture of 2-(4-(4-chlorophenyl)thiazol-2-yl)acetic acid (155 mg, 0.611 mmol) in CH_2Cl_2 (3 mL) was added HATU (348 mg, 0.916 mmol), DIPEA (320 μl, 1.833 mmol) and 2,5-dimethoxyaniline (103 mg, 0.672 mmol). The reaction mixture was stirred for 1h at room temperature. The reaction mixture was diluted with water and CH_2Cl_2, extracted (2x15 mL), the organic layers were combined, dried with magnesium sulfate, concentrated and purified via silica gel chromatography to afford 2-(4-(4-chlorophenyl)thiazol-2-yl)-N-(2,5-dimethoxyphenyl)acetamide as a solid; LCMS: *m/z* $(M+H)^+$ = 389.

Step 2: **3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-6-methylpyridin-2(1H)-one (**Table 1**; Compound 3):** To a mixture of 2-(4-(4-chlorophenyl)thiazol-2-yl)-N-(2,5-dimethoxyphenyl)acetamide (74mg, 0.190 mmol), (E)-4-methoxybut-3-en-2-one (38.8 μl, 0.381 mmol) and potassium 2-methylpropan-2-olate (21.35 mg, 0.190 mmol) and heated 80 °C for 3.5 hr. The reaction mixture was diluted with methanol/CH_2Cl_2/water and to alleviate the emulsion acidify with 1N HCl and extract with EtOAc and concentrated. The crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford as a TFA salt, 3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-6-methylpyridin-2(1H)-one. LCMS: *m/z* $(M+H)^+$ = 521.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (d, *J* = 7.4 Hz, 1H), 8.15 – 8.03 (m, 3H), 7.55 – 7.47 (m, 2H), 7.18 (d, *J* = 9.1 Hz, 1H), 7.07 (dd, *J* = 9.1, 3.1 Hz, 1H), 6.98 (d, *J* = 3.1 Hz, 1H), 6.59 (dd, *J* = 7.5, 0.9 Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 2.03 (d, *J* = 0.8 Hz, 3H); HRMS (ESI) m/z $(M+H)^+$ calcd. for $C_{23}H_{20}ClN_2O_3S$; 439.0878 found 439.0897. Retention Time = 3.822 min.

3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-2(1H)-one (4): To a solution of 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (35 mg, 0.067 mmol) compound **1** in THF (2 mL) was added Lithium Aluminum Hydride (0.101 mL, 0.101 mmol). The reaction mixture stirred at rt for 1 hr then heated at 60 °C for 12 h. The reaction mixture was cooled to 0 °C and quenched with methanol and a bit of water, and diluted with EtOAc, extracted (2x25 mL), the organic layers were combined, dried with magnesium sulfate and concentrated. The crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford as a TFA salt, 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-2(1H)-one. LCMS: *m/z* $(M+H)^+$ = 507.2; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.48 (s, 1H), 8.13 – 8.00 (m, 3H), 7.54 – 7.45 (m, 2H), 7.16 (d, J = 9.1 Hz, 1H), 7.05 (dd, J = 9.1, 3.0 Hz, 1H), 6.87 (d, J = 3.0 Hz, 1H), 3.73 (d, J = 1.4 Hz, 3H), 3.66 (s, 3H), 2.73 (t, J = 6.5 Hz, 2H), 2.09 (d, J = 17.8 Hz, 1H), 1.78 (d, J = 17.8 Hz, 1H), 1.47 (t, J = 6.7 Hz, 2H), 0.88 (s, 3H), 0.84 (s, 3H); HRMS (ESI) m/z $(M+H)^+$ calcd. for $C_{28}H_{28}ClN_2O_3S$; 507.1504 found 507.1509. Retention Time = 4.196 min.



3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinolin-2(1H)-one (5): *Step 1:* To a solution of 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (200 mg, 0.384 mmol) compound **1** in EtOH (10 mL) was added sodium borohydride (29.0 mg, 0.768 mmol). Gas evolution was observed. The reaction mixture stirred at 50 °C for 12 hr. The reaction mixture was cool to rt and diluted with water and EtOAc, extracted (2x25 mL), the organic layers were combined, dried with magnesium sulfate and concentrated. The crude mixture was taken next step without further purification.

Step 2: To a solution of 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-5-hydroxy-7,7-dimethyl-5,6,7,8-tetrahydroquinolin-2(1H)-one (38 mg, 0.073 mmol) in 1,4-Dioxane (10 mL) was added pTSA (1.38 mg, 0.1 eq). The reaction mixture stirred at rt for 4 hr. The organic solvent was concentrated. The crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford as a TFA salt, 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinolin-2(1H)-one. LCMS: *m/z* $(M+H)^+$ = 505.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 2H), 8.01 – 8.23 (m, 6H), 7.54 (m, 2H), 7.18 (d, *J* = 8.61 Hz, 3H), 7.18 – 7.30 (m, 2H), 7.06 – 7.18 (m, 2H), 7.00 (d, *J* = 3.13 Hz, 2H), 6.47 (d, *J* = 9.78 Hz, 2H), 5.63 (d, *J* = 9.78 Hz, 1H), 3.73 (d, *J* = 19.96 Hz, 7H), 2.37 – 2.48 (m, 2H), 2.14 (s, 1H), 0.84 – 1.14 (m, 7H); HRMS (ESI) m/z $(M+H)^+$ calcd. for $C_{28}H_{26}ClN_2O_3S$; 505.1347 found 505.1351. Retention Time = 4.152 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (6): This compound was prepared from **Method 10** using cyclohexane-1,3-dione in **step 1** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 493; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.21 (d, *J* = 1.2 Hz, 1H), 8.11 – 8.02 (m, 2H), 7.57 – 7.46 (m, 2H), 7.21 (d, *J* = 9.1 Hz, 1H), 7.14 – 7.02 (m, 2H), 3.74 (d, *J* = 1.1 Hz, 3H), 3.70 (s, 3H), 2.51 (d, *J* = 1.2 Hz, 2H), 2.47 (m, 4H); HRMS (ESI) m/z $(M+H)^+$ calcd. for $C_{26}H_{22}ClN_2O_4S$; 493.0983 found 493.0973. Retention Time = 3.741 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-6,7-dihydro-1H-cyclopenta[b]pyridine-2,5-dione (7): This compound was prepared from **Method 10** using cyclopentane-1,3-dione in **step 1** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 479.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1H), 8.27 (s, 1H), 8.14 (d, *J* = 8.61 Hz, 2H), 7.54 (d, *J* = 8.61 Hz, 2H), 7.27 (d, *J* = 9.00 Hz, 1H), 7.07 – 7.22 (m, 2H), 3.76 (d, *J* = 12.91 Hz, 5H), 2.77 – 2.92 (m, 1H), 2.55 – 2.77 (m, 3H); HRMS (ESI) m/z $(M+H)^+$ calcd. for $C_{25}H_{20}ClN_2O_4S$; 479.0827 found 479.0840. Retention Time = 3.672 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-5-hydroxyquinolin-2(1H)-one (8): To a solution of 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (25 mg, 0.051 mmol) compound **6** in 1,4-dioxane (3 mL) was added DDQ (17.27 mg, 0.076 mmol). The reaction mixture was stirred at 70 °C for 12 hr. The organic solvent was concentrated. The crude mixture was diluted with DMSO

and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford as a TFA salt, 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-5-hydroxyquinolin-2(1H)-one. LCMS: *m/z* $(M+H)^+$ = 491.2; HRMS (ESI) m/z (M+H)+ calcd. for $C_{26}H_{20}ClN_2O_4S$; 491.0827 found 491.0817. Retention Time = 3.619 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,8-dihydro-1,7-naphthyridine-2,5(1H,6H)-dione (9): This compound was prepared from **Method 10** using *tert*-butyl 3,5-dioxopiperidine-1-carboxylate in **step 1** followed by Boc deprotection after step 3 using TFA to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,8-dihydro-1,7-naphthyridine-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 494.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (s, 1H), 8.30 (s, 1H), 8.14 – 8.07 (m, 2H), 7.59 – 7.52 (m, 2H), 7.29 (d, *J* = 9.2 Hz, 1H), 7.19 (dd, *J* = 9.2, 3.1 Hz, 1H), 7.06 (d, *J* = 3.1 Hz, 1H), 3.98-3.79 (m, 2H), 3.76 (s, 3H), 3.74 (s, 3H); HRMS (ESI) m/z (M+2H) $^{+2}$ calcd. for $C_{25}H_{22}ClN_3O_4S$; 493.0821 found 493.0863. Retention Time = 3.148 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,8-dihydro-1,6-naphthyridine-2,5(1H,6H)-dione (10): This compound was prepared from **Method 10** using *tert*-butyl 2,4-dioxopiperidine-1-carboxylate in **step 1** followed by Boc deprotection using TFA to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,8-dihydro-1,6-naphthyridine-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 494.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.20 (s, 1H), 8.13 – 8.04 (m, 2H), 7.92 (s, 1H), 7.57 – 7.47 (m, 2H), 7.21 (dd, *J* = 8.8, 0.8 Hz, 1H), 7.15 – 7.06 (m, 2H), 3.74 (s, 3H), 3.71 (s, 3H), 3.42 – 3.30 (m, 2H), 2.73 – 2.60 (m, 1H), 2.40 (dt, *J* = 17.6, 6.5 Hz, 1H); HRMS (ESI) m/z (M+Na) + calcd. for $C_{25}H_{20}ClN_3NaO_4S$; 516.0755 found 516.0768. Retention Time = 3.822 min.

1-(2,5-Dimethoxyphenyl)-7,7-dimethyl-3-(4-phenylthiazol-2-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (11): This compound was prepared from **Method 10** using 2-(4-phenylthiazol-2-yl)acetonitrile **N2** in **step 2** to afford 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-3-(4-phenylthiazol-2-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 487.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.25 (s, 1H), 8.18 – 8.11 (m, 2H), 7.57 (dd, *J* = 8.3, 7.0 Hz, 2H), 7.50 – 7.41 (m, 1H), 7.33 (d, *J* = 9.1 Hz, 1H), 7.23 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.14 (d, *J* = 3.0 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 2.72 (d, *J* = 17.8 Hz, 1H), 2.64 – 2.49 (m, 2H), 2.31 (d, *J* = 17.7 Hz, 1H), 1.09 (s, 3H), 1.03 (s, 3H); HRMS (ESI) m/z (M+Na) $^+$ calcd. for $C_{28}H_{26}N_2NaO_4S$; 509.1505 found 509.1529. Retention Time = 3.718 min.

3-(5-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (12): This compound was prepared from **Method 10** using 2-(5-(4-chlorophenyl)thiazol-2-yl)acetonitrile in **step 2** to afford 3-(5-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 521.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.03 (d, *J* = 4.7 Hz, 1H), 8.49 (s, 1H), 7.84 – 7.75 (m, 2H), 7.64 – 7.54 (m, 2H), 7.32 (d, *J* = 9.2 Hz, 1H), 7.26 – 7.17 (m, 1H), 7.13 (d, *J* = 3.1 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 2.71 (d, *J* = 17.7 Hz, 1H), 2.54

(d, *J* = 3.1 Hz, 2H), 2.30 (d, *J* = 17.8 Hz, 1H), 1.08 (s, 3H), 1.02 (s, 3H); HRMS (ESI) m/z $(M+H)^+$ calcd. for $C_{26}H_{24}ClN_2O_4S$; 495.114 found 495.1159. Retention Time = 3.787 min.

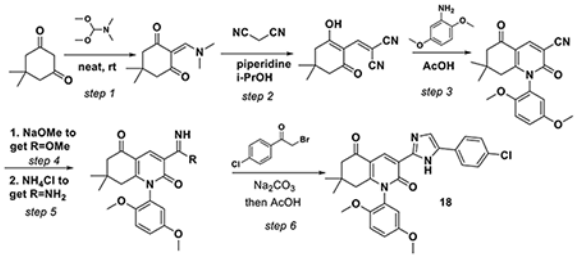
3-(6-Chlorobenzo[d]thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (13): This compound was prepared from **Method 10** using 2-(6-chlorobenzo[d]thiazol-2-yl)acetonitrile **N5** in **step 2** to afford 3-(6-chlorobenzo[d]thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 495.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.27 (d, *J* = 2.1 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 7.56 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.25 (d, *J* = 9.1 Hz, 1H), 7.18 – 7.05 (m, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 2.64-2.60 (m, 2H), 2.35-2.17 (m, 2H), 1.00 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{26}H_{24}ClN_2O_4S$; 495.114 found 495.1138 Retention Time = 3.795 min.

3-(5-Chlorobenzo[d]thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (14): This compound was prepared from **Method 10** using 2-(5-chlorobenzo[d]thiazol-2-yl)acetonitrile *N6* in **step 2** to afford 3-(5-chlorobenzo[d]thiazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 495.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 (s, 1H), 8.20 – 8.12 (m, 2H), 7.46 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.25 (d, *J* = 9.1 Hz, 1H), 7.18 – 7.05 (m, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 2.64 (d, *J* = 17.8 Hz, 1H), 2.24 (d, *J* = 17.8 Hz, 1H), 1.00 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z $(M+Na)^+$ calcd. for $C_{28}H_{25}ClN_2NaO_4S$; 543.1116 found 543.113. Retention Time = 3.811 min.

3-(1-(4-Chlorophenyl)-1H-imidazol-4-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (15): This compound was prepared from **Method 10** using 2-(1-(4-chlorophenyl)-1H-imidazol-4-yl)acetonitrile **N7** in **step 2** to afford 3-(1-(4-chlorophenyl)-1H-imidazol-4-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8 dihydro-quinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 504.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (s, 1H), 8.38 (d, *J* = 1.4 Hz, 1H), 8.20 (d, *J* = 1.4 Hz, 1H), 7.75 – 7.62 (m, 2H), 7.59 – 7.48 (m, 1H), 7.18 (d, *J* = 9.1 Hz, 1H), 7.07 (dd, *J* = 9.1, 3.0 Hz, 1H), 6.94 (d, *J* = 3.0 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 2.63 (dd, *J* = 3.7, 1.9 Hz, 1H), 2.38 (d, *J* = 8.1 Hz, 1H), 2.31 – 2.26 (m, 1H), 0.96 (s, 3H), 0.91 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{27}ClN_3O_4$; 504.1685 found 504.1678. Retention Time = 3.343 min.

1-(2,5-Dimethoxyphenyl)-7,7-dimethyl-3-(4-phenyl-1H-imidazol-1-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (16): This compound was prepared from **Method 10** using 2-(4-phenyl-1H-imidazol-1-yl)acetonitrile **N10** in **step 2** to afford 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-3-(4-phenyl-1H-imidazol-1-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 470.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.35 (s, 1H), 8.27 (s, 1H), 7.88 – 7.80 (m, 2H), 7.41 (dd, *J* = 8.3, 7.1 Hz, 2H), 7.33 – 7.19 (m, 2H), 7.12 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.02 (d, *J* = 3.1 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 2.60 (d, *J* = 17.6 Hz, 1H), 2.44 (d, *J* = 4.1 Hz, 2H), 2.19 (d, *J* = 17.5 Hz, 1H), 0.99 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{28}N_3O_4$; 470.2074 found 470.2095. Retention Time = 3.02 min.

1-(2,5-Dimethoxyphenyl)-7,7-dimethyl-3-(2-phenyl-1H-imidazol-4-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (17): This compound was prepared from **Method 10** using *tert*-Butyl 5-(cyanomethyl)-2-phenyl-1H-imidazole-1-carboxylate **N9** in **step 2** followed by treatment with TFA to afford 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-3-(2-phenyl-1H-imidazol-4-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 470.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.01 (d, *J* = 7.6 Hz, 2H), 7.45 (d, *J* = 31.3 Hz, 3H), 7.18 (d, *J* = 9.1 Hz, 1H), 7.08 (dd, *J* = 9.1, 3.0 Hz, 2H), 6.94 (d, *J* = 3.0 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 2.66 – 2.55 (m, 1H), 2.40 (d, *J* = 8.2 Hz, 1H), 2.29 (p, *J* = 1.9 Hz, 1H), 2.13 (d, *J* = 17.5 Hz, 1H), 0.97 (s, 3H), 0.92 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{28}N_3O_4$; 470.2074 found 470.2054. Retention Time = 2.59 min.



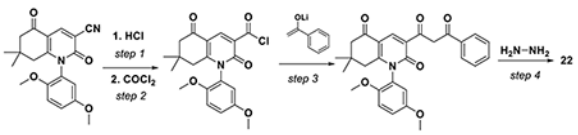
1-(2,5-Dimethoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydro-quinoline-3-carbonitrile dione (18): *Step 1:* Similar to Method 10; *Step 2:* Similar to **Method 10** with stirring only for 1 h. Also, add aniline prior to concentration; *Step 3:* Add acetic acid and stir overnight at rt. The reaction mixture was diluted with water and DCM, extracted (2x), the organic layers were combined, dried with magnesium sulfate, concentrated and purified via silica gel chromatography (10 to 100% EtOAc/hexanes) to afford 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (70% on 2.85 mmol scale); LCMS: *m/z* $(M+H)^+$ = 353.1. *Step 4:* **1-(2,5-dimethoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carboximidamide:** To a mixture of 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (60 mg, 0.170 mmol) in MeOH (1 mL) was added sodium methanolate (398 µl, 1.703 mmol) in MeOH. The reaction mixture was stirred at 45°C for 45 min and then added ammonia hydrochloride (91 mg, 1.703 mmol) and AcOH (1.5 mL). The reaction mixture was stirred at 60°C for 12 h. The reaction mixture was diluted with water and DCM, extracted (2x), the organic layers were combined, dried with magnesium sulfate, concentrated and purified via silica gel chromatography (10 to 100% EtOAc/hexanes) to afford 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carboximidamide; LCMS: *m/z* $(M+H)_+$ = 370.1. *Step 5:* To a mixture of 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carboximidamide (50 mg, 0.135 mmol) in THF (1 mL) was added 2-bromo-1-(4-chlorophenyl)ethan-1-one (135 µl 0.135 mmol) and sodium bicarbonate (11.37 mg, 0.135 mmol). The reaction mixture was stirred at 70 °C for 2 h and then added AcOH (7.75 µl 0.135 mmol) . The reaction mixture was stirred at 70°C for 2 h. The solvent was removed by blowing down under a stream of air with mild heating at 30 °C. The crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to

afford as a TFA salt, 3-(5-(4-chlorophenyl)-1H-imidazol-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione. LCMS: *m/z* $(M+H)_+$ = 504.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.63 (s, 1H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 9.2 Hz, 1H), 7.15 – 6.95 (m, 2H), 3.71 (d, *J* = 13.8 Hz, 6H), 2.66 – 2.54 (m, 2H), 2.42 (d, *J* = 4.5 Hz, 2H), 0.98 (s, 3H), 0.92 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{27}ClN_3O_4$; 504.1685 found 504.1709. Retention Time = 3.171 min.

1-(2,5-Dimethoxyphenyl)-7,7-dimethyl-3-(1-phenyl-1H-pyrazol-3-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (19): This compound was prepared from **Method 10**_using 2-(1-phenyl-1H-pyrazol-3-yl)acetonitrile **N8** in **step 2** to afford 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-3-(1-phenyl-1H-pyrazol-3-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 470.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.51 (d, *J* = 2.5 Hz, 1H), 7.94 – 7.86 (m, 2H), 7.56 – 7.47 (m, 2H), 7.37 – 7.28 (m, 1H), 7.20 (d, *J* = 9.1 Hz, 1H), 7.16 – 7.05 (m, 2H), 6.98 (d, *J* = 3.0 Hz, 1H), 3.75 (s, 3H), 3.71 (s, 3H), 2.56 (d, *J* = 17.6 Hz, 1H), 2.41 (d, *J* = 7.3 Hz, 2H), 2.14 (d, *J* = 17.6 Hz, 1H), 0.98 (s, 3H), 0.93 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{28}N_3O_4$; 470.2074 found 470.2094. Retention Time = 3.539 min.

1-(2,5-Dimethoxyphenyl)-7,7-dimethyl-3-(3-phenyl-1H-pyrazol-1-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (20): This compound was prepared from **Method 10** using 2-(3-phenyl-1H-pyrazol-1-yl)acetonitrile **N11** in **step 2** to afford 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-3-(3-phenyl-1H-pyrazol-1-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 470.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (d, *J* = 2.6 Hz, 1H), 8.51 (s, 1H), 7.96 – 7.88 (m, 2H), 7.50 – 7.41 (m, 2H), 7.41 – 7.32 (m, 1H), 7.22 (d, *J* = 9.1 Hz, 1H), 7.12 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.04 (d, *J* = 3.0 Hz, 1H), 6.96 (d, *J* = 2.6 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.57 (d, *J* = 17.5 Hz, 1H), 2.44 (d, *J* = 4.2 Hz, 2H), 2.16 (d, *J* = 17.6 Hz, 1H), 0.99 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{28}N_3O_4$; 470.2074 found 470.2074. Retention Time = 3.66 min.

1-(2,5-Dimethoxyphenyl)-7,7-dimethyl-3-(4-phenyl-1H-pyrazol-1-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (21): This compound was prepared from **Method 10** using 2-(4-phenyl-1H-pyrazol-1-yl)acetonitrile **N12** in **step 2** to afford 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-3-(4-phenyl-1H-pyrazol-1-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 470.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (d, *J* = 0.8 Hz, 1H), 8.44 (s, 1H), 8.25 (d, *J* = 0.8 Hz, 1H), 7.67 – 7.59 (m, 2H), 7.41 – 7.31 (m, 2H), 7.26 – 7.16 (m, 2H), 7.12 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.04 (d, *J* = 3.1 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.62 – 2.50 (m, 1H), 2.43 (d, *J* = 4.1 Hz, 2H), 2.17 (d, *J* = 17.6 Hz, 1H), 0.99 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{28}N_3O_4$; 470.2074 found 470.208. Retention Time = 3.608 min.



1-(2,5-Dimethoxyphenyl)-7,7-dimethyl-3-(5-phenyl-1H-pyrazol-3-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (22): *Step 1:* A mixture of 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (60 mg, 0.17 mmol) (intermediate after step 3 in the synthesis of compound *18*) in concentrated HCl (3 mL) was heated at 80 °C for 22 h. The reaction mixture was diluted with water, extracted (DCM/MeOH x 3), dried with magnesium sulfate, concentrated to afford 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxylic acid which was used without further purification; LCMS: *m/z* $(M+H)^+$ = 372.1. *Step 2:* To the acid (28 mg, 0.075 mmol) in DCM (3 mL) was added a drop of DMF and oxalyl chloride (0.033 mL, 0.38 mmol). The reaction stirred at rt for 1.2 h. The reaction mixture was concentrated under a stream of argon, rediluted with DCM, and re-concentrated to afford 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonyl chloride; this was verified by LCMS that showed formation of the methyl ester on addition of MeOH to an aliquot from the reaction.

Step 3: To a solution of acetophenone (0.026 mL, 0.23 mmol) in THF (1 mL) that had been cooled to −78 °C was added a solution of LiHMDS (1M THF, 0.225 mL, 0.225 mmol) slowly. The reaction continued to stir at this temperature for 1 h (faint yellow solution) at which point a solution of 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonyl chloride (**VI**) (0.075 mmol) in THF (1.5 mL) was added. The reaction became more yellow and was allowed to warm slowly 1.5 h. The reaction went from yellow to red (likely red is doubly deprotonated trione). *Step 4:* Hydrazine (3 eq) in ethanol was added and stirring resumed for 1 h. Acetic acid (3 drops) was added and the reaction went from red to yellow along with the formation of a precipitate. The reaction was heated at 50 °C for 1 h and stood at rt for 1 week. The crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford as a TFA salt, 1-(2,5-dimethoxyphenyl)-7,7-dimethyl-3-(5-phenyl-1H-pyrazol-3-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 470.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.14 (s, 1H), 8.48 (s, 1H), 7.81 (d, *J* = 7.4 Hz, 1H), 7.74 – 7.66 (m, 1H), 7.45 – 7.31 (m, 1H), 7.27 (dd, *J* = 11.1, 6.7 Hz, 2H), 7.19 (d, *J* = 8.9 Hz, 2H), 7.08 (d, *J* = 9.4 Hz, 1H), 7.01 – 6.93 (m, 1H), 6.47 (s, 0H), 3.73 (s, 3H), 3.69 (s, 3H), 2.51 (s, 3H), 2.14 (d, *J* = 17.8 Hz, 1H), 0.97 (s, 3H), 0.92 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{28}N_3O_4$; 470.2074 found 470.2073. Retention Time = 3.428 min.

3-(4'-Chloro-[1,1'-biphenyl]-3-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (23): This compound was prepared from **Method 10** using 2-(4'-chloro-[1,1'-biphenyl]-3-yl)acetonitrile **N3** in **step 2** to afford 3-(4'-chloro-[1,1'-biphenyl]-3-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 514.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.12 (s, 1H), 7.99 – 7.93 (m, 1H), 7.79 – 7.60 (m, 4H), 7.56 – 7.45 (m, 3H), 7.19 (d, *J* = 9.1 Hz, 1H), 7.08 (dd, *J* = 9.1, 3.1 Hz, 1H), 6.97 (d, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 2.97 (s, 3H), 2.60 – 2.49 (m, 1H), 2.47 – 2.32 (m, 2H), 2.14 (d, *J* = 17.5 Hz, 1H), 0.98 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{31}H_{29}ClNO_4$; 514.178 found 514.1777. Retention Time = 3.835 min.

3-([1,1'-Biphenyl]-4-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (24): This compound was prepared from **Method 10** using 2-([1,1'-biphenyl]-4-yl)acetonitrile in **step 2** to afford 3-([1,1'-biphenyl]-4-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 480.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (s, 1H), 7.83 – 7.75 (m, 2H), 7.74 – 7.65 (m, 4H), 7.51 – 7.42 (m, 2H), 7.40 – 7.31 (m, 1H), 7.20 (d, *J* = 9.2 Hz, 1H), 7.08 (dd, *J* = 9.1, 3.1 Hz, 1H), 6.98 (d, *J* = 3.0 Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 2.45-2.33 (m, 2H), 2.14-2.10 (m, 2H), 0.99 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{31}H_{30}NO_4$; 480.2169 found 480.2176. Retention Time = 3.719 min.

3-(6-(4-Chlorophenyl)pyridin-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (25): This compound was prepared from **Method 10** using 2-(6-(4-chlorophenyl)pyridin-2-yl)acetonitrile **N4** in **step 2** to afford 3-(6-(4-chlorophenyl)pyridin-2-yl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 515.1; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.94 (s, 1H), 8.27 (dd, *J* = 7.2, 1.6 Hz, 1H), 8.16 (d, *J* = 8.6 Hz, 2H), 7.95 – 7.85 (m, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 9.1 Hz, 1H), 7.08 (dd, *J* = 9.1, 3.0 Hz, 1H), 6.99 (d, *J* = 3.0 Hz, 1H), 3.73 (s, 3H), 3.70 (s, 3H), 2.58 (d, *J* = 17.6 Hz, 1H), 2.41 (d, *J* = 7.2 Hz, 2H), 2.15 (d, *J* = 17.6 Hz, 1H), 0.98 (s, 3H), 0.93 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{30}H_{28}ClN_2O_4$; 515.1732 found 515.175. Retention Time = 3.8 min.

N-(4-Chlorobenzyl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamide (26): This compound was prepared from **Method 10** using N-(4-chlorobenzyl)-2-cyanoacetamide in **step 2** to afford N-(4-chlorobenzyl)-1-(2,5-dimethoxyphenyl)-7,7-dimethyl-2,5-dioxo-1,2,5,6,7,8-hexahydroquinoline-3-carboxamide as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 495.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 (t, *J* = 6.0 Hz, 1H), 8.79 (s, 1H), 7.40 – 7.29 (m, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 9.1 Hz, 1H), 7.09 (dd, *J* = 9.1, 3.1 Hz, 1H), 6.99 (d, *J* = 3.0 Hz, 1H), 4.54 – 4.38 (m, 2H), 3.72 (s, 3H), 3.67 (s, 3H), 2.59 (d, *J* = 17.8 Hz, 1H), 2.42 (d, *J* = 2.2 Hz, 2H), 2.17 (d, *J* = 17.8 Hz, 1H), 0.96 (s, 3H), 0.90 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{27}H_{28}ClN_2O_5$; 495.1681 found 495.1691. Retention Time = 3.467 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-phenyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (27): This compound was prepared from **Method 10** using aniline in **step 3** to afford N4-(4-((1H-tetrazol-5-yl)methoxy)-3-chlorophenyl)-N6-([1,1'-biphenyl]-4-yl)pyrimidine-4,6-diamine as a TFA salt. LCMS: *m/z* $(M+H)^+$ =461; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (s, 1H), 8.22 (s, 1H), 8.13 – 8.05 (m, 2H), 7.67 – 7.51 (m, 5H), 7.47 – 7.40 (m, 2H), 2.45 (s, 2H), 2.42 (s, 2H), 0.96 (s, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{26}H_{22}ClN_2O_2S$; 461.1085 found 461.1086. Retention Time = 3.853 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-methoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (28): This compound was prepared from **Method 10** using 2-methoxyaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-methoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as

a TFA salt. LCMS: *m/z* $(M+H)^+$ = 491; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.22 (s, 1H), 8.13 – 8.04 (m, 2H), 7.61 – 7.49 (m, 3H), 7.37 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.31 (dd, *J* = 8.5, 1.2 Hz, 1H), 7.17 (td, *J* = 7.6, 1.2 Hz, 1H), 3.77 (s, 3H), 2.61-2.51 (m, 2H), 2.250-2.20 (m, 2H), 0.98 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{27}H_{24}ClN_2O_3S$; 491.1191 found 491.1203. Retention Time = 3.86 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-ethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (29): This compound was prepared from **Method 10** using 2-ethoxyaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-ethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)_+$ = 505.1; $_1$H NMR (400 MHz, DMSO-*d*6) δ 9.04 (s, 1H), 8.20 (s, 1H), 8.07 (d, *J* = 8.7 Hz, 2H), 7.57 – 7.48 (m, 3H), 7.34 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 4.06 (q, *J* = 6.9 Hz, 2H), 2.60 (d, *J* = 17.8 Hz, 1H), 2.50 (d, *J* = 16.2 Hz, 1H), 2.40 (d, *J* = 16.3 Hz, 1H), 2.16 (d, *J* = 17.7 Hz, 1H), 1.11 (t, *J* = 6.9 Hz, 3H), 0.97 (s, 3H), 0.93 (s, 3H); HRMS (ESI) m/z (M+H) + calcd. for C28H26ClN2O3S; 505.1347 found 505.1354. Retention Time = 3.927 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-isopropoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (30): This compound was prepared from **Method 10** using 2-isopropoxyaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-isopropoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 519.2; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.03 (d, *J* = 1.3 Hz, 1H), 8.19 (d, *J* = 1.4 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 2H), 7.56 – 7.46 (m, 3H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 7.12 (t, *J* = 7.0 Hz, 1H), 4.63 (h, *J* = 6.0 Hz, 1H), 2.62 (d, *J* = 17.7 Hz, 1H), 2.50 (d, *J* = 16.1 Hz, 1H), 2.40 (d, *J* = 16.3 Hz, 1H), 2.15 (d, *J* = 17.7 Hz, 1H), 1.13 (d, *J* = 5.9 Hz, 3H), 1.04 (d, *J* = 6.0 Hz, 3H), 0.97 (s, 3H), 0.93 (s, 3H); HRMS (ESI) m/z (M+H) + calcd. for C29H28ClN2O3S; 519.1504 found 519.1492. Retention Time = 4.026 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(o-tolyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (31): This compound was prepared from **Method 10** using o-toluidine in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(o-tolyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 475.1; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.07 (s, 1H), 8.21 (s, 1H), 8.07 (d, *J* = 8.2 Hz, 2H), 7.60 – 7.39 (m, 5H), 7.32 (d, *J* = 7.6 Hz, 1H), 2.56 (d, *J* = 17.8 Hz, 1H), 2.46 (d, *J* = 8.1 Hz, 2H), 2.12 (d, *J* = 17.9 Hz, 1H), 2.00 (s, 3H), 0.97 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H) + calcd. for $C_{27}H_{24}ClN_2O_2S$; 475.1242 found 475.1249. Retention Time = 3.934 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-ethylphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (32): This compound was prepared from **Method 10** using 2-ethylaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-ethylphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 489.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.22 (s, 1H), 8.13 – 8.05 (m, 2H), 7.58 – 7.49 (m, 4H), 7.49 – 7.41 (m, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 2.63 – 2.50 (m, 1H), 2.49 – 2.40 (m, 2H), 2.34 (dd, *J* = 15.1, 7.5 Hz, 1H), 2.32 – 2.19 (m, 1H), 2.14 (d, *J*

= 17.9 Hz, 1H), 1.08 (t, *J* = 7.6 Hz, 3H), 0.98 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H) + calcd. for $C_{28}H_{26}ClN_2O_2S$; 489.1398 found 489.1417. Retention Time = 4.023 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-isopropylphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (33): This compound was prepared from **Method 10** using 2-isopropylaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-isopropylphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 503.1; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.07 (s, 1H), 8.20 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.64 – 7.49 (m, 4H), 7.46 – 7.37 (m, 1H), 7.28 (d, *J* = 7.4 Hz, 1H), 2.63 (d, *J* = 17.9 Hz, 1H), 2.55 – 2.38 (m, 3H), 2.08 (d, *J* = 17.9 Hz, 1H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.97 (s, 3H), 0.92 (s, 3H); HRMS (ESI) m/z (M+H) + calcd. for $C_{29}H_{28}ClN_2O_2S$; 503.1555 found 503.1558. Retention Time = 4.121 min.

1-([1,1'-Biphenyl]-2-yl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (34): This compound was prepared from **Method 10** using [1,1'-biphenyl]-2-amine in **step 3** to afford 1-([1,1'-Biphenyl]-2-yl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 537.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.22 (s, 1H), 8.13 – 7.99 (m, 2H), 7.75 – 7.58 (m, 2H), 7.58 – 7.44 (m, 2H), 7.24 (qq, *J* = 7.1, 3.8, 3.0 Hz, 7H), 2.56 (d, *J* = 18.0 Hz, 1H), 2.40 (s, 1H), 2.18 (d, *J* = 16.2 Hz, 1H), 2.00 (d, *J* = 18.0 Hz, 1H), 0.91 (s, 3H), 0.48 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{32}H_{26}ClN_2O_2S$; 537.139 found 537.1398. Retention Time = 4.037 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-hydroxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (35): This compound was prepared from **Method 10** using 2-aminophenol in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-hydroxyphenyl)-7,7-dimethyl-7,8-dihydro-quinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 477.1; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 10.14 (s, 1H), 9.03 (s, 1H), 8.20 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.33 (m, 1H), 7.24 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.99 (t, *J* = 7.6 Hz, 1H), 2.57 (d, *J* = 17.8 Hz, 1H), 2.45 (s, 2H), 2.29 (d, *J* = 17.7 Hz, 1H), 0.97 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H) + calcd. for $C_{26}H_{22}ClN_2O_3S$; 477.1034 found 477.1046. Retention Time = 3.642 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(2-phenoxyphenyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (36): This compound was prepared from **Method 10** using 2-phenoxyaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(2-phenoxyphenyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 553.1; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 8.99 (s, 1H), 8.20 (s, 1H), 8.05 (d, *J* = 8.3 Hz, 2H), 7.60 – 7.48 (m, 4H), 7.34 (dt, *J* = 18.2, 7.6 Hz, 3H), 7.08 (dt, *J* = 7.6, 3.3 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 2.68 (d, *J* = 17.8 Hz, 1H), 2.53 – 2.35 (m, 3H), 1.01 (s, 3H), 0.89 (s, 3H); HRMS (ESI) m/z (M+H) + calcd. for $C_{32}H_{26}ClN_2O_3S$; 553.1347 found 553.1347. Retention Time = 4.048 min.

1-(2-(Benzyloxy)phenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (37): This compound was

prepared from **Method 10** using 2-(benzyloxy)aniline in **step 3** to afford 1-(2-(benzyloxy)phenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 567.1; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.02 (s, 1H), 8.21 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 2H), 7.58 – 7.49 (m, 3H), 7.43 – 7.34 (m, 2H), 7.19 (dd, *J* = 7.4, 3.7 Hz, 6H), 5.22 – 5.09 (m, 2H), 2.58 (d, *J* = 17.8 Hz, 1H), 2.46 (d, *J* = 16.1 Hz, 1H), 2.35 (d, *J* = 16.2 Hz, 1H), 2.17 (d, *J* = 17.9 Hz, 1H), 0.95 (s, 3H), 0.82 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for C33H28ClN2O3S; 567.1504 found 567.1516. Retention Time = 3.99 min.

1-(2-Aminophenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (38): This compound was prepared from **Method 10**_using benzene-1,2-diamine in **step 3** to afford 1-(2-aminophenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 476.1; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.00 (s, 1H), 8.18 (s, 1H), 8.07 (d, *J* = 8.2 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 7.1 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.66 (t, *J* = 7.5 Hz, 1H), 5.30 (s, 2H), 2.57 (d, *J* = 17.7 Hz, 1H), 2.47 (s, 1H), 2.35 (d, *J* = 16.3 Hz, 1H), 2.25 (d, *J* = 17.7 Hz, 1H), 0.96 (s, 6H); HRMS (ESI) m/z (M+H)+ calcd. for C26H23ClN3O2S; 476.1194 found 476.1207. Retention Time = 3.721 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(2-(methylamino)phenyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (39): This compound was prepared from **Method 10** using N1-methylbenzene-1,2-diamine in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(2-(methylamino)phenyl)-7,8 dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 490.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (d, *J* = 1.5 Hz, 1H), 8.19 (d, *J* = 1.4 Hz, 1H), 8.12 – 8.02 (m, 2H), 7.59 – 7.47 (m, 2H), 7.37 – 7.27 (m, 1H), 7.01 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.80 – 6.64 (m, 2H), 5.51 (q, *J* = 4.7 Hz, 1H), 2.69 – 2.51 (m, 5H), 2.40 – 2.30 (m, 1H), 2.13 (d, *J* = 17.7 Hz, 1H), 0.94 (d, *J* = 7.9 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for C27H25ClN3O2S; 490.1351 found 490.136. Retention Time = 3.845 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-(dimethylamino)phenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (40): This compound was prepared from **Method 10** using N1,N1-dimethylbenzene-1,2-diamine in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-(dimethylamino)phenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 504.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.06 (d, *J* = 1.4 Hz, 1H), 8.21 (d, *J* = 1.5 Hz, 1H), 8.13 – 8.02 (m, 2H), 7.57 – 7.42 (m, 2H), 7.24 (ddd, *J* = 7.7, 5.0, 1.5 Hz, 3H), 7.15 (td, *J* = 7.5, 1.4 Hz, 1H), 2.52 (d, *J* = 1.4 Hz, 7H), 2.44 (s, 1H), 2.33 – 2.26 (m, 2H), 0.94 (d, *J* = 3.8 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{27}ClN_3O_2S$; 504.1507 found 504.1516. Retention Time = 4.019 min.

2-(3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8--tetrahydro-quinolin-1(2H)-yl)benzoic acid (41): This compound was prepared from **Method 10** using 2-aminobenzoic acid in **step 3** to afford 2-(3-(4-(4-chlorophenyl)thiazol-2-

yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)benzoic acid as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 505.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.21 (s, 1H), 9.04 (s, 1H), 8.19 (s, 1H), 8.13 (d, *J* = 7.5 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 2H), 7.80 (s, 1H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 7.6 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.41 – 2.27 (m, 2H), 2.14 (d, *J* = 17.7 Hz, 1H), 0.97 (s, 3H), 0.89 (s, 3H); HRMS (ESI) m/z (M+H) + calcd. for C27H22ClN2O4S; 505.0983 found 505.1001. Retention Time = 3.523 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-fluorophenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (42): This compound was prepared from **Method 10** using 2-fluoroaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-fluorophenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 479.1; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.06 (s, 1H), 8.23 (s, 1H), 8.07 (d, *J* = 8.4 Hz, 2H), 7.71 – 7.49 (m, 5H), 7.49 – 7.42 (m, 1H), 2.61 (d, *J* = 17.8 Hz, 1H), 2.48 (d, *J* = 2.0 Hz, 2H), 2.31 (d, *J* = 17.7 Hz, 1H), 0.99 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H) + calcd. for C26H21ClFN2O2S; 479.0991 found 479.0991. Retention Time = 3.885 min.

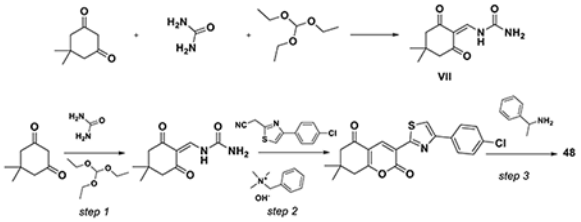
1-(2-Chlorophenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (43): This compound was prepared from **Method 10** using 2-chloroaniline in **step 3** to afford 1-(2-chlorophenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 495.1; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.07 (s, 1H), 8.23 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 2H), 7.83 – 7.76 (m, 1H), 7.63 (dd, *J* = 3.4, 1.9 Hz, 3H), 7.53 (d, *J* = 8.3 Hz, 2H), 2.60 (d, *J* = 17.8 Hz, 1H), 2.47 (s, 2H), 2.12 (d, *J* = 17.8 Hz, 1H), 0.98 (s, 3H), 0.95 (s, 3H); HRMS (ESI) m/z (M+H) + calcd. for $C_{26}H_{21}Cl_2N_2O_2S$; 495.0695 found 495.0716. Retention Time = 3.956 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(2-(trifluoromethyl)phenyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (44): This compound was prepared from **Method 10** using 2-(trifluoromethyl)aniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(2-(trifluoromethyl)phenyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 529.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (d, *J* = 1.5 Hz, 1H), 8.23 (d, *J* = 1.6 Hz, 1H), 8.10 – 8.01 (m, 3H), 7.97 (t, *J* = 7.8 Hz, 1H), 7.84 (t, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.57 – 7.48 (m, 2H), 2.70 – 2.55 (m, 2H), 2.42 – 2.27 (m, 1H), 2.10 (d, *J* = 17.9 Hz, 1H), 0.98 (s, 3H), 0.90 (s, 3H); HRMS (ESI) m/z (M+H) + calcd. for $C_{27}H_{21}ClF_3N_2O_2S$; 529.0959 found 529.0976. Retention Time = 3.936 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(2-(trifluoromethoxy)phenyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (45): This compound was prepared from **Method 10** using 2-(trifluoromethoxy)aniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(2-(trifluoromethoxy)phenyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+Na)^+$ = 545.1; HRMS (ESI) m/z (M+H)+ calcd. for $C_{27}H_{20}ClF_3N_2NaO_3S$; 567.0727 found 567.0755. Retention Time = 3.96 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(pyridin-2-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (46): This compound was prepared from **Method 10**_using pyridin-2-amine in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(pyridin-2-yl)-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 462.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.72 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1H), 8.24 (s, 1H), 8.16 (td, *J* = 7.7, 1.9 Hz, 1H), 8.12 – 8.06 (m, 2H), 7.73 – 7.62 (m, 2H), 7.58 – 7.50 (m, 2H), 2.60 (d, *J* = 17.8 Hz, 1H), 2.47 (s, 2H), 2.12 (d, *J* = 17.8 Hz, 1H), 0.98 (s, 3H), 0.96 (s, 3H); HRMS (ESI) m/z (M+H) + calcd. for $C_{25}H_{21}ClN_3O_2S$; 462.1038 found 462.1057. Retention Time = 3.723 min.

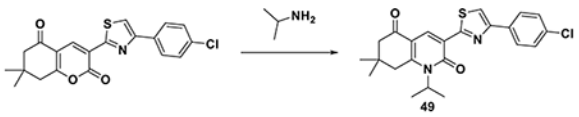
3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-methoxybenzyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (47): This compound was prepared from **Method 10** using (2-methoxyphenyl)methanamine in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-methoxybenzyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 505.1; ^{1}H NMR (400 MHz, DMSO-*d*6) δ 9.03 (s, 1H), 8.20 (s, 1H), 8.07 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 5.39 (s, 2H), 3.88 (s, 3H), 2.85 (s, 2H), 2.46 (d, *J* = 11.6 Hz, 2H), 0.94 (s, 6H); HRMS (ESI) m/z (M+H) + calcd. for C28H26ClN2O3S; 505.1347 found 505.1334. Retention Time = 3.997 min.



3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(1-phenylethyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione (48): *Step 1* **1-((4,4-Dimethyl-2,6-dioxocyclohexylidene)methyl)urea:** To a solution of triethyl *ortho*formate (0.89 mL, 5.35 mmol) and urea (214 mg, 3.57 mmol) in DMF (1.5 mL) was added isopropanol (10 mL). The resulting solution was heated at 80 °C for 2 h and cooled to 0 °C. A white precipitate formed and was removed by filtration (washed with water and hexanes). 1-((4,4-Dimethyl-2,6-dioxocyclohexylidene)methyl)urea was isolated as a white solid (480 mg, 64%); LCMS: *m/z* $(M+H)^+$ = 211.1.

Step 2 **3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-7,8-dihydro-2H-chromene-2,5(6H)-dione:** A mixture of 1-((4,4-dimethyl-2,6-dioxocyclohexylidene)methyl)urea (40 mg, 0.19 mmol), nitrile **1** (54 mg, 0.23 mmol), and a solution of benzyltrimethylammonium hydroxide solution (40% in MeOH, 0.113 mL, 0.285 mmol) in DMF/MeOH (1:1-1 mL) was heated at 140 °C for 1 h 20 min. Upon cooling, the mixture was diluted with water, acidified at 0 °C with 1N HCl, stirred overnight, and filtered to afford a brown solid (3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-7,8-dihydro-2H-chromene-2,5(6H)-dione, 61 mg, 91%); LCMS: *m/z* $(M+H)^+$ = 386.0;

Step 3 **(48):** A solution of 3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-7,8-dihydro-2H-chromene-2,5(6H)-dione (34 mg, 0.088 mmol) and 1-phenylethan-1-amine (20.6 mg, 0.17 mmol) in DMF (1.0 mL) was heated at 150 °C for 2 h. The crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford as a TFA salt 3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-1-(1-phenylethyl)-7,8-dihydroquinoline-2,5(1H,6H)-dione. LCMS: *m/z* $(M+H)^+$ = 489.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.00 (s, 1H), 8.19 (s, 1H), 8.09 – 8.02 (m, 2H), 7.55 – 7.48 (m, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.19 (m, 3H), 3.06 (m, 1H), 2.69 – 2.51 (m, 2H), 2.12 (d, *J* = 17.7 Hz, 2H),1.93 (d, *J* = 6.9 Hz, 3H), 0.95 (s, 3, H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{26}ClN_2O_2S$; 489.1398 found 489.1375. Retention Time = 4.042 min.



3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-isopropyl-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (49): This compound was prepared according to the method used to make compound **48** using isopropylamine in step 3 to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-isopropyl-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 427.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.21 (s, 1H), 8.12 – 8.03 (m, 2H), 7.57 – 7.48 (m, 2H), 4.81 (br s, 1H), 3.08 (s, 2H), 2.45 (s, 2H), 1.60 (d, *J* = 6.7 Hz, 6H), 1.08 (s, 6H); HRMS (ESI) m/z (M+H) + calcd. for $C_{23}H_{24}ClN_2O_2S$; 427.1242 found 427.1242. Retention Time = 3.952 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-cyclohexyl-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (50): This compound was prepared from **Method 10** using cyclohexanamine in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-cyclohexyl-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 467.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.19 (s, 1H), 8.05 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 4.35 – 4.20 (m, 1H), 2.73 – 2.66 (m, 3H), 2.54 – 2.39 (m, 2H), 1.81 (d, *J* = 12.8 Hz, 2H), 1.68 (t, *J* = 14.3 Hz, 3H), 1.43 (d, *J* = 13.2 Hz, 2H), 1.22 (d, *J* = 9.9 Hz, 2H), 1.6 (s, 6H); HRMS (ESI) m/z (M+H) + calcd. for $C_{26}H_{28}ClN_2O_2S$; 467.1555 found 467.1555. Retention Time = 4.193 min.

Methyl 2-(3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)thiophene-3-carboxylate (51): This compound was prepared from **Method 10** using methyl 2-aminothiophene-3-carboxylate in **step 3** to afford methyl 2-(3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)thiophene-3-carboxylate as a TFA salt. LCMS: *m/z* $(M+H)^+$ =525.07; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.02 – 7.95 (m, 2H), 7.61 (d, J = 5.7 Hz, 1H), 7.58 (s, 1H), 7.50 (t, J = 6.0 Hz, 1H), 7.45 – 7.39 (m, 2H), 3.71 (s, 3H), 2.61 – 2.45 (m, 4H), 1.08 (d, J = 9.4 Hz, 6H). Aliphatic region complicated significantly by amide

rotamers; HRMS (ESI) m/z (M+H)+ calcd. for $C_{26}H_{22}ClN_2O_4S_2$; 525.0704 found 525.071. Retention Time = 3.812 min.

2-(3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)thiophene-3-carbonitrile (52): This compound was prepared from **Method 10** using 2-aminothiophene-3-carbonitrile in **step 3** to afford 2-(3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)thiophene-3-carbonitrile as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 492.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.27 (s, 1H), 8.08 (d, *J* = 8.7 Hz, 2H), 8.04 (d, *J* = 5.7 Hz, 1H), 7.65 (d, *J* = 5.7 Hz, 1H), 7.53 (d, *J* = 8.6 Hz, 2H), 2.68 (d, *J* = 17.8 Hz, 2H), 2.51 (m, 2H), 1.02 (s, 3H), 1.00 (s, 3H); HRMS (ESI) m/z (M+H) + calcd. for C25H19ClN3O2S2; 492.0602 found 492.0606. Retention Time = 3.776 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,3-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (53): This compound was prepared from *Method 10* using 2,3-dimethoxyaniline in *step 3* to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,3-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 521.13; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.00 (d, J = 7.8 Hz, 2H), 7.57 (d, J = 0.9 Hz, 1H), 7.42 (d, J = 7.7 Hz, 2H), 7.26 (s, 1H), 7.12 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 7.9 Hz, 1H), 3.97 (d, J = 0.6 Hz, 3H), 3.76 (d, J = 0.9 Hz, 3H), 2.53 – 2.36 (m, 4H), 1.07 (t, J = 9.8 Hz, 6H). Aliphatic region complicated significantly by amide rotamers; HRMS (ESI) m/z (M+H) + calcd. for $C_{28}H_{26}ClN_2O_4S$; 521.1296 found 521.1272. Retention Time = 3.908 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,4-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (54): This compound was prepared from **Method 10** using 2,4-dimethoxyaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,4-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 521.13; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.03 – 7.96 (m, 2H), 7.56 (s, 1H), 7.42 (dd, J = 8.8, 2.2 Hz, 2H), 7.11 (d, J = 9.1 Hz, 1H), 6.70 – 6.64 (m, 2H), 3.90 (s, 3H), 3.78 (s, 3H), 2.55 – 2.45 (m, 3H), 2.34 (d, J = 17.9 Hz, 1H), 1.06 (d, J = 6.4 Hz, 6H). Aliphatic region complicated significantly by amide rotamers; HRMS (ESI) m/z (M+H) + calcd. for $C_{28}H_{26}ClN_2O_2S$; 521.1296 found 521.1308. Retention Time = 3.882 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (55): This compound was prepared from **Method 10** using 2,6-dimethoxyaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 521.13; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.22 (s, 1H), 8.13 – 8.04 (m, 2H), 7.58 – 7.49 (m, 3H), 6.91 (d, *J* = 8.6 Hz, 2H), 3.75 (s, 6H), 2.52 – 2.46 (m, 3H), 2.35 (d, J = 17.9 Hz, 1H), 0.96 (s, 6H); HRMS (ESI) m/z (M+H) + calcd. for $C_{28}H_{26}ClN_2O_4S$; 521.1296 found 521.1318. Retention Time = 3.864 min.

3-(3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)-2-methoxybenzoic acid (56): This

compound was prepared from **Method 10** using 3-amino-2-methoxybenzoic acid in **step 3** to afford 3-(3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)-2-methoxybenzoic acid as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 535.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.33 (s, 1H), 9.08 (s, 1H), 8.24 (s, 1H), 8.13 – 8.04 (m, 2H), 7.93 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.64 (d, *J* = 7.4 Hz, 1H), 7.58 – 7.49 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 1H), 3.62 (s, 3H), 2.57 (d, *J* = 17.8 Hz, 1H), 2.53 (s, 1H), 2.46 – 2.40 (m, 1H), 2.32 (d, *J* = 17.8 Hz, 1H), 0.99 (s, 3H), 0.96 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{24}ClN_2O_5S$; 535.1089 found 535.1078. Retention Time = 3.604 min.

4-(3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)-3-methoxybenzoic acid (57): This compound was prepared from **Method 10** using 4-amino-3-methoxybenzoic acid in **step 3** to afford 4-(3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)-3-methoxybenzoic acid as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 535.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.37 (s, 1H), 9.06 (s, 1H), 8.23 (s, 1H), 8.12 – 8.05 (m, 2H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.53 (dd, *J* = 8.2, 6.3 Hz, 3H), 3.84 (s, 3H), 2.62 – 2.50 (m, 2H), 2.49 – 2.40 (m, 1H), 2.22 (d, *J* = 17.7 Hz, 1H), 0.99 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{24}ClN_2O_5S$; 535.1089 found 535.1099. Retention Time = 3.643 min.

3-(3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)-4-methoxybenzoic acid (58): This compound was prepared from **Method 10** using 3-amino-4-methoxybenzoic acid in **step 3** to afford 3-(3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8, tetrahydroquinolin-1(2H)-yl)-4-methoxybenzoic acid as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 535.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 9.05 (s, 1H), 8.23 (s, 1H), 8.15 (dd, *J* = 8.7, 2.2 Hz, 1H), 8.12 – 8.05 (m, 2H), 7.94 (d, *J* = 2.2 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.41 (d, *J* = 8.8 Hz, 1H), 3.86 (s, 3H), 2.62 (d, *J* = 17.9 Hz, 1H), 2.55 – 2.49 (m, 1H), 2.47 – 2.39 (m, 1H), 2.19 (d, *J* = 17.8 Hz, 1H), 0.99 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{24}ClN_2O_5S$; 535.1089 found 535.1112. Retention Time = 3.596 min.

2-(3-(4-(4-Chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)-3-methoxybenzoic acid (59): This compound was prepared from **Method 10** using 2-amino-3-methoxybenzoic acid in **step 3** to afford 2-(3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-2,5-dioxo-5,6,7,8-tetrahydroquinolin-1(2H)-yl)-3-methoxybenzoic acid as a TFA salt. LCMS: *m/z* $(M+H)^+$ =535.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.19 (s, 1H), 9.05 (s, 1H), 8.21 (s, 1H), 8.12 – 8.04 (m, 2H), 7.76 – 7.65 (m, 2H), 7.61 – 7.50 (m, 3H), 3.81 (s, 3H), 2.58 – 2.49 (m, 2H), 2.37 (d, *J* = 2.8 Hz, 2H), 0.97 (s, 3H), 0.94 (s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{24}ClN_2O_5S$; 535.1089 found 535.1099. Retention Time = 3.547 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-methoxy-6-methylphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (60): This compound was prepared from **Method 10** using 2-methoxy-6-methylaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,3-dimethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a

TFA salt. LCMS: *m/z* $(M+H)^+$ = 505.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 1H), 8.23 (s, 1H), 8.13 – 8.02 (m, 2H), 7.58 – 7.42 (m, 3H), 7.16 – 7.03 (m, 2H), 3.74 (s, 3H), 2.48-2.37 (m, 2H), 2.269m, 2H), 1.99 (s, 3H), 0.96 (s, 3H), 0.95(s, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{26}ClN_2O_3S$; 505.1347 found 505.135. Retention Time = 3.963 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-methoxypyridin-3-yl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (61): This compound was prepared from **Method 10** using 2-methoxypyridin-3-amine in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-methoxypyridin-3-yl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ =492.11; ^{1}H NMR (400 MHz, CD3OD) δ 9.04 (s, 1H), 8.39-8.38 (m, 1H), 8.22 (s, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.91-7.89 (m, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 1H), 3.86 (s, 3H), 3.66-3.53 (m, 1H), 3.47-3.32 (m, 1H), 2.57 (d, J = 20 Hz, 1H), 2.23 (d, J = 20 Hz, 1H), 1.19-0.94 (m, 6H). Aliphatic region complicated significantly by amide rotamers; HRMS (ESI) m/z (M+H) + calcd. for C26H23ClN3O3S; 492.1143 found 492.116. Retention Time = 3.836 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(4-methoxypyridin-3-yl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (62): This compound was prepared from **Method 10** using 4-methoxypyridin-3-amine in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(4-methoxypyridin-3-yl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 492.11; ^{1}H NMR (400 MHz, CD3OD) δ 9.01 (s, 1H), 8.21-8.19 (m, 2H), 8.08-8.06 (m, 2H), 7.88-7.86 (m, 1H), 7.52 (d, J = 8.4 Hz, 2H), 6.48 (d, J = 8.4 Hz, 1H), 3.76 (s, 3H), 3.68-3.64 (m, 1H), 2.77-2.73 (m, 2H), 2.41-2.41 (m, 1H), 1.20-0.96 (m, 6H). Aliphatic region complicated significantly by amide rotamers; HRMS (ESI) m/z (M+H) + calcd. for $C_{26}H_{23}ClN_3O_3S$; 492.1143 found 492.1148. Retention Time = 3.133 min.

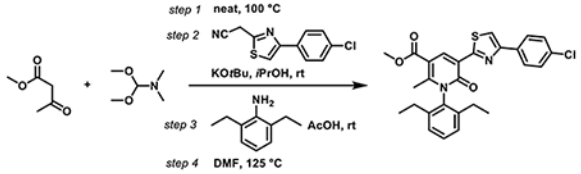
3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,5-diethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (63): This compound was prepared from **Method 10** using 2,5-diethoxyaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,5-diethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 549.16; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.03 – 7.97 (m, 2H), 7.57 (s, 1H), 7.42 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 1.6 Hz, 2H), 6.78 – 6.75 (m, 1H), 4.10 – 3.95 (m, 4H), 2.50 (d, J = 18.4 Hz, 3H), 2.36 (d, J = 18.0 Hz, 1H), 1.42 (t, J = 7.0 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H), 1.07 (t, J = 7.3 Hz, 6H). Aliphatic region complicated significantly by amide rotamers; HRMS (ESI) m/z (M+H) + calcd. for $C_{30}H_{30}ClN_2O_4S$; 549.1603 found 549.1609. Retention Time = 4.023 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (64): This compound was prepared from **Method 10** using 2,6-diethoxyaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethoxyphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 549.16; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.03 – 7.97 (m, 2H), 7.56 (s, 1H), 7.45 – 7.34 (m, 3H), 6.70 (dd, J = 8.5, 3.8 Hz, 2H), 4.06 (hd, J = 9.8, 7.2 Hz, 4H), 2.49 (s, 2H), 2.40 (s, 2H), 1.22 (t, J = 7.0 Hz, 6H), 1.07 (d, J = 11.2

Hz, 6H). Aliphatic region complicated significantly by amide rotamers; HRMS (ESI) m/z (M+H)+ calcd. for $C_{30}H_{30}ClN_2O_4S$; 549.161 found 549.1609. Retention Time = 4.023 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-ethyl-6-methylphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (65): This compound was prepared from **Method 10** using 2-ethyl-6-methylaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-ethyl-6-methylphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 503.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.10 (s, 1H), 8.22 (s, 1H), 8.08 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 2H), 2.50 (d, *J* = 2.8 Hz, 2H), 2.32 (d, *J* = 14.0 Hz, 3H), 2.21 – 2.10 (m, 1H), 1.96 (s, 3H), 1.16 – 1.01 (m, 3H), 0.95 (s, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{29}H_{28}ClN_2O_2S$; 503.1555 found 503.1562. Retention Time = 4.101 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione (66): This compound was prepared from **Method 10** using 2-(4-(4-chlorophenyl)thiazol-2-yl)acetonitrile in **step 2** and 2,6-diethylaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-7,7-dimethyl-7,8-dihydroquinoline-2,5(1H,6H)-dione as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 517.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.11 (s, 1H), 8.23 (s, 1H), 8.12 – 8.05 (m, 2H), 7.59 – 7.47 (m, 3H), 7.38 (d, *J* = 7.7 Hz, 2H), 2.51 (s, 2H), 2.40 – 2.26 (m, 4H), 2.16 (dq, *J* = 15.0, 7.5 Hz, 2H), 1.07 (t, *J* = 7.5 Hz, 6H), 0.95 (s, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{30}H_{30}ClN_2O_2S$; 517.1711 found 517.1699. Retention Time = 4.187 min.



Method 11:

Methyl 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (67): *Step 1:* In a vial, methyl 3-oxobutanoate (0.385 mL, 3.57 mmol) and DMF-DMA (0.474 mL, 3.57 mmol) were mixed and heated neat at 100 °C for 15 min. The reaction mixture became a red oil.

Step 2: To the mixture was added *i*-PrOH (40 mL), 2-(4-(4-chlorophenyl)thiazol-2-yl)acetonitrile **N1**/**IVa** (837 mg, 3.57 mmol), and potassium tert-butoxide (400 mg, 3.57 mmol). The reaction was allowed to stir at rt for 2 h at which point the solvent was removed.

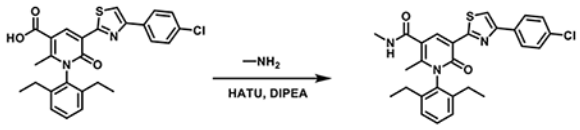
Step 3: To the resulting residue were added acetic acid (30 mL) and 2,6-dimethylaniline (646 μL, 3.9 mmol). The reaction stirred for 15 min and the mixture was diluted with water, extracted (EtOAc x 2). The organic layers were combined (not dried with magnesium sulfate) and concentrated.

Step 4: The residue was taken up in DMF (40 mL) and heated at 125 °C for 1.5 h. The reaction mixture was diluted with water and EtOAc, extracted (2x), the organic layers were

combined, dried with Na_2SO_4, and concentrated. The crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford as a TFA salt, methyl 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (1.05 g, 60%); LCMS: *m/z* $(M+H)^+$ = 493.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 (s, 1H), 8.22 (s, 1H), 8.12 – 8.03 (m, 2H), 7.59 – 7.44 (m, 3H), 7.36 (d, *J* = 7.7 Hz, 2H), 3.89 (s, 3H), 3.31 (s, 7H), 2.61 – 2.50 (m, 1H), 2.47 – 2.34 (m, 3H), 2.33 – 2.07 (m, 8H), 1.05 (t, *J* = 7.5 Hz, 6H), 1.00 (t, *J* = 7.6 Hz, 0H), 0.82 (s, 1H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{27}H_{26}ClN_2O_3S$; 493.1347 found 493.1338. Retention Time = 4.247 min.

5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid (68): To a solution of methyl 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylate (1.0 g, 2.03 mmol, **compound 67**) in THF (10 ml) and MeOH (10 ml) was added lithium hydroxide (0.168 g, 14.22 mmol) and the mixture became yellow. Stirred 1 h at 70 °C. Concentrated with a stream of air and dilute with DCM. Adjusted pH of aqueous layer to pH 7 using 1N HCl, extracted 2 x 25 mL DCM, dry organic layers Na_2SO_4, and concentrated. The crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid; LCMS: *m/z* $(M+H)^+$ = 478.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.33 (s, 1H), 9.17 (s, 1H), 8.19 (s, 1H), 8.11 – 8.02 (m, 2H), 7.57 – 7.42 (m, 3H), 7.35 (d, *J* = 7.7 Hz, 2H), 2.34 – 2.19 (m, 5H), 2.14 (dq, *J* = 15.1, 7.5 Hz, 2H), 1.04 (t, *J* = 7.6 Hz, 6H); HRMS (ESI) m/z (M+H) + calcd. for $C_{26}H_{24}ClN_2O_3S$; 479.1191 found 479.1186. Retention Time = 3.835 min.

Ethyl 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-oxo-2-phenyl-1,6-dihydro-pyridine-3-carboxylate (): This compound was prepared from **Method 11** using ethyl 3-oxo-3-phenylpropanoate in **step 1** to afford ethyl 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-oxo-2-phenyl-1,6-dihydropyridine-3-carboxylate. LCMS: *m/z* $(M+H)^+$ = 569.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.28 (s, 1H), 8.15 – 8.02 (m, 2H), 7.62 – 7.46 (m, 2H), 7.26 – 7.01 (m, 8H), 3.91 (q, *J* = 7.1 Hz, 2H), 2.60 – 2.48 (m, 1H), 2.47 – 2.15 (m, 6H), 1.04 (t, *J* = 7.5 Hz, 6H), 0.78 (t, *J* = 7.1 Hz, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{33}H_{30}ClN_2O_3S$; 569.166 found 569.1643. Retention Time = 4.366 min.



Method 12:

5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-N,2-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (70): To a solution of 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxylic acid, **compound 68**, (250 mg, 0.522 mmol) in DMF (Volume: 5

ml) was added 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (397 mg, 1.044 mmol) and N-ethyl-N-isopropylpropan-2-amine (365 µl, 2.088 mmol) and methanamine (1044 µl, 2.088 mmol) mixture became yellow the reaction mixture was stirred for 6 hrs at 60 °C and dilute with water and extract with 3 x 10 mL DCM, washed with brine. The organic layer was dried and concentrated. The crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-N,2-dimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide; LCMS: *m/z* $(M+H)^+$ = 492.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (s, 1H), 8.54 (d, *J* = 4.7 Hz, 1H), 8.18 (s, 1H), 8.13 – 8.05 (m, 2H), 7.56 – 7.48 (m, 2H), 7.46 (dd, *J* = 8.3, 7.1 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 2H), 2.96 (s, 1H), 2.78 (d, *J* = 4.5 Hz, 3H), 2.27 (dt, *J* = 15.2, 7.6 Hz, 2H), 2.14 (dq, *J* = 15.1, 7.5 Hz, 2H), 2.01 (s, 3H), 1.05 (t, *J* = 7.6 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{27}H_{27}ClN_3O_2S$; 492.1507 found 492.1506. Retention Time = 3.75 min.

5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-N,N,2-trimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide (71): This compound was prepared from **Method 12** using dimethylamine to afford 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-N,N,2-trimethyl-6-oxo-1,6-dihydropyridine-3-carboxamide. LCMS: *m/z* $(M+H)^+$ = 506.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.19 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 2H), 7.56 −7.47 (m, 2H), 7.49 – 7.41 (m, 1H), 7.35 (s, 1H), 7.33 (s, 1H), 3.01 (s, 3H), 2.96 (s, 3H), 2.29 (dq, *J* = 15.2, 7.6 Hz, 2H), 2.16 (dq, *J* = 15.0, 7.5 Hz, 2H), 1.84 (s, 3H), 1.06 (t, J = 7.6 Hz, 6H); HRMS (ESI) m/z (M+H) + calcd. for $C_{28}H_{29}ClN_3O_2S$; 506.1664 found 506.1659. Retention Time = 3.819 min.

5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-N-isopropyl-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (72): This compound was prepared from **Method 12** using propan-2-amine to afford 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-N-isopropyl-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide. LCMS: *m/z* $(M+H)^+$ = 520.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.49 (d, *J* = 7.5 Hz, 1H), 8.20 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.48 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.37 (s, 1H), 7.35 (s, 1H), 4.06 (dq, *J* = 13.4, 6.7 Hz, 1H), 2.32 (dq, *J* = 15.2, 7.6 Hz, 2H), 2.18 (dq, *J* = 15.1, 7.5 Hz, 2H), 2.00 (s, 3H), 1.20 (d, *J* = 6.6 Hz, 6H), 1.08 (t, J = 7.5 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{29}H_{31}ClN_3O_2S$; 520.182 found 520.1817. Retention Time = 3.916 min.

N-(*tert*-Butyl)-5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (73): This compound was prepared from *Method 12* using 2-methylpropan-2-amine to afford N-(tert-butyl)-5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide. LCMS: *m/z* $(M+H)^+$ = 534.1; *1*H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.49 (d, *J* = 7.5 Hz, 1H), 8.20 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.48 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.37 (s, 1H), 7.35 (s, 1H), 4.06 (dq, *J* = 13.4, 6.7 Hz, 1H), 2.32 (dq, *J* = 15.2, 7.6 Hz, 2H), 2.18 (dq, *J* = 15.1, 7.5 Hz, 2H), 2.00 (s, 3H), 1.20 (d, *J* = 6.6 Hz, 6H), 1.08 (t, *J* = 7.5 Hz, 6H); HRMS (ESI) m/z (M+H) + calcd. for $C_{30}H_{33}ClN_3O_2S$; 534.1977 found 534.1983. Retention Time = 4.032 min.

5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-N-isobutyl-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (74): This compound was prepared from **Method 12** using 2-methylpropan-1-amine to afford 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-N-isobutyl-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide. LCMS: *m/z* $(M+H)^+$ = 534.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.61 (t, *J* = 5.8 Hz, 1H), 8.18 (d, *J* = 0.6 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.46 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.35 (s, 1H), 7.33 (s, 1H), 3.08 (dd, *J* = 6.8, 5.8 Hz, 2H), 2.29 (dq, *J* = 15.2, 7.6 Hz, 2H), 2.15 (dq, *J* = 15.1, 7.5 Hz, 2H), 2.00 (s, 3H), 1.83 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.6 (t, *J* = 7.5 Hz, 6H), 0.91 (d, *J* = 6.6 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for C30H33ClN3O2S; 534.1977 found 534.1974. Retention Time = 4.012 min.

5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-N-(2-hydroxyethyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (75): This compound was prepared from *Method 12* using 2-aminoethan-1-ol to afford 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-N-(2-hydroxyethyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide. LCMS: *m/z* $(M+H)^+$ = 522.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.61 (t, *J* = 5.6 Hz, 1H), 8.18 (d, *J* = 0.6 Hz, 1H), 8.15 - 8.00 (m, 2H), 7.56 – 7.48 (m, 2H), 7.46 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.35 (s, 1H), 7.33 (s, 1H), 3.53 (t, *J* = 6.1 Hz, 2H), 3.35 – 3.30 (m, 2H), 3.14 (s, 1H), 2.29 (dd, J = 15.1, 7.6 Hz, 2H), 2.15 (dq, *J* = 15.1, 7.5 Hz, 2H), 2.00 (s, 3H), 1.08 – 1.2 (m, 6H); HRMS (ESI) m/z (M+H) + calcd. for C28H29C1N3O3S; 522.1613 found 522.1627. Retention Time = 3.505 min.

5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-N-(2-methoxyethyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (76): This compound was prepared from *Method 12* using 2-methoxyethan-1-amine to afford 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-N-(2-methoxyethyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide. LCMS: *m/z* $(M+H)^+$ = 536.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (d, *J* = 4.7 Hz, 2H), 8.21 (s, 1H), 8.11 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.48 (dd, *J* = 8.2, 7.1 Hz, 1H), 7.37 (s, 1H), 7.35 (s, 1H), 3.50 (td, *J* = 5.4, 1.3 Hz, 2H), 3.47 – 3.39 (m, 2H), 3.31 (s, 3H), 2.39 – 2.26 (m, 2H), 2.18 (dq, *J* = 15.1, 7.5 Hz, 2H), 2.02 (s, 3H), 1.08 (t, *J* = 7.5 Hz, 6H); HRMS (ESI) m/z (M+H) + calcd. for $C_{29}H_{31}ClN_3O_3S$; 536.1769 found 536.1774. Retention Time = 3.789 min.

(5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl)glycine (77): *Step 1*: Followed *Method 12* using methyl glycinate.

Step 2: To a solution of the crude acid from step 1 in 1:1 THF/MeOH (~0.3 mM) was added lithium hydroxide (~10 eq) and stirred 1 h at 70 °C. Concentrated with a stream of air and dilute with DCM. Adjusted pH of aqueous layer to pH 7 using 1N HCl, extracted 2 x DCM, dry organic layers Na_2SO_4, and concentrated. The crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford compound *77*. LCMS: *m/z* $(M+H)^+$ = 536.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.69 (s, 1H), 9.00 (t, *J* = 5.9 Hz, 1H), 8.77 (s, 1H), 8.21 (d, *J* = 0.6 Hz, 1H), 8.14 – 8.07 (m, 2H), 7.57 – 7.52 (m, 2H), 7.49 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 2H), 3.96 (d, *J* = 5.9 Hz, 2H), 2.32 (dq, *J* = 15.2, 7.6 Hz, 2H), 2.18 (dq, *J* = 15.1, 7.5 Hz, 2H), 2.08 (s, 3H), 1.08

(td, *J* = 7.6, 0.6 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{27}ClN_3O_4S$; 536.1405 found 536.1417. Retention Time = 3.491 min.

N-(2-Aminoethyl)-5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (78): This compound was prepared from *Method 12* using ethane-1,2-diamine to afford N-(2-aminoethyl)-5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 521.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.77 (t, *J* = 5.6 Hz, 1H), 8.23 (d, *J* = 0.6 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 7.81 (s, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.53 – 7.45 (m, 1H), 7.38 (s, 1H), 7.36 (s, 1H), 3.51 (q, *J* = 6.1 Hz, 2H), 3.4 (q, *J* = 5.9 Hz, 2H), 2.31 (dd, J = 15.2, 7.5 Hz, 2H), 2.17 (dq, *J* = 15.1, 7.5 Hz, 2H), 2.08 (s, 3H), 1.13 – 1.04 (m, 6H); HRMS (ESI) m/z (M+H) + calcd. for $C_{28}H_{30}ClN_4O_2S$; 517.1711 found 521.1773. Retention Time = 2.669 min.

5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-N-(2-(methylamino)-ethyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (79): This compound was prepared from *Method 12* using *tert*-butyl (2-aminoethyl)(methyl)carbamate to afford tert-butyl (2-(5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydro-pyridine-3-carboxamido)ethyl)(methyl)carbamate followed by Boc deprotection using TFA in DCM to afford 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-N-(2-(methylamino)ethyl)-6-oxo-1,6-dihydropyridine-3-carboxamide as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 535.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.83 (t, *J* = 5.7 Hz, 1H), 8.44 (s, 1H), 8.23 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.54 – 7.45 (m, 1H), 7.39 (s, 1H), 7.37 (s, 1H), 3.55 (q, *J* = 6.0 Hz, 2H), 3.14 (s, 2H), 2.70 – 2.63 (m, 3H), 2.31 (dq, *J* = 15.2, 7.6 Hz, 2H), 2.17 (dq, *J* = 15.1, 7.5 Hz, 2H), 2.09 (s, 3H), 1.08 (t, *J* = 7.5 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{29}H_{32}ClN_4O_2S$; 535.1929 found 535.1938. Retention Time = 2.712 min.

N-(2-Amino-2-oxoethyl)-5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (80): This compound was prepared from *Method 12* using 2-aminoacetamide to afford N-(2-amino-2-oxoethyl)-5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide. LCMS: *m/z* $(M+H)^+$ = 535.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (d, *J* = 7.6Hz, 2H), 8.21 (s, 1H), 8.11 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.36 (d, J = 7.7 Hz, 2H), 7.06 (s, 2H), 3.84 (d, *J* = 5.8 Hz, 2H), 2.32 (dq, *J* = 15.2, 7.6 Hz, 2H), 2.18 (dq, *J* = 15.2, 7.5 Hz, 2H), 2.08 (s, 3H), 1.08 (t, *J* = 7.5 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{28}H_{28}ClN_4O_3S$; 535.1565 found 535.155. Retention Time = 3.378 min.

5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-N-(3-(methylamino)propyl)-6-oxo-1,6-dihydropyridine-3-carboxamide (81): This compound was prepared from *Method 12* using tert-butyl (3-aminopropyl)(methyl)carbamate followed by boc deprotection using TFA in DCM to afford 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-N-(3-(methylamino)propyl)-6-oxo-1,6-dihydropyridine-3-carboxamide as

a TFA salt. LCMS: *m/z* $(M+H)^+$ = 549.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (d, *J* = 2.8 Hz, 2H), 8.34 (s, 1H), 8.23 (s, 1H), 8.11 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.38 (s, 1H), 7.36 (s, 1H), 3.34 (q, *J* = 6.5, 6.1Hz, 2H), 2.99 (p, J = 6.6 Hz, 2H), 2.60 (t, J= 5.4 Hz, 3H), 2.31 (dq, *J* = 15.2, 7.6 Hz, 2H), 2.17 (dq, *J* = 15.1, 7.5 Hz, 2H), 2.05 (s, 3H), 1.86 (p, *J* = 7.0 Hz, 2H), 1.08 (t, *J* = 7.5 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{30}H_{33}ClN_4NaO_2S$; 571.1905 found 571.1919. Retention Time = 2.708 min.

5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide (82): This compound was prepared from *Method 12* using aniline to afford 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-N-phenyl-1,6-dihydropyridine-3-carboxamide. LCMS: *m/z* $(M+H)^+$ = 554.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (s, 1H), 8.88 (s, 1H), 8.23 (s, 1H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 7.9 Hz, 2H), 7.57 – 7.45 (m, 3H), 7.43 – 7.32 (m, 4H), 7.18 – 7.09 (m, 1H), 2.42 – 2.28 (m, 2H), 2.21 (dq, *J* = 15.1, 7.5 Hz, 2H), 2.09 (s, 3H), 1.10 (t, *J* = 7.5 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{32}H_{29}ClN_3O_2S$; 554.1664 found 554.1682. Retention Time = 4.043 min.

***N*-Benzyl-5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (83):** This compound was prepared from *Method 12* using phenylmethanamine to afford N-benzyl-5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide. LCMS: *m/z* $(M+H)^+$ = 567.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (t, *J* = 5.9 Hz, 1H), 8.77 (s, 1H), 8.18 (s, 1H), 8.12 – 8.04 (m, 2H), 7.57 – 7.41 (m, 3H), 7.41 – 7.21 (m, 7H), 4.48 (d, *J* = 5.9 Hz, 2H), 2.22 (ddq, *J* = 56.8, 15.1, 7.5 Hz, 4H), 2.02 (s, 3H), 1.05 (t, *J* = 7.5 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{33}H_{31}ClN_3O_2S$; 568.182 found 568.1842. Retention Time = 3.966 min.

5-(4-(4-Chlorophenyl)thiazol-2-yl)-N-cyclohexyl-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (84): This compound was prepared from *Method 12* using cyclohexanamine to afford 5-(4-(4-chlorophenyl)thiazol-2-yl)-N-cyclohexyl-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide. LCMS: *m/z* $(M+H)^+$ = 567.7; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (s, 1H), 8.46 (d, *J* = 7.7 Hz, 1H), 8.17 (s, 1H), 8.11 – 8.04 (m, 2H), 7.56 – 7.41 (m, 3H), 7.33 (d, *J* = 7.7 Hz, 2H), 3.72 (dd, *J* = 7.4, 3.6 Hz, 0H), 2.30 (dq, *J* = 15.2, 7.6 Hz, 2H), 2.15 (dq, *J* = 15.1, 7.5 Hz, 2H), 1.97 (s, 3H), 1.88 (d, *J* = 9.6 Hz, 2H), 1.71 (s, 2H), 1.58 (d, *J* = 13.0 Hz, 1H), 1.35 – 1.22 (m, 4H), 1.05 (t, *J* = 7.5 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{32}H_{35}ClN_3O_2S$; 560.2133 found 560.2134. Retention Time = 4.151 min.

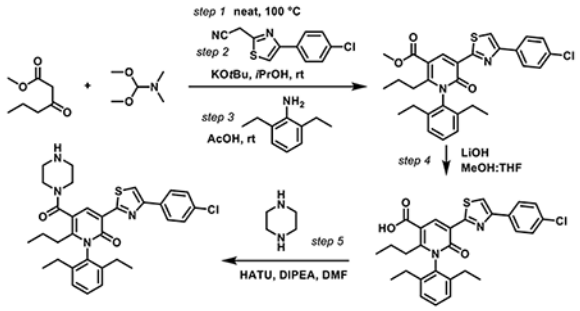
3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-methyl-5-(piperidine-1-carbonyl)pyridin-2(1H)-one (85): This compound was prepared from *Method 12* using piperidine to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-methyl-5-(piperidine-1-carbonyl)pyridin-2(1H)-one. LCMS: *m/z* $(M+H)^+$ = 546.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (d, *J* = 0.8 Hz, 1H), 8.22 (d, *J* = 0.9 Hz, 1H), 8.17 – 8.06 (m, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.51 −7.46 (m, 1H), 7.38 (s, 1H), 7.36 (s, 1H), 3.65 (s, 2H), 3.45 (s, 4H), 2.39 – 2.15 (m,

4H), 1.88 (d, *J* = 0.8 Hz, 3H), 1.63 (s, 4H), 1.12 – 1.05 (m, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{31}H_{33}ClN_3O_2S$; 546.1977 found 546.1998. Retention Time = 4.064 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-methyl-5-(morpholine-4-carbonyl)pyridin-2(1H)-one (86): This compound was prepared from *Method 12* using morpholine to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-methyl-5-(morpholine-4-carbonyl)pyridin-2(1H)-one. LCMS: *m/z* $(M+H)^+$ = 548.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.19 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 7.48 – 7.43 (m, 1H), 7.35 (s, 1H), 7.33 (s, 1H), 3.62 (m, 8H), 2.36 – 2.12 (m, 4H), 1.86 (d, *J* = 1.6 Hz, 3H), 1.11 – 1.01 (m, 6H); HRMS (ESI) m/z (M+Na)+ calcd. for $C_{30}H_{30}ClN_3NaO_3S$; 570.1589 found 570.1605. Retention Time = 3.787 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-methyl-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (87): This compound was prepared from *Method 12* using piperazine to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-methyl-5-(piperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 547.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.19 (s, 1H), 8.16 – 8.03 (m, 2H), 7.57 – 7.36 (m, 3H), 7.34 (d, *J* = 7.7 Hz, 2H), 3.57 (s, 2H), 3.28 (s, 4H), 2.70 (d, *J* = 14.8 Hz, 1H), 2.52 (p, *J* = 1.9 Hz, 0H), 2.26 (dt, *J* = 15.2, 7.4 Hz, 2H), 2.17 (s, 3H), 1.85 (s, 3H), 1.06 (t, *J* = 7.5 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{30}H_{32}ClN_4O_2S$; 547.1929 found 547.1942. Retention Time = 2.691 min.

N-Benzyl-5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (88): This compound was prepared from *Method 12* using 1-methylpiperazine to afford N-benzyl-5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 561.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.23 (s, 1H), 8.12 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.52 – 7.47 (m, 1H), 7.38 (s, 1H), 7.37 (s, 1H), 3.42 (m, 8H), 2.84 (s, 3H), 2.39 −3.15 (m, 4H), 1.90 (s, 3H), 1.09 (t, *J* = 7.5 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{31}H_{34}ClN_4O_2S$; 561.2086 found 561.2076. Retention Time = 2.74 min.



Method 13:

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(piperazine-1-carbonyl)-6-propylpyridin-2(1H)-one (89): *Steps 1-3:* A mixture of ethyl 3-oxohexanoate (0.674 g, 4.26 mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine (0.566 ml, 4.26 mmol)

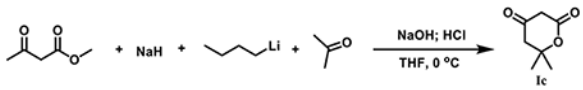
was stirred for 1 h at 100 °C. The mixture was diluted with IPA (10 ml). Added 2-(4-(4-chlorophenyl)thiazol-2-yl)acetonitrile (1.00 g, 4.26 mmol) and K^{t}OBu (0.478 g, 4.26 mmol) and stirred at 50 °C for 3 hrs. The solvent was removed. To the residue was added 2,6-diethylaniline (0.772 ml, 4.69 mmol) and AcOH (6.10 ml, 107 mmol), sonicated to a homogeneous mixture. The reaction mixture was stirred at 70°C for 4 hrs, cooled to room temperature, diluted with EtOAc and washed with water. The organic layer was dried, concentrated and purified by column chromatography to afford ethyl 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-oxo-2-propyl-1,6-dihydro-pyridine-3-carboxylate; LCMS: *m/z* (M+H)+ = 535.3.

Step 4-5: To a solution of ethyl 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-oxo-2-propyl-1,6-dihydropyridine-3-carboxylate (1.5 g, 2.8 mmol) in THF (10 ml) and MeOH (10 ml) was added lithium hydroxide (0.470 g, 19.6 mmol). The reaction mixture was stirred at 60 °C for 3 hrs. The solvent was removed by rotovap, diluted with DCM, quenched with 1N HCl and washed with brine (2 x 50 mL), dried over $MgSO_4$ and concentrated to afford the 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-oxo-2-propyl-1,6-dihydropyridine-3-carboxylic acid; LCMS: *m/z* $(M+H)^+$ = 507.0. Without further purification, to the crude acid (1.00 g, 1.97 mmol) was added 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (1.125 g, 2.96 mmol), DMF (5 ml), N-ethyl-N-isopropylpropan-2-amine (0.689 ml, 3.94 mmol) and piperazine (0.255 g, 2.96 mmol) (mixture became yellow). The reaction was stirred for 1 hr at rt, diluted with water, extracted with 3 x 10 mL DCM, washed with brine. The organic layer was dried and concentrated. The crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford as a TFA salt, 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(piperazine-1-carbonyl)-6-propylpyridin-2(1H)-one; LCMS: *m/z* $(M+H)^+$ = 575.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.54 (d, *J* = 2.1 Hz, 1H), 8.18 (d, *J* = 2.0 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 2H), 7.49 (dd, *J* = 16.9, 7.7 Hz, 4H), 7.34 (d, *J* = 7.9 Hz, 2H), 3.63 (s, 1H), 3.55 (s, 1H), 3.28 (d, *J* = 4.1 Hz, 2H), 3.28 (s, 4H), 2.81 (s, 1H), 2.70 (s, 5H), 2.61 (s, 1H), 2.29 (dt, *J* = 15.3, 7.3 Hz, 4H), 2.14 (s, 4H), 1.27 (s, 2H), 1.07 (t, *J* = 7.4 Hz, 8H), 0.60 (t, *J* = 7.1 Hz, 4H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{32}H_{36}ClN_4O_2S$; 575.2242 found 575.2223. Retention Time = 2.804 min.

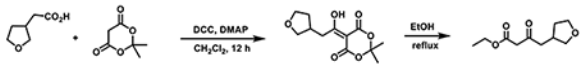
3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-isopropyl-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (90): This compound was prepared via *Method 13* using methyl 4-methyl-3-oxopentanoate in *step 1* to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-isopropyl-5-(piperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 575.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (s, 1H), 8.68 (s, 1H), 8.23 (d, *J* = 0.6 Hz, 1H), 8.19 −8.10 (m, 2H), 7.59 – 7.51 (m, 2H), 7.49 (t, *J* = 7.7 Hz, 1H), 7.37 (dd, *J* = 7.6, 4.5 Hz, 2H), 4.08 (d, *J* = 14.1 Hz, 1H), 3.78 (d, *J* = 14.7 Hz, 1H), 3.73 – 3.61 (m, 1H), 3.60 – 3.48 (m, 1H), 3.49 – 3.38 (m, 1H), 3.26 – 3.13 (m, 1H), 3.10 (d, *J* = 6.0 Hz, 1H), 2.43 – 2.29 (m, 2H), 2.25 (td, *J* = 15.0, 7.5 Hz, 1H), 2.11 (dd, *J* = 14.9, 7.4 Hz, 1H), 1.10 (q, J = 7.1 Hz, 14H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{32}H_{36}ClN_4O_2S$; 575.2242 found 575.2225. Retention Time = 2.79 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-isobutyl-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (91): This compound was prepared via *Method 13* using methyl 5-methyl-3-oxohexanoate in **step 1** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-isobutyl-5-(piperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 589.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.73 (d, *J* = 0.7 Hz, 1H), 8.24 (d, *J* = 0.7 Hz, 1H), 8.18 - 8.10 (m, 2H), 7.59 – 7.52 (m, 2H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 4.06 (s, 1H), 3.81 (s, 1H), 3.64 (m, 2H), 3.16 (m, 5H), 2.45 – 1.91 (m, 3H), 1.34 (dq, J = 13.5, 6.7 Hz, 1H), 1.10 (d, *J* = 7.9 Hz, 8H), 0.63 (d, *J* = 6.5 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{33}H_{38}ClN_4O_2S$; 589.2399 found 589.2381. Retention Time = 1.982 min.

Synthesis of Intermediates

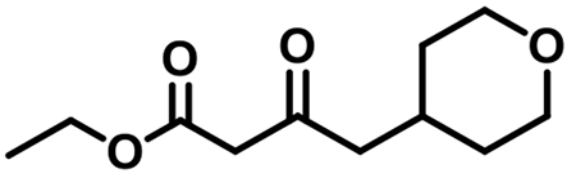


6,6-Dimethyldihydro-2H-pyran-2,4(3H)-dione (Ic): To NaH (1.92 g, 80 mmol) in anhydrous THF (200 mL) was added, at 0 °C methyl acetoacetate (9.28 g, 80 mmol) dropwise. After 10 min. of stirring *n*-BuLi (32 mL, 2.5M solution in hexanes, 80 mmol) was added dropwise, and the orange solution was stirred at 0 °C for 10 more min. Dry acetone (7.5 mL, 82 mmol) was added at once, and the mixture was stirred for 10 min. at 0 °C. NaOH (80 mL, 2.5M solution in water) was then added, and the mixture was stirred for 12 h at room temperature, whereupon it was acidified (2.5M HCl solution) and extracted with ether (3x200 mL). The organic layer was washed with brine and dried with Na_2SO_4. After filtration, the solvent was evaporated with rotovap. The residue was dissolved in a minimum of CH_2Cl_2, and precipitated with pentane as brownish solid, yield (62%) m.p. 126-127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.48 (s, 6H); 2.66 (s, 2H); 3.40 (s, 2H).

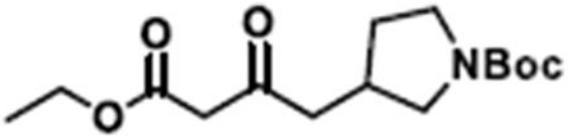


Method D:

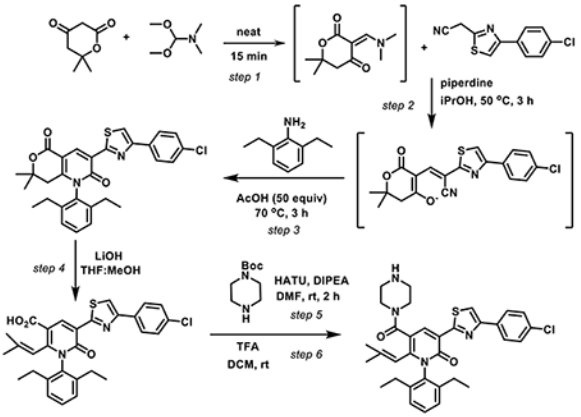
Ethyl 3-oxo-4-(tetrahydrofuran-3-yl)butanoate: To a solution of 2-(tetrahydrofuran-3-yl)acetic acid (1.00 g , 7.68 mmol) in DCM (10 ml), was added DMAP (1.408 g, 11.53 mmol) and DCC (2.378 g, 11.53 mmol) and then 2,2-dimethyl-1,3-dioxane-4,6-dione (1.107 g, 7.68 mmol) was added and the mixture was stirred for 12 h at room temperature. The insoluble urea was then removed by filtration over Celite, and the solvent was evaporated under reduced pressure. The crude product was re-dissolved in ethyl acetate and washed with 1 M HCl. The organic phase was dried over Na_2SO_4, filtered and evaporated. The crude product was used without further purification. The crude product was dissolved in Ethanol (20 mL) and refluxed for 6 hrs. The organic solvent was evaporated under reduced pressure and purified by column chromatography to afford ethyl 3-oxo-4-(tetrahydrofuran-3-yl) butanoate.



Ethyl 3-oxo-4-(tetrahydro-2H-pyran-4-yl)butanoate: This compound was prepared from **Method 14**using 2-(tetrahydro-2H-pyran-4-yl)acetic acid to afford ethyl 3-oxo-4-(tetrahydro-2H-pyran-4-yl)butanoate.



***tert*-Butyl 3-(4-ethoxy-2,4-dioxobutyl)pyrrolidine-1-carboxylate:** This compound was prepared from **Method 14**using 2-(1-(tert-butoxycarbonyl)pyrrolidin-3-yl)acetic acid to afford tert-butyl 3-(4-ethoxy-2,4-dioxobutyl)pyrrolidine-1-carboxylate.



Method 15:

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (92): *Steps 1-3:* A mixture of 6,6-dimethyldihydro-2H-pyran-2,4(3H)-dione (3.03 g, 21.30 mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine (2.83 ml, 21.30 mmol) was stirred for 15 min at room temperature. The reaction mixture became a yellow solid. To the mixture was added with 2-propanol (50 mL), 2-(4-(4-chlorophenyl)thiazol-2-yl)acetonitrile (5.00 g, 21.3 mmol) and piperidine (8.4 ml, 85 mmol) and then sonicated to get a homogeneous mixture. The mixture was stirred at 70 °C for 4 h. The solvent was removed by rotovap. To the residue was added 2,6-diethylaniline (3.86 ml, 23.4 mmol) and acetic acid (61.00 ml, 1065 mmol) and the reaction mixture was sonicated to dissolve solids. The mixture was stirred at 70 °C for 4 h and cooled to room temperature and diluted with DCM and washed with water, sat $NaHCO_3$ solution and brine solution. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (10:90

EA/Hex to 100% EA) to afford the product, 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-7,7-dimethyl-7,8-dihydro-2H-pyrano[4,3-b]pyridine-2,5(1H)-dione; LCMS: *m/z* $(M+H)^+$ = 520.2.

Step 4: To a solution of 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-7,7-dimethyl-7,8-dihydro-1H-pyrano[4,3-b]pyridine-2,5-dione (3.5 g, 6.74 mmol) in THF (25 mL) and MeOH (25 mL) was added lithium hydroxide (1.13 g, 47.2 mmol) and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed and diluted with DCM and quenched with acetic acid (2.70 ml, 47.2 mmol). The organic layer was washed several times with brine and dry over Na_2SO_4 and concentrated to afford the crude 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid; LCMS: *m/z* $(M+H)^+$ = 519.2. Yield ~95%. The crude acid was used in the next step without further purification.

Steps 5 and 6: To a solution of 5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid (2.0 g, 3.85 mmol) was added HATU (2.198 g, 5.78 mmol), DMF (Volume: 10 ml), DIPEA (1.346 ml, 7.71 mmol) and piperazine (1.077 g, 5.78 mmol). The reaction mixture was stirred for 1 hr at rt, diluted with water, extracted with 3 x 10 mL DCM, washed with brine. The organic layer was dried and concentrated. The crude was product (without further purification) was diluted with DCM (10 ml) and TFA (10.39 ml, 135 mmol), stirred for 1 hr at rt. The solvent was concentrated under vacuum, the crude mixture was diluted with DMSO and purified by reverse phase chromatography (**Standard Acidic Gradient Method**) to afford as a TFA salt, 3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one; LCMS: *m/z* $(M+H)^+$ = 587.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.8 – 8.02 (m, 2H), 7.95 (s, 1H), 7.53 – 7.43 (m, 3H), 7.39 – 7.29 (m, 2H), 5.39 (s, 1H), 4.38 (s, 1H), 3.78 (s, 2H), 3.52 (d, J = 29.4 Hz, 3H), 3.24 (s, 1H), 2.31 (d, J = 61.9 Hz, 4H), 1.67 (dd, J = 21.3, 1.1 Hz, 6H), 1.31 (s, 2H), 1.26 – 1.06 (m, 6H). Aliphatic region complicated significantly by amide rotamers; HRMS (ESI) m/z (M+H)+ calcd. for $C_{33}H_{36}ClN_4O_2S$; 587.2242 found 587.2243. Retention Time = 2.781 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-6-(cyclopropylmethyl)-1-(2,6-diethylphenyl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (93): This compound was prepared from **Method 13** using ethyl 4-cyclopropyl-3-oxobutanoate in **step 1** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-6-(cyclopropylmethyl)-1-(2,6-diethylphenyl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 587.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (br s, 2H), 8.73 (s, 1H), 8.21 (s, 1H), 8.16 – 8.07 (m, 2H), 7.55 – 7.44 (m, 3H), 7.34 (d, J = 7.7 Hz, 2H), 4.07 (m, 1H), 3.74 (m, 1H), 3.51 (m, 3H), 3.12 (m, 3H), 2.35 (m, 2H), 2.12 (m, 5H), 1.07 (t, J = 7.5 Hz, 6H), 0.52 – 0.12 (m, 2H), −0.05 (m, 1H), −0.27 (m, 1H); HRMS (ESI) m/z $(M+H)^+$ calcd. for $C_{26}H_{28}ClN_{14}O$; 587.2254 found 587.2255. Retention Time = 2.803 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methoxyethyl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (94): This compound was

prepared from *Method 13* using methyl 5-methoxy-3-oxopentanoate in **step 1** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methoxyethyl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 591.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (d, *J* = 0.5 Hz, 2H), 8.24 (d, *J* = 0.5 Hz, 1H), 8.18 – 8.10 (m, 2H), 7.58 – 7.47 (m, 3H), 7.39 (s, 1H), 7.37 (s, 1H), 4.04 (s, 1H), 3.85 – 3.43 (m, 3H), 3.16 (d, *J* = 35.4 Hz, 6H), 3.02 (d, *J* = 0.6 Hz, 3H), 2.85 (s, 1H), 2.33 (t, *J* = 1.9 Hz, 2H), 2.17 (s, 2H), 1.11 (s, 7H). Aliphatic region complicated significantly by amide rotamers; HRMS (ESI) m/z (M+H)+ calcd. for $C_{32}H_{36}ClN_4O_3S$; 591.2191 found 591.2195. Retention Time = 3.741 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(piperazine-1-carbonyl)-6-(3,3,3-trifluoropropyl)pyridin-2(1H)-one (95): This compound was prepared from **Method 13** using ethyl 6,6,6-trifluoro-3-oxohexanoate in **step 1** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(piperazine-1-carbonyl)-6-(3,3,3-trifluoropropyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 629.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (m, 3H), 8.24 (s, 1H), 8.16 – 8.08 (m, 2H), 7.55 – 7.47 (m, 3H), 7.38 (d, J = 7.7 Hz, 2H), 3.72 (br m, 5H), 3.17 (br m, 2H), 2.36 (dt, J = 15.1, 7.6 Hz, 2H), 2.02 (br m, 3H), 1.08 (t, J = 7.5 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{32}H_{33}ClF_3N_4O_2S$; 629.1959 found 629.195. Retention Time = 2.851 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(piperazine-1-carbonyl)-6-((tetrahydrofuran-3-yl)methyl)pyridin-2(1H)-one (96): This compound was prepared from **Method 13** using ethyl 3-oxo-4-(tetrahydrofuran-3-yl)butanoate in **step 1** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(piperazine-1-carbonyl)-6-((tetrahydrofuran-3-yl)methyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 617.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (s, 1H), 8.18 (s, 1H), 8.10 – 8.05 (m, 2H), 7.48 – 7.41 (m, 3H), 7.31 (d, *J* = 7.7 Hz, 2H), 3.98 (s, 1H), 3.72 (s, 1H), 3.46 (d, *J* = 17.9 Hz, 2H), 3.07 – 2.95 (m, 6H), 2.57 – 2.49 (m, 1H), 2.16-1.90 (m, 6H), 1.71 (d, *J* = 21.7 Hz, 1H), 1.59 (d, *J* = 10.6 Hz, 2H), 1.38-135 (m, 1H), 1.02 (d, *J* = 9.1 Hz, 6H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{34}H_{38}ClN_4O_3S$; 617.2348 found 617.2332. Retention Time = 2.722 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(piperazine-1-carbonyl)-6-((tetrahydro-2H-pyran-4-yl)methyl)pyridin-2(1H)-one (97): This compound was prepared from **Method 13** using ethyl 3-oxo-4-(tetrahydro-2H-pyran-4-yl)butanoate in **step 1** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(piperazine-1-carbonyl)-6-((tetrahydro-2H-pyran-4-yl)methyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 631.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 8.19 (s, 1H), 8.8 (d, *J* = 8.6 Hz, 2H), 7.51 – 7.41 (m, 3H), 7.33 (d, *J* = 7.7 Hz, 2H), 4.00 (s, 1H), 3.67 – 3.60 (m, 3H), 2.95 (td, *J* = 11.6, 2.4 Hz, 2H), 2.37 – 2.23 (m, 2H), 2.22 – 1.98 (m, 4H), 1.22 – 0.88 (m, 16H); HRMS (ESI) m/z (M+Na)+ calcd. for $C_{35}H_{39}ClN_4NaO_3S$; 653.2324 found 653.2336. Retention Time = 2.746 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(piperazine-1-carbonyl)-6-(pyrrolidin-3-ylmethyl)pyridin-2(1H)-one (98): This compound was prepared

from **Method 13** using *tert*-butyl 3-(4-ethoxy-2,4-dioxobutyl)pyrrolidine-1-carboxylate in **step 1** followed by Boc deprotection using TFA in DCM to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(piperazine-1-carbonyl)-6-(pyrrolidin-3-ylmethyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 616.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.96 (br s, 2H), 8.74 (s, 1H), 8.54 (br s, 2H), 8.24 (s, 1H), 8.16 – 8.01 (m, 2H), 7.60 – 7.44 (m, 3H), 7.37 (d, J = 7.7 Hz, 2H), 4.19 – 2.56 (m, 10H), 2.44 – 1.94 (m, 5H), 1.63 (dd, J = 101.3, 45.9 Hz, 5H), 1.39 – 1.15 (m, 1H), 1.10 (t, J = 7.5 Hz, 6H); HRMS (ESI) m/z (M+H) + calcd. for $C_{29}H_{34}ClF_3N_9O$; 616.2521 found 616.2524. Retention Time = 2.321 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(3-methylpiperazine-1-carbonyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one (99): This compound was prepared from **Method 15** using *tert*-butyl 2-methylpiperazine-1-carboxylate in **step 5** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(3-methylpiperazine-1-carbonyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 601.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.73 (d, *J* = 9.4 Hz, 1H), 8.25 (s, 1H), 8.09 (dd, *J* = 8.9, 2.3 Hz, 2H), 7.53 (dd, *J* = 8.7, 2.3 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.29 (dd, *J* = 22.5, 7.7 Hz, 2H), 5.30 (s, 1H), 4.55 (dd, *J* = 32.5, 13.8 Hz, 1H), 4.33-4.23 (m, 1H), 3.72-3.48 (m, 1H), 3.23 – 2.62 (m, 3H), 2.42 – 2.24 (m, 2H), 2.16-1.97 (m, 2H), 1.63 – 1.52 (m, 6H), 1.24 (dd, *J* = 12.0, 6.4 Hz, 1H), 1.11 (dt, *J* = 11.5, 7.3 Hz, 6H), 0.98 (t, *J* = 7.5 Hz, 3H); HRMS (ESI) m/z (M+H) + calcd. for $C_{34}H_{38}ClN_4O_2S$; 601.2399 found 601.2395. Retention Time = 2.805 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(2-methylpiperazine-1-carbonyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one (100): This compound was prepared from **Method 15** using *tert*-butyl 3-methylpiperazine-1-carboxylate in **step 5** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(3-methylpiperazine-1-carbonyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 601.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (s, 1H), 8.25 (s, 1H), 8.13 – 8.05 (m, 2H), 7.53 (dd, *J* = 8.9, 2.3 Hz, 2H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.35 – 7.21 (m, 2H), 5.28 (s, 1H), 4.94 (s, 1H), 3.59 (d, *J* = 14.1 Hz, 1H), 3.27 – 2.93 (m, 5H), 2.42 – 2.21 (m, 2H), 2.10 (dp, *J* = 26.2, 7.5 Hz, 2H), 1.63 – 1.47 (m, 6H), 1.38 – 1.19 (m, 1H), 1.17 – 1.06 (m, 6H), 0.99 (t, *J* = 7.5 Hz, 3H); HRMS (ESI) m/z (M+H) + calcd. for $C_{34}H_{38}ClN_4O_2S$; 601.2399 found 601.2388. Retention Time = 2.824 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(3-ethylpiperazine-1-carbonyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one (101): This compound was prepared from **Method 15** using *tert*-butyl 2-ethylpiperazine-1-carboxylate in **step 5** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(3-ethylpiperazine-1-carbonyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 615.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.25 (s, 1H), 8.14 – 8.05 (m, 2H), 7.57 – 7.50 (m, 2H), 7.47 – 7.40 (m, 1H), 7.37 – 7.22 (m, 2H), 5.29 (s, 1H), 4.67-4.52 (m, 1H), 3.72-3.64 (m, 1H), 3.23-3.05 (m, 2H), 3.01 – 2.61 (m, 2H), 2.45 – 2.20 (m, 2H), 2.14-1.99 (m, 2H), 1.66 – 1.51 (m,

9H), 1.16 – 1.06 (m, 3H), 1.02-0.94 (m, 3H), 0.87-0.79 (m, 2H); HRMS (ESI) m/z (M+H) + calcd. for C35H40ClN4O2S; 615.2555 found 615.2525. Retention Time = 2.848 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(3-propylpiperazine-1-carbonyl)pyridin-2(1H)-one (102): This compound was prepared from **Method 15** using *tert*-butyl 2-propylpiperazine-1-carboxylate in **step 5** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(3-propylpiperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 629.3; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.75 (s, 1H), 8.25 (s, 1H), 8.16 – 8.05 (m, 2H), 7.53 (dt, J = 9.7, 2.9 Hz, 2H), 7.49 – 7.38 (m, 1H), 7.29 (dd, J = 22.4, 7.9 Hz, 2H), 5.28 (s, 1H), 4.66 – 4.31 (m, 2H), 3.72-3.67 (m, 1H), 3.23 – 2.94 (m, 2H), 2.89 – 2.52 (m, 2H), 2.43 – 2.19 (m, 2H), 2.15-1.99 (m, 2H), 1.65 – 1.50 (m, 6H), 1.37 (d, J = 1.2 Hz, 1H), , 1.16 – 1.05 (m, 4H), 1.04 – 0.82 (m, 8H); HRMS (ESI) m/z (M+H) + calcd. for $C_{36}H_{39}ClFN_4O_3$; 629.2689 found 629.2701. Retention Time = 2.889 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(4,7-diazaspiro[2.5]octane-7-carbonyl)pyridin-2(1H)-one (103): This compound was prepared from **Method 15** using *tert*-butyl 4,7-diazaspiro[2.5]octane-4-carboxylate in **step 5** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(4,7-diazaspiro[2.5]octane-7-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 613.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (s, 1H), 8.41 (s, 1H), 8.29 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.48 – 7.21 (m, 3H), 5.33 (s, 1H), 4.43-4.33 (m, 1H), 3.70 – 3.37 (m, 3H), 3.07-2.90 (m, 2H), 2.71 – 2.59 (m, 2H), 2.44 – 1.90 (m, 4H), 1.58 (d, *J* = 10.3 Hz, 6H), 1.26 – 0.72 (m, 9H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{35}H_{38}ClN_4O_2S$; 613.2399 found 613.2427. Retention Time = 2.85 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(3-(hydroxymethyl)piperazine-1-carbonyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one (104): This compound was prepared from **Method 15** using *tert*-butyl 2-(hydroxymethyl)piperazine-1-carboxylate in **step 5** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-5-(3-(hydroxymethyl)piperazine-1-carbonyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 617.2; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.73 (s, 1H), 8.25 (s, 1H), 8.09 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.43 (t, J = 7.7 Hz, 1H), 7.29 (dd, J = 20.5, 7.7 Hz, 2H), 5.29 (s, 1H), 4.63-4.53 (m, 1H), 3.73 – 3.39 (m, 3H), 3.21 – 2.63 (m, 2H), 2.44 – 2.18 (m, 4H), 2.16-1.99 (m, 2H), 1.63 – 1.51 (m, 7H), 1.16 – 1.05 (m, 3H), 0.98 (t, J = 7.5 Hz, 3H); HRMS (ESI) m/z (M+H) + calcd. for $C_{34}H_{38}ClN_4O_3S$; 617.2348 found 617.2376. Retention Time = 2.743 min.

4-(5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-2-one (105): This compound was prepared from **Method 15** using *tert*-butyl 2-oxopiperazine-1-carboxylate in **step 5** to afford 4-(5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazin-2-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 601.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ

8.70 (d, *J* = 8.2 Hz, 1H), 8.24 (d, *J* = 1.8 Hz, 1H), 8.17 – 7.97 (m, 3H), 7.58 – 7.36 (m, 4H), 5.23 (s, 1H), 3.89-3.79 (s, 2H), 3.26 – 2.95 (m, 4H), 2.41 – 2.00 (m, 4H), 1.61 – 1.42 (m, 7H), 1.20 – 0.86 (m, 6H); HRMS (ESI) m/z (M+H) + calcd. for $C_{33}H_{34}ClN_4O_3S$; 601.2035 found 601.2049. Retention Time = 3.612 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(3-(trifluoromethyl)piperazine-1-carbonyl)pyridin-2(1H)-one (106): This compound was prepared from **Method 15** using *tert*-butyl 2-(trifluoromethyl)piperazine-1-carboxylate in **step 5** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(3-(trifluoromethyl)piperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ =655.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.24 (s, 1H), 8.10 (dd, *J* = 9.1, 2.5 Hz, 2H), 7.57 – 7.48 (m, 2H), 7.43 (td, *J* = 7.7, 4.6 Hz, 1H), 7.30 (dd, *J* = 18.6, 7.0 Hz, 2H), 5.25 (s, 1H), 4.52-4.44 (m, 1H), 4.15-3.98 (m, 1H), 3.23 – 2.56 (m, 5H), 2.38 – 2.17 (m, 2H), 2.16-1.99 (m, 2H), 1.56 (d, *J* = 11.2 Hz, 6H), 1.16 – 0.91 (m, 6H); HRMS (ESI) m/z (M+H) + calcd. for $C_{34}H_{35}ClF_3N_4O_2S$; 655.2116 found 655.214. Retention Time = 3.952 min.

4-(5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-2-carbonitrile (107): This compound was prepared from **Method 15** using *tert*-butyl 2-cyanopiperazine-1-carboxylate in **step 5** to afford 4-(5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-2-carbonitrile as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 612.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (d, *J* = 8.6 Hz, 1H), 8.24 (s, 1H), 8.09 (dd, *J* = 8.3, 1.7 Hz, 2H), 7.58 – 7.48 (m, 2H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.29 (dd, *J* = 17.7, 7.3 Hz, 2H), 5.24 (d, *J* = 8.0 Hz, 1H), 4.45 – 4.12 (m, 1H), 3.23 – 2.97 (m, 2H), 2.93 – 2.63 (m, 4H), 2.44 – 2.20 (m, 2H), 2.20 – 2.01 (m, 2H), 1.67 – 1.50 (m, 6H), 1.11 (t, *J* = 12.8, 7.4, Hz, 3H), 1.00 (t, *J* = 7.4 Hz, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{34}H_{35}ClN_5O_2S$; 612.2195 found 612.22. Retention Time = 3.776 min.

4-(5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-2-carboxylic acid (108): This compound was prepared from **Method 15** using 1-(tert-butyl) 2-methyl piperazine-1,2-dicarboxylate in **step 5** followed by ester hydrolysis using LiOH in THF:MeOH and Boc deprotection using TFA in DCM to afford 4-(5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-2-carboxylic acid as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 631.1; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (s, 1H), 8.25 (s, 1H), 8.09 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.53 (dd, *J* = 8.6, 2.3 Hz, 2H), 7.43 (td, *J* = 7.7, 5.6 Hz, 1H), 7.36 – 7.18 (m, 2H), 5.28 (s, 1H), 4.58-4.48 (m, 1H), 4.20-4.04 (m, 1H), 3.87 – 3.57 (m, 1H), 3.12 – 2.62 (m, 2H), 2.44 – 2.17 (m, 2H), 2.20 – 1.99 (m, 2H), 1.63 – 1.49 (m, 6H), 1.24 – 1.05 (m, 3H), 1.03 – 0.94 (m, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{27}H_{28}Cl\ N_{14}O_3$; 631.214 found 631.2151. Retention Time = 3.038 min.

4-(5-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-2-carboxamide (109): This compound was prepared from **Method 15** using piperazine-2-carboxamide in **step 5** to afford 4-(5-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-2-carboxamide as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 630.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (s, 1H), 8.26 (s, 1H), 8.09 (dd, *J* = 8.0, 6.0 Hz, 2H), 7.53 (dd, *J* = 8.0, 6.2 Hz, 2H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.37 – 7.20 (m, 2H), 5.29 (d, *J* = 9.5 Hz, 1H), 4.72-4.55 (m, 1H), 4.02-3.72 (m, 1H), 3.66-3.54 (m, 1H), 3.17 – 2.99 (m, 2H), 2.82 (t, *J* = 13.0 Hz, 1H), 2.68-2.62 (m, 1H), 2.42 – 2.22 (m, 2H), 2.15-1.99 (m, 2H), 1.67 – 1.50 (m, 6H), 1.11 (t, *J* = 7.5 Hz, 3H), 1.05 – 0.91 (m, 3H); HRMS (ESI) m/z (M+H) + calcd. for $C_{34}H_{34}ClF_5N_3O$; 630.2305 found 630.2311. Retention Time = 2.753 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(2,6-diazaspiro[3.3]heptane-2-carbonyl)pyridin-2(1H)-one (110): This compound was prepared from **Method 15** using *tert*-butyl 2,6-diazaspiro[3.3]heptane-2-carboxylate in **step 5** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(2,6-diazaspiro[3.3]heptane-2-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 599.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, *J* = 4.2 Hz, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 8.07 (dd, *J* = 8.7, 2.3 Hz, 2H), 7.56 – 7.49 (m, 2H), 7.42 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 5.30 (s, 1H), 4.08 (t, *J* = 11.4 Hz, 4H), 2.70 – 2.59 (m, 2H), 2.24-2.09 (m, 6H), 1.58 (s, 6H), 1.08-1.02 (m, 6H). HRMS (ESI) m/z (M+H)+ calcd. for $C_{34}H_{36}ClN_4O_2S$; 599.2242 found 599.225. Retention Time = 2.749 min.

5-((1R,5S)-3,8-Diazabicyclo[3.2.1]octane-3-carbonyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one (111): This compound was prepared from **Method 15** using *tert*-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-8-carboxylate in **step 5** to afford 5-((1R,5S)-3,8-diazabicyclo[3.2.1]octane-3-carbonyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 613.2; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.73 (s, 1H), 8.24 (s, 1H), 8.15 – 8.04 (m, 2H), 7.58 – 7.48 (m, 2H), 7.42 (t, J = 7.7 Hz, 1H), 7.29 (dd, J = 26.3, 7.7 Hz, 2H), 5.23 (s, 1H), 4.44 (d, J = 14.0 Hz, 1H), 4.14-3.86 (m, 2H), 3.61 – 3.34 (m, 2H), 2.96 (d, J = 14.0 Hz, 1H), 2.65 (p, J = 1.9 Hz, 1H), 2.44 – 2.27 (m, 2H), 2.15 – 1.97 (m, 2H), 1.96 – 1.71 (m, 3H), 1.55 (dd, J = 10.4, 1.3 Hz, 6H), 1.14 (t, J = 7.7 Hz, 3H), 0.96 (t, J = 7.5 Hz, 3H); HRMS (ESI) m/z (M+Na) + calcd. for $C_{35}H_{37}ClN_4NaO_2S$; 635.2218 found 635.2206. Retention Time = 2.823 min.

5-(3,8-Diazabicyclo[3.2.1]octane-8-carbonyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one (112): This compound was prepared from **Method 15** using *tert*-butyl (1R,5S)-3,8-diazabicyclo[3.2.1]octane-3-carboxylate in **step 5** to afford 5-(3,8-diazabicyclo[3.2.1]octane-8-carbonyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2,6-diethylphenyl)-6-(2-methylprop-1-en-1-yl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 613.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (s, 1H), 8.08

(d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.27 (dd, *J* = 13.8, 7.7 Hz, 2H), 5.24 (s, 1H), 3.98-3.92 (m, 2H), 3.25 – 3.05 (m, 4H), 2.78 – 2.53 (m, 4H), 2.37 – 2.02 (m, 4H),1.90 (s, 3H), 1.55 (s, 3H), 1.04-0.97 (m, 6H); HRMS (ESI) m/z (M+H) + calcd. for $C_{35}H_{38}ClN_4O_2S$; 613.2399 found 613.2389. Retention Time = 2.798 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-6-(2-methylprop-1-en-1-yl)-1-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (113): This compound was prepared from **Method 15** using aniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-6-(2-methylprop-1-en-1-yl)-1-phenyl-5-(piperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 531.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (s, 1H), 8.06 – 8.01 (m, 2H), 7.93 (d, J = 1.8 Hz, 1H), 7.61 – 7.49 (m, 3H), 7.48 – 7.42 (m, 2H), 7.37 (s, 1H), 7.19 (s, 1H), 5.59 (s, 1H), 4.25 (s, 2H), 3.84 (s, 2H), 3.64 (d, J = 18.3 Hz, 2H), 3.14 (s, 2H), 1.63 (dd, J = 9.4, 1.1 Hz, 6H). Aliphatic region complicated significantly by amide rotamers; HRMS (ESI) m/z (M+H) + calcd. for $C_{29}H_{28}ClN_4O_2S$; 531.1616 found 531.1631. Retention Time = 2.583 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-ethylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (114): This compound was prepared from **Method 15** using 2-ethylaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-ethylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 559.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.04 (d, J = 8.7 Hz, 2H), 7.94 (s, 1H), 7.53–7.47 (m, 2H), 7.45 (d, J = 8.6 Hz, 2H), 7.44–7.00 (m, 2H), 5.62–5.42 (m, 1H), 4.35–4.25 (m, 2H), 3.90–3.50 (m, 4H), 3.35–3.10 (m, 2H), 2.50–2.25 (m, 2H), 1.67–1.57 (m, 6H), 1.25–1.05 (m, 3H). Aliphatic region complicated significantly by amide rotamers; HRMS (ESI) m/z (M+H)>+ calcd. for $C_{31}H_{32}ClN_4O_2S$; 559.1929 found 559.1937. Retention Time = 2.675 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-ethyl-6-methylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (115): This compound was prepared from **Method 15** using 2-ethyl-6-methylaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-ethyl-6-methylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 533.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 2H), 8.71 (d, J = 6.5 Hz, 1H), 8.22 (s, 1H), 8.12 (d, J = 8.6 Hz, 2H), 7.52 (t, J = 8.4 Hz, 2H), 7.43 (t, J = 7.6 Hz, 1H), 7.33 (dd, J = 15.7, 8.1 Hz, 2H), 3.57 (d, J = 87.5 Hz, 4H), 3.16 (t, J = 47.1 Hz, 4H), 2.20 (t, J = 39.9 Hz, 1H), 1.98 (s, 3H), 1.90 (s, 3H), 1.08 (t, J = 7.5 Hz, 3H). Aliphatic region complicated significantly by amide rotamers; HRMS (ESI) m/z (M+H)+ calcd. for $C_{29}H_{30}ClN_4O_2S$; 533.1773 found 533.1792. Retention Time = 2.6 min.

1-(2-Chloro-6-ethylphenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (116): This compound was prepared from **Method 15** using 2-chloro-6-ethylaniline in **step 3** to afford 1-(2-chloro-6-ethylphenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 593.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.03 (d, J = 8.7 Hz, 2H), 7.94

(s, 1H), 7.55–7.39 (m, 5H), 5.55–5.35 (m, 1H), 4.40–4.20 (m, 1H), 3.85–3.70 (m, 1H), 3.60–3.45 (m, 2H), 3.35–3.10 (m, 4H), 2.60–2.25 (m, 2H), 1.74–1.63 (m, 6H), 1.30–1.05 (m, 3H). Aliphatic region complicated significantly by amide rotamers; HRMS (ESI) m/z (M+H)+ calcd. for $C_{31}H_{31}Cl_2N_4O_2S$; 593.1539 found 593.1528. Retention Time = 4.187 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-ethyl-5-methylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (117): This compound was prepared from **Method 15** using 2-ethyl-5-methylaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-ethyl-5-methylphenyl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 573.2; ^{1}H NMR (400 MHz, CD3OD) ? 8.86 (s, 1H), 8.04 (d, J = 8.44 Hz, 2H), 7.94 (s, 1H), 7.45 (d, J = 8.8 Hz, 2H), 7.37-7.27 (m, 2H), 7.17-7.03 (m, 1H), 5.66-5.41 (m, 1H), 4.42-4.20 (m, 1H), 3.91-3.74 (m, 1H), 3.65-3.49 (m, 2H), 3.25-3.13 (m, 3H), 2.50-2.18 (m, 6H), 1.71-1.61 (m, 6H), 1.23-1.05 (m, 3H). Aliphatic region complicated significantly by amide rotamers; HRMS (ESI) m/z (M+H)+ calcd. for $C_{32}H_{34}ClN_4O_2S$; 573.2086 found 573.2082. Retention Time = 2.735 min.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-1-(2-ethyl-5-methoxyphenyl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (118): This compound was prepared from **Method 15** using 2-ethyl-5-methoxyaniline in **step 3** to afford 3-(4-(4-chlorophenyl)thiazol-2-yl)-1-(2-ethyl-5-methoxyphenyl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 589.3; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (s, 1H), 8.24 (s, 1H), 8.10 (d, J = 8.2 Hz, 2H), 7.57 – 7.50 (m, 3H), 7.04 (d, J = 7.2 Hz, 2H), 5.53 (s, 1H), 3.78 (s, 3H), 3.72-3.67 (m, 2H), 3.45-3.37 (m, 2H), 3.20-3.01 (m, 2H), 2.65 (q, J = 1.9 Hz, 2H), 2.09-2.03 (m, 2H), 1.61 – 1.52 (m, 6H), 1.15 – 0.90 (m, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{32}H_{34}ClN_4O_3S$; 589.2035 found 589.2024. Retention Time = 2.709 min.

In Method 15, after step 5, using a preparative CHIRALCEL® ODH Column and a hexanes/EtOH/DEA (70/30/0.04) mobile phase at a flow rate of 35 mL/min, Boc-**55** could be separated into two isomers with ee >98% and ee 80.9%. These were subjected to Boc deprotection with TFA to yield **(+)-118** and **(−)-(118**) respectively.

(+)-118: ^{1}H NMR (400 MHz, Chloroform-d) δ 8.82 (bs, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.58 (s, 1H), 7.44 – 7.36 (m, 3H), 7.30 (d, J = 8.6 Hz, 1H), 6.98 (dd, J = 8.7, 2.7 Hz, 1H), 6.68 – 6.46 (m, 1H, rotameric), 5.60 – 5.28 (m, 1H, rotameric), 4.16 – 2.84 (m, 9H), 2.42 - 2.02 (m, 2H), 1.70 – 1.60 (m, 6H), 1.16 – 0.81 (m, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{32}H_{34}ClN_4O_3S$; 589.2035 found 589.2021. Retention Time = 2.582 min.

(−)-118: ^{1}H NMR (400 MHz, Chloroform-d) δ 8.81 (bs, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.57 (s, 1H), 7.44 – 7.34 (m, 3H), 7.30 (d, J = 8.6 Hz, 1H), 6.97 (dd, J = 8.7, 2.7 Hz, 1H), 6.67 – 6.49 (m, 1H, rotameric), 5.61 – 5.29 (m, 1H, rotameric), 4.14 – 2.86 (m, 9H), 2.41 - 2.03 (m, 2H), 1.71 – 1.61 (m, 6H), 1.17 – 0.80 (m, 3H); HRMS (ESI) m/z (M+Na)+ calcd. for $C_{32}H_{33}ClN_4NaO_3S$; 611.1854 found 611.1875. Retention Time = 2.685 min.

1-(5-Chloro-2-ethylphenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one (119): This compound was prepared from **Method 15** using 2-ethyl-5-chloroaniline in **step 3** to afford 1-(5-chloro-2-ethylphenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one as a TFA salt. LCMS: *m/z* $(M+H)^+$ = 593.2; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.21 (s, 1H), 8.09 (d, J = 8.2 Hz, 2H), 7.70 – 7.26 (m, 5H), 5.50 – 5.26 (m, 1H, rotameric), 3.67 – 3.55 (m, 1H), 3.41 – 3.11 (m, 3H), 2.78 – 2.53 (m, 4H), 2.37 – 2.02 (m, 2H), 1.57 (s, 3H), 1.55 (s, 3H), 1.15 – 0.91 (m, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{31}H_{31}Cl_2N_4O_2S$ 593.1533 found 593.1539. Retention Time = 2.747 min.

Synthesis of isobutylene analogs (+)-119 and (−)-119 as per Scheme 3

1-(5-Chloro-2-ethylphenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-7,8-dihydro-2H-pyrano[4,3-b]pyridine-2,5(1*H*)-dione (VIIb): A mixture of 6,6-dimethyldihydro-2H-pyran-2,4(3*H*)-dione **Ic** (6.06 g, 42.6 mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine **II** (5.66 mL, 42.6 mmol) was stirred for 15 min at rt. The reaction mixture became a yellow solid. To the mixture was added with 2-propanol (100 mL) followed by 2-(4-(4-chlorophenyl)thiazol-2-yl)acetonitrile **N1/IVa** (10.0 g, 42.6 mmol) and piperidine (16.9 mL, 170 mmol). The mixture was stirred at 70 °C for 4 h, brought to rt and the solvent was removed by rotovap. To the residue was added 5-chloro-2-ethylaniline (6.63 g, 42.6 mmol) and acetic acid (122.0 mL, 2130 mmol). The mixture was stirred at 70 °C for 4 h, cooled to room temperature, diluted with DCM, washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (10:90 EA/Hex to 100% EA) to afford the product, 1-(5-chloro-2-ethylphenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-7,7-dimethyl-7,8-dihydro-2H-pyrano[4,3-b]pyridine-2,5(1H)-dione **VIIb** as a yellow solid; LCMS: *m/z* $(M+H)^+$ = 525.0. Yield ~75%.

***tert*-Butyl 4-(1-(5-chloro-2-ethylphenyl)-5-(4-(4-chlorophenyl)thiazol-2-yl)-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carbonyl)piperazine-1-carboxylate (VIIIa):** To a solution of **X** (10 g, 19 mmol) in THF (100 mL) and MeOH (100 mL) was added lithium hydroxide (2.3 g, 95 mmol) and the reaction mixture was stirred at rt for 1 h. The solvent was removed, the reaction was diluted with DCM and quenched with acetic acid (5.45 mL, 95 mmol). The organic layer was washed several times with brine, dried over Na_2SO_4 and concentrated to afford crude 1-(5-chloro-2-ethylphenyl)-5-(4-(4-chlorophenyl)thiazol-2-yl)-2-(2-methylprop-1-en-1-yl)-6-oxo-1,6-dihydropyridine-3-carboxylic acid **VIIc**; LCMS: *m/z* $(M+H)^+$ = 525.0. Yield ~95%.

To a solution of the crude unpurified acid **VIIc** in DMF (25 mL) was added HATU (10.9 g, 28.5 mmol) and N-ethyl-N-isopropylpropan-2-amine (9.97 mL, 57.1 mmol) and *tert*-butyl piperazine-1-carboxylate (5.32 g, 28.5 mmol). The reaction mixture became yellow and it was stirred for 1h at rt, diluted with water, extracted with 3 x 100 mL DCM, and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated. The organic solvent was concentrated and purified by reverse-phase flash chromatography (100% water to 100%

acetonitrile in 0.1% TFA) to afford **VIIIa**. It was dissolved in DCM (100 ml) and washed with sat aq $NaHCO_3$ (3 x 100 mL) solution to remove any residual TFA (this step was important to prevent conversion of **VIIIa** back to **VIIb**), dried over Na_2SO_4, filtered; the organic solvent was removed by rotovap and then high vacuum to afford pure **VIIIa**, LCMS: *m/z* $(M+H)^+$ = 693.0. Yield ~90%.

Atropisomer Separation: Using preparative CHIRALCEL ODH Column and a hexanes/EtOH (70/30) mobile phase at a flow rate of 1mL/min, **VIIIa** clearly separated into two isomers and ee >98% that were designated as **1st_pos** (ee > 98%) and **2nd_neg** (ee 98.0%).

***S*)-1-(5-chloro-2-ethylphenyl)-3-(4-(4-chlorophenyl)thiazol-2-yl)-6-(2-methylprop-1-en-1-yl)-5-(piperazine-1-carbonyl)pyridin-2(1H)-one ((+)-119):** To a solution of active atropisomer **1st_pos** (5.00 g, 7.21 mmol) in DCM (50 ml) was added 2,2,2-trifluoroacetic acid (19.44 ml, 252.4 mmol) the reaction mixture was stirred for 1 h at rt (after Boc deprotection). The solvent was concentrated, and the material purified by reverse-phase flash chromatography (gradient of 100% water to 100% acetonitrile in 0.1% TFA) to provide **(+)-119** the TFA salt . This was dissolved in DCM (100 mL) and washed with sat aq $NaHCO_3$ (3 x 100 mL) to afford the free base. The organic layer was dried over Na_2SO_4 concentrated by rotovap and dried under high vacuum to afford pure **(+)-119** aka **NCATS-SM5637**, **NSC 791985**. Yield ~92%, LCMS: *m/z* $(M+H)^+$ = 593.0. ^1H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 8.23 (s, 1H), 8.14 – 8.05 (d, J = 8.2 Hz, 2H), 7.70 – 7.35 (m, 5H), 5.50-5.30 (2 br s 1H, rotameric), 3.64 – 3.54 (m, 1H), 3.65-3.10 (m, 3H), 2.80 – 2.56 (m, 4H), 2.22 – 2.05 (m, 2H), 1.62 – 1.55 (m, 6H), 1.13 – 0.95 (m, 3H); HRMS (ESI) m/z (M+H)+ calcd. for $C_{31}H_{31}Cl_2N_4O_2S$; 593.1539 found 593.1561. Retention Time = 2.747 min. 98% ee as determined by HPLC analysis using Chiracel OD-H column, 10% i-PrOH in hexane, 0.5 ml/min 254nm, t_r (min):16.4 (major), t_r 18.6 (minor).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AAALACi	American Association for Accreditation of Laboratory Animal Care international
ATCC	American Type Culture Collection

bodipy	boron difluoride dipyrromethene
CBC	Chemical Biology Consortium
CCD	Charged-coupled device
CETSA	Cellular Thermal Shift Assay
DI	Deionized
DMEM	Dulbecco's Modified Eagle Medium
DPBS	Dulbecco's phosphate-buffered saline
EtOAc	Ethyl acetate
G6PDH	Glucose-6-Phosphate Dehydrogenase
HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
2-HG	R-2-hydroxyglutarate
IDH1	isocitrate dehydrogenase 1
KG	ketoglutarate
KOtBu	Potassium tert-butoxide
mIDH1	mutant isocitrate dehydrogenase 1
NCATS	National Center for Advancing Translational Sciences
NExT	Institute's (NCI) Experimental Therapeutics
NSC	(Cancer Chemotherapy) National Service Center
qHTS	quantitative high-throughput screen
RH	Relative Humidity
RLM	Rat Liver Microsomes

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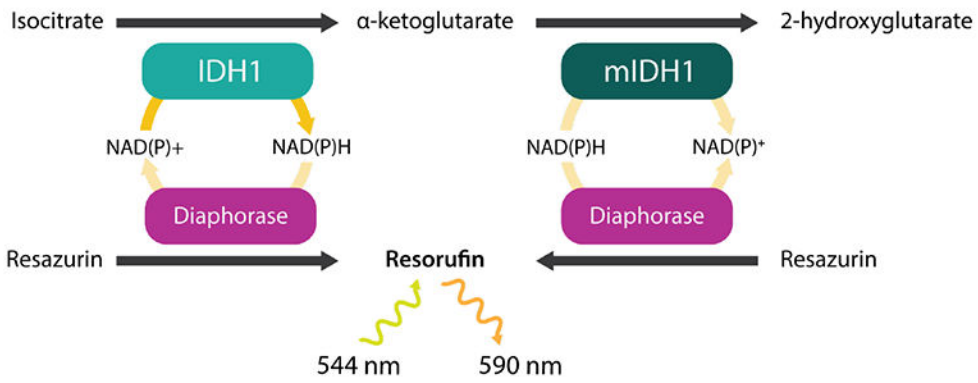
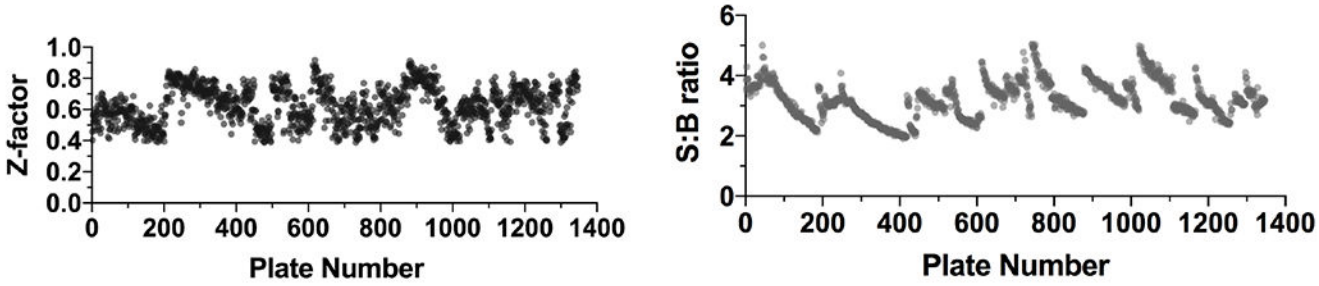
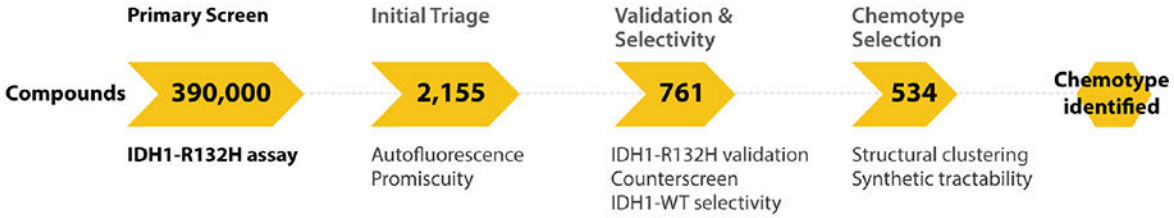
A



B



C



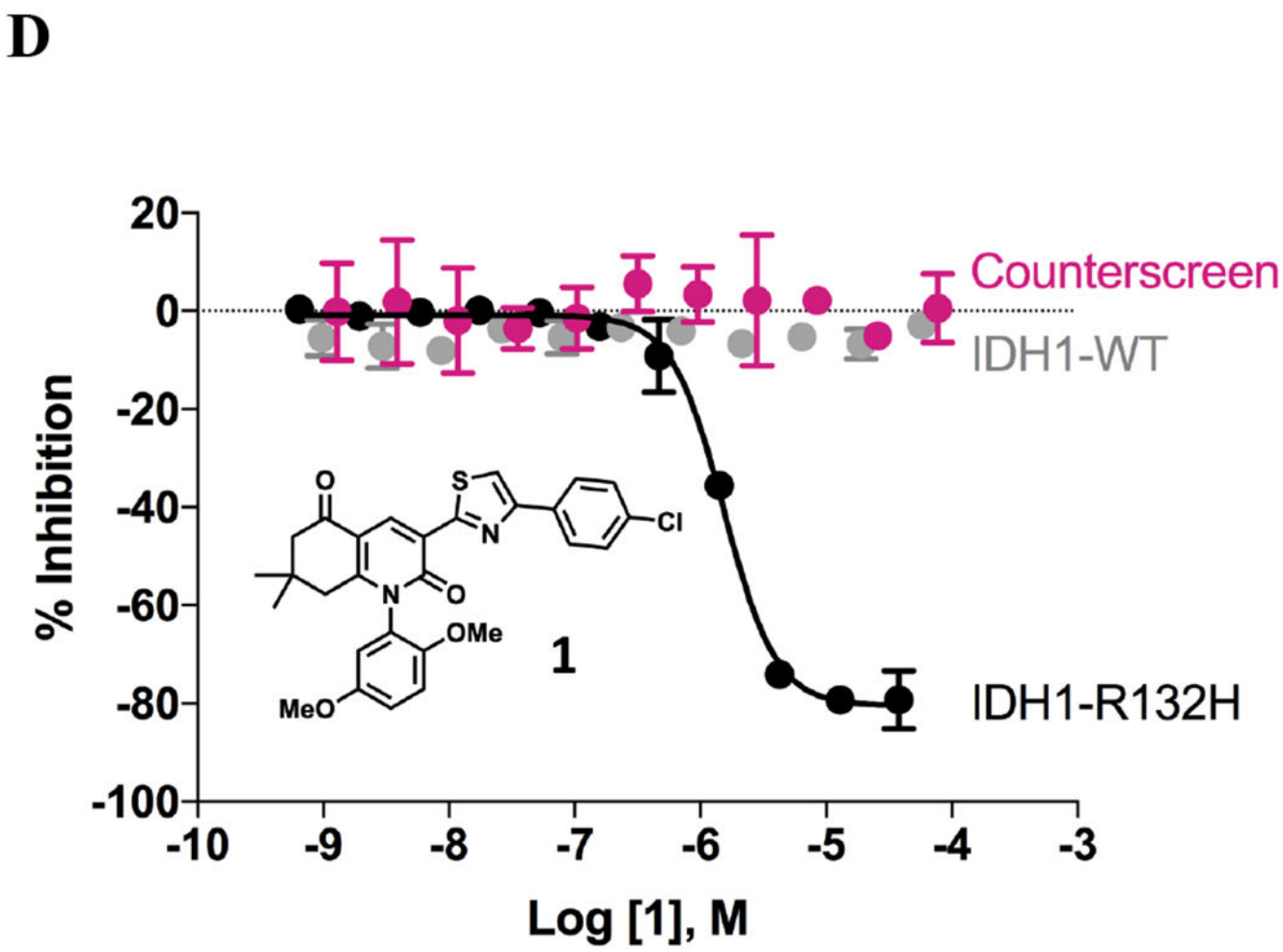
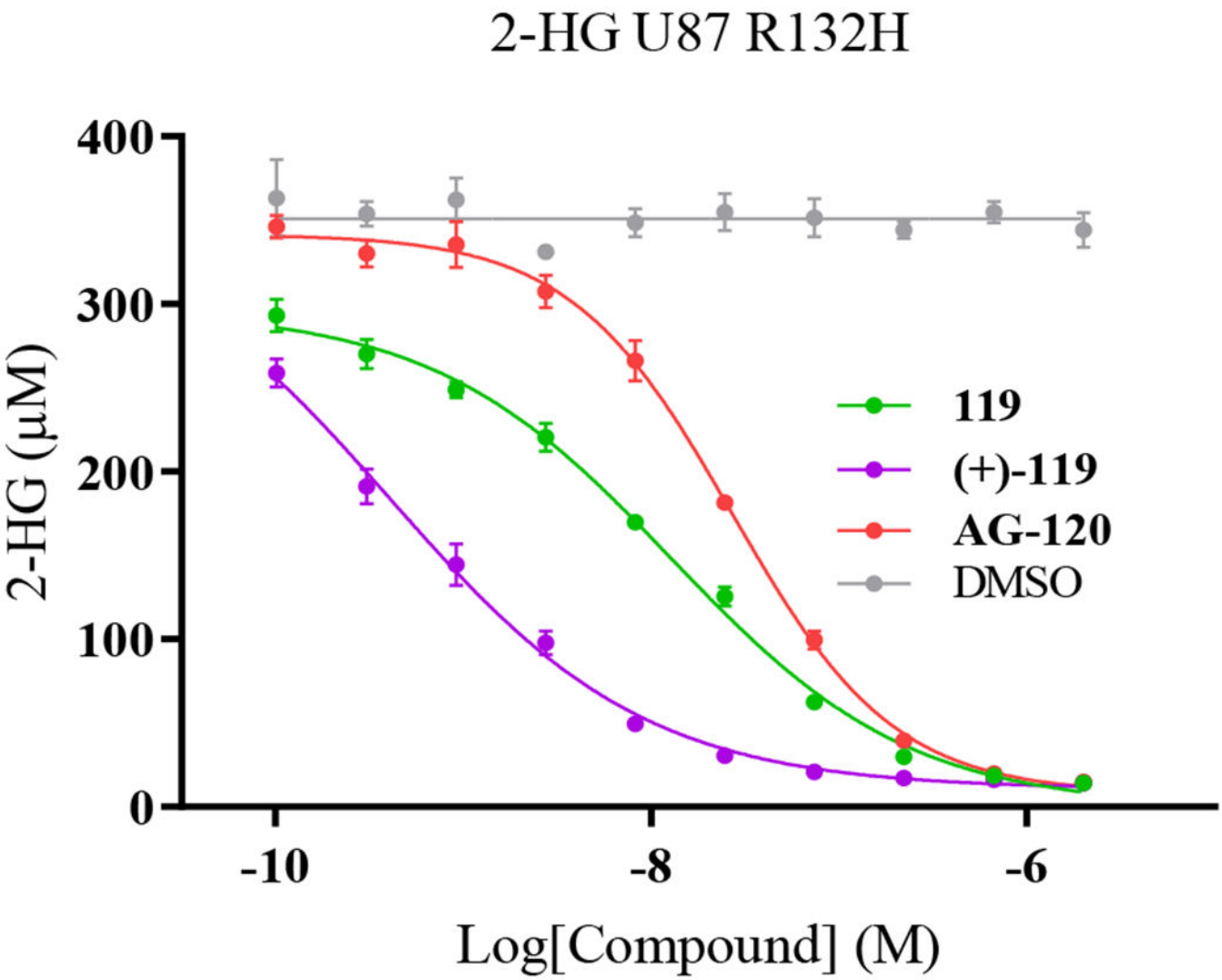


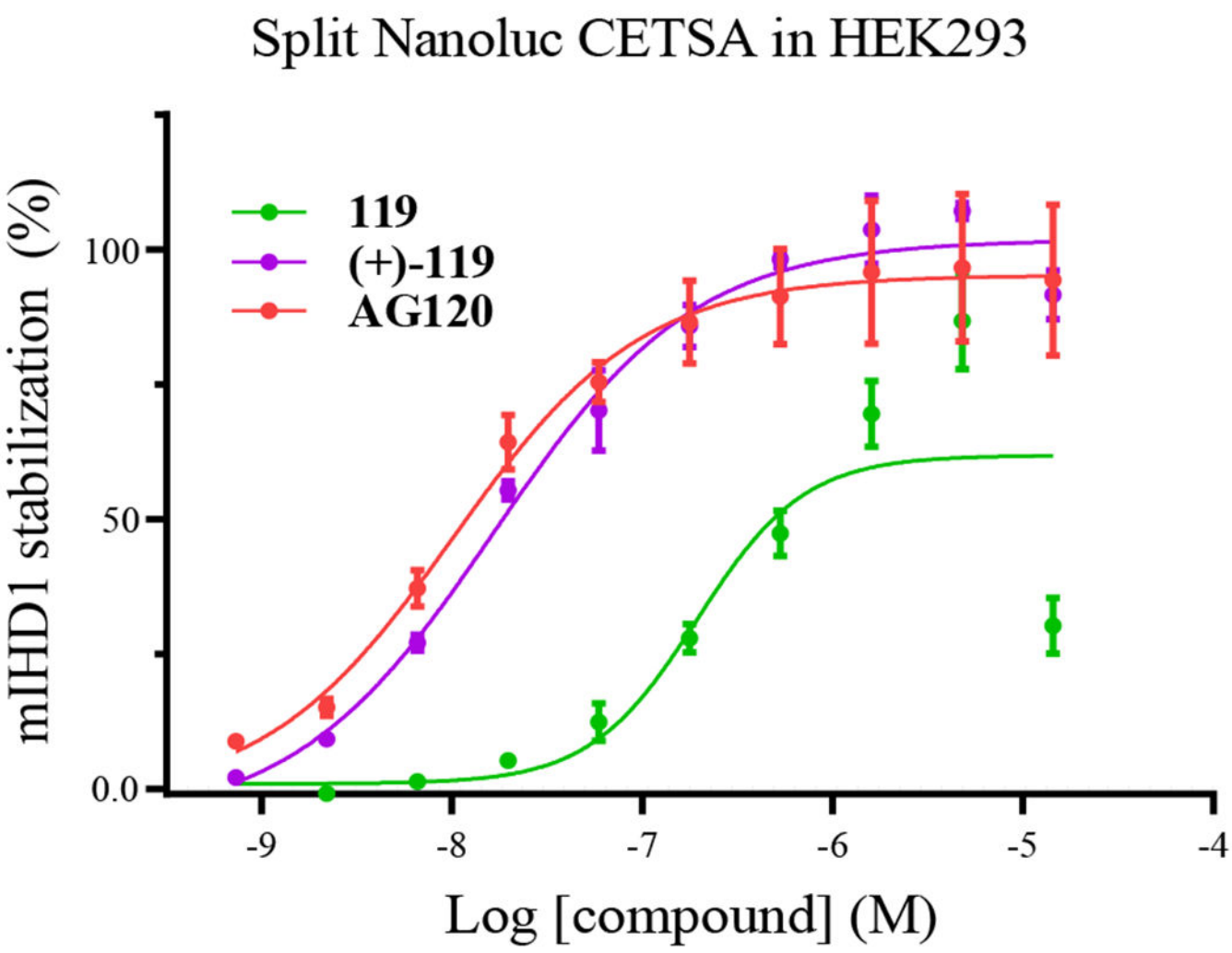
Figure 1.

A. Schematic for primary biochemical qHTS assay; **B**. Assay performance as measured by Z' factor and S:B ratio; **C**. Workflow for the identification of small molecule inhibitors of mutant IDH1; **D**. Dose-dependent activity of hit **1** against R132H mIDH1, IDH-WT, and in a readout interference counterscreen.



	IC_{50} (nM)
119	13.04 ± 3.56
(+)-119	0.43 ± 0.40
AG-120	27.23 ± 4.16

Figure 2.
Dose-dependent reduction of 2-HG in U87-mIDH1 (R132H) cells (N=3)



	EC_{50} (nM)
119	250.22 ± 223.70
(+)-119	18.02 ± 9.67
AG-120	12.47 ± 10.19

Figure 3.
Dose dependent stabilization of NanoLuc-tagged R132H mIDH1 in HEK293 cells (N=3)

PK parameters	Brain	Plasma
T_{max} (h)	6	4
C_{max} (ng/g or ng/mL)	594.67	2013.33
C_{max} (μmol/kg or μM)	1.00	3.39
AUC_{last} (h*ng/g or mL)	6996 ± 797	24371 ± 779
AUC_{last} ratio (P/B)	3.52 ± 0.43	
C_{max} ratio (P/B)	3.68 ± 0.13	

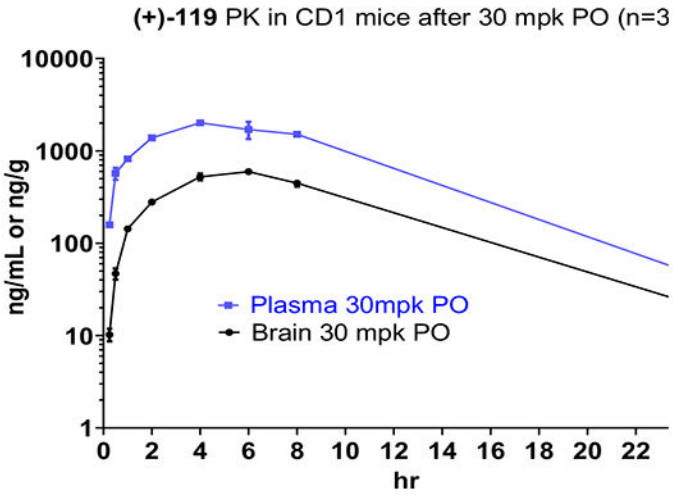


Figure 4.

Pharmacokinetic parameters and conc vs. time profiles in brain and plasma of CD1 mice (n=3) after a single of 30 mpk oral dose of **(+)-119** formulated as a solution in 20% PEG300, 40% of Solutol® solution (30% w/w in water), and 40% DI water.

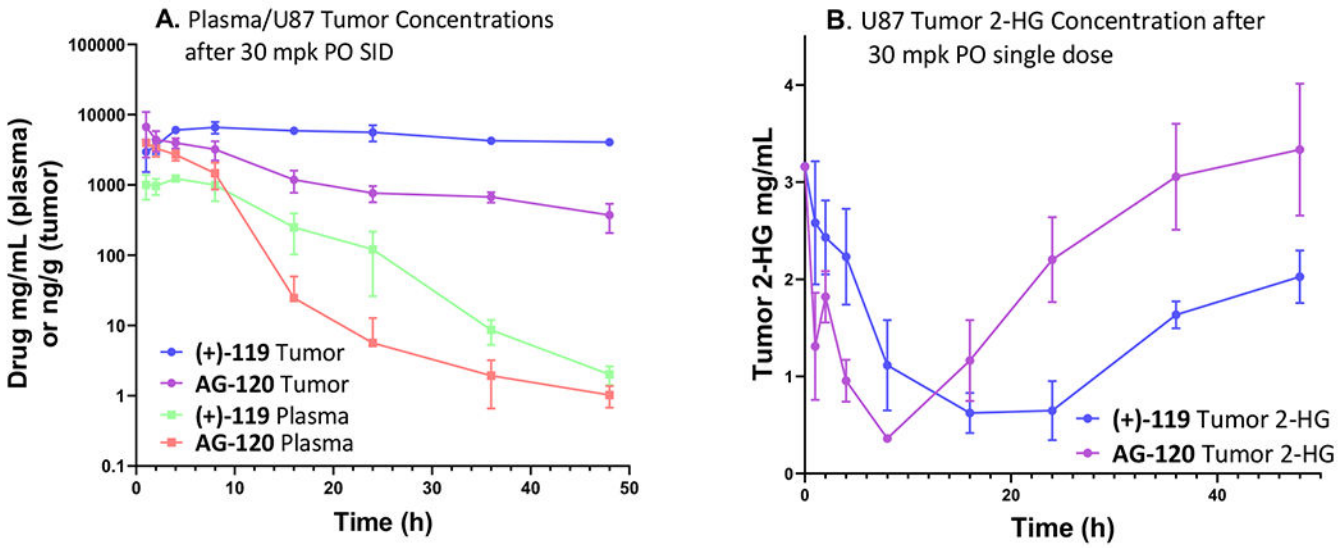
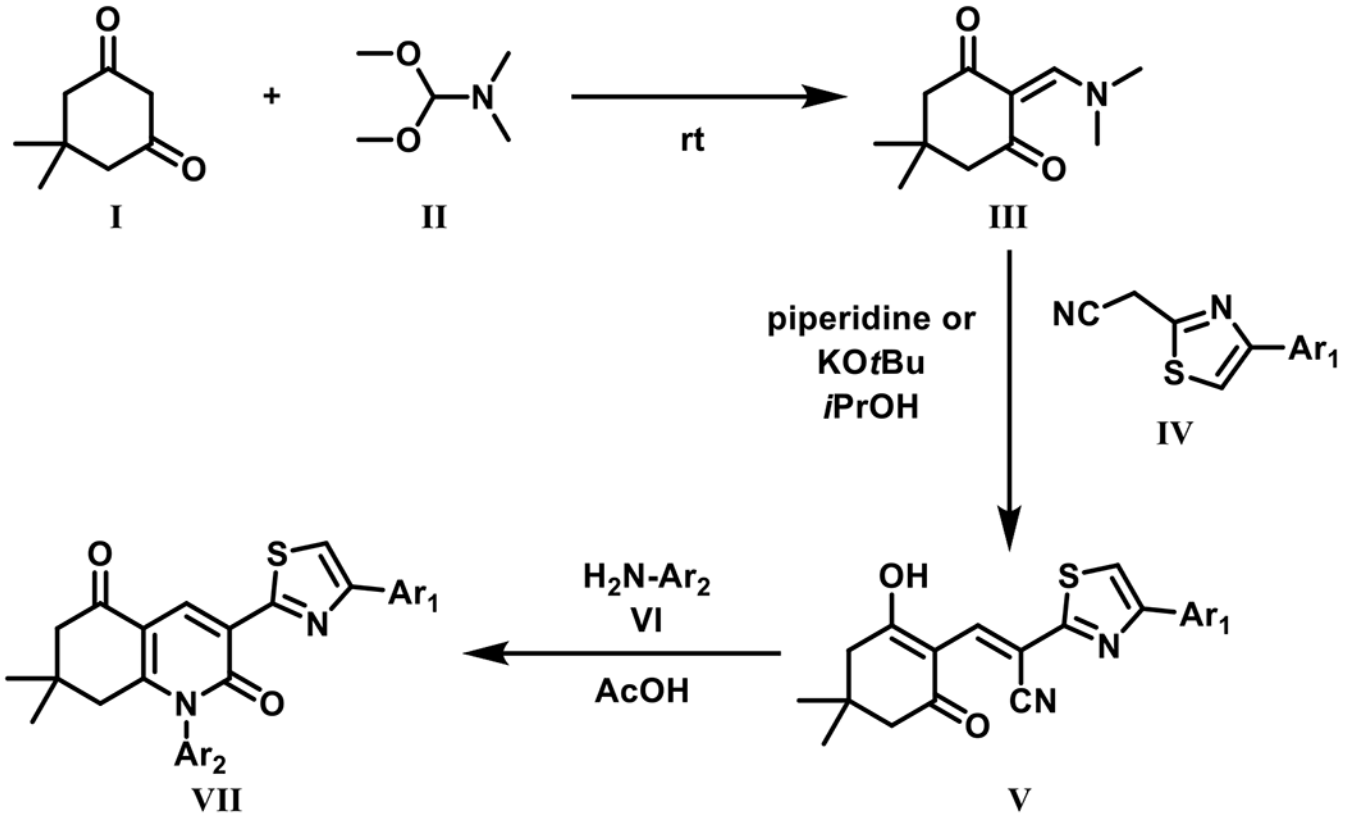
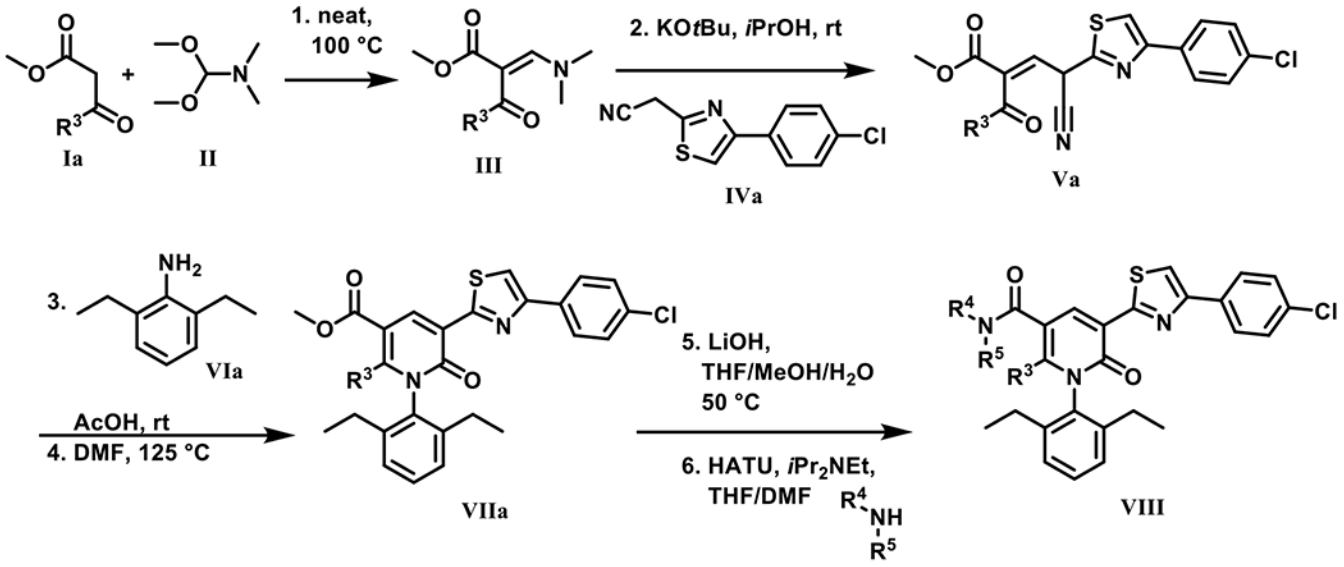


Figure 5.

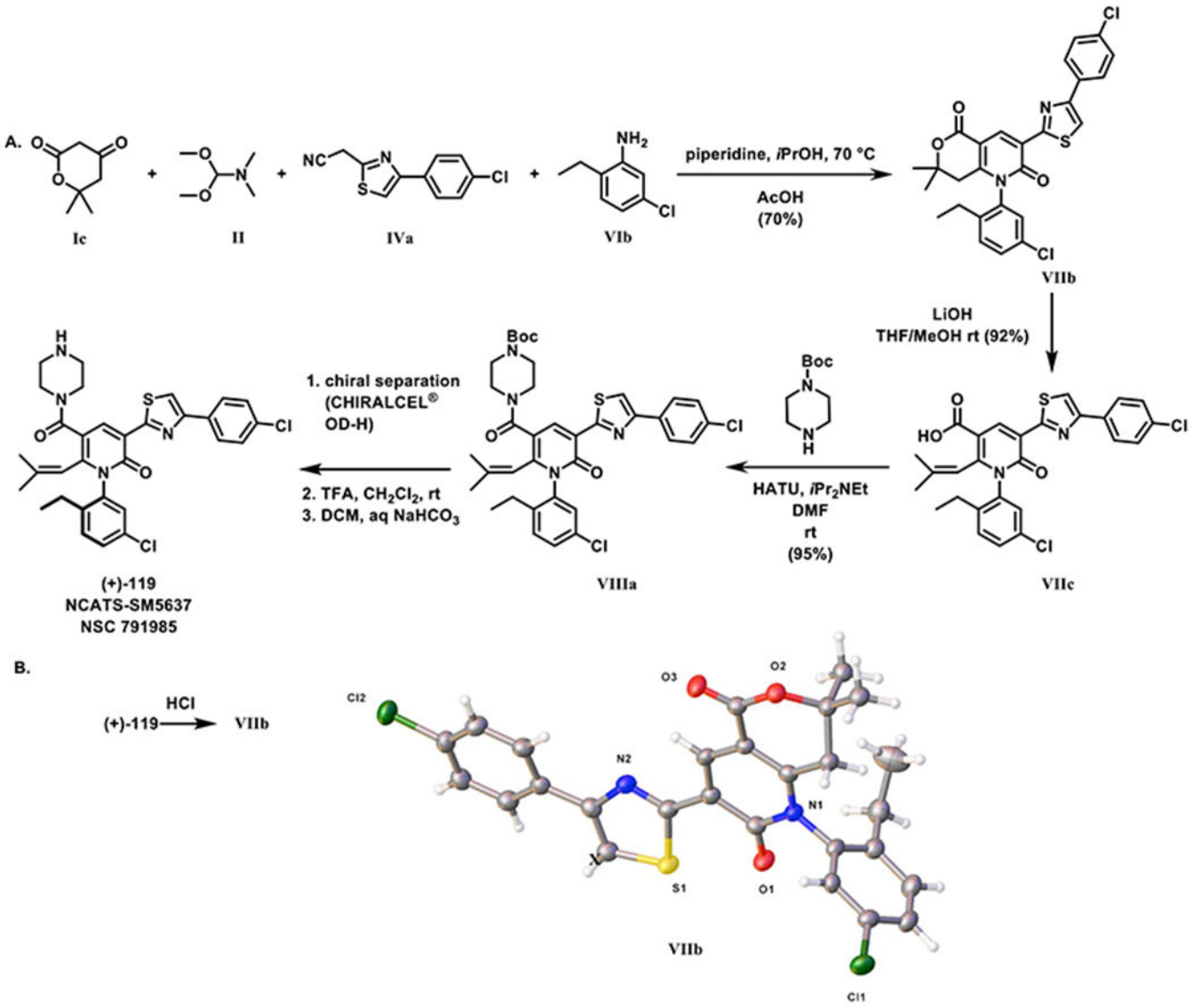
PK/PD in a U87 R132H mIDH-based xenograft mouse model: **A**. Concentrations of **(+)-119** or AG-120 in plasma and tumor after administration of a single 30 mpk PO dose. **B**. Concentrations of 2-HG in tumor.



Scheme 1.
General analog synthesis.



Scheme 2.
General amide synthesis.

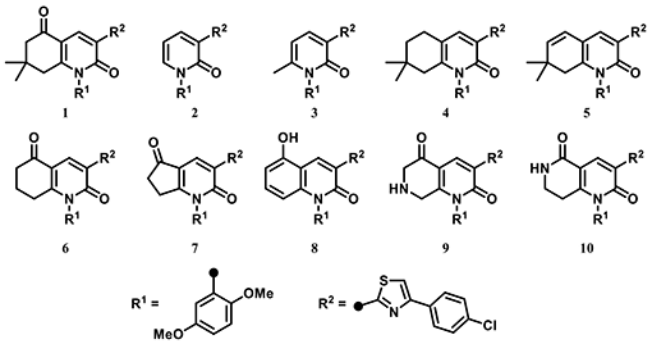


Scheme 3.

A. Synthesis of isobutylene analog **(+)-119** including separation of atropisomers. **B**. Formation of **VIIb** from **(+)-119** and its X-ray coordinates of its single crystal.

Table 1.

Core modifications and SAR.

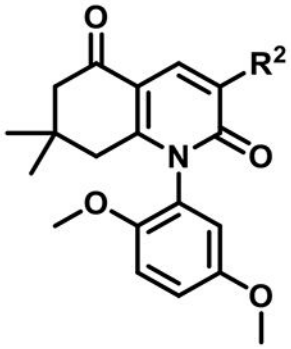


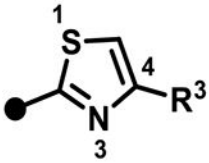
Biochemical	IDH1 R132H		IDH1 R132C	
Compound	**IC_{50}(μM) ± SD[a]**	**% inhibition ± SD at 38 μM**	**IC_{50}(μM) ± SD[a]**	**% inhibition ± SD at 38 μM**
1	1.6 ± 0.2	84 ± 7	1.0 ± 0.3	85 ± 9
2	> 38	-	> 38	-
3	> 38	-	> 38	-
4	3.6 ± 0.5	87 ± 3	-	64 ± 5
5	3.0 ± 0.3	96 ± 4	1.7 ± 0.2	76 ± 2
6	-	62 ± 1	-	43 ± 1
7	-	38 ± 1	-	29 ± 4
8	-	35 ± 0	-	36 ± 2
9	8.0 ± 2.4	75 ± 15	-	32 ± 3
10	2.3 ± 0.0	84 ± 1	-	65 ± 4

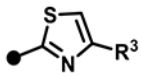
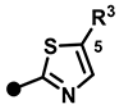
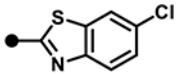
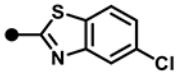
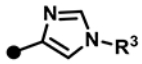
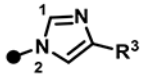
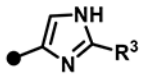
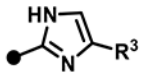
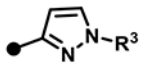
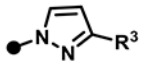
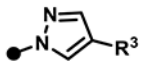
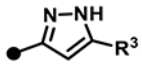
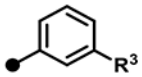
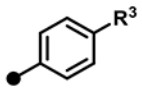
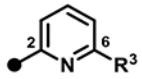
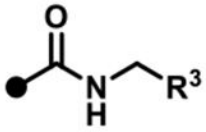
[a] IC_{50} values were determined utilizing the diaphorase and resazurin-coupled R132H and R132C mIDH1 assays (average of $N = 3$). IC_{50} values are reported only for compounds where ≥75% inhibition of enzyme activity was observed at the highest concentration tested (38 μM).

Table 2.

Thiazole substitution SAR.



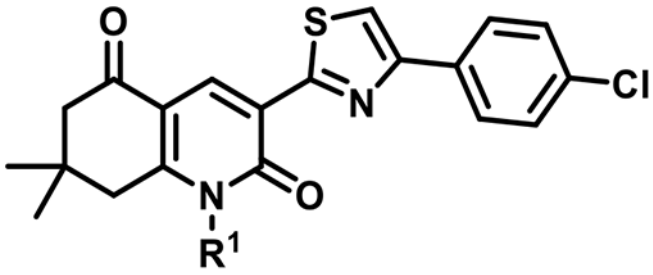
Biochemical			IDH1 R132H		IDH1 R132C	
Compd	R^2	R^3	IC_{50}(μM) ± SD[a]	% inhibition ± SD at 38 μM	IC_{50}(μM) ± SD[a]	% inhibition ± SD at 38 μM
1		4-Cl-Ph	1.6 ± 0.2	84 ± 7	1.0 ± 0.3	85 ± 9

11		Ph	1.2 ± 0.1	77 ± 2	-	59 ± 3
12		4-Cl-Ph	> 38	-	> 38	-
13		-	-	50 ± 1	2.5 ± 1.6	94 ± 21
14		-	> 38	-	> 38	-
15		4-Cl-Ph	-	41 ± 14	> 38	-
16		Ph	-	59 ± 5	-	44 ± 6
17		Ph	2.1 ± 0.1	75 ± 3	-	39 ± 5
18		4-Cl-Ph	2.2 ± 0.1	82 ± 1	2.5 ± 0.2	77 ± 21
19		Ph	3.1 ± 0.2	84 ± 7	-	46 ± 2
20		Ph	-	71 ± 2	-	41 ± 2
21		Ph	-	31 ± 7	> 38	-
22		Ph	-	47 ± 6	-	41 ± 10
23		4-Cl-Ph	> 38	-	> 38	-
24		Ph	> 38	-	> 38	-
25		4-Cl-Ph	-	67 ± 3	-	46 ± 6
26		4-Cl-Ph	-	35 ± 1	> 38	-

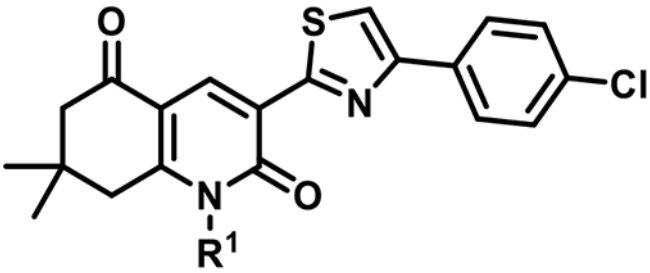
[a] IC_{50} values were determined utilizing the diaphorase and resazurin-coupled R132H and R132C mIDH1 assays (average of $N = 3$). IC_{50} values are reported only for compounds where ≥75% inhibition of enzyme activity was observed at the highest concentration tested (38 μM).

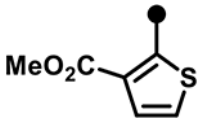
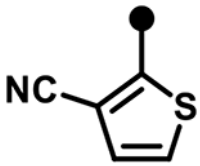
Table 3.

Pyridone Aryl Substituent SAR



Biochemical		IDH1 R132H		IDH1 R132C	
Compd	**R^1**	**IC_{50}(μM) ± SD[a]**	**% inhibition ± SD at 38 μM**	**IC_{50}(μM) ± SD[a]**	**% inhibition ± SD at 38 μM**
1	2,5-$(OMe)_2$Ph	1.6 ± 0.2	84 ± 7	1.0 ± 0.3	85 ± 9
27	Ph	-	47 ± 3	-	38 ± 2
28	2-OMe-Ph	2.4 ± 0.5	76 ± 3	-	65 ± 2
29	2-OEt-Ph	0.51 ± 0.03	88 ± 6	0.41 ± 0.03	81 ± 3
30	2-O*i*Pr-Ph	1.1 ± 0.2	80 ± 2	0.47 ± 0.05	77 ± 1
31	2-Me-Ph	-	74 ± 4	-	64 ± 2
32	2-Et-Ph	2.0 ± 0.1	91 ± 1	0.87 ± 0.28	83 ± 7
33	2-*i*Pr-Ph	-	62 ± 3	-	61 ± 6
34	2-Ph-Ph	-	59 ± 2	-	67 ± 2
35	2-OH-Ph	-	71 ± 1	-	61 ± 3
36	2-OPh-Ph	-	30 ± 1	-	60 ± 2
37	2-OBn-Ph	-	38 ± 2	-	61 ± 2
38	2-NH_2-Ph	-	57 ± 0	-	42 ± 2
39	2-NHMe-Ph	-	59 ± 3	-	43 ± 1
40	2-NMe_2-Ph	-	56 ± 4	-	57 ± 7
41	2-CO_2H-Ph	4.6 ± 0.3	96 ± 5	11 ± 1	105 ± 7
42	2-F-Ph	-	65 ± 5	-	49 ± 3
43	2-Cl-Ph	1.3 ± 0.1	83 ± 1	-	70 ± 1
44	2-CF_3-Ph	0.27 ± 0.00	96 ± 2	0.20 ± 0.01	87 ± 2
45	2-OCF_3-Ph	0.57 ± 0.04	98 ± 2	0.28 ± 0.02	78 ± 13
46	2-Py	-	47 ± 2	-	39 ± 1
47	2-OMeBn	-	61 ± 12	-	53 ± 1
48	α-MeBn	> 38	-	-	34 ± 1
49	*i*Pr	-	31 ± 8	-	33 ± 1
50	cyclohexyl	> 38	-	> 38	-

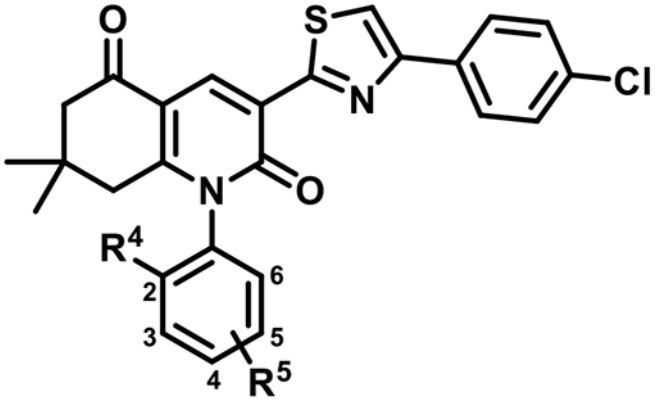


Biochemical		IDH1 R132H		IDH1 R132C	
Compd	**R[1]**	**IC_{50}(μM) ± SD[a]**	**% inhibition ± SD at 38 μM**	**IC_{50}(μM) ± SD[a]**	**% inhibition ± SD at 38 μM**
51		0.47 ± 0.01	94 ± 1	0.47 ± 0.01	83 ± 4
52		0.26 ± 0.02	100 ± 1	0.25 ± 0.02	90 ± 2

[a] IC_{50} values were determined utilizing the diaphorase and resazurin-coupled R132H and R132C mIDH1 assays (average of $N = 3$). IC_{50} values are reported only for compounds where ≥75% inhibition of enzyme activity was observed at the highest concentration tested (38 μM).

Table 4.

Pyridone Aryl Substituent SAR continued.

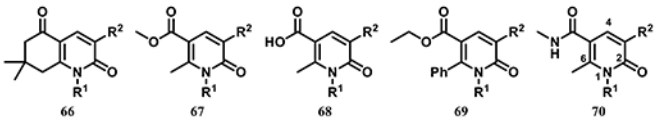


Biochemical			IDH1 R132H		IDH1 R132C	
Compd	**R^4**	**R^5**	**IC_{50}(μM) ± SD[a]**	**% inhibition ± SD at 38 μM**	**IC_{50}(μM) ± SD[a]**	**% inhibition ± SD at 38 μM**
1	OMe	5-OMe	1.6 ± 0.2	84 ± 7	1.0 ± 0.3	85 ± 9
53	OMe	3-OMe	-	64 ± 17	-	35 ± 3
54	OMe	4-OMe	> 38	-	> 38	-
55	OMe	6-OMe	2.4 ± 0.1	87 ± 2	1.6 ± 0.2	75 ± 7
56	OMe	3-CO_2H	14 ± 1	82 ± 2	-	65 ± 2
57	OMe	4-CO_2H	> 38	-	-	43 ± 6
58	OMe	5-CO_2H	12 ± 1	108 ± 2	14 ± 1	86 ± 4
59	OMe	6-CO_2H	0.91 ± 0.06	102 ± 3	2.0 ± 0.1	108 ± 1
60	OMe	6-Me	2.1 ± 0.1	81 ± 2	-	72 ± 1
61	OMe	3-N (Py)	1.0 ± 0.1	97 ± 1	1.3 ± 0.2	80 ± 1
62	OMe	5-N (Py)	> 38	-	> 38	-
63	OEt	5-OEt	0.16 ± 0.01	85 ± 1	0.064 ± 0.004	75 ± 1
64	OEt	6-OEt	0.39 ± 0.03	76 ± 4	0.16 ± 0.02	86 ± 7
65	Et	6-Me	0.79 ± 0.18	89 ± 1	0.50 ± 0.09	86 ± 3
66	Et	6-Et	0.69 ± 0.05	89 ± 2	0.24 ± 0.05	82 ± 4

[a] IC_{50} values were determined utilizing the diaphorase and resazurin-coupled R132H and R132C mIDH1 assays (average of $N = 3$). IC_{50} values are reported only for compounds where ≥75% inhibition of enzyme activity was observed at the highest concentration tested (38 μM).

Table 5.

Ring-opened core modifications.



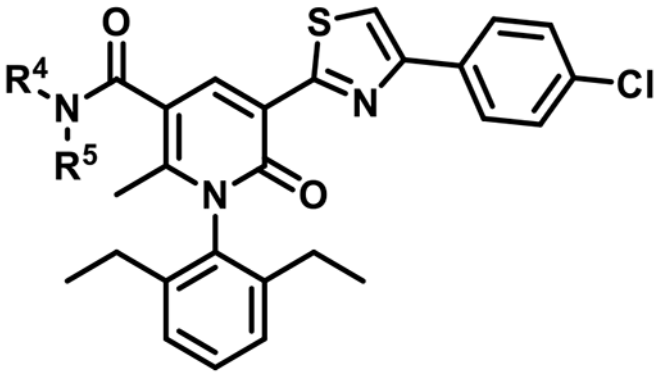
R^1 = 2,6-diethylphenyl
R^2 = 4-(4-chlorophenyl)thiazol-2-yl

Biochemical	IDH1 R132H		IDH1 R132C	
Core	**IC_{50}(μM) ± SD[a]**	**% inhibition ± SD at 38 μM**	**IC_{50}(μM) ± SD[a]**	**% inhibition ±SD at 38 μM**
1	1.6 ± 0.2	84 ± 7	1.0 ± 0.3	85 ± 4
10	2.3 ± 0.0	84 ± 1		65 ± 4
66	0.69 ± 0.05	89 ± 2	0.24 ± 0.05	82 ± 4
67	> 38	-	> 38	-
68	7.2 ± 0.5	102 ± 1		72 ± 3
69	> 38	-	> 38	-
70	1.5 ± 0.0	87 ± 3		64 ± 5

[a] IC_{50} values were determined utilizing the diaphorase and resazurin-coupled R132H and R132C mIDH1 assays. IC_{50} is reported only for compounds with >75% inhibition at 38μM, the highest concentration tested.

Table 6.

Amide substitution SAR.

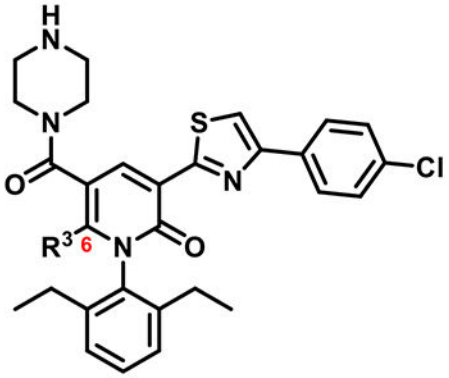


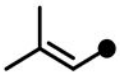
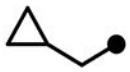
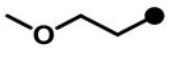
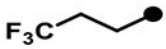
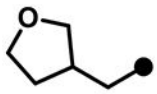
	Biochemical		IDH1 R132H		IDH1 R132C	
Compd	**R^4**	**R^5**	**IC_{50}(μM) ± SD[a]**	**% inhibition ± SD at 38 μM**	**IC_{50}(μM) ± SD[a]**	**% inhibition ± SD at 38 μM**
70	Me	H	1.5 ± 0.0	87 ± 3		64 ± 5
71	Me	Me	1.2 ± 0.1	98 ± 3	2.0 ± 0.1	86 ± 1
72	*i*Pr	H	2.8 ± 0.2	47 ± 1		54 ± 2
73	*t*Bu	H		65 ± 5		49 ± 4
74	*i*Bu	H	> 38		0.81 ± 0.05	56 ± 1
75	CH_2CH_2OH	H	0.42 ± 0.00	104 ± 3	2.0 ± 0.1	96 ± 2
76	CH_2CH_2OMe	H	2.1 ± 0.0	92 ± 2	0.73 ± 0.10	102 ± 5
77	CH_2CO_2H	H	1.2 ± 0.0	106 ± 2	11 ± 1	87 ± 4
78	$CH_2CH_2NH_2$	H	0.38 ± 0.00	97 ± 1	2.0 ± 0.1	89 ± 1
79	CH_2CH_2NHMe	H	0.87 ± 0.06	101 ± 3	0.32 ± 0.02	96 ± 2
80	CH_2CONH_2	H	1.6 ± 0.1	105 ± 3	3.8 ± 0.0	77 ± 14
81	$CH_2CH_2CH_2NHMe$	H	1.0 ± 0.1	104 ± 3	0.91 ± 0.06	95 ± 0
82	Ph	H		40 ± 21		69 ± 11
83	CH_2Ph	H	> 38			41 ± 1
84	cyclohexyl	H	> 38			31 ± 7
85	*N*-piperidine			51 ± 0		65 ± 3
86	*N*-morpholine		4.2 ± 0.0	82 ± 4	4.1 ± 0.3	71 ± 2
87	*N*-piperazine		0.21 ± 0.00	103 ± 3	1.5 ± 0.0	93 ± 2
88	*N*-4-Me-piperazine		2.9 ± 0.2	88 ± 1	1.2 ± 0.1	86 ± 3

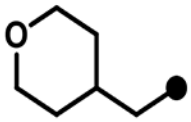
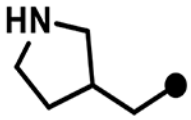
[a] IC_{50} values were determined utilizing the diaphorase and resazurin-coupled mIDH1 R132H and R132C assays. IC_{50} is reported for compounds with >75% inhibition at 38μM, the highest concentration tested.

Table 7.

Pyridinone 6-position SAR.



Biochemical		IDH1 R132H		IDH1 R132C	
Compd	R^3	$IC_{50}(\mu M) \pm SD^a$	% inhibition ± SD at 38 μM	$IC_{50}(\mu M) \pm SD^a$	% inhibition ± SD at 38 μM
87	Me	0.21 ± 0.00	103 ± 3	1.5 ± 0.0	93 ± 2
89	*n*Pr	0.075 ± 0.000	97 ± 2	0.10 ± 0.01	82 ± 13
90	*i*Pr	0.42 ± 0.00	102 ± 4	0.39 ± 0.05	92 ± 3
91	*i*Bu	0.11 ± 0.01	98 ± 2	0.12 ± 0.03	83 ± 14
92		0.044 ± 0.003	101 ± 1	0.058 ± 0.010	97 ± 11
93		0.055 ± 0.004	107 ± 2	0.049 ± 0.003	96 ± 3
94		0.14 ± 0.01	102 ± 6	0.34 ± 0.04	92 ± 8
95		0.24 ± 0.00	101 ± 3	0.60 ± 0.07	82 ± 12
96		0.075 ± 0.000	105 ± 3	0.13 ± 0.01	91 ± 1

97		1.1 ± 0.1	93 ± 2	0.98 ± 0.07	79 ± 3
98		10 ± 1	81 ± 2		52 ± 3

[a] IC_{50} values were determined utilizing the diaphorase and resazurin-coupled mIDH1 R132H and R132C assays. IC_{50} is reported for compounds with >75% inhibition at 38μM, the highest concentration tested.

Table 8.

In vitro drug-like properties of analogs with >10-fold increase in R132C mIDH1 potency over compound **87**

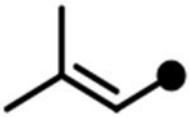
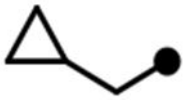
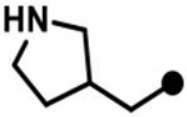
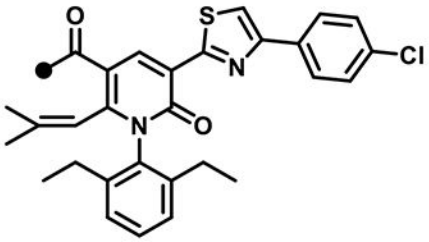
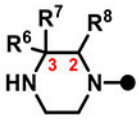
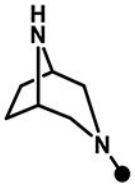
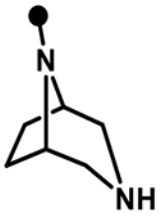
Compd	R^3	IDH1 R132H IC_{50} Fold improvement over 87	IDH1 R132C IC_{50} Fold improvement over 87	Single Point RLM ($t_{1/2}$, min)	PAMPA (10^{-6} cm/s)	Solubility (μg/mL)
89	*n*Pr	2.8	15	27	134	<1
91	*i*Bu	1.9	13	17	16	<1
92		4.8	26	14	225	<1
93		3.8	31	17	43	<1
98		2.8	12	7	24	<1

Table 9.

Piperazine SAR.



Biochemical					IDH1 R132H	IDH1 R132C
Compd	Carbonyl Substitution	R^6	R^7	R^8	$IC_{50}(\mu M) \pm SD^a$	$IC_{50}(\mu M) \pm SD^b$
92		H	H	H	0.044 ± 0.003	0.058 ± 0.010
99[c]		Me	H	H	0.044 ± 0.003	0.046 ± 0.003
100[c]		H	H	Me	0.039 ± 0.003	0.053 ± 0.006
101[c]		Et	H		0.10 ± 0.01	0.072 ± 0.005
102[c]		*n*Pr			0.13 ± 0.01	0.082 ± 0.014
103		CH_2-CH_2			0.078 ± 0.005	0.048 ± 0.006
104[c]		CH_2-OH	H		0.049 ± 0.003	0.060 ± 0.013
105		O (ketone)		H	0.035 ± 0.002	0.039 ± 0.003
106[c]		CF_3			0.36 ± 0.02	0.13 ± 0.00
107[c]		CN	H		0.16 ± 0.01	0.056 ± 0.010
108[c]		CO_2H			0.055 ± 0.004	0.064 ± 0.004
109[c]		$CONH_2$			0.094 ± 0.000	0.042 ± 0.000
110					0.24 ± 0.00	0.064 ± 0.021
111					0.094 ± 0.000	0.060 ± 0.007

112		0.062 ± 0.004	0.049 ± 0.003

IC_{50} values were determined utilizing the diaphorase and resazurin-coupled mIDH1 R132H and R132C assays.

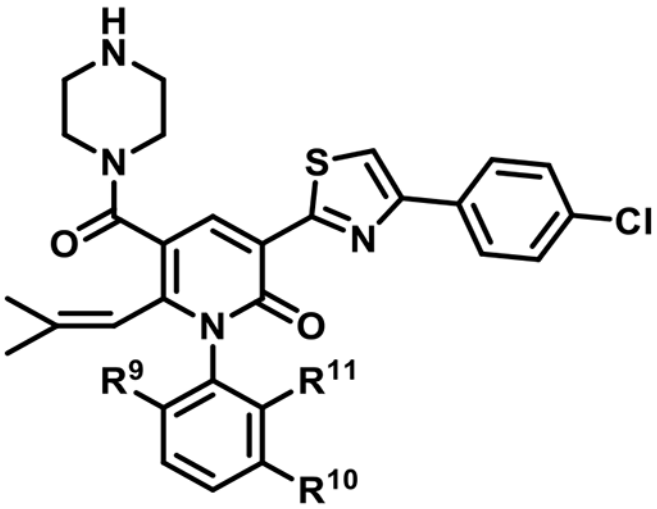
[a] Compounds showed >97% inhibition at 38 μM, the highest concentration tested.

[b] Compounds showed >85% inhibition at 38 μM, the highest concentration tested.

[c] Compounds are racemic.

Table 10.

SAR at the pyridinone N1-aryl ring.



Biochemical				IDH1 R132H	IDH1 R132C	
Compd	**R^9**	**R^{10}**	**R^{11}**	**IC_{50}(μM) ± SD[a]**	**IC_{50}(μM)± SD[a]**	
92	Et	H	Et	0.044 ± 0.003	0.058 ± 0.010	
113	H	H	H	0.33 ± 0.00	3.2 ± 0.6	
114	Et	H	H	0.056 ± 0.004	0.16 ± 0.01	
115	Et	H	Me	0.27 ± 0.00	2.2 ± 0.2	
116	Et	H	Cl	0.044 ± 0.003	0.055 ± 0.004	
117	Et	Me	H	0.044 ± 0.003	0.11 ± 0.02	
118				0.114 ± 0.007	0.075 ± 0.000	
(+)−118				0.12 ± 0.02	0.13 ± 0.03	
(−)−118	Et	OMe	H	0.42 ± 0.05	0.67 ± 0.04	
119				0.114 ± 0.007	0.10 ± 0.01	
(+)−119				0.081± 0.005	0.072 ± 0.005	**NCATS-SM5637, NSC 791985**
(−)−119	Et	Cl	H	0.25 ± 0.04	0.54 ± 0.10	
AG-120				0.065 ± 0.009	0.063 ± 0.015	

[a] IC_{50} values were determined utilizing the diaphorase and resazurin-coupled R132H and R132C mIDH1 assays. All compounds showed >80% inhibition at 38 μM, the highest concentration tested.

Table 11.

2-HG levels (% of vehicle control) in U87-mIDH1 (R132H) cells after 48h incubation with compound compared to DMSO and drug-like properties.

	% 2-HG[a]		IDH1 R132H[b]	Single Point	PAMPA	Solubility
Compd	**100 nM**	**500 nM**	**IC_{50}(μM)± SD**	**RLM ($t_{1/2}$, min)**	**(10^{-6} cm/s)**	**(μg/mL)**
91	33 ± 25	12 ± 6.4	0.11 ± 0.01	17	16	<1
92	13 ± 3.1	16 ± 1.1	0.044 ± 0.003	14	225	<1
99	11 ± 5.5	8 ± 2.3	0.044 ± 0.003	25	213	<1
100	14 ± 5.1	11 ± 5.3	0.039 ± 0.003	17	40	<1
103	17 ± 3.8	14 ± 0.81	0.078 ± 0.005	12	48	<1
105	23 ± 4.2	13 ± 3.1	0.035 ± 0.002	2	275	<1
108	29 ± 16	10 ± 8.6	0.055 ± 0.004	23	<1	16
111	11 ± 3.1	10 ± 3.4	0.094 ± 0.000	>30	89	<1
112	32 ± 8.4	18 ± 2.8	0.062 ± 0.004	9	99	<1
118	40 ± 1.7	19 ± 3.7	0.114 ± 0.007	>30	549	<1
(−)−119	ND	ND	0.25 ± 0.04	>30	255	<1
(+)−119	5.9 ± 0.16	4.1 ± 0.17	0.081 ± 0.005	>30	434	<1

[a] Values represent % 2-HG after 48 h incubation with inhibitor, where 100% is normalized to 2-HG levels in DMSO-treated control.

[b] The enzymatic R132H IC_{50} has been re-introduced in the table to visualize the entire data set for all compounds in this table.

ND: Not Determined.