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Synthesis, structure-activity relationship and antimalarial efficacy of 6-chloro-2-arylvinylquinolines

Guang Huang [a, †], Claribel Murillo Solano [b, †], Joel Melendez [b], Justin Shaw [b], Jennifer Collins [b], Robert Banks [c], Arash Keshavarzi Arshadi [b], Rachasak Boonhok [d, e], Hui Min [d], Jun Miao [d], Debopam Chakrabarti [b, *], Yu Yuan [a, *]

[a] Department of Chemistry, University of Central Florida, Orlando, FL 32816, USA

[b] Division of Molecular Microbiology, Burnett School of Biomedical Sciences, University of Central Florida, Orlando, FL 32826, USA

[c] Research Program Services, University of Central Florida, Orlando, FL 32816, USA

[d] Department of Internal Medicine, Morsani College of Medicine, University of South Florida, Tampa, FL 33612, USA

[e] Department of Medical Technology, School of Allied Health Science, Walailak University, Nakhon Si Thammarat 80160, Thailand

ABSTRACT

There is an urgent need to develop new efficacious antimalarials to address the emerging drug-resistant clinical cases. Our previous phenotypic screening identified styrylquinoline **UCF501** as a promising antimalarial compound. To optimize **UCF501**, we herein report a detailed structure-activity relationship study of 2-arylvinylquinolines, leading to the discovery of potent, low nanomolar antiplasmodial compounds against a *P. falciparum* CQ-resistant Dd2 strain, with excellent selectivity profiles (RI < 1 and SI > 200). Several metabolically stable 2-arylvinylquinolines are identified as fast-acting agents that kill asexual blood stage parasites at the trophozoite phase, and the most promising compound

24 also demonstrates transmission blocking potential. Additionally, the monophosphate salt of **24** exhibits excellent *in vivo* antimalarial efficacy in the murine model without noticeable toxicity. Thus, the 2-arylvinylquinolines represent a promising class of antimalarial drug leads.

KEYWORDS: malaria, antiplasmodial activity, 2-arylvinylquinolines, structure-activity relationship, fast-acting, parasitocidal, dual-stage activity

INTRODUCTION

Malaria afflicts almost half of the world's population, causing estimated 228 million clinical cases and 405,000 deaths in 2018. Predominant mortality was among children below age of five and pregnant women in Africa.[1] Significant progress has been made, over the last decade, to reduce the global malaria burden using ACTs and long-lasting insecticide treated nets as well as indoor residual spraying for vector control. However, the loss of efficacy of ACTs in the CQ-resistant malaria strains underscores the fragility of gains accomplished in the global effort for malaria eradication. To mitigate this alarming situation and achieve the eventual elimination of malaria, it is important to develop inexpensive chemical entities against drug-resistant malaria parasite strains, ideally those that possess transmission-blocking properties.

Important strategies to develop new antimalarial compounds involve structural re-engineering of exiting drugs such as CQ, a landmark 4-aminoquinoline compound due to its efficacy against all types of human malaria parasites, long half-life, low cost and a favorable safety profiles.[2] However, CQ has lost it efficacy due to mutations in the gene

encoding the DV membrane protein PfCRT, leading to reduced drug accumulation in its site of action and ultimately CQ resistance.[3] Based on this premise, numerous CQ analogues with conformational rigid nitrogen-containing side chains[4-6] and CQ hybrids (CQ-resistance reverse agents,[7-9] CQ-artemisinin,[10-12] CQ-synthetic peroxide,[13-15] CQ-ferrocene,[16, 17] CQ-chalcone,[17-19] CQ-*N*-contained heterocyclic compound,[9, 20-22] etc.) have been developed to overcome the resistance and improve the antimalarial activity. Piperaquine and Ferroquine are examples of re-engineered CQ analogues. The former containing two 7-chloro-aminoquinoline moieties is extensively used in Southeast Asia for prophylaxis and treatment.[23] The latter, a 7-chloroaminoquinoline covalently linked to an aminoferrocenyl group, is in phase II pilot clinical trials.[24, 25] Thus, the quinoline scaffold is a privileged structure that can be reengineered to design new antimalarial candidates.[2, 9, 26-28]

Within the quinoline class, styrylquinoline derivatives display a wide spectrum of pharmacological properties, such as antileishmanial,[29] anticancer,[30] anti-HIV[31] and anti-Alzheimer's activity.[32] Recently, we reported the discovery of styrylquinoline **UCF501** with promising *in vitro* and *in vivo* antiplasmodial activity.[33] In particular, it exhibited a more potent inhibitory activity against CQ-resistant strain than that against CQ-sensitive strain. From a mechanistic perspective, **UCF501** may in fact act differently from CQ, while its exact molecular target remained elusive. Although a number of analogues were reported in the previous investigation, a detailed account is highly desirable to elucidate the SAR of this chemotype. Notably, all of them were less active than the lead compound **UCF501**. Herein, we describe a comprehensive medicinal chemistry study on arylvinylquinolines (Fig. 1), report the key structural determinants for the antimalarial activity, and identify

new compounds that show improved microsomal stability over **UCF501**. In addition, we disclose the details of the specific stage action, the rate of killing, and an *in vivo* evaluation of the frontrunner compounds.

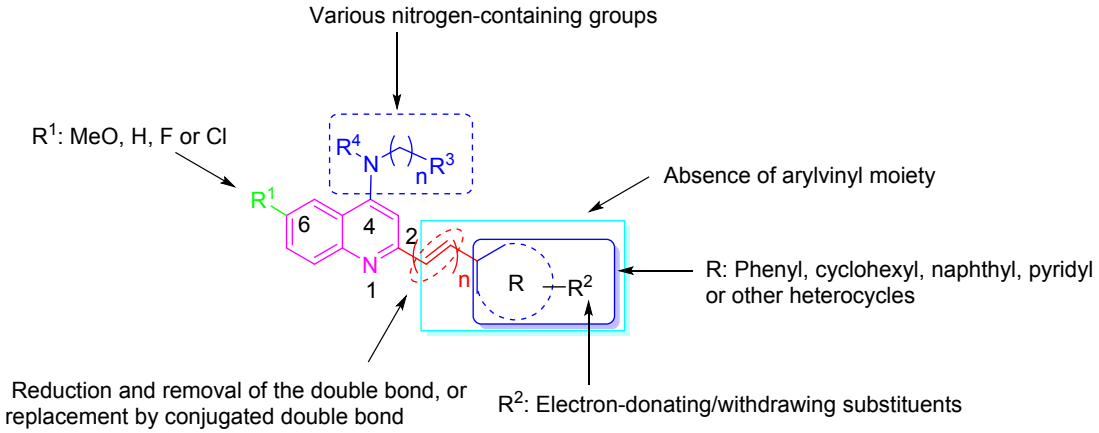


Figure 1. SAR strategy around the quinoline scaffold.

RESULTS AND DISCUSSION

Chemistry

The synthesis of compounds **8-37** (Scheme 1 and Table 1) started from commercially available anilines **1a-d**. The reaction of aniline **1a** with ethyl acetoacetate **2** in the presence of acetic acid afforded an imine intermediate, which was converted to hydroxyquinoline **3a** at elevated temperature.[34] Alternatively, hydroxyquinolines **3a-d** were synthesized by mixing anilines **1a-d** with **2** in the presence of PPA.[35] The chlorination of hydroxyquinolines **3a-d** with phosphorus oxychloride gave 4-chloroquinolines **4a-d** in quantitative yields, which were then reacted with neat *N*,*N*-dimethylaminoalkylamines **5a-b** via nucleophilic substitution to produce the aminoquinolines **6a-6e** in excellent yields. Subsequent olefination of **6a-6e** with appropriate aromatic aldehydes **7a-l** using *p*-$TsNH_2$ as a catalyst were carried out in xylene to afford (*E*)-styrylquinolines **8-37**.[33]

To study the effect of heterocycles and carbocycles other than benzenoid on the antiplasmodial potency, 2-arylvinylquinolines **39-57** (Scheme 2 and Table 2) were synthesized from 2-methylquinolines **6a-c**, following the same synthetic sequence as shown for styrylquinolines **8-37**.

To investigate the influence of the double bond on the antimalarial activity, 2-pyridylethylquinolines **58** and **59** were prepared in good yields (Scheme 3 and Table 3) through the reduction of 2-pyridylvinylquinolines (**41** and **50)** with hydrazine hydrate at 80 °C.[36]

To understand the effect of the C4-amino group on the antimalarial potency, arylvinylquinoline derivatives **62-72**, **81-87** and **90-96** were synthesized (Table 4). The synthetic route of **62-72** is depicted in Scheme 4, using a similar chemistry as described in Scheme 1. A growing number of studies demonstrated that the isonitrile group displays good antimalarial activity,[37-40] and thus, we prepared compound **64** for the antimalarial evaluation. Initially, we employed the direct olefination reaction to construct the arylvinylquinoline motif, but no discernable amount of **64** was detected. Therefore, an alternative synthetic route was adopted to prepare isonitrile **64** (Scheme 5). In detail, benzyl bromide **73** was reacted with a stoichiometric amount of triethylphosphite to give the phosphonate **74** via an Arbuzov reaction,[41] which was then converted to amine **75** by the reduction of the nitro group. Isonitrile **76** was then obtained by treatment of amine **75** with chloroform in the presence of a base. Subsequently, aldehyde **77**, derived from selenium dioxide oxidation of 2-methylquinoline **61a**,[42] was reacted with phosphonate **76** to afford isonitrile **64** in moderate yield via a Horner-Wadsworth-Emmons reaction.[43]

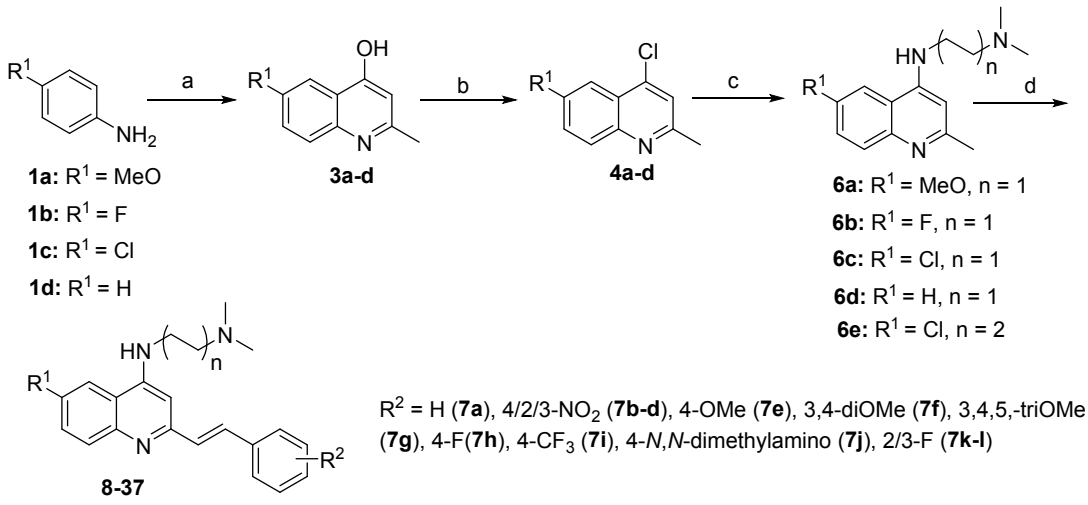
Diversification of the amino group was achieved through nucleophilic substitutions. For examples, aminoquinolines **80a-c** were prepared by mixing chloroquinoline **4c** with the aminoalcohol followed by mesylation and substitution. With aminoquinolines **80a-c** in hand, 2-arylvinylquinolines **81-87** were obtained by reacting with appropriate aldehydes (Scheme 6).

The designed compounds **90-96**, containing propylamine and butylamine moieties, were synthesized in two steps (Scheme 7). First, treatment of quinoline **4c** with appropriate amines **88a-c** furnished aminoquinolines **89a-c**, and second, aminoquinolines **89a-c** were converted to **90-96** by the corresponding olefination reaction.

Next, we turned our attention to the analogues containing various fluorinated substituents and conjugated double bonds. The synthesis of arylvinylquinolines **98-114** were commenced from methylquinoline **89b** and the appropriate aldehydes **7i** or **97a-p** (Scheme 8 and Table 5), using the identical procedures described for compounds **90-96**.

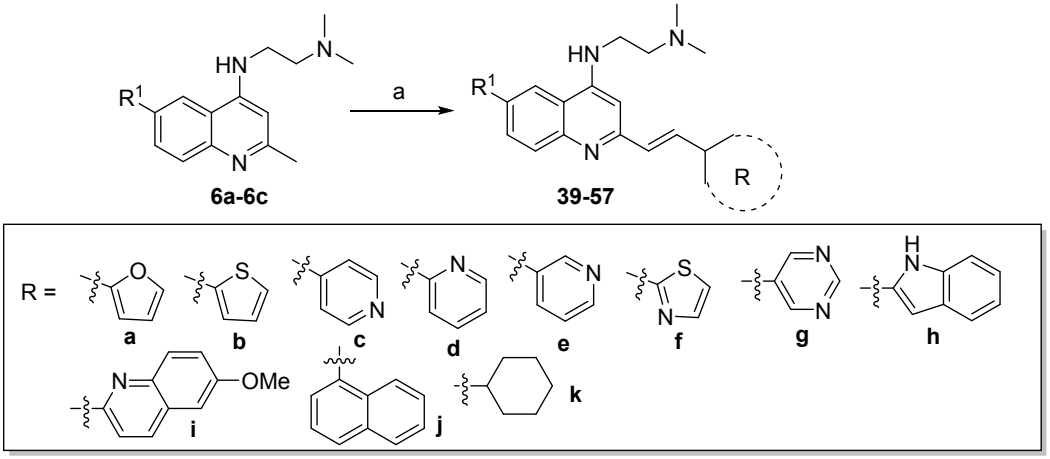
To evaluate the importance of the double bond, arylquinolines **119** and **120** were synthesized from 4-chloroaniline **1c** (Scheme 9 and Table 5). Briefly, aniline **1c** and ethyl benzoylacetate **115** or ethyl isonicotinoyl acetate **116** were condensed in the presence of PPA to give hydroxyquinolines **117a** or **117b**, which were transformed into chloroarylquinolines **118a** or **118b**. Subsequent nucleophilic substitution with 4-morpholinobutanamine furnished 4-aminoarylvinylquinolines **119** and **120**, respectively.

Scheme 1. Synthesis of 6-substituted 2-styrylquinolines 8-37 [α]



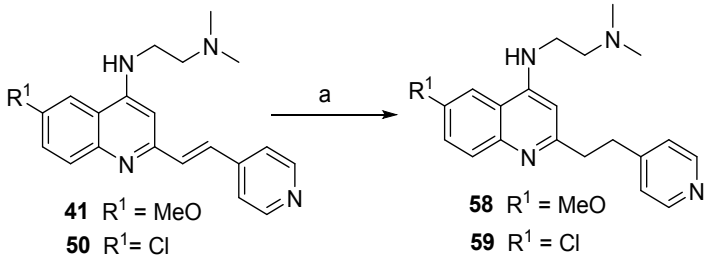
[α]Reagents and conditions: a) method A for **3a**: i. *p*-anisidine **1a**, ethyl acetoacetate **2**, acetic acid, anhydrous magnesium sulfate, ethanol, 90 °C, 6 h; ii. Dowtherm, 270 °C, 30 min, 43% for 2 steps; method B for **3a-d**: anilines **1a-d**, ethyl acetoacetate **2**, PPA, 150 °C, 2 h, 57-68%; b) phosphorus oxychloride, 105 °C, 2 h, 85-90%; c) *N*,*N*-dimethylaminoalkylamines **5a-b**, 130 °C, 24 h, 87-93%; d) aromatic aldehydes **7a-l**, *p*-$TsNH_2$, xylene, 130 °C, 12 h, 60-89%.

Scheme 2. Synthesis of 6-substituted 2-arylvinylquinolines 39-57 [α]



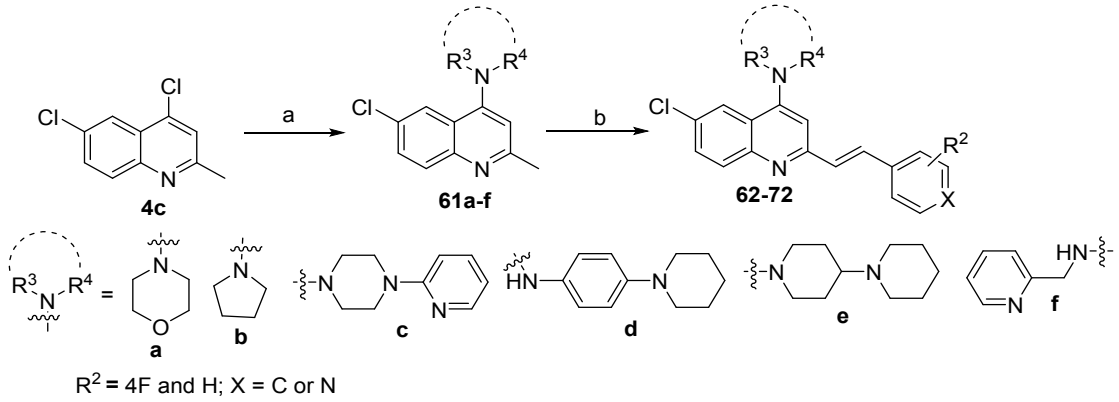
[α]Reagents and conditions: a) *p*-$TsNH_2$, aldehydes **38a-k**, xylene, 130 °C, 12 h, 48-86%.

Scheme 3. Synthesis of 6-substituted 2-alkylquinolines 58-59 [α]



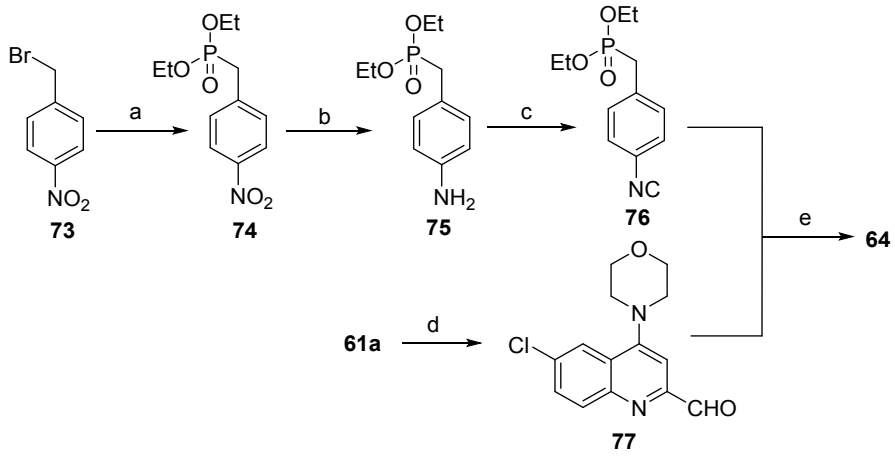
[α]Reagents and conditions: a) hydrazine hydrate, EtOH, 80 °C, 36 h, 81-83%.

Scheme 4. Synthesis of 4-substituted-arylvinylquinolines 62-72 [α]



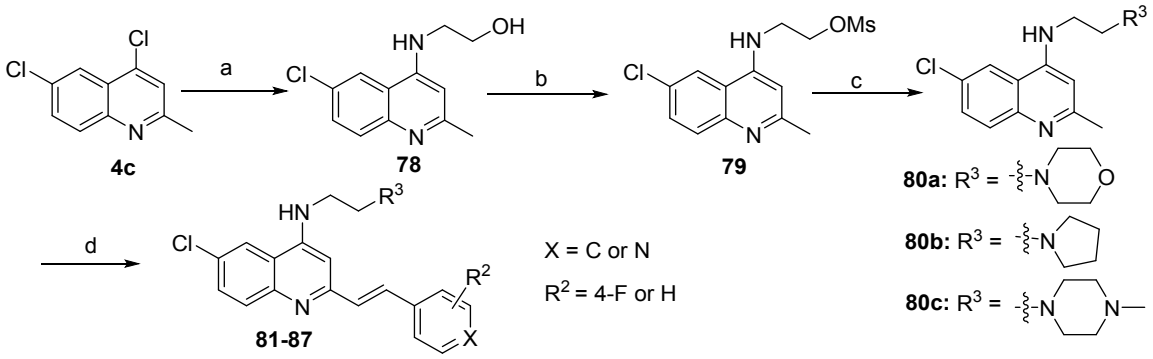
[α]Reagents and conditions: a) amines **60a-f** ,130 °C, EtOH, 12 h, 73-92%; b) aldehydes **7a**, **7h** or **38c**, *p*-$TsNH_2$, xylene, 130 °C, 12 h, 48-89%.

Scheme 5. Synthesis of isonitrile styrylquinoline 64 [α]



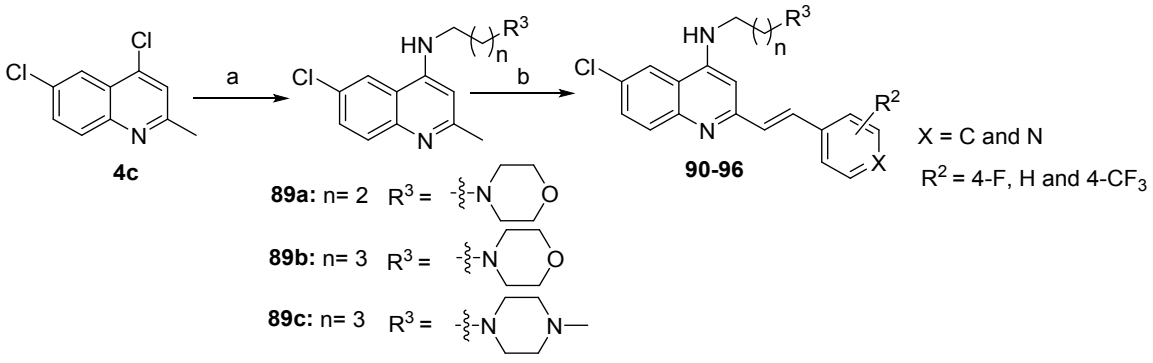
[α]Reagents and conditions: a) triethylphosphite, reflux, 20 h, 88%; b) Pd/C, H_2, MeOH, overnight, 75%; c) 50% NaOH, $CHCl_3$, tetrabutylammonium bromide, DCM, rt to 40 °C, 2 h, 80%; d) SeO_2, 1,4-dioxane, 80 °C, 6 h, 32%; e) potassium *tert*-butoxide, anhydrous DMF, rt, 1 h, 58%.

Scheme 6. Synthesis of 4-aminoarylvinylquinolines 81-87 [α]



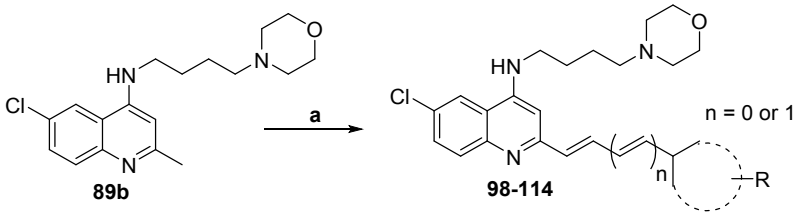
[α]Reagents and conditions: a) 2-aminoethanol, EtOH, 130 °C, 48 h, 97%; b) MsCl, Et_3N, THF, 0 °C, 1 h, 72%; c) K_2CO_3, amines, anhydrous CH_3CN, reflux, overnight, 80-94%; d) aldehydes **7a**, **7h** or **38c**, *p*-$TsNH_2$, xylene, 130 °C, 12 h, 79-91%.

Scheme 7. Synthesis of 4-aminoarylvinylquinolines 90-96 [α]



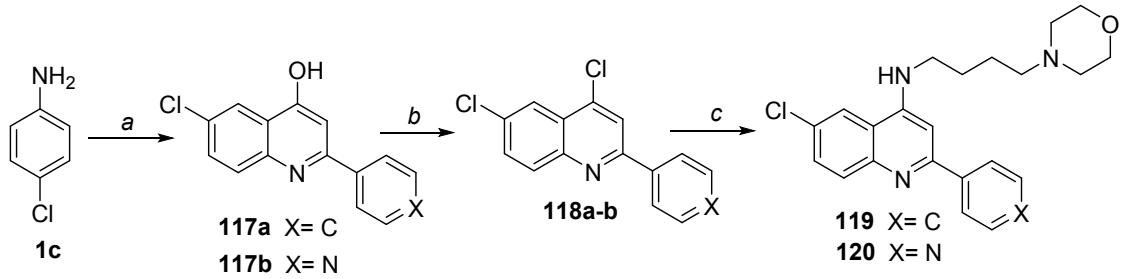
[α]Reagents and conditions: a) aliphatic amines **88a-c**, 130 °C, 24 h, 86-93%; b) aldehydes **7a**, **7h**, **7j** or **38c**, *p*-$TsNH_2$, xylene, 130 °C, 12 h, 67-88%.

Scheme 8. Synthesis of 4-morpholinobutylaminoarylvinylquinolines 98-114 [α]



[α]Reagents and conditions: a) aldehydes **7i** and **97a-p**, *p*-$TsNH_2$, xylene, 130 °C, 12 h, 52-92%.

Scheme 9. Synthesis of 4-morpholinobutylaminoarylquinolines 119-120 [α]



[α]Reagents and conditions: a) ethyl benzoylacetate **115** or ethyl isonicotinoyl acetate **116**, 150 °C, PPA, 6 h; b) phosphorus oxychloride, 105 °C, 2 h, 20-45% for two steps; c) 4-morpholinobutanamine, 130 °C, 24 h, 43-49%.

Biology

In vitro Antiplasmodial Activity and Cytotoxicity

The SAR studies were focused on improving the *in vitro* activity of 2-arylvinylquinolines against the CQ-resistant *Pf* Dd2 strain.

SAR1 Targets. A series of styrylquinoline analogues **8-34** bearing various C6 substituents (R^1) and benzenoid substituents (R^2) were evaluated for their *in vitro* activity against Dd2 strain (Table 1).

In the C6-methoxy series, compound **9** (R^2 = 4-NO_2, EC_{50} = 28.6 ± 0.9 nM) exhibited slightly higher inhibitory activity than the unsubstituted compound **8** (R^2 = H, EC_{50} = 41.2 ± 5.3 nM). Moving the nitro group from the *para*-position to *ortho*- or *meta*-position led to decreased activity, as seen with compound **10** (EC_{50} = 56.3 ± 8.1 nM) and **11** (EC_{50} = 49.5 ± 4.0 nM). Replacement of the nitro group with 4-methxoy, 3,4-dimethoxy and 3,4,5-trimethxoy groups afforded compounds **12**-**14**, respectively, which were less potent than compound **9**.

The introduction of a fluorine atom at the C6 position improved antiplasmodial activity over the corresponding methoxylated analogues. For instance, compound **16** (R^2 = H, EC_{50} = 21.0 ± 2.1 nM) and compound **21** (R^2 = 3,4,5-trimethoxy, EC_{50} = 38.6 ± 1.8 nM) showed almost 2-fold greater activity than the counterparts **8** and **14**. Another noteworthy observation was that fluorinated analogue **20** with a 3,4-dimethoxy group exhibited approximately 4.5-fold improved activity as compared to compound **13**.

Substitution of the fluorine atom by a chlorine atom led to further enhancement of the antiplasmodial activity. Chlorostyrylquinolines bearing a fluoro or trifluoromethyl group on the benzene ring showed potent activity against Dd2 strain. Among these analogues, compound **29** (R^2 = 4-F) was the most active one with an EC_{50} value of 4.8 ± 2.0 nM, which was almost 14-fold more potent than **UCF501**. Compared with compound **29**, compound **24** and **31** demonstrated slightly lower inhibitory activity with EC_{50} values of 10.9 ± 1.9 and 5.9 ± 1.4 nM, respectively. However, altering the fluorine atom from the *para* position to *ortho* position led to 5-fold decrease in activity as observed in compound **30** (EC_{50} = 26.0 ± 0.9 nM). For all styrylquinolines (R^1 = -OMe, -F and -Cl), the introduction of electron-rich groups (R^2) proved to be detrimental to the antiplasmodial

potency, as seen with compounds **12-14**, **19-21** and **25-28**, which were less active relative to their analogues (R^2 = H and 4-NO_2).

Removal of the C6-substituent (R^1 = H) caused a significant drop in the antiplasmodial activity. For example, compound **32** (R^1 = H, EC_{50} = 80.7 ± 22.4 nM) exhibited a much lower activity than the corresponding analogues **8** (R^1 = MeO), **16** (R^1 = F) and **22** (R^1 = Cl). Therefore, the general trend of the substituents at the C6 position in the order of improved potency is H < OMe < F < Cl.

We also briefly investigated the spacing parameter for the C4 amino side-chain of styrylquinolines. As shown in Table 1, significant loss of potency was observed for the compounds containing a dimethylaminobutyl group. It appeared that, for styrylquinolines, dimethylaminoethylamine was a superior side-chain to dimethylaminobutylamine.

SAR2 Targets. Having determined the impacts of dimethylaminoalkyl and halogen substituents on the antiplasmodial activity, we next tested if the replacement of the phenyl ring (R) with heterocycles and non-benzenoid carbocycles would affect the inhibitory activity against Dd2 strain (Table 2). Substitutions of the benzenoid motif by five-membered aromatic heterocycles including furan (compounds **39**, **44** and **47**), thiophene (compounds **40**, **45** and **48**) and thiazole (compound **49**) led to the reduced antiplasmodial activity. However, replacement of the phenyl group with a 4-pyridyl group (compounds **41**, **46** and **50**) retained the antiplasmodial potency. Importantly, the position of nitrogen atom significantly influenced the antiplasmodial activity. For instance, 4-pyridylvinylquinoline **50** was approximately 2-fold more active than compound **51** bearing 2-pyridylvinyl group. This manifestation became more evident for methoxylated

pyridylvinylquinolines since the activity difference was up to 30-fold, e.g. compound **41** (R = 4-pyridyl, EC_{50} = 33.6 ± 5.8 nM) and **42** (R = 2-pyridyl, EC_{50} = 1032.8 ± 232.9 nM).

Moreover, chlorinated arylvinylquinolines were more potent than the corresponding fluorinated and methoxylated analogues in this series. For instance, compound **47** (R^1 = Cl, EC_{50} = 37.0 ± 4.3 nM) showed a 2-fold higher activity than compounds **39** (R^1 = MeO, EC_{50} = 88.7 ± 2.3 nM) and **44** (R^1 = F, EC_{50} = 82.6 ± 9.4 nM). Accordingly, this work provided further supports that the chlorine atom at the C6 position was superior to fluorine atom and methoxy substituent for the antiplasmodial potency.

In addition, we found that replacement of pyridine by other heterocycles such as pyrimidine, indole and quinoline resulted in a marked loss of potency, as seen with the corresponding arylvinylquinolines **53** (EC_{50} = 155.0 ± 11.6 nM), **54** (EC_{50} = 95.9 ± 6.7 nM) and **55** (EC_{50} = 281.3 ± 40.3 nM). Unfortunately, our search for compounds more active than **22** by incorporating carbocycles, such as naphthalene and saturated cyclohexane, to the vinylquinoline scaffold was unsuccessful.

SAR3 Targets. Compared with 4-aminoquinolines, e.g. CQ, a unique feature of our lead compound is the vinyl group that bridges the quinoline core and the aromatic ring. In this series, we intended to assess the impacts of the double bond on antiplasmodial activity. As illustrated in Table 3, in the absence of arylvinyl group, aminoquinolines **6a**, **6c** and **6e** were inactive against the Dd2 strain. Even with an aromatic group, the saturated analogues showed almost an order of magnitude weaker activity than the vinyl analogues, as demonstrated by pyridylethylquinoline **58** (EC_{50} = 708.7 ± 58.2 nM) vs **41** (EC_{50} = 38.8 ± 4.7 nM) and pyridylethylquinolines **59** (EC_{50} = 259.0 ± 15.5 nM) vs **50** (EC_{50} = 28.8 ± 5.0

nM). Therefore, these data indicated that the absence of the 2-arylvinyl moiety severely reduced the antiplasmodial activity, which was in line with recent studies.[29, 44]

SAR4 Targets. Having identified the optimal substituent at the C6 position and the aromatic motif (phenyl and pyridyl) at C2 position, we shifted our focus on exploring nitrogen-containing groups at C4 position. As a result, the first subset of analogues **62**-**72** were prepared by incorporating morpholine, pyrrolidine, 1-(2-pyridyl)piperazine, 4-piperidinoaniline and bipiperidine directly to the arylvinylquinoline scaffold, and they were screened for their antiplasmodial activity (Table 4). These compounds generally showed moderate to low activity against the Dd2 strain, with EC_{50} values ranging from 428.0 ± 15.0 to 6753.3 ± 1076.0 nM. Unexpectedly, the isonitrile compound **64** did not show significant antiplasmodial activity (EC_{50} > 1000 nM). Meanwhile, we found that the arylvinylquinoline (R^1 = 4-NC) containing *N*,*N*-dimethylaminoethylamino group was less potent than compound **29** (data not shown). Compound **72** bearing a 2-picolylmethylamine moiety, the most active compound in this subset, had an EC_{50} value of 155.5 ± 34.5 nM.

Inspired by the above-mentioned results, the second subset of analogues **81**-**96** were synthesized by attaching different alkylamines. These analogues displayed promising activities with EC_{50} values below 100 nM, and the majority of them were more potent than the positive control **UCF501**. The nitrogen atom spacing was also screened in this subset of analogues. For the morpholinylalkylamine series, arylvinylquinolines with a tetramethylene linker showed a much higher activity than that of di- or trimethylene linkers as demonstrated by the most potent compounds **92** (EC_{50} = 2.4 ± 1.1 nM) and **93** (EC_{50} = 9.9 ± 1.3 nM), displaying almost a 2-fold and 13-fold improved potency as compared with the counterparts **81** and **82**, respectively. However, this linker length preference was

inconclusive for the *N*-methylpiperazinylalkylamine series. For example, compound **96**, containing a 4-carbon linker, was slightly more active compared to the corresponding analogue **87**. Whereas compound **86** bearing a 2-carbon linker was nearly 2.5-fold more potent than analogue **95**.

SAR5 Targets. After C4-substitution optimization, we used arylvinylquinolines containing a 4-morpholinobutanamine motif (**92** and **93**) as benchmark molecules for further investigation. In this series, we focused on the C2 modification by fluorine-containing aromatics. Given the wide use of fluorine substitution in drug discovery to improve biological activity, permeability, pharmacokinetic issues,[45-47] and in light of morpholine as a privileged structure with advantageous physicochemical, biological, and metabolic properties,[48] it was expected to produce synergistic effects when these two motifs were combined. For this reason, we prepared arylvinylquinolines **98**-**114** with the optimal 4-morpholinobutanamine at the C4 position to evaluate their capability to suppress the growth of the Dd2 strain. The results are summarized in Table 5. Compound **100** with a 3-trifluoromethyl group showed comparable activity to its *para* positional isomer **98**, which was 3-fold more potent than the *ortho* isomer **99** (EC_{50} = 103.6 ± 7.2 nM). This result provided additional evidence that introducing *ortho*-substituents at the phenyl ring may compromise the antiplasmodial potency. Replacement of the 4-trifluoromethyl group by 4-trifluoromethoxy substituent afforded compound **101** with a slightly decreased activity. A noteworthy observation was that the introduction of di-substituted fluorinated phenyl ring caused a significant loss of antiplasmodial potency as observed in analogues **102**-**105**. We also observed that compounds **105** and **104** were nearly 7-fold and 2.5-fold more active than **103**, respectively, confirming that the fluorine substituent at the *para*

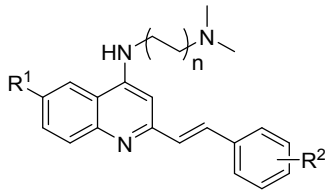
position of phenyl ring was favorable to improve the antiplasmodial activity. Further fluorination on the phenyl ring dramatically reduced the activity, rendering compounds **106-108** less active than the benchmark molecule **92**. Collectively, the SAR study demonstrated that monofluorination at the *para*-position is the best choice within current scope of screening and any positional deviation or excessive fluorination is disadvantageous for the antiplasmodial potency. Additionally, these results suggested that there is limited space available for the target interactions, with the substituent *ortho*-position and steric effects being particularly sensitive.

Deviating from our expectations, the introduction of a fluorine atom at the pyridine ring did not increase the antiplasmodial activity. For instance, compound **109** with a 3-fluoro substituent (EC_{50} = 79.6 ± 11.8 nM) was almost 7.5-fold less active than the counterpart **93** (Table 4, EC_{50} = 9.9 ± 1.3 nM). Interestingly, both pyridylvinylquinolines **109** and **111** demonstrated much weaker inhibitory activity than compound **110** (EC_{50} = 54.6 ± 16.5 nM). Additionally, among this series, compound **112** bearing 3-fluoropyridine moiety displayed the weakest inhibitory effect on the Dd2 strain with an EC_{50} value of 197.1 ± 16.5 nM. Again, these results implied that the *ortho* substitution at the aromatic ring could intervene the target interactions that were quite sensitive to the steric effect and the orientation of the aromatic ring.

Analogues with a different number of double bonds (**113-114** and **119-120**) were also assessed for their *in vitro* antiplasmodial activity. Compounds **113** and **114** with two double bonds exhibited a much lower activity than the benchmark compounds, implying that a single double bond is a better choice for improving the antimalarial potency. Additional support for the crucial role of vinyl group came from the evaluation of analogues without

any double bond. As shown in Table 5, a loss of activity was observed in arylquinolines **119** and **120** (EC_{50} > 400 nM). Thus, we concluded that a single double bond between the quinoline core and the aromatic ring is required for the antiplasmodial activity, highlighting the uniqueness of our chemical scaffold.

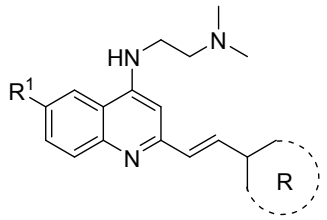
Table 1. Antiplasmodial activity of SAR1 targets against Dd2 strain

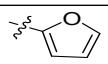
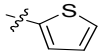


Compd	R^1	n	R^2	EC_{50} (nM)
8	MeO	1	H	41.2 ± 5.3
9	MeO	1	4-NO_2	28.6 ± 0.9
10	MeO	1	2-NO_2	56.3 ± 8.1
11	MeO	1	3-NO_2	49.5 ± 4.0
12	MeO	1	4-OMe	43.6 ± 2.0
13	MeO	1	3,4-diOMe	187.3 ± 13.6
14	MeO	1	3,4,5-triOMe	74.2 ± 8.8
15	MeO	1	4-F	32.9 ± 5.1
16	F	1	H	21.0 ± 2.1
17	F	1	4-NO_2	30.9 ± 5.9
18	F	1	4-F	30.9 ± 5.5
19	F	1	4-OMe	37.8 ± 8.7
20	F	1	3,4-diOMe	41.1 ± 0.6
21	F	1	3,4,5-triOMe	38.6 ± 1.8
22	Cl	1	H	22.4 ± 2.0
23	Cl	1	4-NO_2	28.7 ± 3.8
24	Cl	1	4-CF_3	10.9 ± 1.9

25	Cl	1	4-OMe	34.8 ± 7.9
26	Cl	1	3,4-diOMe	38.9 ± 7.8
27	Cl	1	3,4,5-triOMe	44.4 ± 3.6
28	Cl	1	4-*N*,*N*-dimethylamino	88.3 ± 2.2
29	Cl	1	4-F	4.8 ± 2.0
30	Cl	1	2-F	26.0 ± 0.9
31	Cl	1	3-F	5.9 ± 1.4
32	H	1	H	80.7 ± 22.4
33	H	1	4-NO_2	47.9 ± 9.5
34	H	1	4-F	25.5 ± 7.1
35	Cl	2	H	68.0 ± 9.0
36	Cl	2	4-NO_2	52.5 ± 2.0
37	Cl	2	4-F	51.2 ± 1.6
UCF501				67.0 ± 8.0
CQ				174.0 ± 15.5

Table 2. Antiplasmodial activity of SAR 2 targets against Dd2 strain



Compd	R^1	R	EC_{50} (nM)
39	MeO		88.7 ± 2.3
40	MeO		80.0 ± 7.0

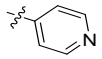
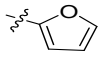
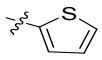
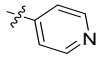
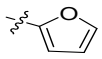
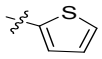
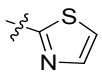
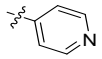
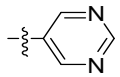
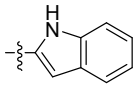
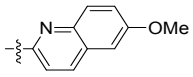
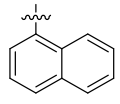
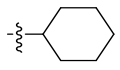
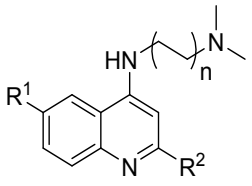
41	MeO		38.8 ± 4.7
42	MeO		1032.8 ± 232.9
43	MeO		71.0 ± 27.5
44	F		82.6 ± 9.4
45	F		110.9 ± 29.1
46	F		36.1 ± 2.1
47	Cl		37.0 ± 4.3
48	Cl		29.7 ± 4.6
49	Cl		239.7 ± 30.6
50	Cl		28.8 ± 5.0
51	Cl		67.5 ± 1.9
52	Cl		33.6 ± 5.8
53	Cl		155.0 ± 11.6
54	Cl		95.9 ± 6.7
55	Cl		281.3 ± 40.3
56	Cl		373.0 ± 19.0
57	Cl		394.0 ± 40.0

Table 3. Antiplasmodial activity of SAR 3 targets against Dd2 strain



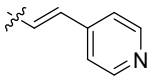
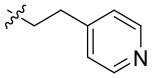
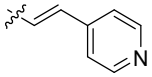
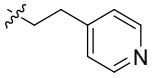
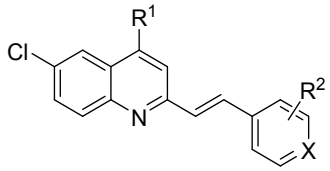
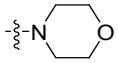
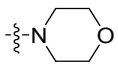
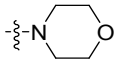
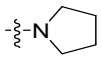
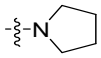
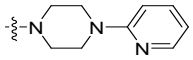
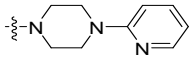
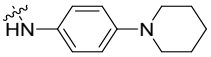
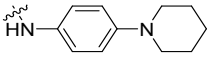
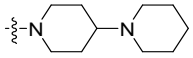
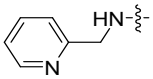
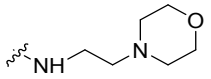
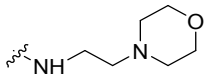
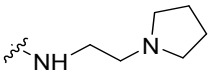
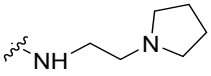
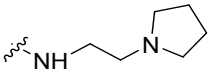
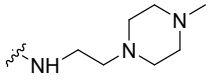
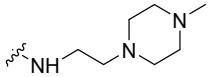
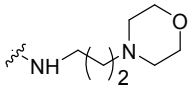
Compd	R^1	n	R^2	EC_{50} (nM)
6a	MeO	1	Me	5516.0 ± 571.3
6c	Cl	1	Me	731.6 ± 107.1
6e	Cl	2	Me	1245.0 ± 139.2
41	MeO	1		38.8 ± 4.7
58	MeO	1		708.7 ± 58.2
50	Cl	1		28.8 ± 5.0
59	Cl	1		259.0 ± 15.5

Table 4. Antiplasmodial activity of SAR 4 targets against Dd2 strain



Compd	R^1	X	R^2	EC_{50} (nM)
62		C	4-F	6753.3 ± 1076.0
63		N	H	3590.0 ± 870.0

64		C	4-NC	1007.6 ± 84.2
65		C	4-F	428.0 ± 15.0
66		N	H	1185.0 ± 175.0
67		C	4-F	3300.0 ± 60.0
68		N	H	2570.0 ± 610.0
69		C	4-F	666.7 ± 116.7
70		N	H	793.3 ± 81.3
71		C	4-F	486.7 ± 69.5
72		C	4-F	155.5 ± 34.5
81		C	4-F	24.2 ± 0.8
82		N	H	136.9 ± 14.6
83		C	4-F	92.3 ± 5.8
84		C	H	106.9 ± 8.4
85		N	H	67.7 ± 11.6
86		C	4-F	15.3 ± 3.4
87		N	H	53.3 ± 8.5
90		C	4-F	40.8 ± 5.6

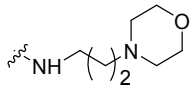
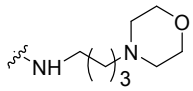
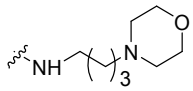
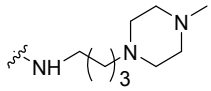
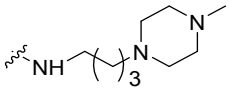
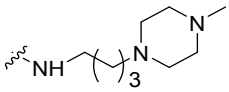
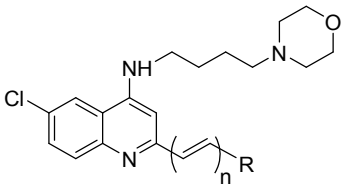
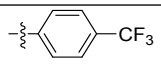
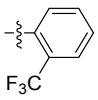
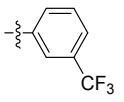
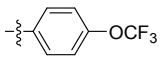
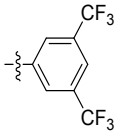
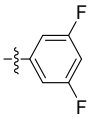
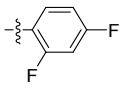
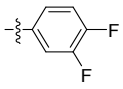
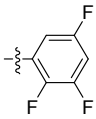
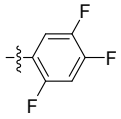
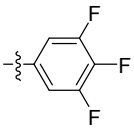
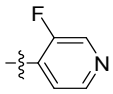
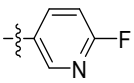
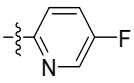
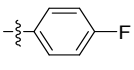
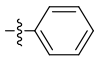
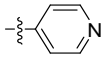
91		C	4-CF_3	84.8 ± 6.3
92		C	4-F	2.4 ± 1.1
93		N	H	9.9 ± 1.3
94		C	H	58.9 ± 8.8
95		C	4-F	43.0 ± 7.5
96		N	H	33.4 ± 5.4

Table 5. Antiplasmodial activity of SAR 5 targets against Dd2 strain



Compd	n	R	EC_{50} (nM)
98	1		30.7 ± 5.2
99	1		103.6 ± 7.2
100	1		33.9 ± 1.4
101	1		56.6 ± 7.6

102	1		108.0 ± 8.0
103	1		185.3 ± 34.1
104	1		72.6 ± 17.2
105	1		25.5 ± 6.1
106	1		587.5 ± 255.5
107	1		196.7 ± 39.7
108	1		130.1 ± 34.9
109	1		79.6 ± 11.8
110	1		54.6 ± 16.5
111	1		73.1 ± 11.9
112	1		197.1 ± 81.2
113	2		96.5 ± 24.4
114	2		142.7 ± 18.6

119	0		422.7 ± 62.7
120	0		796.3 ± 161.3

Upon completion of the SAR study on Dd2 strain, several bioactive arylvinylquinolines were selected for further antiplasmodium activity assay using the CQ-sensitive 3D7 strain (Table S1 and Table 6). Methoxylated styrylquinolines (**8** and **13-14**) bearing dimethylaminoethylamine moiety exhibited much stronger inhibitory activity against CQ-sensitive 3D7 strain than CQ-resistant Dd2 strain (RI ≥ 1.5), whereas all fluorinated and chlorinated analogues were more potent against Dd2 strain than 3D7 (RI < 1), except for compounds **28** (RI = 1.3), indicative of no cross-resistance induced by these vinylquinolines between the CQ-resistant and CQ-sensitive parasites. By contrast, RI of CQ is almost 10. In this series, the SAR trends observed for the 3D7 strain were similar to that observed for the Dd2 strain. For instance, compound **30** with a 2-fluoro group (EC_{50} = 55.9 ± 9.5 nM) showed remarkably diminished potency as compared to the corresponding 4-fluoro (compound **29**, EC_{50} = 8.7 ± 0.5 nM) or 3-fluoro analogues (compound **31**, EC_{50} = 23.0 ± 2.8 nM). Besides, removal of methoxy group or fluorine atom at C6 position of styrylquinoline scaffold resulted in the decreased activity, as seen with compounds **32** vs **8** and **32** vs **16**. In addition, 2-pyridylvinylquinoline **51** were less potent than its corresponding isomers **50** and **52** against 3D7 strain. All pyridylvinylquinolines demonstrated highly potent activity against Dd2 strain as compared to 3D7 strain (RI < 1), as seen with compounds **41**, **46** and **50-52**. Interestingly, substitution of pyridine in compound **50** by other nitrogen-containing heterocycles (e.g. pyrimidine, indole and quinoline) and carbocycles (e.g. naphthalene and cyclohexane) led to respective

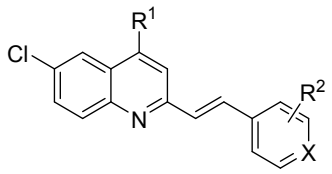
compounds **53-57**, which displayed significantly stronger growth-inhibitory effect on 3D7 strain than Dd2 strain (RI ≥ 1.3) (Table S1). These results indicated that, for R group, phenyl and pyridyl are favorable to overcome cross-resistance.

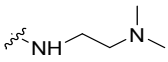
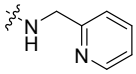
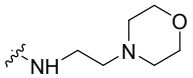
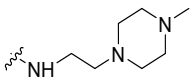
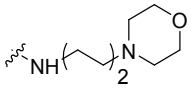
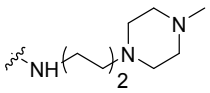
A similar observation was that arylvinylquinolines (**64** and **67-72**) devoid of the methylene linker exhibited moderate to low activity against the 3D7 strain with EC_{50} values in the ranger of 155.0 ± 6.0 to 2643.1 ± 214.8 nM (Table S1). By comparison, incorporation of morpholinoalkylamino or *N*-methylpiperazinylalkylamino group to the arylvinylquinoline scaffold markedly enhanced the antiplasmodial activity against 3D7 strain. These results further confirmed that the introduction of flexible alkylamine moiety on the arylvinylquinoline scaffold was beneficial to the antiplasmodium activity. It was worth noting that, among this subset, arylvinylquinolines (**106-107**, **110** and **112**) containing 4-morpholinobutanamino motif showed significantly improved inhibitory activity against 3D7 strain relative to Dd2 strain. In addition, compound **110** was almost 5-fold more potent than compound **112** against 3D7 strain, further corroborating the result that the positional effect of nitrogen atom and fluorine atom on the pyridyl ring dramatically influenced the antiplasmodial activity.

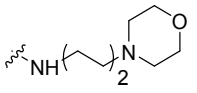
Selected compounds were also evaluated for their cytotoxicity against HepG2 cells (Table 6). In most cases the cytotoxicity profiles of these compounds correlated well with their antiplasmodial activity, as demonstrated by compounds **24** vs **29**, **29** vs **72** vs **81**, **72** vs **81** vs **86**, **81** vs **92**, **86** vs **96**, **93** vs **96** and **98** vs **105**. For instance, compound **92** containing a tetramethylene linker exhibited nearly 6-fold increase in inhibitory activity against the 3D7 strain and a 4.8-fold increase in cytotoxicity relative to compound **81**. Nevertheless, the cytotoxic activity of compound **24** was comparable to compound **98**,

although compound **24** demonstrated more potent antiparasitic activity. Additionally, we observed that the position of fluorine atom at the phenyl ring has a marginal effect on their cytotoxicity, as seen with compounds **29-31**. Notably, all compounds tested showed high selectivity profiles (SI > 120), especially for compounds **24**, **29** and **92** (SI > 1000), indicating good safety windows.

Table 6. Selectivity and resistance indices of synthesized analogues.



Compd	R^1	X	R^2	Antiplasmodium activity EC_{50} (nM)			Cytotoxic activity EC_{50} (nM)	
				Dd2	3D7	RI [a]	HepG2	SI [b]
24			4-CF_3	10.9 ± 1.9	16.8 ± 0.8	0.6	11235.3 ± 1855.0	1031
29		C	4-F	4.8 ± 2.0	8.7 ± 0.5	0.6	5331.6 ± 964.9	1110
30			2-F	26.0 ± 0.9	55.9 ± 9.5	0.5	4827.3 ± 1072.0	186
31			3-F	5.9 ± 1.4	23.0 ± 2.8	0.3	4777.4 ± 1588.0	810
50		N	H	28.8 ± 5.0	56.6 ± 11.3	0.5	6110.6 ± 1046.0	212
72				155.5 ± 34.5	248.3 ± 35.1	0.6	19760.6 ± 3272.0	127
81				24.2 ± 0.8	41.8 ± 12.7	0.6	17204.6 ± 3299.0	711
86		C	4-F	15.3 ± 3.4	15.7 ± 2.9	1.0	3195.2 ± 490.8	209
92		C	4-F	2.4 ± 1.1	6.9 ± 1.3	0.3	3547.0 ± 384.1	1478
93		N	H	9.9 ± 1.3	20.8 ± 4.4	0.5	5670.1 ± 1162.0	561
96		N	H	33.4 ± 5.4	36.1 ± 11.3	0.9	8377.7 ± 2576.0	251

98		C	4-CF_3	30.7 ± 5.2	73.8 ± 9.7	0.4	10178.2 ± 2391.0	332
105			3,4-diF	25.5 ± 6.1	27.6 ± 1.2	0.9	6135.2 ± 1222.0	241
UCF501	-			67.0 ± 8.0	119.0 ± 3.0	0.6	7019.1 ± 244.5	105
CQ	-			174.0 ± 15.5	17.8 ± 5.5	9.8	10430.0 ± 860.0	60

[a] RI = Dd2 EC_{50} / 3D7 EC_{50}; [b] SI = HepG2 EC_{50} / Dd2 EC_{50}

Metabolic Stability and Preliminary Metabolite Identification.

To assess the metabolic stability, selected compounds listed in Table 7 were subjected to an *in vitro* microsomal turnover assay with mouse liver microsomal preparations. This assay determines the percentage of the parent compound residues after 60 min incubation (Table 7). We identified that compounds bearing the 4-trifluoromethyl group on the phenyl ring exhibited a better metabolic stability than that with 4-fluoro group, as demonstrated by compounds **24** ($t_{1/2}$ = 104.2 min) vs **29** ($t_{1/2}$ = 55.2 min) and **92** ($t_{1/2}$ = 22.2 min) vs **98** ($t_{1/2}$ = 64.9 min). The intrinsic stability of the *N*, *N*-dimethylaminoethylamino moiety was superior to the 2-pyridinemethanamino or 2-(4-methylpiperaziyl)ethanamino groups, e.g. compounds **29** vs **72** ($t_{1/2}$ = 65.3 min) and **86** ($t_{1/2}$ = 60.3 min). The morpholine motif appeared to be the most labile group upon enzymatic degradation as seen with compound **92** which had the shortest half-life time ($t_{1/2}$ = 22.2 min) in this series. Additionally, we observed that replacing the phenyl ring with pyridine in arylvinylquinoline rendered the compound more susceptible to hepatic metabolism, such as in the case of compounds **50** ($t_{1/2}$ = 22.3 min) and compound **93** ($t_{1/2}$ = 14.4 min). This suggested that the pyridyl ring had no advantages over benzenoids in the microsomal stability. The assay indicated that the C4 amino side-chain and the arylvinyl group significantly influenced compound metabolic stability.

In the context of the present study, the metabolite mixture was analyzed by LC-MS after 15, 30, 60 min incubations. *N*-dealkylation from the tertiary terminal amine and oxidation of arylvinylquinoline scaffold appeared to be the major pathways for the metabolic decomposition, which is consistent with the previous studies on 4-aminoquinolines metabolism,[4, 8, 49] and P450 mediated oxidation in liver microsomes.[8, 50] For example, the microsomal metabolites of **UCF501** were primarily derived from *N*-deethylation of the tertiary amine (monodeethyl **UCF501**, **UCF501-M1**), *O*-demethylation (**UCF501-M2**), oxidation of styrylquinoline (**UCF501-M3**) and the reduction of the nitro group (three minor metabolites, Figure S1). The tentatively assigned metabolites of compound **29** included monodemethylated (**29-M1**), bidemethylated (**29-M2**) and oxidized products (**29-M3**) (Figure S3). The same decomposition pathway was not observed for compound **24** containing an identical C4 side-chain (Figure S2), which could explain the different metabolic stability profiles of **24**, **29** and **UCF501**. Although *N*-demethylation was the primary metabolic route for compound **24**, its half-life time was acceptable as compared to related compounds in other literature reports.[8, 27, 51, 52]

Demethylated (**86-M1**) and oxidized products (**86-M2**) were identified as the possible metabolites of compound **86** (Figure S4). The metabolic instability of arylvinylquinolines **92**, **93**, **98** and **105** was largely attributed to the breakage of the morpholine ring (alkanolamine metabolite **M1** and primary amine metabolite **M2**). Among this series, compound **93** was the most susceptible to hepatic metabolism, and oxidative metabolites **93-M3** and **93-M4** were observed in addition to ring-opening metabolites **M1** and **M2** (Figure S5).

Table 7. *In vitro* metabolism in mouse liver microsomes

Compd	% remaining after 60 min	Projected $t_{1/2}$ (min)	Clint (μL/min/mg)
24	67.1	104.2	13.3
29	47.1	55.2	25.1
31	38.2	43.2	32.1
50	15.5	22.3	62.2
72	52.9	65.3	21.2
86	50.2	60.3	23.0
92	15.4	22.2	62.4
93	5.6	14.4	96.2
98	52.7	64.9	21.4
105	19.9	25.8	53.7
UCF501	36.7	41.5	33.4
	47.8[a]	56.2[a]	-

[a] Values reported from the initial study.[33]

2-Arylvinylquinolines Blocks Trophozoite Stage in *Pf* Asexual Life Cycle

To understand the antiplasmodial activity of 2-arylvinylquinolines, we decided to establish the developmental stage specific action of the most promising compounds **24**, **29** and **86** by microscopic and flow cytometric analysis.[33, 53] Tightly synchronized cultures were exposed to 5 × EC_{50} concentration of compound **24** at 6, 18, 30 and 42 h post-invasion (HPI) of the merozoites. DHA (50 nM), atovaquone (6.6 nM), and DMSO vehicle were included as controls. Microscopic analysis of Giemsa-stained-thin smears and flow cytometric evaluation were performed at 12 h intervals. As seen in Figure 2A, the untreated control cultures underwent normal cell cycle progress through trophozoite (18 HPI), early schizont (30 HPI), late schizont/segmenter (42 HPI) and reinvaded ring (54 HPI) with an increased peak height (Figure 2A-B). In contrast to untreated cultures, the cycle

progression of compound **24**-treated cultures was blocked when compound was added at 6, 18, and 30 HPI (Figure 2A-B). However, the main effect seems to be in the transition between late trophozoite and schizont stages. In contrast, the addition of compound **24** at a later stage (42 HPI) did not affect the schizont maturation or the reinvasion of new merozoites occurred (Figure 2A-B). Similarly, compounds **29** and **86** demonstrated stage-specific action at the late trophozoite phase in Dd2 cultures (Figure S6 and S7). The stage-specific inhibition in the DHA and Atovaquone-treated cultures replicated the expected pattern, inhibition of all stages in the case of DHA and no inhibition in late stages with atovaquone (Figure S8 and S9). Thus, these results indicated that 2-arylvinylquinolines inhibit blood stage parasites by acting in the late trophozoite phase in the *Pf* asexual life cycle.

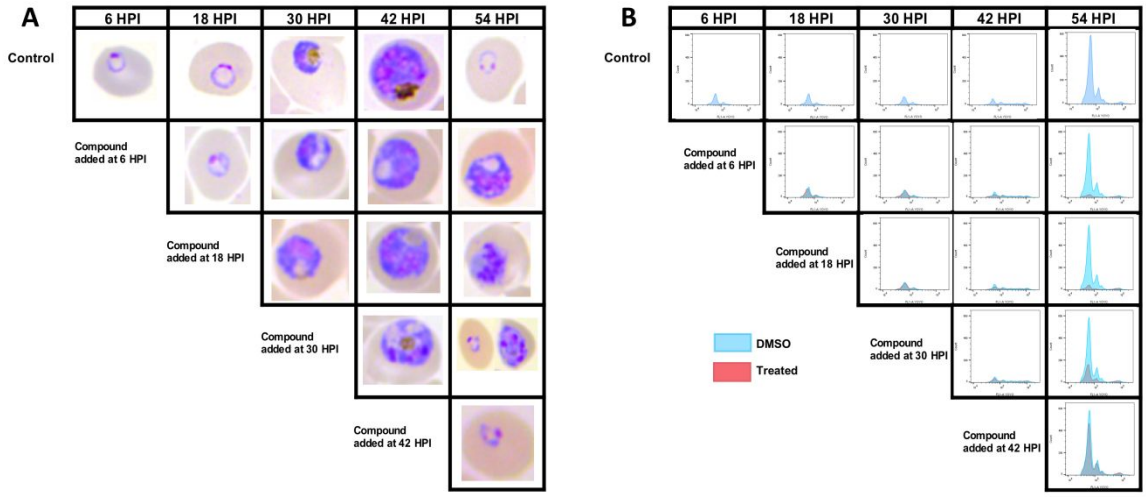


Figure 2. Stage-specific inhibition of *Pf* growth by compound **24**. Tightly synchronized Dd2 parasites were treated at 6, 18, 30 and 42 h post-invasion (HPI) with compound **24** at 5 × EC_{50} concentration. Samples for Giemsa staining and flow cytometry were collected every 12 h following compound addition. (A) Microscopic images of Giemsa-stained thin smears. (B) Histogram plot of YOYO-1 labeled cells from flow cytometric analysis. Results shown are representative of three independent biological replicates.

Ultrastructural Effects of 2-Arylvinylquinolines

A notable morphological change in parasites upon exposure to compound **24** is the appearance of large vacuoles. To explore those morphological changes, parasites were exposed to **24** at 5 × EC_{50} for 1.5, 3, 6 and 12 h and processed for TEM. Micrographs revealed the appearance of membrane bound structures within the parasite DV (Figure 3). These structures were observed as early as 1.5 h following compound exposure in the late trophozoite-early schizont stages and persisted until 12 h post exposure (Figure 3). The enlarged food vacuoles observed in the Giemsa-stained parasites may be due to the accumulation of undegraded hemoglobin as has been reported previously in parasites treated with inhibitors targeting proteases in the parasite food vacuole.[54] Similar morphological alterations observed in the DV in TEM images have been reported in parasite treated with piperaquine.[55] Although the mechanism of action of the piperaquine has not been elucidated, genetic changes in Plasmepsin II and III have been associated with clinical resistance to this drug.[56] Plasmepsin II is a key enzyme in the degradation of host hemoglobin.[57] The presence of this phenotype in parasites treated with compound **24** and the fact that the compound acts on the trophozoite when most hemoglobin degradation occurs, suggests that hemoglobin digestion could be a potential cellular target of **24**.

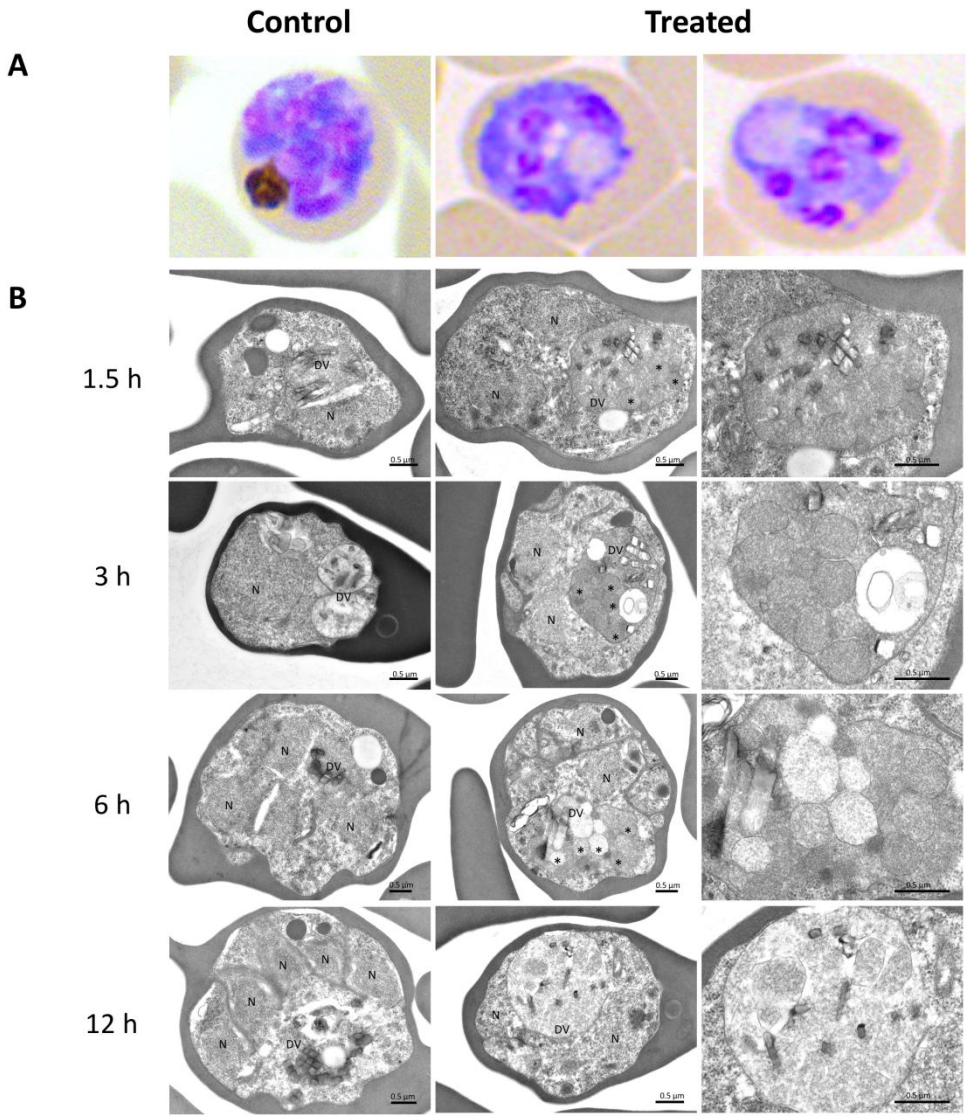


Figure 3. Transmission electron micrograph of *Pf* Dd2 exposed to 5 × EC_{50} compound **24**. (A) Giemsa stained image of representative parasites processed for TEM. A large vacuole is observed in the cytosol of treated parasites. (B) Micrographs of parasite after treatment with compound **24** for increasing periods of time. Parasites treated with 0.15% DMSO used as a control. Micrographs of treated parasite show membrane-bound structures within DV (*) suggesting undigested hemoglobin vesicles. Details of DV from treated parasite with undigested vesicles (*) and hemozoin crystals are shown in the far-right panel. Scale bar is 0.5 µm.

2-Arylvinylquinolines Are Fast-acting Parasitocidal Agents

To study whether 2-arylvinylquinolines exerted their antiplasmodial activity through a parasitocidal or parasitostatic mechanism, time kill kinetic experiments using the Dd2 strain were performed.[33] Asynchronously growing Dd2 cultures were treated with 5 × EC_{50} concentrations of 2-arylvinylquinolines **24**, **29**, **86**, DHA (50 nM) and atovaquone (6.6 nM) for different lengths of time (6, 12, 24 or 48 h). After removal of the inhibitors after the specified incubation times, culture growth was assessed for 96 h. DHA and atovaquone were used as references for fast- and slow-acting compounds, respectively. A notable reduction in parasitemias was observed following all treatment durations with compounds **24**, **29** and **86**, which was similar to the kill kinetic profile of DHA (Figure 4A-D).[58] In contrast, as can be seen from Figure 4A-D, parasites exposed to atovaquone required a longer exposure (48 h) to induce a reduction in the parasitemias, confirming its slow-acting antiplasmodial activity. Overall, these results suggested that 2-arylvinylquinolines produced rapid parasite clearance through a parasitocidal mechanism, making them ideal drug candidates.

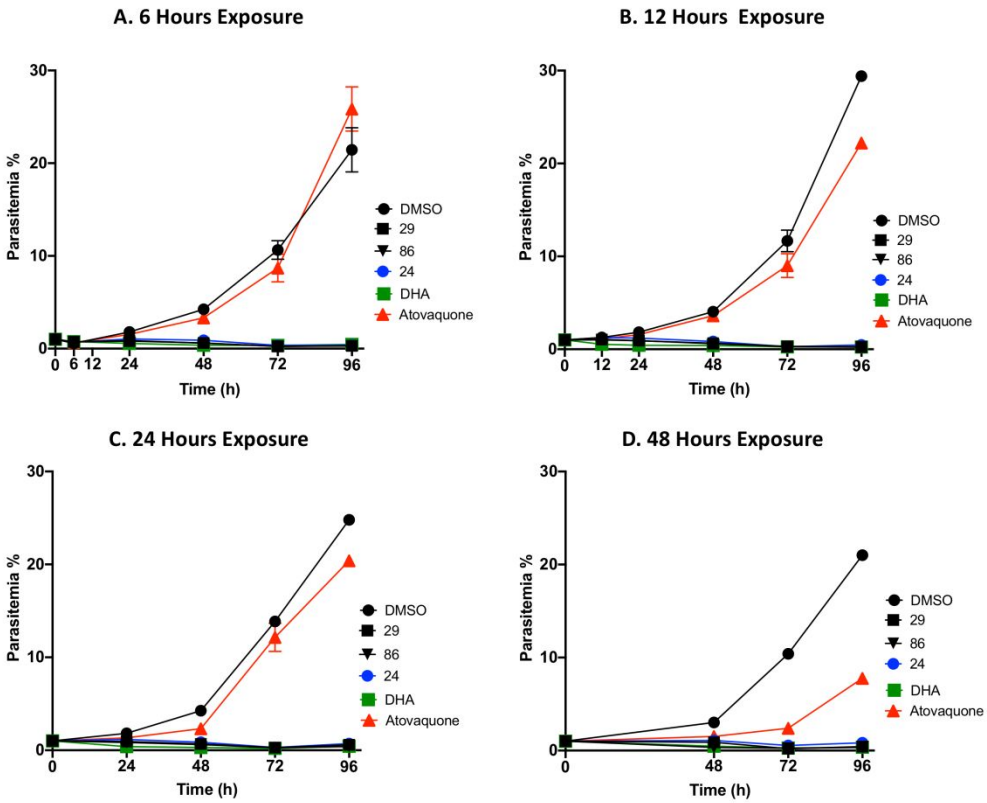


Figure 4. Parasitocidal activity of 2-arylvinylquinolines. Asynchronous Dd2 parasite culture was exposed to 5 × EC_{50} concentrations of test compounds for (A) 6, (B) 12, (C) 24, and (D) 48 h followed bycompound removal. Parasite growth was then monitored daily for 96 h. DHA and Atovaquone (50 nM and 6.6 nM) were included as fast and slow acting controls, respectively. Parasitemia was determined by microscopy of Giemsa stained smear. Results shown are representative of three independent biological replicates. Mean ± SEM of 3 independent readings.

In Vitro Gametocytocidal Activity of 2-Arylvinylquinolines

The *in vitro* gametocytocidal activity of 2-arylvinylquinolines **24**, **29** and **86** is summarized in Table 8. All three compounds demonstrated potent inhibitory activity toward early stage (II-III) gametocytes with submicromolar EC_{50} values. Late stage (IV-V) gametocytes are more refractory to antimalarial drugs than early-stage gametocytes and blood stage parasites, and thus only few compounds are effective against late stage *Pf*

gametocytes.[59] Encouragingly, all compounds tested displayed strong inhibitory activity toward late-stage gametocytes, among which **24** was the most active molecule with an EC_{50} value of 393.6 ± 99.4 nM (Table 8 and Figure 5). Therefore, 2-arylvinylquinolines represent promising leads as new antimalarials with promising dual stage (blood and gametocyte) activity.

Table 8. Inhibition of Early and Late Stage Gametocytes

Compd	Early stage EC_{50} (nM) [a]	Late stage EC_{50} (nM) [a]
24	471.5 ± 18.4	393.6 ± 99.4
29	590.7 ± 118.7	2049.3 ± 113.6
86	909.9 ± 314.2	2495.7 ± 423.8
Methylene blue	74.7 ± 21.9	107.2 ± 46.3
DHA	17.4 ± 3.7	37.4 ± 8.9

[a] EC_{50} data represent the means and SEMs of three separate experiments.

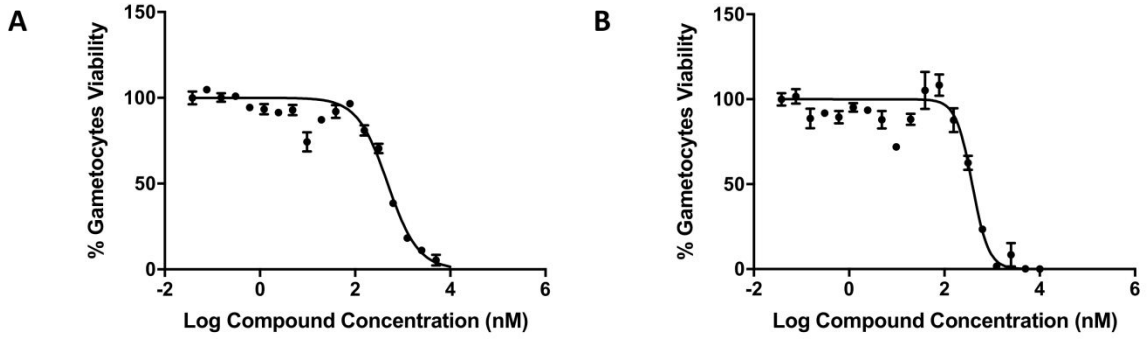


Figure 5. Activity of compound **24** on 3D7 *P. falciparum* gametocyte stages. The viability of gametocytes after the exposure of compound **24** was evaluated on early (A) or late (B) gametocytes stages of 3D7 expressing luciferase parasite. EC_{50} data represents the means and SEMs of three experiments.

β-Hematin Inhibition Activity of 2-Arylvinylquinolines

CQ and other aminoquinolines are known to act on the malaria parasites by blocking hematin biocrystallization (hemozoin formation) through the π-π stacking. As a result, the

accumulated toxic heme causes the death of parasites by inducing oxidative membrane damage.[9, 60] We performed β-hematin inhibition experiments to determine the possible mode of actions of arylvinylquinolines. As shown in Figure 6A-B, CQ strongly inhibited β-hematin formation. Within the three tested compounds, **29** and **86** also showed inhibitory activity towards β-hematin formation in a concentration-dependent manner, although their activity was much weaker than that of CQ. In contrast, compound **24** demonstrated very low activity against β-hematin crystal formation even at the highest concentration tested (200 μM). These results suggested that the potent antimalarial activity of 2-arylvinylquinolines could associate with mechanisms other than the inhibition of heme detoxification.

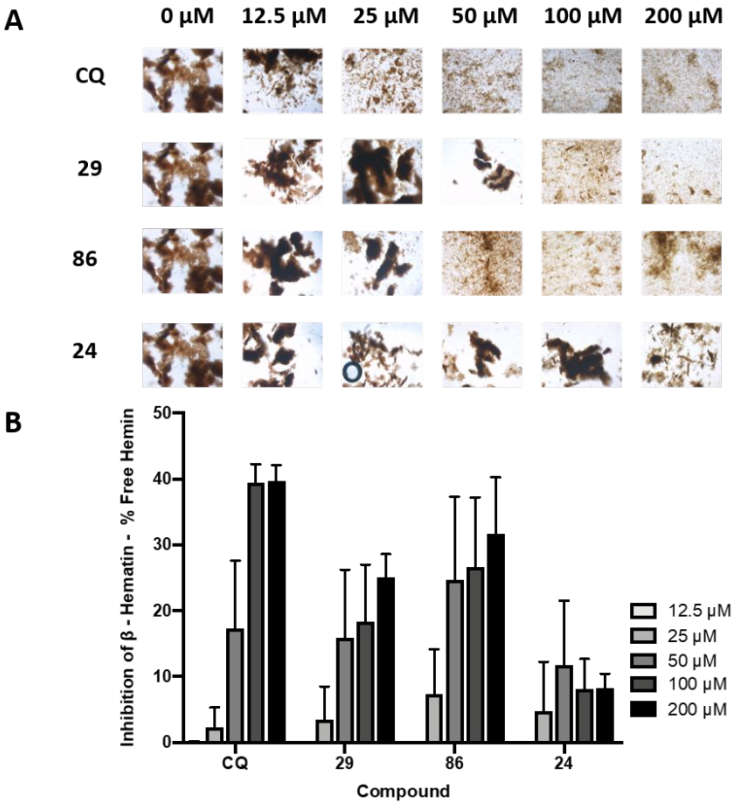


Figure 6. Effect of the 2-arylvinylaminequinoline derivatives on the β-hematin crystal formation. (**A**) Images of β-hematin crystals following incubation of 100 μM hemin, propionate buffer, phosphatidylcholine and, varying concentrations of compound for 16 h at 37 °C. Images were taken using a Nikon Eclipse TE200 (B) Free hemin, as indicative of inhibition of β-hematin crystal formation, was determined using a linear calibration curve. Data represents mean ± SEM of three independent experiments.

2-Arylvinylquinolines Are Well Tolerated and Active in an *in vivo* Model.

Given the robust antiplasmodial potency of 2-arylvinylquinolines against Dd2 and 3D7 strains and the good microsomal stability profiles of **24**, **29** and **86**, we assessed the *in vivo* efficacy of these compounds using the rodent malaria model. The monophosphate salts of **24**, **29** and **86** were used in female Swiss Webster mice infected with *P. berghei* ANKA strain. As observed from Figure 7A-B, all of these compounds completely cured malaria infection in mice when exposed to 100 mg/kg daily by p.o. administration in a standard Peters' four-day test, and no parasite bioluminescence was detected in any of the tested mice (Figure 7A). Although a lower dose of the monophosphate salt of the compound **86** (**86s**) was ineffective for malarial infected mice, monophosphate salts of **29** and **24** effectively cleared the parasites at 25 mg/kg. While a marginal luminescence signal was detected in compound **29s**-treated mice, this signal could arise from a small amount of circulating or dying parasites. Significantly, we found that **24s** provided full protection and cure at 25 mg/kg with no bioluminescence signals detected after treatment.

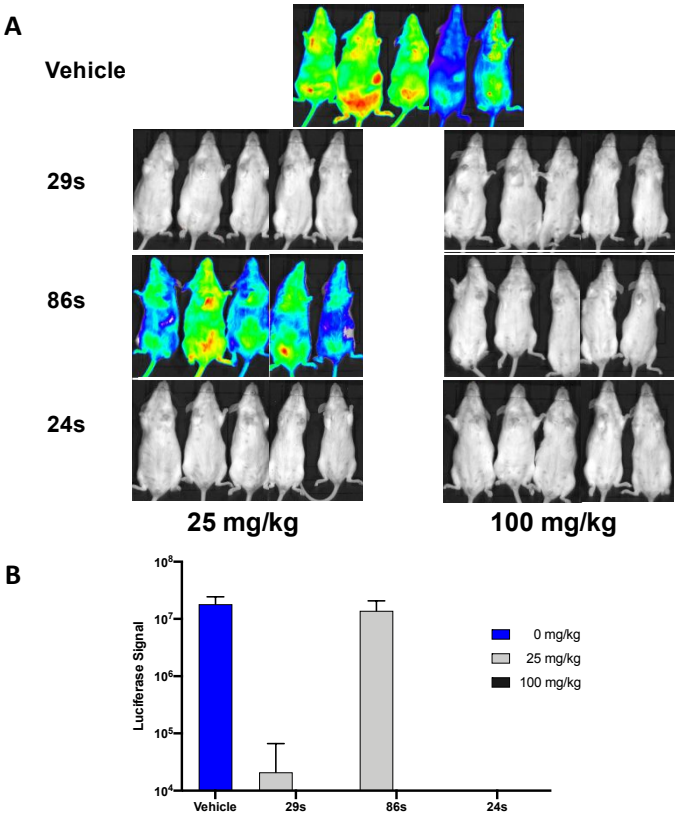


Figure 7. Curative property of 2-arylvinylquinoline derivatives. (A) Swiss Webster female mice were infected with *P. berghei* ANKA luciferase expressing strain and treated with 25 and 100 mg/kg orally once daily 48 h post-infection. 7 days after infection, bioluminescence was detected (A) and quantified (B) using an *in vivo* imaging system (IVIS).

To assess the curative property of compound **24s**, we monitored the survival of *P. berghe*i ANKA infected mice for 30 days following oral administration of 25 and 100 mg/kg. The monophosphate salt of **24** was well tolerated and did not display apparent adverse symptoms such as hunched posture, hypotrichosis, or reduced mobility. In addition, the administration of **24s** by these dosing regiments caused no significant weight loss, whereas the body weight of control groups decreased sharply (Figure S10). The mean survivability in the control group was 8 days (Figure 8A). In contrast, administration of **24s** at 100 mg/kg prolonged the lives of the mice by 22 days (the end of experiment, 30

days), and no parasites were detected in Giemsa-stained thin blood smears. Importantly, with p.o. administration of **24s** at a lower dose (25 mg/kg), 3 out of 4 mice survived without detection of any malaria parasites in thin blood smears, while all mice succumbed in the control group. Similar results have been reported with CQ administered at 30 mg/kg (MSD: 24 days).[61] The curative dose for piperaquine and ferroquine are better (16 mg/kg and 30 mg/kg, respectively with a single oral dose) compared to **24s** and CQ (Sergio Wittlin, Swiss Tropical Institute, personal communication). In comparison, **UCF501** cured malaria infection in 4/5 mice when they were exposed to a high dose 100 mg/kg twice daily p.o. administration in our previous study,[33] suggesting good *in vivo* efficacy improvement with **24s**. This improvement can be explained, to some extent, by the enhanced metabolic stability of **24**.

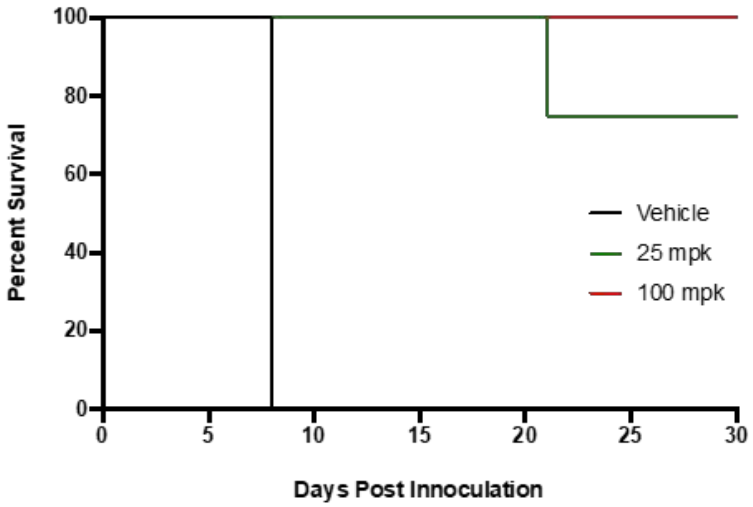


Figure 8. Effect of compound **24s** on the survivability of *P. berghei* ANKA infected mice. BALB/c females were infected with a *P. berghei* ANKA luciferase expressing strain and treated 4 h post-infection with 25 or 100 mg/kg given orally once daily for 4 days. There was not statistically significant difference between the 25 mg/kg and 100 mg/kg treatment groups log-rank (Mantel-Cox) test ($p = 0.2636$).

CONCLUSIONS

In this work, in-depth SAR studies were performed around a quinoline scaffold leading to the generation of 6-chloro-arylvinylquinolines. The SAR trends are summarized in Figure 9. Many promising arylvinylaminoquinolines exhibited more potent antimalarial activity than the positive controls (**CQ** and **UCF501**), the most active of which being compounds **24**, **29**, **31**, **86**, **92** and **93** with $EC_{50} \leq 15$ nM. The inhibitory activity of all compounds tested against the CQ-resistant strain were higher than inhibition of the CQ-susceptible strain (RI < 1), suggesting no cross-resistance induced by this chemotype.

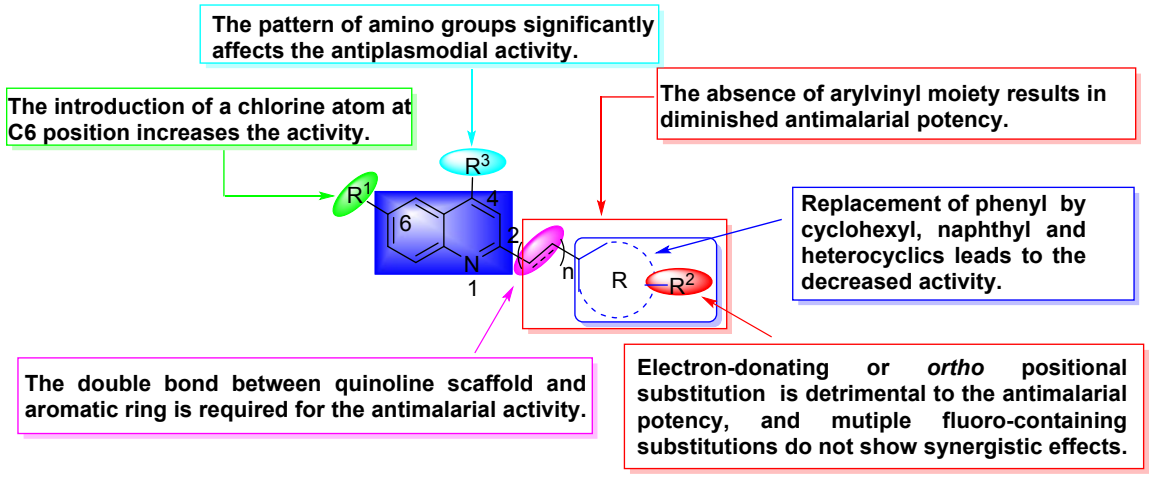


Figure 9. Summary of SAR trends

The most promising compound **24**, (EC_{50} = 10.9 ± 1.9 nM against Dd2 strain; $t_{1/2}$ = 104.2 min), is a fast-acting parasitocidal agent with robust blood and gametocyte stage activity, demonstrating stage specific action at the trophozoite phase in the *Pf* asexual life cycle. Importantly, **24s** displayed remarkable efficacy in the rodent malaria model, resulting in 100% reduction of parasitemia in 5/5 mice at 100 mg/kg, p.o. and 3/4 mice at 25 mg/kg, p.o., with no apparent signs of toxicity. Future studies will focus on assessment of pharmacokinetic and toxicological liabilities, if any, of **24s**. Additionally, compound **24**

showed a weaker inhibitory activity towards β-hematin formation as compared with CQ, indicating that the potent antimalarial activity of **24** may associate with different mode of actions. In particular, the accumulations of membrane-bound structures inside the FV in treated parasites suggests that compound **24** interferes with the hemoglobin digestion process. Collectively, 6-chloro-arylvinylquinolines **24** can be considered as a promising lead for the development of new antimalarials.

EXPERIMENTAL SECTION

Chemistry.

Synthesis of compounds. All reagents were commercially available and used without further purification. Nuclear magnetic resonance spectra were recorded in $CDCl_3$, MeOD and DMSO solutions. ^{1}H, ^{13}C NMR and ^{19}F NMR were recorded on Bruker spectrometers operating at 400 and 500 MHz. Data are reported as follows: chemical shift (δ), multiplicity, integrated intensity, and coupling constant (J) in hertz. Melting points were measured on a Stuart SMP20 melting point apparatus and were uncorrected. High-resolution mass spectroscopy (HRMS) images were obtained on an Agilent 6230 FOF/LC/MS. High-performance liquid chromatography (HPLC) analysis was performed on an Agilent 1260 system using a ZORBAX C18 column (150 × 4.6 mm, 3.5 μm) at room temperature with a gradient elution using the mobile phase (A) nanopure water containing 0.1% formic acid and (B) acetonitrile containing 0.1% formic acid. HPLC condition **A**: 10-70% of B at 0–7 min, 70-95% of B at 7–7.3 min, 95% of B at 7.3–9.3 min, 95-10% of B at 9.3-10 min and 10% of B at 10-13 min, flow rate of 0.8 mL min^{-1}; HPLC condition **B**: 45-95% of B at 0–7 min, 95% of B at 7–9.3 min, 95-45% of B at 9.3-10 min and 45% of B at 10-13 min, flow rate of 0.5 mL min^{-1}. All compounds used for biological evaluation have purity of ≥ 95%.

General procedure 1: synthesis of hydroxyquinolines (3a-d)

Method 1A: A mixture of 4-methoxyaniline (24.4 mmol), ethylacetoacetate (3.49 g, 26.8 mmol), anhydrous magnesium sulfate (3.51 g, 29.2 mmol) and acetic acid (0.2 mL) in ethanol (30 mL) was heated to 90 °C for 6 h. Once the reaction was completed as monitored by TLC, the resultant mixture was filtered, and the resultant solvent was concentrated under reduced pressure to give a pale brown liquid. This crude product was purified by silica gel column chromatography to afford imine (3.2 g, 56% yield). Then a solution of imine (3.1 g, 13.2 mmol) in Dowtherm (5 mL) was heated to 270 °C for 20 min. After cooling, the reaction mixture was diluted in ethyl acetate. The solid was collected by filtration, washed with water, and dried in a vacuum oven to give the hydroxyquinoline **3a** (1.9 g, 76% yield) as an off-white solid.

Method 1B: Polyphosphoric acid (80.6 g) was added to a solution of anilines (0.1 mol) and ethyl acetoacetate, (12.6 mL, 0.1 mol). The reaction mixture was stirred at 150 °C for 2 h. Upon completion, the reaction mixture was poured into ice water with vigorous stirring. The precipitated solid was collected by filtration and dried *in vacuum* oven to get hydroxyquinolines **3a-d**. The crude products were then used for the next reaction without further purification.

General procedure 2 for synthesis of chlorinated quinolines (chlorination of hydroxyquinolines) (4a-d)

The hydroxyquinolines (0.10 mol) in phosphorous oxychloride (60 mL) was heated to 105 °C for 2 h. Upon completion, the excess of phosphorous oxychloride was removed under reduced pressure. The residue was quenched into crushed ice and neutralized using a saturated solution of sodium bicarbonate. The solid obtained was then collected by

filtration and dried *in vacuum* to afford chlorinated quinolines **4a-d**. The crude products were used for the next step without further purification.

General procedure 3 for synthesis of aminoquinolines (nucleophilic substitution of chlorinated quinolines) (6a-e, 61a-f, and 89a-c)

Method 3A: Chlorinated quinolines (2.4 mmol) and amine (3.0 mL) in a pressure tube were heated at 140 °C for 24 h. Upon completion, water was added to the resultant content.

The precipitated solid was collected by filtration and dried *in vacuum* to afford aminoquinolines.

Method 3B: Chlorinated quinolines (3.0 mmol), secondary amine (27 mmol) and EtOH (2.0 mL) were heated in a pressure tube at 130 °C for 36 h. Upon completion, the resultant solvent was removed to dryness. The residue was dissolved in dichloromethane and washed with water and brine. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic extracts were then dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the desired aminoquinolines.

***N*^{1}-(6-Methoxy-2-methylquinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (6a)**

The title compound was synthesized from **4a** and N^1,N^1-dimethylethane-1,2-diamine (**5a**) according to the method described for procedure 3A. Isolated yield: 92%; Off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 9.2 Hz, 1H), 7.31 (dd, J = 9.2, 2.8 Hz, 1H), 7.13 (d, J = 2.8 Hz, 1H), 6.25 (s, 1H), 3.95 (s, 3H), 3.39 – 7.35 (m, 2H), 2.74 (t, J = 6.0 Hz, 2H), 2.69 (s, 3H), 2.34 (s, 6H).

***N*^{1}-(6-Fluoro-2-methylquinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (6b)**

The title compound was synthesized from **4b** and N^1,N^1-dimethylethane-1,2-diamine (**5a**) according to the method described for procedure 3A. Isolated yield: 89%; Off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 9.2 Hz, 1H), 7.44 – 7.37 (m, 2H), 6.31 (s, 1H), 3.32 (t, J = 5.8 Hz, 2H), 2.71 (t, J = 6.0 Hz, 2H), 2.66 (s, 3H), 2.33 (s, 6H).

N^1-(6-Chloro-2-methylquinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (6c)

The title compound was synthesized from **4c** and N^1,N^1-dimethylethane-1,2-diamine (**5a**) according to the method described for procedure 3A. Isolated yield: 93%; Off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 9.0 Hz, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.53 (dd, J = 9.0, 2.4 Hz, 1H), 6.31 (s, 1H), 3.38 (q, J = 6.0 Hz, 2H), 2.69 (t, J = 6.0 Hz, 2H), 2.60 (s, 3H), 2.32 (s, 6H).

N^1,N^1-Dimethyl-N^2-(2-methylquinolin-4-yl)ethane-1,2-diamine (6d)

The title compound was synthesized from **4d** and N^1,N^1-dimethylethane-1,2-diamine (**5a**) according to the method described for procedure 3B. Isolated yield: 92%; yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.52 (t, J = 8.4 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 6.22 (s, 1H), 3.25 – 3.21 (m, 2H), 2.63 – 2.60 (m, 2H), 2.54 (s, 3H), 2.24 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 150.0, 148.0, 129.1, 128.7, 123.8, 119.7, 117.5, 99.1, 57.2, 45.1, 40.0, 25.5.

N^1-(6-Chloro-2-methylquinolin-4-yl)-N^4,N^4-dimethylbutane-1,4-diamine (6e)

The title compound was synthesized from **4c** and N^1,N^1-dimethylbutane-1,4-diamine (**5b**) according to the method described for procedure 3A. Isolated yield: 87%; Off-white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 9.0 Hz, 1H), 7.77 (d, J = 2.2 Hz, 1H), 7.51 (dd, J = 9.0, 2.2 Hz, 1H), 6.27 (s, 1H), 3.26 – 3.21 (m, 2H), 2.60 (s, 3H), 2.40 (t, J = 6.4 Hz, 2H), 2.31 (s, 6H), 1.94 – 1.89 (m, 2H), 1.75 – 1.69 (m, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 160.0, 150.4, 146.6, 130.5, 130.0, 129.4, 120.1, 118.8, 99.4, 59.9, 45.9, 43.9, 27.2, 26.3, 25.8.

4-(6-Chloro-2-methylquinolin-4-yl)morpholine (61a)

The title compound was synthesized from **4c** and **60a** according to the method described for procedure 3A. Isolated yield: 90%; Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.86 (m, 2H), 7.53 (dd, J = 9.0, 2.4 Hz, 1H), 6.74 (s, 1H), 3.96 (t, J = 5.6 Hz, 4H), 3.15 (t, J = 5.6 Hz, 4H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 156.3, 148.0, 131.2, 130.9, 130.3, 122.9, 122.7, 110.6, 67.2, 52.9, 25.9.

6-Chloro-2-methyl-4-(pyrrolidin-1-yl)quinoline (61b)

The title compound was synthesized from **4c** and **60b** according to the method described for procedure 3A. Isolated yield: 92%; Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 2.4 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.48 (dd, J = 9.0, 2.4 Hz, 1H), 6.37 (s, 1H), 3.67 – 3.63 (m, 4H), 2.58 (s, 3H), 2.06 – 2.03 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 152.4, 148.7, 130.8, 129.5, 128.0, 124.4, 120.8, 104.0, 52.4, 26.3, 25.8.

6-Chloro-2-methyl-*N*-(4-(piperidin-1-yl)phenyl)quinolin-4-amine (61c)

The title compound was synthesized from **4c** and **60c** according to the method described for procedure 3B. Isolated yield: 73%; Green solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 9.08 (s, 1H), 8.25 (d, J = 9.0 Hz, 1H), 7.47 (dd, J = 9.0, 1.8 Hz, 1H), 7.23 (d, J = 9.0 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 6.38 (s, 1H), 3.16 – 3.12 (m, 4H), 2.60 (s, 3H), 1.72 – 1.67 (m, 4H), 1.62 – 1.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 154.0, 151.4, 137.8, 133.6, 132.5, 127.6, 126.7, 123.7, 122.3, 117.7, 116.8, 100.3, 50.3, 26.0, 24.5, 20.7.

6-Chloro-2-methyl-4-(4-(pyridin-2-yl)piperazin-1-yl)quinoline (61d)

The title compound was synthesized from **4c** and **60d** according to the method described for procedure 3B. Isolated yield: 86%; Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, J = 4.9, 2.8 Hz, 1H), 7.98 (d, J = 2.4 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.58 – 7.55 (m, 1H), 7.55 – 7.52 (m, 1H), 6.80 (s, 1H), 6.74 (d, J = 8.6 Hz, 1H), 6.71 – 6.68 (m, 1H), 3.83 – 3.79 (m, 4H), 3.32 – 3.29 (m, 4H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 159.8, 156.4, 148.4, 148.0, 138.0, 131.2, 130.9, 130.3, 123.1, 122.8, 114.3, 110.8, 107.7, 52.4, 45.8, 25.9.

6-Chloro-2-methyl-*N*-(pyridin-2-ylmethyl)quinolin-4-amine (61f)

The title compound was synthesized from **4c** and **60f** according to the method described for procedure 3B. Isolated yield: 80%; Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, J = 5.4 Hz, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.72 – 7.68 (m, 1H), 7.53 – 7.51 (m, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.26 (t, J = 6.8 Hz, 1H), 6.34 (s, 1H), 4.56 (d, J = 4.4 Hz, 2H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 155.9, 150.0, 148.9, 147.0, 137.2, 130.9, 130.1, 129.9, 123.0, 122.1, 119.6, 118.8, 100.5, 47.8, 26.0.

6-Chloro-2-methyl-*N*-(3-morpholinopropyl)quinolin-4-amine (89a)

The title compound was synthesized from **4c** and 3-morpholinopropan-1-amine (**88a**) according to the method described for procedure 3B. Isolated yield: 93%; Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 2.2 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.52 (dd, J = 9.0, 2.2 Hz, 1H), 6.26 (s, 1H), 3.95 – 3.93 (m, 4H), 3.40 – 3.37 (m, 2H), 2.66 – 2.60 (m, 6H), 2.59 (s, 3H), 1.98 – 1.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 150.1, 147.0, 131.0, 129.9, 129.6, 119.9, 118.8, 99.3, 67.2, 59.8, 54.5, 44.8, 26.1, 23.5.

6-Chloro-2-methyl-*N*-(4-morpholinobutyl)quinolin-4-amine (89b)

The title compound was synthesized from **4c** and 4-morpholinobutan-1-amine (**88b**) according to the method described for procedure 3B. Isolated yield: 88%; Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 2.2 Hz, 1H), 7.52 (dd, J = 9.0, 2.2 Hz, 1H), 6.33 (s, 1H), 3.78 – 3.75 (m, 4H), 3.32 (q, J = 6.7 Hz, 2H), 2.61 (s, 3H), 2.48 – 2.42 (m, 6H), 1.87 – 1.81 (m, 2H), 1.73 – 1.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 149.4, 146.9, 131.0, 130.1, 129.8, 119.1, 100.0, 67.3, 58.5, 54.1, 43.6, 26.8, 24.7.

6-Chloro-2-methyl-*N*-(4-(4-methylpiperazin-1-yl)butyl)quinolin-4-amine (89c)

The title compound was synthesized from **4c** and 4-(4-methylpiperazin-1-yl)butan-1-amine (**88c**) according to the method described for procedure 3B. Isolated yield: 86%; Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 9.0 Hz, 1H), 7.77 (d, J = 2.2 Hz, 1H), 7.51 (dd, J = 9.0, 2.2 Hz, 1H), 6.27 (s, 1H), 3.26 – 3.21 (m, 2H), 2.60 (s, 3H), 2.57 – 2.47 (m, 6H), 2.43 (t, J = 6.4 Hz, 4H), 2.31 (s, 3H), 1.94 – 1.89 (m, 2H), 1.75 – 1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 150.4, 146.6, 130.5, 130.0, 129.4, 120.1, 118.8, 99.4, 59.9, 45.9, 43.9, 27.2, 26.3, 25.8.

General procedure 4 for synthesis of arylvinylquinolines (olefination reaction) (8-37, 39-57, 62-63, 65-72, 81-87, 90-96 and 98-114)

A mixture of 2-methylquinolines (0.20 mmol), p-$TsNH_2$ (34 mg, 0.20 mmol), and appropriate aldehyde (1.0 mmol) in m-xylene (2.0 mL) was stirred at 140 °C for 12 h. Upon completion, the cooled mixture was directly loaded and purified on a silica gel column chromatography to afford arylvinylquinolines.

(E)-N^1-(6-Methoxy-2-styrylquinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (8)

The title compound was synthesized from **6a** and **7a**. Isolated yield: 85%; Yellow solid; MP: 153 – 156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 9.2 Hz, 1H), 7.77 (d,

J = 16.4 Hz, 1H), 7.55 (dd, *J* = 6.8, 3.2 Hz, 3H), 7.35 (d, *J* = 16.4 Hz, 1H), 7.31 – 7.27 (m, 3H), 7.20 (dd, *J* = 9.2, 2.6 Hz, 1H), 6.56 (s, 1H), 3.91 (s, 3H), 3.65 (t, *J* = 6.2 Hz, 2H), 2.98 (t, *J* = 6.0 Hz, 2H), 2.48 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 150.6, 143.6, 142.6, 140.9, 133.1, 129.4, 127.8, 126.6, 126.3, 122.6, 121.8, 118.9, 101.0, 96.7, 57.1, 56.3, 45.3, 40.6; HRMS (ESI) *m/z* calcd. for $C_{22}H_{26}N_3O$ 348.2076 $[M + H]^+$; found: 348.2049; retention time 5.478 min (HPLC condition A).

(E)-*N*^{1}-(6-Methoxy-2-(4-nitrostyryl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (9)

The title compound was synthesized from **6a** and **7b**. Isolated yield: 82%; Yellow solid; MP: > 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 16.2 Hz, 1H), 7.41 (d, *J* = 16.2 Hz, 1H), 7.33 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.05 (d, *J* = 2.8 Hz, 1H), 6.65 (s, 1H), 3.95 (s, 3H), 3.41 (q, *J* = 6.0, 5.8 Hz, 2H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 153.2, 149.9, 147.4, 144.2, 143.9, 134.6, 131.5, 130.1, 127.7, 124.5, 120.9, 119.6, 100.3, 98.0, 57.5, 56.0, 45.5, 40.6; HRMS (ESI) *m/z* calcd. for $C_{22}H_{25}N_4O_3$ 393.1927 $[M + H]^+$; found: 393.1936; retention time 2.664 min (HPLC condition B).

(E)-*N*^{1}-(6-Methoxy-2-(2-nitrostyryl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (10)

The title compound was synthesized from **6a** and **7c**. Isolated yield: 80%; Yellow solid; MP: 168 – 170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 4.0 Hz, 1H), 7.96 (d, *J* = 16.4 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.63 (t, *J* = 8.2 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.33 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.16 (d, *J* = 2.6 Hz, 1H), 6.72 (s, 1H), 3.96 (s, 3H), 3.47 (t, *J* = 6.2 Hz, 2H), 2.81 (t, *J* = 6.2 Hz, 2H), 2.39 (s, 6H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 157.8, 152.5, 150.7, 148.5, 141.4, 133.8, 133.1, 132.5, 129.2, 129.0, 125.2, 121.7, 119.3, 100.8, 95.9, 57.3, 56.2, 45.4, 40.5; HRMS (ESI) *m/z* calcd. for $C_{22}H_{25}N_4O_3$ 393.1927 $[M + H]^+$; found: 393.1901; retention time 5.795 min (HPLC condition A).

(E)-*N*^{1}-(6-Methoxy-2-(3-nitrostyryl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (11)

The title compound was synthesized from **6a** and **7d**. Isolated yield: 83%; Yellow solid; MP: 183 – 185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (t, *J* = 2.2 Hz, 1H), 8.13 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.91 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 16.2 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 16.2 Hz, 1H), 7.34 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.07 (d, *J* = 2.6 Hz, 1H), 6.65 (s, 1H), 3.96 (s, 3H), 3.43 – 3.39 (m, 2H), 2.76 (t, *J* = 6.2 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 153.4, 149.9, 149.1, 144.2, 139.2, 133.1, 131.5, 130.1, 130.0, 122.8, 121.8, 120.8, 119.5, 100.3, 98.0, 57.5, 56.0, 45.5, 40.6; HRMS (ESI) *m/z* calcd. for $C_{22}H_{25}N_4O_3$ 393.1927 $[M + H]^+$; found: 393.1901; retention time 5.771 min (HPLC condition A).

(E)-*N*^{1}-(6-Methoxy-2-(4-methoxystyryl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (12)

The title compound was synthesized from **6a** and **7e**. Isolated yield: 60%; Yellow solid; MP: 171 – 173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 9.2 Hz, 1H), 7.57 (d, *J* = 16.4 Hz, 1H), 7.51 *J* = 8.6 Hz, 2H), 7.23 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.15 (d, *J* = 16.4 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 6.55 (s, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.43 (t, *J* = 6.0 Hz, 2H), 2.76 (t, *J* = 6.0 Hz, 2H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 159.5, 157.3, 153.1, 150.8, 134.6, 131.0, 129.3, 129.1, 121.5, 118.8, 114.5, 113.9, 101.0, 96.2,

57.4, 56.2, 55.7, 45.5, 40.8; HRMS (ESI) *m/z* calcd. for $C_{23}H_{28}N_3O_2$ 378.2182 $[M + H]^+$; found: 378.2155; retention time 5.649 min (HPLC condition A).

(E)-*N*^{1}-(2-(3,4-Dimethoxystyryl)-6-methoxyquinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (13)

The title compound was synthesized from **6a** and **7f**. Isolated yield: 64%; Yellow solid; MP: > 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 9.2 Hz, 1H), 7.61 (d, J = 16.2 Hz, 1H), 7.25 – 7.21 (m, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 10.0 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.55 (s, 1H), 5.29 (s, 3H), 3.92 (s, 3H), 3.91 (s, 3H), 3.50 (t, J = 5.8 Hz, 2H), 2.80 (t, J = 6.0 Hz, 2H), 2.37 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.3, 150.5, 149.5, 149.1, 129.8, 129.4, 122.7, 121.9, 121.1, 112.5, 111.4, 109.6, 101.2, 100.7, 95.7, 57.2, 56.3, 53.8, 45.5, 45.4, 40.8; HRMS (ESI) *m/z* calcd. for $C_{24}H_{30}N_3O_3$ 408.2287 $[M + H]^+$; found: 408.2273; retention time 2.609 min (HPLC condition B).

(E)-*N*^{1}-(6-Methoxy-2-(3,4,5-trimethoxystyryl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (14)

The title compound was synthesized from **6a** and **7g**. Isolated yield: 75%; Yellow solid; MP: > 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 9.2 Hz, 1H), 7.56 (d, J = 16.4 Hz, 1H), 7.25 – 7.18 (m, 3H), 6.83 (s, 2H), 6.56 (s, 1H), 3.90 (s, 3H), 3.89 (s, 6H), 3.87 (s, 3H), 3.48 (t, J = 6.0 Hz, 2H), 2.78 (t, J = 6.0 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 153.7, 153.2, 152.1, 151.2, 139.3, 135.5, 132.0, 127.5, 125.3, 121.9, 118.7, 104.9, 101.1, 95.9, 61.3, 57.2, 56.5, 56.3, 45.4, 40.8; HRMS (ESI) *m/z* calcd. for $C_{25}H_{32}N_3O_4$ 438.2393 $[M + H]^+$; found: 438.2405; retention time 2.527 min (HPLC condition B).

(E)-N^1-(2-(4-Fluorostyryl)-6-methoxyquinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (15)

The title compound was synthesized from **6a** and **7h**. Isolated yield: 71%; Yellow solid; MP: 161 – 164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 9.2 Hz, 1H), 7.60 (d, J = 16.4 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.29 (dd, J = 9.2, 2.8 Hz, 1H), 7.21 (d, J = 16.4 Hz, 1H), 7.08 (d, J = 2.6 Hz, 1H), 7.07– 7.02 (m, 2H), 6.59 (s, 1H), 3.93 (s, 3H), 3.42 (t, J = 6.0 Hz, 2H), 2.76 (t, J = 6.0 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, J = 247.0 Hz), 157.3, 153.3, 150.5, 142.0, 133.1 (d, J = 3.0 Hz), 132.9, 129.6, 129.2 (d, J = 8.0 Hz), 127.8, 121.2, 119.0, 116.1 (d, J = 21.0 Hz), 100.7, 96.8, 57.4, 56.1, 45.5, 40.7; HRMS (ESI) *m/z* calcd. for $C_{22}H_{25}FN_3O$ 366.1982 $[M + H]^+$; found: 366.1957; retention time 5.684 min (HPLC condition A).

(E)-N^1-(6-Fluoro-2-styrylquinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (16)

The title compound was synthesized from **6b** and **7a**. Isolated yield: 75%; Yellow solid; MP: 114 – 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 9.2, 5.6 Hz, 1H), 7.68 – 7.60 (m, 3H), 7.42 (dd, J = 10.2, 2.4 Hz, 1H), 7.40 – 7.35 (m, 3H), 7.33 – 7.27 (m, 2H), 6.65 (s, 1H), 3.41 (t, J = 5.8 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (d, J = 242.0 Hz), 155.8, 150.4 (d, J = 4.0 Hz), 145.0, 136.9, 134.2, 131.6 (d, J = 9.0 Hz), 129.1, 128.8, 127.6, 119.5 (d, J = 25.0 Hz), 119.1 (d, J = 9.0 Hz), 104.6 (d, J = 23.0 Hz), 97.4, 57.3, 45.4, 40.3; HRMS (ESI) *m/z* calcd. for $C_{21}H_{23}FN_3$ 336.1876 $[M + H]^+$; found: 336.1848; retention time 4.999 min (HPLC condition A).

(E)-N^1-(6-Fluoro-2-(4-nitrostyryl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (17)

The title compound was synthesized from **6b** and **7b**. Isolated yield: 79%; Yellow solid; MP: > 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 9.0 Hz, 2H), 7.98 (dd, J = 9.6, 5.6 Hz, 1H), 7.74 – 7.66 (m, 3H), 7.45 – 7.36 (m, 3H), 6.62 (s, 1H), 3.36 (q, J = 5.8 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (d, J = 245.0 Hz), 154.9, 150.3 (d, J = 5.0 Hz), 147.5, 145.8, 143.6, 134.4, 132.4 (d, J = 8.0 Hz), 130.9, 127.9, 124.5, 119.6 (d, J = 25.0 Hz), 119.4 (d, J = 9.0 Hz), 104.5 (d, J = 23.0 Hz), 98.3, 57.3, 45.4, 40.3; HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}FN_4O_2$ 381.1727 $[M + H]^+$; found: 381.1709; retention time 2.666 min (HPLC condition B).

(E)-N^1-(6-Fluoro-2-(4-fluorostyryl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (18)

The title compound was synthesized from **6b** and **7h**. Isolated yield: 88%; Yellow solid; MP: 120 – 122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, J = 10.0, 5.4 Hz, 1H), 7.70 (d, J = 16.2 Hz, 1H), 7.60 – 7.56 (m, 2H), 7.52 (dd, J = 9.8, 2.4 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.23 (d, J = 16.4 Hz, 1H), 7.05 (t, J = 8.6 Hz, 2H), 6.64 (s, 1H), 3.52 (t, J = 5.8 Hz, 2H), 2.89 (t, J = 6.0 Hz, 2H), 2.45 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (d, J = 247.0 Hz), 160.0 (d, J = 244.0 Hz), 155.7, 150.3 (d, J = 5.0 Hz), 145.2, 133.2 (d, J = 3.0 Hz), 132.8, 129.1 (d, J = 8.0 Hz), 119.6 (d, J = 25.0 Hz), 119.1, 116.2, 116.0, 115.4, 115.2, 104.7 (d, J = 23.0 Hz), 97.3, 57.1, 45.1, 40.2; ; HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}F_2N_3$ 354.1782 $[M + H]^+$; found: 354.1754; retention time 5.223 min (HPLC condition A).

(E)-N^1-(6-Fluoro-2-(4-methoxystyryl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (19)

The title compound was synthesized from **6b** and **7e**. Isolated yield: 86%; Yellow solid; MP: 141 – 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 10.0, 5.4 Hz, 1H),

7.60 (d, J = 16.2 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.41 – 7.37 (m, 2H), 7.16 (d, J = 16.2 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.63 (s, 1H), 3.85 (s, 3H), 3.38 (t, J = 5.8 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.8 (d, J = 244.0 Hz), 159.5, 150.2 (d, J = 4.0 Hz), 149.2, 133.6, 132.0 (d, J = 9.0 Hz), 131.1, 129.8, 128.9, 119.4 (d, J = 25.0 Hz), 119.2, 114.6, 113.8, 104.5 (d, J = 22.0 Hz), 97.3, 57.4, 55.7, 45.4, 40.4; HRMS (ESI) *m/z* calcd. for $C_{22}H_{25}FN_3O$ 366.1982 $[M + H]^+$; found: 366.1954; retention time 5.034 min (HPLC condition A).

(E)-N^1-(2-(3,4-Dimethoxystyryl)-6-fluoroquinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (20)

The title compound was synthesized from **6b** and **7f**. Isolated yield: 83%; Yellow solid; MP: > 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 9.0, 5.6 Hz, 1H), 7.39 (dd, J = 9.0, 2.0 Hz, 2H), 6.97 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 12.6 Hz, 1H), 6.78 (s, 1H), 6.76 (d, J = 5.0 Hz, 1H), 6.41 (s, 1H), 3.87 (s, 3H), 3.62 (s, 3H), 2.99 (t, J = 5.8 Hz, 2H), 2.57 (t, J = 6.0 Hz, 2H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (d, J = 245.0 Hz), 156.5, 149.6 (d, J = 6.0 Hz), 149.2, 148.7, 134.5, 131.3, 129.8, 129.3, 122.8, 119.6 (d, J = 26.0 Hz), 118.7 (d, J = 9.0 Hz), 112.6, 111.1, 104.6 (d, J = 23.0 Hz), 51.1, 56.2, 56.0, 45.3, 40.0; HRMS (ESI) *m/z* calcd. for $C_{23}H_{27}FN_3O_2$ 396.2087 $[M + H]^+$; found: 396.2048; retention time 2.552 min (HPLC condition A).

(E)-N^1-(6-Fluoro-2-(3,4,5-trimethoxystyryl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (21)

The title compound was synthesized from **6b** and **7g**. Isolated yield: 80%; Yellow solid; MP: > 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 9.0, 5.6 Hz, 1H), 7.57 (d, J = 16.2 Hz, 1H), 7.44 – 7.37 (m, 2H), 7.22 (d, J = 16.2 Hz, 1H), 6.86 (s, 2H), 6.67 (s, 1H),

3.91 (s, 6H), 3.88 (s, 3H), 3.41 (t, J = 5.8 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0 (d, J = 245.0 Hz), 155.5, 153.7, 153.2, 150.5 (d, J = 4.0 Hz), 139.1, 134.3 (d, J = 7.0 Hz), 132.5, 131.1, 128.2, 119.7 (d, J = 25.0 Hz), 119.0 (d, J = 8.0 Hz), 106.8, 104.7 (d, J = 23.0 Hz), 96.8, 61.3, 57.2, 56.5, 45.4, 40.4; HRMS (ESI) *m/z* calcd. for $C_{24}H_{29}FN_3O_3$ 426.2193 $[M + H]^+$; found: 426.2173; retention time 5.251 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-styrylquinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (22)

The title compound was synthesized from **6c** and **7a**. Isolated yield: 82%; Yellow solid; MP: 135 – 136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 9.0 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.66 (d, J = 13.6 Hz, 1H), 7.62 (d, J = 6.8 Hz, 2H), 7.56 (dd, J = 9.0, 2.4 Hz, 1H), 7.42 – 7.37 (m, 2H), 7.32 (d, J = 7.4 Hz, 1H), 7.29 (d, J = 16.0 Hz, 1H), 6.65 (s, 1H), 3.40 – 3.35 (m, 2H), 2.75 – 2.71 (m, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 149.8, 147.2, 137.0, 134.1, 131.4, 130.4, 130.2, 129.8, 129.1, 128.8, 127.6, 119.6, 98.0, 57.4, 45.5, 40.4; HRMS (ESI) *m/z* calcd. for $C_{21}H_{23}ClN_3$ 352.1581 $[M + H]^+$; found: 352.1580; retention time 5.818 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(4-nitrostyryl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (23)

The title compound was synthesized from **6c** and **7b**. Isolated yield: 85%; Yellow solid; MP: > 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 9.0 Hz, 2H), 7.93 (d, J = 9.0 Hz, 1H), 7.76 – 7.71 (m, 4H), 7.59 (dd, J = 9.0, 2.4 Hz, 1H), 7.38 (d, J = 16.2 Hz, 1H), 6.63 (s, 1H), 3.40 – 3.35 (m, 2H), 2.77 – 2.72 (m, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 150.0, 147.6, 143.6, 134.2, 131.7, 131.3, 130.8, 130.7, 127.92, 124.5,

119.6, 98.7, 57.3, 45.4, 40.4; HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}ClN_4O_2$ 397.1431 $[M + H]^+$; found: 397.1403; retention time 6.526 min (HPLC condition A).

(E)-*N*^{1}-(6-Chloro-2-(4-(trifluoromethyl)styryl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (24)

The title compound was synthesized from **6c** and **7i**. Isolated yield: 83%; Yellow solid; MP: 171 – 172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 2.2 Hz, 1H), 7.72 (d, J = 6.4 Hz, 1H), 7.70 – 7.63 (m, 4H), 7.57 (dd, J = 9.0, 2.2 Hz, 1H), 7.33 (d, J = 16.2 Hz, 1H), 6.64 (s, 1H), 3.39 (t, J = 5.6 Hz, 2H), 2.74 (t, J = 6.0 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 149.9, 147.2, 140.5, 132.3, 132.1, 131.5, 130.6, 130.5, 127.6, 126.0 (q, J = 4.0 Hz), 123.1, 119.6, 119.5, 98.3, 57.3, 45.4, 40.4; HRMS (ESI) *m/z* calcd. for $C_{22}H_{22}ClF_3N_3$ 420.1454 $[M + H]^+$; found: 420.1463; retention time 2.399 min (HPLC condition B).

(E)-*N*^{1}-(6-Chloro-2-(4-methoxystyryl)quinolin-4-yl)-N^2,*N*^{2}-dimethylethane-1,2-diamine (25)

The title compound was synthesized from **6c** and **7e**. Isolated yield: 79%; Yellow solid; MP: 166 – 168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 9.0 Hz, 1H), 7.71 (d, J = 2.2 Hz, 1H), 7.61 (d, J = 16.2 Hz, 1H), 7.58 – 7.53 (m, 3H), 7.14 (d, J = 16.2 Hz, 1H), 6.92 (d, J = 8.8 Hz, 2H), 6.63 (s, 1H), 3.85 (s, 3H), 3.37 (q, J = 6.0 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 159.5, 156.3, 150.2, 133.6, 131.1, 130.3, 129.8, 128.9, 119.5, 114.6, 113.8, 104.6, 100.6, 97.3, 57.4, 55.7, 45.4, 40.4; HRMS (ESI) *m/z* calcd. for $C_{22}H_{25}ClN_3O$ 382.1686 $[M + H]^+$; found: 382.1656; retention time 5.988 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(3,4-dimethoxystyryl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (26)

The title compound was synthesized from **6c** and **7f**. Isolated yield: 81%; Yellow solid; MP: > 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 9.0 Hz, 1H), 7.71 (d, J = 2.2 Hz, 1H), 7.57 (d, J = 16.2 Hz, 1H), 7.56 (dd, J = 9.0, 2.4 Hz, 1H), 7.22 (d, J = 2.0 Hz, 1H), 7.16 (d, J = 16.2 Hz, 1H), 7.14 (dd, J = 4.0, 2.2 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.66 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.40 – 3.35 (m, 2H), 2.75 – 2.71 (m, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 150.0, 149.5, 148.9, 133.9, 131.4, 130.2, 122.9, 121.5, 119.6, 112.6, 111.5, 111.0, 109.3, 100.9, 57.3, 56.2, 56.0, 45.3, 40.1; HRMS (ESI) *m/z* calcd. for $C_{23}H_{27}ClN_3O_2$ 412.1792 $[M + H]^+$; found: 412.1775; retention time 5.910 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(3,4,5-trimethoxystyryl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (27)

The title compound was synthesized from **6c** and **7g**. Isolated yield: 75%; Yellow solid; MP: 187 – 189 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 9.0 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.56 (dd, J = 9.0, 2.4 Hz, 1H), 7.54 (d, J = 16.2 Hz, 1H), 7.19 (d, J = 16.2 Hz, 1H), 6.87 (s, 2H), 6.67 (s, 1H), 3.92 (s, 6H), 3.89 (s, 3H), 3.41 – 3.36 (m, 2H), 2.75 – 2.71 (m, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 153.8, 149.7, 147.3, 139.0, 133.9, 132.7, 131.4, 130.4, 130.2, 129.4, 119.6, 119.5, 104.6, 97.5, 61.3, 57.4, 56.5, 45.5, 40.4; HRMS (ESI) *m/z* calcd. for $C_{24}H_{29}ClN_3O_3$ 442.1897 $[M + H]^+$; found: 442.1868; retention time 6.390 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(4-(dimethylamino)styryl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (28)

The title compound was synthesized from **6c** and **7j**. Isolated yield: 84%; Red solid; MP: 159 – 162 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (d, J = 2.2 Hz, 1H), 7.69 – 7.65 (m, 3H), 7.40 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 16.2 Hz, 1H), 6.81 (d, J = 8.2 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 6.60 (s, 1H), 3.65 (t, J = 5.6 Hz, 2H), 2.97 (s, 6H), 2.81 (t, J = 5.6 Hz, 2H), 2.43 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 154.0, 152.9, 152.1, 140.1, 132.4, 131.0, 130.7, 129.5, 123.5, 123.2, 121.6, 118.2, 115.9, 111.9, 95.1, 56.7, 44.3, 40.7, 39.2; HRMS (ESI) *m/z* calcd. for $C_{23}H_{28}ClN_4$ 395.2002 $[M + H]^+$; found: 395.1984; retention time 7.245 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(4-fluorostyryl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (29)

The title compound was synthesized from **6c** and **7h**. Isolated yield: 88%; Yellow solid; MP: 177 – 179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 2.2 Hz, 1H), 7.63 (d, J = 16.2 Hz, 1H), 7.60 – 7.55 (m, 3H), 7.18 (d, J = 16.2 Hz, 1H), 7.10 – 7.05 (m, 2H), 6.62 (s, 1H), 3.38 (q, J = 6.0 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, J = 247.0 Hz), 156.7, 149.8, 147.2, 133.2, 132.8, 131.4, 130.5, 129.5, 129.1 (d, J = 8.0 Hz), 119.6, 119.5, 116.1 (d, J = 22.0 Hz), 98.0, 57.3, 45.4, 40.4; HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}ClFN_3$ 370.1486 $[M + H]^+$; found: 370.1496; retention time 2.341 min (HPLC condition B).

(E)-N^1-(6-Chloro-2-(2-fluorostyryl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (30)

The title compound was synthesized from **6c** and **7k**. Isolated yield: 82%; Yellow solid; MP: 116 – 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 9.0 Hz, 1H), 7.78 (d, J = 16.4 Hz, 1H), 7.74 (d, J = 2.2 Hz, 1H), 7.70 (dd, J = 7.6, 1.8 Hz, 1H), 7.55 (dd, J = 7.6,

2.2 Hz, 1H), 7.35 (d, *J* = 16.4 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.17 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.14 – 7.08 (m, 1H), 6.67 (s, 1H), 3.38 (t, *J* = 5.6 Hz, 2H), 2.74 (t, *J* = 6.0 Hz, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1 (d, *J* = 249.0 Hz), 156.7, 149.9, 147.0, 132.0, 131.3, 130.5, 130.4, 130.0 (d, *J* = 8.0 Hz), 128.2 (d, *J* = 3.0 Hz), 126.4 (d, *J* = 3.0 Hz), 124.9 (d, *J* = 12.0 Hz), 124.7 (d, *J* = 4.0 Hz), 119.6, 119.5, 116.2 (d, *J* = 22.0 Hz), 97.8, 57.3, 45.4, 40.4; HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}ClFN_3$ 370.1486 $[M + H]^+$; found: 370.1463; retention time 5.710 min (HPLC condition A).

(E)-*N*^{1}-(6-Chloro-2-(3-fluorostyryl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (31)

The title compound was synthesized from **6c** and **7l**. Isolated yield: 82%; Yellow solid; MP: 154 – 157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 9.0 Hz, 1H), 7.73 (d, *J* = 2.2 Hz, 1H), 7.62 (d, *J* = 16.2 Hz, 1H), 7.56 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.39 – 7.29 (m, 4H), 7.24 (d, *J* = 16.2 Hz, 1H), 6.61 (s, 1H), 3.37 (t, *J* = 5.6 Hz, 2H), 2.74 (t, *J* = 6.0 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (d, *J* = 244.0 Hz), 156.3, 149.9, 147.1, 139.4 (d, *J* = 7.0 Hz), 132.8 (d, *J* = 3.0 Hz), 131.4, 130.9, 130.5 (d, *J* = 2.0 Hz), 130.4 (d, *J* = 8.0 Hz), 123.5 (d, *J* = 3.0 Hz), 119.6, 119.5, 115.5 (d, *J* = 22.0 Hz), 113.8 (d, *J* = 22.0 Hz), 98.2, 57.3, 45.4, 40.4; HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}ClFN_3$ 370.1486 $[M + H]^+$; found: 370.1459; retention time 5.803 min (HPLC condition A).

(E)-*N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(2-styrylquinolin-4-yl)ethane-1,2-diamine (32)

The title compound was synthesized from **6d** and **7a**. Isolated yield: 89%; Yellow solid; MP: 158 – 161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 16.2 Hz, 1H), 7.62 (d, *J* = 4.0 Hz, 1H), 7.59 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.41 – 7.36 (m, 2H), 7.33 – 7.28 (m, 3H), 6.64 (s, 1H), 3.53 (t, *J* = 6.0 Hz, 2H),

2.80 (t, J = 6.0 Hz, 2H), 2.38 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 152.4, 143.6, 137.3, 136.0, 131.4, 129.6, 129.1, 128.0, 125.7, 120.8, 117.6, 96.1, 57.0, 45.4, 40.4; HRMS (ESI) *m/z* calcd. for $C_{21}H_{24}N_3$ 318.1970 $[M + H]^+$; found: 318.1955; retention time 6.292 min (HPLC condition A).

(E)-N^1,N^1-Dimethyl-N^2-(2-(4-nitrostyryl)quinolin-4-yl)ethane-1,2-diamine (33)

The title compound was synthesized from **6d** and **7b**. Isolated yield: 87%; Yellow solid; MP: 152 – 154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.76 – 7.72 (m, 3H), 7.69 – 7.64 (m, 1H), 7.46 – 7.41 (m, 2H), 6.65 (s, 1H), 3.40 (t, J = 5.8 Hz, 2H), 2.75 (t, J = 5.8 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 150.9, 147.5, 143.6, 134.2, 131.3, 130.1, 129.7, 127.9, 125.3, 124.4, 120.1, 118.8, 97.9, 57.4, 45.4, 40.3; HRMS (ESI) *m/z* calcd. for $C_{21}H_{23}N_4O_2$ 363.1821 $[M + H]^+$; found: 363.1798; retention time 6.133 min (HPLC condition A).

(E)-N^1-(2-(4-Fluorostyryl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (34)

The title compound was synthesized from **6d** and **7h**. Isolated yield: 84%; Yellow solid; MP: 194 – 198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 16.2 Hz, 1H), 7.64 – 7.55 (m, 3H), 7.39 (t, J = 7.4 Hz, 1H), 7.26 (d, J = 16.2 Hz, 1H), 7.00 (t, J = 8.6 Hz, 2H), 6.64 (s, 1H), 3.46 (t, J = 5.8 Hz, 2H), 2.75 (t, J = 5.8 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (d, J = 247.0 Hz), 155.6, 151.2, 133.6, 133.3 (d, J = 3.0 Hz), 130.3, 129.3 (d, J = 8.0 Hz), 128.4, 128.1, 125.0, 120.2, 118.3, 116.1 (d, J = 21.0 Hz), 96.9, 57.3, 45.4, 40.4; HRMS (ESI) *m/z* calcd. for $C_{21}H_{23}FN_3$ 336.1876 $[M + H]^+$; found: 336.1853; retention time 6.245 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-styrylquinolin-4-yl)-N^4,N^4-dimethylbutane-1,4-diamine (35)

The title compound was synthesized from **6e** and **7a**. Isolated yield: 85%; Yellow solid; MP: 102 – 105 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (d, J = 2.2 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.60 – 7.57 (m, 2H), 7.56 (d, J = 5.8 Hz, 1H), 7.51 (dd, J = 9.0, 2.2 Hz, 1H), 7.35 (d, J = 5.8 Hz, 1H), 7.31 (d, J = 16.4 Hz, 1H), 7.15 (d, J = 16.4 Hz, 1H), 6.71 (s, 1H), 3.36 (t, J = 6.8 Hz, 2H), 2.64 (t, J = 6.8 Hz, 2H), 2.44 (s, 6H), 1.77 – 1.68 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 156.2, 151.3, 145.3, 136.6, 135.1, 130.5, 130.1, 128.9, 128.8, 128.4, 127.4, 127.3, 120.8, 119.2, 96.3, 58.7, 46.7, 43.7, 25.9, 24.0; HRMS (ESI) *m/z* calcd. for $C_{23}H_{27}ClN_3$ 380.1894 $[M + H]^+$; found: 380.1876; retention time 6.078 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(4-nitrostyryl)quinolin-4-yl)-N^4,N^4-dimethylbutane-1,4-diamine (36)

The title compound was synthesized from **6e** and **7b**. Isolated yield: 76%; Yellow solid; MP: > 200 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.17 (d, J = 8.8 Hz, 2H), 8.15 (d, J = 2.2 Hz, 1H), 7.78 (dd, J = 8.8, 3.6 Hz, 3H), 7.72 (d, J = 16.4 Hz, 1H), 7.59 (dd, J = 9.0, 2.2 Hz, 1H), 7.36 (d, J = 16.4 Hz, 1H), 6.86 (s, 1H), 3.50 (t, J = 6.4 Hz, 2H), 3.03 (t, J = 6.4 Hz, 2H), 2.75 (s, 6H), 1.87 – 1.82 (m, 2H);^{13}C NMR (100 MHz, CD_3OD) δ 155.2, 151.5, 147.8, 145.3, 143.1, 132.6, 131.7, 130.8, 130.6, 128.6, 127.9, 123.9, 120.9, 97.1, 58.0, 42.8, 42.4, 25.5, 22.9; HRMS (ESI) *m/z* calcd. for $C_{23}H_{26}ClN_4O_2$ 425.1744 $[M + H]^+$; found: 425.1724; retention time 6.177 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(4-fluorostyryl)quinolin-4-yl)-N^4,N^4-dimethylbutane-1,4-diamine (37)

The title compound was synthesized from **6e** and **7h**. Isolated yield: 81%; Yellow solid; MP: 145 – 147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 2.2 Hz, 1H), 7.65 (d, J = 16.4 Hz, 1H), 7.59 (d, J = 5.8 Hz, 1H), 7.58 (d, J = 5.8 Hz, 1H), 7.53 (dd, J = 9.0, 2.0 Hz, 1H), 7.18 (d, J = 16.4 Hz, 1H), 7.06 (t, J = 8.6 Hz, 2H), 6.55 (s, 1H), 3.32 (t, J = 6.8 Hz, 2H), 2.45 (t, J = 6.8 Hz, 2H), 2.35 (s, 6H), 1.97 – 1.92 (m, 2H), 1.78 – 1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, J = 247.0 Hz), 156.4, 150.7, 146.7, 133.2 (d, J = 3.0 Hz), 133.0, 130.7, 130.4, 130.0, 129.2 (d, J = 8.0 Hz), 120.3, 119.6, 116.1 (d, J = 21.0 Hz), 97.3, 59.8, 45.8, 43.9, 27.1, 26.2; HRMS (ESI) *m/z* calcd. for $C_{23}H_{26}ClFN_3$ 398.1799 $[M + H]^+$; found: 398.1779; retention time 6.641 min (HPLC condition A).

(E)-N^1-(2-(2-(Furan-2-yl)vinyl)-6-methoxyquinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (39)

The title compound was synthesized from **6e** and **38a**. Isolated yield: 62%; Yellow solid; MP: 114 – 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 9.2 Hz, 1H), 7.52 (d, J = 16.2 Hz, 1H), 7.43 (d, J = 1.8 Hz, 1H), 7.20 (dd, J = 9.2, 2.8 Hz, 1H), 7.16 (d, J = 2.6 Hz, 1H), 7.07 (d, J = 16.2 Hz, 1H), 6.51 (d, J = 3.4 Hz, 1H), 6.44 – 6.41 (m, 2H), 3.89 (s, 3H), 3.40 (t, J = 6.2 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 2.32 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 152.9, 152.3, 151.0, 143.7, 129.2, 128.4, 126.4, 122.3, 121.7, 118.8, 112.4, 101.0, 100.9, 97.1, 57.3, 56.2, 45.5, 40.8; HRMS (ESI) *m/z* calcd. for $C_{20}H_{24}N_3O_2$ 338.1869 $[M + H]^+$; found: 338.1867; retention time 2.497 min (HPLC condition B).

(E)-N^1-(6-Methoxy-2-(2-(thiophen-2-yl)vinyl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (40)

The title compound was synthesized from **6e** and **38b**. Isolated yield: 64%; Yellow solid; MP: 123 – 126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 9.2 Hz, 1H), 7.74 (d, J = 16.2 Hz, 1H), 7.25 – 7.19 (m, 3H), 7.14 (d, J = 2.8 Hz, 1H), 7.04 – 6.99 (m, 2H), 6.45 (s, 1H), 3.89 (d, J = 1.2 Hz, 3H), 3.39 (t, J = 6.0 Hz, 2H), 2.74 (t, J = 6.0 Hz, 2H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 152.8, 150.6, 142.4, 141.8, 129.1, 128.4, 128.2, 127.3, 127.1, 126.3, 121.4, 119.0, 100.8, 96.8, 57.4, 56.1, 45.5, 40.8; HRMS (ESI) *m/z* calcd. for $C_{20}H_{24}N_3OS$ 354.1640 $[M + H]^+$; found: 354.1617; retention time 5.373 min (HPLC condition A).

(E)-*N*^{1}-(6-Methoxy-2-(2-(pyridin-4-yl)vinyl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (41)

The title compound was synthesized from **6e** and **38c**. Isolated yield: 80%; Yellow solid; MP: 168 – 170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 5.2 Hz, 2H), 7.96 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 7.44 (d, J = 16.4 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.23 (s, 1H), 6.65 (s, 1H), 3.89 (s, 3H), 3.59 (t, J = 6.0 Hz, 2H), 2.89 (t, J = 6.0 Hz, 2H), 2.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 150.6, 143.6, 142.6, 140.9, 129.4, 126.6, 126.3, 122.6, 121.8, 118.9, 101.0, 96.7, 57.1, 56.3, 45.3, 40.6; HRMS (ESI) *m/z* calcd. for $C_{21}H_{25}N_4O$ 349.2028 $[M + H]^+$; found: 349.2056; retention time 2.355 min (HPLC condition B).

(E)-*N*^{1}-(6-Methoxy-2-(2-(pyridin-2-yl)vinyl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (42)

The title compound was synthesized from **6e** and **38d**. Isolated yield: 83%; Brown solid; MP: 147 – 150 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.63 (dd, J = 4.8, 2.4 Hz, 1H), 7.97 (d, J = 16.4 Hz, 1H), 7.90 – 7.85 (m, 1H), 7.83 (d, J = 9.2 Hz, 1H), 7.76 (d, J = 2.6

Hz, 1H), 7.71 – 7.67 (m, 2H), 7.51 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.19 (s, 1H), 3.99 (s, 3H), 3.29 – 3.28 (m, 4H), 2.77 (s, 6H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.0, 154.5, 153.5, 150.0, 149.1, 137.8, 125.0, 124.7, 124.6, 122.6, 118.6, 102.1, 95.9, 56.0, 43.5, 39.5; HRMS (ESI) *m/z* calcd. for $C_{21}H_{25}N_4O$ 349.2028 $[M + H]^+$; found: 349.2009; retention time 2.744 min (HPLC condition A).

(E)-*N*^{1}-(6-Methoxy-2-(2-(pyridin-3-yl)vinyl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (43)

The title compound was synthesized from **6e** and **7e**. Isolated yield: 76%; Brown solid; MP: 127 – 129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (d, *J* = 2.2 Hz, 1H), 8.51 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.95 – 7.92 (m, 1H), 7.62 (d, *J* = 16.4 Hz, 1H), 7.37 (d, *J* = 16.4 Hz, 1H), 7.32 (dd, *J* = 9.2, 2.6 Hz, 2H), 7.12 (d, *J* = 2.6 Hz, 1H), 6.65 (s, 1H), 3.95 (s, 3H), 3.48 – 3.44 (m, 2H), 2.81 (t, *J* = 5.6 Hz, 2H), 2.38 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 150.8, 150.5, 149.6, 149.4, 148.7, 136.7, 133.6, 132.7, 130.2, 124.0, 123.2, 121.4, 119.2, 100.7, 97.1, 57.4, 56.2, 45.4, 40.6; HRMS (ESI) *m/z* calcd. for $C_{21}H_{25}N_4O$ 349.2028 $[M + H]^+$; found: 349.2001; retention time 2.918 min (HPLC condition A).

(E)-*N*^{1}-(6-Fluoro-2-(2-(furan-2-yl)vinyl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (44)

The title compound was synthesized from **6b** and **38a**. Isolated yield: 65%; Yellow solid; MP: 107 – 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 9.0, 5.6 Hz, 1H), 7.56 (d, *J* = 16.0 Hz, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 7.42 – 7.35 (m, 2H), 7.14 (d, *J* = 16.0 Hz, 1H), 6.54 (s, 1H), 6.52 (d, *J* = 3.6 Hz, 1H), 6.46 (dd, *J* = 3.6, 1.8 Hz, 1H), 3.37 (t, *J* = 5.8 Hz, 2H), 2.74 (t, *J* = 6.0 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9

(d, *J* = 244.0 Hz), 155.2, 153.2 , 150.4 (d, *J* = 4.0 Hz), 143.4, 131.4 (d, *J* = 6.0 Hz), 126.8, 121.9, 119.6 (d, *J* = 25.0 Hz), 119.0 (d, *J* = 9.0 Hz), 112.3, 111.4, 104.6 (d, *J* =23.0 Hz), 98.1, 57.3, 45.4, 40.3; HRMS (ESI) *m/z* calcd. for $C_{19}H_{21}FN_3O$ 326.1669 $[M + H]^+$; found: 326.1649; retention time 4.859 min (HPLC condition A).

(E)-*N*^{1}-(6-Fluoro-2-(2-(thiophen-2-yl)vinyl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (45)

The title compound was synthesized from **6b** and **38b**. Isolated yield: 69%; Yellow solid; MP: 121 – 123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 9.0, 5.6 Hz, 1H), 7.83 (d, *J* = 16.0 Hz, 1H), 7.43 – 7.36 (m, 2H), 7.27 (d, *J* = 5.6 Hz, 1H), 7.22 (d, *J* = 3.6 Hz, 1H), 7.07 (d, *J* = 16.0 Hz, 1H), 7.03 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.56 (s, 1H), 3.38 (t, *J* = 5.8 Hz, 2H), 2.75 (t, *J* = 6.0 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (d, *J* = 244.0 Hz), 155.3, 150.4 (d, *J* = 4.0 Hz), 145.0, 142.5, 131.4 (d, *J* = 9.0 Hz), 128.3, 128.1, 127.3, 126.2, 119.6 (d, *J* = 25.0 Hz), 119.0 (d, *J* = 9.0 Hz), 104.6 (d, *J* = 23.0 Hz), 97.6, 57.3, 45.4, 40.3; HRMS (ESI) *m/z* calcd. for $C_{19}H_{21}FN_3S$ 342.1440 $[M + H]^+$; found: 342.1421; retention time 4.899 min (HPLC condition A).

(E)-*N*^{1}-(6-Fluoro-2-(2-(pyridin-4-yl)vinyl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (46)

The title compound was synthesized from **6b** and **38c**. Isolated yield: 84%; Yellow solid; MP: 167 – 169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 5.8 Hz, 2H), 8.03 (dd, *J* = 9.6, 5.6 Hz, 1H), 7.60 (d, *J* = 16.2 Hz, 1H), 7.47 (d, *J* = 2.2 Hz, 2H), 7.46 – 7.39 (m, 3H), 6.65 (s, 1H), 3.41 (t, *J* = 5.8 Hz, 2H), 2.73 (t, *J* = 6.0 Hz, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (d, *J* = 245.0 Hz), 154.9, 150.6, 150.3 (d, *J* = 5.0 Hz), 145.7, 144.4, 134.2, 132.3 (d, *J* = 9.0 Hz), 130.8, 121.7, 119.7 (d, *J* = 24.0 Hz), 119.4 (d, *J* = 9.0

Hz), 104.6 (d, J = 23.0 Hz), 98.1, 57.3, 45.4, 40.3; HRMS (ESI) *m/z* calcd. for $C_{20}H_{22}FN_4$ 337.1828 $[M + H]^+$; found: 337.1812; retention time 2.430 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(2-(furan-2-yl)vinyl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (47)

The title compound was synthesized from **6c** and **38a**. Isolated yield: 69%; Yellow solid; MP: 118 – 120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 9.0 Hz, 1H), 7.71 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 2.2 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.14 (d, J = 16.2 Hz, 1H), 6.53 (s, 1H), 6.52 (d, J = 3.8 Hz, 1H), 6.46 (dd, J = 3.6, 1.8 Hz, 1H), 3.34 (q, J = 6.0 Hz, 2H), 2.72 (t, J = 6.0 Hz, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 153.3, 149.8, 147.3, 143.3, 131.4, 130.4, 130.0, 127.6, 121.6, 119.5, 119.4, 112.2, 111.2, 98.7, 57.4, 45.4, 40.3; HRMS (ESI) *m/z* calcd. for $C_{19}H_{21}ClN_3O$ 342.1373 $[M + H]^+$; found: 342.1350; retention time 5.965 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(2-(thiophen-2-yl)vinyl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (48)

The title compound was synthesized from **6c** and **38b**. Isolated yield: 65%; Yellow solid; MP: 131 – 132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 16.2 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 9.0, 2.4 Hz, 1H), 7.28 (s, 1H), 7.22 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 11.6 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.56 (s, 1H), 3.36 (q, J = 6.0 Hz, 2H), 2.73 (t, J = 6.0 Hz, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 149.8, 147.2, 142.6, 131.3, 130.5, 130.1, 128.9, 128.2, 128.1, 127.1, 126.1, 119.6, 98.1, 57.3, 45.4, 40.4; HRMS (ESI) *m/z* calcd. for $C_{19}H_{21}ClN_3S$ 358.1145 $[M + H]^+$; found: 358.1113; retention time 6.280 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(2-(thiazol-2-yl)vinyl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (49)

The title compound was synthesized from **6c** and **38f**. Isolated yield: 62%; Yellow solid; MP: 108 – 110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 9.0 Hz, 1H), 7.87 (s, 1H), 7.84 (d, J = 16.2 Hz, 1H), 7.76 (d, J = 2.2 Hz, 1H), 7.57 (dd, J = 4.0, 2.2 Hz, 1H), 7.54 (d, J = 16.2 Hz, 1H), 7.33 (d, J = 3.2 Hz, 1H), 6.66 (s, 1H), 3.35 (t, J = 5.6 Hz, 2H), 2.74 (t, J = 5.6 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 155.4, 149.9, 147.2, 144.2, 135.2, 131.6, 130.8, 130.6, 126.4, 119.7, 119.6, 98.3, 57.3, 45.4, 40.3; HRMS (ESI) *m/z* calcd. for $C_{18}H_{20}ClN_4S$ 359.1097 $[M + H]^+$; found: 359.1073; retention time 3.304 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(2-(pyridin-4-yl)vinyl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (50)

The title compound was synthesized from **6c** and **38c**. Isolated yield: 85%; Yellow solid; MP: 174 – 175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 6.2 Hz, 2H), 7.92 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 16.2 Hz, 1H), 7.14 (dd, J = 4.0, 2.2 Hz, 1H), 7.46 (d, J = 6.4 Hz, 2H), 7.42 (d, J = 16.2 Hz, 1H), 6.63 (s, 1H), 3.39 – 3.34 (m, 2H), 2.76 – 2.71 (m, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 150.7, 150.0, 147.3, 144.4, 134.2, 131.7, 131.1, 130.7, 130.6, 121.7, 119.6, 119.6, 98.5, 57.3, 45.4, 40.4; HRMS (ESI) *m/z* calcd. for $C_{20}H_{22}ClN_4$ 353.1533 $[M + H]^+$; found: 353.1530; retention time 2.784 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(2-(pyridin-2-yl)vinyl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (51)

The title compound was synthesized from **6c** and **38d**. Isolated yield: 83%; Yellow solid; MP: 114 – 116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 4.8 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 7.77 (d, J = 16.2 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.69 (dd, J = 8.0, 2.4 Hz, 1H), 6.69 (s, 1H), 7.57 (d, J = 2.2 Hz, 1H), 7.55 (m, 1H), 3.34 (t, J = 5.8 Hz, 2H), 2.73 (t, J = 5.8 Hz, 2H), 2.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 155.5, 150.1, 150.0, 137.0, 133.6, 133.3, 131.4, 130.5, 123.1, 119.7, 119.5, 99.0, 57.3, 45.4, 40.3; HRMS (ESI) *m/z* calcd. for $C_{20}H_{22}ClN_4$ 353.1533 $[M + H]^+$; found: 353.1530; retention time 2.844 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(2-(pyridin-3-yl)vinyl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (52)

The title compound was synthesized from **6c** and **38e**. Isolated yield: 86%; Yellow solid; MP: 128 – 132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 1.8 Hz, 1H), 8.53 (d, J = 4.8 Hz, 1H), 7.93 (d, J = 4.8 Hz, 1H), 7.91 (d, J = 16.2 Hz, 1H), 7.76 (d, J = 2.2 Hz, 1H), 7.65 (d, J = 16.2 Hz, 1H), 7.56 (dd, J = 9.0, 2.2 Hz, 1H), 7.33 – 7.29 (m, 2H), 6.64 (s, 1H), 3.41 (t, J = 5.8 Hz, 2H), 2.78 (t, J = 5.8 Hz, 2H), 2.38 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 150.1, 149.7, 149.5, 146.7, 133.7, 132.6, 131.3, 131.0, 130.8, 130.7, 130.6, 124.0, 119.8, 119.4, 98.1, 57.2, 45.4, 40.3; HRMS (ESI) *m/z* calcd. for $C_{20}H_{22}ClN_4$ 353.1533 $[M + H]^+$; found: 353.1520; retention time 2.844 min (HPLC condition A).

(E)-N^1-(6-Chloro-2-(2-(pyrimidin-5-yl)vinyl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (53)

The title compound was synthesized from **6c** and **38g**. Isolated yield: 67%; Yellow solid; MP: 171 – 173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.09 (s, 2H), 9.07 (s, 1H), 8.29 (d, J = 2.2 Hz, 1H), 7.81 (d, J = 6.0 Hz, 1H), 7.77 (d, J = 16.2 Hz, 1H), 7.62 (dd, J = 9.0,

2.2 Hz, 2H), 7.52 (d, *J* = 16.2 Hz, 1H), 6.93 (s, 1H), 3.68 (t, *J* = 5.6 Hz, 2H), 3.28 (t, *J* = 5.6 Hz, 2H), 2.76 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.2, 156.0, 155.7, 150.4, 147.3, 133.6, 132.4, 131.6, 131.1, 130.8, 129.6, 127.3, 121.9, 120.0, 98.9, 55.5, 43.7, 40.5; HRMS (ESI) *m/z* calcd. for $C_{19}H_{21}ClN_5$ 354.1485 $[M + H]^+$; found: 354.1463; retention time 3.162 min (HPLC condition A).

(E)-*N*^{1}-(2-(2-(1H-indol-2-yl)vinyl)-6-chloroquinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (54)

The title compound was synthesized from **6c** and **38h**. Isolated yield: 63%; Green solid; MP: 148 – 150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.0 Hz, 1H), 7.78 (d, *J* = 2.2 Hz, 1H), 7.68 – 7.66 (dd, *J* = 4.0, 2.2 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 6.81 (d, *J* = 13.2 Hz, 1H), 6.71 (s, 1H), 6.45 (s, 1H), 6.39 (d, *J* = 13.2 Hz, 1H), 3.35 (t, *J* = 6.0 Hz, 2H), 2.73 (t, *J* = 6.0 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 150.0, 146.0, 137.3, 136.9, 130.9, 130.4, 129.8, 129.0, 126.4, 125.3, 123.3, 121.2, 119.8, 118.8, 112.1, 107.6, 102.5, 57.2, 45.4, 40.2; HRMS (ESI) *m/z* calcd. for $C_{23}H_{24}ClN_4$ 391.1689 $[M + H]^+$; found: 391.1680; retention time 6.631 min (HPLC condition A).

(E)-*N*^{1}-(6-Chloro-2-(2-(6-methoxyquinolin-2-yl)vinyl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (55)

The title compound was synthesized from **6c** and **38i**. Isolated yield: 66%; Brown solid; MP: 151 – 154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.6 Hz, 1H), 7.98 (dd, *J* = 9.0, 2.2 Hz, 2H), 7.86 (d, *J* = 16.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 16.4 Hz, 2H), 7.57 (dd, *J* = 9.2, 2.2 Hz, 1H), 7.38 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.08 (d, *J* = 2.8 Hz, 1H), 6.85 (s, 1H), 3.95 (s, 3H), 3.40 (t, *J* = 6.0 Hz, 2H), 2.78 (t, *J* = 6.0 Hz, 2H), 2.38 (s,

6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.3, 153.5, 150.0, 147.0, 146.6, 144.6, 135.6, 134.8, 133.9, 131.1, 130.7, 129.0, 122.9, 120.1, 119.8, 119.6, 105.6, 97.6, 57.3, 56.0, 45.4, 40.4; HRMS (ESI) *m/z* calcd. for $C_{25}H_{26}ClN_4O$ 433.1795 $[M + H]^+$; found: 433.1812; retention time 6.204 min (HPLC condition A).

(E)-*N*^{1}-(6-Chloro-2-(2-(naphthalen-1-yl)vinyl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (56)

The title compound was synthesized from **6c** and **38j**. Isolated yield: 60%; Brown solid; MP: 113 – 115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J = 16.0 Hz, 1H), 8.36 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.87 (q, J = 9.2, 8.2 Hz, 4H), 7.74 (d, J = 2.2 Hz, 1H), 7.59 (dd, J = 5.8 Hz, 2.2 Hz, 1H), 7.55 (dd, , J = 5.8 Hz, 2.2 Hz, 1H), 7.53 – 7.49 (m, 2H), 7.33 (d, J = 16.0 Hz, 1H), 6.72 (s, 1H), 3.42 (t, J = 7.0 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 2.36 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 150.0, 147.0, 134.5, 134.1, 132.3, 131.9, 131.3, 130.5, 130.3, 129.2, 129.0, 126.6, 126.3, 126.0, 124.5, 124.3, 119.6, 119.4, 98.3, 57.3, 45.5, 40.4; HRMS (ESI) *m/z* calcd. for $C_{25}H_{25}ClN_3$ 402.1737 $[M + H]^+$; found: 402.1723; retention time 5.609 min (HPLC condition A).

(E)-*N*^{1}-(6-Chloro-2-(2-cyclohexylvinyl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (57)

The title compound was synthesized from **6c** and **38k**. Isolated yield: 48%; Yellow solid; MP: 88 – 91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 2.2 Hz, 1H), 7.54 (dd, J = 9.2, 2.2 Hz, 1H), 6.82 (d, J = 16.2 Hz, 1H), 6.60 (d, J = 16.2 Hz, 1H), 6.51 (s, 1H), 3.39 (t, J = 6.0 Hz, 2H), 2.75 (t, J = 6.0 Hz, 2H), 2.41 – 2.38 (m, 1H), 2.35 (s, 6H), 1.88 – 1.76 (m, 6H), 1.35 – 1.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 144.9, 142.3, 131.0, 130.5, 129.1, 127.3, 126.7, 119.8, 119.0, 96.6, 57.1, 45.4,

41.6, 32.8, 30.1, 26.3; HRMS (ESI) *m/z* calcd. for $C_{21}H_{29}ClN_3$ 358.2050 $[M + H]^+$; found: 358.2024; retention time 6.114 min (HPLC condition A).

(E)-4-(6-Chloro-2-(4-fluorostyryl)quinolin-4-yl)morpholine (62)

The title compound was synthesized from **61a** and **7h**. Isolated yield: 89%; Yellow solid; MP: 173 – 175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 2.2 Hz, 1H), 7.64 (d, J = 16.2 Hz, 1H), 7.61 – 7.57 (m, 3H), 7.21 (d, J = 16.2 Hz, 1H), 7.11 – 7.07 (m, 3H), 4.03 – 4.00 (m, 4H), 3.26 – 3.23 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (d, J = 247.0 Hz), 156.8, 156.6, 148.4, 133.6, 132.9 (d, J = 4.0 Hz), 131.8, 131.4, 130.7, 129.3, 129.2, 128.9 (d, J = 3.0 Hz), 123.8, 122.8, 116.2 (d, J = 22.0 Hz), 108.3, 67.2, 53.0; HRMS (ESI) calculated for $C_{21}H_{19}ClFN_2O$ $[M+H]^+$ m/z 369.1170, found 369.1153; retention time 8.342 min (HPLC condition A).

(E)-4-(6-Chloro-2-(2-(pyridin-4-yl)vinyl)quinolin-4-yl)morpholine (63)

The title compound was synthesized from **61a** and **38c**. Isolated yield: 84%; Yellow solid; MP: 195 – 198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 5.4 Hz, 2H), 7.98 (d, J = 9.0 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H), 7.62 – 7.58 (m, 2H), 7.46 – 7.43 (m, 3H), 7.09 (s, 1H), 4.03 – 4.00 (m, 4H), 3.26 – 3.23 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 155.7, 150.7, 148.4, 144.0, 133.5, 132.0, 131.9, 130.9, 124.0, 122.8, 121.7, 108.7, 67.2, 53.0; HRMS (ESI) calculated for $C_{20}H_{19}ClN_3O$ $[M+H]^+$ m/z 352.1217, found 352.1196; retention time 6.309 min (HPLC condition A).

(E)-6-Chloro-2-(4-fluorostyryl)-4-(pyrrolidin-1-yl)quinoline (65)

The title compound was synthesized from **61b** and **7h**. Isolated yield: 85%; Yellow solid; MP: 161 – 163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 2.2 Hz, 1H), 7.89 (d, J = 9.0 Hz, 1H), 7.61 (d, J = 16.2 Hz, 1H), 7.59 – 7.56 (m, 2H), 7.51 (dd, J = 8.6, 2.2 Hz,

1H), 7.14 (d, *J* = 16.2 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 2H), 6.64 (s, 1H), 3.72 – 3.68 (m, 4H), 2.08 – 2.06 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (d, *J* = 247.0 Hz), 155.8, 152.6, 149.1, 133.3 (d, *J* = 3.0 Hz), 132.4, 131.4, 129.8, 129.5 (d, *J* = 3.0 Hz), 129.1, 129.0, 128.4, 124.5, 121.6, 116.1 (d, *J* = 22.0 Hz), 102.3, 52.5, 26.3; HRMS (ESI) calculated for $C_{21}H_{19}ClFN_2$ $[M+H]^+$ m/z 353.1221, found 353.1205; retention time 8.792 min (HPLC condition A).

(E)-6-Chloro-2-(2-(pyridin-4-yl)vinyl)-4-(pyrrolidin-1-yl)quinoline (66)

The title compound was synthesized from **61b** and **38c**. Isolated yield: 81%; Yellow solid; MP: 175 – 177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 6.0 Hz, 2H), 8.19 (d, *J* = 2.2 Hz, 1H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.60 (d, *J* = 16.2 Hz, 1H), 7.54 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.46 (d, *J* = 6.0 Hz, 2H), 7.40 (d, *J* = 16.2 Hz, 1H), 6.68 (s, 1H), 3.76 – 3.73 (m, 4H), 2.12 – 2.08 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 150.6, 144.4, 134.0, 131.4, 131.0, 130.1, 129.0, 124.5, 121.7, 102.7, 52.6, 26.4; HRMS (ESI) calculated for $C_{20}H_{19}ClN_3$ $[M+H]^+$ m/z 336.1268, found 336.1241; retention time 6.372 min (HPLC condition A).

(E)-6-Chloro-2-(4-fluorostyryl)-4-(4-(pyridin-2-yl)piperazin-1-yl)quinoline (67)

The title compound was synthesized from **61c** and **7h**. Isolated yield: 74%; Yellow solid; MP: 154 – 155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 1H), 8.00 (d, *J* = 2.4 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.67 (s, 1H), 7.62 – 7.53 (m, 5H), 7.22 (d, *J* = 16.2 Hz, 1H), 7.11 (s, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.76 (d, *J* = 8.6 Hz, 1H), 6.72 (ddd, *J* = 7.2, 5.0, 0.8 Hz, 1H), 3.87 – 3.83 (m, 4H), 3.38 – 3.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (d, *J* = 248.0 Hz), 159.8, 156.8, 156.7, 148.4, 138.0, 133.5, 133.0 (d, *J* = 4.0 Hz), 131.8, 131.4, 130.7, 129.3, 129.2, 129.0 (d, *J* = 2.0 Hz), 124.0, 122.9,

116.2 (d, J = 22.0 Hz), 114.4, 108.5, 107.7, 52.4, 45.9; HRMS (ESI) calculated for $C_{26}H_{23}ClFN_4$ $[M+H]^+$ m/z 445.1595, found 445.1588; retention time 7.497 min (HPLC condition A).

(E)-6-Chloro-4-(4-(pyridin-2-yl)piperazin-1-yl)-2-(2-(pyridin-4-yl)vinyl)quinoline (68)

The title compound was synthesized from **61c** and **38c**. Isolated yield: 71%; Brown solid; MP: 163 – 166 °C; ^{1}H NMR (400 **38f**Hz, $CDCl_3$) δ 8.65 (d, J = 3.2 Hz, 2H), 8.26 (ddd, J = 5.0, 2.0, 0.8 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.64 (d, J = 2.4 Hz, 1H), 7.60 (d, J = 4.2 Hz, 1H), 7.58 – 7.54 (m, 1H), 7.49 – 7.45 (m, 3H), 7.14 (s, 1H), 6.77 (d, J = 8.6 Hz, 1H), 6.72 (ddd, J = 7.2, 5.0, 0.8 Hz, 1H), 3.87 – 3.84 (m, 4H), 3.40 – 3.37 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 157.0, 150.7, 148.4, 144.0, 138.0, 133.5, 132.0, 131.9, 130.9, 124.2, 123.0, 121.7, 114.4, 108.9, 107.8, 52.4, 45.9; HRMS (ESI) calculated for $C_{25}H_{23}ClN_5$ $[M+H]^+$ m/z 428.1642, found 428.1621; retention time 5.680 min (HPLC condition A).

(E)-6-Chloro-2-(4-fluorostyryl)-*N*-(4-(piperidin-1-yl)phenyl)quinolin-4-amine (69)

The title compound was synthesized from **61d** and **7h**. Isolated yield: 48%; Yellow solid; MP: 154 – 156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 9.0 Hz, 1H), 7.85 (d, J = 2.2 Hz, 1H), 7.59 (dd, J = 9.0, 2.2 Hz, 1H), 7.55 (d, J = 5.4 Hz, 1H), 7.53 (d, J = 2.8 Hz, 1H), 7.51 (d, J = 16.2 Hz, 1H), 7.22 (d, J = 7.0 Hz, 2H), 7.09 – 7.02 (m, 5H), 6.92 (s, 1H), 3.24 – 3.21 (m, 4H), 1.80 – 1.74 (m, 4H), 1.65 – 1.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, J = 247.0 Hz), 156.5, 150.7, 149.0, 133.1, 131.4, 130.8, 130.5, 129.2 (d, J = 8.0 Hz), 129.0, 125.9, 119.6, 119.3, 117.7, 116.1 (d, J = 21.0 Hz), 100.5, 51.0, 26.2,

24.6; HRMS (ESI) calculated for $C_{28}H_{26}ClFN_3$ $[M+H]^+$ m/z 458.1799, found 458.1787; retention time 9.254 min (HPLC condition A).

(E)-6-Chloro-*N*-(4-(piperidin-1-yl)phenyl)-2-(2-(pyridin-4-yl)vinyl)quinolin-4-amine (70)

The title compound was synthesized from **61c** and **38c**. Isolated yield: 45%; Brown solid; MP: > 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, br., 2H), 7.96 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 2.2 Hz, 1H), 7.62 (dd, J = 9.0, 2.2 Hz, 1H) 7.48 (d, J = 16.2 Hz, 1H), 7.41 (d, J = 5.6 Hz, 2H), 7.31 (d, J = 16.2 Hz, 1H), 7.22 (d, J = 9.0 Hz, 2H), 7.04 (d, J = 9.0 Hz, 2H), 6.93 (s, 1H), 3.25 – 3.22 (m, 4H), 1.80 – 1.74 (m, 4H), 1.66 – 1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 150.8, 150.6, 149.3, 147.7, 144.3, 133.9, 131.8, 131.3, 131.2, 130.9, 130.3, 126.1, 121.7, 119.4, 117.7, 101.0, 51.0, 26.2, 24.6; HRMS (ESI) calculated for $C_{27}H_{26}ClN_4$ $[M+H]^+$ m/z 441.1846, found 441.1805; retention time 6.342 min (HPLC condition A).

(E)-4-([1,4'-Bipiperidin]-1'-yl)-6-chloro-2-(4-fluorostyryl)quinoline (71)

The title compound was synthesized from **61d** and **7h**. Isolated yield: 65%; Yellow solid; MP: > 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 1H), 7.84 (d, J = 2.2 Hz, 1H), 7.62 (d, J = 16.2 Hz, 1H), 7.60 – 7.55 (m, 3H), 7.18 (d, J = 16.2 Hz, 1H), 7.10 – 7.05 (m, 3H), 3.69 – 3.66 (m, 2H), 2.98 – 2.86 (m, 7H), 2.31 – 2.28 (m, 2H), 2.10 – 2.04 (m, 2H), 1.98 – 1.91 (m, 4H), 1.64 – 1.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (d, J = 247.0 Hz), 156.7, 156.5, 133.6, 132.9 (d, J = 3.0 Hz), 131.8, 131.4, 130.6, 129.3, 129.2, 128.9 (d, J = 3.0 Hz), 123.9, 122.7, 116.2 (d, J = 19.0 Hz), 108.6, 63.7, 52.1, 50.6, 27.5, 24.8, 23.9; HRMS (ESI) calculated for $C_{27}H_{30}ClFN_3$ $[M+H]^+$ m/z 450.2112, found 450.2064; retention time 6.414 min (HPLC condition A).

(E)-6-Chloro-2-(4-fluorostyryl)-*N*-(pyridin-2-ylmethyl)quinolin-4-amine (72)

The title compound was synthesized from **61d** and **7h**. Isolated yield: 58%; Yellow solid; MP: 188 – 190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 5.0 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.74 – 7.70 (m, 1H), 7.60 – 7.55 (m, 3H), 7.53 (d, J = 3.2 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.29 (dd, J = 4.8, 3.6 Hz, 1H), 7.13 (d, J = 16.2 Hz, 1H), 7.08 – 7.03 (m, 2H), 6.62 (s, 1H), 4.63 (d, J = 4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (d, J = 247.0 Hz), 156.8, 156.6, 148.4, 133.6, 132.9 (d, J = 4.0 Hz), 131.8, 131.4, 130.7, 129.3, 129.2, 128.9 (d, J = 3.0 Hz), 122.8, 116.2 (d, J = 22.0 Hz), 108.3, 67.2, 53.0; HRMS (ESI) calculated for $C_{23}H_{18}ClFN_3$ $[M+H]^+$ m/z 390.1173, found 390.1150; retention time 7.926 min (HPLC condition A).

(E)-6-Chloro-2-(4-fluorostyryl)-*N*-(2-morpholinoethyl)quinolin-4-amine (81)

The title compound was synthesized from **80a** and **7h**. Isolated yield: 80%; Yellow solid; MP: 147 – 149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 2.2 Hz, 1H), 7.60 (s, 1H), 7.59 – 7.55 (m, 3H), 7.16 (d, J = 16.2 Hz, 1H), 7.07 (t, J = 8.7 Hz, 2H), 6.61 (s, 1H), 3.79 (t, J = 4.6 Hz, 4H), 3.40 (q, J = 5.4 Hz, 2H), 2.84 – 2.80 (m, 2H), 2.59 – 2.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, J = 246.0 Hz), 156.7, 149.7, 147.1, 133.1 (d, J = 3.0 Hz), 133.0, 131.4, 130.5, 130.4, 129.3, 129.1 (d, J = 8.0 Hz), 119.4, 119.3, 116.1 (d, J = 22.0 Hz), 98.1, 67.4, 56.4, 53.5, 39.2; HRMS (ESI) *m/z* calcd. for $C_{23}H_{24}ClFN_3O$ 412.1592 $[M + H]^+$; found: 412.1565; retention time 6.037 min (HPLC condition A).

(E)-6-Chloro-*N*-(2-morpholinoethyl)-2-(2-(pyridin-4-yl)vinyl)quinolin-4-amine (82)

The title compound was synthesized from **80a** and **38c**. Isolated yield: 83%; Yellow solid; MP: > 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 6.0 Hz, 2H), 7.93 (d, J =

9.0 Hz, 1H), 7.70 (d, *J* = 2.2 Hz, 1H), 7.60 (d, *J* = 2.2 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 6.2 Hz, 2H), 7.41 (d, *J* = 16.2 Hz, 1H), 6.64 (s, 1H), 5.86 (t, *J* = 4.2 Hz, 1H), 3.81 – 3.78 (m, 4H), 3.43 – 3.39 (m, 2H), 2.83 (t, *J* = 6.8 Hz, 2H), 2.59 – 2.56 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 150.7, 149.8, 147.2, 144.3, 134.1, 131.7, 131.3, 130.7, 121.7, 119.4, 98.7, 67.4, 56.4, 53.5, 39.2; HRMS (ESI) *m/z* calcd. for $C_{22}H_{24}ClN_4O$ 395.1639 $[M + H]^+$; found: 395.1613; retention time 2.839 min (HPLC condition A).

(E)-6-Chloro-2-(4-fluorostyryl)-*N*-(2-(pyrrolidin-1-yl)ethyl)quinolin-4-amine (83)

The title compound was synthesized from **80b** and **7h**. Isolated yield: 88%; Yellow solid; MP: 157 – 159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 9.0 Hz, 1H), 7.79 (d, *J* = 2.2 Hz, 1H), 7.64 (d, *J* = 16.2 Hz, 1H), 7.59 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.55 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.17 (d, *J* = 16.2 Hz, 1H), 7.07 (t, *J* = 8.6 Hz, 2H), 6.62 (s, 1H), 3.47 (t, *J* = 6.0 Hz, 2H), 2.98 (t, *J* = 6.0 Hz, 2H), 2.73 – 2.68 (m, 4H), 1.91 – 1.86 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, *J* = 247.0 Hz), 156.4, 150.0, 146.7, 133.2, 133.1 (d, *J* = 4.0 Hz), 130.9, 130.6, 130.4, 129.2 (d, *J* = 8.0 Hz), 128.9, 119.9, 116.1 (d, *J* = 22.0 Hz), 97.8, 54.2, 41.6, 30.1, 23.9; HRMS (ESI) *m/z* calcd. for $C_{23}H_{24}ClFN_3$ 396.1643 $[M + H]^+$; found: 396.1618; retention time 6.000 min (HPLC condition A).

(E)-6-Chloro-*N*-(2-(pyrrolidin-1-yl)ethyl)-2-styrylquinolin-4-amine (84)

The title compound was synthesized from **80b** and **7a**. Isolated yield: 90%; Yellow solid; MP: 164 – 166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 9.0 Hz, 1H), 8.36 (s, 1H), 8.24 (d, *J* = 16.2 Hz, 1H), 8.18 (d, *J* = 7.7 Hz, 2H), 8.12 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.95 (t, *J* = 7.5 Hz, 2H), 7.90 – 7.81 (m, 2H), 6.63 (s, 1H), 4.05 (t, *J* = 5.8 Hz, 2H), 3.55 (t, *J* = 5.8 Hz, 2H), 3.30 – 3.24 (m, 4H), 2.48 – 2.43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 150.0, 146.9, 136.9, 134.3, 131.1, 130.5, 130.3, 129.4, 129.1, 128.9, 127.6, 119.8,

119.5, 97.8, 54.2, 41.7, 23.9; HRMS (ESI) *m/z* calcd. for $C_{23}H_{25}ClN_3$ 378.1737 $[M + H]^+$; found: 378.1750, retention time 5.904 min (HPLC condition A).

(E)-6-Chloro-2-(2-(pyridin-4-yl)vinyl)-*N*-(2-(pyrrolidin-1-yl)ethyl)quinolin-4-amine (85)

The title compound was synthesized from **80b** and **38c**. Isolated yield: 91%; Yellow solid; MP: 197 – 199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 6.0 Hz, 2H), 7.92 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 2.2 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 2.8 Hz, 1H), 7.47 – 7.45 (m, 2H), 7.42 (d, J = 16.2 Hz, 1H), 6.64 (s, 1H), 3.50 – 3.46 (m, 2H), 3.01 – 2.97 (m, 2H), 2.72 (t, J = 6.2 Hz, 4H), 1.92 – 1.87 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 150.6, 150.0, 147.1, 134.1, 131.5, 131.2, 131.2, 130.8, 130.7, 121.7, 119.9, 119.6, 98.4, 54.2, 54.1, 41.5, 23.9; HRMS (ESI) *m/z* calcd. for $C_{22}H_{24}ClN_4$ 379.1689 $[M + H]^+$; found: 379.1664; retention time 2.908 min (HPLC condition A).

(E)-6-Chloro-2-(4-fluorostyryl)-*N*-(2-(4-methylpiperazin-1-yl)ethyl)quinolin-4-amine (86)

The title compound was synthesized from **80c** and **7h**. Isolated yield: 84%; Yellow solid; MP: 157 – 159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (t, J = 8.0 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 7.74 (d, J = 2.2 Hz, 1H), 7.64 (d, J = 16.2 Hz, 1H), 7.58 – 7.51 (m, 3H), 7.17 (d, J = 16.2 Hz, 1H), 7.05 (t, J = 7.4 Hz, 2H), 6.58 (s, 1H), 3.45 (m, 2H), 2.78 (t, J = 6.0 Hz, 2H), 2.69 – 2.61 (m, 8H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (d, J = 247.0 Hz), 155.9, 150.3, 134.0, 132.9 (d, J = 3.0 Hz), 132.4, 132.3, 130.9, 130.7, 129.3 (d, J = 8.0 Hz), 127.8, 119.8, 119.2, 116.2, 116.0, 115.2 (d, J = 21.0 Hz), 97.6, 55.7, 55.0, 52.4, 45.7, 39.6; HRMS (ESI) *m/z* calcd. for $C_{24}H_{27}ClFN_4$ 425.1908 $[M + H]^+$; found: 425.1908; retention time 2.319 min (HPLC condition B).

(E)-6-Chloro-*N*-(2-(4-methylpiperazin-1-yl)ethyl)-2-(2-(pyridin-4-yl)vinyl)quinolin-4-amine (87)

The title compound was synthesized from **80c** and **38c**. Isolated yield: 79%; Yellow solid; MP: > 200 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (d, J = 6.0 Hz, 2H), 8.08 (d, J = 2.2 Hz, 1H), 7.75 (s, 1H), 7.60 (d, J = 16.2 Hz, 1H), 7.58 (d, J = 1.6 Hz, 2H), 7.56 (dd, J = 6.8 Hz, J = 1.6 Hz, 1H), 7.42 (d, J = 16.2 Hz, 1H), 6.85 (s, 1H), 3.54 (t, J = 6.8 Hz, 2H), 2.78 (t, J = 6.8 Hz, 2H), 2.74 – 2.65 (m, 8H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 155.3, 151.2, 149.5, 145.7, 145.3, 133.1, 131.6, 130.7, 129.1, 122.0, 120.8, 119.4, 97.2, 55.7, 54.4, 52.0, 44.4, 40.0; HRMS (ESI) *m/z* calcd. for $C_{23}H_{27}ClN_5$ 408.1955 $[M + H]^+$; found: 408.1958; retention time 3.101 min (HPLC condition A).

(E)-6-Chloro-2-(4-fluorostyryl)-N-(3-morpholinopropyl)quinolin-4-amine (90)

The title compound was synthesized from **89a** and **7h**. Isolated yield: 88%; Yellow solid; MP: 170 – 171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 2.2 Hz, 1H), 7.65 (d, J = 16.4 Hz, 1H), 7.60 (d, J = 5.4 Hz, 1H), 7.58 – 7.55 (m, 2H), 7.18 (d, J = 16.2 Hz, 1H), 7.07 (t, J = 8.6 Hz, 2H), 6.55 (s, 1H), 3.96 (t, J = 4.8 Hz, 4H), 3.48 (q, J = 5.4 Hz, 2H), 2.70 – 2.67 (m, 2H), 2.65 – 2.61 (m, 2H), 2.04 – 1.98 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2 (d, J = 247.0 Hz), 153.4, 150.7, 133.3, 133.2, 133.1 (d, J = 4.0 Hz), 130.9, 130.6, 130.3, 129.2 (d, J = 8.0 Hz), 120.1, 119.4, 116.1 (d, J = 22.0 Hz), 97.1, 67.2, 59.9, 54.6, 45.0, 23.3; HRMS (ESI) *m/z* calcd. for $C_{24}H_{26}ClFN_3O$ 426.1748 $[M + H]^+$; found: 426.1718; retention time 6.087 min (HPLC condition A).

(E)-6-Chloro-*N*-(3-morpholinopropyl)-2-(4-(trifluoromethyl)styryl)quinolin-4-amine (91)

The title compound was synthesized from **89a** and **7i**. Isolated yield: 84%; Yellow solid; MP: 144 – 146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.91 (m, 2H), 7.71 (d, J = 3.2 Hz, 1H), 7.69 – 7.62 (m, 4H), 7.58 – 7.55 (m, 1H), 7.32 (d, J = 16.2 Hz, 1H), 6.57 (s, 1H), 3.96 (t, J = 4.8 Hz, 4H), 3.47 (q, J = 5.8 Hz, 2H), 2.67 (t, J = 5.4 Hz, 2H), 2.63 – 2.60 (m, 2H), 2.03 – 1.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 150.6, 147.1, 140.5, 132.3, 132.2, 131.5 , 130.4 (d, J = 4.0 Hz), 130.1, 127.6, 126.0 (q, J = 4.0 Hz), 123.1, 120.1, 119.6, 97.58 , 67.2, 59.9, 54.6, 45.0, 23.3; HRMS (ESI) *m/z* calcd. for $C_{25}H_{26}ClF_3N_3O$ 476.1716 $[M + H]^+$; found: 476.1692; retention time 6.598 min (HPLC condition A).

(E)-6-Chloro-2-(4-fluorostyryl)-*N*-(4-morpholinobutyl)quinolin-4-amine (92)

The title compound was synthesized from **89b** and **7h**. Isolated yield: 78%; Yellow solid; MP: 185 – 187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 1H), 7.71 (d, J = 2.2 Hz, 1H), 7.64 (d, J = 16.2 Hz, 1H), 7.58 (dd, J = 8.8, 5.6 Hz, 2H), 7.53 (dd, J = 9.0, 2.2 Hz, 1H), 7.16 (d, J = 16.2 Hz, 1H), 7.08 (d, J = 8.6 Hz, 2H), 6.58 (s, 1H), 3.78 – 3.75 (m, 4H), 3.42 – 3.38 (m, 2H), 2.50 – 2.44 (m, 6H), 1.90 – 1.85 (m, 2H), 1.76 – 1.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3 (d, J = 247.0 Hz), 156.1, 150.0, 133.5, 133.0 (d, J = 3.0 Hz), 130.8, 130.7, 130.5, 129.5 (d, J = 8.0 Hz), 128.5, 119.5, 119.1, 116.1 (d, J = 21.0 Hz), 97.7, 67.3, 58.5, 54.1, 43.7, 26.7, 24.7; HRMS (ESI) *m/z* calcd. for $C_{25}H_{28}ClFN_3O$ 440.1905 $[M + H]^+$; found: 440.1878; retention time 6.257 min (HPLC condition A).

(E)-6-Chloro-*N*-(4-morpholinobutyl)-2-(2-(pyridin-4-yl)vinyl)quinolin-4-amine (93)

The title compound was synthesized from **89b** and **38c**. Isolated yield: 73%; Yellow solid; MP: 174 – 176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 6.0 Hz, 2H), 8.02 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.67 (d, J = 16.4 Hz, 1H), 7.54 (dd, J = 9.0, 2.2

Hz, 1H), 7.46 – 7.42 (m, 3H), 6.62 (s, 1H), 3.79 – 3.76 (m, 4H), 3.42 – 3.38 (m, 2H), 2.55 – 2.48 (m, 6H), 1.92 – 1.85 (m, 2H), 1.79 – 1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 150.6, 150.1, 146.8, 144.2, 133.7, 131.5, 131.4, 130.8, 124.1, 121.7, 119.5, 119.4, 98.4, 67.2, 58.5, 54.1, 43.7, 26.7, 24.7; HRMS (ESI) *m/z* calcd. for $C_{24}H_{28}ClN_4O$ 423.1952 $[M + H]^+$; found: 423.1941; retention time 2.812 min (HPLC condition A).

(E)-6-Chloro-*N*-(4-(4-methylpiperazin-1-yl)butyl)-2-styrylquinolin-4-amine (94)

The title compound was synthesized from **89c** and **7a**. Isolated yield: 74%; Yellow solid; MP: 122 – 123 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.24 (d, J = 2.2 Hz, 1H), 7.80 (d, J = 5.4 Hz, 1H), 7.77 (d, J = 16.4 Hz, 1H), 7.68 – 7.65 (m, 1H), 7.63 (dd, J = 7.8, 1.6 Hz, 2H), 7.39 – 7.34 (m, 3H), 7.20 (d, J = 16.4 Hz, 1H), 6.88 (s, 1H), 3.51 (t, J = 7.0 Hz, 2H), 3.20 – 3.15 (m, 2H), 2.76 – 2.69 (m, 6H), 2.57 (t, J = 7.0 Hz, 2H), 2.43 (s, 3H), 1.83 – 1.78 (m, 2H), 1.73 – 1.67 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 153.5, 153.1, 141.2, 138.1, 135.9, 132.2, 129.7, 129.0, 127.7, 125.0, 123.3, 121.5, 118.4, 96.3, 57.4, 53.8, 51.7, 44.1, 43.2, 25.9, 23.6; HRMS (ESI) *m/z* calcd. for $C_{26}H_{32}ClN_4$ 435.2315 $[M + H]^+$; found: 435.2290; retention time 5.789 min (HPLC condition A).

(E)-6-Chloro-2-(4-fluorostyryl)-*N*-(4-(4-methylpiperazin-1-yl)butyl)quinolin-4-amine (95)

The title compound was synthesized from **89b** and **7h**. Isolated yield: 71%; Yellow solid; MP: 133 – 135 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.21 (d, J = 2.2 Hz, 1H), 7.79 (d, J = 9.4 Hz, 1H), 7.75 (d, J = 16.4 Hz, 1H), 7.67 (d, J = 2.2 Hz, 1H), 7.66 – 7.63 (m, 2H), 7.12 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 9.0 Hz, 2H), 6.86 (s, 1H), 3.51 (t, J = 7.0 Hz, 2H), 3.21 – 3.15 (m, 2H), 2.79 – 2.70 (m, 6H), 2.61 – 2.57 (m, 2H), 2.45 (s, 3H), 1.83 – 1.77 (m, 2H), 1.74 – 1.68 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 163.8 (d, J = 248.0 Hz),

153.4, 153.1, 141.1, 136.7, 132.3 (d, J = 3.0 Hz), 132.2, 131.2, 129.7 (d, J = 8.0 Hz), 125.0, 123.2, 121.5, 118.4, 115.8 (d, J = 22.0 Hz), 96.3, 57.4, 53.8, 51.7, 44.0, 43.2, 25.9, 23.6; HRMS (ESI) *m/z* calcd. for $C_{26}H_{31}ClN_4F$ 453.2221 $[M + H]^+$; found: 453.2222; retention time 6.115 min (HPLC condition A).

(E)-6-Chloro-*N*-(4-(4-methylpiperazin-1-yl)butyl)-2-(2-(pyridin-4-yl)vinyl)quinolin-4-amine (96)

The title compound was synthesized from **89b** and **38c**. Isolated yield: 67%; Brown solid; MP: > 200 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (d, J = 6.2 Hz, 2H), 8.16 (d, J = 2.2 Hz, 1H), 7.78 (d, J = 9.4 Hz, 1H), 7.62 (d, J = 16.4 Hz, 1H), 7.60 (d, J = 2.2 Hz, 1H), 7.58 (dd, J = 5.6, 1.8 Hz, 2H), 7.44 (d, J = 16.4 Hz, 1H), 6.83 (s, 1H), 3.45 (t, J = 6.8 Hz, 2H), 3.20 – 3.14 (m, 2H), 2.74 – 2.66 (m, 6H), 2.57 (t, J = 7.6 Hz, 2H), 2.42 (s, 3H), 1.81 – 1.76 (m, 2H), 1.72 – 1.67 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 154.7, 151.8, 149.6, 145.2, 145.1, 132.5, 131.9, 130.9, 130.7, 128.5, 122.0, 121.0, 119.3, 97.2, 57.5, 53.9, 51.8, 44.1, 42.8, 26.0, 23.7; HRMS (ESI) *m/z* calcd. for $C_{25}H_{31}ClN_5$ 436.2268 $[M + H]^+$; found: 436.2254; retention time 2.741 min (HPLC condition A).

(E)-6-Chloro-*N*-(4-morpholinobutyl)-2-(4-(trifluoromethyl)styryl)quinolin-4-amine (98)

The title compound was synthesized from **89b** and **7i**. Isolated yield: 87%; Brown solid; MP: 153 – 155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 9.0 Hz, 1H), 7.71 (d, J = 1.3 Hz, 1H), 7.71 – 7.67 (m, 4H), 7.62 (d, J = 8.2 Hz, 2H), 7.56 (dd, J = 9.0, 2.2 Hz, 1H), 7.31 (d, J = 16.2 Hz, 1H), 6.63 (s, 1H), 3.79 – 3.76 (m, 4H), 3.40 (d, J = 4.9 Hz, 2H), 2.50 – 2.44 (m, 6H), 1.91 – 1.86 (m, 2H), 1.76 – 1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 149.9, 146.9, 140.4, 132.6, 131.8, 131.4, 130.7 (d, J = 3.0 Hz), 130.5, 130.2, 127.6,

126.0 (d, J = 4.0 Hz), 123.1, 119.3 (d, J = 4.0 Hz), 98.3, 67.3, 58.5, 54.1, 43.7, 26.7, 24.8; HRMS (ESI) *m/z* calcd. for $C_{26}H2_8ClF_3N_3O$ 490.1873 $[M + H]^+$; found: 490.1838; retention time 6.612 min (HPLC condition A).

(E)-6-Chloro-*N*-(4-morpholinobutyl)-2-(2-(trifluoromethyl)styryl)quinolin-4-amine (99)

The title compound was synthesized from **89b** and **97a**. Isolated yield: 83%; Brown solid; MP: 110 – 112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 2.8 Hz, 1H), 7.90 (s, 1H), 7.72 (d, J = 2.2 Hz, 2H), 7.57 (dd, J = 9.0, 2.2 Hz, 2H), 7.42 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 16.2 Hz, 2H), 6.70 (s, 1H), 3.78 – 3.76 (m, 4H), 3.44 – 3.40 (m, 2H), 2.51 – 2.48 (m, 4H), 2.46 (d, J = 7.2 Hz, 2H), 1.92 – 1.86 (m, 2H), 1.78 – 1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 149.9, 146.6, 135.9, 133.5, 132.4, 131.3, 130.8, 130.7, 130.0, 129.1, 128.4, 127.9, 127.2, 126.3 (d, J = 6.0 Hz), 119.3, 97.0, 67.3, 58.5, 54.1, 46.7, 26.7, 24.7; HRMS (ESI) *m/z* calcd. for $C_{26}H_{28}ClF_3N_3O$ 490.1873 $[M + H]^+$; found: 490.1837; retention time 6.324 min (HPLC condition A).

(E)-6-Chloro-*N*-(4-morpholinobutyl)-2-(3-(trifluoromethyl)styryl)quinolin-4-amine (100)

The title compound was synthesized from **89b** and **97b**. Isolated yield: 81%; Brown solid; MP: 130 – 132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 9.0 Hz, 1H), 7.87 (s, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.57 (dd, J = 9.0, 2.2 Hz, 2H), 7.51 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 16.2 Hz, 1H), 6.64 (s, 1H), 3.79 – 3.77 (m, 4H), 3.44 – 3.39 (m, 2H), 2.52 – 2.49 (m, 4H), 2.48 (t, J = 7.8 Hz, 2H), 1.92 – 1.87 (m, 2H), 1.78 – 1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 149.9, 146.9, 137.7, 132.6, 131.7, 131.4, 130.6 (d, J = 3.0 Hz), 129.6, 125.8, 125.2 (d, J = 3.0 Hz), 124.1 (q, J = 4.0 Hz), 123.1, 119.3 (d,

J = 3.0 Hz), 98.1, 67.2, 58.5, 54.1, 43.7, 26.7, 24.7; HRMS (ESI) *m/z* calcd. for $C_{26}H2_8ClF_3N_3O$ 490.1873 $[M + H]^+$; found: 490.1868; retention time 6.606 min (HPLC condition A).

(E)-6-Chloro-*N*-(4-morpholinobutyl)-2-(4-(trifluoromethoxy)styryl)quinolin-4-amine (101)

The title compound was synthesized from **89b** and **97c**. Isolated yield: 80%; Brown solid; MP: 140 – 142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 9.0 Hz, 1H), 7.73 (d, *J* = 2.2 Hz, 1H), 7.67 (d, *J* = 16.2 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.55 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.25 (d, *J* = 16.2 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 2H), 6.60 (s, 1H), 3.79 – 3.76 (m, 4H), 3.43 – 3.39 (m, 2H), 2.51 – 2.45 (m, 6H), 1.91 – 1.86 (m, 2H), 1.77 – 1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 150.12, 149.6 (d, *J* = 2.0 Hz), 146.8, 135.5, 133.1, 130.8, 130.6, 128.9, 122.1, 121.5 (d, *J* = 2.0 Hz), 119.5 (d, *J* = 3.0 Hz), 119.1, 97.9, 67.2, 58.5, 54.1, 43.8, 26.7, 25.7. HRMS (ESI) *m/z* calcd. for $C_{26}H_{28}ClF_3N_3O_2$ 506.1822 $[M + H]^+$; found: 506.1789; retention time 6.712 min (HPLC condition A).

(E)-2-(3,5-Bis(trifluoromethyl)styryl)-6-chloro-*N*-(4-morpholinobutyl)quinolin-4-amine (102)

The title compound was synthesized from **89b** and **97d**. Isolated yield: 74%; Yellow solid; MP: 143 – 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 2H), 7.92 (d, *J* = 9.0 Hz, 1H), 7.79 (s, 1H), 7.73 (d, *J* = 16.2 Hz, 1H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.58 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.36 (d, *J* = 16.2 Hz, 1H), 6.63 (s, 1H), 3.79 – 3.76 (m, 4H), 3.42 – 3.38 (m, 2H), 2.51 – 2.45 (m, 6H), 1.91 – 1.86 (m, 2H), 1.77 – 1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 149.8, 147.3, 139.2, 133.5, 132.6, 132.3, 131.8, 130.8, 130.6 (d, *J* = 7.0 Hz), 127.1 (q, *J* = 4.0 Hz), 125.0, 121.8 (q, *J* = 4.0 Hz), 119.4, 119.2, 98.5, 67.3, 58.5, 54.1, 43.7, 26.8,

24.8; ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0; HRMS (ESI) *m/z* calcd. for $C_{27}H_{27}ClF_6N_3O$ 558.1747 $[M + H]^+$; found: 558.1719; retention time 7.321 min (HPLC condition A).

(E)-6-Chloro-2-(3,5-difluorostyryl)-*N*-(4-morpholinobutyl)quinolin-4-amine (103)

The title compound was synthesized from **89b** and **97e**. Isolated yield: 86%; Yellow solid; MP: 120 – 122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 2.2 Hz, 1H), 7.60 (d, J = 10.6 Hz, 1H), 7.57 (dd, J = 8.0, 2.2 Hz, 1H), 7.22 (d, J = 16.2 Hz, 1H), 7.13 – 7.10 (m, 2H), 6.78 – 6.73 (m, 1H), 6.60 (s, 1H), 3.78 (t, J = 4.8 Hz, 4H), 3.42 – 3.37 (m, 2H), 2.50 – 2.48 (m, 4H), 2.47 (s, 2H), 1.91 – 1.86 (m, 2H), 1.77 – 1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (dd, J = 246.0, 3.0 Hz), 155.8, 149.7, 147.3, 132.2, 131.8, 131.7, 130.6 (d, J = 3.0 Hz), 119.4, 119.2, 110.1 (d, J = 26.0 Hz), 103.9 (t, J = 26.0 Hz), 98.5, 67.3, 58.5, 54.1, 43.7, 26.8, 24.8; HRMS (ESI) *m/z* calcd. for $C_{25}H_{27}ClF_2N_3O$ 458.1811 $[M + H]^+$; found: 458.1775; retention time 6.418min (HPLC condition A).

(E)-6-Chloro-2-(2,4-difluorostyryl)-*N*-(4-morpholinobutyl)quinolin-4-amine (104)

The title compound was synthesized from **89b** and **97f**. Isolated yield: 82%; Yellow solid; MP: 105 – 106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.01 (s, 1H), 7.91 (d, J = 9.8 Hz, 1H), 7.75 (d, J = 16.8 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.42 (dd, J = 8.6, 1.8 Hz, 1H), 7.24 (d, J = 16.8 Hz, 1H), 6.86 (dd, J = 7.8, 3.8 Hz, 1H), 6.29 (s, 1H), 3.83 – 3.81 (m, 4H), 3.43 (t, J = 6.6 Hz, 2H), 2.73 – 2.68 (m, 4H), 2.65 (t, J = 7.6 Hz, 2H), 1.91 – 1.86 (m, 2H), 1.84 – 1.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (dd, J = 251.0, 11.0 Hz), 161.5 (dd, J = 244.0, 12.0 Hz), 153.1, 151.8, 139.6, 133.8, 133.7, 132.3, 131.9, 130.2, 124.6, 122.3, 118.2, 112.5 (d, J = 25.0 Hz), 111.2 (d, J = 24.0 Hz), 104.8 (d, J = 26.0 Hz), 94.5,

66.4, 58.1, 53.4, 43.8, 26.0, 23.6; HRMS (ESI) *m/z* calcd. for $C_{25}H_{27}ClF_2N_3O$ 458.1811 [M + H]$^+$; found: 458.1785; retention time 6.296 min (HPLC condition A).

(E)-6-Chloro-2-(3,4-difluorostyryl)-*N*-(4-morpholinobutyl)quinolin-4-amine (105)

The title compound was synthesized from **89b** and **97g**. Isolated yield: 80%; Yellow solid; MP: 146 – 147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 9.0 Hz, 1H), 7.69 (d, J = 2.2 Hz, 1H), 7.59 (d, J = 11.9 Hz, 1H), 7.57 – 7.55 (m, 1H), 7.45 – 7.40 (m, 1H), 7.33 – 7.30 (m, 1H), 7.20 – 7.12 (m, 2H), 6.59 (s, 1H), 3.79 – 3.76 (m, 4H), 3.42 – 3.38 (m, 2H), 2.51 – 2.48 (m, 4H), 2.46 (t, J = 7.2 Hz, 2H), 1.91 – 1.86 (m, 2H), 1.77 – 1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 152.0, 149.8, 147.1, 134.2 (t, J = 5.0 Hz), 131.9, 131.5, 130.6, 130.5, 124.0, 123.9 (d, J = 5.0 Hz), 119.3, 119.2, 117.9 (dd, J = 13.0, 6.0 Hz), 115.7 (dd, J = 15.0, 3.0 Hz), 98.2, 67.3, 58.5, 54.1, 43.7, 26.8, 24.8; HRMS (ESI) *m/z* calcd. for $C_{25}H_{27}ClF_2N_3O$ 458.1811 [M + H]$^+$; found: 458.1787; retention time 6.345 min (HPLC condition A).

(E)-6-Chloro-*N*-(4-morpholinobutyl)-2-(2,3,5-trifluorostyryl)quinolin-4-amine (106)

The title compound was synthesized from **89b** and **97h**. Isolated yield: 73%; Yellow solid; MP: 125 – 126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 16.4 Hz, 1H), 7.68 (d, J = 2.2 Hz, 1H), 7.57 (dd, J = 9.0, 2.2 Hz, 1H), 7.31 (d, J = 16.4 Hz, 1H), 7.19 – 7.14 (m, 1H), 6.90 – 6.83 (m, 1H), 6.62 (s, 1H), 3.79 – 3.75 (m, 4H), 3.40 (q, J = 6.6 Hz, 2H), 2.51 – 2.48 (m, 4H), 2.45 (t, J = 7.2 Hz, 2H), 1.92 – 1.86 (m, 2H), 1.77 – 1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (m), 156.8 (m), 155.7, 152.3 (m), 149.8, 147.2, 134.4 (d, J = 5.0 Hz), 131.8, 130.8, 130.6, 124.2 (d, J = 4.0 Hz), 119.4, 119.2, 108.8 (d, J = 24.0 Hz), 105.2 (d, J = 21.0 Hz), 105.1 (d, J = 21.0 Hz), 98.3, 67.3, 58.5, 54.1, 43.7, 26.8, 24.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.4, -133.5, -147.0; HRMS (ESI) *m/z*

calcd. for $C_{25}H_{26}ClF_3N_3O$ 476.1716 $[M + H]^+$; found: 476.1689; retention time 6.239 min (HPLC condition A).

(E)-6-Chloro-*N*-(4-morpholinobutyl)-2-(2,4,5-trifluorostyryl)quinolin-4-amine (107)

The title compound was synthesized from **89b** and **97h**. Isolated yield: 78%; Yellow solid; MP: 150 – 152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 9.0 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.56 (dd, J = 9.0, 2.2 Hz, 1H), 7.53 – 7.46 (m, 1H), 7.22 (d, J = 16.4 Hz, 1H), 7.01 – 6.94 (m, 1H), 6.62 (s, 1H), 3.79 – 3.76 (m, 4H), 3.42 – 3.38 (m, 2H), 2.51 – 2.48 (m, 4H), 2.47 (t, J = 7.2 Hz, 2H), 1.91 – 1.86 (m, 2H), 1.77 – 1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 149.8, 147.2, 132.8, 131.8, 130.6 (d, J = 6.0 Hz), 124.3, 119.4, 119.2, 115.4 (d, J = 5.0 Hz), 115.2 (d, J = 4.0 Hz), 106.4 (d, J = 20.0 Hz), 106.2 (d, J = 20.0 Hz), 98.1, 67.3, 58.5, 54.1, 43.7, 26.8, 24.7; HRMS (ESI) *m/z* calcd. for $C_{25}H_{26}ClF_3N_3O$ 476.1716 $[M + H]^+$; found: 476.1691; retention time 6.304 min (HPLC condition A).

(E)-6-Chloro-*N*-(4-morpholinobutyl)-2-(3,4,5-trifluorostyryl)quinolin-4-amine (108)

The title compound was synthesized from **89b** and **97j**. Isolated yield: 71%; Yellow solid; MP: 158 – 159 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 2.2 Hz, 1H), 7.58 – 7.56 (m, 1H), 7.54 (d, J = 16.0 Hz, 1H), 7.21 (dd, J = 8.8, 6.6 Hz, 2H), 7.13 (d, J = 16.0 Hz, 1H), 6.57 (s, 1H), 3.79 – 3.76 (m, 4H), 3.41 – 3.36 (m, 2H), 2.51 – 2.48 (m, 4H), 2.47 (t, J = 7.2 Hz, 2H), 1.91 – 1.87 (m, 2H), 1.77 – 1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 153.0 (m), 150.5 (m), 149.8, 147.2, 133.3, 131.8, 131.7, 130.9, 130.6, 130.5, 119.2 (d, J = 6.0 Hz), 119.1 (d, J = 5.0 Hz), 98.5, 67.3, 58.5, 54.1, 43.7, 26.8, 24.8; HRMS (ESI) *m/z* calcd. for $C_{25}H_{26}ClF_3N_3O$ 476.1716 $[M + H]^+$; found: 476.1688; retention time 5.946 min (HPLC condition A).

(E)-6-Chloro-2-(2-(3-fluoropyridin-4-yl)vinyl)-*N*-(4-morpholinobutyl)quinolin-4-amine (109)

The title compound was synthesized from **89b** and **97k**. Isolated yield: 79%; Yellow solid; MP: 140 – 142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 2.4 Hz, 1H), 8.42 (d, J = 5.0 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.74 (d, J = 16.4 Hz, 1H), 7.70 (d, J = 2.2 Hz, 1H), 7.58 (dd, J = J = 7.4, 1.6 Hz, Hz, 1H), 7.55 (d, J = 4.0 Hz, 1H), 7.51 (d, J = 16.4 Hz, 1H), 6.66 (s, 1H), 3.79 – 3.76 (m, 4H), 3.43 – 3.39 (m, 2H), 2.51 – 2.45 (m, 6H), 1.91 – 1.87 (m, 2H), 1.78 – 1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 154.3, 149.9, 147.2, 146.24 (d, J = 5.0 Hz), 139.2 (d, J = 25.0 Hz), 136.6 (d, J = 6.0 Hz), 132.0, 131.8, 131.0, 130.7, 123.7 (d, J = 3.0 Hz), 121.6, 119.5, 119.3, 98.5, 67.27, 58.5, 54.1, 43.7, 26.7, 24.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ -131.7; HRMS (ESI) *m/z* calcd. for $C_{24}H_{27}ClFN_4O$ 441.1857 $[M + H]^+$; found: 441.1846; retention time 5.365 min (HPLC condition A).

(E)-6-Chloro-2-(2-(6-fluoropyridin-3-yl)vinyl)-*N*-(4-morpholinobutyl)quinolin-4-amine (110)

The title compound was synthesized from **89b** and **97l**. Isolated yield: 84%;Yellow solid; MP: 129 – 130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 2.2 Hz, 1H), 8.07 – 8.03 (m, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H), 7.65 (d, J = 16.2 Hz, 1H), 7.57 (dd, J = 9.0, 2.2 Hz, 1H), 7.23 (d, J = 16.2 Hz, 1H), 6.97 (dd, J = 8.6, 2.8 Hz, 1H), 6.61 (s, 1H), 3.79 – 3.76 (m, 4H), 3.43 – 3.39 (m, 2H), 2.51 – 2.45 (m, 6H), 1.91 – 1.86 (m, 2H), 1.78 – 1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (d, J = 240.0 Hz), 155.6, 150.0, 147.3, 147.1, 138.8 (d, J = 8.0 Hz), 131.3, 131.1, 130.9 (d, J = 4.0 Hz), 130.8, 130.7, 129.1, 119.4, 119.3, 110.4, 110.0, 98.1, 67.2, 58.5, 54.1, 43.7, 26.7, 24.7; HRMS

(ESI) *m/z* calcd. for $C_{24}H_{27}ClFN_4O$ 441.1857 $[M + H]^+$; found: 441.1875; retention time 5.741 min (HPLC condition A).

（E)-6-Chloro-2-(2-(5-fluoropyridin-2-yl)vinyl)-*N*-(4-morpholinobutyl)quinolin-4-amine (111)

The title compound was synthesized from **89b** and **97m**. Isolated yield: 92%; Brown solid; MP: 132 – 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, J = 3.0 Hz, 1H), 7.94 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 16.4 Hz, 1H), 7.73 (d, J = 2.4 Hz, 1H), 7.59 (d, J = 16.4 Hz, 1H), 7.55 (d, J = 5.3 Hz, 1H), 7.53 (dd, J = 7.4, 1.6 Hz, 1H), 7.44 – 7.39 (m, 1H), 6.65 (s, 1H), 3.77 – 3.75 (m, 4H), 3.39 – 3.35 (m, 2H), 2.50 – 2.47 (m, 4H), 2.44 (t, J = 7.0 Hz, 2H), 1.87 – 1.82 (m, 2H), 1.73 – 1.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (d, J = 256.0 Hz), 155.6, 151.8, 150.1, 146.5, 138.4 (d, J = 24.0 Hz), 132.6 (d, J = 7.0 Hz), 131.0, 130.72 , 130.7 (d, J = 5.0 Hz), 124.0 (d, J = 4.0 Hz), 123.8, 123.7, 119.5, 119.2, 98.8, 67.3, 58.5, 54.1, 43.7, 26.7, 24.6; HRMS (ESI) *m/z* calcd. for $C_{24}H_{27}ClFN_4O$ 441.1857 $[M + H]^+$; found: 441.1835; retention time 5.666 min (HPLC condition A).

(E)-6-Chloro-2-(2-(3-fluoropyridin-2-yl)vinyl)-*N*-(4-morpholinobutyl)quinolin-4-amine (112)

The title compound was synthesized from **89b** and **97n**. Isolated yield: 90%; Brown solid; MP: 113 – 115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 4.6 Hz, 1H), 7.01 (d, J = 16.2 Hz, 1H), 7.96 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 16.2 Hz, 1H), 7.73 (d, J = 2.2 Hz, 1H), 7.55 – 7.52 (m, 1H), 7.45 – 7.40 (m, 1H), 7.26 – 7.22 (m, 1H), 6.65 (s, 1H), 3.78 – 3.76 (m, 4H), 3.41 – 3.37 (m, 2H), 2.52 – 2.49 (m, 4H), 2.47 (t, t, J = 7.6 Hz, 2H), 1.89 – 1.85 (m, 2H), 1.76 – 1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0 (d, J = 261.0 Hz), 155.5, 150.1, 145.8 (d, J = 6.0 Hz), 143.9, 143.8, 134.5, 131.3, 130.7, 125.9, 124.3 (d, J =

4.0 Hz), 123.9, 123.7, 119.5, 119.3, 99.5, 67.2, 58.5, 54.1, 43.7, 26.7, 24.6; HRMS (ESI) *m/z* calcd. for $C_{24}H_{27}ClFN_4O$ 441.1857 $[M + H]^+$; found: 441.1852; retention time 5.642 min (HPLC condition A).

6-Chloro-2-((1E,3E)-4-(4-fluorophenyl)buta-1,3-dien-1-yl)-*N*-(4 morpholinobutyl)-quinolin-4-amine (113)

The title compound was synthesized from **89b** and **97o**. Isolated yield: 58%; Brown solid; MP: 141 – 144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.6 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.54 – 7.48 (m, 1H), 7.44 (dd, J = 8.6, 5.4 Hz, 2H), 7.06 (t, J = 8.6 Hz, 2H), 6.92 (d, J = 15.4 Hz, 1H), 6.86 (d, J = 15.4 Hz, 1H), 6.78 (d, J = 15.4 Hz, 1H), 6.49 (s, 1H), 3.78 – 3.76 (m, 4H), 3.40 (t, J = 7.8 Hz, 2H), 2.51 – 2.48 (m, 4H), 2.47 (s, 2H), 1.90 – 1.85 (m, 2H), 1.75 – 1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (d, J = 246.0 Hz), 157.3, 149.6, 136.3, 135.4, 131.4, 130.4, 128.9, 128.8 (d, J = 8.0 Hz), 126.8, 119.4, 118.5, 116.0 (d, J = 22.0 Hz), 101.2, 67.2, 58.5, 54.1, 43.7, 26.7, 24.6; HRMS (ESI) *m/z* calcd. for $C_{27}H_{30}ClFN_3O$ 466.2061 $[M + H]^+$; found: 466.2039; retention time 6.383 min (HPLC condition A).

6-Chloro-*N*-(4-morpholinobutyl)-2-((1E,3E)-4-phenylbuta-1,3-dien-1-yl)quinolin-4-amine (114)

The title compound was synthesized from **89b** and **97p**. Isolated yield: 52%; Brown solid; MP: 135 – 137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.6 Hz, 1H), 7.57 – 7.47 (m, 3H), 7.44 (d, J = 8.6 Hz, 2H), 7.35 (t, J = 8.6 Hz, 2H), 7.29 (d, J = 7.2 Hz, 1H), 7.01(d, J = 15.4 Hz, 1H), 6.89 (d, J = 15.4 Hz, 1H), 6.76 (d, J = 15.4 Hz, 1H), 6.36 (s, 1H), 3.76 (t, J = 5.6 Hz, 4H), 3.41 (t, J = 7.2 Hz, 2H), 2.52 – 2.46 (m, 4H), 1.89 – 1.84 (m, 2H), 1.75 – 1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 150.0, 145.7, 138.0, 137.6,

135.9, 130.7, 129.1, 129.0, 128.5, 128.4, 127.4, 127.3, 126.5, 119.7, 118.4, 100.9, 67.1, 58.4, 53.9, 43.6, 26.6, 24.4; HRMS (ESI) *m/z* calcd. for $C_{27}H_{31}ClN_3O$ 448.2156 $[M + H]^+$; found: 448.2133; retention time 6.203 min (HPLC condition A).

General Procedure (hydrazine hydrate reduction reaction) for synthesis of compounds 58 and 59

A solution of pyridylvinylquinolines (0.2 mmol) and hydrazine hydrate (1.50 mL) in EtOH (6.0 mL) was heated at 80 °C for 36 h. After completion of the reaction, the solvents were removed to dryness. The residue was dissolved in dichloromethane and washed with water and brine. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography.

***N*^{1}-(6-Methoxy-2-(2-(pyridin-4-yl)ethyl)quinolin-4-yl)-*N*^{2},*N*^{2}-dimethylethane-1,2-diamine (58)**

The title compound was synthesized from pyridylvinylquinoline **40**. Isolated yield: 81%; White solid; MP: 104 – 106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 5.2 Hz, 2H), 8.29 (d, J = 9.2 Hz, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.33 (dd, J = 9.2, 2.6 Hz, 1H), 7.22 (d, J = 6.0 Hz, 2H), 6.19 (s, 1H), 3.97 (s, 3H), 3.49 (t, J = 6.0 Hz, 2H), 3.34 – 3.30 (m, 2H), 3.22 – 3.18 (m, 2H), 2.89 (t, J = 6.0 Hz, 2H), 2.47 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 156.2, 155.0, 150.2, 149.9, 126.1, 124.4, 122.8, 117.9, 101.3, 98.4, 56.8, 56.4, 45.2, 40.4, 36.9, 35.4; HRMS (ESI) calculated for $C_{21}H_{27}N_4O$ $[M+H]^+$ m/z 351.2185, found 351.2162; retention time 2.078 min (HPLC condition A).

N^1-(6-Chloro-2-(2-(pyridin-4-yl)ethyl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine (59)

The title compound was synthesized from pyridylvinylquinoline **49**. Isolated yield: 83%; White solid; MP: 115 – 117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J = 5.6 Hz, 2H), 8.13 (d, J = 9.0 Hz, 1H), 7.94 (d, J = 2.2 Hz, 1H), 7.58 (dd, J = 9.0, 2.2 Hz, 1H), 7.20 (d, J = 6.0 Hz, 2H), 6.21 (s, 1H), 3.35 (t, J = 6.0 Hz, 2H), 3.27 – 3.23 (m, 2H), 3.20 – 3.16 (m, 2H), 2.78 (t, J = 6.8 Hz, 2H), 2.47 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 150.7, 150.4, 150.1, 145.4, 130.9, 130.6, 129.9, 124.4, 119.8, 118.6, 99.5, 57.0, 46.1, 45.3, 40.2, 35.3; HRMS (ESI) calculated for $C_{20}H_{24}ClN_4$ $[M+H]^+$ m/z 355.1689, found 355.1667; retention time 2.203 min (HPLC condition A).

Diethyl (4-nitrobenzyl)phosphonate (74)

The mixture of 1-(bromomethyl)-4-nitrobenzene (**73**) (2.44 g, 11.3 mmol) and triethylphosphite (5.0 mL, 28.79 mmol) was reflux under a nitrogen atmosphere for 20 h. After cooling, the reaction mixture was evaporated in vacuo to give the product **74** (2.72 g, 88% yield) as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.8 Hz, 2H), 7.47 (dd, J = 8.8, 2.6 Hz, 2H), 4.09 – 4.01 (m, 4H), 3.24 (d, J = 22.4 Hz, 2H), 1.26 (t, J = 7.0 Hz, 6H).

Diethyl (4-aminobenzyl)phosphonate (75)

Diethyl (4-nitrobenzyl)phosphonate (**74**) (273 mg, 1.0 mmol) was dissolved in MeOH (20 mL) under an inert atmosphere. Then 10% Pd/C (108 mg, 10% mol) were added carefully. After being stirred at room temperature overnight, the reaction mixture was filtered off on a celite pad and washed with MeOH. The resultant solvents were evaporated under vacuum to give compound **75** (190 mg, 76% yield) as a yellow oil. ^{1}H NMR (400

MHz, $CDCl_3$) δ 6.96 (dd, J = 8.4, 2.6 Hz, 2H), 6.52 (d, J = 8.4 Hz, 2H), 3.95 – 3.85 (m, 4H), 2.94 (d, J = 22.0 Hz, 2H), 1.14 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9 (d, J = 3.0 Hz), 130.8 (d, J = 7.0 Hz), 120.8 (d, J = 9.0 Hz), 115.5 (d, J = 3.0 Hz), 62.3 (d, J = 6.0 Hz), 33.0 (d, J = 138.0 Hz), 16.7 (d, J = 6.0 Hz).

Diethyl (4-isocyanobenzyl)phosphonate (76)

To a stirred solution of aniline (150 mg, 0.62 mmol), chloroform (50 µL, 0.62 mmol), benzyltriethylammonium chloride (2.0 mg) in DCM (3.0 mL) was added 50% aqueous NaOH solution (0.71 mmol) dropwise. Then the reaction mixture was refluxed for 2 h. Upon completion, the resultant content was diluted with water (5 mL) and extracted with dichloromethane. The combined organic layers were washed with water, brine and dried over Na_2SO_4. The resultant solvents were evaporated to give compound **76** (125 mg, 80% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, br., 4H), 4.02 – 3.97 (m, 4H), 3.12 (d, J = 22.0 Hz, 2H), 1.22 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.0 (d, J = 9.0 Hz), 131.1 (d, J = 7.0 Hz), 130.9 (d, J = 7.0 Hz), 126.8 (d, J = 3.0 Hz), 115.6 (d, J = 3.0 Hz), 62.6 (d, J = 7.0 Hz), 33.9 (d, J = 137.0 Hz), 16.7 (d, J = 5.0 Hz).

6-Chloro-4-morpholinoquinoline-2-carbaldehyde (77)

To a solution of 4-(6-chloro-2-methylquinolin-4-yl)morpholine (**61a**) (150 mg, 0.55 mmol) in dioxane (5 mL) was added SeO_2 (443 mg, 3.99 mmol) slowly. The resultant mixture was heated at 80 °C for 6 h under a nitrogen atmosphere. After cooling, the resultant solvents were removed *in vacuo*. The residue was purified by column chromatography to furnish compound **77** (50 mg, 32% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 8.15 (d, J = 9.4 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.70 (dd, J = 9.0, 2.4 Hz, 1H), 7.51 (s, 1H), 4.01 (t, J = 5.6 Hz, 4H), 3.28 (t, J = 5.6 Hz, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 157.5, 153.7, 148.1, 134.5, 133.0, 131.4, 126.1, 123.3, 105.9, 67.1, 52.9.

(E)-4-(6-Chloro-2-(4-isocyanostyryl)quinolin-4-yl)morpholine (64)

A solution of quinoline-2-carbaldehyde **77** (43 mg, 0.16 mmol) and diethyl (4-isocyanobenzyl)phosphonate (**76**) (18 mg, 0.16 mmol) in anhydrous DMF (1.5 mL) were added dropwise to a solution of potassium tert-butoxide (46 mg, 0.28 mmol) in anhydrous DMF (1.5 mL). The resultant mixture was stirred at room temperature for 1 h and then poured onto crushed ice. The precipitated solid was collected by filtration and dried. The crude product obtained was purified by silica gel column chromatography to give compound **64** (35 mg, 58% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 9.0 Hz, 1H), 7.95 (d, J = 2.2 Hz, 1H), 7.66 (d, J = 16.2 Hz, 1H), 7.63 (dd, J = 4.0, 2.4 Hz, 2H), 7.61 (dd, J = 9.0, 2.4 Hz, 2H), 7.41 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 16.2 Hz, 1H), 7.09 (s, 1H), 4.02 (t, J = 5.6 Hz, 4H), 3.26 (t, J = 5.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 156.8, 156.1, 148.4, 138.0, 132.7, 131.9, 131.8, 131.4, 130.8, 128.4, 127.2, 123.9, 122.8, 108.6, 67.2, 53.0; HRMS (ESI) calculated for $C_{22}H_{19}ClN_3O$ $[M+H]^+$ m/z 376.1217, found 376.1186; retention time 5.905 min (HPLC condition B).

2-((6-Chloro-2-methylquinolin-4-yl)amino)ethyl methanesulfonate (79)

A mixture of 4,6-dichloroquinoline (840 mg, 4.0 mol), EtOH (1.0 mL) and 2-aminoethanol (6.0 mL, 99.4 mmol) were heated with stirring at 130 °C for 48 h. After cooling, the reaction mixture was poured into ice water. The resulting precipitate was collected by filtration and dried to give **78** (920 mg, 97% yield) as an off-white solid.

To a suspension of **78** (700 mg, 2.96 mmol) in anhydrous THF (12 mL) under a nitrogen atmosphere was added triethylamine (820 μL, 5.92 mmol). The mixture was

cooled to below 0 °C. Methanesulfonyl chloride (365 μL, 4.74 mmol) was added slowly keeping the temperature below 5 °C, and the reaction mixture was stirred in an ice bath for 1 h. Then, the reaction contents were quenched by the addition of saturated solution of sodium bicarbonate and brine. The reaction contents were then transferred to a separatory funnel, diluting with ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were then dried over Na_2SO_4, filtered, and evaporated to give **79** (172 mg, 72% yield) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 9.0 Hz, 1H), 7.73 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 9.0, 2.2 Hz, 1H), 6.35 (s, 1H), 4.59 – 4.56 (m, 2H), 3.70 (q, J = 5.0 Hz, 2H), 3.09 (s, 3H), 2.62 (s, 3H).

General Procedure for synthesis of 2-methyl-4-aminoquinolines (80a-c)

A mixture of 2-((6-chloro-2-methylquinolin-4-yl)amino)ethyl methanesulfonate (**79**) (172 mg, 0.5 mmol), appropriate amines (2.5 mmol) and potassium carbonate (415 mg, 3.0 mmol) in anhydrous CH_3CN (6 mL) was stirred at 82 °C overnight. Upon completion, the resultant mixture was cooled down to room temperature. The resultant solvents were removed. The residue was dissolved in dichloromethane and washed with water and brine. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were then dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel.

6-Chloro-2-methyl-*N*-(2-morpholinoethyl)quinolin-4-amine (80a)

The title compound was synthesized from precursor **79** and morpholine. Isolated yield: 94%; Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 2.2 Hz, 1H), 7.52 (dd, J = 9.0, 2.2 Hz, 1H), 6.30 (s, 1H), 3.76 (t, J = 6.4 Hz, 4H), 3.30 (d, J =

6.2 Hz, 2H), 2.76 (t J = 6.8 Hz, 2H), 2.59 (s, 3H), 2.55 – 2.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 149.3, 146.9, 131.0, 130.1, 129.8, 119.2, 118.7, 100.3, 67.4, 56.5, 53.5, 39.1, 26.0.

6-Chloro-2-methyl-*N*-(2-(pyrrolidin-1-yl)ethyl)quinolin-4-amine (80b)

The title compound was synthesized from precursor **79** and pyrrolidine. Isolated yield: 92%; Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 9.0 Hz, 1H), 7.70 (d, J = 2.2 Hz, 1H), 7.52 (dd, J = 8.9, 2.2 Hz, 1H), 6.31 (s, 1H), 3.34 – 3.30 (m, 2H), 2.88 – 2.85 (m, 2H), 2.60 (t, J = 6.4 Hz, 7H), 1.85 – 1.82 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 149.8, 147.0, 130.9, 130.0, 129.6, 119.5, 118.7, 100.1, 54.2, 54.2, 41.7, 26.0, 23.9.

6-Chloro-2-methyl-*N*-(2-(4-methylpiperazin-1-yl)ethyl)quinolin-4-amine (80c)

The title compound was synthesized from precursor **79** and *N*-methylpiperidine. Isolated yield: 80%; Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.8 Hz, 1H), 7.63 (s, 1H), 7.44 (d, J = 8.0 Hz, 1H), 6.22 (s, 1H), 5.83 (s, 1H), 3.25 – 3.19 (m, 2H), 2.69 (t, J = 6.4 Hz, 2H), 2.52 (s, 3H), 2.51 – 2.27 (m, 8H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 149.5, 146.7, 130.7, 130.0, 129.7, 119.4, 118.7, 100.1, 55.8, 55.5, 52.9, 46.4, 39.4, 25.8.

General procedure for synthesis of 4,6-dichloro-2-arylquinolines (118a-b)

A stirred mixture of 4-chloroaniline (2.6 g, 20.4 mmol) and appropriate ethyl acetates (2.60 mmol) in PPA (14 g) was heated at 150 °C for 6 h. After cooling, the reaction mixture was poured into ice water with vigorous stirring. The resulting precipitate was collected by filtration, washed with water, and dried *in vacuum* oven to give 2-arylhydroxyquinolines **117a** or **117b**.

2-Arylhydroxyquinolines (2.0 mol) in phosphorous oxycholoride (2.0 mL) was heated to 105 ^{o}C for 2 h. The excess of phosphorous oxychloride was removed under reduced pressure. The residue was quenched into crushed ice, neutralized using saturated solution of sodium bicarbonate and extracted with extracted with dichloromethane. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtrated and evaporated. The residue was purified by column chromatography on silica gel.

4,6-Dichloro-2-phenylquinoline (118a)

Isolated yield: 20% (for 2 steps); Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 2.4 Hz, 1H), 8.15 (dd, J = 6.6, 1.8 Hz, 2H), 8.12 (d, J = 9.0 Hz, 1H), 7.99 (s, 1H), 7.73 – 7.70 (m, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.52 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 147.8, 142.4, 138.5, 133.6, 132.1, 131.9, 130.4, 129.4, 127.8, 126.4, 123.3, 120.1.

4,6-Dichloro-2-(pyridin-4-yl)quinoline (118b)

Isolated yield: 45% (for 2 steps); Brown solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J = 6.0 Hz, 2H), 8.25 (d, J = 2.4 Hz, 1H), 8.15 (d, J = 9.0 Hz, 1H), 8.04 (d, J = 1.6 Hz, 1H), 8.03 (s, 2H), 7.76 (dd, J = 9.0, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 151.0, 147.8, 145.5, 143.1, 134.8, 132.3, 130.3, 127.0, 123.4, 121.7, 119.7.

6-Chloro-*N*-(4-morpholinobutyl)-2-phenylquinolin-4-amine (119)

The title compound was synthesized from **118a** according to the method described for procedure 3B. Isolated yield: 43%; White solid; MP: 141 – 143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J = 8.2, 1.4 Hz, 2H), 8.02 (d, J = 9.0 Hz, 1H), 7.76 (d, J = 2.2 Hz, 1H), 7.56 (dd, J = 9.0, 2.4 Hz, 1H), 7.52 – 7.48 (m, 2H), 7.47 – 7.43 (m, 1H), 6.84 (s, 1H), 3.78 – 3.75 (m, 4H), 3.45 – 3.40 (m, 2H), 2.51 – 2.45 (m, 6H), 1.90 – 1.86 (m, 2H), 1.77 – 1.71

(m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 150.2, 146.7, 140.3, 131.5, 130.5, 129.7, 129.1, 127.9, 119.3, 97.6, 67.2, 58.5, 54.1, 43.7, 26.7, 24.6; HRMS (ESI) *m/z* calcd. for $C_{23}H_{27}ClN_3O$ 396.1843 $[M + H]^+$; found: 396.1830; retention time 5.243 min (HPLC condition A).

6-Chloro-*N*-(4-morpholinobutyl)-2-(pyridin-4-yl)quinolin-4-amine (120)

The title compound was synthesized from **118b** according to the method described for procedure 3B. Isolated yield: 49%; White solid; MP: 185 – 186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 6.4 Hz, 2H), 7.97 (t, J = 7.2 Hz, 3H), 7.76 (d, J = 2.2 Hz, 1H), 7.58 (dd, J = 9.0, 2.2 Hz, 1H), 6.84 (s, 1H), 3.77 – 3.74 (m, 4H), 3.43 – 3.38 (m, 2H), 2.49 – 2.43 (m, 6H), 1.90 – 1.84 (m, 2H), 1.76 – 1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 150.6, 150.3, 148.1, 147.4, 132.4, 131.2, 130.6, 122.1, 119.4, 119.3, 97.0, 67.2, 58.5, 54.1, 43.7, 26.7, 24.7; HRMS (ESI) *m/z* calcd. for $C_{22}H_{26}ClN_4O$ 397.1795 $[M + H]^+$; found: 397.1771; retention time 2.651 min (HPLC condition A).

General procedure for preparation of the monophosphate of 2-arylvinylaminoquinolines (24s, 29s and 86s)

To a 50 mL signal flask were charged 2-arylethenylaminoquinolines (0.81 mmol), acetonitrile (13.0 mL) and 0.1 M phosphoric acid (10 mL, 1.0 mmol). The reaction mixture was stirred at room temperature for 24 h. Then the resultant solution was filtered, and the solvents were dried with a lyophilizer *under vacuum* (0.135 mbar) with the temperature of - 46°C for 48 h to afford phosphate salts **24s**, **29s** and **86s**.

(E)-N^1-(6-Chloro-2-(4-(trifluoromethyl)styryl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine monophosphate salt (24s)

The title compound was synthesized from compound **24**. Yield: 90%; Light-yellow solid; MP: > 200 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.77 (d, J = 16.2 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 7.55 (dd, J = 9.0, 2.4 Hz, 1H), 7.41 (d, J = 16.2 Hz, 1H), 7.28 (s, 1H), 6.83 (s, 1H), 3.50 (t, J = 6.0 Hz, 2H), 2.80 (t, J = 6.0 Hz, 2H), 2.39 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 155.9, 150.2, 147.2, 141.1, 132.8, 131.7, 131.3, 130.2, 128.9, 128.1, 126.1 (q, J = 4.0 Hz), 123.7, 121.5, 119.6, 98.6, 56.5, 44.8, 40.3; HRMS (ESI) *m/z* calcd. for $C_{22}H_{22}ClF_3N_3$ 420.1454 $[M + H]^+$; found: 420.1463; retention time 2.399 min (HPLC condition B).

(E)-N^1-(6-Chloro-2-(4-fluorostyryl)quinolin-4-yl)-N^2,N^2-dimethylethane-1,2-diamine monophosphate salt (29s)

The title compound was synthesized from compound **29**. Yield: 83%; Light-yellow solid; MP: > 200 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.24 (d, J = 2.2 Hz, 1H), 7.70 (d, J = 6.6 Hz, 1H), 7.71 – 7.64 (m, 4H), 7.52 (dd, J = 9.0, 2.2 Hz, 1H), 7.22 – 7.16 (m, 3H), 7.01 (t, J = 5.2 Hz, 1H), 6.71 (s, 1H), 3.38 – 3.34 (m, 2H), 2.53 (t, J = 6.8 Hz, 2H), 2.18 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.3 (d, J = 245.0 Hz), 156.4, 150.2, 147.4, 133.6, 132.0, 131.4, 130.1, 129.9, 129.5 (d, J = 8.0 Hz), 128.4, 121.4, 119.5, 116.2 (d, J = 23.0 Hz), 98.1, 57.5, 45.8, 41.1; HRMS (ESI) *m/z* calcd. for $C_{21}H_{22}ClFN_3$ 370.1486 $[M + H]^+$; found: 370.1502; retention time 2.070 min (HPLC condition B).

(E)-6-Chloro-2-(4-fluorostyryl)-*N*-(2-(4-methylpiperazin-1-yl)ethyl)quinolin-4-amine monophosphate salt (86s)

The title compound was synthesized from compound **86**. Yield: 80%; Light-yellow solid; MP: > 200 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.23 (d, J = 2.2 Hz, 1H), 7.71 – 7.65 (m, 4H), 7.52 (dd, J = 9.0, 2.2 Hz, 1H), 7.21 – 7.16 (m, 3H), 7.04 (t, J = 5.4 Hz, 1H),

6.73 (s, 1H), 3.40 – 3.36 (m, 2H), 3.30 – 3.25 (m, 2H), 2.60 (t, J = 6.8 Hz, 2H), 2.51 – 2.45 (m, 2H), 2.40 – 2.28 (m, 4H), 2.14 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 163.6 (d, J = 245.0 Hz), 161.2, 156.4, 147.3, 133.6, 132.0, 131.3, 130.0, 129.8 (d, J = 9.0 Hz), 129.5, 128.5, 121.3, 119.5, 116.2 (d, J = 21.0 Hz), 98.2, 56.3, 55.0, 53.0, 45.9, 40.7; HRMS (ESI) *m/z* calcd. for $C_{24}H_{27}ClFN_4$ 425.1908 $[M + H]^+$; found: 425.1910; retention time 2.334 min (HPLC condition B).

Biology

***In vitro* Antiplasmodial Activity**

Antiplasmodial activity was assessed by SYBR green I fluorescence as described previously.[33] Two-fold serial dilutions of compounds were incubated with *P. falciparum* cultures at 1% parasitemia and 1% hematocrit in 96 well plates (Santa Cruz Biotechnology, Dallas, TX) at 37 °C under a 5% CO_2 humidified atmosphere. The maximum DMSO concentration in assays was 0.1%. DMSO and CQ were used as growth and inhibition controls, respectively. After 72 h of incubation, plates were frozen at -80 °C, thawed, and incubated with 100 µL of lysis buffer (20 mM Tris-HCl, 0.08% saponin, 5 mM EDTA, 0.8% Triton X-100 and 0.01% SYBR Green I). Following incubation in the dark at room temperature for 1 h, the fluorescence signal was measured at 485 nM excitation and 530 nM emission using a Synergy Neo2 multi-mode reader (BioTek, Winooski, VT, USA). GraphPad Prism 8.0 software was used to generate a non-linear dose-response curves and calculate the EC_{50} values for each compound.

In vitro Cytotoxicity Assay

Test compounds were screened for cytotoxic activity in human hepatocyte cells (HepG2) seeded in 384-well clear bottom plates (Santa Cruz Biotechnology) at 2,250 cells

per well for 24 h at 37 °C in 5% CO_2 humidified atmosphere. Serial dilutions of test compounds were added starting at 25 μM, and plates were incubated for an additional 48 h. Subsequently, 10 μL of [(3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) (MTS, CellTiter 96® Aqueous One, Promega, Madison, WI) was added to each well and cell viability was determined after 3 h of incubation at 37 °C by measuring the absorbance at 490 nm using a Synergy Neo2 multi-mode reader (BioTek, Winooski, VT, USA). GraphPad Prism 8.0 software was used to generate non-linear dose-response curves and calculate the EC_{50} values for each compound.

In vitro Gametocytocidal Activity

Highly synchronous gametocyte cultures of the *P. falciparum* 3D7 line luc7 were obtained using an established method of gametocyte induction.[62, 63] Briefly, gametocytes induced by nutrient starvation were continually cultured in heparin treated medium to eliminate asexual stage parasites. Gametocytes at early stage (II-III) and late stage (IV-V) were purified via Percoll gradient centrifugation. 100 μL of culture containing 50,000 gametocytes was added into each well in black 96-well plate and exposed for 72 h to a 19-point dose-response gradient of test compounds (concentration range of 0.038 nM to 10 μM). Luciferase expression was determined using the ONE-Glo luciferase assay system (Promega, Madison, WI, USA) according to manufacturer instructions. 100 μL of reagent was added to the culture, incubated for 5 min and mixed well before luciferase intensity detection by a plate reader (PerkinElmer). EC_{50} values were determined in GraphPad Prism 8.0 software using a nonlinear dose-response curve fitting model.

In vitro Metabolic Stability

The metabolic stability of compounds was evaluated in mouse liver microsomes (Sigma-Aldrich) with an NADPH-regenerating system.[64] Microsomes were suspended in a 0.1 M phosphate buffer (pH = 7.4) at a final protein concentration of 0.5 mg/mL and incubated with test compounds (1 μM) at 37 °C. An NADPH-regenerating system (1.3 mM NADP, 3.3 mM glucose 6-phosphate, 3.3 mM $MgCl_2$ and 0.4 U/mL glucose 6-phosphate dehydrogenase in 0.1 M potassium phosphate buffer, pH=7.4) was added to initiate the metabolic reactions. The mixture was incubated on a shaking platform at 37 °C, and aliquots were withdrawn then quenched with the addition of an equal volume of cold acetonitrile at different time periods. Additionally, samples were incubated in the absence of the NADPH-regenerating system to monitor for noncytochrome P450-mediated metabolism in the microsomal matrix. To remove debris, samples were centrifuged at 14,000 g for 10 min at 20 °C and the amount of parent compound remaining in the supernatant was monitored via LC-MS. The compound stability is calculated as the percent remaining of the unchanged parent compound at each time point (T = 60 min) relative to the peak area at T = 0 min.

Stage Specific Action

P. falciparum Dd2 cultures tightly synchronized by magnetic separation and sorbitol treatment were exposed to test compounds at 5 × EC_{50} at 6, 18, 30, or 42 h post-invasion.[33] DHA (Sigma-Aldrich) (50 nM), atovaquone (Sigma-Aldrich) (6.6 nM), and DMSO (Sigma-Aldrich), (0.1%) were included as controls. Samples were taken after treatment at 12 h intervals to prepare Giemsa-stained thin smears for microscopic assessment of intraerythrocytic development. Simultaneously, samples were collected and processed for flow cytometric cell cycle analysis using a method previously described.[65] Briefly, samples

were fixed with 0.0075% glutaraldehyde (Sigma-Aldrich) and 4% paraformaldehyde (Sigma-Aldrich) in PBS, permeabilized with 0.25% Triton X-100, treated with RNAse (Sigma-Aldrich) (50 μg/mL) and stained with YOYO-1 DNA binding dye (Invitrogen, Waltham, MA, USA) at final concentration of 500 nM. Flow data were acquired using the CytoFLEX flow cytometer with 500,000 events per sample (Beckman Coulter, Indianapolis, IN, USA) and analyzed with the FlowJo software (FlowJo LLC, Ashland, OR, USA).

In vitro Killing Profile

P. falciparum Dd2 asynchronous cultures at 1% parasitemia and 2% hematocrit were exposed to 5 × EC_{50} of test compounds for 6, 12, 24, or 48 h. Parasites treated with 0.15% DMSO, DHA (50 nM), and atovaquone (6.6 nM), were included as negative, fast-acting, and slow-acting controls respectively. After exposure, compounds were removed through 3 washes with RPMI. Parasitemia was followed for 4 days after the addition of compounds via Giemsa-Stained thin smears.

β-Hematin Formation

Interference of the test compounds in the β-hematin crystal formation was evaluated under physiological conditions in the presence of lipid catalyst using a 96-well plate assay as previously described.[66] A mixture of 10 μL of 2 mM hemin (Sigma-Aldrich, St. Louis, MO) was dissolved in 0.1 M NaOH, 180 μL of propionate buffer at pH 5.2, and 10 μL of a previously sonicated phosphatidylcholine (Sigma-Aldrich, St. Louis, MO) suspension (10 mg/mL) was incubated with different concentrations of the test compound at 37 °C with gentle shaking for 16 h. DMSO and CQ were used as controls. After the incubation, the reaction was stopped by the addition of 100 μL of a solution of SDS 7.5% (w/v)

dissolved in 0.1 M bicarbonate buffer (pH 9.1). Plates were gently mixed and incubated at room temperature for 10 min. An aliquot of 50 µL from each well was transferred to a second plate pre-loaded with 200 µL/well of SDS solution (2.5% w/v in 0.1 M bicarbonate buffer), and the absorbance at 405 nm was read using a Synergy Neo2 multi-mode reader (BioTek). Free hemin in solution (as indicative of inhibition of β -hematin formation) was estimated by a linear calibration curve determined for each assay. Hemin stocks with concentrations ranging from 0 to 16 µM were freshly prepared in 2.5% SDS-0.1 M bicarbonate buffer (pH 9.1). Images of crystals were taken before quenching the reaction with SDS using a Nikon Eclipse TE200 inverted microscope.

***In vivo* Antimalarial Activity**

Effect on the elimination of existing infection. This evaluation was conducted at the Anti-Infectives Screening Core at New York Langone Medical Center, New York University (NYU). Briefly, Swiss-Webster female mice were injected with 10^3 red blood cells infected with *P. berghei* ANKA strain expressing luciferase. 48 h post-infection, mice were separated in groups of 5 mice and treated with compounds **24s**, **29s** or **86s**. Compounds were administrated via oral gavage in 200 µL aliquots of a vehicle containing 2% methylcellulose (Sigma-Aldrich, St. Louis, MO) and 0.5% Tween 80 (Sigma-Aldrich, St. Louis, MO) once daily for 5 days. Compounds were tested at 25 and 100 mg/kg. Compound vehicle was administered to the control mice group. On day 7 post-infection, mice were injected with 150 mg/kg of D-luciferin potassium salt in PBS (Goldbio, St. Louis, MO) and luminescence was detected using an IVIS® Lumina II imager. Results were expressed as the luciferin signal which is proportional to the load of parasites.

Protocol used was approved by the NYU institutional animal care and use committee (IACUC).

Assessment of curative property. BALB/c female mice (10 weeks old, ~20 g) were inoculated intraperitoneally with 10^6 parasitized red blood cells with *P. berghei* ANKA 676m1cl1 (MRA-868, BEI Resources, Manassas,VA). Three experimental groups of 5 animals each were included: vehicle control, compound **24s** at 25, and 100 mg/kg dose. Treatment was administrated once daily via oral gavage in the same vehicle previously mentioned for 4 days starting at 4 h post-infection. Infection was monitored from day 4 post-inoculation by Giemsa-stained thin smear of blood collected from the tail vein. Animals were sacrificed when parasitemia reached 40% or when symptoms of severe malaria were present. Animals with a negative blood smear 30 days post infection were considered cured. Survival data was analyzed using the Kaplan-Meier statistical method with Log-Rank significance test. The Protocol used in the study was approved by UCF institutional animal care and use committee (IACUC).

Transmission Electron Microscopy

P. falciparum Dd2 cultures were exposed to compound **24** at 5 × EC_{50} for 1.5, 3, 6 or 12 h. Culture treated with 0.15% DMSO was included as a control. For ultrastructural analysis, samples at each time-point were centrifuged at low speed and washed once with PBS (pH=7.4), then resuspended in 1 mL of 2% paraformaldehyde / 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer at a pH of 7.4 (Electron Microscopy Sciences, Hatfield, PA) and incubated at room temperature for 2 hours with gently shaking. Following incubation, cells were pelleted and gently resuspended in 0.2 M sodium cacodylate buffer (pH=7.4) (Electron Microscopy Sciences, Hatfield, PA). Subsequently, buffer was

replaced for 1% osmium tetroxide (Polysciences Inc.) and incubated for 1 h. Samples were then rinsed extensively in dH_2O prior to en bloc staining with 1% aqueous uranyl acetate (Ted Pella Inc., Redding, CA) for 1 h. Following several rinses in dH_2O, samples were dehydrated in a graded series of ethanol solutions and embedded in Eponate 12 resin (Ted Pella Inc.). Sections of 95 nm were cut with a Leica Ultracut UCT ultramicrotome (Leica Microsystems Inc., Bannockburn, IL), stained with uranyl acetate and lead citrate, and viewed on a JEOL 1200 EX transmission electron microscope (JEOL USA Inc., Peabody, MA) equipped with an AMT 8 megapixel digital camera and AMT Image Capture Engine V602 software (Advanced Microscopy Techniques, Woburn, MA).

ASSOCIATED CONTENT

Supporting information

- Molecular formula strings and associated biological data (CSV)
- Antiplasmodium activity of synthesized analogues (Table S1)
- Metabolic stability profiles of selected compounds **UCF501**, **24**, **29**, **86** and **93** (Figure S1-S5); Stage specific action of compounds **29** (Figure S6), **86** (Figure S7), DHA (Figure S8), and Atovaquone (Figure S9); Mice body weight data for compound **24s** (Figure S10).
- ^{1}H NMR, ^{13}C NMR spectra and LCMS data of selected compounds.

AUTHOR INFORMATION

Corresponding author

Debopam.Chakrabarti@ucf.edu (D. Chakrabarti), Yu.Yuan@ucf.edu (Y.Yuan)

ORCID

Yu Yuan: 0000-0001-5441-8742

Debopam Chakrabarti: 0000-0002-4554-3119

Guang Huang: 0000-0001-7226-5743

Claribel Murillo Solano: 0000-0002-8116-7181

Author Contributions

† G.H. and C.M.S. contributed equally to this work. Y.Y., D.C., G.H. and C.M.S. designed the research and wrote the manuscript; G.H. synthesized new compounds and conducted NMR/HRMS analysis; C.M.S., J.S., J.C., and A.K.A. screened compounds for antimalarial activity; C.M.S performed biochemical killing profile of compounds and the stage specific assays; C.M.S, J.S., J.C. and R.B. conducted the *in vivo* experiments. G.H., J.M. and C.S. carried out the microsomal stability assay; J.M., R Boonhok and H.M conducted anti-gametocyte activity assay. All the authors discussed the results and commented on the manuscript.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

Pf, *Plasmodium falciparum*; CQ, Chloroquine; ACTs, artemisinin-based combination therapies; DV, digestive vacuole; PfCRT, *Plasmodium falciparum* chloroquine resistance transporter; RI, resistance index; SI, selectivity index; FV, food vacuole; TEM, transmission electron microscopy; SAR, structure-activity relationship; DHA, dihydroartemisinin; PPA, polyphosphoric acid; *p*-$TsNH_2$, *p*-toluenesulfonamide; p.o., per os; MSD, mean survival time (in days).

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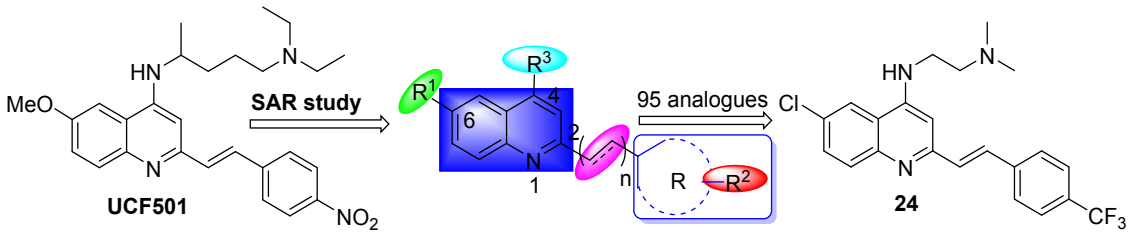
Table of Content (TOC) Graphic



Pf Asexual EC_{50} = 67.0 ± 8.0 nM (Dd2 strain)
SI = 105, RI = 0.6
Microsomal stability(MLM): $t_{1/2}$ = 41.5 min
In vivo efficacy: 100 mg/kg twice daily, p.o.

Pf Asexual EC_{50} =10.9 ± 1.9 nM (Dd2 strain)
SI = 1031, RI = 0.6
Pf Gametocyte EC_{50} = 471.5 ± 18.4 nM (early stage)
EC_{50} = 393.6 ± 99.4 nM (late stage)
Microsomal stability (MLM): $t_{1/2}$ = 104.2 min
In vivo efficacy (24s): 25 mg/kg once daily, p.o.