

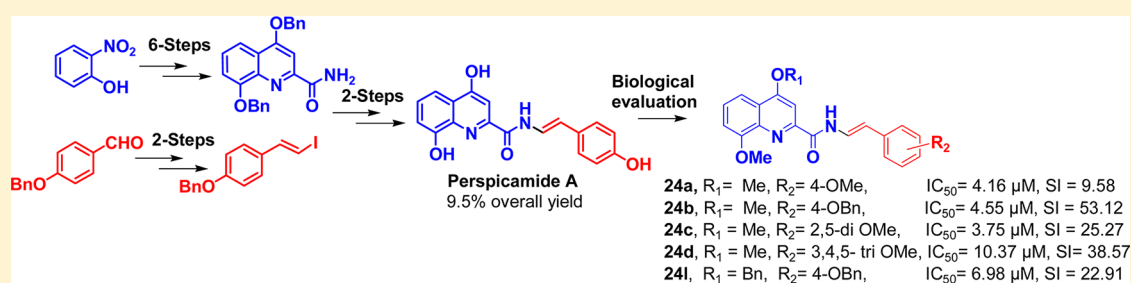
Synthesis of Perspicamide A and Related Diverse Analogues: Their Bioevaluation as Potent Antileishmanial Agents

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S Supporting Information



ABSTRACT: The first protocol for the synthesis of perspicamide A and related diverse analogues has been developed from economical and readily available starting materials. Furthermore, a few synthesized analogues, **24a**, **24b**, **24c**, **24d**, and **24l**, exhibited potent activity against *Leishmania donovani* with IC₅₀ values ranging from 3.75 to 10.37 μM and a selectivity index (SI) ranging from 9.58 to 53.12, which is improved compared to the standard drug Miltefosine (IC₅₀ 12.4 μM and SI 4.1).

INTRODUCTION

Throughout the history of medicinal chemistry and pharmaceutical drug development, small-molecule natural products (SMNPs) have played and continue to play an invaluable role in drug discovery and have inspired ingenuity owing to their drug like assets.¹ Usually it is found that active SMNPs have relatively poor drug properties,² and thus some chemical manipulations are required to address such deficiencies.³ In this context, several drugs have emerged, such as topotecan, irinotecan (from camptothecin), taxotere (from taxol), etoposide, teniposide (podophyllotoxin derivatives), etc. upon modification of natural leads, and many more are in various stages of research.⁴

The quinoline nucleus containing metabolite perspicamide A (**1**) and B (**2**) (Figure 1), first isolated from the Australian ascidian *Botrylloides perspicuum* in 2005 by Quinn et al.,⁵ has attracted much attention as it is found in many drug-like compounds.⁶ The presence of the quinoline and enamide systems (separately) in a large number of functionalized molecules with wide variety of applications including medicinal chemistry,⁷ material science,⁸ and several reaction intermediates⁹ is well documented. From a medicinal point of view, macrolactone bearing an enamide side chain, such as salicylilalamide A and B (**3** and **4**, inhibitors of mammalian VATPases),¹⁰ CJ-12950 (**5**),¹¹ and lobatamide A (**6**)¹² (Figure 1) are well-known for their potent antitumor activity. Other important enamides include protease inhibitor TMC-95-A-D,¹³

sedative and anti-inflammatory peptide frangulofoline,¹⁴ etc. Perhaps even more importantly, quinoline-based molecules are landmarks for a broad range of biological activities including antimalarial,¹⁵ antibacterial,¹⁶ cytotoxic,¹⁷ DNA binding property,¹⁸ anti-inflammatory,¹⁹ and antileishmanial,²⁰ etc. To the best of our knowledge and belief, the synthesis and medicinal utility of perspicamide A and related analogues has not been reported yet. Our group has also been engaged in the synthesis of small drug-like molecules using metal-catalyzed coupling protocols,²¹ condensation reactions,²² and a multicomponent approach.²³ Thus, herein we disclose the first synthesis of perspicamide A and a wide range of structurally related analogues and their biological evaluation as potential antileishmanial agent employing an efficient and flexible route via Cu-mediated cross-coupling reaction under mild condition.

Retrosynthesis. The idea for the synthetic route to perspicamide A (**1**) was developed by taking incremental steps backward from the final structure (Figure 2), where the synthons **7**, **14**, and **25** would be an obvious choice for the preparation of desired molecule. With regard to the construction of the desired architecture, benzyl protection, reduction, subsequent aza-Michael reaction, cyclization, benzyl protection, amidation, and finally copper-mediated cross-coupling reaction followed by selective deprotection may lead

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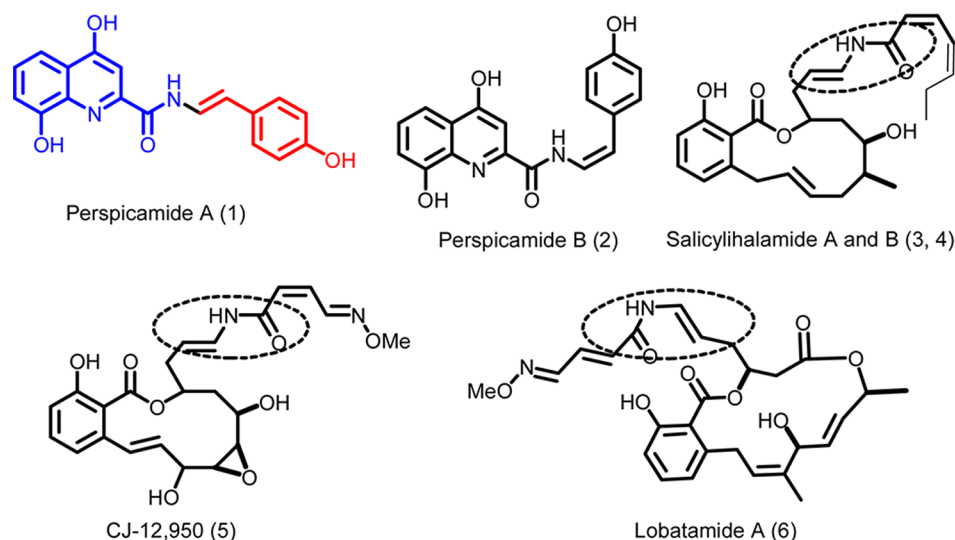


Figure 1. Perspicamide A and B (1, 2) and other biologically significant enamides (3–6).

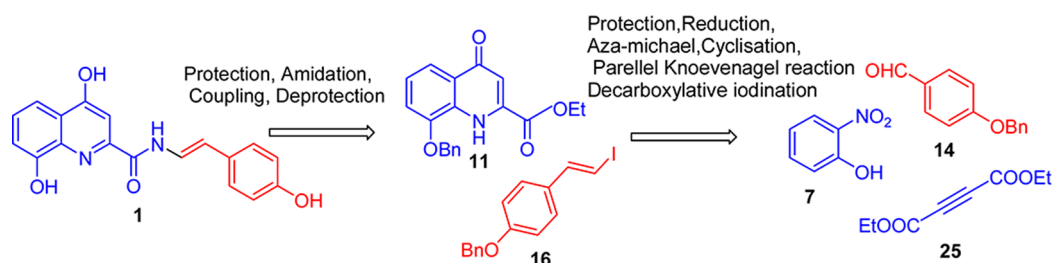
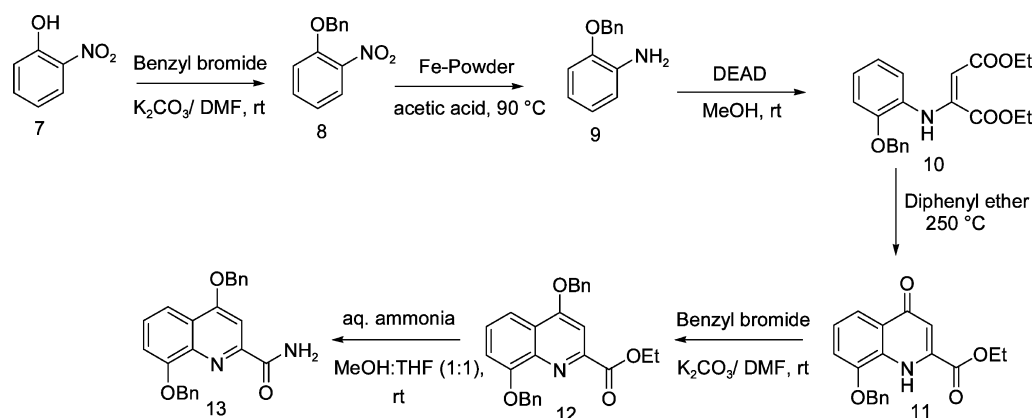


Figure 2. Retrosynthetic analysis of perspicamide A (1).

Scheme 1. Synthesis of Quinoline Carboxamide (13)

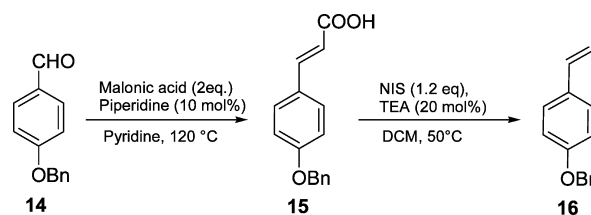


to the formation of perspicamide A (1). The counterpart of the excised fragment, e.g., styryl iodide (16), is easily accessible, starting from 4-benzyloxy benzaldehyde (14).

RESULTS AND DISCUSSION

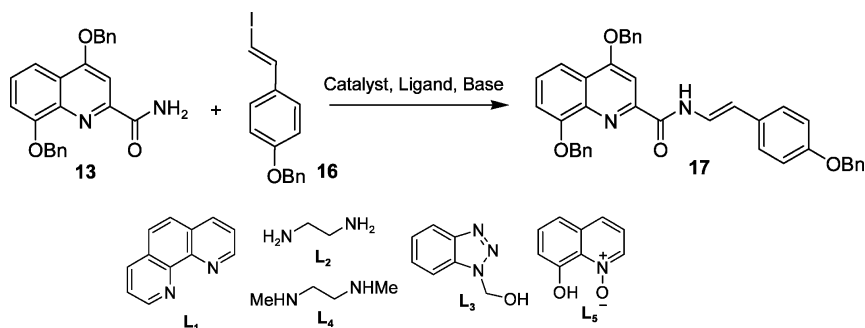
The synthetic route for both the fragments is given in Schemes 1 and 2. 2-Nitrophenol (7), used as precursor, was protected with benzyl bromide in presence of K_2CO_3 in DMF and reduced with Fe/acetic acid to give the corresponding 2-benzyloxy aniline (9) in overall 65% yield. This aniline 9 was coupled to diethyl acetylenedicarboxylate (DEAD) in MeOH via aza-Michael reaction to afford 10 in 84% yield.²⁴ This early stage of the synthesis provides our first diversification point

Scheme 2. Synthesis of Styryl Iodide (16)



(Figure 2) and paves the way for the synthesis of perspicamide A and related analogues.

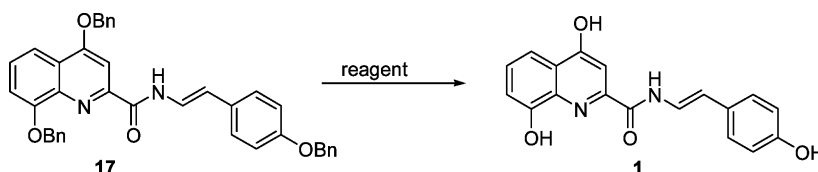
The intermediate 10 was subsequently cyclized in diphenylether (Ph_2O) at 250 °C to get the desired skeleton,

Table 1. Optimization of the Coupling Reaction of Quinoline 2-Carboxamide (13) and Styryl Iodide (16)^a

Structure of ligands (L) used

entry	catalyst	L	base	time (h)	yield (%) ^b
1			CS ₂ CO ₃	15	nr ^c
2	CuI		CS ₂ CO ₃	15	nr ^c
3	CuI	L ₁	CS ₂ CO ₃	15	trace
4	CuI	L ₂	CS ₂ CO ₃	15	62
5	CuI	L ₂	K ₂ CO ₃	15	nr ^c
6	CuI	L ₃	CS ₂ CO ₃	15	trace
7	CuI	L ₄	CS ₂ CO ₃	10	74
8	Cu ₂ O	L ₄	CS ₂ CO ₃	8	82
9	CuTC	L ₄	CS ₂ CO ₃	9	76
10	Cu(OAc) ₂	L ₄	CS ₂ CO ₃	15	15
11	Cu ₂ O	L ₅	CS ₂ CO ₃	15	nr ^c
12	Cu(OTf) ₂	L ₂	CS ₂ CO ₃	15	nr ^c

^aReaction conditions: 13 (0.4 mmol), 16 (0.4 mmol), catalyst (15 mol %), ligand (20 mol %), base (1 mmol), and solvent (5 mL), under nitrogen atmosphere at 85 °C. ^bIsolated yield. ^cNo product formation.

Table 2. Deprotection of Benzylated Analogue^a to Perspicamide A (1)

entry	reagent	equiv	solvent	temp (°C)	time (min)	(%)1 ^b
1	Pd/C	10 ^c	MeOH	rt	15	0
2	Pd/C	10 ^c	MeOH	rt	30	0
3	Pd/C	10 ^c	MeOH	rt	60	0
4	BBr ₃	3	DCM	35	30	<i>d</i>
5	BBr ₃	6	DCM	35	60	<i>d</i>
6	BCl ₃	6	DCM	35	60	32
7	BCl ₃	9	DCM	35	60	48
8	BCl ₃	12	DCM	35	120	15

^aReaction condition: substrate 17 (1.0 equiv), reagent, and solvent (5 mL) under argon atmosphere. ^bIsolated yield. ^cWeight percent used. ^dMixture of uncharacterised product.

ethyl 4-hydroxyquinoline-2-carboxylate (11) in good yield (69%),²⁵ which upon a second benzyl protection followed by amidation with aqueous ammonia in MeOH/THF (1:1) led to the formation of the desired key intermediate 4,8-bis(benzyloxy)quinoline-2-carboxamide (13) in 79% yield. The other excised fragment 16, e.g., styryl iodide, was prepared from 4-benzyloxy benzaldehyde (14) in two steps: (i) the Knoevenagel condensation of malonic acid with 4-benzyloxy benzaldehyde (14) using 10 mol % piperidine as catalyst in pyridine at reflux conditions,²⁶ and (ii) decarboxylative iodination with *N*-iodosuccinimide (NIS) using 20 mol %

Et₃N as catalyst in DCM at reflux conditions (inert atmosphere) in overall 49% yield (Scheme 2).²⁷

With both the key intermediates, 4,8-bis(benzyloxy)-quinoline-2-carboxamide (13) and 4-benzyloxy styryl iodide (16) in hand, we were ready to attempt the key coupling reaction with concomitant construction of benzyl protected perspicamide A (17). The coupling protocol for the desired molecule was optimized to obtain the best reaction conditions so that the efficiency of the protocol could be maintained. Several catalyst and ligands along with bases were optimized and the results are summarized in Table 1.

Table 3. Synthesized Perspicamide A Related Analogues^a

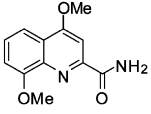
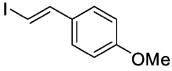
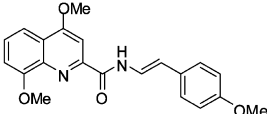
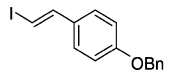
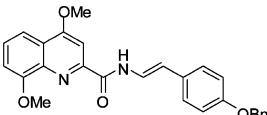
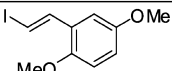
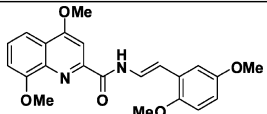
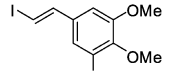
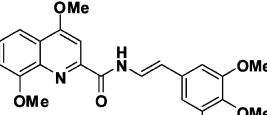
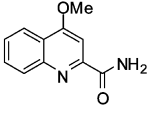
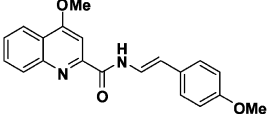
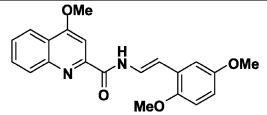
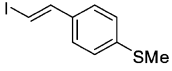
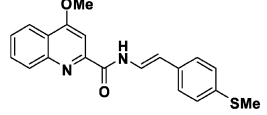
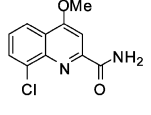
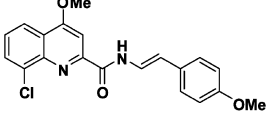
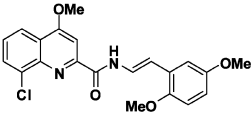
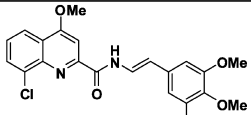
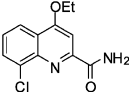
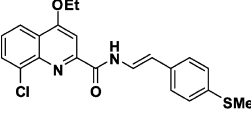
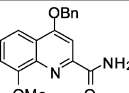
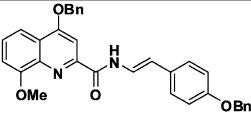
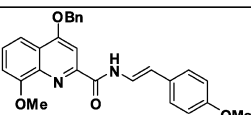
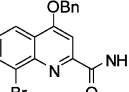
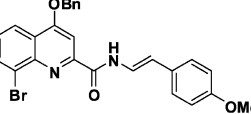
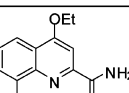
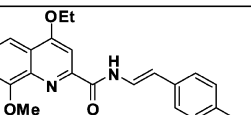
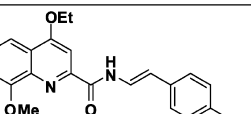
entry	substrate A	substrate B	product	yield (%) ^b
1	 22a	 16a	 24a	88
2	22a	 16b	 24b	78
3	22a	 16c	 24c	84
4	22a	 16d	 24d	88
5	 22b	16a	 24e	81
6	22b	16c	 24f	86
7	22b	 16e	 24g	91
8	 22c	16a	 24h	82

Table 3. continued

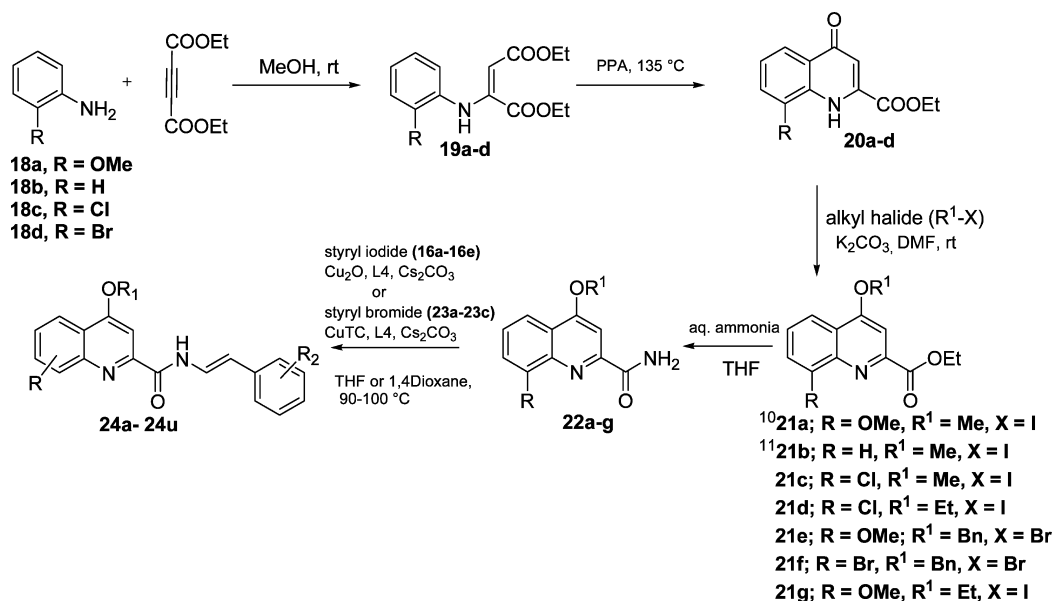
entry	substrate A	substrate B	product	yield (%) ^b
9	22c	16c	 24i	84
10	22c	16d	 24j	88
11	 22d	16e	 24k	86
12	 22e	16b	 24l	75
13	22e	16a	 24m	78
14	 22f	16a	 24n	76
15	 22g	16e	 24o	88
16	22g	16a	 24p	84

^aReaction conditions: substrate A (2.47 mmol), substrate B (2.47 mmol), Cu₂O (15 mol %), DMEDA (20 mol %), Cs₂CO₃ (6.17 mmol), and THF (10 mL) under nitrogen atmosphere at 85 °C for 8–10 h. ^bIsolated yield.

The Cu-catalyzed C–N coupling of amides with styryl halides, the modified Goldberg reaction, is the most widely applicable reaction for the synthesis of enamides framework of natural products.²⁸ The first enamide synthesis via metal-

catalyzed coupling was reported by Porco et al. where they used CuTC as catalyst.²⁹ Later Buchwald et al. used CuI as catalyst and DMEDA as ligand to achieve the same.³⁰ Further, Ma used dimethyl glycine as ligand to promote a similar reaction.³¹

Scheme 3. Synthesis of Perspicamide A Related Analogues 24a–24u



However, during optimization of catalyst, we found that Cu₂O is more effective and economic compared to CuI, along with DMEDA as ligand and Cs₂CO₃ as base (entry 8, Table 1). Thus, coupling of 4,8-bis(benzyloxy)quinoline-2-carboxamide (**13**) with styryl halide (**16**) under the optimized reaction conditions (entry 8, Table 1) led to the formation of benzyl-protected perspicamide A, which upon subsequent deprotection led to the formation of perspicamide A in 48% yield (Table 2). In the overall synthetic maneuver, relative stereochemistry was found to be in favor of the desired *trans*-diastereoisomer.

During the initial efforts of deprotection, the methylated analogue of perspicamide A (**24a**, Table 3, entry 1) was subjected to a deprotection reaction employing several Lewis acids, such as BBr₃, Br₂ in acetic acid, etc., and unfortunately this afforded a mixture of unidentified products (monitored by TLC). This might be due to the sensitive nature of the enamide bond in such a functional system. Therefore, we opted to use a protecting group that could be easily unmasked under mild conditions. Even though the easily cleavable benzyl group is used for protection, still the deprotection of *O*-benzylated perspicamide was optimized (Table 2), where 9.0 equiv of BCl₃ in DCM under argon atmosphere was found to be the best reaction condition for deprotection.³²

The structure of the synthesized natural product was confirmed by ¹H and ¹³C NMR (see Supporting Information) and HRMS and by comparison with literature.⁵ The synthetic protocol for perspicamide A related analogues is delineated in Scheme 3.

The synthesis of these analogues was started with substituted anilines, the first point of diversification in the designed library. The second diversity point evolved during the syntheses of styryl halides where different aromatic aldehydes were used as precursor. Furthermore, during the hydroxyl protection a third diversity point arose where different alkyl halides are used for derivatization. Thus, the designed library holds several merits with a high level of diversity in synthesized molecules (Table 3).

Unfortunately our catalytic system failed in the case of the less reactive styryl bromide, and hence further screening of

catalyst was carried out, where CuTC was found as efficient catalyst for the coupling of quinoline carboxamide with styryl bromide (see Supporting Information Table S1). After optimization of the catalytic system in the coupling reaction with different styryl halides as iodide and less reactive bromide, we were able to synthesize the related analogues of perspicamide A bearing other functionalities in excellent yields (Table 4).

Biological Screening Results. All of the synthesized compounds were evaluated for their antileishmanial activity where analogues **24a**, **24b**, **24c**, **24d**, and **24l** were found to be potentially active with IC₅₀ values or 4.16, 4.55, 3.75, 10.37, and 6.98 μM and SI values or 9.58, 53.12, 25.27, 38.57, and 22.91, respectively, which seems more promising than values for the standard drug Miltefosine (IC₅₀ 12.4 μM and SI 4.41) (Table 5).

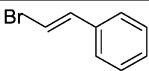
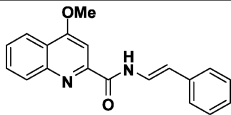
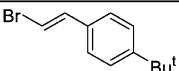
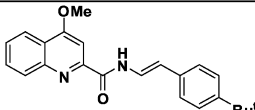
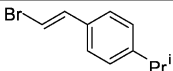
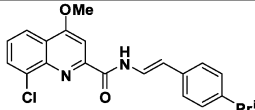
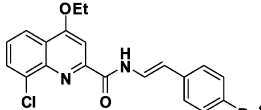
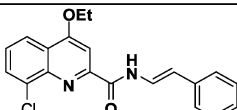
CONCLUSION

In conclusion, we have described the first synthesis of perspicamide A and related analogues and their potential utility as antileishmanial agents. A combination of well-optimized, easy-to-operate methodologies and only a small number of synthetic transformations increases both the practicability and efficiency of the synthesis. This strategy would allow an extremely valuable approach for a variety of substitution patterns and offers the chance of a future bioactivity-directed synthesis of defined perspicamide library.

EXPERIMENTAL SECTION

Material and Method for Biological Screening. Antiamastigote Activity. To assess the activity of compounds against the amastigote stage of the parasite, mouse macrophage cell line (J774A.1) infected with WHO reference strain (MHOM/IN/80/Dd8) of promastigotes (expressing luciferase firefly reporter gene) was used. Cells were seeded in a 96-well plate (4 × 10³ cell/100 μL/well) in RPMI-1640 containing 10% fetal calf serum, and the plates were incubated at 37 °C in a CO₂ incubator. After 24 h, the medium was replaced with fresh medium containing stationary-phase promastigotes (4 × 10⁴/100 μL/well). Promastigotes invade the macrophage and are transformed into amastigotes. The test compounds were added at 2-fold dilutions up to 7 points in complete medium starting from 40 μM

Table 4. Synthesized Perspicamide A Related Analogues via Styryl Bromide Substrate^a

entry	substrate C	substrate D	product	yield (%) ^b
1	22b	 23a	 24q	72
2	22b	 23b	 24r	77
3	22c	 23c	 24s	74
4	22d	23b	 24t	76
5	22d	23a	 24u	73

^aReaction conditions: substrate C (1.0 mmol), substrate D (1.1 mmol), CuTC (15 mol %), DMEDA (20 mol %), Cs₂CO₃ (2.5 mmol), and THF (10 mL) or 1,4-dioxane (5 mL) under nitrogen atmosphere at 100 °C for 12 h, ^bIsolated yield.

concentration after replacing the previous medium, and the plates were incubated at 37 °C in a CO₂ incubator for 72 h. After incubation, the drug-containing medium was decanted, and 50 μ L of PBS was added in each well and mixed with an equal volume of Steady Glo reagent. After gentle shaking for 1–2 min, the reading was recorded in a luminometer.³³ The values are expressed as relative luminescence units (RLU), and the data were transformed into a graphic program (Excel). The IC₅₀ of antileishmanial activity was calculated by nonlinear regression analysis of the concentration response curve using the four parameter Hill equations.

Cytotoxicity Assay. The cell viability was determined using the MTT assay.³⁴ Exponentially growing cells (Vero Cell line) (1×10^5

cells/100 μ L/well) were incubated with test compounds for 72 h. The test compounds were added at 3-fold dilutions up to 7 points in complete medium starting from 400 μ M concentration and were incubated at 37 °C in a humidified mixture of CO₂ and 95% air in an incubator. Podophyllotoxin was used as a reference drug, and control wells containing dimethyl sulfoxide (DMSO) without compounds were also included in the experiment. Stock solutions of compounds were initially dissolved in DMSO and further diluted with fresh complete medium. After incubation, 25 μ L of MTT reagent (5 mg/mL) in PBS medium, followed by syringe filtration, was added to each well and incubated at 37 °C for 2 h. At the end of the incubation period, the supernatant was removed by inverting the plate completely

Table 5. *In Vitro* Antileishmanial Activity of Perspicamide Analogues against Intracellular Amastigotes and Their Cytotoxicity^a

compd no.	antiamastigote activity IC ₅₀ (μM)	cytotoxicity CC ₅₀ (μM)	selectivity index (SI) ^b	compd no.	antiamastigote activity IC ₅₀ (μM)	cytotoxicity CC ₅₀ (μM)	selectivity index (SI) ^b
1	>40	NA	NA	24l	6.98	159.97	22.91
17	>40	NA	NA	24m	ND	ND	NA
24a	4.16	39.86	9.58	24n	ND	ND	NA
24b	4.55	241.74	53.12	24o	toxic	ND	NA
24c	3.75	94.77	25.27	24p	toxic	ND	NA
24d	10.37	>400	>38.57	24q	ND	ND	NA
24e	>40	ND	NA	24r	ND	ND	NA
24f	>40	ND	NA	24s	>20	ND	NA
24g	14.08	ND	NA	24t	ND	ND	NA
24h	12.39	ND	NA	24u	ND	ND	NA
24i	13.81	ND	NA	MF	12.4	54.75	4.41
24j	>20	ND	NA	SSG	71.90	398.26	5.53
24k	20.73	ND	NA				

^aMF (Miltefosine) and SSG (Sodium Stibo-gluconate): Standard antileishmanial drugs IC₅₀ >15 μM = inactive; IC₅₀ > 5–15 μM = moderately active; IC₅₀ < 5 μM = active compounds. ND = not done, NA = not available. ^bSI for each compound was calculated as ratio between, CC₅₀ and IC₅₀ against *Leishmania* amastigotes.

without disturbing the cell layer, and 150 μL of pure DMSO was added to each well. After 15 min of shaking the readings were recorded as absorbance at 544 nm on a micro plate reader. The cytotoxic effect were expressed as 50% lethal dose, i.e., as the concentration of a compound that provoked a 50% reduction in cell viability compared to cells in culture medium alone. CC₅₀ values were estimated as described by Huber and Koella.³⁵

General Chemistry. NMR spectra were recorded on 300, 400, or 600 MHz spectrometers for ¹H NMR and 50, 75, 100, or 150 MHz for ¹³C NMR in CDCl₃ or DMSO-*d*₆ with TMS as internal reference wherever mentioned. Chemical shifts (δ) are reported in parts per million (ppm) for ¹H and ¹³C NMR spectra. Coupling constants *J* are reported in hertz (Hz). Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). HRMS analyses were carried out on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry. The reaction progress was routinely monitored by thin-layer chromatography (TLC) on precoated silica gel plates. Column chromatography was performed over silica gel (60–120) and (100–200) mesh. All compounds were characterized by TLC, ¹H and ¹³C NMR, IR, and HRMS.

Experimental Procedure for the Synthesis of Fragment 13. **2-(Benzyloxy)nitrobenzene (8).** To a stirred solution of 2-nitrophenol (7) (2.0 g, 14.4 mmol) in DMF (5 mL) was added K₂CO₃ (4.0 g, 28.8 mmol) at room temperature, and the mixture was allowed to stir for 15 min followed by the addition of benzyl bromide (1.71 mL, 14.4 mmol). The reaction was allowed to stir at room temperature for 2 h. After completion (monitored by TLC), the reaction mixture was poured into water and extracted with ethyl acetate (4 × 20 mL). The combined organic layers were washed with saturated brine solution, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to get the titled compound 8 as a brown solid. Yield 2.89 g, 88%.³⁶

2-(Benzyloxy)aniline (9). To a solution of 2-benzyloxy nitrobenzene (8) (2.89 g, 12.60 mmol) in acetic acid (10 mL) was added iron powder (3.55 g, 63.00 mmol). The reaction mixture was heated at 90 °C for 40 min. After completion of reaction (monitored by TLC), the reaction mixture was filtered through a Celite pad followed by neutralization with 10% sodium bicarbonate solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure, and the crude product was purified by column chromatography using 60–120 mesh silica gel with CHCl₃/hexane (1:1) as eluent to get the intermediate 9 as a gummy solid. Yield 1.86 g, 74%.³⁷

Diethyl 2-(2-(Benzyloxy)phenylamino)maleate (10). A solution of 2-benzyloxy aniline (9) (1.86 g, 9.36 mmol) in anhydrous methanol was treated with diethylethylenedicarboxylate (DEAD)

(1.80 mL, 11.23 mmol), and the reaction was allowed to stir for 6 h at room temperature. After completion of the reaction, the solvent was evaporated under reduced pressure followed by column chromatography using 60–120 mesh silica gel using 2% ethyl acetate/hexane as eluent to get intermediate 10 as yellow oil. Yield 2.90 g, 84%; IR (cm⁻¹) 3448, 1732, 1618, 1216, 768, 697, 668; ¹H NMR (300 MHz, CDCl₃) δ 9.90 (s, 1H), 7.57 (d, *J* = 7.0 Hz, 2H), 7.49–7.39 (m, 3H), 7.09–6.95 (m, 4H), 5.53 (s, 1H), 5.22 (s, 2H), 4.34–4.21 (m, 4H), 1.42 (t, *J* = 6.8 Hz, 3H), 1.21 (t, *J* = 6.9 Hz, 3H) ppm; ¹³C NMR (50 MHz, CDCl₃) δ 169.4, 164.3, 149.8, 148.0, 136.7, 130.2, 128.5, 127.8, 127.0, 124.4, 121.0, 120.7, 113.2, 93.2, 70.6, 61.8, 59.8, 14.4, 13.6 ppm; HRMS (EI) calcd for [M + H]⁺ C₂₁H₂₄NO₃ 370.1576, found 370.1583.

Ethyl 8-(Benzyloxy)-4-oxo-1,4-dihydroquinoline-2-carboxylate (11). The above aza-Michael product (10) (2.90 g, 7.85 mmol) was dissolved in diphenylether (DPE) and refluxed in a preheated oil bath at 250 °C for 10 min to provide cyclized quinolone ester 11. The crude reaction mixture was purified by column chromatography using 60–120 mesh silica gel with CHCl₃ as eluent to get 11 as a red solid, mp 118–122 °C. Yield 1.75 g, 69%; IR (cm⁻¹) 3349, 1718, 1559, 1332, 1252; ¹H NMR (300 MHz, CDCl₃) δ 7.89 (d, *J* = 8.1 Hz, 1H), 7.43–7.36 (m, 4H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.18–7.11 (m, 2H), 7.00 (s, 1H), 5.25 (s, 2H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.43 (t, *J* = 7.1 Hz, 3H) ppm; ¹³C NMR (50 MHz, CDCl₃) δ 179.7, 162.5, 147.5, 136.1, 135.6, 130.7, 129.0, 128.7, 127.5, 127.0, 124.3, 117.6, 113.1, 111.6, 71.3, 63.4, 14.1 ppm; HRMS (EI) calcd for [M + H]⁺ C₁₉H₁₈NO₄ 324.1158, found 324.1167.

Ethyl 4,8-Bis(benzyloxy)-quinoline-2-carboxylate (12). To a stirring solution of quinolone 2-ester (11) (1.75 g, 5.41 mmol) in DMF (5 mL), was added K₂CO₃ (1.50 g, 10.82 mmol), and the mixture was allowed to stir for 15 min at room temperature, followed by the addition of benzyl bromide (0.64 mL, 5.41 mmol). The reaction mixture was heated at 70 °C for 6 h. After completion (monitored by TLC), the reaction mixture was poured into water and extracted with ethyl acetate (5 × 15 mL). The combined organic layers were washed with saturated brine solution, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure to get the titled compound 12 as a brown solid, mp 113–117 °C. Yield 1.81 g, 81%; IR (cm⁻¹) 1718, 1508, 1258, 1220, 1045, 767, 697; ¹H NMR (300 MHz, CDCl₃) δ 7.85 (d, *J* = 8.3 Hz, 1H), 7.69 (s, 1H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.51 (d, *J* = 7.1 Hz, 2H), 7.44–7.29 (m, 7H), 7.12 (d, *J* = 7.5 Hz, 1H), 5.38 (s, 2H), 5.32 (s, 2H), 4.53 (q, *J* = 7.1 Hz, 2H), 1.51 (t, *J* = 7.0 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 166.0, 162.2, 155.2, 148.3, 141.0, 137.0, 135.5, 128.8, 128.5, 127.9, 127.7, 127.2, 123.6, 114.0, 111.5, 101.6, 71.2, 70.7, 62.1, 14.3 ppm; HRMS (EI) calcd for [M + H]⁺ C₂₆H₂₄NO₄ 414.1627, found 414.1636.

4,8-Bis(benzyloxy)-quinoline-2-carboxamide (13). To a stirring solution of **12** (1.39 g, 10.0 mmol) in MeOH/THF (1:1) (10 mL) was added 10 mL of aq ammonia (30% solution). The reaction mixture was allowed to stir at room temperature for 12 h (monitored by TLC). Solvent was removed under reduced pressure and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with saturated brine solution and dried over anhydrous Na₂SO₄. The crude product was purified by column chromatography using 60–120 mesh silica gel with 1% MeOH/CHCl₃ as eluent to get **13** as a brown solid, mp 167–170 °C. Yield 1.33 g, 79%; IR (cm⁻¹) 3387, 1632, 1553, 1457, 1041, 821; ¹H NMR (300 MHz, CDCl₃) δ 8.27 (s, 1H), 7.91–7.86 (m, 2H), 7.55–7.43 (m, 11H), 7.18 (d, J = 6.2 Hz, 1H), 6.00 (s, 1H), 5.36 (s, 4H) ppm; ¹³C NMR (50 MHz, CDCl₃ + DMSO-*d*₆) δ 171.8, 167.0, 159.2, 154.7, 144.7, 143.8, 141.7, 140.4, 133.4, 133.3, 133.1, 132.6, 132.3, 132.0, 128.0, 118.9, 116.2, 103.9, 75.6, 75.2 ppm; HRMS (EI) calcd for [M + H]⁺ C₂₄H₂₁N₂O₃ 385.1552, found 385.1567.

(E)-3-(4-(Benzyloxy)-phenyl)-acrylic Acid (15). This compound was obtained by the condensation of 4-(benzyloxy) benzaldehyde (**14**) (2.00 g, 9.43 mmol) and malonic acid (1.96 g, 18.86 mmol) with piperidine (0.19 mL, 1.18 mmol) in pyridine (10 mL) solvent for 3 h at 120 °C. After completion of reaction (monitored by TLC), the reaction mixture was poured into a chilled solution of 10% aq hydrochloric acid. The corresponding cinnamic acid appeared as a white precipitate. The precipitate was filtered and washed with water to get **15** as a white solid. Yield 1.07 g, 89%.³⁸

(E)-1-(Benzyloxy)-4-(2-iodovinyl)-benzene (16). To a stirred solution of (E)-3-(4-(benzyloxy)phenyl) acrylic acid (**15**) (1.07 g, 4.21 mmol) in DCM (10 mL) was added Et₃N (0.13 mL, 0.84 mmol) over a period of 10 min under argon atmosphere followed by the addition of *N*-iodosuccinimide (NIS) (1.14 g, 5.05 mmol), and the reaction mixture was allowed reaction for 30 min at 45 °C. The reaction was cooled, and solvent was evaporated at low temperature under reduced pressure. The crude product was purified by column chromatography using 60–120 mesh silica gel with 2% EtOAc/hexane as eluent to get the titled compound **16** as a white solid. Yield 0.78 g, 55%.³⁹

(E)-4,8-Bis(benzyloxy)-N-(4-(benzyloxy)-styryl)-quinoline-2-carboxamide (17). To a oven-dried double neck round-bottom flask (rbf) equipped with magnetic stirring bar and 4,8-bis(benzyloxy)-quinoline-2-carboxamide (**13**) (1.33 g, 3.46 mmol) in dry THF (10 mL) were added (E)-1-(benzyloxy)-4-(2-iodovinyl)benzene (**16**) (1.16 g, 3.46 mmol), Cu₂O (0.74 mg, 0.52 mmol), DMEDA (0.074 mL, 0.69 mmol), and Cs₂CO₃ (2.81 mg, 8.65 mmol) under an argon atmosphere. Then reaction mixture was degassed and backfilled several times with argon before being heated to 85 °C and allowed reaction to reflux for 8 h. The flask was then cooled to room temperature, the reaction mixture was filtered through a Celite pad, and the solution was evaporated under reduced pressure followed by column chromatography using 100–200 mesh silica gel with 15% EtOAc/hexane as eluent to get the titled compound **17** as a yellow solid, mp 210–213 °C. Yield 1.68 g, 82%; IR (cm⁻¹) 3458, 1643, 1502, 769; ¹H NMR (300 MHz, CDCl₃) δ 10.31 (d, J = 11.3 Hz, 1H), 7.90–7.84 (m, 2H), 7.63–7.52 (m, 5H), 7.49–7.31 (m, 14H), 7.20 (d, J = 7.6 Hz, 1H), 6.96 (d, J = 8.4 Hz, 2H), 6.27 (d, J = 14.5 Hz, 1H), 5.38 (s, 4H), 5.08 (s, 2H) ppm; ¹³C NMR (50 MHz, CDCl₃) δ 162.7, 161.6, 157.8, 154.5, 149.0, 139.9, 137.0, 135.5, 129.3, 128.8, 128.7, 128.6, 128.5, 128.0, 127.9, 127.7, 127.4, 127.3, 127.1, 126.8, 123.6, 120.8, 115.1, 114.5, 114.1, 111.7, 111.4, 99.3, 71.1, 70.8, 70.0 ppm; HRMS (EI) calcd for [M + H]⁺ C₃₉H₃₃N₂O₄ 593.2440, found 593.2448.

(E)-4,8-Dihydroxy-N-(4-hydroxystyryl)-quinoline-2-carboxamide (1). To a stirred solution of **17** (500 mg, 0.84 mmol) in dry DCM (5 mL) at 0 °C was added BCl₃ (1.0 M solution in methylene chloride) (0.67 mL, 7.6 mmol) dropwise for 15 min under nitrogen atmosphere, followed by stirring at room temperature for 1 h. After completion (monitored by TLC), the reaction was quenched with methanol (10 mL) followed by evaporation under vacuum on a rotavapor and column chromatography using 100–200 mesh silica gel with 2% MeOH/CHCl₃ as eluent to get the titled compound **1** as a yellow solid, mp >250 °C. Yield 130 mg, 48%; IR (cm⁻¹) 3435, 1641, 1524, 1216, 766; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.88 (s, 1H),

11.25 (d, J = 12.8 Hz, 1H), 10.01 (s, 1H), 9.45 (s, 1H), 7.59–7.57 (m, 2H), 7.47–7.42 (m, 2H), 7.27 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 7.6 Hz, 1H), 6.75 (d, J = 8.6 Hz, 2H), 6.54 (d, J = 14.2 Hz, 1H) ppm; ¹³C NMR (150 MHz, DMSO-*d*₆) δ 162.8, 161.5, 156.4, 153.5, 147.8, 138.2, 127.6, 127.2, 126.6, 122.1, 120.6, 115.7, 114.1, 111.8, 111.7, 102.0 ppm; HRMS (EI) calcd for [M + H]⁺ C₁₈H₁₅N₂O₄ 323.1032, found 323.1036.⁵

General Procedure for the Preparation of 19a–19e. Different anilines (**18a–18d**) (20.0 mmol) were dissolved in 10 mL of anhydrous methanol followed by dropwise addition of DEAD (24.0 mmol), and the reaction was allowed to run for 4 h at room temperature. After completion of reaction as indicated by TLC, the resulting mixture was evaporated under reduced pressure, and the residue was purified by column chromatography using 60–120 mesh silica gel (eluent hexane/EtOAc) affording the corresponding aza-Michael product **19a–19d** in 80–85% yield.^{40a–c}

Diethyl 2-(2-Bromophenylamino)-maleate (19d). Yellow oil. Yield 83%; IR (cm⁻¹) 3461, 3278, 1733, 1668, 1616, 1277, 1215, 1148, 1035, 760; ¹H NMR (300 MHz, CDCl₃) δ 9.71 (s, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.20 (t, J = 6.9 Hz, 1H), 6.95 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 5.54 (s, 1H), 4.25–4.15 (m, 4H), 1.32 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 169.3, 164.1, 147.1, 139.1, 133.2, 127.8, 125.1, 121.6, 116.1, 96.4, 62.3, 60.4, 14.5, 13.8 ppm; HRMS (EI) calcd for [M + H]⁺ C₁₄H₁₇BrNO₄ 342.0341, found 342.0349.

General Procedure for the Preparation of 20a–20d. Different substituted diethyl 2-(phenylamino) maleate (7.50 mmol) was added to neat polyphosphoric acid (PPA) and allowed reaction to run for 2 h at 135 °C. The reaction mixture was neutralized with sodium bicarbonate, and the product was purified by simple washing with cold water or extracted with CHCl₃ from aqueous solution. The organic layer was dried with Na₂SO₄ and evaporated under reduced pressure provided **20a–20d** in 75–85% yield.⁴¹

Ethyl 8-Bromo-4-oxo-1,4-dihydroquinoline-2-carboxylate (20d). Brown solid, mp 150–153 °C. Yield 83%; IR (cm⁻¹) 3367, 1719, 1634, 1523, 1272, 768, 600; ¹H NMR (300 MHz, CDCl₃) δ 9.39 (s, 1H), 8.30 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.27–7.22 (m, 1H), 6.99 (s, 1H), 4.54 (q, J = 7.1 Hz, 2H), 1.48 (t, J = 7.1 Hz, 3H) ppm; ¹³C NMR (50 MHz, CDCl₃) δ 178.8, 162.2, 136.58, 136.56, 135.8, 127.3, 125.8, 124.7, 112.1, 111.7, 63.4, 14.0 ppm; HRMS (EI) calcd for [M + H]⁺ C₁₂H₁₁BrNO₃ 295.9922, found 295.9924.

General Procedure for the Preparation of 21a–21g. To a stirred solution of different substituted quinolone 2-ester (**20a–20d**) (5.0 mmol) in DMF (5 mL) was added K₂CO₃ (10.0 mmol) followed by addition of alkyl halide (methyl or ethyl iodide 10.0 mmol or benzyl bromide 5.0 mmol), and the reaction allowed to run for 4–6 h. After completion of reaction, the mixture was poured into water and extracted with ethyl acetate, and the organic layer was dried with Na₂SO₄ and evaporated under reduced pressure to provide a solid mass of product (**21a–21g**) in 85–95% yield.^{42,43}

Ethyl 8-Chloro-4-methoxy-quinoline-2-carboxylate (21c). Brown solid, mp 125–128 °C. Yield 89%; IR (cm⁻¹) 1718, 1626, 1276, 1070, 712, 756; ¹H NMR (600 MHz, CDCl₃) δ 8.13 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 7.3 Hz, 1H), 7.59 (s, 1H), 7.48 (t, J = 8.1 Hz, 1H), 4.53 (q, J = 7.0 Hz, 2H), 4.11 (s, 3H), 1.50 (t, J = 7.1 Hz, 3H) ppm; ¹³C NMR (150 MHz, CDCl₃) δ 165.5, 163.6, 149.8, 144.8, 134.3, 130.6, 127.2, 123.5, 120.8, 100.8, 62.5, 56.3, 14.2 ppm; HRMS (EI) calcd for [M + H]⁺ C₁₃H₁₃ClNO₃ 266.0584, found 266.0595.

Ethyl 8-Chloro-4-ethoxy-quinoline-2-carboxylate (21d). Brown solid, mp 108 °C. Yield 88%; IR (cm⁻¹) 1721, 1622, 1269, 1068, 759, 686; ¹H NMR (300 MHz, CDCl₃) δ 8.19 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 6.7 Hz, 1H), 7.58 (s, 1H), 7.50 (t, J = 7.7 Hz, 1H), 4.54 (q, J = 6.5 Hz, 2H), 4.39 (q, J = 6.5 Hz, 2H), 1.61 (t, J = 6.0 Hz, 3H), 1.50 (t, J = 7.0 Hz, 3H) ppm; ¹³C NMR (150 MHz, CDCl₃) δ 165.8, 163.2, 150.0, 145.0, 134.4, 130.8, 127.3, 123.8, 121.2, 101.6, 65.2, 62.7, 14.5, 14.4 ppm; HRMS (EI) calcd for [M + H]⁺ C₁₄H₁₅ClNO₃ 280.0740, found 280.0747.

Ethyl 4-(Benzyloxy)-8-methoxyquinoline-2-carboxylate (21e). Creamy color solid, mp 157–153 °C. Yield 83%; IR (cm⁻¹) 1714, 1268, 1228, 1068, 754, 698; ¹H NMR (300 MHz, DMSO-*d*₆) δ

7.74 (d, $J = 7.8$ Hz, 1H), 7.67 (s, 1H), 7.61–7.56 (m, 3H), 7.47–7.38 (m, 3H), 7.28 (d, $J = 7.4$ Hz, 1H), 5.46 (s, 2H), 4.45 (q, $J = 7.0$ Hz, 2H), 3.98 (s, 3H), 1.39 (t, $J = 7.0$ Hz, 3H) ppm; ^{13}C NMR (50 MHz, CDCl_3) δ 165.7, 161.8, 156.3, 148.1, 140.3, 136.4, 129.1, 128.9, 128.7, 128.2, 123.1, 113.2, 110.1, 102.4, 70.6, 61.9, 56.2, 14.7 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+ \text{C}_{20}\text{H}_{20}\text{NO}_4$ 338.1392, found 338.1398.

Ethyl 4-(Benzyloxy)-8-bromo quinoline-2-carboxylate (21f). Light brown solid, mp 152–155 °C. Yield 82%; IR (cm^{-1}) 1715, 1629, 1259, 1064, 696; ^1H NMR (300 MHz, CDCl_3) δ 8.27 (d, $J = 8.0$ Hz, 1H), 8.10 (d, $J = 6.8$ Hz, 1H), 7.72 (s, 1H), 7.51–7.42 (m, 6H), 5.36 (s, 2H), 4.56 (q, $J = 6.6$ Hz, 2H), 1.53 (t, $J = 6.6$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 165.5, 162.6, 150.1, 145.8, 135.1, 134.3, 128.8, 128.7, 127.8, 125.8, 123.6, 121.8, 101.8, 71.1, 62.4, 14.2 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+ \text{C}_{19}\text{H}_{17}\text{BrNO}_3$ 386.0392, found 386.0396.

Ethyl 4-Ethoxy-8-methoxy-quinoline-2-carboxylate (21g). Brown solid, mp 132–135 °C. Yield 88%; IR (cm^{-1}) 1719, 1633, 1257, 1053, 759, 682; ^1H NMR (300 MHz, CDCl_3) δ 7.81 (d, $J = 8.4$ Hz, 1H), 7.59 (s, 1H), 7.52 (t, $J = 7.9$ Hz, 1H), 7.07 (d, $J = 7.7$ Hz, 1H), 4.54 (q, $J = 6.9$ Hz, 2H), 4.38 (q, $J = 7.1$ Hz, 2H), 4.05 (s, 3H), 1.60 (t, $J = 6.9$ Hz, 3H), 1.52 (t, $J = 7.1$ Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 165.6, 162.2, 155.5, 147.9, 140.1, 127.5, 123.1, 113.0, 108.1, 101.0, 64.3, 61.9, 55.6, 14.1, 14.0 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+ \text{C}_{15}\text{H}_{18}\text{NO}_4$ 276.1236, found 276.1244.

General Procedure for the Preparation of 22a–22g. To a stirred solution of different substituted quinoline 2-esters (5.0 mmol) in MeOH/THF (1:1) (10 mL) was added 30% NH_4OH solution (15 mL) followed by stirring for 12 h at room temperature, converting the ester to amide. Solvent was removed on a rotary evaporator and extracted with ethyl acetate followed by washing with brine solution. The combined organic layers dried over Na_2SO_4 provided substituted quinoline 2-carboxamide. Purification through crystallization with ethanol provided quinoline 2-carboxamides in 80–90% yield.⁴⁴

4,8-Dimethoxy Quinoline-2-carboxamide (22a). Brown solid, mp 162–165 °C. Yield 90%; IR (cm^{-1}) 3439, 1642, 1391, 767; ^1H NMR (CDCl_3 , 400 MHz): δ 8.25 (s, 1H), 7.80 (d, $J = 8.4$ Hz, 1H), 7.72 (s, 1H), 7.50 (t, $J = 8$ Hz, 1H), 7.09 (d, $J = 7.7$ Hz, 1H), 5.78 (s, 1H), 4.11 (s, 3H), 4.05 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 167.6, 163.9, 155.6, 150.0, 139.9, 127.6, 123.7, 114.0, 109.1, 98.9, 56.5, 56.3 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+ \text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3$ 233.0848, found 233.0857.

8-Chloro-4-methoxyquinoline-2-carboxamide (22c). Brown solid, mp 225–230 °C. Yield 89%; IR (cm^{-1}) 3444, 1638, 1399, 770; ^1H NMR (300 MHz, CDCl_3) δ 8.23 (s, 1H), 8.18 (d, $J = 8.4$ Hz, 1H), 7.86 (d, $J = 7.5$ Hz, 1H), 7.75 (s, 1H), 7.50 (t, $J = 8.3$ Hz, 1H), 5.77 (s, 1H), 4.14 (s, 3H) ppm; ^{13}C NMR (150 MHz, $\text{CDCl}_3 + \text{DMSO}-d_6$) δ 171.4, 168.7, 156.1, 148.6, 138.2, 135.2, 131.5, 128.2, 125.8, 103.2, 61.2 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+ \text{C}_{11}\text{H}_{10}\text{ClN}_2\text{O}_2$ 237.0431, found 237.0442.

8-Chloro-4-ethoxyquinoline-2-carboxamide (22d). Dark brown solid, mp 209–212 °C. Yield 88%; IR (cm^{-1}) 3456, 1613, 1388, 774; ^1H NMR (600 MHz, CDCl_3) δ 8.23 (s, 1H), 8.17 (d, $J = 8.3$ Hz, 1H), 7.83 (d, $J = 7.3$ Hz, 1H), 7.70 (s, 1H), 7.46 (t, $J = 8.0$ Hz, 1H), 5.87 (s, 1H), 4.38 (q, $J = 6.8$ Hz, 2H), 1.58 (t, $J = 6.9$ Hz, 3H) ppm; ^{13}C NMR (150 MHz, CDCl_3) δ 167.0, 163.4, 151.1, 144.1, 133.7, 130.6, 126.8, 123.8, 121.3, 99.1, 65.2, 14.6 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+ \text{C}_{12}\text{H}_{12}\text{ClN}_2\text{O}_2$ 251.0587, found 251.0594.

4-(Benzyloxy)-8-methoxyquinoline-2-carboxamide (22e). Light brown solid, mp 192–195 °C. Yield 82%; IR (cm^{-1}) 3468, 1615, 1364, 748; ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 8.12 (s, 1H), 7.76 (s, 1H), 7.75–7.73 (m, 2H), 7.57–7.54 (m, 3H), 7.45 (t, $J = 7.5$ Hz, 2H), 7.39 (t, $J = 7.3$ Hz, 1H), 7.27 (d, $J = 7.8$ Hz, 1H), 5.46 (s, 2H), 3.99 (s, 3H) ppm; ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$) δ 166.3, 161.6, 154.95, 150.1, 138.8, 135.8, 128.5, 128.1, 127.7, 127.5, 122.4, 112.9, 109.5, 99.4, 69.9, 55.7 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+ \text{C}_{18}\text{H}_{17}\text{N}_2\text{O}_3$ 309.1239, found 309.1243.

4-(Benzyloxy)-8-bromo-quinoline-2-carboxamide (22f). Creamy white solid, mp 185–188 °C. Yield 80%; IR (cm^{-1}) 3464, 1628, 1365, 771; ^1H NMR (300 MHz, CDCl_3) δ 8.27 (d, $J = 8.1$ Hz, 2H), 8.07 (d, $J = 7.3$ Hz, 1H), 7.83 (s, 1H), 7.52 (d, $J = 6.8$ Hz, 2H),

7.46–7.37 (m, 4H), 5.90 (s, 1H), 5.37 (s, 2H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 166.8, 163.1, 151.2, 144.9, 135.3, 134.2, 128.9, 128.8, 127.9, 127.5, 125.1, 123.7, 122.1, 99.5, 71.3 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+ \text{C}_{17}\text{H}_{14}\text{BrN}_2\text{O}_2$ 357.0239, found 357.0247.

4-Ethoxy-8-methoxyquinoline-2-carboxamide (22g). Brown solid, mp 167–170 °C. Yield 88%; IR (cm^{-1}) 3472, 1635, 1362, 743; ^1H NMR (600 MHz, CDCl_3) δ 8.20 (s, 1H), 7.81 (d, $J = 8.3$ Hz, 1H), 7.68 (s, 1H), 7.48 (t, $J = 7.9$ Hz, 1H), 7.07 (d, $J = 7.6$ Hz, 1H), 5.83 (s, 1H), 4.36 (q, $J = 6.9$ Hz, 2H), 4.04 (s, 3H), 1.57 (t, $J = 6.9$ Hz, 3H) ppm; ^{13}C NMR (150 MHz, CDCl_3) δ 167.5, 162.9, 155.4, 149.8, 139.8, 127.3, 123.6, 114.0, 108.9, 99.2, 64.8, 56.2, 14.6 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+ \text{C}_{13}\text{H}_{15}\text{N}_2\text{O}_3$ 247.1083, found 247.1087.

General Procedure for Styryl Iodide (16a–16e). Starting material cinnamic acids are available commercially, although some of the substrates used were prepared in our laboratory. Different cinnamic acids (only substrates with electron-donating groups on the aromatic ring) (4.0 mmol) were dissolved in dichloromethane (6 mL), subsequently Et_3N (0.8 mmol) was added followed by addition of *N*-iodosuccinimide (NIS) (4.80 mmol), and the reaction was allowed to run for 15–30 min. After completion of reaction, evaporated the solvent at low temperature on a rotavapor followed by column chromatography using 60–120 mesh silica gel provided the corresponding substituted (*E*)-styryl iodide (16a–16e) in 50–70% yield.²⁷

General Procedure for Styryl Bromide (23a–23c). Different cinnamic acids (4.0 mmol) were dissolved in dichloromethane (6 mL), subsequently Et_3N (0.8 mmol) was added followed by addition of *N*-bromosuccinimide (NBS) (4.80 mmol), and the reaction was allowed to run for 15–30 min. Evaporation of the solvent at low temperature on a rotavapor followed by column chromatography using 60–120 mesh silica gel provided the corresponding substituted (*E*)-styryl bromide (23a–23c) in 60–85% yield.²⁷

General Procedure for Coupling Product (24a–24p). To a oven-dried double-neck rbf equipped with magnetic stirring bar and substituted quinoline-2-carboxamide (22a–22g) (2.47 mmol) in dry THF (10 mL) were added different (*E*)-styryl iodides (16a–16e) (2.47 mmol), Cu_2O (0.37 mmol), DMEDA (0.49 mmol), and Cs_2CO_3 (6.17 mmol) under argon atmosphere. Then reaction mixture was degassed and backfilled several times with argon before being heated to 85 °C, and the reaction mixture was allowed to reflux for 8–10 h. The flask was then cooled to room temperature and filtered through a Celite pad, and the solution was evaporated under reduced pressure followed by column chromatography using 100–200 mesh silica gel with 20% ethyl acetate/hexane as eluent to get the titled compounds 24a–24p as a yellow solids. Yield 75–91%.

(E)-4,8-Dimethoxy-N-(4-methoxy-styryl)-quinoline-2-carboxamide (24a). Yellow solid, mp 175–178 °C. Yield 88%; IR (cm^{-1}) 3471, 2366, 1653, 1504, 1074, 752; ^1H NMR (CDCl_3 , 400 MHz): δ 10.11 (d, $J = 11.0$ Hz, 1H), 7.81 (d, $J = 8.4$ Hz, 1H), 7.76 (s, 1H), 7.63 (dd, $J_1 = 11.2$ Hz, $J_2 = 14.5$ Hz, 1H), 7.52 (t, $J = 7.9$ Hz, 1H), 7.36 (d, $J = 8.5$ Hz, 2H), 7.12 (d, $J = 7.7$ Hz, 1H), 6.88 (d, $J = 8.6$ Hz, 2H), 6.46 (d, $J = 14.6$ Hz, 1H), 4.13 (s, 3H), 4.10 (s, 3H), 3.81 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 164.4, 162.2, 158.9, 155.6, 149.6, 139.7, 129.4, 127.7, 127.2, 123.7, 121.1, 114.7, 114.5, 114.1, 109.2, 99.0, 56.6, 56.3, 55.6 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+ \text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_4$ 365.1501, found 365.1501.

(E)-N-(4-(Benzyloxy)-styryl)-4,8-dimethoxy-quinoline-2-carboxamide (24b). Yellow solid, mp 157–159 °C. Yield 78%; IR (cm^{-1}) 3456, 1649, 1566, 1207, 784; ^1H NMR (CDCl_3 , 300 MHz): δ 10.15 (d, $J = 10.5$ Hz, 1H), 7.84–7.79 (m, 2H), 7.67–7.36 (m, 9H), 7.15 (d, $J = 7.1$ Hz, 1H), 6.98 (d, $J = 7.9$ Hz, 2H), 6.48 (d, $J = 14.4$ Hz, 1H), 5.10 (s, 2H), 4.16 (s, 3H), 4.13 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 163.6, 161.8, 157.8, 155.2, 149.2, 139.4, 137.0, 129.3, 128.6, 127.9, 127.4, 126.8, 123.4, 120.8, 115.1, 114.4, 113.8, 108.9, 98.6, 70.0, 56.2, 56.0 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+ \text{C}_{27}\text{H}_{25}\text{N}_2\text{O}_4$ 441.1814, found 441.1811.

(E)-4,8-Dimethoxy-N-(2,5-dimethoxystyryl)-quinoline-2-carboxamide (24c). Yellow solid, mp 128–131 °C. Yield 84%; IR (cm^{-1}) 3408, 1667, 1547, 1222, 789; ^1H NMR (CDCl_3 , 300 MHz): δ 10.20 (d, $J = 11.1$ Hz, 1H), 7.84–7.75 (m, 3H), 7.55 (t, $J = 7.9$ Hz,

1H), 7.15 (d, $J = 7.7$ Hz, 1H), 7.08 (d, $J = 2.8$ Hz, 1H), 6.86–6.72 (m, 3H), 4.16 (s, 3H), 4.14 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 163.6, 161.9, 155.3, 153.8, 150.9, 149.2, 139.4, 127.4, 126.2, 123.4, 123.2, 113.7, 112.9, 112.3, 111.3, 109.7, 108.9, 98.6, 56.3, 56.2, 56.0, 55.8 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_5$ 395.1607, Found 395.1611.

(E)-4,8-Dimethoxy-N-(3,4,5-trimethoxystyryl)-quinoline-2-carboxamide (24d). Yellow solid, mp 198–200 °C. Yield 88%; IR (cm^{-1}) 3344, 1676, 1469, 1234, 760; ^1H NMR (CDCl_3 , 300 MHz): 10.19 (d, $J = 11.1$ Hz, 1H), 7.85–7.78 (m, 2H), 7.71 (dd, $J_1 = 11.5$ Hz, $J_2 = 14.4$ Hz, 1H), 7.56 (t, $J = 8.0$ Hz, 1H), 7.16 (d, $J = 7.7$ Hz, 1H), 6.66 (s, 2H), 6.46 (d, $J = 14.5$ Hz, 1H), 4.17 (s, 3H), 4.13 (s, 3H), 3.92 (s, 6H), 3.87 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 163.6, 162.0, 155.1, 153.3, 149.0, 132.1, 127.4, 123.4, 121.9, 114.7, 113.7, 108.8, 102.8, 98.5, 60.8, 56.1, 56.0 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_6$ 425.1713, found 425.1722.

(E)-4-Methoxy-N-(4-methoxystyryl)-quinoline-2-carboxamide (24e). Yellow solid, mp 124–127 °C. Yield 81%; IR (cm^{-1}) 3447, 2357, 1663, 1544, 742; ^1H NMR (CDCl_3 , 300 MHz): 10.08 (d, $J = 11.0$ Hz, 1H), 8.25 (d, $J = 8.1$ Hz, 1H), 8.08 (d, $J = 8.4$ Hz, 1H), 7.78–7.72 (m, 2H), 7.64 (m, 2H), 7.37 (d, $J = 8.5$ Hz, 2H), 6.89 (d, $J = 8.6$ Hz, 2H), 6.45 (d, $J = 14.6$ Hz, 1H), 4.14 (s, 3H), 3.82 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 75 MHz) δ 162.7, 160.6, 157.5, 149.2, 146.3, 129.4, 128.0, 127.8, 126.0, 125.8, 121.1, 121.0, 119.5, 113.2, 113.1, 96.8, 56.2, 54.2 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_3$ 335.1396, found 335.1407.

(E)-N-(2,5-Dimethoxystyryl)-4-methoxyquinoline-2-carboxamide (24f). Yellow solid, mp 144–147 °C. Yield 86%; IR (cm^{-1}) 3449, 1663, 1563, 736; ^1H NMR (CDCl_3 , 300 MHz): 10.17 (d, $J = 11.2$ Hz, 1H), 8.52 (d, $J = 8.1$ Hz, 1H), 8.09 (d, $J = 8.3$ Hz, 1H), 7.82–7.72 (m, 3H), 7.60 (t, $J = 7.5$ Hz, 1H), 7.06 (d, $J = 2.7$ Hz, 1H), 6.84 (m, 3H), 4.14 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 162.7, 160.7, 152.7, 149.8, 149.2, 146.4, 129.4, 128.1, 126.1, 124.9, 122.1, 121.2, 121.0, 111.9, 111.1, 110.2, 108.5, 96.8, 55.2, 54.8 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{21}\text{H}_{21}\text{N}_2\text{O}_4$ 365.1501, found 365.1490.

(E)-4-Methoxy-N-(4-methylthio)-styryl)-quinoline-2-carboxamide (24g). Yellow solid, mp 139–142 °C. Yield 91%; IR (cm^{-1}) 3474, 2196, 1661, 1542, 782; ^1H NMR (CDCl_3 , 400 MHz) δ 10.05 (d, $J = 10.8$ Hz, 1H), 8.17 (d, $J = 8.1$ Hz, 1H), 8.00 (d, $J = 8.3$ Hz, 1H), 7.98–7.65 (m, 3H), 7.60 (t, $J = 14.9$ Hz, 1H), 7.35 (d, $J = 8.0$ Hz, 2H), 7.23 (d, $J = 8.0$ Hz, 2H), 6.35 (d, $J = 14.6$ Hz, 1H), 4.06 (s, 3H), 2.41 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz) δ 164.1, 162.1, 150.5, 147.8, 137.0, 133.7, 130.8, 129.4, 127.4, 126.4, 122.6, 122.4, 122.3, 114.3, 98.2, 56.6, 16.4 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{20}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$ 351.1167, found 351.1176.

(E)-8-Chloro-4-methoxy-N-(4-methoxystyryl)-quinoline-2-carboxamide (24h). Yellow solid, mp 178–181 °C. Yield 82%; IR (cm^{-1}) 3434, 2372, 1656, 1477, 1219, 772; ^1H NMR (CDCl_3 , 300 MHz): 10.15 (d, $J = 11.4$ Hz, 1H), 8.18 (d, $J = 8.3$ Hz, 1H), 7.88 (d, $J = 7.3$ Hz, 1H), 7.77 (s, 1H), 7.64 (dd, $J_1 = 11.4$ Hz, $J_2 = 14.5$ Hz, 1H), 7.51 (t, $J = 7.7$ Hz, 1H), 7.38 (d, $J = 8.5$ Hz, 2H), 6.90 (d, $J = 8.6$ Hz, 2H), 6.45 (d, $J = 14.6$ Hz, 1H), 4.16 (s, 3H), 3.82 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 164.2, 161.3, 158.7, 150.6, 133.5, 130.6, 128.8, 126.9, 126.8, 123.6, 121.1, 120.5, 114.7, 114.2, 98.6, 56.5, 55.3 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{20}\text{H}_{18}\text{ClN}_2\text{O}_3$ 369.1006, found 369.1012.

(E)-8-Chloro-N-(2,5-dimethoxystyryl)-4-methoxyquinoline-2-carboxamide (24i). Yellow solid, mp 221–224 °C. Yield 84%; IR (cm^{-1}) 3441, 2344, 1638, 1543, 742; ^1H NMR (CDCl_3 , 300 MHz): 10.23 (d, $J = 11.6$ Hz, 1H), 8.19 (d, $J = 8.0$ Hz, 1H), 7.89 (d, $J = 7.0$ Hz, 1H), 7.82 (t, $J = 12.4$ Hz, 2H), 7.52 (t, $J = 7.9$ Hz, 1H), 7.07 (d, $J = 2.8$ Hz, 1H), 6.85–6.69 (m, 3H), 4.16 (s, 3H), 3.87 (s, 3H), 3.82 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 164.1, 161.4, 153.7, 150.8, 150.4, 143.7, 139.2, 133.6, 130.6, 126.9, 125.8, 123.5, 123.0, 121.1, 114.0, 113.0, 112.1, 111.3, 110.0, 98.6, 56.5, 56.2, 55.8 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{21}\text{H}_{20}\text{ClN}_2\text{O}_4$ 399.1112, found 399.1114.

(E)-8-Chloro-4-methoxy-N-(3,4,5-trimethoxystyryl)-quinoline-2-carboxamide (24j). Yellow solid, mp 234–236 °C. Yield 84%; mp 236 °C; ^1H NMR (CDCl_3 , 300 MHz): 10.21 (d, $J =$

11.1, 1H), 8.20 (d, $J = 8.1$ Hz, 1H), 7.89 (d, $J = 7.4$ Hz, 1H), 7.77 (s, 1H), 7.68 (dd, $J_1 = 11.4$ Hz, $J_2 = 14.4$ Hz, 1H), 7.52 (t, $J = 7.9$ Hz, 1H), 6.65 (s, 2H), 6.43 (d, $J = 14.5$ Hz, 1H), 4.18 (s, 3H), 3.91 (s, 6H), 3.86 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 163.2, 160.3, 152.4, 149.3, 142.6, 136.3, 132.5, 130.8, 129.6, 125.9, 122.5, 120.6, 120.1, 114.0, 101.8, 97.5, 59.9, 55.5, 55.1 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{22}\text{H}_{22}\text{ClN}_2\text{O}_5$ 429.1217, found 429.1207.

(E)-8-Chloro-4-ethoxy-N-(4-methylthio)-styryl)-quinoline-2-carboxamide (24k). Yellow solid, mp 125–128 °C. Yield 86%; IR (cm^{-1}) 3426, 2367, 1652, 1587, 1435, 1023, 667; ^1H NMR (CDCl_3 , 400 MHz): 10.19 (d, $J = 11.2$ Hz, 1H), 8.21 (d, $J = 8.3$ Hz, 1H), 7.88 (d, $J = 7.3$ Hz, 1H), 7.73 (s, 1H), 7.71 (dd, $J_1 = 11.5$ Hz, $J_2 = 14.4$ Hz, 1H), 7.50 (t, $J = 7.9$ Hz, 1H), 7.36 (d, $J = 8.1$ Hz, 2H), 7.23 (d, $J = 8.1$ Hz, 2H), 6.43 (d, $J = 14.6$ Hz, 1H), 4.43 (q, $J = 6.8$ Hz, 2H), 2.49 (s, 3H), 1.62 (t, $J = 6.9$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 163.8, 161.8, 150.7, 144.1, 137.0, 133.8, 133.6, 130.9, 127.4, 127.1, 126.4, 124.0, 122.1, 121.6, 114.6, 99.4, 65.5, 16.3, 14.7 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{21}\text{H}_{20}\text{ClN}_2\text{O}_5\text{S}$ 399.0856, found 399.0859.

(E)-4-(Benzyloxy)-N-(4-(benzyloxy)-styryl)-8-methoxyquinoline-2-carboxamide (24l). Yellow solid, mp 179–182 °C. Yield 75%; IR (cm^{-1}) 3422, 2306, 1639, 1541, 767; ^1H NMR (CDCl_3 , 300 MHz): 10.14 (d, $J = 11.1$ Hz, 1H), 7.89 (s, 2H), 7.55–7.14 (m, 14H), 7.16 (d, $J = 7.3$ Hz, 1H), 6.98 (d, $J = 8.0$ Hz, 2H), 6.49 (d, $J = 14.5$ Hz, 1H), 5.41 (s, 2H), 5.10 (s, 2H), 4.14 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 162.7, 161.8, 157.8, 155.3, 149.2, 139.5, 137.0, 135.5, 129.3, 128.7, 128.6, 128.5, 127.9, 127.7, 127.4, 126.8, 123.5, 120.8, 115.2, 114.3, 114.0, 109.0, 99.6, 70.8, 70.1, 56.0 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{33}\text{H}_{29}\text{N}_2\text{O}_4$ 517.2127, Found 517.2129.

(E)-4-(Benzyloxy)-8-methoxy-N-(4-methoxystyryl)-quinoline-2-carboxamide (24m). Yellow solid, mp 155–158 °C. Yield 78%; $R_f = 0.70$ (30% EtOAc: Hexane); IR (cm^{-1}) 3444, 2317, 1639, 1543, 759; ^1H NMR (CDCl_3 , 400 MHz) δ 10.21 (d, $J = 10.9$ Hz, 1H), 7.87–7.85 (m, 2H), 7.63–7.33 (m, 9H), 7.12 (d, $J = 7.6$ Hz, 1H), 6.88–6.86 (d, 2H), 6.47 (d, $J = 14.6$ Hz, 1H), 5.37 (s, 2H), 4.10 (s, 3H), 3.81 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 163.0, 162.1, 158.9, 155.5, 149.6, 139.9, 135.8, 129.4, 129.1, 128.8, 128.0, 127.7, 127.2, 123.8, 121.1, 114.7, 114.5, 114.3, 109.3, 100.0, 71.1, 56.3, 55.6 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{27}\text{H}_{25}\text{N}_2\text{O}_4$ 441.1814, Found 441.1811.

(E)-4-(Benzyloxy)-8-bromo-N-(4-methoxystyryl)-quinoline-2-carboxamide (24n). Yellow solid, mp 148–151 °C. Yield 76%; IR (cm^{-1}) 3429, 2298, 1634, 1504, 769; ^1H NMR (CDCl_3 , 300 MHz): 10.17 (d, $J = 11.1$ Hz, 1H), 8.27 (d, $J = 8.2$ Hz, 1H), 8.11 (d, $J = 7.3$ Hz, 1H), 7.87 (s, 1H), 7.65–7.37 (m, 9H), 6.91 (d, $J = 8.4$ Hz, 2H), 6.46 (d, $J = 14.5$ Hz, 1H), 5.41 (s, 2H), 3.84 (s, 3H) ppm; ^{13}C NMR (CDCl_3 , 75 MHz): δ 163.1, 161.1, 158.7, 150.5, 144.5, 135.1, 134.2, 128.8, 128.6, 127.7, 127.4, 126.9, 124.8, 123.5, 122.0, 120.4, 114.6, 114.2, 99.4, 71.2, 55.3 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{26}\text{H}_{22}\text{BrN}_2\text{O}_3$ 489.0814, Found 489.0819.

(E)-4-Ethoxy-8-methoxy-N-(4-methylthio)-styryl)-quinoline-2-carboxamide (24o). Yellow solid, mp 147–150 °C. Yield 88%; IR (cm^{-1}) 3458, 1685, 1647, 1349, 1069, 746; ^1H NMR (CDCl_3 , 400 MHz): 10.25 (d, $J = 11.1$ Hz, 1H), 7.84 (d, $J = 8.4$ Hz, 1H), 7.71–7.65 (m, 2H), 7.51 (t, $J = 7.9$ Hz, 1H), 7.33–7.31 (m, 2H), 7.21–7.19 (m, 2H), 7.11 (d, $J = 7.7$ Hz, 1H), 6.45 (d, $J = 14.6$ Hz, 1H), 4.39 (q, $J = 6.9$ Hz, 2H), 4.09 (s, 3H), 2.48 (s, 3H), 1.60 (t, $J = 6.9$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 163.3, 162.4, 155.5, 149.5, 139.8, 136.8, 133.9, 127.6, 127.4, 126.4, 123.8, 122.4, 114.4, 114.3, 109.2, 99.5, 65.1, 56.3, 16.4, 14.7 ppm; HRMS (EI) calcd for $[\text{M} + \text{H}]^+$ $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_5\text{S}$ 395.1429, found 395.1439.

(E)-4-Ethoxy-8-methoxy-N-(4-methoxystyryl)-quinoline-2-carboxamide (24p). Yellow solid, mp 107–110 °C. Yield 84%; IR (cm^{-1}) 3445, 2337, 1669, 1513, 738; ^1H NMR (CDCl_3 , 400 MHz): 10.27 (d, $J = 11.0$ Hz, 1H), 7.83 (d, $J = 8.4$ Hz, 1H), 7.71 (s, 1H), 7.62 (dd, $J_1 = 11.2$ Hz, $J_2 = 14.5$ Hz, 1H), 7.50 (t, $J = 7.9$ Hz, 1H), 7.35–7.33 (m, 2H), 7.11 (d, $J = 7.7$ Hz, 1H), 6.87 (m, 2H), 6.47 (d, $J = 14.6$ Hz, 1H), 4.39 (q, $J = 6.9$ Hz, 2H), 4.09 (s, 3H), 3.80 (s, 3H), 1.59 (t, $J = 6.9$ Hz, 3H) ppm; ^{13}C NMR (CDCl_3 , 100 MHz): δ 163.2, 162.3, 158.9, 155.5, 149.7, 139.8, 129.5, 127.5, 127.1, 123.8, 121.2, 114.7,

114.5, 114.3, 109.2, 99.6, 65.1, 56.3, 55.6, 14.8 ppm; HRMS (EI) calcd for $[M + H]^+$ $C_{22}H_{23}N_2O_4$ 379.1580, found 379.1592.

General Procedure for the Preparation of 24q–24u. To an oven-dried double neck rbf equipped with magnetic stirring bar and substituted quinoline-2-carboxamide (2.47 mmol) in 1,4-dioxane (5 mL) or dry THF (10 mL) were added different (*E*)-styryl bromides (2.47 mmol), CuTC (0.37 mmol), DMEDA (0.49 mmol), and Cs_2CO_3 (6.17 mmol) under argon atmosphere. Then reaction mixture was degassed and backfilled several times with argon before being heated to 100 °C, and the reaction mixture was allowed to reflux for 8–12 h. After consumption of starting material as indicated by thin layer chromatography (TLC), the flask was then cooled to room temperature and filtered through a Celite pad, and the solution was evaporated under reduced pressure followed by column chromatography using 100–200 mesh silica gel with 20% ethyl acetate/exane as eluent to afford the corresponding enamide products **24q–24u** in 72–77% yield.

(E)-4-Methoxy-N-styrylquinoline-2-carboxamide (24q). Yellow solid, mp 128–131 °C. Yield 72%; IR (cm^{-1}) 3617, 1655, 1224, 761; 1H NMR ($CDCl_3$, 600 MHz): δ 10.13 (d, J = 10.9 Hz, 1H), 8.24 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.77–7.70 (m, 3H), 7.59 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 7.4 Hz, 2H), 7.34 (t, J = 7.3 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 6.47 (d, J = 14.5 Hz, 1H), 4.14 (s, 3H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 164.0, 162.0, 150.4, 147.6, 136.4, 130.7, 129.3, 128.8, 127.3, 126.9, 125.8, 122.5, 122.4, 122.2, 114.6, 98.1, 56.4 ppm; HRMS (EI) calcd for $[M + H]^+$ $C_{19}H_{17}N_2O_2$ 305.1290, found 305.1296.

(E)-N-(4-tert-Butylstyryl)-4-methoxyquinoline-2-carboxamide (24r). Yellow solid, mp 142–145 °C. Yield 77%; IR (cm^{-1}) 3628, 1649, 1222, 763; 1H NMR ($CDCl_3$, 600 MHz): 10.10 (d, J = 11.2 Hz, 1H), 8.23 (d, J = 7.9 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 7.76 (t, J = 8.1 Hz, 1H), 7.72–7.67 (m, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.37 (q, J = 8.5 Hz, 4H), 6.45 (d, J = 14.6 Hz, 1H), 4.13 (s, 3H), 1.32 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.9, 161.9, 150.4, 150.0, 147.6, 133.6, 130.6, 129.2, 127.2, 125.8, 125.6, 122.4, 122.2, 121.8, 114.5, 98.0, 56.4, 34.7, 31.4 ppm; HRMS (EI) calcd for $[M + H]^+$ $C_{23}H_{25}N_2O_2$ 361.1838, found 361.1842.

(E)-8-Chloro-N-(4-isopropylstyryl)-4-methoxyquinoline-2-carboxamide (24s). Yellow solid, mp 152–155 °C. Yield 74%; IR (cm^{-1}) 3622, 1661, 1212, 767; 1H NMR ($CDCl_3$, 400 MHz): 10.16 (d, J = 11.1 Hz, 1H), 8.17 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 7.3 Hz, 1H), 7.76 (s, 1H), 7.71 (dd, J_1 = 11.5 Hz, J_2 = 14.3 Hz, 1H), 7.50 (t, J = 7.9 Hz, 1H), 7.38 (m, 2H), 7.21 (m, 2H), 6.47 (d, J = 14.6 Hz, 1H), 4.16 (s, 3H), 2.94 (m, 1H), 1.27 (d, J = 6.8 Hz, 6H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.5, 161.7, 150.8, 148.0, 144.1, 134.0, 133.9, 131.0, 127.2, 127.1, 126.1, 123.9, 121.7, 121.4, 115.2, 98.9, 56.9, 34.1, 24.2 ppm; HRMS (EI) calcd for $[M + H]^+$ $C_{22}H_{22}ClN_2O_2$ 381.1370, found 381.1388.

(E)-N-(4-tert-Butylstyryl)-8-chloro-4-ethoxyquinoline-2-carboxamide (24t). Yellow solid, mp 188–191 °C. Yield 76%; IR (cm^{-1}) 3616, 1654, 1216, 761; 1H NMR ($CDCl_3$, 600 MHz): 10.17 (d, J = 11.3 Hz, 1H), 8.19 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 7.4 Hz, 1H), 7.73 (s, 1H), 7.71 (dd, J_1 = 11.5 Hz, J_2 = 14.5 Hz, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.39 (q, J = 8.4 Hz, 4H), 6.46 (d, J = 14.5 Hz, 1H), 4.41 (q, J = 6.9 Hz, 2H), 1.61 (t, J = 7.1 Hz, 3H), 1.33 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.6, 161.6, 150.6, 150.1, 143.9, 133.6, 133.5, 130.7, 126.9, 125.8, 125.6, 123.8, 121.7, 121.4, 114.9, 99.2, 65.3, 34.7, 31.4, 14.6 ppm; HRMS (EI) calcd for $[M + H]^+$ $C_{24}H_{26}ClN_2O_2$ 409.1683, found 409.1680.

(E)-8-Chloro-4-ethoxy-N-styryl quinoline-2-carboxamide (24u). Yellow solid, mp 152–155 °C. Yield 73%; IR (cm^{-1}) 3618, 1655, 1216, 764; 1H NMR ($CDCl_3$, 600 MHz): 10.17 (d, J = 11.1 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 7.3 Hz, 1H), 7.73–7.69 (m, 2H), 7.48 (t, J = 7.7 Hz, 1H), 7.43 (d, J = 7.5 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.2 Hz, 1H), 6.46 (d, J = 14.5 Hz, 1H), 4.40 (q, J = 6.9 Hz, 2H), 1.60 (t, J = 6.9 Hz, 3H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ 163.6, 161.6, 150.5, 143.9, 136.4, 133.6, 131.6, 130.7, 128.8, 128.1, 126.96, 126.94, 125.9, 123.8, 122.3, 121.4, 121.2, 115.0, 104.4, 99.2, 65.3, 14.6 ppm; HRMS (EI) calcd for $[M + H]^+$ $C_{20}H_{18}ClN_2O_2$ 353.1057, found 353.1051.

■ ASSOCIATED CONTENT

§ Supporting Information

1H and ^{13}C NMR data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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