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

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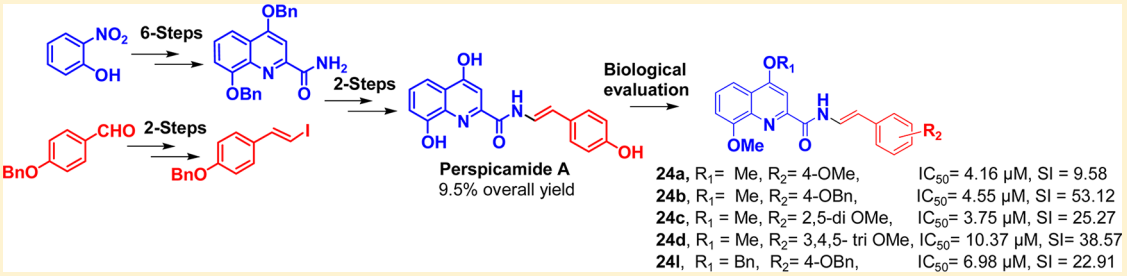
Supporting Information



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 IC_{50} 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 (IC_{50} 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 defficiencies.[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 persipicuum* 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 intermediates[9] is well documented. From a medicinal point of view, macrolactone bearing an enamide side chain, such as salicylihalamide A and B (**3** and **4**, inhibitors of mamalian 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 frangufoline,[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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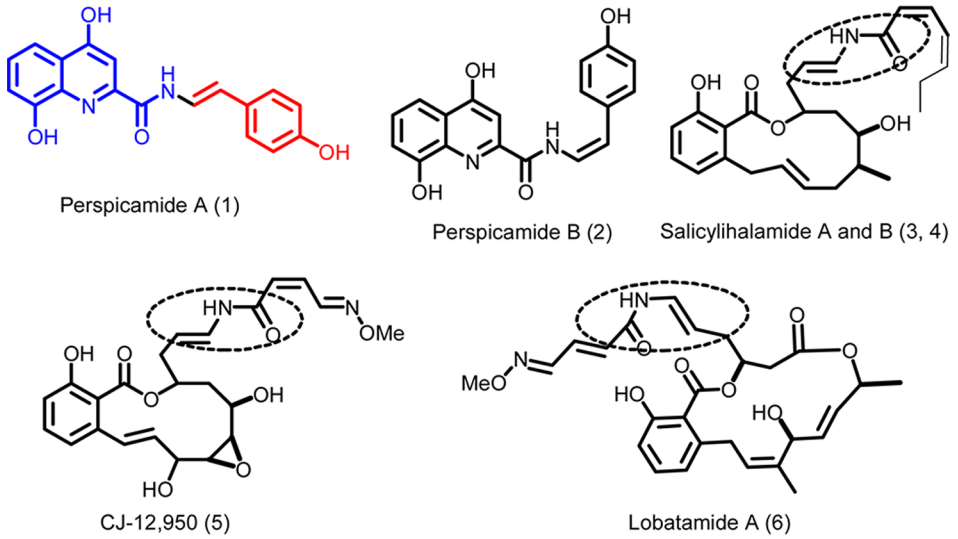


Figure 1. Perspicamide A and B (**1**, **2**) and other biologically significant enamides (**3**–**6**).

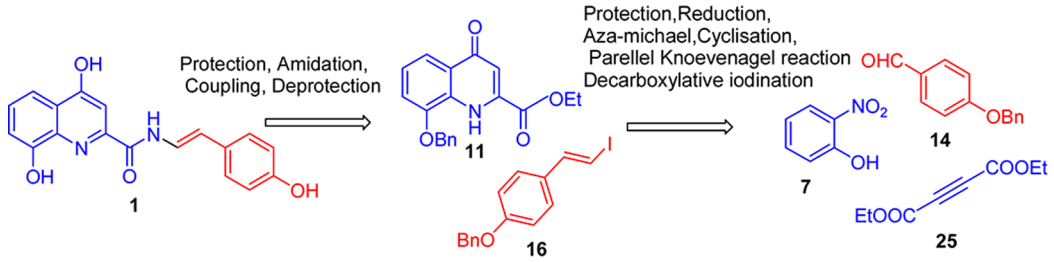
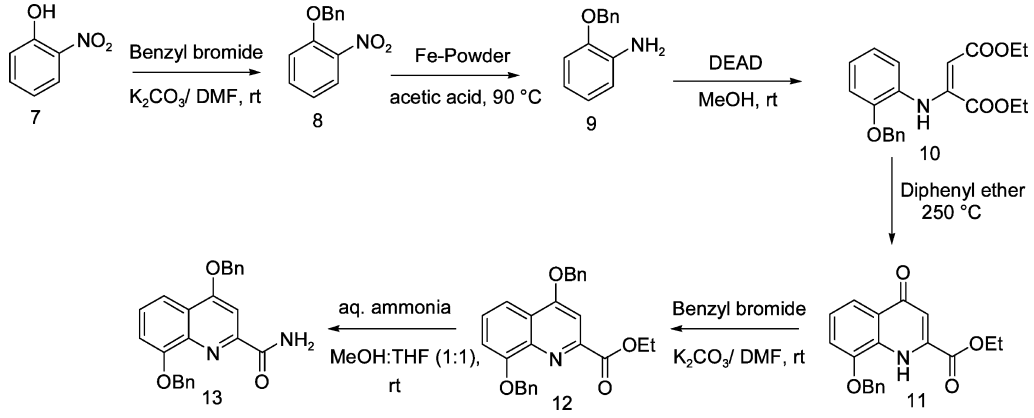


Figure 2. Retrosynthetic analysis of perspicamide A (**1**).

Scheme 1. Synthesis of Quinoline Carboxamide (13)

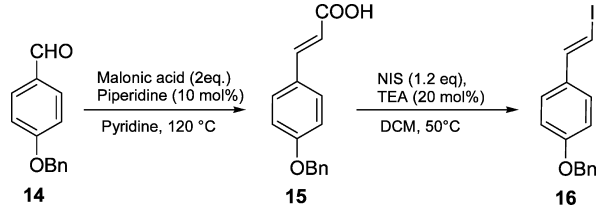


to the formation of perspicamide A (**1**). The counterpart of the excised fragment, e.g., styryl iodide (**16**), is easily accessible, starting from 4-benzyloxy benzaldehyde (**14**).

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

Scheme 2. Synthesis of Styryl Iodide (16)



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

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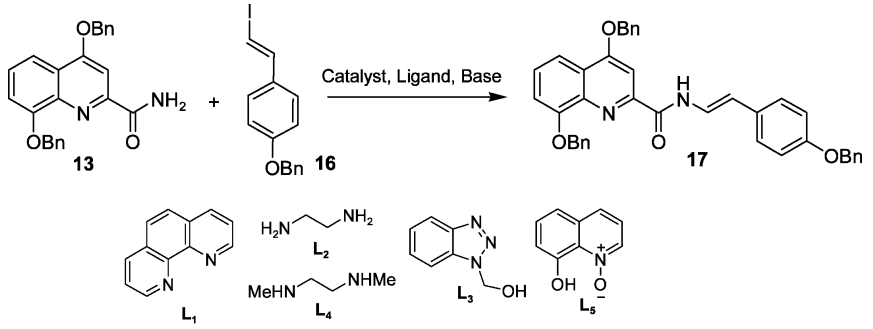
Table 1. Optimization of the Coupling Reaction of Quinoline 2-Carboxamide (13) and Styryl Iodide (16)[a]

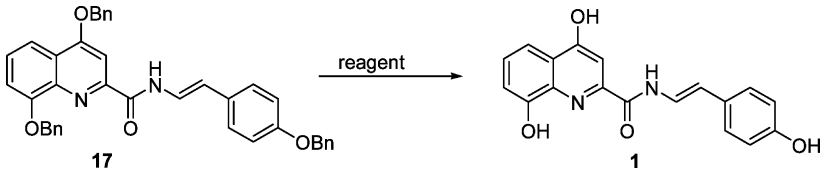


Structure of ligands (L) used

entry	catalyst	L	base	time (h)	yield (%)[b]
1			Cs_2CO_3	15	nr[c]
2	CuI		Cs_2CO_3	15	nr[c]
3	CuI	L_1	Cs_2CO_3	15	trace
4	CuI	L_2	Cs_2CO_3	15	62
5	CuI	L_2	K_2CO_3	15	nr[c]
6	CuI	L_3	Cs_2CO_3	15	trace
7	CuI	L_4	Cs_2CO_3	10	74
8	**Cu_2O**	**L_4**	**Cs_2CO_3**	**8**	**82**
9	CuTC	L_4	Cs_2CO_3	9	76
10	$Cu(OAc)_2$	L_4	Cs_2CO_3	15	15
11	Cu_2O	L_5	Cs_2CO_3	15	nr[c]
12	$Cu(OTf)_2$	L_2	Cs_2CO_3	15	nr[c]

[a]Reaction 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. [b]Isolated yield. [c]No 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	*d*
5	BBr_3	6	DCM	35	60	*d*
6	BCl_3	6	DCM	35	60	32
7	**BCl_3**	**9**	**DCM**	**35**	**60**	**48**
8	BCl_3	12	DCM	35	120	15

[a]Reaction condition: substrate **17** (1.0 equiv), reagent, and solvent (5 mL) under argon atmosphere. [b]Isolated yield. [c]Weight percent used. [d]Mixture 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*-iodosuccinamide (NIS) using 20 mol % Et_3N 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.

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Table 3. Synthesized Perspicamide A Related Analogues[a]

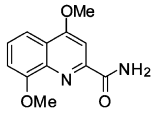
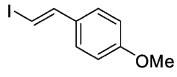
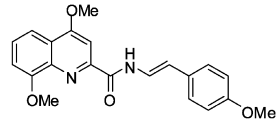
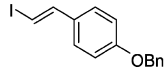
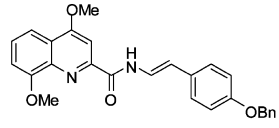
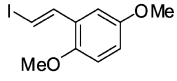
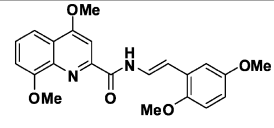
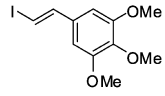
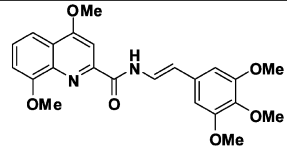
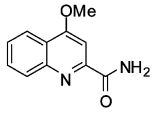
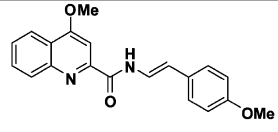
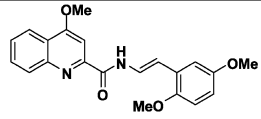
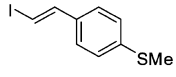
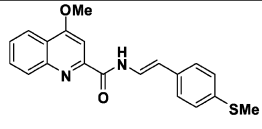
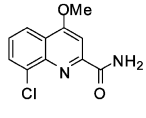
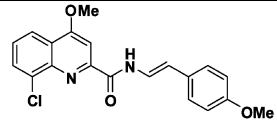
entry	substrate A	substrate B	product	yield (%)[b]
1	 22a	 16a	 24a	88
2	22a	 16b	 24b	78
3	22a	 16c	 24c	84
4	22a	 16d	 24d	88
5	 22b	16a	 24e	81
6	22b	16c	 24f	86
7	22b	 16e	 24g	91
8	 22c	16a	 24h	82

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Table 3. continued

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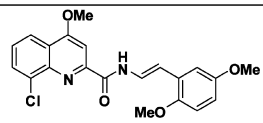
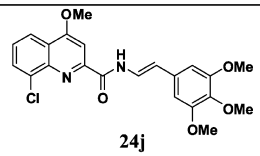
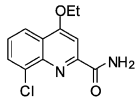
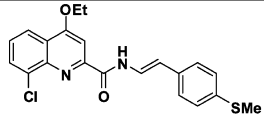
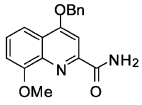
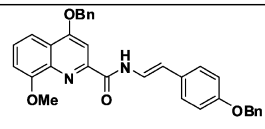
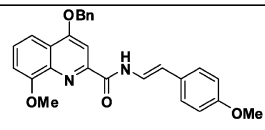
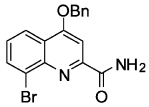
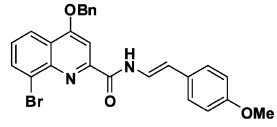
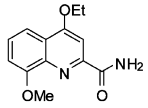
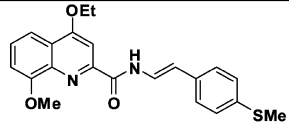
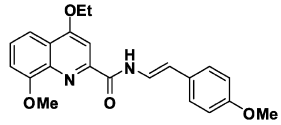
9	22c	16c	 24i	84
10	22c	16d	 24j	88
11	 22d	16e	 24k	86
12	 22e	16b	 24l	75
13	22e	16a	 24m	78
14	 22f	16a	 24n	76
15	 22g	16e	 24o	88
16	22g	16a	 24p	84

[a]Reaction conditions: substrate A (2.47 mmol), substrate B (2.47 mmol), Cu_2O (15 mol %), DMEDA (20 mol %), Cs_2CO_3 (6.17 mmol), and THF (10 mL) under nitrogen atmosphere at 85 °C for 8−10 h. [b]Isolated 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]

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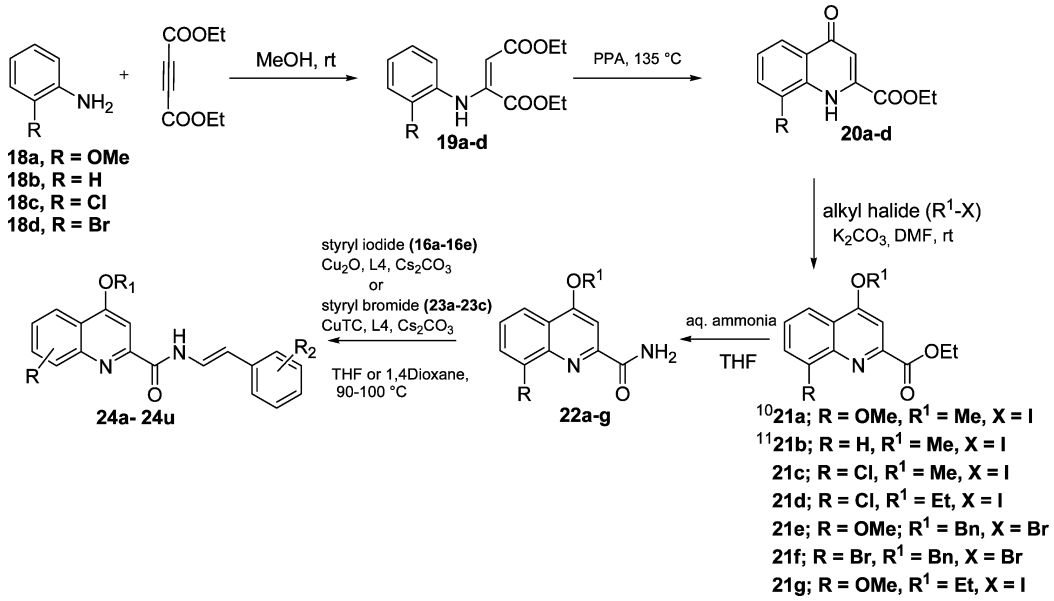
Scheme 3. Synthesis of Perspicamide A Related Analogues 24a−24u



However, during optimization of catalyst, we found that Cu_2O is more effective and economic compared to CuI, along with DMEDA as ligand and Cs_2CO_3 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 BBr_3, Br_2 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 BCl_3 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 ^{13}C 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 funtionalities 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 IC_{50} 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 (IC_{50} 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 (4×10^3 cell/100 μL/well) in RPMI-1640 containing 10% fetal calf serum, and the plates were incubated at 37 °C in a CO_2 incubator. After 24 h, the medium was replaced with fresh medium containing stationary-phase promastigotes (4×10^4/100 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

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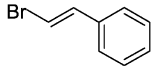
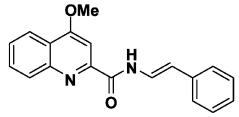
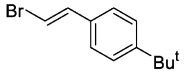
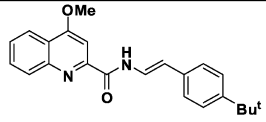
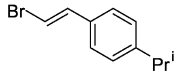
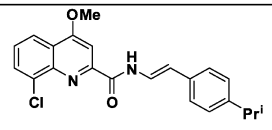
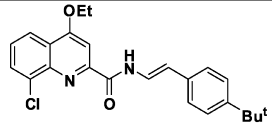
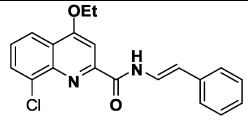
Table 4. Synthesized Perspicamide A Related Analogues via Styryl Bromide Substrate[a]

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

[a]Reaction conditions: substrate C (1.0 mmol), substrate D (1.1 mmol), CuTC (15 mol %), DMEDA (20 mol %), Cs_2CO_3 (2.5 mmol), and THF (10 mL) or 1,4-dioxane (5 mL) under nitrogen atmosphere at 100 °C for 12 h, [b]Isolated yield.

concentration after replacing the previous medium, and the plates were incubated at 37 °C in a CO_2 incubator for 72 h. After incubation, the drug-containing medium was decanted, and 50 μL 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 IC_{50} 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 μL/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 μM concentration and were incubated at 37 °C in a humidified mixture of CO_2 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 μL 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

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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				

[a]MF (Miltefosine) and SSG (Sodium Stibo-gluconate): Standard antileishmanial drugs IC_{50} >15 μM = inactive; IC_{50} > 5−15 μM = moderately active; IC_{50} < 5 μM = active compounds. ND = not done, NA = not available. [b]SI for each compound was calculated as ratio between, CC_{50} and IC_{50} 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. CC_{50} values were estimated as described by Huber and Koella.[35]

General Chemistry. NMR spectra were recorded on 300, 400, or 600 MHz spectrometers for ^{1}H NMR and 50, 75, 100, or 150 MHz for ^{13}C NMR in $CDCl_3$ or DMSO-d_6 with TMS as internal reference wherever mentioned. Chemical shifts (δ) are reported in parts per million (ppm) for ^{1}H and ^{13}C 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, ^{1}H and ^{13}C NMR, IR, and HRMS.

Experimental Procedure for the Synthesis of Fragment 13. 2-(Benzyloxy)nitrobenzene (8). To a stirred solution of 2-nitro phenol (7) (2.0 g, 14.4 mmol) in DMF (5 mL) was added K_2CO_3 (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 Na_2SO_4, 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 Na_2SO_4 and concentrated under reduced pressure, and the crude product was purified by column chromatography using 60−120 mesh silica gel with $CHCl_3$/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; ^{1}H NMR (300 MHz, $CDCl_3$) 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; ^{13}C NMR (50 MHz, $CDCl_3$) 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 $[M + H]^+$ $C_{21}H_{24}NO_5$ 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 $CHCl_3$ 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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; ^{13}C NMR (50 MHz, $CDCl_3$) 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 $[M + H]^+$ $C_{19}H_{18}NO_4$ 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 K_2CO_3 (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 Na_2SO_4, 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; ^{1}H NMR (300 MHz, $CDCl_3$) 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; ^{13}C NMR (75 MHz, $CDCl_3$) 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 $[M + H]^+$ $C_{26}H_{24}NO_4$ 414.1627, found 414.1636.

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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 Na_2SO_4. The crude product was purified by column chromatography using 60−120 mesh silica gel with 1% MeOH/$CHCl_3$ 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, $CDCl_3$) 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; ^{13}C NMR (50 MHz, $CDCl_3$ + 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 $[M + H]^+$ $C_{24}H_{21}N_2O_3$ 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 Et_3N (0.13 mL, 0.84 mmol) over a period of 10 min under argon atmosphere followed by the addition of *N*-iodosuccinamide (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), Cu_2O (0.74 mg, 0.52 mmol), DMEDA (0.074 mL, 0.69 mmol), and Cs_2CO_3 (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, $CDCl_3$) 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; ^{13}C NMR (50 MHz, $CDCl_3$) 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 $[M + H]^+$ $C_{39}H_{33}N_2O_4$ 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 BCl_3 (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/ $CHCl_3$ 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; ^{13}C 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 $[M + H]^+$ $C_{18}H_{15}N_2O_4$ 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, $CDCl_3$) 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; ^{13}C NMR (75 MHz, $CDCl_3$) 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 $[M + H]^+$ $C_{14}H_{17}BrNO_4$ 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 $CHCl_3$ from aqueous solution. The organic layer was dried with Na_2SO_4 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, $CDCl_3$) 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; ^{13}C NMR (50 MHz, $CDCl_3$) 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 $[M + H]^+$ $C_{12}H_{11}BrNO_3$ 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 K_2CO_3 (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 Na_2SO_4 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, $CDCl_3$) 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; ^{13}C NMR (150 MHz, $CDCl_3$) 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 $[M + H]^+$ $C_{13}H_{13}ClNO_3$ 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, $CDCl_3$) 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; ^{13}C NMR (150 MHz, $CDCl_3$) 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 $[M + H]^+$ $C_{14}H_{15}ClNO_3$ 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

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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 $[M + H]^+$ $C_{20}H_{20}NO_4$ 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; ^{1}H 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 $[M + H]^+$ $C_{19}H_{17}BrNO_3$ 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; ^{1}H 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 $[M + H]^+$ $C_{15}H_{18}NO_4$ 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; ^{1}H NMR ($CDCl_3$, 400 MHz): 8.25 (s, 1H), 7.80 (d, J = 8.4, 1H), 7.72 (s, 1H), 7.50 (t, J = 8, 1H), 7.09 (d, J = 7.7, 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, 56.37 ppm; HRMS (EI) calcd for $[M + H]^+$ $C_{12}H_{12}N_2O_3$ 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; ^{1}H 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, $CDCl_3$ + 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 $[M + H]^+$ $C_{11}H_{10}ClN_2O_2$ 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; ^{1}H 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 $[M + H]^+$ $C_{12}H_{12}ClN_2O_2$ 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; ^{1}H NMR (600 MHz, 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, 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 $[M + H]^+$ $C_{18}H_{17}N_2O_3$ 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; ^{1}H 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 $[M + H]^+$ $C_{17}H_{14}BrN_2O_2$ 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; ^{1}H 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 $[M + H]^+$ $C_{13}H_{15}N_2O_3$ 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*-iodosuccinamide (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*-bromosuccinamide (NBS) (4.80 mmol), and the reaction was allowed to run for 15−30 min. Evaporattion 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 sthe olution was evaporated under reduced pressure followed by column chromatography using 100−200 mess 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; ^{1}HNMR ($CDCl_3$, 400 MHz): 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, 2H), 7.12 (d, J = 7.7, 1H), 6.88 (d, J = 8.6, 2H), 6.46 (d, J = 14.6, 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 $[M + H]^+$ $C_{21}H_{21}N_2O_4$ 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; ^{1}HNMR ($CDCl_3$, 300 MHz): 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 $[M + H]^+$ $C_{27}H_{25}N_2O_4$ 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; ^{1}H 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,

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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 $[M + H]^+$ $C_{22}H_{23}N_2O_5$ 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; ^{1}H 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 $[M + H]^+$ $C_{23}H_{25}N_2O_6$ 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; ^{1}HNMR ($CDCl_3$, 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 $[M + H]^+$ $C_{20}H_{19}N_2O_3$ 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; ^{1}HNMR ($CDCl_3$, 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 (CDCl3, 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 $[M + H]^+$ $C_{21}H_{21}N_2O_4$ 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; ^{1}H 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 $[M + H]^+$ $C_{20}H_{19}N_2O_2S$ 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; ^{1}HNMR ($CDCl_3$, 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 $[M + H]^+$ $C_{20}H_{18}ClN_2O_3$ 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; ^{1}HNMR ($CDCl_3$, 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): δ164.1, 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 $[M + H]^+$ $C_{21}H_{20}ClN_2O_4$ 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; ^{1}HNMR ($CDCl_3$, 300 MHz): 10.21 (d, J = 11.1, 1H), 8.20 (d, J = 8.1, 1H), 7.89 (d, J = 7.4, 1H), 7.77 (s, 1H), 7.68 (dd, J_1 = 11.4, J_2 = 14.4, 1H), 7.52 (t, J = 7.9, 1H), 6.65 (s, 2H), 6.43 (d, J = 14.5, 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 $[M + H]^+$ $C_{22}H_{22}ClN_2O_5$ 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; ^{1}H 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 $[M + H]^+$ $C_{21}H_{20}ClN_2O_2S$ 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; ^{1}H 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 $[M + H]^+$ $C_{33}H_{29}N_2O_4$ 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; ^{1}H 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 $[M + H]^+$ $C_{27}H_{25}N_2O_4$ 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; ^{1}H 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 $[M + H]^+$ $C_{26}H_{22}BrN_2O_3$ 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; ^{1}HNMR ($CDCl_3$, 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 $[M + H]^+$ $C_{22}H_{23}N_2O_3S$ 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; ^{1}HNMR ($CDCl_3$, 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,

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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 mess 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; δ ^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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(6) See Supporting Information Table S3 for drug likeness (*Lipinski parameter*) of synthesized molecule calculated via www.molinspiration.com.

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