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Total Synthesis of Pyrrolo[2,3-*c*]quinoline Alkaloid: Trigonoine B

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Abstract

The first total synthesis of pyrrolo[2,3-*c*]quinoline alkaloid trigonoine B (**1**) was accomplished via a six-step sequence involving the construction of an *N*-substituted 4-aminopyrrolo[2,3-*c*]quinoline framework via electrocyclization of 2-(pyrrol-3-yl)benzene containing a carbodiimide moiety as a 2-azahexatriene system. The employed six-step sequence afforded trigonoine B (**1**) in 9.2% overall yield. The described route could be employed for the preparation of various *N*-substituted 4-aminopyrroloquinolines with various biological activities.

Keywords

pyrrolo[2,3-*c*]quinoline; trigonoine B; electrocyclization; 2-azahexatiriene system; carbodiimide

Introduction

In 2011, two novel alkaloids, namely trigonoine A and B, were isolated from the leaves of *Trigonostemon lii* by Hao and co-workers [1]. The structures of the compounds were elucidated through 1D and 2D NMR spectroscopy. It was determined that trigonoine A was a β-carboline alkaloid containing a 2,8-diazabicyclo[3.3.1]nonane ring system, while trigonoine B (**1**) was formed by a combination of 2,3-dihydroquinolin-4-one and 3*H*-pyrrolo[2,3-*c*]quinoline rearranged from a β-carboline skeleton (Fig. 1).

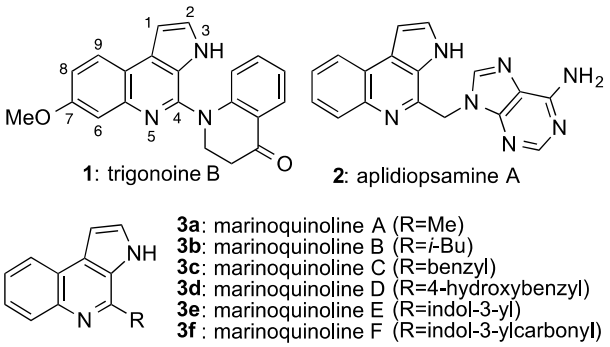


Figure 1: Natural products possessing the pyrrolo[2,3-*c*]quinoline skeleton.

Additionally, the anti-hepatitis B virus (HBV) activity of the alkaloids was evaluated *in vitro* using an HBV-transfected HepG2 cell line. The anti-human immunodeficiency virus (HIV) properties were also investigated to determine whether trigonoine A and B could prevent the cytopathic effects of HIV-1_{IIIB} in C8166 cells. Notably, it was found that both natural products exhibited anti-HIV activity.

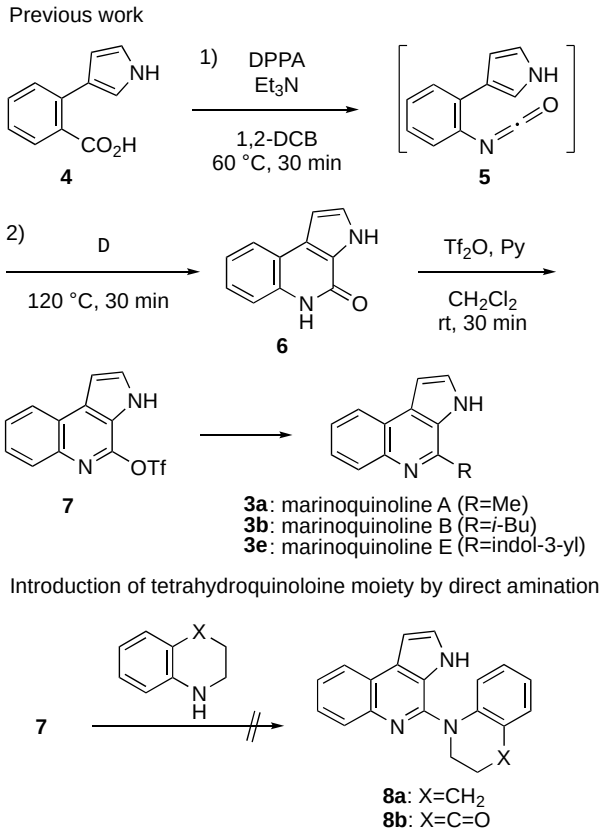
In addition to trigonoine B, aplidiopsamine A [2] (**2**) and marinoquinolines [3] (**3**) are the natural products that possess the pyrrolo[2,3-*c*]quinoline skeleton (Fig. 1). These pyrrolo[2,3-*c*]quinolines have been demonstrated to show antimalarial and

antibacterial biological activities [2,3]. Thus, the development of a convenient and efficient synthetic route to the pyrrolo[2,3-*c*]quinoline skeleton has attracted considerable attention from organic and medicinal chemists. The total syntheses of aplidiopsamine A [4,5] (**2**) and marinoquinolines [5,6] (**3**) have been achieved by various synthetic strategies. Nevertheless, the total synthesis of trigonoine B (**1**) has not yet been reported.

We have been interested in the synthesis of heterocyclic compounds by constructing fused pyridine ring systems based on a thermal electrocyclization of an azahexatriene moiety [7]. It has been hoped that the development of compounds with enhanced biological activity would be possible using these natural products and their derivatives [8]. We have previously reported the total syntheses of indolo[3,2-*c*]quinoline (isocryptolepine) [9], azaanthracenones (kalasinamide, marcanine A, and geovanine) [10], imidazo[4',5':4,5]pyrido[2,3-*b*]indole (grossularine-1 and -2) [11], imidazo[4,5-*b*]pyridine (2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine and 2-amino-1,6-dimethylimidazo[4,5-*b*]pyridine) [12], and imidazo[4,5-*c*]quinoline (imiquimod) [13] based on electrocyclization of 2-azahexatriene involving an isocyanate moiety as the key intermediate.

In addition, we recently reported the total syntheses of marinoquinolines A (**3a**), B (**3b**), and E (**3e**) comprising the pyrrolo[2,3-*c*]quinoline skeleton [14]. As demonstrated in the Scheme 1, Curtius rearrangement of carboxylic acid **4** resulted in the formation of isocyanate **5**, followed by electrocyclization of **5** to furnish pyrrolo[2,3-*c*]quinoline **6**. Intermediate **6** was subsequently transformed into triflate **7**, and the total syntheses of marinoquinolines **3a**, **3b**, and **3e** were accomplished by introducing different substituents at the C4 position. However, despite our efforts to introduce dihydroquinoline derivatives into the triflate **7** using various conditions, the synthesis of

8 could not be achieved. Consequently, we decided to develop a new synthetic strategy for the preparation of trigonoine B (**1**).



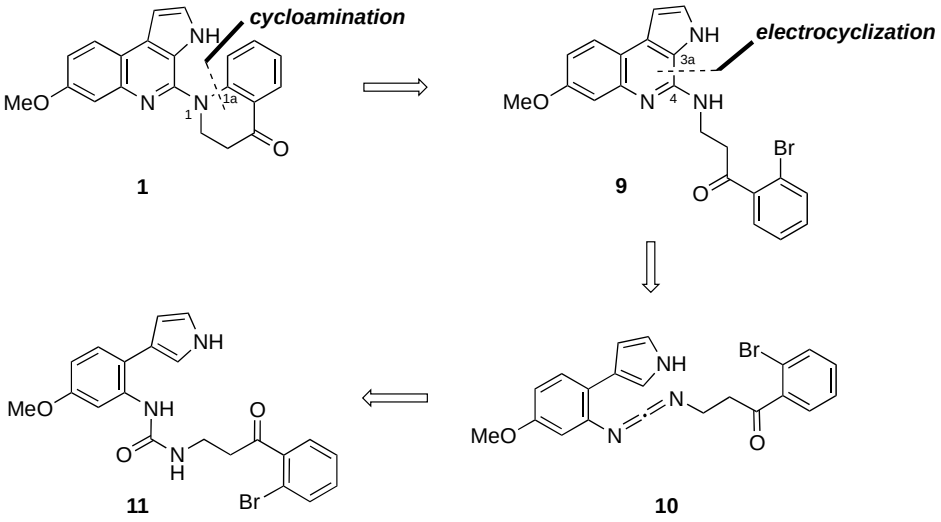
Scheme 1: Total synthesis of marinoquinolines and introduction of tetrahydroquinoline moiety by direct amination to triflate **7**.

Carbodiimides are valuable synthetic intermediates that can be obtained by an aza-Wittig reaction of isocyanates with iminophosphoranes or by dehydration of urea [15]. Molina et al. previously reported the synthesis of 2-aminopyridine derivatives by electrocyclization of conjugated carbodiimides derived from aza-Wittig reaction of iminophosphoranes and isocyanates [16]. We also achieved the preparation of mutagenic amino-α-carbolines 2-amino-9*H*-pyrido[2,3-*b*]indole (AαC) and MeAαC by the electrocyclization of 3-alkenyl-2-carbodiimidoindole derivatives obtained by an aza-Wittig reaction of indol-2-yl iminophosphoranes and isocyanates [17].

In this work, we report the first total synthesis of trigonoine B (**1**) involving the construction of a pyrrolo[2,3-*c*]quinoline framework by electrocyclization of 2-(pyrrol-3-yl)benzene containing a carbodiimide moiety as a 2-azahexatriene system.

Results and Discussion

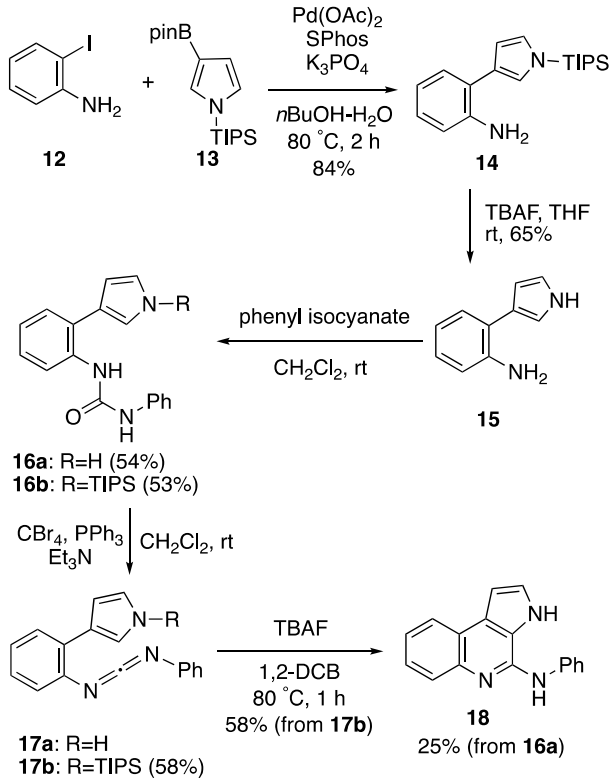
Scheme 2 illustrates the retrosynthetic strategy designed to synthesize triogonoine B (**1**). It was speculated that the dihydroquinoline moiety of trigonoine B (**1**) could be constructed through a cycloamination reaction between positions C1a and N1. The synthesis of precursor pyrroloquinoline **9** possessing a substituted amino group at the 4-position could be achieved by electrocyclization of pyrrol-3-ylbenzene **10** containing a carbodiimide moiety as a 2-azahexatriene system. Lastly, it was proposed that carbodiimide **10** could be derived from urea **11**.



Scheme 2: Retrosynthetic analysis of pyrrolo[2,3-*c*]quinoline ring construction.

Therefore, we investigated the electrocyclization of pyrrol-3-ylbenzene containing a carbodiimide moiety. First, 2-(pyrrol-3-yl)aniline **14** was synthesized by the Suzuki–Miyaura coupling reaction of 2-iodoaniline (**12**) and 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-[tris(1-methylethyl)silyl]-1*H*-pyrrole (**13**) according to Pratt's

conditions (Scheme 3) [18]. Subsequently, to remove the triisopropylsilyl (TIPS) protecting group, **14** was treated with tetra-*n*-butylammonium fluoride (TBAF) in THF, affording aniline **15** in 65% yield. Treatment of **15** with phenyl isocyanate in CH_2Cl_2 gave urea **16a** in 54% yield. To obtain carbodiimide **17a**, **16a** was treated with carbon tetrabromide (CBr_4), PPh_3, and Et_3N in CH_2Cl_2. The reaction was monitored by TLC, which confirmed the complete consumption of the starting material. However, after the work up, extraction, and removal of solvent (in vacuo), the appearance of the TLC plate changed due to the formation of various byproducts. Then, the reaction mixture was purified, but the desired carbodiimide **17a** was not obtained, and an aminopyrroloquinoline **18** in which electrocyclization of **17a** proceeded was afforded in 25% yield. Notably, it was found that electrocyclization of **17a** proceeded easily at low temperature (~60 °C).



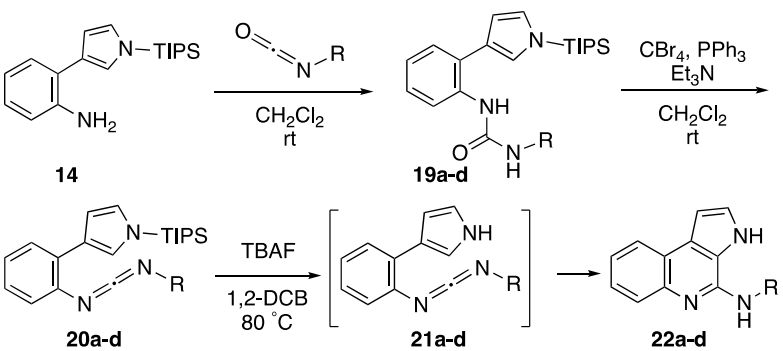
Scheme 3: Synthesis of *N*-substituted 4-aminopyrrolo[3,2-*c*]quinoline **18**.

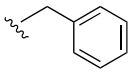
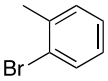
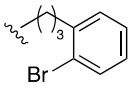
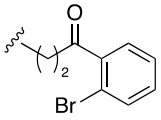
Although we tried to optimize the reaction conditions to improve the yield of **18**, the yield could not be improved owing to the generation of numerous byproducts in the

reaction of **16a** with CBr_4, PPh_3, and Et_3N. Using the same procedure, carbodiimide **17b** was then synthesized in 58% yield starting from aniline **14** via urea **16b**. Based on the above results, it was speculated that the electrocyclization of **17b** would proceed continuously following the removal of the TIPS group. When **17b** was heated with TBAF in 1,2-dichlorobenzene (1,2-DCB) at 80 °C, the expected reaction proceeded and the desired pyrroloquinoline **18** was obtained in 58% yield.

We subsequently examined the versatility of the electrocyclization of carbodiimides **20a**–**d** as 2-azahexatriene systems (Table 1). First, urea derivatives **19a**–**d** were synthesized by reacting 2-(pyrrol-3-yl)aniline **14** with isocyanates, which were commercially available or prepared from an appropriate carboxylic acid through the Curtius rearrangement reaction (50–98% yield). Treatment of urea derivatives **19a**–**d** with CBr_4, PPh_3, and Et_3N afforded carbodiimides **20a**–**d** in 64%–75% yield. Compounds **21a**–**d** were obtained in situ following the removal of the TIPS protecting group in **20a**–**d** by TBAF in 1,2-DCB at 80 °C. The electrocyclization then proceeded immediately, affording the desired pyrroloquinolines **22a**–**c** in 49%–90% yield (entries 1–3). However, the cyclization of **20d** only gave a mixture of unidentified products (entry 4).

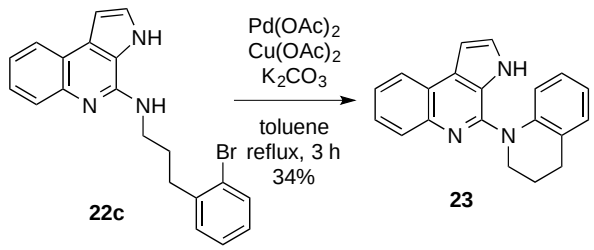
Table 1: Synthesis of *N*-subsutituted 4-aminopyrrolo[3,2-*c*]quinolines **22** by electrocyclization of carbodiimides **20**.



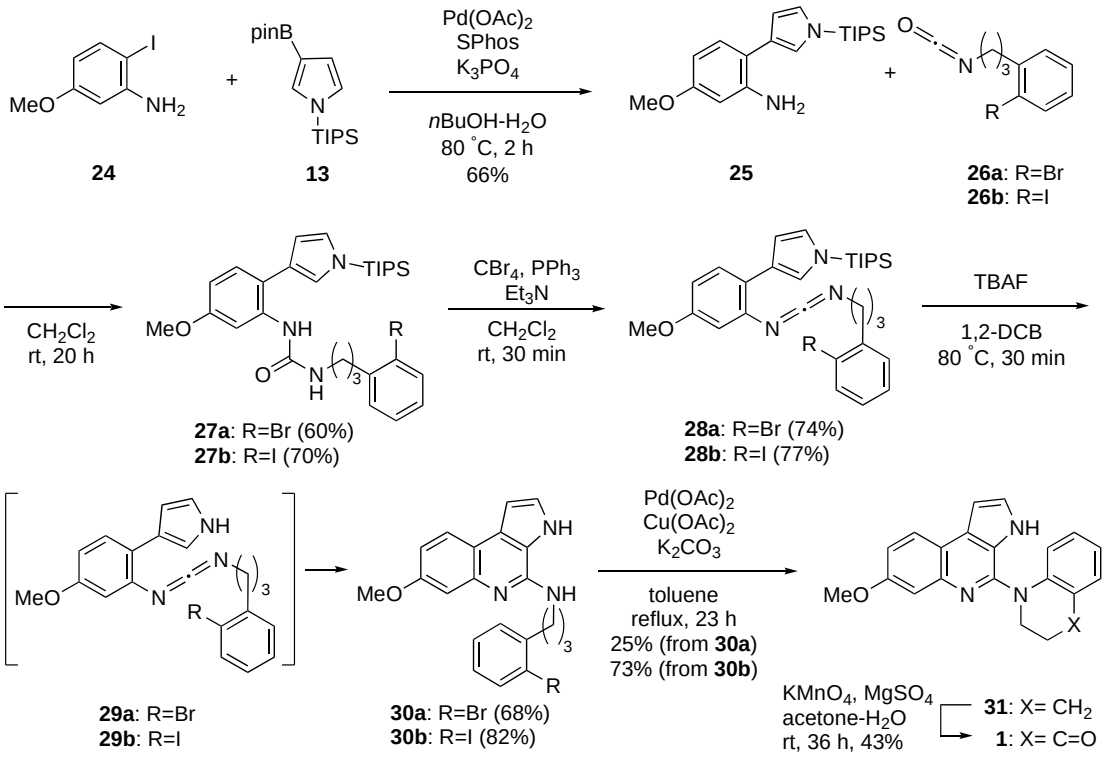
entry	R		19		20		22	
			Time (h)	Yield (%)	Time (h)	Yield (%)	Time (h)	Yield (%)
1		**a**	12	50	4	64	2	90
2		**b**	12	96	1	–[a]	2	49[b]
3		**c**	20	64	2	75	1	61
4		**d**	18	98	0.5	68	1	–[c]

[a] Since the carbodiimide **20b** was unstable, the next reaction was carried out without purification. [b] yield from **19b**. [c] unknown compounds.

Hence, we decided to evaluate the synthesis of 2,3-dihydroquinolin-4-one moiety of trigonoine B (**1**) by cycloamination of **22c** (Scheme 4). The Buchwald–Hartwig amination of **22c** was conducted in the presence of *t*BuONa, BINAP, and $Pd_2(dba)_3.CHCl_3$; however, the desired tetrahydroquinoline **23** was not obtained and only **22c** was recovered. We then examined the conditions reported by Orito and co-workers [19]. The treatment of **22c** with $Pd(OAc)_2$, $Cu(OAc)_2$, and K_2CO_3 afforded **23** in 34% yield.



Scheme 4: Synthesis of tetrahydroquinoline moiety by cycloamination.



Scheme 5: Synthesis of trigonoine B (**1**).

The focus subsequently shifted to the total synthesis of trigonoine B (**1**) (Scheme 5). The key starting material, 2-iodo-5-methoxyaniline (**24**), was synthesized according to the procedure previously reported by Wetzel and co-workers [20]. Suzuki–Miyaura coupling of 2-iodoaniline derivative **24** and pyrrole-3-boronic acid pinacol ester **13** was carried out in the presence of $Pd(OAc)_2$ and SPhos, followed by the treatment of the resulting 2-(pyrrol-3-yl)aniline **25** with 3-(2-bromophenyl)propyl isocyanate **26a**, which afforded urea **27a** in a 60% yield. Treatment of urea **27a** with CBr_4 and PPh_3 in the presence of Et_3N then gave carbodiimide **28a** in a good yield of 74%. Following the reaction of **28a** with TBAF in 1,2-DCB and desilylation, the electrocyclization of **29a** proceeded smoothly to afford the desired 4-aminopyrroloquinoline **30a** in 68% yield. Subsequently, cycloamination of **30a** in the presence of $Pd(OAc)_2$, $Cu(OAc)_2$, and K_2CO_3 gave tetrahydroquinoline **31** in a 25% yield. However, although attempts were

made to optimize the cycloamination reaction conditions, the yield could not be improved. We hypothesized that the low yield could be attributed to be the low reactivity of the bromo group. Thus, the same reaction was performed using a compound bearing a more reactive iodo group.

Accordingly, 4-aminopyrroloquinoline **30b** was synthesized from the 2-(pyrrol-3-yl)aniline **25** and 3-(2-iodophenyl)propyl isocyanate **26b** in 3 steps using same procedures. Subsequently, cycloamination of **30b** gave the tetrahydroquinoline **31** in 73% yield, resulting in a significant improvement in yield.

Finally, the oxidation of tetrahydroquinoline **31** were examined. As a result. Following the evaluation of various reaction conditions [21], the best outcome was obtained upon treatment of **31** with $KMnO_4$ and $MgSO_4$ in an acetone–H_2O solvent system [22]. Employing these conditions, trigonoine B (**1**) was obtained in 43% yield. The acquired physical and spectroscopic data of trigonoine B (**1**) synthesized herein are consistent with those of natural trigonoine B [1]. Thus, in this study, we successfully achieved the first total synthesis of trigonoine B.

Conclusion

The total synthesis of a pyrrolo[2,3-*c*]quinoline alkaloid, trigonoine B (**1**), was achieved for the first time through electrocyclization of 2-(pyrrol-3-yl)benzene bearing a carbodiimide moiety as a 2-azahexatriene system. The employed six-step sequence afforded **1** in 9.2% overall yield. Notably, the developed synthetic route could be used for the synthesis of various *N*-substituted 4-aminopyrroloquinolines. The biological activity of trigonoine B and its derivatives is under evaluation.

Experimental

General Experimental Details. All non-aqueous reactions were carried out under an atmosphere of nitrogen in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Analytical thin-layer chromatography was performed with Silica gel $60PF_{254}$ (Merck). Silica gel column chromatography was performed with Silica gel 60 (70–230 mesh, Kanto Chemical Co. Lit.). All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL AL-300 at 300 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00). Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); quin (quintet); sept (septet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL AL-300 at 75 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0) and DMSO-d_6 (δ 39.7). Infrared spectra were recorded with ATR method using a Shimadzu FTIR-8000 spectrophotometer and Technologies DuraScop. Low and High-resolution mass spectra were recorded on JEOL JMS-700 spectrometers by direct inlet system.

2-(1-Triisopropylsilyl-*1H*-pyrrol-3-yl)aniline (14). A mixture of 2-iodoaniline (**12**) (249 mg, 1.1 mmol), 1-(triisopropylsilyl)-*1H*-pyrrole-3-boronic acid pinacol ester (**13**) (500 mg, 1.4 mmol), K_3PO_4 (485 mg, 2.3 mmol), $Pd(OAc)_2$ (9 mg, 0.04 mmol), and SPhos (33 mg, 0.08 mmol) in *n*-BuOH/H_2O (4 mL/ 2 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The reaction mixture was quenched with water, and then was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc–hexane (1:5 *v*/*v*) as an eluent to give the 2-(pyrrol-3-yl)aniline **14** (248 mg, 84%). Yellow oil; IR (ATR) ν: 3290 cm^{-1}; ^{1}H NMR (300 MHz,

$CDCl_3$) δ 7.25 (dd, *J* = 7.5 and 1.7 Hz, 1H), 7.05 (td, *J* = 7.5 and 1.7 Hz, 1H), 6.95 (dd, *J* = 2.2 and 1.5 Hz, 1H), 6.84 (dd, *J* = 2.8 and 2.2 Hz, 1H), 6.79 (td, *J* = 7.5 and 1.7 Hz, 1H), 6.74 (dd, *J* = 7.5 and 1.7 Hz, 1H), 6.51 (dd, *J* = 2.8 and 1.5 Hz, 1H), 3.93 (br s, 2H), 1.47 (sept, *J* = 7.3 Hz, 3H), 1.13 (d, *J* = 7.3 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 129.7, 126.9, 124.7, 123.8, 122.6, 122.3, 118.6, 115.5, 110.7, 17.8, 11.7; HRMS (EI) *m/z*: [M^+] calcd for $C_{19}H_{30}N_2Si$, 314.2178; found, 314.2180.

2-(*1H*-Pyrrol-3-yl)aniline (15). A solution of TBAF (1.0 M in THF, 0.21 mL, 0.21 mmol) was added dropwise to a solution of 2-(pyrrol-3-yl)aniline **14** (56 mg, 0.178 mmol) in THF (5 mL) at 0 °C under N_2 atmosphere. After stirring at rt for 10 min, the reaction mixture was quenched with water, and then was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated *in vacuo.* The residue was purified by column chromatography using EtOAc-hexane (1:4, *v/v*) as an eluent to give the 2-(1*H*-pyrrol-3-yl)aniline (**15**) (65 mg, 65%). Yellow oil; IR (ATR) ν: 3406 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (br s, 1H) , 7.24 (dd, *J* = 7.5 and 1.7 Hz, 1H), 7.07 (td, *J* = 7.5 and 1.7 Hz, 1H) , 6.98–7.00 (m, 1H), 6.87–6.89 (m, 1H) , 6.79 (td, *J* = 7.5 and 1.7 Hz, 1H), 6.75 (dd, *J* = 7.5 and 1.7 Hz, 1H) , 6.44–6.46 (m, 1H), 3.94 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 129.9, 127.2, 122.2, 121.9, 118.6, 118.4, 116.1, 115.5, 108.7; HRMS (EI) *m/z*: [M^+] calcd for $C_{10}H_{10}N_2$, 158.0844; found, 158.0848.

***N*-Phenyl-*N'*-[2-(1*H*-pyrrol-3-yl)phenyl]urea (16a)**. A solution of phenyl isocyanate (62 µL, 0.57 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of aniline **14** (60 mg, 0.38 mmol) in CH_2Cl_2 (2 mL) at rt under N_2 atmosphere. After stirring at rt for 12 h, the reaction mixture was evaporated *in vacuo.* The residue was purified by column chromatography using EtOAc-hexane (3:7, v/v) as an eluent to give the urea **16a** (57 mg, 54%). White solid; mp: 160–161 °C; IR (ATR) ν: 3325, 3286,1631 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.09 (br s, 1H), 9.17 (s, 1H), 7.81 (dd, *J* = 7.8 and

1.7 Hz, 1H), 7.75 (br s, 1H), 7.44 (dd, *J* = 7.8 and 1.7 Hz, 2H), 7.23–7.32 (m, 3H), 7.14 (td, *J* = 7.8 and 1.7 Hz, 1H), 6.99–7.05 (m, 2H), 6.89–6.95 (m, 2H), 6.27–6.30 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.9, 140.1, 135.1 129.2, 128.8, 127.9, 125.7, 123.0, 122.4, 121.6, 119.5, 118.7, 117.9, 116.7, 107.9; HRMS (EI) *m/z*: [M^+] calcd for $C_{17}H_{15}N_3O$, 277.1215; found, 277.1227.

***N*-Phenyl-*N'*-[2-(1-(triisopropylsilyl)-1*H*-pyrrol-3-yl)phenyl]urea (16b)**. The same procedure as above was carried out using aniline **15** (300 mg, 0.96 mmol) to give the urea **16b** (220 mg, 53%). White solid; mp: 199–201 °C; IR (ATR) ν: 3325, 1651 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.96 (br s, 1H), 7.74 (br s, 1H), 7.61 (dd, *J* = 7.4 and 1.7 Hz, 1H), 7.38–7.44 (m, 3H), 7.23–7.28 (m, 2H), 7.17 (td, *J* = 7.4 and 1.7 Hz, 1H), 7.07–7.12 (m, 2H), 6.91–6.96 (m, 2H), 6.51 (dd, *J* = 2.8 and 1.5 Hz, 1H), 1.48 (sept, *J* = 7.4 Hz, 3H), 1.05 (d, *J* = 7.4 Hz, 18H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.2, 140.1, 134.5, 129.2, 129.0, 128.7, 125.8, 124.90, 124.85, 124.1, 122.9, 122.6, 121.5, 117.8, 110.6, 17.6, 10.9; HRMS (EI) *m/z*: [M^+] calcd for $C_{26}H_{35}N_3OSi$, 433.2549; found, 433.2553.

***N*-Phenyl-*N'*-[2-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)phenyl]carbodiimide (17b)**. A solution of CBr_4 (380 mg, 1.2 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of urea **16b** (100 mg, 0.23 mmol), PPh_3 (303 mg, 1.2 mmol), and Et_3N (0.32 mL, 2.3 mmol) in CH_2Cl_2 (8 mL) at 0 °C. After stirring at rt for 2 h, the reaction mixture was then evaporated *in vacuo*. The residue was washed with EtOAc/hexane (1:4, v/v) at 3 times and the filtrate was evaporated *in vacuo* to give the carbodiimide **17b** (56 mg, 58%). Yellow oil; IR (ATR) ν: 2133 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.70 (m, 1H), 7.51–7.55 (m, 1H), 7.46–7.49 (m, 1H), 7.34 (dd, *J* = 2.2 and 1.5 Hz, 1H), 7.26–7.35 (m, 2H), 7.11–7.17 (m, 4H), 6.80 (dd, *J* = 2.8 and 2.2 Hz, 1H), 6.71 (dd, *J* = 2.8 and 1.5 Hz, 1H), 1.46 (sept, *J* = 7.4 Hz, 3H), 1.12 (d, *J* = 7.4 Hz, 18H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 134.1, 132.1, 130.7, 129.4, 128.8, 128.6, 128.5, 126.2, 125.9, 125.7, 125.0, 124.3, 124.0, 123.0, 110.6, 17.8, 11.7; HRMS (EI) *m/z*: [M^+] calcd for $C_{26}H_{33}N_3Si$, 415.2444; found, 415.2448.

***N*-Phenyl-3*H*-pyrrolo[2,3-*c*]quinolin-4-amine (18)**. A solution of TBAF (1.0 M in THF, 80 µL, 0.080 mmol) was added dropwise to a solution of carbodiimide **17b** (28 mg, 0.067 mmol) in 1,2-dichlorobenzene (2.0 mL) under N_2 atmosphere. After stirring at 80 °C for 1 h, the reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (1:5, v/v) as an eluent to give the pyrroloquinoline **18** (10 mg, 58%). Yellow oil; IR (ATR) ν: 3332 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.8 and 1.5 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.46 (td, *J* = 7.8 and 1.5 Hz, 1H), 7.37 (td, *J* = 7.8 and 1.5 Hz, 1H), 7.28–7.35 (m, 4H), 7.18 (d, *J* = 2.9 Hz, 1H), 7.05–7.09 (m, 1H), 6.95 (d, *J* = 2.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 141.2, 140.9, 129.8, 129.4, 126.5, 125.3, 125.1, 123.7, 123.2, 122.7, 121.5, 121.1, 120.1, 102.1; HRMS (EI) *m/z*: [M^+] calcd for $C_{17}H_{13}N_3$, 259.1109; found, 259.1117.

***N*-Benzyl-*N'*-[2-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)phenyl]urea (19a)**. A solution of benzyl isocyanate (0.29 mL, 2.4 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of 2-(1*H*-pyrrol-3-yl)aniline **14** (500 mg, 1.6 mmol) in CH_2Cl_2 (10 mL) at rt under N_2 atmosphere. After stirring at rt for 12 h, the reaction mixture was evaporated *in vacuo.* The residue was purified by column chromatography using EtOAc-hexane (1:4, v/v) as an eluent to give the urea **19a** (355 mg, 50%). White solid; mp: 136–138 °C; IR (ATR) ν: 3290, 1624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.5 and 1.4 Hz, 1H), 7.39 (dd, *J* = 7.5 and 1.4 Hz, 1H), 7.26–7.32 (m, 3H), 7.19–7.24 (m, 3H), 7.12 (td, *J* = 7.5 and 1.4 Hz, 1H), 6.96 (dd, *J* = 2.0 and 1.6 Hz, 1H), 6.84 (dd, *J* = 2.8 and 2.0 Hz, 1H), 6.46–6.47 (m, 2H), 4.84 (t, *J* = 6.1 Hz, 1H), 4.42 (d, *J* = 6.1 Hz, 1H), 1.45

(sept, *J* = 7.4 Hz, 3H), 1.11 (d, *J* = 7.4 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 139.0, 134.7, 129.1, 129.6, 128.6, 127.5, 127.3, 126.9, 125.2, 124.5, 123.3, 123.0, 122.7, 110.6, 44.3, 17.8, 11.6; HRMS (EI) *m/z*: [M^+] calcd for $C_{27}H_{37}N_3OSi$, 447.2706; found, 447.2714.

***N*-(2-Bromophenyl)-*N'*-[2-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)phenyl]urea (19b)**. The same procedure as above was carried out using aniline **14** (347 mg, 1.11 mmol) to give the urea **19b** (526 mg, 98%). White solid; mp: 99–100 °C; IR (ATR) ν: 3294, 1655 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 7.8 and 1.5 Hz, 1H), 7.77 (dd, *J* = 7.8 and 1.5 Hz, 1H), 7.43–7.48 (m, 2H), 7.28–7.31 (m, 1H), 7.20 (td, *J* = 7.8 and 1.5 Hz, 1H), 6.97–6.99 (m, 2H), 6.91 (td, *J* = 7.8 and 1.5 Hz, 1H), 6.83 (dd, *J* = 2.8 and 2.2 Hz, 1H), 6.68 (br s, 1H), 6.49 (dd, *J* = 2.8 and 1.5 Hz, 1H), 1.45 (sept, *J* = 7.5 Hz, 3H), 1.11 (d, *J* = 7.5 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 136.3, 133.7, 132.5, 132.1, 130.1, 129.8 128.2, 127.0, 125.5, 125.3, 124.2, 124.1, 123.1, 122.5, 121.5, 113.5, 110.7, 17.8, 11.6; HRMS (EI) *m/z*: [M^+] calcd for $C_{26}H_{34}BrN_3OSi$, 511.1655; found, 511.1665.

***N*-[3-(2-Bromophenyl)propyl]-*N'*-[2-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)phenyl] urea (19c)**. To a solution of 4-(2-bromophenyl)butanoic acid (300 g, 1.2 mmol) in toluene (15 mL) was added diphenylphosphoryl azide (0.3 mL, 1.6 mmol) and Et_3N (0.25 mL, 1.8 mmol). After stirring at rt for 30 min, the reaction mixture was evaporated *in vacuo* to give isocyanate as yellow oil. The isocyanate was used in the next reaction without purification. A solution of isocyanate in CH_2Cl_2 (3.0 mL) was added dropwise to a solution of aniline **14** (193 mg, 0.62 mmol) in CH_2Cl_2 (3.0 mL) at rt under N_2 atmosphere. After stirring at rt for 20 h, the reaction mixture was evaporated *in vacuo.* The residue was purified by column chromatography using EtOAc-hexane (1:4, v/v) as an eluent to give the urea **19c** (215 mg, 64%). White solid; mp: 134–135 °C; IR (ATR)

ν: 3294, 1624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 8.0 and 1.1 Hz, 1H), 7.48 (dd, *J* = 8.0 and 1.1 Hz, 1H), 7.42 (dd, *J* = 8.0 and 1.1 Hz, 1H), 7.16–7.26 (m, 3H), 7.14 (td, *J* = 8.0 and 2.2 Hz, 1H), 7.00–7.06 (m, 1H), 6.96 (dd, *J* = 2.9 and 1.5 Hz, 1H), 6.83 (dd, *J* = 2.9 and 2.0 Hz, 1H), 6.49 (dd, *J* = 2.9 and 1.5 Hz, 1H), 6.33 (br s, 1H), 4.64 (t, *J* = 6.0 Hz, 1H), 3.25 (dt *J* = 7.2 and 6.0 Hz, 2H), 2.72 (t, *J* = 7.2 Hz, 2H), 1.78 (quin, *J* = 7.2 Hz, 2H), 1.47 (sept, *J* = 7.5 Hz, 3H), 1.11 (d, *J* = 7.5 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 140.8, 134.7, 132.7, 130.3, 129.62, 129.57, 127.6, 127.5, 126.8, 125.1, 124.7, 124.3, 123.9, 123.0, 122.7, 110.7, 39.7, 33.3, 30.2, 17.8, 11.6; HRMS (EI) *m/z*: [M^+] calcd for $C_{29}H_{40}BrN_3OSi$, 553.2124; found, 553.2128.

***N*-[3-(2-Bromophenyl)-3-oxopropyl]-*N'*-[2-(1-triisopropylsilyl-1*H*-pyrrol-3-yl) phenyl]urea (19d)**. The same procedure as above was carried out using aniline **14** (73 mg, 0.23 mmol) and 4-(2-bromophenyl)-4-oxobutanoic acid (120 mg, 0.47 mmol) to give the urea **19d** (62 mg, 98%). White solid; mp: 121–123 °C; IR (ATR) ν: 3317, 1705, 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.59 (dd, *J* = 8.0 and 1.2 Hz, 1H), 7.35–7.39 (m, 3H), 7.29–7.33 (m, 1H), 7.23 (td, *J* = 8.0 and 1.2 Hz, 1H), 7.11 (td, *J* = 8.0 and 1.2 Hz, 1H), 6.92 (dd, *J* = 2.2 and 1.5 Hz, 1H), 6.84 (dd, *J* = 2.8 and 2.2 Hz, 1H), 6.45 (dd, *J* = 2.8 and 1.5 Hz, 1H), 6.42 (br s, 1H), 5.15 (t, *J* = 6.5 Hz, 1H), 3.63 (dt *J* = 6.5 and 6.1 Hz, 2H), 3.18 (t, *J* = 6.1 Hz, 2H), 1.47 (sept, *J* = 7.5 Hz, 3H), 1.12 (d, *J* = 7.5 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.4, 155.8, 140.8, 134.9, 133.9, 131.8, 129.7, 128.7, 128.5, 127.5, 126.9, 125.3, 124.3, 123.0, 122.8, 122.7, 118.7, 110.7, 42.8, 35.2, 17.8, 11.6; HRMS (EI) *m/z*: [M^+] calcd for $C_{29}H_{38}BrN_3O_2Si$, 567.1917; found, 567.1923.

***N*-Benzyl-*N'*-[2-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)phenyl]carbodiimide (20a)**. A solution of CBr_4 (148 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) was added dropwise to a solution of urea **19a** (100 mg, 0.22 mmol), PPh_3 (117 mg, 0.45 mmol), and Et_3N (0.12

mL, 0.90 mmol) in CH_2Cl_2 (8 mL) at 0 °C. After stirring at rt for 4 h, the reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (1:9, v/v) as an eluent to give the carbodiimide **20a** (62 mg, 64%). Yellow oil; IR (ATR) ν: 2137 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45–7.48 (m, 1H), 7.34–7.36 (m, 4H), 7.28–7.30 (m, 2H), 7.03–7.11 (m, 3H), 6.79 (dd, *J* = 2.8 and 2.1 Hz, 1H), 6.66 (dd, *J* = 2.8 and 1.5 Hz, 1H), 4.52 (s, 2H), 1.47 (sept, *J* = 7.3 Hz, 3H), 1.12 (d, *J* = 7.3 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 136.8, 135.8, 130.3, 128.7, 127.6, 127.5, 127.3, 126.0, 125.2, 125.0, 124.1, 123.2, 110.6, 50.4, 17.9, 11.7; HRMS (EI) *m/z*: [M^+] calcd for $C_{27}H_{35}N_3Si$, 429.2600; found, 429.2610.

***N*-(2-Bromophenyl)-*N'*-[2-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)phenyl]carbodiimide (20b)**. A solution of CBr_4 (119 mg, 0.361 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of urea **19b** (35 mg, 0.072 mmol), PPh_3 (94 mg, 0.36 mmol), and Et_3N (0.1 mL, 0.72 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After stirring at rt for 2 h, the reaction mixture was evaporated *in vacuo* to give the crude carbodiimide **20b**. The carbodiimide **20b** was used in the next reaction without purification, because it was unstable.

***N*-(2-Bromophenyl)-3*H*-pyrrolo[2,3-*c*]quinolin-4-amine (22b).** A solution of TBAF (1.0 M in THF, 86 µL, 0.0864 mmol) was added dropwise to a solution of the crude carbodiimide **20b** in 1,2-dichlorobenzene (3 mL) under N_2 atmosphere. After stirring at 80 °C for 1 h, the reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (3:7, v/v) as an eluent to give the pyrroloquinolin **22b** (12 mg, 49%). Colorless oil; IR (ATR) ν: 2962 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.99 (br s, 1H), 8.33 (br s, 1H), 8.03–8.13 (m, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.60–7.63 (m, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.29–7.46 (m, 3H), 7.03–713 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 142.9, 141.6, 138.1, 132.7, 128.4, 127.8, 126.8,

126.3, 126.0, 125.5, 124.9, 122.54, 122.46, 121.3, 119.4, 116.5, 101.6; HRMS (EI) *m/z*: [M^+] calcd for $C_{17}H_{12}BrN_3$, 337.0215; found, 337.0225.

***N*-[3-(2-Bromophenyl)propyl]-*N'*-[2-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)phenyl] carbodiimide (20c)**. A solution of CBr_4 (1.70 g, 5.1 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of urea **19c** (568 mg, 1.03 mmol), PPh_3 (1.34 g, 5.1 mmol), and Et_3N (1.4 mL, 10.3 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After stirring at rt for 2 h, the reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (1:4, v/v) as an eluent to give the carbodiimide **20c** (411 mg, 75%). Yellow oil; IR (ATR) ν: 2137 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48–7.54 (m, 2H), 7.34 (dd, *J* = 2.0 and 1.5 Hz, 1H), 7.20–7.23 (m, 3H), 7.03–7.14 (m, 3H), 6.79 (dd, *J* = 2.7 and 2.0 Hz, 1H), 6.70 (dd, *J* = 2.7 and 1.5 Hz, 1H), 3.41 (t, *J* = 6.6 Hz, 2H), 2.86 (dt *J* = 6.6 and 6.1 Hz, 2H), 1.95 (t, *J* = 6.1 Hz, 2H), 1.47 (sept, *J* = 7.5 Hz, 3H), 1.13 (d, *J* = 7.5 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 136.3, 135.7, 132.9, 130.5, 130.2, 128.7, 127.8, 127.5, 126.0, 125.0, 124.8, 124.4, 124.0, 123.3, 110.6, 46.1, 33.4, 31.3, 17.8, 11.7; HRMS (EI) *m/z*: [M^+] calcd for $C_{29}H_{38}BrN_3Si$, 535.2018; found, 535.2012.

***N*-[3-(2-Bromophenyl)-3-oxopropyl]-*N'*-[2-(1-triisopropylsilyl-1*H*-pyrrol-3-yl) phenyl] carbodiimide (20d)**. A solution of CBr_4 (443 mg, mmol) in CH_2Cl_2 (5 mL) was added dropwise to a solution of urea **19d** (152 mg, 0.27mmol), PPh_3 (351 mg, 1.34 mmol), and Et_3N (0.4 mL, 2.68 mmol) in CH_2Cl_2 (4 mL) at 0 °C. After stirring at rt for 30 min, the reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (1:9, v/v) as an eluent to give the carbodiimide **20d** (99 mg, 68%). Brown oil; IR (ATR) ν: 2133 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–7.61 (m, 1H), 7.45–7.49 (m, 1H), 7.36–7.41 (m, 1H), 7.28–7.32 (m, 3H), 7.17–7.21 (m, 1H), 7.07–7.13 (m, 2H), 6.79 (dd, *J* = 2.8 and 2.2 Hz, 1H), 6.68 (dd, *J* =

2.8 and 1.5 Hz, 1H), 3.79 (t, *J* = 6.8 Hz, 2H), 3.26 (t *J* = 6.8 Hz, 2H), 1.45 (sept, *J* = 7.6 Hz, 3H), 1.12 (d, *J* = 7.6 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.4, 141.1, 136.1, 135.7, 133.7, 131.8, 130.3, 128.8, 128.7, 127.5, 126.1, 125.3, 125.0, 124.0, 123.2, 118.7, 110.6, 43.8, 41.7, 17.8, 11.7; HRMS (EI) *m/z*: [M^+] calcd for $C_{29}H_{35}BrN_3OSi$, 549.1811; found, 549.1823.

***N*-Benzyl-3*H*-pyrrolo[2,3-*c*]quinolin-4-amine (22a)**. A solution of TBAF (1.0 M in THF, 0.14 mL, 0.14 mmol) was added dropwise to a solution of carbodiimide **19a** (50 mg, 0.12 mmol) in 1,2-dichlorobenzene (10 mL) under N_2 atmosphere. After stirring at 80 °C for 2 h, the reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (1:9, v/v) as an eluent to give the pyrroloquinolin **22a** (26 mg, 90%). Brown solid; mp: 145–146 °C; IR (ATR) ν: 3329 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.06–7.19 (m, 6H), 6.86 (d, *J* = 2.8 Hz, 1H), 4.72 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.9, 142.3, 138.5, 128.8, 128.5, 127.9, 127.3, 126.3, 125.4, 124.8, 122.7, 122.6, 120.5, 119.1, 102.4, 45.6; HRMS (EI) *m/z*: [M^+] calcd for $C_{18}H_{15}N_3$, 273.1266; found, 273.1276.

***N*-[3-(2-bromophenyl)propyl]-3*H*-pyrrolo[2,3-*c*]quinolin-4-amine (22c).** The same procedure as above was carried out using carbodiimide **19c** (102 mg, 0.19 mmol) to give the pyrroloquinoline **22c** (45 mg, 61%). White solid; mp: 158–159 °C; IR (ATR) ν: 3309 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.37 (dd, *J* = 8.3 Hz, 1H), 7.33 (d, *J* = 2.8 Hz, 1H), 7.22–7.27 (m, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.98 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 2.8 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 5.20 (br s, 1H), 3.30 (t, *J* = 7.2 Hz, 2H), 2.29 (t, *J* = 7.2 Hz, 2H), 1.28 (quin, *J* = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 142.6, 140.5, 132.5, 130.1, 128.7, 127.5, 127.3, 126.3, 125.1, 124.8, 124.3, 122.8, 122.4, 120.9,

119.7, 102.5, 41.1, 33.0, 28.7; HRMS (EI) *m/z*: [M^+] calcd for $C_{20}H_{18}BrN_3$, 379.0684; found, 379.0692.

4-[1,2,3,4-Tetrahydroquinolin-1-yl)]-3*H*-pyrrolo[2,3-*c*]quinoline (23). A mixture of pyrrolo[2,3-*c*]quinolin **22c** (38 mg, 0.10 mmol), $Pd(OAc)_2$ (1.12 mg, 5.0 μmol), $Cu(OAc)_2$ (9.1 mg, 50 μmol) and K_2CO_3 (69 mg, 0.50 mmol) in toluene (2.0 mL) was refluxed for 3 h under N_2 atmosphere. The reaction mixture was filtered through Celite pad and the organic layer was evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc–hexane (1:4 v/v) as an eluent to give the tetrahydroquinoline **23** (10 mg, 34%). Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 7.8 and 1.6 Hz, 1H), 8.00 (dd, *J* = 7.8 and 1.6 Hz, 1H), 7.91 (br s, 1H), 7.54 (td, *J* = 7.8 and 1.6 Hz, 1H), 7.45 (td, *J* = 7.8 and 1.6 Hz, 1H), 7.22 (dd, *J* = 7.8 and 1.6 Hz, 1H), 7.14 (t, *J* = 2.8 Hz, 1H), 7.03 (td, *J* = 8.0 and 1.6 Hz, 1H), 6.93–6.98 (m, 2H), 6.75 (dd, *J* = 7.8 and 1.6 Hz, 1H), 4.19 (t, *J* = 6.2 Hz, 2H), 2.92 (t, *J* = 6.2 Hz, 2H), 1.12 (quin, *J* = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 142.8, 141.2, 130.1, 129.2, 129.1, 127.6, 126.3, 126.2, 124.4, 123.9, 122.5, 122.0, 121.9, 121.7, 118.7, 101.6, 47.3, 27.5, 24.1; HRMS (EI) *m/z*: [M^+] calcd for $C_{20}H_{17}N_3$, 299.1422; found, 299.1432.

5-Methoxy-2-(1-triisopropylsilyl-*1H*-pyrrol-3-yl)aniline (25). A mixture of 2-iodo-5-methoxyaniline (**24**) (249 mg, 1.1 mmol), 1-(triisopropylsilyl)-*1H*-pyrrole-3-boronic acid pinacol ester (**13**) (500 mg, 1.4 mmol), K_3PO_4 (486 mg, 2.3 mmol), $Pd(OAc)_2$ (13 mg, 57 μmol), and SPhos (47 mg, 114 μmol) in *n*-BuOH/H_2O (6 mL/3 mL) was stirred at 80 °C for 2 h under N_2 atmosphere. The reaction mixture was quenched with water, and then the mixture was extracted with EtOAc. The EtOAc layer was washed with water and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc–hexane (1:4 *v*/*v*) to give the 2-(pyrrol-3-yl)aniline **25** (227 mg, 66%). Brown oil; IR (ATR) ν: 2943 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17

(d, *J* = 8.3 Hz, 1H), 6.87-6.89 (m, 1H), 6.83 (t, *J* = 2.5 Hz, 1H), 6.44-6.46 (m, 1H), 6.35–6.40 (m, 2H), 3.78 (s, 3H), 1.47 (sept, *J* = 7.6 Hz, 3H), 1.12 (d, *J* = 7.6 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 144.6, 130.5, 124.6, 123.4, 121.9, 115.8, 110.7, 104.0, 101.0, 55.1, 17.8, 11.6; HRMS (EI) *m/z*: [M^+] calcd for $C_{19}H_{30}N_2Si$, 314.2178; found, 314.2184.

***N*-[3-(2-Bromophenyl)propyl]-*N'*-[5-methoxy-2-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)phenyl] urea (27a)**. To a solution of 4-(2-bromophenyl)butanoic acid (620 mg, 2.6 mmol) in toluene (15 mL) was added diphenylphosporyl azide (0.70 mL, 3.3 mmol) and Et_3N (0.50 mL, 3.4 mmol). After stirring at rt for 30 min, the reaction mixture was evaporated *in vacuo* to give isocyanate as yellow oil. The isocyanate was used in the next reaction without purification. A solution of the isocyanate in CH_2Cl_2 (11 mL) dropwise to a solution of aniline **25** (438 mg, 1.3 mmol) in CH_2Cl_2 (10 mL) at rt under N_2 atmosphere. After stirring at rt for 20 h, the reaction mixture was evaporated *in vacuo.* The residue was purified by column chromatography using EtOAc-hexane (1:4, v/v) as an eluent to give the urea **27a** (448 mg, 60%). White solid; mp: 117–118 °C; IR (ATR) ν: 3298, 1631 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.3 Hz, 1H), 7.45 (d, *J* = 2.6 Hz, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 7.17–7.21 (m, 2H), 7.00–7.06 (m, 1H), 6.86 (t, *J* = 1.5 Hz, 1H), 6.82 (t, *J* = 2.6 Hz, 1H), 6.68 (dd, *J* = 8.3 and 2.6 Hz, 1H), 6.55 (br s, 1H), 6.41 (dd, *J* = 2.6 and 1.5 Hz, 1H), 4.69 (br s, 1H), 3.83 (s, 3H), 3.22–3.26 (m, 2H), 2.73 (t, *J* = 7.5 Hz, 2H), 1.78 (quin, *J* = 7.5 Hz, 2H) 1.46 (sept, *J* = 7.4 Hz, 3H), 1.11 (d, *J* = 7.4 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 155.7, 140.7, 136.1, 132.7, 130.4, 130.3, 127.7, 127.5, 125.1, 124.3, 122.6, 122.4, 120.9, 110.6, 110.3, 107.5, 55.4, 39.8, 33.3, 30.2, 17.8, 11.6; HRMS (EI) *m/z*: [M^+] calcd for $C_{30}H_{42}BrN_3O_2Si$, 583.2230; found, 583.2237.

***N*-[3-(2-Iodophenyl)propyl]-*N'*-[5-methoxy-2-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)phenyl] urea (27b)**. The same procedure as above was carried out using aniline **25** (50 mg, 0.145 mmol) and 4-(2-bromophenyl)butanoic acid (105 mg, 0.362 mmol) to give the urea **27b** (66 mg, 70%). White solid; mp: 124–125 °C; IR (ATR) ν: 3275, 1624 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 7.8 and 1.2 Hz, 1H), 7.46 (d, *J* = 2.8 Hz, 1H), 7.26–7.28 (m, 1H), 7.20 (td, *J* = 7.8 and 1.2 Hz, 1H), 6.82–6.89 (m, 3H), 6.68 (dd, *J* = 8.3 and 2.8 Hz, 1H), 6.48 (br s, 1H), 6.42 (dd, *J* = 2.5 and 1.3 Hz, 1H), 4.65 (t, *J* = 5.8 Hz, 1H), 3.83 (s, 3H), 3.27 (dt, *J* = 7.9 and 5.8 Hz, 2H), 2.72 (t, *J* = 7.9 Hz, 1H), 1.76 (quin, *J* = 7.9 Hz, 2H) 1.46 (sept, *J* = 7.8 Hz, 3H), 1.11 (d, *J* = 7.8 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 155.7, 144.0, 139.4, 136.1, 130.4, 129.4, 128.4, 127.8, 125.1, 122.6, 122.4, 121.0, 110.7, 110.3, 107.6, 100.5, 55.4, 39.8, 38.0, 30.6, 17.8, 11.6; HRMS (EI) *m/z*: [M^+] calcd for $C_{30}H_{42}IN_3O_2Si$, 631.2091; found, 631.2097.

***N*-[3-(2-Bromophenyl)propyl]-*N'*-[5-methoxy-2-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)phenyl] carbodiimide (28a)**. A solution of CBr_4 (1.53 g, 4.6 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of urea **27a** (540 mg, 0.92 mmol), PPh_3 (1.21 g, 4.6 mmol), and Et_3N (1.3 mL, 9.2 mmol) in CH_2Cl_2 (21 mL) at 0 °C. After stirring at rt for 30 min, the reaction mixture was evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (1:4, v/v) as an eluent to give the carbodiimide **28a** (387 mg, 74%). Yellow oil; IR (ATR) ν: 2866 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.20–7.22 (m, 3H), 7.03–7.08 (m, 1H), 6.77 (dd, *J* = 2.8 and 1.5 Hz, 1H), 6.76 (d, *J* = 2.5 Hz, 1H), 6.69 (dd, *J* = 8.5 and 2.7 Hz, 1H), 6.63 (dd, *J* = 2.8 and 1.5 Hz, 1H), 3.83 (s, 3H), 3.39 (t, *J* = 7.9 Hz, 2H), 2.85 (t, *J* = 7.5 Hz, 2H), 1.94 (quin, *J* = 7.5 Hz, 2H), 1.46 (sept, *J* = 7.4 Hz, 3H), 1.12 (d, *J* = 7.4 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 140.4, 137.2, 135.2, 132.8, 130.5, 129.5, 127.7, 127.4, 124.3, 123.8, 123.4, 123.1, 123.0, 110.9, 110.5,

109.9, 55.3, 45.9, 33.3, 31.2, 17.8, 11.6; HRMS (EI) *m/z*: [M^+] calcd for $C_{30}H_{40}BrN_3OSi$, 565.2124; found, 565.2128.

***N*-[3-(2-Iodophenyl)propyl]-*N'*-[5-methoxy-2-(1-triisopropylsilyl-1*H*-pyrrol-3-yl)phenyl] carbodiimide (28b)**. The same procedure as above was carried out using the urea **27b** (350 mg, 0.56 mmol) to give the carbodiimide **28b** (262 mg, 77%). Yellow oil; IR (ATR) ν: 2133 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 7.8 and 1.4 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 7.25 (s, 1H), 7.20–7.22 (m, 2H), 6.88 (td, *J* = 7.8 and 1.4 Hz, 1H), 6.78 (t, *J* = 8.5 Hz, 1H), 6.75 (d, *J* = 2.8 Hz, 1H), 6.69 (dd, *J* = 8.5 and 2.7 Hz, 1H), 6.62 (dd, *J* = 2.8 and 1.5 Hz, 1H), 3.80 (s, 3H), 3.40 (t, *J* = 6.6 Hz, 2H), 2.83 (t, *J* = 6.6 Hz, 1H), 1.91 (quin, *J* = 6.6 Hz, 2H) 1.46 (sept, *J* = 7.6 Hz, 3H), 1.12 (d, *J* = 7.6 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 143.7, 139.6, 137.3, 135.2, 129.63, 129.58, 128.4, 127.9, 123.9, 123.5, 123.2, 123.0, 111.0, 110.5, 110.0, 100.4, 55.4, 46.0, 37.9, 31.6, 17.9, 11.7; HRMS (EI) *m/z*: [M^+] calcd for $C_{30}H_{40}IN_3OSi$, 613.1985; found, 613.1990.

***N*-[3-(2-Bromophenyl)propyl]-7-methoxy-3*H*-pyrrolo[2,3-*c*]quinolin-4-amine (30a)**. A solution of TBAF (1.0 M in THF, 0.6 mL, 0.60 mmol) was added dropwise to a solution of carbodiimide **28a** (281 mg, 0.50 mmol) in 1,2-dichlorobenzene (25 mL) under N_2 atmosphere. After stirring at 80 °C for 30 min, the reaction mixture evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (3:2, v/v) as an eluent to give the pyrroloquinoline-4-amine **30a** (138 mg, 68%). Yellow oil; IR (ATR) ν: 3309 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.5 Hz, 1H), 7.48 (dd, *J* = 8.0 and 1.3 Hz, 1H), 7.29 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 2.8 Hz, 1H), 7.14 (td, *J* = 7.6 and 1.1 Hz, 1H), 7.04–7.08 (m, 2H), 6.94 (dd, *J* = 8.5 and 2.4 Hz, 1H), 6.85 (d, *J* = 2.8 Hz, 1H), 3.85 (s, 3H), 3.62 (t, *J* = 7.2 Hz, 2H), 2.70 (t, *J* = 7.2 Hz, 1H), 1.83 (quin, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 147.6, 143.4, 140.4, 132.5,

130.0, 129.0, 127.4, 127.2, 125.4, 124.3, 123.9, 118.6, 114.9, 112.2, 106.3, 101.9, 55.3, 41.2, 33.0, 28.6; HRMS (EI) *m/z*: [M^+] calcd for $C_{21}H_{20}BrN_3O$, 409.0790; found, 409.0791.

***N*-[3-(2-Iodophenyl)propyl]-7-methoxy-3*H*-pyrrolo[2,3-*c*]quinolin-4-amine (30b)**. The same procedure as above was carried out using the carbodiimide **28b** (40 mg, 0.065 mmol) to give the pyrroloquinoline-4-amine **30b** (24 mg, 82%). Yellow oil; IR (ATR) ν: 3313 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.29 (d, *J* = 2.8 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.91 (dd, *J* = 8.7 and 2.4 Hz, 1H), 6.83 (d, *J* = 2.8 Hz, 1H), 6.79 (t, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 5.46 (br s, 1H), 3.77 (s, 3H), 3.36 (t, *J* = 7.6 Hz, 2H), 2.32 (t, *J* = 7.6 Hz, 1H), 1.36 (quin, *J* = 7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 147.4, 143.83, 143.76, 139.3, 129.3, 129.0, 128.2, 127.7, 125.1, 123.8, 118.7, 115.0, 112.4, 106.6, 102.1, 100.6, 55.3, 41.2, 37.9, 29.3; HRMS (EI) *m/z*: [M^+] calcd for $C_{21}H_{20}IN_3O$, 457.0651; found, 457.0653.

7-Methoxy-4-(1,2,3,4-tetrahydroquinolin-1-yl)-3*H*-pyrrolo[2,3-*c*]quinoline (31). A mixture of pyrroloquinoline-4-amine **30a** (147 mg, 0.36 mmol), $Pd(OAc)_2$ (4.0 mg, 0.018 mmol), $Cu(OAc)_2$ (33 mg, 0.18 mmol) and K_2CO_3 (248 mg, 1.8 mmol) in toluene (7 mL) was refluxed for 23 h under N_2 atmosphere. The reaction mixture was filtered through Celite pad and the organic layer was evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc–hexane (1:4 *v*/*v*) as an eluent to give the tetrahydroquinoline **31** (30 mg, 25%). Yellow solid; mp: 159–160 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.8 Hz, 1H), 7.82 (br s, 1H), 7.42 (d, *J* = 2.8 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 2.8 Hz, 1H), 7.10 (t, *J* = 2.8 Hz, 1H), 7.02 (td, *J* = 7.8 and 1.9 Hz, 1H), 6.95 (td, *J* = 7.2 and 1.3 Hz, 1H), 6.87–6.88 (m, 1H), 6.74 (dd, *J* = 8.8 and 1.9 Hz, 1H), 4.17 (t, *J* = 6.2 Hz, 2H), 3.95 (s, 3H), 2.91 (t, *J* = 6.2 Hz, 2H), 2.11

(sept, *J* = 6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 145.4, 144.2, 141.2, 130.5, 129.2, 129.0, 126.3 124.7, 123.5, 121.6, 121.1, 118.7, 116.1, 115.3, 107.6, 101.1, 55.4, 47.3, 27.5, 24.0; HRMS (EI) *m/z*:[M^+] calcd for $C_{21}H_{19}N_3O$, 329.1528; found, 329.1533.

Synthesis of 31 from 30b. The same procedure as above was carried out using the pyrroloquinoline-4-amine **30b** (90 mg, 0.196 mmol) to give the tetrahydroquinoline **31** (47 mg, 73%).

Trigonoine B (1). To a solution of tetrahydroquinoline **31** (27 mg, 0.082 mmol) in acetone (0.5 mL) at 0 °C was added anhydrous $MgSO_4$ (25 g, 0.21 mmol) and H_2O (0.2 mL). Subsequently, $KMnO_4$ (54 mg, 0.45 mmol) was added in small portions over 30 min. After stirring at rt for 36 h, the reaction mixture was quenched with a saturated solution of $K_2S_2O_5$. The reaction mixture was filtered through Celite pad, and washed with CH_2Cl_2 and H_2O. The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography using EtOAc-hexane (1:5, v/v) to give trigonoine B (**1**) (12 mg, 43 %). Yellow solid; mp: 277–278 °C; IR (ATR) ν: 1674 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.63 (br s, 1H), 8.20 (d, *J* = 8.8 Hz, 1H), 7.88 (dd, *J* = 7.8 and 1.7 Hz, 1H), 7.51–7.54 (m, 1H), 7.36 (d, *J* = 2.6 Hz, 1H), 7.27 (td, *J* = 7.8 and 1.7 Hz, 1H), 7.19 (dd, *J* = 8.8 and 2.6 Hz, 1H), 7.09 (dd, *J* = 2.9 and 2.0 Hz, 1H), 6.92 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 4.21 (t, *J* = 7.0 Hz, 2H), 3.88 (s, 3H), 2.89 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 193.5, 157.8, 149.2, 144.5, 143.5, 134.7, 134.7, 130.5, 128.0, 127.2, 124.1, 122.7, 121.0, 119.4, 117.1, 116.3, 116.2, 108.1, 101.0, 55.2, 48.3; HRMS (EI) *m/z*:[M^+] calcd for $C_{21}H_{17}N_3O_2$, 343.1321; found, 343.1327.

Supporting Information

Supporting Information File 1: ^{1}H NMR and ^{13}C NMR spectra of all new compounds.

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