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Article

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The Povarov reaction of cycloiminium formed *in situ* via hydroamination cycloisomerization of homopropargylic amines with electron-rich olefins

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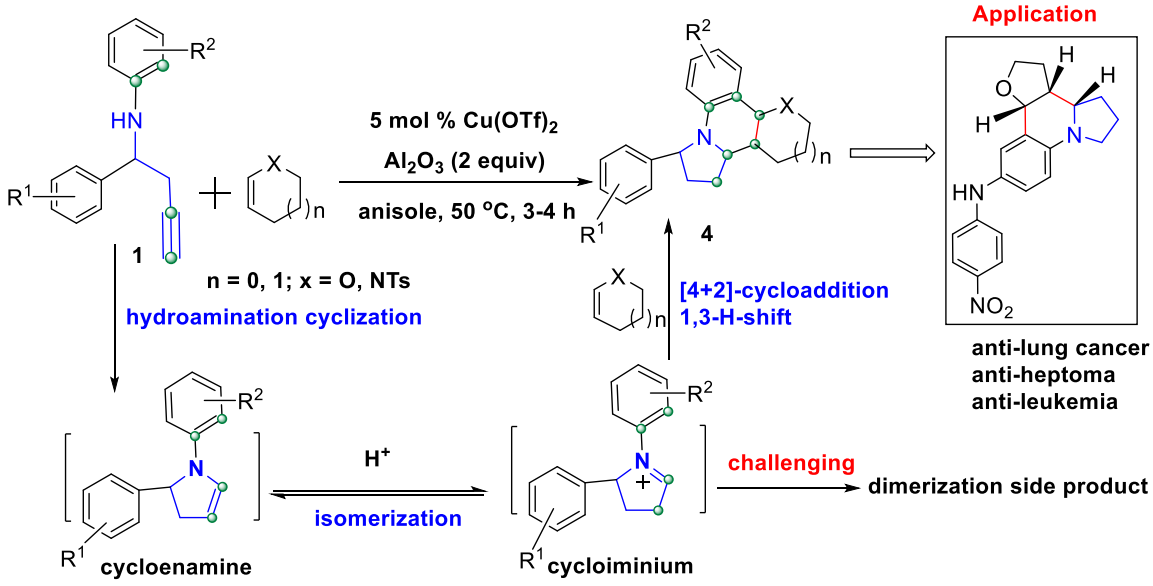


ABSTRACT

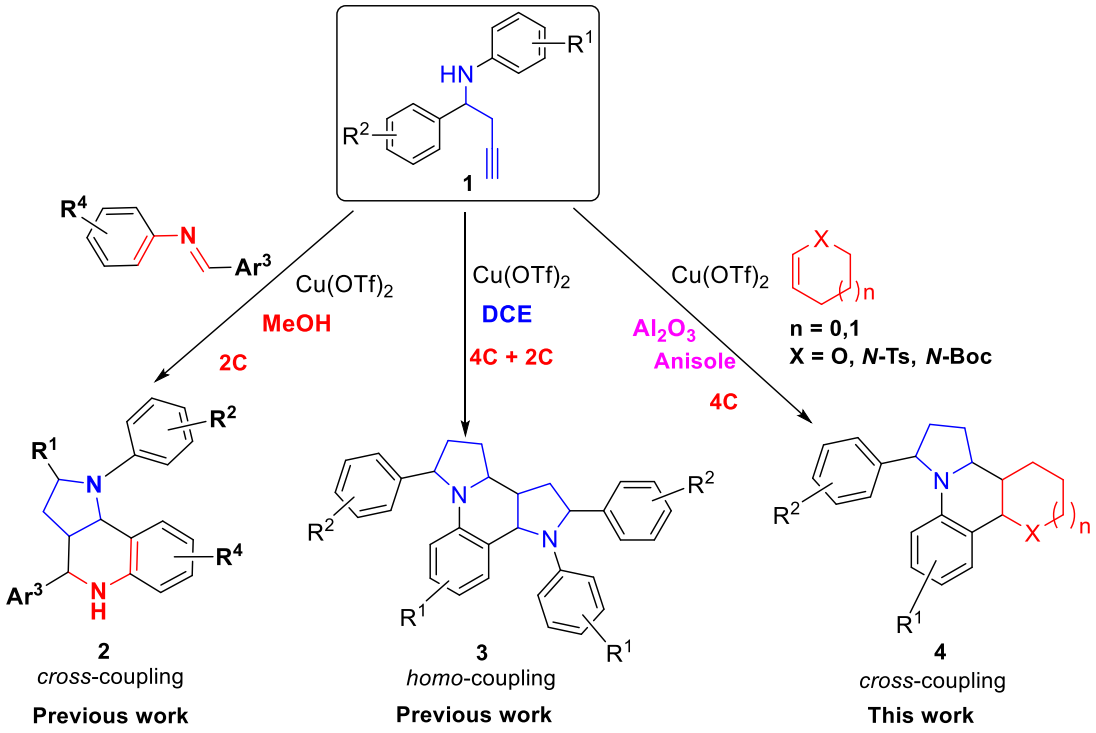
A new one pot cascade reaction of homopropargylic amines with electron-rich olefins is developed in the presence of $Cu(OTf)_2$, and affords a series of octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline derivatives in yields of 38 to 80%. This reaction proceeds through an intramolecular hydroamination cyclization of homopropargylic amine, to generate a highly reactive cycloenamine intermediate *in situ*, which subsequently isomerizes to cycloiminium cation, and followed by the Povarov-type reaction with dihydrofuran, dihydropyran or dihydropyrrole. Notably, the Al_2O_3 additive plays a key role for the effective inhibition of competitive *self*-dimerization of homoproargylic amines.

INTRODUCTION

The Povarov reaction of *N*-arylimines with electron-rich olefins, an inverse electron-demand *aza*-Diels-Alder (IEDDA), has been extensively explored.[1] For the *N*-arylimines, various strategies have been developed to access them, including cyclic amines. For example, a typical condensation *in situ* or preparation in advance from aldehydes (or ketones) and aromatic amines,[2] or oxidation *in situ* of *N*-arylamines with active α-H,[3] or reduction of nitrobenzene derivatives.[4] The former is the most classical and has been widely used to comprise two-component methods or three-component approaches. As a comparison, the latter two tactics were sparse. Especially, cycloiminium or oxidation of cyclic amine enables the formation of polycyclic compounds.[5] Therefore, it is highly

desirable to develop novel *N*-arylimine equivalents or precursors as dienes in the Povarov reaction for the construction of diverse tetrahydroquinoline derivatives, which are ubiquitous scaffolds with a wide range of biological activities such as antifungal, antimicrobial, anti-HIV, antibacterial, anti-inflammatory and anticancer.[6] Our research group has developed several cascade reactions of simple homopropargylic amines. It was found that the homopropargylic amines could act as potential both **2C** and **4C** synthons. Moreover, the dual roles of **4C** and **2C** synthons or a single role of **2C** synthon has been realized with the addition of other appropriate substrate molecules, respectively (Scheme 1).[7] Based on these results, we envisioned that the single **4C** synthon identity may be also accessible. In fact, to achieve a single **4C** synthon role of the homopropargylic amine, it is full of great challenging and more difficult than the single **2C** synthon role-play. It is because that once cycloiminium cation is generated through isomerization of cycloenamine formed *in situ* via an intramolecular hydroamination cyclization of homopropargylic amine, it will inevitably react with its isomer cycloenamine to give a *formal* dimerized compound. In spite of this, we believe that this competitive side reaction can be reduced as low as possible through controlling the reaction conditions or introducing additional higher reactivity substrates. Thus, the electron-rich cyclic alkenes were herein employed to react with homopropargylic amines. To our delight, we could obtain the expected cycloaddition product **4** in good yields through the great amount of experimental parameters screenings (Scheme 1, this work).

Scheme 1. The diverse reactions of homopropargylic amines



RESULTS AND DISCUSSION

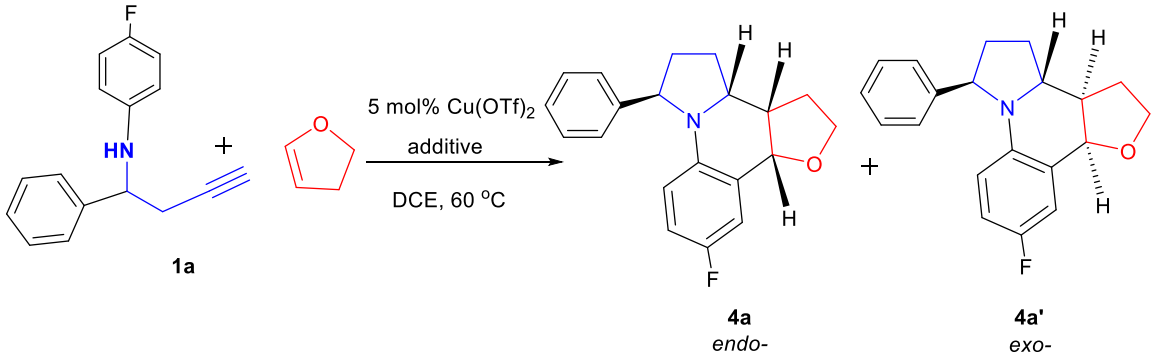
In our initial study, the dihydrofuran was selected as a model substrate to react with the simple homopropargylic amine **1a** under previously developed standard reaction conditions. Consequently, the *cross*-cycloaddition products **4a** and **4a'** were obtained in a low yield (24%) but with the major *self*-dimerization compound **3a** (Table 1, entry 1). In order to inhibit the *self*-dimerization of homopropargylic amine **1a**, we attempted to introduce some additives (Table 1). Acid additives were firstly selected to accelerate the isomerization of cycloenamine to cycloiminium cation. For example, the strong acid, CF_3COOH, and weak acid, CH_3COOH and PhCOOH, could indeed increase the desired

product's yield (entries 2-4). The Lewis acid $Sc(OTf)_3$ was also examined (entry 5). However, no further improved results were obtained. Other microenvironment adjustment was then considered through adding NaCl,[8] silica gel[9] and acidic Al_2O_3[10] into the reaction system (entries 6-8). Surprisingly, this reaction gave obviously increased yield of *cross*-cycloaddition product **4a** and **4a'** with the addition of silica gel or Al_2O_3. More interestingly, using the Al_2O_3 activated by water, a slightly higher yield of target compound was generated (entry 9). It is noteworthy that the target compounds were obtained with *endo*/*exo*-configuration in 63:37 diastereomeric ratio and the *self*-dimerization product **3a** was accompanied in more or less in all cases (Table 1).

Why was the Al_2O_3 competent auxiliary in this reaction? With this question in our mind, some explored experiments were further performed (Table 1, entries 10-14). The types and levels activated by water of Al_2O_3 were subtly examined. As shown in table 1, it was found that the I-activated level of acidic Al_2O_3 gave higher yield of *cross*-cycloaddition product than neutral and basic Al_2O_3 (entries 10-13). These results demonstrated that the acidic microenvironment was favor to the isomerization of cycloenamine to cycloiminium cation. Additionally, a metal oxide, CuO, acting as a Lewis acid, was tested. As a result, this reaction could also smoothly proceed and afford the corresponding product in moderate yield (Table 1, entry 14). Obviously, the Al_2O_3 was superior to the CuO in this reaction. In view of these results, we surmised that the unique reticular structure property and Lewis acidity as well as weak protonic acidity of Al_2O_3 endow it special catalytic activity in this

reaction, accelerating the isomerization of cycloenamine formed *in situ* to cycloiminium cation, and thus impeding the occurrence of *self*-dimerization.

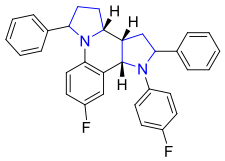
Table 1. The screening of additives in the cascade reaction of homopropargylic amine 1a and dihydrofuran[a]



1a **4a** *endo-* **4a'** *exo-*

entry	Additive (equiv)	Total yield (**4a** + **4a'**) (%)[c]	*Self*-dimerized product yield (**3a**) (%)[f]
1	-	24	42
2	CF_3COOH (0.2)	31	33
3	CH_3COOH (0.2)	55	21
4	PhCOOH (0.2)	48	25
5	$Sc(OTf)_3$ (0.1)	48	15
6	NaCl (2.0)	51	28
7	Silica gel (2.0)	62	20
8	Al_2O_3 (2.0)	65	9

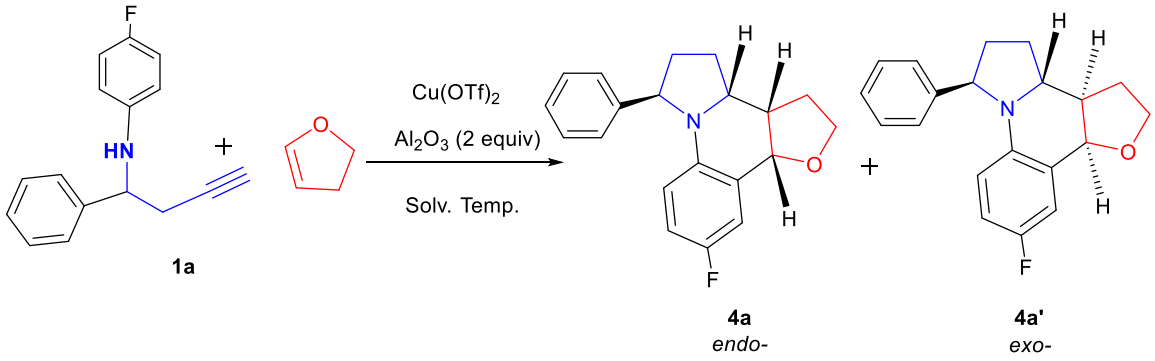
9[d]	Al_2O_3 (2.0)	68	11
10	Acidic Al_2O_3 (2.0)	72	8
11	Neutral Al_2O_3 (2.0)	52	14
12	Basic Al_2O_3 (2.0)	57	11
13[e]	Acidic Al_2O_3 (2.0)	68	10
14	CuO (2.0)	54	18

[a] Reaction conditions: **1a** (24 mg, 0.1 mmol, 1.2 equiv), dihydrofuran (21 mg, 0.3 mmol, 3.0 equiv), 5 mol % $Cu(OTf)_2$ (0.005 mmol, 1.8 mg, 5 mol%), a certain amount of additive and DCE (1 mL) were sequentially added into a tube. The reaction was carried out under the given reaction conditions and the products were subsequently detected by TLC; [b] The diastereomeric ratios were determined based upon NMR analysis of the crude products; [c] Isolated yield; [d] the 1mmol Al_2O_3 was activated by 25 ul H_2O; [e] The Al_2O_3 was activated and named as II-activated level (1 mmol Al_2O_3 + 50 ul H_2O), the above Al_2O_3 was activated and named as I-activated level (1 mmol Al_2O_3 + 25 ul H_2O) (acidic, neutral, basic); [f] The side product is  (**3a**).

Then the other experimental parameters, such as solvents, reaction temperature and the amount of catalyst and electron-rich olefins were investigated (Table 2). As a result, the anisole displays advantage over other common used organic solvents (entries 1-8). And the

60 °C was the optimal (entries 9-10). In addition, whether increasing or reducing the loading of $Cu(OTf)_2$, the reaction gave decreased yield of target compound (Table 2, entries 11-15). In the case of 30 mol% $Cu(OTf)_2$, most of the homopropargylic amine **1a** suffered decomposed (entry 14). Moreover, no obvious improved results were obtained in the case of the increased amount of dihydrofuran (entries 16-17). Based on the above results, the optimal reaction conditions were 5 mol% $Cu(OTf)_2$, 2 equiv Al_2O_3, 3 equiv dihydrofuran at 60 °C in the anisole.

Table 2. The other experimental parameters screening in the reaction of homopropargylic amine 1a and dihydrofuran[a]



1a **4a** *endo-* **4a'** *exo-*

entry	Solv.	Temp. (°C)	$Cu(OTf)_2$ (mol%)	^{1}H NMR Yield (%)[b]	*dr* (endo:exo)[c]	Isolated Yield (%)
1	DCE	60	5	-	62:38	72
2	MeOH	60	5	34/42[d]	62:38	-
3	CH_3CN	60	5	trace/51[d]	--	-

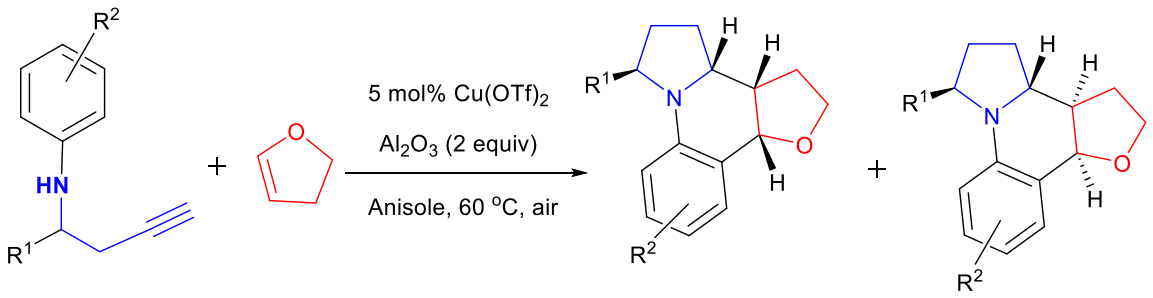
4	PhMe	60	5	72/10 [d]	58:42	-
5	PhOMe	60	5	-	67:33	72
6	THF	60	5	53/34 [d]	62:38	-
7	DMF	60	5	trace/67 [d]	--	-
8	1,4-dioxane	60	5	22/48 [d]	58:42	-
9	PhOMe	85	5	-	67:33	52
10[e]	PhOMe	r.t.	5	-	67:33	50
11	PhOMe	60	10	-	67:33	60
12	PhOMe	60	15	-	67:33	55
13	PhOMe	60	20	-	67:33	38
14	PhOMe	60	30	-	67:33	15
15	PhOMe	60	2	-	67:33	52
16[f]	PhOMe	60	5	-	67:33	69
17[g]	PhOMe	60	5	-	67:33	71

[a] Reaction conditions: **1a** (24 mg, 0.1 mmol), dihydrofuran (21 mg, 0.3 mmol, 3.0 equiv), a certain amount of $Cu(OTf)_2$, Al_2O_3 (0.2 mmol, 20.4 mg, 2.0 equiv) and solvent (1 mL) were sequentially added into a tube. The reaction was carried out under the given reaction conditions and the products were subsequently detected by TLC (generally 3-4 h); [b] The NMR yield was calculated by adding a certain amount of DMF as an internal

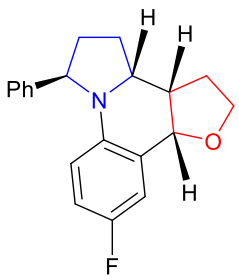
standard; [c] The diastereomeric ratios were determined based upon ^{1}H NMR analysis of the crude products; [d] the yield of *self*-dimerized side product; [e] the reaction time was 6 h; [f] the amount of dihydrofuran was 0.4 mmol (4.0 equiv); [g] the amount of dihydrofuran was 0.5 mmol (5.0 equiv).

Having established the optimized reaction conditions, the scope of homopropargylic amines was scrutinized by performing the reaction with dihydrofuran (Table 3). Generally, all tested homopropargylic amines were able to tolerate this catalytic system to afford the desired product **4a**-**o** and **4a'-o'** in moderate to good yields (38%-80%). It should be noted that all these reactions were traced by thin layer chromatography (TLC) with the small amount of *self*-dimerization side products. And in the case of 4-CF_3-substituted *N*-aryl homopropargylic amine, only the *self*-dimerization competitive side product was obtained in 78% yield. For the homopropargylic amine with R^1 = 4-NO_2-C_6H_4, the corresponding products contained four diastereoisomers. In addition, all products were racemic. And the *endo* or *exo*-configuration of the target compound was confirmed according to the x-ray single crystal diffraction of *exo*-**4q'** and theirs ^{1}H NMR. And the *endo* or *exo*-configurational product contains the extremely small amount of diastereoisomers, respectively.

Table 3. The scope of homopropargylic amines and dihydrofuran[a]



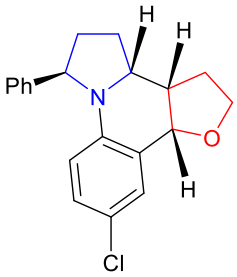
1 **4** *endo-* **4'** *exo-*



4a/4a'

endo:exo = 63:37

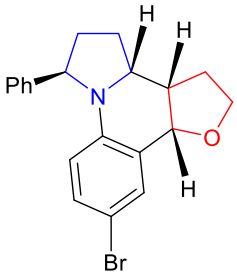
total yield 72%



4b/4b'

endo:exo = 57:43

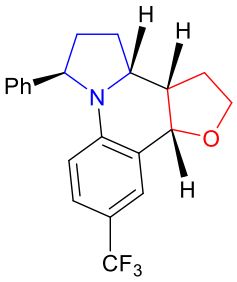
total yield 75%



4c/4c'

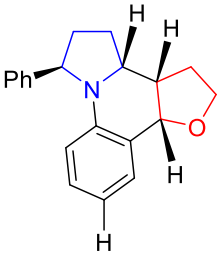
endo:exo = 67:33

total yield 71%



4d/4d'

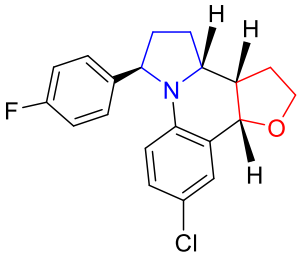
total yield 0%[b]



4e/4e'

endo:exo = 63:37

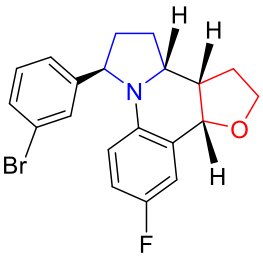
total yield 64%



4f/4f'

endo:exo = 63:37

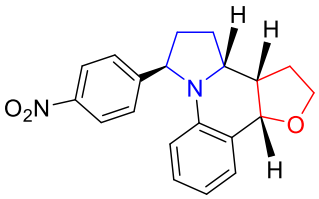
total yield 64%



4g/4g'

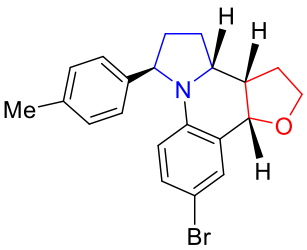
endo:exo = 67:33

total yield 57%



4h/4h'

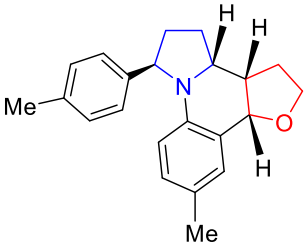
total yield 80%[c]



4i/4i'

endo:exo = 70:30

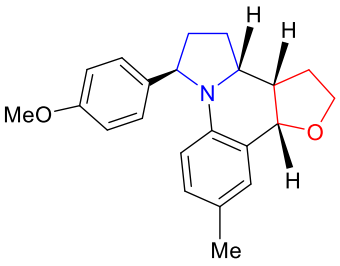
total yield 38%



4j/4j'

endo:exo = 64:36

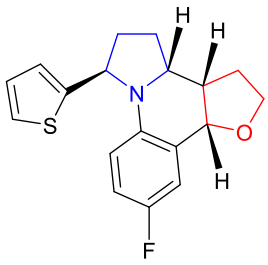
total yield 74%



4k/4k'

endo:exo = 67:33

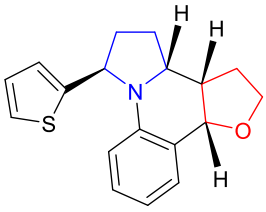
total yield 66%



4l/4l'

endo:exo = 63:37

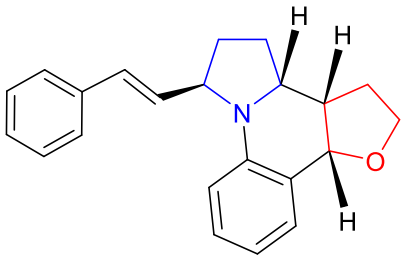
total yield 50%



4m/4m'

endo:exo = 61:39

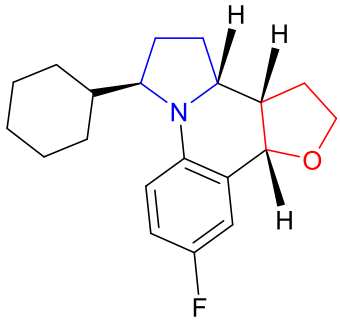
total yield 55%



4n/4n'

endo:exo = 63:37

total yield 62%



4o/4o'

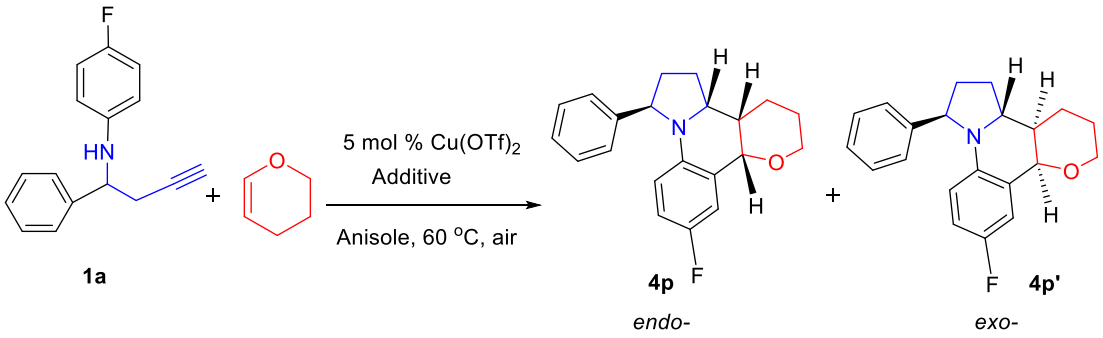
endo:exo = 62:38

total yield 71%

[a] Reaction conditions: Homopropargylic amines **1** (0.1 mmol), dihydrofuran (21 mg, 0.3 mmol, 3.0 equiv), $Cu(OTf)_2$ (0.005 mmol, 1.8 mg, 5 mol%), Al_2O_3 (0.2 mmol, 20.4 mg, 2.0 equiv) and anisole (1 mL) were sequentially added into a tube. The reaction was carried out at 60 °C in the air and the products were subsequently detected by TLC (generally 3-4 h); [b] The product was the *self*-dimerization compound (yield 78%); [c] The products contained four diastereoisomers (The diastereomeric ratios were determined based upon NMR analysis of the crude products).

Several other electron-rich olefins were further employed to test this methodology application (Scheme 2). Under the above optimized reaction conditions, the reaction resulted in the expected octahydro-2H-pyrano[3,2-c]pyrrolo[1,2-a]quinoline product in low yield (27%) in the case of dihydropyran. Therefore, further additive screening experiments were carried out as shown in Table 4. Interestingly, the $Sc(OTf)_3$ exhibited the best catalytic activity for the reaction of dihydropyran and homopropargylic amine **1a** (Table 4). And this reaction gave only one *endo*-configurational product **4p** with excellent diastereoselectivity (*dr* > 25:1) (Scheme 2, eq 1). Similarly, the *N*-Ts protected dihydropyrrole rendered the corresponding products **4q** and **4q'** in 80% yield with $Cu(OTf)_2$ and $Sc(OTf)_3$ as cocatalysts. The exact configuration of *exo*-**4q'** was unambiguously determined by a single crystal X-ray diffraction (Figure 1).[11] However, this catalytic system was incompatible with vinyl *n*-butyl ether or vinyl *t*-butyl ether (4r-s). Fortunately, using our developed methodology, a lung cancer inhibitor **4t** could be facilely synthesized in good yield (Scheme 2, eq 2)[12].

Table 4. The additive effect on the reaction of homopropargylic amine 1a and dihydropyran[a]



Entry	Additive (equiv)	Isolated yield (%)[b]	*dr* (endo:exo)[c]
1	Al_2O_3 (2.0)	27	>25:1
2	$Sc(OTf)_3$ (0.1)	62	>25:1
3	$Y(OTf)_3$ (0.05)	51	>25:1
4	$Y(OTf)_3$ (0.1)	55	>25:1
5	$Yb(OTf)_3$ (0.1)	60	>25:1
6	$In(OTf)_3$ (0.1)	30	>25:1
7	$Zn(OTf)_2$ (0.1)	44	>25:1
8	$SnCl_2$ (1.0)	41	>25:1
9	$SnCl_2$ (2.0)	36	>25:1
10	BF_3·OEt (0.1)	48	>25:1

[a] Reaction conditions: **1a** (24 mg, 0.1 mmol), dihydropyran (25.2 mg, 0.3 mmol, 3.0 equiv), 5 mol% $Cu(OTf)_2$ (1.8 mg), additive and anisole (1 mL) were sequentially added into a tube. The reaction was carried out under the given reaction conditions and the products were subsequently detected by TLC; [b] Isolated yield; [c] The diastereomeric ratios were determined based upon NMR analysis of the crude products.

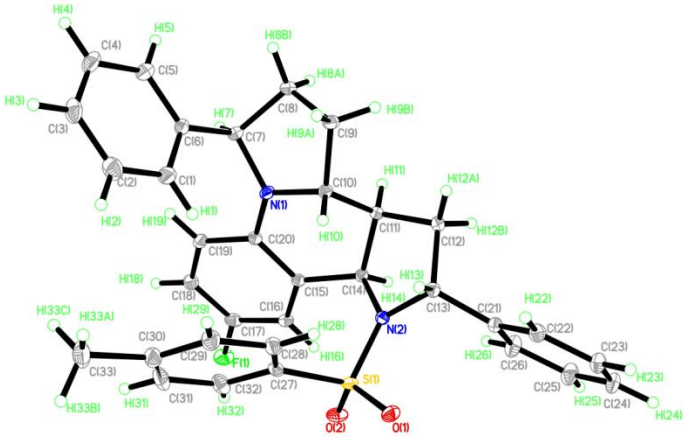
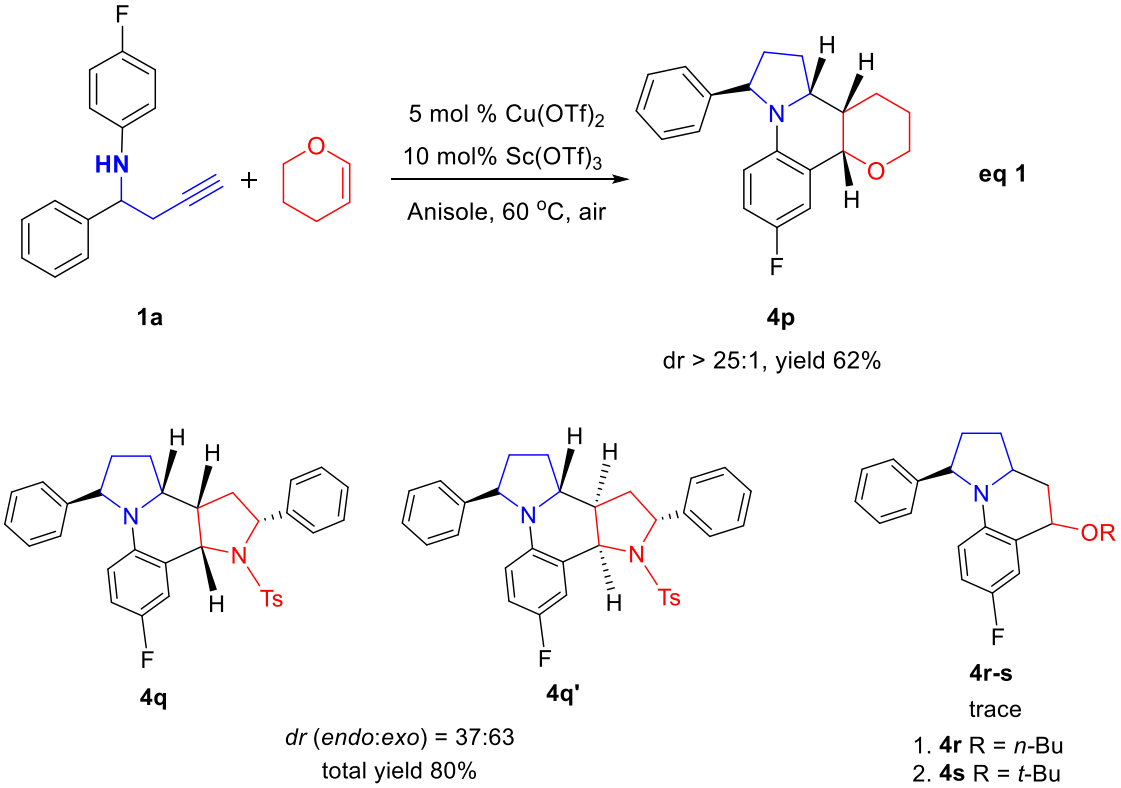
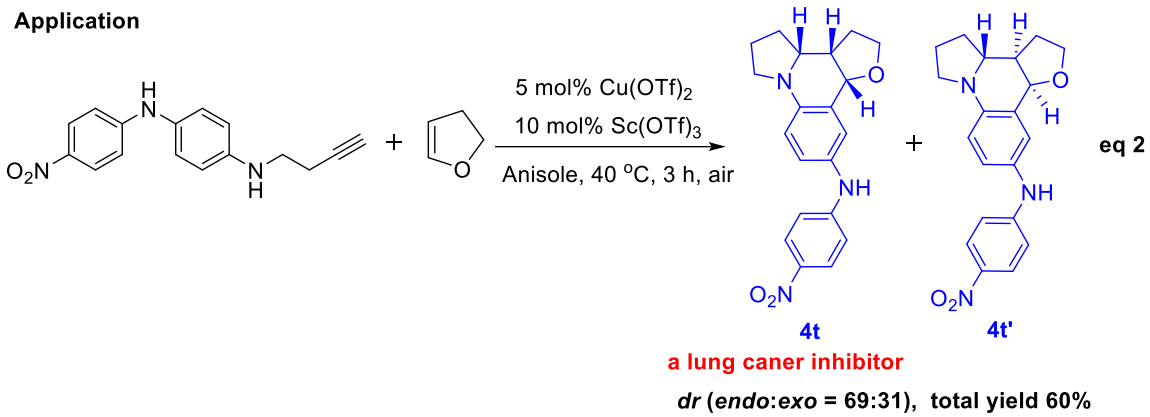


Figure 1. The ORTEP drawing (30% thermal ellipsoids) of *exo*-4q'

Scheme 2. The reactions of homopropargylic amine 1a and other electron-rich olefins.



Application



CONCLUSION

In summary, a novel Povarov reaction of cycloiminium with electron-rich olefins was developed for the preparation of octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline derivatives. The cycloiminium was formed *in situ* via a simple and efficient Cu-catalyzed intramolecular hydroamination cycloisomerization reactions of homopropargylic amines. Various homopropargylic amines were well tolerated in this methodology to give the corresponding desired products in moderate to good yields. More importantly, the inevitable competitive *self*-dimerization of homopropargylic amines could be effectively reduced through introducing the Al_2O_3 additive or $Sc(OTf)_2$ as a cocatalyst.

EXPERIMENTAL SECTION

1. General Information

The ^1H NMR and ^{13}C NMR spectra were recorded at 400 MHz or 600 MHz. ^1H and ^{13}C NMR Chemical shifts were calibrated to tetramethylsilane as an internal reference.

Chemical shifts are given in (ppm) and coupling constants (J) in Hz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet: t, triplet; q, quartet; m, multiplet; High resolution mass spectra (HRMS) were measured on a mass spectrometer equipped with a TOF system and an electrospray ionization (ESI) ion source.

2. Synthesis and Characterization of *N*-(4-nitrophenyl)benzene-1,4-diamine[13]

The 1-fluoro-4-nitrobenzene (5 mmol, 705 mg), Na_2CO_3 (5.0 mmol, 530 mg), 1,4-phenylenediamine (10 mmol, 1.08 g) and 7 mL of water were sequentially added into a flask and refluxed for 10 h. Then the reaction mixture was cold and 10 mL of toluene were added and stirred vigorously for another 1 h. The precipitated product was collected by filtration and washed thoroughly with water and toluene. The *N*-(4-nitrophenyl) benzene-1,4-diamine was obtained as an orange solid with 1.1 g, yield 78%, m.p. 210-211 ^{o}C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.03-7.98 (m, 2H), 6.95-6.89 (m, 2H), 6.79-6.73 (m, 2H), 6.64-6.58 (m, 2H), 5.10 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 153.2, 146.4, 136.4, 127.7, 126.4, 124.8, 114.6, 111.7. HRMS (ESI$^+$) calculated for $C_{12}H_{12}N_3O_2$ (M+H$^+$) 230.0930; found 230.0926.

3. Synthesis and Characterization of Homopropargylic Amines

The homopropargylic amines were prepared according to the known procedures[7]. Because our research group has synthesized a series of homopropargylic amines, we herein directly used or synthesized these substrates through using well-developed methods. And these substrates are all known, the characterizations are consistent with that of our synthesized compounds.

General procedure for Homopropargylic Amines (1a-1o)

An aluminum amalgam was prepared from aluminum powder (0.5 g, 18.0 mmol) and a catalytic amount of mercuric chloride (10 mg) in 7.5 mL anhydrous THF by vigorously stirring at room temperature for 1 h under a N_2 atmosphere. A solution of propargylic bromide (18.0 mmol) in 12.5 mL of anhydrous THF was then slowly added to the suspension at such a rate as to maintain the temperature between 30-40 ^oC. After the addition, the reaction mixture was continued to stir until a dark grey solution was formed. The generated propargylic aluminum sesqui-bromide solution was added to a solution of imine (6.0 mmol) in 20.0 mL of anhydrous THF at 0 ^oC under N_2 atmosphere. The reaction mixture was stirred at 0 ^oC for about 1 h, then warmed to room temperature and continued to stir for additional 3-4 h (monitored by TLC). The mixture was quenched by adding saturated NH_4Cl aqueous solution, and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$, and then filtered, the filtration was concentrated in vacuo to give the residue. The residue was purified by flash chromatography over silica gel (gradient elution of EtOAc /petroleum ether, PE : EA = 50 : 1).

***N*-(1-phenylbut-3-yn-1-yl)-4-(trifluoromethyl)aniline 1d**

White solid, 1.44 g, yield 83%, m.p. 34.7-35.8 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.17 (m, 7H), 6.47 (d, *J* = 8.5 Hz, 2H), 4.66 (s, 1H), 4.49 (dd, *J* = 7.0, 5.2 Hz, 1H), 2.72 (ddd, *J* = 16.9, 5.3, 2.7 Hz, 1H), 2.58 (ddd, *J* = 16.9, 7.0, 2.7 Hz, 1H), 2.01 (t, *J* = 2.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 141.3, 129.0, 128.0, 126.6 (d, *J* = 3.8 Hz), 126.4, 113.0, 79.9, 72.0, 56.1, 28.2. HRMS (ESI^-) calculated for $C_{17}H_{13}F_3N$ ($M\text{-}H^+$) 288.1000; found 288.1033.

***N*-(1-(4-nitrophenyl)but-3-yn-1-yl)aniline 1h**

Orange oil liquid, 1.06 g, yield 78%. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.03 (t, *J* = 7.7 Hz, 2H), 6.63 (t, *J* = 7.3 Hz, 1H), 6.41 (d, *J* = 8.0 Hz, 2H), 4.55 (t, *J* = 6.0 Hz, 1H), 4.41 (s, 1H), 2.73 (ddd, *J* = 16.9, 5.5, 2.7 Hz, 1H), 2.60 (ddd, *J* = 16.9, 6.5, 2.6 Hz, 1H), 2.03 (t, *J* = 2.7 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 149.8, 147.5, 146.3, 129.4, 127.5, 124.1, 118.6, 113.8, 79.1, 77.5, 77.2, 76.8, 72.5, 55.9, 27.9. HRMS (ESI$^-$) calculated for $C_{16}H_{13}N_2O_2$ (M-H$^+$) 265.0977; found 265.0981.

4-bromo-*N*-(1-(*p*-tolyl)but-3-yn-1-yl)aniline 1i

Light yellow oil liquid, 1.41 g, yield 75%, m.p. 85.5-87.9 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 7.2, 2.0 Hz, 2H), 7.19 (ddd, *J* = 10.2, 8.4, 2.0 Hz, 4H), 6.45 (dd, *J* = 8.7, 2.1 Hz, 2H), 4.59-4.39 (m, 1H), 2.87-2.57 (m, 2H), 2.36 (d, *J* = 1.9 Hz, 3H), 2.11 (q, *J* = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.1, 138.6, 137.5, 132.0, 129.6, 126.3, 115.4, 109.6, 80.3, 71.7, 56.3, 28.2, 21.3. HRMS (ESI+) calculated for $C_{17}H_{17}BrN$ (M+H$^+$) 314.0544; found 314.0543.

***N*-(1-(thiophen-2-yl)but-3-yn-1-yl)aniline 1m**

Orange oil liquid, 845.6 mg, yield 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.18 (m, 3H), 7.12 (d, *J* = 3.5 Hz, 1H), 7.02 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 4.93 (t, *J* = 5.9 Hz, 1H), 4.41 (s, 1H), 2.96-2.79 (m, 2H), 2.15 (t, *J* = 2.7 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 146.7, 127.0, 124.5, 124.2, 118.6, 114.1, 80.0, 71.9, 52.7, 28.1. HRMS (ESI+) calculated for $C_{14}H_{14}NS$ (M+H$^+$) 228.0847; found 228.0845.

2-phenyl-1-tosyl-2,3-dihydro-1H-pyrrole

The synthesis of 2-phenyl-1-tosyl-2,3-dihydro-1H-pyrrole was performed according to the previously reported procedure[14]

White solid, 61.5 mg, yield 70%, m.p. 103-105 °C, ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (d, *J* = 7.9 Hz, 2H), 7.45-7.24 (m, 7H), 6.55 (d, *J* = 4.0 Hz, 1H), 5.14 (d, *J* = 4.0 Hz, 1H), 4.74 (dd, *J* = 11.0, 6.3 Hz, 1H), 2.94 (dd, *J* = 16.6, 11.2 Hz, 1H), 2.51 (d, *J* = 6.2 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 142.8, 134.0, 130.9, 129.7, 128.9, 128.6, 127.7, 127.6, 126.4, 110.3, 63.1, 40.8, 21.7. HRMS (ESI+) calculated for $C_{17}H_{18}NO_2S$ ($M+H^+$) 300.1058; found 300.1056.

Synthesis and Characterization of Homopropargylic Amines (1q)

N-(4-nitrophenyl)benzene-1,4-diamine (4 mmol, 916.9 mg) was added to the Ar-purged flask in DMF (24 mL). K_2CO_3 (4.2 mmol, 580.3 mg) and 4-bromo-1-butyne (4.1 mmol, 545.3 mg) were added to the reaction system and the reaction mixture was stirred at 85 °C for 12 h. The mixture was then quenched by saturated NH_4Cl aqueous solution and extracted with ethyl acetate for three times, the combined organic layers were washed with brine and dried with anhydrous $MgSO_4$. Then the extracts were filtered and the filtration was concentrated to give a yellow liquid residue. The residue was purified by flash column chromatography on silica gel (EtOAc /petroleum ether, PE : EA = 1 : 10) to afford the orange solid **1q**, 382.6 mg, yield 34%, m.p. 55-57 °C. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.09-8.02 (m, 2H), 7.09-7.01 (m, 2H), 6.76-6.63 (m, 4H), 6.15 (s, 1H), 4.05 (s, 1H), 3.33 (t, *J* = 6.6 Hz, 2H), 2.53 (td, *J* = 6.5, 2.7 Hz, 2H), 2.07 (t, *J* = 2.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 146.0, 138.8, 129.3, 126.5, 126.3, 114.0, 112.4, 81.7, 70.4, 42.7, 19.2. HRMS (ESI+) calculated for $C_{16}H_{16}N_3O_2$ ($M+H^+$) 282.1243; found 282.1242.

4. The general procedure of this cascade reaction of homopropargylic amines with olefins

$Cu(OTf)_2$ (1.81 mg, 5 mol %) was added to a solution of homopropargylic amines (0.1 mmol), Al_2O_3 (0.2 mmol, 20.4 mg, 2.0 equiv) and 2,3-dihydrofuran (21 mg, 0.3 mmol) in

1 mL anisole, and the mixture was stirred at 60 °C until the complete disappearance of the starting material (monitored by TLC). The mixture was passed through a short kieselguhr column by using CH_2Cl_2, the filtration was concentrated in vacuo and purified by column chromatography with gradient elution (Silica gel, petroleum ether : EtOAc, gradient from 50 : 1 to 10 : 1) to give the final products **4**. All the products are racemic. And the *endo* or *exo*-configurational product contains the extremely small amount of diastereoisomers, respectively.

10-fluoro-6-phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4a (*endo*)

Orange oil liquid, 14.03 mg, yield 45%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dt, *J* = 7.3, 4.6 Hz, 2H), 7.17-7.10 (m, 1H), 7.07 (d, *J* = 7.3 Hz, 2H), 6.99 (dt, *J* = 9.0, 2.9 Hz, 1H), 6.61 (m, 1H), 6.06 (m, 1H), 4.70 (m, 1H), 4.37 (t, *J* = 3.3 Hz, 1H), 4.06-3.87 (m, 1H), 3.80 (m, 1H), 3.32 (m, 1H), 2.45-2.29 (m, 1H), 2.19 (m, 2H), 1.79 (m, 3H), 1.71-1.60 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (d, *J* = 235.3), 144.3, 139.9, 128.7, 126.8, 125.8, 117.4 (d, *J* = 21.6), 116.0 (d, *J* = 22.1), 113.7 (d, *J* = 7.1), 120.0 (d, *J* = 8.1 Hz), 76.8, 65.0, 64.7, 57.7, 39.8, 34.3, 29.7, 29.0. HRMS (ESI+) calculated for $C_{20}H_{20}FNO$ ($M+H^+$) 310.1607; found 310.1600.

10-fluoro-6-phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4a' (*exo*)

Orange oil liquid, 8.24 mg, yield 27%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.2 Hz, 2H), 7.15 (q, *J* = 7.6 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 2H), 6.98 (dd, *J* = 9.4, 3.0 Hz, 1H), 6.50 (td, *J* = 8.4, 2.8 Hz, 1H), 5.88 (dd, *J* = 4.4, 4.4 Hz, 1H), 5.10 (d, *J* = 7.2 Hz, 1H), 4.66 (dd, *J* = 7.8, 5.2 Hz, 1H), 4.19 (m, 1H), 3.85-3.69 (m, 3H), 2.67-2.57 (m, 1H), 2.53-2.41 (m, 1H), 2.08 (m, 1H), 1.92-1.58 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (d, *J* = 253.3), 144.7, 138.8, 128.9, 126.8, 125.7, 115.2 (d, *J* = 23.0), 114.8 (d, *J* = 22.0), 112.3 (d, *J* = 7.0), 122.5 (d, *J* = 6.1 Hz), 75.7, 66.6, 63.7, 56.7, 41.6, 35.9, 29.7, 24.8. HRMS (ESI+) calculated for $C_{20}H_{21}FNO$ ($M+H^+$) 310.1607; found 310.1600.

10-chloro-6-phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4b (*endo*)

Colorless liquid, 13.9 mg, yield 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.11 (m, 4H), 7.10-7.02 (m, 2H), 6.84 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.07 (d, *J* = 8.8 Hz, 1H), 4.74 (dd, *J* = 7.9, 3.8 Hz, 1H), 4.38 (d, *J* = 4.3 Hz, 1H), 3.98 (m, 1H), 3.84 (m, 1H), 3.34 (m, 1H), 2.42 (m, 1H), 2.22 (m, 2H), 1.81 (m, 3H), 1.67 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 141.9, 131.1, 129.1, 128.8, 126.9, 125.8, 120.5, 114.1, 76.7, 65.0, 64.4, 57.7, 39.9, 34.5, 29.7, 29.3. HRMS (ESI+) calculated for $C_{20}H_{21}ClNO$ ($M+H^+$) 326.1312; found 326.1303.

10-chloro-6-phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4b' (*exo*)

Colorless liquid, 10.5 mg, yield 32%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 7.28-7.21 (m, 1H), 7.17 (dd, *J* = 7.0, 1.7 Hz, 2H), 6.82 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.99 (d, *J* = 8.7 Hz, 1H), 5.20 (d, *J* = 7.1 Hz, 1H), 4.77 (dd, *J* = 7.8, 5.6 Hz, 1H), 4.29 (td, *J* = 8.8, 3.5 Hz, 1H), 3.97-3.81 (m, 2H), 2.74 (m, 1H), 2.59 (m, 1H), 2.25-2.13 (m, 1H), 2.01-1.68 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 140.9, 129.0, 128.7, 128.1, 126.9, 125.7, 122.9, 121.0, 112.9, 75.4, 66.6, 63.4, 56.7, 41.3, 36.0, 29.8, 24.8. HRMS (ESI+) calculated for $C_{20}H_{21}ClNO$ ($M+H^+$) 326.1312; found 326.1303.

10-bromo-6-phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4c (*endo*)

Colorless liquid, 17.6 mg, yield 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 5.0 Hz, 1H), 7.19 (m, 3H), 7.11-7.03 (d, *J* = 7.2 Hz, 2H), 6.96 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.02 (d, *J* = 8.8 Hz, 1H), 4.73 (dd, *J* = 7.9, 3.9 Hz, 1H), 4.38 (d, *J* = 4.0 Hz, 1H), 3.98 (m, 1H), 3.84 (m, 1H), 3.38-3.29 (m, 1H), 2.42 (m, 1H), 2.22 (m, 2H), 1.88-1.76 (m, 3H), 1.73-1.62 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 142.3, 134.0, 131.9, 128.8, 126.9, 125.8, 121.1, 114.6, 107.5, 76.7, 65.0, 64.4, 57.7, 39.9, 34.5, 29.8, 29.3. HRMS (ESI+) calculated for $C_{20}H_{21}BrNO$ ($M+H^+$) 370.0807; found 370.0794.

10-bromo-6-phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4c' (*exo*)

Colorless liquid, 8.7 mg, yield 23%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.33 (d, *J* = 2.0 Hz, 1H), 7.28-7.12 (m, 4H), 7.10-7.03 (m, 2H), 6.85 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.84 (d, *J* = 8.8 Hz, 1H), 5.10 (d, *J* = 7.1 Hz, 1H), 4.66 (dd, *J* = 7.8, 5.6 Hz, 1H), 4.18 (td, *J* = 7.6, 3.2 Hz, 1H), 3.87-3.71 (m, 2H), 2.64 (m, 1H), 2.49 (m, 1H), 2.14-2.04 (m, 1H), 1.93-1.57 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.2, 141.2, 131.5, 130.9, 129.0, 126.9, 125.7, 123.4, 113.4, 108.1, 75.4, 66.6, 63.4, 56.7, 41.3, 36.0, 29.8, 24.8. HRMS (ESI+) calculated for $C_{20}H_{21}BrNO$ ($M+H^+$) 370.0807; found 370.0793.

6-phenyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4e and 4e'

Colorless liquid, 18.6 mg, yield 64%, *dr (endo:exo)* = 63:37. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.18 (m, 6H), 7.18-7.07 (m, 5H), 6.95-6.88 (m, 1H), 6.83-6.77 (m, 0.51H), 6.54 (m, 1.48H), 6.17 (d, *J* = 8.2 Hz, 1H), 5.99 (d, *J* = 8.2 Hz, 0.53H), 5.17 (d, *J* = 7.3 Hz, 0.55H), 4.78 (dd, *J* = 8.0, 3.5 Hz, 1H), 4.72 (dd, *J* = 7.9, 5.1 Hz, 0.59H), 4.45 (d, *J* = 4.3 Hz, 1H), 4.22 (td, *J* = 7.1, 3.5 Hz, 0.56H), 3.99 (m, 1H), 3.89-3.71 (m, 2H), 3.38 (m, 1H), 2.69-2.59 (m, 0.42H), 2.53 -2.34 (m, 1.56H), 2.30-2.13 (m, 1.81H), 2.08 (m, 0.46H), 1.90-1.74 (m, 4H), 1.74-1.62 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.7, 144.4, 143.4, 142.4, 131.6, 129.3, 129.0, 128.8, 128.7, 128.2, 126.7, 125.9, 125.8, 121.3, 119.1, 116.2, 115.8, 113.0, 111.8, 75.8, 66.5, 65.0, 64.4, 63.4, 57.6, 56.6, 41.8, 39.8, 35.8, 34.4, 29.9, 29.6, 29.2, 24.9. HRMS (ESI+) calculated for $C_{20}H_{22}NO$ ($M+H^+$) 292.1701; found 292.1698.

6-(4-chlorophenyl)-10-fluoro-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4f (*endo*)

Light green oil liquid, 13.9 mg, yield 40%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 -7.23 (m, 2H), 7.15-7.08 (m, 3H), 6.76 (td, *J* = 8.6, 3.0 Hz, 1H), 6.13 (dd, *J* = 9.0, 4.6 Hz, 1H), 4.79 (dd, *J* = 7.9, 3.1 Hz, 1H), 4.49 (d, *J* = 4.4 Hz, 1H), 4.08 (m, 1H), 3.94 (m, 1H), 3.42 (m, 1H), 2.51 (m, 1H), 2.41-2.20 (m, 2H), 1.99-1.74 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8 (d, *J* = 253.3), 142.9, 139.7, 132.5, 128.9, 127.3, 117.6 (d, *J* = 21.2), 116.1 (d, *J* = 22.2), 113.7 (d, *J* = 7.1), 120.2 (d, *J* = 6.1 Hz), 76.8, 65.1, 64.2, 57.7, 39.8, 34.3, 29.8, 29.0. HRMS (ESI+) calculated for $C_{20}H_{20}ClFNO$ ($M+H^+$) 344.1217; found 344.1217.

6-(4-chlorophenyl)-10-fluoro-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4f' (*exo*)

Light green oil liquid, 8.1 mg, yield 24%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 2H), 7.06-6.95 (m, 3H), 6.52 (td, *J* = 8.6, 3.1 Hz, 1H), 5.83 (dd, *J* = 8.9, 4.5 Hz, 1H), 5.09 (d, *J* = 7.2 Hz, 1H), 4.63 (dd, *J* = 8.1, 4.9 Hz, 1H), 4.17 (td, *J* = 7.0, 3.5 Hz, 1H), 3.81 (q, *J* = 8.1 Hz, 1H), 3.73 (td, *J* = 9.0, 3.5 Hz, 1H), 2.63 (m, 1H), 2.48 (m, 1H), 2.13-2.03 (m, 1H), 1.86 (m 1H), 1.78-1.59 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3 (d, J = 253.3), 143.2, 138.6, 132.5, 129.1, 127.2, 115.4 (d, *J* = 22.2), 114.8 (d, *J* = 22.2), 112.2 (d, *J* = 7.1), 122.7 (d, *J* = 6.1 Hz), 75.6, 66.6, 63.2, 56.7, 41.5, 35.9, 29.7, 24.8. HRMS (ESI+) calculated for $C_{20}H_{20}ClFNO$ ($M+H^+$) 344.1217; found 344.1220.

6-(3-bromophenyl)-10-fluoro-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4g (*endo*)

Yellowish-green liquid, 14.8 mg, yield 38%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 -7.25 (m, 2H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.01 (m, 2H), 6.67 (td, *J* = 8.6, 3.1 Hz, 1H), 6.05 (dd, *J* = 8.9, 4.6 Hz, 1H), 4.67 (dd, *J* = 7.9, 3.1 Hz, 1H), 4.39 (d, *J* = 4.4 Hz, 1H), 3.98 (td, *J* = 8.6, 6.3 Hz, 1H), 3.83 (td, *J* = 9.5, 5.7 Hz, 1H), 3.33 (m, 1H), 2.46-2.33 (m, 1H), 2.30-2.12 (m, 2H), 1.86-1.64 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.5 (d, *J* = 236.3 Hz), 147.0, 140.0, 130.4, 130.1, 128.9, 124.4, 123.0, 120.2 (d, *J* = 6.1 Hz), 117.6 (d, *J* = 22.2 Hz), 116.2 (d, *J* = 22.2 Hz), 113.8 (d, *J* = 7.1 Hz), 76.7, 65.1, 64.6, 57.7, 39.6, 34.2, 29.7, 28.8. HRMS (ESI+) calculated for $C_{20}H_{20}BrFNO$ ($M+H^+$) 388.0712; found 388.0712.

6-(3-bromophenyl)-10-fluoro-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4g' (*exo*)

Yellowish-green liquid, 7.4 mg, yield 19%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.22 (m, 2H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.00 (m, 2H), 6.53 (td, *J* = 8.6, 3.1 Hz, 1H), 5.85 (dd, *J* = 8.9, 4.5 Hz, 1H), 5.11 (d, *J* = 7.1 Hz, 1H), 4.61 (dd, *J* = 7.8, 5.0 Hz, 1H), 4.19 (td, *J* = 6.9, 3.5 Hz, 1H), 3.82 (q, *J* = 8.1 Hz, 1H), 3.74 (td, *J* = 9.0, 3.4 Hz, 1H), 2.63 (m, 1H), 2.54-2.43 (m, 1H), 2.09 (m, 1H), 1.86 (m, 1H), 1.80-1.51 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (d, *J* = 235.3 Hz), 147.4, 138.5, 130.6, 130.1, 130.0, 128.8, 124.3, 123.1, 122.7 (d, *J* = 6.1 Hz), 115.3 (d, J = 22.2 Hz), 114.9 (d, *J* = 22.2 Hz), 112.1 (d, *J* = 7.1 Hz), 75.6, 66.6,

63.5, 56.7, 41.5, 35.8, 29.7, 24.8. HRMS (ESI+) calculated for $C_{20}H_{20}BrFNO$ ($M+H^+$) 388.0712; found 388.0696.

6-(4-nitrophenyl)-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4h and 4h'

Orange liquid, 26.9 mg, *dr* (*endo*:*exo*) = 69:31, yield 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (t, *J* = 1.8 Hz, 0.52H), 8.10 (m, 6H), 7.39-7.24 (m, 8H), 7.10-6.99 (m, 2H), 6.96-6.88 (m, 1.41H), 6.83-6.77 (m, 0.56H), 6.64-6.50 (m, 3H), 6.36 (t, *J* = 7.2, 0.49H), 6.14 (d, *J* = 8.1 Hz, 0.39H), 6.03 (d, *J* = 8.2 Hz, 1H), 5.91-5.86 (m, 0.51H), 5.64 (d, *J* = 6.1 Hz, 0.55H), 5.19 (d, *J* = 5.4 Hz, 0.43H), 5.09 (dd, *J* = 8.5, 3.4 Hz, 0.50H), 5.01 (dd, *J* = 4.4, 1.5 Hz, 0.55H), 4.92-4.83 (m, 1.67H), 4.76 (q, *J* = 7.4 Hz, 1H), 4.46 (d, *J* = 4.2 Hz, 1H), 4.39-4.30 (m, 0.58H), 4.00 (td, *J* = 8.6, 6.3 Hz, 1H), 3.87 (m, 1H), 3.79 (dd, *J* = 7.5, 5.9 Hz, 1.29H), 3.65-3.53 (m, 0.93H), 3.44-3.29 (m, 1.73H), 2.79 (m, 0.47H), 2.65 (m, 0.80H), 2.57-2.46 (m, 1H), 2.43 (td, *J* = 7.1, 1.8 Hz, 1H), 2.36-2.14 (m, 2.48H), 2.12-1.92 (m, 0.77H), 1.92-1.64 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.7, 152.4, 152.2, 147.4, 147.1, 147.0, 146.1, 142.7, 141.5, 131.9, 129.8, 129.5, 129.4, 129.1, 128.7, 128.35, 128.3, 127.4, 127.2, 126.7, 126.5, 126.4, 124.5, 124.4, 124.2, 124.1, 121.8, 121.5, 119.4, 117.7, 117.5, 116.7, 116.6, 115.8, 115.7, 114.7, 114.1, 112.8, 111.6, 111.5, 103.9, 77.4, 77.0, 67.1, 66.2, 66.1, 65.1, 64.0, 63.7, 61.0, 60.3, 58.7, 57.7, 57.2, 57.1, 41.2, 39.9, 39.7, 36.9, 35.8, 35.1, 34.6, 34.3, 33.2, 32.4, 29.8, 29.8, 29.4, 23.6, 22.8. HRMS (ESI+) calculated for $C_{20}H_{21}N_2O_3$ ($M+H^+$) 337.1552; found 337.1553.

10-bromo-6-(p-tolyl)-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4i (*endo*)

Yellowish-green liquid, 10.2 mg, yield 27%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 2.4 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.98-6.93 (m, 3H), 6.04 (d, *J* = 8.7 Hz, 1H), 4.70 (dd, *J* = 7.9, 3.8 Hz, 1H), 4.37 (d, *J* = 4.3 Hz, 1H), 3.97 (m, 1H), 3.88-3.77 (m, 1H), 3.31 (ddd, *J* = 11.2, 7.4, 5.7 Hz, 1H), 2.46-2.31 (m, 1H), 2.25 (s, 3H), 2.19 (ddd, *J* = 12.5, 8.4, 4.3 Hz, 1H), 1.84-1.73 (m, 3H), 1.66 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 140.8, 136.5, 133.9, 131.9, 129.5, 125.7, 121.1, 114.5, 107.4, 76.7, 65.0, 64.1, 57.6, 39.9, 34.6, 29.8, 29.3, 21.2. HRMS (ESI+) calculated for $C_{21}H_{23}BrNO$ ($M+H^+$) 384.0963; found 384.0960.

10-bromo-6-(p-tolyl)-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4i' (*exo*)

Yellowish-green liquid, 4.4 mg, yield 11%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 2.4, 1H), 7.04 (d, *J* = 7.8 Hz, 2H), 6.95 (d, *J* = 7.8 Hz, 2H), 6.85 (dd, *J* = 8.7, 2.5 Hz, 1H), 5.86 (d, *J* = 8.7 Hz, 1H), 5.09 (d, *J* = 7.1 Hz, 1H), 4.63 (dd, *J* = 7.7, 5.6 Hz, 1H), 4.16 (td, *J* = 6.8, 2.4 Hz, 1H), 3.86-3.71 (m, 3H), 2.68-2.57 (m, 1H), 2.53-2.42 (m, 1H), 2.25 (s, 3H), 2.14-2.02 (m, 1H), 1.91-1.59 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.3, 141.1, 136.5, 131.5, 130.9, 129.6, 125.6, 123.4, 113.4, 108.0, 75.4, 66.6, 63.1, 56.6, 41.3, 36.0, 29.8, 24.7, 21.2. HRMS (ESI+) calculated for $C_{21}H_{23}BrNO$ ($M+H^+$) 384.0963; found 384.0950.

10-methyl-6-(p-tolyl)-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4j and 4j'

Light green liquid, 23.6 mg, yield 74%, *dr (endo:exo)* = 64:36. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.06 (m, 1.59H), 7.05-6.95 (m, 5.62H), 6.73 (dd, *J* = 8.4, 1H), 6.62 (dd, *J* = 8.0, 0.46H), 6.10 (d, *J* = 8.4 Hz, 1H), 5.92 (d, *J* = 8.0 Hz, 0.44H), 5.14 (d, *J* = 7.2 Hz, 0.45H), 4.70 (m, 1.47H), 4.41 (d, *J* = 4.4 Hz, 1H), 4.18 (td, *J* = 7.0, 3.3 Hz, 0.48H), 3.97 (m, 1H), 3.80 (m, 2H), 3.33 (m, 1H), 2.61 (m, 0.21H), 2.49-2.30 (m, 1H), 2.24 (m, 5H), 2.11 (s, 3H), 1.78 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 141.6, 141.2, 140.3, 136.2, 136.2, 131.9, 129.9, 129.5, 129.4, 129.3, 128.8, 125.8, 125.8, 125.0, 124.8, 121.3, 119.0, 113.0, 111.9, 77.2, 76.0, 66.6, 65.0, 64.2, 63.1, 57.6, 56.6, 42.1, 39.9, 35.8, 34.4, 29.9, 29.5, 29.0, 25.0, 21.2, 20.5, 20.3. HRMS (ESI+) calculated for $C_{22}H_{26}NO$ ($M+H^+$) 320.2014; found 320.2008.

6-(4-methoxyphenyl)-10-methyl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo [1,2-a]quinoline 4k and 4k'

White solid, 22.1 mg, yield 66%, m.p. 169.8-172.4 ºC, *dr (endo:exo)* = 67:33. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (m, 1.78H), 7.01 (m, 3H), 6.77-6.70 (m, 4H), 6.62 (d, *J* = 8.0, 0.55H), 6.11 (d, *J* = 8.3 Hz, 1H), 5.93 (d, *J* = 8.2 Hz, 0.54H), 5.13 (d, *J* = 7.3 Hz, 0.54H), 4.68 (m, 1.66H), 4.41 (d, *J* = 4.4 Hz, 1H), 3.97 (td, *J* = 8.4, 6.3 Hz, 1H), 3.81 (m, 1H), 3.70 (s, 5H), 3.32 (m, 1H), 2.61 (m, 0.58H), 2.49-2.39 (m, 0.51H), 2.34 (m, 0.91H), 2.21 (m,

1.45H), 2.11 (s, 5H), 2.05 (m, 0.52H), 1.89-1.60 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 141.2, 140.3, 136.9, 136.6, 131.9, 129.9, 129.4, 128.8, 127.0, 126.9, 125.0, 124.8, 121.3, 119.0, 114.1, 114.0, 113.0, 111.9, 76.0, 66.6, 65.0, 63.9, 62.8, 57.5, 56.5, 55.4, 42.1, 39.9, 35.9, 34.4, 29.9, 29.4, 29.0, 25.0, 20.5, 20.3. HRMS (ESI+) calculated for $C_{22}H_{26}NO_2$ ($M+H^+$) 336.1964; found 336.1965.

10-fluoro-6-(thiophen-2-yl)-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4l and 4l'

Colorless liquid , 15.8 mg, yield 50%, *dr (endo:exo)* = 63:37. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (m, 2H), 6.99 (m, 2H), 6.86 (m, 2H), 6.77 (t, *J* = 4.5 Hz, 2H), 6.71 (td, *J* = 8.4, 2.8 Hz, 1H), 6.59 (td, *J* = 8.4, 2.8 Hz, 1H), 6.38 (dd, *J* = 9.0, 4.6 Hz, 1H), 6.20 (dd, *J* = 8.9, 4.6 Hz, 1H), 5.08 (d, *J* = 7.5 Hz, 1H), 4.98 (m, 2H), 4.37 (d, *J* = 4.6 Hz, 1H), 4.09 (td, *J* = 7.2, 3.3 Hz, 1H), 3.96 (m, 1H), 3.85-3.69 (m, 4H), 3.26 (m, 1H), 2.63 (m, 1H), 2.50-2.12 (m, 5H), 1.98-1.62 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1 (d, *J* = 236.3 Hz), 148.8, 139.9, 130.7, 127.11, 127.07, 127.0, 126.9, 124.0, 123.7, 123.46, 122.7, 120.8 (d, *J* = 7.1 Hz), 120.6, 117.4 (d, *J* = 21.2 Hz), 116.0 (d, *J* = 23.2 Hz), 115.5 (d, *J* = 22.2 Hz), 114.9 (d, *J* = 22.2 Hz), 114.1 (d, *J* = 7.1 Hz), 113.8, 117.7 (d, *J* = 7.1 Hz), 100.2, 76.6, 75.9, 67.2, 66.8, 65.1, 61.0, 59.3, 58.3, 56.6, 55.8, 41.9, 39.9, 35.4, 35.1, 34.2, 32.4, 29.8, 29.7, 29.1, 28.9, 28.4, 24.7, 23.5. HRMS (ESI+) calculated for $C_{18}H_{19}FNOS$ ($M+H^+$) 316.1171; found 316.1169.

6-(thiophen-2-yl)-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4m and 4m'

Colorless liquid, 16.4 mg, yield 55%, *dr (endo:exo)* = 61:39. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.24 (d, *J* = 7.6, 1H), 7.07 (m, 1H), 7.04 – 6.95 (m, 1H), 6.94-6.86 (m, 1H), 6.84 (m, 2H), 6.78 (m, 2H), 6.59 (m, 2H), 6.46 (dd, J = 8.2, 1.0 Hz, 1H), 6.30 (dd, *J* = 8.2, 1.1 Hz, 1H), 5.14 (d, *J* = 7.5 Hz, 1H), 5.06-4.99 (m, 2H), 4.42 (d, *J* = 4.4 Hz, 1H), 4.11 (m, 1H), 3.96 (m, 1H), 3.85-3.69 (m, 3H), 3.29 (m, 1H), 2.64 (m, 1H), 2.30 (m, 2H), 2.26-2.11 (m, 2H), 1.98-1.67 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7, 143.3, 142.4, 131.6, 129.3, 129.2, 128.3, 126.9, 126.8, 123.88, 123.86, 123.6, 123.5, 122.7, 122.1, 119.7, 116.9, 116.6, 113.2, 112.0, 76.9, 76.0, 66.6, 65.0, 60.7, 59.0, 56.4, 55.7, 42.0, 39.8, 35.4, 34.2, 29.8, 28.9, 28.5, 24.8. HRMS (ESI+) calculated for $C_{18}H_{20}NOS$ ($M+H^+$) 298.1266; found 298.1266.

(*E*)-6-styryl-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4n and 4n'

Colorless liquid , 19.7 mg, yield 62%, *dr (endo:exo)* = 63:37. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.17 (m, 16H), 7.13 (t, *J* = 7.1 Hz, 3H), 7.04 (t, *J* = 7.9 Hz, 2H), 6.95 (t, *J* = 7.9 Hz, 1H), 6.59 (t, *J* = 7.3 Hz, 4H), 6.48 (d, *J* = 8.1 Hz, 1H), 6.41 (m, 3H), 6.15 (d, *J* = 5.9 Hz, 1H), 6.11 (d, *J* = 6.2 Hz, 1H), 6.07 (d, *J* = 6.6 Hz, 0.41H), 5.13 (d, *J* = 7.6 Hz, 1H), 4.41 (t, *J* = 6.5 Hz, 5H), 4.24 (t, *J* = 6.6 Hz, 1H), 3.95 (m, 3H), 3.78 (m, 4H), 3.18 (m, 1.55H),

2.69-2.55 (m, 1H), 2.31-1.98 (m, 7H), 1.74 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 143.1, 137.0, 136.9, 131.6, 131.2, 130.1, 129.9, 129.4, 129.2, 128.7, 128.4, 127.5, 127.5, 126.5, 126.4, 122.0, 119.3, 116.4, 116.0, 113.1, 112.0, 77.1, 76.0, 66.6, 64.9, 62.1, 60.8, 56.3, 55.6, 41.8, 39.9, 32.0, 30.9, 29.8, 29.0, 28.9, 24.8. HRMS (ESI+) calculated for $C_{18}H_{19}FNOS$ ($M+H^+$) 316.1171; found 316.1169.

6-cyclohexyl-10-fluoro-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2-a]quinoline 4o and 4o'

Yellowish-green liquid, 22.4 mg, yield 71%, *dr (endo:exo)* = 62:38. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (m, 2H), 6.82 (td, *J* = 8.7, 3.0 Hz, 1H), 6.71 (td, *J* = 8.7, 3.0 Hz, 1H), 6.44 (dd, *J* = 9.0, 4.5 Hz, 1H), 6.26 (dd, *J* = 9.0, 4.5 Hz, 1H), 4.98 (d, *J* = 7.0 Hz, 1H), 4.29 (d, *J* = 4.2 Hz, 1H), 3.91 (q, *J* = 7.9 Hz, 1H), 3.79 (m, 4H), 3.64 (m, 4H), 3.08-2.94 (m, 1H), 2.54-2.44 (m, 1H), 2.26-2.12 (m, 3H), 2.00 (m, 1H), 1.82 (m, 8H), 1.73-1.39 (m, 11H), 1.18 (m, 3H), 1.10-0.88 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (d, *J* = 234.3.3 Hz), 139.3, 121.9 (d, *J* = 5.1 Hz), 117.8 (d, *J* = 22.2 Hz), 116.0 (d, *J* = 22.2 Hz), 115.3 (d, *J* = 22.2 Hz), 114.8 (d, *J* = 22.2 Hz), 111.0 (d, *J* = 6.1 Hz), 75.5, 66.3, 64.9, 63.5, 56.6, 55.3, 41.4, 40.3, 40.0, 39.8, 30.4, 30.2, 30.2, 29.9, 29.8, 27.8, 27.2, 26.8, 26.7, 26.69, 26.66, 26.4, 26.3, 25.5, 24.8, 24.3. HRMS (ESI+) calculated for $C_{20}H_{27}FNO$ ($M+H^+$) 316.2077; found 316.2073.

11-fluoro-7-phenyl-3,4,4a,4b,5,6,7,12b-octahydro-2H-pyrano[3,2-c]pyrrolo[1,2-a]quinoline 4p

White solid, 47 mg, yield 51%, m.p. 158-160 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.17 (m, 2H), 7.16-7.10 (m, 3H), 6.84 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.56 (td, *J* = 8.7, 3.1 Hz, 1H), 5.90 (dd, *J* = 9.0, 4.6 Hz, 1H), 4.61 (t, *J* = 7.6 Hz, 1H), 4.25-4.15 (m, 2H), 4.12-4.04 (m, 1H), 3.67 (m, 1H), 2.49 (m, 1H), 2.18 (m, 1H), 1.88 (m, 3H), 1.75 (m, 1H), 1.62-1.48 (m, 2H), 1.41-1.34 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.2 (d, *J* = 235.3 Hz), 144.9, 139.7, 128.9, 126.8, 125.7, 121.3 (d, *J* = 6.1 Hz), 117.1 (d, *J* = 21.2 Hz), 116.0 (d, *J* = 22.2 Hz), 122.2 (d, *J* = 8.1 Hz), 76.1, 69.2, 64.0, 55.9, 37.2, 36.1, 31.4, 24.8, 21.6. HRMS (ESI+) calculated for $C_{21}H_{23}FNO$ ($M+H^+$) 324.1764; found 324.1757.

10-fluoro-2,6-diphenyl-1-tosyl-2,3,3a,3b,4,5,6,11b-octahydro-1H-dipyrrolo[1,2-a:3',2'-c]quinoline 4q and 4q'

Wight solid, 43.1 mg, yield 80%, m.p. 188.3-191.2 °C, *dr (endo:exo)* = 37:63. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 10.3, 2.9 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.23 (t, *J* = 7.3 Hz, 4H), 7.19-7.14 (m, 1H), 7.09 (m, 3H), 7.05-6.86 (m, 9H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.56 (m, 2H), 5.93 (dd, *J* = 9.0, 4.7 Hz, 1H), 5.81 (dd, *J* = 9.0, 4.6 Hz, 1H), 5.48 (d, *J* = 6.3 Hz, 1H), 5.21 (t, *J* = 8.4 Hz, 1H), 4.81 (d, *J* = 3.9 Hz, 1H), 4.66-4.60 (m, 1H), 4.47 (dd, *J* = 7.6, 5.4 Hz, 1H), 4.24 (m, 1H), 3.46 (dt, *J* = 11.4, 6.4 Hz, 1H), 2.92 -2.82 (m, 1H), 2.48-2.27 (m, 3H), 2.24 (s, 5H), 2.12 (m, 2H), 1.88-1.65 (m, 2H), 1.62-

1.47 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8 (d, *J* = 233.3 Hz), 154.1, 144.5, 144.5, 142.3, 141.9, 141.2, 140.6, 139.4, 139.2, 139.1, 128.93, 128.87, 128.7, 128.0, 127.5, 127.2, 126.9, 126.8, 126.4, 126.0, 125.6, 125.5, 120.6, 120.4, 117.2 (d, *J* = 24.3 Hz), 116.4 (d, *J* = 22.2 Hz), 115.1 (d, *J* = 22.2 Hz), 114.4 (d, *J* = 7.1 Hz), 112.5 (d, *J* = 7.1 Hz), 112.3 (d, *J* = 7.1 Hz), 66.3, 64.2, 62.9, 62.4, 61.8, 61.4, 57.0, 56.7, 41.2, 39.5, 38.2, 35.8, 35.0, 34.9, 29.8, 29.4, 21.7, 21.5. HRMS (ESI+) calculated for $C_{33}H_{31}FN_2NaO_2S$ ($M+Na^+$) 561.1988; found 561.1988.

_N_-(4-nitrophenyl)-2,3,3a,3b,4,5,6,11b-octahydrofuro[3,2-c]pyrrolo[1,2a]quinolin-10-amine 4t and 4t'

Orange solid, 46.5 mg, yield 44%, m.p. 160-162 °C, ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (d, *J* = 3.2 Hz, 1H), 8.01 (dt, *J* = 9.4, 2.4 Hz, 2H), 7.09 (t, *J* = 2.8 Hz, 1H), 7.04 (dq, *J* = 8.0, 2.6 Hz, 1H), 6.79 (dt, *J* = 9.3, 2.4 Hz, 2H), 6.54 (dt, *J* = 8.7, 2.5 Hz, 1H), 4.40 (q, *J* = 3.2, 1.9 Hz, 1H), 3.89-3.75 (m, 1H), 3.70 (tt, *J* = 9.0, 3.6 Hz, 1H), 3.14 (dq, *J* = 10.3, 5.0, 4.6 Hz, 1H), 2.67 (tt, *J* = 9.2, 3.6 Hz, 1H), 2.26-2.13 (m, 2H), 2.07-1.72 (m, 5H), 1.51 (p, *J* = 11.3, 10.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.9, 142.4, 136.6, 127.6, 126.4, 126.3, 124.6, 121.2, 112.0, 111.9, 76.2, 64.3, 57.5, 46.7, 40.8, 30.7, 29.1, 22.5. HRMS (ESI+) calculated for $C_{24}H_{31}N_2O_2$ ($M+H^+$) 379.2386; found 379.2371.

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SUPPORTING INFORMATION

The characterization data, NMR and HR-MS spectra of all pyrroloquinoline derivatives as well as the X-ray data of compound *exo*-**4q'** are all provided in supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Crystal data for the compound *exo*-**4q'**: C33H31FN2O2S, MW) 538.66, Tetragonal, P-42(1)c. Final R indices [I>2ó(I)], R1) 0.0262, wR2) 0.0707, R indices (all data) R1) 0.0284, wR2) 0.0720, a) 23.493(17) Å, b) 23.493(17) Å, c) 9.703(9) Å, V) 5355.2(7) Å3, T) 113 (2) K, Z) 8. Reflections collected/unique: 67777/6129 [R(int) 0.0444], number of observations [>2ó(I)] 6129, parameters) 353, Goodness-of-fit on F^2) 1.037. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center. CCDC 1503242.

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