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ARTICLE TYPE

Design, synthesis, and anticancer activities of new compounds bearing the quinone-pyran-lactone tricyclic pharmacophore

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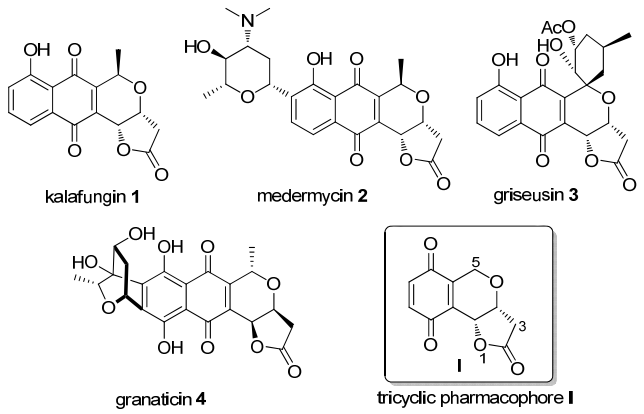
A simple and more effective four-step synthesis of tricyclic quinone-pyran-lactone skeleton was developed. Subsequent structural modification led to several series of derivatives. Regio- and diastereo-characteristics of these compounds was elucidated, and their antitumor activities against several cancer cells were investigated.

Introduction

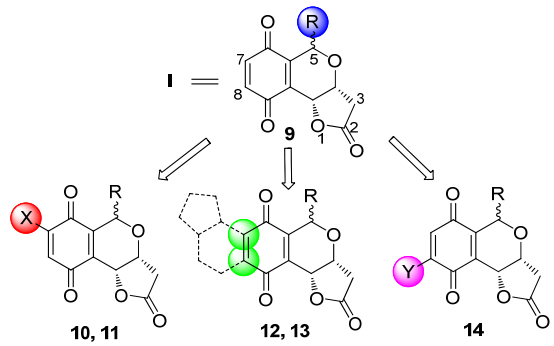
The furanone-fused pyranonaphthoquinones (PNQs) are a class of natural products displaying a range of interesting biological activities, and have served as challenging chemical entities for both synthetic and medicinal chemistry studies.[1] For instance, kalafungin **1** (Scheme 1), extracted from the fermentation broth of *Streptomyces tanashiensis*, possesses inhibitory activity against various pathogenic bacteria, fungi, yeasts, and protozoa, as well as against L5178Y mouse leukemic cells and AKT kinase.[2] Medermycin **2** exhibits significant activity against gram-positive bacteria and is cytotoxic against K562 human myeloid leukemia, P-388 murine leukemia and L5178Y murine lymphoblastoma cell lines.[3] Moderate activity against gram-positive bacteria *in vitro* was also reported for the spiro-natural product, Griseusin **3**.[4] Granaticin **4** bearing a more complex skeleton shows inhibitory activity against protozoa, bacteria, and cytotoxicity against KB cells.[5]



Scheme 1 The representative natural products bearing the furanone-fused pyranonaphthoquinone skeleton

The mechanism of the antibacterial and cytotoxic activities of these furanone-fused pyranonaphthoquinones is proposed to be related to the quinone-pyran-lactone core that can generate reactive oxygen species, such as superoxide and hydrogen peroxide, *via* a one-electron transfer process, or a bioreductive alkylation process after ring opening of the γ-lactone.[6] Therefore, the tricyclic quinone-pyran-lactone framework (**I**) is the key pharmacophore of these complex natural products and is critical to their biological activity (Scheme 1).[2c,6,7] To date, many synthetic methods have been developed,[1b,1c,8] while asymmetric approaches to assemble compounds bearing this tricyclic pharmacophore are limited.[9] Meanwhile, most of the reported structural modifications were focused on the 5-position substituents[2c], and the SAR study on other positions of tricyclic pharmacophore **I** is scarce.

Considering the unique structure of the tricyclic pharmacophore **I**, along with the limited structure-activity relationship (SAR), we decide to develop a more convenient and efficient strategy to construct the core structure **I**, and then conduct a structural modification to prepare a diverse compound library for preliminary biological screening (Scheme 2). As most known PNQs are tetracyclic compounds, particular attention has been paid to tricyclic and pentacyclic ring systems. Besides, nitrogen atom were introduced to this pharmacophore. Herein, we present our synthesis and the activity study of new analogues against several tumor cell lines.

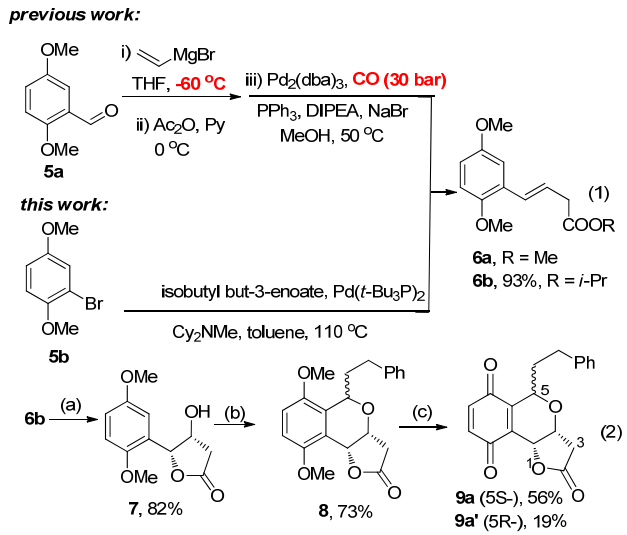


Scheme 2 Proposed new compounds bearing the trycyclic pharmacophore **I**.

Results and discussion

Among the synthetic methods reported to assemble structure **I**[8,9], we considered the Sharpless asymmetric dihydroxylation followed by oxa-Pictet-Spengler reaction[8b] to be the most efficient approach to construct the pyran-lactone component. Yet, the synthesis of Sharpless dihydroxylation substrate **6a** reported by Koert in 2012 required three steps from the starting material **5a**, during which harsh conditions such as -60 °C, CO (30 bar)

were necessary (Scheme 3, eq1).[9f] In order to develop a shorter synthetic route with milder conditions for substrate **6**, we decided to take advantage of Heck reaction[8b] using commercially available 2-bromo-1,4-dimethoxybenzene **5b** as the starting material. As shown in scheme 3, after screening of the temperature, solvent and catalyst, alkene **6b** was achieved in only one step with up to 93% yield by coupling of bromide **5b** with isobutyl but-3-enoate under the catalysis of Pd(*t*-$Bu_3P)_2$/Cy_2NMe[8b] (Scheme 3, eq1).



Scheme 3 Synthesis of **9a** and **9a'**. Reagents and conditions: (a) $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, $K_2O_5O_4$, *t*-BuOH-H_2O, 0 °C to rt, 12 h; (b) phenylpropionaldehyde, $BF_3.OEt_2$, CH_2Cl_2, 0 °C to rt, 2 h; (c) CAN, MeCN/H_2O, rt, 10 min.

Subsequent Sharpless dihydroxylation of alene **6b** with $(DHQD)_2PHAL$ was conducted by following a standard condition[8b] led to hydroxylactone **7** in 82% yield (Scheme 3, eq 2). The absolute configuration was confirmed by comparing the optical rotation value of **7** ($[\alpha]_D^{20}$ = -40, c = 1.05, $CHCl_3$) with its known enantiomer reported by Koert ($[\alpha]_D^{20}$ = +47, c = 1.05, $CHCl_3$).[9f] Next, the oxa-Pictet-Spengler reaction of **7** with phenylpropionaldehyde in the presence of boron trifluoride etherate afforded tricyclic compound **8** in 73% yield. Subsequent oxidation of **8** with cerium ammonium nitrate (CAN) provided the tricyclic core structure **9a** in 56% yield with a 5S- and (3a,5)-*trans*-configuration, while the diastereomer **9a'** bearing a 5R- and (3a,5)-*cis*-configuration was also obtained as a minor product in 19% isolated yield. The configurations at the 5-position in **9a** and **9a'** were determined by their NOE correlations (Figure 1).

In the NOE analysis of **9a** (Figure 1), irradiation of the proton signal at chemical shift of 4.31 ppm corresponding to H_{3a} led to an enhancement of the proton signal with chemical shift at 5.10 ppm corresponding to H_{9b} proton. Further, an enhancement of the H_5 proton signal with chemical shift of 4.61 ppm was also observed. This result indicated that the H_{3a}, H_{9b}, and H_5 protons are *cis*-oriented with respect to each other. In contrast, irradiation of the H_{3a} proton signal of compound **9a'** at 4.52 ppm only led to an enhancement of the H_{9b} signal (δ_H = 5.08 ppm), and no significant enhancement was observed on the proton of H_5, suggesting that protons of H_{3a} and H_5 are *trans*-oriented (Figure 1).

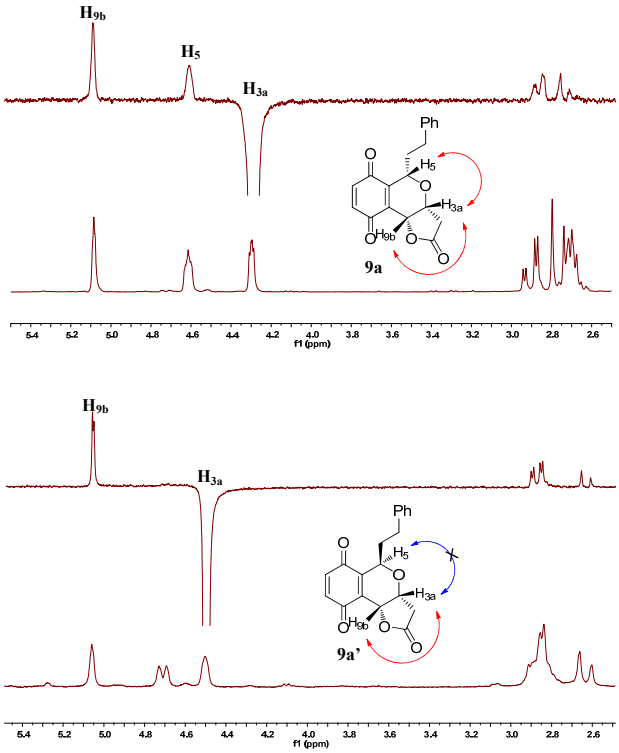
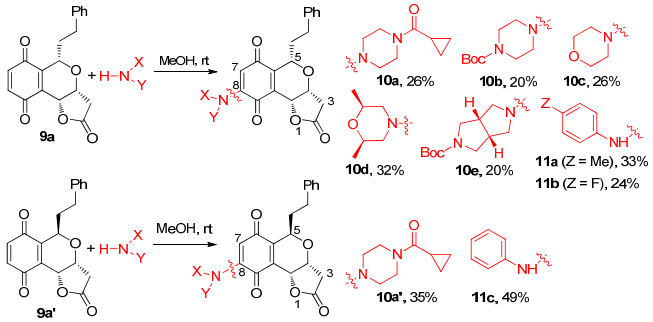


Figure 1 NOE spectrum of **9a** and **9a'**.

With the core structures of **9a** and **9a'** in hand, we decided to synthesize analogues by introducing a series of amino groups into the oxygen-rich pharmacophore. As illustrated in scheme 4, several aliphatic and aromatic amines were reacted with pyranoquinone lactones **9a** or **9a'** in MeOH at rt leading to corresponding 8-amino analogues **10a-e**, **10a'**, and **11a-c** in moderate yields. The relatively lower yields (20-49%) were mostly due to the instability of the lactone fragment in the reaction process as well as during the silica gel column chromatography. In comparison with aliphatic amines, the nucleophilic substitution reaction with aromatic amines took longer reaction time while gave slightly higher yields (**11a-c** *vs* **10a-d**).



Scheme 4 Synthesis of amino-substituted derivatives **10a-e, 10a' and 11a-c**.

The regiochemistry of the newly introduced amino group in the products was determined by the 1D and 2D NMR spectroscopic analysis. For instance, in the HMBC spectrum of **10d** (Figure 2), the long-range correlation between H-7 (δ_H = 5.53 ppm) and C-5a (δ_C = 148.5 ppm) suggested that the amino group was on C-8

position. Otherwise, a long-range correlation between H-7 (δ_H = 5.53 ppm) and C-9a (δ_C = 131.2 ppm) should be observed (see ESI for full details).

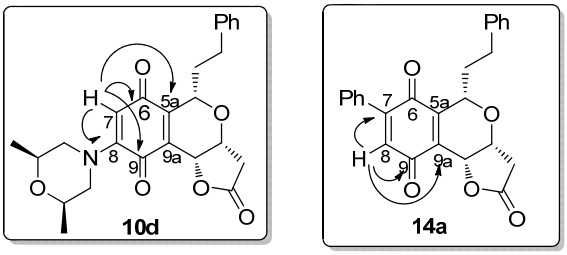
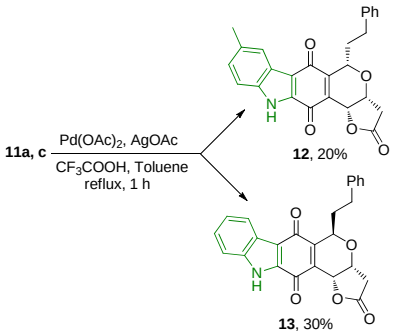


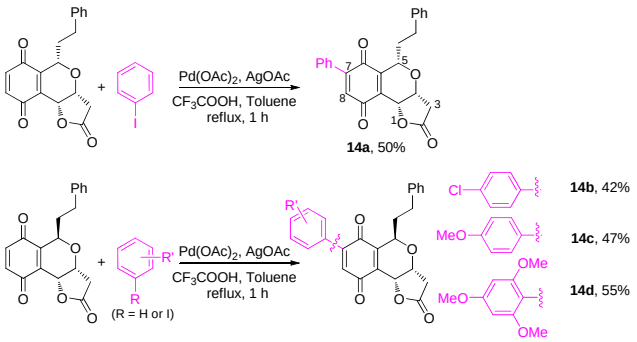
Figure 2 HMBC spectrum of **10d** and **14a**.

The aromatic amine substituted products **11a** and **11c** could be further used to form pentacyclic derivatives **12** and **13** by means of Pd-catalyzed intramolecular cross-dehydrogenative coupling (CDC) reaction. As shown in scheme 5, upon several attempts, carbazole derivatives **12** and **13** were obtained in 20% and 30% yields, respectively by treating **11a** or **11c** with $Pd(OAc)_2$ (0.1 equiv) as the catalyst, AgOAc (2 equiv) as the oxidant, CF_3COOH (0.5 equiv) as the additive, and toluene as the solvent under 110 ^oC in 1 h.



Scheme 5 Synthesis of carbazoles **12** and **13**.

Under a similar catalytic system, Pd-catalyzed intermolecular coupling of intermediate **9a** or **9a'** with a subseries of aryl iodides were conducted in refluxing toluene (Scheme 6). The corresponding products **14a-c** were generated in 42-50% yields (scheme 6). It is worth mentioning that 1,3,5-trimethoxybenzene rather than its iodide could react with **9a'** directly to form **14d** in 55% yield through an intermolecular dehydrogenative coupling reaction.



Scheme 6 Synthesis of **14a-d**.

The regiochemistry of the coupling products **14a-d** distinctly different from that in analogues **10** and **11** was determined by the ^1H NMR, ^{13}C NMR and HMBC. For instance, in the HMBC spectrum of **14a** (Figure 2), the observed correlations between H-8 (δ_H = 6.65 ppm) and C-9 (δ_C = 183.43 ppm), H-8 and C-9a (δ_C = 145.51 ppm) suggested that the aryl group was on C-7 position. Otherwise, correlations between H-8 (δ_H = 6.65 ppm) and C-5a (δ_C = 132.85 ppm), H-8 (δ_H = 6.65 ppm) and C-6 (δ_C = 185.87 ppm) should be detected (see ESI for full details).

The different regiochemistry between the amino (**10a-e**, **10a'**, **11a-c**) and aryl (**14a-d**) analogues is likely due to the differences of the electron densities on C-7 position and C-8 in compound **9a** or **9a'**. The reaction of amines with **9a** or **9a'** occurs through a nucleophilic substitution manner, where the amino group tends to attack the C-8 carbon center with lower electron density. On the other hand, in Pd-catalyzed intermolecular cross-coupling of aryl iodides with **9a** or **9a'**, the Pd(II) complex is electrophilic and tends to attack the electron-rich position (C-7). In order to differentiate the electron charge distribution of **9a**, the density functional theory (DFT) calculations were performed with the Gaussian-09 software package.[10] As shown in Figure 3, NBO (Natural Bond Orbital) charge values of C_7 and C_8 are – 0.246 and – 0.236, respectively, indicating that electronic density on the C-7 position is slightly higher than that on the C-8 position, which was in agreement with our experiment results.

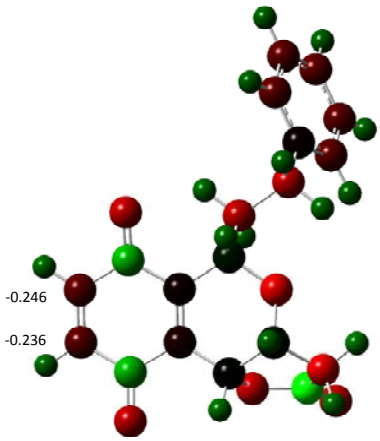


Figure 3 Calculated charge distribution of **9a**.

With all these new synthetic derivatives in hand, we decided to conduct a preliminary bioassay on these compounds to guide our further structural optimization. Compounds **9a, 9a', 10a, 10a', 11c, 13, 14a,** and **14c** were selected as the representatives and evaluated for their antiproliferative effects against several cancer cell lines[11,12] including: squamous carcinoma KB cells, vincristine-resistant KB/VCR cells, human lung cancer A549 cells, and human leukemia HL60 cells. As shown in Table 1, tricyclic compounds without substituents on the quinone part (compounds **9a**, **9a'**) displayed poor potency in the cellular assay with IC_{50} values of greater than 6.48 μg/mL. Surprisingly, introduction of an aliphatic amino group into the tricyclic pharmacophore **9a** or **9a'** yielded compounds **10a** and **10a'** showing dramatically increased cytotoxicity. Both compounds exhibited IC_{50} values less than 5 μg/mL against all the tested cell lines. Compound **10a** has the highest potency of 0.66 μg/mL against KB cells, whereas compound **10a'** is most potent against A549 cells with an IC_{50} value of 0.62 μg/mL. Both compounds also showed good potency against the vincristine-resistant KB/VCR cells with IC_{50} values of 1.62 and 1.28 μg/mL, respectively. The corresponding aromatic amine derivative **11c** was much less potent against KB, A549, and HL60 cells with IC_{50} values more than 5 μg/mL. However, good inhibitory effects

of the cyclized compound **13** were observed against both KB and KB/VCR cells with IC_{50} values of 0.99 and 1.84 μg/mL, respectively. The aryl substituted products **14a,c** showed poor cytotoxic activities against both KB and KB/VCR cells (> 8 μg/mL).

Table 1. Cytotoxic activities[11,12]

	(IC_{50}, μg/mL)			
Compd	**KB**	**KB/VCR**	**A549**	**HL60**
9a	> 6.48	> 6.48	> 6.48	> 6.48
9a'	> 6.48	> 6.48	> 6.48	> 6.48
10a	0.66	1.62	4.21	1.90
10a'	4.05	1.28	0.62	1.73
11c	4.31	2.21	6.58	4.45
13	0.99	1.84	4.81	4.68
14a	> 8.00	> 8.00	> 8.00	> 8.00
14c	> 8.60	8.52	4.49	4.46
Vincristine	0.46	0.26	12.09	
Adriamycin				0.02

Conclusions

In summary, we have developed a simple and more effective four-step synthesis of tricyclic quinone-pyran-lactone skeleton. Subsequent structural modification led to several series of derivatives. Preliminary antitumor activities of these new compounds against several cancer cell lines were evaluated. Compounds **10a** and **10a'** bearing a piperazinyl substituent showed high antiproliferative effects against most of the tested cell lines.

Experimental

General experimental information

All reactions were performed in glassware containing a Tefloncoated stir bar. Solvents and chemical reagents were obtained from commercial sources and used without further purifications. Optical rotations were measured on Autopol VI, serial number 90079, manufactured by Rudolph Research Analytical, Hackettstown, NJ. ^{1}H and ^{13}C spectra were recorded on Varian Mercury 300 MHz or Mercury 400 MHz and the data were recorded using $CDCl_3$ as the solvent. Chemical shifts (δ) were reported in ppm downfield from an internal TMS standard. Low and high-resolution mass spectra were obtained in the ESI and EI mode. Flash column chromatography on silica gel (200-300 mesh) was used for the routine purification of reaction products. The column output was monitored by TLC on silica gel (100-200 mesh) precoated on glass plates (15 x 50 mm), and spots were visualized by UV light at 254 or 365 nM. HMBC, NOE were used in the structural assignment.

(*E*)-Isobutyl 4-(2,5-Dimethoxyphenyl)but-3-enoate (6b)

To a solution of 2-bromo-1,4-dimethoxybenzene (5.43 g, 25 mmol), isobutyl vinylacetate (0.98 mL, 62.5 mmol), and *N*, *N*-dicyclohexylmethyl amine (8.04 mL, 37.5 mmol) in toluene (30 mL) was added bis(tri-*t*-butylphosphine)palladium (1.28 g, 2.5 mmol) under nitrogen, and the mixture was refluxed for 12 h. The reaction was concentrated under vacuum and the residue purified *via* silica column chromatography with petroleum ether/ethyl acetate (50/1) as the eluent provided compound **6b** (6.46 g, 93%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.80 – 6.75 (m, 3H), 6.36 – 6.22 (m, 1H), 3.88 (d, J = 6.7 Hz, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 3.26 (d, J = 7.1 Hz, 2H), 2.02 – 1.84 (m, 1H), 0.93 (d, J = 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.8, 153.7, 151.0, 128.0, 126.8, 122.8, 113.7, 112.2, 112.1, 70.9, 56.2, 55.8, 38.9, 27.7, 19.1; MS (ESI) 301.00 $[M + Na]^+$; HRMS (ESI) calcd for $C_{16}H_{22}O_4Na$ $[M + Na]^+$, 301.1410, found, 301.1413.

(4*R*,5*R*)-5-(2,5-Dimethoxyphenyl)-4-hydroxydihydrofuran-2(3*H*)-one (7)

To a stirred solution of $K_3Fe(CN)_6$ (11.53 g, 35 mmol), $NaHCO_3$ (4.84 g, 35 mmol), $(DHQD)_2PHAL$ (77.9 mg, 0.1 mmol), potassium osmate dehydrate (22.39 mg, 0.05 mmol), and methanesulfonamide (1.14 g, 12 mmol) in water (75 mL) and *tert*-butanol (40 mL) at 0 °C, was added a solution of **6b** (2.78 g, 10 mmol) in *tert*-butanol (40 mL) in one portion. The mixture was warmed to room temperature overnight. Sodium sulfite (18 g) was added, and the aqueous layer was extracted with EtOAc. The combined organic portion was washed with 1N HCl (40 mL) and brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. Purification by silica column chromatography with petroleum ether/ethyl acetate (10/1) as the eluent provided compound **7** (1.95 g, 82%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.89 – 6.80 (s, 2H), 5.72 (d, J = 3.3 Hz, 1H), 4.82 – 4.75 (m, 1H), 3.80 (s, 3H), 3.77 (m, 3H), 2.87 (dd, J = 17.6, 5.2 Hz, 1H), 2.68 (d, J = 17.7 Hz, 1H), 1.46 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 154.0, 149.7, 122.2, 115.1, 113.0, 111.5, 81.9, 68.8, 56.0, 55.9, 38.2; MS (ESI) 239.0 $[M + H]^+$; HRMS (ESI) calcd for $C_{12}H_{15}O_5$ $[M + H]^+$, 239.0914, found, 239.0910. $[\alpha]_D^{20}$ = -40 (c 1.05, $CHCl_3$).

(3a*R*,9b*R*)-5-Phenethyl-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromene-2,6,9(5*H*,9b*H*)-triones 9a and (3a*R*,5*R*,9b*R*)-5-Phenethyl-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromene-2,6,9(5*H*,9b*H*)-trione 9a'

To a solution of **7** (500 mg, 2.1 mmol) and 3-phenylpropanal (422 mg, 3.15 mmol) in dichloromethane (75 mL) at 0 °C was added boron trifluoride etherate (0.5 mL, 4.2 mmol) dropwise. The reaction was allowed to warm to room temperature for 4 h. saturated aqueous sodium bicarbonate was added, and the mixture was extracted with CH_2Cl_2. The combined organic portion was dried with anhydrous Na_2SO_4 and concentrated in vacuo. Purification by silica column chromatography with petroleum ether/ethyl acetate (5/1) as the eluent provided compound **8** (542 mg, 73%) as a white solid.

A solution of compound **8** (100 mg, 0.28 mmol) in acetonitrile (5 mL) at 0 °C was treated with a solution of ammonium cerium nitrate (309 mg, 0.56 mmol) in water (3 mL) in one portion. The reaction was quenched after 10 min with EtOAc and water. The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica column chromatography using petroleum ether/ethyl acetate (5/1) to afford diastereomers **9a** (51 mg, 56%) and **9a'** (17 mg, 19%) as yellow solid.

For **9a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 2H), 7.14 – 7.10 (m, 3H), 6.70 (d, J = 10.2 Hz, 1H), 6.60 (d, J = 10.2 Hz, 1H), 5.08 (d, J = 1.7 Hz, 1H), 4.67 – 4.55 (m, 1H), 4.31 – 4.29 (m, 1H), 2.91 (dd, J = 17.5, 4.4 Hz, 1H), 2.77 (d, J = 17.4 Hz, 1H), 2.73 – 2.60 (m, 2H), 2.44 – 2.19 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 185.8, 183.9, 174.4, 147.3, 140.7, 137.0, 135.8, 132.8, 129.3, 128.5, 126.1, 71.1, 70.9, 69.3, 37.2, 33.9, 30.5; EI-MS

(m/z) 324 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{16}O_5$, 324.0998; found, 324.0997. $[\alpha]_D^{20}$ = 86 (c 0.06, $CHCl_3$).

For **9a':** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.278(m, 2H), 7.24 – 7.19(m, 3H), 6.85 (d, *J* = 10.2 Hz, 1H), 6.79 (d, *J* = 10.2 Hz, 1H), 5.08 (d, *J* = 3.0 Hz, 1H), 4.75 – 4.71 (m, 1H), 4.53 – 4.51 (m, 1H), 2.93 – 2.83 (m, 3H), 2.66 (d, *J* = 17.7 Hz, 1H), 2.12 – 2.01 (m, 1H), 1.95 – 1.85 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.2, 184.3, 174.0, 146.6, 140.5, 136.6, 136.5, 132.4, 128.5 (×2C), 126.3, 69.5, 68.4, 66.3, 36.8, 33.0, 32.4. EI-MS (m/z) 324.0 (M^+); HRMS (EI): m/z [M^+] calcd for $C_{19}H_{16}O_5$, 324.0998, found, 324.0996. $[\alpha]_D^{20}$ = 41.11 (c 0.09, $CHCl_3$).

General procedure for synthesis of 10a-e and 11a-c

To a solution of **9a** or **9a'** (1.0 equiv.) in MeOH (20 mL) was added an appropriate aliphatic amine or aromatic amine (1.2 equiv.) at 0 °C. The resulting mixture was stirred at room temperature for 2h, concentrated in vacuo. The residue was purified by silica column chromatography using petroleum ether/ethyl acetate (3/1) provided corresponding products **10a-e** and **11a-c** in 20-50% yields.

(3a*R*,5*S*,9b*R*)-8-(4-(Cyclopropanecarbonyl)piperazin-1-yl)-5-phenethyl-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromene-2,6,9(5*H*,9b*H*)-trione (10a): deep red solid (26%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 – 7.18 (m, 2H), 7.14 – 7.10 (m, 3H), 5.54 (s, 1H), 5.16 (d, *J* = 1.9 Hz, 1H), 4.63 – 4.57 (m, 1H), 4.27 – 4.25 (m, 1H), 3.792 – 3.63 (m, 6H), 3.50 – 3.30 (m, 2H), 2.90 (dd, *J* = 17.6, 4.5 Hz, 1H), 2.76 (d, *J* = 17.4 Hz, 1H), 2.73 – 2.65 (m, 2H), 2.39 – 2.27(m, 2H), 1.75 – 1.67 (m, 1H), 1.04 – 1.00 (m, 2H), 0.83 – 0.80 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.5, 181.8, 174.6, 172.6, 150.9, 148.7, 141.1, 131.2, 129.2, 128.3, 125.8, 107.4, 71.5, 71.1, 69.6, 47.9, 37.3, 34.5, 30.7, 8.0, 7.9; MS (ESI) 477.2 [M + H]$^+$; HRMS (ESI) calcd for $C_{27}H_{29}N_2O_6$ [M + H]$^+$, 477.2020, found, 477.2016. $[\alpha]_D^{20}$ = -11.11 (c 0.018, $CHCl_3$).

(3a*R*,5*R*,9b*R*)-8-(4-(Cyclopropanecarbonyl)piperazin-1-yl)-5-phenethyl-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromene-2,6,9(5*H*,9b*H*)-trione (10a'): deep red solid (35%);^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 – 7.20(m, 5H), 5.70 (s, 1H), 5.12 (d, *J* = 2.6 Hz, 1H), 4.76 – 4.72 (m, 1H), 4.49 – 4.46(m, 1H), 3.92 – 3.36 (m, 8H), 2.92 – 2.79 (m, 3H), 2.64 (d, *J* = 17.8 Hz, 1H), 2.20 – 2.08(m, 1H), 1.91 – 1.79 (m, 1H), 1.75 – 1.66 (m, 1H), 1.06 – 0.96 (m, 2H), 0.82 – 0.80 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.8, 182.2, 174.2, 172.5, 151.0, 147.5, 140.8, 130.8, 128.5 (×2C), 126.2, 108.0, 70.1, 68.6, 66.4, 48.2, 36.8, 33.1, 32.5, 29.7, 11.0, 7.9 (×2C); MS (ESI) 477.2 [M + H]$^+$; HRMS (ESI) calcd for $C_{27}H_{29}N_2O_6$ [M + H]$^+$, 477.2020, found, 477.2016. $[\alpha]_D^{20}$ = 640 (c 0.01, $CHCl_3$).

***tert*-Butyl 4-((3a*R*,5*S*,9b*R*)-2,6,9-Trioxo-5-phenethyl-3,3a,5,6,9,9b-hexahydro-2*H*-furo[3,2-*c*]isochromen-8-yl)piperazine-1-carboxylate (10b):** deep red solid (20%);^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.13 (m, 2H), 7.11 – 7.07 (m, 3H), 5.53 (s, 1H), 5.16 (d, *J* = 3.0 Hz, 1H), 4.61 – 4.57 (m, 1H), 4.26 – 4.23 (m, 1H), 3.63 – 3.49 (m, 6H), 3.38 – 3.31 (m, 2H), 2.89 (dd, *J* = 17.6, 4.6 Hz, 1H), 2.75 (d, *J* = 17.5 Hz, 1H), 2.68 (dd, *J* = 14.2, 6.8 Hz, 2H), 2.30 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.5, 181.8, 174.6, 154.5, 151.2, 148.6, 141.1, 131.2, 129.2, 128.3, 125.8, 107.6, 80.6, 71.4, 71.1, 69.7, 48.0, 37.3, 34.5, 30.7, 28.4; MS (ESI) 531.1 [M + Na]$^+$; HRMS (ESI) calcd for $C_{28}H_{32}N_2O_7Na$ [M + Na]$^+$, 531.2107, found, 531.2106. $[\alpha]_D^{20}$ = -100 (c 0.005, $CHCl_3$).

(3a*R*,5*S*,9b*R*)-8-Morpholino-5-phenethyl-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromene-2,6,9(5*H*,9b*H*)-trione (10c): deep red solid (26%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.18 (m, 2H), 7.14 – 7.11 (m, 3H), 5.54 (s, 1H), 5.16 (d, *J* = 2.1 Hz, 1H), 4.60 – 4.57 (m, 1H), 4.25 – 4.23 (m, 1H), 3.84 – 3.77 (m, 4H), 3.49 – 3.45 (m, 2H), 3.34 – 3.29 (m, 2H), 2.89 (dd, *J* = 17.5, 4.6 Hz, 1H), 2.75 (d, *J* = 17.6 Hz, 1H), 2.72 – 2.64 (m, 2H), 2.38 – 2.24 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.6, 181.8, 174.7, 151.5, 148.5, 141.1, 131.3, 129.2, 128.3, 125.9, 107.9, 71.4, 71.1, 69.6, 66.3, 48.6, 37.3, 34.5, 30.7; MS (ESI) 432.2 [M + Na]$^+$; HRMS (ESI) calcd for $C_{23}H_{23}NO_6Na$ [M + Na]$^+$, 432.1423, found, 432.1425. $[\alpha]_D^{20}$ = -120 (c 0.01, $CHCl_3$).

(3a*R*,5*S*,9b*R*)-8-((2*S*,6*R*)-2,6-Dimethylmorpholino)-5-phenethyl-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromene-2,6,9(5*H*,9b*H*)-trione (10d): deep red solid (32%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.24 (m, 2H), 7.18 – 7.13 (m, 3H), 5.58 (s, 1H), 5.21 – 5.20 (m, 1H), 4.63 – 4.61 (m, 1H), 4.29 – 4.28 (m, 1H), 3.93 – 3.65 (m, 4H), 2.93 (dd, *J* = 17.6, 4.7 Hz, 1H), 2.79 (d, *J* = 17.5 Hz, 1H), 2.74 – 2.58 (m, 4H), 2.43 – 2.38 (m, 1H), 2.35 – 2.28 (m, 1H), 1.25 (d, *J* = 2.4 Hz, 3H), 1.24 (d, *J* = 2.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.5, 181.9, 174.7, 151.1, 148.5, 141.2, 131.2, 129.2, 128.3, 125.8, 107.4, 71.5, 71.4, 71.1, 69.7, 53.8, 53.5, 37.3, 34.6, 30.7, 18.8, 18.7; MS (ESI) 460.2 [M + Na]$^+$; HRMS (ESI) calcd for $C_{27}H_{27}NO_6Na$ [M + Na]$^+$, 460.1736, found, 460.1736. $[\alpha]_D^{20}$ = -50 (c 0.014, $CHCl_3$).

(3a*R*,6a*S*)-*tert*-Butyl-5-((3a*R*,5*S*,9b*R*)-2,6,9-Trioxo-5-phenethyl-3,3a,5,6,9,9b-hexahydro-2*H*-furo[3,2-*c*]isochromen-8-yl)hexahydropyrrolo[3,4-c]pyrrole-2(1*H*)-carboxylate (10e): deep red solid (20%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25– 7.11(m, 5H), 5.35 (s, 1H), 5.15 (s, 1H), 4.67– 4.64 (m, 1H), 4.29– 4.25 (m, 1H), 3.74– 2.91 (m, 10H), 2.85 (dd, *J* = 15.6, 10.0 Hz, 2H), 2.76 – 2.65 (m, 2H), 2.46 – 2.25 (m, 2H), 1.46 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 182.3, 182.1, 174.8, 154.4, 149.7, 147.1, 141.3, 129.0, 128.3, 125.7, 103.0, 80.0, 71.7, 71.1, 70.0, 49.7, 49.4, 37.3, 34.9, 31.6, 30.8, 28.5; MS (ESI) 557.1 [M + Na]$^+$; HRMS (ESI) calcd for $C_{30}H_{34}N_2O_7Na$ [M + Na]$^+$, 557.2264, found, 557.2252. $[\alpha]_D^{20}$ = -528.57 (c 0.014, $CHCl_3$).

(3a*R*,5*S*,9b*R*)-5-Phenethyl-8-(p-tolylamino)-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromene-2,6,9(5*H*,9b*H*)-trione (11a): yellow solid (33%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 6.0 Hz, 2H), 7.19 (d, *J* = 2.8 Hz, 2H), 7.17 – 7.12(m, 3H), 7.08 (d, *J* = 6.0 Hz, 2H), 5.98 (s, 1H), 5.13 (s, 1H), 4.69–4.65 (m, 1H), 4.31– 4.29 (m, 1H), 2.90 (dd, *J* = 17.4, 4.5 Hz, 2H), 2.78 (d, *J* = 17.4 Hz, 1H), 2.76 – 2.68 (m, 2H), 2.44 (dd, *J* = 9.9, 5.6 Hz, 1H), 2.36 (s, 3H), 2.34 – 2.25 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.1, 181.3, 174.6, 150.7, 143.0, 141.1, 136.0, 134.3, 130.3, 129.5, 129.2, 128.4, 125.9, 122.4, 101.1, 71.8, 71.0, 69.9, 37.3, 35.1, 30.8, 21.0; MS (ESI) 452.1 [M + H]$^+$; HRMS (ESI) calcd for $C_{26}H_{23}NO_5Na$ [M + Na]$^+$, 452.1474, found, 452.1469. $[\alpha]_D^{20}$ = -35 (c 0.02, $CHCl_3$).

(3a*R*,5*S*,9b*R*)-8-((4-Fluorophenyl)amino)-5-phenethyl-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromene-2,6,9(5*H*,9b*H*)-trione (11b): yellow solid (24%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 – 7.12 (m, 10H), 5.88 (s, 1H), 5.13 (s, 1H), 4.68 – 4.63 (m, 1H), 4.36 – 4.27 (m, 1H), 2.92 (dd, *J* = 17.4, 4.5 Hz, 1H), 2.78 (d, *J* = 17.8 Hz, 1H), 2.75 – 2.61 (m, 2H), 2.46 – 2.27 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.2, 181.1, 174.7, 160.4 (d, *J*=247 Hz), 150.6, 143.3, 141.0, 132.9, 129.6, 129.2, 128.4, 125.9, 124.7 (d, *J*=9 Hz, 2), 116.7, (d, *J*= 24 Hz, 2), 101.1, 71.7, 71.0, 69.8, 37.3,

35.0, 30.7; MS (ESI) 431.9 $[M - H]^-$; HRMS (ESI) calcd for $C_{25}H_{19}NO_5F$ $[M - H]^-$, 432.1247, found, 432.1248. $[\alpha]_D^{20}$ = -50 (c 0.014, $CHCl_3$).

(3a*R*,5*R*,9b*R*)-5-Phenethyl-8-(phenylamino)-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromene-2,6,9(5*H*,9b*H*)-trione (11c): yellow solid (49%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.38(m, 3H), 7.32 – 7.27 (m, 2H), 7.24 – 7.19(m, 6H), 6.14 (s, 1H), 5.10 (d, *J* = 3.0 Hz, 1H), 4.82 – 4.78(m, 1H), 4.53 – 4.51 (m, 1H), 2.95 – 2.82 (m, 3H), 2.66 (d, *J* = 17.8 Hz, 1H), 2.20 – 2.09 (m, 1H), 1.96 – 1.84 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.4, 181.5, 174.1, 149.7, 143.0, 140.8, 136.9, 129.7, 128.9, 128.5, 128.4, 126.2, 126.0, 122.6, 100.9, 70.3, 68.7, 66.3, 36.8, 33.3, 32.5; MS (ESI) 438.1 $[M + Na]^+$; HRMS (ESI) calcd for $C_{25}H_{21}NO_5Na$ $[M + Na]^+$, 438.1317, found, 438.1316. $[\alpha]_D^{20}$ = 135.29 (c 0.017, $CHCl_3$).

General procedure for synthesis of compounds 12 and 13

A solution of pyanoquinone lactone aniline **11a** or **11c** in trifluoroacetic acid (40 mL mmol^{-1}) was added to a mixture of palladium diacetate (0.1 mol equiv.) and silver acetate (2 mol equiv.). The resulting mixture was stirred at 90 °C for 1 h, cooled to room temperature and quenched by saturated sodium bicarbonate and extracted with dichloromethane. The combined organic layers were washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. After removal of the solvents, the residue was purified by silica column chromatography using petroleum ether/ethyl acetate (1/1) provided corresponding products **12** and **13** in 20-30% yields.

(3a*R*,5*S*,12b*R*)-8-Methyl-5-phenethyl-3,3a dihydrofuro[2',3':5,6]pyrano[4,3-*b*]carbazole 2,6,12(5*H*,11*H*,12b*H*)-trione (12): deep red solid (20%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.94 (s, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.28 – 7.08 (m, 5H), 6.94 (d, *J* = 6.9 Hz, 1H), 5.20 (d, *J* = 2.5 Hz, 1H), 4.79 – 4.77 (m, 1H), 4.33 – 4.31(m, 1H), 2.93 (dd, *J* = 17.5, 4.3 Hz, 1H), 2.82 (d, *J* = 17.4Hz, 1H), 2.80 – 2.71 (m, 2H), 2.49 (s, 3H), 2.46 – 2.16 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 181.7, 176.9, 174.8, 150.0, 141.0, 135.6, 134.8, 134.2, 131.6, 129.6, 129.1, 128.2, 125.6, 124.4, 122.3, 116.9, 112.7, 71.8, 70.9, 70.2, 37.4, 35.3, 30.8, 21.6; MS (ESI) 450.1 $[M + Na]^+$; HRMS (ESI) calcd for $C_{26}H_{21}NO_5Na$ $[M + Na]^+$, 450.1317, found, 450.1311. $[\alpha]_D^{20}$ = -67 (c 0.024, $CHCl_3$).

(3a*R*,5*R*,12b*R*)-5-Phenethyl-3,3a-dihydrofuro[2',3':5,6]pyrano[4,3-*b*]carbazole-2,6,12(5*H*,11*H*,12b*H*)-trione (13): deep red solid (30%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.51 – 7.22 (m, 7H), 5.20 (d, *J* = 3.0 Hz, 1H), 4.91 – 4.87 (m, 1H), 4.58 – 4.52 (m, 1H), 3.00 – 2.89 (m, 3H), 2.71 (d, *J* = 17.7 Hz, 1H), 2.26 – 2.21 (m, 1H), 2.01 – 1.94 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 180.7, 177.4, 174.4, 149.2, 140.7, 137.2, 134.4, 130.8, 128.6, 128.5, 127.7, 126.2, 124.9, 124.0, 122.9, 116.9, 113.2, 70.3, 69.1, 66.3, 36.9, 33.5, 32.6; MS (ESI) 414.2 $[M + H]^+$; HRMS (ESI) calcd for $C_{25}H_{20}NO_5$ $[M + H]^+$, 414.1333, found, 414.1336. $[\alpha]_D^{20}$ = 600 (c 0.015, $CHCl_3$).

General procedure for synthesis of compounds 14a-d

To a solution of **9a** or **9a'** (1.0 equiv.) in toluene (20 mL mmol^{-1}), was added an appropriate iodobenzene (2 equiv.), palladium diacetate (0.1 equiv.), and silver acetate (2 equiv.). The resulting mixture was stirred at 80 °C for 2h, cooled to room temperature, concentrated in vacuo and extracted with EtOAc. The combined extracts were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by silica column chromatography using petroleum ether/ethyl acetate (3/1) provided corresponding products **14a-d** in 40 - 60% yields.

(3a*R*,5*S*,9b*R*)-5-Phenethyl-7-phenyl-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromene-2,6,9(5*H*,9b*H*)-trione (14a): yellow solid (50%);^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 5H), 7.20 – 7.04 (m, 5H), 6.65 (s, 1H), 5.20 (s, 1H), 4.69 – 4.66 (m, 1H), 4.34 – 4.31 (m, 1H), 2.94 (dd, *J* = 17.5, 4.5 Hz, 1H), 2.82 (d, *J* = 6.6 Hz, 1H), 2.79 – 2.71 (m, 2H), 2.43 – 2.35 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 185.9, 183.4, 174.5, 147.2, 145.5, 140.7, 132.9, 132.6, 132.0, 130.4, 129.5, 129.3, 128.6, 128.4, 126.0, 71.3, 70.9, 69.7, 37.3, 33.8, 30.5; MS (ESI) 423.1 $[M + Na]^+$; HRMS (ESI) calcd for $C_{25}H_{20}O_5Na$ $[M + Na]^+$, 423.1207, found, 423.1203. $[\alpha]_D^{20}$ = 22 (c 0.05, $CHCl_3$).

(3a*R*,5*R*,9b*R*)-7-(4-Chlorophenyl)-5-phenethyl-3,3a-dihydro-2*H*-furo[3,2-c]isochromene-2,6,9(5*H*,9b*H*)-trione (14b): yellow solid (42%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 – 7.37 (m, 4H), 7.32 – 7.27 (m, 3H), 7.21 – 7.18 (m, 2H), 6.84 (s, 1H), 5.16 (d, *J* = 2.8 Hz, 1H), 4.78 – 4.72 (m, 1H), 4.54 – 4.52 (m, 1H), 2.94 – 2.84 (m, 3H), 2.66 (d, *J* = 17.8 Hz, 1H), 2.15 – 2.05 (m, 1H), 1.99 – 1.88 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.0, 183.7, 173.9, 146.5, 145.0, 140.5, 137.0, 132.6, 132.3, 130.7, 130.5, 129.0, 128.5, 126.3, 69.5, 68.6, 66.5, 36.8, 33.0, 32.4; MS (ESI) 457.1 $[M + Na]^+$; HRMS (ESI) calcd for $C_{25}H_{29}ClO_5Na$ $[M + Na]^+$, 457.0921, found, 457.0924. $[\alpha]_D^{20}$ = 125 (c 0.004, $CHCl_3$).

(3a*R*,5*R*,9b*R*)-7-(4-Methoxyphenyl)-5-phenethyl-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromene-2,6,9(5*H*,9b*H*)-trione (14c): yellow solid (47%);^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.7 Hz, 2H), 7.32 – 7.24 (m, 3H), 7.23 – 7.17 (m, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.79 (s, 1H), 5.16 (d, *J* = 2.8 Hz, 1H), 4.76 – 4.72 (m, 1H), 4.53 – 4.50 (m, 1H), 3.83 (s, 3H), 2.88 (dt, *J* = 15.3, 6.4 Hz, 4H), 2.65 (d, *J* = 17.7 Hz, 1H), 2.13 – 2.02 (m, 1H), 1.92 (dd, *J* = 11.2, 6.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.2, 184.4, 174.1, 161.7, 146.2, 145.4, 140.6, 132.4, 131.1, 130.6, 128.5 (×2C), 126.2, 124.5, 114.2, 69.5, 68.7, 66.5, 55.4, 36.8, 33.0, 32.4; MS (ESI) 453.1 $[M + Na]^+$; HRMS (ESI) calcd for $C_{26}H_{22}O_6Na$ $[M + Na]^+$, 453.1314, found, 423.1301. $[\alpha]_D^{20}$ = 35.7 (c 0.021, $CHCl_3$).

(3a*R*,5*R*,9b*R*)-5-Phenethyl-7-(2,4,6-trimethoxyphenyl)-3,3a-dihydro-2*H*-furo[3,2-*c*]isochromene-2,6,9(5*H*,9b*H*)-trione (14d): yellow solid (55%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (m, 2H), 7.23 – 7.18 (m, 3H), 6.75 (s, 1H), 6.16 (s, 2H), 5.18 (d, *J* = 2.5 Hz, 1H), 4.78 – 4.75 (m, 1H), 4.53 – 4.50 (m, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.68 (s, 3H), 2.92 – 2.85 (dd, *J* = 16.2, 5.9 Hz, 1H), 2.66 (d, *J* = 17.7 Hz, 0H), 2.21 – 2.07 (m, 0H), 2.01 – 1.82 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.5, 183.2, 174.3, 162.9, 159.2, 158.7, 145.7, 143.3, 140.8, 135.9, 132.8, 128.5 (×2C), 126.2, 103.6, 91.0, 90.9, 69.7, 68.8, 66.4, 56.0, 55.8, 55.5, 37.0, 33.0, 32.5; MS (ESI) 513.1 $[M + Na]^+$; HRMS (ESI) calcd for $C_{28}H_{26}O_8Na$ $[M + Na]^+$, 513.1525, found, 513.1517. $[\alpha]_D^{20}$ = 140.91 (c 0.011, $CHCl_3$).

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A simple and effective synthesis of tricyclic quinone-pyran-lactone skeleton was developed and subsequent structural modification was conducted.