An Efficient Synthesis of Isoindolo[2,1-*a*]quinoline Derivatives via Imino Diels–Alder and Intramolecular Diels–Alder Reactions with Furan

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Abstract: The straightforward synthesis of new isoindolo[2,1-*a*]quinoline derivatives from 2,4-disubstituted 1,2,3,4-tetrahydroquinolines bearing a furan fragment via the intramolecular Diels–Alder reaction is reported. The synthesis of key precursors was realized with excellent levels of diastereoselectivity either by Povarov reaction or by a multicomponent condensation approach.

Key words: Povarov reaction, quinolines, furans, intramolecular Diels–Alder reaction, isoindolo[2,1-*a*]quinolines

The chemistry of tetrahydroquinoline derivatives has long been an area of interest for organic chemists due to the presence of these scaffolds within the framework of numerous biologically interesting natural products and pharmaceutical agents. Many new methods for the synthesis of tetrahydroquinoline derivatives have been developed.[1,2] The most attractive strategy for these derivatives is the acid-promoted imino Diels–Alder (Povarov) reaction between *N*-aryl-substituted aldimines and electron-rich alkenes, which is a route that has been a topic of continuing interest for the last forty years.[3,4] The synthesis of such compounds by three-component reaction of a substituted aniline, an benzaldehyde derivative, and an electron-rich alkene in the presence of various Lewis acid catalysts has become more popular.[5] The synthesis of tetrahydroquinoline derivatives has been studied extensively in solution, as well as on solid phase, using [4+2]-cycloaddition reactions.[6] Moreover, the imino Diels–Alder reaction of *N*-benzylidenanilines and enamides was synthetically useful in the rapid construction of the 4-amidotetrahydroquinoline system.[7] These processes are well documented, mainly due to synthetic efforts towards the martinelline alkaloid[8] that acts as a nonpeptide bradykinin receptor antagonist and 4-amido-2-carboxytetrahydroquinolines as a selective glycine antagonists.[9] On the other hand, the intramolecular Diels–Alder reaction with furan as the diene partner is a very powerful synthetic tool for the construction of rigid tricyclic nitrogen heterocycles.[10] With these facts in mind and taking into consideration that the 2-furyl-1,2,3,4-tetrahydroquinoline synthesis and chemistry have been poorly explored,[11] we consider that tetrahydroquinolines with furan moiety show interesting features that make them attractive for synthetic and pharmacological use. As part of our ongoing research program, searching for bioactive polyheterocycles containing a nitrogen atom from accessible aldimines,[12] we were interested in an efficient synthesis of isoindolo[2,1-*a*]quinoline derivatives, a class of molecules that possess an array of biological activities.[13] Recently, we reported the straightforward synthesis of 1,3-disubstituted 11-oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic acids, from 2,4-disubstituted 1,2,3,4-tetrahydroquinolines bearing a furan fragment via the intramolecular Diels–Alder reaction.[14] Herein, we wish to report our detailed study on this theme.

Syntheses of oxoisoindolo[2,1-*a*]quinoline derivatives are not numerous; various 11-oxo- and 5,11-dioxoisoindolo[2,1-*a*]quinolines have been prepared from 1*H*-isoindole derivatives,[13a,15,16] 2-(quinol-2-yl)benzoic acid and its esters,[17] or 2′-amino-2-methoxyacetophenones.[13b] Recently, an efficient two-step synthesis of these heterocyclic derivatives from 4-(arylamino)-4-(2-furyl)but-1-enes has been reported.[18]

Initially, freshly distilled *N*-furfurylidenanilines **3a–k** (readily obtained from various anilines **1** and 2-furaldehydes **2**) and *N*-vinylpyrrolidin-2-one were used in the intermolecular imino Diels–Alder reaction (Scheme 1). The reactions proceeded smoothly in the presence of boron trifluoride–diethyl ether complex (20 mol%) at room temperature (23–25°C) in dichloromethane to give the corresponding tetrahydroquinolines **4a–k** in excellent yields and with a highly level of selectivity. A simple purification process by recrystallization gave pure *cis*-2-(2-furyl)tetrahydroquinolines **4a–k** as stable crystalline substances (Table 1).

Cycloaddition of aldimine **3h** with *N*-vinylpyrrolidin-2-one gave a mixture of four isomers of 6,7-dichloro- and 5,6-dichlorotetrahydroquinoline derivatives in the crude reaction as observed by GC-EIMS analysis. The diastereomeric 6,7-dichlorotetrahydroquinoline derivative **4h** was separated using column chromatography (silica gel, heptane–EtOAc, 2:1), from which the *cis*-isomer was obtained by recrystallization.

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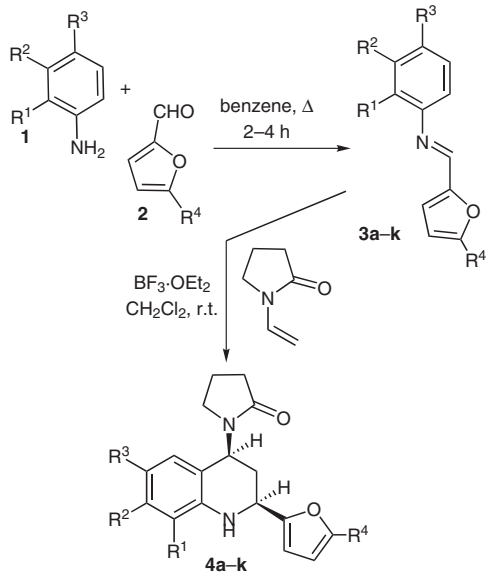
Table 1 Synthesis of *cis*-2-(2-Furyl)-4-(2-oxopyrrolidin-1-yl)quinolines **4a–k** Using the Povarov Reaction

Entry	Product	R^1	R^2	R^3	R^4	Ratio[a] *cis*/*trans*	Yield[b] (%)
1	**4a**	H	H	H	H	98:2	98
2	**4b**	H	H	Me	H	96:4	96
3	**4c**	H	H	OMe	H	96:4	90
4	**4d**	OMe	H	OMe	H	98:2	94
5	**4e**	H	H	Br	H	98:2	96
6	**4f**	H	H	Cl	H	98:2	96
7	**4g**	H	H	F	H	95:5	92
8	**4h**	H	Cl	Cl	H	90:10	77[c]
9	**4i**	Me	H	H	H	90:10	89
10	**4j**	OMe	H	H	H	85:15	82
11	**4k**	OMe	H	OMe	Me	76:24	75

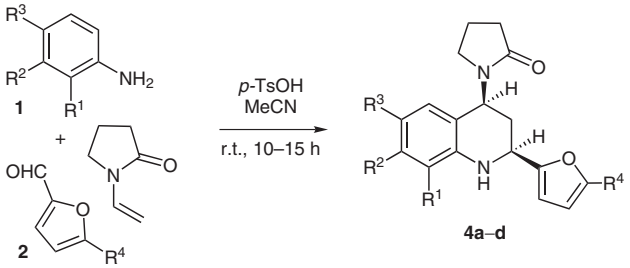
[a] Determined by GC-EIMS.
[b] Of the pure *cis*-isomer.
[c] All data are given for the *cis*-6,7-dichlorotetrahydroquinoline.

The relative configuration of the newly created stereocenters is *cis*-(2*e*,4*e*), indicating the *endo*-approach of *N*-vinylpyrrolidin-2-one. The structural elucidation of tetrahydroquinolines **4a–k** was made on basis of ^{1}H NMR. The relative *trans* orientation of H2, H3, and H4 was established from the large vicinal coupling constants $J_{2,3}$~$J_{3,4}$ = 10.0–11.5 Hz (Table 3).



Scheme 1

As multicomponent condensations have emerged as a powerful tool for delivering the molecular diversity needed in combinatorial approaches for the preparation of bioactive compounds, we examined the three-component Povarov reaction between *p*-toluidine, 2-furaldehyde, and *N*-vinylpyrrolidin-2-one to afford the tetrahydroquinoline **4b** (Scheme 2) using various conditions. These condensations were carried out in various solvents (CH_2Cl_2, MeCN, toluene, etc.) at room temperature in the presence of various water-tolerant acidic catalysts. This cycloaddition proceeded smoothly in the presence of Lewis (BF_3·OEt_2, $AlCl_3$, $BiCl_3$) and Brönsted (TsOH, TFA, oxalic acid) acids (10–20 mol%) in acetonitrile, dichloromethane, toluene, and diethyl ether. 4-Toluenesulfonic acid (20 mol%) was the best catalyst in this multicomponent condensation, giving the final product **4b** in 80% yield in 20 hours in acetonitrile at room temperature. Thus, this multicomponent condensation between selected anilines, 2-furaldehyde, and *N*-vinylpyrrolidin-2-one under these chosen conditions afforded the key tetrahydroquinoline precursors **4a–c** in good yields (Table 2). However, in the case of 2,4-dimethoxyaniline, the desired tetrahydroquinoline **4d** was obtained in very poor yield.



Scheme 2

In next step, the *cis*-tetrahydroquinolines **4a–i** were readily converted into the corresponding 11-oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic acids **5a–i** and their

Table 2 Three-Component Synthesis of Synthesis of *cis*-2-(2-Furyl)-4-(2-oxopyrrolidin-1-yl)quinolines **4a–d**

Entry	Product	R^1	R^2	R^3	R^4	Yield[a] (%)
1	**4a**	H	H	H	H	65
2	**4b**	H	H	Me	H	80
3	**4c**	H	H	OMe	H	75
4	**4d**	OMe	H	OMe	H	10

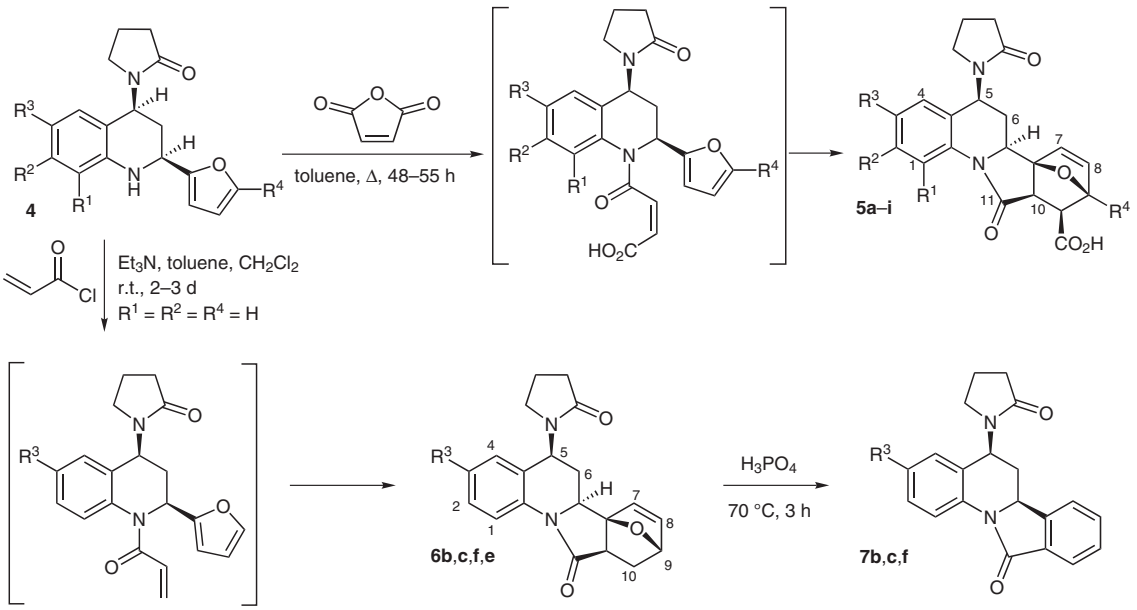
[a] Purified by column chromatography as the *cis*-isomer.

analogues, epoxyisoindolo[2,1-*a*]quinolines **6b**,**c**,**f**,**e** (Scheme 3). The N-acylation of 2-(2-furyl)tetrahydroquinolines **4** with maleic anhydride in toluene at 60 °C and subsequent intramolecular Diels–Alder reaction with the furan moiety provided the final polycyclic products *exo*-adducts **5** in high yields and with an excellent level of selectivity. The N-acylation of 2-furyltetrahydroquinolines **4b**,**c**,**f**,**e** with acryloyl chloride resulted in the formation of the corresponding 11-oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-6b,9-epoxyisoindolo[2,1-*a*]quinolines **6** in good yields. Carboxylic acids **5** are stable colorless crystalline substances, sparingly soluble in most organic solvents and with high melting points. Their analogues **6** are also colorless crystalline substances, but soluble in common solvents (Table 4).

Homonuclear and inverse-detected 2D NMR experiments allowed the assignment of all the signals and correlations, corroborating the obtained epoxyisoindolo[2,1-*a*]quinoline core. From the ^{1}H NMR spectra of compounds **5a**–**i**, the configuration of the proton H6a was judged to be axial,[12] but the orientation of this proton relative to the 6b,9-epoxy bridge remained unclear (Table 5).

The NOE experiments did not give a definitive answer to this question. The attempts to obtain a monocrystal of a sample of one of the carboxylic acids **5** failed because of their extremely low solubility in the vast majority of organic solvents.

To determine orientation of the H6a proton in compounds **5**–**7**, a single crystal of the compound **6e** was grown. An X-ray crystal structure analysis was carried out, the resulting structure is shown on Figure 1.[19,20] The molecular structure of **6e** consists of a pyrrolo[1,2-*a*]quinoline condensed with an oxabicyclo[2.2.1]heptane fragment. The central hexahydropyrrolo[1,2-*a*]quinoline fragment has *exo*-fusion [C(15)–C(16) *exo*-bond] with a oxabicyclo[2.2.1]heptene (crystallographic numbering used). The central six-membered cycle N(1)–C(1)–C(6)–C(9) is folded and has a conformation envelope with C(8) deviating (0.63 Å) from a least-squares plane defined by five other atoms. The 2-oxopyrrolidin-1-yl group occupies a pseudoequatorial position and both protons H(7) and H(9) (≡ H5 and H6a) are in the pseudoaxial position in the tetrahydroquinoline. The geometry of the 7-oxabicyclo[2.2.1]hept-2-ene is normal, with the dihedral angle



Scheme 3

Table 3 ^{1}H NMR Data of Compounds **4a–k**

	^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ, *J* (Hz)
4a	2.02 (m, 2 H, CH_2), 2.23 (m, 2 H, CH_2), 2.49 (m, 2 H, CH_2), 3.20 (m, 2 H, CH_2), 4.10 (s, 1 H, NH), 4.67 (dd, *J* = 10.0, 4.0, 1 H, CH), 5.68 (dd, *J* = 10.5, 8.0, 1 H, CH), 6.26 (d, *J* = 3.0, 1 H_{arom}), 6.35 (dd, *J* = 3.0, 2.0, 1 H_{arom}), 6.58 (dd, *J* = 8.0, 1.0, 1 H_{arom}), 6.71 (td, *J* = 7.5, 7.5, 1.0, 1 H_{arom}), 6.86 (dd, *J* = 7.5, 1.0, 1 H_{arom}), 7.04 (tt, *J* = 7.5, 7.5, 2.0, 1 H_{arom}), 7.38 (dd, *J* = 2.0, 1.0, 1 H_{arom})
4b	2.01 (m, 2 H, CH_2), 2.19 (s, 3 H, CH_3), 2.21 (m, 2 H, CH_2), 2.49 (m, 2 H, CH_2), 3.19 (dm, 2 H, CH_2), 4.01 (s, 1 H, NH), 4.60 (dd, *J* = 10.5, 3.5, 1 H, CH), 5.64 (dd, *J* = 11.0, 7.0, 1 H, CH), 6.24 (d, *J* = 3.0, 1 H_{arom}), 6.33 (dd, *J* = 3.0, 2.0, 1 H_{arom}), 6.50 (d, *J* = 8.0, 1 H_{arom}), 6.65 (s, 1 H_{arom}), 6.84 (d, *J* = 8.0, 1 H_{arom}), 7.37 (dd, *J* = 2.0, 1.0, 1 H_{arom})
4c	1.99 (m, 2 H, CH_2), 2.21 (m, 2 H, CH_2), 2.48 (m, 2 H, CH_2), 3.20 (dm, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 4.90 (s, 1 H, NH), 4.58 (dd, *J* = 11.0, 3.0, 1 H, CH), 5.66 (dd, *J* = 11.5, 6.5, 1 H, H), 6.24 (dd, *J* = 3.0, 1.0, 1 H_{arom}), 6.33 (dd, *J* = 3.0, 2.0, 1 H_{arom}), 6.45 (dd, *J* = 2.5, 1.0, 1 H_{arom}), 6.55 (d, *J* = 8.0, 1 H_{arom}), 6.65 (dd, *J* = 9.0, 2.5, 1 H_{arom}), 7.37 (dd, *J* = 2.0, 1.0, 1 H_{arom})
4d	1.98 (m, 2 H, CH_2), 2.24 (m, 2 H, CH_2), 2.48 (m, 2 H, CH_2), 3.20 (dm, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 4.25 (s, 1 H, NH), 4.55 (dd, *J* = 11.0, 3.0, 1 H, CH), 5.68 (dd, *J* = 11.0, 7.0, 1 H, CH), 6.06 (d, *J* = 2.0, 1 H_{arom}), 6.27 (d, *J* = 3.0, 1 H_{arom}), 6.34 (d, *J* = 2.0, 1 H_{arom}), 6.34 (d, *J* = 1.5, 1 H_{arom}), 7.37 (dd, *J* = 2.0, 1.0, 1 H_{arom})
4e	2.04 (m, 2 H, CH_2), 2.20 (m, 2 H, CH_2), 2.50 (m, 2 H, CH_2), 3.20 (m, 2 H, CH_2), 4.19 (s, 1 H, NH), 4.63 (m, 1 H, CH), 5.61 (t, *J* = 9.0, 8.9, 1 H, CH), 6.25 (d, *J* = 3.3, 1 H, CH), 6.34 (dd, *J* = 3.2, 1.9, 1 H, CH), 6.45 (d, *J* = 8.5, 1 H_{arom}), 6.93 (dd, *J* = 2.2, 1.0, 1 H_{arom}), 7.11 (ddd, *J* = 8.5, 2.3, 0.7, 1 H_{arom}), 7.37 (dd, *J* = 1.8, 0.8, 1 H_{arom})
4f	2.03 (m, 2 H, CH_2), 2.21 (m, 2 H, CH_2), 2.50 (m, 2 H, CH_2), 3.21 (dm, 2 H, CH_2), 4.14 (s, 1 H, NH), 4.64 (m, 1 H, CH), 5.62 (t, *J* = 9.0, 1 H, CH), 6.25 (d, *J* = 3.0, 1 H_{arom}), 6.35 (dd, *J* = 3.0, 2.0, 1 H_{arom}), 6.51 (d, *J* = 8.0, 1 H_{arom}), 6.80 (d, *J* = 2.0, 1 H_{arom}), 6.99 (dq, *J* = 8.0, 2.5, 1.0, 1 H_{arom}), 7.38 (dd, *J* = 2.0, 1.0, 1 H_{arom})
4g	2.03 (m, 2 H, CH_2), 2.21 (m, 2 H, CH_2), 2.50 (m, 2 H, CH_2), 3.22 (dm, 2 H, CH_2), 4.04 (s, 1 H, NH), 4.62 (dd, *J* = 10.5, 3.5, 1 H, CH), 5.64 (dd, *J* = 11.0, 7.0, 1 H, CH), 6.25 (d, *J* = 3.0, 1 H_{arom}), 6.34 (dd, *J* = 3.0, 2.0, 1 H_{arom}), 6.53 (dd, *J* = 4.0, 4.0, 1 H_{arom}), 6.58 (dd, *J* = 3.0, 1.0, 1 H_{arom}), 6.77 (dddd, *J* = 10.0, 7.0, 3.0, 1.0, 1 H_{arom}), 7.38 (dd, *J* = 2.0, 1.0, 1 H_{arom})
4h	1.17 (dm, 2 H, CH_2), 2.31 (m, 2 H, CH_2), 2.45 (dm, 2 H, CH_2), 2.74 (m, 2 H, CH_2), 4.47 (s, 1 H, NH), 4.52 (m, 1 H, CH), 5.47 (t, *J* = 6.5, 6.5, 1 H, CH), 6.20 (dt, *J* = 3.0, 1.0, 1 H_{arom}), 6.33 (dd, *J* = 3.0, 2.0, 1 H_{arom}), 6.53 (d, *J* = 9.0, 1 H_{arom}), 7.11 (dd, *J* = 9.0, 1.0, 1 H_{arom}), 7.37 (dt, *J* = 1.0, 1 H_{arom})
4i	2.00 (m, 2 H, CH_2), 2.11 (s, 3 H, CH_3), 2.24 (m, 2 H, CH_2), 2.49 (m, 2 H, CH_2), 3.19 (dm, 2 H, CH_2), 3.91 (s, 1 H, NH), 4.68 (dd, *J* = 10.0, 4.0, 1 H, CH), 5.71 (dd, *J* = 11.0, 7.0, 1 H, CH), 6.29 (d, *J* = 3.0, 1 H_{arom}), 6.37 (dd, *J* = 3.0, 2.0, 1 H_{arom}), 6.66 (dd, *J* = 7.0, 6.0, 1 H_{arom}), 6.75 (d, *J* = 8.0, 1 H_{arom}), 6.95 (dt, *J* = 6.0, 1.0, 1 H_{arom}), 7.40 (dd, *J* = 2.0, 1.0, 1 H_{arom})
4j	1.98 (m, 2 H, CH_2), 2.25 (m, 2 H, CH_2), 2.48 (m, 2 H, CH_2), 3.18 (dm, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 4.47 (s, 1 H, NH), 4.62 (dd, *J* = 7.7, 6.1, 1 H, CH), 5.70 (dd, *J* = 9.1, 8.8, 1 H, CH), 6.27 (d, *J* = 3.2, 1 H_{arom}), 6.34 (dd, *J* = 3.2, 1.8, 1 H_{arom}), 6.51 (m, 1 H_{arom}), 6.65 (s, 1 H_{arom}), 6.66 (d, *J* = 0.6, 1 H_{arom}), 7.37 (dd, *J* = 1.8, 0.8, 1 H_{arom})
4k	1.96 (m, 2 H, CH_2), 2.21 (m, 2 H, CH_2), 2.24 (s, 3 H, CH_3), 2.45 (m, 2 H, CH_2), 3.16 (dm, 2 H, CH_2), 3.67 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 4.19 (s, 1 H, NH), 4.44 (m, 1 H, CH), 5.64 (t, *J* = 9.5, 1 H, CH), 5.87 (dd, *J* = 2.5, 1 H_{arom}), 6.03 (d, *J* = 3.0, 1 H_{arom}), 6.10 (d, *J* = 3.0, 1 H_{arom}), 6.30 (d, *J* = 2.0, 1 H_{arom})

between the planes C(10)–C(13) and C(10)–C(13)–C(14)–C(15) equal 108.2°. The C(10)–O(1)–C(13) epoxy bridge and H(9) (≡ H6a) are in the *trans*-position.

Acid treatment (H_3PO_4, 70 °C, 3 h) of the crude epoxyisoindolo[2,1-*a*]quinolines **6** gave the corresponding 3-substituted 11-oxo-5-(2-oxopyrrolidinyl)isoindolo[2,1-*a*]quinolines **7**, the final products in our investigation (Scheme 3). Their structures were confirmed by ^{1}H and ^{13}C NMR spectra and MS data.

In summary, the synthesis described herein provides diverse isoindolo[2,1-*a*]quinoline derivatives: epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic acids, epoxyisoindolo[2,1-*a*]quinolines, and 11-oxo-5-(2-oxopyrrolidin-1-yl)isoindolo[2,1-*a*]quinolines, useful in the preparation of interesting small drug-like molecules. These polyheterocycles are available in two-steps or three-steps and in good yields from commercial and inexpensive *N*-vinylpyrrolidin-2-one, anilines, and 2-furaldehydes or their respective aldimines. Some chemical transformations of these interesting molecules for the preparation of functionalized 11-oxoisoindolo[2,1-*a*]quinolines are under way in our laboratories.

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were obtained on a Nicolet Avatar 360-FTIR spectrophotometer as KBr pellets. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-400 spectrometer (400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR), using $CDCl_3$ or DMSO-d_6 as the solvent. TMS was used as an internal standard. A Hewlett-Packard (HP) 5890 A series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector with an HP MS ChemStation Data system was used for MS identification at 70 eV using a 60-m capillary column coated with HP-5 [5%-phenylpoly(dimethylsiloxane)]. Elemental analyses were performed on a Perkin Elmer 2400 Series II analyzer. The reaction progress was monitored using TLC on a Silufol UV 254 TLC aluminum sheets. Column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). All reagents were purchased from Merck, Sigma, and Aldrich and used

Table 4 Straightforward Synthesis of Epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic Acids **5**, Their Analogues **6**, and Isoindolo[2,1-*a*]quinolines **7** from Tetrahydroquinolines **4**

Entry	Product	R^1	R^2	R^3	R^4	Yield (%)	Mp (°C)
1	**5a**	H	H	H	H	80	264–265
2	**5b**	H	H	Me	H	83	>300
3	**5c**	H	H	OMe	H	75	268–269
4	**5d**	OMe	H	OMe	H	70	243–244
5	**5f**	H	H	Cl	H	63	267–268
6	**5g**	H	H	F	H	70	265–266
7	**5i**	Me	H	H	H	60	266–267
8	**6b**	H	H	Me	H	82	nd[a]
9	**6c**	H	H	OMe	H	60	nd[a]
10	**6e**	H	H	Br	H	72	nd[a]
11	**6f**	H	H	Cl	H	87	nd[a]
12	**7b**	H	H	Me	H	95	205–206
13	**7c**	H	H	OMe	H	98	231–232
14	**7f**	H	H	Cl	H	84	233–234

[a] Not determined, used crude in the following step.

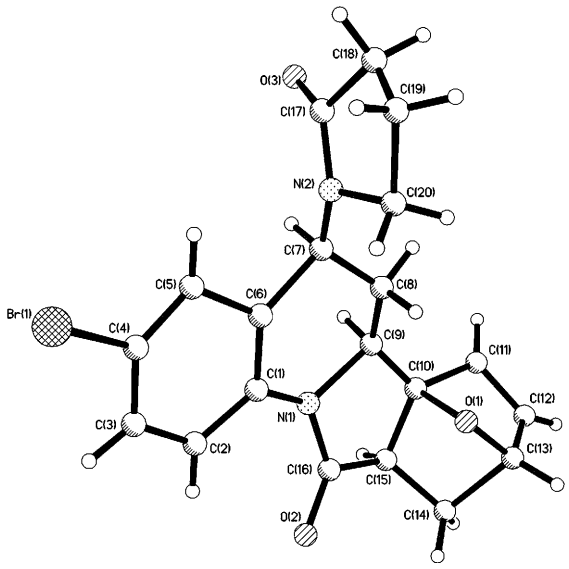


Figure 1 X-ray crystal structures of compound **6e**

without further purification. Final purification of all products for elemental analyses was performed by recrystallization. The X-ray data for **6e** were collected on an Inraf-Nonius Cad-4 diffractometer (graphite monochromator, 293(2)K, α-scanning technique). The structure was solved by direct and Fourier techniques, and refined by full-matrix least-squares on F^2 with anisotropic thermal parameters for all non-hydrogen atoms. The positions of the hydrogen atoms of the molecule were calculated geometrically and refined using the riding model. The crystals of **6e** proved to be twinned crystals, monoclinic with β ~90°, that emulated an orthorhombic system. Twinned crystals (with taking into account of racemic twinning) of **6e** were refined using the SHELXL-97[20] program by a literature method.[21]

2-(2-Furyl)-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinolines 4; General Procedure

A soln of aldimine **3** (8.3 mmol) in anhyd CH_2Cl_2 (15 mL) was cooled to 0 °C. Over a period of 20 min, $BF_3{\cdot}OEt_2$ (0.36 mL, 2.8 mmol) was added dropwise. The resulting mixture was allowed to warm to 25°C and *N*-vinylpyrrolidin-2-one (1.02 g, 9.1 mmol) in CH_2Cl_2 (10 mL) was then added with vigorous stirring. The mixture was stirred at r.t. for 12 h and then poured into H_2O. The organic layer was separated and dried (Na_2SO_4). The organic solvent was removed in vacuo. The residue, which was analyzed by GC-MS, was purified by recrystallization (CH_2Cl_2–EtOAc, 2:1) to afford *cis*-tetrahydroquinolines **4** (Table 1).

***cis*-2-(2-Furyl)-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (4a)**

Mp 115–116 °C.

IR (KBr): 3320, 1670, 1147 cm^{-1}.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.2, 31.2, 31.4, 42.3, 47.7, 49.6, 105.5, 110.2, 115.2, 118.5, 119.0, 126.9, 128.2, 142.0, 145.1, 155.1, 175.8.

GC-EIMS (70 eV): t_R = 35.01 min, *m/z* (%) = 282 (M^+, 6), 198 ($M^+ - C_4H_6NO$, 12), 197 ($M^+ - C_4H_7NO$, 66), 196 ($M^+ - C_4H_8NO$, 100), 168 (15), 130 ($M^+ - C_8H_{10}NO_2$, 13), 77 (6), 41 (5).

***cis*-2-(2-Furyl)-6-methyl-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (4b)**

Mp 194–195 °C.

IR (KBr): 3330, 1670, 1145 cm^{-1}.

Table 5 ^{1}H NMR Data of Compounds **5** and **6**

	^{1}H NMR (400 MHz, DMSO-d_6) δ, *J* (Hz)
5a	1.96 (m, 2 H, CH_2), 2.00 (m, 2 H, CH_2), 2.37 (m, 2 H, CH_2), 2.59 (d, *J* = 9.0, 1 H, CH), 3.08 (dm, 2 H, CH_2), 3.13 (d, *J* = 9.0, 1 H, CH), 4.88 (dd, *J* = 11.0, 3.0, 1 H, CH), 5.05 (d, *J* = 2.0, 1 H, CH), 5.50 (m, 1 H, CH), 6.51 (dd, *J* = 5.5, 1.5, 1 H, CH), 6.61 (d, *J* = 5.0, 1 H, CH), 6.97 (d, *J* = 8.0, 1 H_{arom}), 7.08 (t, *J* = 7.5, 1 H_{arom}), 7.24 (t, *J* = 8.0, 1 H_{arom}), 8.54 (d, *J* = 7.5, 1 H_{arom}), 12.30 (s, 1 H, CO_2H)
5b	1.96 (m, 2 H, CH_2), 2.04 (m, 2 H, CH_2), 2.24 (s, 3 H, CH_3), 2.39 (m, 2 H, CH_2), 2.57 (d, *J* = 9.0, 1 H, CH), 3.11 (dm, 2 H, CH_2), 3.10 (d, *J* = 9.0, 1 H, CH), 4.83 (dd, *J* = 11.5, 2.5, 1 H, CH), 5.03 (d, *J* = 2.0, 1 H, CH), 5.45 (m, 1 H, CH), 6.50 (dd, *J* = 6.0, 1.0, 1 H, CH), 6.60 (d, *J* = 6.0, 1 H, CH), 6.76 (s, 1 H_{arom}), 7.05 (d, *J* = 8.0, 1 H_{arom}), 8.51 (d, *J* = 8.0, 1 H_{arom}), 12.28 (s, 1 H, CO_2H)
5c	1.95 (m, 2 H, CH_2), 1.98 (m, 2 H, CH_2), 2.38 (m, 2 H, CH_2), 2.57 (d, *J* = 9.0, 1 H, CH), 3.09 (dm, 2 H, CH_2), 3.10 (d, *J* = 9.0, 1 H, CH), 3.70 (s, 3 H, OCH_3), 4.82 (dd, *J* = 11.5, 2.5, 1 H, CH), 5.03 (d, *J* = 1.0, 1 H, CH), 5.45 (m, 1 H, CH), 6.44 (d, *J* = 2.0, 1 H_{arom}), 6.50 (dd, *J* = 6.0, 1.0, 1 H, CH), 6.59 (d, *J* = 6.0, 1 H, CH), 6.88 (dd, *J* = 8.0, 2.5, 1 H_{arom}), 8.58 (d, *J* = 8.0, 1 H_{arom}), 12.19 (s, 1 H, CO_2H)
5d	1.93 (m, 2 H, CH_2), 2.19 (dm, 2 H, CH_2), 2.42 (m, 2 H, CH_2), 2.55 (d, *J* = 9.0, 1 H, CH), 2.95 (d, *J* = 9.0, 1 H, CH), 3.05 (dm, 2 H, CH_2), 3.67 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 4.24 (dd, *J* = 12.5, 2.5, 1 H, CH), 5.07 (d, *J* = 1.6, 1 H, CH), 5.52 (dd, *J* = 10.0, 8.0, 1 H, CH), 6.09 (d, *J* = 2.0, 1 H_{arom}), 6.48 (dd, *J* = 6.0, 1.6, 1 H, CH), 6.52 (d, *J* = 2.0, 1 H_{arom}), 6.70 (d, *J* = 6.0, 1 H, CH), 12.29 (s, 1 H, CO_2H)
5f	2.01 (m, 2 H, CH_2), 2.11 (m, 2 H, CH_2), 2.40 (m, 2 H, CH_2), 2.60 (d, *J* = 9.0, 1 H, CH), 3.15 (d, *J* = 9.0, 1 H, CH), 3.16 (dm, 2 H, CH_2), 4.89 (dd, *J* = 10.0, 4.0, 1 H, CH), 5.05 (d, *J* = 2.0, 1 H, CH), 5.47 (m, 1 H, CH), 6.52 (dd, *J* = 6.0, 1.0, 1 H, CH), 6.64 (d, *J* = 4.0, 1 H, CH), 6.95 (d, *J* = 1.0, 1 H_{arom}), 7.33 (dd, *J* = 9.0, 2.0, 1 H_{arom}), 8.66 (d, *J* = 9.0, 1 H_{arom}), 12.31 (s, 1 H, CO_2H)
5g	1.99 (m, 2 H, CH_2), 2.09 (m, 2 H, CH_2), 2.36 (m, 2 H, CH_2), 2.59 (d, *J* = 9.0, 1 H, CH), 3.13 (dm, 2 H, CH_2), 3.14 (d, *J* = 9.0, 1 H, CH), 4.89 (dd, *J* = 11.0, 3.0, 1 H, CH), 5.05 (d, *J* = 2.0, 1 H, CH), 5.47 (m, 1 H, CH), 6.52 (dd, *J* = 6.0, 2.0, 1 H, CH), 6.61 (d, *J* = 6.0, 1 H, CH), 6.78 (dd, *J* = 8.5, 2.5, 1 H_{arom}), 7.13 (td, *J* = 8.5, 2.5, 1 H_{arom}), 8.68 (dd, *J* = 9.0, 2.0, 1 H_{arom}), 12.27 (s, 1 H, CO_2H)
5i	1.91 (q, 2 H, CH_2), 2.15 (s, 3 H, CH_3), 2.35 (m, 2 H, CH_2), 2.47 (dm, 2 H, CH_2), 2.62 (d, *J* = 9.0, 1 H, CH), 3.02 (d, *J* = 9.0, 1 H, CH), 3.07 (dm, 2 H, CH_2), 4.38 (dd, *J* = 13.0, 2.0, 1 H, CH), 5.11 (d, *J* = 1.5, 1 H, CH), 5.61 (dd, *J* = 10.0, 8.0, 1 H, CH), 6.49 (dd, *J* = 6.0, 1.5, 1 H, CH), 6.76 (d, *J* = 6.0, 1 H, CH), 6.85 (t, *J* = 6.0, 1 H_{arom}), 7.12 (m, 2 H_{arom}), 12.28 (s, 1 H, CO_2H)
6b[a]	1.62 (dd, *J* = 11.9, 8.8, 1 H_{endo}, CH), 1.99 (m, 2 H, CH_2), 2.12 (m, 2 H, CH_2), 2.23 (m, 1 H_{exo}, CH), 2.25 (s, 3 H, CH_3), 2.48 (m, 2 H, CH_2), 2.62 (dd, *J* = 8.7, 3.4, 1 H_{endo}, CH), 3.12 (dm, 2 H, CH_2), 4.58 (dd, *J* = 10.9, 3.6, 1 H, CH), 5.07 (dd, *J* = 4.5, 1.5, 1 H, CH), 5.61 (dd, *J* = 11.5, 6.8, 1 H, CH), 6.39 (d, *J* = 5.8, 1 H, CH), 6.43 (dd, *J* = 5.8, 1.7, 1 H, CH), 6.74 (s, 1 H_{arom}), 7.03 (dd, *J* = 8.5, 1.9, 1 H_{arom}), 8.54 (d, *J* = 8.5, 1 H_{arom})
6c[a]	1.63 (dd, *J* = 11.8, 8.8, 1 H_{endo}, CH), 2.00 (m, 2 H, CH_2), 2.13 (m, 2 H, CH_2), 2.24 (m, 1 H_{exo}, CH), 2.48 (m, 2 H, CH_2), 2.63 (dd, *J* = 8.7, 3.3, 1 H_{endo}, CH), 3.14 (dm, 2 H, CH_2), 3.73 (s, 3 H, CH_3), 4.57 (dd, *J* = 10.8, 3.7, 1 H, CH), 5.07 (dd, *J* = 4.3, 1.0, 1 H, CH), 5.62 (dd, *J* = 11.4, 6.9, 1 H, CH), 6.39 (d, *J* = 5.8, 1 H, CH), 6.44 (dd, *J* = 5.8, 1.4, 1 H,CH), 6.50 (dd, *J* = 2.6, 1 H_{arom}), 6.79 (dd, *J* = 9.2, 2.8, 1 H_{arom}), 8.63 (d, *J* = 9.1, 1 H_{arom})
6e	1.55 (dd, *J* = 11.6, 8.8, 1 H_{endo}, CH), 1.97 (m, 5 H, CH, $2CH_2$), 2.38 (m, 2 H, CH_2), 2.74 (dd, *J* = 8.7, 3.3, 1 H_{endo}, CH), 3.09 (dm, 2 H, CH_2), 4.92 (dd, *J* = 8.0, 6.5, 1 H, CH), 5.07 (dd, *J* = 4.5, 1.5, 1 H, CH), 5.46 (t, *J* = 8.3, 1 H, CH), 6.48 (dd, *J* = 5.8, 1.7, 1 H, CH), 6.54 (d, *J* = 5.8, 1 H, CH), 7.06 (dd, *J* = 2.2, 0.9, 1 H_{arom}), 7.45 (ddd, *J* = 6.5, 2.4, 0.6, 1 H_{arom}), 8.59 (d, *J* = 9.0, 1 H_{arom})
6f[a]	1.64 (dd, *J* = 11.9, 8.8, 1 H_{endo}, CH), 2.03 (m, 2 H, CH_2), 2.13 (m, 2 H, CH_2), 2.23 (m, 1 H_{exo}, CH), 2.50 (m, 2 H, CH_2), 2.63 (dd, *J* = 8.7, 3.3, 1 H_{endo}, CH), 3.13 (dm, 2 H, CH_2), 4.60 (dd, *J* = 10.6, 3.9, 1 H, CH), 5.07 (dd, *J* = 4.5, 1.5, 1 H, CH), 5.60 (dd, *J* = 11.1, 7.2, 1 H, CH), 6.39 (d, *J* = 5.8, 1 H), 6.44 (dd, *J* = 5.8, 1.6, 1 H, CH), 6.91 (dd, *J* = 2.4, 1.0, 1 H_{arom}), 7.18 (ddd, *J* = 7.1, 2.5, 0.6, 1 H_{arom}), 8.65 (d, *J* = 9.0, 1 H_{arom})

[a] The solvent was $CDCl_3$/TMS.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.2, 20.5, 31.1, 31.3, 42.2, 47.7, 49.7, 105.3, 110.1, 115.4, 119.0, 127.1, 127.8, 128.9, 141.9, 142.7, 155.2, 175.7.

GC-EIMS (70 eV): t_R = 36.51 min, *m/z* (%) = 296 (M^+, 5), 212 ($M^+ - C_4H_6NO$, 10), 211($M^+ - C_4H_7NO$, 50), 210 ($M^+ - C_4H_8NO$, 100), 196 (5), 182 (7), 167 (7), 144 ($M^+ - C_8H_{10}NO_2$, 10), 130 (5), 115 (6), 91 (6), 81 (6), 44 (10).

***cis*-2-(2-Furyl)-6-methoxy-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (4c)**

Mp 169–170 °C.

IR (KBr): 3349, 1679, 1116 cm^{-1}.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.2, 31.3, 31.3, 42.3, 48.0, 50.0, 55.8, 105.4, 110.2, 112.2, 114.5, 116.6, 120.4, 139.2, 141.9, 152.9, 155.2, 175.7.

GC-EIMS (70 eV): t_R = 40.98 min, *m/z* (%) = 312 (M^+, 9), 228 ($M^+ - C_4H_6NO$, 8), 227 ($M^+ - C_4H_7NO$, 42), 226 ($M^+ - C_4H_8NO$, 100), 212 (6), 198 (5), 183 (5), 160 ($M^+ - C_8H_{10}NO_2$, 7), 117 (6), 81 (8), 41 (5).

***cis*-2-(2-Furyl)-6,8-dimethoxy-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (4d)**

Mp 178–179 °C.

IR (KBr): 3392, 1681, 1153 cm^{-1}.

Table 6 COSY Correlations of Compounds **6**

	COSY correlations [δ_H/δ_H (H/H)]
6b	1.62/2.23 ($10_{endo}/10_{exo}$), 1.62/2.62 ($10_{endo}/10a_{endo}$), 1.99/2.48 (4″/3″), 1.99/3.17 (4″/5″), 2.12/4.58 (6/6a), 2.12/5.61 (6/5), 2.23/1.62 ($10_{exo}/10_{endo}$), 2.23/2.62 ($10_{exo}/10a_{endo}$), 2.23/5.07 (10_{exo}/9), 2.48/1.99 (3″/4″), 2.62/1.62 ($10a_{endo}/10_{endo}$), 2.62/2.23 ($10a_{endo}/10_{exo}$), 3.12/1.99 (5″/4″), 4.58/2.12 (6a/6), 5.07/2.23 (9/10_{exo}), 5.07/6.43 (9/8), 5.61/2.12 (5/6), 6.39/6.43 (7/8), 6.43/5.07 (8/9), 6.43/6.39 (8/7), 6.74/7.03 (4/2), 7.03/6.74 (2/4), 7.03/8.54 (2/1), 8.54/7.03 (1/2)
6c	1.63/2.24 ($10_{endo}/10_{exo}$), 1.63/2.63 ($10_{endo}/10a_{endo}$), 2.00/2.48 (4″/3″), 2.00/3.14 (4″/5″), 2.13/4.57 (6/6a), 2.13/5.62 (6/5), 2.24/1.63 ($10_{exo}/10_{endo}$), 2.24/2.63 ($10_{exo}/10a_{endo}$), 2.24/5.07 (10_{exo}/9), 2.48/2.00 (3″/4″), 2.63/1.63 ($10a_{endo}/10_{endo}$), 2.63/2.24 ($10a_{endo}/10_{exo}$), 3.14/2.00 (5″/4″), 4.57/2.13 (6a/6), 5.07/2.24 (9/10_{exo}), 5.07/6.44 (9/8), 5.62/2.13 (5/6), 6.39/6.44 (7/8), 6.44/5.07 (8/9), 6.44/6.39 (8/7), 6.50/6.79 (4/2), 6.79/6.50 (2/4), 6.79/8.63 (2/1), 8.63/6.79 (1/2)
6e	[M[a] = 4″, 6, 10_{exo}], 1.55/1.97 ($10_{endo}/10_{exo}$[M]), 1.55/2.74 ($10_{endo}/10a_{endo}$), 1.97/1.55 (M/10_{endo}), 1.97/1.97 (M/M), 2.38/1.97 (3″/M), 2.74/1.55 ($10a_{endo}/10_{endo}$), 2.74/1.97 ($10a_{endo}/10_{exo}$[M]), 3.09/1.97 (5″/4″[M]), 4.92/1.97 (6a/6[M]), 5.07/1.97 (9/10_{exo}[M]), 5.07/6.48 (9/8), 5.46/1.97 (5/6[M]), 6.48/5.07 (8/9), 6.48/6.54 (8/7), 6.54/6.48 (7/8), 7.06/7.45 (4/2), 7.45/7.06 (2/4), 7.45/8.59 (2/1), 8.59/7.45 (1/2)
6f	1.64/2.23 ($10_{endo}/10_{exo}$), 1.64/2.63 ($10_{endo}/10a_{endo}$), 2.03/2.50 (4″/3″), 2.03/3.13 (4″/5″), 2.13/4.60 (6/6a), 2.13/5.60 (6/5), 2.23/1.64 ($10_{exo}/10_{endo}$), 2.23/2.63 ($10_{exo}/10a_{endo}$), 2.23/5.07 (10_{exo}/9), 2.50/2.03 (3″/4″), 2.63/1.64 ($10a_{endo}/10_{endo}$), 2.63/2.23 ($10a_{endo}/10_{exo}$), 3.13/2.03 (5″/4″), 4.60/2.13 (6a/6), 5.07/2.23 (9/10_{exo}), 5.07/6.44 (9/8), 5.60/2.13 (5/6), 6.39/6.44 (7/8), 6.44/5.07 (8/9), 6.44/6.39 (8/7), 6.91/7.18 (4/2), 7.18/6.91 (2/4), 7.18/8.65 (2/1), 8.65/7.18 (1/2)

[a] Multiplet of H4 pyrrolidine ring and H6, and H10_{exo} of the epoxyisoindolo[2,1-*a*]quinoline core.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.3, 31.4, 31.5, 42.4, 48.0, 49.7, 55.5, 55.8, 98.0, 101.7, 105.4, 110.1, 119.6, 129.4, 141.9, 147.9, 152.6, 155.4, 175.7.

GC-EIMS (70 eV): t_R = 46.66 min, *m*/*z* (%) = 342 (M^+, 15), 258 ($M^+ - C_4H_6NO$, 8), 257 ($M^+ - C_4H_7NO$, 33), 256 ($M^+ - C_4H_8NO$, 100), 242 (11), 190 ($M^+ - C_8H_{10}NO_2$, 6), 81 (6), 41 (5).

***cis*-6-Bromo-2-(2-furyl)-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (4e)**
Mp 205–206 °C.

IR (KBr): 3327, 1667, 1145 cm^{-1}.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.1, 30.6, 31.1, 42.1, 47.4, 49.4, 105.7, 110.0, 110.2, 116.7, 120.9, 129.1, 131.0, 142.0, 144.0, 154.5, 175.7.

GC-EIMS (70 eV): t_R = 49.03 min, *m*/*z* (%) = 362 (M^+, 6), 278 ($M^+ - C_4H_6NO$, 11), 277 ($M^+ - C_4H_7NO$, 66), 276 ($M^+ - C_4H_8NO$, 100), 210 ($M^+ - C_8H_{10}NO_2$, 9), 196 (25), 167 (24), 129 (8), 81 (10).

***cis*-6-Chloro-2-(2-furyl)-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (4f)**
Mp 192–193 °C.

IR (KBr): 3326, 1672, 1145 cm^{-1}.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.2, 30.7, 31.2, 42.2, 47.5, 49.6, 105.7, 110.3, 116.4, 120.6, 123.2, 126.3, 128.3, 142.1, 143.6, 154.6, 175.8.

GC-EIMS (70 eV): t_R = 41.78 min, *m*/*z* (%) = 316 (M^+, 6), 232 ($M^+ - C_4H_6NO$, 42), 231 ($M^+ - C_4H_7NO$, 65), 230 ($M^+ - C_4H_8NO$, 100), 196 (15), 167 (18), 164 ($M^+ - C_8H_{10}NO_2$, 13), 81 (10), 41 (9).

***cis*-6-Fluoro-2-(2-furyl)-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (4g)**
Mp 161–162 °C.

IR (KBr): 3367, 1670, 1149 cm^{-1}.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.1, 30.8, 31.2, 42.2, 47.8, 49.8, 105.6, 110.2, 112.9, 115.1, 116.2, 120.5, 127.7, 141.3, 154.8, 155.2, 175.8.

GC-EIMS (70 eV): t_R = 34.85 min, *m*/*z* (%) = 300 (M^+, 6), 216 ($M^+ - C_4H_6NO$, 10), 215 ($M^+ - C_4H_7NO$, 61), 214 ($M^+ - C_4H_8NO$, 100), 198 (4), 186 (15), 148 ($M^+ - C_8H_{10}NO_2$, 11), 81 (5), 41 (3).

***cis*-6,7-Dichloro-2-(2-furyl)-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (4h)**
Mp 154–155 °C.

IR (KBr): 3307, 1670, 1128 cm^{-1}.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.1, 30.9, 31.2, 43.7, 46.4, 47.9, 105.6, 110.4, 114.5, 117.5, 121.8, 129.9, 133.2, 142.1, 145.6, 154.9, 175.0.

GC-EIMS (70 eV): t_R = 68.06 min, *m*/*z* (%) = 350 (M^+, 9), 315 (M^+ – Cl, 100), 266 ($M^+ - C_4H_6NO$, 40), 265 ($M^+ - C_4H_7NO$, 46), 264 ($M^+ - C_4H_8NO$, 59), 230 ($M^+ - C_4H_7ClNO$, 49), 198 ($M^+ - C_8H_{10}NO_2$, 26), 166 (8), 81 (43), 69 (9), 53 (10), 41 (34).

***cis*-2-(2-Furyl)-8-methyl-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (4i)**
Mp 120–121 °C.

IR (KBr): 3344, 1681, 1149 cm^{-1}.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 17.4, 18.2, 31.0, 31.4, 42.3, 48.0, 49.7, 105.5, 110.2, 117.8, 118.5, 122.2, 124.6, 129.3, 142.0, 143.1, 155.3, 175.7.

GC-EIMS (70 eV): t_R = 44.71 min, *m*/*z* (%) = 296 (M^+, 5), 212 ($M^+ - C_4H_6NO$, 11), 211 ($M^+ - C_4H_7NO$, 57), 210 ($M^+ - C_4H_8NO$, 100), 196 (4), 182 (9), 167 (4), 144 ($M^+ - C_8H_{10}NO_2$, 11), 81 (9), 41 (7).

***cis*-2-(2-Furyl)-8-methoxy-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (4j)**
Mp 151–152 °C.

IR (KBr): 3419, 1681, 1116 cm^{-1}.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.3, 31.2, 31.5, 42.4, 47.9, 49.5, 55.5, 105.6, 108.6, 110.3, 117.5, 118.8, 119.2, 135.1, 142.0, 146.8, 155.5, 175.8.

GC-EIMS (70 eV): t_R = 51.24 min, *m*/*z* (%) = 312 (M^+, 7), 228 ($M^+ - C_4H_6NO$, 10), 227 ($M^+ - C_4H_7NO$, 46), 226 ($M^+ - C_4H_8NO$, 100), 212 (9), 196 (9), 184 (5), 160 ($M^+ - C_8H_{10}NO_2$, 7), 145 (5), 81 (8), 41 (8).

cis-6,8-Dimethoxy-2-(5-methyl-2-furyl)-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (4k)
Mp 140–141 °C.

IR (KBr): 3401, 1704, 1122 cm^{-1}.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 13.4, 18.1, 31.3, 31.4, 42.3, 48.0, 49.6, 55.3, 55.6, 97.9, 101.7, 105.8, 106.0, 119.5, 129.5, 147.8, 151.3, 152.4, 153.4, 175.5.

GC-EIMS (70 eV): t_R = 75.26 min, *m*/*z* (%) = 356 (M^+, 16), 272 ($M^+ - C_4H_6NO$, 7), 271($M^+ - C_4H_7NO$, 32), 270 ($M^+ - C_4H_8NO$, 100), 256 (11), 240 (6), 190 ($M^+ - C_8H_{10}NO_2$, 7), 95 (6), 85 (5), 43 (11).

2-(2-Furyl)tetrahydroquinolines 4a–d by Three-Component Condensation; General Procedure
A mixture of aniline **1** (3.2 mmol) and 2-furaldehyde **2** (3.8 mmol) in anhyd MeCN (20 mL) was stirred at r.t. for 30 min. TsOH (20 mol%) was added. Over a period of 20 min, a soln *N*-vinylpyrrolidin-2-one (5.6 mmol) in MeCN (10 mL) was added dropwise. The resulting mixture was stirred for 10–14 h. On completion of the reaction as indicated by TLC, the mixture was diluted with H_2O (30 mL) and extracted with EtOAc (3 × 15 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo and the resulting product was purified by column chromatography (silica gel, petroleum ether–EtOAc) to afford pure *cis*-tetrahydroquinolines **4a–d**.

11-Oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic Acids 5; General Procedure
Corresponding tetrahydroquinoline **4** (1.5 mmol) was dissolved in toluene (10 mL). Then an equimolar amount of maleic anhydride (1.5 mmol) was added in one portion to the soln. The mixture was stirred at 100 °C for 1–5 d. Then the crystalline product was filtered off, washed with toluene (3 × 5 mL) and anhyd MeOH (1 × 5 mL), and dried at 100°C to give desired products **5** as white solids (Table 4).

11-Oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (5a)
IR (KBr): 1733, 1693, 1639, 972 cm^{-1}.

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 17.8, 25.4, 30.6, 41.7, 45.2, 47.4, 51.0, 55.5, 81.0, 89.3, 118.1, 123.4, 123.6, 126.3, 127.9, 134.3, 137.4, 137.8, 169.9, 173.1, 175.0.

3-Methyl-11-oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (5b)
IR (KBr): 1729, 1704, 1650, 977 cm^{-1}.

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 17.9, 20.6, 25.5, 30.7, 42.9, 45.1, 47.4, 51.0, 55.4, 81.0, 89.4, 118.1, 123.5, 126.4, 128.4, 132.4, 134.3, 135.0, 137.7, 169.6, 173.1, 175.0.

3-Methoxy-11-oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (5c)
IR (KBr): 1735, 1689, 1639, 918 cm^{-1}.

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 17.9, 25.5, 30.6, 41.8, 45.0, 47.6, 51.0, 55.2, 55.3, 80.9, 89.3, 111.2, 112.9, 119.5, 125.3, 130.8, 134.3, 137.7, 155.1, 169.1, 173.0, 175.0.

1,3-Dimethoxy-11-oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (5d)
IR (KBr): 1741, 1675, 970 cm^{-1}.

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 17.6, 28.2, 30.6, 41.7, 45.1, 47.7, 48.8, 55.3, 56.0, 56.9, 81.3, 90.2, 99.4, 102.8, 119.8, 129.7, 134.0, 136.9, 154.3, 158.0, 168.0, 172.6, 174.5.

3-Chloro-11-oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (5f)
IR (KBr): 1733, 1706, 1654, 975 cm^{-1}.

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 17.8, 25.0, 30.5, 42.3, 45.1, 48.5, 51.0, 55.4, 81.0, 89.2, 119.8, 125.6, 126.3, 127.3, 127.8, 134.1, 136.3, 137.8, 170.1, 172.9, 175.1.

3-Fluoro-11-oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (5g)
IR (KBr): 1741, 1693, 1637, 975 cm^{-1}.

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 17.8, 25.2, 30.5, 42.4, 45.1, 51.0, 55.4, 81.0, 89.3, 112.5, 114.5, 124.4, 126.6, 128.2, 133.9, 134.2, 137.8, 156.8, 169.8, 173.0, 175.1.

1-Methyl-11-oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline-10-carboxylic Acid (5i)
IR (KBr): 1712, 1635, 1591, 972 cm^{-1}.

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 17.5, 18.9, 28.2, 30.6, 41.6, 45.1, 47.7, 49.2, 57.6, 81.6, 90.2, 124.3, 125.7, 128.0, 129.9, 133.4, 134.3, 135.3, 136.7, 169.1, 172.6, 174.5.

11-Oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinolines 6; General Procedure
The corresponding tetrahydroquinoline **4** (1.5 mmol) was dissolved in toluene–CH_2Cl_2 (10 mL) and stirred in presence of Et_3N. Then acryloyl chloride (3 mmol) was added in one portion to the soln. The mixture was stirred at r.t. for 2–3 d. Then, it was treated with CH_2Cl_2 and the organic layer was washed with H_2O (3 × 10 mL) and dried (Na_2SO_4). Finally, the organic layer was filtered through a flash column (silica gel) and then concentrated by evaporation to afford the products **6** as melt solids (Table 4).

3-Methyl-11-oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline (6b)
IR (KBr): 1681, 1611, 1073, 829 cm^{-1}.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.1, 20.8, 25.9, 28.2, 31.1, 42.1, 47.8, 48.3, 56.7, 78.7, 89.8, 119.2, 122.8, 126.6, 129.0, 132.2, 133.2, 134.7, 137.8, 172.2, 175.9.

3-Methoxy-11-oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline (6c)
IR (KBr): 1682, 1621, 1037, 826 cm^{-1}.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.2, 25.9, 28.2, 31.1, 42.1, 47.9, 48.4, 55.3, 56.7, 78.8, 89.8, 111.8, 113.2, 120.7, 124.7, 130.7, 132.3, 137.8, 155.7, 171.9, 175.8.

3-Bromo-11-oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline (6e)
IR (KBr): 1684, 1589, 1074, 825 cm^{-1}.

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 14.7, 18.0, 20.1, 28.5, 37.4, 45.8, 67.7, 79.4, 104.8, 109.9, 116.2, 118.1, 120.3, 122.1, 126.1, 127.1, 132.1, 135.4, 172.7, 174.6.

3-Chloro-11-oxo-5-(2-oxopyrrolidin-1-yl)-6,6a,9,10,10a,11-hexahydro-5*H*-6b,9-epoxyisoindolo[2,1-*a*]quinoline (6f)
IR (KBr): 1686, 1593, 1072, 826 cm^{-1}.

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.1, 25.5, 28.3, 30.9, 42.1, 47.7, 48.3, 56.7, 78.8, 89.7, 120.7, 125.0, 126.0, 128.4, 128.9, 132.0, 135.8, 138.0, 172.6, 176.0.

11-Oxo-5-(2-oxopyrrolidin-1-yl)-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinolines 7; General Procedure

The corresponding epoxyisoindolo[2,1-*a*]quinoline **6** (1 g) was dissolved in $CHCl_3$ (10 mL). Then the mixture was cooled and 85% H_3PO_4 (3 mL) was added at once to the soln. The mixture was stirred at 70 °C for 3 h. Finally, the mixture was neutralized and treated with $CHCl_3$ (3 × 20 mL). The organic layer was dried (Na_2SO_4) and the solvent removed under vacuum to afford the crude product, which was purified by column chromatography (silica gel, petroleum ether–EtOAc) to give the desired products **7** as white solids (Table 4).

3-Methyl-11-oxo-5-(2-oxopyrrolidin-1-yl)-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline (7b)

IR (KBr): 1678, 1498, 1287 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71 (q, *J* = 12.3 Hz, 1 H, CH), 2.01 (m, 2 H, CH_2), 2.30 (s, 3 H, CH_3), 2.51 (m, 2 H, CH_2), 2.63 (ddd, *J* = 12.6, 6.4, 2.6 Hz, 1 H, CH), 3.07 (t, *J* = 7.0 Hz, 2 H, CH_2), 4.87 (dd, 12.4, 2.4, 1 H, CH), 5.76 (dd, *J* = 12.0, 6.3 Hz, 1 H, CH), 6.85 (s, 1 H_{arom}), 7.14 (dd, *J* = 8.4, 12.0 Hz, 1 H_{arom}), 7.46 (dd, *J* = 7.5, 0.8 Hz, 1 H_{arom}), 7.50 (t, *J* = 7.4 Hz, 1 H_{arom}), 7.59 (td, *J* = 7.5, 1.2 Hz, 1 H_{arom}), 7.91 (d, *J* = 7.5 Hz, 1 H_{arom}), 8.40 (d, *J* = 8.4 Hz, 1 H_{arom}).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.2, 21.1, 31.2, 31.5, 42.3, 47.9, 58.1, 120.5, 120.8, 123.3, 124.2, 127.0, 128.8, 129.2, 132.1, 132.5, 134.0, 134.3, 143.6, 165.6, 175.8.

GC-EIMS (70 eV): t_R = 33.18 min, *m*/*z* (%) = 332 (M^+, 5), 247 ($M^+ - C_4H_7NO$, 100), 232 ($M^+ - C_5H_{10}NO$, 15), 218 ($M^+ - C_6H_{12}NO$, 5), 204 ($M^+ - C_7H_{14}NO$, 3), 191 ($M^+ - C_7H_{13}N_2O$, 1), 177 ($M^+ - C_8H_{15}N_2O$, 1), 115 (5), 77 (3), 51 (2).

3-Methoxy-11-oxo-5-(2-oxopyrrolidin-1-yl)-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline (7c)

IR (KBr): 1682, 1496, 1283 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69 (q, *J* = 12.3 Hz, 1 H, CH), 1.99 (m, 2 H, CH_2), 2.49 (m, 2 H, CH_2), 2.62 (ddd, *J* = 12.4, 6.3, 2.5 Hz, 1 H, CH), 3.08 (t, *J* = 7.0 Hz, 2 H, CH_2), 3.76 (s, 3 H, CH_3), 4.85 (dd, *J* = 12.3, 2.4 Hz, 1 H, CH), 5.75 (dd, *J* = 12.0, 6.26 Hz, 1 H, CH), 6.59 (dd, *J* = 2.9, 0.9 Hz, 1 H_{arom}), 6.89 (dd, *J* = 9.0, 2.6 Hz, 1 H_{arom}), 7.46 (dd, *J* = 7.5, 0.5 Hz, 1 H_{arom}), 7.49 (t, *J* = 7.5 Hz, 1 H_{arom}), 7.57 (td, *J* = 7.5, 1.1 Hz, 1 H_{arom}), 7.89 (d, *J* = 7.5 Hz, 1 H_{arom}), 8.44 (d, *J* = 9.0 Hz, 1 H_{arom}).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 18.2, 31.1, 31.4, 42.4, 48.1, 55.5, 58.1, 112.2, 113.5, 121.8, 121.9, 124.2, 125.1, 128.8, 130.2, 132.0, 132.5, 143.5, 156.4, 165.5, 175.8.

GC-EIMS (70 eV): t_R = 21.54 min, *m*/*z* (%) = 348 (M^+, 9), 263 ($M^+ - C_4H_7NO$, 100), 248 ($M^+ - C_5H_{10}NO$, 18), 232 ($M^+ - C_5H_{10}NO_2$, 12), 220 ($M^+ - C_7H_{14}NO$, 10), 204 ($M^+ - C_7H_{14}NO$, 3), 193 ($M^+ - C_8H_{15}N_2O$, 6), 177 ($M^+ - C_8H_{15}N_2O$, 1), 115 (2), 77 (6), 51 (2).

3-Chloro-11-oxo-5-(2-oxopyrrolidin-1-yl)-5,6,6a,11-tetrahydroisoindolo[2,1-*a*]quinoline (7f)

IR (KBr): 1684, 1481, 1288 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72 (q, *J* = 12.3 Hz, 1 H, CH), 2.03 (m, 2 H, CH_2), 2.51 (m, 2 H, CH_2), 2.63 (ddd, *J* = 12.5, 6.2, 2.5 Hz, 1 H, CH), 3.08 (m, 2 H, CH_2), 4.90 (dd, *J* = 12.3, 2.4 Hz, 1 H, CH), 5.79 (dd, *J* = 12.0, 6.2 Hz, 1 H, CH), 7.03 (dd, *J* = 2.4, 1.0 Hz, 1 H_{arom}), 7.28 (ddd, *J* = 8.9, 2.5 Hz, 0.8, 1 H_{arom}), 7.48 (dd, *J* = 7.5, 0.8 Hz, 1 H_{arom}), 7.51 (t, *J* = 7.4 Hz, 1 H_{arom}), 7.61 (td, *J* = 7.5, 1.1 Hz, 1 H_{arom}), 7.90 (d, *J* = 7.6 Hz, 1 H_{arom}), 8.49 (d, *J* = 8.9 Hz, 1 H_{arom}).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.2, 18.1, 31.0, 42.3, 47.8, 58.0, 60.3, 121.9, 124.4, 125.5, 126.5, 128.6, 129.0, 129.7, 132.0, 132.5, 135.3, 143.4, 165.8, 175.8.

GC-MS (70 eV): t_R = 35.22 min, *m*/*z* (%) = 352 (M^+, 5), 267 ($M^+ - C_4H_7NO$, 100), 232 ($M^+ - C_4H_7ClNO_2$, 15), 204 ($M^+ - C_6H_{11}ClNO$, 7), 177 ($M^+ - C_7H_{12}ClN_2O$, 3), 115 (1), 77 (5), 51 (2).

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