Design, Synthesis, and Biological Activity of Novel Polycyclic Aza-Amide FKBP12 Ligands

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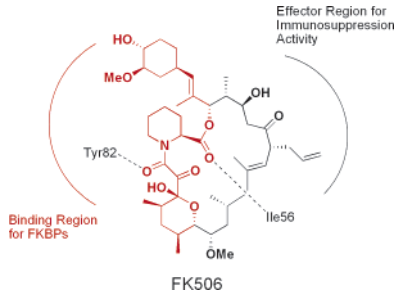
Since the discovery that FK-506 promotes neurite outgrowth, considerable attention has been focused on the development of potent nonimmunosuppressive ligands for FK-506 binding proteins (FKBPs). Such neuroimmunophilin agents have been reported to show neuroregenerative activity in a variety of cell and animal models including neurite outgrowth, age-related cognitive decline, Parkinson's disease, peripheral nerve injury, optic nerve degeneration, and diabetic neuropathy. We have designed and synthesized a unique series of tetracyclic aza-amides that have been shown to be potent FKBP12 rotamase inhibitors. The structure−activity relationships established in this study have demonstrated diverse structural modifications that result in potent rotamase inhibitory activity.

Introduction

The macrolide lactone FK506 (Tacrolimus) originally isolated from *Streptomyces tsukubaensis* has been shown to be a powerful immunosuppressant agent used to prevent organ transplant rejection.[1,2] FK506 is bifunctional in nature, having an effector region, responsible for immunosuppression, and a protein-binding region (Figure 1).[3] The proteins that bind FK506 were subsequently named FK506 binding proteins or FKBPs. In 1994, Snyder, et al. reported that FK506 could promote neurite outgrowth in PC-12 cells and rat sensory ganglia.[4,5] Hamilton, et al. demonstrated that the effector region, responsible for the immunosuppressive properties of FK506, was not required to facilitate neurite outgrowth.[6] Small molecule mimics that maintained interactions with FKBPs, were shown to promote neurite outgrowth. Since long-term continuous treatment with FK506 has been shown to promote undesirable side effects, such as immune deficiency, considerable efforts are underway to develop compounds that elicit neuroprotective and neurorestorative effects without having immunosuppressant activity.[7−9]

The mechanism by which neuroimmunophilin ligands elicit neurite outgrowth is not well understood; however, the ability to bind FKBPs, in particular FKBP52, does appear to correlate with neurite outgrowth.[10−12] In addition, FKBP12 is known to facilitate the cis−trans isomerization of peptide linkages adjacent to proline residues (PPIase or rotamase inhibitory activity).[13,14] While not directly associated with neurite outgrowth, rotamase inhibitory activity does provide a convenient assay for the binding ability of small molecules to FKBP12. Neuroimmunophilin agents capable of promoting neurite outgrowth have a number of potential therapeutic targets including Parkinson's disease, Alzheimer's disease, spinal cord injury, traumatic brain injury, stroke, diabetic neuropathy, and peripheral neuropathy.



FK506

Figure 1. Bifunctional nature of FK506.

Two key hydrogen bond interactions are evident from the crystal structure analysis of FK506 complexed with FKBP12 (Figure 1).[15−17] The first is the interaction between the backbone NH of Ile-56 and the pipecolinic ester carbonyl. The second is a hydrogen bond between the amide carbonyl and Tyr-82. Additionally, a small hydrophobic, electropositive cavity is formed by Tyr-26, Phe-36, and Phe-99. Previous work in this area demonstrated that compound **1** is a potent inhibitor of FKBP rotamase activity.[18] The aim of our current structure−activity relationship (SAR) studies was to further elucidate the structural modifications necessary that lead to potent FKBP12 rotamase inhibitory activity.

Results and Discussion

Initial structural modifications of compound **1** revolved around incorporation of a tetrahydroisoquinoline moiety to limit the flexibility of these compounds in an effort to better match the hydrophobic binding cavity seen in the FK506−FKBP12 crystal structure complex. The proposed structural motif would allow the preparation of a number of analogues varying the substitution of the A and B ring as depicted in Figure 2 for rapid SAR evaluation.

The novel polycyclic derivatives were prepared in five steps starting from 2,6-pyridine dicarboxylic acid as shown in Scheme 1. Reduction with Rh/Al followed by protection of the amine during workup afforded the *cis*-diacid **2**. Treatment with acetic

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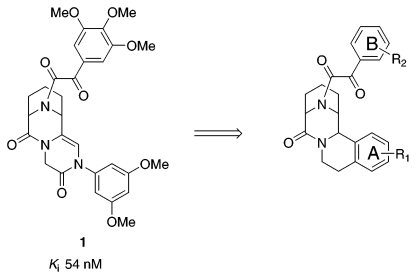
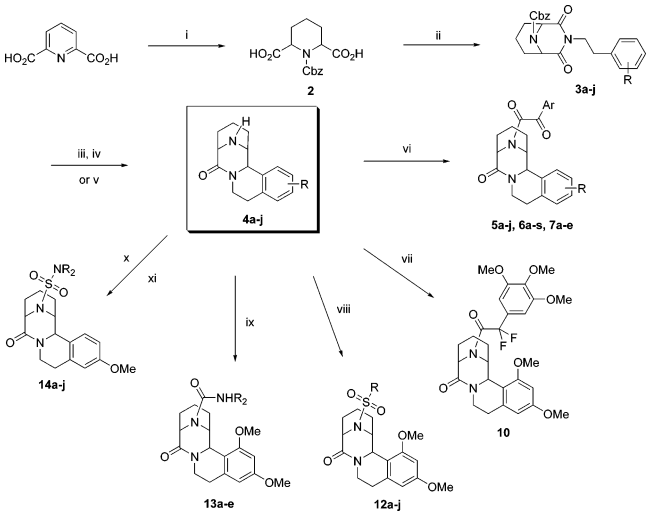


Figure 2. Structural modifications for initial SAR exploration.

Scheme 1[a]



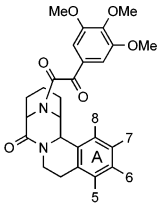
[a] Reagents and conditions: (i) Rh-Al, 50 psi H_2, NaOH (aq) followed by CbzCl; (ii) acetic anhydride, toluene, reflux followed by phenethylamine; (iii) sodium borohydride, methanol, 0 °C; (iv) trifluoroacetic acid, CH_2Cl_2 0 °C; (v) Li(HBEt$_3$), BF3OEt2; (vi) keto-acid, EDC-HCl, HOBt, triethylamine, CH_2Cl_2, 0 °C to room temperature; (vii) α,α-difluoro acid, EDC-HCl, DMAP, CH_3CN; (viii) *N*-methylmorpholine, sulfonyl chloride, CH_2Cl_2; (ix) R_2NH, ethyl isocyanate, DMF; (x) $ClSO_3H$, Et_3N, CH_2Cl_2; (xi) 3,5-lutidine, aniline, CH_2Cl_2.

anhydride provided the cyclic anhydride that upon workup could be reacted with a variety of phenethylamines to provide **3a**−**j**. Partial reduction of the imide could be accomplished by treatment with sodium borohydride, and the cyclization induced with trifluoroacetic acid. Benzyl carbamate deprotection afforded the desired amines **4a**−**j**. Alternatively, a one-pot cyclization/deprotection was accomplished by addition of trifluoroboraneetherate to the cyclization reaction, which afforded the desired template in higher yield and purity compared to the two-step process. This penultimate intermediate was elaborated to incorporate a significant number of linker modifications. A variety of keto-amide, sulfonamide, sulfamide, urea, and α,α-difluoro amides were prepared and evaluated to determine the structural requirements necessary to maintain FKBP12 binding.

In an effort to first optimize the substitution of the tetrahydroisoquinoline moiety, we chose to preserve the 3,4,5-trimethoxy substitution on the B-ring and the keto-amide functionality that had proven successful for compound **1**. The most promising substitution on the A ring was then chosen as a basis for further SAR exploration of the B ring substitution and linker modification. The effect of A ring modification on rotamase activity, exhibited by compounds **5a**−**j**, is highlighted in Table 1. Incorporation of a variety of substituents resulted in less than a 4-fold difference in activity with the 6,8-dimethoxy derivative, **5a**, being most potent at 69 nM.

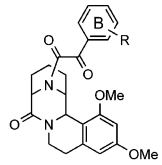
After determining that the 6,8-dimethoxy substitution of the tetrahydroisoquinoline was most active, we explored the SAR

Table 1. Tetrahydroisoquinoline Substitution and the Effect on Activity



Compd	Substitution	FKBP12 K_i (nM)	Compd	Substitution	FKBP12 K_i (nM)
5a	6,8-di-OMe	69	5f	5-Cl	152
5b	7-Me	85	5g	6-Cl	171
5c	5-OMe	105	5h	8-F	201
5d	7-Cl	126	5i	(H)	217
5e	6-OMe	143	5j	7-F	225

Table 2. Aryl Substitution and the Effect on Activity



Compd	Substitution	FKBP12 K_i (nM)	Compd	Substitution	FKBP12 K_i (nM)
5a	3,4,5-tri-OMe	69	6j	4-OMe	131
6a	3,4-di-Cl	34	6k	2,4-di-Cl	153
6b	3,5-di-OMe	34	6l	2-OH	238
6c	3-Cl	46	6m	2,3-di-Cl	282
6d	3,4-di-OMe	60	6n	2-Cl	583
6e	4-Br	71	6o	2,4-di-Cl	586
6f	4-Cl	72	6p		1000
6g	(H)	100	6q	2,5-di-Cl	8100
6h	4-F	110	6r	3,5-di-*t*-Bu,4-OH	20800
6i	4-Et	123			

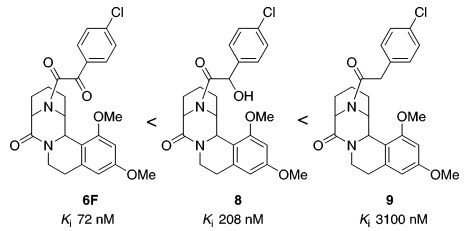


Figure 3. Effects of oxidation state on activity.

surrounding the keto-amide functionality. A variety of substitutions were made on the B-ring system to provide **6a**−**r** (Table 2). The 3,4-di-Cl derivative, **6a**, proved one of the most active at 34 nM. Incorporation of bulky substituents, such as 3,5-di-*t*-bu-4-OH in **6r**, led to a decrease in activity. In general, meta/para substitution was favored over ortho substitution for the compounds tested. A variety of heterocyclic replacements for the simple aromatic ring in **7a**−**e** proved to be potent rotamase inhibitors (Table 3).

The keto-amide motif was retained from FK506 in previous work due to the hydrogen bond between the amide carbonyl and Tyr-82 in the FK506−FKBP12 crystal structure. In an effort to explore the necessity of the keto-amide in the polycyclic structures, we synthesized compounds **8** and **9**. Activity diminished as the oxidation state of the α-carbon decreased (Figure 3). However, α,α-difluoro substitution resulted in compound **10**, which is nearly equipotent to keto-amide **5a**; this is an analogous result to what was seen with 2-aryl-2,2-difluoroacetamide proline and pipecolate derivatives (Figure 4).[19]

The necessity of other possible sites of hydrogen bonding interactions was tested. Compound **11** was synthesized by LAH

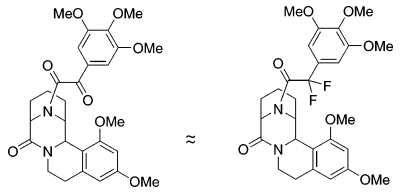


Figure 4. α,α-Difluoro substitution and the effect on activity.

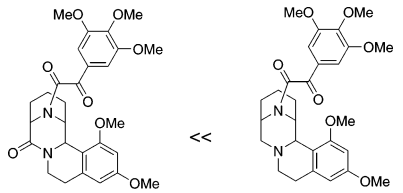
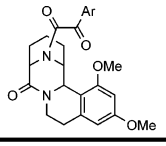


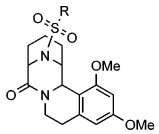
Figure 5. Effects of removing a hydrogen bond acceptor.

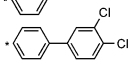
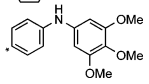
Table 3. Aryl Replacement and the Effect on Activity



Compd	Substitution	FKBP12 K_i (nM)	Compd	Substitution	FKBP12 K_i (nM)
7a	2-Thiophene	107	7d	2-Furan	279
7b	3-Pyridyl	110	7e	2-Indole	2300
7c	4-Pyridyl	114			

Table 4. Effects of Incorporation of a Sulfonamide Linkage

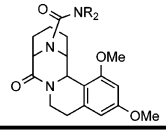


Compd	R	FKBP12 K_i (nM)	Compd	R	FKBP12 K_i (nM)
12a		54	12f		104
12b		82	12g		156
12c		84	12h		244
12d		88	12i		266
12e		92	12j		288

reduction of the penultimate amine derivative followed by standard coupling conditions. The loss of this hydrogen bond acceptor site resulted in nearly complete loss of rotamase inhibitory activity (Figure 5). Further SAR investigations preserved this key site of oxidation.

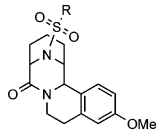
An alternative to the keto-amide was explored with the intention of maintaining hydrogen-bonding possibility. A series of compounds **12a**−**j** were synthesized via coupling of the penultimate amine with a sulfonyl chloride in the presence of base. The sulfonamide proved to be an effective replacement, as all compounds demonstrated respectable levels of rotamase activity (Table 4). In an analogous fashion, a urea linkage was introduced in compounds **13a**−**e** by treatment of the amine with an isocyanate. This series of compounds demonstrated decreased

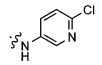
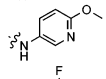
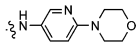
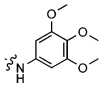
Table 5. Effects of Incorporation of a Urea Linkage



Compd	R	FKBP12 K_i (nM)	Compd	R	FKBP12 K_i (nM)
13a	2-MePh	330	13d	Ph	2700
13b	2-OMePh	357	13e	2,4-di-FPh	7000
13c	4-NO_2Ph	772			

Table 6. Effects of Incorporation of a Sulfamide Linkage



Compd	R	FKBP12 K_i (nM)	Compd	R	FKBP12 K_i (nM)
14a		123	14f		360
14b		150	14g		360
14c		183	14h		590
14d		210	14i		591
14e		236	14j		640

levels of activity (Table 5). Last, the incorporation of a sulfamide linkage was explored. A number of analogues **14a**−**j** exhibited potent activity (Table 6).

Conclusions

Extensive SAR exploration of a polyclic aza-amide has identified many compounds with potent FKBP12 rotamase inhibitory activity. Incorporation of a rigid tetrahydroisoquinoline framework resulted in several compounds with increased activity compared to previous studies. Replacement of the keto-amide functionality by a sulfonamide or sulfamide linkage proved successful.

Experimental Section

Biochemistry. Compounds were evaluated for their ability to inhibit FKBP12 rotamase activity via the following procedure. In a quartz cuvette, a final 1 mL buffer concentration was reached (50 mM Hepes, 100 mM NaCl, pH 8.0). Within this final reaction volume, 3.5 μL of 20 μM FKBP-12 (in 50 mM Hepes, 100 mM NaCl, pH 8.0) and 10 μL of test compound in DMSO were added. The reaction was initiated by adding 10 μL of chymotrypsin (100 mg/mL in 1 mM HCl) followed by 5 μL (4−10 mM succinyl-Ala-Leu-Pro-Phe-pNA in 240 mM LiCl/TFE) at 15 °C. The absorbance at 390 nM versus time was monitored for up to 400 s. Rate constants were generated from the absorbance versus time plots at 8−12 compound concentrations. Additionally, a no enzyme control rate constant was determined. The K_{iapp} was determined from the corrected rate constants using an IC_{50} equation or a tight-binding equation by Morrison.[20] Typical error in measurement of the K_{iapp} was less than 25%.

The syntheses of compounds **2**, **3a**−**c**, **3e**, **3i**, **3j, 4a**−**c, 4e, 4j, 5c**, **8**−**11**, **12a**−**j**, **13a**−**e**, and **14a**−**j** have previously been described.[21,22]

General Procedure A for Synthesis of 3a−j. A suspension of **2** (1.0 equiv) in acetic anhydride (0.08 M) was heated at 65 °C for 30 min. The mixture was cooled to RT and concentrated, dissolved in 20 mL of toluene, and concentrated again. The toluene treatment was repeated three additional times to remove all traces of acetic anhydride. The residual oil was dissolved in toluene (0.45 M), and the desired phenethylamine (1.1 equiv) was added and stirred for 1.5 h at RT. Acetic anhydride (5 M with respect to phenethylamine) was added and stirred at RT for 16 h. The reaction mixture concentrated to an oil and purified by MPLC (hexane/ethyl acetate gradient 90:10 to 40:60). Fractions containing the desired product were combined and concentrated to give the desired product as an oil.

3-[2-(4-Chloro-phenyl)-ethyl]-2,4-dioxo-3,9-diaza-bicyclo[3.3.1]-nonane-9-carboxylic acid benzyl ester (3d). 1.96 g (68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.37 (m, 2 H), 1.77 (m, 3 H), 1.92 (m, 2 H), 2.78 (t, $J = 7.69$ Hz, 2 H), 3.96 (m, 2 H), 4.93 (m, 2 H), 5.14 (s, 2 H), 7.12 (d, $J = 8.55$ Hz, 2 H), 7.21 (m, 2 H), 7.33 (s, 5 H). MS (APCI) *m/z* 427.1 ($M^+ + 1$).

3-[2-(2-Chloro-phenyl)-ethyl]-2,4-dioxo-3,9-diaza-bicyclo[3.3.1]-nonane-9-carboxylic acid benzyl ester (3f). 4.59 g (79%). MS (APCI) *m/z* 427.1 ($M^+ + 1$).

3-[2-(3-Chloro-phenyl)-ethyl]-2,4-dioxo-3,9-diaza-bicyclo[3.3.1]-nonane-9-carboxylic acid benzyl ester (3g). 2.52 g (87%). MS (APCI) *m/z* 427.1 ($M^+ + 1$).

3-[2-(3-Fluoro-phenyl)-ethyl]-2,4-dioxo-3,9-diaza-bicyclo[3.3.1]-nonane-9-carboxylic acid benzyl ester (3h). 4.22 g (76%). MS (APCI) *m/z* 411.1 ($M^+ + 1$).

General Procedure B for Synthesis of 4a−j. A solution of **3** in THF (0.2 M) was cooled to −78 °C prior to addition of Li-($HBEt_3$) (1.7 equiv). After 30 min at −78 °C, methanol was added, and the reaction mixture was warmed to 0 °C. After 10 min, $NaHCO_3$ (sat'd aq.) and 30% H_2O_2 were added and the sample was stirred for 30 min at RT. The solution was concentrated, diluted with water, extracted with CH_2Cl_2, and the organics were combined, dried, and concentrated. The residual oil was taken up in dry CH_2Cl_2 and TFA (0.02 M) was added and the sample was stirred for 15 h. $BF_3{\cdot}OEt_2$ was added, and the mixture was stirred until ring closure and deprotection were complete as determined by mass spectrometry. The reaction mixture was then neutralized with $NaHCO_3$ (sat'd aq.), extracted with CH_2Cl_2, dried and concentrated onto silica, and purified by MPLC (CH_2Cl_2/MeOH 99:1 to 70:30).

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,5,6,9,10,11,-12,13,13a-octahydro-2-chloro (4d). 0.323 g (90%). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.56 (m, 1 H), 1.68 (m, 1 H), 1.84 (m, 1 H), 1.97 (m, 2 H), 2.09 (m, 1 H), 2.73 (m, 1 H), 2.83 (m, 1 H), 3.06 (m, 1 H), 3.86 (m, 1 H), 4.50 (m, 2 H), 4.96 (s, 1 H), 7.20 (d, $J = 8.06$ Hz, 1 H), 7.30 (d, $J = 8.06$ Hz, 1 H), 7.56 (s, 1 H). MS (APCI) *m/z* 277.0 ($M^+ + 1$).

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,5,6,9,10,11,-12,13,13a-octahydro-4-chloro (4f). 1.08 g (60%). MS (APCI) *m/z* 276.9 ($M^+ + 1$).

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,5,6,9,10,11,-12,13,13a-octahydro-3-chloro (4g). 1.31 g (99%). MS (APCI) *m/z* 277.0 ($M^+ + 1$).

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,5,6,9,10,11,-12,13,13a-octahydro-1-fluoro (4h). 1.29 g (75%). MS (APCI) *m/z* 261.0 ($M^+ + 1$).

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,5,6,9,10,11,-12,13,13a-octahydro (4i). A solution of **3i** in MeOH (0.065 M) was cooled to −5 °C prior to portion-wise addition of $NaBH_4$ (2.5 equiv) over 30 min. The sample was warmed to RT over 1 h, acidified to pH 2 by dropwise addition of HCl (4 N in dioxane), and stirred for 2 h. A small portion of Na_2CO_3 (sat'd aq.) was added, and the mixture was then concentrated, diluted with $NaHCO_3$ (sat'd aq.), and extracted with EtOAc. The combined organics were washed with NH_4Cl (sat'd aq.) and then brine, dried, and concentrated. The residual oil was purified by flash chromatography on silica using EtOAc/Hexanes (1:1) as eluent. The desired fractions were combined and concentrated, and the residual oil was taken up in dry CH_2Cl_2/TFA (1:2) and cooled to 0 °C. After the sample was stirred at 0 °C for 1 h, the mixture was allowed to warm to RT over 15 h and then was partitioned between $NaHCO_3$ (sat'd aq.) and EtOAc. The combined organics were washed with water and then brine, dried, and concentrated. The residual oil was purified on silica using a gradient of (1:1) to (3:1) EtOAc/hexanes as eluent. The desired fractions were combined and concentrated. The residue was taken up in EtOAc/MeOH (1:1) and treated with a catalytic amount of Pd on carbon (10%) and stirred under a hydrogen atmosphere for 2 h. The mixture was filtered through Celite and the filtrate concentrated to give **4i** in an overall 26% yield. This material was subsequently used without further purification.

General Procedure C for Synthesis of 5a−j, 6a−r, 7a−e. A solution of **4** (1.0 equiv) in CH_2Cl_2 was treated sequentially with the appropriate acid (1.2 equiv), EDC·HCl (1.2 equiv), HOBt (1.2 equiv), and Et_3N (1.2 equiv) at RT, and stirred overnight. The reaction mixture was concentrated onto silica gel, and purified by MPLC (hexane/ethyl acetate 90:10−40:60). Fractions containing the desired compounds were combined and concentrated to give the desired product.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,4,5-trimethoxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (5a). 0.407 g (47%). ^{1}H NMR (major rotamer, 400 MHz, $CDCl_3$) δ ppm 1.85−2.02 (m, 4 H), 2.13 (s, 1 H), 2.49 (s, 1 H), 2.66 (s, 1 H), 2.90 (s, 1 H), 3.50 (s, 3 H), 3.64 (s, 3 H), 3.73 (s, 6 H), 3.89 (s, 3 H), 4.57 (s, 1 H), 4.86 (s, 1 H), 5.15 (s, 1 H),5.65 (s, 1 H), 6.04 (s, 1 H), 6.71 (s, 2 H), 7.24 (s, 2 H). MS (APCI) *m/z* 525.2 ($M^+ + 1$). Anal. ($C_{28}H_{32}N_2O_8$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,4,5-trimethoxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-2-methyl (5b). 0.127 g (68%). MS (APCI) *m/z* 479.1 ($M^+ + 1$). Anal. ($C_{27}H_{30}N_2O_6$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,4,5-trimethoxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-2-chloro (5d). 0.073 g (51%). MS (APCI) *m/z* 499.0 ($M^+ + 1$). Anal. ($C_{26}H_{27}ClN_2O_6{\cdot}0.36CH_3OH$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,4,5-trimethoxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-3-methoxy (5e). 0.19 g (83%). MS (APCI) *m/z* 495.2 ($M^+ + 1$). Anal. ($C_{27}H_{30}N_2O_7{\cdot}0.2H_2O$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,4,5-trimethoxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-4-chloro (5f). 0.058 g (30%). MS (APCI) *m/z* 499.1 ($M^+ + 1$). Anal. ($C_{26}H_{27}ClN_2O_6{\cdot}0.15C_6H_{14}{\cdot}0.25CH_2Cl_2$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,4,5-trimethoxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-3-chloro (5 g). 0.173 g (64%). MS (APCI) *m/z* 498.0 ($M^+ - 1$). Anal. ($C_{26}H_{27}ClN_2O_6{\cdot}0.07CH_2Cl_2$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,4,5-trimethoxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1-fluoro (5h). 0.086 g (46%). MS (APCI) *m/z* 483.2 ($M^+ + 1$). Anal. ($C_{26}H_{27}FN_2O_6{\cdot}0.15CH_2Cl_2{\cdot}0.3C_4H_8O$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,4,5-trimethoxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro (5i). 0.120 g (31%). MS (APCI) *m/z* 465.2 ($M^+ + 1$). Anal. ($C_{26}H_{28}N_2O_6{\cdot}0.2\ H_2O$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,4,5-trimethoxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-2-fluoro (5j). 0.073 g (53%). MS (APCI) *m/z* 483.1 ($M^+ + 1$). Anal. ($C_{26}H_{27}FN_2O_6{\cdot}0.8H_2O$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,4-dichloro)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6a). 0.042 g (31%). MS (APCI) *m/z* 503.0 ($M^+ + 1$). Anal. ($C_{25}H_{24}Cl_2N_2O_5$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,5-dimethoxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6b). 0.058 g (45%). MS (APCI) *m/z* 495.1 ($M^+ + 1$). Anal. ($C_{27}H_{30}N_2O_7$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3-chloro)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6c). 0.057 g (36%). MS (APCI) *m/z* 469.1 ($M^+ + 1$). Anal. ($C_{25}H_{25}Cl_1N_2O_5{\cdot}0.05C_6H_{14}$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,4-dimethoxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6d). 0.044 g (34%). MS (APCI) *m/z* 495.1 ($M^+ + 1$). Anal. ($C_{27}H_{30}N_2O_7 \cdot 0.50CH_2Cl_2$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(4-bromo)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6e). 0.058 g (36%). MS (APCI) *m/z* 515.0 ($M^+ + 1$). Anal. ($C_{25}H_{25}BrN_2O_5 \cdot 0.15CH_2Cl_2$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(4-chloro)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6f). 0.033 g (21%). MS (APCI) *m/z* 469.1 ($M^+ + 1$). Anal. ($C_{25}H_{25}ClN_2O_5 \cdot 0.75H_2O$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy Name (6 g). 0.13 g (38%). MS (APCI) *m/z* 435.2 ($M^+ + 1$). Anal. ($C_{25}H_{26}N_2O_5$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(4-fluoro)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6h). 0.020 g (9%). MS (APCI) *m/z* 453.2 ($M^+ + 1$). Anal. ($C_{25}H_{25}FN_2O_5 \cdot 1.20H_2O \cdot 0.15C_6H_{14}$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(4-ethyl)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6i). 0.044 g (28%). MS (APCI) *m/z* 463.1 ($M^+ + 1$). Anal. ($C_{27}H_{30}N_2O_5 \cdot 0.05H_2O$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(4-methoxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6j). 0.036 g (23%). MS (APCI) *m/z* 465.1 ($M^+ + 1$). Anal. ($C_{26}H_{28}N_2O_6 \cdot 0.15C_4H_8O_2$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(2,5-dichloro)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6k). 0.063 g (19%). MS (APCI) *m/z* 503.0 ($M^+ + 1$). Anal. ($C_{25}H_{24}Cl_2N_2O_5 \cdot 0.05C_6H_{14}$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(2-hydroxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6l). 0.123 g (55%). MS (APCI) *m/z* 451.2 ($M^+ + 1$). Anal. ($C_{25}H_{26}N_2O_6 \cdot 0.30H_2O$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(2,3-dichloro)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6m). 0.052 g (32%). MS (APCI) *m/z* 503.0 ($M^+ + 1$). Anal. ($C_{25}H_{24}Cl_2N_2O_5 \cdot 0.45C_6H_{14}$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(2-chloro)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6n). 0.049 g (31%). MS (APCI) *m/z* 469.1 ($M^+ + 1$). Anal. ($C_{25}H_{25}Cl_1N_2O_5 \cdot 0.05C_6H_{14} \cdot 0.15H_2O$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(2,4-dichloro)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6o). 0.012 g (12%). MS (APCI) *m/z* 503.1 ($M^+ + 1$). Anal. ($C_{25}H_{24}Cl_2N_2O_5 \cdot 0.6C_6H_{14} \cdot 0.15H_2O \cdot 0.30CH_2Cl_2$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(4-diethylamino)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6p). 0.054 g (13%). MS (APCI) *m/z* 506.2 ($M^+ + 1$). Anal. ($C_{29}H_{35}N_3O_5 \cdot 0.15C_6H_{14} \cdot 0.30H_2O$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(2,5-dichloro)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6q). 0.062 g (10%). MS (APCI) *m/z* 503.0 ($M^+ + 1$). Anal. ($C_{25}H_{24}Cl_2N_2O_5 \cdot 0.45C_6H_{14}$) C, H, N.

9,13-Imino-8H-azocino [2,1-a] isoquinolin-8-one,14-[2-oxo-(3,5-di-*tert*-butyl-4-hydroxy)phenylacetate]-5,6,9,10,11,12,13,13a-octahydro-1,3-dimethoxy (6r). 0.058 g (39%). MS (APCI) *m/z* 563.2 ($M^+ + 1$). Anal. ($C_{33}H_{42}N_2O_6 \cdot 0.07H_2O$) C, H, N.

Supporting Information Available: Experimental details for **7a**−**7e** and combustion analysis of the final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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