Solution-Phase Parallel Annulation of (Thio)hydantoins to Tetrahydroisoquinolines and Tetrahydro-β-carbolines Containing the 2-Arylethyl Amine Scaffold

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The one-step solution-phase parallel synthesis of two structurally diverse libraries of pharmacologically important compounds is described. The presented compounds combine three privileged structures: the *2-arylethyl amine* moiety, a tetrahydro(hetero)areno[*c*]pyridine, and a (thio)hydantoin. These compounds are synthesized by annulation of a hydantoin or a 2-thiohydantoin ring to tri- or tetracyclic scaffolds, containing the 2-arylethyl amine moiety and a tetrahydroisoquinoline, a tetrahydro-β-carboline, or a tetrahydrofuro[3,2-*c*]-pyridine. The annulation leads to pharmacologically relevant structural motifs such as imidazopyrroloisoquinolines, dioxoloimidazopyrroloisoquinolines, furoimidazopyrrolopyridines, and imidazopyrrolopyridoindoles. Both libraries were obtained with quantitative yields. The 36-membered hydantoin library was obtained with purities from 57 to 100% (90% average) and the 32-membered thiohydantoin library with purities from 73 to 100% (94% average).

Introduction

The *2-arylethyl amine* moiety **1** (Figure 1) is an important privileged structure, which is encountered in numerous natural and synthetic products active in the central nervous system. This moiety is present in neurotransmitters (dopamine, epinephrine, norepinephrine, and serotonin),[1] in medicines (salmeterol[2] and venlafaxine,[3] two of the ten best-selling prescription drugs in 2006),[4] and also in many hallucinogenic drugs [LSD, MDMA (ecstasy), mescaline, and psilocybin (magic mushrooms)].[5]

The tetrahydro(hetero)areno[*c*]pyridines **2** (e.g., tetrahydroisoquinolines **3** and tetrahydro-β-carbolines **4**; Figure 1) are another class of privileged core structures found in nature and often show a wide range of biological and pharmacological effects.[6] Finally, (thio)hydantoins **5** (Figure 1) are also present in a wide range of biologically active compounds including antiarrhythmic,[7] antiepileptic,[8] antitumor,[9] anxiolytic,[10] anticarcinogenic,[11] and anti-HIV agents.[12]

The combination of privileged structures can lead to new compounds, which may have pharmacological relevance as demonstrated in the following two examples: tetrahydroisoquinoline-hydantoin **6**, which selectively binds to the guinea pig σ_1 receptor,[13] and tetrahydro-β-carboline-hydantoin **7**, which demonstrates antimitotic activity (Figure 2).[14]

The aim of the present study is the generation of tetra- and pentacyclic compounds that combine three of the aforementioned privileged structures, which may lead to potentially relevant compounds (Scheme 1).

Results and Discussion

The starting compounds for the synthesis of our libraries are the four scaffolds **8**−**11** depicted in Figure 3. Each compound was obtained by a Pictet−Spengler cyclization from the corresponding β-aryl amines as previously reported.[15]

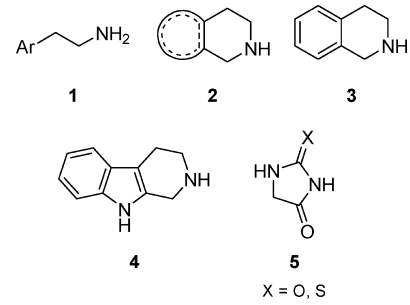

Figure 1. 2-Arylethyl amine **1**, tetrahydro(hetero)areno[*c*]pyridine **2**, tetrahydroisoquinoline **3**, tetrahydro-β-carboline **4**, and (thio)-hydantoin **5**.

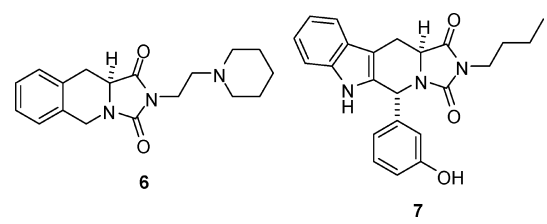

Figure 2. Tetrahydroisoquinoline-hydantoin **6** and tetrahydro-β-carboline-hydantoin **7**.

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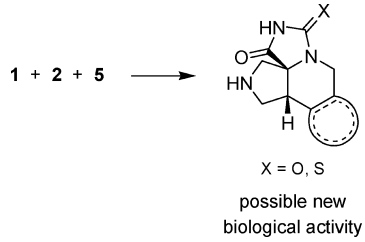
Scheme 1



Conversion of substrates **8**−**11** to chemsets **13**−**16** was accomplished using annulation of a hydantoin ring with reagent chemset **12**. Nine isocyanates **12**{*a*−*i*} (alkyl, electron-rich aryl, electron-poor aryl, and heteroaryl isocyanates; Figure 4) were selected for the generation of a 36-compound library.

The annulation of a hydantoin ring to tetrahydroisoquinolines has been well studied by Sergheraert and co-workers. They found that treatment of methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate with an alkyl or an aryl isocyanate in dichloromethane at room temperature using a large excess of DIPEA gave the desired tetrahydroisoquinoline-hydantoins.[16] We found for substrates **8**−**11** that there was no need for the addition of an external base (DIPEA), since all the scaffolds possess a tertiary amine within the structure. The conversion of these compounds into chemsets **13**−**16** took place within 40 h (although most of the reactions with the more reactive aromatic isocyanates[17] were finished after 5−20 h) in dichloromethane at room temperature for the aromatic isocyanates and at reflux for the aliphatic isocyanates (Scheme 2).

It was observed that only one equivalent of isocyanate per equivalent of substrate was needed for the reaction to proceed, except in the case of **12**{*a*}, where 1.2 equiv was

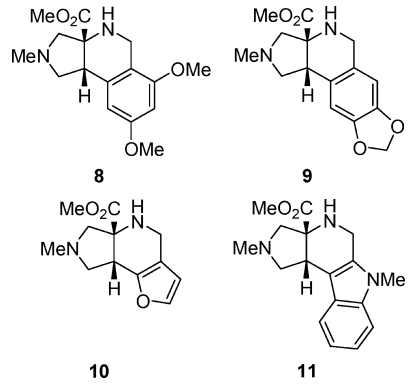


Figure 3. Four scaffolds **8**−**11** used for the library synthesis.

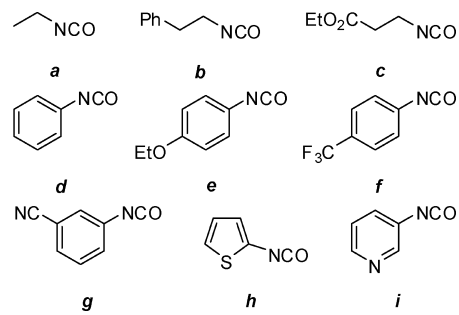
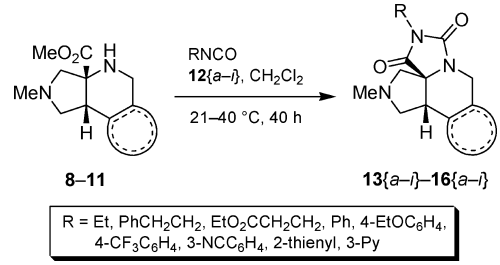


Figure 4. Isocyanates **12**{*a*−*i*} used for the annulation to substrates **8**−**11**.

Scheme 2



used. This transformation consisted of two steps: the addition of the free amine to the isocyanate to form a urea and the cyclization between the urea and the ester to form the hydantoin. The urea formation took place in 1−8 h in all cases, but the cyclization was much slower (especially for the alkyl ureas because of their lower acidity) occurring in 3−30 h. Thus, compounds **13**{*a*−*i*}−**16**{*a*−*i*} were obtained after evaporation of dichloromethane, methanol (the leaving group from the ester), and any excess reagents with purities from 57 to 100% (90% average) according to LC-MS analysis (confirmed by ^{1}H NMR spectroscopy) and with quantitative yields (based on mass recovery; Table 1). All reactions using the aromatic isocyanates **12**{*d*−*i*} were clean and resulted in products with purity >90% (except **12**{*g*}). The aliphatic isocyanates **12**{*a*−*c*} gave products with purities in the range 57−89%, probably due to partial isocyanate decomposition under the reflux conditions. Compounds **8**−**11** were also treated with *tert*-butyl isocyanate, but the reaction stopped after carbamoylation of the substrates so that only the corresponding ureas were detected. Addition of DIPEA to aid the reaction was ineffective and KOBu^t gave a mixture of the ureas, the hydantoins, and other unidentified compounds.

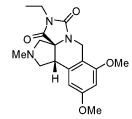
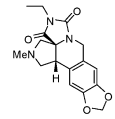
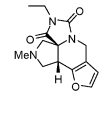
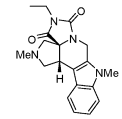
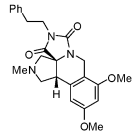
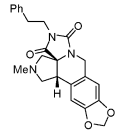
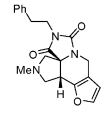
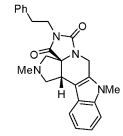
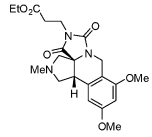
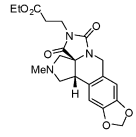
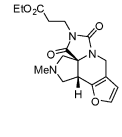
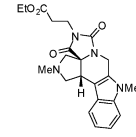
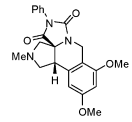
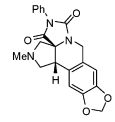
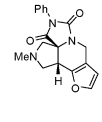
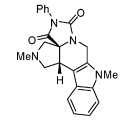
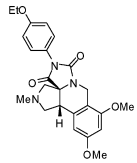
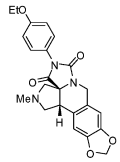
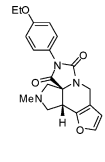
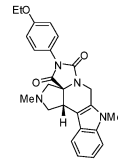
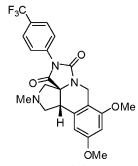
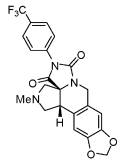
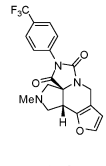
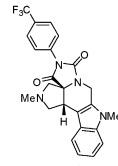
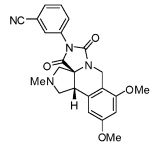
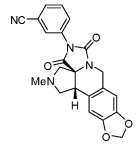
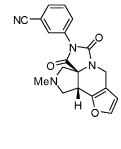
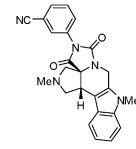
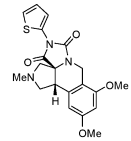
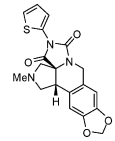
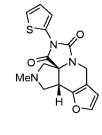
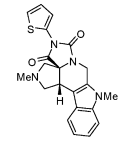
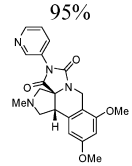
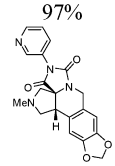
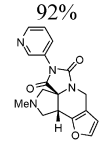
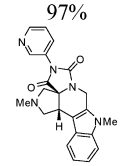
Following a similar procedure, conversion of the tri- and tetracyclic substrates **8**−**11** to chemsets **18**−**21** was achieved using annulation of a 2-thiohydantoin ring with reagent chemset **17**. In this case, eight isothiocyanates **17**{*a*−*h*} (alkyl, electron-rich aryl, electron-poor aryl, and heteroaryl isocyanates; Figure 5) were selected for the generation of a 32-compound library.

The reactions were performed under similar reaction conditions as for the hydantoin formation but using dimethylformamide as the solvent.[18] One equivalent of the isothiocyanates was used, except in case of **17**{*a*}, where 1.2 equiv was used. The corresponding thioureas were not observed and compounds **18**{*a*−*h*}−**21**{*a*−*h*} were cleanly obtained after evaporation of dimethylformamide, methanol, and any excess reagents with purities from 73 to 100% (94% average) according to LC-MS analysis (confirmed also by ^{1}H NMR spectroscopy) and with quantitative yields (based on mass recovery, except for **17**{*a*}; Scheme 3 and Table 2). All reactions using aromatic isothiocyanates **17**{*d*−*h*} finished within 20 h at room temperature. The reactions with aliphatic isothiocyanates **17**{*a*−*c*} were slower[19] and required 40 h at 40 °C, whereas the reaction with **17**{*a*} did not go to completion.

Conclusions

A highly efficient method for the synthesis of two small libraries (36 + 32 compounds) creating an array of completely

Table 1. Purities for Hydantoin Annulation to Substrates **8**−**11**[a,b]

Reagent	Substrate 8	9	10	11
	Product			
EtNCO **12a**	 **13a** 87%	 **14a** 89%	 **15a** 80%	 **16a** 81%
$PhCH_2CH_2NCO$ **12b**	 **13b** 78%	 **14b** 82%	 **15b** 57%	 **16b** 83%
$EtO_2CCH_2CH_2NCO$ **12c**	 **13c** 87%	 **14c** 87%	 **15c** 76%	 **16c** 83%
PhNCO **12d**	 **13d** 95%	 **14d** 98%	 **15d** 91%	 **16d** 97%
$4\text{-}EtOC_6H_4NCO$ **12e**	 **13e** 88%	 **14e** 95%	 **15e** 92%	 **16e** 95%
$4\text{-}CF_3C_6H_4NCO$ **12f**	 **13f** 94%	 **14f** 96%	 **15f** 94%	 **16f** 98%
$3\text{-}NCC_6H_4NCO$ **12g**	 **13g** 88%	 **14g** 90%	 **15g** 81%	 **16g** 88%
2-ThienylNCO **12h**	 **13h** 95%	 **14h** 97%	 **15h** 92%	 **16h** 97%
3-PyNCO **12i**	 **13i** 99%	 **14i** 100%	 **15i** 100%	 **16i** 95%

[a] % = Purity determined by LC-MS at 215 nm. [b] Quantitative yields based on mass recovery.

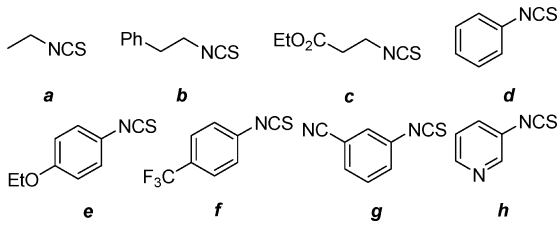
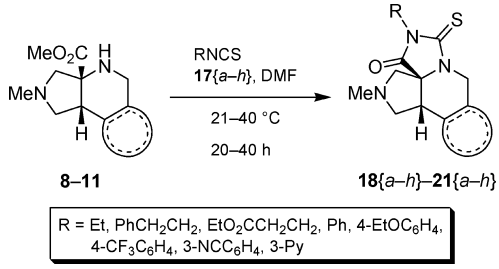


Figure 5. Isothiocyanates **17**{*a*−*h*} used for the annulation to substrates **8**−**11**.

Scheme 3



new pharmaceutically important scaffolds; such as hexahydroimidazo[1,5-*b*]pyrrolo[3,4-*c*]isoquinolines (**13** and **18**), hexahydro[1,3]dioxolo[4,5-*g*]imidazo[1,5-*b*]pyrrolo[3,4-*c*]-isoquinolines (**14** and **19**), hexahydrofuro[2,3-*d*]imidazo[1,5-*a*]pyrrolo[3,4-*b*]pyridines (**15** and **20**), and octahydroimidazo[1′,5′:1,6]pyrrolo[3′,4′:5,6]pyrido[3,4-*b*]indoles (**16** and **21**); has been described. The novel compounds combine three privileged structures: the 2-arylethyl amine moiety, a tetrahydro(hetero)areno[*c*]pyridine, and a (thio)hydantoin.

Experimental Section

Reagents were obtained from commercial suppliers and used without purification. Dichloromethane was distilled from CaH_2 under nitrogen immediately before use and dimethylformamide was used without distillation (99.8%, water <50 ppm, extra dry, ACROS). IR spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer. NMR spectra were recorded on a Bruker DMX 300 (300 MHz) and a Varian 400 (400 MHz) spectrometer in $CDCl_3$ solutions. Chemical shifts are given in parts per million (ppm) with respect to tetramethylsilane (0.00 ppm) as internal standard. Coupling constants are reported as *J* values in hertz (Hz). Multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and b (broad). Peak assignment in ^{13}C spectra are based on 2D gHSQC and gHMBC spectra, and DEPT 135 when needed. Chain numbering corresponds to IUPAC nomenclature, so unprimed atoms belong to the principal chain, primed atoms belong to the first named substituent, doubled-primed atoms to the second named substituent, etc. LC-MS measurements were run on a Shimadzu LC-10A VP series liquid chromatography system, equipped with an SPD-10A VP UV−vis detector and a LCMS-2010A mass spectrometer. The column used for the LC analysis was an Agilent Zorbax Extend C_{18} (3.5 μm, 4.6 × 150 mm) and it was eluted at 1 mL/min with a gradient made up of two solvent mixtures. Solvent A consisted of 0.1% trifluoroacetic acid in water and solvent B consisted of 0.1% trifluoroacetic acid in acetonitrile. The gradient was run as follows: $t = 0$ min, 50% A; $t = 5$ min, 5% A; $t = 10$ min, 5% A; $t = 12.5$ min, 50% A; $t = 20$ min, 50% A. A wavelength of 215 nm was selected for the analysis of purity.

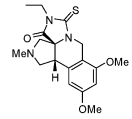
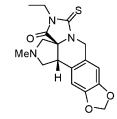
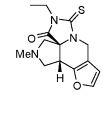
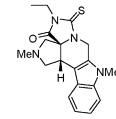
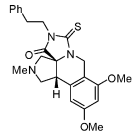
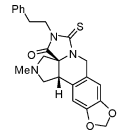
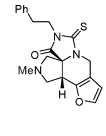
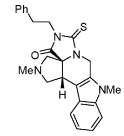
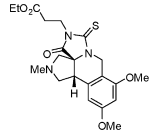
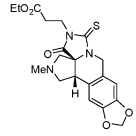
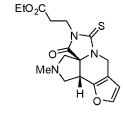
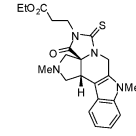
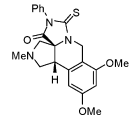
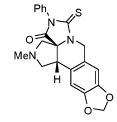
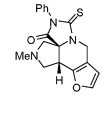
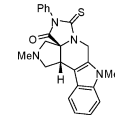
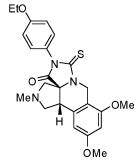
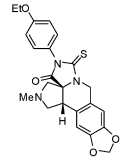
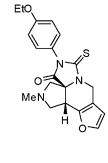
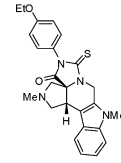
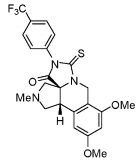
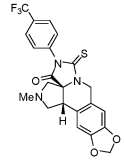
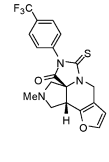
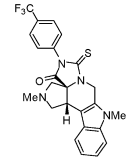
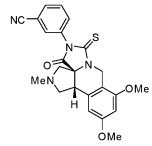
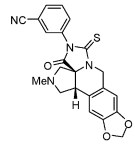
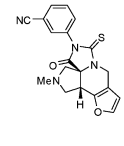
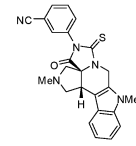
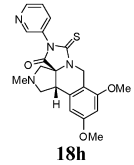
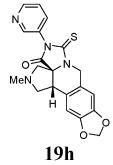
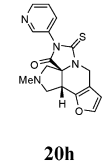
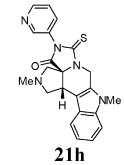
General Procedure for Hydantoin Annulation. Solutions of **12**{*a*−*i*} (0.1 mmol, 0.12 mmol for **12**{*a*}) from a 0.3 M stock solution in dichloromethane (except for **12**{*g*,*i*}, which are insoluble and were used as a solid) were added to nine separate solutions of **8** (0.1 mmol) in dichloromethane (1.5 mL). The resulting reaction mixture was stirred at 40 °C for **12**{*a*−*c*} and at room temperature for **12**{*d*−*i*} for 40 h. After that time, the solvent was evaporated, and the samples were analyzed.

(±)-Ethyl 3-{(3a*R*,12b*R*)-9,11-Dimethoxy-2-methyl-4,6-dioxo-2,3,5,6,8,12b-hexahydro-1*H*,4*H*-imidazo[1,5-*b*]pyrrolo[3,4-*c*]isoquinolin-5-yl}propanoate 13c. ^1H NMR [300 MHz, δ (ppm), $CDCl_3$]: 6.31 (d, $J = 2.4$ Hz, 1 ^1H, 10′-C*H*), 6.23 (d, $J = 2.4$ Hz, 1 ^1H, 12′-C*H*), 5.23 (d, $J = 16.5$ Hz, 1 ^1H, 8′-CH*H*), 4.08 (q, $J = 7.2$ Hz, 2 ^1H, CH_2CH_3), 3.90 (d, $J = 16.5$ Hz, 1 ^1H, 8′-C*H*H), 3.80 (s, 3 ^1H, 9′-OCH_3), 3.77 (s, 3 ^1H, 11′-OCH_3), 3.81−3.74 (m, 2 ^1H, 3-CH_2), 3.60 (dd; $J = 7.5$, 5.1 Hz; 1 ^1H, 12′b-C*H*), 3.15 (dd; $J = 9.0$, 7.5 Hz; 1 ^1H, 1′-CH*H*), 3.02 (bs, 2 ^1H, 3′-CH_2), 2.76−2.66 (m, 1 ^1H, 1′-C*H*H), 2.62 (t, $J = 7.2$ Hz, 2 ^1H, 2-CH_2), 2.36 (bs, 3 ^1H, NCH_3), 1.20 (t, $J = 7.2$ Hz, 3 ^1H, CH_2CH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 176.0 (4′-*C*O), 170.8 (*C*O_2), 160.0 (11′-*C*), 156.8 (9′-*C*), 155.1 (6′-*C*O), 136.8 (12′a-*C*), 114.9 (8′a-*C*), 104.3 (12′-*C*), 96.9 (10′-*C*), 67.6 (3′a-*C*), 65.4 (1′-*C*), 63.5 (3′-*C*), 60.9 (*C*H_2CH_3), 55.6 (9′-O*C*H_3), 55.5 (11′-O*C*H_3), 45.1 (12′b-*C*), 41.8 (N*C*H_3), 35.0 (3-*C*), 34.8 (8′-*C*), 32.6 (2-*C*), 14.2 (CH_2*C*H_3). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2928, 2849, 2785, 1769, 1710, 1607, 832. MS [APCI (*m*/*z*)] calcd for $(C_{21}H_{27}N_3O_6 + H)^+ = 418$, found 418.

(±)-(3a*R*,12b*R*)-9,11-Dimethoxy-2-methyl-5-phenyl-2,3,8,12b-tetrahydro-1*H*,4*H*-imidazo[1,5-*b*]pyrrolo[3,4-*c*]-isoquinoline-4,6(5*H*)-dione 13d. ^1H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.46−7.28 (m, 5 ^1H, Ph), 6.33 (d, $J = 2.4$ Hz, 1 ^1H, 10-C*H*), 6.27 (d, $J = 2.4$ Hz, 1 ^1H, 12-C*H*), 5.33 (d, $J = 16.2$ Hz, 1 ^1H, 8-CH*H*), 3.99 (d, $J = 16.2$ Hz, 1 ^1H, 8-C*H*H), 3.81 (s, 3 ^1H, 9-OCH_3), 3.78 (s, 3 ^1H, 11-OCH_3), 3.71 (dd; $J = 7.2$, 4.5 Hz; 1 ^1H, 12b-C*H*), 3.14 (dd; $J = 9.0$, 7.2 Hz; 1 ^1H, 1-CH*H*), 3.10 (s, 2 ^1H, 3-CH_2), 2.73 (dd; $J = 9.0$, 4.5 Hz; 1 ^1H, 1-C*H*H), 2.35 (s, 3 ^1H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 175.3 (4-*C*O), 160.1 (11-*C*), 156.9 (9-*C*), 154.3 (6-*C*O), 137.3 (12a-*C*), 132.0 (1′-*C*), 129.0 (3′-*C* + 5′-*C*), 128.1 (4′-*C*), 126.0 (2′-*C* + 6′-*C*), 115.0 (8a-*C*), 104.4 (12-*C*), 96.9 (10-*C*), 67.6 (3a-*C*), 65.8 (1-*C*), 64.3 (3-*C*), 55.6 (9-OCH_3), 55.5 (11-OCH_3), 45.6 (12b-*C*), 41.8 (NCH_3), 35.0 (8-*C*). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2942, 2839, 2787, 1772, 1716, 1607, 834, 763, 690. MS [APCI (*m*/*z*)] calcd. for $(C_{22}H_{23}N_3O_4 + H)^+ = 394$, found 394.

(±)-(3a*R*,13b*R*)-5-Ethyl-2-methyl-2,3,8,13b-tetrahydro-1*H*,4*H*,11*H*-[1,3]dioxolo[4,5-*g*] imidazo[1,5-*b*]pyrrolo[3,4-*c*]-isoquinoline-4,6(5*H*)-dione 14a. ^1H NMR [300 MHz, δ (ppm), $CDCl_3$]: 6.65 (s, 1 ^1H, 9-C*H*), 6.57 (s, 1 ^1H, 13-C*H*), 5.92 (s, 2 ^1H, 11-CH_2), 4.83 (d, $J = 15.9$ Hz, 1 ^1H, 8-CH*H*), 4.17 (d, $J = 15.9$ Hz, 1 ^1H, 8-C*H*H), 3.63−3.45 (m, 3 ^1H, 13b-C*H* + CH_2CH_3), 3.14−3.01 (m, 2 ^1H, 1-CH*H* + 3-CH*H*), 2.92 (d, $J = 10.2$ Hz, 1 ^1H, 3-C*H*H), 2.56 (dd; $J = 7.5$, 6.0 Hz; 1 ^1H, 1-C*H*H), 2.34 (s, 3 ^1H, NCH_3), 1.17 (t, $J = 7.2$ Hz, 3 ^1H,

Table 2. Purities for Thiohydantoin Annulation to Substrates **8**−**11**[a,b,c]

Reagent	Substrate 8	9	10	11
	Product			
EtNCS **17a**	 **18a** 80%[d]	 **19a** 94%[e]	 **20a** 73%[f]	 **21a** 90%[g]
$PhCH_2CH_2NCS$ **17b**	 **18b** 95%	 **19b** 99%	 **20b** 95%	 **21b** 96%
$EtO_2CCH_2CH_2NCS$ **17c**	 **18c** 94%	 **19c** 87%	 **20c** 89%	 **21c** 98%
PhNCS **17d**	 **18d** 93%	 **19d** 96%	 **20d** 98%	 **21d** 98%
$4\text{-}EtOC_6H_4NCS$ **17e**	 **18e** 95%	 **19e** 98%	 **20e** 98%	 **21e** 98%
$4\text{-}CF_3C_6H_4NCS$ **17f**	 **18f** 93%	 **19f** 96%	 **20f** 93%	 **21f** 97%
$3\text{-}NCC_6H_4NCS$ **17g**	 **18g** 88%	 **19g** 95%	 **20g** 92%	 **21g** 99%
3-PyNCS **17h**	 **18h** 87%	 **19h** 100%	 **20h** 93%	 **21h** 99%

[a] % = Purity determined by LC-MS at 215 nm. [b] Purity percentage calculated excluding residual DMF peak (1−12%) when present. [c] Quantitative yields based on mass recovery, except for **17**{*a*}. [d] Plus 10% **8**. [e] Plus 6% **9**. [f] Plus 14% **10**. [g] Plus 8% **11**.

CH_2CH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 175.9 (4-*C*O), 156.1 (6-*C*O), 147.4 (12a-*C*), 146.6 (9a-*C*), 128.4 (13a-*C*), 127.0 (8a-*C*), 109.1 (13-*C*), 106.9 (9-*C*), 101.3 (11-*C*), 67.9 (3a-*C*), 65.7 (1-*C*), 64.2 (3-*C*), 45.5 (13b-*C*), 41.7 (NCH_3), 40.6 (8-*C*), 34.3 (CH_2CH_3), 13.6 (CH_2CH_3). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2928, 2850, 2783, 1768, 1708, 1035, 933. MS [APCI (*m*/*z*)] calcd. for $(C_{17}H_{19}N_3O_4 + H)^+ = 330$, found 330.

(±)-3-{(3a*R*,13b*R*)-2-Methyl-4,6-dioxo-2,3,5,6,8,13b-hexahydro-1*H*,4*H*,11*H*-[1,3]dioxolo[4,5-*g*]imidazo[1,5-*b*]pyrrolo[3,4-*c*]isoquinolin-5-yl}benzonitrile 14g. ^1H NMR [300

MHz, δ (ppm), $CDCl_3$]: 7.83 (t, $J = 1.6$ Hz, 1 ^{1}H, 2-C*H*), 7.75 (dt; $J = 7.8$, 1.6 Hz; 1 ^{1}H, 4-C*H*), 7.61 (dt; $J = 7.8$, 1.3 Hz; 1 ^{1}H, 6-C*H*), 7.54 (t, $J = 7.8$ Hz, 1 ^{1}H, 5-C*H*), 6.69 (s, 1 ^{1}H, 9′-C*H*), 6.62 (s, 1 ^{1}H, 13′-C*H*), 5.94 (s, 2 ^{1}H, 11′-CH_2), 4.92 (d, $J = 15.6$ Hz, 1 ^{1}H, 8′-CH*H*), 4.31 (d, $J = 15.6$ Hz, 1 ^{1}H, 8′-C*H*H), 3.72 (dd; $J = 7.5$, 5.1 Hz; 1 ^{1}H, 13′b-C*H*), 3.15 (d, $J = 10.5$ Hz, 1 ^{1}H, 3′-CH*H*), 3.12 (dd; $J = 9.0$, 7.5 Hz; 1 ^{1}H, 1′-CH*H*), 3.05 (d, $J = 10.5$ Hz, 1 ^{1}H, 3′-C*H*H), 2.65 (dd; $J = 9.0$, 5.1 Hz; 1 ^{1}H, 1′-C*H*H), 2.37 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 174.5 (4′-*C*O), 153.9 (6′-*C*O), 147.7 (12′a-*C*), 146.9 (9′a-*C*), 133.0 (3-*C*), 131.4 (6-*C*), 130.0 (5-*C*), 129.8 (4-*C*), 129.0 (2-*C*), 128.4 (13′a-*C*), 126.7 (8′a-*C*), 118.0 (*C*N), 113.3 (1-*C*), 109.1 (13′-*C*), 106.9 (9′-*C*), 101.4 (11′-*C*), 68.1 (3′a-*C*), 65.8 (1′-*C*), 64.8 (3′-*C*), 46.0 (13′b-*C*), 41.6 (N*C*H$_3$), 40.9 (8′-*C*). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2943, 2842, 2786, 2230, 1776, 1718, 1037, 932, 730. MS [APCI (*m*/*z*)] calcd. for $(C_{22}H_{18}N_4O_4 + H)^+ = 403$, found 403.

(±)-(3a*R*,11b*R*)-2-Methyl-5-[4-(trifluoromethyl)phenyl]-2,3,8,11b-tetrahydro-1*H*,4*H*-furo[2,3-*d*]imidazo[1,5-*a*]pyrrolo[3,4-*b*]pyridine-4,6(5*H*)-dione 15f. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.77−7.69 (m, 2 ^{1}H, 3′-C*H* + 5′-C*H*), 7.68−7.60 (m, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 7.37 (d, $J = 1.8$ Hz, 1 ^{1}H, 10-C*H*), 6.31 (d, $J = 1.8$ Hz, 1 ^{1}H, 9-C*H*), 5.07 (dd; $J = 15.9$, 1.5 Hz; 1 ^{1}H, 8-CH*H*), 4.19 (dd; $J = 15.9$, 1.8 Hz; 1 ^{1}H, 8-C*H*H), 3.63 (d, $J = 5.4$ Hz, 1 ^{1}H, 11b-C*H*), 3.30 (d, $J = 10.5$ Hz, 1 ^{1}H, 3-CH*H*), 3.26 (d, $J = 9.3$ Hz, 1 ^{1}H, 1-CH*H*), 2.90 (dd; $J = 9.3$, 5.4 Hz; 1 ^{1}H, 1-C*H*H), 2.89 (d, $J = 10.5$ Hz, 1 ^{1}H, 3-C*H*H), 2.37 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 174.2 (4-*C*O), 153.3 (6-*C*O), 147.5 (11a-*C*), 142.6 (10-*C*), 134.9 (q, $J = 1.4$ Hz, 1′-*C*), 130.0 (q, $J = 32.7$ Hz, 4′-*C*), 126.3 (q, $J = 3.7$ Hz, 3′-*C* + 5′-*C*), 125.9 (2′-*C* + 6′-*C*), 123.9 (q, $J = 270.5$ Hz, *C*F$_3$), 115.7 (8a-*C*), 108.2 (9-*C*), 68.4 (3a-*C*), 62.2 (3-*C*), 60.0 (1-*C*), 42.2 (11b-*C*), 41.8 (N*C*H$_3$), 36.2 (8-*C*). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2945, 2843, 2794, 1777, 1721, 1324, 842, 739. MS [APCI (*m*/*z*)] calcd. for $(C_{19}H_{16}F_3N_3O_3 + H)^+ = 392$, found 392.

(±)-(3a*R*,11b*R*)-2-Methyl-5-(3-pyridyl)-2,3,8,11b-tetrahydro-1*H*,4*H*-furo[2,3-*d*]imidazo[1,5-*a*]pyrrolo[3,4-*b*]pyridine-4,6(5*H*)-dione 15i. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 8.78 (d, $J = 2.4$ Hz, 1 ^{1}H, 2′-C*H*), 8.60 (dd; $J = 4.8$, 1.5 Hz; 1 ^{1}H, 6′-C*H*), 7.83 (ddd; $J = 8.1$, 2.4, 1.5 Hz; 1 ^{1}H, 4′-C*H*), 7.41 (ddd; $J = 8.1$, 4.8, 0.6 Hz; 1 ^{1}H, 5′-C*H*), 7.36 (d, $J = 1.8$ Hz, 1 ^{1}H, 10-C*H*), 6.31 (d, $J = 1.8$ Hz, 1 ^{1}H, 9-C*H*), 5.07 (dd; $J = 15.9$, 1.5 Hz; 1 ^{1}H, 8-CH*H*), 4.19 (dd; $J = 15.9$, 1.8 Hz; 1 ^{1}H, 8-C*H*H), 3.64 (d, $J = 5.4$ Hz, 1 ^{1}H, 11b-C*H*), 3.29 (d, $J = 10.8$ Hz, 1 ^{1}H, 3-CH*H*), 3.24 (d, $J = 9.3$ Hz, 1 ^{1}H, 1-CH*H*), 2.90 (d, $J = 10.8$ Hz, 1 ^{1}H, 3-C*H*H), 2.89 (dd; $J = 9.3$, 5.7 Hz; 1 ^{1}H, 1-C*H*H), 2.37 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 174.2 (4-*C*O), 153.3 (6-*C*O), 148.9 (6′-*C*), 147.6 (11a-*C*), 146.8 (2′-*C*), 142.6 (10-*C*), 133.1 (4′-*C*), 128.9 (3′-*C*), 123.7 (5′-*C*), 115.6 (8a-*C*), 108.2 (9-*C*), 68.6 (3a-*C*), 62.3 (3-*C*), 60.1 (1-*C*), 42.2 (11b-*C*), 41.8 (N*C*H$_3$), 36.2 (8-*C*). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2946, 2840, 2791, 1775, 1717, 732, 705. MS [APCI (*m*/*z*)] calcd. for $(C_{17}H_{16}N_4O_3 + H)^+ = 325$, found 325.

(±)-(3a*R*,13c*R*)-2,9-Dimethyl-5-phenethyl-1,2,3,8,9,13c-hexahydro-4*H*-imidazo[1′,5′:1,6]pyrrolo[3′,4′:5,6]pyrido[3,4-*b*]indole-4,6(5*H*)-dione 16b. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.42 (d, $J = 7.8$ Hz, 1 ^{1}H, 13-C*H*), 7.29 (d, $J = 8.1$ Hz, 1 ^{1}H, 10-C*H*), 7.25−7.08 (m, 7 ^{1}H, 11-C*H* + 12-C*H* + Ph), 5.21 (dd; $J = 16.2$, 0.6 Hz; 1 ^{1}H, 8-CH*H*), 4.37 (d, $J = 16.2$ Hz, 1 ^{1}H, 8-C*H*H), 3.78 (t, $J = 7.2$ Hz, 2 ^{1}H, 1′-CH_2), 3.68 (s, 3 ^{1}H, 9-NCH_3), 3.64 (d, $J = 5.7$ Hz, 1 ^{1}H, 13c-C*H*), 3.22 (d, $J = 10.5$ Hz, 1 ^{1}H, 3-CH*H*), 3.18 (d, $J = 9.3$ Hz, 1 ^{1}H, 1-CH*H*), 2.98−2.89 (m, 3 ^{1}H, 1-C*H*H + 2′-CH_2), 2.73 (d, $J = 10.5$ Hz, 1 ^{1}H, 3-C*H*H), 2.32 (s, 3 ^{1}H, 2-NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 175.9 (4-*C*O), 155.5 (6-*C*O), 137.8 (1″-*C*), 137.6 (9a-*C*), 131.7 (8a-*C*), 129.1 (2″-*C* + 6″-*C*), 128.6 (3″-*C* + 5″-*C*), 126.8 (4″-*C*), 125.5 (13a-*C*), 122.1 (11-*C*), 119.7 (12-*C*), 118.0 (13-*C*), 109.4 (10-*C*), 108.0 (13b-*C*), 68.1 (3a-*C*), 62.35 (1-*C*), 62.28 (3-*C*), 41.9 (2-N*C*H$_3$), 40.8 (13c-*C*), 40.3 (1′-*C*), 34.9 (8-*C*), 34.0 (2′-*C*), 29.8 (9-N*C*H$_3$). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2946, 2851, 2789, 1768, 1709, 760, 742, 699. MS [APCI (*m*/*z*)] calcd. for $(C_{25}H_{26}N_4O_2 + H)^+ = 415$, found 415.

(±)-(3a*R*,13c*R*)-5-(4-Ethoxyphenyl)-2,9-dimethyl-1,2,3,8,9,13c-hexahydro-4*H*-imidazo[1′,5′:1,6]pyrrolo[3′,4′:5,6]pyrido[3,4-*b*]indole-4,6(5*H*)-dione 16e. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.48 (d, $J = 7.8$ Hz, 1 ^{1}H, 13-C*H*), 7.34−7.20 (m, 4 ^{1}H, 10-C*H* + 11-C*H* + 2′-C*H* + 6′-C*H*), 7.15−7.09 (m, 1 ^{1}H, 12-C*H*), 6.98−6.90 (m, 2 ^{1}H, 3′-C*H* + 5′-C*H*), 5.33 (dd; $J = 16.2$, 0.9 Hz; 1 ^{1}H, 8-CH*H*), 4.43 (dd; $J = 16.2$, 0.9 Hz; 1 ^{1}H, 8-C*H*H), 4.04 (q, $J = 6.9$ Hz, 2 ^{1}H, CH_2CH$_3$), 3.95 (dd; $J = 6.0$, 1.2 Hz; 1 ^{1}H, 13c-C*H*), 3.70 (s, 3 ^{1}H, 9-NCH_3), 3.31 (d, $J = 10.5$ Hz, 1 ^{1}H, 3-CH*H*), 3.20 (d, $J = 9.0$ Hz, 1 ^{1}H, 1-CH*H*), 3.01 (dd; $J = 9.0$, 6.0 Hz; 1 ^{1}H, 1-C*H*H), 2.95 (d, $J = 10.5$ Hz, 1 ^{1}H, 3-C*H*H), 2.34 (s, 3 ^{1}H, 2-NCH_3), 1.41 (t, $J = 6.9$ Hz, 3 ^{1}H, CH$_2$CH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 175.5 (4-*C*O), 158.8 (4′-*C*), 154.9 (6-*C*O), 137.5 (9a-*C*), 131.5 (8a-*C*), 127.6 (2′-*C* + 6′-*C*), 125.5 (13a-*C*), 124.3 (1′-*C*), 122.1 (11-*C*), 119.8 (12-*C*), 118.1 (13-*C*), 115.0 (3′-*C* + 5′-*C*), 109.4 (10-*C*), 108.6 (13b-*C*), 68.3 (3a-*C*), 63.8 (*C*H$_2$CH$_3$), 63.2 (3-*C*), 62.7 (1-*C*), 42.0 (2-N*C*H$_3$), 41.2 (13c-*C*), 35.1 (8-*C*), 29.9 (9-N*C*H$_3$), 14.9 (CH$_2$*C*H$_3$). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2936, 2841, 2788, 1772, 1714, 735. MS [APCI (*m*/*z*)] calcd. for $(C_{25}H_{26}N_4O_3 + H)^+ = 431$, found 431.

(±)-(3a*R*,13c*R*)-2,9-Dimethyl-5-(2-thienyl)-1,2,3,8,9,13c-hexahydro-4*H*-imidazo[1′,5′:1,6]pyrrolo[3′,4′:5,6]pyrido[3,4-*b*]indole-4,6(5*H*)-dione 16h. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.53 (dd; $J = 3.9$, 1.2 Hz; 1 ^{1}H, 3′-C*H*), 7.45 (d, $J = 7.8$ Hz, 1 ^{1}H, 13-C*H*), 7.30 (d, $J = 8.1$ Hz, 1 ^{1}H, 10-C*H*), 7.26−7.20 (m, 1 ^{1}H, 11-C*H*), 7.15 (dd; $J = 5.4$, 1.2 Hz; 1 ^{1}H, 5′-C*H*), 7.14−7.08 (m, 1 ^{1}H, 12-C*H*), 6.99 (dd; $J = 5.4$, 3.9 Hz; 1 ^{1}H, 4′-C*H*), 5.33 (d, $J = 15.9$ Hz, 1 ^{1}H, 8-CH*H*), 4.44 (d, $J = 15.9$ Hz, 1 ^{1}H, 8-C*H*H), 3.95 (d, $J = 6.0$ Hz, 1 ^{1}H, 13c-C*H*), 3.70 (s, 3 ^{1}H, 9-NCH_3), 3.28 (d, $J = 10.5$ Hz, 1 ^{1}H, 3-CH*H*), 3.18 (d, $J = 9.0$ Hz, 1 ^{1}H, 1-CH*H*), 3.03 (dd; $J = 9.0$, 6.0 Hz; 1 ^{1}H, 1-C*H*H), 2.95 (d, $J = 10.5$ Hz, 1 ^{1}H, 3-C*H*H), 2.34 (s, 3 ^{1}H, 2-NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 173.6 (4-*C*O), 153.4 (6-*C*O), 137.5 (9a-*C*), 132.5 (2′-*C*), 131.1 (8a-*C*), 125.4 (13a-*C*), 125.2 (4′-*C*), 122.2 (11-*C*), 121.7 (5′-*C*), 119.9 (3′-*C*), 119.8 (12-*C*), 118.1 (13-*C*), 109.4 (10-*C*), 108.6 (13b-*C*), 68.1 (3a-*C*), 63.2 (3-*C*), 62.7 (1-*C*), 41.9 (2-N*C*H$_3$), 41.3 (13c-*C*), 35.3 (8-*C*), 29.9 (9-N*C*H$_3$). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2937, 2841, 2790, 1773,

1716, 910, 733, 698. MS [APCI (*m*/*z*)] calcd. for $(C_{21}H_{20}N_4O_2S + H)^+ = 393$, found 393.

General Procedure for Thiohydantoin Annulation. Solutions of **17**{*a*−*h*} (0.1 mmol, 0.12 mmol for **17**{*a*}) from a 0.3 M stock solution in dimethylformamide were added to eight separate solutions of **8** (0.1 mmol) in dimethylformamide (1.5 mL). The resulting reaction mixture was stirred at 40 °C for 40 h for **17**{*a*−*c*} and at room temperature for 20 h for **17**{*d*−*h*}. After that time, the solvent was evaporated and the samples were analyzed.

(±)-(3a*R*,12b*R*)-9,11-Dimethoxy-2-methyl-5-phenethyl-6-thioxo-2,3,5,6,8,12b-hexahydro-1*H*,4*H*-imidazo[1,5-*b*]pyrrolo[3,4-*c*]isoquinolin-4-one 18b. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.26−7.14 (m, 5 ^{1}H, Ph), 6.33 (d, J = 2.4 Hz, 1 ^{1}H, 10-C*H*), 6.20 (d, J = 2.4 Hz, 1 ^{1}H, 12-C*H*), 5.90 (d, J = 16.2 Hz, 1 ^{1}H, 8-CH*H*), 4.17 (d, J = 16.2 Hz, 1 ^{1}H, 8-C*H*H), 4.09−4.00 (m, 2 ^{1}H, 1′-CH_2), 3.83 (s, 3 ^{1}H, 9-OCH_3), 3.78 (s, 3 ^{1}H, 11-OCH_3), 3.43 (dd; J = 6.6, 3.3 Hz; 1 ^{1}H, 12b-C*H*), 3.04–2.96 (m, 4 ^{1}H, 1-CH*H* + 3-CH*H* + 2′-CH_2), 2.77 (dd; J = 9.3, 3.3 Hz; 1 ^{1}H, 1-C*H*H), 2.68 (d, J = 10.5 Hz, 1 ^{1}H, 3-C*H*H), 2.28 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 180.4 (6-*C*S), 176.5 (4-*C*O), 160.1 (11-*C*), 156.9 (9-*C*), 138.0 (1″-*C*), 137.4 (12a-*C*), 129.2 (2″-*C* + 6″-*C*), 128.5 (3″-*C* + 5″-*C*), 126.6 (4″-*C*), 114.5 (8a-*C*), 104.1 (12-*C*), 96.9 (10-*C*), 69.5 (3a-*C*), 65.6 (1-*C*), 63.6 (3-*C*), 55.7 (9-O*C*H$_3$), 55.5 (11-O*C*H$_3$), 46.6 (12b-*C*), 42.9 (1′-*C*), 41.6 (N*C*H$_3$), 38.8 (8-*C*), 33.6 (2′-*C*). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2938, 2837, 2786, 1741, 1673, 1603, 1149, 834, 747, 699. MS [APCI (*m*/*z*)] calcd. for $(C_{24}H_{27}N_3O_3S + H)^+ = 438$, found 438.

(±)-(3a*R*,12b*R*)-9,11-Dimethoxy-2-methyl-6-thioxo-5-[4-(trifluoromethyl)phenyl]-2,3,5,6,8,12b-hexahydro-1*H*,4*H*-imidazo[1,5-*b*]pyrrolo[3,4-*c*]isoquinolin-4-one 18f. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.77−7.69 (m, 2 ^{1}H, 3′-C*H* + 5′-C*H*), 7.52−7.44 (m, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 6.36 (d, J = 2.4 Hz, 1 ^{1}H, 10-C*H*), 6.29 (d, J = 2.4 Hz, 1 ^{1}H, 12-C*H*), 5.99 (d, J = 16.5 Hz, 1 ^{1}H, 8-CH*H*), 4.29 (d, J = 16.5 Hz, 1 ^{1}H, 8-C*H*H), 3.84 (s, 3 ^{1}H, 9-OCH_3), 3.79 (s, 3 ^{1}H, 11-OCH_3), 3.77 (dd; J = 6.9, 3.6 Hz; 1 ^{1}H, 12b-C*H*), 3.26 (d, J = 10.5 Hz, 1 ^{1}H, 3-CH*H*), 3.13 (dd; J = 9.0, 6.9 Hz; 1 ^{1}H, 1-CH*H*), 3.00 (d, J = 10.5 Hz, 1 ^{1}H, 3-C*H*H), 2.89 (dd; J = 9.0, 3.3 Hz; 1 ^{1}H, 1-C*H*H), 2.35 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 179.4 (6-*C*S), 175.8 (4-*C*O), 160.3 (11-*C*), 157.0 (9-*C*), 137.2 (12a-*C*), 136.4 (q, J = 1.4 Hz, 1′-*C*), 131.0 (q, J = 32.7 Hz, 4′-*C*), 129.0 (2′-*C* + 6′-*C*), 126.2 (q, J = 3.7 Hz, 3′-*C* + 5′-*C*), 123.8 (q, J = 270.8 Hz, *C*F$_3$), 114.3 (8a-*C*), 104.1 (12-*C*), 97.0 (10-*C*), 70.1 (3a-*C*), 65.7 (1-*C*), 64.1 (3-*C*), 55.8 (9-O*C*H$_3$), 55.5 (11-O*C*H$_3$), 46.9 (12b-*C*), 41.6 (N*C*H$_3$), 39.2 (8-*C*). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2939, 2841, 2788, 1751, 1672, 1608, 1320, 1151, 840. MS [APCI (*m*/*z*)] calcd. for $(C_{23}H_{22}F_3N_3O_3S + H)^+ = 478$, found 478.

(±)-(3a*R*,13b*R*)-5-Ethyl-2-methyl-6-thioxo-2,3,5,6,8,13b-hexahydro-1*H*,4*H*,11*H*-[1,3]dioxolo[4,5-*g*]imidazo[1,5-*b*]pyrrolo[3,4-*c*]isoquinolin-4-one 19a. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 6.67 (s, 1 ^{1}H, 9-C*H*), 6.57 (s, 1 ^{1}H, 13-C*H*), 5.92 (s, 2 ^{1}H, 11-CH_2), 5.54 (d, J = 15.3 Hz, 1 ^{1}H, 8-CH*H*), 4.47 (d, J = 15.3 Hz, 1 ^{1}H, 8-C*H*H), 3.86 (q, J = 7.2 Hz, 2 ^{1}H, CH_2CH$_3$), 3.61 (dd; J = 6.9, 3.9 Hz; 1 ^{1}H, 13b-C*H*), 3.04 (dd; J = 9.0, 6.9 Hz; 1 ^{1}H, 1-CH*H*), 3.04 (d, J = 10.2 Hz, 1 ^{1}H, 3-CH*H*), 2.92 (d, J = 10.2 Hz, 1 ^{1}H, 3-C*H*H), 2.72 (dd; J = 9.0, 3.9 Hz; 1 ^{1}H, 1-C*H*H), 2.33 (s, 3 ^{1}H, NCH_3), 1.21 (t, J = 7.2 Hz, 3 ^{1}H, CH$_2$CH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 181.2 (6-*C*S), 176.3 (4-*C*O), 147.6 (12a-*C*), 146.7 (9a-*C*), 128.8 (13a-*C*), 126.5 (8a-*C*), 108.7 (13-*C*), 107.0 (9-*C*), 101.3 (11-*C*), 69.8 (3a-*C*), 65.9 (1-*C*), 64.2 (3-*C*), 46.8 (13b-*C*), 44.2 (8-*C*), 41.6 (N*C*H$_3$), 37.3 (*C*H$_2$CH$_3$), 13.1 (CH$_2$*C*H$_3$). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2938, 2843, 2785, 1738, 1673, 1035, 932. MS [APCI (*m*/*z*)] calcd for $(C_{17}H_{19}N_3O_3S + H)^+ = 346$, found 346.

(±)-3-{(3a*R*,13b*R*)-2-Methyl-4-oxo-6-thioxo-2,3,5,6,8,13b-hexahydro-1*H*,4*H*,11*H*-[1,3]dioxolo[4,5-*g*]imidazo[1,5-*b*]pyrrolo[3,4-*c*]isoquinolin-5-yl}benzonitrile 19g. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.73−7.65 (m, 2 ^{1}H, 2-C*H* + 6-C*H*), 7.63−7.54 (m, 2 ^{1}H, 5-C*H* + 4-C*H*), 6.70 (s, 1 ^{1}H, 9′-C*H*), 6.63 (s, 1 ^{1}H, 13′-C*H*), 5.94 (s, 2 ^{1}H, 11′-CH_2), 5.60 (d, J = 15.3 Hz, 1 ^{1}H, 8′-CH*H*), 4.59 (d, J = 15.3 Hz, 1 ^{1}H, 8′-C*H*H), 3.77 (dd; J = 6.9, 3.9 Hz; 1 ^{1}H, 13′b-C*H*), 3.21 (d, J = 10.2 Hz, 1 ^{1}H, 3′-CH*H*), 3.08 (dd; J = 9.3, 6.9 Hz; 1 ^{1}H, 1′-CH*H*), 3.04 (d, J = 10.2 Hz, 1 ^{1}H, 3′-C*H*H), 2.80 (dd; J = 9.3, 3.9 Hz; 1 ^{1}H, 1′-C*H*H), 2.37 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 179.6 (6′-*C*S), 175.3 (4′-*C*O), 147.8 (12′a-*C*), 146.9 (9′a-*C*), 134.1 (3-*C*), 133.0 (4-*C*), 132.5 (6-*C*), 132.1 (2-*C*), 129.9 (5-*C*), 128.6 (13′a-*C*), 126.1 (8′a-*C*), 117.8 (*C*N), 113.3 (1-*C*), 108.8 (13′-*C*), 107.1 (9′-*C*), 101.4 (11′-*C*), 70.5 (3′a-*C*), 65.9 (1′-*C*), 64.7 (3′-*C*), 47.2 (13′b-*C*), 44.6 (8′-*C*), 41.4 (N*C*H$_3$). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2939, 2844, 2788, 2230, 1752, 1670, 1036, 932, 733. MS [APCI (*m*/*z*)] calcd. for $(C_{22}H_{18}N_4O_3S + H)^+ = 419$, found 419.

(±)-(3a*R*,11b*R*)-2-Methyl-5-phenyl-6-thioxo-2,3,5,6,8,11b-hexahydro-1*H*,4*H*-furo[2,3-*d*]imidazo[1,5-*a*]pyrrolo[3,4-*b*]pyridin-4-one 20d. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.54−7.43 (m, 3 ^{1}H, 3′-C*H* + 4′-C*H* + 5′-C*H*), 7.38 (d, J = 1.8 Hz, 1 ^{1}H, 10-C*H*), 7.35−7.28 (m, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 6.33 (d, J = 1.8 Hz, 1 ^{1}H, 9-C*H*), 5.78 (dd; J = 15.9, 1.5 Hz; 1 ^{1}H, 8-CH*H*), 4.39 (dd; J = 15.9, 2.1 Hz; 1 ^{1}H, 8-C*H*H), 3.68 (d, J = 5.1 Hz, 1 ^{1}H, 11b-C*H*), 3.36 (d, J = 10.5 Hz, 1 ^{1}H, 3-CH*H*), 3.29 (d, J = 9.0 Hz, 1 ^{1}H, 1-CH*H*), 2.91 (dd; J = 9.0, 5.1 Hz; 1 ^{1}H, 1-C*H*H), 2.86 (d, J = 10.5 Hz, 1 ^{1}H, 3-C*H*H), 2.38 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 180.9 (6-*C*S), 175.5 (4-*C*O), 147.2 (11a-*C*), 142.8 (10-*C*), 133.2 (1′-*C*), 129.4 (4′-*C*), 129.2 (3′-*C* + 5′-*C*), 128.5 (2′-*C* + 6′-*C*), 115.6 (8a-*C*), 108.4 (9-*C*), 70.6 (3a-*C*), 62.0 (3-*C*), 59.5 (1-*C*), 43.1 (11b-*C*), 41.8 (N*C*H$_3$), 40.3 (8-*C*). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2939, 2845, 2791, 1749, 1671, 742, 732, 692. MS [APCI (*m*/*z*)] calcd. for $(C_{18}H_{17}N_3O_2S + H)^+ = 340$, found 340.

(±)-(3a*R*,11b*R*)-5-(4-Ethoxyphenyl)-2-methyl-6-thioxo-2,3,5,6,8,11b-hexahydro-1*H*,4*H*-furo[2,3-*d*]imidazo[1,5-*a*]pyrrolo[3,4-*b*]pyridin-4-one 20e. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.37 (d, J = 1.8 Hz, 1 ^{1}H, 10-C*H*), 7.24−7.17 (m, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 7.02−6.93 (m, 2 ^{1}H, 3′-C*H* + 5′-C*H*), 6.32 (d, J = 1.8 Hz, 1 ^{1}H, 9-C*H*), 5.77 (dd; J = 15.9, 1.5 Hz; 1 ^{1}H, 8-CH*H*), 4.38 (dd; J = 15.9, 1.8 Hz; 1 ^{1}H, 8-C*H*H), 4.06 (q, J = 6.9 Hz, 2 ^{1}H, CH_2CH$_3$), 3.66 (d, J = 5.4 Hz, 1 ^{1}H, 11b-C*H*), 3.34 (d, J = 10.5 Hz, 1 ^{1}H, 3-CH*H*), 3.29 (d, J = 9.3 Hz, 1 ^{1}H, 1-CH*H*), 2.92 (dd; J = 9.3, 5.4

Hz; 1 ^{1}H, 1-C*H*H), 2.85 (d, J = 10.5 Hz, 1 ^{1}H, 3-C*H*H), 2.37 (s, 3 ^{1}H, NCH_3), 1.42 (t, J = 6.9 Hz, 3 ^{1}H, CH_2CH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 181.4 (6-*C*S), 175.7 (4-*C*O), 159.5 (4′-*C*), 147.2 (11a-*C*), 142.8 (10-*C*), 129.6 (2′-*C* + 6′-*C*), 125.6 (1′-*C*), 115.6 (8a-*C*), 115.0 (3′-*C* + 5′-*C*), 108.4 (9-*C*), 70.5 (3a-*C*), 63.8 (*C*H_2CH$_3$), 62.0 (3-*C*), 59.5 (1-*C*), 43.0 (11b-*C*), 41.8 (N*C*H$_3$), 40.4 (8-*C*), 14.9 (CH_2*C*H$_3$). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2936, 2840, 2791, 1747, 1671, 733. MS [APCI (*m*/*z*)] calcd. for $(C_{20}H_{21}N_3O_3S + H)^+$ = 384, found 384.

(±)-Ethyl 3-{(3a*R*,13c*R*)-2,9-dimethyl-4-oxo-6-thioxo-1,2,3,5,6,8,9,13c-octahydro-4*H*-imidazo[1′,5′:1,6]pyrrolo-[3′,4′:5,6]pyrido[3,4-*b*]indol-5-yl}propanoate 21c. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.44 (d, J = 7.8 Hz, 1 ^{1}H, 13′-C*H*), 7.30 (d, J = 8.1 Hz, 1 ^{1}H, 10′-C*H*), 7.31−7.19 (m, 1 ^{1}H, 11′-C*H*), 7.14−7.08 (m, 1 ^{1}H, 12′-C*H*), 5.99 (dd; J = 16.2, 0.9 Hz; 1 ^{1}H, 8′-CH*H*), 4.57 (dd; J = 16.2, 1.2 Hz; 1 ^{1}H, 8′-C*H*H), 4.16 (t, J = 7.2 Hz, 2 ^{1}H, 3-CH_2), 4.12 (q, J = 7.2 Hz, 2 ^{1}H, CH_2CH$_3$), 3.87 (d, J = 5.1 Hz, 1 ^{1}H, 13′c-C*H*), 3.71 (s, 3 ^{1}H, 9′-NCH_3), 3.25 (d, J = 10.5 Hz, 1 ^{1}H, 3′-CH*H*), 3.20 (d, J = 9.0 Hz, 1 ^{1}H, 1′-CH*H*), 3.00 (dd; J = 9.0, 6.0 Hz; 1 ^{1}H, 1′-C*H*H), 2.80 (d, J = 10.5 Hz, 1 ^{1}H, 3′-C*H*H), 2.81−2.64 (m, 2 ^{1}H, 2-CH_2), 2.32 (s, 3 ^{1}H, 2′-NCH_3), 1.23 (t, J = 7.2 Hz, 1 ^{1}H, CH_2CH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 180.8 (6′-*C*S), 176.4 (4′-*C*O), 170.9 (*C*O_2), 137.8 (9′a-*C*), 131.0 (8′a-*C*), 125.2 (13′a-*C*), 122.2 (11′-*C*), 119.8 (12′-*C*), 118.1 (13′-*C*), 109.5 (10′-*C*), 108.6 (13′b-*C*), 70.5 (3′a-*C*), 62.6 (3′-*C*), 62.2 (1′-*C*), 61.0 (*C*H_2CH$_3$), 41.91 (2′-N*C*H$_3$), 41.89 (13′c-*C*), 39.1 (8′-*C*), 37.9 (3-*C*), 32.3 (2-*C*), 29.9 (9′-N*C*H$_3$), 14.3 (CH_2*C*H$_3$). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2938, 2840, 2789, 1736, 1674, 739. MS [APCI (*m*/*z*)] calcd. for $(C_{22}H_{26}N_4O_3S + H)^+$ = 427, found 427.

(±)-(3a*R*,13c*R*)-2,9-Dimethyl-5-(3-pyridyl)-6-thioxo-1,2,3,5,6,8,9,13c-octahydro-4*H*-imidazo[1′,5′:1,6]pyrrolo[3′,4′:5,6]pyrido[3,4-*b*]indol-4-one 21h. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 8.66 (dd; J = 4.8, 1.5 Hz; 1 ^{1}H, 6′-C*H*), 8.63 (d, J = 2.4 Hz, 1 ^{1}H, 2′-C*H*), 7.71 (ddd; J = 8.1, 2.4, 1.5 Hz; 1 ^{1}H, 4′-C*H*), 7.49 (d, J = 7.8 Hz, 1 ^{1}H, 13-C*H*), 7.43 (ddd; J = 8.1, 4.8, 0.6 Hz; 1 ^{1}H, 5′-C*H*), 7.33 (d, J = 8.1 Hz, 1 ^{1}H, 10-C*H*), 7.28−7.22 (m, 1 ^{1}H, 11-C*H*), 7.17−7.11 (m, 1 ^{1}H, 12-C*H*), 6.10 (dd; J = 16.2, 0.9 Hz; 1 ^{1}H, 8-CH*H*), 4.68 (dd; J = 16.2, 1.2 Hz; 1 ^{1}H, 8-C*H*H), 4.05 (d, J = 5.1 Hz, 1 ^{1}H, 13c-C*H*), 3.74 (s, 3 ^{1}H, 9-NCH_3), 3.41 (d, J = 10.5 Hz, 1 ^{1}H, 3-CH*H*), 3.25 (d, J = 9.0 Hz, 1 ^{1}H, 1-CH*H*), 3.04 (dd; J = 9.0, 5.7 Hz; 1 ^{1}H, 1-C*H*H), 2.94 (d, J = 10.5 Hz, 1 ^{1}H, 3-C*H*H), 2.36 (s, 3 ^{1}H, 2-NCH_3) ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 180.4 (6-*C*S), 175.8 (4-*C*O), 150.0 (6′-*C*), 149.4 (2′-*C*), 137.8 (9a-*C*), 136.0 (4′-*C*), 130.9 (8a-*C*), 130.3 (3′-*C*), 125.2 (13a-*C*), 123.7 (5′-*C*), 122.3 (11-*C*), 120.0 (12-*C*), 118.1 (13-*C*), 109.6 (10-*C*), 108.6 (13b-*C*), 71.1 (3a-*C*), 63.1 (3-*C*), 62.3 (1-*C*), 42.4 (13c-*C*), 41.8 (2-N*C*H$_3$), 39.5 (8-*C*), 30.0 (9-N*C*H$_3$). FTIR [$\bar{\nu}$ (cm^{-1}), neat]: 2937, 2841, 2790, 1749, 1670, 733, 703. MS [APCI (*m*/*z*)] calcd for $(C_{22}H_{21}N_5OS + H)^+$ = 404, found 404.

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Supporting Information Available. Experimental copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **13c**, **13d**, **14a**, **14i**, **15f**, **15i**, **16b**, **16e**, **16h**, **18b**, **18f**, **19a**, **19g**, **20d**, **20e**, **21c**, and **21h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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