Synthesis of Hydantoins and Thiohydantoins Spiro-Fused to Pyrrolidines: Druglike Molecules Based on the 2-Arylethyl Amine Scaffold

Daniel Blanco-Ania,[†] Pedro H. H. Hermkens,[‡] Leo A. J. M. Sliedregt,[§] Hans W. Scheeren,[†] and Floris P. J. T. Rutjes*,[†]

Institute for Molecules and Materials, Radboud University Nijmegen, Toernooiveld 1, 6525 ED Nijmegen, The Netherlands, Schering-Plough, P.O. Box 20, 5340 BH Oss, The Netherlands, and Solvay Pharmaceuticals, Sector Discovery Weesp, P.O. Box 900, 1380 DA Weesp, The Netherlands

Received November 22, 2008

The synthesis of a 144-compound library of hydantoins and thiohydantoins spiro-fused to pyrrolidines is described. These compounds are synthesized from β-aryl pyrrolidines, providing products with the *2-arylethyl amine* moiety, a structural feature often encountered in compounds active in the central nervous system. All possible stereoisomers of the two-stereocenter products are synthesized. The 80-membered hydantoin sublibrary was obtained with yields ranging from 58 to 100% (87% average) and purities from 51 to 100% (87% average) and the 64-membered thiohydantoin sublibrary was obtained with yields ranging from 65 to 100% (89% average) and purities from 67 to 100% (93% average).

Introduction

The *2-arylethyl amine* moiety **1** (Figure 1) is an important pharmacophore, which is encountered in numerous compounds active in the central nervous system (CNS). This privileged structure is present in neurotransmitters such as dopamine, epinephrine, norepinephrine, and serotonin.[1] Salmeterol[2] and venlafaxine,[3] two of the ten best-selling prescription drugs in 2006,[4] also contain this moiety. In addition, the 2-arylethyl amine unit occurs in many hallucinogenic drugs, such as LSD, MDMA (ecstasy), mescaline, and psilocybin (magic mushrooms).[5]

Hydantoins **2** and 2-thiohydantoins **3** (Figure 1) are also present in a wide range of biologically active compounds including antiarrhythmic,[6] antiepileptic,[7] antitumor,[8] anxiolytic,[9] anticarcinogenic,[10] and anti-HIV agents.[11] A well-known example of a drug featuring a hydantoin is phenytoin (5,5-diphenylhydantoin, Dilantin), which has been used for decades to treat epilepsy.[12]

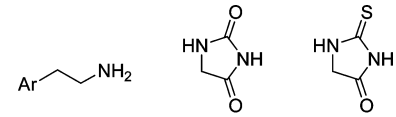
One approach used to determine the relationship of conformational structure to biological activity of small molecules is to minimize the flexibility of the potential drug through the use of conformationally restricted analogues.[13] Herein we present the synthesis of a library comprised of compounds combining all the above features (Scheme 1). First, these compounds possess a β-aryl pyrrolidine with a conformationally constrained 2-arylethyl amine. Second, they are semirigid structures because of the spiro fusion to a (thio)hydantoin.

These new spiro compounds are potential CNS ligands. In the course of our research, several publications on this new scaffold have been published.[14] The reported compounds possess the substructure **4** and were shown to be LFA-1 antagonists. Although this is not a CNS application, it demonstrates the potential of this class of compounds to bind to complex biomolecules. We constructed our library from compounds having structures based on **4** and **5** and also **6** and **7** (which include the thiohydantoin moiety; Figure 2), and in each case, all combinations of stereoisomers were generated.

Results and Discussion

The basis of this research is the synthesis of substrates **12**{*1*−*4*} and **13**{*1*−*4*} (Figure 3), which has been described in a recent article.[15]

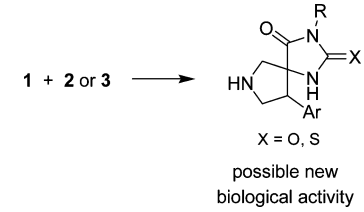
The synthetic approach to substrates **12**{*1*−*4*} and **13**{*1*−*4*} involved the use of the Knoevenagel condensa-



1 **2** **3**

Figure 1. 2-Arylethyl amine **1**, hydantoin **2**, and 2-thiohydantoin **3**.

Scheme 1. Combination of Two Privileged Structures to Generate a Product with Increased Rigidity



* To whom correspondence should be addressed. E-mail: f.rutjes@science.ru.nl.
† Radboud University Nijmegen.
‡ Schering-Plough.
§ Solvay Pharmaceuticals.

10.1021/cc800190z CCC: $40.75
Published on Web 05/27/2009

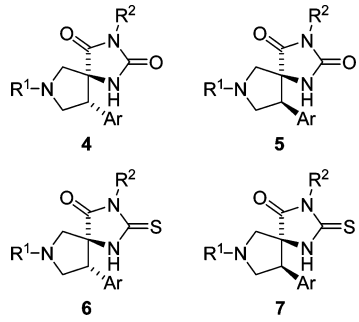


Figure 2. 9-Aryl spiro[hydantoin-5,3′-pyrrolidines], **4** and **5**, and 9-aryl spiro[pyrrolidine-3,5′-thiohydantoins], **6** and **7**.

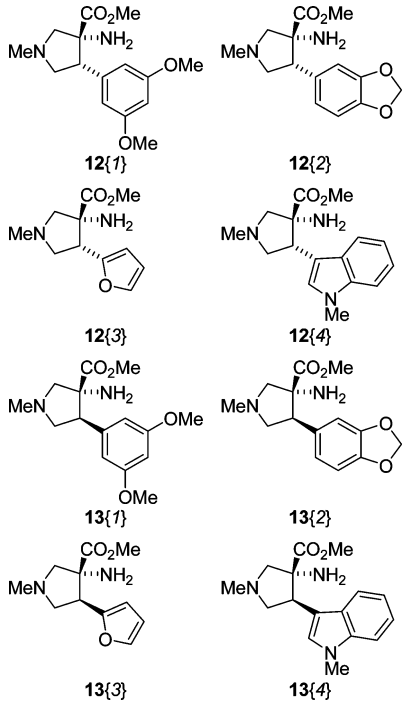


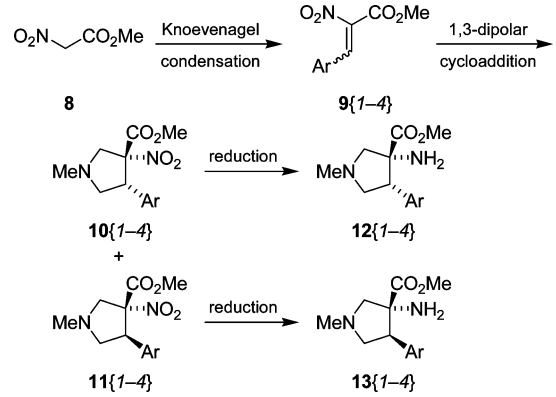
Figure 3. Scaffolds **12**{*1*−*4*} and **13**{*1*−*4*} for the library synthesis.

tion[16] of methyl nitroacetate **8** with various aromatic aldehydes[17] (or their corresponding imines)[18] to obtain the α-nitro acrylates **9**{*1*−*4*}. Subsequent 1,3-dipolar cycloaddition reactions[19] of **9**{*1*−*4*} with the azomethine ylide $CH_2{=}N^+(Me)CH_2^-$(generated in situ)[20] gave a 1:1 diastereomeric mixture of the racemic pyrrolidine core structures **10**{*1*−*4*} and **11**{*1*−*4*}. After separation of the diastereoisomers, reduction of the nitro group to the amine under catalytic hydrogenation conditions completed the synthesis (Scheme 2).

Conversion of chemsets **12** and **13** to chemsets **15** and **16** was accomplished using annulation of a hydantoin or a thiohydantoin ring with reagent chemset **14**. Ten isocyanates **14**{*1*−*10*} and eight isothiocyanates **14**{*11*−*18*} (alkyl, electron-rich aryl, electron-poor aryl, and heteroaryl iso(thio)-cyanates; Figure 4) were selected for the generation of a 144-compound library.

One possible route to the formation of a (thio)hydantoin ring from an α-amino ester is through the formation of a (thio)urea by addition of the amino group onto an iso(thio)-cyanate. Depending on the reactivity of the ester and the acidity of the (thio)urea, the cyclization step to form the

Scheme 2. Formation of Substrates **12**{*1*−*4*} and **13**{*1*−*4*}



hydantoin can take place spontaneously, on standing at room temperature or at reflux, or with the help of a base or an acid. We started with the synthesis of the spiro hydantoins, which were obtained after treating substrates **12**{*1*−*4*} and **13**{*1*−*4*} with chemset **14**{*1*−*10*} in dichloromethane. It was observed that, after 15 h at room temperature, the reactions with **14**{*1*−*4*} afforded the corresponding ureas, the reactions with **14**{*5*−*7*} afforded a mixture of the ureas and the spiro hydantoins, and the reactions with **14**{*8*−*10*} had residual substrate (even after refluxing). The slowness of the reaction with reagent **14**{*8*} was most likely a result of the electron-donating effect of the ethoxy group and in the case of **14**{*9*,*10*} was probably due to the low solubility in dichloromethane. Therefore, dimethylformamide at 80 °C for 15 h was used as the solvent for the reactions with these last three reagents. After evaporation of the solvent, the crude mixture was dissolved in tetrahydrofuran and 1 M $KOBu^t$ in tetrahydrofuran (1 equiv) was added. The reactions were stirred at room temperature for 15 h (except for reactions with **14**{*4*}, which were only stirred for 3 h to avoid secondary reactions), followed by evaporation of the solvent and liquid−liquid extraction, to afford all the expected 80 new 9-aryl spiro[hydantoin-5,3′-pyrrolidines] **15**{*1*−*4*,*1*−*10*} and **16**{*1*−*4*,*1*−*10*} with yields from 58 to 100% (87% average) and with purities from 51 to 100% (87% average; Scheme 3 and Table 1).

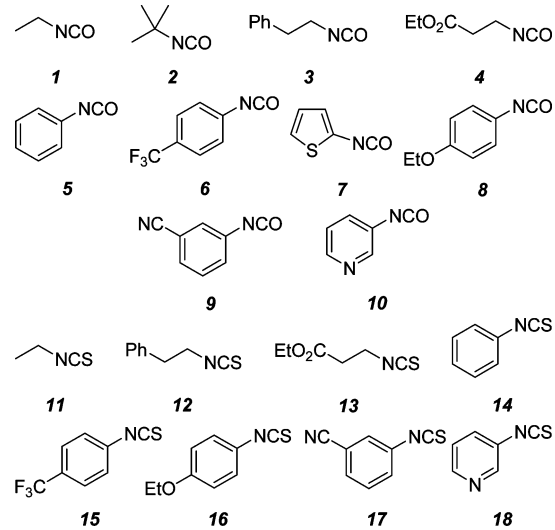
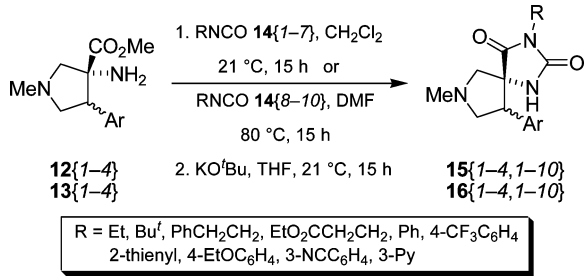


Figure 4. Isocyanates and isothiocyanates **14**{*1*−*18*} used with substrates **12**{*1*−*4*} and **13**{*1*−*4*}.

Scheme 3. Spiro Hydantoin Formation from Substrates **12**{*1−4*} and **13**{*1−4*}



The reactions carried out in dichloromethane gave products with purities in the range 77 to 100% (93% average), whereas the purities of the products from the reactions run in dimethylformamide were in the range 51 to 96% (76% average). The lower purities could be caused by partial decomposition of the isocyanates at the temperature used for the reactions in dimethylformamide. Although the reactions with **14**{*4*} were only run for 3 h, a mixture of methyl and ethyl esters was found (entries 4, 14, 24, 34, 44, 54, 64, and 74). This mixture results from transesterification of the ethyl ester on the R group by methoxide, which was formed in the cyclization.

The next step in the synthesis of the spiro thiohydantoins was conducted as above, and it was observed that for the formation of **15**{*1−4,11−18*} and **16**{*1−4,11−18*} no external base was required under any of the conditions. Thioureas are approximately 10^6 times more acidic than ureas,[21] meaning that as soon as they were formed, they were deprotonated by the tertiary amine within the molecule so that the cyclization took place without actually observing the thioureas. In the first instance, the reactions were run in dichloromethane, but those containing the aliphatic isothiocyanates **14**{*11−13*} did not go to completion at any temperature, even with an excess of the reagent. On the contrary, all the reactions with the aromatic isothiocyanates **14**{*14−18*} were complete within 40 h at room temperature. Second, it was found that all the reactions, except with **14**{*11*}, went to completion very cleanly in dimethylformamide[22] at 40 °C for 40 h (most of the reactions with aromatic isothiocyanates finished within 3−15 h). Evaporation of the solvent yielded the 64 new 9-aryl spiro[pyrrolidine-3,5′-thiohydantoins] **15**{*1−4,11−18*} and **16**{*1−4,11−18*} (Scheme 4). It also appeared that compounds **16**{*1−4,11−18*} were very insoluble in diethyl ether. Thus, the crude mixture of these compounds was washed with 1 mL of diethyl ether per 0.05 mmol of product (for **16**{*3,11−18*}, 1 mL per 0.075 mmol of product) to improve the purity. Compounds **15**{*1−4,11−18*} were better soluble and the washing step was carried out with 1 mL of diethyl ether per 0.1 mmol of product. Compounds **15**{*3,11−13*} and **15**{*3,15*} were not washed with diethyl ether because of their high solubility in this solvent and were analyzed immediately after evaporation of the solvent. Thus, spiro thiohydantoins **15**{*1−4,11−18*} and **16**{*1−4,11−18*} were obtained with yields from 65 to 100% (89% average) and purities from 67 to 100% (93% average; Table 2). It can be seen from the table that the use of the more reactive aryl isothiocyanates[23] **14**{*14−18*} did not result in a big difference in reactivity between the more hindered amines **12**{*1−4*} and amines **13**{*1−4*}. The reaction with the alkyl isothiocyanates **14**{*11−13*}, however, worked better with the less hindered amines **13**{*1−4*} (see, for example, entries 1, 9, 17, and 25 where residual substrate was present).

Conclusions

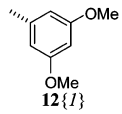
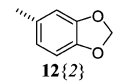
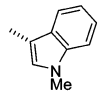
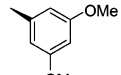
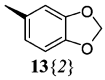
In conclusion, we have developed an efficient method for the synthesis of a library containing all possible stereoisomers of hydantoins and 2-thiohydantoins spiro-fused to the 3-position of pyrrolidines. These products all present the privileged 2-arylethyl amine moiety, rigidified in the pyrrolidine ring, in combination with a (thio)hydantoin, another common pharmacophore. We have shown that these aryl groups could be 3,5-dimethoxyphenyl, 1,3-benzodioxol-5-yl, 2-furyl, and 1-methylindol-3-yl. As a result, we anticipate that this methodology can be successfully applied for a wide range of aromatic groups. All 144 compounds were synthesized in moderate to good yields and purities.

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 (CD_3SOCD_3 for **16**{*2,17*}). 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), b (broad), and app (apparent). 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.

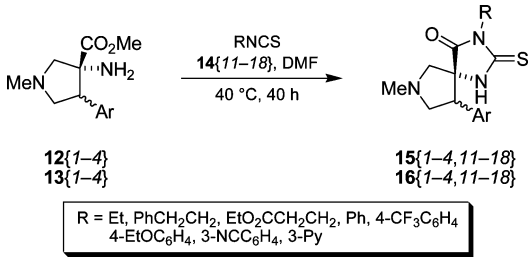
General Procedure 1 for Spiro Hydantoin Formation. Solutions of **14**{*1−7*} (0.1 mmol, 0.12 mmol for **14**{*1,2*}) from a 0.3 M stock solution in dichloromethane were added to seven separate solutions of **12**{*1*} (0.1 mmol) in dichloromethane (1.5 mL). The resulting reaction mixture was stirred at room temperature for 15 h. After that time,

Table 1. Results of Spiro Hydantoin Formation from Substrates **12**{*1*−*4*} and **13**{*1*−*4*}

Entry	Substrate (Ar)	R	Product	Yield (%)[a]	Purity (%)[b]	Method[c]
1	 **12**{*1*}	CH_2CH_3	**15**{*1,1*}	100	90	1
2		$C(CH_3)_3$	**15**{*1,2*}	64	78	1
3		CH_2CH_2Ph	**15**{*1,3*}	100	78	1
4		$CH_2CH_2CO_2Et$	**15**{*1,4*}	76	99[d]	1
5		Ph	**15**{*1,5*}	77	96	1
6		4-$CF_3C_6H_4$	**15**{*1,6*}	100	89	1
7		2-Thienyl	**15**{*1,7*}	93	97	1
8		4-$EtOC_6H_4$	**15**{*1,8*}	100	60	2
9		3-NCC_6H_4	**15**{*1,9*}	85	74	2
10		3-Py	**15**{*1,10*}	73	90	2
11	 **12**{*2*}	CH_2CH_3	**15**{*2,1*}	99	99	1
12		$C(CH_3)_3$	**15**{*2,2*}	68	92	1
13		CH_2CH_2Ph	**15**{*2,3*}	100	80	1
14		$CH_2CH_2CO_2Et$	**15**{*2,4*}	75	100[d]	1
15		Ph	**15**{*2,5*}	74	92	1
16		4-$CF_3C_6H_4$	**15**{*2,6*}	100	91	1
17		2-Thienyl	**15**{*2,7*}	100	98	1
18		4-$EtOC_6H_4$	**15**{*2,8*}	69	73	2
19		3-NCC_6H_4	**15**{*2,9*}	85	85	2
20		3-Py	**15**{*2,10*}	74	82	2
21	 **12**{*3*}	CH_2CH_3	**15**{*3,1*}	100	100	1
22		$C(CH_3)_3$	**15**{*3,2*}	59	98	1
23		CH_2CH_2Ph	**15**{*3,3*}	100	94	1
24		$CH_2CH_2CO_2Et$	**15**{*3,4*}	78	100[d]	1
25		Ph	**15**{*3,5*}	60	90	1
26		4-$CF_3C_6H_4$	**15**{*3,6*}	100	97	1
27		2-Thienyl	**15**{*3,7*}	95	96	1
28		4-$EtOC_6H_4$	**15**{*3,8*}	88	96	2
29		3-NCC_6H_4	**15**{*3,9*}	82	88	2
30		3-Py	**15**{*3,10*}	62	87	2
31	 **12**{*4*}	CH_2CH_3	**15**{*4,1*}	88	97	1
32		$C(CH_3)_3$	**15**{*4,2*}	72	80	1
33		CH_2CH_2Ph	**15**{*4,3*}	97	83	1
34		$CH_2CH_2CO_2Et$	**15**{*4,4*}	78	99[d]	1
35		Ph	**15**{*4,5*}	79	93	1
36		4-$CF_3C_6H_4$	**15**{*4,6*}	100	90	1
37		2-Thienyl	**15**{*4,7*}	100	94	1
38		4-$EtOC_6H_4$	**15**{*4,8*}	100	90	2
39		3-NCC_6H_4	**15**{*4,9*}	97	65	2
40		3-Py	**15**{*4,10*}	90	52	2
41	 **13**{*1*}	CH_2CH_3	**16**{*1,1*}	83	89	1
42		$C(CH_3)_3$	**16**{*1,2*}	84	85	1
43		CH_2CH_2Ph	**16**{*1,3*}	93	93	1
44		$CH_2CH_2CO_2Et$	**16**{*1,4*}	70	94[d]	1
45		Ph	**16**{*1,5*}	96	97	1
46		4-$CF_3C_6H_4$	**16**{*1,6*}	100	93	1
47		2-Thienyl	**16**{*1,7*}	97	97	1
48		4-$EtOC_6H_4$	**16**{*1,8*}	100	80	2
49		3-NCC_6H_4	**16**{*1,9*}	95	74	2
50		3-Py	**16**{*1,10*}	87	51	2
51	 **13**{*2*}	CH_2CH_3	**16**{*2,1*}	83	96	1
52		$C(CH_3)_3$	**16**{*2,2*}	95	94	1
53		CH_2CH_2Ph	**16**{*2,3*}	93	94	1
54		$CH_2CH_2CO_2Et$	**16**{*2,4*}	58	98[d]	1
55		Ph	**16**{*2,5*}	93	95	1
56		4-$CF_3C_6H_4$	**16**{*2,6*}	99	92	1
57		2-Thienyl	**16**{*2,7*}	95	98	1
58		4-$EtOC_6H_4$	**16**{*2,8*}	100	74	2
59		3-NCC_6H_4	**16**{*2,9*}	91	70	2
60		3-Py	**16**{*2,10*}	83	69	2
61	 **13**{*3*}	CH_2CH_3	**16**{*3,1*}	81	99	1
62		$C(CH_3)_3$	**16**{*3,2*}	94	97	1
63		CH_2CH_2Ph	**16**{*3,3*}	92	97	1
64		$CH_2CH_2CO_2Et$	**16**{*3,4*}	60	100[d]	1
65		Ph	**16**{*3,5*}	100	96	1
66		4-$CF_3C_6H_4$	**16**{*3,6*}	96	92	1
67		2-Thienyl	**16**{*3,7*}	89	99	1
68		4-$EtOC_6H_4$	**16**{*3,8*}	94	91	2
69		3-NCC_6H_4	**16**{*3,9*}	89	70	2
70		3-Py	**16**{*3,10*}	78	74	2
71	 **13**{*4*}	CH_2CH_3	**16**{*4,1*}	76	98	1
72		$C(CH_3)_3$	**16**{*4,2*}	84	77	1
73		CH_2CH_2Ph	**16**{*4,3*}	99	84	1
74		$CH_2CH_2CO_2Et$	**16**{*4,4*}	58	96[d]	1
75		Ph	**16**{*4,5*}	99	92	1
76		4-$CF_3C_6H_4$	**16**{*4,6*}	98	91	1
77		2-Thienyl	**16**{*4,7*}	100	97	1
78		4-$EtOC_6H_4$	**16**{*4,8*}	97	88	2
79		3-NCC_6H_4	**16**{*4,9*}	88	69	2
80		3-Py	**16**{*4,10*}	82	60	2

[a] Crude yield based on mass recovery. [b] Purity determined by LC-MS at 215 nm. [c] 1 = (a) RNCO, CH_2Cl_2, 21 °C, 15 h; (b) $KOBu^t$, THF, 21 °C, 15 h. 2 = (a) RNCO, DMF, 80 °C, 15 h, (b) $KOBu^t$, THF, 21 °C, 15 h. [d] Mixture of methyl and ethyl esters.

Scheme 4. Spiro Thiohydantoin Formation from Substrates **12**{*1*−*4*} and **13**{*1*−*4*}



the solvent was evaporated, and tetrahydrofuran (1.5 mL) and 1 M KOBu^t in tetrahydrofuran (0.1 mmol) were added. The reaction mixture was then stirred at room temperature for 15 h (3 h for **14**{*4*}). A saturated solution of $NaHCO_3$ (0.6 mL) was then added, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 1.5 mL), and the combined organic layers were evaporated to dryness under vacuum.

General Procedure 2 for Spiro Hydantoin Formation. Solutions of **14**{*8*−*10*} (0.1 mmol) from a 0.3 M stock solution in dimethylformamide were added to three separate solutions of **12**{*1*} (0.1 mmol) in dimethylformamide (1.5 mL). The resulting reaction mixture was stirred at 80 °C for 15 h. After that time, the solvent was evaporated, and tetrahydrofuran (1.5 mL) and 1 M KOBu^t in tetrahydrofuran (0.1 mmol) were added. The reaction mixture was then stirred at room temperature for 15 h. A saturated solution of $NaHCO_3$ (0.6 mL) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 1.5 mL), and the combined organic layers were evaporated to dryness under vacuum.

(±)-(5*R*,9*R*)-9-(3,5-Dimethoxyphenyl)-7-methyl-3-phenyl-1,3,7-triazaspiro[4.4]nonane-2,4-dione 15{*1*,*5*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.48−7.40 (m, 2 ^{1}H, 3″-C*H* + 5″-C*H*), 7.39−7.28 (m, 3 ^{1}H, 2″-C*H* + 4″-C*H* + 6″-C*H*), 6.36 (s, 3 ^{1}H, 2′-C*H* + 4′-C*H* + 6′-C*H*), 6.27 (bs, 1 ^{1}H, N*H*), 3.95 (dd; J = 9.0, 5.7 Hz; 1 ^{1}H, 9-C*H*), 3.73 (s, 6 ^{1}H, 2 × OCH_3), 3.30 (dd; J = 9.9, 5.7 Hz; 1 ^{1}H, 8-CH*H*), 3.11−3.03 (m, 2 ^{1}H, 6-CH_2), 2.92 (app t, J = 9.5 Hz, 1 ^{1}H, 8-C*H*H), 2.45 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 173.9 (4-*C*O), 161.4 (3′-*C* + 5′-*C*), 154.9 (2-*C*O), 139.3 (1′-*C*), 131.7 (1″-*C*), 129.2 (3″-*C* + 5″-*C*), 128.3 (4″-*C*), 126.2 (2″-*C* + 6″-*C*), 106.3 (2′-*C* + 6′-*C*), 99.3 (4′-*C*), 70.3 (5-*C*), 65.7 (6-*C*), 59.8 (8-*C*), 55.5 (2 × OCH_3), 53.1 (9-*C*), 41.9 (NCH_3). FTIR [ν^- (cm^{-1}), neat]: 3189, 2938, 2838, 2791, 1776, 1714, 1595, 1203, 1153, 857, 763, 702. MS [APCI (*m*/*z*)] calcd for $(C_{21}H_{23}N_3O_4 + H)^+$ = 382, found 382.

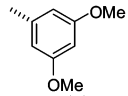
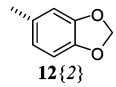
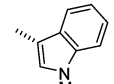
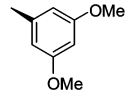
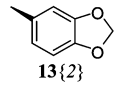
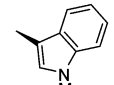
(±)-(5*R*,9*R*)-9-(3,5-Dimethoxyphenyl)-7-methyl-3-(2-thienyl)-1,3,7-triazaspiro[4.4] nonane-2,4-dione 15{*1*,*7*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.45 (dd; J = 3.9, 1.2 Hz; 1 ^{1}H, 3″-C*H*), 7.15 (dd; J = 5.4, 1.2 Hz; 1 ^{1}H, 5″-C*H*), 6.98 (dd; J = 5.4, 3.9 Hz; 1 ^{1}H, 4″-C*H*), 6.37 (bs, 1 ^{1}H, N*H*), 6.34 (t, J = 2.1 Hz, 1 ^{1}H, 4′-C*H*), 6.31 (d, J = 2.1 Hz, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 3.94 (dd; J = 9.0, 5.4 Hz; 1 ^{1}H, 9-C*H*), 3.70 (s, 6 ^{1}H, 2 × OCH_3), 3.30 (dd; J = 9.9, 5.4 Hz; 1 ^{1}H, 8-CH*H*), 3.08−3.01 (m, 2 ^{1}H, 6-CH_2), 2.92 (app t, J = 9.5 Hz, 1 ^{1}H, 8-C*H*H), 2.45 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 172.5 (4-*C*O), 161.4 (3′-*C* + 5′-*C*), 153.6 (2-*C*O), 139.1 (1′-*C*), 132.2 (2″-*C*), 125.2 (4″-*C*), 121.8 (5″-*C*), 120.1 (3″-*C*), 106.2 (2′-*C* + 6′-*C*), 99.5 (4′-*C*), 70.0 (5-*C*), 65.8 (6-*C*), 59.9 (8-*C*), 55.4 (2 × OCH_3), 53.1 (9-*C*), 41.9 (NCH_3). FTIR [ν^- (cm^{-1}), neat]: 3194, 2937, 2838, 2789, 1778, 1719, 1595, 1203, 1156, 834, 691. MS [APCI (*m*/*z*)] calcd for $(C_{19}H_{21}N_3O_4S + H)^+$ = 388, found 388.

(±)-(5*R*,9*R*)-9-(1,3-Benzodioxol-5-yl)-3-ethyl-7-methyl-1,3,7-triazaspiro[4.4]nonane-2,4-dione 15{*2*,*1*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 6.70 (d, J = 8.1 Hz, 1 ^{1}H, 7′-C*H*), 6.68 (d, J = 1.8 Hz, 1 ^{1}H, 4′-C*H*), 6.56 (dd; J = 8.1, 1.8 Hz; 1 ^{1}H, 6′-C*H*), 6.16 (bs, 1 ^{1}H, N*H*), 5.93 (s, 2 ^{1}H, 2′-CH_2), 3.81 (dd; J = 9.0, 6.0 Hz; 1 ^{1}H, 9-C*H*), 3.56−3.42 (m, 2 ^{1}H, CH_2CH$_3$), 3.17 (dd; J = 9.9, 6.0 Hz; 1 ^{1}H, 8-CH*H*), 2.98 (d, J = 9.9 Hz, 1 ^{1}H, 6-CH*H*), 2.91 (d, J = 9.9 Hz, 1 ^{1}H, 6-C*H*H), 2.89 (app t, J = 9.3 Hz, 1 ^{1}H, 8-C*H*H), 2.43 (s, 3 ^{1}H, NCH_3), 1.13 (t, J = 7.2 Hz, 3 ^{1}H, CH_2CH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 174.7 (4-*C*O), 156.0 (2-*C*O), 148.2 (3′a-*C*), 147.2 (7′a-*C*), 130.7 (5′-*C*), 121.5 (6′-*C*), 108.5 (7′-*C*), 108.2 (4′-*C*), 101.3 (2′-*C*), 70.4 (5-*C*), 65.3 (6-*C*), 60.4 (8-*C*), 52.4 (9-*C*), 42.0 (NCH_3), 33.7 (CH_2CH_3), 13.5 (CH_2CH_3). FTIR [ν^- (cm^{-1}), neat]: 3270, 2940, 2841, 2788, 1771, 1703, 1253, 1236, 1037, 928. MS [APCI (*m*/*z*)] calcd for $(C_{16}H_{19}N_3O_4 + H)^+$ = 318, found 318.

(±)-(5*R*,9*R*)-9-(1,3-Benzodioxol-5-yl)-3-*tert*-butyl-7-methyl-1,3,7-triazaspiro[4.4] nonane-2,4-dione 15{*2*,*2*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 6.72 (d, J = 8.1 Hz, 1 ^{1}H, 7′-C*H*), 6.69 (d, J = 1.8 Hz, 1 ^{1}H, 4′-C*H*), 6.58 (dd; J = 8.1, 1.8 Hz; 1 ^{1}H, 6′-C*H*), 5.94 (s, 2 ^{1}H, 2′-CH_2), 5.55 (bs, 1 ^{1}H, N*H*), 3.76 (dd; J = 9.0, 5.7 Hz; 1 ^{1}H, 9-C*H*), 3.13 (dd; J = 9.9, 5.7 Hz; 1 ^{1}H, 8-CH*H*), 2.93 (d, J = 9.6 Hz, 1 ^{1}H, 6-CH*H*), 2.87 (d, J = 9.6 Hz, 1 ^{1}H, 6-C*H*H), 2.85 (app t, J = 9.3 Hz, 1 ^{1}H, 8-C*H*H), 2.41 (s, 3 ^{1}H, NCH_3), 1.53 (s, 9 ^{1}H, C(CH_3)$_3$). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 175.8 (4-*C*O), 156.8 (2-*C*O), 148.2 (3′a-*C*), 147.1 (7′a-*C*), 131.1 (5′-*C*), 121.4 (6′-*C*), 108.5 (7′-*C*), 108.2 (4′-*C*), 101.3 (2′-*C*), 69.2 (5-*C*), 65.6 (6-*C*), 60.5 (8-*C*), 57.9 (*C*(CH$_3$)$_3$), 52.8 (9-*C*), 42.0 (NCH_3), 28.7 (C(*C*H$_3$)$_3$). FTIR [ν^- (cm^{-1}), neat]: 3226, 2936, 2841, 2786, 1764, 1702, 1253, 1235, 1037, 927. MS [APCI (*m*/*z*)] calcd for $(C_{18}H_{23}N_3O_4 + H)^+$ = 346, found 346.

(±)-(5*R*,9*R*)-9-(2-Furyl)-7-methyl-3-phenethyl-1,3,7-triazaspiro[4.4]nonane-2,4-dione 15{*3*,*3*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.35−7.17 (m, 6 ^{1}H, 5′-C*H* + Ph), 6.41 (bs, 1 ^{1}H, N*H*), 6.27 (dd; J = 3.0, 1.8 Hz; 1 ^{1}H, 4′-C*H*), 6.06 (d, J = 3.0 Hz, 1 ^{1}H, 3′-C*H*), 3.93 (dd; J = 9.3, 6.3 Hz; 1 ^{1}H, 9-C*H*), 3.74 (t, J = 7.6 Hz, 2 ^{1}H, NCH_2CH$_2$), 3.21 (dd; J = 9.6, 6.3 Hz; 1 ^{1}H, 8-CH*H*), 2.98−2.87 (m, 2 ^{1}H, NCH$_2$CH_2), 2.87 (d, J = 9.6 Hz, 1 ^{1}H, 6-CH*H*), 2.86 (app t, J = 9.6 Hz, 1 ^{1}H, 8-C*H*H), 2.79 (d, J = 9.6 Hz, 1 ^{1}H, 6-C*H*H), 2.38 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 174.3 (4-*C*O), 156.1 (2-*C*O), 151.0 (2′-*C*), 142.9 (5′-*C*), 137.9 (1″-*C*), 129.0 (2″-*C* + 6″-*C*), 128.6 (3″-*C* + 5″-*C*), 126.7 (4″-*C*), 110.4 (4′-*C*), 107.9 (3′-*C*), 69.7 (5-*C*), 65.4 (6-*C*), 58.1 (8-*C*), 46.0 (9-*C*), 41.8 (NCH_3), 39.9 (NCH_2CH$_2$), 34.0 (NCH$_2$*C*H$_2$). FTIR [ν^- (cm^{-1}), neat]: 3266,

Table 2. 2. Results of Spiro Thiohydantoin Formation from Substrates **12**{*1*−*4*} and **13**{*1*−*4*}

Entry	Substrate (Ar)	R	Product	Yield (%)[a]	Purity (%)[b]
1	 **12**{*1*}	CH_2CH_3	**15**{*1,11*}	69	67[c]
2		CH_2CH_2Ph	**15**{*1,12*}	65	73
3		$CH_2CH_2CO_2Et$	**15**{*1,13*}	73	75
4		Ph	**15**{*1,14*}	95	83
5		4-$CF_3C_6H_4$	**15**{*1,15*}	85	96
6		4-$EtOC_6H_4$	**15**{*1,16*}	92	90
7		3-NCC_6H_4	**15**{*1,17*}	98	87
8		3-Py	**15**{*1,18*}	95	96
9	 **12**{*2*}	CH_2CH_3	**15**{*2,11*}	70	78[d]
10		CH_2CH_2Ph	**15**{*2,12*}	68	76
11		$CH_2CH_2CO_2Et$	**15**{*2,13*}	71	86
12		Ph	**15**{*2,14*}	90	92
13		4-$CF_3C_6H_4$	**15**{*2,15*}	83	96
14		4-$EtOC_6H_4$	**15**{*2,16*}	98	95
15		3-NCC_6H_4	**15**{*2,17*}	97	96
16		3-Py	**15**{*2,18*}	97	93
17	 **12**{*3*}	CH_2CH_3	**15**{*3,11*}	100	85[e]
18		CH_2CH_2Ph	**15**{*3,12*}	100	94
19		$CH_2CH_2CO_2Et$	**15**{*3,13*}	100	92
20		Ph	**15**{*3,14*}	76	98
21		4-$CF_3C_6H_4$	**15**{*3,15*}	100	98
22		4-$EtOC_6H_4$	**15**{*3,16*}	90	97
23		3-NCC_6H_4	**15**{*3,17*}	100	93
24		3-Py	**15**{*3,18*}	98	100
25	 **12**{*4*}	CH_2CH_3	**15**{*4,11*}	79	82[f]
26		CH_2CH_2Ph	**15**{*4,12*}	86	93
27		$CH_2CH_2CO_2Et$	**15**{*4,13*}	81	94
28		Ph	**15**{*4,14*}	82	97
29		4-$CF_3C_6H_4$	**15**{*4,15*}	84	97
30		4-$EtOC_6H_4$	**15**{*4,16*}	90	93
31		3-NCC_6H_4	**15**{*4,17*}	82	93
32		3-Py	**15**{*4,18*}	95	96
33	 **13**{*1*}	CH_2CH_3	**16**{*1,11*}	89	94
34		CH_2CH_2Ph	**16**{*1,12*}	84	100
35		$CH_2CH_2CO_2Et$	**16**{*1,13*}	94	95
36		Ph	**16**{*1,14*}	93	98
37		4-$CF_3C_6H_4$	**16**{*1,15*}	73	100
38		4-$EtOC_6H_4$	**16**{*1,16*}	90	100
39		3-NCC_6H_4	**16**{*1,17*}	100	100
40		3-Py	**16**{*1,18*}	97	94
41	 **13**{*2*}	CH_2CH_3	**16**{*2,11*}	85	85
42		CH_2CH_2Ph	**16**{*2,12*}	86	97
43		$CH_2CH_2CO_2Et$	**16**{*2,13*}	98	97
44		Ph	**16**{*2,14*}	98	100
45		4-$CF_3C_6H_4$	**16**{*2,15*}	95	100
46		4-$EtOC_6H_4$	**16**{*2,16*}	99	99
47		3-NCC_6H_4	**16**{*2,17*}	100	97
48		3-Py	**16**{*2,18*}	100	100
49	 **13**{*3*}	CH_2CH_3	**16**{*3,11*}	91	95
50		CH_2CH_2Ph	**16**{*3,12*}	88	98
51		$CH_2CH_2CO_2Et$	**16**{*3,13*}	89	96
52		Ph	**16**{*3,14*}	95	99
53		4-$CF_3C_6H_4$	**16**{*3,15*}	79	96
54		4-$EtOC_6H_4$	**16**{*3,16*}	93	99
55		3-NCC_6H_4	**16**{*3,17*}	93	99
56		3-Py	**16**{*3,18*}	100	100
57	 **13**{*4*}	CH_2CH_3	**16**{*4,11*}	88	90
58		CH_2CH_2Ph	**16**{*4,12*}	88	83
59		$CH_2CH_2CO_2Et$	**16**{*4,13*}	85	93
60		Ph	**16**{*4,14*}	85	96
61		4-$CF_3C_6H_4$	**16**{*4,15*}	75	99
62		4-$EtOC_6H_4$	**16**{*4,16*}	97	96
63		3-NCC_6H_4	**16**{*4,17*}	99	97
64		3-Py	**16**{*4,18*}	100	96

[a] Crude yield based on mass recovery. [b] Purity determined by LC-MS at 215 nm. [c] Plus 16% **12**{*1*}. [d] Plus 8% **12**{*2*}. [e] Plus 15% **12**{*3*}. [f] Plus 12% **12**{*4*}.

2943, 2841, 2796, 1770, 1709, 766, 739, 699. MS [APCI (*m*/*z*)] calcd for $(C_{19}H_{21}N_3O_3 + H)^+ = 340$, found 340.

(±)-(5*R*,9*R*)-9-(2-Furyl)-7-methyl-3-(3-pyridyl)-1,3,7-triazaspiro[4.4]nonane-2,4-dione 15{*3,10*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 8.73 (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*), 7.78 (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*), 7.37 (d, $J = 1.8$ Hz, 1 ^{1}H, 5′-C*H*), 6.60 (bs, 1 ^{1}H, N*H*), 6.33 (dd; $J = 3.0$, 1.8 Hz; 1 ^{1}H, 4′-C*H*), 6.21 (d, $J = 3.0$ Hz, 1 ^{1}H, 3′-C*H*), 4.12 (dd; $J = 9.6$, 6.9 Hz; 1 ^{1}H, 9-C*H*), 3.28 (dd; $J = 9.6$, 6.9 Hz; 1 ^{1}H, 8-CH*H*), 3.14 (d, $J = 9.9$ Hz, 1 ^{1}H, 6-CH*H*), 3.02 (d, $J = 9.9$ Hz, 1 ^{1}H, 6-C*H*H), 2.98 (app t, $J = 9.6$ Hz, 1 ^{1}H, 8-C*H*H), 2.46 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 173.1 (4-*C*O), 154.3 (2-*C*O), 150.7 (2′-*C*), 149.0 (6″-*C*), 147.1 (2″-*C*), 143.2 (5′-*C*), 133.3 (4″-*C*), 128.9 (3″-*C*), 123.7 (5″-*C*), 110.6 (4′-*C*),

108.2 (3′-*C*), 70.0 (5-*C*), 65.2 (6-*C*), 57.8 (8-*C*), 47.0 (9-*C*), 41.8 (N*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 3233, 2945, 2849, 2795, 1777, 1719, 716. MS [APCI (*m*/*z*)] calcd for ($C_{16}H_{16}N_4O_3$ + H)$^+$ = 313, found 313.

(±)-(5*R*,9*R*)-7-Methyl-9-(1-methyl-1*H*-indol-3-yl)-3-[4-(trifluoromethyl)phenyl]-1,3,7-triazaspiro[4.4]nonane-2,4-dione 15{*4*,*6*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.69−7.60 (m, 2 ^{1}H, 3″-C*H* + 5″-C*H*), 7.46 (d, *J* = 8.1 Hz, 1 ^{1}H, 4′-C*H*), 7.35−7.30 (m, 2 ^{1}H, 2″-C*H* + 6″-C*H*), 7.28 (d, *J* = 8.1 Hz, 1 ^{1}H, 7′-C*H*), 7.25−7.19 (m, 1 ^{1}H, 6′-C*H*), 7.07−7.01 (m, 1 ^{1}H, 5′-C*H*), 6.99 (s, 1 ^{1}H, 2′-C*H*), 6.17 (bs, 1 ^{1}H, N*H*), 4.36 (dd; *J* = 9.0, 6.9 Hz; 1 ^{1}H, 9-C*H*), 3.73 (s, 3 ^{1}H, 1′-NC*H*$_3$), 3.27 (dd; *J* = 9.6, 6.9 Hz; 1 ^{1}H, 8-CH*H*), 3.24 (d, *J* = 9.9 Hz, 1 ^{1}H, 6-CH*H*), 3.07 (app t, *J* = 9.3 Hz, 1 ^{1}H, 8-C*H*H), 3.04 (d, *J* = 9.9 Hz, 1 ^{1}H, 6-C*H*H), 2.50 (s, 3 ^{1}H, 7-NC*H*$_3$). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 174.1 (4-*C*O), 154.4 (2-*C*O), 137.3 (7′a-*C*), 134.8 (q, *J* = 1.4 Hz, 1″-*C*), 130.0 (q, *J* = 32.7 Hz, 4″-*C*), 127.4 (3′a-*C*), 127.2 (2′-*C*), 126.3 (2″-*C* + 6″-*C*), 126.1 (q, *J* = 3.7 Hz, 3″-*C* + 5″-*C*), 123.9 (q, *J* = 270.5 Hz, *C*F$_3$), 122.5 (6′-*C*), 119.9 (5′-*C*), 118.6 (4′-*C*), 109.9 (3′-*C* + 7′-*C*), 70.0 (5-*C*), 65.7 (6-*C*), 60.2 (8-*C*), 45.3 (9-*C*), 42.0 (7-N*C*H$_3$), 33.0 (1′-N*C*H$_3$). FTIR [ν- (cm^{-1}), neat]: 3228, 2938, 2842, 2790, 1776, 1716, 1323, 840, 738. MS [APCI (*m*/*z*)] calcd for ($C_{23}H_{21}F_3N_4O_2$ + H)$^+$ = 443, found 443.

(±)-(5*R*,9*R*)-3-(4-Ethoxyphenyl)-7-methyl-9-(1-methyl-1*H*-indol-3-yl)-1,3,7-triazaspiro [4.4]nonane-2,4-dione 15{*4*,*8*}. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 7.51 (d, *J* = 7.9 Hz, 1 ^{1}H, 4″-C*H*), 7.28 (d, *J* = 8.2 Hz, 1 ^{1}H, 7″-C*H*), 7.24−7.19 (m, 1 ^{1}H, 6″-C*H*), 7.10−7.01 (m, 1 ^{1}H, 5″-C*H*), 7.00 (s, 1 ^{1}H, 2″-C*H*), 7.01−6.96 (m, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 6.89−6.84 (m, 2 ^{1}H, 3′-C*H* + 5′-C*H*), 6.04 (bs, 1 ^{1}H, N*H*), 4.35 (dd; *J* = 8.9, 7.0 Hz; 1 ^{1}H, 9-C*H*), 4.00 (q, *J* = 7.0 Hz, 2 ^{1}H, C*H*$_2$CH$_3$), 3.73 (s, 3 ^{1}H, 1″-NC*H*$_3$), 3.28 (dd; *J* = 9.3, 7.0 Hz; 1 ^{1}H, 8-CH*H*), 3.22 (d, *J* = 10.0 Hz, 1 ^{1}H, 6-CH*H*), 3.07 (app t, *J* = 9.1 Hz, 1 ^{1}H, 8-C*H*H), 3.05 (d, *J* = 9.7 Hz, 1 ^{1}H, 6-C*H*H), 2.50 (s, 3 ^{1}H, 7-NC*H*$_3$), 1.39 (t, *J* = 7.0 Hz, 3 ^{1}H, CH$_2$C*H*$_3$). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 174.6 (4-*C*O), 158.8 (4′-*C*), 155.5 (2-*C*O), 137.3 (7″a-*C*), 127.7 (2′-*C* + 6′-*C*), 127.5 (3″a-*C*), 127.2 (2″-*C*), 124.0 (1′-*C*), 122.4 (6″-*C*), 119.9 (5″-*C*), 118.8 (4″-*C*), 115.0 (3′-*C* + 5′-*C*), 110.1 (3″-*C*), 109.8 (7″-*C*), 69.9 (5-*C*), 65.8 (6-*C*), 63.8 (*C*H$_2$CH$_3$), 60.3 (8-*C*), 45.0 (9-*C*), 42.0 (7-N*C*H$_3$), 33.0 (1″-N*C*H$_3$), 14.9 (CH$_2$*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 3236, 2933, 2846, 2793, 1771, 1715, 827, 741. MS [APCI (*m*/*z*)] calcd for ($C_{24}H_{26}N_4O_3$ + H)$^+$ = 419, found 419.

(±)-(5*R*,9*S*)-9-(3,5-Dimethoxyphenyl)-7-methyl-3-phenyl-1,3,7-triazaspiro[4.4]nonane-2,4-dione 16{*1*,*5*}. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.42 (bs, 1 ^{1}H, N*H*), 7.36−7.24 (m, 3 ^{1}H, 3″-C*H* + 4″-C*H* + 5″-C*H*), 6.88−6.81 (m, 2 ^{1}H, 2″-C*H* + 6″-C*H*), 6.43 (d, *J* = 2.2 Hz, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 6.39 (t, *J* = 2.2 Hz, 1 ^{1}H, 4′-C*H*), 3.71 (s, 6 ^{1}H, 2 × OC*H*$_3$), 3.66 (dd; *J* = 12.2, 6.2 Hz; 1 ^{1}H, 9-C*H*), 3.37 (d, *J* = 11.0 Hz, 1 ^{1}H, 6-CH*H*), 3.33 (dd; *J* = 9.1, 6.2 Hz; 1 ^{1}H, 8-CH*H*), 3.12 (dd; *J* = 12.2, 9.4 Hz; 1 ^{1}H, 8-C*H*H), 3.12 (d, *J* = 10.7 Hz, 1 ^{1}H, 6-C*H*H), 2.57 (s, 3 ^{1}H, NC*H*$_3$). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 173.4 (4-*C*O), 160.9 (3′-*C* + 5′-*C*), 156.0 (2-*C*O), 136.6 (1′-*C*), 131.4 (1″-*C*), 129.0 (3″-*C* + 5″-*C*), 128.2 (4″-*C*), 126.3 (2″-*C* + 6″-*C*), 106.0 (2′-*C* + 6′-*C*), 100.0 (4′-*C*), 70.7 (5-*C*), 63.7 (6-*C*), 58.5 (8-*C*), 56.0 (9-*C*), 55.5 (2 × O*C*H$_3$), 41.7 (N*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 3187, 2939, 2839, 2795, 1777, 1714, 1595, 1203, 1153, 857, 774, 694. MS [APCI (*m*/*z*)] calcd for ($C_{21}H_{23}N_3O_4$ + H)$^+$ = 382, found 382.

(±)-(5*R*,9*S*)-9-(3,5-Dimethoxyphenyl)-7-methyl-3-(2-thienyl)-1,3,7-triazaspiro[4.4] nonane-2,4-dione 16{*1*,*7*}. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.36 (bs, 1 ^{1}H, N*H*), 7.09 (dd; *J* = 5.5, 1.3 Hz; 1 ^{1}H, 5″-C*H*), 6.97 (dd; *J* = 3.8, 1.3 Hz; 1 ^{1}H, 3″-C*H*), 6.88 (dd; *J* = 5.5, 3.9 Hz; 1 ^{1}H, 4″-C*H*), 6.37 (d, *J* = 2.2 Hz, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 6.34 (t, *J* = 2.2 Hz, 1 ^{1}H, 4′-C*H*), 3.70 (s, 6 ^{1}H, 2 × OC*H*$_3$), 3.62 (dd; *J* = 12.2, 6.0 Hz; 1 ^{1}H, 9-C*H*), 3.34 (d, *J* = 10.4 Hz, 1 ^{1}H, 6-CH*H*), 3.35−3.31 (m, 1 ^{1}H, 8-CH*H*), 3.12 (d, *J* = 11.1 Hz, 1 ^{1}H, 6-C*H*H), 3.13−3.07 (m, 1 ^{1}H, 8-C*H*H), 2.57 (s, 3 ^{1}H, NC*H*$_3$). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 172.2 (4-*C*O), 160.9 (3′-*C* + 5′-*C*), 154.9 (2-*C*O), 136.3 (1′-*C*), 131.6 (2″-*C*), 125.3 (4″-*C*), 122.7 (5″-*C*), 121.5 (3″-*C*), 105.8 (2′-*C* + 6′-*C*), 100.3 (4′-*C*), 70.6 (5-*C*), 64.0 (6-*C*), 58.6 (8-*C*), 56.1 (9-*C*), 55.4 (2 × O*C*H$_3$), 41.7 (N*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 3195, 2940, 2839, 2797, 1780, 1722, 1595, 1203, 1153, 834, 691. MS [APCI (*m*/*z*)] calcd for ($C_{19}H_{21}N_3O_4S$ + H)$^+$ = 388, found 388.

(±)-(5*R*,9*S*)-9-(1,3-Benzodioxol-5-yl)-3-*tert*-butyl-7-methyl-1,3,7-triazaspiro[4.4] nonane-2,4-dione 16{*2*,*2*}. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 7.63−7.44 (m, 1 ^{1}H, N*H*), 6.73 (d, *J* = 1.5 Hz, 1 ^{1}H, 4′-C*H*), 6.73 (d, *J* = 8.1 Hz, 1 ^{1}H, 7′-C*H*), 6.67 (dd; *J* = 8.1, 1.5 Hz; 1 ^{1}H, 6′-C*H*), 5.91 (d, *J* = 1.5 Hz, 1 ^{1}H, 2′-CH*H*), 5.91 (d, *J* = 1.5 Hz, 1 ^{1}H, 2′-C*H*H), 3.43 (dd; *J* = 12.2, 6.1 Hz; 1 ^{1}H, 9-C*H*), 3.22−3.17 (m, 1 ^{1}H, 8-CH*H*), 3.18 (d, *J* = 10.2 Hz, 1 ^{1}H, 6-CH*H*), 3.00 (d, *J* = 10.7 Hz, 1 ^{1}H, 6-C*H*H), 2.97 (dd; *J* = 12.4, 9.0 Hz; 1 ^{1}H, 8-C*H*H), 2.51 (s, 3 ^{1}H, NC*H*$_3$), 1.26 (s, 9 ^{1}H, C(C*H*$_3$)). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 175.4 (4-*C*O), 157.8 (2-*C*O), 147.7 (3′a-*C*), 147.3 (7′a-*C*), 128.2 (5′-*C*), 121.6 (6′-*C*), 108.7 (4′-*C*), 108.2 (7′-*C*), 101.1 (2′-*C*), 69.5 (5-*C*), 63.7 (6-*C*), 58.8 (8-*C*), 57.4 (*C*(CH$_3$)$_3$), 56.0 (9-*C*), 41.8 (N*C*H$_3$), 28.4 (C(*C*H$_3$)$_3$). FTIR [ν^- (cm^{-1}), neat]: 3251, 2937, 2846, 2784, 1762, 1702, 1253, 1231, 1037, 928. MS [APCI (*m*/*z*)] calcd for ($C_{18}H_{23}N_3O_4$ + H)$^+$ = 346, found 346.

(±)-(5*R*,9*S*)-9-(1,3-Benzodioxol-5-yl)-7-methyl-3-phenethyl-1,3,7-triazaspiro[4.4] nonane-2,4-dione 16{*2*,*3*}. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.02 (bs, 1 ^{1}H, N*H*), 7.28−7.22 (m, 2 ^{1}H, 3″-C*H* + 5″-C*H*), 7.21−7.15 (m, 1 ^{1}H, 4″-C*H*), 7.12−7.07 (m, 2 ^{1}H, 2″-C*H* + 6″-C*H*), 6.75 (d, *J* = 1.3 Hz, 1 ^{1}H, 4′-C*H*), 6.71 (d, *J* = 8.0 Hz, 1 ^{1}H, 7′-C*H*), 6.68 (dd; *J* = 8.0, 1.3 Hz; 1 ^{1}H, 6′-C*H*), 5.87 (s, 2 ^{1}H, 2′-C*H*$_2$), 3.53 (dd; *J* = 12.2, 6.2 Hz; 1 ^{1}H, 9-C*H*), 3.43 (t, *J* = 8.0 Hz, 2 ^{1}H, NC*H*$_2$CH$_2$), 3.24 (dd; *J* = 9.1, 6.3 Hz; 1 ^{1}H, 8-CH*H*), 3.21 (d, *J* = 11.1 Hz, 1 ^{1}H, 6-CH*H*), 3.03 (dd; *J* = 12.2, 9.1 Hz; 1 ^{1}H, 8-C*H*H), 2.95 (d, *J* = 10.8 Hz, 1 ^{1}H, 6-C*H*H), 2.52 (s, 3 ^{1}H, NC*H*$_3$), 2.48 (dt; *J* = 13.6, 8.0 Hz; 1 ^{1}H, NCH$_2$CH*H*), 2.32 (dt; *J* = 13.5, 7.8 Hz; 1 ^{1}H, NCH$_2$C*H*H). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 174.2 (4-*C*O), 156.7 (2-*C*O), 147.8 (3′a-*C*), 147.4 (7′a-*C*), 138.0 (1″-*C*), 128.8 (2″-*C* + 6″-*C*), 128.6 (3″-*C* + 5″-*C*), 127.9 (5′-*C*), 126.6 (4″-*C*), 121.6 (6′-*C*), 108.6 (4′-*C*), 108.3 (7′-*C*), 101.2 (2′-*C*), 70.7 (5-*C*), 63.7 (6-*C*), 59.0 (8-*C*), 55.3

(9-*C*), 41.7 (N*C*H$_3$), 39.5 (N*C*H$_2$CH$_2$), 33.8 (NCH$_2$*C*H$_2$). FTIR [ν^- (cm^{-1}), neat]: 3258, 2941, 2842, 2789, 1770, 1706, 1253, 1236, 1037, 928, 769, 699. MS [APCI (*m*/*z*)] calcd for $(C_{22}H_{23}N_3O_4 + H)^+ = 394$, found 394.

(±)-Ethyl 3-{(5*R*,9*S*)-9-(2-furyl)-7-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]nonan-3-yl} propanoate 16{*3*,*4*}. ^{1}H NMR [400 MHz, δ (ppm), CDCl$_3$]: 7.52 (bs, 1 ^{1}H, N*H*), 7.29 (s, 1 ^{1}H, 5″-C*H*), 6.30 (dd; *J* = 3.2, 1.8 Hz; 1 ^{1}H, 4″-C*H*), 6.15 (d, *J* = 3.2 Hz, 1 ^{1}H, 3″-C*H*), 4.12 (q, *J* = 7.2 Hz, 2 ^{1}H, C*H*$_2$CH$_3$), 3.69 (dd; *J* = 11.7, 6.6 Hz; 1 ^{1}H, 9′-C*H*), 3.67−3.60 (m, 2 ^{1}H, 3-C*H*$_2$), 3.34 (dd; *J* = 8.9, 7.0 Hz; 1 ^{1}H, 8′-CH*H*), 3.18 (d, *J* = 10.5 Hz, 1 ^{1}H, 6′-CH*H*), 2.93 (d, *J* = 10.5 Hz, 1 ^{1}H, 6′-C*H*H), 2.84 (dd; *J* = 11.5, 9.3 Hz; 1 ^{1}H, 8′-C*H*H), 2.48 (s, 3 ^{1}H, NC*H*$_3$), 2.46−2.29 (m, 2 ^{1}H, 2-C*H*$_2$), 1.24 (t, *J* = 7.2 Hz, 3 ^{1}H, CH$_2$C*H*$_3$). ^{13}C NMR [75 MHz, δ (ppm), CDCl$_3$]: 173.4 (4′-*C*O), 170.7 (*C*O$_2$), 156.3 (2′-*C*O), 149.7 (2″-*C*), 142.2 (5″-*C*), 110.6 (4″-*C*), 107.5 (3″-*C*), 69.8 (5′-*C*), 64.3 (6′-*C*), 60.9 (*C*H$_2$CH$_3$), 58.3 (8′-*C*), 49.8 (9′-*C*), 41.6 (N*C*H$_3$), 34.2 (3-*C*), 32.3 (2-*C*), 14.3 (CH$_2$*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 3313, 2949 2846, 2793, 1774, 1710, 747. MS [APCI (*m*/*z*)] calcd for $(C_{16}H_{21}N_3O_5 + H)^+ = 336$, found 336.

(±)-(5*R*,9*S*)-3-(4-Ethoxyphenyl)-9-(2-furyl)-7-methyl-1,3,7-triazaspiro[4.4]nonane-2,4-dione 16{*3*,*8*}. ^{1}H NMR [400 MHz, δ (ppm), CDCl$_3$]: 7.33 (d, *J* = 1.3 Hz, 1 ^{1}H, 5″-C*H*), 7.14 (bs, 1 ^{1}H, N*H*), 6.99−6.94 (m, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 6.90−6.84 (m, 2 ^{1}H, 3′-C*H* + 5′-C*H*), 6.34 (dd; *J* = 3.2, 1.8 Hz; 1 ^{1}H, 4″-C*H*), 6.21 (d, *J* = 3.2 Hz, 1 ^{1}H, 3″-C*H*), 4.01 (q, *J* = 7.0 Hz, 2 ^{1}H, C*H*$_2$CH$_3$), 3.81 (dd; *J* = 11.6, 6.5 Hz; 1 ^{1}H, 9-C*H*), 3.38 (dd; *J* = 8.9, 6.7 Hz; 1 ^{1}H, 8-CH*H*), 3.32 (d, *J* = 10.7 Hz, 1 ^{1}H, 6-CH*H*), 3.04 (d, *J* = 10.5 Hz, 1 ^{1}H, 6-C*H*H), 2.92 (dd; *J* = 11.6, 9.3 Hz; 1 ^{1}H, 8-C*H*H), 2.51 (s, 3 ^{1}H, NC*H*$_3$), 1.39 (t, *J* = 7.0 Hz, 3 ^{1}H, CH$_2$C*H*$_3$). ^{13}C NMR [75 MHz, δ (ppm), CDCl$_3$]: 173.0 (4-*C*O), 158.7 (4′-*C*), 155.9 (2-*C*O), 149.9 (2″-*C*), 142.3 (5″-*C*), 127.5 (2′-*C* + 6′-*C*), 124.0 (1′-*C*), 115.0 (3′-*C* + 5′-*C*), 110.7 (4″-*C*), 107.7 (3″-*C*), 69.9 (5-*C*), 64.1 (6-*C*), 63.8 (*C*H$_2$CH$_3$), 58.2 (8-*C*), 50.3 (9-*C*), 41.7 (N*C*H$_3$), 14.9 (CH$_2$*C*H$_3$). FTIR [ν- (cm^{-1}), neat]: 3284, 2930, 2849, 2791, 1776, 1714, 826, 734. MS [APCI (*m*/*z*)] calcd for $(C_{19}H_{21}N_3O_4 + H)^+ = 356$, found 356.

(±)-(5*R*,9*S*)-3-Ethyl-7-methyl-9-(1-methyl-1*H*-indol-3-yl)-1,3,7-triazaspiro[4.4]nonane-2,4-dione 16{*4*,*1*}. ^{1}H NMR [400 MHz, δ (ppm), CDCl$_3$]: 8.07 (bs, 1 ^{1}H, N*H*), 7.51 (d, *J* = 7.9 Hz, 1 ^{1}H, 4′-C*H*), 7.23 (d, *J* = 8.2 Hz, 1 ^{1}H, 7′-C*H*), 7.19−7.13 (m, 1 ^{1}H, 6′-C*H*), 7.08−7.02 (m, 1 ^{1}H, 5′-C*H*), 6.96 (s, 1 ^{1}H, 2′-C*H*), 4.06 (dd; *J* = 12.2, 6.2 Hz; 1 ^{1}H, 9-C*H*), 3.73 (s, 3 ^{1}H, 1′-NC*H*$_3$), 3.38 (dd; *J* = 9.3, 6.4 Hz; 1 ^{1}H, 8-CH*H*), 3.30 (d, *J* = 10.7 Hz, 1 ^{1}H, 6-CH*H*), 3.14−3.04 (m, 2 ^{1}H, C*H*$_2$CH$_3$), 3.05 (d, *J* = 10.7 Hz, 1 ^{1}H, 6-C*H*H), 2.99 (dd; *J* = 12.2, 9.2 Hz; 1 ^{1}H, 8-C*H*H), 2.58 (s, 3 ^{1}H, 7-NC*H*$_3$), 0.25 (t, *J* = 7.2 Hz, 3 ^{1}H, CH$_2$C*H*$_3$). ^{13}C NMR [75 MHz, δ (ppm), CDCl$_3$]: 174.5 (4-*C*O), 156.8 (2-*C*O), 136.8 (7′a-*C*), 127.8 (3′a-*C*), 127.2 (2′-*C*), 122.0 (6′-*C*), 119.7 (5′-*C*), 118.6 (4′-*C*), 109.3 (7′-*C*), 107.8 (3′-*C*), 71.0 (5-*C*), 64.3 (6-*C*), 60.2 (8-*C*), 48.4 (9-*C*), 41.8 (7-N*C*H$_3$), 32.9 (1′-N*C*H$_3$ + *C*H$_2$CH$_3$), 12.1 (CH$_2$*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 3298, 2934, 2841, 2794, 1770, 1705, 730. MS [APCI (*m*/*z*)] calcd for $(C_{18}H_{22}N_4O_2 + H)^+ = 327$, found 327.

(±)-(5*R*,9*S*)-7-Methyl-9-(1-methyl-1*H*-indol-3-yl)-3-[4-(trifluoromethyl)phenyl]-1,3,7-triazaspiro[4.4]nonane-2,4-dione 16{*4*,*6*}. ^{1}H NMR [400 MHz, δ (ppm), CDCl$_3$]: 8.26 (bs, 1 ^{1}H, N*H*), 7.59 (d, *J* = 7.9 Hz, 1 ^{1}H, 4′-C*H*), 7.45−7.38 (m, 2 ^{1}H, 3″-C*H* + 5″-C*H*), 7.28 (d, *J* = 8.2 Hz, 1 ^{1}H, 7′-C*H*), 7.24−7.18 (m, 1 ^{1}H, 6′-C*H*), 7.12−7.06 (m, 1 ^{1}H, 5′-C*H*), 6.98 (s, 1 ^{1}H, 2′-C*H*), 6.63−6.57 (m, 2 ^{1}H, 2″-C*H* + 6″-C*H*), 4.17 (dd; *J* = 12.0, 6.3 Hz; 1 ^{1}H, 9-C*H*), 3.73 (s, 3 ^{1}H, 1′-NC*H*$_3$), 3.46 (dd; *J* = 9.2, 6.6 Hz; 1 ^{1}H, 8-CH*H*), 3.43 (d, *J* = 10.7 Hz, 1 ^{1}H, 6-CH*H*), 3.16 (d, *J* = 10.7 Hz, 1 ^{1}H, 6-C*H*H), 3.01 (dd; *J* = 12.0, 9.4 Hz; 1 ^{1}H, 8-C*H*H), 2.62 (s, 3 ^{1}H, 7-NC*H*$_3$). ^{13}C NMR [75 MHz, δ (ppm), CDCl$_3$]: 173.4 (4-*C*O), 155.3 (2-*C*O), 137.3 (7′a-*C*), 134.8 (q, *J* = 1.4 Hz, 1″-*C*), 130.0 (q, *J* = 32.7 Hz, 4″-*C*), 127.4 (3′a-*C*), 127.2 (2′-*C*), 126.3 (2″-*C* + 6″-*C*), 126.1 (q, *J* = 3.7 Hz, 3″-*C* + 5″-*C*), 123.9 (q, *J* = 270.5 Hz, *C*F$_3$), 122.5 (6′-*C*), 119.9 (5′-*C*), 118.6 (4′-*C*), 109.9 (3′-*C* + 7′-*C*), 70.0 (5-*C*), 65.7 (6-*C*), 60.2 (8-*C*), 45.3 (9-*C*), 42.0 (7-N*C*H$_3$), 33.0 (1′-N*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 3228, 2938, 2842, 2790, 1776, 1716, 1323, 840, 738. MS [APCI (*m*/*z*)] calcd for $(C_{23}H_{21}F_3N_4O_2 + H)^+ = 443$, found 443.

General Procedure for Spiro Thiohydantoin Formation. Solutions of **14**{*11*−*18*} (0.1 mmol, 0.12 mmol for **14**{*11*}) from a 0.3 M stock solution in dimethylformamide were added to eight separate solutions of **12**{*1*} (0.1 mmol) in dimethylformamide (1.5 mL). The resulting reaction mixture was stirred at 40 °C for 40 h. After that time, the solvent was evaporated.

For the washing step, to the crude mixture of compounds **16**{*1*−*4*,*11*−*18*} was added diethyl ether (2 mL) (for **16**{*3*,*11*−*18*}, only 1.2 mL). The mixture was shaken until a white precipitate was formed. The sample was centrifuged, the solvent carefully eliminated with a pipet, and the resulting white or off-white solid was analyzed. For compounds **15**{*1*−*4*,*11*−*18*}, the washing step was carried out with only 1 mL of diethyl ether. For compounds **15**{*3*,*11*−*13*} and **15**{*3*,*15*}, there was no washing step, and they were analyzed immediately after evaporation of the solvent.

(±)-(5*R*,9*R*)-9-(3,5-Dimethoxyphenyl)-3-(4-ethoxyphenyl)-7-methyl-2-thioxo-1,3,7-triazaspiro[4.4]nonan-4-one 15{*1*,*16*}. ^{1}H NMR [300 MHz, δ (ppm), CDCl$_3$]: 7.46 (bs, 1 ^{1}H, N*H*), 7.10−7.04 (m, 2 ^{1}H, 2″-C*H* + 6″-C*H*), 6.97−6.91 (m, 2 ^{1}H, 3″-C*H* + 5″-C*H*), 6.39 (t, *J* = 2.1 Hz, 1 ^{1}H, 4′-C*H*), 6.38 (d, *J* = 2.1 Hz, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 4.05 (q, *J* = 6.9 Hz, 2 ^{1}H, C*H*$_2$CH$_3$), 3.93 (dd; *J* = 9.0, 5.7 Hz; 1 ^{1}H, 9-C*H*), 3.77 (s, 6 ^{1}H, 2 × OC*H*$_3$), 3.34 (dd; *J* = 9.9, 5.7 Hz; 1 ^{1}H, 8-CH*H*), 3.13 (d, *J* = 9.9 Hz, 1 ^{1}H, 6-CH*H*), 3.06 (d, *J* = 9.9 Hz, 1 ^{1}H, 6-C*H*H), 2.95 (app t, *J* = 9.6 Hz, 1 ^{1}H, 8-C*H*H), 2.49 (s, 3 ^{1}H, NC*H*$_3$), 1.42 (t, *J* = 6.9 Hz, 3 ^{1}H, CH$_2$C*H*$_3$). ^{13}C NMR [75 MHz, δ (ppm), CDCl$_3$]: 182.5 (2-*C*S), 174.5 (4-*C*O), 161.5 (3′-*C* + 5′-*C*), 159.5 (4″-*C*), 138.7 (1′-*C*), 129.4 (2″-*C* + 6″-*C*), 125.2 (1″-*C*), 115.0 (3″-*C* + 5″-*C*), 106.3 (2′-*C* + 6′-*C*), 99.7 (4′-*C*), 72.8 (5-*C*), 64.7 (6-*C*), 63.8 (*C*H$_2$CH$_3$), 59.6 (8-*C*), 55.6 (2 × OC*H*$_3$), 54.0 (9-*C*), 41.8 (N*C*H$_3$), 14.9 (CH$_2$*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 3142, 2936, 2839, 2790, 1748, 1596, 1203,

1155, 837. MS [APCI (*m*/*z*)] calcd for $(C_{23}H_{27}N_3O_4S + H)^+$ = 442, found 442.

(±)-(5*R*,9*R*)-9-(3,5-Dimethoxyphenyl)-7-methyl-3-(3-pyridyl)-2-thioxo-1,3,7-triazaspiro [4.4]nonan-4-one 15{*1*,*18*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 8.65 (dd; *J* = 4.8, 1.2 Hz; 1 ^{1}H, 6″-C*H*), 8.49 (d, *J* = 2.4 Hz, 1 ^{1}H, 2″-C*H*), 7.57 (dt; *J* = 8.1, 1.8 Hz; 1 ^{1}H, 4″-C*H*), 7.41 (dd; *J* = 8.1, 4.8 Hz; 1 ^{1}H, 5″-C*H*), 6.41 (t, *J* = 2.1 Hz, 1 ^{1}H, 4′-C*H*), 6.37 (d, *J* = 2.1 Hz, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 3.94 (dd; *J* = 9.0, 6.3 Hz; 1 ^{1}H, 9-C*H*), 3.77 (s, 6 ^{1}H, 2 × OCH_3), 3.37 (dd; *J* = 9.9, 6.0 Hz; 1 ^{1}H, 8-CH*H*), 3.17 (d, *J* = 9.9 Hz, 1 ^{1}H, 6-CH*H*), 3.10 (d, *J* = 9.9 Hz, 1 ^{1}H, 6-C*H*H), 2.97 (app t, *J* = 9.6 Hz, 1 ^{1}H, 8-C*H*H), 2.51 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 181.1 (2-*C*S), 174.0 (4-*C*O), 161.5 (3′-*C* + 5′-*C*), 150.0 (6″-*C*), 149.2 (2″-*C*), 138.2 (1′-*C*), 135.9 (4″-*C*), 129.8 (3″-*C*), 123.7 (5″-*C*), 106.3 (2′-*C* + 6′-*C*), 99.7 (4′-*C*), 73.2 (5-*C*), 64.4 (6-*C*), 59.4 (8-*C*), 55.6 (2 × O*C*H_3), 54.2 (9-*C*), 41.8 (N*C*H_3). MS [APCI (*m*/*z*)] calcd for $(C_{20}H_{22}N_4O_3S + H)^+$ = 399, found 399.

(±)-(5*R*,9*R*)-9-(1,3-Benzodioxol-5-yl)-7-methyl-3-phenyl-2-thioxo-1,3,7-triazaspiro[4.4] nonan-4-one 15{*2*,*14*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 8.34 (bs, 1 ^{1}H, N*H*), 7.51−7.36 (m, 3 ^{1}H, 3′-C*H* + 4″-C*H* + 5″-C*H*), 7.20−7.11 (m, 2 ^{1}H, 2″-C*H* + 6″-C*H*), 6.81 (d, *J* = 1.8 Hz, 1 ^{1}H, 4′-C*H*), 6.77 (d, *J* = 7.8 Hz, 1 ^{1}H, 7′-C*H*), 6.67 (dd; *J* = 7.8, 1.8 Hz; 1 ^{1}H, 6′-C*H*), 5.96 (s, 2 ^{1}H, 2′-CH_2), 3.94 (dd; *J* = 8.7, 6.9 Hz; 1 ^{1}H, 9-C*H*), 3.27 (dd; *J* = 9.6, 6.9 Hz; 1 ^{1}H, 8-CH*H*), 3.17 (d, *J* = 10.2 Hz, 1 ^{1}H, 6-CH*H*), 3.11 (d, *J* = 10.2 Hz, 1 ^{1}H, 6-C*H*H), 3.00 (app t, *J* = 9.3 Hz, 1 ^{1}H, 8-C*H*H), 2.49 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 181.9 (2-*C*S), 174.4 (4-*C*O), 148.3 (3′a-*C*), 147.5 (7′a-*C*), 132.8 (1″-*C*), 129.5 (5′-*C*), 129.3 (4″-*C*), 129.2 (3″-*C* + 5″-*C*), 128.4 (2″-*C* + 6″-*C*), 121.6 (6′-*C*), 108.6 (7′-*C*), 108.2 (4′-*C*), 101.3 (2′-*C*), 73.3 (5-*C*), 64.2 (6-*C*), 57.7 (8-*C*), 54.1 (9-*C*), 41.9 (N*C*H_3). FTIR [ν^- (cm^{-1}), neat]: 3156, 2940, 2846, 2789, 1746, 1253, 1236, 1036, 931, 756, 694. MS [APCI (*m*/*z*)] calcd for $(C_{20}H_{19}N_3O_3S + H)^+$ = 382, found 382.

(±)-(5*R*,9*R*)-9-(1,3-Benzodioxol-5-yl)-7-methyl-3-(3-pyridyl)-2-thioxo-1,3,7-triazaspiro [4.4]nonan-4-one 15-{*2*,*18*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 8.65 (dd; *J* = 4.8, 1.5 Hz; 1 ^{1}H, 6″-C*H*), 8.47 (d, *J* = 2.4 Hz, 1 ^{1}H, 2″-C*H*), 7.57 (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*), 6.78 (d, *J* = 7.8 Hz, 1 ^{1}H, 7′-C*H*), 6.78 (d, *J* = 1.8 Hz, 1 ^{1}H, 4′-C*H*), 6.66 (dd; *J* = 7.8, 1.8 Hz; 1 ^{1}H, 6′-C*H*), 5.98 (s, 2 ^{1}H, 2′-CH_2), 3.95 (dd; *J* = 9.0, 5.7 Hz; 1 ^{1}H, 9-C*H*), 3.30 (dd; *J* = 9.6, 5.7 Hz; 1 ^{1}H, 8-CH*H*), 3.18 (d, *J* = 9.9 Hz, 1 ^{1}H, 6-CH*H*), 3.08 (d, *J* = 9.9 Hz, 1 ^{1}H, 6-C*H*H), 2.97 (app t, *J* = 9.6 Hz, 1 ^{1}H, 8-C*H*H), 2.50 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 181.5 (2-*C*S), 174.3 (4-*C*O), 150.4 (6″-*C*), 149.7 (2″-*C*), 149.0 (3′a-*C*), 148.1 (7′a-*C*), 136.3 (4″-*C*), 130.2 (3″-*C*), 130.1 (5′-*C*), 124.1 (5″-*C*), 121.9 (6′-*C*), 109.3 (7′-*C*), 108.5 (4′-*C*), 101.9 (2′-*C*), 73.8 (5-*C*), 64.8 (6-*C*), 60.3 (8-*C*), 54.6 (9-*C*), 42.2 (N*C*H_3). FTIR [ν^- (cm^{-1}), neat]: 3069, 2940, 2848, 2787, 1748, 1253, 1236, 1036, 930, 707. MS [APCI (*m*/*z*)] calcd for $(C_{19}H_{18}N_4O_3S + H)^+$ = 383, found 383.

(±)-(5*R*,9*R*)-9-(2-Furyl)-7-methyl-3-phenethyl-2-thioxo-1,3,7-triazaspiro[4.4]nonan-4-one 15{*3*,*12*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.76 (bs, 1 ^{1}H, N*H*), 7.36−7.18 (m, 6 ^{1}H, 5′-C*H* + Ph), 6.29 (dd; *J* = 3.3, 1.8 Hz; 1 ^{1}H, 4′-C*H*), 6.10 (d, *J* = 3.3 Hz, 1 ^{1}H, 3′-C*H*), 4.07−3.97 (m, 2 ^{1}H, NCH_2CH$_2$), 3.94 (dd; *J* = 9.3, 6.9 Hz; 1 ^{1}H, 9-C*H*), 3.25 (dd; *J* = 9.6, 6.9 Hz; 1 ^{1}H, 8-CH*H*), 3.02−2.85 (m, 5 ^{1}H, 6-CH_2 + 8-C*H*H + NCH$_2$CH_2), 2.43 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 182.5 (2-*C*S), 174.2 (4-*C*O), 150.2 (2′-*C*), 143.0 (5′-*C*), 137.9 (1″-*C*), 129.1 (2″-*C* + 6″-*C*), 128.6 (3″-*C* + 5″-*C*), 126.7 (4″-*C*), 110.5 (4′-*C*), 108.0 (3′-*C*), 71.6 (5-*C*), 64.4 (6-*C*), 58.0 (8-*C*), 46.7 (9-*C*), 42.4 (N*C*H$_2$CH$_2$), 41.8 (N*C*H_3), 33.6 (NCH$_2$*C*H$_2$). FTIR [ν^- (cm^{-1}), neat]: 3283, 2941, 2846, 2793, 1740, 743, 700. MS [APCI (*m*/*z*)] calcd for $(C_{19}H_{21}N_3O_2S + H)^+$ = 356, found 356.

(±)-(5*R*,9*R*)-9-(2-Furyl)-7-methyl-2-thioxo-3-[4-(trifluoromethyl)phenyl]-1,3,7-triazaspiro[4.4]nonan-4-one 15-{*3*,*15*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 8.52 (bs, 1 ^{1}H, N*H*), 7.79−7.71 (m, 2 ^{1}H, 3″-C*H* + 5″-C*H*), 7.51−7.43 (m, 2 ^{1}H, 2″-C*H* + 6″-C*H*), 7.40 (d, *J* = 1.8 Hz, 1 ^{1}H, 5′-C*H*), 6.35 (dd; *J* = 3.3, 1.8 Hz; 1 ^{1}H, 4′-C*H*), 6.23 (d, *J* = 3.3 Hz, 1 ^{1}H, 3′-C*H*), 4.12 (dd; *J* = 9.0, 7.8 Hz; 1 ^{1}H, 9-C*H*), 3.35 (dd; *J* = 9.6, 7.8 Hz; 1 ^{1}H, 8-CH*H*), 3.20−3.13 (m, 2 ^{1}H, 6-CH_2), 3.05 (app t, *J* = 9.6 Hz, 1 ^{1}H, 8-C*H*H), 2.49 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 181.6 (2-*C*S), 173.6 (4-*C*O), 149.9 (2′-*C*), 143.2 (5′-*C*), 136.1 (q, *J* = 1.4 Hz, 1″-*C*), 131.1 (q, *J* = 32.7 Hz, 4″-*C*), 128.9 (2″-*C* + 6″-*C*), 126.3 (q, *J* = 3.7 Hz, 3″-*C* + 5″-*C*), 123.8 (q, *J* = 270.8 Hz, *C*F$_3$), 110.6 (4′-*C*), 108.2 (3′-*C*), 72.4 (5-*C*), 64.0 (6-*C*), 57.4 (8-*C*), 47.6 (9-*C*), 41.9 (N*C*H_3). MS [APCI (*m*/*z*)] calcd for $(C_{18}H_{16}F_3N_3O_2S + H)^+$ = 396, found 396.

(±)-3-{(5*R*,9*R*)-9-(2-Furyl)-7-methyl-4-oxo-2-thioxo-1,3,7-triazaspiro[4.4]nonan-3-yl} benzonitrile 15{*3*,*17*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 8.30 (bs, 1 ^{1}H, N*H*), 7.76−7.70 (m, 1 ^{1}H, 6-C*H*), 7.64 (t, *J* = 1.5 Hz, 1 ^{1}H, 2-C*H*), 7.62−7.55 (m, 2 ^{1}H, 4-C*H* + 5-C*H*), 7.41 (d, *J* = 1.8 Hz, 1 ^{1}H, 5″-C*H*), 6.36 (dd; *J* = 3.3, 1.8 Hz; 1 ^{1}H, 4″-C*H*), 6.24 (d, *J* = 3.3 Hz, 1 ^{1}H, 3″-C*H*), 4.12 (dd; *J* = 9.0, 7.5 Hz; 1 ^{1}H, 9′-C*H*), 3.35 (dd; *J* = 9.6, 7.5 Hz; 1 ^{1}H, 8′-CH*H*), 3.19−3.11 (m, 2 ^{1}H, 6′-CH_2), 3.04 (app t, *J* = 9.6 Hz, 1 ^{1}H, 8′-C*H*H), 2.50 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 181.3 (2′-*C*S), 173.4 (4′-*C*O), 149.9 (2″-*C*), 143.3 (5″-*C*), 133.8 (3-*C*), 133.0 (4-*C*), 132.6 (6-*C*), 132.1 (2-*C*), 130.1 (5-*C*), 117.8 (*C*N), 113.4 (1-*C*), 110.7 (4″-*C*), 108.2 (3″-*C*), 72.4 (5′-*C*), 64.0 (6′-*C*), 57.4 (8′-*C*), 47.7 (9′-*C*), 41.8 (N*C*H_3). MS [APCI (*m*/*z*)] calcd for $(C_{18}H_{16}N_4O_2S + H)^+$ = 353, found 353.

(±)-(5*R*,9*R*)-3-Ethyl-7-methyl-9-(1-methyl-1*H*-indol-3-yl)-2-thioxo-1,3,7-triazaspiro [4.4]nonan-4-one 15{*4*,*11*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.46 (d, *J* = 7.8 Hz, 1 ^{1}H, 4′-C*H*), 7.29 (d, *J* = 8.1 Hz, 1 ^{1}H, 7′-C*H*), 7.24−7.17 (m, 1 ^{1}H, 6′-C*H*), 7.10−7.04 (m, 1 ^{1}H, 5′-C*H*), 6.98 (s, 1 ^{1}H, 2′-C*H*), 4.24 (dd; *J* = 9.0, 6.6 Hz; 1 ^{1}H, 9-C*H*), 3.75 (s, 3 ^{1}H, 1′-NCH_3), 3.76−3.68 (m, 2 ^{1}H, CH_2CH$_3$), 3.32 (dd; *J* = 9.3, 6.6 Hz; 1 ^{1}H, 8-CH*H*), 3.09 (d, *J* = 10.2 Hz, 1 ^{1}H, 6-CH*H*), 3.07 (app t, *J* = 9.3 Hz, 1 ^{1}H, 8-C*H*H), 3.04 (d, *J* = 10.2 Hz, 1 ^{1}H, 6-C*H*H), 2.52 (s, 3 ^{1}H, 7-NCH_3), 1.03 (t,

J = 7.2 Hz, 3 ^{1}H, CH_2CH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 182.4 (2-*C*S), 175.1 (4-*C*O), 137.2 (7′a-*C*), 127.3 (3′a-*C*), 127.2 (2′-*C*), 122.4 (6′-*C*), 119.9 (5′-*C*), 118.6 (4′-*C*), 109.7 (3′-*C* + 7′-*C*), 72.2 (5-*C*), 64.7 (6-*C*), 60.5 (8-*C*), 45.4 (9-*C*), 41.9 (7-NCH_3), 36.4 (CH_2CH_3), 33.0 (1′-NCH_3), 12.8 (CH_2CH_3). FTIR [ν^- (cm^{-1}), neat]: 3171, 2937, 2841, 2787, 1735, 739. MS [APCI (*m*/*z*)] calcd for ($C_{18}H_{22}N_4OS$ + H)$^+$ = 343, found 343.

(±)-Ethyl 3-{(5*R*,9*R*)-7-methyl-9-(1-methyl-1*H*-indol-3-yl)-4-oxo-2-thioxo-1,3,7-triazaspiro[4.4]nonan-3-yl}propanoate 15{*4*,*13*}. ^{1}H NMR [300 MHz, δ (ppm), $CDCl_3$]: 7.46 (d, J = 8.1 Hz, 1 ^{1}H, 4″-C*H*), 7.28 (d, J = 8.4 Hz, 1 ^{1}H, 7″-C*H*), 7.25−7.18 (m, 1 ^{1}H, 6″-C*H*), 7.12−7.06 (m, 1 ^{1}H, 5″-C*H*), 7.08 (s, 1 ^{1}H, 2″-C*H*), 4.30 (dd; J = 9.0, 6.9 Hz; 1 ^{1}H, 9′-C*H*), 4.09 (q, J = 7.2 Hz, 2 ^{1}H, CH_2CH$_3$), 3.98−3.87 (m, 2 ^{1}H, 3-CH_2), 3.76 (s, 3 ^{1}H, 1″-NCH_3), 3.53 (dd; J = 9.6, 6.9 Hz; 1 ^{1}H, 8′-CH*H*), 3.27 (d, J = 10.2 Hz, 1 ^{1}H, 6′-CH*H*), 3.17 (d, J = 10.2 Hz, 1 ^{1}H, 6′-C*H*H), 3.15 (app t, J = 9.4 Hz, 1 ^{1}H, 8′-C*H*H), 2.63 (s, 3 ^{1}H, 7′-NCH_3), 2.48−2.35 (m, 2 ^{1}H, 2-CH_2), 1.24 (t, J = 7.2 Hz, 3 ^{1}H, CH_2CH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 182.2 (2′-*C*S), 174.9 (4′-*C*O), 171.2 (*C*O$_2$), 137.6 (7″a-*C*), 128.1 (2″-*C*), 127.6 (3″a-*C*), 122.9 (6″-*C*), 120.4 (5″-*C*), 118.8 (4″-*C*), 110.3 (7″-*C*), 109.0 (3″-*C*), 72.5 (5′-*C*), 64.6 (6′-*C*), 61.3 (CH_2CH_3), 60.6 (8′-*C*), 45.7 (9′-*C*), 42.3 (7′-NCH_3), 37.3 (3-*C*), 33.5 (1″-NCH_3), 32.3 (2-*C*), 14.7 (CH_2CH_3). MS [APCI (*m*/*z*)] calcd for ($C_{21}H_{26}N_4O_3S$ + H)$^+$ = 415, found 415.

(±)-(5*R*,9*S*)-9-(3,5-Dimethoxyphenyl)-3-ethyl-7-methyl-2-thioxo-1,3,7-triazaspiro[4.4] nonan-4-one 16{*1*,*11*}. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 9.29 (bs, 1 ^{1}H, N*H*), 6.33 (t, J = 2.2 Hz, 1 ^{1}H, 4′-C*H*), 6.29 (d, J = 2.2 Hz, 2 ^{1}H, 2′-C*H* + 6′-C*H*), 3.73 (s, 6 ^{1}H, 2 × OCH_3), 3.64 (dd; J = 12.2, 6.2 Hz; 1 ^{1}H, 9-C*H*), 3.63 (dq; J = 13.4, 7.2 Hz; 1 ^{1}H, CH*H*CH$_3$), 3.48 (dq; J = 13.6, 7.0 Hz; 1 ^{1}H, C*H*HCH$_3$), 3.38 (dd; J = 9.4, 6.2 Hz; 1 ^{1}H, 8-CH*H*), 3.33 (d, J = 11.1 Hz, 1 ^{1}H, 6-CH*H*), 3.08 (dd; J = 12.2, 9.4 Hz; 1 ^{1}H, 8-C*H*H), 2.99 (d, J = 11.1 Hz, 1 ^{1}H, 6-C*H*H), 2.63 (s, 3 ^{1}H, NCH_3), 0.70 (t, J = 7.0 Hz, 1 ^{1}H, CH_2CH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 183.1 (2-*C*S), 174.1 (4-*C*O), 160.9 (3′-*C* + 5′-*C*), 135.9 (1′-*C*), 105.5 (2′-*C* + 6′-*C*), 100.4 (4′-*C*), 72.4 (5-*C*), 63.5 (6-*C*), 58.1 (8-*C*), 55.5 (2 × OCH_3), 55.4 (9-*C*), 42.1 (NCH_3), 36.0 (CH_2CH_3), 12.3 (CH_2CH_3). FTIR [ν^- (cm^{-1}), neat]: 3186, 2938, 2837, 2792, 1737, 1595, 1203, 1153, 846. HRMS [ESI (*m*/*z*)] calcd for ($C_{17}H_{23}N_3O_3S$ + H)$^+$ = 350.15384, found 350.15322 (|Δ| = 1.8 ppm).

(±)-(5*R*,9*S*)-9-(3,5-Dimethoxyphenyl)-7-methyl-3-phenethyl-2-thioxo-1,3,7-triazaspiro [4.4]nonan-4-one 16{*1*,*12*}. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 9.39 (bs, 1 ^{1}H, N*H*), 7.29−7.23 (m, 2 ^{1}H, 3″-C*H* + 5″-C*H*), 7.22−7.16 (m, 1 ^{1}H, 4″-C*H*), 7.16−7.10 (m, 2 ^{1}H, 2″-C*H* + 6″-C*H*), 6.32 (s, 3 ^{1}H, 2′-C*H* + 4′-C*H* + 6′-C*H*), 3.81−3.73 (m, 1 ^{1}H, NCH*H*CH$_2$), 3.73 (s, 6 ^{1}H, 2 × OCH_3), 3.69−3.59 (m, 2 ^{1}H, 9-C*H* + NC*H*HCH$_2$), 3.40 (dd; J = 9.2, 6.1 Hz; 1 ^{1}H, 8-CH*H*), 3.33 (d, J = 11.2 Hz, 1 ^{1}H, 6-CH*H*), 3.09 (dd; J = 12.2, 9.4 Hz; 1 ^{1}H, 8-C*H*H), 2.94 (d, J = 11.1 Hz, 1 ^{1}H, 6-C*H*H), 2.63 (s, 3 ^{1}H, NCH_3), 2.55 (ddd; J = 12.7, 11.4, 5.8 Hz; 1 ^{1}H, NCH$_2$CH*H*), 2.14 (ddd; J = 12.9, 11.6, 5.0 Hz; 1 ^{1}H, NCH$_2$C*H*H). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 183.0 (2-*C*S), 174.1 (4-*C*O), 161.0 (3′-*C* + 5′-*C*), 138.1 (1″-*C*), 136.0 (1′-*C*), 128.9 (2″-*C* + 6″-*C*), 128.6 (3″-*C* + 5″-*C*), 126.7 (4″-*C*), 105.7 (2′-*C* + 6′-*C*), 100.3 (4′-*C*), 72.5 (5-*C*), 63.6 (6-*C*), 58.1 (8-*C*), 55.6 (2 × OCH_3), 55.3 (9-*C*), 42.1 (NCH_2CH_2), 42.0 (NCH_3), 33.2 (NCH$_2$$CH_2$). FTIR [$\nu^-$ (cm^{-1}), neat]: 3192, 2940, 2837, 2794, 1740, 1595, 1202, 1152, 846, 697. HRMS [ESI (*m*/*z*)] calcd for ($C_{23}H_{27}N_3O_3S$ + H)$^+$ = 426.18514, found 426.18460 (|Δ| = 1.3 ppm).

(±)-Ethyl 3-{(5*R*,9*S*)-9-(1,3-benzodioxol-5-yl)-7-methyl-4-oxo-2-thioxo-1,3,7-triazaspiro[4.4]nonan-3-yl}propanoate 16{*2*,*13*}. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.58 (bs, 1 ^{1}H, N*H*), 6.72 (d, J = 8.0 Hz, 1 ^{1}H, 7″-C*H*), 6.66 (d, J = 1.4 Hz, 1 ^{1}H, 4″-C*H*), 6.62 (dd; J = 8.0, 1.4 Hz; 1 ^{1}H, 6″-C*H*), 5.94 (s, 2 ^{1}H, 2″-CH_2), 4.09 (q, J = 7.1 Hz, 2 ^{1}H, CH_2CH$_3$), 3.87 (ddd; J = 13.6, 10.3, 5.8 Hz; 1 ^{1}H, 3-CH*H*), 3.74 (ddd; J = 13.6, 10.3, 5.3 Hz; 1 ^{1}H, 3-C*H*H), 3.65 (dd; J = 12.1, 6.0 Hz; 1 ^{1}H, 9′-C*H*), 3.35 (d, J = 11.2 Hz, 1 ^{1}H, 6′-CH*H*), 3.36−3.32 (m, 1 ^{1}H, 8′-CH*H*), 3.03 (dd; J = 11.9, 9.8 Hz; 1 ^{1}H, 8′-C*H*H), 2.99 (d, J = 11.1 Hz, 1 ^{1}H, 6′-C*H*H), 2.60 (s, 3 ^{1}H, NCH_3), 2.27 (ddd; J = 16.4, 10.3, 5.8 Hz; 1 ^{1}H, 2-CH*H*), 1.92 (ddd; J = 16.2, 10.4, 5.3 Hz; 1 ^{1}H, 2-C*H*H), 1.23 (t, J = 7.1 Hz, 3 ^{1}H, CH_2CH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 182.3 (2′-*C*S), 173.9 (4′-*C*O), 170.5 (*C*O$_2$), 148.0 (3″a-*C*), 147.8 (7″a-*C*), 126.9 (5″-*C*), 121.5 (6″-*C*), 108.5 (7″-*C*), 108.3 (4″-*C*), 101.4 (2″-*C*), 72.6 (5′-*C*), 63.1 (6′-*C*), 60.8 (CH_2CH_3), 58.6 (8′-*C*), 55.4 (9′-*C*), 41.9 (NCH_3), 36.3 (3-*C*), 31.6 (2-*C*), 14.3 (CH_2CH_3). FTIR [ν^- (cm^{-1}), neat]: 3282, 2948, 2842, 2784, 1741, 1731, 1252, 1236, 1036, 928. HRMS [ESI (*m*/*z*)] calcd for ($C_{19}H_{23}N_3O_5S$ + H)$^+$ = 406.14367, found 406.14128 (|Δ| = 5.9 ppm).

(±)-3-{(5*R*,9*S*)-9-(1,3-Benzodioxol-5-yl)-7-methyl-4-oxo-2-thioxo-1,3,7-triazaspiro[4.4] nonan-3-yl}benzonitrile 16{*2*,*17*}. ^{1}H NMR [400 MHz, δ (ppm), CD_3SOCD_3]: 11.2 (bs, 1 ^{1}H, N*H*), 7.86 (dt; J = 7.8, 1.3 Hz; 1 ^{1}H, 6-C*H*), 7.63 (t, J = 8.0 Hz, 1 ^{1}H, 5-C*H*), 7.07 (dt; J = 8.0, 1.4 Hz; 1 ^{1}H, 4-C*H*), 7.00 (t, J = 1.4 Hz, 1 ^{1}H, 2-C*H*), 6.91 (d, J = 8.0 Hz, 1 ^{1}H, 7″-C*H*), 6.72 (d, J = 1.4 Hz, 1 ^{1}H, 4″-C*H*), 6.66 (dd; J = 8.0, 1.4 Hz; 1 ^{1}H, 6″-C*H*), 6.02−6.00 (m, 2 ^{1}H, 2″-CH_2), 3.71 (dd; J = 11.7, 6.2 Hz; 1 ^{1}H, 9′-C*H*), 3.27 (d, J = 11.2 Hz, 1 ^{1}H, 6′-CH*H*), 3.12 (dd; J = 8.9, 6.2 Hz; 1 ^{1}H, 8′-CH*H*), 2.92 (dd; J = 11.7, 9.4 Hz; 1 ^{1}H, 8′-C*H*H), 2.88 (d, J = 11.1 Hz, 1 ^{1}H, 6′-C*H*H), 2.38 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), CD_3SOCD_3]: 180.5 (2′-*C*S), 173.9 (4′-*C*O), 147.1 (3″a-*C*), 146.7 (7″a-*C*), 133.7 (3-*C*), 133.4 (4-*C*), 132.4 (6-*C*), 131.7 (2-*C*), 130.2 (5-*C*), 128.3 (5″-*C*), 121.2 (6″-*C*), 117.7 (*C*N), 111.6 (1-*C*), 108.1 (7″-*C*), 107.9 (4″-*C*), 101.1 (2″-*C*), 73.5 (5′-*C*), 61.7 (6′-*C*), 57.1 (8′-*C*), 53.7 (9′-*C*), 41.7 (NCH_3). FTIR [ν^- (cm^{-1}), neat]: 3282, 2948, 2842, 2784, 1741, 1731, 1252, 1236, 1036, 928. HRMS [ESI (*m*/*z*)] calcd for ($C_{21}H_{18}N_4O_3S$ + H)$^+$ = 407.11779, found 407.11531 (|Δ| = 6.1 ppm).

(±)-(5*R*,9*S*)-9-(2-Furyl)-7-methyl-3-phenyl-2-thioxo-1,3,7-triazaspiro[4.4]nonan-4-one 16{*3*,*14*}. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 9.17 (bs, 1 ^{1}H, N*H*), 7.46−7.35 (m, 4 ^{1}H, 5′-C*H* + 3″-C*H* + 4″-C*H* + 5″-C*H*), 7.06−6.99 (m, 2 ^{1}H, 2″-C*H* + 6″-C*H*), 6.36 (dd; J = 3.3, 2.0 Hz; 1 ^{1}H, 4′-C*H*), 6.23 (d, J = 3.3 Hz, 1 ^{1}H, 3′-C*H*), 3.91 (dd; J = 11.7, 6.6 Hz; 1 ^{1}H, 9-C*H*), 3.50 (dd; J = 9.3, 6.7 Hz; 1 ^{1}H, 8-CH*H*), 3.43 (d, J = 10.9 Hz, 1 ^{1}H, 6-CH*H*), 3.06 (d, J =

10.8 Hz, 1 ^{1}H, 6-C*H*H), 2.94 (dd; J = 11.6, 9.5 Hz; 1 ^{1}H, 8-C*H*H), 2.59 (s, 3 ^{1}H, NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 183.0 (2-*C*S), 173.3 (4-*C*O), 149.1 (2′-*C*), 142.5 (5′-*C*), 132.8 (1″-*C*), 129.2 (4″-*C*), 129.1 (3″-*C* + 5″-*C*), 128.3 (2″-*C* + 6″-*C*), 110.9 (4′-*C*), 108.2 (3′-*C*), 72.2 (5-*C*), 63.9 (6-*C*), 57.9 (8-*C*), 50.2 (9-*C*), 41.8 (N*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 3110, 2948, 2847, 2794, 1753, 760, 732, 691. HRMS [ESI (*m*/*z*)] calcd for $(C_{17}H_{17}N_3O_2S + H)^+$ = 328.11197, found 328.11137 (|Δ| = 1.8 ppm).

(±)-(5*R*,9*S*)-3-(4-Ethoxyphenyl)-9-(2-furyl)-7-methyl-2-thioxo-1,3,7-triazaspiro[4.4] nonan-4-one 16{*3*,*16*}. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 9.46 (bs, 1 ^{1}H, N*H*), 7.38 (dd; J = 1.8, 0.6 Hz; 1 ^{1}H, 5″-C*H*), 6.94−6.86 (m, 4 ^{1}H, 2′-C*H* + 3′-C*H* + 5′-C*H* + 6′-C*H*), 6.35 (dd; J = 3.2, 1.8 Hz; 1 ^{1}H, 4″-C*H*), 6.23 (d, J = 3.2 Hz, 1 ^{1}H, 3″-C*H*), 4.02 (q, J = 7.0 Hz, 2 ^{1}H, CH_2CH$_3$), 3.88 (dd; J = 11.7, 6.4 Hz; 1 ^{1}H, 9-C*H*), 3.49 (dd; J = 9.2, 6.7 Hz; 1 ^{1}H, 8-CH*H*), 3.41 (d, J = 10.8 Hz, 1 ^{1}H, 6-CH*H*), 3.05 (d, J = 10.8 Hz, 1 ^{1}H, 6-C*H*H), 2.93 (dd; J = 11.7, 9.4 Hz; 1 ^{1}H, 8-C*H*H), 2.59 (s, 3 ^{1}H, NCH_3), 1.40 (t, J = 7.0 Hz, 3 ^{1}H, CH$_2$CH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 183.5 (2-*C*S), 173.5 (4-*C*O), 159.4 (4′-*C*), 149.2 (2″-*C*), 142.4 (5″-*C*), 129.3 (2′-*C* + 6′-*C*), 125.2 (1′-*C*), 114.9 (3′-*C* + 5′-*C*), 110.8 (4″-*C*), 108.1 (3″-*C*), 72.1 (5-*C*), 64.0 (6-*C*), 63.8 (*C*H$_2$CH$_3$), 58.0 (8-*C*), 50.2 (9-*C*), 41.9 (N*C*H$_3$), 14.9 (CH$_2$*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 3278, 2937, 2841, 2795, 1750, 821, 732. HRMS [ESI (*m*/*z*)] calcd for $(C_{19}H_{21}N_3O_3S + H)^+$ = 372.13819, found 372.13606 (|Δ| = 5.7 ppm).

(±)-(5*R*,9*S*)-7-Methyl-9-(1-methyl-1*H*-indol-3-yl)-2-thioxo-3-[4-(trifluoromethyl)phenyl]-1,3,7-triazaspiro[4.4]nonan-4-one 16{*4*,*15*}. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 7.60 (d, J = 7.9 Hz, 1 ^{1}H, 4′-C*H*), 7.44−7.38 (m, 2 ^{1}H, 3″-C*H* + 5″-C*H*), 7.32 (d, J = 8.2 Hz, 1 ^{1}H, 7′-C*H*), 7.29−7.23 (m, 1 ^{1}H, 6′-C*H*), 7.18−7.11 (m, 1 ^{1}H, 5′-C*H*), 6.97 (s, 1 ^{1}H, 2′-C*H*), 6.37−6.29 (m, 2 ^{1}H, 2″-C*H* + 6″-C*H*), 4.33 (dd; J = 12.2, 6.3 Hz; 1 ^{1}H, 9-C*H*), 3.73 (s, 3 ^{1}H, 1′-NCH_3), 3.65 (dd; J = 9.2, 6.5 Hz; 1 ^{1}H, 8-CH*H*), 3.60 (d, J = 10.8 Hz, 1 ^{1}H, 6-CH*H*), 3.19 (d, J = 11.3 Hz, 1 ^{1}H, 6-C*H*H), 3.08 (dd; J = 12.2, 9.5 Hz; 1 ^{1}H, 8-C*H*H), 2.75 (s, 3 ^{1}H, 7-NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 182.2 (2-*C*S), 173.4 (4-*C*O), 137.0 (7′a-*C*), 135.8 (q, J = 1.4 Hz, 1″-*C*), 130.9 (q, J = 32.5 Hz, 4″-*C*), 128.6 (2″-*C* + 6″-*C*), 127.5 (2′-*C*), 127.1 (3′a-*C*), 126.0 (q, J = 3.7 Hz, 3″-*C* + 5″-*C*), 123.7 (q, J = 270.5 Hz, *C*F$_3$), 122.6 (6′-*C*), 120.4 (5′-*C*), 118.7 (4′-*C*), 109.6 (7′-*C*), 107.0 (3′-*C*), 73.5 (5-*C*), 64.0 (6-*C*), 59.4 (8-*C*), 49.3 (9-*C*), 42.2 (7-N*C*H$_3$), 33.1 (1′-N*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 3289, 2948, 2829, 2795, 1751, 1321, 840, 737. HRMS [ESI (*m*/*z*)] calcd for $(C_{23}H_{21}F_3N_4OS + H)^+$ = 459.14664, found 459.14440 (|Δ| = 4.9 ppm).

(±)-(5*R*,9*S*)-7-Methyl-9-(1-methyl-1*H*-indol-3-yl)-3-(3-pyridyl)-2-thioxo-1,3,7-triazaspiro[4.4]nonan-4-one 16{*4*,*18*}. ^{1}H NMR [400 MHz, δ (ppm), $CDCl_3$]: 8.44 (dd; J = 4.8, 1.5 Hz; 1 ^{1}H, 6″-C*H*), 7.58 (d, J = 7.9 Hz, 1 ^{1}H, 4′-C*H*), 7.44 (d, J = 2.0 Hz, 1 ^{1}H, 2″-C*H*), 7.32 (d, J = 8.2 Hz, 1 ^{1}H, 7′-C*H*), 7.29−7.23 (m, 1 ^{1}H, 6′-C*H*), 7.17−7.11 (m, 1 ^{1}H, 5′-C*H*), 7.11 (dd; J = 8.2, 4.8 Hz; 1 ^{1}H, 5″-C*H*), 6.98 (s, 1 ^{1}H, 2′-C*H*), 6.61 (dt; J = 8.2, 1.8 Hz; 1 ^{1}H, 4″-C*H*), 4.29 (dd; J = 12.0, 6.2 Hz; 1 ^{1}H, 9-C*H*), 3.73 (s, 3 ^{1}H, 1′-NCH_3), 3.61 (dd; J = 8.9, 6.4 Hz; 1 ^{1}H, 8-CH*H*), 3.55 (d, J = 11.1 Hz, 1 ^{1}H, 6-CH*H*), 3.16 (d, J = 11.0 Hz, 1 ^{1}H, 6-C*H*H), 3.03 (dd; J = 12.0, 9.5 Hz; 1 ^{1}H, 8-C*H*H), 2.72 (s, 3 ^{1}H, 7-NCH_3). ^{13}C NMR [75 MHz, δ (ppm), $CDCl_3$]: 182.4 (2-*C*S), 173.5 (4-*C*O), 149.6 (6″-*C*), 149.0 (2″-*C*), 136.9 (7′a-*C*), 135.8 (4″-*C*), 129.6 (3″-*C*), 127.4 (2′-*C*), 127.1 (3′a-*C*), 123.4 (5″-*C*), 122.6 (6′-*C*), 120.4 (5′-*C*), 118.5 (4′-*C*), 109.7 (7′-*C*), 107.2 (3′-*C*), 73.7 (5-*C*), 64.3 (6-*C*), 59.6 (8-*C*), 49.5 (9-*C*), 42.3 (7-N*C*H$_3$), 33.1 (1′-N*C*H$_3$). FTIR [ν^- (cm^{-1}), neat]: 3312, 2948, 2842, 2794, 1751, 731, 708. HRMS [ESI (*m*/*z*)] calcd for $(C_{21}H_{21}N_5OS + H)^+$ = 392.15451, found 392.15151 (|Δ| = 7.6 ppm).

Acknowledgment. We would like to thank Dr. Richard H. Blaauw and Chiralix B.V. (Nijmegen, The Netherlands) for the use of their parallel-synthesis facilities.

Supporting Information Available. Experimental copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **15**{*1*,*5*}, **15**{*1*,*7*}, **15**{*1*,*16*}, **15**{*1*,*18*}, **15**{*2*,*1*}, **15**{*2*,*2*}, **15**{*2*,*14*}, **15**{*2*,*18*}, **15**{*3*,*3*}, **15**{*3*,*10*}, **15**{*3*,*12*}, **15**{*3*,*15*}, **15**{*3*,*17*}, **15**{*4*,*6*}, **15**{*4*,*8*}, **15**{*4*,*11*}, **15**{*4*,*13*}, **16**{*1*,*5*}, **16**{*1*,*7*}, **16**{*1*,*11*}, **16**{*1*,*12*}, **16**{*2*,*2*}, **16**{*2*,*3*}, **16**{*2*,*13*}, **16**{*2*,*17*}, **16**{*3*,*4*}, **16**{*3*,*8*}, **16**{*3*,*14*}, **16**{*3*,*16*}, **16**{*4*,*1*}, **16**{*4*,*6*}, **16**{*4*,*15*}, and **16**{*4*,*18*}. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) von Bohlen und Halbach, O.; Dermietzel, R. *Neurotransmitters and Neuromodulators: Handbook of Receptors and Biological Effects*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2006.

(2) (a) Campbell, L. M. *Int. J. Clin. Pract.* **2002**, *56*, 783–790. (b) Skidmore, I. F.; Lunts, L. H. C.; Finch, H.; Naylor, A. Phenethanolamin-Verbindungen, Verfahren zu Ihrer Herstellung und Diese Verbindungen Enthaltende Arzneimittel. DE 3414752, October 18, 1984; *Chem. Abstr.* **1985**, *102*, 95383.

(3) (a) Johnson, D. S.; Li, J. J. *The Art of Drug Synthesis*; Wiley-Interscience: New York, 2007. (b) Yardley, J. P.; Husbands, G. E. M.; Stack, G.; Butch, J.; Bisckler, J.; Moyer, J. A.; Muth, E. A.; Andree, T.; Fletcher, H., III.; James, M. N. G.; Sieleck, A. R. *J. Med. Chem.* **1990**, *33*, 2899–2905. (c) Husbands, G. E. M.; Yardley, J. P.; Muth, E. A. 2-Phenyl-2-(1-hydroxycycloalkyl or 1-hydroxycycloalk-2-enyl)ethylamine Derivatives. U.S. Patent 4535186, August 13, 1985; *Chem. Abstr.* **1985**, *102*, 5895.

(4) Carlucci, D. R.; Aitken, M. IMS Intelligence.360, 2007. IMS Health Home Page. http://www.imshealth.com/ims/portal/front/articleC/0,2777,6266_41382706_81567488,00.html (accessed Jun 20, 2008).

(5) (a) Shulgin, A.; Shulgin, A. *Pihkal: A Chemical Love Story*; Transform Press, 1991. (b) Shulgin, A.; Shulgin, A. *Tihkal: The Continuation*; Transform Press, 1997.

(6) Matsukura, M.; Daiku, Y.; Ueda, K.; Tanaka, S.; Igarashi, T.; Minami, N. *Chem. Pharm. Bull.* **1992**, *40*, 1823–1827.

(7) (a) Brouillette, W. J.; Jestkov, V. P.; Brown, M. L.; Akhtar, M. S.; DeLorey, T. M.; Brown, G. B. *J. Med. Chem.* **1994**, *37*, 3289–3293. (b) Brouillette, W. J.; Brown, G. B.; DeLorey, T. M.; Liang, G. *J. Pharm. Sci.* **1990**, *79*, 871–874.

(8) Struck, R. F.; Kirk, M. C.; Rice, L. S.; Suling, W. J. *J. Med. Chem.* **1986**, *29*, 1319–1321.

(9) López-Rodríguez, M. L.; Rosado, M. L.; Benhamú, B.; Morcillo, M. J.; Sanz, A. M.; Orensanz, L.; Beneitez, M. E.; Fuentes, J. A.; Manzanares, J. *J. Med. Chem.* **1996**, *39*, 4439–4450.

(10) Al-Obaid, A. M.; El-Subbagh, H. I.; Khodair, A. I.; Eleazar, M. M. *Anticancer Drugs* **1996**, *7*, 873.

(11) Khodair, A. I.; El-Subbagh, H. I.; El-Emam, A. A. *Boll. Chim. Farm.* **1997**, *136*, 561–567.
(12) McNamara, J. O. Drugs Effective in the Therapy of the Epilepsies. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 10th ed.; Hardman, J. G., Limbird, L. E., Gilman, A. G., Eds.; McGraw-Hill: New York, 2001; Chapter 21, pp 528−531.
(13) (a) Boger, D. L.; Labroli, M. A.; Marsilje, T. H.; Jin, Q.; Hedrick, M. P.; Baker, S. J.; Shim, J. H.; Benkovic, S. J. *Bioorg. Med. Chem.* **2000**, *8*, 1075–1086. (b) Hruby, V. J. *Life Sci.* **1982**, *31*, 189–199.
(14) (a) Potin, D.; Launay, M.; Monatlik, F.; Malabre, P.; Fabreguettes, M.; Fouquet, A.; Maillet, M.; Nicolai, E.; Dorgeret, L.; Chevallier, F.; Besse, D.; Dufort, M.; Caussade, F.; Ahmad, S. Z.; Stetsko, D. K.; Skala, S.; Davis, P. M.; Balimane, P.; Patel, K.; Yang, Z.; Marathe, P.; Postelneck, J.; Townsend, R. M.; Goldfarb, V.; Sheriff, S.; Einspahr, H.; Kish, K.; Malley, M. F.; DiMarco, J. D.; Gougoutas, J. Z.; Kadiyala, P.; Cheney, D. L.; Tejwani, R. W.; Murphy, D. K.; Mcintyre, K. W.; Yang, X.; Chao, S.; Leith, L.; Xiao, Z.; Mathur, A.; Chen, B.-C.; Wu, D.-R.; Traeger, S. C.; McKinnon, M.; Barrish, J. C.; Robl, J. A.; Iwanowicz, E. J.; Suchard, S. J.; Dhar, T. G. M. *J. Med. Chem.* **2006**, *49*, 6946–6949. (b) Dhar, T. G. M.; Launay, M.; Potin, D.; Watterson, S. H.; Xiao, Z. Pyridyl-Substituted Spiro-Hydantoin Compounds and Use Thereof. Int. Patent WO 2006065919, June 22, 2006; *Chem. Abstr.* **2006**, *145*, 83333. (c) Delmonte, A. J.; Dhar, T. G. M.; Galella, M.; Gleeson, M.; Gougoutas, J. Z.; McLeod, D. D.; Zhang, H.; Chen, B.-C. Crystalline Forms of 6-[(5*S*,9*R*)-9-(4-Cyanophenyl)-3-(3,5-dichlorophenyl)-1-methyl-2,4-dioxo-1,3,7-triazaspiro[4.4]non-7-yl]nicotinic Acid. Int. Patent WO 2006065908, June 22, 2006; *Chem. Abstr.* **2006**, *145*, 83332. (d) Delmonte, A. J.; Dhar, T. G. M.; Fan, Y.; Gougoutas, J. Z.; Malley, M. F.; McLeod, D. D.; Waltermire, R. E.; Wei, C. Crystalline Forms and Process for Preparing Spiro-Hydantoin Compounds. Int. Patent WO 2006039639, April 13, 2006; *Chem. Abstr.* **2006**, *144*, 370092. (e) Dhar, T. G. M.; Potin, D.; Maillet, M. J. B.; Launay, M.; Nicolai, E. A.; Iwanowicz, E. J. Spiro-Hydantoin Compounds Useful as Anti-Inflammatory Agents. Int. Patent WO 03029245, April 10, 2003; *Chem. Abstr.* **2003**, *138*, 304285.
(15) Blanco-Ania, D.; Hermkens, P. H. H.; Sliedregt, L. A. J. M.; Scheeren, H. W.; Rutjes, F. P. J. T. *Tetrahedron*, [Online early access]. DOI: 10.1016/j.tet.2009.04.059. Published online: April 24, 2009.
(16) For a review about Knoevenagel condensation, see: Tietze, L. F.; Beifuss, U. The Knoevenagel Reaction. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, pp 341−394.
(17) Fornicola, R. S.; Oblinger, E.; Montgomery, J. *J. Org. Chem.* **1998**, *63*, 3528–3529.
(18) Kuster, G. J. T.; van Berkom, L. W. A.; Kalmoua, M.; van Loevezijn, A.; Sliedregt, L. A. J. M.; van Steen, B. J.; Kruse, C. G.; Rutjes, F. P. J. T.; Scheeren, H. W. *J. Comb. Chem.* **2006**, *8*, 85–94.
(19) (a) For a review of 1,3-dipolar cycloaddition reactions, see: Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1, pp 1−176. (b) For an excellent review of intramolecular 1,3-dipolar cycloaddition reactions with azomethine ylides, see: Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765–2809.
(20) For the formation of the ylide, see: Grigg, R.; Idle, J.; McMeekin, P.; Surendrakumar, S.; Vipond, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2703–2713 and references cited therein.
(21) Bordwell, F. G.; Algrim, D. J.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 5903–5904.
(22) Fuentes, J.; Salameh, B. A. B.; Pradera, M. A.; Fernández de Cordoba, F. J.; Gasch, C. *Tetrahedron* **2006**, *62*, 97–111.
(23) Mukerjee, A. K.; Ashare, R. *Chem. Rev.* **1991**, *91*, 1–24.

CC800190Z