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Novel and efficient synthesis of 4,7-dihydro-1*H*-pyrrolo[2,3-*b*] pyridine derivatives via one-pot, three-component approach from *N*-substituted 5-amino-3-cyanopyrroles, various carbonyl and active methylene compounds

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ABSTRACT

An efficient route to novel 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridines with incorporated tetrahedral fragment in the position-4 via three-component reaction of *N*-substituted 5-amino-3-cyanopyrroles, various carbonyl and active methylene compounds has been developed. In the same time, by using developed methods here, the 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridines with fused 4-spiro-frameworks were synthesized starting from isatins and a set of 1,2-dicarbonyl compounds. The reactions were carried out under mild conditions using ethanol, acetic acid or 1,4-dioxane as solvent.

1. Introduction

Multicomponent reactions (MCRs) make it possible to synthesize target molecules with great efficiency and atom economy.[1] Using this approach more than two adducts can be converted directly into product by one-pot simultaneous or sequential reaction. In contrast with multistep synthesis they are more efficient because several bonds are formed in one sequence without isolation of any intermediates.[2] Even when the first MCRs are dated by the middle of 19th century, a new interest has renewed for such reactions, not just because of minimization of waste, but also solvents, reagents, adsorbents, and energy are dramatically decreased. Because of the significant therapeutic potential associated with heterocyclic compounds such reactions, coupled with high-throughput biological screening, are one of the best tools to generate large compound-libraries for evaluation as lead or hit compounds in drug discovery.[1g]

1*H*-Pyrrolo[2,3-*b*]pyridine heterocyclic system can be considered as bioisosteres of the indole moiety, which represents important structure class in drug discovery.[3] The 1*H*-pyrrolo[2,3-*b*] pyridine framework is present in several natural products.[4] Despite of that this heterocyclic system has attracted considerable interest of the scientific community due its physicochemical and pharmacological properties.[5] For instance variolins, a group of marine heterocycle substances isolated from the Antarctic sponge *Kirkpatrickia variolosa*, have exhibited a potent cytotoxic activity against P388 murine leukaemia cell lines, particularly variolin B.[6,7] In addition azaindoles have also found applications in synthesis as prominent materials for electronic devices due to their luminescence properties,[8] and in coordination chemistry.[9] In contrary, the correspondent dihydro-analogues, namely 4,7-dihydro-1*H*-pyrrolo [2,3-*b*]pyridines are rear in the literature. Nevertheless, some scarce information indicates handful representatives manly containing 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine scaffold incorporated into the more complex polycyclic structure.[10] The 4-

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spiro-fused 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridines are not known to date.

Recently we have demonstrated the one-pot, three-component synthesis of 7-azaindole derivatives from *N*-substituted 5-amino-1*H*-pyrrole-3-carbonitriles, various aldehydes, and active methylene compounds.[11] As intermediates in some cases we have detected and succeed to isolate many 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridines. To our best knowledge this was the first synthetic method towards 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridines by multicomponent reaction as well as the first application of 5-aminopyrroles in multicomponent synthesis. Current work is a logical continuation of our previous research regarding the synthesis libraries of 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine derivatives; herein we detail a three-component reaction using different active ketones, 5-aminopyrroles and 1,3-dicarbonyl compounds to afford the 4-fused 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridines derivatives. The method discussed vide infra also can be applied to the construction 4-spiro-fused dihydro-1*H*-pyrrolo[2,3-*b*]pyridine libraries.

2. Results and discussion

During the last decade Iaroshenko's group[11] developed a series of new cyclocondensation reactions of electron-rich aminoheterocycles with 1,3-CCC- and 1,3-CNC-dielectrophiles, these resulted in the synthesis of many purines, purine-like scaffolds and purine isosteres. Using our recent experience[12] we have concentrated on developing synthetic methods towards the 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridines frameworks containing tetrahedral carbon nuclei in the postion-4 of the annulated 1,4-dihydropyridine ring. We have assumed the novelty of this scaffold and as result its possible application in the medicine chemistry and drug design as a potential target for the combinatorial aspect of biology-oriented synthesis (BIOS),[13] for the creation of natural-product-derived and natural-product-inspired compound libraries.

Previous reports have also shown that diverse spirocyclic compounds as well as pharmacologically relevant 3-spiro-fused oxindoles can be generated by using 5-aminopyrazoles.[14] However, to the best of our knowledge, the combinatorial synthesis of spiroxindoles fused with a 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine framework has not been reported hitherto. Thus, we envisioned that these scaffolds could be synthesized by a one-pot reaction of *N*-substituted 5-amino-3-cyanopyrroles, commercially available isatins and adequate 1,3-dicarbonyl compounds, such as Meldrum's acid **1a**, tetronic acid **1b**, 1,3-dimedione **1c** and 4-hydroxycoumarin **1d** (Fig. 1). To further explore the potential of this synthetic protocol, we also investigated the reactions with other 1,2-dicarbonyl compounds **2i**–**l** (Figs. 2 and 3).

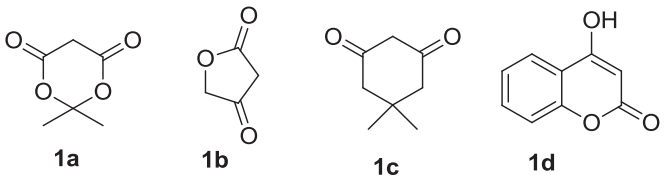

Fig. 1. 1,3-Dicarbonyl compounds **1** used for the synthesis of 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridines.

In our initial studies various conditions were evaluated to find an appropriate medium for the synthesis of spiroxindole derivatives. Initially, we tested the reaction of isatin **2a**, 5-amino-1-*tert*-butyl-pyrrole-3-carbonitrile **3a** and Meldrum's[15] acid **1a** in different solvents, including ethanol, dimethylformamide (DMF), acetic acid, acetic acid/proline,[11] acetic acid/ammonium acetate, and 1,4-dioxane. All the reactions of this model system were carried out first at room temperature, than the temperature was slowly increased until the reflux. The progress of the reaction was monitored by TLC. Performing the reaction in 1,4-dioxane the lowest yield of 30% for compound **4aa** was obtained, in contrary using DMF and ethanol we have reached 42 and 60% yields of the corresponding product **4aa**, respectively. Based on our previous work,[11] we thought that the using of ethanol as a solvent of choice and L-proline as a catalyst would be the best reaction condition for the current reaction, however, to our great disappointment the yield remained unchanged. When the reaction was conducted in acetic acid, surprisingly the yield of **4aa** aroused up to 70%. As a next logical step of our study, we decided to test the systems: acetic acid/L-proline and acetic acid/ammonium acetate as a reaction medium, the latest reaction conditions delivered product **4aa** in a yield of 81%. These were our solvent/base of choice to afford the required spiroxindoles derivatives **4** (Scheme 1, Table 1).

The procedure was simple and easy to operate, generally the reaction was completed after 6–8 h and precipitate, corresponding to the product, was formed in almost all the cases and was separated by simple filtration. As can be seen in Tables 1 and 2, the method probed into work with a wide variety of isatin substrates **2**, containing electron withdrawing or electron donating groups such as bromine, chlorine, nitro or trifluoromethoxy. *N*-Methyl substituted isatins also showed to be suitable for the reaction (Table 1, entries 2 and 8, and Table 2 entries 2, 6, 7 and 9). In all these cases good yields in the range from 51 to 86% were obtained (Table 1), except when 5-amino-1-cyclohexyl-1*H*-pyrrole-3-carbonitrile **3b** was used, in this case the yield went down to 30% (Table 2, entry 7). Previously, similar reaction mode has been reported with aminopyrazoles,[16] nevertheless the usage of 5-amino-3-cyanopyrroles **3** in the reactions of this type has not been documented in the literature. In the same time different cyclic active methylene compounds like **1b**, **c** were also used; the reaction in all cases delivered desired spiroxindoles **5** and **6** (Scheme 2). On the other hand, the introduction of 4-hydroxycoumarin **1d** in this reaction, as active β-dicarbonyl compound, afforded the spiroxindoles **7**. Previous reports have shown that when 4-hydroxycoumarin **1d** has been used, a cleavage of the coumarone ring can be possible.[17] As we have observed in this study, the reaction occurs via rupture of the C–O bond and consequent ring opening delivering corresponding products **7** (Scheme 2, Table 2). This reaction took place only in ethanol under reflux; other reaction conditions experienced a failure.

To explore the scope of this reaction to form new spiroheterocyclic derivatives, we investigated the use of acenaphtylene-1,2-dione **2i** to afford the *N*-substituted-2,6′-dioxo-1′,5′,6′,7′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitriles **8**–**10** (Scheme 3). As expected the reaction proceeded with fair to good yields using ethanol as a solvent and the reactions were under reflux (Table 3). In this case our standard reaction conditions, namely the acetic acid/ammonium acetate have shown less efficiency.

Finally, we decided to expand the versatility of this methodology using acyclic 1,2-dicarbonyl compounds **2j**–**l** such as methyl 2-oxo-2-phenylacetate **2j**, 3,4-hexadione **2k** and ethyl 2-oxopropanoate **2l** (Scheme 4). Unfortunately our optimal reaction condition developed for the synthesis of 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine series **4**–**10** experienced a failure when we set 1,2-dicarbonyl compounds **2j**–**l** under investigation.

On this stage we had to renovate the search of suitable reaction conditions. In order to find the optimal reaction medium we tested different solvents including ethanol, DMF, 1,4-dioxane and acetic acid. When we reacted methyl 2-oxo-2-phenylacetate **2j** with **1a** and **3b**, the acetic acid was in this case the best solvent isolated product **11ba** with 42% yield. Nevertheless when we carried out the reaction in two steps, first the condensation of Meldrum's acid with

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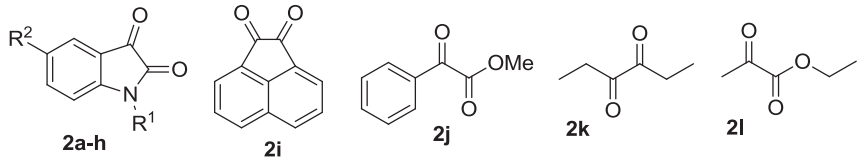


Isatins 2a-h	R^1	R^2
2a	H	H
2b	CH_3	H
2c	H	Cl
2d	H	OCF_3
2e	H	Br
2f	H	F
2g	H	NO_2
2h	Ph	H

Fig. 2. 1,2-Dicarbonyl compounds **2** used for the synthesis of 4,7-dihydro-1*H*-pyrrolo[2,3-*b*]pyridines.

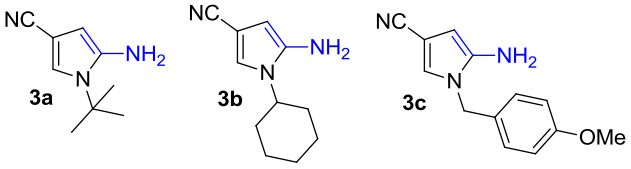


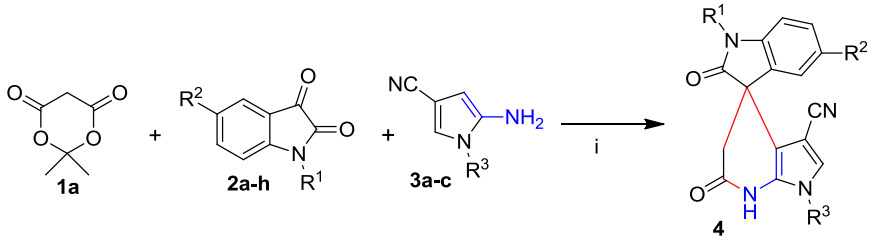
Fig. 3. 5-Aminopyrroles **3a**–**c** used for the synthesis of 4,7-dihydro-1*H*-pyrrolo[2,3-*b*] pyridines.

Table 1
Synthesis of compounds **4**

Entry	R^1	R^2	R^3	Product	Yield (%)
1	H	H	*tert*-Bu	**4aa**	81
2	CH_3	H	*tert*-Bu	**4ab**	73
3	H	Cl	*tert*-Bu	**4ac**	86
4	H	OCF_3	*tert*-Bu	**4ad**	52
5	H	Br	*tert*-Bu	**4ae**	51
6	H	F	*tert*-Bu	**4af**	75
7	H	NO_2	*tert*-Bu	**4af**	70
8	Ph	H	*tert*-Bu	**4ah**	55
9	H	F	Cyclohexyl	**4bf**	57
10	H	H	*p*-OMe–benzyl	**4cb**	58

methyl 2-oxo-2-phenylacetate **2j** in the presence of $TiCl_4$, according to the literature procedure,[18] and then cyclization with **3** in ethanol, the yield raised up to 77% (entry 4, Table 4). As following, with this reaction conditions in hand we synthesized the series of compounds **11aa**–**11cb**. In contrary, for the synthesis of compounds **12b**, **c** the best solvent was 1,4-dioxane; for all reactions good yields were obtained, however the use of methyl 2-oxo-2-phenylacetate **2j** and 3,4-hexadione **2k** showed to be more difficult to handle particularly with dimedone **1c** and 4-hydroxycoumarin **1d**. Next we have concentrated on the combination of dimedone **1c** and 4-hydroxycumarin **1d** with 1,2-dicarbonyl compounds **2j**–**l** and 5-aminopyrroles **3a**–**c** correspondingly. In these two cases the best reaction medium appeared to be ethanol and 1,4-dioxane under reflux (Table 4). Here it was not possible to gain excellent yields; nevertheless we succeed the synthesis of scaffolds **14** and **15** with fair yields in the range of 34–67%.

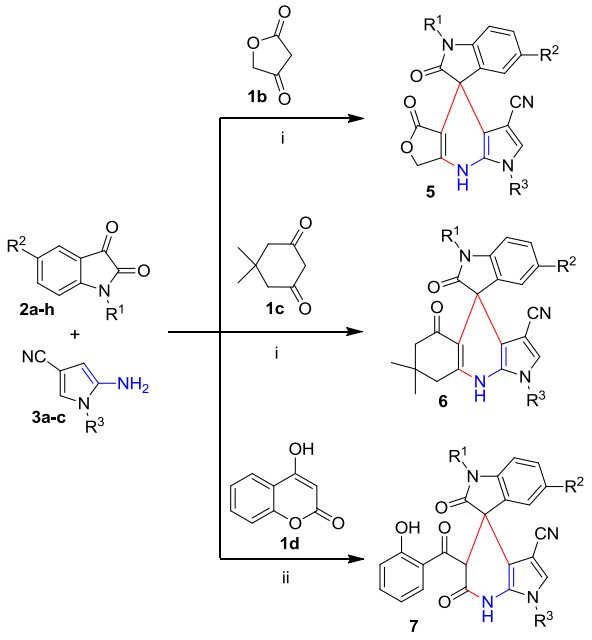
We tested also other compounds, on the first glance suitable for the multicomponent reactions, such as 3-thioisatin, ninhydrin and 2,2,2-trifluoro-1-phenylethanone. In the case of 3-thioisatin, even when it can be considered as an analogue of isatin, the reactivity of the carbonyl groups is completely different. The carbonyl group in the position-3 of the isatin is the reactive entity of the molecule, because of the carbonyl group in the position-2 belongs to an amide functionality and shows less reactivity. Contrary, the carbonyl groups in the 3-thioisatin are equally reactive or susceptible to suffer nucleophilic attacks with the equal velocity, resulting after reaction in a complex mixture that was not possible to separate, even when it was carried out at −10 °C. We wanted to probe the scope of the reaction by using a tricarbonyl compound. For that reason we took ninhydrin instead of isatin, but the reaction was unsuccessful. Then we tried the reaction in two steps, first the condensation with tetronic acid **1b**[19] and then the cyclization with the 5-aminopyrrole. Unfortunately, the latter step failed. The trifluoromethyl group, attached to the β-position of 1,2-dicetones, activates neighbouring carbonyl group; we thought that such compounds would be appropriate substrates for this chemistry, however the reaction did not work neither with 2,2,2-trifluoro-1-phenylethanone nor with 1,1,1-trifluoropropan-2-one under any of mentioned before conditions as well as by the protracted reflux in toluene, benzene, dichloromethane or chloroform with the set of



Scheme 1. Reactions of Meldrum's acid **1a** with isatins **2a**–**h** and 5-amino-3-cyanopyrroles **3**. Reaction conditions: (i) AcOH/$AcONH_4$, reflux.

Table 2
Synthesis of compounds **5**, **6**, **7**

Entry	R^1	R^2	R^3	Product	Yield (%)
1	H	H	*tert*-Bu	**5aa**	57
2	CH_3	H	*tert*-Bu	**5ab**	63
3	H	OCF_3	*tert*-Bu	**5ad**	37
4	H	Br	*tert*-Bu	**5ae**	64
5	H	F	*tert*-Bu	**5af**	61
6	Ph	H	*tert*-Bu	**5ah**	37
7	CH_3	H	Cyclohexyl	**5bb**	30
8	H	H	*tert*-Bu	**6aa**	79
9	CH_3	H	*tert*-Bu	**6ab**	57
10	H	Cl	*tert*-Bu	**6ac**	65
11	H	OCF_3	*tert*-Bu	**6ad**	64
12	H	NO_2	*tert*-Bu	**6ag**	66
13	H	H	Cyclohexyl	**6ba**	41
14	H	OCF_3	*tert*-Bu	**7ad**	69
15	H	NO_2	*tert*-Bu	**7ag**	38
16	H	H	Cyclohexyl	**7ba**	59



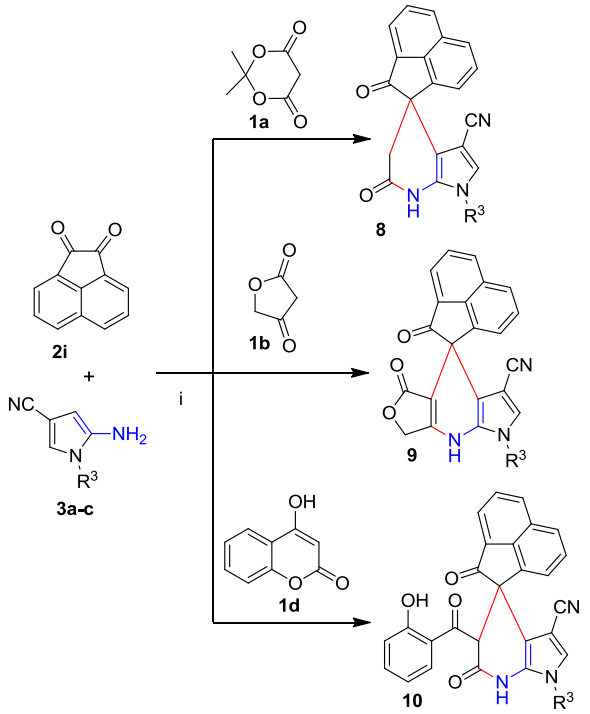
Scheme 2. Reactions of active methylene compounds **1b**–**d** with isatins **2a**–**h** and 5-amino-3-cyanopyrroles **3a**–**c**. Reaction conditions: (i) AcOH/$AcONH_4$, reflux; (ii) EtOH, reflux.

acidic catalysts such as PTSA, $TiCl_4$, $AlCl_3$, $AlBr_3$, AgO_2CCF_3, AgOTrf, $Bi(OTrf)_3$, $Zn(OTrf)_2$, and many other salts. Simple ketones, such as 1*H*-inden-2(3*H*)-one, cyclopropyl(phenyl)methanone as well as hydroxyketones such as 2-hydroxy-1,2-diphenylethanone did also not work, even after we tested the reaction in a variety of conditions.

Finally, the structures of several scaffolds synthesized, namely compounds **9bb** and **11cb** were corroborated by the means of 1D and 2D NMR methods and X-ray analysis (Figs. 1 and 2 in Supplementary data).[20]

3. Conclusion

In summary we have developed an efficient synthetic route to access in a one-pot manner new spirocyclic heterocyclic scaffolds containing 1,4-dihydropyridine framework. Furthermore we illustrated the versatility of this multicomponent reaction by using cyclic and non-cyclic 1,2-dicarbonyl substrates. In total about 50 new compounds, that can be used as substrates for both organic and medicinal research, were synthesized.



Scheme 3. Reactions of active methylene compounds **1a**, **b** and **1d** with 5-amino-3-cyanopyrroles **3** and **2i**. Reaction conditions: (i) EtOH, reflux.

Table 3
Synthesis of compounds **8**, **9**, **10**

Entry	R_3	Product	Yield (%)
1	*tert*-Bu	**8aa**	71
2	Cyclohexyl	**8ba**	55
3	*tert*-Bu	**9ab**	82
4	Cyclohexyl	**9bb**	73
5	*p*-MeO–benzyl	**9bd**	38
6	*tert*-Bu	**10ad**	65
7	Cyclohexyl	**10bd**	56
8	*p*-MeO–benzyl	**10dd**	35

4. Experimental part

4.1. General

The dry solvents ethanol and 1,4-dioxane were purchased directly from ACROS as AcroSeal bottles. Acetic acid was purchased from VWR. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane) or electrospray ionization (ESI). For preparative scale chromatography silica gel 60 (0.063–0.200 mm, 70–230 mesh) was used. Compounds **3** were obtained by method described previously; 1,2- and 1,3-dicarbonyl are commercially available compounds.

4.2. Procedure A—general procedure for the synthesis of compounds 4, 5, 6 and 7

A mixture of the corresponding 1,3-dicarbonyl compound (1 equiv), the corresponding isatin (1 equiv), 5-amino-1*H*-pyrrole-3-carbonitrile (1 equiv) and ammonium acetate (5 equiv) was refluxed in acetic acid for 4–6 h. For compounds **7** ethanol was used as a solvent without any base. The precipitate was collected and, if necessary, purified by column chromatography (eluent: *n*-heptane/ethylacetate).

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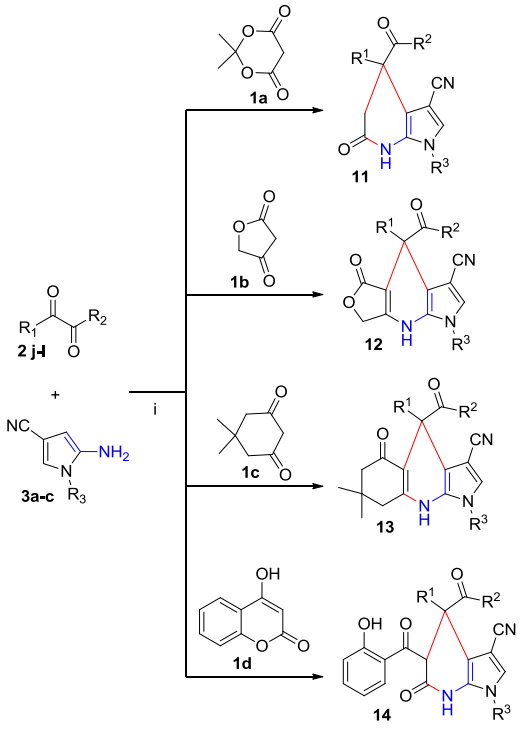

2	R^1	R^2
2j	Ph	OCH_3
2i	CH_3	OCH_2CH_3
2l	CH_3CH_2	CH_3CH_2

Scheme 4. Reactions of active methylene compounds **1a**–**d** with 5-amino-3-cyanopyrroles **3** and **2j**–**l**. Reaction conditions: (i) see the notes of Table 4.

Table 4
Synthesis of compounds **11**, **12**, **13**, **14**

Entry	R^1	R^2	R^3	Product	Yield (%)
1	Ph	OCH_3	*tert*-Bu	**11aa**	70[a]
2	CH_3	OCH_2CH_3	*tert*-Bu	**11ab**	73[a]
3	CH_3CH_2	CH_3CH_2	*tert*-Bu	**11ac**	70[a]
4	Ph	OCH_3	Cyclohexyl	**11ba**	77[a] (42)[b]
5	CH_3	OCH_2CH_3	Cyclohexyl	**11bb**	57[a]
6	Ph	OCH_3	*p*-MeO–benzyl	**11ca**	65[a]
7	CH_3	OCH_2CH_3	*p*-MeO–benzyl	**11cb**	68[a]
8	Ph	OCH_3	*tert*-Bu	**12aa**	42[c]
9	CH_3	OCH_2CH_3	*tert*-Bu	**12ab**	67[c]
10	CH_3	OCH_2CH_3	Cyclohexyl	**12bb**	40[c]
11	CH_3	OCH_2CH_3	*p*-MeO-benzyl	**12cb**	64[c]
12	CH_3	OCH_2CH_3	*tert*-Bu	**13ab**	55[d]
13	CH_3	OCH_2CH_3	Cyclohexyl	**13bb**	58[d]
14	CH_3	OCH_2CH_3	*tert*-Bu	**14ab**	67[c]
15	CH_3	OCH_2CH_3	Cyclohexyl	**14bb**	34[c]
16	CH_3	OCH_2CH_3	*p*-MeO-benzyl	**14cb**	47[c]

[a] Two-step sequential reaction after Ref. 18.
[b] AcOH reflux.
[c] 1,4-Dioxane reflux.
[d] EtOH reflux.

4.3. Procedure B—general procedure for the synthesis of compounds 8, 9, 10

A mixture of Meldrum's acid (1 equiv), the corresponding 1,2-dicarbonyl compound (1 equiv) and 5-amino-1*H*-pyrrole-3-carbonitrile derivative (1 equiv) was refluxed in ethanol 4–6 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent: *n*-heptane/ethylacetate).

4.4. Procedure C—general procedure for the synthesis of compounds 11, 12, 13 and 14

A mixture of the corresponding carbonyl compound (1 equiv), the corresponding 1,2-dicarbonyl compounds (1 equiv) and 5-amino-1*H*-pyrrole-3-carbonitrile (1 equiv) was added to 10 mL of ethanol (compounds **13**), 1,4-dioxane (compounds **14**), or acetic acid (compounds **12**) and heated under reflux for 4–6 h. The precipitate was collected and, if necessary, purified by column chromatography (eluent: *n*-heptane/ethylacetate).

For the preparation of compounds **11** the method communicated in Ref. 18 has particularly been used.

5. Analytical data

5.1. 1′-*tert*-Butyl-2,6′-dioxo-1′,5′,6′,7′-tetrahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (4aa)

The product was isolated as a light yellow solid, yield 81%, mp 291–293 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.56 (9H, s, $(CH_3)_3$), 2.66 (1H, d, J=15.8 Hz, CH_2), 2.81 (1H, d, J=15.8 Hz, CH_2), 6.89 (2H, m, Ar–H), 7.18 (2H, m, Ar–H), 7.35 (1H, s, Ar–H), 10.14 (1H, s, NH), 10.61 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 29.2 $(CH_3)_3$, 40.3 (CH_2), 46.2 (C–), 57.8 (C–), 86.1 (C–), 103.5 (C–), 109.8 (CH–), 114.6 (C–), 122.0 (CH–), 123.1 (CH–), 123.6 (CH–), 128.8 (CH–), 131.2 (C–), 131.4 (C–), 141.5 (C–), 168.4 (C–), 177.7 (C–); MS (GC, 70 eV): m/z (%) 334 (M^+, 49), 277 (89), 250 (68); HRMS (ESI): calcd for $C_{19}H_{19}N_4O_2$ (M+1) 335.1503, found 335.1507; IR (ATR, cm^{-1}): 3172 (w), 2230 (w), 1715 (s), 1672 (s), 1471 (m), 1208 (m), 748 (s), 606 (s).

5.2. 1′-*tert*-Butyl-1-methyl-2,6′-dioxo-1′,5′,6′,7′-tetrahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (4ab)

The product was isolated as a white solid, yield 73%, mp 326–327 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.59 (9H, s, $(CH_3)_3$), 2.77 (1H, d, J=15.7 Hz, CH_2), 2.84 (1H, d, J=15.7 Hz, CH_2), 3.19 (3H, s, NCH_3), 7.10 (2H, m, Ar–H), 7.20 (1H, d, J=7 Hz, Ar–H), 7.32–7.41 (2H, m, Ar–H), 10.23 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 26.1 (CH_3), 29.2 $(CH_3)_3$, 39.9 (CH_2), 45.8 (C–), 57.8 (C–), 86.0 (C–), 103.5 (C–), 108.9 (CH), 114.5 (C–), 122.7 (CH–), 123.0 (CH–), 123.2 (CH–), 128.9 (CH–), 130.8 (C–), 131.2 (C–), 142.8 (C–), 168.4 (C–), 175.9 (C–); MS (GC, 70 eV): m/z (%) 348 (M^+, 44), 291 (100), 250 (36); HRMS (ESI): calcd for $C_{20}H_{21}N_4O_2$ (M+1) 349.1659, found 349.1664; IR (ATR, cm^{-1}): 3140 (w), 2220 (w), 1704 (s), 1668 (s), 1614 (w), 1469 (m), 1347 (s), 1208 (m), 1008 (w), 742 (s), 626 (w).

5.3. 1′-*tert*-Butyl-5-chloro-2,6′-dioxo-1′,5′,6′,7′-tetrahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (4ac)

The product was isolated as a white solid, yield 86%, mp 334–335 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.59 (9H, s, $(CH_3)_3$), 2.68 (1H, d, J=15.7 Hz, CH_2), 3.03 (1H, d, J=15.7 Hz, CH_2), 6.93 (1H, d, J=8.3 Hz, Ar–H), 7.31 (2H, m, Ar–H), 7.41 (1H, s, Ar–H), 10.15 (1H, s, NH), 10.75 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 29.2 $(CH_3)_3$, 39.6 (CH_2), 46.4 (C–), 57.9 (C–), 86.0 (C–), 102.8 (C–), 111.2 (CH–), 114.5 (C–), 123.2 (CH–), 124.0 (CH–), 125.9 (C–), 128.8 (CH–), 131.4 (C–), 133.1 (C–), 140.7 (C–), 168.3 (C–), 177.5 (C–); MS (GC, 70 eV): m/z (%) 368 (M^+, 34), 311 (64), 284 (34); HRMS (ESI): calcd for $C_{19}H_{18}N_4O_2^{35}Cl$ (M+1) 369.1113, found 369.1114; IR (ATR, cm^{-1}): 3280 (w), 2229 (w), 1727 (s), 1698 (s), 1614 (w), 1471 (m), 1199 (m), 821 (s), 615 (w).

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5.4. 1′-*tert*-Butyl-2,6′-dioxo-5-(trifluoromethoxy)-1′,5′,6′,7′-tetrahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (4ad)

The product was isolated as white a solid, yield 52%, mp 299–300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.61 (9H, s, $(CH_3)_3$), 2.66 (1H, d, J=15.9 Hz, CH_2), 3.14 (1H, d, J=15.7 Hz, CH_2), 7.01 (1H, d, J=8.3 Hz, Ar–H), 7.24–7.35 (2H, m, Ar–H), 7.41 (1H, s, Ar–H), 10.17 (1H, s, NH), 10.78 (1H, s, NH); ^{19}F NMR (DMSO-d_6): δ −57.19; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 29.2 $(CH_3)_3$, 39.4 (CH_2), 46.6 (C–), 57.9 (C–), 86.1 (C–), 102.6 (C–), 110.6 (CH–), 114.0–126.2 (C–F, q, $^1J_{C-F}$=255.4 Hz), 114.3 (C–), 117.9 (CH–), 122.2 (CH–), 123.1 (CH–), 131.5 (C–), 132.6 (C–), 141.2 (C–), 143.5–143.4 (C–F, q, $^3J_{C-F}$=1.8 Hz), 168.3 (C–), 177.9 (C–); MS (GC, 70 eV): m/z (%) 418 (M^+, 28), 361 (46), 334 (24); HRMS (ESI): calcd for $C_{20}H_{18}F_3N_4O_3$ (M+1) 419.1326, found 419.1329; IR (ATR, cm^{-1}): 3202 (w), 2225 (w), 1714 (m), 1681 (s), 1482 (m), 1247 (m), 1206 (s), 1166 (s), 614 (w).

5.5. 5-Bromo-1′-*tert*-butyl-2,6′-dioxo-1′,5′,6′,7′-tetrahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (4ae)

The product was isolated as a white solid, yield 51%, mp 309–310 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.59 (9H, s, $(CH_3)_3$), 2.72 (1H, d, J=15.9 Hz, CH_2), 2.97 (1H, d, J=15.9 Hz, CH_2), 6.97 (1H, t, J=8.1 Hz, Ar–H), 7.20 (1H, d, J=7.0 Hz, Ar–H), 7.41 (1H, s, Ar–H), 7.46 (1H, dd, J_1=8.1 Hz, J_2=1 Hz, Ar–H), 10.20 (1H, s, NH), 10.94 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 29.2 $(CH_3)_3$, 40.0 (CH_2), 47.3 (C–), 57.9 (C–), 86.1 (C–), 102.1 (C–), 102.8 (C–), 114.5 (C–), 122.9 (CH–), 123.2 (CH–), 123.7 (CH–), 131.4 (C–), 131.8 (CH–), 132.9 (C–), 141.1 (C–), 168.2 (C–), 177.6 (C–); MS (GC, 70 eV): m/z (%) 412 (M^+, 22), 357 (38), 314 (25); HRMS (ESI): calcd for $C_{19}H^{79}_{18}BrN_4O_2$ (M+1) 413.0608, found 430.0612; IR (ATR, cm^{-1}): 3152 (w), 2227 (w), 1727 (s), 1677 (s), 1469 (m), 1321 (m), 1201 (m), 736 (s).

5.6. 1′-*tert*-Butyl-5-fluoro-2,6′-dioxo-1′,5′,6′,7′-tetrahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (4af)

The product was isolated as a brown solid, yield 75%, mp 277–279 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.59 (9H, s, $(CH_3)_3$), 2.64 (1H, d, J=15.7 Hz, CH_2), 3.04 (1H, d, J=15.7 Hz, CH_2), 6.90 (1H, dd, J_1=8.3 Hz, J_2=4.3 Hz, Ar–H), 7.11 (2H, m, Ar–H), 7.40 (1H, s, Ar–H), 10.14 (1H, s, NH), 10.62 (1H, s, NH); ^{19}F NMR (DMSO-d_6): δ −121.1; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 29.2 $(CH_3)_3$, 39.7 (CH_2–), 46.6–46.7 (C–F, d, $^{4'}J_{C-F}$=1.8 Hz), 57.9 (C–), 86.1 (C–), 102.9 (C–), 110.6–110.7 (C–F, d, $^{3'}J_{C-F}$=7.8 Hz), 111.7–111.9 (C–F, d, $^{2'}J_{C-F}$=24.7 Hz), 114.5 (C–), 115.0–115.4 (C–F, d, $^2J_{C-F}$=23.4 Hz), 123.2 (CH–), 131.4 (C–), 132.6–132.7 (C–F, d, $^3J_{C-F}$=8.2 Hz), 138.0–138.1 (C–F, d, $^4J_{C-F}$=1.83 Hz), 156.3–160.1 (C–F, d, $^1J_{C-F}$=237 Hz), 177.8 (C–), 168.3 (C–); MS (GC, 70 eV): m/z (%) 352 (M^+, 44), 295 (67), 268 (40); HRMS (ESI): calcd for $C_{19}H_{18}FN_4O_2$ (M+1) 353.1408, found 353.1412; IR (ATR, cm^{-1}): 3207 (w), 2220 (w), 1657 (s), 1651 (s), 1486 (m), 1200 (m), 821 (w), 612 (w).

5.7. 1′-*tert*-Butyl-5-nitro-2,6′-dioxo-1′,5′,6′,7′-tetrahydrospiro [indoline-3,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (4ag)

The product was isolated as a brown solid, yield 70%, mp 331–333 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.60 (9H, s, $(CH_3)_3$), 2.73 (1H, d, J=15.7 Hz, CH_2), 3.27 (1H, d, J=15.7 Hz, CH_2), 7.13 (1H, d, J=8.7 Hz, Ar–H), 7.43 (1H, s, Ar–H), 8.18 (1H, d, J=2.3 Hz, Ar–H), 8.27 (1H, dd, J_1=8.7 Hz, J_2=2.3 Hz, Ar–H), 10.25 (1H, s, NH), 11.33 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 29.2 $(CH_3)_3$, 38.9 (CH_2–), 46.2 (C–), 58.0 (C–), 85.8 (C–), 102.1 (C–), 110.1 (CH–), 114.5 (C–), 119.9 (CH–), 123.4 (CH–), 126.3 (CH–), 131.7 (C–), 132.0 (C–), 142.4 (C–), 148.6 (C–), 168.2 (C–), 178.3 (C–); HRMS (ESI): calcd for $C_{19}H_{18}N_5O_4$ (M+1) 380.1353, found 380.1357; IR (ATR, cm^{-1}): 3212 (w), 2227 (w), 1748 (m), 1690 (s), 1326 (s), 1202 (s), 1079 (w).

5.8. 1′-*tert*-Butyl-2,6′-dioxo-1-phenyl-1′,5′,6′,7′-tetrahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (4ah)

The product was isolated as a white solid, yield 55%, mp 310–312 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.62 (9H, s, $(CH_3)_3$), 2.97 (1H, d, J=15.7 Hz, CH_2), 3.03 (1H, d, J=15.7 Hz, CH_2), 6.78 (1H, d, J=7.7 Hz, Ar–H), 7.14 (1H, m, Ar–H), 7.30 (2H, m, Ar–H), 7.45 (1H, s, Ar–H), 7.52 (3H, m, Ar–H), 7.63 (2H, m, Ar–H), 10.31 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 29.2 $(CH_3)_3$, 40.1 (CH_2–), 46.1 (C–), 57.9 (C–), 85.9 (C–), 103.7 (C–), 109.3 (CH–), 114.9 (C–), 123.2 (CH–), 123.3 (CH–), 123.6 (CH–), 126.9 (CH–), 128.3 (CH–), 129.0 (CH–), 129.6 (CH–), 130.8 (C–), 131.2 (C–), 134.1 (C–), 142.7 (C–), 168.3 (C–), 175.5 (C–); MS (GC, 70 eV): m/z (%) 410 (M^+, 45), 353 (100), 325 (64); HRMS (ESI): calcd for $C_{25}H_{23}N_4O_2$ (M+1) 411.1816, found 411.1818; IR (ATR, cm^{-1}): 3149 (w), 2220 (w), 1725 (s), 1678 (s), 1605 (m), 1495 (m), 1327 (m), 1204 (m), 752 (s), 693 (m).

5.9. 1′-Cyclohexyl-5-fluoro-2,6′-dioxo-1′,5′,6′,7′-tetrahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (4bf)

The product was isolated as a white solid, yield 55%, mp 235–237 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16–1.28 (1H, m, *c*-Hex–H), 1.33–1.49 (2H, m, *c*-Hex–H), 1.54–1.73 (3H, m, *c*-Hex–H), 1.77–2.00 (4H, m, *c*-Hex–H), 2.63 (1H, d, J=15.9 Hz, CH_2), 3.08 (1H, d, J=15.9 Hz, CH_2), 4.08–4.22 (1H, m, *c*-Hex–H), 6.91 (1H, dd, J_1=8.2 Hz, J_2=4.3 Hz, Ar–H), 7.14 (2H, m, Ar–H), 7.44 (1H, s, Ar–H), 10.60 (1H, s, NH), 10.77 (1H, s, OH); ^{19}F NMR (DMSO-d_6): δ −121.3; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.5 (CH_2–), 24.9 (CH_2), 24.9 (CH_2), 32.8 (CH_2), 32.9 (CH_2), 46.9–47.0 (C–F, d, $^{4'}J_{C-F}$=1.4 Hz), 54.1 (CH_2), 87.2 (C–), 99.6 (C–), 110.6–110.5 (C–F, d, $^{3'}J_{C-F}$=8.2 Hz), 111.9–111.6 (C–F, d, $^2J_{C-F}$=24.7 Hz), 114.5 (C–), 115.3–114.9 (C–F, d, $^{2'}J_{C-F}$=23.4 Hz), 121.7 (CH–), 131.5 (C–), 132.9–132.7 (C–F, d, $^3J_{C-F}$=8.2 Hz), 138.08–138.1 (C–F, d, $^4J_{C-F}$=1.4 Hz), 160.1–156.3 (C–F, d, $^1J_{C-F}$=237.1 Hz), 168.1 (C–), 178.1 (C–); MS (GC, 70 eV): m/z (%) 378 (M^+, 100), 295 (44), 268 (45); HRMS (EI): calcd for $C_{21}H_{19}N_4FO_2$ (M+1) 378.1487, found 378.1487; IR (ATR, cm^{-1}): 3220 (w), 2220 (w), 1720 (s), 1705 (s), 1486 (s), 1175 (m), 600 (s). Anal. Calcd for $C_{21}H_{19}FN_4O_2$: C, 66.66; H, 5.06; N, 14.81. Found: C, 66.27; H, 5.07; N, 14.84.

5.10. 1′-(4-Methoxybenzyl)-1-methyl-2,6′-dioxo-1′,5′,6′,7′-tetrahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (4cb)

The product was isolated as a white solid, yield 58%, mp 224–226 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.69–2.75 (1H, dd, J=16.1 Hz, CH_2), 2.88–2.94 (1H, dd, J=15.9 Hz, CH_2), 3.18 (3H, s, NCH_3), 3.77 (3H, s, OCH_3), 5.14 (2H, s, CH_2), 6.98 (2H, d, J=8.5 Hz, Ar–H), 7.10 (2H, m, Ar–H), 7.24 (3H, m, Ar–H), 7.37 (2H, m, Ar–H), 10.96 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 26.1 (CH_3), 39.9 (CH_2), 46.1 (C–), 48.3 (CH_2), 55.1 (OCH_3–), 87.3 (C–), 100.8 (CH–), 108.8 (C–), 114.1 (CH–), 114.2 (C–), 122.7 (CH–), 123.2 (CH–), 124.8 (CH–), 128.4 (C–), 128.9 (CH–), 129.0 (CH–), 130.7 (C–), 131.9 (C–), 143.0 (C–), 158.9 (C–), 168.2 (C–), 176.1 (C–); MS (GC, 70 eV): m/z (%) 412 (M^+, 10), 121 (100); HRMS (ESI): calcd for $C_{24}H_{20}N_4O_3$ (M+1) 413.1608, found 413.1600; IR (ATR, cm^{-1}): 3102 (w), 2217 (w), 1688 (s), 1682 (s), 1606 (m), 1515 (m), 1288 (m), 1256 (m), 1173

(m), 1131 (m), 757 (s). Anal. Calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.59; H, 4.84; N, 13.51.

5.11. 1-*tert*-Butyl-2′,5-dioxo-1,5,7,8-tetrahydrospiro[furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine-4,3′-indoline]-3-carbonitrile (5aa)

The product was isolated as a white solid, yield 57%, mp 302–304 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.62 (9H, s, $(CH_3)_3$), 5.00 (2H, s, CH_2), 6.88 (3H, m, Ar–H), 7.19 (1H, m, Ar–H), 7.40 (1H, s, Ar–H), 10.06 (1H, s, NH), 10.54 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 28.9 $(CH_3)_3$, 47.7 (C–), 57.5 (C–), 65.9 (CH_2), 86.5 (C–), 95.5 (C–), 103.5 (C–), 109.3 (CH–), 114.3 (C–), 121.7 (CH–), 124.1 (CH–), 124.4 (CH–), 128.4 (CH–), 129.6 (C–), 134.6 (C–), 141.8 (C–), 158.1 (C–), 170.2 (C–), 177.7 (C–); MS (GC, 70 eV): *m*/*z* (%) 372 (M^+, 36), 316 (100), 274 (64); HRMS (ESI): calcd for $C_{21}H_{19}N_4O_3$ (M+1) 375.1452, found 375.1451; IR (ATR, cm^{-1}): 3265 (w), 2224 (w), 1710 (s), 1638 (s), 1536 (s), 1512 (s), 1469 (m), 1332 (s), 1199 (m), 1056 (m), 759 (s). Anal. Calcd for $C_{21}H_{18}N_4O_3$: C, 67.37; H, 4.85; N, 14.88. Found: C, 67.07; H, 4.85; N, 15.04.

5.12. 1-*tert*-Butyl-1′-methyl-2′,5-dioxo-1,5,7,8-tetrahydrospiro[furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine-4,3′-indoline]-3-carbonitrile (5ab)

The product was isolated as a white solid, yield 63%, mp 327–329 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.58 (9H, s, $(CH_3)_3$), 3.16 (3H, s, CH_3), 4.99 (2H, s, CH_2), 6.98 (3H, m, Ar–H), 7.26 (1H, m, Ar–H), 7.36 (1H, s, Ar–H), 10.10 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 26.1 (CH_3–), 28.9 $(CH_3)_3$, 47.2 (C–), 57.5 (C–), 66.0 (CH_2–), 86.2 (C–), 95.0 (C–), 103.8 (C–), 108.2 (CH–), 114.3 (C–), 122.5 (CH–), 124.0 (CH–), 128.6 (CH–), 129.4 (C–), 133.9 (C–), 143.0 (C–), 158.4 (C–), 170.2 (C–), 176.1 (C–); MS (GC, 70 eV): *m*/*z* (%) 388 (M^+, 68), 360 (37), 304 (67); HRMS (ESI): calcd for $C_{22}H_{21}N_4O_3$ (M+1) 389.1611, found 389.1608; IR (ATR, cm^{-1}): 3260 (w), 2230 (w), 1738 (s), 1687 (s), 1641 (s), 1539 (m), 1514 (m), 1029 (m), 752 (s). Anal. Calcd for $C_{21}H_{18}N_4O_3$: C, 68.03; H, 5.34; N, 14.42. Found: C, 67.60; H, 5.34; N, 14.23.

5.13. 1-*tert*-Butyl-2′,5-dioxo-5′-(trifluoromethoxy)-1,5,7,8-tetrahydrospiro[furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine-4,3′-indoline]-3-carbonitrile (5ad)

The product was isolated as a white solid, yield 37%, mp 303–305 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.63 (9H, s, $(CH_3)_3$), 5.02 (2H, s, CH_2), 6.95 (2H, m, Ar–H), 7.23 (1H, dd, J_1=8 Hz, J_2=1 Hz, Ar–H), 7.44 (1H, s, Ar–H), 10.14 (1H, br s, NH), 10.76 (1H, s, NH); ^{19}F NMR (DMSO-d_6): δ −57.13; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 28.8 $(CH_3)_3$, 48.1 (C–), 57.5 (C–), 66.0 (CH_2–), 86.2 (C–), 94.7 (C–), 102.6 (C–), 110.1 (CH–), 114.0–126.2 (C–F, q, $^1J_{C-F}$=251.7 Hz), 114.1 (C–), 118.0 (CH–), 121.7 (CH–), 124.3 (CH–), 129.7 (C–), 135.8 (C–), 141.1 (C–), 143.4–143.5 (C–F, q, $^3J_{C-F}$=1.8 Hz), 158.5 (C–), 170.2 (C–), 177.8 (C–); MS (GC, 70 eV): *m*/*z* (%) 456 (M^+, 27), 400 (100), 358 (44); HRMS (ESI): calcd for $C_{22}H_{18}N_4O_4F_4$ (M+1) 459.1275, found 459.1272; IR (ATR, cm^{-1}): 3271 (w), 2224 (w), 1714 (s), 1639 (s), 1537 (m), 1515 (m), 1199 (s), 1053 (m), 1024 (m), 803 (m). Anal. Calcd for $C_{22}H_{17}N_4O_4F_4$: C, 57.64; H, 3.74; N, 12.22. Found: C, 57.35; H, 3.67; N, 11.82.

5.14. 5′-Bromo-1-*tert*-butyl-2′,5-dioxo-1,5,7,8-tetrahydrospiro[furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine-4,3′-indoline]-3-carbonitrile (5ae)

The product was isolated as a yellow solid, yield 64%, mp 287–289 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.62 (9H, s, $(CH_3)_3$), 5.00 (2H, s, CH_2), 6.82 (1H, d, J=8.3 Hz, Ar–H), 7.10 (1H, d, J=2.1 Hz, Ar–H), 7.38 (1H, dd, J_1=8.1 Hz, J_2=2.1 Hz, Ar–H), 7.43 (1H, s, Ar–H), 10.12 (1H, s, NH), 10.70 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 28.8 $(CH_3)_3$, 47.8 (C–), 57.5 (C–), 66.0 (CH_2), 86.2 (C–), 94.8 (C–), 102.7 (C–), 111.3 (CH–), 113.4 (C–), 114.3 (C–), 124.3 (CH–), 127.2 (CH–), 129.7 (C–), 131.3 (CH–), 136.7 (C–), 141.1 (C–), 158.4 (C–), 170.2 (C–), 177.3 (C–); MS (GC, 70 eV): *m*/*z* (%) 452 (M^+, 33), 394 (100), 352 (38); HRMS (ESI): calcd for $C_{21}H_{18}N_4O_3Br$(M+1) 453.0556, found 453.0555; IR (ATR, cm^{-1}): 3163 (w), 2227 (w), 1711 (s), 1632 (s), 1537 (s), 1516 (s), 1199 (m), 813 (m).

5.15. 1-*tert*-Butyl-5′-fluoro-2′,5-dioxo-1,5,7,8-tetrahydrospiro[furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine-4,3′-indoline]-3-carbonitrile (5af)

The product was isolated as a white solid, yield 61%, mp 274–276 °C. ^{1}H NMR (250 MHz, DMSO-d_6): δ 1.63 (9H, s, $(CH_3)_3$), 5.01 (2H, s, CH_2), 6.85 (2H, m, Ar–H), 7.01–7.02 (1H, m, Ar–H), 7.43 (1H, s, Ar–H), 10.11 (1H, s, NH), 10.53 (1H, s, NH); ^{19}F NMR (DMSO-d_6): δ −122.01; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 34.1 $(CH_3)_3$, 53.4 (C–), 53.3–53.4 (C–F, d, $^{4'}J_{C-F}$=1.8 Hz), 62.7 (C–), 71.2 (CH_2), 91.5 (C–), 100.2 (C–), 108.1 (C–), 115.3–115.2 (C–F, d, $^3J_{C-F}$=7.8 Hz), 117.5–117.1 (C–F, d, $^2J_{C-F}$=24.3 Hz), 119.5 (C–), 120.2–119.8 (C–F, d, $^{2'}J_{C-F}$=23.4 Hz), 129.5 (CH), 134.9 (C–), 141.3–141.1 (C–F, d, $^{3'}J_{C-F}$=7.3 Hz), 143.3–143.2 (C–F, d, $^4J_{C-F}$=1.8 Hz), 161.6–165.4 (C–F, d, $^1J_{C-F}$=237.1 Hz), 175.4 (C–), 163.6 (C–), 183.0 (C–); MS (GC, 70 eV): *m*/*z* (%) 390 (M^+, 36), 334 (100), 292 (51); HRMS (ESI): calcd for $C_{21}H_{18}FN_4O_3$ (M+1) 393.1357, found 393.1353; IR (ATR, cm^{-1}): 3169 (w), 2229 (w), 1712 (s), 1630 (s), 1537 (s), 1486 (s), 1198 (m), 1026 (m), 800 (m).

5.16. 1-*tert*-Butyl-2′,5-dioxo-1′-phenyl-1,5,7,8-tetrahydrospiro[furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine-4,3′-indoline]-3-carbonitrile (5ah)

The product was isolated as a light yellow solid, yield 37%, mp 327–329 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.64 (9H, s, $(CH_3)_3$), 5.06 (2H, s, CH_2), 6.68 (1H, d, J=7.7 Hz, Ar–H), 7.07 (2H, m, Ar–H), 7.24 (1H, m, Ar–H), 7.50 (4H, m, Ar–H), 7.63 (2H, m, Ar–H), 10.19 (5H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 28.9 $(CH_3)_3$, 47.5 (C–), 57.6 (C–), 66.2 (CH_2), 86.3 (C–), 95.5 (C–), 103.6 (C–), 108.5 (CH–), 114.7 (C–), 123.1 (CH–), 124.3 (CH–), 124.7 (CH–), 126.9 (CH–), 128.2 (CH–), 128.7 (CH–), 129.6 (CH–), 129.7 (C–), 133.5 (C–), 134.6 (C–), 142.9 (C–), 158.2 (C–), 170.3 (C–), 175.6 (C–); MS (GC, 70 eV): *m*/*z* (%) 3450 (M^+, 85), 422 (96), 366 (100); HRMS (ESI): calcd for $C_{27}H_{22}N_4O_3$ (M) 450.1686, found 450.1688; IR (ATR, cm^{-1}): 3273 (w), 2224 (w), 1747 (m), 1690 (s), 1655 (s), 1533 (m), 1513 (m), 1197 (m), 1030 (s), 765 (m). Anal. Calcd for $C_{27}H_{22}N_4O_3$: C, 71.99; H, 4.92; N, 12.44. Found: C, 71.61; H, 5.06; N, 12.14.

5.17. 1-Cyclohexyl-1′-methyl-2′,5-dioxo-1,5,7,8-tetrahydrospiro[furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine-4,3′-indoline]-3-carbonitrile (5bb)

The product was isolated as a light yellow solid, yield 30%, mp 352–355 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14–1.29 (1H, m, CH), 1.33–1.49 (2H, m, CH), 1.56–1.75 (3H, m, CH), 1.83–1.93 (4H, m, CH), 3.19 (3H, s, CH_3), 3.86–4.22 (1H, m, CH), 5.05 (2H, s, CH_2), 7.02 (3H, m, Ar–H), 7.30 (1H, m, Ar–H), 7.45 (1H, s, Ar–H), 10.75 (1H, br s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.5 (CH_2), 25.0 (CH_2), 26.0 (CH_3), 32.6 (CH_2), 47.2 (C–), 54.8 (CH), 65.4 (CH_2), 87.4 (C–), 95.3 (C–), 101.7 (C–), 108.2 (CH–), 114.3 (C–), 122.5 (CH–), 122.7 (CH–), 124.0 (CH–), 128.6 (CH–), 129.7 (C–), 133.8 (C–), 142.9 (C–), 158.6 (C–), 170.2 (C–), 176.1 (C–); MS (GC, 70 eV): *m*/*z* (%) 414 (M^+, 83), 386 (100), 370 (48); HRMS (ESI): calcd for $C_{24}H_{22}N_4O_3$ (M+1) 414.1686, found 414.1696; IR (ATR, cm^{-1}): 3136 (w), 2229 (w), 1744 (m), 1725 (m), 1681 (s), 1647 (s), 1551 (s), 1334 (m), 1222 (m), 1027 (m), 757 (s).

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5.18. 1′-*tert*-Butyl-7′,7′-dimethyl-2,5′-dioxo-1′,5′,6′,7′,8′,9′-hexahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]quinoline]-3′-carbonitrile (6aa)

The product was isolated as a orange solid, yield 79%, mp 304–305 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.04 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.63 (9H, s, $(CH_3)_3$), 1.97–2.20 (2H, m, CH_2), 2.72 (2H, d, J=16.1 Hz, CH_2), 6.80 (3H, m, Ar–H), 7.10 (1H, m, Ar–H), 7.32 (1H, s, Ar–H), 8.77 (1H, br s, NH), 10.26 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 26.7 (CH_3–), 28.4 (CH_3–), 29.2 $(CH_3)_3$, 32.0 (C–), 41.0 (CH_2–), 49.3 (CH_2–), 50.3 (C–), 57.3 (C–), 86.1 (C–), 104.1 (C–), 106.1 (C–), 108.7 (CH–), 114.5 (C–), 120.9 (CH–), 122.7 (CH–), 123.8 (CH–), 127.2 (CH), 127.9 (C–), 137.2 (C–), 142.0 (C–), 151.8 (C–), 179.3 (C–), 193.1 (C–); MS (GC, 70 eV): m/z (%) 412 (M^+, 14), 370 (42), 314 (100); HRMS (ESI): calcd for $C_{25}H_{27}N_4O_2$ (M+1) 415.2128, found 415.2122; IR (ATR, cm^{-1}): 3314 (w), 3115 (w), 2219 (w), 1708 (s), 1613 (s), 1524 (s), 1505 (s), 1469 (m), 1329 (m), 1209 (m), 747 (m).

5.19. 1′-*tert*-Butyl-1,7′,7′-trimethyl-2,5′-dioxo-1′,5′,6′,7′,8′,9′-hexahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]quinoline]-3′-carbonitrile (6ab)

The product was isolated as a light yellow solid, yield 57%, mp 300–307 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.61 (9H, s, $(CH_3)_3$), 2.02 (2H, dd, J_1=34.5 Hz, J_2=13 Hz, CH_2), 2.72 (2H, dd, J_1=17 Hz, J_2=7.6 Hz, CH_2), 3.16 (3H, s, CH_3), 6.86 (3H, m, Ar–H), 7.20 (1H, m, Ar–H), 7.30 (1H, s, Ar–H), 8.83 (1H, br s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 25.6 (CH_3), 26.6 (CH_3), 28.5 (CH_3), 29.1 $(CH_3)_3$, 32.0 (C–), 40.9 (CH_2), 48.9 (C–), 50.2 (CH_2), 57.3 (C–), 85.8 (C–), 104.5 (C–), 105.7 (C–), 107.5 (CH–), 114.7 (C–), 121.7 (CH–), 122.4 (CH–), 123.7 (CH–), 127.4 (CH–), 127.9 (C–), 136.4 (C–), 143.0 (C–), 152.1 (C–), 177.8 (C–), 193.1 (C–); HRMS (ESI): calcd for $C_{26}H_{29}N_4O_2$ (M+1) 429.2285, found 429.2286; IR (ATR, cm^{-1}): 3301 (w), 2220 (w), 1693 (s), 1606 (s), 1525 (s), 1504 (s), 1327 (m), 1207 (s), 746 (s).

5.20. 1′-*tert*-Butyl-5-chloro-7′,7′-dimethyl-2,5′-dioxo-1′,5′,6′,7′,8′,9′-hexahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]quinoline]-3′-carbonitrile (6ac)

The product was isolated as a white solid, yield 65%, mp 312–315 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.61 (9H, s, $(CH_3)_3$), 2.07 (2H, dd, J=1 Hz, CH_2), 2.70 (9H, dd, J=1 Hz, CH_2), 6.76 (2H, m, Ar–H), 7.14 (1H, dd, J_1=8 Hz, J_2=2 Hz, Ar–H), 7.33 (1H, s, Ar–H), 8.82 (1H, br s, NH), 10.41 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 27.1 (CH_3–), 28.0 (CH_3–), 29.1 $(CH_3)_3$, 32.0 (C–), 40.9 (CH_2–), 49.7 (C–), 50.2 (CH_2–), 57.4 (C–), 85.9 (C–), 103.2 (C–), 105.6 (C–), 110.1 (CH–), 114.4 (C–), 122.7 (CH–), 124.1 (CH–), 124.8 (C–), 127.1 (CH–), 128.0 (C–), 139.0 (C–), 141.2 (C–), 152.3 (C–), 179.0 (C–), 193.3 (C–); MS (GC, 70 eV): m/z (%) 446 (M^+, 16), 404 (41), 348 (100); HRMS (ESI): calcd for $C_{25}H_{26}ClN_4O_2$ (M+1) 449.1740, found 449.1746; IR (ATR, cm^{-1}): 3311 (w), 2216 (w), 1711 (s), 1614 (s), 1525 (s), 1506 (s), 1208 (m), 811 (m), 559 (s).

5.21. 1′-*tert*-Butyl-7′,7′-dimethyl-5′-methylene-2-oxo-5-(trifluoromethoxy)-1′,5′,6′,7′,8′,9′-hexahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]quinoline]-3′-carbonitrile (6ad)

The product was isolated as a yellow solid, yield 64%, mp 230–232 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.62 (9H, s, $(CH_3)_3$), 2.08 (2H, dd, J_1=17.2 Hz, J_2=22.5 Hz, CH_2), 2.70 (2H, dd, J_1=16.5 Hz, J_2=45.5 Hz CH_2), 6.73 (1H, s, Ar–H), 6.84 (1H, d, J=8.3 Hz, Ar–H), 7.10 (1H, d, J=7.4 Hz, Ar–H), 7.34 (1H, s, Ar–H), 8.91 (1H, br s, NH), 10.47 (1H, s, NH); ^{19}F NMR (DMSO-d_6): δ –57.27; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 26.4 (CH_3), 28.4 (CH_3), 29.1 (CH_3), 32.0 (C–), 41.1 (CH_2), 49.8 (C–), 50.2 (CH_2), 57.4 (C–), 85.9 (C–), 103.1 (C–), 105.4 (C–), 109.3 (CH–), 114.0 (C–), 114.4–126.2 (C–F, q, J_{C-F}=254.9 Hz), 116.2 (CH–), 120.3 (CH–), 124.0 (CH–), 128.4 (C–), 138.6 (C–), 141.3 (C–), 142.9–142.8 (C–F, q, $^3J_{C-F}$=1.9 Hz), 152.4 (C–), 179.4 (C–), 193.1 (C–); MS (GC, 70 eV): m/z (%) 496 (M^+, 15), 454 (27), 398 (100); HRMS (ESI): calcd for $C_{26}H_{26}F_3N_4O_3$ (M+1) 499.1951, found 499.1458; IR (ATR, cm^{-1}): 3290 (w), 2224 (w), 1710 (s), 1608 (s), 1526 (s), 1504 (s), 1486 (m), 1262 (s), 1191 (m).

5.22. 1′-*tert*-Butyl-7′,7′-dimethyl-5-nitro-2,5′-dioxo-1′,5′,6′,7′,8′,9′-hexahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]quinoline]-3′-carbonitrile (6ag)

The product was isolated as a yellow solid, yield 66%, mp 273–275 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.04 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.63 (9H, s, $(CH_3)_3$), 2.09 (2H, dd, J_1=16.2 Hz, J_2=20.1 Hz, CH_2), 2.76 (2H, dd, J_1=26.5 Hz, J_2=17.2 Hz, CH_2), 7.00 (1H, d, J=8.7 Hz, Ar–H), 7.38 (1H, s, Ar–H), 7.62 (1H, d, J=1.9 Hz, Ar–H), 8.13 (1H, dd, J_1=8.5 Hz, J_2=2.1 Hz, Ar–H), 11.10 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 27.2 (CH_3), 27.8 (CH_3), 29.1 $(CH_3)_3$, 32.1 (C–), 40.8 (CH_2), 50.0 (CH_2), 57.6 (C–), 85.7 (C–), 102.4 (C–), 105.2 (C–), 108.9 (CH–), 114.4 (C–), 118.0 (CH–), 124.4 (CH–), 125.1 (CH–), 128.2 (C–), 137.9 (C–), 141.8 (C–), 149.0 (C–), 152.8 (C–), 171.9 (C–), 179.8 (C–), 193.6 (C–); HRMS (ESI): calcd for $C_{25}H_{26}N_5O_4$ (M+1) 460.1979, found 460.1988; IR (ATR, cm^{-1}): 3324 (w), 2216 (w), 1722 (s), 1614 (s), 1526 (s), 1512 (s), 1335 (s), 1209 (m), 1189 (m).

5.23. 1′-Cyclohexyl-7′,7′-dimethyl-2,5′-dioxo-1′,5′,6′,7′,8′,9′-hexahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]quinoline]-3′-carbonitrile (6ba)

The product was isolated as a white solid, yield 41%, mp 274–277 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.20 (1H, m, CH), 1.35–1.74 (5H, m, CH), 1.80–1.95 (4H, m, CH), 2.01–2.18 (2H, m, CH_2), 2.55–2.66 (2H, m, CH_2), 4.17–4.22 (1H, m, CH), 6.78 (3H, m, Ar–H), 7.07 (1H, m, Ar–H), 7.36 (1H, s, Ar–H), 9.67 (1H, s, NH), 10.2 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.6 (CH_2), 25.1 (CH_2), 26.8 (CH_3), 28.3 (CH_3), 32.1 (C–), 32.8 (CH_2), 40.9 (CH_2), 49.5 (C–), 50.4 (CH_2), 53.9 (CH–), 87.5 (C–), 101.6 (C–), 106.3 (C–), 108.7 (CH–), 114.6 (C–), 121.0 (CH–), 122.4 (CH–), 122.7 (CH–), 127.1 (CH–), 128.1 (C–), 137.3 (C–), 142.0 (C–), 151.7 (C–), 179.4 (C–), 192.9 (C–); MS (GC, 70 eV): m/z (%) 440 (M^+, 51), 396 (71), 348 (88); HRMS (ESI): calcd for $C_{27}H_{28}N_4O_2$ (M+1) 440.2206, found 440.2201; IR (ATR, cm^{-1}): 3276 (w), 2224 (w), 1693 (s), 1616 (s), 1532 (s), 1326 (m), 1217 (m), 744 (s).

5.24. 1′-*tert*-Butyl-5′-(2-hydroxybenzoyl)-2,6′-dioxo-5-(trifluoromethoxy)-1′,5′,6′,7′-tetrahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (7ad)

The product was isolated as a white solid, yield 69%, mp 234–236 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.61 (9H, s, $(CH_3)_3$), 6.04 (1H, s, CH), 6.93 (3H, m, Ar–H), 7.21 (1H, m, Ar–H), 7.45 (3H, m, Ar–H), 7.89 (1H, m, Ar–H), 10.43 (1H, s, NH), 10.60 (1H, s, NH), 11.17 (1H, s, OH); ^{19}F NMR (DMSO-d_6): δ –57.35; ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 29.3 $(CH_3)_3$, 48.2 (C–), 56.1 (C–), 58.2 (CH–), 86.2 (C–), 104.7 (C–), 110.2 (CH–), 113.7 (C–), 114.0–126.2 (C–F, q, J_{C-F}=255.4 Hz), 117.5 (CH–), 117.7 (CH–), 119.2 (CH–), 122.0 (C–), 122.4 (CH–), 123.4 (CH–), 130.4 (C–), 130.6 (C–), 131.2 (CH–), 136.1 (CH–), 142.9 (C–), 143.0–143.1 (C–F, q, $^3J_{C-F}$=1.9 Hz), 159.8 (C–), 167.1 (C–), 177.4 (C–), 198.0 (C–); HRMS (ESI): calcd for $C_{27}H_{22}F_3N_4O_5$ (M+1) 539.1536, found 539.1535; IR (ATR, cm^{-1}): 3163 (w), 2224 (w), 1714 (s), 1682 (m), 1487 (m), 1253 (m), 615 (m).

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5.25. 1′-*tert*-Butyl-5′-(2-hydroxybenzoyl)-5-nitro-2,6′-dioxo-1′,5′,6′,7′-tetrahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (7ag)

The product was isolated as a brown solid, yield 38%, mp 310 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.63 (9H, s, $(CH_3)_3$), 6.23 (1H, s, CH), 6.95 (2H, m, Ar–H), 7.11 (1H, d, J=8.7 Hz, Ar–H), 7.51 (2H, m, Ar–H), 7.87 (2H, d, J=7.7 Hz, Ar–H), 8.24 (2H, dd, J_1=8.5 Hz, J_2=1.7 Hz, Ar–H), 8.35 (1H, m, Ar–H), 10.50 (1H, br s, OH), 11.15 (1H, s, NH), 11.22 (1H, br s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 29.3 $(CH_3)_3$, 47.7 (C–), 56.0 (C–), 58.3 (CH–), 86.0 (C–), 104.1 (C–), 109.7 (CH–), 113.9 (C–), 117.6 (CH–), 119.2 (CH–), 119.8 (CH–), 122.0 (C–), 123.8 (CH–), 126.6 (CH–), 130.1 (C–), 130.8 (C–), 131.3 (CH–), 136.2 (CH–), 142.0 (C–), 150.4 (C–), 159.8 (C–), 166.9 (C–), 177.9 (C–), 197.7 (C–); HRMS (ESI): calcd for $C_{26}H_{22}N_5O_6$ (M+1) 500.1564, found 500.1561; IR (ATR, cm^{-1}): 3155 (w), 2226 (w), 1726 (s), 1682 (s), 1525 (m), 1332 (s), 1194 (m), 1157 (m), 709 (s), 555 (s).

5.26. 1′-Cyclohexyl-5′-(2-hydroxybenzoyl)-2,6′-dioxo-1′,5′,6′,7′-tetrahydrospiro[indoline-3,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (7ba)

The product was isolated as a yellow solid, yield 59%, mp 297–299 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.25 (1H, m, CH_2), 1.44 (2H, m, CH_2), 1.57–1.76 (3H, m, CH_2), 1.89–1.98 (4H, m, CH_2), 4.02–4.29 (1H, m, CH), 6.03 (1H, br s, CH), 6.92 (4H, s, Ar–H), 7.27 (2H, m, Ar–H), 7.52 (2H, m, Ar–H), 7.98 (1H, m, Ar–H), 10.42 (1H, br s, OH), 11.00 (1H, br s, NH), 11.29 (1H, br s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.5 (CH_2), 25.0 (CH_2), 32.7 (CH_2), 48.2 (C–), 54.4 (CH–), 56.4 (CH–), 87.5 (C–), 102.3 (C–), 109.4 (CH–), 114.0 (C–), 117.5 (CH–), 119.2 (CH–), 121.4 (CH–), 121.7 (CH–), 122.0 (C–), 123.3 (CH–), 128.8 (C–), 128.9 (CH–), 130.6 (C–), 131.3 (CH–), 136.1 (CH–), 143.6 (C–), 159.9 (C–), 167.3 (C–), 177.6 (C–), 198.2 (C–); HRMS (ESI): calcd for $C_{28}H_{25}N_4O_4$ (M+1) 481.1870, found 481.1879; IR (ATR, cm^{-1}): 3137 (w), 2222 (w), 1713 (s), 1682 (s), 1471 (m), 1191 (m), 744 (s). Anal. Calcd for $C_{28}H_{24}N_4O_4$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.27; H, 5.20; N, 11.41.

5.27. 1′-*tert*-Butyl-2,6′-dioxo-1′,5′,6′,7′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (8aa)

The product was isolated as a yellow solid, yield 71%, mp 330 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.61 (9H, s, $(CH_3)_3$), 2.83 (1H, d, J=15.7 Hz, CH_2), 3.13 (1H, d, J=15.7 Hz, CH_2), 7.35 (1H, s, Ar–H), 7.57 (1H, d, J=7 Hz, Ar–H), 7.75 (1H, m, Ar–H), 7.91 (1H, m, Ar–H), 8.04 (2H, m, Ar–H), 8.37 (1H, d, J=7.9 Hz, Ar–H), 10.28 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 29.2 $(CH_3)_3$, 39.9 (CH_2), 51.0 (C–), 57.9 (C–), 86.1 (C–), 104.5 (C–), 114.5 (C–), 120.6 (CH–), 122.4 (CH–), 123.1 (CH–), 125.0 (CH–), 128.8 (CH–), 128.9 (CH–), 130.3 (C–), 130.8 (C–), 131.2 (C–), 132.5 (CH–), 140.2 (C–), 140.6 (C–), 168.6 (C–), 203.3 (C–); MS (GC, 70 eV): m/z (%) 369 (M$^+$, 75), 313 (50), 284 (100); HRMS (EI): calcd for $C_{23}H_{19}N_3O_2$ (M+1) 369.1472, found 369.1474; IR (ATR, cm^{-1}): 3153 (w), 2221 (w), 1710 (s), 1673 (s), 1341 (s), 1204 (m), 776 (s).

5.28. 1′-Cyclohexyl-2,6′-dioxo-1′,5′,6′,7′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (8ba)

The product was isolated as a yellow solid, yield 55%, mp 335–337 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.13–1.31 (1H, m, CH_2), 1.34–1.55 (2H, m, CH_2), 1.55–1.76 (3H, m, CH_2), 1.83–1.98 (4H, m, CH_2), 2.85 (1H, d, J=15.9 Hz, CH_2), 3.19 (1H, d, J=15.9 Hz, CH_2), 4.21 (1H, m, CH), 7.40 (1H, br s, Ar–H), 7.62 (1H, d, J=6.4 Hz, Ar–H), 7.79 (1H, m, Ar–H), 7.92 (1H, m, Ar–H), 8.08 (2H, m, Ar–H), 8.40 (1H, d, J=7.9 Hz, Ar–H), 10.91 (1H, br s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.5 (CH_2), 24.9 (CH_2), 32.8 (CH_2), 40.1 (CH_2), 51.2 (C–), 54.1 (CH–), 87.3 (C–), 101.3 (C–), 114.5 (C–), 120.6 (CH–), 121.6 (CH–), 122.4 (CH–), 125.0 (CH–), 128.8 (CH–), 128.9 (CH–), 130.3 (C–), 130.6 (C–), 131.3 (C–), 132.4 (CH–), 140.2 (C–), 140.7 (C–), 168.4 (C–), 203.5 (C–); MS (GC, 70 eV): m/z (%) 395 (M$^+$, 100), 366 (28), 284 (59); HRMS (ESI): calcd for $C_{25}H_{21}N_3O_2$ (M+1) 395.1628, found 395.1629; IR (ATR, cm^{-1}): 3280 (w), 2218 (w), 1713 (s), 1683 (s), 1494 (m), 1326 (s), 1178 (m), 784 (s).

5.29. 1′-*tert*-Butyl-2,5′-dioxo-1′,5′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine]-3′-carbonitrile (9ab)

The product was isolated as a yellow solid, yield 82%, mp 259–263 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.65 (9H, s, $(CH_3)_3$), 5.08 (2H, br s, CH_2), 7.35 (2H, m, Ar–H), 7.88 (4H, m, Ar–H), 8.34 (1H, d, J=7.9 Hz, Ar–H), 10.17 (1H, br s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 28.9 $(CH_3)_3$, 52.4 (C–), 57.5 (C–), 66.2 (CH_2), 86.3 (C–), 96.4 (C–), 104.6 (C–), 114.2 (C–), 121.1 (CH–), 122.1 (CH–), 124.2 (CH–), 124.7 (CH–), 128.6 (CH–), 129.0 (CH–), 129.6 (C–), 129.6 (C–), 131.8 (CH–), 132.1 (C–), 141.5 (C–), 142.6 (C–), 158.5 (C–), 170.5 (C–), 203.6 (C–); MS (GC, 70 eV): m/z (%) 365 (M$^+$, 24), 309 (100), 280 (16); IR (ATR, cm^{-1}): 3270 (w), 2220 (w), 1713 (s), 1640 (s), 1532 (s), 1513 (s), 1328 (m), 1201 (m), 1048 (m), 784 (s). Anal. Calcd for $C_{25}H_{19}N_3O_3$: C, 73.34; H, 4.68; N, 10.26. Found: C, 73.49; H, 4.87; N, 9.85.

5.30. 1′-Cyclohexyl-2,5′-dioxo-1′,5′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine]-3′-carbonitrile (9bb)

The product was isolated as a yellow solid, yield 73%, 295–297 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16–1.33 (1H, m, CH_2), 1.45 (2H, q, J=11.4 Hz, CH_2), 1.55–1.81 (3H, m, CH_2), 1.91–2.12 (4H, m, CH_2), 4.10 (1H, m, CH), 5.12 (2H, s, CH_2), 7.34 (1H, d, J=6.6 Hz, Ar–H), 7.44 (1H, s, Ar–H), 7.71 (1H, t, J=7.5 Hz, Ar–H), 7.88 (1H, m, Ar–H), 7.94–8.11 (2H, m, Ar–H), 8.35 (1H, d, J=7.9 Hz, Ar–H), 10.82 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.5 (CH_2), 25.1 (CH_2), 32.6 (CH_2), 52.3 (C–), 54.8 (CH), 65.5 (CH_2), 87.5 (C–), 96.7 (C–), 102.5 (C–), 114.2 (C–), 121.0 (CH), 122.0 (CH), 122.9 (CH), 124.6 (CH), 128.6 (CH), 128.9 (CH), 129.6 (C–), 129.8 (C–), 131.8 (CH), 132.0 (C–), 141.4 (C–), 142.5 (C–), 158.6 (C–), 170.5 (C–), 203.5 (C–); MS (GC, 70 eV): m/z (%) 435 (M$^+$, 30), 391 (71), 309 (100); HRMS (EI): calcd for $C_{27}H_{21}N_3O_3$ (M+1) 435.1577, found 435.1576; IR (ATR, cm^{-1}): 3136 (w), 2220 (w), 1750 (s), 1682 (s), 1651 (s), 1545 (s), 1330 (s), 1210 (m), 1023 (m), 780 (s).

5.31. 1′-(4-Methoxybenzyl)-2,5′-dioxo-1′,5′,7′,8′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine]-3′-carbonitrile (9cb)

The product was isolated as a yellow solid, yield 38%, mp 275–278 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.79 (3H, s, OCH_3), 5.10 (2H, br s, CH_2), 5.17 (2H, s, CH_2), 7.01 (2H, d, J=8.5 Hz, Ar–H), 7.33 (4H, m, Ar–H), 7.71 (1H, m, Ar–H), 7.88 (1H, m, Ar–H), 8.04 (2H, m, Ar–H), 8.34 (1H, d, J=8.1 Hz, Ar–H), 10.93 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 48.5 (CH_2), 52.4 (C–), 55.1 (OCH_3), 65.5 (CH_2), 87.8 (C–), 96.8 (C–), 103.0 (C–), 113.8 (C–), 114.2 (CH), 121.0 (CH), 122.1 (CH), 124.7 (CH), 126.0 (CH), 128.1 (CH), 128.6 (C–), 128.7 (C–), 129.0 (CH), 129.6 (C–), 130.5 (C–), 131.8 (CH), 131.9 (C–), 141.4 (C–), 142.4 (C–), 158.7 (C–), 159.0 (C–), 170.5 (C–), 203.4 (C–); MS (GC, 70 eV): m/z (%) 473 (M$^+$, 14), 429 (21), 121 (100); HRMS (EI): calcd for $C_{29}H_{19}N_3O_4$ (M+1) 473.1370, found 473.1364; IR (ATR, cm^{-1}): 3026 (w), 2220 (w), 1739 (s), 1694 (s), 1650 (s), 1548 (s), 1514 (s), 1325 (m), 1250 (s), 1173 (m), 1026 (m), 782 (s).

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5.32. 1′-*tert*-Butyl-5′-(2-hydroxybenzoyl)-2,6′-dioxo-1′,5′,6′,7′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (10ad)

The product was isolated as a yellow solid, yield 65%, mp 270–272 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.64 (9H, s, $(CH_3)_3$), 6.29 (1H, s, CH), 6.91 (2H, d, J=8.3 Hz, Ar–H), 7.38 (1H, s, Ar–H), 7.47 (1H, m, Ar–H), 7.63 (2H, m, Ar–H), 7.88 (2H, m, Ar–H), 8.00 (2H, m, Ar–H), 8.29 (1H, d, J=8.1 Hz, Ar–H), 10.55 (1H, s, NH), 11.01 (1H, s, OH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 29.3 $(CH_3)_3$, 52.4 (C–), 58.0 (CH–), 58.2 (C–), 86.6 (C–), 106.1 (C–), 113.6 (C–), 117.6 (CH–), 119.2 (CH–), 120.5 (CH–), 121.7 (CH–), 121.9 (C–), 123.4 (CH–), 125.3 (CH–), 128.5 (CH–), 128.6 (CH–), 130.1 (C–), 130.3 (C–), 131.2 (CH–), 131.4 (CH–), 131.9 (C–), 136.1 (CH–), 138.1 (C–), 141.7 (C–), 159.7 (C–), 167.6 (C–), 197.4 (C–), 201.4 (C–); MS (GC, 70 eV): m/z (%) 489 (M^+, 35), 368 (6), 312 (100); HRMS (EI): calcd for $C_{30}H_{23}N_3O_4$ (M+1) 489.1683, found 489.1678; IR (ATR, cm^{-1}): 3153 (w), 2220 (w), 1673 (s), 1634 (s), 1493 (s), 1343 (m), 1469 (m), 1194 (m), 1160 (m), 782 (s).

5.33. 1′-Cyclohexyl-5′-(2-hydroxybenzoyl)-2,6′-dioxo-1′,5′,6′,7′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (10bd)

The product was isolated as a yellow solid, yield 56%, mp 290–292 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14–1.27 (1H, m, CH_2), 1.34–1.48 (2H, m, CH_2), 1.57–1.73 (3H, m, CH_2), 1.80–2.01 (4H, m, CH_2), 4.11–4.23 (1H, m, CH), 6.35 (1H, s, CH), 6.91 (2H, m, Ar–H), 7.40 (1H, s, Ar–H), 7.48 (1H, m, Ar–H), 7.66 (2H, m, Ar–H), 7.89 (2H, m, Ar–H), 8.01 (2H, m, Ar–H), 8.29 (1H, d, J=7.9 Hz, Ar–H), 11.02 (1H, s, NH), 11.13 (1H, s, OH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.5 (CH_2), 25.0 (CH_2), 32.8 (CH_2), 52.7 (C–), 54.5 (CH), 58.1 (CH), 87.6 (C–), 103.0 (C–), 113.7 (C–), 117.5 (CH–), 119.2 (CH–), 120.4 (CH–), 121.8 (CH–), 121.9 (CH–), 125.3 (CH–), 128.5 (CH–), 128.6 (CH–), 130.1 (C–), 130.3 (C–), 131.3 (CH–), 131.4 (CH–), 131.8 (C–), 136.1 (CH–), 138.0 (C–), 141.7 (C–), 159.8 (C–), 167.4 (C–), 197.7 (C–), 201.6 (C–); MS (GC, 70 eV): m/z (%) 515 (M^+, 31), 394 (100), 312 (55); IR (ATR, cm^{-1}): 3125 (w), 2220 (w), 1722 (s), 1670 (s), 1634 (s), 1340 (w), 1155 (m), 755 (s).

5.34. 5′-(2-Hydroxybenzoyl)-1′-(4-methoxybenzyl)-2,6′-dioxo-1′,5′,6′,7′-tetrahydro-2*H*-spiro[acenaphthylene-1,4′-pyrrolo[2,3-*b*]pyridine]-3′-carbonitrile (10dd)

The product was isolated as a yellow solid, yield 35%, mp 248–250 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.88 (3H, br s, OCH_3), 4.96–5.53 (2H, m, CH_2), 6.40 (1H, br s, CH), 6.97 (4H, m, Ar–H), 7.41–8.1 (10 H, m, Ar–H), 8.37 (1H, br s, Ar–H), 11.03 (1H, br s, NH), 11.35 (1H, br s, OH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 48.5 (CH_2), 52.9 (C–), 55.1 (OCH_3–), 58.1 (CH–), 87.7 (C–), 103.4 (C–), 113.4 (C–), 114.2 (CH–), 117.5 (CH–), 119.2 (CH–), 120.4 (CH–), 121.8 (CH–), 122.0 (C–), 124.9 (CH–), 125.3 (CH–), 128.2 (C–), 128.5 (CH–), 128.6 (CH–), 129.3 (CH–), 130.1 (C–), 130.8 (C–), 130.9 (C–), 131.2 (CH–), 131.4 (CH–), 131.8 (C–), 136.1 (C–), 137.9 (C–), 141.7 (C–), 159.0 (C–), 159.6 (C–), 167.3 (C–), 197.4 (C–), 201.6 (C–); MS (GC, 70 eV): m/z (%) 253 (100), 226 (16); HRMS (ESI): calcd for $C_{34}H_{24}N_3O_5$ (M+1) 554.1710, found 554.1718; IR (ATR, cm^{-1}): 3182 (w), 2224 (w), 1712 (s), 1699 (s), 1638 (s), 1515 (m), 1239 (m), 1176 (m), 1153 (m), 748 (m).

5.35. Methyl 1-*tert*-butyl-3-cyano-6-oxo-4-phenyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (11aa)

The product was isolated as a yellow solid, yield 70%, mp 85 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.57 (9H, s, $(CH_3)_3$), 3.03 (1H, d, J=15.5 Hz, CH_2), 3.19 (1H, d, J=15.5 Hz, CH_2), 3.70 (3H, s, OCH_3), 7.18 (2H, m, Ar–H), 7.34 (3H, m, Ar–H), 7.54 (1H, s, Ar–H), 10.07 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 29.1 $(CH_3)_3$, 43.5 (CH_2), 50.5 (C–), 52.4 (OCH_3–), 57.8 (C–), 88.0 (C–), 104.6 (C–), 115.6 (C–), 124.0 (CH–), 126.9 (CH–), 127.3 (CH–), 128.3 (CH–), 130.2 (C–), 140.2 (C–), 168.0 (C–), 172.5 (C–); MS (GC, 70 eV): m/z (%) 351 (M^+, 18), 292 (27), 236 (100); HRMS (EI): calcd for $C_{20}H_{21}N_3O_3$ (M+1) 351.1580, found 351.1577; IR (ATR, cm^{-1}): 3231 (w), 2222 (w), 1731 (m), 1681 (s), 1674 (s), 1494 (m), 1199 (m), 698 (m).

5.36. Ethyl 1-*tert*-butyl-3-cyano-4-methyl-6-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (11ab)

The product was isolated as a white solid, yield 73%, mp 210–212 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.19 (3H, t, J=6 Hz, CH_3), 1.57 (9H, s, $(CH_3)_3$), 1.62 (3H, s, CH_3), 2.62 (1H, d, J=15.5 Hz, CH_2), 2.79 (1H, d, J=15.5 Hz, CH_2), 4.11 (2H, q, CH_2), 7.46 (1H, s, Ar–H), 9.98 (1H, br s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 13.7 (CH_3), 22.3 (CH_3), 29.1 $(CH_3)_3$, 41.0 (C–), 42.1 (CH_2), 57.5 (C–), 60.7 (CH_2), 86.5 (C–), 105.4 (C–), 116.5 (C–), 123.3 (CH–), 129.7 (C–), 168.7 (C–), 173.2 (C–); IR (ATR, cm^{-1}): 3219 (w), 2216 (w), 1722 (s), 1674 (s), 1352 (m), 1209 (m), 1156 (m), 1131 (m), 629 (s).

5.37. 1-*tert*-Butyl-4-ethyl-6-oxo-4-propionyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonitrile (11ac)

The product was isolated as a white solid, yield 70%, mp 257–259 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (6H, m, J=7.6 Hz, J=7.2 Hz, CH_3), 1.53 (9H, s, $(CH_3)_3$), 1.97 (1H, m, CH_2), 2.24 (1H, m, CH_2), 2.42 (1H, d, J=15.5 Hz, CH_2), 2.48 (2H, q, 7.4 Hz), 2.75 (1H, d, J=15.7 Hz, CH_2), 7.52 (1H, s, Ar–H), 9.86 (4H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 8.3 (CH_3), 8.4 (CH_3), 26.4 (CH_2), 29.0 $(CH_3)_3$, 29.2 (CH_2), 37.8 (CH_2), 51.4 (C–), 57.7 (C–), 86.5 (C–), 103.5 (C–), 117.1 (C–), 124.1 (CH–), 130.6 (C–), 169.4 (C–), 209.3 (C–); MS (GC, 70 eV): m/z (%) 301 (M^+, 2), 244 (34), 188 (100); HRMS (ESI): calcd for $C_{17}H_{23}N_3O_2$ (M+1) 301.1787, found 301.1785; IR (ATR, cm^{-1}): 3149 (w), 2215 (w), 1705 (s), 1668 (s), 1346 (s), 1207 (s).

5.38. Methyl 3-cyano-1-cyclohexyl-6-oxo-4-phenyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (11ba)

The product was isolated as a white solid, yield 77%, mp 310–312 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.22 (1H, m, CH_2), 1.39 (2H, m, CH_2), 1.52–1.74 (3H, m, CH_2), 1.75–1.99 (4H, m, CH_2), 2.94 (1H, d, J=15.8 Hz, CH_2), 3.20 (1H, d, J=15.8 Hz, CH_2), 3.70 (3H, s, OCH_3), 3.99–4.23 (1H, m, CH), 7.18 (2H, d, J=7.3 Hz, Ar–H), 7.36 (3H, m, Ar–H), 7.58 (1H, s, Ar–H), 10.73, (1H, br s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 24.5 (CH_2), 24.9 (CH_2), 32.7 (CH_2), 44.0 (CH_2), 50.9 (C–), 52.4 (OCH_3–), 54.1 (CH–), 89.4 (C–), 100.8 (C–), 115.8 (C–), 122.7 (CH–), 126.6 (CH–), 127.3 (CH–), 128.4 (CH–), 130.5 (C–), 140.7 (C–), 167.8 (C–), 172.6 (C–); MS (GC, 70 eV): m/z (%) 377 (M^+, 15), 318 (100), 236 (41); HRMS (EI): calcd for $C_{22}H_{23}N_3O_3$ (M+1) 377.1733, found 377.1736; IR (ATR, cm^{-1}): 3253 (w), 2940 (w), 2224 (w), 1724 (s), 1692 (s), 1529 (m), 1500 (m), 1290 (w), 1231 (m), 1175 (m), 1065 (m), 759 (s), 702 (s), 607 (s). Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 69.81; H, 6.08; N, 11.27.

5.39. Ethyl 3-cyano-1-cyclohexyl-4-methyl-6-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (11bb)

The product was isolated as a white solid, yield 57%, mp 263–265 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (3H, t, J=7.1 Hz, CH_3), 1.17–1.45 (3H, m, CH_2), 1.46–1.73 (6H, m, CH_2), 1.73–2.03 (4H, m, CH_2), 2.60 (1H, d, J=15.9 Hz, CH_2), 2.62 (3H, s, CH_3), 2.75

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(1H, d, J=15.9 Hz, CH_2), 3.91–4.24 (m, 3 H, $CHCH_2$), 7.45 (1H, s, Ar–H), 10.55 (1 H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 13.7 (CH_3), 22.3 (CH_3), 24.5 (CH_2), 24.8 (CH_2), 32.9 (CH_2), 41.3 (C–), 42.4 (CH_2), 53.9 (CH), 60.7 (CH_2), 87.9 (C–), 102.2 (C–), 116.5 (C–), 121.9 (CH), 129.8 (C–), 168.6 (C–), 173.3 (C–); MS (GC, 70 eV): m/z (%) 329 (M^+, 15), 256 (100), 174 (57); HRMS (EI): calcd for $C_{18}H_{23}N_3O_3$ (M+1) 329.1733, found 329.1735; IR (ATR, cm^{-1}): 3131 (w), 2938 (w), 2217 (w), 1723 (s), 1673 (s), 1544 (s), 1351 (s), 1187 (m), 1098 (m), 1015 (m), 773 (s), 621 (s). Anal. Calcd for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.74; H, 6.98; N, 12.97.

5.40. Methyl 3-cyano-1-(4-methoxybenzyl)-6-oxo-4-phenyl-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (11ca)

The product was isolated as a yellow solid, yield 65%, mp 102–104 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.87 (1H, d, J=15.9 Hz, CH_2), 3.12 (1H, d, J=15.9 Hz, CH_2), 3.66 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 5.09 (2H, s), 6.93 (2H, m, Ar–H), 7.15 (4H, m, Ar–H), 7.33 (3H, m, Ar–H), 7.48 (1H, s, Ar–H), 10.81 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 44.0 (CH_2), 48.3 (CH_2), 51.1 (OCH_3), 52.5 (OCH_3), 55.1 (C–), 89.7 (C–), 101.4 (C–), 114.2 (C–), 115.5 (C–), 126.0 (CH–), 126.6 (CH–), 127.4 (CH–), 128.3 (C–), 128.5 (CH–), 128.9 (CH–), 131.1 (C–), 140.6 (C–), 158.9 (C–), 167.7 (C–), 172.5 (C–); MS (GC, 70 eV): m/z (%) 415 (M^+, 6), 121 (100); HRMS (EI): calcd for $C_{24}H_{21}N_3O_4$ (M+1) 415.1526, found 415.1525; IR (ATR, cm^{-1}): 3126 (w), 2224 (w), 1728 (m), 1513 (s), 1245 (s), 1175 (m), 699 (m). Anal. Calcd for $C_{24}H_{21}N_3O_4$: C, 69.39; H, 5.10; N, 10.11. Found: C, 69.54; H, 5.45; N, 9.85.

5.41. Ethyl 3-cyano-1-(4-methoxybenzyl)-4-methyl-6-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (11cb)

The product was isolated as a white solid, yield 68%, mp 139–142 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (3H, t, J=7.1 Hz, CH_3), 1.59 (3H, s, CH_3), 2.58 (1H, d, J=15.9 Hz, CH_2), 2.74 (1H, d, J=15.9 Hz, CH_2), 3.75 (3H, s, OCH_3), 4.06 (2H, m, CH_2), 5.07 (2H, dd, J_1=15.3 Hz, J_2=34.6 Hz, CH_2), 6.94 (2H, d, J=8.7 Hz, Ar–H), 7.20 (2H, d, J=8.7 Hz, Ar–H), 7.41 (1H, s, Ar–H), 10.66 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 13.7 (CH_3–), 22.1 (CH_3–), 41.4 (C–), 42.2 (CH_2–), 48.1 (CH_2–), 55.0 (OCH_3–), 60.8 (CH_2–), 88.0 (C–), 102.7 (C–), 114.1 (CH–), 116.2 (C–), 125.2 (CH–), 128.4 (C–), 128.9 (CH–), 130.4 (C–), 158.9 (C–), 168.6 (C–), 173.3 (C–); MS (GC, 70 eV): m/z (%) 367 (M^+, 5), 121 (100); HRMS (ESI): calcd for $C_{20}H_{21}N_3O_4$ (M+1) 367.1526, found 367.1527; IR (ATR, cm^{-1}): 3286 (w), 2222 (w), 1695 (s), 1511 (s), 1460 (m), 1251 (s), 810 (s). Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.57; H, 5.78; N, 11.55.

5.42. Methyl 1-*tert*-butyl-3-cyano-5-oxo-4-phenyl-4,5,7,8-tetrahydro-1*H*-furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine-4-carboxylate (12aa)

The product was isolated as a white solid, yield 42%, mp 225–227 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.63 (9H, s, $(CH_3)_3$), 4.91 (2H, dd, J=16.4 Hz, CH_2), 7.24 (5H, m, Ar–H), 7.53 (1H, s, Ar–H), 10.00 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 28.8 $(CH_3)_3$, 51.3 (C–), 52.2 (OCH_3), 57.4 (C–), 65.1 (CH_2), 88.4 (C–), 97.5 (C–), 102.9 (C–), 115.4 (C–), 125.0 (CH–), 126.4 (CH–), 127.4 (CH–), 127.9 (CH–), 129.5 (C–), 142.5 (C–), 156.0 (C–), 170.5 (C–), 171.4 (C–); MS (GC, 70 eV): m/z (%) 331 (32), 275 (100), 246 (59); HRMS (ESI): calcd for $C_{22}H_{22}N_3O_4$ (M+1) 392.1604, found 392.1605; IR (ATR, cm^{-1}): 3296 (w), 2227 (w), 1754 (s), 1727 (s), 1658 (s), 1531 (s), 1506 (s), 1224 (m), 1197 (s), 1031 (s), 1010 (s), 693 (s).

5.43. Ethyl 1-*tert*-butyl-3-cyano-4-methyl-5-oxo-4,5,7,8-tetrahydro-1*H*-furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine-4-carboxylate (12ab)

The product was isolated as a white solid, yield 67%, mp 248–251 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (3H, t, J=7.1 Hz, CH_3), 1.58 (9H, s, $(CH_3)_3$), 1.72 (3H, s, CH_3), 4.00–4.19 (2H, m, CH_2), 4.90 (2H, s, CH_2), 7.45 (1H, s, Ar–H), 9.78 (1H, br s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 13.9 (CH_3), 24.1 (CH_3), 28.8 $(CH_3)_3$, 41.8 (C–), 57.3 (C–), 60.8 (CH_2), 65.4 (CH_2), 86.7 (C–), 97.7 (C–), 105.4 (C–), 115.8 (C–), 124.2 (CH–), 128.1 (C–), 156.8 (C–), 171.1 (C–), 172.0 (C–); MS (GC, 70 eV): m/z (%) 269 (M^+, 25), 213 (100), 184 (67); HRMS (ESI): calcd for $C_{18}H_{21}N_3O_4$ (M+1) 344.1604, found 344.1603; IR (ATR, cm^{-1}): 3382 (m), 2979 (w), 2221 (m), 1727 (w), 1703 (s), 1643 (s), 1533 (s), 1515 (s), 1205 (s), 999 (s).

5.44. Ethyl 3-cyano-1-cyclohexyl-4-methyl-5-oxo-4,5,7,8-tetrahydro-1*H*-furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine-4-carboxylate (12bb)

The product was isolated as a white solid, yield 40%, mp 298–300 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.14 (3H, t, J=7 Hz, CH_3), 1.17–1.44 (3H, m, CH_2), 1.44–1.66 (3H, m, CH_2), 1.68 (3H, s, CH_3), 1.75–1.94 (4H, m, CH_2), 3.87–4.00 (1H, m, CH), 4.06 (2H, q, J=6.8 Hz, CH_2), 4.88 (2H, dd, J_1=16.4 Hz, J_2=18.7 Hz, CH_2), 7.47 (1H, s, Ar–H); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 13.9 (CH_3), 24.1 (CH_3), 24.5 (CH_2), 25.0 (CH_2), 32.7 (CH_2), 42.0 (C–), 54.4 (CH), 60.7 (CH_2), 64.9 (CH_2), 88.0 (C–), 97.6 (C–), 103.1 (C–), 115.9 (C–), 122.8 (CH), 129.2 (C–), 157.6 (C–), 171.3 (C–), 172.1 (C–); MS (GC, 70 eV): m/z (%) 295 (32), 213 (100), 184 (30); HRMS (ESI): calcd for $C_{20}H_{24}N_3O_4$ (M+1) 370.1761, found 370.1758; IR (ATR, cm^{-1}): 3217 (w), 2221 (w), 1748 (s), 1691 (s), 1652 (s), 1551 (s), 1452 (m), 1332 (m), 1278 (m), 990 (s), 575 (m).

5.45. Ethyl 3-cyano-1-(4-methoxybenzyl)-4-methyl-5-oxo-4,5,7,8-tetrahydro-1*H*-furo[3,4-*b*]pyrrolo[3,2-*e*]pyridine-4-carboxylate (12cb)

The product was isolated as a yellow solid, yield 64%, mp 221–223 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.17 (3H, t, J=6.9 Hz, CH_3), 1.74 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 4.11 (2H, q, J=6.9 Hz, CH_2), 4.85 (2H, dd, J_1=16.4 Hz, J_2=19.2 Hz, CH_2), 5.09 (2H, s, CH_2), 6.97 (2H, d, J=8.3 Hz, Ar–H), 7.22 (2H, d, J=8.3 Hz, Ar–H), 7.49 (1H, s, Ar–H), 10.53 (1H, br s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 13.9 (CH_3), 24.0 (CH_3), 42.0 (C–), 48.4 (CH_2), 55.1 (OCH_3), 60.8 (CH_2), 64.8 (CH_2), 88.3 (C–), 98.1 (C–), 103.8 (C–), 114.2 (CH), 115.5 (C–), 126.1 (CH), 128.1 (C–), 128.7 (CH), 129.1 (C–), 157.1 (C–), 159.0 (C–), 171.1 (C–), 171.9 (C–); MS (GC, 70 eV): m/z (%) 407 (M^+, 2), 334 (25), 121 (100); HRMS (ESI): calcd for $C_{22}H_{22}N_3O_5$ (M+1) 408.1554, found 408.1549; IR (ATR, cm^{-1}): 3203 (w), 2223 (w), 1712 (s), 1625 (s), 1541 (s), 1513 (s), 1328 (m), 1254 (m), 1027 (m), 1009 (m), 611 (m). Anal. Calcd for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.20; N, 10.31. Found: C, 65.00; H, 5.20; N, 10.46.

5.46. Ethyl 1-*tert*-butyl-3-cyano-4,7,7-trimethyl-5-oxo-4,5,6,7,8,9-hexahydro-1*H*-pyrrolo[2,3-*b*]quinoline-4-carboxylate (13ab)

The product was isolated as a white solid, yield 55%, mp 201–204 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.04 (3H, s, CH_3), 1.05 (3H, s, CH_3), 1.13 (3H, t, J=7.1 Hz, CH_3), 1.55 (3H, s, CH_3), 1.57 (9H, s, $(CH_3)_3$), 2.12 (2H, dd, J=15.9 Hz, CH_2), 2.60 (2H, dd, J=17 Hz, CH_2), 3.82–4.14 (2H, m, CH_2), 7.35 (1H, s, Ar–H), 8.47 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 13.9 (CH_3), 25.9 (CH_3), 27.4 (CH_3), 27.6 (CH_3), 29.1 $(CH_3)_3$, 32.0 (C–), 40.8 (CH_2), 42.9 (C–), 50.6 (CH_2), 57.2 (C–), 59.8 (CH_2), 86.1 (C–), 106.2 (C–), 109.3 (C–), 115.6 (C–), 123.7 (CH–), 126.9 (C–), 150.3 (C–), 173.1 (C–), 194.1 (C–); IR (ATR,

cm^{-1}): 3307 (w), 2220 (w), 1731 (s), 1617 (s), 1523 (s), 1504 (s), 1326 (m), 1098 (m).

5.47. Ethyl 3-cyano-1-cyclohexyl-4,7,7-trimethyl-5-oxo-4,5,6,7,8,9-hexahydro-1*H*-pyrrolo[2,3-*b*]quinoline-4-carboxylate (13bb)

The product was isolated as a yellow solid, yield 58%, mp 246–248 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02 (6H, br s, CH_3), 1.09 (3H, t, J=7 Hz, CH_3), 1.14–1.25 (1H, m, CH_2), 1.26–1.51 (3H, m, CH_2), 1.54 (3H, s, CH_3), 1.57–1.71 (2H, m, CH_2), 1.73–1.92 (4H, m, CH_2), 2.10 (2H, dd, J_1=15.7 Hz, J_2=29.7 Hz, CH_2), 2.41 (2H, dd, J_1=16.2 Hz, J_2=29.8 Hz, CH_2), 3.83–4.18 (3H, m, CH), 7.38 (1H, s, Ar–H), 9.35 (1H, br s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 14.0 (CH_3), 24.6 (CH_2), 25.0 (CH_2), 25.9 (CH_3), 27.2 (CH_3), 27.9 (CH_3), 32.2 (CH_2), 32.6 (C–), 40.8 (CH_2), 43.2 (C–), 50.7 (CH_2), 53.8 (CH), 59.8 (CH_2), 87.6 (C–), 103.7 (C–), 109.5 (C–), 115.7 (C–), 122.3 (CH), 127.2 (C–), 150.3 (C–), 173.2 (C–), 193.8 (C–); MS (GC, 70 eV): m/z (%) 409 (M^+, 9), 336 (100), 254 (77); HRMS (ESI): calcd for $C_{24}H_{31}N_3O_3$ (M+1) 409.2359, found 409.2364; IR (ATR, cm^{-1}): 3302 (w), 2942 (w), 2224 (m), 1725 (s), 1642 (m), 1628 (m), 1531 (s), 1508 (m), 1423 (m), 1327 (m), 1222 (m), 1102 (m).

5.48. Ethyl 1-*tert*-butyl-3-cyano-5-(2-hydroxybenzoyl)-4-methyl-6-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (14ab)

The product was isolated as a white solid, yield 67%, mp 258–260 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.10 (3H, t, J=7 Hz, CH_3), 1.59 (12H, s, CH_3), 4.08 (2H, m, CH_2), 5.25 (1H, s, CH), 6.99 (2H, m, Ar–H), 7.51 (2H, m, Ar–H), 7.93 (1H, d, J=7.7 Hz, Ar–H), 10.26 (1H, br s, NH), 11.38 (1H, br s, OH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 13.6 (CH_3), 19.6 (CH_3), 29.1 (CH_3), 42.9 (C–), 57.9 (C–), 58.6 (CH–), 60.3 (CH_2), 86.1 (C–), 105.6 (C–), 116.5 (C–), 117.6 (CH–), 119.2 (CH–), 122.7 (C–), 123.8 (CH–), 130.0 (C–), 131.3 (CH–), 136.0 (CH–), 159.9 (C–), 167.6 (C–), 172.3 (C–), 198.8 (C–); MS (GC, 70 eV): m/z (%) 331 (M^+, 35), 275 (100), 246 (59); IR (ATR, cm^{-1}): 3218 (w), 2227 (w), 1725 (s), 1674 (s), 1634 (s), 1349 (m), 1219 (m), 1188 (m), 1158 (m), 752 (s), 619 (s). Anal. Calcd for $C_{23}H_{25}N_3O_5$: C, 65.24; H, 5.95; N, 9.92. Found: C, 64.99; H, 5.97; N, 9.81.

5.49. Ethyl 3-cyano-1-cyclohexyl-5-(2-hydroxybenzoyl)-4-methyl-6-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (14bb)

The product was isolated as a white solid, yield 34%, mp 252–255 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.09 (3H, t, J=7.1 Hz), 1.16–1.47 (3H, m, CH_2), 1.53–1.71 (6H, m, CH), 1.77–1.96 (4H, m, CH), 3.96–4.13 (3H, m, CH), 5.26 (1H, s, CH), 6.96 (2H, m, Ar–H), 7.53 (2H, m, Ar–H), 7.93 (1H, dd, J_1=8.1 Hz, J_2=1.3 Hz, Ar–H), 10.86 (1H, s, OH), 11.39 (1H, s, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 13.6 (CH_3), 19.5 (CH_3), 24.5 (CH_2), 24.8 (CH_2), 32.7 (CH_2), 32.9 (C–), 43.3 (C–), 54.2 (CH), 59.0 (CH), 60.3 (CH_2), 87.3 (C–), 102.6 (C–), 116.5 (C–), 117.6 (CH), 119.1 (CH), 122.3 (CH), 122.6 (C–), 130.0 (C–), 131.4 (CH), 136.1 (CH), 160.0 (C–), 167.5 (C–), 172.5 (C–), 199.1 (C–); HRMS (ESI): calcd for $C_{25}H_{28}N_3O_5$ (M+1) 450.2023, found 450.2023; IR (ATR, cm^{-1}): 2931 (w), 2219 (w), 1723 (m), 1687 (s), 1634 (m), 1444 (w), 1339 (m), 1215 (m), 751 (s). Anal. Calcd for $C_{25}H_{27}N_3O_5$: C, 66.80; H, 6.05; N, 9.35. Found: C, 66.78; H, 6.04; N, 9.54.

5.50. Ethyl 3-cyano-5-(2-hydroxybenzoyl)-1-(4-methoxybenzyl)-4-methyl-6-oxo-4,5,6,7-tetrahydro-1*H*-pyrrolo[2,3-*b*]pyridine-4-carboxylate (14cb)

The product was isolated as a white solid, yield 47%, mp 199–201 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11 (3H, t, J=7.1 Hz, CH_3), 1.60 (3H, s, CH_3), 3.78 (3H, s, OCH_3), 4.00–4.15 (2H, m, CH_2), 5.05 (1H, d, J=15.3 Hz, CH_2), 5.20 (1H, d, J=15.3 Hz, CH_2), 5.27 (1H, s, CH), 6.96 (4H, m, Ar–H), 7.24 (2H, m, Ar–H), 7.47 (1H, s, Ar–H), 7.52 (1H, m, Ar–H), 7.89 (1H, dd, J_1=8.0 Hz, J_2=1.42 Hz, Ar–H); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 13.6 (CH_3), 19.4 (CH_3), 43.4 (C–), 48.3 (CH_2), 55.1 (OCH_3), 58.9 (CH), 60.4 (CH_2), 87.5 (C–), 103.1 (C–), 114.1 (CH–), 116.1 (C–), 117.5 (CH–), 119.2 (CH–), 122.8 (C–), 125.5 (CH–), 128.3 (C–), 129.0 (CH–), 130.5 (C–), 131.3 (CH–), 136.0 (CH–), 158.9 (C–), 159.8 (C–), 167.4 (C–), 172.5 (C–), 198.7 (C–); MS (GC, 70 eV): m/z (%) 487 (M^+, 1), 325 (6), 121 (100); HRMS (ESI): calcd for $C_{27}H_{26}N_3O_6$ (M+1) 488.1816, found 488.1803; IR (ATR, cm^{-1}): 3030 (w), 2222 (w), 1679 (s), 1635 (m), 1246 (s), 1208 (s), 1153 (s), 1029 (m), 750 (s). Anal. Calcd for $C_{27}H_{25}N_3O_6$: C, 66.52; H, 5.17; N, 8.62. Found: C, 66.56; H, 5.14; N, 8.85.

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Supplementary data

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of all compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.04.115.

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20. Crystallographic data (excluding structure factors) for the structure **9bb** and **11cb**, reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 916825 and 916826 and can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif.

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