Tetrahedron 67 (2011) 3519–3523

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Novel four-component route to the synthesis of spiro[indoline-3,4′-pyridine]-3′-carboxylate derivatives

Abdolali Alizadeh *, Javad Mokhtari

Department of Chemistry, Tarbiat Modares University, PO Box 14115-175 Tehran, Iran

ARTICLE INFO

Article history:
Received 18 November 2010
Received in revised form 24 February 2011
Accepted 14 March 2011
Available online 21 March 2011

Keywords:
Isatin
Ylide
Benzylamine
Alkyl acetoacetate
Multicomponent reaction

ABSTRACT

An effective route to spiro[indoline-3,4′-pyridine]-3′-carboxylate derivatives is described. This involves reaction of isatin, 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone, and benzylamine derivatives or aliphatic amines in the presence of alkyl acetoacetate (1,3-dicarbonyl compounds) in dry methanol under reflux conditions. The reactive 1:1 enaminone, which is obtained from the addition of the amine to 1,3-dicarbonyl compound, adds to the α,β-unsaturated ketone, which is formed from the reaction of isatin and 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone, to produce the alkyl 1′-benzyl-2′-methyl-2-oxo-6′-phenyl-1′*H*-spiro[indoline-3,4′-pyridine]-3′-carboxylate derivatives in excellent yields.

1. Introduction

Exploring novel pharmacological agents with the minimum number of synthetic steps and less time is a major challenge for chemists.[1] In general, the conventional approach involves the use of multistep reaction sequences, which are typically associated with low yields, high cost, and tedious isolation and purification of the resulting products. However, as a significant strategy, superior to the conventional one, multicomponent reactions (MCRs) offer a valuable solution for such a situation.[2–7] MCRs constitute a highly effective one-pot procedure that has many advantages, including atom economy[8] and facile synthesis of molecules that have interesting biological properties using readily available starting materials.

The indole core represents an interesting pharmacophore, which displays wide-ranging biological and pharmacological properties.[9] Furthermore, 3′-spirooxindoles, formed by sharing of the 3-carbon atom, have been of interest to organic chemists because they exhibit interesting biological properties.[10–12] For instance, spirotryprostatin B, a natural alkaloid isolated from the fermentation broth of *Aspergillus fumigatus*, has been identified as a novel inhibitor of microtubule assembly,[13] and pteropodine and isopteropodine have been shown to modulate the function of muscarinic serotonin receptors (Fig. 1).[14] Therefore, a number of methods have been reported for the preparation of spirooxindole derivatives.[15–17]

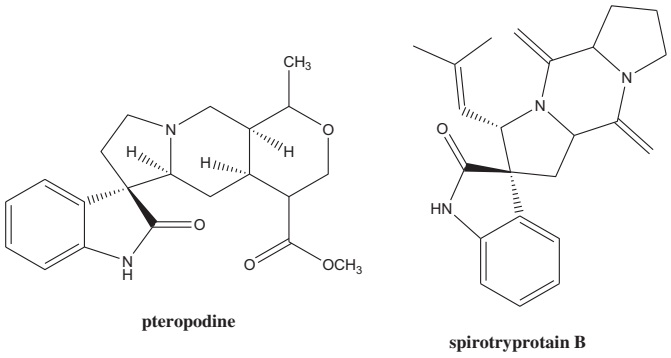


Fig. 1. Naturally occurring and biologically active spirocyclic oxindoles.

Hantzsch 1,4-dihydropyridines are easily prepared from the Hantzsch reaction or its modifications.[18,19] In recent years, it was found that drugs, such as nifedipine and niguldipine undergo redox processes during their metabolism catalyzed by cytochrome P-450 in the liver.[20] Furthermore, 1,4-dihydropyridines are well-known compounds as a consequence of their pharmacological profile as the most important calcium channel modulators.[21,22] For example, amlodipine besylate, nifedipine, and related dihydropyridines are Ca^{2+} channel blockers, are rapidly emerging as one of the most important classes of drugs for the treatment of cardiovascular diseases including hypertension.

* Corresponding author. Tel.: +98 21 8800663; fax: +98 21 88006544; e-mail addresses: abdol_alizad@yahoo.com, aalizadeh@modares.ac.ir.

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.03.032

The preparation of new 1,4-dihydropyridines with special properties is an active and attractive ongoing interdisciplinary research area. Herein, as a part of our research program, which aims to develop libraries of the aforementioned bioactive compounds, and in a continuation of our interest in one-pot and multicomponent reactions (MCRs),[23] we now report a four-component reaction of isatin, 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone, and amine **1** in the presence of 1,3-dicarbonyl compound **2** in dry methanol at reflux to afford a series of spirooxindole derivatives **3** containing indoline-3,4′-pyridine-3′-carboxylate fragments in 74–85% yields (Table 1).

Table 1
Synthetic results of **3a** under different reactions conditions

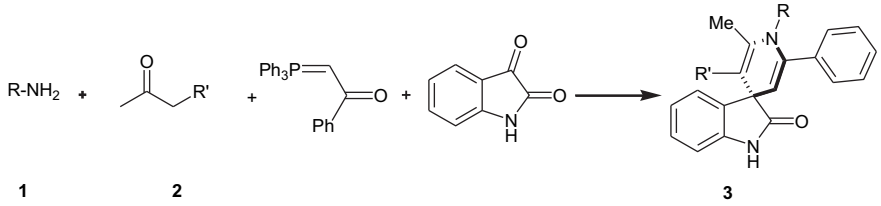
Entry	Solvent	Temp/°C	Time/h	Isolated yield (%)
1	Methanol	Reflux	3	80
2	Ethanol	Reflux	3	72
3	Acetonitrile	Reflux	5	64
4	THF	Reflux	6	48
5	Dichloromethane	Reflux	6	12

2. Results and discussion

The choice of an appropriate reaction medium is of crucial importance for successful synthesis. Initially, the four-component reaction of isatin, 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone, benzylamine, and methyl acetoacetate as a simple model substrate was investigated to establish the feasibility of the strategy and to optimize the reaction conditions (Scheme 1).

Table 2
Synthetic results of spiro[indoline-3,4′-pyridine]-3′-carboxylate **3a–l** via four-component reaction

Entry	R	R′	Time (h)	Product	Yield (%)
1	$PhCH_2$	CO_2Me	2	**3a**	80
2	$PhCH_2$	CO_2Et	3	**3b**	84
3	p-$ClC_6H_4CH_2$	CO_2Me	3	**3c**	81
4	p-$ClC_6H_4CH_2$	CO_2Et	3	**3d**	78
5	o-$ClC_6H_4CH_2$	CO_2Me	2	**3e**	85
6	o-$ClC_6H_4CH_2$	CO_2Et	3	**3f**	82
7	p-$MeC_6H_4CH_2$	CO_2Me	2	**3g**	79
8	p-$MeC_6H_4CH_2$	CO_2Et	3	**3h**	74
9	Propyl	CO_2Me	4	**3i**	79
10	*iso*-Butyl	CO_2Et	4	**3j**	81
11	$PhCH_2$	Me	6	**3k**	78
12	p-$MeOC_6H_5$	CO_2Me	5	**3l**	80
13	$PhCH_2$	Ph	12	**3m**	—
14	Allyl	Ph	12	**3n**	—



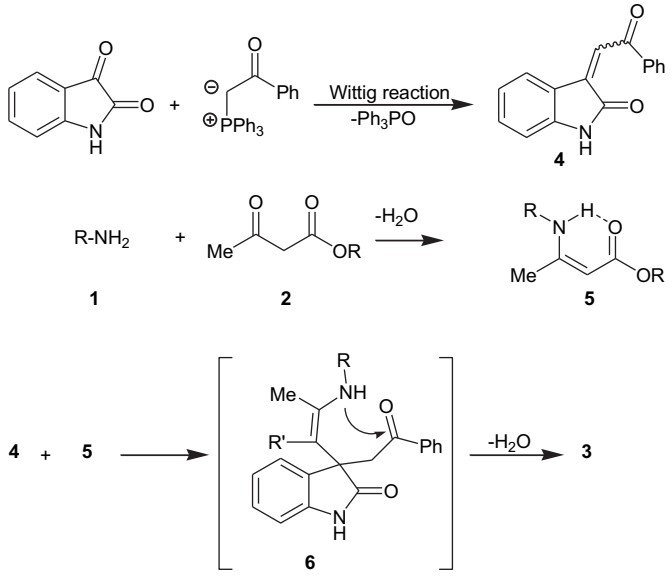
Scheme 1. Synthesis of spiro[indoline-3,4′-pyridine]-3′-carboxylate derivatives.

Different solvents, such as methanol, ethanol, acetonitrile, tetrahydrofuran (THF), and dichloromethane were explored. The results are summarized in Table 1. As can be seen from Table 1, the best results were obtained by heating the reaction mixture in methanol at reflux, which yielded product **3a** in high yield (Table 1, entry 1).

Encouraged by this success, we investigated the scope of the reaction of isatin, 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone, amines **1**, and 1,3-dicarbonyl compound **2**. The corresponding spiro[indoline-3,4′-pyridine]-3′-carboxylates **3a–l** were synthesized in high yields (74–85%), and the results are summarized in Table 2. It can be seen from Table 2 that the nature of the aryl substituent in the benzylamines had no significant effect on the final yield of the products. It was found that the reaction with 1-phenylpropan-2-one does not occur (entries 13 and 14).

The structures of compounds **3a–l** were deduced from their elemental analysis, mass, IR, and high-field ^1H and ^{13}C NMR spectra. The mass spectrum of **3a** displayed the molecular ion peak at m/z 436, which is in agreement with the proposed structure. The IR spectrum of this compound showed absorption bands due to the one NH group at 3172 cm^{-1} and the carbonyl groups at 1702 cm^{-1}. The ^1H NMR spectrum of **3a** showed five sharp singlets for $2CH_3$, CH_2, CH, and NH groups (δ=2.43, 3.35, 4.52, 5.05, and 8.36 ppm), and the aromatic moieties gave rise to multiplets in the aromatic region of the spectrum (δ=6.87–6.93 ppm). The ^1H-decoupled ^{13}C NMR spectrum of **3a** showed 23 distinct resonances in agreement with the suggested structure.

Although we have not established the mechanism of the reaction experimentally, a possible explanation is proposed in Scheme 2. Compound **3** could result from the initial addition of the benzylamine to alkyl acetoacetate and subsequent attack of the resulting reactive enaminone **5** on the compound **4** to yield intermediate **6**. Cyclization of the intermediate **6** and subsequent loss of H_2O leads to compound **3**.



Scheme 2. Proposed mechanism.

3. Conclusion

In conclusion, an efficient, clean, and simple method for the preparation of spiro[indoline-3,4′-pyridine]-3′-carboxylate derivatives using readily available starting materials is reported. These types of heterocycles contain a number of functional groups that may be lead to the biological activity of the title compounds. The reaction proceeds under neutral conditions with no bases or catalysts in high yield and simple purification of the products are the advantages of our work. The simplicity of the present procedure makes it an interesting alternative to the complex multistep approaches.

4. Experimental

4.1. General

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded at 500.1 and 125.7 MHz, respectively, on a BRUKER DRX 500-AVANCE FT-NMR instrument with DMSO-d_6 as a solvent. The reagents and solvents were obtained from Fluka (Buchs, Switzerland) and used without further purification.

4.2. General procedure for the preparation of compounds 3a–l, exemplified by 3a

A solution of 1-phenyl-2-(1,1,1-triphenyl-λ^5-phosphanylidene)-1-ethanone (0.38 g, 1 mmol) and isatin (0.15 g, 1 mmol) was magnetically stirred in MeOH (3 mL) for 20 min. Then, benzylamine (0.11 g, 1 mmol) and alkyl acetoacetate (1.2 mmol) were added simultaneously. The reaction mixture was stirred for 3 h under reflux conditions and the progress of the reaction was followed by thin layer chromatography. After completion, the solvent was removed under reduced pressure and the residue was purified by column chromatography (*n*-hexane/EtOAc, 3:1).

*4.2.1. Methyl 1′-benzyl-2′-methyl-2-oxo-6′-phenyl-1′H-spiro[indoline-3,4′-pyridine]-3′-carboxylate (**3a**).* White powder, mp=218–221 °C, 0.35 g, yield 80%. IR (KBr) (ν_{max}, cm^{-1}): 3172 (NH), 1702 (C=O), 1455 (Ar). Anal. Calcd for $C_{28}H_{24}N_2O_3$ (436.51): C, 77.05; H, 5.54; N, 6.42%. Found: C, 76.8; H, 5.51; N, 6.38%. MS (EI, 70 eV): *m*/*z* (%)=438 (M^+, 4), 404 (75), 313 (87), 296 (12), 154 (15), 91 (100), 69 (32), 57 (41). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=2.43 (3H, s, CH_3), 3.35 (3H, s, CH_3), 4.52 (1H, s, CH), 5.05 (2H, s, CH_2N), 6.87–6.93 (5H, m, 5CH of Ar), 7.14–7.16 (1H, m, CH of Ar), 7.25–7.34 (8H, m, 5CH of Ar), 8.36 (1H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=11.3 (CH_3), 45.1 (CH_2N), 47.5 (OCH_3), 49.17 (C_{spiro^2}), 108.4 (CH), 109.4 (*C*=CMe), 114.4 (CH of Ar), 121.1 (CH of Ar), 122.3 (CH of Ar), 125.2 (4CH of Ar), 126.7 (CH of Ar), 126.8 (CH of Ar), 128.1 (CH of Ar), 128.3 (2CH of Ar), 130.5 (CH of Ar), 131.1 (C_{ipso}), 131.3 (*C*=CH), 135.8 (C_{ipso}), 136.9 (C_{ipso}), 137.1 (*C*–Me), 140.8 (C_{ipso}), 164.6 (NC=O), 179.6 ppm (C=O).

*4.2.2. Ethyl 1′-benzyl-2′-methyl-2-oxo-6′-phenyl-1′H-spiro[indoline-3,4′-pyridine]-3′-carboxylate (**3b**).* White powder, mp=210–214 °C, 0.38 g, yield 84%. IR (KBr) (ν_{max}, cm^{-1}): 3183 (NH), 1700 (C=O), 1461 (Ar). Anal. Calcd for $C_{29}H_{26}N_2O_3$ (450.53): C, 77.31; H, 5.82; N, 6.22%. Found: C, 77.27; H, 5.76; N, 6.17%. MS (EI, 70 eV): *m*/*z* (%)=450 (M^+, 4), 404 (29), 313 (45), 220 (16), 105 (50), 91 (75), 69 (100), 55 (79). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=0.94 (3H, t, $^3J_{HH}$=6.8 Hz, CH_3), 2.45 (3H, s, CH_3), 3.88–3.92 (2H, m, CH_2), 4.53 (1H, s, CH), 5.05 (2H, s, CH_2N), 6.89–7.55 (14H, m, 14CH of Ar), 8.90 (1H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=11.4 (CH_3), 13.6 (CH_3), 45.4 (CH_2N), 47.5 (OCH_2), 58.4 (C_{spiro^2}), 108.7 (CH), 109.7 (*C*=CMe), 114.3 (CH of Ar), 121.3 (CH of Ar), 122.4 (CH of Ar), 125.2 (4CH of Ar), 126.7 (2CH of Ar), 126.9 (CH of Ar), 128.1 (CH of Ar), 128.4 (2CH of Ar), 130.2 (CH of Ar), 131.2 (C_{ipso}), 131.4 (*C*=CH), 135.80 (C_{ipso}), 137.0 (C_{ipso}), 137.1 (*C*–Me), 141.1 (C_{ipso}), 164.3 (NC=O), 178.0 ppm (C=O).

*4.2.3. Methyl 1′-(4-chlorobenzyl)-2′-methyl-2-oxo-6′-phenyl-1′H-spiro[indoline-3,4′-pyridine]-3′-carboxylate (**3c**).* White powder, mp=186–189 °C, 0.38 g, yield 81%. IR (KBr) (ν_{max}, cm^{-1}): 3186 (NH), 1702 (C=O), 1462 (Ar). Anal. Calcd for $C_{28}H_{23}ClN_2O_3$(470.95): C, 71.41; H, 4.92; N, 5.95%. Found: C, 71.35; H, 4.88; N, 5.93%. MS (EI, 70 eV): *m*/*z* (%)=470 (M^+, 8), 438 (58), 313 (95), 154 (16), 125 (79), 83 (100), 61 (16). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=2.43 (3H, s, CH_3), 3.34 (3H, s, CH_3), 4.49 (1H, s, CH), 5.00 (2H, s, CH_2N), 6.83–7.35 (13H, m, 13CH of Ar), 8.73 (1H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=11.2 (CH_3), 45.2 (CH_2N), 46.5 (OCH_3), 49.2 (C_{spiro^2}), 108.5 (CH), 109.6 (*C*=CMe), 114.7 (CH of Ar), 121.3 (CH of Ar), 122.4 (CH of Ar), 126.5 (4CH of Ar), 126.8 (CH of Ar), 128.3 (2CH of Ar), 128.6 (2CH of Ar), 130.0 (CH of Ar), 130.8 (C_{ipso}), 130.9 (C_{ipso}), 132.8 (*C*=CH), 135.4 (C_{ipso}), 135.7 (C_{ipso}), 136.9 (*C*–Me), 140.9 (C_{ipso}), 164.6 (NC=O), 179.8 ppm (C=O).

*4.2.4. Ethyl 1′-(4-chlorobenzyl)-2′-methyl-2-oxo-6′-phenyl-1′H-spiro[indoline-3,4′-pyridine]-3′-carboxylate (**3d**).* White powder, mp=168–170 °C, 0.38 g, yield 78%. IR (KBr) (ν_{max}, cm^{-1}): 3178 (NH), 1699 (C=O), 1465 (Ar). Anal. Calcd for $C_{29}H_{25}ClN_2O_3$ (484.98): C, 71.82; H, 5.20; N, 5.78. Found: C, 71.78; H, 5.17; N, 5.76%. MS (EI, 70 eV): *m*/*z* (%)=484 (M^+, 8), 438 (70), 313 (100), 154 (16), 125 (91), 105 (16), 89 (20). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=0.95 (3H, t, $^3J_{HH}$=7.0 Hz, CH_3), 2.44 (3H, s, CH_3), 3.92 (2H, q, $^3J_{HH}$=3.8 Hz, CH_2), 4.50 (1H, s, CH), 5.00 (2H, s, CH_2N), 6.84–7.51 (13H, m, 13CH of Ar), 8.35 (1H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=11.4 (CH_3), 13.6 (CH_3), 45.2 (CH_2N), 46.9 (OCH_2), 58.5 (C_{spiro^2}), 108.5 (CH), 110.0 (*C*=CMe), 114.6 (CH of Ar), 121.4 (CH of Ar), 122.4 (CH of Ar), 126.6 (4CH of Ar), 126.7 (CH of Ar), 128.2 (2CH of Ar), 128.5 (2CH of Ar), 130.0 (CH of Ar), 130.8 (C_{ipso}), 131.0 (*C*=CH), 132.7 (C_{ipso}), 135.4 (C_{ipso}), 135.7 (C_{ipso}), 136.7 (*C*–Me), 140.9 (C_{ipso}), 164.2 (NC=O), 179.3 ppm (C=O).

*4.2.5. Methyl 1′-(2-chlorobenzyl)-2′-methyl-2-oxo-6′-phenyl-1′H-spiro[indoline-3,4′-pyridine]-3′-carboxylate (**3e**).* White powder, mp=192–195 °C, 0.40 g, yield 85%. IR (KBr) (ν_{max}, cm^{-1}): 3205 (NH), 1702 (C=O), 1441 (Ar). Anal. Calcd for $C_{28}H_{23}ClN_2O_3$(470.95): C, 71.41; H, 4.92; N, 5.95%. Found: C, 71.38; H, 4.85; N, 5.91%. MS (EI, 70 eV): *m*/*z* (%)=470 (M^+, 8), 438 (75), 313 (100), 296 (12), 154 (16), 125 (83), 105 (12), 89 (25), 71 (12). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=2.40 (3H, s, CH_3), 3.36 (3H, s, CH_3), 4.53 (1H, s, CH), 5.07 (2H, s, CH_2N), 6.63 (1H, d, $^3J_{HH}$=7.2 Hz, CH of Ar), 6.88 (1H, d, $^3J_{HH}$=7.6 Hz, CH of Ar), 6.94 (2H, t, $^3J_{HH}$=6.2 Hz, 2CH of Ar), 7.15 (2H, t, $^3J_{HH}$=6.2 Hz, 2CH of Ar), 7.22–7.36 (7H, m, 7CH of Ar), 8.29 (1H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=11.0 (CH_3), 45.1 (CH_2N), 45.4 (OCH_3), 49.2 (C_{spiro^2}), 108.4 (CH), 109.7 (*C*=CMe), 114.8 (CH of Ar), 121.5 (CH of Ar), 122.5 (CH of Ar), 126.3 (4CH of Ar), 126.8 (CH of Ar), 127.0 (CH of Ar), 128.1 (CH of Ar), 128.3 (CH of Ar), 128.9 (CH of Ar), 129.8 (CH of Ar), 130.7 (C_{ipso}), 131.2 (C_{ipso}), 131.3 (*C*=CH), 134.5 (C_{ipso}), 135.8 (C_{ipso}), 137.0 (*C*–Me), 140.8 (C_{ipso}), 164.6 (NC=O), 179.4 ppm (C=O).

*4.2.6. Ethyl 1′-(2-chlorobenzyl)-2′-methyl-2-oxo-6′-phenyl-1′H-spiro[indoline-3,4′-pyridine]-3′-carboxylate (**3f**).* White powder, mp=208–211 °C, 0.39 g, yield 82%. IR (KBr) (ν_{max}, cm^{-1}): 3168 (NH), 1703 (C=O), 1448 (Ar). Anal. Calcd for $C_{29}H_{25}ClN_2O_3$ (484.98): C, 71.82; H, 5.20; N, 5.78. Found: C, 71.76; H, 5.15; N, 5.77%. MS (EI, 70 eV): *m*/*z* (%)=484 (M^+, 8), 438 (91), 411 (8), 313 (100), 296 (12), 125 (95), 89 (25). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=0.96 (3H, t, $^3J_{HH}$=7.05 Hz, CH_3), 2.41 (3H, s, CH_3), 3.92 (2H, q, $^3J_{HH}$=6.80 Hz, CH_2), 4.53 (1H, s, CH), 5.07 (2H, s, CH_2N), 6.66 (1H, d, $^3J_{HH}$=7.3 Hz, CH of Ar), 6.88 (1H, d, $^3J_{HH}$=7.6 Hz, CH of Ar), 6.94 (2H, d, $^3J_{HH}$=4.2 Hz, 2CH of Ar),

7.14–7.36 (9H, m, 9CH of Ar), 8.45 (1H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=11.2 (CH_3), 13.6 (CH_3), 45.2 (CH_2N), 52.9 (OCH_2), 58.5 (C_{spiro^2}), 108.6 (CH), 110.0 (*C*=CMe), 114.6 (CH of Ar), 121.4 (CH of Ar), 122.4 (CH of Ar), 126.3 (4CH of Ar), 126.7 (CH of Ar), 127.0 (CH of Ar), 128.1 (CH of Ar), 128.3 (CH of Ar), 128.9 (CH of Ar), 129.8 (CH of Ar), 130.6 (C_{ipso}), 131.2 (C_{ipso}), 131.3 (*C*=CH), 134.5 (C_{ipso}), 135.8 (C_{ipso}), 136.9 (*C*–Me), 140.9 (C_{ipso}), 164.2 (NC=O), 179.5 ppm (C=O).

*4.2.7. Methyl 2′-methyl-1′-(4-methylbenzyl)-2-oxo-6′-phenyl-1′H-spiro[indoline-3,4′-pyridine]-3′-carboxylate (**3g**).* White powder, mp=201–203 °C, 0.36 g, yield 79%. IR (KBr) (ν_{max}, cm^{-1}): 3189 (NH), 1699 (C=O), 1456 (Ar). Anal. Calcd for $C_{29}H_{26}N_2O_3$ (450.53): C, 77.31; H, 5.82; N, 6.22%. Found: C, 77.23; H, 5.78; N, 6.15%. MS (EI, 70 eV): *m*/*z* (%)=450 (M^+, 8), 418 (70), 313 (100), 285 (8), 105 (54), 77 (12). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=2.35 (3H, s, CH_3), 2.45 (3H, s, CH_3), 3.35 (3H, s, CH_3), 4.54 (1H, s, CH), 5.02 (2H, s, CH_2), 6.83 (2H, d, $^3J_{HH}$=7.7 Hz, 2CH of Ar), 6.92–6.94 (3H, m, 3CH of Ar), 7.14 (2H, d, $^3J_{HH}$=7.7 Hz, 2CH of Ar), 7.17 (1H, m, CH of Ar) 7.35 (3H, m, 3CH of Ar), 7.59 (1H, m, CH of Ar), 9.32 (1H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=11.8 (CH_3), 21.1 (CH_3), 45.9 (CH_2N), 47.8 (OCH_3), 50.8 (C_{spiro^2}), 109.2 (CH), 109.9 (*C*=CMe), 114.9 (CH of Ar), 121.9 (CH of Ar), 122.9 (CH of Ar), 125.6 (4CH of Ar), 127.2 (CH of Ar), 128.6 (2CH of Ar), 129.5 (2CH of Ar), 130.7 (CH of Ar), 131.3 (C_{ipso}), 131.7 (C_{ipso}), 134.4 (*C*=CH), 136.3 (C_{ipso}), 137.0 (C_{ipso}), 137.8 (*C*–Me), 141.7 (C_{ipso}), 165.2 (NC=O), 180.9 ppm (C=O).

*4.2.8. Ethyl 2′-methyl-1′-(4-methylbenzyl)-2-oxo-6′-phenyl-1′H-spiro[indoline-3,4′-pyridine]-3′-carboxylate (**3h**).* White powder, mp=214–216 °C, 0.34 g, yield 74%. IR (KBr) (ν_{max}, cm^{-1}): 3167 (NH), 1700 (C=O), 1452 (Ar). Anal. Calcd for $C_{30}H_{28}N_2O_3$ (464.56): C, 77.56; H, 6.07; N, 6.03%. Found: C, 77.52; H, 6.03, N, 6.01%. MS (EI, 70 eV): *m*/*z* (%)=464 (M^+, 12), 418 (100), 391 (4), 313 (83), 296 (8), 105 (58), 77 (8). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=0.94 (3H, t, $^3J_{HH}$=6.8 Hz, CH_3), 2.35 (3H, s, CH_3), 2.34 (3H, s, CH_3), 3.88–3.95 (2H, m, OCH_2), 4.52 (1H, s, CH), 5.00 (2H, s, CH_2N), 6.82–7.34 (13H, m, 13CH of Ar), 8.63 (1H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=11.5 (CH_3), 13.6 (CH_3), 20.5 (CH_3), 43.7 (CH_2), 47.3 (OCH_2), 58.4 (C_{spiro^2}), 108.6 (CH), 109.7 (*C*=CMe), 114.2 (CH of Ar), 121.3 (CH of Ar), 122.5 (CH of Ar), 125.1 (4CH of Ar), 126.7 (CH of Ar), 128.1 (2CH of Ar), 129.0 (2CH of Ar), 130.4 (CH of Ar), 130.9 (C_{ipso}), 131.2 (C_{ipso}), 133.9 (*C*=CH), 135.8 (C_{ipso}), 136.5 (C_{ipso}), 137.1 (*C*–Me), 140.9 (C_{ipso}), 164.3 (NC=O), 179.7 ppm (C=O).

*4.2.9. Methyl 2′-methyl-2-oxo-6′-phenyl-1′-propyl-1′H-spiro[indoline-3,4′-pyridine]-3′-carboxylate (**5i**).* White powder, mp=212–214 °C, 0.31 g, yield 79%. IR (KBr) (ν_{max}, cm^{-1}): 3162 (NH), 2932 (CH), 1697 (C=O), 1469 (Ar). Anal. Calcd for $C_{24}H_{24}N_2O_3$ (388.46): C, 74.21; H, 6.23; N, 7.21%. Found: C, 74.16; H, 6.20, N, 7.12%. MS (EI, 70 eV): *m*/*z* (%)=388 (M^+, 8), 356 (45), 313 (24), 296 (8), 149 (35), 77 (64), 57 (100). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=0.77 (3H, t, $^3J_{HH}$=7.3 Hz, CH_3), 1.55–1.59 (2H, m, CH_2), 2.53 (3H, s, CH_3), 3.31 (3H, s, CH_3), 3.72–3.75 (2H, m, NCH_2), 4.41 (1H, s, CH), 6.86–6.91 (3H, m, 3CH of Ar), 7.10–7.56 (6H, m, 6CH of Ar), 8.93 (1H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=11.09 (CH_3), 11.62 (CH_3), 23.92 (CH_2), 43.73 (CH_2), 45.66 (NCH_2), 46.06 (CH_3), 49.47 (C_{spiro^2}), 108.98 (CH), 109.19 (*C*=CMe), 114.62 (CH of Ar), 121.80 (CH of Ar), 122.94 (CH of Ar), 127.10 (2CH of Ar), 128.51 (2CH of Ar), 131.07 (CH of Ar), 131.66 (C_{ipso}), 131.95 (CH of Ar), 135.50 (*C*=CH), 137.03 (C_{ipso}), 137.03 (*C*–Me), 141.43 (C_{ipso}), 165.21 (NC=O), 179.87 ppm (C=O).

*4.2.10. Ethyl 1′-isobutyl-2′-methyl-2-oxo-6′-phenyl-1′H-spiro[indoline-3,4′-pyridine]-3′-carboxylate (**5j**).* White powder, mp=210–212 °C, 0.34 g, yield 81%. IR (KBr) (ν_{max}, cm^{-1}): 3291 (NH), 2958 (CH), 1703 (C=O), 1468 (Ar). Anal. Calcd for $C_{26}H_{28}N_2O_3$ (416.52): C, 74.98; H, 6.78; N, 6.73%. Found: C, 74.84; H, 6.65, N, 6.69%. MS (EI, 70 eV): *m*/*z* (%)=416 (M^+, 25), 370 (100), 327 (15), 313 (20), 154 (12), 127 (8), 77 (8), 57 (16). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=0.69 (3H, d, $^3J_{HH}$=2.5 Hz, CH_3), 0.71 (3H, d, $^3J_{HH}$=2.5 Hz, CH_3), 0.92 (3H, t, $^3J_{HH}$=7.05 Hz, CH_3), 1.75–1.80 (1H, m, CH), 2.56 (3H, s, CH_3), 3.68 (2H, d, $^3J_{HH}$=7.1 Hz, NCH_2), 3.87 (2H, q, $^3J_{HH}$=6.9, 14.0 Hz, CH_2), 4.42 (1H, s, CH), 6.85–6.92 (3H, m, 3CH of Ar), 7.11–7.51 (6H, m, 6CH of Ar), 8.50 (1H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=12.62 (CH_3), 14.08 (CH_3), 19.88 (CH_3), 19.92 (CH_3), 29.32 ($CH(CH_3)_2$), 45.66 (CH_2), 51.41 (NCH_2), 58.73 (C_{spiro^2}), 108.95 (CH), 109.56 (*C*=CMe), 114.61 (CH of Ar), 121.77 (CH of Ar), 122.90 (CH of Ar), 127.07 (2CH of Ar), 128.35 (2CH of Ar), 128.78 (C_{ipso}), 131.75 (CH of Ar), 132.04 (CH of Ar), 135.84 (*C*=CH), 137.39 (C_{ipso}), 137.03 (*C*–Me), 144.93 (C_{ipso}), 164.82 (NC=O), 179.48 ppm (C=O).

*4.2.11. 3′-Acetyl-1′-benzyl-2′-methyl-6′-phenyl-1′H-spiro[indoline-3,4′-pyridin]-2-one (**5k**).* White powder, mp=204–206 °C, 0.33 g, yield 78%. IR (KBr) (ν_{max}, cm^{-1}): 3266 (NH), 1710 (C=O), 1625 (C=O), 1418 (Ar). Anal. Calcd for $C_{28}H_{24}N_2O_2$ (420.51): C, 79.98; H, 5.75; N, 6.66%. Found: C, 79.91; H, 5.68; N, 6.62%. MS (EI, 70 eV): *m*/*z* (%)=420 (M^+, 4), 199 (20), 183 (16), 118 (25), 84 (100), 51 (65). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=2.28 (3H, s, CH_3), 2.41 (3H, s, CH_3), 4.46 (1H, s, CH), 5.07 (2H, s, CH_2N), 6.88–6.95 (5H, m, 5CH of Ar), 7.28–7.69 (9H, m, 9CH of Ar), 7.71 (1H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=13.39 (CH_3), 30.58 (CH_3), 45.52 (NCH_2), 52.82 (C_{spiro^2}), 108.98 (CH), 121.55 (CH of Ar), 122.47 (CH of Ar), 125.58 (4CH of Ar), 127.18 (CH of Ar), 127.43 (CH of Ar), 128.41 (2CH of Ar), 128.51 (2CH of Ar), 128.70 (C_{ipso}), 128.91 (2CH of Ar), 130.48 (C_{ipso}), 131.87 (*C*–Me), 131.89 (*C*=CH), 132.04 (C_{ipso}), 132.12 (C_{ipso}), 137.33 (C_{ipso}), 165.14 (NC=O), 180. 18 ppm (C=O).

*4.2.12. Methyl 1′-(4-methoxyphenyl)-2′-methyl-2-oxo-6′-phenyl-1′H-spiro[indoline-3,4′-pyridine]-3′-carboxylate (**5l**).* White powder, mp=254–256 °C, 0.35 g, yield 80%. IR (KBr) (ν_{max}, cm^{-1}): 3170 (NH), 1703 (C=O), 1508 (Ar). Anal. Calcd for $C_{27}H_{22}N_2O_3$ (452.51): C, 74.32; H, 5.35; N, 6.19%. Found: C, 74. 68; H, 5.20; N, 6.17%. MS (EI, 70 eV): *m*/*z* (%)=452 (M^+, 4), 420 (25), 391 (8), 313 (10), 216 (12), 127 (15), 108 (46), 92 (75), 77 (100). ^{1}H NMR (500.13 MHz, $CDCl_3$): δ_H=2.34 (3H, s, CH_3), 3.37 (3H, s, CH_3), 3.79 (3H, s, CH_3), 4.66 (1H, s, CH), 6.79–6.98 (5H, m, 5CH of Ar), 7.14–7.28 (8H, m, 8CH of Ar), 8.40 (1H, s, NH). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C=12.77 (CH_3), 45.62 (CH_3), 49.77 (OCH_3), 53.39 (C_{spiro^2}), 108.91 (CH), 109.99 (*C*=CMe), 114.10 (2CH of Ar), 121.97 (CH of Ar), 123.16 (CH of Ar), 127.23 (2CH of Ar), 127.65 (CH of Ar), 128.17 (2CH of Ar), 129.46 (CH of Ar), 129.82 (CH of Ar),130.43 (*C*=CH), 130.88 (C_{ipso}), 131.01 (2CH of Ar), 131.55 (*C*–Me), 136.48 (C_{ipso}), 138.62 (C_{ipso}), 141.28 (C_{ipso}), 159.01 (C–OMe),165.24 (NC=O), 180.22 ppm (C=O).

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.03.032. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Schreiber, S. L. *Science* **2000**, *287*, 1964–1969; (b) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 303–313.
2. Terrett, N. K. *Combinatorial Chemistry*; Oxford University Press: New York, NY, 1998.
3. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123–131.
4. Tietze, L. F.; Lieb, M. E. *Curr. Opin. Chem. Biol.* **1998**, *2*, 363–371.
5. Dax, S. L.; McNally, J. J.; Youngman, M. A. *Curr. Med. Chem.* **1999**, *6*, 255–270.
6. Plunkett, M.; Ellman, J. A. *Sci. Am.* **1997**, *276*, 68–73.
7. Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366–374.
8. Weber, L. *Drug Discovery Today* **2002**, *7*, 143–147.
9. Sundberg, R. J. *The Chemistry of Indoles*; Academic: New York, NY, 1996.
10. (a) Joshi, K. C.; Chand, P. *Pharmazie* **1982**, *37*, 1–12; (b) Da-Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273–324; (c) Abdel-Rahman, A. H.; Keshk, E. M.; Hanna, M. A.; El-Bady, S. M. *Bioorg. Med. Chem.* **2006**, *12*, 2483–2488.
11. Kobayashi, J.; Tsuda, M.; Agemi, K.; Shigemori, H.; Ishibashi, M.; Sasaki, T.; Mikami, Y. *Tetrahedron* **1991**, *47*, 6617–6622.

12. James, D. M.; Kunze, H. B.; Faulkner, D. J. *J. Nat. Prod.* **1991**, *54*, 1137–1140.
13. (a) Khafagy, M. M.; El-Wahas, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. *Farmaco* **2002**, *57*, 715–722; (b) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667.
14. Kang, T. H.; Matsumoto, K.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H. *Eur. J. Pharmacol.* **2002**, *444*, 39–45.
15. Manian, R. D. R. S.; Jayashankaran, J.; Raghunathan, R. *Synth. Commun.* **2003**, *33*, 4053–4061.
16. Lo, M. M. C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077–16086.
17. Poornachandran, M.; Muruganantham, R.; Raghunathan, R. *Synth. Commun.* **2006**, *36*, 141–150.
18. Litvic, M.; Cepanec, I.; Filipan, M.; Kos, K.; Bartolincic, A.; Druskovic, V.; Tibi, M. M.; Vinkovic, V. *Heterocycles* **2005**, *65*, 23–35.
19. Liu, Z.; Han, B.; Liu, Q.; Zhang, W.; Yang, L.; Liu, Z. L.; Yu, W. *Synlett* **2005**, 1579–1580.
20. Sabitha, G.; Reddy, G. S. K. K.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2003**, *44*, 4129–4131.
21. Harper, J. L.; Camerini-Otero, C. S.; Li, A. H.; Kim, S. A.; Jacobson, K. A.; Daly, J. W. *Biochem. Pharmacol.* **2003**, *65*, 329–338.
22. Zarghi, A.; Sadeghi, H.; Fassihi, A.; Faizi, M.; Shafiee, A. *Farmaco* **2003**, *58*, 1077–1081.
23. (a) Zohreh, N.; Alizadeh, A.; Bijanzadeh, H. R.; Zhu, L. G. *J. Comb. Chem.* **2010**, *12*, 497; (b) Rostamnia, S.; Alizadeh, A.; Zhu, L. G. *J. Comb. Chem.* **2009**, *11*, 143; (c) Alizadeh, A.; Rezvanian, A. *Tetrahedron* **2010**, *66*, 6924; (d) Alizadeh, A.; Noaparast, Z.; Sabahnoo, H.; Zohreh, N. *Synlett* **2010**, *10*, 1496; (e) Alizadeh, A.; Sabahnoo, H.; Noaparast, Z.; Zohreh, N.; Mikaeili, A. *Synlett* **2010**, 1854; (f) Alizadeh, A.; Rostamnia, S.; Zhu, L. G. *Tetrahedron Lett.* **2010**, *51*, 4750.