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3-Aryl β-carbolin-1-ones as a new class of potent inhibitors of tumor cell proliferation: synthesis and biological evaluation

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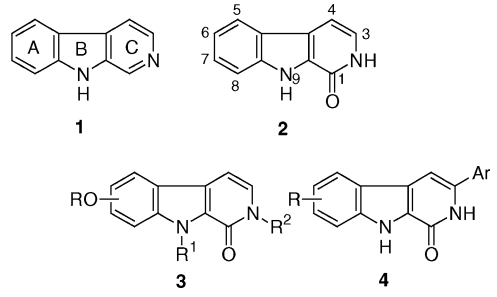
Received 23rd August 2004, Accepted 11th January 2005
First published as an Advance Article on the web 7th February 2005

A novel three-step synthesis of 3-aryl β-carbolin-1-ones from non-indole starting materials has been developed. The two nitrogen atoms in β-carbolin-1-one were introduced efficiently by Michael addition of ethyl acetamidocyanoacetate to chalcone. The desired pyridone and indole rings were assembled by an intramolecular ketone–nitrile annulation mediated by aqueous HCl–HOAc and a Cu(I)-catalyzed intramolecular *N*-arylation of the amide, respectively. The target compounds were found to possess significant activity against tumor cell proliferaton.

Introduction

β-Carboline (**1**, Scheme 1) is a key pharmacophore present in a number of biologically important natural tricyclic alkaloids.[1,2] Its structural variant β-carbolin-1-one (**2**) has served as an important intermediate for the preparation of complex alkaloids[3] and has been found to possess potent bioactivities on the central nervous system.[4] In 2001, some A-ring alkoxy-substituted β-carbolin-1-ones (**3**) were first reported in a patent literature to inhibit colon and lung tumor.[5] Subsequently, we have found that 3-aryl β-carbolin-1-ones (**4**) display strong anti-tumor activities.[6] Herein we report a novel synthetic route for the preparation of derivatives of **4**[7] and their activities on HeLa cell proliferation.

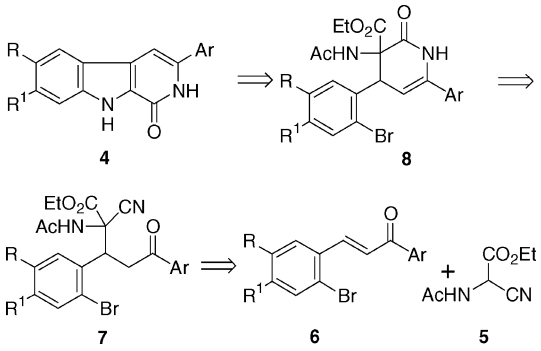


Scheme 1 β-Carboline and β-carbolin-1-ones.

Significant efforts have been made to construct the skeleton of β-carbolin-1-one (**2**) over recent years. Two major synthetic strategies have been adopted for this purpose, initiated directly or indirectly with a few indole derivatives. The first is to build pyridone rings by using acid- or Pd-catalyzed intramolecular cyclization of indole-2-carboxylic acid amides,[5,8–9] or intramolecular Heck reaction of 3-iodoindole-2-carboxylic acid amides.[10] The other is to modify the corresponding tricyclic precursors,[11–13] by for example dehydrogenation of polyhydro-β-carbolin-1-one[3a–b] or oxidation of β-carboline (**1**) to yield the corresponding *N*-oxides, followed by a thermal rearrangement.[3e,g–i] For our purpose to synthesize 3-aryl β-carbolin-1-one (**4**), these methods suffered from either inaccessible starting materials or elaborate multi-step syntheses.

As a number of lactams are readily prepared by ketone–nitrile annulation[14] and the *N*-arylation of amide can be achieved *via* catalysis by Pd[15] and/or Cu(I),[16] a novel three-step synthetic route for 3-aryl β-carbolin-1-one (**4**) from non-indole starting materials was designed, as shown in Scheme 2.

The two nitrogen atoms in target compound **4** were introduced efficiently by Michael addition of ethyl acetamidocyanoacetate (**5**) to chalcone (**6**), followed by the assembly of the pyridone and indole rings by an intramolecular ketone–nitrile annulation and a Cu(I)-catalyzed intramolecular *N*-arylation of amide, respectively.



Scheme 2 *Retro*-Synthesis of 3-aryl β-carbolin-1-one **4**.

Results and discussion

Assembly of adduct 7 by Michael addition

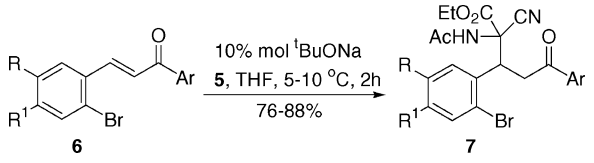
Although ethyl acetamidocyanoacetate (**5**) has a suitable structure to be a nucleophilic donor for Michael addition, it has rarely been employed for this purpose in the literature.[17] One of its nitrogen-containing groups was often "wasted" in other applications.[18] When we treated the mixture of **5** and chalcone **6a** with an equimolar amount of EtONa in EtOH at room temperature for 2 h, the desired adduct **7a** was obtained in 32% yield, with a tedious separation by chromatography. To optimize the yield of this reaction, the bases and solvents used were altered (Table 1) and **7a** was obtained in 86% yield when the reaction was carried out in THF with catalytic amount of *t*-BuONa (10% mol) at 5–10 °C for 2 h. As shown in Scheme 3 and Table 2, the additions of **5** to other chalcones **6b–i** yielded the corresponding adducts **7b–i** in 76–88% yields under similar conditions.

For the atom-saving, attempts were made to use *N*-(cyanomethyl)acetamide (**9**) as an alternative to **5** during Michael addition (Scheme 4). Unfortunately, Michael addition between **9** and **6j** gave 1:2-adduct **10** as a unique or a major product under a variety of conditions (such as NaOH, $NaHCO_3$,

DOI: 10.1039/b412921k

Table 1 Effect of bases and solvents on the yield of **7a**

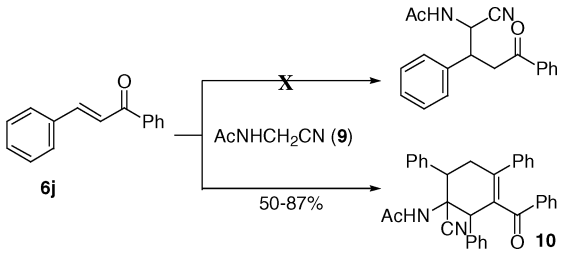
Entry	Base/mol	Solvent	Temp./°C	Yield of **7a** (%)
1	EtONa (1.0)	EtOH	25–30	32
2	EtONa (1.0)	THF	25–30	45
3	*t*-BuONa (1.0)	*t*-BuOH	25–30	47
4	*t*-BuONa (1.0)	THF	25–30	70
5	*t*-BuONa (0.5)	THF	25–30	74
6	*t*-BuONa (0.1)	THF	25–30	75
7	*t*-BuONa (0.1)	THF	5–10	86



Scheme 3 Introduction of two nitrogen atoms by Michael addition.

Table 2 The preparation of compounds **7**, **8** and **4**

				Yields (%)		
6,7,8,4	R	R^1	Ar	**7**	**8**	**4**
a	H	H	C_6H_5	86	80	68
b	H	H	4-ClC_6H_4	88	77	67
c	H	H	4-MeC_6H_4	76	67	70
d	OCH_2O		C_6H_5	77	84	60
e	OCH_2O		4-ClC_6H_4	83	81	64
f	OCH_2O		4-MeC_6H_4	81	76	62
g	MeO	MeO	C_6H_5	76	88	65
h	MeO	MeO	4-ClC_6H_4	84	80	72
i	MeO	MeO	4-MeC_6H_4	77	80	60



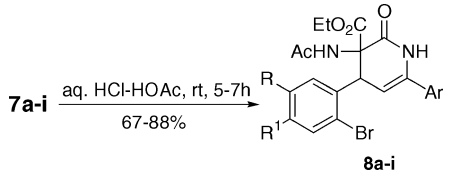
Scheme 4 1:2-adduct **10** as a unique or major product.

pyridine or piperidine as base, THF or EtOH as solvent), because two acidic protons on the methylene in **9** were involved in the reaction.

The construction of dihydropyridone 8 by intramolecular ketone–nitrile annulation

The intermediate **7** can be further elaborated by two possible pathways: the indole ring is built first by an intramolecular *N*-arylation of amide, or the pyridone ring is constructed preferentially by an intramolecular ketone–nitrile annulation. Unfortunately, **7a** did not result in any indole product in the intramolecular *N*-arylation of amide catalyzed by $Pd(OAc)_2$–P(*o*-tolyl)$_3$–Cs_2CO_3[15b] or $Pd(OAc)_2$–DPEphos–Cs_2CO_3[15d] at 100 °C in toluene for 10 h, while chalcone **6a** was recovered in almost quantitative yield. A control experiment revealed that this result arose from *retro*-Michael addition of **7a** catalyzed by Cs_2CO_3. Moreover, we found that compound **7a** was extremely sensitive to base and that the *retro*-Michael addition can take place even in the presence of Na_2CO_3.

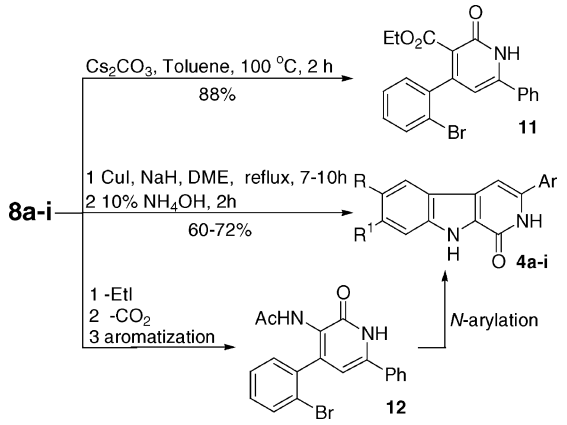
Next, a neutral ketone–nitrile annulation of **7a** catalyzed by $RuH_2(PPh_3)_4$[14d–e] in aqueous DME gave an unseparated mixture. Finally, we found that acid-catalyzed ketone–nitrile annulation of **7a** mediated by H_3PO_4–P_2O_5[14b–c] or EtOH–H_2SO_4[14a,f] proceeded smoothly to give the desired product dihydopyridone **8a** as white crystals, but associated with low yields (24–46%) largely due to the poor solubility of both substrate and product in the solvent used. In our improved procedure, the best yield of **8a** (80%) was obtained by standing the mixture of **7a** in aqueous HCl–HOAc at room temperature for 5–7 h. Using the same procedure, compounds **7b–i** were converted to the corresponding products **8b–i** in 67–88% yields (Scheme 5, Table 2). We observed that **8a–i** are pure regioisomers in two groups **8a–g** and **8h–i**, resulting from the stereochemistry of bromophenyl substituent. Since the stereochemistry will disappear automatically in next step, they were therefore not defined.



Scheme 5 Efficient ketone–nitrile annulation.

Preparation of 2-aryl β-carbolin-1-one 4 by Cu(I)-promoted intramolecular *N*-arylation of amide

When compound **8a** was treated with $Pd(OAc)_2$–P(*o*-tolyl)$_3$–Cs_2CO_3, a crystalline product was obtained in good yield. However, instead of an *N*-arylation product, the product was assigned as 4-(2-bromophemyl)-2-oxo-6-phenyl-1,2-dihydro-pyridine-3-carboxylic acid ethyl ester (**11**, Scheme 6). Since **11** was also obtained without $Pd(OAc)_2$ and P(*o*-tolyl)$_3$, its formation must result from a Cs_2CO_3 promoted elimination of acetoamino group.[19]



Scheme 6 Cu(I)-catalyzed intramolecular *N*-arylation of amide.

Fortunately, when compound **8a** was treated under improved Goldberg reaction conditions (CuI–NaH–DMF at 90 °C for 2 h), the target compound 3-phenyl β-carbolin-1-one (**4a**) was obtained in 20% yield. By varying the reaction conditions, we found that the yield of **4a** was affected significantly by the solvents and the amount of NaH used. As shown in Table 3, the best yield (68%) was obtained by refluxing the mixture of **8a**–CuI–NaH (1 : 2 : 4 by mole) in DME followed by work-up with 10% aqueous NH_4OH. Under similar conditions, **8b–i** were converted into the corresponding **4b–i** smoothly and in moderate yields (60–72%, Table 2). The structure of **4g** was confirmed by its single crystal X-ray diffraction analysis (Fig. 1).[20]†

Since *N*-[4-(2-bromophenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-yl]acetamide (**12**) was captured during the reaction and it can be converted into **4a** with CuI–NaH, a tandem reaction

† CCDC reference number 254765. See http://www.rsc.org/suppdata/ob/b4/b412921k/ for crystallographic data in .cif or other electronic format.

Table 3 Effect of solvent and NaH on the yield of **4a**[a]

Solvent	NaH : **4a**/mol : mol)	Temp./°C	Time/h[b]	Yield (%)
DMF	2	90	2	20
DMF	4	90	2	45
Pyridine	4	110	4	< 10
DMA	4	90	4	< 10
DME	4	84	7	68

[a] Two equivalents of CuI was used. [b] The time at which **8a** was exhausted.

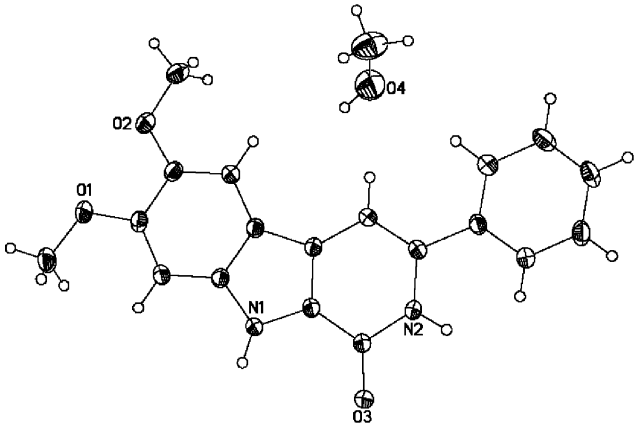


Fig. 1 The X-ray crystal structure of compound **4g**.

sequenced by the cleavage of the ester, a decarboxylation–aromatization and an *N*-arylation of the amide was proposed (Scheme 6). CuI played a critical role in both the initiation step to cleave the ester and in the end step to promote the intramolecular *N*-arylation of intermediate **12** to give target compound **4**.

Biological evaluation

The compounds **4a–i** were tested in a tumor cell proliferation assay using the HeLa cell line. Although compound **2** is inactive against HeLa cells, addition of an aromatic group at C3 of compound **2** gave rise to potent inhibitors of HeLa cell proliferation with IC_{50} values in the low micromolar range (Table 4 and Experimental section). Substitution at the C6 and C7 positions decreased (**4d–f**) or completely eliminated (**4g–i**) activity. Together, these results indicate that the compounds accessible through the method disclosed in this manuscript have potential as inhibitors of tumor cell growth. The experiments also prove that the aromatic groups substituted on C3 in **4** are essential for their bioactivities.

Conclusion

A novel three-step synthetic route to a group of bioactive 3-aryl β-carbolin-1-ones (**4**) was developed by using non-indole starting materials. Ethyl acetamidocyanoacetate (**5**) was employed as a nucleophilic donor in a Michael addition for the introduction of two nitrogen-containing functional groups to the adduct **7**. An intramolecular ketone–nitrile annulation of **7** mediated by aqueous HCl–HOAc yielded dihydopyridone **8** conveniently. Finally, the target compound **4** was obtained by a Cu(I)-catalyzed intramolecular *N*-arylation of the amide. The resulting compounds **4a–i** were tested in a tumor cell proliferation assay using the HeLa cell line and the results proved that the aromatic groups substituted on C3 in **4** are essential for their bioactivities.

Experimental

The IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer as KBr pellets. The ^1H NMR spectra were recorded on a Bruker ACF-300 spectrometer in $CDCl_3$ with TMS as internal reference. The *J* values are given in Hz. MS spectra were obtained on a VG-ZAB-HS mass spectrometer with 70 eV. The elemental analyses were performed on a Perkin-Elmer 240C instrument.

General procedure for the preparation of 7a–i by Michael addition

To a cold solution (ice–water bath) of ethyl acetamidocyanoacetate (**5**, 3.4 g, 20 mmol) and chalcone (**6**, 10 mmol) in anhydrous THF (50 mL) was added solid *t*-BuONa (96 mg, 1.0 mmol) in one portion. After the resultant mixture was stirred at 5–10 °C for 2 h (monitored by TLC), the solvent was removed under a vacuum. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous solution of Na_2CO_3. The organic layer was dried over Na_2SO_4 and removal of the solvent gave the crude product, which was purified by chromatography [silica gel, 50% EtOAc in petroleum ether (60–90 °C)] to yield pure compound **7**.

2-Acetylamino-2-cyano-3-(2-bromophenyl)-5-oxo-5-phenylpentanoic acid ethyl ester (7a). Mp 166–170 °C (EtOH); (found: C, 57.71; H, 4.85; N, 6.15%. $C_{22}H_{21}BrN_2O_4$ requires: C, 57.78; H, 4.63; N, 6.13%); ν_{max}/cm^{-1} 3360, 2981, 2247, 1757, 1689, 1673, 1596; δ_H 8.35 (1H, s), 8.01–7.88 (3H, m), 7.65–7.44 (5H, m), 7.23–7.20 (1H, m), 4.83 (1H, dd, $J = 8.0$, 2.9), 4.14–3.90 (3H, m), 3.72 (1H, dd, $J = 19.3$, 2.8), 2.12 (3H, s), 0.95 (3H, t, $J = 7.2$); *m/z* 458 (M + 2, 0.1%), 105 (100).

2-Acetylamino-2-cyano-3-(2-bromophenyl)-5-oxo-5-(4-chlorophenyl)pentanoic acid ethyl ester (7b). Mp 152–156 °C (EtOH); (found: C, 53.74; H, 4.14; N, 5.75%. $C_{22}H_{20}BrClN_2O_4$ requires: C, 53.73; H, 4.10; N, 5.70%); ν_{max}/cm^{-1} 3252, 2972, 2246, 1762, 1685, 1665; δ_H 8.18 (1H, s), 7.97–7.94 (2H, m), 7.88 (1H, dd, $J = 7.9$, 1.4), 7.59 (1H, dd, $J = 8.0$, 1.3), 7.50–7.48 (2H, m), 7.44–7.39 (1H, m), 7.23–7.19 (1H, m), 4.81 (1H, dd, $J = 7.9$, 3.1), 4.09–3.91 (3H, m), 3.68 (1H, dd, $J = 19.1$, 3.1), 2.12 (3H, s), 0.95 (3H, t, $J = 7.1$); *m/z* 492 (M^+, 1.2%), 241 (100).

2-Acetylamino-2-cyano-3-(2-bromophenyl)-5-oxo-5-(4-methylphenyl)pentanoic acid ethyl ester (7c). Mp 146–148 °C (EtOH); (found: C, 58.62; H, 4.73; N, 6.06%. $C_{23}H_{23}BrN_2O_4$ requires: C, 58.61; H, 4.92; N, 5.94%); ν_{max}/cm^{-1} 3371, 2987, 2247, 1760, 1692, 1669, 1604; δ_H 8.41 (1H, s), 7.92–7.89 (3H, m), 7.58 (1H, dd, $J = 8.0$, 1.3), 7.44–7.39 (1H, m), 7.31–7.28 (2H, m), 7.23–7.17 (1H, m), 4.81 (1H, dd, $J = 8.2$, 2.7), 4.10–3.91 (3H, m), 3.68 (1H, dd, $J = 19.2$, 2.8), 2.45 (3H, s), 2.11 (3H, s), 0.92 (3H, t, $J = 7.1$); *m/z* 470 (M^+, 0.9%), 119 (100).

Table 4 The inhibition of HeLa cell proliferation by compounds **4a–i** and **2**

Compound	$IC_{50}/\mu M$	STDEV/μM	Compound	$IC_{50}/\mu M$	STDEV/μM
4a	1.50	±0.48	**4f**	2.11	±0.046
4b	1.17	±0.087	**4g**	NA[a]	—
4c	1.20	±0.087	**4h**	NA[a]	—
4d	>30	—	**4i**	>30	—
4e	17.11	±2.13	**2**	NA[a]	—

[a] No inhibition was observed at 30 μM.

2-Acetylamino-2-cyano-3-(2-bromo-4,5-methylenedioxy)-5-oxo-5-phenylpentanoic acid ethyl ester (7d). Mp 196–200 °C (EtOH); (found: C, 55.15, H, 4.28; N, 5.57%. $C_{23}H_{21}BrN_2O_6$ requires: C, 55.10; H, 4.22; N, 5.59%); ν_{max}/cm^{-1} 3251, 3030, 2246, 1758, 1682, 1654, 1598; δ_H 8.24 (1H, s), 8.02 (2H, d, J = 7.3), 7.69–7.62 (1H, m), 7.52 (2H, t, J = 7.5), 7.35 (1H, s), 7.07 (1H, s), 6.03 (2H, s), 4.75 (1H, dd, J = 8.1, 2.7), 4.09–4.0 (3H, m), 3.67 (1H, dd, J = 19.2, 2.7), 2.12 (3H, s), 1.08 (3H, t, J = 7.1); m/z 502 (M + 2, 4.4%), 500 (M^+, 4.7), 105 (100).

2-Acetylamino-2-cyano-3-(2-bromo-4,5-methylenedioxy)-5-oxo-5-(4-chlorophenyl)pentanoic acid ethyl ester (7e). Mp 168–172 °C (EtOH); (found: C, 51.53, H, 3.76; N, 5.43%. $C_{23}H_{20}BrClN_2O_6$ requires: C, 51.56; H, 3.76; N, 5.23%); ν_{max}/cm^{-1} 3251, 3035, 2246, 1760, 1684, 1655, 1589; δ_H 8.07 (1H, s), 7.97–7.93 (2H, m), 7.51–7.47 (2H, m), 7.31 (1H, s), 7.00 (1H, s), 6.03 (2H, s), 4.73 (1H, dd, J = 7.9, 3.2), 4.09–3.95 (3H, m), 3.62 (1H, dd, J = 19.1, 3.2), 2.06 (3H, s), 1.08 (3H, t, J = 7.1); m/z 536 (M + 2, 0.1%), 139 (100).

2-Acetylamino-2-cyano-3-(2-bromo-4,5-methylenedioxy)-5-oxo-5-(4-methylphenyl)pentanoic acid ethyl ester (7f). Mp 180–184 °C (EtOH); (found: C, 55.90; H, 4.69; N, 5.25%. $C_{24}H_{23}BrN_2O_6$ requires: C, 55.94; H, 4.50; N, 5.44%); ν_{max}/cm^{-1} 3257, 3035, 2247, 1761, 1678, 1655, 1607; δ_H 8.33 (1H, s), 7.91 (2H, d, J = 8.2), 7.36 (1H, s), 7.31 (2H, d, J = 8.0), 7.00 (1H, s), 6.03 (2H, s), 4.73 (1H, dd, J = 8.2, 2.7), 4.09–3.95 (3H, m), 3.63 (1H, dd, J = 19.1, 2.8), 2.43 (3H, s), 2.10 (3H, s), 1.07 (3H, t, J = 7.1); m/z 516 (M + 2, 0.1%), 514 (M^+, 0.2), 119 (100).

2-Acetylamino-2-cyano-3-(2-bromo-4,5-dimethoxyphenyl)-5-oxo-5-phenylpentanoic acid ethyl ester (7g). Mp 214–216 °C (EtOH); (found: C, 55.61; H, 5.00; N, 5.46%. $C_{24}H_{25}BrN_2O_6$ requires: C, 55.72; H, 4.87; N, 5.41%); ν_{max}/cm^{-1} 3377, 2987, 2248, 1757, 1683, 1665, 1602; δ_H 8.36 (1H, s), 8.03–8.0 (2H, m), 7.66 (1H, t, J = 7.2), 7.52 (2H, J = 7.9), 7.43 (1H, s), 6.98 (1H, s), 4.70 (1H, dd, J = 8.1, 2.7), 4.14–3.95 (6H, m), 3.87 (3H, s), 3.70 (1H, dd, J = 19.1, 2.7), 2.11 (3H, s), 1.01 (3H, t, J = 7.1); m/z 518 (M + 2, 1.3%), 516 (M^+, 1.2), 105 (100).

2-Acetylamino-2-cyano-3-(2-bromo-4,5-dimethoxyphenyl)-5-oxo-5-(4-chlorophenyl)pentanoic acid ethyl ester (7h). Mp 196–198 °C (EtOH); (found: C, 52.13; H, 4.32; N, 5.28%. $C_{24}H_{24}BrClN_2O_6$ requires: C, 52.24; H, 4.38; N, 5.08%); ν_{max}/cm^{-1} 3265, 3068, 2247, 1758, 1688, 1660, 1590; δ_H 8.22 (1H, s), 7.97 (2H, d, J = 8.5), 7.50 (2H, d, J = 8.4), 7.42 (1H, s), 6.99 (1H, s), 4.68 (1H, dd, J = 8.1, 2.5), 4.05–3.91 (6H, m), 3.87 (3H, s), 3.65 (1H, dd, J = 19.1, 2.5), 2.11 (3H, s), 1.02 (3H, t, J = 7.1); m/z 552 (M + 2, 0.5%), 139 (100).

2-Acetylamino-2-cyano-3-(2-bromo-4,5-dimethoxyphenyl)-5-oxo-5-(4-methylphenyl)pentanoic acid ethyl ester (7i). Mp 184–188 °C (EtOH); (found: C, 56.57; H, 5.10; N, 5.40%. $C_{25}H_{27}BrN_2O_6$ requires: C, 56.51; H, 5.12; N, 5.27%); ν_{max}/cm^{-1} 3268, 2995, 2247, 1760, 1682, 1661, 1606; δ_H 8.45 (1H, s), 7.92 (2H, d, J = 8.0), 7.44 (1H, s), 7.31 (2H, d, J = 8.0), 6.98 (1H, s), 4.68 (1H, dd, J = 6.8, 2.5), 4.04–3.95 (6H, m), 3.87 (3H, s), 3.67 (1H, dd, J = 19.1, 1.6), 2.45 (3H, s), 2.11 (3H, s), 1.01 (3H, t, J = 7.1); m/z 532 (M + 2, 1.3%), 530 (M^+, 1.2), 119 (100).

General procedure for the preparation of 2-pyridone 8a–i

To a cold solution (ice–water bath) of aqueous HCl (37%, 5 mL) and HOAc (50 mL) was added solid compound **7** (10 mmol) in one portion. After the resultant mixture was stirred at room temperature for 5–7 h (monitored by TLC), it was poured into ice–water. The mixture was neutralized to pH 7 by solid $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and dried over Na_2SO_4. The solvent was removed to yield a residue, which was purified by recrystallization to give pure compound **8**.

3-Acetylamino-4-(2-bromophenyl)-2-oxo-6-phenyl-1,2,3,4-tetrohydropyridine-3-carboxylic acid ethyl ester (8a). Mp 212–216 °C (EtOAc); (found: C, 57.62; H, 4.59; N, 6.08%. $C_{22}H_{21}BrN_2O_4$ requires: C, 57.78; H, 4.63; N, 6.13%); ν_{max}/cm^{-1} 3416, 3373, 1734, 1704, 1674, 1599; δ_H 7.62 (1H, s), 7.59 (1H, s), 7.55–7.46 (2H, m), 7.45–7.40 (3H, m), 7.27–7.25 (2H, m), 7.19–7.15 (1H, m), 6.72 (1H, s), 5.57 (1H, d, J = 2.5), 5.26 (1H, s), 4.27–4.06 (2H, m), 2.13 (3H, s), 1.27 (3H, t, J = 7.2); m/z 458 (M + 2, 0.2%), 456 (M^+, 0.2), 290 (100).

3-Acetylamino-4-(2-bromophenyl)-2-oxo-6-(4-chlorophenyl)-1,2,3,4-tetrohydropyridine-3-carboxylic acid ethyl ester (8b). Mp 228–230 °C (EtOAc); (found: C, 53.81; H, 4.10; N, 5.72%. $C_{22}H_{20}BrClN_2O_4$ requires: C, 53.73; H, 4.10; N, 5.70%); ν_{max}/cm^{-1} 3409, 3266, 1740, 1704, 1660; δ_H 7.62 (1H, d, J = 1.0), 7.59 (1H, s), 7.41 − 7.38 (4H, m), 7.27–7.16 (3H, m), 6.69 (1H, s), 5.56 (1H, d, J = 2.5), 5.25 (1H, s), 4.27–4.09 (2H, m), 2.12 (3H, s), 1.28 (3H, t, J = 7.2); m/z 492 (M + 2, 0.4%), 490 (M^+, 0.4), 324 (100).

3-Acetylamino-4-(2-bromophenyl)-2-oxo-6-(4-methylphenyl)-1,2,3,4-tetrohydropyridine-3-carboxylic acid ethyl ester (8c). Mp 246–248 °C (EtOAc); (found: C, 58.53; H, 4.80; N, 5.79%. $C_{23}H_{23}BrN_2O_4$ requires: C, 58.61; H, 4.92; N, 5.94%); ν_{max}/cm^{-1} 3414, 3368, 1733, 1704, 1675; δ_H 7.62–7.59 (1H, m), 7.39–7.33 (3H, m), 7.27–7.20 (4H, m), 7.18–7.12 (1H, m), 6.70 (1H, s), 5.56 (1H, d, J = 2.5), 5.23 (1H, s), 4.25–4.09 (2H, m), 2.40 (3H, s), 2.13 (3H, s), 1.27 (3H, t, J = 7.2); m/z 472 (M + 2, 0.2%), 470 (M^+, 0.2), 304 (100).

3-Acetylamino-4-(2-bromo-4,5-methylenedioxyphenyl)-2-oxo-6-phenyl-1,2,3,4-tetrohydropyridine-3-carboxylic acid ethyl ester (8d). Mp 248–250 °C (EtOAc); (found: C, 55.22; H, 4.28; N, 5.67%. $C_{23}H_{21}BrN_2O_6$ requires: C, 55.10; H, 4.22; N, 5.59%); ν_{max}/cm^{-1} 3421, 3239, 1748, 1703, 1676, 1651; δ_H 7.50–7.41 (6H, m), 7.03 (1H, s), 6.73 (1H, s), 6.72 (1H, s), 5.98 (2H, s), 5.46 (1H, d, J = 2.5), 5.21 (1H, s), 4.30–4.13 (2H, m), 2.13 (3H, s), 1.30 (3H, t, J = 7.2); m/z 502 (M + 2, 0.1%), 500 (M^+, 0.1), 334 (100).

3-Acetylamino-4-(2-bromo-4,5-methylenedioxyphenyl)-2-oxo-6-(4-chlorophenyl)-1,2,3,4-tetrohydropyridine-3-carboxylic acid ethyl ester (8e). Mp 256–260 °C (EtOAc); (found: C, 51.65; H, 3.93; N, 5.25%. $C_{23}H_{20}BrClN_2O_6$ requires: C, 51.56; H, 3.76; N, 5.23%); ν_{max}/cm^{-1} 3404, 3297, 1739, 1704, 1658; δ_H 7.48–7.41 (5H, m), 7.03 (1H, s), 6.71 (1H, s), 6.69 (1H, s), 5.98 (2H, s), 5.45 (1H, d, J = 2.5), 5.20 (1H, s), 4.30–4.11 (2H, m), 2.13 (3H, s), 1.27 (3H, t, J = 7.1); m/z 538 (M + 4, 0.3%), 537 (M + 3, 0.3), 536 (M + 2, 0.3), 535 (M + 1, 0.2), 534 (M^+, 0.3), 368 (100).

3-Acetylamino-4-(2-bromo-4,5-methylenedioxyphenyl)-2-oxo-6-(4-methylphenyl)-1,2,3,4-tetrohydropyridine-3-carboxylic acid ethyl ester (8f). Mp 214–216 °C (EtOAc); (found: C, 55.85; H, 4.46; N, 5.62%. $C_{24}H_{23}BrN_2O_6$ requires: C, 55.93; H, 4.50; N, 5.44%); ν_{max}/cm^{-1} 3384, 3223, 1730, 1703, 1662; δ_H 7.38–7.35 (3H, m), 7.24 (2H, d, J = 8.0), 7.03 (1H, s), 6.72 (1H, s), 6.71 (1H, s), 5.98 (2H, s), 5.45 (1H, d, J = 2.5), 5.17 (1H, s), 4.31–4.10 (2H, m), 2.40 (3H, s), 2.13 (3H, s), 1.27 (3H, t, J = 7.1); m/z 516 (M + 2, 0.2%), 514 (M^+, 0.2), 348 (100).

3-Acetylamino-4-(2-bromo-4,5-dimethoxyphenyl)-2-oxo-6-phenyl-1,2,3,4-tetrohydropyridine-3-carboxylic acid ethyl ester (8g). Mp 216–220 °C (EtOAc); (found: C, 55.74; H, 4.84; N, 5.51%. $C_{24}H_{25}BrN_2O_6$ requires: C, 55.72; H, 4.87; N, 5.41%); ν_{max}/cm^{-1} 3366, 3219, 1746, 1704, 1658; δ_H7.48–7.40 (6H, m), 7.04 (1H, s), 6.73 (1H, s), 6.71 (1H, s), 5.47 (1H, d, J = 2.5), 5.24 (1H, d, J = 6.3), 4.32–4.09 (2H, m), 3.89 (3H, s), 3.79 (3H, s), 2.13 (3H, s), 1.27 (3H, t, J = 7.2); m/z 518 (M + 2, 4.0%), 516 (M^+, 4.5), 378 (100).

3-Acetylamino-4-(2-bromo-4,5-dimethoxyphenyl)-2-oxo-6-(4-chlorophenyl)-1,2,3,4-tetrohydropyridine-3-carboxylic acid ethyl

ester (8h). Mp 238–242 °C (EtOAc); (found: C, 52.19; H, 4.44; N, 5.07%. $C_{24}H_{24}BrClN_2O_6$ requires: C, 52.24; H, 4.38; N, 5.08%); ν_{max}/cm^{-1} 3369, 3219, 1756, 1704, 1664; δ_H 7.46 (1H, s), 7.38(4H, s), 7.03 (1H, s), 6.72 (1H, s), 6.42 (1H, s), 5.67 (1H, d, $J = 5.0$), 5.23 (1H, d, $J = 6.1$), 4.32–4.26 (2H, m), 3.86 (3H, s), 3.75 (3H, s), 1.88 (3H, s), 1.27 (3H, t, $J = 7.1$); *m/z* 554 (M + 4, 3.4%), 552 (M + 2, 11.2), 550 (M^+, 8.4), 412 (100).

3-Acetylamino-4-(2-bromo-4,5-dimethoxyphenyl)-2-oxo-6-(4-methylphenyl)-1,2,3,4-tetrohydropyridine-3-carboxylic acid ethyl ester (8i). Mp 228–230 °C (EtOAc); (found: C, 56.53; H, 5.28; N, 5.47%. $C_{25}H_{27}BrN_2O_6$ requires: C, 56.51; H, 5.12; N, 5.27%); ν_{max}/cm^{-1} 3364, 3242, 1749, 1705, 1662; δ_H 7.34–7.32 (3H, m), 7.22 (2H, d, $J = 8.0$), 7.04 (1H, s), 6.75 (1H, s), 6.39 (1H, s), 5.67 (1H, d, $J = 5.7$), 5.22 (1H, d, $J = 6.2$), 4.36–4.24 (2H, m), 3.88 (3H, s), 3.75 (3H, s), 2.38 (3H, s), 1.90 (3H, s), 1.27 (3H, t, $J = 7.1$); *m/z* 532 (M + 2, 7.0%), 530 (M^+, 6.1), 392 (100).

General procedure for the preparation of 3-phenyl-2,9-dihydro-1*H*-pyrido [3,4-*b*]indol-1-one (4a–i)

A mixture of **8** (5 mmol), CuI (1.9 g, 10 mmol) and NaH (480 mg, 20 mmol) in anhydrous DME (100 mL) was heated to reflux under N_2 for 7–10 h (minitored by TLC). After the most of DME was removed under a vacuum, 10% aqueous solution of NH_4OH (100 mL) was added. The resultant mixture was stirred for 2 h at room temperature and the solid was collected. The crude product was purified by chromatography (silica gel, 10% MeOH in EtOAc) to give pure compound **4**.

3-Phenyl-2,9-dihydro-β-carbolin-1-one (4a)[44a]. Mp 300–302 °C (MeOH); (found: C, 78.44; H, 4.65; N, 10.61%. $C_{17}H_{12}N_2O$ requires: C, 78.44; H, 4.65; N, 10.76%); ν_{max}/cm^{-1} 3110, 3051, 1636, 1620, 1598; δ_H (500 MHz, DMSO-d_6)11.96 (1H, s), 11.60 (1H, s), 8.10 (1H, d, $J = 8.0$), 7.77 (2H, d, $J = 7.5$), 7.54 (1H, d, $J = 8.5$), 7.47 (2H, t, $J = 8.5$), 7.47 (2H, t, $J = 7.0$), 7.43–7.39 (2H, m), 7.37 (1H, s), 7.19 (1H, t, $J = 7.5$); δ_C (500 MHz, DMSO-d_6) 157.0, 140.3, 137.2, 135.5, 129.6, 129.2, 128.0, 127.4, 125.7, 123.1, 122.4, 120.5, 113.4, 99.6; *m/z* 262 (M + 2, 6.2%), 261 (M + 1, 60.5), 260 (M^+, 100).

3-(4-Chlorophenyl)-2,9-dihydro-β-carbolin-1-one (4b). Mp 344–346 °C (MeOH); (found: C, 69.26; H, 3.77; N, 9.40%. $C_{17}H_{11}ClN_2O$ requires: C, 69.28; H, 3.76; N, 9.50%); ν_{max}/cm^{-1} 3115, 2971, 1635; δ_H (DMSO-d_6) 12.05 (1H, s), 11.66 (1H, s), 8.11 (1H, d, $J = 7.9$), 7.83 (2H, dd, $J = 6.8, 1.9$), 7.56–7.53 (3H, m), 7.46–7.42 (2H, m), 7.23 (1H, t, $J = 7.2$); *m/z* 297 (M + 3, 5.8%), 296 (M + 2, 33.1), 294 (M^+, 100).

3-(4-Methylphenyl)-2,9-dihydro-β-carbolin-1-one (4c). Mp 326–328 °C (MeOH); (found: C, 78.80; H, 5.05; N, 10.00%. $C_{18}H_{14}N_2O$ requires: C, 78.81; H, 5.14; N, 10.21%); ν_{max}/cm^{-1} 3141, 2972, 1635; δ_H (DMSO-d_6) 11.98 (1H, s), 11.55 (1H, s), 8.11 (1H, d, $J = 7.9$), 7.70 (2H, d, $J = 8.1$), 7.53 (1H, d, $J = 8.3$), 7.43 (1H, t, $J = 7.2$), 7.37 (1H, s), 7.30 (2H, d, $J = 8.1$), 7.20 (1H, t, $J = 7.2$), 2.37 (3H, s); *m/z* 276 (M + 2, 1.6%), 275 (M + 1, 19.8), 274 (M^+, 100).

3-Phenyl-6,7-methylenedioxy-2,9-dihydro-β-carbolin-1-one (4d). Mp 342–344 °C (MeOH); (found: C, 71.03; H, 3.91; N, 9.08%. $C_{18}H_{12}N_2O_3$ requires: C, 71.05; H, 3.97; N, 9.21%); ν_{max}/cm^{-1} 3084, 2893, 1635, 1613; δ_H (DMSO-d_6) 11.85 (1H, s), 11.41 (1H, s), 7.79–7.76 (2H, m), 7.57 (1H, d, $J = 0.2$), 7.51–7.41 (3H, m), 7.28 (1H, s), 6.97 (1H, s), 6.06 (2H, s); *m/z* 306 (M + 2, 2.7%), 305 (M + 1, 20.8), 304 (M^+, 100).

3-(4-Chlorophenyl)-6,7-methylenedioxy-2,9-dihydro-β-carbolin-1-one (4e). Mp 334–336 °C (MeOH); (found: C, 64.05; H, 3.51; N, 8.16%. $C_{18}H_{11}ClN_2O_3$ requires: C, 63.82; H, 3.27; N, 8.27%); ν_{max}/cm^{-1} 3181, 3101, 2975, 1635, 1619; δ_H (DMSO-d_6) 11.90 (1H, s), 11.48 (1H, s), 7.79 (2H, dd, $J = 8.5, 1.4$), 7.56–7.52 (3H, m), 7.31 (1H, d, $J = 1.4$), 6.97 (1H, s), 6.06 (2H, s); *m/z* 341 (M + 3, 7.0%), 340 (M + 2, 35.0), 339 (M + 1, 22.3), 338 (M^+, 100).

3-(4-Methylphenyl)-6,7-methylenedioxy-2,9-dihydro-β-carbolin-1-one (4f). Mp 338–340 °C (MeOH); (found: C, 71.71; H, 4.49; N, 8.57%. $C_{19}H_{14}N_2O_3$ requires: C, 71.69; H, 4.43; N, 8.80%); ν_{max}/cm^{-1} 3092, 2972, 1638; δ_H (DMSO-d_6) 11.84 (1H, s), 11.37 (1H, s), 7.66 (2H, dd, $J = 7.9, 1.2$), 7.57 (1H, d, $J = 1.3$), 7.28 (2H, d, $J = 7.4$), 7.24 (1H, d, $J = 1.5$), 6.96 (1H, d, $J = 1.3$), 6.06 (2H, s), 2.35 (3H, s); *m/z* 320 (M + 2, 3.2%), 319 (M + 1, 21.2), 318 (M^+, 100).

3-Phenyl-6,7-dimethoxy-2,9-dihydro-β-carbolin-1-one (4g). Mp 306–308 °C (MeOH); (found: C, 71.24; H, 5.08; N, 8.56%. $C_{19}H_{16}N_2O_3$ requires: C, 71.24; H, 5.03; N, 8.74%); ν_{max}/cm^{-1} 3392, 3174, 1635, 1596; δ_H (DMSO-d_6) 11.75 (1H, s), 11.40 (1H, s), 7.79 (2H, d, $J = 7.3$), 7.64 (1H, s), 7.51–7.46 (2H, m), 7.42–7.37 (1H, m), 7.35 (1H, s), 6.98 (1H, s), 3.85 (3H, s), 3.84 (3H, s); *m/z* 322 (M + 2, 2.2%), 321 (M + 1, 22.6), 320 (M^+, 100).

3-(4-Chlorophenyl)-6,7-dimethoxy-2,9-dihydro-β-carbolin-1-one (4h). Mp 316–318 °C; (found: C, 64.40; H, 4.25; N, 7.75%. $C_{19}H_{15}ClN_2O_3$ requires: C, 64.30; H, 4.26; N, 7.89%); ν_{max}/cm^{-1} 3114, 1633, 1607; δ_H (DMSO-d_6) 11.79 (1H, s), 11.47 (1H, s), 7.81 (2H, dd, $J = 8.6, 1.8$), 7.63 (1H, s), 7.54 (2H, dd, $J = 8.7, 1.8$), 7.38 (1H, s), 6.97 (1H, s), 3.85 (3H, s), 3.84 (3H, s); *m/z* 357 (M + 3, 7.0%), 356 (M + 2, 33.2), 355 (M + 1, 26.1), 354 (M^+, 100).

3-(4-Methylphenyl)-6,7-dimethoxy-2,9-dihydro-β-carbolin-1-one (4i). Mp 330–332 °C (MeOH); (found: C, 71.79; H, 5.45; N, 8.32%. $C_{20}H_{18}N_2O_3$ requires: C, 71.84; H, 5.43; N, 8.38%); ν_{max}/cm^{-1} 3166, 1630, 1603; δ_H (DMSO-d_6) 11.72 (1H, s), 11.36 (1H, s), 7.69 (2H, d, $J = 7.9$), 7.63 (1H, s), 7.31–7.27 (3H, m), 6.97 (1H, s), 3.84 (6H, s), 2.39 (3H, s); *m/z* 336 (M + 2, 3.3%), 335 (M + 1, 23.0), 334 (M^+, 100).

***N*-(3-Benzoyl-1-cyano-2,4,6-triphenylcyclohex-3-enyl)acetamide (10).** Mp 188–190 °C (EtOAc–PE); (found: C, 82.20; H, 5.70; N, 5.51%. $C_{34}H_{28}N_2O_2$ requires: C, 82.23; H, 5.68; N, 5.64%); ν_{max}/cm^{-1} 3300, 1640, 1600, 1580; δ_H 9.58 (1H, s), 7.66–7.02 (18H, m), 6.59 (2H, d, $J = 6.4$), 5.81 (1H, d, $J = 6.8$), 5.61 (1H, d, $J = 3.8$), 5.26 (1H, d, $J = 2.9$), 4.93 (1H, d, $J = 6.9$), 1.56 (3H, s); *m/z* 496 (M^+, 12.8%), 391 (100), 349 (22.1), 332 (5.4), 271 (16.0), 191 (20.1), 115 (12.1), 105 (88.3), 43 (40.4).

4-(2-Bromophemyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-carboxylic acid ethyl ester (11). A mixture of **8a** (457 mg, 1 mmol) and Cs_2CO_3 (652 mg, 2 mmol) in toluene (10 mL) was stirred at 100 °C for 10 h and cooled to room temperature. Then it was poured into 2% aqueous solution of HCl and extracted with diethyl ether. The combined organic layers were washed with H_2O and dried over Na_2SO_4. The solvent was removed to give crude product, which was purified by chromatography to give 350 mg (88%) of pure product **11**; mp 200–202 °C (EtOAc–PE); (found: C, 60.30; H, 4.00; N, 3.60%. $C_{20}H_{16}BrNO_3$ requires: C, 60.32; H, 4.05; N, 3.53%); ν_{max}/cm^{-1} 1738, 1627, 1608; δ_H 7.97–7.93 (2H, m), 7.67 (1H, d, $J = 7.8$), 7.51–7.49 (3H, m), 7.36 (1H, d, $J = 1.1$), 7.31–7.28 (2H, m), 6.78 (1H, s), 4.12–4.04 (2H, m), 0.92 (3H, t, $J = 7.1$); *m/z* 399 (M + 2, 1.6%), 397 (M^+, 1.6), 290 (100).

***N*-[4-(2-Bromophenyl)-2-oxo-6-phenyl-1,2-dihydropyridine-3-yl]acetamide (12).** The compound was captured as an intermediate by quenching the reaction of **8a** to **4a** after it was carried out for 2 h and was separated by column chromatography under the exact same conditions by which **4a** was separated; mp 228–230 °C (EtOAc–PE); (found: C, 59.56; H, 4.04; N, 7.33%. $C_{19}H_{15}BrN_2O_2$ requires: C, 59.55; H, 3.95; N, 7.31%); ν_{max}/cm^{-1}3261, 2924, 2853, 1640, 1529, 759; δ_H (DMSO-d_6) 1.75 (s, 3H), 6.45 (s, 1H), 7.31 (d, 2H, $J = 4.9$), 7.40 (d, 1H, $J = 7.4$), 7.45–7.47 (m, 3H), 7.69 (d, 1H, $J = 7.9$),

7.77 (t, 2H, $J = 3.6$), 9.05 (s, 1H), 12.16 (s, 1H); δ_C (DMSO-d_6) 169.3, 161.7, 148.4, 144.3, 139.2, 134.0, 133.4, 130.9, 130.7, 130.5, 129.7, 128.1, 127.6, 124.9, 122.0, 107.2, 23.3. m/z 384 (M + 2, 14.3%), 382 (M^+, 13.6), 342 (100).

Materials and methods in a tumor cell proliferation assay using the HeLa cell line

Cells were grown in a humidified incubator at 37 °C in an atmosphere of 5% CO_2. Bovine Aortic Endothelial Cells (BAECs) were obtained from Clonetics (San Diego) and cultured in DMEM with 10% fetal bovine serum (FBS) and 50 units ml^{-1} penicillin, plus 50 μg mL^{-1} streptomycin (P/S). HeLa cells were obtained from American Type Culture Collection (ATCC) and cultured in RPMI 1640 containing 10% fetal bovine serum (FBS) and 50 units ml^{-1} penicillin plus 50 μg mL^{-1} streptomycin (P/S).

Cell proliferation assay

Proliferating cells were seeded into a 96-well plate and grown in the presence of varying concentrations of testing compounds or carrier solvent (0.1% DMSO) for 24 h. Cells were pulsed with [^{3}H]thymidine (6.7 Ci $mmol^{-1}$, 1 μCi per well) for an additional 6 h and harvested with a semiautomated cell harvester onto glass fiber papers for scintillation counting. All assays were performed in triplicate and are presented as the mean ±SD.

Acknowledgements

We are grateful to the National Natural Science Foundation of China for financial support.

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20 Crystal data for compound **4g**: $C_{19}H_{15}N_2O_3{\cdot}CH_3OH$, $M = 351.37$, monoclinic; $a = 9.2371(6)$ Å, $b = 7.4210(5)$ Å, $c = 25.1558(17)$ Å; $V = 1714.9(2)$ A^3, $T = 293$ K; space group: $P21/n$; $Z = 4$; absorption coefficient: 0.096 mm^{-1}, 10 057 reflections measured, 3970 unique [R(int) = 0.0438]; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0646$, $wR_2 = 0.1930$; R indices (all data): $R_1 = 0.0783$, $wR_2 = 0.2036$.