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Domino Reactions of 1-Aroyl-3,4-dihydroisoquinolines with α,β-Unsaturated Aldehydes

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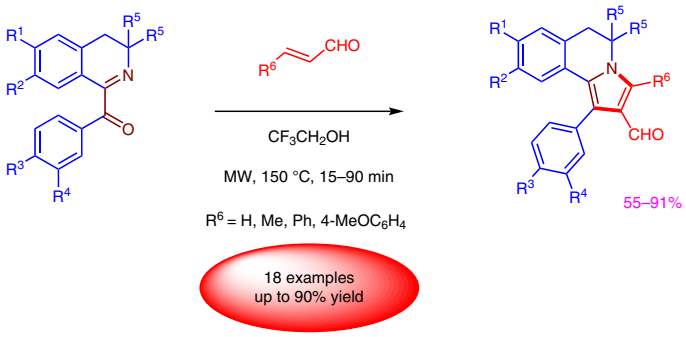

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Abstract An efficient synthesis of pyrrolo[2,1-*a*]isoquinolines by a domino reaction from a variety of 3,4-dihydropyrrolo[2,1-*a*]isoquinolines and α,β-unsaturated aldehydes in the absence of catalyst in good yields under microwave irradiation, is reported.

Key words domino reaction, dihydroisoquinolines, aldehydes, microwave irradiation, cytotoxic activity

Michael addition of the sp^3-hybridized nitrogen atom is a well-studied process[1] that is widely used in chemistry, including for the construction of heterocyclic compounds.[2] The addition of an sp^2-hybridized nitrogen atom to activated double and triple bonds has been much less studied. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) with an sp^2-hybridized nitrogen atom are used as catalysts in the Baylis–Hillman reaction between electron-deficient olefins and carbonyl compounds or their derivatives.[3] The presence of a carbonyl group in the α-position to the sp^2-hybridized nitrogen atom may lead to the formation of a pyrrole ring. According to this scheme, the attachment of electron-deficient alkenes to 1-aroyl-3,4-dihydroisoquinolines with an iminoketone fragment for the formation of 3,4-dihydropyrrolo[2,1-*a*]isoquinolines is possible. This type of transformation can be regarded as a domino reaction. Related precedence was published by Basavaiah et al. using aromatic isoquinoline derivatives in the reaction with activated ketones in the presence of Lewis acid.[4]

The heterocyclic system of 3,4-dihydropyrrolo[2,1-*a*]isoquinolines is a structural fragment of the alkaloids criptaustoline and cryptovoline,[5] as well as lamellarin-type alkaloids, which were first isolated from the prosobranch mollusc Lamellaria.[6] Pyrrolo[2,1-*a*]isoquinolines inhibit phosphodiesterase 10A,[7] are follicle-stimulating hormone (FSH) receptor activators,[8] and exhibit antiplasmodial[9] and antitumor[10] activities.

There are two principle approaches to construct the skeleton of 3,4-dihydropyrrolo[2,1-*a*]isoquinolines. The first, most common method is annulation of the pyrrole ring to isoquinoline derivatives by oxidative/cycloaddition/aromatization.[11] The second approach involves formation of an isoquinoline fragment based on pyrrole derivatives.[12]

In this paper, we describe results of domino reactions of 1-*p*-fluorobenzoyl (**1**), 1-*p*-chlorobenzoyl (**2**), and 3',4'-dimethoxybenzoyl (**3**) 6,7-dimethoxy-3,4-dihydroisoquinolines, drotaveraldine (**4**) and 3,3,7-trimethyl-3,4-dihydroisoquinoline (**5**) with α,β-unsaturated aldehydes in 2,2,2-trifluoroethanol (Figure 1). 1-Aroylisoquinolines **1**–**3** were prepared by the Bischler–Napieralski reaction,[13,14] and the intermediate 1-benzyl-3,4-dihydroisoquinolines were oxidized by sparging with oxygen gas in ethyl acetate.

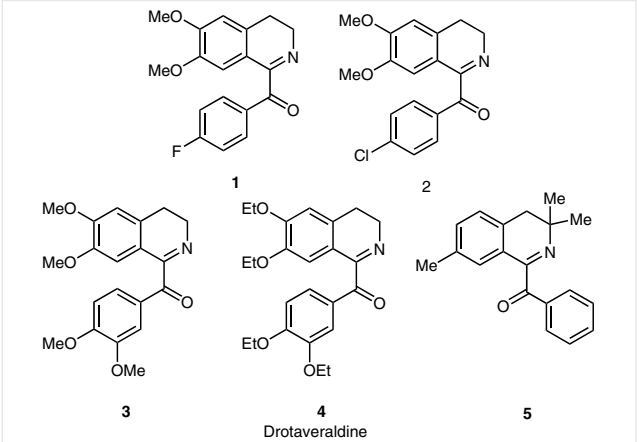
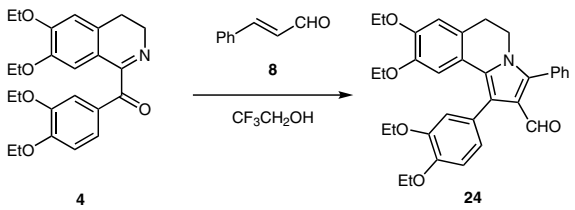


Figure 1 1-Aroyl-3,4-dihydroisoquinolines **1**–**5**

Table 1 Optimization of the Reaction Conditions[a]

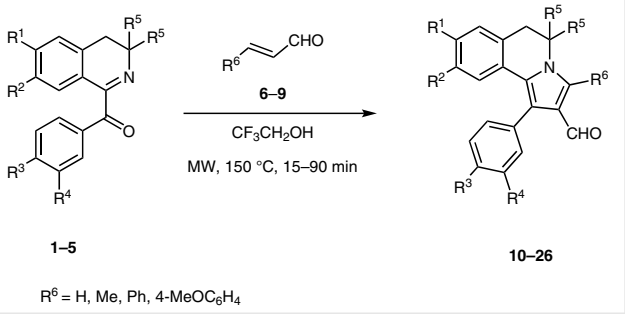


Entry	Conditions	Yield (%)
1	MeOH, reflux, 48 h	53
2	EtOH, reflux, 24 h	64
3	TFE, reflux, 3 h	69
4	$(CF_3)_2CHOH$, reflux, 24 h	39
5	EtOH, MW, 100 °C, 1 h	70
6	EtOH, AcOH, MW, 100 °C, 1 h	68
7	TFE, MW, 100 °C, 1 h	72
8	TFE, MW, 150 °C, 1 h	76
9	TFE, MW, 150 °C, 80 min	80
10	TFE, MW, 180 °C, 1 h	68
11	TFE, AcOH, MW, 150 °C, 80 min	60

[a] Reaction conditions: **4** (0.24 mmol), **8** (0.36 mmol).

Drotaveraldine **4** was recovered from drotaverine hydrochloride, which was spontaneously oxidized by air oxygen. Isoquinoline **5** was synthesized through the Ritter reaction of 2-methyl-1-(4-methylphenyl)propan-2-ol and benzoyl cyanide.[15]

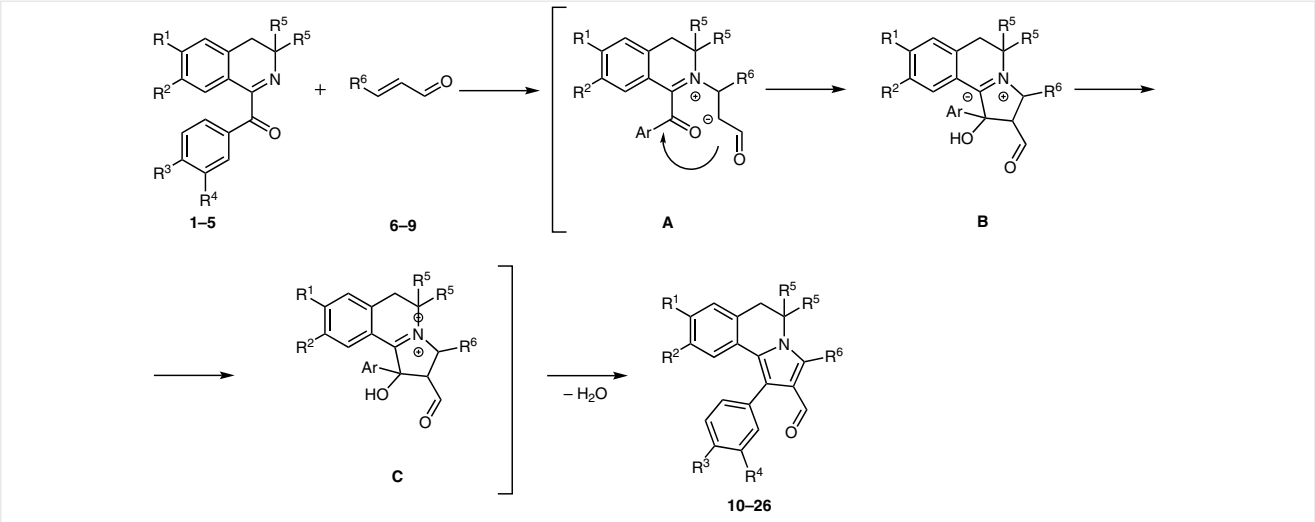
Reaction conditions were optimized by the reaction of drotaveraldine (**4**) and cinnamaldehyde (**8**) to produce pyrrolo[2,1-*a*]isoquinoline **24** (Table 1). It was found that the reactions do not occur in such aprotic solvents as ether and benzene. Replacement of the solvent with methanol, ethanol, 2,2,2-trifluoroethanol, or hexafluoroisopropanol resulted in the interaction, but in trifluoroethanol the reaction proceeds faster and with an increased yield of **24**. Microwave (MW) activation can significantly reduce the reaction time. Soft acid catalysis under microwave conditions was ineffective. Finally, optimal conditions were established at 150 °C for 80 minutes, leading to 80% yield of the desired pyrrolo[2,1-*a*]isoquinoline **24** (Table 1, entry 9).



Scheme 1 Synthesis of pyrrolo[2,1-*a*]isoquinolines **10–26** under MW

The optimal conditions were used in the reactions of 1-benzoylisoquinolines **1–5** with acrolein (**6**), crotonaldehyde (**7**), cinnamaldehyde (**8**), and 4-methoxycinnamaldehyde (**9**) (Scheme 1). Yields of pyrrolo[2,1-*a*]isoquinolines **10–26** in the reaction with unsaturated aldehydes **6–9** carried out in TFE under MW conditions for 15–90 minutes at 150 °C are shown in Table 2.

The reaction begins with nucleophilic addition by the imine nitrogen onto the activated double bond of aldehydes, which generates zwitterion **A**. Next follows the closure of the five-membered ring and the formation of zwitterion **B**. The process is completed by the formation of ylide **C**, the dehydration of which leads to the synthesis of pyrrolo[2,1-*a*]isoquinolines **10–26** (Scheme 2).



Scheme 2 Proposed mechanism for the formation of pyrrolo[2,1-*a*]-isoquinolines **10–26**

Table 2 Yields of Products **10–26**[a]

Entry	R^1	R^2	R^3	R^4	R^5	R^6	Product	MW time (min)	Yield (%)
1	OMe	OMe	F	H	H	H	**10**	20	60
2	OMe	OMe	F	H	H	Me	**11**	30	65
3	OMe	OMe	F	H	H	Ph	**12**	90	70
4	OMe	OMe	F	H	H	*p*-$MeOC_6H_4$	**13**	90	55
5	OMe	OMe	Cl	H	H	H	**14**	25	91
6	OMe	OMe	Cl	H	H	Me	**15**	30	68
7	OMe	OMe	Cl	H	H	Ph	**16**	80	80
8	OMe	OMe	Cl	H	H	*p*-$MeOC_6H_4$	**17**	80	60
9	OMe	OMe	OMe	OMe	H	H	**18**	10	86
10	OMe	OMe	OMe	OMe	H	Me	**19**	20	75
11	OMe	OMe	OMe	OMe	H	Ph	**20**	50	80
12	OMe	OMe	OMe	OMe	H	*p*-$MeOC_6H_4$	**21**	60	63
13	OEt	OEt	OEt	OEt	H	H	**22**	10	80
14	OEt	OEt	OEt	OEt	H	Me	**23**	30	72
15	OEt	OEt	OEt	OEt	H	Ph	**24**	80	80
16	OEt	OEt	OEt	OEt	H	*p*-$MeOC_6H_4$	**25**	90	69
17	H	Me	H	H	Me	H	**26**	20	61

[a] Reaction conditions: benzoylisoquinoline (1.0 mmol), aldehyde (1.5 mmol), 2,2,2-trifluoroethanol (3 mL), MW (300 W, 150 °C).

The substituent R^6 in the reagent affects the rate of formation of the target products **10–26**. Reactions with acrolein in progress rapidly for 0.5 hour, but reactions with 4-methoxycinnamicaldehyde take about a week without microwave radiation. The reaction is sensitive, first of all, to the steric biases of substituent R^6, which correlates with the proposed reaction mechanism. This is confirmed by the observation that 3,3-dimethyl-1-benzoyl-3,4-dihydroisoquinoline **5** reacts only with acrolein. With other α,β-unsaturated aldehydes, the reaction does not begin because of steric hindrance during the formation of intermediate **A**.

The structures of pyrrolo[2,1-*a*]isoquinolines **10–26** were confirmed based on ^1H and ^{13}C NMR, IR spectroscopy, and mass spectrometry. Additionally, the structure of compound **17** was established by using single-crystal X-ray diffraction data (Figure 2).

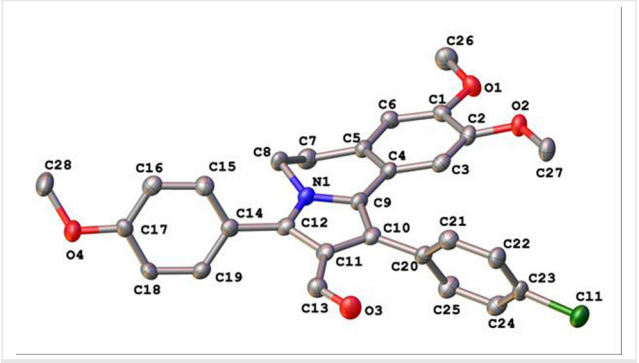


Figure 2 Molecular structure of **17** presented in ADP ellipsoids at 50% probability

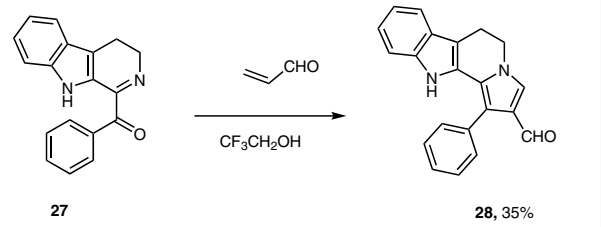
It has been shown[16] that 2-aryl-5,6-dihydropyrrolo[2,1-*a*]isoquinolines exhibit cytotoxic activity against certain lines of human cancer cells, such as breast cancer in women, liver, and lung cancer. In this report, compounds **22–25** were tested on human cell cultures A549 (lung carcinoma), HCT116 (intestinal carcinoma), RD (rhabdomyosarcoma), and HeLa (cervical adenocarcinoma). The obtained data are presented in Table 3.

Comparing the data, it can be concluded that pyrrolo[2,1-*a*]isoquinolines **22–25** possess some cytotoxicity, although not sufficient to compete with the structures known in this pharmacological group. However, compounds **22** and **25** show a more pronounced effect, which allows them to be considered as prospective objects of further study.

To determine the synthetic limits of the reaction, 1-benzoyl-3,4-dihydro-β-carboline **27**[17] was reacted with acrolein in trifluoroethanol heated at reflux. Indoloindolizine **28** was obtained as a result with a 35% yield (Scheme 3). The structure of indoloindolizine **28** was confirmed using ^1H and ^{13}C NMR, IR spectroscopy, and mass spectrometry. Thus, we have confirmed the possibility of the formation of the pyrrole ring with an imino-ketone moiety and unsaturated aldehydes.

Table 3 IC_{50} Values

Compound	IC_{50} (μM)			
	RD	HCT116	HeLa	A549
22	21.31 ± 1.22	11.82 ± 0.03	44.54 ± 1.98	19.69 ± 0.26
23	61.13 ± 1.60	66.60 ± 0.90	–	251.27 ± 20.77
24	365.20 ± 22.95	183.35 ± 0.03	–	228.51 ± 20.83
25	12.25 ± 0.90	23.87 ± 1.12	103.69 ± 6.5	43.66 ± 2.35
daunorubicin	2.45 ± 0.07	0.21 ± 0.00	–	1.44 ± 0.31
doxorubicin	0.53 ± 0.03	0.19 ± 0.01	–	–



27 **28**, 35%

Scheme 3 Synthesis of 1-phenyl-6,11-dihydro-5*H*-indolizino[8,7-*b*]-indole-2-carbaldehyde **28**

In summary, a new method for the synthesis of pyrrolo[2,1-*a*]isoquinolines by the domino reaction of 1-aroyl-substituted 3,4-dihydroisoquinolines with α,β-unsaturated aldehydes has been developed. The simple reaction setup and the variety of commercially available starting materials are additional merits of this method.

All reagents were purchased from Merck, J.T. Baker, or Sigma–Aldrich Chemical Co. and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions at 25 °C, with a 600 MHz NMR spectrometer; peak positions are given in parts per million (δ) referenced to the appropriate solvent residual peak. Mass spectra were recorded with an LCMS-8040 Triple quadrupole liquid chromatograph–mass spectrometer from Shimadzu.

Pyrrolo[2,1-*a*]isoquinolines 10–26; General Procedure

1-Benzoylisoquinoline (1.0 mmol), the corresponding aldehyde (1.2 mmol), and 2,2,2-trifluoroethanol were added to a flask that was suitable for a microwave oven. The mixture was irradiated at 150 °C for 10–90 min. The reaction progress was monitored by TLC (Sorbfil, 2:1 EtOAc–hexane). The solvent was removed under vacuum, and the residue was recrystallized from EtOAc–hexane to give pyrroloisoquinolines **10**–**26**.

1-(4-Fluorophenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (10)

Yield: 211 mg (60%); beige solid; mp 155–157 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.61 (s, 1 H), 7.42–7.40 (m, 2 H), 7.38 (s, 1 H), 7.15–7.09 (m, 2 H), 6.69 (s, 1 H), 6.49 (s, 1 H), 4.12 (t, *J* = 6.5 Hz, 2 H), 3.85 (s, 3 H), 3.37 (s, 3 H), 3.04 (t, *J* = 6.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 186.0, 162.4 (d, *J* = 247.1 Hz, 1 C), 147.9, 147.8, 132.6 (d, *J* = 7.2 Hz, 2 C), 130.4 (d, *J* = 4.3 Hz, 1 C), 127.7, 126.0, 124.5, 124.2, 121.0, 120.3, 115.6 (d, *J* = 21.7 Hz, 2 C), 111.3, 107.7, 56.0, 52.3, 45.4, 29.2.

MS (LCMS): *m*/*z* = 352 [M + H]$^+$.

Anal. Calcd for $C_{21}H_{18}FNO_3$: C, 71.78; H, 5.16; N, 3.99. Found: C, 71.44; H, 5.05; N, 3.82.

1-(4-Fluorophenyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (11)

Yield: 231 mg (65%); beige solid; mp 168–169 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.64 (s, 1 H), 7.39–7.37 (m, 2 H), 7.13–7.11 (m, 2 H), 6.68 (s, 1 H), 6.43 (s, 1 H), 3.99 (t, *J* = 6.4 Hz, 2 H), 3.85 (s, 3 H), 3.36 (s, 3 H), 3.02 (t, *J* = 6.4 Hz, 2 H), 2.63 (s, 3 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 187.0, 162.3 (d, *J* = 247.1 Hz, 1 C), 147.8, 147.6, 135.4 (d, *J* = 7.2 Hz, 2 C), 132.7, 130.5 (d, *J* = 4.3 Hz, 1 C), 125.7, 124.1, 121.2, 121.1, 120.6, 115.6 (d, *J* = 20.2 Hz, 2 C), 111.1, 107.5, 56.0, 55.2, 40.8, 28.9, 11.0.

MS (LCMS): *m*/*z* = 366 [M + H]$^+$.

Anal. Calcd for $C_{22}H_{20}FNO_3$: C, 72.31; H, 5.52; N, 3.83. Found: C, 72.15; H, 5.24; N, 3.75.

1-(4-Fluorophenyl)-8,9-dimethoxy-3-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (12)

Yield: 299 mg (70%); beige solid; mp 230–232 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.62 (s, 1 H), 7.52–7.48 (m, 3 H), 7.47–7.45 (m, 2 H), 7.45–7.42 (m, 2 H), 7.13–7.11 (m, 2 H), 6.69 (s, 1 H), 6.49 (s, 1 H), 3.97 (t, *J* = 6.3 Hz, 2 H), 3.85 (s, 3 H), 3.37 (s, 3 H), 2.96 (t, *J* = 6.3 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 186.5, 162.3 (d, *J* = 247.1 Hz, 1 C), 148.0, 147.7, 141.4, 132.5 (d, *J* = 8.7 Hz, 2 C), 131.2 (d, *J* = 4.3 Hz, 1 C), 131.0 (s, 2 C), 129.23, 129.16, 128.6 (s, 2 C), 127.5, 125.2, 121.5, 121.0, 119.3, 115.4 (d, *J* = 21.7 Hz, 2 C), 111.0, 108.2, 56.0, 55.2, 42.5, 29.3.

MS (LCMS): *m*/*z* = 428 [M + H]$^+$.

Anal. Calcd for $C_{27}H_{22}FNO_3$: C, 75.86; H, 5.19; N, 3.28. Found: C, 75.59; H, 4.96; N, 3.07.

1-(4-Fluorophenyl)-8,9-dimethoxy-3-(4-methoxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (13)

Yield: 251 mg (55%); beige solid; mp 203–205 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.61 (s, 1 H), 7.44–7.42 (m, 2 H), 7.39 (d, *J* = 8.7 Hz, 2 H), 7.13–7.10 (m, 2 H), 7.03 (d, *J* = 8.7 Hz, 2 H), 6.68 (s, 1 H), 6.47 (s, 1 H), 3.96 (t, *J* = 6.3 Hz, 2 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.37 (s, 3 H), 2.96 (t, *J* = 6.3 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 186.5, 162.3 (d, *J* = 247.1 Hz, 1 C), 160.4, 147.9, 147.7, 141.4, 132.5 (d, *J* = 8.7 Hz, 2 C), 132.3 (s, 2 C), 131.2 (d, *J* = 4.3 Hz, 1 C), 127.3, 125.2, 121.4, 121.2, 121.1, 119.2, 115.4 (d, *J* = 20.2 Hz, 2 C), 114.1 (s, 2 C), 111.0, 108.1, 56.0, 55.2, 55.5, 42.3, 29.3.

MS (LCMS): *m*/*z* = 458 $[M + H]^+$.

Anal. Calcd for $C_{28}H_{24}FNO_4$: C, 73.51; H, 5.29; N, 3.06. Found: C, 73.40; H, 5.12; N, 2.96.

1-(4-Chlorophenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (14)

Yield: 334 mg (91%); beige solid; mp 244–247 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.63 (s, 1 H), 7.41–7.38 (m, 4 H), 7.38 (s, 1 H), 6.69 (s, 1 H), 6.48 (s, 1 H), 4.12 (t, *J* = 6.5 Hz, 2 H), 3.85 (s, 3 H), 3.38 (s, 3 H), 3.04 (t, *J* = 6.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 185.9, 148.0, 147.8, 133.5, 133.0, 132.3 (s, 2 C), 128.8 (s, 2 C), 127.8, 126.2, 124.6, 124.1, 121.0, 120.0, 111.3, 107.7, 56.0, 55.3, 45.4, 29.1.

MS (LCMS): *m*/*z* = 368 $[M + H]^+$.

Anal. Calcd for $C_{21}H_{18}ClNO_3$: C, 68.57; H, 4.93; N, 3.81. Found: C, 68.91; H, 5.18; N, 3.62.

1-(4-Chlorophenyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (15)

Yield: 259 mg (68%); beige solid; mp 231–232 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.65 (s, 1 H), 7.40 (d, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 8.4 Hz, 2 H), 6.68 (s, 1 H), 6.42 (s, 1 H), 3.99 (t, *J* = 6.4 Hz, 2 H), 3.85 (s, 3 H), 3.36 (s, 3 H), 3.02 (t, *J* = 6.4 Hz, 2 H), 2.63 (s, 3 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 186.8, 147.8, 147.7, 135.6, 133.4, 133.2, 132.5 (s, 2 C), 128.8 (s, 2 C), 125.8, 124.2, 121.1, 120.7, 120.4, 111.1, 107.6, 56.0, 55.2, 40.9, 29.0, 11.0.

MS (LCMS): *m*/*z* = 382 $[M + H]^+$.

Anal. Calcd for $C_{22}H_{20}ClNO_3$: C, 69.20; H, 5.28; N, 3.67. Found: C, 69.41; H, 5.05; N, 3.77.

1-(4-Chlorophenyl)-8,9-dimethoxy-3-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (16)

Yield: 354 mg (80%); beige solid; mp 206–208 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.62 (s, 1 H), 7.52–7.48 (m, 3 H), 7.46–7.45 (m, 2 H), 7.42–7.39 (m, 4 H), 6.69 (s, 1 H), 6.46 (s, 1 H), 3.97 (t, *J* = 6.2 Hz, 2 H), 3.85 (s, 3 H), 3.38 (s, 3 H), 2.96 (t, *J* = 6.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 186.4, 148.0, 147.7, 141.7, 133.9, 133.2, 132.3 (s, 2 C), 131.0 (s, 2 C), 129.3, 129.0, 128.7 (s, 2 C), 128.6 (s, 2 C), 127.6, 125.3, 121.3, 120.8, 118.9, 111.0, 108.2, 56.0, 55.2, 42.5, 29.2.

MS (LCMS): *m*/*z* = 444 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{22}ClNO_3$: C, 73.05; H, 5.00; N, 3.16. Found: C, 72.95; H, 5.27; N, 3.28.

1-(4-Chlorophenyl)-8,9-dimethoxy-3-(4-methoxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (17)

Yield: 284 mg (60%); beige solid; mp 201–203 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.61 (s, 1 H), 7.41–7.39 (m, 4 H), 7.38 (d, *J* = 8.4 Hz, 2 H), 7.03 (d, *J* = 8.4 Hz, 2 H), 6.68 (s, 1 H), 6.45 (s, 1 H), 3.96 (t, *J* = 6.4 Hz, 2 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.37 (s, 3 H), 2.95 (t, *J* = 6.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 186.4, 160.4, 147.9, 147.7, 141.7, 133.9, 133.1, 132.3 (s, 2 C), 132.3 (s, 2 C), 128.6 (s, 2 C), 127.4, 125.2, 121.2, 121.1, 120.9, 118.9, 114.1 (s, 2 C), 111.0, 106.2, 56.0, 55.5, 55.2, 42.3, 29.3.

MS (LCMS): *m*/*z* = 474 $[M + H]^+$.

Anal. Calcd for $C_{28}H_{24}ClNO_4$: C, 70.96; H, 5.10; N, 2.96. Found: C, 71.87; H, 5.21; N, 3.12.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo-[2,1-*a*]isoquinoline-2-carbaldehyde (18)

Yield: 338 mg (86%); beige solid; mp 177–179 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.67 (s, 1 H), 7.40 (s, 1 H), 7.03 (dd, *J* = 1.8, 8.3 Hz, 1 H), 6.98 (d, *J* = 1.8 Hz, 1 H), 6.96 (d, *J* = 8.3 Hz, 1 H), 6.71 (s, 1 H), 6.67 (s, 1 H), 4.14 (t, *J* = 6.5 Hz, 2 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.41 (s, 3 H), 3.07 (t, *J* = 6.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 186.6, 149.0, 148.5, 147.7, 127.3, 126.6, 125.1, 124.4 (s, 2C), 124.3, 123.3, 121.7, 121.2, 114.0, 111.4, 111.2, 107.8, 56.09, 56.06, 56.0, 55.4, 45.4, 29.2.

MS (LCMS): *m*/*z* = 394 $[M + H]^+$.

Anal. Calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 72.05; H, 5.56; N, 3.41.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (19)

Yield: 305 mg (75%); beige solid; mp 163–165 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.66 (s, 1 H), 6.96 (dd, *J* = 1.8, 8.1 Hz, 1 H), 6.94 (s, 1 H), 6.92 (d, *J* = 8.1 Hz, 1 H), 6.68 (s, 1 H), 6.59 (s, 1 H), 3.99 (t, *J* = 6.6 Hz, 2 H), 3.90 (s, 3 H), 3.86 (s, 3 H), 3.81 (s, 3 H), 3.36 (s, 3 H), 3.02 (t, *J* = 6.6 Hz, 2 H), 2.64 (s, 3 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 187.7, 149.0, 148.4, 147.7, 147.4, 135.0, 126.8, 125.4, 124.0, 123.5, 122.2, 121.4, 120.6, 114.1, 111.4, 110.9, 107.5, 56.1, 56.06, 55.98, 55.4, 40.8, 28.9, 11.1.

MS (LCMS): *m*/*z* = 408 $[M + H]^+$.

Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.74; H, 6.18; N, 3.44. Found: C, 70.96; H, 6.07; N, 3.58.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-3-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (20)

Yield: 375 mg (80%); beige solid; mp 150–152 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.64 (s, 1 H), 7.53–7.42 (m, 5 H), 7.03 (dd, *J* = 1.9, 8.3 Hz, 1 H), 7.01 (d, *J* = 1.9 Hz, 1 H), 6.94 (d, *J* = 8.3 Hz, 1 H), 6.68 (s, 1 H), 6.63 (s, 1 H), 3.96 (t, *J* = 6.4 Hz, 2 H), 3.90 (s, 3 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.38 (s, 3 H), 2.96 (t, *J* = 6.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 186.6, 149.0, 148.4, 147.8, 147.7, 140.6, 131.0, 129.4, 129.1, 128.5 (s, 3C), 127.4, 127.3, 125.0, 123.2, 121.5, 121.3, 120.7, 114.0, 111.1, 110.9, 108.2, 56.06, 56.05, 55.98, 55.4, 42.5, 29.3.

MS (LCMS): *m*/*z* = 470 $[M + H]^+$.

Anal. Calcd for $C_{29}H_{27}NO_5$: C, 74.18; H, 5.80; N, 2.98. Found: C, 74.09; H, 5.90; N, 2.85.

1-(3,4-Dimethoxyphenyl)-8,9-dimethoxy-3-(4-methoxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (21)

Yield: 314 mg (63%); beige solid; mp 147–149 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.64 (s, 1 H), 7.39–7.37 (m, 2 H), 7.03–7.01 (m, 3 H), 7.00 (d, *J* = 2.1 Hz, 1 H), 6.94 (d, *J* = 8.3 Hz, 1 H), 6.67 (s, 1 H), 6.62 (s, 1 H), 3.95 (t, *J* = 6.4 Hz, 2 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.83 (s, 3 H), 3.37 (s, 3 H), 2.95 (t, *J* = 6.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 186.7, 160.3, 149.0, 148.3, 147.7, 147.6, 140.6, 132.2 (s, 3 C), 127.5, 127.0, 125.0, 123.2, 121.5, 121.4, 120.6, 114.1 (s, 2 C), 114.0, 111.4, 110.9, 108.2, 56.06, 56.05, 55.98, 55.5, 55.4, 42.3, 29.3.

MS (LCMS): *m*/*z* = 500 [M + H]$^+$.

Anal. Calcd for $C_{30}H_{29}NO_6$: C, 72.13; H, 5.85; N, 2.80. Found: C, 72.27; H, 6.04; N, 2.90.

1-(3,4-Diethoxyphenyl)-8,9-diethoxy-5,6-dihydropyrrolo-[2,1-*a*]isoquinoline-2-carbaldehyde (22)

Yield: 359 mg (80%); beige solid; mp 125–128 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.62 (s, 1 H), 7.35 (s, 1 H), 6.95–6.92 (m, 3 H), 6.68 (s, 1 H), 6.65 (s, 1 H), 4.14–4.09 (m, 4 H), 4.07–4.02 (m, 4 H), 3.60 (q, *J* = 7.0 Hz, 2 H), 3.01 (t, *J* = 6.4 Hz, 2 H), 1.46 (t, *J* = 7.0 Hz, 3 H), 1.43–1.39 (m, 6 H), 1.18 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 186.9, 148.9, 148.1, 147.37, 147.34, 127.9, 126.7, 124.7, 124.3, 124.2, 123.2, 122.0, 121.3, 116.0, 113.7, 113.2, 109.4, 64.8, 64.7, 64.6, 63.9, 45.5, 29.1, 14.94, 14.92, 14.8, 14.6.

MS (LCMS): *m*/*z* = 450 [M + H]$^+$.

Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95; N, 3.12. Found: C, 72.35; H, 6.79; N, 3.23.

1-(3,4-Diethoxyphenyl)-8,9-diethoxy-3-methyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (23)

Yield: 333 mg (72%); beige solid; mp 115–117 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.63 (s, 1 H), 6.93–6.90 (m, 3 H), 6.67 (s, 1 H), 6.59 (s, 1 H), 4.12 (q, *J* = 7.0 Hz, 2 H), 4.06–4.00 (m, 4 H), 3.97 (t, *J* = 6.4 Hz, 2 H), 3.57 (q, *J* = 7.0 Hz, 2 H), 2.98 (t, *J* = 6.4 Hz, 2 H), 2.52 (s, 3 H), 1.45 (t, *J* = 7.0 Hz, 3 H), 1.42–1.38 (m, 6 H), 1.16 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 187.9, 148.9, 148.0, 147.3, 147.0, 134.7, 127.0, 125.4, 123.8, 123.4, 122.4, 121.6, 120.7, 116.1, 113.8, 113.0, 109.2, 64.8, 64.7, 64.6, 63.9, 40.9, 28.8, 14.9, 14.9 (s, 2 C), 14.6, 11.1.

MS (LCMS): *m*/*z* = 464 [M + H]$^+$.

Anal. Calcd for $C_{28}H_{33}NO_5$: C, 72.55; H, 7.18; N, 3.02. Found: C, 72.32; H, 6.97; N, 3.14.

1-(3,4-Diethoxyphenyl)-8,9-diethoxy-3-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (24)

Yield: 420 mg (80%); beige solid; mp 107–109 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.63 (s, 1 H), 7.50–7.44 (m, 5 H), 6.99–6.96 (m, 2 H), 6.93–6.92 (m, 1 H), 6.67 (s, 1 H), 6.64 (s, 1 H), 4.14 (q, *J* = 7.0 Hz, 2 H), 4.07–4.04 (m, 4 H), 3.95 (t, *J* = 6.2 Hz, 2 H), 3.59 (q, *J* = 7.0 Hz, 2 H), 2.93 (t, *J* = 6.2 Hz, 2 H), 1.46 (t, *J* = 7.0 Hz, 3 H), 1.43–1.39 (m, 6 H), 1.19 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 186.6, 148.9, 148.0, 147.4, 140.1, 131.0 (s, 3C), 129.6, 129.0, 128.4 (s, 2C), 127.5, 127.2, 124.8, 123.1, 121.4, 121.3, 120.9, 116.3, 113.8, 112.9, 109.8, 64.8, 64.6, 64.5, 63.8, 42.5, 29.2, 15.0, 14.92, 14.91, 14.6.

MS (LCMS): *m*/*z* = 526 [M + H]$^+$.

Anal. Calcd for $C_{33}H_{35}NO_5$: C, 75.40; H, 6.71; N, 2.66. Found: C, 75.18; H, 6.37; N, 2.22.

1-(3,4-Diethoxyphenyl)-8,9-diethoxy-3-(4-methoxyphenyl)-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (25)

Yield: 383 mg (69%); beige solid; mp 99–102 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.62 (s, 1 H), 7.38–7.37 (m, 2 H), 7.02–7.01 (m, 2 H), 6.98–6.95 (m, 2 H), 6.93 (d, *J* = 8.1 Hz, 1 H), 6.67 (s, 1 H), 6.63 (s, 1 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 4.06 (q, *J* = 7.0 Hz, 4 H), 3.94 (t, *J* = 6.4 Hz, 2 H), 3.87 (s, 3 H), 3.59 (q, *J* = 7.0 Hz, 2 H), 2.92 (t, *J* = 6.4 Hz, 2 H), 1.46 (t, *J* = 6.9 Hz, 3 H), 1.43–1.39 (m, 6 H), 1.18 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 186.7, 160.2, 148.9, 148.0, 147.3, 140.1, 132.2 (s, 3 C), 127.6, 127.0, 124.8, 123.1, 121.7, 121.5, 121.3, 121.0, 116.2, 114.0 (s, 2 C), 113.7, 113.0, 110.0, 64.8, 64.7, 64.6, 63.9, 55.5, 42.4, 29.2, 15.0, 14.94, 14.91, 14.7.

MS (LCMS): *m*/*z* = 556 [M + H]$^+$.

Anal. Calcd for $C_{34}H_{37}NO_6$: C, 73.49; H, 6.71; N, 2.52. Found: C, 73.17; H, 6.57; N, 2.66.

5,5,9-Trimethyl-1-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-2-carbaldehyde (26)

Yield: 192 mg (61%); beige solid; mp 102–105 °C.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.61 (s, 1 H), 7.64 (s, 1 H), 7.43–7.40 (m, 4 H), 7.40–7.37 (m, 1 H), 7.05 (d, *J* = 7.7 Hz, 1 H), 6.91 (dd, *J* = 1.1, 7.7 Hz, 1 H), 6.77 (s, 1 H), 2.94 (s, 2 H), 2.03 (s, 3 H), 1.48 (s, 6 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 187.0, 136.3, 134.1, 130.7, 128.6 (s, 2 C), 128.4, 128.3, 127.9, 127.5, 127.4 (s, 2 C), 126.9, 125.0, 124.4, 124.3, 121.1, 55.5, 43.0, 27.8 (s, 2 C), 21.3.

MS (LCMS): *m*/*z* = 316 [M + H]$^+$.

Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.64; H, 6.54; N, 4.35.

1-Phenyl-6,11-dihydro-5*H*-indolizino[8,7-*b*]indole-2-carbaldehyde (28)

The acrolein was added with stirring to a solution of 1-benzoyl-3,4-dihydro-β-carboline **27** in 2,2,2-trifluoroethanol. The reaction was conducted at reflux for 6 h. The reaction progress was monitored by TLC (Sorbfil; EtOAc–hexane, 2:1). The solvent was removed under vacuum, to give indolizino[8,7-*b*]indole **28** as an amorphous mass, isolation was done by silica gel column chromatography (EtOAc–hexane, 1:10).

Yield: 109 mg (35%); amorphous mass.

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 9.71 (s, 1 H), 7.78 (s, 1 H), 7.56–7.55 (m, 2 H), 7.54–7.51 (m, 2 H), 7.50 (s, 1 H), 7.49–7.46 (m, 2 H), 7.18 (d, *J* = 8.3 Hz, 1 H), 7.13–7.09 (m, 2 H), 4.28 (t, *J* = 6.9 Hz, 2 H), 3.22 (t, *J* = 6.9 Hz, 2H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 185.8, 136.2, 133.3, 132.2, 131.0, 130.7, 130.2 (s, 2 C), 129.6, 129.1 (s, 2 C), 128.1, 128.0, 127.1, 126.1, 122.5, 120.3, 118.1, 111.3, 46.3, 29.8.

MS (LCMS): *m*/*z* = 313 [M + H]$^+$.

Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.54; H, 5.36; N, 8.85.

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Supporting Information

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