Ugi Four-Component Reaction with Tandem Deprotection, Cyclization and Pictet–Spengler Reaction: A Concise Route to N-Fused Polycyclic Indolediketopiperazine Alkaloid Analogues

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Abstract: Aza-fused polycyclic indolediketopiperazine alkaloids are of potential interest due to their broad range of biological activities. Traditionally, a number of methods have been used to generate N-fused polycyclic indolediketopiperazine skeletons, but the need to develop novel, concise methods with which to modify the substitution pattern continues. Herein, we describe the two-step formation of N-fused polycyclic indolediketopiperazine alkaloid analogues by the application of the Ugi four-component reaction with tandem deprotection, cyclization and Pictet–Spengler reaction.

Key words: alkaloids, Ugi reaction, tandem reactions, deprotection, cyclization, Pictet–Spengler reaction

Polycyclic indole alkaloids containing the aza-fused diketopiperazine motif are highly significant in view of their widespread biological activities and have therefore attracted considerable attention.[1] For example, Fumitremorgine C (**1**) and Demethoxyfumitremorgine C (**2**), both isolated from *Aspergillus fumigates*, show antifungal activity and enhance the cytotoxicity of several anticancer agents in vitro (Figure 1). Tadalafil (**3**) and its analogue **4** exhibit antimalarial activity, and the potent vasodilator amauromine (**5**) and the insecticidal okaramine C (**6**) also possess the N-fused indolediketopiperazine as a key structural motif.[2]

Although a number of methods have been developed to generate the N-fused polycyclic indolediketopiperazine skeleton, novel, concise methods with which to modify the substitution pattern remain in strong demand.[3]

Over the past few decades, isocyanide-based multicomponent reactions (IMCRs) followed by other synthetic transformations have attracted considerable attention because that approach can allow the construction of complex molecules in a small number of steps, usually from readily obtainable starting materials.[4] Recently, combination of the isocyanide-based Ugi-MCR and the Pictet–Spengler reaction has emerged as a promising strategy for the creation of highly diverse natural-product-like compounds (Scheme 1).[5] We have also reported the synthesis of N-fused polycyclic heterocycles through Ugi type MCR followed by acid-catalyzed tandem de-*tert*-butylation and Pictet–Spengler reaction (Scheme 1).[6]

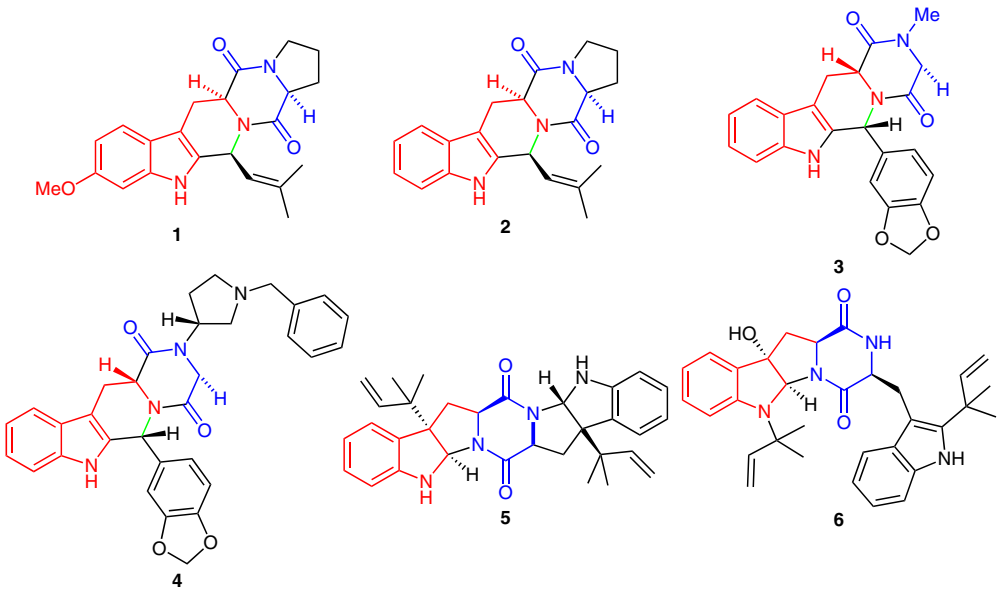

Figure 1 Representative N-fused indolediketopiperazine alkaloids

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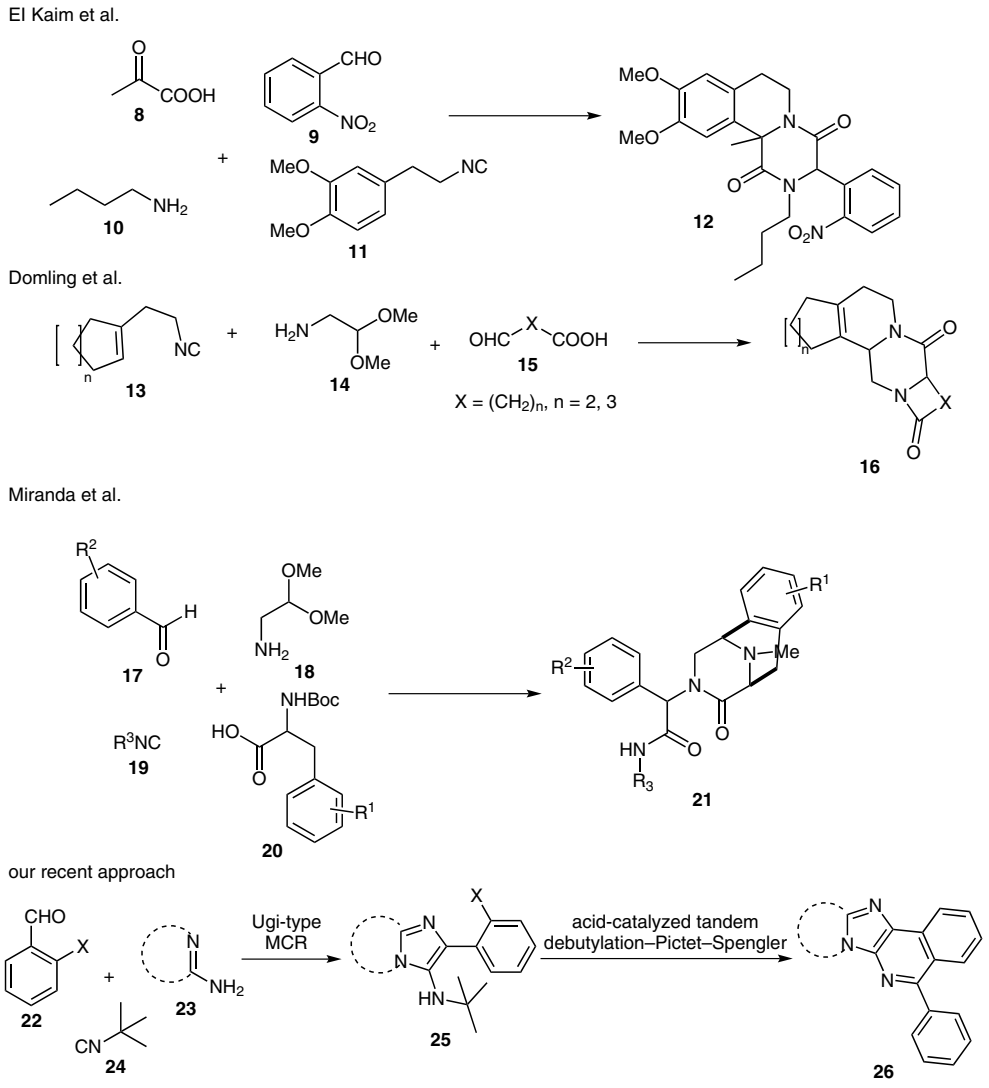
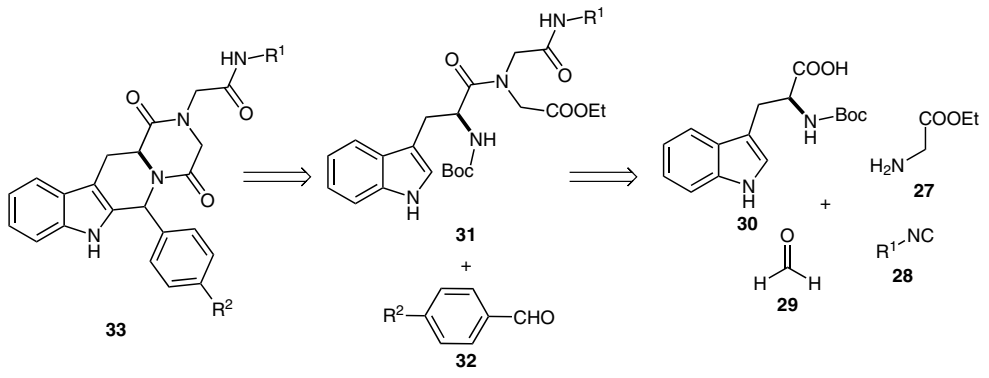


Scheme 1 Sequential Ugi and Pictet–Spengler reactions for the synthesis of N-fused polycyclic heterocycles

Based on our interest in the synthesis of biologically important heterocycles through IMCRs with other synthetic transformations,[7] we turned our attention towards the synthesis of diverse N-fused polycyclic indolediketopiperazine alkaloid analogues using the Ugi-MCR followed by tandem deprotection, cyclization and Pictet–Spengler reactions. An interesting feature of this methodology involves tandem deprotection, cyclization and Pictet–Spengler reaction. To the best of our knowledge, there is no report available on this type of tandem cyclization sequence.

We envisaged that the product **31** (Scheme 2) might be constructed by the Ugi four-component condensation of



Scheme 2 Retrosynthetic analysis

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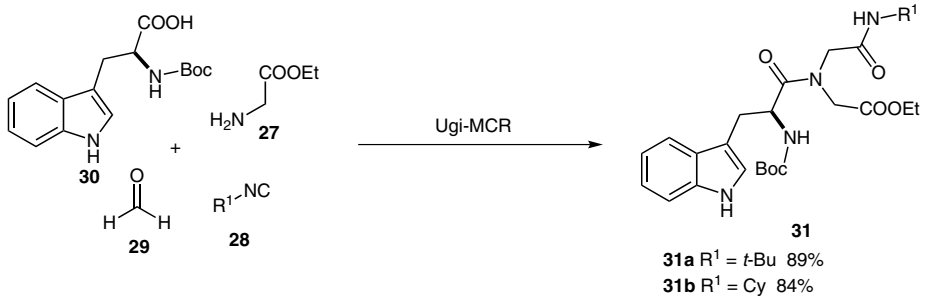


Scheme 3 Four-component Ugi reaction

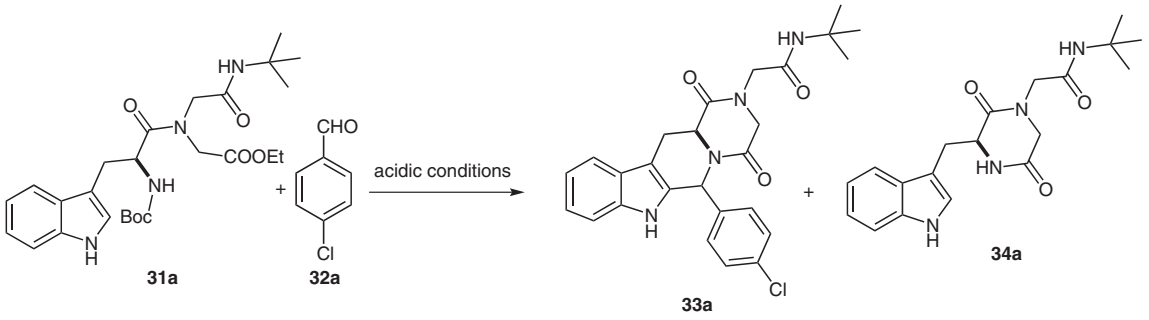
N-Boc protected tryptophan **30**, amine **27**, aldehyde **29**, and isocyanide **28**. The Ugi product **31** can undergo tandem deprotection/cyclization/Pictet–Spengler reactions with aldehydes **32** under the acidic conditions to generate N-fused polycyclic indolediketopiperazine alkaloid analogues.

To test the feasibility of the proposed methodology towards the synthesis of N-fused polycyclic indolediketopiperazine alkaloid analogues, Ugi-4CR of *N*-Boc protected L-tryptophan (**30**), formaldehyde **29**, and glycine ester **27** with two different isocyanides **28** was considered (Scheme 3). Initially, the Ugi reaction was carried out at room temperature, and it was found that the reaction required 24 hours to reach the completion, however, the reaction was complete within 30–35 minutes when performed at 60 °C using microwave irradiation; the products **31a** and **31b** were furnished in 89 and 84% yields, respectively (Scheme 3).

To optimize the acidic conditions for the tandem deprotection, cyclization and Pictet–Spengler reaction (Scheme 4), we selected Ugi intermediate **31a** and 4-chlorobenzaldehyde **32a** as a model system. Initially, we applied our previously optimized acidic conditions (10% TFA in DCE at reflux) but, unfortunately, product **33a** was only formed in low yield, with deprotected and cyclized product **34a** being furnished in very good yield (Table 1, entry 4). Interestingly, when these acidic conditions were applied under the microwave irradiation, product **33a** was formed in 61% yield (Table 1, entry 6). The product **33a** was formed as a mixture of two diastereomers, the *trans*-diastereomer being strongly preferred over the *cis*-diastereomer, and the major product was separated by column chromatography on silica gel. The stereochemical assignment of these diastereomers was achieved on the basis of NOE experiments (see the Supporting Information).[8]

We next explored the ability of Ugi intermediates **31a** and **31b** to undergo tandem deprotection, cyclization and Pictet–Spengler reaction with a variety of aldehydes **32a**–**j** (Table 2).[9] The reaction proceeded smoothly with electron-rich benzaldehydes (Table 2, entry 1–9), whereas

Table 1 Optimization of Acidic Conditions for the Tandem Cyclization Reaction[a]



Entry	Solvent	TFA (%)	Yield **33a** (%)	Yield **34a** (%)
1	CH_2Cl_2	5	trace	39
2	CH_2Cl_2	10	18	43
3	DCE	5	trace	46
4	DCE	10	23	51
5	THF	10	14	32
6[b]	DCE	10	61	trace

[a] Reaction conditions: **31a** (1 equiv), **32a** (1.2 equiv).
[b] Reaction conditions: microwave irradiation, 90 °C, 15 min.

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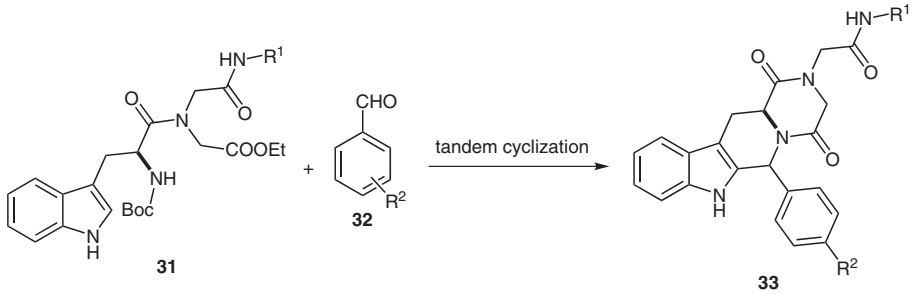


Scheme 4 Tandem cyclization reaction using Ugi-MCR synthesized precursors

the use of electron-withdrawing benzaldehydes did not afford the desired Pictet–Spengler products and instead led only to deprotection and cyclization to afford products **34a** and **34b** (Table 2, entries 10–12).

In summary, we have described a two-step protocol for the synthesis of N-fused polycyclic indolediketopiperazine alkaloid analogues by application of the Ugi four-component reaction with tandem deprotection, cyclization and Pictet–Spengler reaction. This synthetic strategy has the advantages of fewer reaction steps, good yields, and operational simplicity, ultimately leading to N-fused polycyclic indolediketopiperazine alkaloid analogues with diverse substitution patterns, with the *trans*-isomers being formed with high stereoselectivity. Biological screenings of the synthesized compounds are in progress in our lab and will be reported in due course.

Table 2 Scope of the Two-Step Reaction Protocol[a]

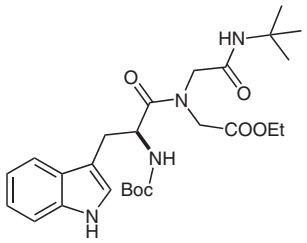
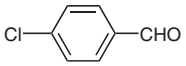
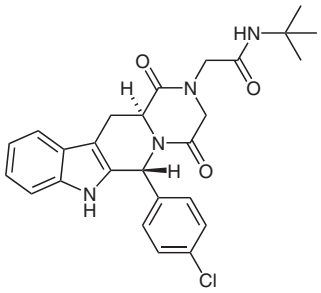
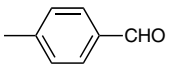
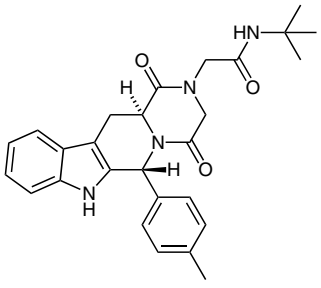
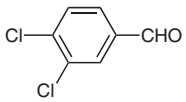
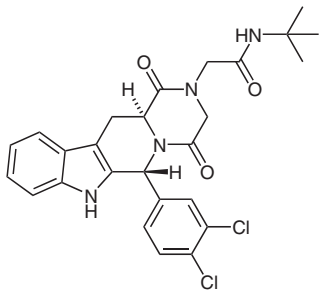
Entry	Ugi intermediate **31**	Aldehyde **32**	Cyclized product **33**	Yield (%)[b]
1	 **31a**	 **32a**	 **33a**	61
2	**31a**	 **32b**	 **33b**	54
3	**31a**	 **32c**	 **33c**	47

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Table 2 Scope of the Two-Step Reaction Protocol[a] (continued)

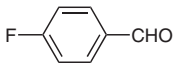
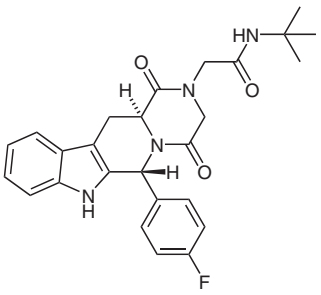
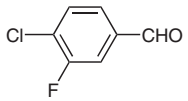
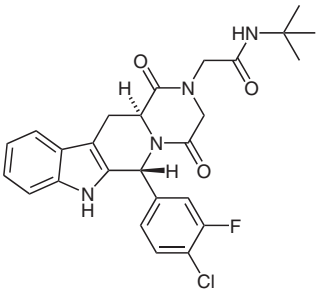
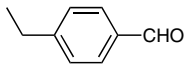
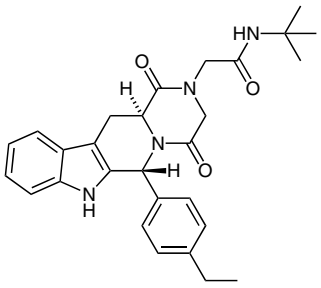
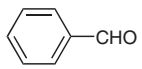
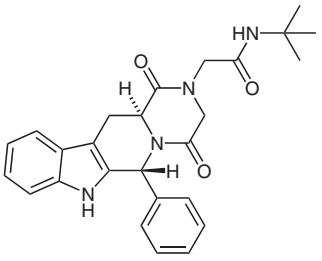
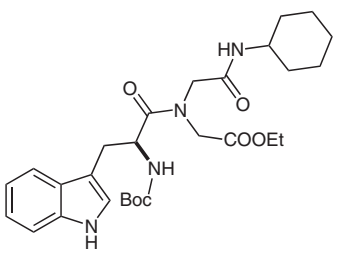
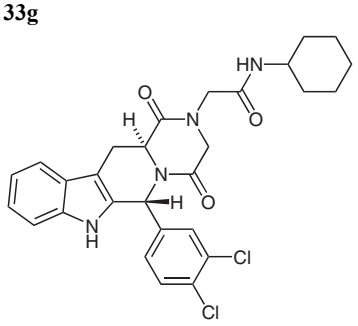
Entry	Ugi intermediate **31**	Aldehyde **32**	Cyclized product **33**	Yield (%)[b]
4	**31a**	 **33d**	 **33d**	39
5	**31a**	 **33e**	 **33e**	42
6	**31a**	 **33f**	 **33f**	57
7	**31a**	 **33g**	 **33g**	60
8	 **31b**	**32c**	 **33h**	43

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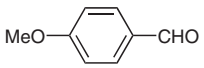
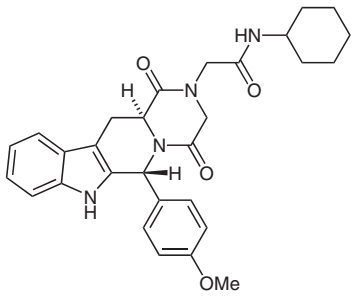
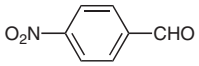
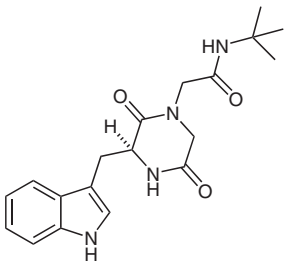
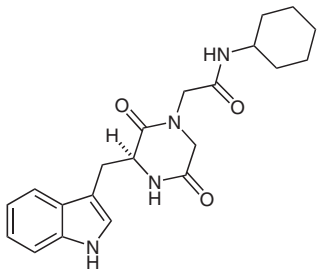
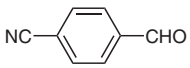
Table 2 Scope of the Two-Step Reaction Protocol[a] (continued)

Entry	Ugi intermediate **31**	Aldehyde **32**	Cyclized product **33**	Yield (%)[b]
9	**31b**	 **32h**	 **33i**	47
10	**31b**	 **32i**	 **34a**	69
11	**31a**	**32i**	 **34b**	67
12	**31a**	 **32j**	**34a**	65

[a] Reaction conditions: Ugi intermediate **31** (1 equiv), aldehyde **32** (1.2 equiv), 90 °C, microwave, 15 min.
[b] Yield of separated *trans*-isomer.

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(8) See the Supporting Information.

(9) **Synthesis of Ugi Products 31a and 31b; General Procedure:** To a solution of *N*-Boc protected L-tryptophan **30** (1 mmol), glycine ester **27** (1 mmol), and paraformaldehyde **29** (1.2 mmol) in methanol (3 mL) was added isocyanide **28** (1 mmol) in a 10 mL reaction glass vial containing a stirring bar. The vial was sealed tightly with a Teflon cap and placed in a microwave cavity (33 W) for 30 min at a pre-selected temperature of 60 °C. After completion of the reaction (indicated by TLC), the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexane–EtOAc) to afford the corresponding products.

Synthesis of Cyclized Products 33a–i; General Procedure: The Ugi-4CR products (1 mmol) were dissolved in 10% TFA in DCE (3 mL) and the corresponding aromatic aldehydes (1.5 mmol) were added in a 10 mL reaction glass vial containing a stirring bar, the vial was sealed tightly with a Teflon cap and placed in a microwave cavity for 15 min at a pre-selected temperature of 90 °C. The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was evaporated and the residue was neutralized with saturated $NaHCO_3$, extracted with EtOAc (20 mL) and the combined organic layer was washed with water (10 mL) and dried over sodium sulfate. EtOAc was removed under reduced pressure and the crude material was purified by column chromatography ($CHCl_3$–MeOH) to afford the cyclized products **33a–i** in 61–39% yield.

Spectroscopic Data for 33a: Yield: 61%; solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (s, 1 H), 7.56 (d, *J* = 7.2 Hz, 1 H), 7.34–7.15 (m, 7 H), 7.05 (s, 1 H), 5.69 (s, 1 H), 4.55–3.98 (m, 4 H), 3.74–3.51 (m, 2 H), 3.09 (t, *J* = 12.3 Hz, 1 H), 1.37 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 166.1, 162.2, 137.0, 136.7, 135.2, 130.4, 129.4, 126.5, 123.2, 120.5, 118.8, 111.5, 109.5, 52.8, 52.2, 51.7, 51.2, 50.4, 29.1, 27.8; HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{28}ClN_4O_3$: 479.1850; found: 479.1842.

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