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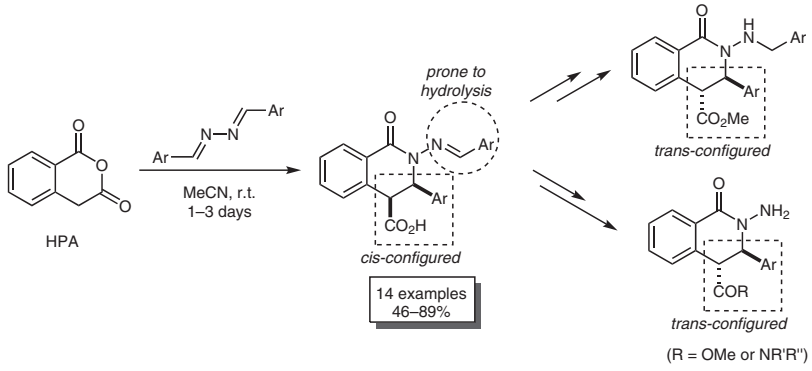
Aldazines in the Castagnoli–Cushman Reaction

Alexander Mikheyev
Grigory Kantin
Mikhail Krasavin*

Saint Petersburg State University, Saint Petersburg, 199034, Russian Federation
m.krasavin@spbu.ru



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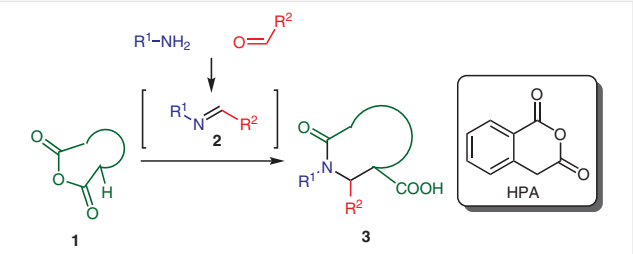
Abstract Aldazines were employed in the Castagnoli–Cushman reaction of homophthalic anhydride for the first time. The reaction proved to be distinctly diastereoselective when conducted at room temperature in acetonitrile, yielding predominantly the kinetic *cis*-configured adduct as a racemate. Thermodynamically more stable *trans*-configuration could be attained either via heating the *cis*-configured product in DMSO or via the action of a base (imidazole) in the course of CDI-promoted esterification or amidation of the carboxylic acid function in the initial adducts. Further manipulation of the remaining *N*-acylhydrazone moiety in the latter led to *N*-alkyl- or fully unprotected *N*-aminolactams.

Key words aldazines, symmetrical, non-symmetrical, Castagnoli–Cushman reaction, homophthalic anhydride, hydrazone reduction, hydrazone cleavage, *N*-aminolactams

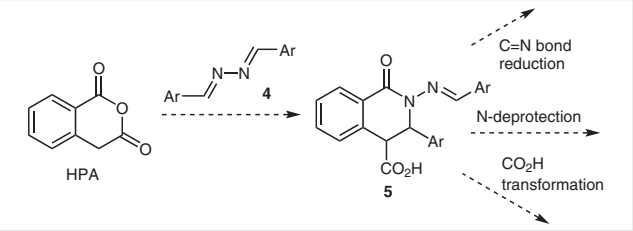
Replacement of the imine component with its hydrazone surrogate in the Ugi multicomponent reaction (MCR)[2] has proven to be a productive diversity-generating[3] strategy, which had substantial consequences for the product's conformational organization and hydrolytic stability.[4] Moreover, it created an opportunity for synthesizing hitherto unaccessible 'forked' peptidomimetic structures.[5] Recently, we have actively engaged in researching the synthetic potential of another MCR, the Castagnoli–Cushman reaction (CCR),[6] that is, the formal cycloaddition of an α-C–H cyclic anhydride **1** [most prominently of homophthalic anhydride (HPA)][7] and an imine **2** (generated in situ or prepared in a separate chemical step) leading to the formation of lactam **3** containing a carboxylic acid function (Scheme 1).

Recently, we employed a reactant replacement strategy,[8] which involved unprotected oximes in the CCR of HPA.[9] It then came to our attention that a similar replacement of the imine component with a hydrazone has not been systematically studied in the CCR. In this work, we investigated



Scheme 1 The Castagnoli–Cushman reaction

the possibility of using easy-to-prepare symmetrical aldazines **4** in the CCR of HPA as well as the prospects of subsequent manipulation of the resulting initial cycloadducts **5** (Scheme 2).

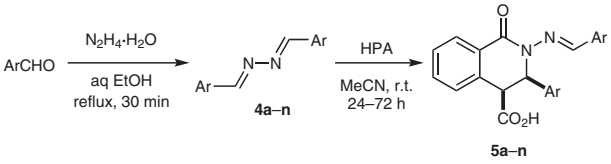


Scheme 2 The scope of this work: aldazine **4** as a replacement of imine **2**

A series of known symmetrical aldazines **4a–n** were prepared according to the literature procedure[10] and were deemed sufficiently pure (>95%) for the reaction with HPA. The latter was conducted in anhydrous acetonitrile, which we had previously found[11] to be a suitable solvent for CCR of HPA as it is conducive to the precipitation of the product isoquinolonic acids from the reaction mixture. This drives the reaction forward and also facilitates the product isolation and purification.

To our delight, treatment of aldazines **4a–n** with HPA indeed furnished good to excellent yields of the expected *N*-(arylmethylideneamino)tetrahydroisoquinolonic acids **5a–n** obtained predominantly as a single, racemic *cis*-isomer (in three cases small amounts of the *trans*-isomer were also formed, Table 1). It should be noted that the HPA reaction with aldazines containing electron-poor aromatic groups (e.g., 4-NO_2, 4-CO_2Et) yielded no product **5**.

Table 1 *N*-(Arylmethylideneamino)tetrahydroisoquinolonic Acids **5a–n** Prepared



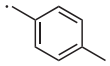
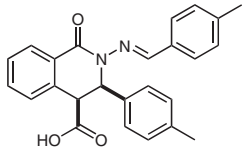
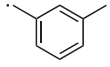
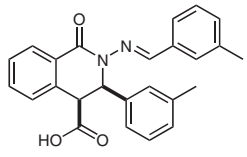
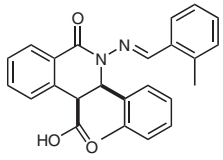
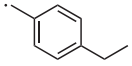
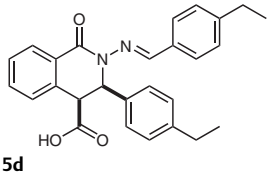
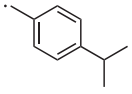
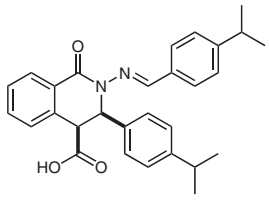
Entry	Starting aldazine	Ar	Product structure	Isolated yield (%)
1	**4a**		 **5a**	86
2	**4b**		 **5b**	60
3	**4c**		 **5c**	78
4	**4d**		 **5d**	59
5	**4e**		 **5e**	52

Table 1 (continued)

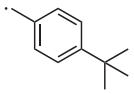
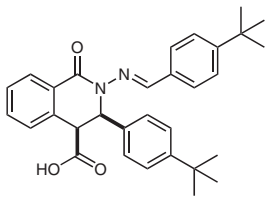
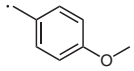
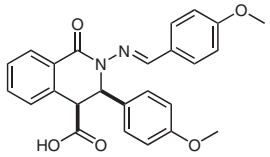
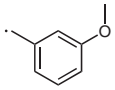
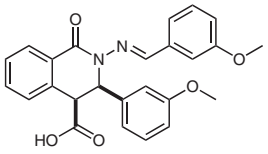
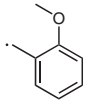
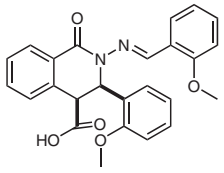
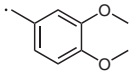
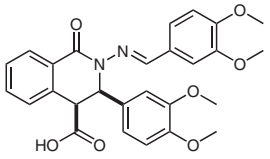
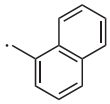
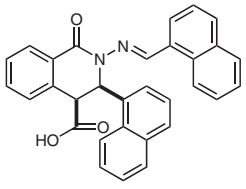
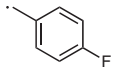
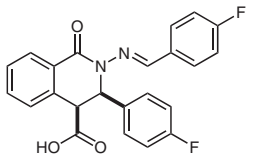
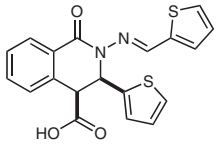
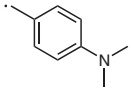
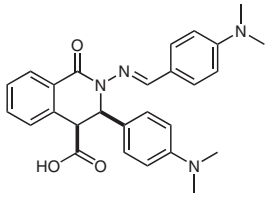
Entry	Starting aldazine	Ar	Product structure	Isolated yield (%)
6	**4f**		 **5f**	72
7	**4g**		 **5g**	86
8	**4h**		 **5h**	54
9	**4i**		 **5i**	86
10	**4j**		 **5j**	86[a]
11	**4k**		 **5k**	89[b]
12	**4l**		 **5l**	46[c]

Table 1 (continued)

Entry	Starting aldazine	Ar	Product structure	Isolated yield (%)
13	**4m**		 **5m**	72
14	**4n**		 **5n**	77

[a] *cis*/*trans* ratio: 100:5.
[b] *cis*/*trans* ratio: 100:8.
[c] *cis*/*trans* ratio: 100:4.

The stereochemical assignment was initially done on the basis of the coupling constants between H-3 and H-4 in the range of 5.1–6.1 Hz, which is in full accordance with the literature data for *cis*-tetrahydroisoquinolonic acids.[12] On the contrary, *trans*-configured tetrahydroisoquinolonic acids generally display H-3/H-4 coupling constants of less than 2.0 Hz (Figure 1).[13]

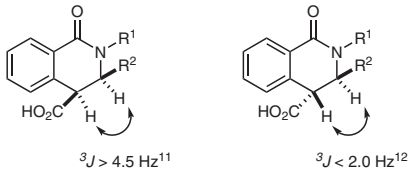
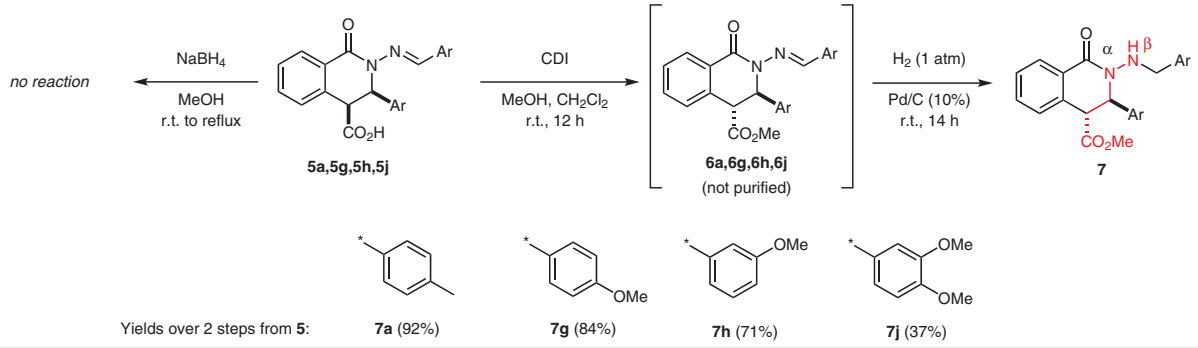


Figure 1 The characteristic H-3/H-4 coupling constant allowing for stereochemical assignment of tetrahydroisoquinolonic acids **5a–n**

The *cis*-configured CCR products **5a–n** are likely the kinetic products of the formal aldazine-HPA cycloaddition. They are promptly removed from the reaction mixture by precipitation at room temperature, before it becomes possible for them to isomerize into its thermodynamically more stable *trans*-configured counterpart. Notably, reactions between **4a–n** and HPA in refluxing acetonitrile led to substantial by-product formation and lower diastereoselectivity. The latter aspect is consistent with higher solubility of the kinetic *cis*-configured product in acetonitrile at elevated temperature and its greater propensity to equilibrate into the *trans*-diastereomer. Moreover, when **5a** was dissolved in DMSO-d_6 and its behavior was observed by ^{1}H NMR spectroscopy, slow ambient-temperature isomerization into *trans*-**5a** was observed (1:1 *cis*/*trans* ratio was obtained after keeping the solution at room temperature for 8 days). The isomerization was much faster at 70 °C: a 1:10 *cis*/*trans* ratio was achieved in only 23 hours. From the latter mixture, a crystal of thermodynamically more stable *trans*-**5a** was obtained and its X-ray structure determined (for isomerization data and single-crystal X-ray structure – see Supporting Information).

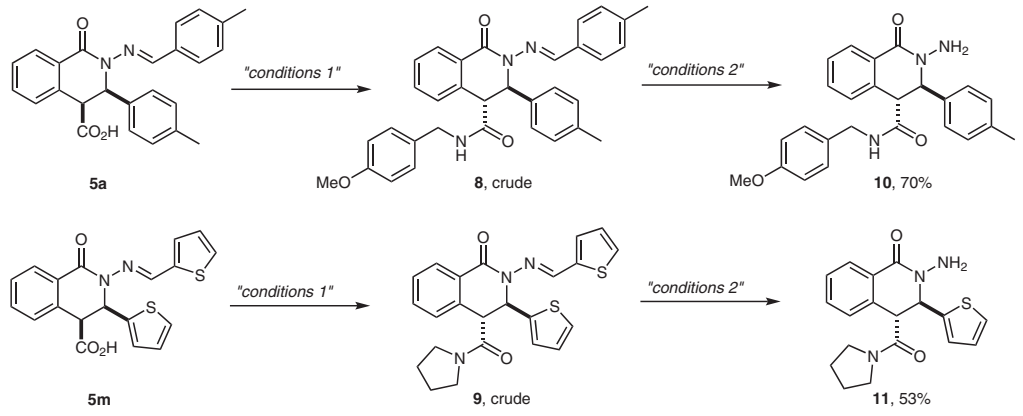
To involve the remaining hydrazone moiety in the bulky, lipophilic **5a–n** in a second CCR with HPA, even under forcing conditions (such as reflux for 72 h), was not feasible, most likely due to steric reasons. The hydrazone linkage (especially *N*-acylhydrazone as is the case in **5a–n**) is prone to undergo hydrolysis[14] and can be viewed as a weak spot from the drug design point of view. Therefore, our intention was to reduce the *N*-acylahydrazone moiety in **5**. Attempted reduction of carboxylic acids **5** with excess sodium borohydride in methanol did not produce any conversion whatsoever, even at reflux temperatures. A workable alternative was found in esterifying a selection of carboxylic acids **5a**, **5g**, **5h**, and **5j** on treatment with 1,1′-carbonyldiimidazole (CDI) in methanol/dichloromethane and subsequent hydrogenation of the resulting material over 10% Pd on carbon in THF (Scheme 3).[15] Interestingly, the relative configuration of compounds **7** (containing the α-hydrazinocarboxylic ester motif, shown in red, and a free β-NH for further modification) thus obtained was identified to be *trans* (according to the rules summarized in Figure 1). This is likely due to base-promoted isomerization at the ester synthesis step (via the action of imidazole liberated from CDI) and not at the hydrogenation step. ^{1}H NMR analysis of two representative crude hydrazone esters **6a** and **6g** confirmed them indeed to be *trans*-configured.



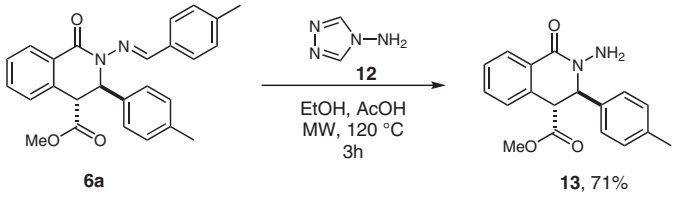
Scheme 3 Esterification and reduction of selected *N*-acylhydrazone CCR adducts **5**

Besides transforming the hydrolytically prone *N*-acylhydrazone moiety in **5** into an *N*-alkylhydrazide motif in **7**, we sought to remove the arylidene group from the terminal nitrogen in **5** altogether. This would allow considering one of the arylidene groups in aldazines **4** as a protecting group. Attempted use of excess hydrazine hydrate[16] on free carboxylic acids **5** resulted only in a salt formation and no further transformation of the *N*-acylhydrazone group (even under microwave irradiation at 120 °C for 4 h). A somewhat daring attempt to selectively remove arylidene moiety in crude **6a** with hydrazine hydrate only led to predominant transformation of the ester moiety. However, when representative carboxylic acids **5a** and **5m** were converted to secondary **8** and tertiary **9** amides (with reversal of stereochemistry to *trans* for reasons likely similar to the discussed above for ester **6** synthesis), this allowed clean and resonably good-yielding removal of the arylidene groups in crude **8** and **9** on treatment with excess hydrazine hydrate in THF under microwave irradiation at 120 °C for 4 hours to produce *N*-aminolactams **10** and **11**, respectively, without affecting the amide moiety (Scheme 4).

We also found the hydrazone moiety in the crude ester **6a** to be cleaved cleanly and efficiently with a 10-fold excess of 4*H*-1,2,4-triazol-4-amine (**12**) under microwave irradiation in ethanol containing acetic acid (Scheme 5). To



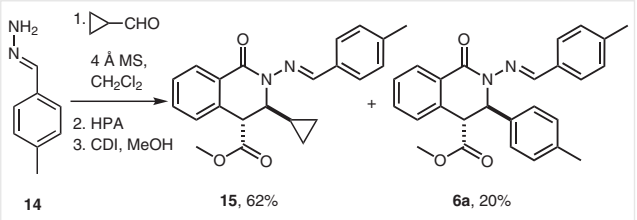
Scheme 4 Synthesis of amides **8** and **9** and arylidene group removal with hydrazine hydrate. *Reagents and conditions 1*: CDI (2 equiv), CH_2Cl_2, 40 °C, 2 h; then 1° or 2° amine (2.5–3.0 equiv), r.t., 12 h (1° amine) or 24 h (2° amine). *Reagents and conditions 2*: hydrazine hydrate (3 mL/mmol), THF, MW, 120 °C, 4 h.



Scheme 5 Hydrazone cleavage with 4*H*-1,2,4-triazol-4-amine (**12**)

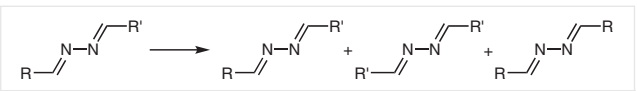
the best of our knowledge, the use of **12** to remove arylidene groups from *N*-acylhydrazones has not been described todate.

We were also curious to see if non-symmetrical aldazines would display some regiospecificity in the CCR with HPA. To that end, known[17] 4-methylbenzylidene hydrazine (**14**) was condensed with cyclopropanecarboxaldehyde in the presence of 4Å molecular sieves and when **14** was fully consumed in 3 hours, the resulting material was brought into reaction with HPA. At the end of the reaction (3 days), it was obvious, according to TLC analysis, that more than one product was obtained. Therefore, the reaction mixture was esterified (CDI/MeOH), in order to facilitate chromatographic separation of the initially formed carboxylic acid products. As a result, two products **15** and **6a** were obtained (Scheme 6). Both esters were *trans*-configured, as judged by the coupling constants, which was consistent with previous observations.



Scheme 6 CCR product distribution obtained with a non-symmetrical aldazine

The predominant formation of **15** in this reaction sequence (and the absence of the product that would result from the CCR at the 'aromatic' end of the putative unsymmetrical aldazine) is consistent with the generally higher electrophilicity of aliphatic hydrazones relative to aromatic. The formation of **6a** can be justified by the known[18] tendency of unsymmetrical aldazines to exchange their 'aldehyde' portions and give an equilibrium mixture of three possible aldazines: the starting non-symmetrical and two symmetrical ones (Scheme 7). The absence of a 'bis-cyclopropyl' product in the first reaction mixture can likely be justified by the volatility of either the respective symmetrical aldazine or cyclopropanecarboxaldehyde, which escaped the reaction medium before being captured by the putative cyclopropylmethylene hydrazine.



Scheme 7 'Scrambling' of a non-symmetrical aldazine into a mixture of three aldazines

In summary, we have reported the first example of using aldazines as imine components in the Castagnoli–Cushman reaction (CCR) with homophthalic anhydride (HPA). The symmetrical bis-aromatic aldazines gave good to excellent yields of kinetic *cis*-configured CCR adducts, which could be equilibrated into more thermodynamically stable *trans*-isomer when heated in DMSO. The same reversal of relative stereochemistry was achieved in base-promoted fashion when the carboxylic acid function in the initial CCR adducts was transformed into an amide or esterified (presumably, by the action of imidazole released from CDI). The double CCR could not be achieved for steric reasons. However, the remaining *N*-acylhydrazone portion of the initial CCR aducts could be, after esterification of the latter, hydrogenated to give an *N*-alkyl *N*-amino lactam. The arylidene portion in the initial CCR adducts could be viewed as an N-protecting group which can be removed, after amidation or esterification of the carboxylic acid function, by action of hydrazine hydrate (amides) or 4*H*-1,2,4-triazol-4-amine (esters). The use of the latter for *N*-acylhydrazone cleavage has not been described. Unsymmetrical aldazines generally do not allow obtaining a single product due to a 'scrambling' of the aldazine periphery groups. However, an expected preference for an aliphatic over aromatic aldazine portion in such aldazines was observed. These findings substantially expand the scope of the chemical space amenable via the Castagnoli–Cushman reaction.

All commercial reagents were used without further purification. MeCN and CH_2Cl_2 were distilled after refluxing with P_2O_5 and stored over 3 Å MS. NMR spectra were recorded using Bruker Avance III spectrometer (^{1}H: 400.13 MHz; ^{13}C: 100.61 MHz; chemical shifts are reported as parts per million (δ, ppm); the residual solvent peaks were used as internal standards: 7.26 and 2.50 ppm for ^{1}H in $CDCl_3$ and DMSO-d_6, respectively, 39.52 and 77.16 ppm for ^{13}C in DMSO-d_6 and $CDCl_3$, respectively. Multiplicities are abbreviated according to standard abbreviations; coupling constants *J* are reported in Hz). Mass spectra were recorded using Bruker microTOF spectrometer (ionization by electrospray, positive ions detection). Melting points were determined in open capillary tubes on Stuart SMP50 Automatic Melting Point Apparatus. Column chromatography was performed on an Isolera Prime Biotage station. Single-crystal X-ray diffraction experiments were carried out using a diffractometer with monochromated MoKα radiation. The structures had been solved by the ShelXS[19] and Superflip[20] structure solution programs using Direct Methods and Charge Flipping, respectively, and refined by means of the ShelXL program, incorporated in the OLEX2 program package.[21]

Carboxylic Acids 5a–n; General Procedure

Aldazine **4**[10] (1 mmol) and homophthalic anhydride (194 mg, 1.2 mmol) were combined in anhyd MeCN (13 mL). The reaction mixture was stirred at r.t. for 24–72 h. The precipitate formed was collected by filtration, washed with MeCN (2 × 2 mL), and dried at 65 °C.

cis-(*E*)-2-[(4-Methylbenzylidene)amino]-1-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5a)

Yield: 1.45 g (86%); white solid; mp 209.1–211.8 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.95–13.20 (br s, 1 H, CO_2H), 8.70 (s, 1 H, HC=N), 8.12 (dd, *J* = 7.7, 1.0 Hz, CH_{Ar}), 7.55–7.67 (m, 4 H, CH_{Ar}), 7.51 (t, *J* = 7.4 Hz, 1 H, CH_{Ar}), 7.24 (d, *J* = 8.0 Hz, 2 H, CH_{Ar}), 7.01 (s, 4 H,

CH_{Ar}), 5.77 (d, *J* = 5.8 Hz, 1 H, CH), 4.89 (d, *J* = 5.7 Hz, 1 H, CH), 2.33 (s, 3 H, CH_3), 2.19 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.6, 161.2, 152.9, 140.9, 137.7, 134.2, 134.1, 132.9, 132.0, 129.8 (2 C), 129.6, 129.2 (2 C), 128.5, 128.3, 128.2, 128.1 (2 C), 128.0 (2 C), 62.6, 49.2, 21.5, 21.0.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{23}N_2O_3$ [M + H]$^+$: 399.1703; found: 399.1705.

cis-(*E*)-2-[(3-Methylbenzylidene)amino]-1-oxo-3-(*m*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5b)

Yield: 0.119 g (60%); white solid; mp 177.2–179.0 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.30–14.00 (br s, 1 H, CO_2H), 8.70 (s, 1 H, HC=N), 8.13 (d, *J* = 7.5 Hz, 1 H, CH_{Ar}), 7.56–7.67 (m, 2 H, CH_{Ar}), 7.45–7.55 (m, 3 H, CH_{Ar}), 7.31 (t, *J* = 7.5 Hz, 1 H, CH_{Ar}), 7.24 (d, *J* = 7.3 Hz, 1 H, CH_{Ar}), 7.09 (t, *J* = 7.5 Hz, 1 H, CH_{Ar}), 6.96–7.06 (m, 2 H, CH_{Ar}), 6.90 (d, *J* = 7.4 Hz, 1 H, CH_{Ar}), 5.79 (d, *J* = 5.7 Hz, 1 H, CH), 4.90 (d, *J* = 5.4 Hz, 1 H, CH), 2.31 (s, 3 H, CH_3), 2.17 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.7, 161.3, 152.6, 138.5, 137.6, 137.0, 134.7, 134.2, 133.0, 131.7 (2 C), 129.6, 129.2, 129.1, 128.9, 128.6 (2 C), 128.3, 128.2, 125.4, 125.2, 62.7, 49.2, 21.6, 21.3.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{23}N_2O_3$ [M + H]$^+$: 399.1703; found: 399.1706.

cis-(*E*)-2-[(2-Methylbenzylidene)amino]-1-oxo-3-(*o*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5c)

Yield: 0.156 g (78%); white solid; mp 186.0–188.4 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.64–13.15 (br s, 1 H, CO_2H), 8.97 (s, 1 H, HC=N), 8.14 (dd, *J* = 7.6, 1.0 Hz, CH_{Ar}), 7.63 (td, *J* = 7.5, 1.2 Hz, 1 H, CH_{Ar}), 7.60–7.52 (m, 2 H, CH_{Ar}), 7.49 (d, *J* = 7.6 Hz, 1 H, CH_{Ar}), 7.27–7.34 (m, 1 H, CH_{Ar}), 7.17–7.24 (m, 3 H, CH_{Ar}), 7.09–7.15 (m, 1 H, CH_{Ar}), 6.93–7.02 (m, 2 H, CH_{Ar}), 6.00 (d, *J* = 6.1 Hz, 1 H, CH), 4.75 (d, *J* = 6.1 Hz, 1 H, CH), 2.49 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.0, 161.7, 155.2, 137.8, 136.4, 136.2, 134.8, 133.1, 132.7, 131.3, 130.9, 130.7, 129.5, 128.6, 128.5, 128.2, 128.0, 127.8, 126.9, 126.6, 126.2, 59.8, 48.9, 19.6, 19.5.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{23}N_2O_3$ [M + H]$^+$: 399.1703; found: 399.1707.

cis-(*E*)-2-[(4-Ethylbenzylidene)amino]-3-(4-ethylphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5d)

Yield: 0.253 g (59%); white solid; mp 164.2–166.5 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.18–14.00 (br s, 1 H, CO_2H), 8.73 (s, 1 H, HC=N), 8.13 (d, *J* = 7.4 Hz, 1 H, CH_{Ar}), 7.55–7.70 (m, 4 H, CH_{Ar}), 7.51 (t, *J* = 7.4 Hz, 1 H, CH_{Ar}), 7.26 (d, *J* = 8.0 Hz, 2 H, CH_{Ar}), 7.05 (s, 4 H, CH_{Ar}), 5.79 (d, *J* = 5.7 Hz, 1 H, CH), 4.71 (d, *J* = 5.7 Hz, 1 H, CH), 2.62 (q, *J* = 7.5 Hz, 2 H, CH_2), 2.49 (q, *J* = 7.6 Hz, 2 H, CH_2), 1.17 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.09 (t, *J* = 7.5 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.6, 161.2, 152.8, 147.1, 143.9, 134.3, 134.2, 132.9, 132.3, 129.6, 128.7 (2 C), 128.5, 128.3, 128.1 (3 C), 128.0 (4 C), 62.6, 49.1, 28.6, 28.1, 15.8, 15.6.

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{27}N_2O_3$ [M + H]$^+$: 427.2016; found: 427.2017.

cis-(*E*)-2-[(4-Isopropylbenzylidene)amino]-3-(4-isopropylphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5e)

Yield: 0.118 g (52%); white solid; mp 121.0–122.8 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.94–13.26 (br s, 1 H, CO_2H), 8.78 (s, 1 H, HC=N), 8.13 (d, *J* = 7.5 Hz, 1 H, CH_{Ar}), 7.55–7.71 (m, 4 H, CH_{Ar}), 7.51 (t, *J* = 7.4 Hz, 1 H, CH_{Ar}), 7.30 (d, *J* = 8.0 Hz, 2 H, CH_{Ar}), 7.00–7.13 (m, 4 H, CH_{Ar}), 5.78 (d, *J* = 5.8 Hz, 1 H, CH), 4.94 (d, *J* = 5.7 Hz, 1 H, CH), 2.91 [sept, *J* = 6.8 Hz, 1 H, *HC*$(CH_3)_2$], 2.77 [sept, *J* = 6.9 Hz, 1 H, *HC*$(CH_3)_2$], 1.20 (d, *J* = 6.9 Hz, 6 H, 2 × CH_3), 1.11 (d, *J* = 6.9 Hz, 6 H, 2 × CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.6, 161.2, 152.7, 151.7, 148.5, 134.4, 134.2, 132.9, 132.5, 129.6, 128.5, 128.3, 128.2 (3 C), 128.1 (2 C), 127.2 (2 C), 126.6 (2 C), 62.6, 48.9, 33.9, 33.4, 24.1 (2 C), 24.0 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{31}N_2O_3$ [M + H]$^+$: 455.2329; found: 455.2334.

cis-(*E*)-2-{[4-(*tert*-Butyl)benzylidene]amino}-3-[4-(*tert*-butyl)-phenyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5f)

Yield: 0.361 g (72%); white solid; mp 168.0–170.6 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.85–13.32 (br s, 1 H, CO_2H), 8.81 (s, 1 H, HC=N), 8.13 (d, *J* = 7.5 Hz, 1 H, CH_{Ar}), 7.56–7.73 (m, 4 H, CH_{Ar}), 7.51 (t, *J* = 7.4 Hz, 1 H, CH_{Ar}), 7.45 (d, *J* = 8.3 Hz, 2 H, CH_{Ar}), 7.23 (d, *J* = 8.3 Hz, 2 H, CH_{Ar}), 7.06 (d, *J* = 8.3 Hz, 2 H, CH_{Ar}), 5.79 (d, *J* = 5.8 Hz, 1 H, CH), 4.96 (d, *J* = 5.7 Hz, 1 H, CH), 1.28 (s, 9 H, 3 × CH_3), 1.18 (s, 9 H, 3 × CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.6, 161.2, 153.9, 152.5, 150.8, 134.2, 134.1, 132.9, 132.1, 129.7, 128.5, 128.4, 128.2, 128.0 (2 C), 128.8 (2 C), 126.0 (2 C), 125.5 (2 C), 62.6, 48.7, 35.1, 34.6, 31.43 (3 C), 31.39 (3 C).

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{35}N_2O_3$ [M + H]$^+$: 483.2642; found: 483.2638.

cis-(*E*)-2-[(4-Methoxybenzylidene)amino]-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5g)

Yield: 0.460 g (86%); white solid; mp 191.9–193.8 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.95–13.12 (br s, 1 H, CO_2H), 8.70 (s, 1 H, HC=N), 8.11 (d, *J* = 7.6 Hz, 1 H, CH_{Ar}), 7.61–7.69 (m, 3 H, CH_{Ar}), 7.59 (td, *J* = 7.4, 1.2 Hz, 1 H, CH_{Ar}), 7.51 (t, *J* = 7.4 Hz, 1 H, CH_{Ar}), 7.05 (d, *J* = 8.7 Hz, 2 H, CH_{Ar}), 6.99 (d, *J* = 8.7 Hz, 2 H, CH_{Ar}), 6.77 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 5.72 (d, *J* = 5.8 Hz, 1 H, CH), 4.87 (d, *J* = 5.8 Hz, 1 H, CH), 3.80 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.7, 161.7, 161.1, 159.3, 153.4, 134.2, 132.8, 129.6 (3 C), 129.4 (2 C), 129.0, 128.5, 128.3, 128.1, 127.3, 114.7 (2 C), 114.0 (2 C), 62.4, 55.8, 55.4, 49.2.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{23}N_2O_5$ [M + H]$^+$: 431.1601; found: 431.1607.

cis-(*E*)-2-[(3-Methoxybenzylidene)amino]-3-(3-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5h)

Yield: 0.069 g (54%); white solid; mp 170.4–173.4 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.75 (s, 1 H, HC=N), 8.13 (dd, *J* = 7.6, 0.8 Hz, 1 H, CH_{Ar}), 7.63–7.68 (m, 2 H, CH_{Ar}), 7.60 (td, *J* = 7.4, 1.2 Hz, 1 H, CH_{Ar}), 7.52 (t, *J* = 7.4 Hz, 1 H, CH_{Ar}), 7.34 (t, *J* = 7.9 Hz, 1 H, CH_{Ar}), 7.25–7.31 (m, 2 H, CH_{Ar}), 7.14 (t, *J* = 7.9 Hz, 1 H, CH_{Ar}), 6.97–7.03 (m, 1 H, CH_{Ar}), 6.79 (dd, *J* = 8.0, 2.0 Hz, 1 H, CH_{Ar}), 6.68–6.75 (m, 2 H, CH_{Ar}), 5.82 (d, *J* = 5.8 Hz, 1 H, CH), 4.91 (d, *J* = 5.7 Hz, 1 H, CH), 3.76 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.6, 161.4, 159.9, 159.3, 152.0, 138.5, 136.2, 134.2, 133.0, 130.3, 129.8, 129.5, 128.6, 128.3 (2 C), 120.7, 120.3, 117.0, 114.5, 113.5, 112.4, 62.5, 55.6, 55.3, 49.1.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{23}N_2O_5$ [M + H]$^+$: 431.1601; found: 431.1604.

cis-(*E*)-2-[(2-Methoxybenzylidene)amino]-3-(2-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5i)

Yield: 0.184 g (86%); white solid; mp 196.1–198.8 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.69–12.92 (br s, 1 H, CO_2H), 8.74 (s, 1 H, HC=N), 8.13 (dd, *J* = 7.6, 1.2 Hz, 1 H, CH_{Ar}), 7.73 (dd, *J* = 7.8, 1.7 Hz, 1 H, CH_{Ar}), 7.59 (td, *J* = 7.5, 1.4 Hz, 1 H, CH_{Ar}), 7.52 (t, *J* = 7.5, Hz, 1 H, CH_{Ar}), 7.38–7.44 (m, 1 H, CH_{Ar}), 7.36 (d, *J* = 7.6 Hz, 1 H, CH_{Ar}), 7.16–7.22 (m, 1 H, CH_{Ar}), 7.08 (d, *J* = 8.1 Hz, 1 H, CH_{Ar}), 7.01 (d, *J* = 8.2 Hz, 1 H, CH_{Ar}), 6.96 (t, *J* = 7.5, Hz, 1 H, CH_{Ar}), 6.67–6.72 (m, 2 H, CH_{Ar}), 6.14 (d, *J* = 6.0 Hz, 1 H, CH), 4.80 (d, *J* = 6.0 Hz, 1 H, CH), 3.86 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.6, 161.3, 158.5, 157.3, 146.0, 134.5, 133.0, 132.5, 129.7, 129.6, 128.6, 128.3, 128.0, 127.8, 126.0, 124.5, 122.6, 121.1, 120.5, 112.4, 111.3, 56.2, 56.1, 55.3, 49.0.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{23}N_2O_5$ [M + H]$^+$: 431.1601; found: 431.1603.

cis-(*E*)-2-[(3,4-Dimethoxybenzylidene)amino]-3-(3,4-dimethoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5j)

Yield: 0.126 g (86%, ratio *cis*/*trans*: 100:5); white solid; mp 195.0–197.0 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.82–13.38 (br s, 1 H, CO_2H), 8.69 (s, 1 H, HC=N), 8.11 (dd, *J* = 7.6, 0.9 Hz, 1 H, CH_{Ar}), 7.67 (d, *J* = 7.7 Hz, 1 H, CH_{Ar}), 7.60 (td, *J* = 7.5, 1.2 Hz, 1 H, CH_{Ar}), 7.51 (t, *J* = 7.5 Hz, 1 H, CH_{Ar}), 7.32 (d, *J* = 1.7 Hz, 1 H, CH_{Ar}), 7.26 (dd, *J* = 8.4, 1.7 Hz, 1 H, CH_{Ar}), 7.01 (d, *J* = 8.4 Hz, 1 H, CH_{Ar}), 6.75–6.81 (m, 2 H, CH_{Ar}), 6.63 (dd, *J* = 8.4, 1.9 Hz, 1 H, CH_{Ar}), 5.74 (d, *J* = 5.7 Hz, 1 H, CH), 4.86 (d, *J* = 5.7 Hz, 1 H, CH), 3.79 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3), 3.57 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.8, 161.1, 153.1, 151.5, 149.4, 148.9, 148.5, 134.3, 132.8, 129.8, 129.3, 128.4, 128.2, 128.1, 127.5, 122.6, 120.3, 112.3, 111.9, 111.7, 109.5, 62.4, 56.0, 55.8, 55.7, 55.6, 49.3.

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{26}N_2O_7$ [M + H]$^+$: 491.1813; found: 491.1813.

cis-(*E*)-3-(Naphthalen-1-yl)-2-[(naphthalen-1-ylmethylene)-amino]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5k)

Yield: 0.178 g (89%, ratio *cis*/*trans*: 100:8); white solid; mp 218.0–221.0 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.5–13.5 (br s, 1 H, CO_2H), 9.24 (s, 1 H, HC=N), 8.60 (d, *J* = 8.6 Hz, 1 H, CH_{Ar}), 8.26 (dd, *J* = 7.6, 1.1 Hz, 1 H, CH_{Ar}), 8.12 (d, *J* = 8.6 Hz, 1 H, CH_{Ar}), 7.88–8.02 (m, 3 H, CH_{Ar}), 7.84 (dd, *J* = 6.7, 2.5 Hz, 1 H, CH_{Ar}), 7.64–7.72 (m, 3 H, CH_{Ar}), 7.60 (t, *J* = 7.5 Hz, 2 H, CH_{Ar}), 7.44–7.51 (m, 3 H, CH_{Ar}), 7.31–7.38 (m, 2 H, CH_{Ar}), 7.22–7.29 (m, 1 H, CH_{Ar}), 6.96 (d, *J* = 6.0 Hz, 1 H, CH), 4.92 (d, *J* = 6.0 Hz, 1 H, CH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.0, 162.0, 154.4, 135.0, 133.8 (3 C), 133.2, 131.5, 131.3, 130.6, 129.9, 129.4 (2 C), 129.0, 128.9 (2 C), 128.6, 128.3, 128.2, 127.4, 127.2, 126.6, 126.2 (2 C), 125.8, 125.6, 124.5, 123.5, 58.1, 49.9.

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{22}N_2O_3$ [M + H]$^+$: 471.1703; found: 471.1708.

cis-(*E*)-2-[(4-Fluorobenzylidene)amino]-3-(4-fluorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5l)

Yield: 0.322 g (46%, ratio *cis*/*trans*: 100:4); white solid; mp 173.8–176.2 °C [crystallized from DMF/MeCN 1:6 (v/v)].

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.75–13.50 (br s, 1 H, CO_2H), 8.83 (s, 1 H, HC=N), 8.13 (d, *J* = 7.6 Hz, 1 H, CH_{Ar}), 7.75 (dd, *J* = 5.7, 8.5 Hz, 2 H, CH_{Ar}), 7.62 (d, *J* = 3.9 Hz, 2 H, CH_{Ar}), 7.53 (td, *J* = 4.3, 8.1 Hz, 1 H, CH_{Ar}), 7.27 (t, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.20 (dd, *J* = 5.5, 8.6 Hz, 2 H, CH_{Ar}), 7.08 (t, *J* = 8.8 Hz, 2 H, CH_{Ar}), 5.84 (d, *J* = 5.8 Hz, 1 H, CH), 4.88 (d, *J* = 5.7 Hz, 1 H, CH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.7, 163.9 (d, $^1J_{C,F}$ = 248.7 Hz), 162.2 (d, $^1J_{C,F}$ = 245.0 Hz), 161.3, 152.3, 134.2, 133.5 (d, $^4J_{C,F}$ = 2.9 Hz), 133.1, 131.3 (d, $^4J_{C,F}$ = 2.9 Hz), 130.3 (d, $^3J_{C,F}$ = 8.1 Hz, 2 C), 130.2 (d, $^4J_{C,F}$ = 8.8 Hz, 2 C), 129.3, 128.7, 128.4, 128.3, 116.3 (d, $^2J_{C,F}$ = 22.0 Hz, 2 C), 115.5 (d, $^2J_{C,F}$ = 21.3 Hz, 2 C), 62.3, 49.3.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{17}F_2N_2O_3$ [M + H]$^+$: 407.1202; found: 407.1198.

cis-(*E*)-1-Oxo-3-(thiophen-2-yl)-2-[(thiophen-2-ylmethylene)amino]-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5m)

Yield: 1.26 g (72%); pale yellow solid; mp 183.6–184.2 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 13.13–13.36 (br s, 1 H, CO_2H), 9.22 (s, 1 H, HC=N), 8.06 (dd, *J* = 7.8, 1.2 Hz, 1 H, CH_{Ar}), 7.88 (d, *J* = 7.9 Hz, 1 H, CH_{Ar}), 7.70 (d, *J* = 5.0 Hz, 1 H, CH_{Ar}), 7.65 (td, *J* = 7.6, 1.4 Hz, 1 H, CH_{Ar}), 7.56 (dd, *J* = 3.6, 1.0 Hz, 1 H, CH_{Ar}), 7.52 (t, *J* = 7.6 Hz, 1 H, CH_{Ar}), 7.29 (dd, *J* = 5.0, 1.1 Hz, 1 H, CH_{Ar}), 7.16 (dd, *J* = 5.0, 3.7 Hz, 1 H, CH_{Ar}), 6.96 (dd, *J* = 3.5, 0.8 Hz, 1 H, CH_{Ar}), 6.86 (dd, *J* = 5.0, 3.5 Hz, 1 H, CH_{Ar}), 5.98 (d, *J* = 5.2 Hz, 1 H, CH), 5.06 (d, *J* = 5.1 Hz, 1 H, CH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.2, 161.0, 147.7, 139.7, 139.2, 134.1, 133.1, 132.6, 130.2, 129.6, 128.6, 128.42, 128.37, 128.31, 128.27, 126.8, 126.5, 59.8, 48.2.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{14}N_2O_3S_2$ [M + H]$^+$: 383.0519; found: 383.0521.

cis-(*E*)-2-{[(4-(Dimethylamino)benzylidene]amino}-3-[4-(dimethylamino)phenyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic Acid (5n)

Yield: 0.385 g (77%); orange solid; mp 183.0–185.2 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.31–13.44 (br s, 1 H, CO_2H), 8.59 (s, 1 H, HC=N), 8.09 (dd, *J* = 7.7, 1.0 Hz, 1 H, CH_{Ar}), 7.68 (d, *J* = 7.7 Hz, 1 H, CH_{Ar}), 7.45–7.60 (m, 4 H, CH_{Ar}), 6.91 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 6.72 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 6.51 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 5.56 (d, *J* = 5.8 Hz, 1 H, CH), 4.83 (d, *J* = 5.8 Hz, 1 H, CH), 2.97 (s, 6 H, 2 × CH_3), 2.80 (s, 6 H, 2 × CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 170.7, 160.8, 155.3, 152.4, 150.4, 134.3, 132.4, 130.1, 129.4 (3 C), 128.9 (3 C), 128.2 (3 C), 127.9 (2 C), 124.3, 121.9, 112.2 (2 C), 112.1 (2 C), 63.0, 49.2.

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{28}N_4O_3$ [M + H]$^+$: 457.2234; found: 457.2248.

N-(Benzylamino)lactams 7a, 7g, 7h, and 7i; General Procedure

The respective carboxylic acid **5** (0.5 mmol) and *N*,*N*′-carbonyldiimidazole (162 mg, 1 mmol) were combined in anhyd CH_2Cl_2 (3 mL). The reaction mixture was stirred for 1 h at 40 °C and to the resulting suspension MeOH (0.125 mL) was added. After stirring the mixture at r.t. for 12 h, the solution was washed with H_2O (4 × 1 mL). The volatiles were evaporated at reduced pressure. The methyl ester thus obtained was used in the next step without additional purification, the yield was nearly quantitative. Two crude esters **6a** and **6g** were analyzed by

^{1}H NMR to confirm their configuration to be *trans* (see below for NMR data). A stream of H_2 gas was passed for 1 h through a solution of the methyl ester thus obtained (0.5 mmol) in anhyd THF (3 mL) containing a catalytic amount of 10% Pd/C (42 mg, 0.04 mmol). The reaction mixture was stirred in H_2 atmosphere at r.t. for 14 h. The catalyst was separated by centrifugation and washed with THF (3 × 1 mL). The combined organic solutions were filtered through syringe filter unit (PTFE membrane with pores 0.45 μm) and evaporated at reduced pressure to give crude target compounds. The latter were purified by chromatography on silica gel using an appropriate gradient of EtOAc in $CHCl_3$.

Methyl (*E*)-*trans*-2-[(4-Methylbenzylidene)amino]-1-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (6a)

The crude ester **6a** was obtained as described above and was used in the subsequent transformations without further purification and full characterization.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.55 (s, 1 H, HC=N), 8.02 (dd, *J* = 7.6, 1.1 Hz, 1 H, CH_{Ar}), 7.62 (d, *J* = 8.1 Hz, 2 H, CH_{Ar}), 7.52 (td, *J* = 7.3, 1.4 Hz, 1 H, CH_{Ar}), 7.46 (td, *J* = 7.5, 1.2 Hz, 1 H, CH_{Ar}), 7.35 (d, *J* = 7.0 Hz, 1 H, CH_{Ar}), 7.26 (d, *J* = 7.9 Hz, 2 H, CH_{Ar}), 7.06 (d, *J* = 8.7 Hz, 2 H, CH_{Ar}), 7.04 (d, *J* = 8.7 Hz, 2 H, CH_{Ar}), 6.03 (br s, 1 H, CH), 4.57 (d, *J* = 1.1 Hz, 1 H, CH), 3.65 (s, 3 H, CO_2CH_3), 2.34 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3).

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{24}N_2O_3Na$ [M + Na]$^+$: 435.1679; found: 435.1668.

Methyl (*E*)-*trans*-2-[(4-Methoxybenzylidene)amino]-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (6g)

The crude ester **6a** was obtained as described above and was used in subsequent transformations without further purification and full characterization.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.55 (s, 1 H, HC=N), 8.01 (dd, *J* = 7.6, 1.4 Hz, 1 H, CH_{Ar}), 7.69 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.52 (td, *J* = 7.3, 1.5 Hz, 1 H, CH_{Ar}), 7.46 (td, *J* = 7.5, 1.4 Hz, 1 H, CH_{Ar}), 7.36 (dd, *J* = 7.5, 1.1 Hz, 1 H, CH_{Ar}), 7.08 (d, *J* = 8.7 Hz, 2 H, CH_{Ar}), 7.01 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 6.82 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 5.97 (br s, 1 H, CH), 4.55 (d, *J* = 1.5 Hz, 1 H, CH), 3.80 (s, 3 H, OCH_3), 3.65 (s, 6 H, 2 × OCH_3).

Methyl *trans*-2-[(4-Methylbenzyl)amino]-1-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (7a)

Yield: 0.190 g (92%); yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.96 (dd, *J* = 7.4, 1.6 Hz, 1 H, CH_{Ar}), 7.50–7.39 (m, 2 H, CH_{Ar}), 7.28 (dd, *J* = 7.3, 1.4 Hz, 1 H, CH_{Ar}), 7.25 (d, *J* = 7.9 Hz, 2 H, CH_{Ar}), 7.13 (d, *J* = 7.9 Hz, 2 H, CH_{Ar}), 7.04 (d, *J* = 8.1 Hz, 2 H, CH_{Ar}), 6.97 (d, *J* = 8.1 Hz, 2 H, CH_{Ar}), 5.99–5.93 (m, 1 H, NH), 5.45 (s, 1 H, CH), 4.37 (d, *J* = 1.4 Hz, 1 H, CH), 4.04–3.93 (m, 2 H, CH_2), 3.61 (s, 3 H, OCH_3), 2.28 (s, 3 H, CH_3), 2.19 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.4, 163.0, 137.1, 136.7, 136.6, 135.2, 133.3, 132.7, 130.3, 129.5 (2 C), 129.3 (2 C), 129.0 (2 C), 128.8, 128.6, 127.4, 126.4 (2 C), 63.3, 53.5, 53.0, 50.9, 21.2, 20.9.

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{26}N_2O_3Na$ [M + Na]$^+$: 437.1836; found: 437.1846.

Methyl *trans*-2-[(4-Methoxybenzyl)amino]-3-(4-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (7g)

Yield: 0.188 g (84%); white solid; mp 132.1–134.2 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.96 (dd, *J* = 7.5, 1.6 Hz, 1 H, CH_{Ar}), 7.53–7.39 (m, 2 H, CH_{Ar}), 7.33–7.25 (m, 3 H, CH_{Ar}), 7.00 (d, *J* = 8.7 Hz, 2 H, CH_{Ar}), 6.89 (d, *J* = 8.7 Hz, 2 H, CH_{Ar}), 6.79 (d, *J* = 8.7 Hz, 2 H, CH_{Ar}), 5.89 (t, *J* = 6.7 Hz, 1 H, NH), 5.43 (s, 1 H, CH), 4.36 (d, *J* = 1.4 Hz, 1 H, CH), 3.96 (d, *J* = 6.6 Hz, 2 H, CH), 3.74 (s, 3 H, OCH_3), 3.66 (s, 3 H, OCH_3), 3.62 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.5, 162.9, 159.0 (2 C), 133.4, 132.7, 131.4, 130.3 (3 C), 130.2, 128.8, 128.6, 127.7 (2 C), 127.4, 114.3 (2 C), 114.1 (2 C), 62.9, 55.5 (2 C), 53.2, 53.0, 50.9.

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{26}N_2O_5Na$ [M + Na]$^+$: 469.1734; found: 469.1749.

Methyl *trans*-2-[(3-Methoxybenzyl)amino]-3-(3-methoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (7h)

Yield: 0.158 g (71%); colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.97 (dd, *J* = 7.5, 1.6 Hz, 1 H, CH_{Ar}), 7.51–7.40 (m, 2 H, CH_{Ar}), 7.32–7.27 (m, 1 H, CH_{Ar}), 7.24 (t, *J* = 7.9 Hz, 1 H, CH_{Ar}), 7.15 (t, *J* = 7.9 Hz, 1 H, CH_{Ar}), 6.98–6.91 (m, 2 H, CH_{Ar}), 6.86–6.80 (m, 1 H, CH_{Ar}), 6.76 (dd, *J* = 7.9, 2.1 Hz, 1 H, CH_{Ar}), 6.68–6.61 (m, 2 H, CH_{Ar}), 6.12 (dd, *J* = 7.3, 5.7 Hz, 1 H, NH), 5.46 (s, 1 H, CH), 4.41 (d, *J* = 1.4 Hz, 1 H, CH), 4.07 (dd, *J* = 12.8, 5.5, Hz, 1 H, C*H*H), 4.00 (dd, *J* = 12.8, 7.5, Hz, 1 H, CH*H*), 3.74 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.4, 163.0, 159.73, 159.68, 141.3, 140.1, 133.3, 132.7, 130.3, 130.0, 129.7, 128.8, 128.7, 127.4, 121.1, 118.7, 114.4, 113.2, 113.1, 112.7, 63.5, 55.4 (2 C), 53.7, 53.0, 50.8.

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{26}N_2O_5$ [M + H]$^+$: 447.1914; found: 447.1917.

Methyl *trans*-2-[(3,4-Dimethoxybenzyl)amino]-3-(3,4-dimethoxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (7j)

Yield: 0.093 g (37%); colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.97 (dd, *J* = 7.5, 1.5 Hz, 1 H, CH_{Ar}), 7.51–7.40 (m, 2 H, CH_{Ar}), 7.32–7.27 (m, 1 H, CH_{Ar}), 6.98 (d, *J* = 1.4 Hz, 1 H, CH_{Ar}), 6.92–6.85 (m, 2 H, CH_{Ar}), 6.79–6.73 (m, 2 H, CH_{Ar}), 6.47 (dd, *J* = 8.3, 1.9 Hz, 1 H, CH_{Ar}), 5.97 (t, *J* = 6.5 Hz, 1 H, NH), 5.42 (s, 1 H, CH), 4.39 (d, *J* = 1.3 Hz, 1 H, CH), 3.98 (d, *J* = 6.6 Hz, 2 H, CH_2), 3.74 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.65 (s, 6 H, 2 × OCH_3), 3.61 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.5, 163.0, 149.1, 149.0, 148.5 (2 C), 133.4, 132.6, 131.8, 130.8, 130.3, 128.9, 128.6, 127.3, 121.2, 118.4, 112.9, 112.1, 111.9, 110.7, 63.2, 56.0, 55.9, 55.85, 55.8, 53.6, 53.0, 51.0.

HRMS (ESI): *m*/*z* calcd for $C_{28}H_{30}N_2O_7Na$ [M + Na]$^+$: 529.1945; found: 529.1968.

***trans*-2-Amino-*N*-(4-methoxybenzyl)-1-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (10)**

Carboxylic acid **5a** (0.398 g, 1.0 mmol) and *N*,*N*′-carbonyldiimidazole (0.324 g, 2.0 mmol) were combined in anhyd CH_2Cl_2 (5 mL). The reaction mixture was stirred at 40 °C for 1 h. To the resulting suspension 4-methoxybenzylamine (0.411 g, 0.391 mL, 3.0 mmol) was added. After stirring for 24 h at r.t., the precipitate was filtered off, washed with CH_2Cl_2 (2 × 1 mL) and the volatiles were removed in vacuo. The light yellow oil thus obtained was treated with refluxing MeOH for 10 min and then cooled to r.t. The precipitate was collected by centrifugation, washed with MeOH (2 × 4 mL), and dried at 75 °C. The resulting material [containing about 7% of 1,3-bis(4-methoxybenzyl)urea according

to ^{1}H NMR analysis] was used in the next step without full characterization and additional purification. Its ^{1}H NMR, however, confirmed the *trans*-stereochemistry of the intermediate amide **8**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.53 (s, 1 H, HC=N), 8.28–8.35 (m, 2 H, CH_{Ar}), 7.64 (d, *J* = 8.1 Hz, 2 H, CH_{Ar}), 7.45–7.53 (m, 2 H, CH_{Ar}), 7.15–7.21 (m, 3 H, CH_{Ar}), 7.01–7.11 (m, 6 H, CH_{Ar}), 6.79 (d, *J* = 8.7 Hz, 2 H, CH_{Ar}), 6.17 (br s, 1 H, CH), 5.55 (t, *J* = 5.6 Hz, 1 H, NH), 4.25–4.41 (m, 2 H, NCH_2), 4.09 (d, *J* = 1.5 Hz, 1 H, CH), 3.75 (s, 3 H, OCH_3), 2.38 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3).

Crude **8** was placed in a 5 mL Biotage microwave vial and combined with hydrazine hydrate (0.3 mL) and THF (2 mL). The mixture was subjected to microwave irradiation at 120 °C for 4 h. The upper organic layer was carefully separated and the volatiles were removed at reduce pressure. The crude solid product was crystallized from MeOH to provide 0.291 g (70%) of the title compound as a light-green oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28–8.19 (m, 1 H, CH_{Ar}), 7.52–7.42 (m, 2 H, CH_{Ar}), 7.17–7.11 (m, 1 H, CH_{Ar}), 7.05 (d, *J* = 8.1 Hz, 2 H, CH_{Ar}), 7.02 (d, *J* = 8.7 Hz, 2 H, CH_{Ar}), 6.97 (d, *J* = 8.2 Hz, 2 H, CH_{Ar}), 6.82 (d, *J* = 8.7 Hz, 2 H, CH_{Ar}), 5.71 (d, *J* = 1.5 Hz, 1 H, CH), 5.56 (br t, *J* = 5.3 Hz, 1 H, NH), 4.67 (br s, 2 H, NH_2), 4.41 (dd, *J* = 14.8, 6.1 Hz, 1 H, C*H*H), 4.23 (dd, *J* = 14.8, 5.3 Hz, 1 H, CH*H*), 3.90 (d, *J* = 1.9 Hz, 1 H, CH), 3.78 (s, 3 H, OCH_3), 2.27 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 162.9, 159.0, 137.7, 135.4, 132.8, 132.7, 129.6, 129.5 (2 C), 129.1, 128.9, 128.7, 128.5 (3 C), 125.9 (2 C), 114.1 (2 C), 65.2, 55.3, 53.7, 43.5, 21.0.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{16}N_2O_3S$ [M + H]$^+$: 416.1982; found: 416.1969.

trans-2-Amino-4-(pyrrolidine-1-carbonyl)-3-(thiophen-2-yl)-3,4-dihydroisoquinolin-1(2*H*)-one (11)

Carboxylic acid **5m** (0.191 g, 0.5 mmol) and *N*,*N*′-carbonyldiimidazole (0.162 g, 1.0 mmol) were combined in anhyd dichloromethane (3 mL). The reaction mixture was stirred at 40 °C for 2 h. To the resulting suspension, pyrrolidine (0.178 g, 0.205 mL, 2.5 mmol) was added. After stirring for 12 h at r.t., the mixture was diluted with CH_2Cl_2 (2 mL) and the organic layer was washed with H_2O (4 × 3 mL). The volatiles were removed at reduced pressure and the crude product was used in next step without full characterization. Its ^{1}H NMR, however, confirmed the *trans*-stereochemistry of the intermediate amide **9**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.67 (s, 1 H, HC=N), 8.21 (dd, *J* = 7.6, 1.4 Hz, 1 H, CH_{Ar}), 7.44–7.55 (m, 2 H, CH_{Ar}), 7.37 (d, *J* = 5.0 Hz, 1 H, CH_{Ar}), 7.32 (d, *J* = 4.0 Hz, 1 H, CH_{Ar}), 7.12–7.21 (m, 2 H, CH_{Ar}), 7.06 (dd, *J* = 4.9, 3.7 Hz, 1 H, CH_{Ar}), 6.95 (d, *J* = 3.4 Hz, 1 H, CH_{Ar}), 6.86 (dd, *J* = 5.0, 3.7 Hz, 1 H, CH_{Ar}), 5.68 (d, *J* = 3.4 Hz, 1 H, CH), 4.49 (d, *J* = 3.4 Hz, 1 H, CH), 3.62–3.78 (m, 2 H, NCH_2), 3.44–3.61 (m, 2 H, NCH_2), 2.02–2.13 (m, 2 H, CH_2), 1.84–2.00 (m, 2 H, CH_2).

Crude **9** was placed in a 5 mL Biotage microwave vial and combined with hydrazine hydrate (0.3 mL) and THF (2 mL). The mixture was subjected to microwave irradiation at 120 °C for 4 h. The upper organic layer was carefully separated and the volatiles were removed from it at reduce pressure. The crude product was crystallized from MeOH to provide 90 mg (53%) of the title compound as a white crystalline solid; mp 245.1–247.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.26 (m, 1 H, CH_{Ar}), 7.42–7.54 (m, 2 H, CH_{Ar}), 7.21 (dd, *J* = 5.0, 0.9 Hz, 1 H, CH_{Ar}), 7.07–7.15 (m, 1 H, CH_{Ar}), 6.98 (d, *J* = 2.9 Hz, 1 H, CH_{Ar}), 6.92 (dd, *J* = 5.0, 3.7 Hz, 1 H, CH_{Ar}), 5.45 (d, *J* = 5.3 Hz, 1 H, CH), 4.63 (s, 2 H, NH_2), 4.38 (d, *J* = 5.2 Hz, 1 H, CH), 3.41–3.66 [m, 4 H, $N(CH_2)_2$], 1.95–2.10 (m, 2 H, CH_2), 1.84–1.95 (m, 2 H, CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 163.6, 142.4, 134.0, 132.4, 128.8, 128.5, 128.3, 127.1, 126.8, 126.3, 125.3, 62.3, 51.0, 47.2, 46.3, 26.3, 24.3.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{19}N_3O_2SNa$ [M + Na]$^+$: 364.1090; found: 364.1097.

Methyl *trans*-2-Amino-1-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (13)

A mixture of crude ester **6a** (41 mg, 0.1 mmol) and 4*H*-1,2,4-triazol-4-amine (0.084 g, 1.0 mmol) in a mixture of EtOH (1 mL) and AcOH (0.050 mL) was subjected to microwave irradiation at 120 °C for 3 h. The solvent was evaporated in vacuo and the solid residue was extracted with EtOAc (5 mL). The combined organic extracts were concentrated in vacuo and the residue was purified by column chromatography on silica gel using 50% EtOAc in $CHCl_3$ as eluent to provide 0.022 g (71%) of the title compound as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22–8.15 (m, 1 H, CH_{Ar}), 7.49–7.41 (m, 2 H, CH_{Ar}), 7.23–7.16 (m, 1 H, CH_{Ar}), 7.07 (d, *J* = 7.9 Hz, 2 H, CH_{Ar}), 6.97 (d, *J* = 8.1 Hz, 2 H, CH_{Ar}), 5.46 (d, *J* = 1.2 Hz, 1 H, CH), 4.68 (br s, 2 H, NH_2), 4.00 (d, *J* = 1.7 Hz, 1 H, CH), 3.73 (s, 3 H, OCH_3), 2.28 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 163.2, 137.9, 135.3, 132.2, 132.1, 129.6 (2 C), 129.4, 128.5, 128.1, 127.9, 126.0 (2 C), 64.6, 52.9, 51.5, 21.0.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{18}N_2O_3Na$ [M + Na]$^+$: 333.1210; found: 333.1220.

Methyl *trans*-(*E*)-3-Cyclopropyl-2-[(4-methylbenzylidene)amino]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (15)

To a solution of 4-methylbenzylidene hydrazine[17] (0.134 g, 1 mmol) in anhyd CH_2Cl_2 (1.5 mL) containing powdered 4Å molecular sieves (0.2 g) cyclopropanecarboxaldehyde (0.070 g, 0.075 mL, 1 mmol) was added. The reaction mixture was stirred at r.t. for 3 h, filtered through a syringe filter unit (PTFE membrane with pores 0.45 µm) and the precipitate was washed with anhyd CH_2Cl_2 (3 × 0.5 mL). To the combined filtrate and washings, homophthalic anhydride (1.2 mmol, 0.194 g) was added. After stirring at r.t. for 3 days, *N*,*N*′-carbonyldiimidazole (0.324 g, 2 mmol) was added followed by anhyd MeOH (0.25 mL), after an additional hour of stirring. The stirring was continued for 12 h at r.t. The solution was filtered through short plug of silica gel and the sorbent was washed with copious amounts of CH_2Cl_2. The combined filtrate and washings were concentrated in vacuo. From the crude product mixture, 0.224 g (62%) of the title compound was isolated by column chromatography on Isolera Prime Biotage® station using a 60 g silica gel cartridge and 15 → 25% acetone in hexane gradient as eluent; white solid; mp 96.2–97.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.47 (s, 1 H, HC=N), 8.21 (dd, *J* = 7.6, 1.4 Hz, 1 H, CH_{Ar}), 7.68 (d, *J* = 8.1 Hz, 2 H, CH_{Ar}), 7.56 (td, *J* = 7.4, 1.4 Hz, 1 H, CH_{Ar}), 7.49 (td, *J* = 7.5, 1.2 Hz, 1 H, CH_{Ar}), 7.41 (d, *J* = 7.3 Hz, 1 H, CH_{Ar}), 7.24 (d, *J* = 7.9 Hz, 2 H, CH_{Ar}), 4.08 (d, *J* = 1.2 Hz, 1 H, CH), 3.88 (dd, *J* = 9.9, 1.5 Hz, 1 H, CH), 3.67 (s, 3 H, CO_2CH_3), 2.41 (s, 3 H, CH_3), 0.96–1.08 (m, 1 H, CH), 0.82–0.94 (m, 1 H, CH), 0.55–0.65 (m, 1 H, CH), 0.43–0.53 (m, 1 H, CH), 0.27–0.37 (m, 1 H, CH).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 160.8, 155.9, 140.7, 133.1, 132.5, 132.2, 129.7, 129.4, 129.3 (2 C), 128.6, 128.5, 127.7 (2 C), 68.0, 52.8, 49.5, 21.5, 14.6, 5.0, 2.7.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{22}N_2O_3Na$ [M + Na]$^+$: 385.1523; found: 385.1520.

The other methyl ester isolated in 20% yield was identified to be **6a** as it displayed identical ^{1}H NMR and HRMS data to the material previously obtained via esterification of **5a** (vide supra).

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Supporting Information

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(1) Address correspondence to this author at the Laboratory of Chemical Pharmacology, Institute of Chemistry, Saint Petersburg State University, 26 Universitetskii prospekt, Peterhof 198504, Russian Federation.
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