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# Unusually Reactive Cyclic Anhydride Expands the Scope of the Castagnoli-Cushman Reaction

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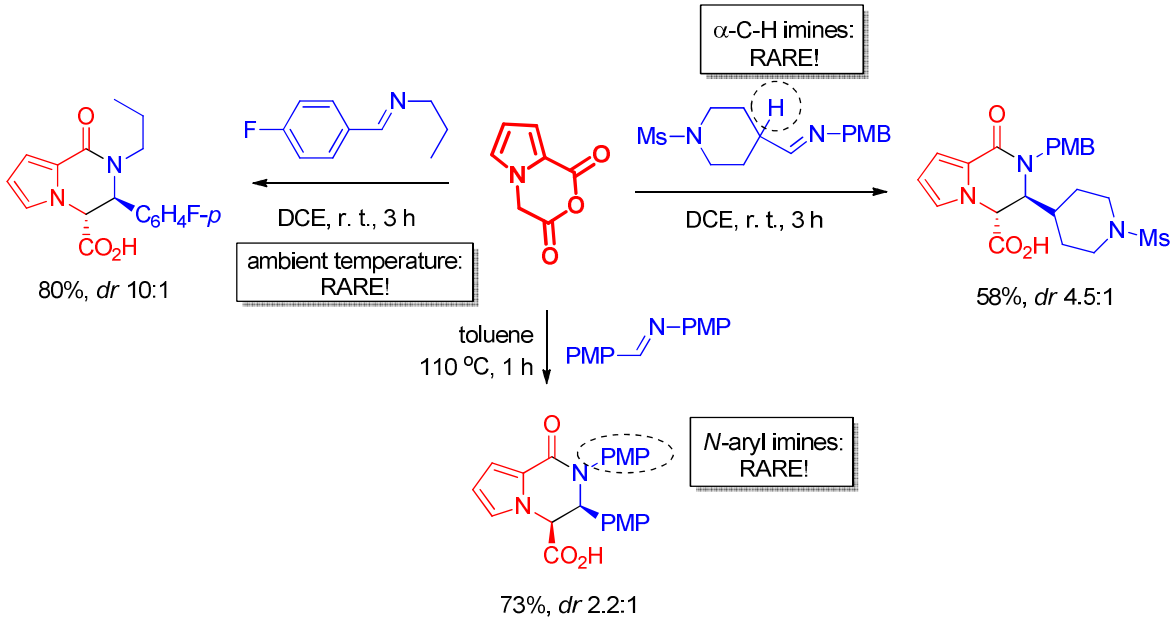



**ABSTRACT:** In the course of synthesizing and testing various 'azole-including' cyclic anhydrides in the Castagnoli-Cushman reaction with imines, a remarkably reactive, pyrrole-based anhydride has been identified. It displayed a remarkably efficient reaction with *N*-alkyl and *N*-aryl imines, in particular, with 'enolizable' α-C-H imines which typically fail to react with a majority of known cyclic anhydrides. The reactivity of this anhydride has been justified by an efficient resonance stabilization of its enol form. This finding expands the existing arsenal of highly reactive cyclic anhydrides and further confirms the importance of anhydride enolization for an efficient Castagnoli-Cushman reaction.

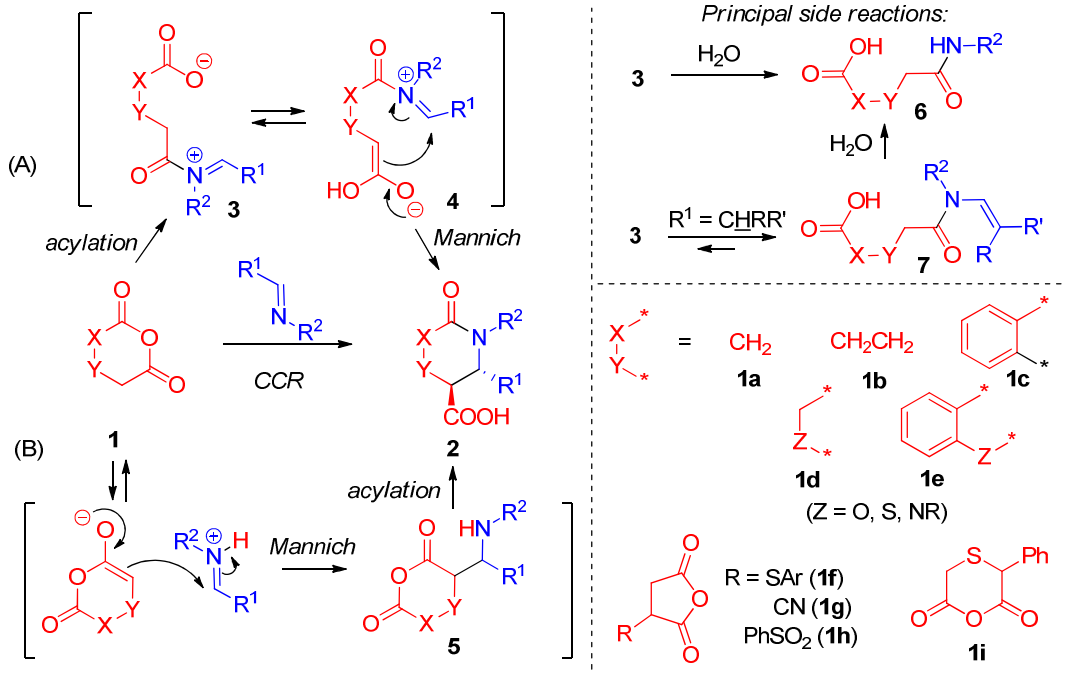
## Introduction

The formal cycloaddition of dicarboxylic acid anhydrides **1** and imines[1] (recently dubbed the Castagnoli-Cushman reaction (CCR) to signify the pioneering work of these researchers[2]) is a remarkably efficient strategy to construct structurally diverse lactams **2** featuring a broad variety of periphery substituents. Two possible mechanisms have been proposed for the CCR and discussed as equally plausible. One of them (A), initially favored by Cushman,[3] implies the initial intermolecular *N*-acylation of the imine component leading to the ring-opened *N*-acyliminium intermediate **3**(**4**) which, in its enol form of alkyl carboxylate anion (shown), undergoes the intramolecular Mannich-type ring closure to give the observed lactam **2**. However, the comprehensive experimental and computational evidence gathered in the recent years speaks for an alternative mechanism (B). It implies a reverse order of events (compared to mechanism A) whereby the enolate form of cyclic anhydride **1** undergoes Mannich-type nucleophilic addition to the protonated imine to give the initial adduct **5**. The latter is perfectly set to undergo the intramolecular *N*-acylation (or aminolysis of the cyclic anhydride) to give lactam **2**. The greater plausibility of mechanism B is supported by the comprehensive computational analysis of both reaction mechanisms (in favor of the latter) by Shaw[4] and the recent isolation[5] as well as trapping[6] of intermediate **5**. The existence, in principle, of the acylation-Mannich pathway A is supported by the frequently observed[7] formation of by-product monoamide **6** which is likely formed via hydrolysis of intermediate **3**. Moreover, with only a few exceptions so far (*vide infra*), it is impossible to involve in the CCR imines derived from α-C-H ('enolizable') aldehydes. The latter promptly tautomerize into enamides **7** (which can be isolated[8] or transformed to **6** on aqueous workup) and steer the reaction away from the productive Mannich-acylation pathway B.

The cyclic anhydrides **1** are the principal source of skeletal diversity of the CCR products **2**.[9] From the earlier examples of the CCR involving succinic (**1a**) and glutaric (**1b**)[2] and homophthalic (HPA, **1c**)[3] anhydrides, the scope of workable anhydrides for the reaction has been

expanded significantly to include heteroatom-containing versions of glutaric anhydride (**1d**)[8] as well as seven-membered versions **1e.**[10] Particularly notable are the highly reactive versions of succinic (**1g**,[11] **1h**,[12] **1i**[13]) and thia-glutaric (**1j**)[14] anhydrides (Figure 1). The enolization of these anhydrides implicated in the productive reaction pathway (B) is highly favored due to enolate stabilization by electron-withdrawing groups and/or negative charge delocalization. Thus, the CCR with these substrates proceeds at ambient temperature – in contrast to toluene or xylene reflux temperatures which are typical for the CCR with less reactive anhydrides.[8]

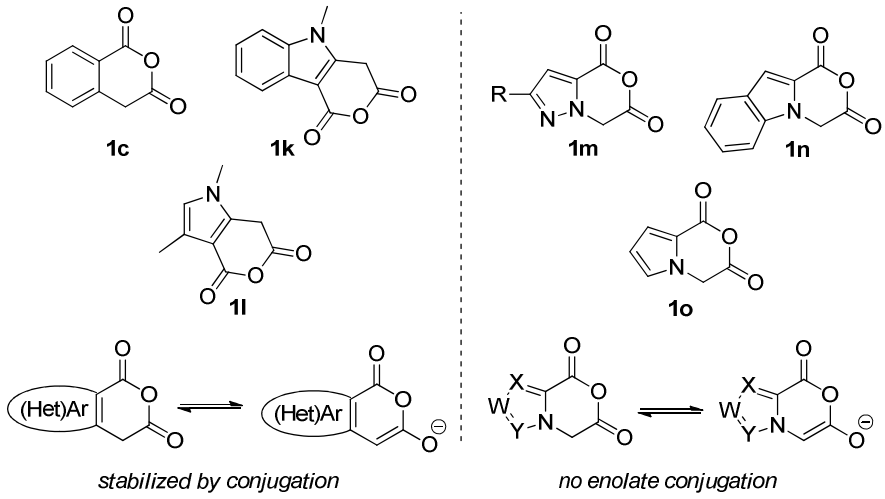
**Figure 1.** The Castagnoli-Cushman reaction, its plausible mechanisms, side products and selected examples of cyclic anhydrides (**1a-i**) reported to-date as partners for the reaction.




HPA (**1c**), however, is also one of the most reactive cyclic anhydrides for the CCR. Indeed, its reactions with imines typically proceed at room temperature. Moreover, it is the only cyclic anhydride to-date that has been reported to give a respectable yield in the CCR with α-C-H imines.[15-18] This aspect is indicative of the non-productive *N*-acylation/Mannich pathway A (primarily leading to enamide side products **7** with α-C-H imines[8]) being essentially shut off for this reactive anhydride. Additional evidence for the high reactivity of **1c** and the importance of

Mannich/acylation reaction pathway B is provided by the fact that **1c** can react in a CCR-like fashion – under mild conditions - with aldehydes (to provide respective lactones);[19] in this reaction, the initial acylation (pathway A) is highly unlikely. This is in contrast to other cyclic anhydrides which normally need to be deprotonated with a strong base[20] or react with aldehydes only with the aid of an organocatalyst[21] or a Lewis acid.[22] Additionally, HPA (**1c**) is more reactive toward *N*-aryl imines which either fail to react with less reactive cyclic anhydrides or require harsh, solvent-free conditions.[23] Thus, it is perhaps unsurprising that the particular suitability of HPA (**1c**) for the CCR inspired Tamura an co-workers to synthesize and use in the same reaction various azole-fused glutaric anhydrides (e. g., **1k-l**).[24] In the latter, one can recognize a possibility for the same type of resonance stabilization of the conjugate enolate as is present in **1c**. Recently, we became interested in exploring a different type of glutaric anhydride variants which we term 'azole-including' (to differentiate it from the azole-fused counterparts **1k-l**) and which to-date have been successfully exemplified by pyrazole (**1m**)[25] and indole (**1n**)[26] cyclic anhydrides. Because no apparent stabilization of the conjugate enolate is possible in these anhydrides (such as the one present in **1c** and **1k-l**), they displayed moderate reactivity and, somewhat predictably, required prolonged heating for the CCR to proceed.

**Figure 2.** Comparison of homophthalic anhydride (HPA, **1c**) to two distinct types of cyclic anhydrides: azole-fused **1k-l** and azole-including **1m**, **1n** and **1o** (investigated in this work).

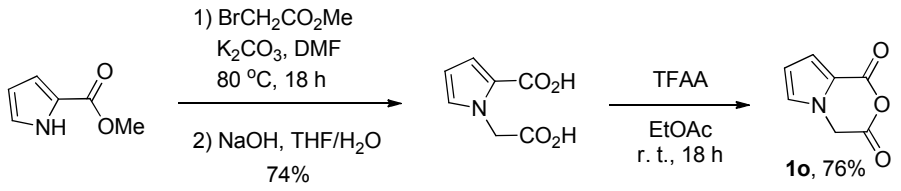


While continuing the exploration of the azole-including cyclic anhydride chemical space, we synthesized and tested, as partner in the CCR, pyrrole-including anhydride **1o** (Figure 2). To our surprise and delight, in the initial experiments it displayed an HPA-like reactivity (reactions going to completion at ambient temperature over only a few hours). Encouraged by this observation, we set off to investigate more fully the reactivity and the synthetic potential of **1o** for the Castagnoli-Cushman reaction. Herein, we present the results of our findings in this regard.

**Results and Discussion**

Anhydride **1o** had not been reported in the literature (though is commercially available according to SciFinder®) and was prepared by a straightforward alkylation of ethyl indole-2-carboxylate followed by double ester hydrolysis and cyclodehydration with trifluoroacetic anhydride (Scheme 1).

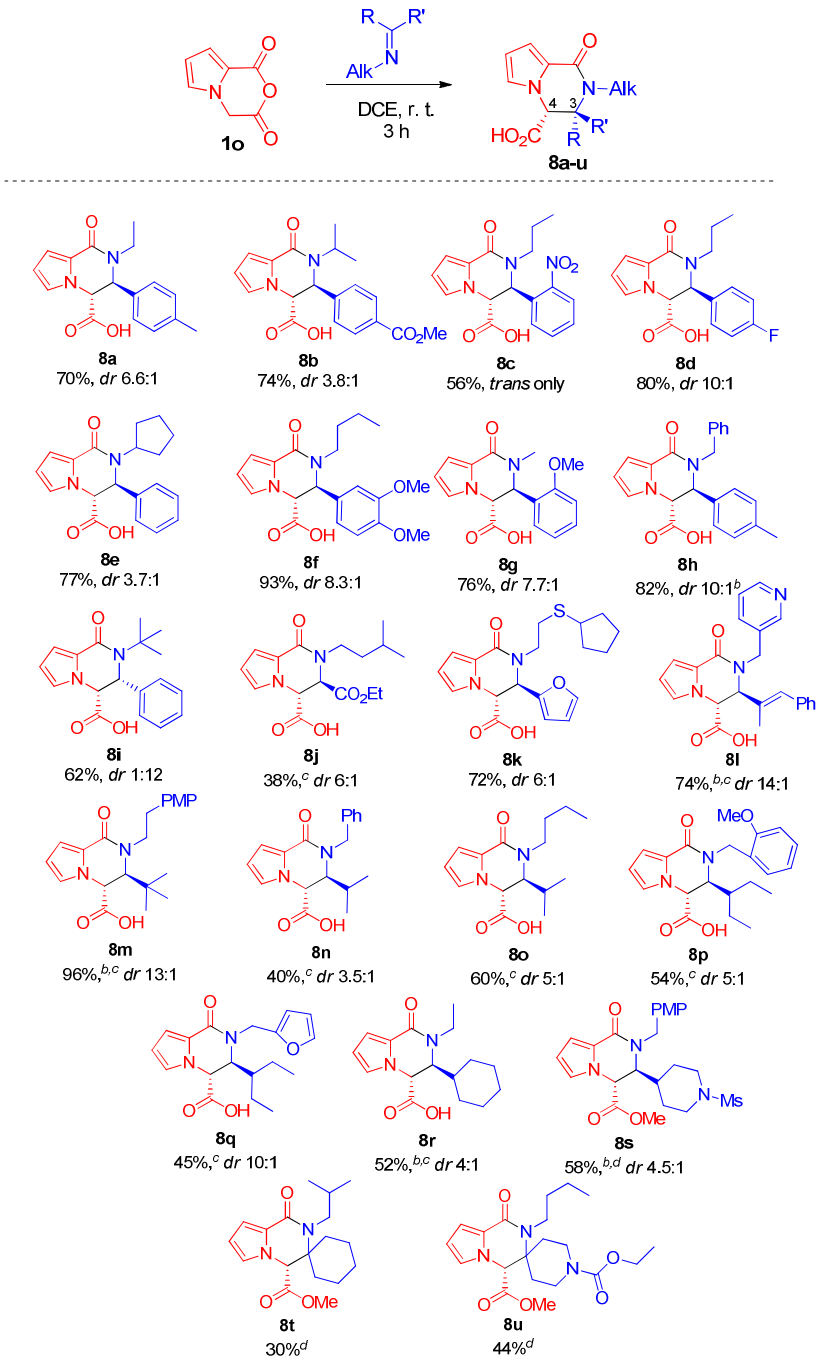
**Scheme 1.** Preparation of 1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,3(4*H*)-dione (**1c**).




Following the discovery that **1o** reacts readily and smoothly with imines at ambient temperature and some preliminary experimentation with various solvents (MeCN, toluene, DMF and EtOAc), we discovered that 1,2-dichloroethane (DCE) provided the best results in terms of conversion and side product profile. Hence, the standard conditions (**1o** : imine = 1:1, DCE 1 mL/mmol, r. t., 3 h) were successfully applied to a range of *N*-alkyl aldimines and ketimines to produce 1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acids **8a-u** in good to excellent yields (Table 1). Besides the mild reaction conditions and the short reaction times, the high, HPA-like reactivity of **1o** manifested itself particularly in its ability to give good yields of the CCR lactam adducts with α-C-H aldimines (compounds **8n-s**). However, the most difficult-to-achieve

extension of the CCR is the ability to involve much less reactive α-C-H ketimines. So far, examples of the CCR with such substrates have been reported for the highly reactive HPA.[5,33-34]

**Table 1.** 1-Oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acids **8a-u** synthesized in this work.[a]

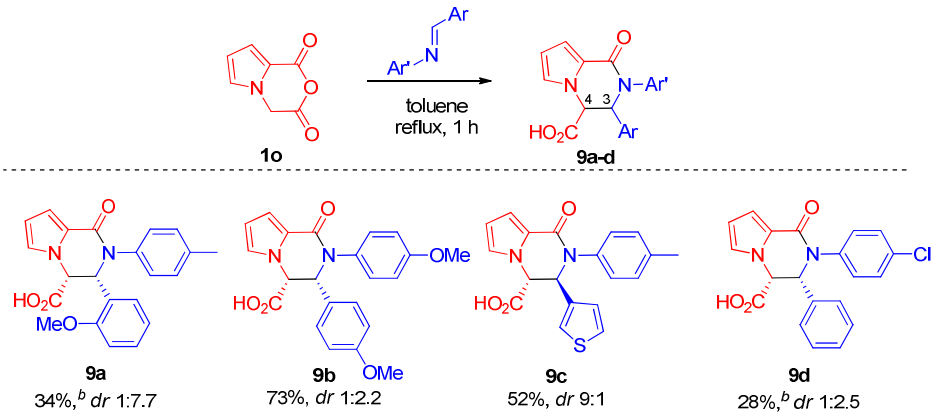



[a] Major diastereomer is shown.
[b] Diastereomers separated and characterized separately.
[c] Isolated by preparative HPLC.
[d] Isolated by column chromatography following esterification ($MeI/K_2CO_3$ – see Experimental Section).

The fact that we were able to obtain products **8t-u** (albeit in a relatively modest yield) clearly attests to the high reactivity of **1o** and a significant contribution of the productive, Mannich-acylation reaction pathway (Figure 1B) in its reactivity mode. Adducts **8a-s** obtained from the reactions of **1o** with aldimines were obtained predominantly as *trans*-isomers (except for the sterically congested *N*-*tert*-butyl product **8i**). The stereochemical assignment was unequivocally performed based on the $^{1}$H NMR spectra and correlated with crystallographic information (*vide infra*). We also sought to improve diastereoselectivity for the reaction leading to **8e** (where the *dr* value observed at room temperature was only 3.8:1). However, neither lowering the reaction temperature (5 ºC, 24 h) nor raising it (40 ºC, 30 min) improved the *dr* value and only led to incomplete conversion or increased byproduct formation as observed by $^{1}$H NMR analysis.

Having established the unexpectedly high (HPA-like) reactivity of anhydride **1o** in the CCR, we were curious to see if *N*-aryl imines (which normally fail to react in the CCR of cyclic anhydrides other than HPA unless harsh temperature regimens are applied[23]) would also turn out to be competent partners for the CCR with anhydride **1o**. While at room temperature, the test reactions with a set of selected *N*-aryl imines displayed low conversions, even at reaction times up to 48 h, performing the same reactions in refluxing toluene gave the complete conversion of anhydride **1o** and the desired products **9a-d** were isolated in modest to good yields (Scheme 2).

**Scheme 2.** Preparation of *N*-aryl 1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acids **9a-d**.[a]

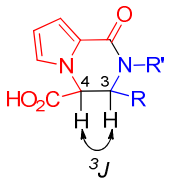



[a] Major diastereomer is shown.
[b] Yield of the pure *cis*-isomer (isolated by crystallization); actual yield may be higher.

The remainder of the reaction mass balance was attributable to a mixture of unidentified by-products observed in each case. The competition of the unwanted course(s) of the reaction is likely due to the reduced reactivity of the anilinic nitrogen atom in initial Mannich-type adduct **5**, which suppresses the subsequent intramolecular aminolysis of the cyclic anhydride moiety in **5** (i. e. the desired course of the reaction) and increases the likelihood of competing side-reactions. Interestingly, in contrast the majority of products **8** obtained with *N*-alkyl imines, *N*-aryl adducts **9** were mostly obtained in *cis*-configured form (except for product **9c**).

As with compounds **8**, the stereochemical assignment of compounds **9** was done on the basis of an apparently higher vicinal coupling constant $^{3}J(H^{3},H^{4})$ generally observed for the *cis*-isomer vs. *trans*-isomer. The generality of this rule was confirmed via single-crystal X-ray analysis of three representative compounds in the *cis*- as well as in the *trans*-series (Table 2).

**Table 2.** Vicinal coupling constants observed in the $^{1}$H NMR spectra of the *cis*- and *trans*-configured adducts **8** and **9** of anhydride **1o** with aldimines.

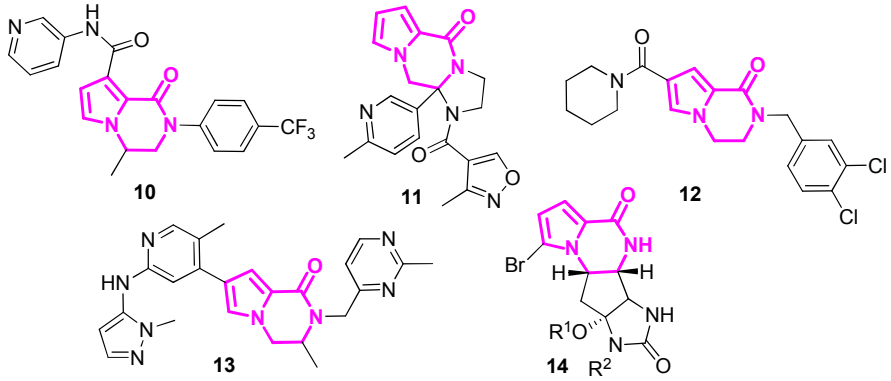



| Compound | $^{3}J$, Hz | | Compound | $^{3}J$, Hz | |
|---|---|---|---|---|---|
| | *cis* | *trans* | | *cis* | *trans* |
| **8a** | 5.1[a] | 1.5 | **8l** | 5.4 | 1.1 |
| **8b** | 4.6 | 1.7 | **8m** | 3.8 | --[b] |
| **8c** | -- | 1.5 | **8n** | 4.1 | 1.1 |
| **8d** | 4.9 | 1.3 | **8o** | 4.2 | 1.1 |
| **8e** | 4.6 | 1.5[a] | **8p** | 4.1 | 1.0 |
| **8f** | 4.8 | 1.6[a] | **8q** | 4.2 | 1.0 |
| **8g** | 5.0 | 1.5 | **8r** | 7.6 | 4.0 |
| **8h** | 5.7 | 1.5 | **8s** | 3.6 | 1.2 |
| **8i** | 4.4 | 2.2 | **9a** | 4.8[a] | 1.2 |
| **8j** | 4.1 | 1.5 | **9b** | 4.8 | --[b] |
| **8k** | 4.5 | 1.6 | **9c** | 4.6 | 1.5[a] |
| | | | **9d** | 4.7[a] | 1.5 |

[a] Single-crystal X-ray structure obtained.
[b] Unresolved doublet.

It should be noted that the 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one core featured in compounds **8a-u** (as well as in their *N*-aryl counterparts **9a-d**) clearly belongs to privileged heterocyclic scaffolds capable of displaying widely variable biological activities depending on the specific molecular periphery employed.[27] Indeed, just by reviewing the biomedical literature over the last 2 years, one can encounter notable examples of mGluR2 receptor antagonist **10**,[28] compound capable of reducing blood uric acid levels **11**,[29] inhibitor of mycobacterial ATP synthase **12**,[30] and ERK1/2 kinase inhibitor **13**;[31] moreover, this core is central to (-)-agelastatin alkaloids of general formula **14**[32] endowed with promising anticancer activity (Figure 3). Thus, besides the remarkably reactive character of **1o** in the context of the CCR, the privileged nature of the 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one motif for drug design clearly adds value to the approach discussed herein. The latter also compares favorably to the earlier described routes in terms of being the only one featuring a one-step construction of the scaffold in question.

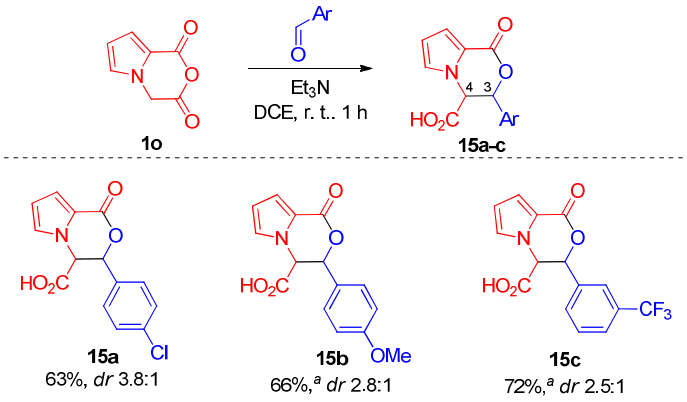
**Figure 3.** Examples of recently reported biologically active compounds featuring 3,4-dihydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one core (highlighted).




To complete the characterization of new anhydride **1o** in formal cycloadditions with electrophiles, we tested it in reactions with aromatic aldehydes. To our delight, in the presence of 1 equiv. of triethylamine, full conversion of **1o** was achieved in 1 hour at ambient temperature and the respective lactone products **15a-c** were isolated as mixtures of diastereomers in moderate to good yields (Scheme 3). Unfortunately, the absence of an apparent difference in the $^{3}J(H^{3},H^{4})$ values of diastereomeric products **15** as well as our being unable to obtain crystals of any of

these compounds for X-ray analysis did not allow performing a straightforward assignment of their relative stereochemistry.

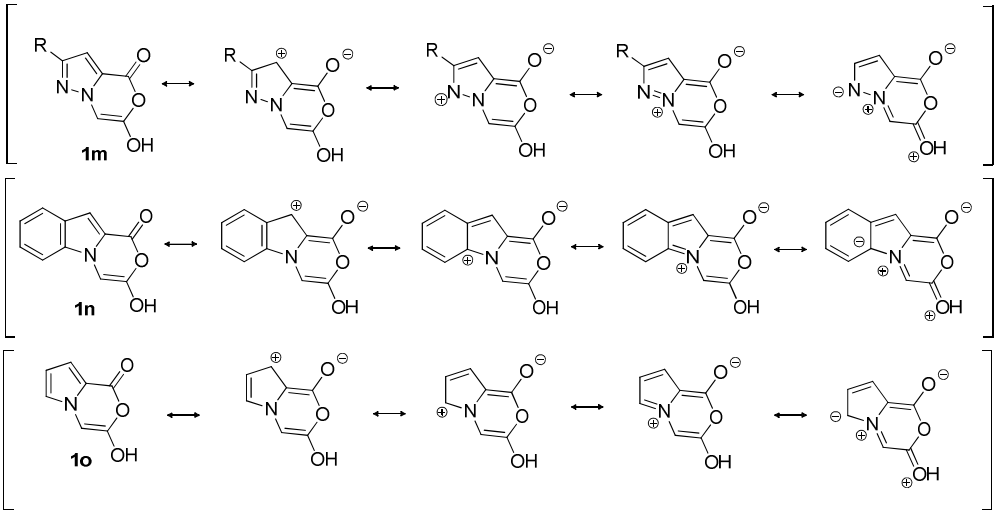
**Scheme 3.** Reaction of anhydride **1o** with aromatic aldehydes.




[a] Isolated by preparative HPLC.

The HPA-like reactivity of **1o** clearly extends the scope of the CCR and the related reaction with aldehydes. Perhaps, the higher reactivity of **1o** compared to its closely related pyrazolo analogs **1m** as well as the 'benzo analog' **1n** can be rationalized even qualitatively by comparing the resonance stabilization of the enol forms of both anhydrides. Indeed, according to the current mechanistic understanding (*vide supra*), the more enolizable a cyclic anhydride is, the more efficiently it will enter the initial Mannich-type addition to the imine (or aldehyde) component and the higher its overall reactivity in the CCR should be. The plausible resonance structures for anhydrides **1m-o** can be drawn out as shown in Figure 4.

**Figure 4.** Possible resonance structures for the enol forms of anhydrides **1m-o**.




All three hybrids appear rather similar. However, in contrast to **1o**, three out of five resonance structures shown for **1n** require the aromatic system of the benzene ring to be destroyed. This alone, in principle, can justify the enol form of **1o** being lower in energy and, hence, the observed higher reactivity of **1o** compared to **1n**. Likewise, the resonance hybrid for **1m** is expected to be higher in energy compared to **1n** owing to the fact that three out of five resonance structures incorporate a positive charge unfavorably located on a nitrogen atom.

In conclusion, we have described a new type of 'azole-including' cyclic anhydride (1*H*-pyrrolo[2,1-*c*][1,4]oxazine-1,3(4*H*)-dione) which displayed a remarkably high reactivity in the Castagnoli-Cushman reaction with *N*-alkyl and *N*-aryl imines as well as a related reaction with aromatic aldehydes. Particularly noteworthy was its reaction with α-C-H aldimines and ketimines that proceeded at room temperature; similar reaction have only been described for homophthalic anhydride but not for other, even highly reactive cyclic anhydrides. This finding clearly expands the diversity of novel anhydrides and potentially paves an avenue for designing new highly reactive anhydrides based on the preliminary analysis of resonance stabilization of the respective enol forms. Such studies are currently underway in our laboratories; the results will be reported in due course.

**Experimental Section**

**General.** All commercial reagents and solvents were used without further purification, unless otherwise noted. 1,2-Dichloroethane (DCE) was distilled over $P_2O_5$ and stored over molecular sieves 4Å. Toluene was distilled after refluxing with sodium-benzophenone and stored over molecular sieves 4Å. NMR spectroscopic data were recorded with a 400 MHz (400.13 MHz for $^1$H and 100.61 MHz for $^{13}$C) and a 500 MHz (500.03 MHz for $^1$H and 125.7 MHz for $^{13}$C) spectrometers in DMSO-$d_6$ or in $CDCl_3$ or in acetone-$d_6$ and were referenced to residual solvent proton signals ($\delta$H = 2.50, 7.26 and 2.05 ppm, respectively) and solvent carbon signals ($\delta$C = 39.5, 77.2 and 206.3 ppm, respectively; multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Coupling constants, $J$ are reported in Hz. The full assignment of signals in $^1$H and $^{13}$C NMR spectra of the obtained new compounds was made, based on 2D-NMR spectroscopy HSQC and HMBC. Mass spectra were recorded with a HRMS-ESI-qTOF spectrometer (electrospray ionization mode). Column chromatography was performed on silica gel 60 (230-400 mesh). For TLC analysis UV254 silica gel coated plates were used. Preparative HPLC was carried out on Shimadzu LC-20AP chromatograph, equipped with spectrophotometric detector. Column: Agilent Zorbax prepHT XDB-C18, 5µm, 21.2×150mm. Eluent: A) 0.1% TFA in water, B) 0.1% TFA in acetonitrile. Flow rate 12 mL/min, temperature – 40 °C, detection UV at 214 and 254 nm. Injection volume – 500µL. Melting points were determined in open capillary tubes on Stuart SMP50 Automatic Melting Point Apparatus.

**1*H*-Pyrrolo[2,1-*c*][1,4]oxazine-1,3(4*H*)-dione (1o).** To a solution of methyl pyrrole-2-carboxylate (12.5 g, 0.1 mol) in DMF (20 mL) was added $K_2CO_3$ (1.5 equiv., 20.7 g, 0.15 mol) and a solution of methyl bromoacetate (1.1 equiv., 11.9 g, 0.11 mol) in DMF (20 mL). The reaction mixture was stirred for 20 minutes at room temperature, then heated at 80 °C for overnight, cooled to room temperature and the solvent was evaporated *in vacuo*. The residue was extracted with DCM (2×20 mL), washed with $H_2O$ (2×20 mL) and brine, passed through a thin layer of silica gel, washing with DCM. The solvent was evaporated under reduced pressure.

*Methyl 1-(2-methoxy-2-oxoethyl)-1H-pyrrole-2-carboxylate* was obtained as a viscous yellow oil (17.4 g, 89%) and was used in the next step without purification. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.99 (dd, *J* = 4.0, 1.8 Hz, 1H), 6.82 – 6.81 (m, 1H), 6.20 (dd, *J* = 4.0, 2.6 Hz, 1H), 5.04 (s, 2H), 3.79 (s, 3H), 3.77 (s, 3H).

To a solution of *methyl 1-(2-methoxy-2-oxoethyl)-1H-pyrrole-2-carboxylate* (2 g, 10.2 mmol) in THF (5 mL) was added a solution of NaOH (4 equiv., 1.6 g, 40.6 mmol) in $H_2O$ (25 mL) and stirred overnight at room temperature. The reaction mixture was acidified with $HCl_{conc}$ to pH 1-2, and cooled. The precipitate was filtered off and air-dried. *1-(Carboxymethyl)-1H-pyrrole-2-carboxylic acid* was obtained as a beige powder (1.4 g, 83%); mp 153 – 155 °C (dec.). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 12.42 (br.s, 2H), 7.06 (t, *J* = 2.2 Hz, 1H), 6.80 (dd, *J* = 3.8, 1.8 Hz, 1H), 6.08 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.00 (s, 2H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 170.3, 161.9, 130.0, 122.5, 117.3, 107.5, 50.0. HRMS *m/z* calcd for $C_7H_6NO_4^-$ $[M–H]^-$: 168.0302, found 168.0312.

To the suspension of *1-(carboxymethyl)-1H-pyrrole-2-carboxylic acid* (1.4 g, 8.3 mmol) in EtOAc (50 mL) was added TFAA (2.2 equiv., 6.8 g, 32.5 mmol) and the mixture was stirred at ambient temperature overnight. The reaction mixture was evaporated almost to dryness under reduced pressure, then filtered off, solid was dried under reduced pressure at 40 °C. *1H-Pyrrolo[2,1-c][1,4]oxazine-1,3(4H)-dione* (**1o**) was obtained as a white powder (0.95 g, 76%); mp 146 – 147 °C (dec.). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 4.1, 1.5 Hz, 1H), 7.02 (t, *J* = 1.9 Hz, 1H), 6.50 (dd, *J* = 4.1, 2.6 Hz, 1H), 5.04 (s, 2H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ 163.8, 153.2, 128.0, 118.3, 113.2, 47.3. HRMS *m/z* calcd for $C_7H_6NO_3^+$ $[M+H]^+$: 152.0342, found 152.0353.

**General procedure for the preparation of aldimines:** A solution of corresponding amine (1 equiv.) and aldehyde (1 equiv.) in dichloromethane (~ 2 mL per mmol) was kept over freshly calcinated $MgSO_4$ (~ 25 g per mol) at room temperature for 1 – 7 days. The progress of reaction was monitored by $^1$H NMR. After completion of the reaction the insoluble material was filtered

and the filtrate was concentrated *in vacuo* to give sufficiently pure imines which were used in reaction with anhydride **1o** without further purification (air-sensitive; store cold).

**General procedure for the preparation of ketimines:** A mixture of corresponding ketone (1 equiv.) and amine (3 equiv.) in toluene (~ 3 mL per mmol) was refluxed with azeotropic removal of water for 30 hours. The resulting mixture was evaporated to dryness to give oily residue which was used in reaction with anhydride **1o** without further purification (air-sensitive; store cold).

**General procedures for the preparation of lactams 8, 9 and lactones 15.**

**General procedure 1:** Anhydride **1o** (0.5 mmol, 76 mg) was added to a solution of corresponding imine (0.5 mmol) in DCE (0.5 mL) and mixture was stirred at room temperature for 3 hours. The resulting mixture was diluted with DCM (2 mL) and extracted with saturated $NaHCO_3$ solution (2×3 mL). The aqueous phase was acidified with $HCl_{conc}$, cooled at 3 °C for an hour. The precipitate was filtered off, and air-dried. In some cases it was recrystallized from MeCN or MeOH or from mixture thereof.

**General procedure 2:** Anhydride **1o** (0.5 mmol, 76 mg) was added to a solution of corresponding imine (0.5 mmol) in DCE (0.5 mL) and mixture was stirred at room temperature for 3 hours. The resulting mixture was evaporated *in vacuo.* The product was isolated using preparative HPLC eluting with $H_2O$–MeCN (with addition 0.1% TFA); gradient: 20% of MeCN (0 – 5 min), 20–90% of MeCN (5 – 40 min), 90–95% of MeCN (40 – 50 min).

**General procedure 3:** Anhydride **1o** (0.5 mmol, 76 mg) was added to the solution of corresponding imine (0.5 mmol) in dry toluene (0.5 mL) and mixture was stirred at 110 °C for 1 hour**.** The resulting mixture was evaporated *in vacuo*. Crude material was diluted with acetone (5 mL), then $K_2CO_3$ (2 equiv., 1 mmol, 138 mg) and MeI (1.5 equiv., 0.75 mmol, 107 mg) were added. Suspension was stirred for 20 hours at ambient temperature. The reaction mixture was evaporated *in vacuo*, extracted with DCM (2×10 mL). The organic layer was washed with $H_2O$

(2×10 mL) and brine (10 mL), dried over anhydrous $Na_2SO_4$ and evaporated. Product was purified by column chromatography on silica gel.

**General procedure 4:** Anhydride **1o** (0.5 mmol, 76 mg) was added to the solution of corresponding imine (0.5 mmol) in dry toluene (0.5 mL) and mixture was stirred at 110 °C for 1 hour. The resulting mixture was diluted with DCM (2 mL) and extracted with saturated $NaHCO_3$ solution (2×3 mL). The aqueous phase was acidified with $HCl_{conc}$, cooled at 3 °C for an hour. The precipitate was filtered off, and air-dried. In some cases it was recrystallized from MeCN or MeOH or from mixture thereof.

**General procedure 5:** Anhydride **1o** (0.3 mmol, 45 mg) and $Et_3N$ (0.3 mmol) were successively added to the solution of corresponding aldehyde (0.3 mmol) in dry DCE (0.3 mL) and mixture was stirred at room temperature for 1 hour. After evaporation of solvent under reduced pressure the product was isolated using preparative HPLC eluting with $H_2O$–MeCN (with addition 0.1% TFA); gradient: 10% B (0 – 10 min), 10–60% B (10 – 40 min), 60–95% B (40 – 55 min).

***trans/cis*-2-Ethyl-1-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (8a)** was prepared according to General procedure 1 from *N*-(4-methylbenzylidene)ethanamine. Yield 104 mg (70%) as mixture of *trans/cis*-diastereomers (6.7:1), colorless solid.

During crystallization from MeCN–MeOH mixture single crystals of two types – prisms and needles – have formed. They were partially separated and the spectral data was obtained for the pure *trans*-isomer (***trans*-8a**). $^1$H NMR (400 MHz, acetone-$d_6$) δ 7.13 (d, $J$ = 8.1 Hz, 2H), 7.05 (d, $J$ = 8.1 Hz, 2H), 6.80 (dd, $J$ = 2.6, 1.6 Hz, 1H, 6-H), 6.76 (dd, $J$ = 3.7, 1.6 Hz, 1H, 7-H), 6.13 (dd, $J$ = 3.7, 2.6 Hz, 1H, 8-H), 5.35 (s, 1H, 3-H), 5.23 (d, $J$ = 1.4 Hz, 1H, 4-H), 4.07 (dq, $J$ = 14.2, 7.2 Hz, 1H, C$\underline{H}$CH$_3$), 2.86 (dq, $J$ = 14.2, 7.2 Hz, 1H, C$\underline{H}$CH$_3$), 2.27 (s, 3H, CH$_3$), 1.09 (t, $J$ = 7.2 Hz, 3H, CH$_2$C$\underline{H}_3$). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ 170.3 ($CO_2H$), 159.1 (1-C), 138.7, 137.1, 130.4, 127.3, 126.1 (8a-C), 125.3 (6-C), 113.2 (7-C), 110.4 (8-C), 63.4 (4-C), 62.4 (3-C),

40.3 ($\underline{C}H_2CH_3$), 21.1 ($CH_3$), 13.9 ($CH_2\underline{C}H_3$). HRMS *m/z* calcd for $C_{17}H_{18}N_2NaO_3^+$ $[M+Na]^+$: 321.1210; found 321.1217.

The spectra of *cis*-diastereomer (***cis*-8a**) contain signals of *trans*-counterpart (*trans/cis* ~ 1:3). $^1$H NMR (400 MHz, acetone-$d_6$) δ (signals *cis*-diastereomer) 7.22 – 7.21 (m, 1H, 6-H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.99 (d, *J* = 8.2 Hz, 2H), 6.85 (dd, *J* = 3.7, 1.5 Hz, 1H, 7-H), 6.22 (m, 1H, 8-H), 5.48 (d, *J* = 4.9 Hz, 1H, 4-H), 5.16 (d, *J* = 4.9 Hz, 1H, 3-H), 3.87 (dq, *J* = 14.2, 7.1 Hz, 1H, C$\underline{H}$CH$_3$), 3.02 (dt, *J* = 14.2, 7.1 Hz, 1H, C$\underline{H}$CH$_3$), 2.25 (s, 3H, $CH_3$), 1.10 (t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H}_3$). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ (signals *cis*-diastereomer) 168.0 ($CO_2H$), 158.6 (1-C), 139.3, 134.7, 130.1, 129.1, 126.6 (8a-C), 125.4 (6-C), 113.8 (7-C), 110.5 (8-C), 62.7 (3-C), 60.9 (4-C), 40.6 ($\underline{C}H_2CH_3$), 21.2 ($CH_3$), 13.9 ($CH_2\underline{C}H_3$). HRMS *m/z* calcd for $C_{17}H_{19}N_2O_3^+$ $[M+H]^+$: 299.1390; found 299.1404.

***trans/cis*-2-Isopropyl-3-(4-(methoxycarbonyl)phenyl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (8b)** was prepared according to General procedure 1 from methyl 4-((isopropylimino)methyl)benzoate. Yield 122 mg (74%), as mixture of *trans/cis*-diastereomers (4:1), colorless solid. $^1$H NMR (400 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 11.87 (br.s, 1H, COOH), 7.93 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 6.80 (dd, *J* = 3.7, 1.5 Hz, 1H, 7-H), 6.75 (dd, *J* = 2.6, 1.6 Hz, 1H, 6-H), 6.12 (dd, *J* = 3.7, 2.6 Hz, 1H, 8-H), 5.52 (s, 1H, 3-H), 5.25 (d, *J* = 1.5 Hz, 1H, 4-H), 4.96 (dt, *J* = 13.8, 6.9 Hz, 1H, C$\underline{H}$(CH$_3$)$_2$), 3.85 (s, 3H, $CO_2CH_3$), 1.20 (d, *J* = 6.8 Hz, 3H, CHC$\underline{H}_3$), 0.88 (d, *J* = 6.8 Hz, 3H, CHC$\underline{H}_3$); observed signals of minor (*cis*) diastereomer: 7.86 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.17 (dd, *J* = 2.5, 1.7 Hz, 1H, 6-H), 6.89 (dd, *J* = 3.7, 1.5 Hz, 1H, 7-H), 6.22 (dd, *J* = 3.7, 2.8 Hz, 1H, 8-H), 5.52 (d, *J* = 4.5 Hz, 1H, 4-H), 5.25 (d, *J* = 4.5 Hz, 1H, 3-H), 4.83 (dt, *J* = 13.8, 6.9 Hz, 1H, C$\underline{H}$(CH$_3$)$_2$), 3.84 (s, 3H, $CO_2CH_3$), 1.33 (d, *J* = 6.8 Hz, 3H, CHC$\underline{H}_3$), 0.87 (d, *J* = 6.8 Hz, 3H, CHC$\underline{H}_3$). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 170.0 ($CO_2H$), 166.8 ($\underline{C}O_2CH_3$), 159.0 (1-C), 147.1, 130.9, 130.6, 127.7, 126.3 (8a-C), 125.1 (6-C), 113.6 (7-C), 110.5 (8-C), 63.8 (4-C), 58.2 (3-C), 52.5 ($CO_2\underline{C}H_3$), 46.1 ($\underline{C}H$(CH$_3$)$_2$), 21.0

(CH<u>C</u>H$_3$), 20.6 (CH<u>C</u>H$_3$); observed signals of minor (*cis*) diastereomer: 167.7 ($CO_2H$), 158.5 (1-C), 144.3, 131.3, 130.3, 129.2, 126.6 (8a-C), 125.4 (6-C), 114.3 (7-C), 110.7 (8-C), 61.4 (4-C), 58.7 (3-C), 46.7 (<u>C</u>H(CH$_3$)$_2$), 21.1 (CH<u>C</u>H$_3$), 20.6 (CH<u>C</u>H$_3$). HRMS *m/z* calcd for $C_{19}H_{21}N_2O_5^+$ $[M+H]^+$: 357.1445; found 357.1436.

***trans*-3-(2-Nitrophenyl)-1-oxo-2-propyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (*trans*-8c)** was prepared according to General procedure 1 from *N*-(2-nitrobenzylidene)propan-1-amine. Yield 96 mg (56%), colorless solid; mp 221 – 222 °C (dec.). $^1$H NMR (400 MHz, acetone-$d_6$) δ 11.99 (br.s, 1H, COOH), 8.18 – 8.14 (m, 2H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.60 (dt, *J* = 7.9, 1.6 Hz, 1H), 6.83 – 6.81 (m, 2H), 6.15 (dd, *J* = 3.7, 2.7 Hz, 1H), 5.65 (d, *J* = 1.6 Hz, 1H), 5.47 (d, *J* = 1.6 Hz, 1H), 4.07 (ddd, *J* = 13.6, 8.5, 7.2 Hz, 1H), 2.81 (ddd, *J* = 13.6, 8.5, 5.1 Hz, 1H), 1.67 – 1.51 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ 169.9, 159.4, 149.6, 142.4,133.64,131.2, 125.70, 125.65, 124.0, 122.7, 113.9, 110.8, 62.8, 62.2, 47.2, 22.3, 11.6. HRMS *m/z* calcd for $C_{17}H_{18}N_3O_5^+$ $[M+H]^+$: 344.1241; found 344.1227.

***trans/cis*-3-(4-Fluorophenyl)-1-oxo-2-propyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (8d)** was prepared according to General procedure 1 from *N*-(4-fluorobenzylidene)propan-1-amine. Yield 127 mg (80%), as mixture of *trans/cis*-diastereomers (10:1), colorless solid. $^1$H NMR (400 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 11.90 (br.s, 1H, COOH), 7.21 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.10 (t, *J* = 8.8 Hz, 2H), 6.81 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.77 (dd, *J* = 3.8, 1.6 Hz, 1H), 6.15 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.41(d, *J* = 1.5 Hz, 1H), 5.28 (d, *J* = 1.6 Hz, 1H), 4.03 (ddd, *J* = 13.5, 8.5, 7.3 Hz, 1H), 2.72 (ddd, *J* = 13.5, 8.4, 5.2 Hz, 1H), 1.64 – 1.48 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H); observed signals of minor (*cis*) diastereomer: 7.02 (t, *J* = 8.8 Hz, 2H), 6.87 (dd, *J* = 3.7, 1.6 Hz, 1H), 6.25 - 6.23 (m, 1H), 5.54 (d, *J* = 4.9 Hz, 1H), 5.22 (d, *J* = 4.9 Hz, 1H), 3.84 (ddd, *J* = 13.6, 8.6, 6.6 Hz, 1H), 2.92 – 2.85 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 170.3, 163.4 (d, *J* = 245.0 Hz), 159.4, 136.1 (d, *J* = 3.2 Hz), 129.5 (d, *J* = 8.4 Hz),

125.5, 116.5 (d, $J$ = 21.8 Hz), 113.6, 110.7, 110.6, 63.2, 62.2, 47.1, 22.3, 11.6. HRMS *m/z* calcd for $C_{17}H_{18}FN_2O_3^+$ $[M+H]^+$: 317.1296; found 317.1301.

***trans/cis*-2-Cyclopentyl-1-oxo-3-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-4-carboxylic acid (8e)** was prepared according to General procedure 1 from *N*-benzylidenecyclopentanamine. Yield 124 mg (77%), as mixture of *trans/cis*-diastereomers (3.7:1), colorless solid. $^1$H NMR (400 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 11.61 (br.s, 1H, COOH), 7.33 – 7.12 (m, 5H), 6.77 – 6.74 (m, 2H, 6,7-H), 6.10 (dd, $J$ = 3.8, 2.6 Hz, 1H, 8-H), 5.41 (d, $J$ = 1.6 Hz, 1H, 3-H), 5.26 (d, $J$ = 1.6 Hz, 1H, 4-H), 4.93 (m, 1H), 1.89 – 1.41 (m, 8H), 1.33 – 1.25 (m, 1H); observed signals of minor (*cis*) diastereomer: 7.18 (dd, $J$ = 2.8, 1.6 Hz, 1H, 6-H), 7.15 – 7.12 (m, 2H), 6.87 (dd, $J$ = 3.7, 1.7 Hz, 1H, 7-H), 6.20 (dd, $J$ = 3.8, 2.8 Hz, 1H, 8-H), 5.49 (d, $J$ = 4.5 Hz, 1H, 4-H), 5.26 (d, $J$ = 4.5 Hz, 1H, 3-H), 4.70 (p, $J$ = 8.6 Hz, 1H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ 170.13 ($CO_2H$), 159.7 (1-C), 141.6 (*ipso*-C), 129.6 (*o*-C), 128.8 (*p*-C), 127.2 (*m*-C), 126.4 (8a-C), 125.0 (6-C), 113.4 (7-C), 110.4 (8-C), 64.0 (4-C), 59.4 (3-C), 55.4, 24.4, 23.8; observed signals of minor (*cis*) diastereomer: 167.8 ($CO_2H$), 159.1 (1-C), 138.7 (*ipso*-C), 129.4 (*o*-C), 129.3 (*p*-C), 128.9 (*m*-C), 126.8 (8a-C), 125.2 (6-C), 114.0 (7-C), 110.5 (8-C), 61.4 (4-C), 60.8 (3-C), 57.6, 24.6, 24.3,. HRMS *m/z* calcd for $C_{19}H_{21}N_2O_3^+$ $[M+H]^+$: 325.1547; found 325.1556.

After recrystallization of diastereomeric mixture from MeCN pure *trans*-diastereomer (***trans*-8e**) was obtained; yield 63 mg (39%); colorless solid; mp 216 – 218 °C (dec.). $^1$H NMR (400 MHz, acetone-$d_6$) δ 7.33 – 7.23 (m, 5H, H-Ph), 6.77 – 6.74 (m, 2H, 6,7-H), 6.10 (dd, $J$ = 3.7, 2.6 Hz, 1H, 8-H), 5.40 (d, $J$ = 1.7 Hz, 1H, 3-C), 5.24 (d, $J$ = 1.7 Hz, 1H, 4-C), 4.98 – 4.90 (m, 1H), 1.79 – 1.44 (m, 8H), 1.32 – 1.25 (m, 1H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ 170.2 ($CO_2H$), 159.6 (1-C), 141.7 (*ipso*-C), 129.6 (*o*-C), 128.8 (*p*-C), 127.2 (*m*-C), 126.5 (8a-C), 125.0 (6-C), 113.3 (7-C), 110.4 (8-C), 64.0 (4-C), 59.4 (3-C), 55.4, 24.4, 23.8. HRMS *m/z* calcd for $C_{19}H_{21}N_2O_3^+$ $[M+H]^+$: 325.1547; found 325.1550.

***trans/cis*-2-Butyl-3-(3,4-dimethoxyphenyl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (8f)** was prepared according to General procedure 1 from *N*-(3,4-dimethoxybenzylidene)butan-1-amine. Yield 173 mg (93%), as mixture of *trans/cis*-diastereomers (8.3:1), colorless solid. $^1$H NMR (400 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 11.85 (br.s, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 6.81 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.77 (dd, *J* = 3.8, 1.6 Hz, 1H), 6.74 (d, *J* = 2.2 Hz, 1H), 6.66 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.15 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.29 (d, *J* = 1.6 Hz, 1H), 5.24 (d, *J* = 1.6 Hz, 1H), 4.09 (dt, *J* = 13.5, 7.8 Hz, 1H), 3.76 (s, 3H), 3.68 (s, 3H), 2.74 (ddd, *J* = 13.5, 7.4, 5.9 Hz, 1H), 1.57 – 1.50 (m, 2H), 1.35 – 1.27 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H); observed signals of minor (*cis*) diastereomer: 7.26 (dd, *J* = 2.8, 1.6 Hz, 1H), 6.61 (d, *J* = 2.2 Hz, 1H), 6.23 (dd, *J* = 3.8, 2.8 Hz, 1H), 5.50 (d, *J* = 4.7 Hz, 1H), 5.11 (d, *J* = 4.7 Hz, 1H), 3.96 – 3.89 (m, 1H), 3.74 (s, 3H), 3.58 (s, 3H), 2.91 (ddd, *J* = 13.8, 8.4, 5.7 Hz, 1H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 170.5, 159.5, 150.7, 150.4, 132.3, 126.1, 125.3, 119.7, 113.2, 112.8, 111.2, 110.4, 63.3, 62.5, 56.20, 56.16, 44.9, 31.3, 20.8, 14.3; observed signals of minor (*cis*) diastereomer: 168.0, 159.0, 150.8, 150.2, 159.6, 126.5, 125.4, 121.8, 113.7, 112.8, 112.4, 110.4,62.9, 60.9, 56.1, 56.0, 45.2, 31.1, 21.0. HRMS *m/z* calcd for $C_{20}H_{25}N_2O_5^+$ $[M+H]^+$: 373.1758; found 373.1757.

After recrystallization of diastereomeric mixture from MeCN pure *trans*-diastereomer (***trans*-8f**) was obtained; yield 65 mg (35%), colorless solid; mp 203 – 205 °C (dec.). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.60 (br.s, 1H), 6.85 – 6.83 (m, 2H), 6.68 – 6.65 (m, 2H), 6.49 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.10 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.27 (d, *J* = 1.6 Hz, 1H), 5.18 (s, 1H), 3.96 (m, 1H), 3.68 (s, 3H), 3.65 (s, 3H), 2.64 (ddd, *J* = 13.2, 7.5, 5.2 Hz, 1H), 1.49 – 1.39 (m, 2H), 1.28 – 1.21 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 170.2, 158.1, 148.8, 148.4, 130.8, 124.7, 124.3, 118.1, 111.7, 111.6, 110.1, 109.1, 61.8, 60.7, 55.4, 55.3, 43.5, 29.9, 19.3, 13.8. HRMS *m/z* calcd for $C_{20}H_{24}N_2NaO_5^+$ $[M+Na]^+$: 395.1577; found 395.1570.

***trans/cis*-3-(2-Methoxyphenyl)-2-methyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (8g)** was prepared according to General procedure 1 from *N*-(2-

methoxybenzylidene)methanamine. Yield 114 mg (76%), as mixture of *trans/cis*-diastereomers (7.7:1), colorless solid. $^1$H NMR (400 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 11.68 (br.s, 1H), 7.30 – 7.26 (m, 1H), 7.08 (dd, *J* = 8.3, 1.1 Hz), 6.84 (dt, *J* = 7.5, 1.1 Hz, 1H), 6.77 (dd, *J* = 2.7, 1.6 Hz, 1H), 6.74 (dd, *J* = 3.8, 1.6 Hz, 1H), 6.71 (dt, *J* = 7.6, 1.1 Hz, 1H), 6.08 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.64 (s, 1H), 5.29 (d, *J* = 1.5 Hz, 1H), 3.97 (s, 3H), 2.98 (s, 3H); observed signals of minor (*cis*) diastereomer: 7.25 – 7.23 (m, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.22 (dd, *J* = 3.7, 2.7 Hz, 1H), 5.71 (d, *J* = 5.0 Hz, 1H), 5.49 (d, *J* = 5.0 Hz, 1H), 3.85 (s, 3H), 2.91 (s, 3H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ 170.7, 160.3, 157.9, 130.5, 127.1, 126.2, 125.7, 125.5, 121.6, 113.3, 112.1, 110.2, 61.0, 60.2, 56.3, 33.3. HRMS *m/z* calcd for $C_{16}H_{17}N_2O_4^+$ $[M+H]^+$: 301.1183; found 301.1172.

***trans/cis*-2-Benzyl-1-oxo-3-(*p*-tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (8h)** was prepared according to General procedure 1 from *N*-(4-methylbenzylidene)-1-phenylmethanamine. Yield 148 mg (82%), as mixture of *trans/cis*-diastereomers (10:1), grey solid. The resulting mixture of diastereomers was recrystallized from MeCN. As a result, two types of crystals were obtained, which were separated manually.

Major (*trans*) diastereomer (***trans*-8h**); colorless crystals; mp 235 – 237 °C (dec.). $^1$H NMR (400 MHz, acetone-$d_6$) δ 12.96 (br.s, 1H, COOH), 7.29 – 6.82 (m, 5H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz), 6.86 (dt, *J* = 3.7, 1.8 Hz, 1H, 7-H), 6.82 (dd, *J* = 2.7, 1.5 Hz, 1H, 6-H), 6.18 (dd, *J* = 3.8, 2.6 Hz, 1H, 8-H), 5.52 (d, *J* = 15.0 Hz, 1H, PhC<u>H</u>), 5.17 (s, 1H), 5.16 (s, 1H), 3.67 (d, *J* = 15.0 Hz, 1H, PhC<u>H</u>), 2.29 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ 170.2 ($CO_2H$), 159.7 (1-C), 139.0, 138.7, 136.5, 130.6, 129.4, 129.1, 128.2, 127.4, 125.8 (8a-C), 125.5 (6-C), 113.8 (7-C), 110.7 (8-C), 63.4 (4-C), 62.2 (3-C), 48.1 ($CH_2$), 21.1 ($CH_3$). HRMS *m/z* calcd for $C_{22}H_{21}N_2O_3^+$ $[M+H]^+$: 361.1547; found 361.1557.

Minor (*cis*) diastereomer (dark crystals) could not be separated completely (*trans/cis* ~ 1:2). $^1$H NMR (400 MHz, acetone-$d_6$) δ (signals of *cis*-diastereomer) 7.37 – 7.33 (m, 4H), 7.28 – 7.26 (m, 1H), 7.26 – 7.25 (m, 1H, 6-H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.95 – 6.93 (m, 3H), 6.27 (m, 1H, 8-H),

5.49 (d, $J$ = 15.2 Hz, 1H, PhC<u>H</u>), 5.44 (d, $J$ = 4.9 Hz, 4-H), 4.95 (d, $J$ = 4.9 Hz, 4-H), 3.66 (d, $J$ = 15.2 Hz, 1H, PhC<u>H</u>), 2.26 (s, 3H, $CH_3$). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ (signals of *cis*-diastereomer) 167.7 ($CO_2H$), 159.0 (1-C), 139.5, 138.8, 133.5, 130.2, 129.6, 129.2, 129.0, 128.4, 126.0 (8a-C), 125.8 (6-C), 114.5 (7-C), 110.7 (8-C), 61.8 (3-C), 60.4 (4-C), 47.5 ($CH_2$), 21.2 ($CH_3$). HRMS *m/z* calcd for $C_{22}H_{21}N_2O_3^+$ $[M+H]^+$: 361.1547; found 361.1550.

***trans/cis*-2-(*tert*-Butyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (8i)** was prepared according to General procedure 1 from *N*-benzylidene-2-methylpropan-2-amine. Yield 97 mg (62%), as mixture of *trans/cis*-diastereomers (1:12), colorless solid. $^1$H NMR (400 MHz, acetone-$d_6$) δ (signals of major (*cis*) diastereomer) 12.07 (br.s, 1H), 7.25 – 7.22 (m, 3H), 7.17 – 7.14 (m, 2H), 7.10 (dd, $J$ = 2.5, 1.7 Hz, 1H), 6.84 (dd, 3.7, 1.7 Hz, 1H), 6.18 (dd, $J$ = 3.7, 2.8 Hz, 1H), 5.52 (d, $J$ = 4.4 Hz, 1H), 5.48 (d, $J$ = 4.4 Hz, 1H), 1.46 (s, 9H); observed signals of minor (*trans*) diastereomer: 6.74 (dd, $J$ = 3.7, 1.6 Hz, 1H), 6.70 (dd, $J$ = 2.6, 1.6 Hz, 1H), 6.08 (dd, $J$ = 3.7, 2.6 Hz, 1H), 5.75 (d, $J$ = 1.7 Hz, 1H), 5.16 (d, $J$ = 1.7 Hz, 1H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ 168.0, 160.1, 138.8, 129.4, 129.31, 123.29, 128.0, 124.5, 113.7, 110.5, 62.1, 30.8, 59.0, 29.2. HRMS *m/z* calcd for $C_{18}H_{21}N_2O_3^+$ $[M+H]^+$: 313.1547; found 313.1557.

After recrystallization from MeCN, pure *cis*-diastereomer (***cis*-8i**) was obtained; yield 47 mg (30%), colorless solid; mp 210 – 211 °C (dec.). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.79 (br.s, 1H), 7.31 – 7.20 (m, 3H), 7.07 – 7.06 (m, 1H), 7.05 – 7.03 (m, 2H), 6.77 (dd, $J$ = 3.6, 1.5 Hz, 1H), 6.18 – 6.16 (m, 1H), 5.46 (d, $J$ = 4.4 Hz, 1H), 5.33 (d, $J$ = 4.4 Hz, 1H), 1.37 (s, 9H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 167.6, 158.7, 137.5, 128.4, 128.2, 127.8, 126.2, 123.6, 112.4, 109.5, 60.7, 59.1, 57.7, 28.4. HRMS *m/z* calcd for $C_{18}H_{21}N_2O_3^+$ $[M+H]^+$: 313.1547; found 313.1548.

***trans/cis*-3-(Ethoxycarbonyl)-2-isopentyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (8j)** was prepared according to General procedure 2 from ethyl 2-(isopentylimino)acetate. Yield 59 mg (38%), as mixture of *trans/cis*-diastereomers (6:1),

colorless transparent oil. $^1$H NMR (400 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 9.99 (br.s, 1H), 7.00 – 6.99 (m, 1H), 6.76 (dd, *J* = 3.7, 1.3 Hz, 1H, 6.17 (dd, *J* = 3.7, 2.8 Hz, 1H), 5.64 (d, *J* = 1.5 Hz, 1H), 5.01 (d, *J* = 1.5 Hz, 1H), 4.23 (dt, *J* = 13.8, 7.9 Hz, 1H), 4.17 – 4.09 (m, 2H), 2.94 (ddd, *J* = 13.8, 8.0, 5.4 Hz, 1H), 1.60 – 1.52 (m, 1H), 1.49 – 1.38 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.90 (t, *J* =6.1 Hz, 6H); observed signals of minor (*cis*) diastereomer: 7.40 – 7.39 (m, 1H), 6.81 (dd, *J* = 3.6, 1.3 Hz, 1H), 5.36 (d, *J* = 4.0 Hz, 1H), 4.89 (d, *J* = 4.0 Hz, 1H), 4.05 (dd, *J* = 14.3, 7.1 Hz, 2H), 3.16 (m, 1H), 1.66 (m, 1H), 1.11 (t, *J* = 7.1 Hz, 3H), 0.94 (dd, *J* = 6.4, 5.0 Hz, 6H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 169.7, 169.4, 159.4, 125.3, 125.2, 113.8, 110.4, 62.7, 61.8, 59.4, 44.1, 37.6, 26.2, 23.1, 22.5, 14.2; observed signals of minor (*cis*) diastereomer: 168.8, 167.6, 159.6, 126.1, 124.9, 114.3, 110.3, 62.5, 61.6, 58.9, 44.8, 26.6, 22.9, 22.7, 14.0. HRMS *m/z* calcd for $C_{16}H_{23}N_2O_5^+$ $[M+H]^+$: 323.1601; found 323.1601.

***trans/cis*-2-(2-(Cyclopentylthio)ethyl)-3-(furan-2-yl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (8k)** was prepared according to General procedure 2 from 2-(cyclopentylthio)-*N*-(furan-2-ylmethylene)ethanamine. Yield 134 mg (72%), as mixture of *trans/cis*-diastereomers (6:1), yellowish viscous oil. $^1$H NMR (400 MHz, $CDCl_3$) δ (signals of major (*trans*) diastereomer) 7.80 (br.s, 1H, COOH+$H_2O$), 7.33 – 7.31 (m, 1H), 6.94 (d, *J* = 3.0 Hz, 1H), 6.75 (s, 1H), 6.27 – 6.17 (m, 2H), 5.97 (d, *J* = 3.2 Hz, 1H), 5.37 (s, 1H), 5.04 (s, 1H), 4.18 – 4.11 (m, 1H), 3.27 – 3.19 (m, 1H), 3.12 (p, *J* = 7.0 Hz, 1H), 2.72 – 2.58 (m, 2H), 1.98 (dt, *J* = 19.4, 6.6 Hz, 2H), 1.72 – 1.69 (m, 2H), 1.56 (dt, *J* = 8.2, 5.5 Hz, 2H), 1.51 – 1.44 (m, 2H); observed signals of minor (*cis*) diastereomer: 7.36 (s, 1H), 7.22 (s, 1H), 7.01 (d, *J* = 3.7 Hz, 1H), 6.18 (dd, *J* = 3.1, 1.8 Hz, 1H), 5.99 (d, *J* = 3.4 Hz, 1H), 5.31 – 5.29 (m, 2H), 2.87 – 2.72 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ (signals of major (*trans*) diastereomer) 169.9, 159.5, 150.4, 143.0, 125.3, 123.2, 115.2, 111.01, 110.96, 108.2, 60.0, 57.4, 46.7, 43.9, 34.1, 34.0, 29.5, 24.91, 24.85; observed signals of minor (*cis*) diastereomer: 167.8, 159.8, 148.5, 143.2, 125.7, 123.9,

115.6, 110.8, 109.6, 58.9, 57.8, 46.3, 44.1, 34.0, 30.3. HRMS *m/z* calcd for $C_{19}H_{22}N_2NaO_4S^+$ $[M+Na]^+$: 397.1192; found 397.1177.

***trans*-(*E*)-1-Oxo-3-(1-phenylprop-1-en-2-yl)-2-(pyridin-3-ylmethyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (*trans*-8l)** was prepared according to General procedure 2 from *N*-((*E*)-2-methyl-3-phenylallylidene)-1-(pyridin-3-yl)methanamine. Yield 134 mg (69%), yellow solid; mp 232 – 233 °C (dec.). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.42 (br.s, 1H), 8.54 (d, $J$ = 1.6 Hz, 1H), 8.46 (dd, $J$ = 4.7, 1.4 Hz, 1H), 7.70 (d, 1H), 7.34 (d, $J$ = 2.5 Hz, 1H), 7.31 (t, $J$ = 6.6 Hz, 2H), 7.22 (t, $J$ = 7.3 Hz, 1H), 7.10 (d, $J$ = 7.4 Hz, 2H), 6.98 – 6.97 (m, 1H), 6.70 (dd, $J$ = 3.7, 1.4 Hz, 1H), 6.17 – 6.15 (m, 2H), 5.37 (s, 1H), 5.14 (d, $J$ = 15.1 Hz, 1H), 4.70 (s, 1H), 4.14 (d, $J$ = 15.1 Hz, 1H), 1.72 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 170.5, 158.5, 149.2, 148.3, 136.2, 135.6, 133.6, 133.5, 128.7, 128.2, 126.9, 126.8, 124.8, 123.6, 123.4, 112.2, 109.3, 65.3, 58.4, 45.6, 14.8. HRMS *m/z* calcd for $C_{23}H_{22}N_3O_3^+$ $[M+H]^+$: 388.1656; found 388.1656.

***cis*-(*E*)-1-Oxo-3-(1-phenylprop-1-en-2-yl)-2-(pyridin-3-ylmethyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (*cis*-8l)** was prepared according to General procedure 2 from *N*-((*E*)-2-methyl-3-phenylallylidene)-1-(pyridin-3-yl)methanamine. Yield 9 mg (5%), yellow amorphous solid. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.77 (br.s, 1H), 8.85 (s, 1H), 8.68 (d, $J$ = 4.4 Hz, 1H), 8.32 (d, $J$ = 7.8 Hz, 1H), 7.75 (dd, $J$ = 7.4, 5.6 Hz, 1H), 7.33 (t, $J$ = 7.4 Hz, 2H), 7.24 (t, $J$ = 7.4 Hz, 1H), 7.19 (s, 1H), 7.09 (d, $J$ = 7.4 Hz, 2H), 6.81 – 6.80 (m, 1H), 6.55 (s, 1H), 6.26 – 6.24 (m, 1H), 5.53 (d, $J$ = 5.5 Hz, 1H), 5.00 (d, $J$ = 15.5 Hz, 1H), 4.72 (d, $J$ = 5.5 Hz, 1H), 4.58 (d, $J$ = 15.5 Hz, 1H), 1.28 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 168.0, 158.1, 144.8, 143.9, 141.5, 136.3, 136.1, 132.8, 132.2, 128.8, 128.2, 127.1, 125.4, 124.6, 123.9, 113.2, 109.8, 65.8, 58.9, 45.4, 12.7. HRMS *m/z* calcd for $C_{23}H_{20}N_3O_3^-$ $[M–H]^-$: 386.1510, found 386.1497.

***trans*-3-(*tert*-Butyl)-2-(4-methoxyphenethyl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (*trans*-8m)** was prepared according to General procedure 2 from

*N*-(2,2-dimethylpropylidene)-2-(4-methoxyphenyl)ethanamine. Yield 164 mg (89%), colorless solid; mp 243 – 244 °C (dec.). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.48 (br.s, 1H), 7.15 (d, $J$ = 8.2 Hz, 2H), 6.98 (s, 1H), 6.87 (d, $J$ = 8.2 Hz, 2H), 6.55 (d, $J$ = 1.5 Hz, 1H), 6.14 – 6.13 (m, 1H), 5.34 (s, 1H), 4.17 (dt, $J$ = 12.2 , 5.7 Hz, 1H), 3.96 (s, 1H), 3.72 (s, 3H), 2.93 (dt, $J$ = 12.2, 5.7 Hz, 1H), 2.61 – 2.55 (m, 2H), 0.78 (s, 9H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 171.7, 128.1, 157.7, 130.6, 129.5, 124.7, 123.4, 113.9, 110.8, 109.2, 66.6, 56.0, 55.0, 49.9, 37.0, 32.9, 26.3. HRMS *m/z* calcd for $C_{21}H_{27}N_2O_4^+$ $[M+H]^+$: 371.1965; found 371.1952.

***cis*-3-(*tert*-Butyl)-2-(4-methoxyphenethyl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (*cis*-8m)** was prepared according to General procedure 2 from *N*-(2,2-dimethylpropylidene)-2-(4-methoxyphenyl)ethanamine. Yield 9 mg (5%), colorless oil. $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.74 (br.s, 1H), 7.41 (m, 1H), 7.17 (d, $J$ = 8.5 Hz, 2H), 6.85 (d, $J$ = 8.5 Hz, 2H), 6.62 (dd, $J$ = 3.6, 1.4 Hz, 1H), 6.14 (m, 1H), 4.69 (d, $J$ = 3.8 Hz, 1H), 4.27 (ddd, $J$ = 13.1, 8.3, 4.2 Hz, 1H), 3.71 (s, 3H), 3.68 (d, $J$ = 3.8 Hz, 1H), 3.15 (dt, $J$ = 13.1, 8.3 Hz, 1H), 2.89 – 2.73 (m, 2H), 0.75 (s, 9H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 169.2, 158.0, 157.8, 131.0, 129.7, 125.6, 122.6, 113.9, 111.6, 109.0, 66.6, 58.0, 55.0, 51.5, 38.1, 32.8, 27.3. HRMS *m/z* calcd for $C_{21}H_{25}N_2O_4^-$ $[M–H]^-$: 369.1820; found 369.1809.

***trans/cis*-2-Benzyl-3-isopropyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (8n)** was prepared according to General procedure 2 from *N*-(2-methylpropylidene)-1-phenylmethanamine. Yield 62 mg (40%), as mixture of *trans/cis*-diastereomers (3.5:1), colorless oil. $^1$H NMR (400 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 7.40 – 7.21 (m, 5H), 6.94 (dd, $J$ = 2.6, 1.6 Hz, 1H), 6.73 (dd, $J$ = 3.8, 1.6 Hz, 1H), 6.19 (dd, $J$ = 3.7, 2.7 Hz, 1H), 5.42 (d, $J$ = 14.9 Hz, 1H), 5.18 (d, $J$ = 1.2 Hz, 1H), 4.05 (d, $J$ = 14.9 Hz, 1H), 3.90 (dd, $J$ = 6.3, 1.3 Hz, 1H), 1.05 (d, $J$ = 7.0 Hz, 3H), 0.77 (d, $J$ = 7.0 Hz, 3H); observed signals of minor (*cis*) diastereomer: 7.42 – 7.19 (m, 6H), 6.78 (dd, $J$ = 3.8, 1.6 Hz, 1H), 6.19 (m, 1H), 5.65 (d, $J$ = 15.1 Hz, 1H), 5.08 (d, $J$ = 4.2 Hz, 1H), 4.07 (d, $J$ = 15.1 Hz, 1H), 3.97 (t, $J$ = 4.2 Hz, 1H), 1.05 (d, $J$ = 7.0 Hz, 3H), 0.74 (d, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ (signals of major

(*trans*) diastereomer) 171.0, 159.1, 139.2, 129.14, 129.10, 128.0, 125.6, 124.5, 113.0, 110.3, 64.5, 57.0, 49.4, 32.1, 19.8, 17.8; observed signals of minor (*cis*) diastereomer: 168.9, 159.5, 139.3, 129.5, 128.8, 128.2, 126.3, 113.8, 110.1, 62.7, 60.3, 50.6, 32.0, 22.4, 18.5. HRMS *m/z* calcd for $C_{18}H_{21}N_2O_3^+$ $[M+H]^+$: 313.1547; found 313.1562.

***trans/cis*-2-Butyl-3-isopropyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (8o)** was prepared according to General procedure 2 from *N*-(2-methylpropylidene)butan-1-amine. Yield 83 mg (60%), as mixture of *trans/cis*-diastereomers (5:1), colorless oil. $^1$H NMR (400 MHz, DMSO-$d_6$) δ (signals of major (*trans*) diastereomer) 13.38 (br.s, 1H), 6.96 (t, *J* = 2.1 Hz, 1H), 6.55 (dd, *J* = 3.7, 1.6 Hz, 1H), 6.11 (dd, *J* = 3.7, 2.6 Hz, 1H), 5.21 (d, *J* = 1.4 Hz, 1H), 4.03 (dt, *J* = 13.5, 7.5 Hz, 1H), 3.73 (dd, *J* = 7.5, 1.4 Hz, 1H), 2.70 (ddd, *J* = 13.5, 8.1, 5.7 Hz, 1H), 1.71 (h, *J* = 6.7 Hz, 1H), 1.61 – 1.34 (m, 2H), 1.22 (h, *J* = 7.3 Hz, 2H), 0.91 (dd, *J* = 7.0, 2.7 Hz, 3H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.74 (d, *J* = 6.8 Hz, 3H); observed signals of minor (*cis*) diastereomer: 13.87 (br.s, 1H), 7.30 – 7.27 (m, 1H), 6.63 (dd, *J* = 3.8, 1.7 Hz, 1H), 6.16 – 6.14 (m, 1H), 5.17 (d, *J* = 4.3 Hz, 1H), 4.12 (ddd, *J* = 13.8, 8.2, 6.2 Hz, 1H), 3.86 (t, *J* = 4.3 Hz, 1H), 2.82 (ddd, *J* = 13.8, 8.1, 6.0 Hz, 1H), 1.92 – 1.84 (m, 1H), 1.54 (tq, *J* = 13.6, 6.2 Hz, 2H), 1.31 (q, *J* = 7.3 Hz, 2H), 0.58 (d, *J* = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ (signals of major (*trans*) diastereomer) 171.3, 157.5, 124.1, 123.9, 111.2, 108.9, 63.8, 56.5, 45.2, 31.3, 31.1, 19.4, 19.1, 18.0, 13.8; observed signals of minor (*cis*) diastereomer: 168.8, 157.9, 125.1, 123.4, 111.9, 109.0, 62.0, 59.0, 46.9, 30.6, 30.2, 21.5, 19.6, 17.8, 13.8. HRMS *m/z* calcd for $C_{15}H_{22}N_2NaO_3^+$ $[M+Na]^+$: 301.1523; found 301.1536.

***trans/cis*-2-(2-Methoxybenzyl)-1-oxo-3-(pentan-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (8p)** was prepared according to General procedure 2 from *N*-(2-ethylbutylidene)-1-(2-methoxyphenyl)methanamine. Yield 99 mg (54%), as mixture of *trans/cis*-diastereomers (5:1), colorless solid. $^1$H NMR (400 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 11.37 (br.s, 1H), 7.31 (dd, *J* = 7.5, 1.7 Hz, 1H), 7.22 (dt, *J* = 7.9, 1.8 Hz, 1H), 6.95 (dd, *J* = 8.3, 1.0 Hz, 1H), 6.92 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.84 (dt, *J* = 7.4, 1.1 Hz, 1H), 6.72 (dd,

*J* = 3.8, 1.6 Hz, 1H), 6.19 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.22 (d, *J* = 14.8 Hz, 1H), 5.12 (d, *J* = 1.1 Hz, 1H), 4.27 (dd, *J* = 5.1, 1.1 Hz, 1H), 4.23 (d, *J* = 14.8 Hz, 1H), 3.86 (s, 3H), 1.72 – 1.61 (m, 2H), 1.42 – 1.34 (m, 1H), 1.33 – 1.18 (m, 1H), 0.97 (d, *J* = 7.2 Hz, 3H), 0.89 – 0.82 (m ,1H), 0.81 – 0.77 (m, 3H); observed signals of minor (*cis*) diastereomer: 11.37 (br.s, 1H), 7.39 (dd, *J* = 7.4, 1.7 Hz, 1H), 7.29 – 7.27 (m, 1H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.74 - 6.72 (m, 1H), 5.26 (d, *J* = 14.7 Hz, 1H), 5.15 (d, *J* = 4.1 Hz, 1H), 4.40 (t, *J* = 4.1 Hz, 1H), 4.17 (d, *J* = 14.7 Hz, 1H), 3.95 (s, 3H), 1.47 (dt, *J* = 12.4, 7.0 Hz, 2H), 1.34 – 1.18 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.79 – 0.76 (m, 3H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 171.4, 159.4, 158.6, 131.2, 129.6, 126.9, 126.0, 124.3, 121.3, 112.7, 111.2, 110.1, 60.6, 56.4, 55.3, 44.9, 42.9, 22.9, 21.5, 12.2, 11.9; observed signals of minor (*cis*) diastereomer: 131.5, 129.6, 127.1, 124.5, 113.6, 111.5, 110.1, 60.6, 60.3, 55.9, 44.5, 24.1, 22.8, 12.4, 11.2. HRMS *m/z* calcd for $C_{21}H_{27}N_2O_4^+$ $[M+H]^+$: 371.1965; found 371.1973.

***trans/cis*-2-(Furan-2-ylmethyl)-1-oxo-3-(pentan-3-yl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (8q)** was prepared according to General procedure 2 from *N*-(2-ethylbutylidene)-1-(furan-2-yl)methanamine. Yield 74 mg (45%), as mixture of *trans/cis*-diastereomers (10:1), colorless solid. $^1$H NMR (400 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 11.53 (br.s, 1H), 7.42 (t, *J* = 1.4 Hz, 1H), 6.93 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.71 (dd, *J* = 3.8, 1.6 Hz, 1H), 6.34 – 6.32 (m, 2H), 6.18 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.25 (d, *J* = 15.6 Hz, 1H), 5.16 (d, *J* = 1.1 Hz, 1H), 4.21 (d, *J* = 15.6 Hz, 1H), 4.22 – 4.20 (m, 1H), 1.66 – 1.54 (m, 2H), 1.37 (dq, *J* = 12.8, 7.5, 7.0 Hz, 1H), 1.23 (ddt, *J* = 14.3, 7.3, 3.0 Hz, 1H), 0.97 (t, *J* = 7.2 Hz, 3H), 0.86 (dddd, *J* = 14.5, 13.2, 7.8, 4.5 Hz, 1H), 0.76 (t, *J* = 7.3 Hz, 3H); observed signals of minor (*cis*) diastereomer: 7.52 (t, *J* = 1.3 Hz, 1H), 7.30 (t, *J* = 2.1 Hz, 1H), 6.77 (dd, *J* = 3.7, 1.6 Hz, 1H), 6.43 – 6.40 (m, 2H), 5.53 (d, *J* = 15.8 Hz, 1H), 5.09 (d, *J* = 4.2 Hz, 1H), 4.07 (d, *J* = 15.8 Hz, 1H), 2.56 (m, 1H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ (signals of major (*trans*) diastereomer) 171.2, 159.0, 152.2, 143.4, 125.8, 124.6, 113.1, 111.3, 110.5, 109.7, 60.5, 56.5, 44.7, 41.7, 22.9, 21.6, 12.2, 11.8; observed signals of minor (*cis*) diastereomer: 143.6, 114.1,

111.5, 110.4, 109.5, 42.7, 24.1, 22.8, 12.5. HRMS *m/z* calcd for $C_{18}H_{23}N_2O_4^+$ $[M+H]^+$: 331.1652; found 331.1661.

***trans*-3-Cyclohexyl-2-ethyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (*trans*-8r)** was prepared according to General procedure 2 from *N*-(cyclohexylmethylene)ethanamine. Yield 58 mg (40%), colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 9.13 (br.s, 1H, $CO_2H+H_2O$), 6.86 (d, *J* = 3.7 Hz, 1H, 7-H), 6.73 (d, *J* = 2.4 Hz, 1H, 6-H), 6.22 (t, *J* = 3.1 Hz, 1H, 8-H), 4.80 (s, 1H, 4-H), 4.18 (dq, *J* = 14.1, 7.1 Hz, 1H, C$\underline{H}_2$CH$_3$), 3.78 (d, *J* = 7.6 Hz, 1H, 3-H), 2.73 (dq, *J* = 14.1, 7.1Hz, 1H, C$\underline{H}_2$CH$_3$), 1.76 – 1.55 (m, 5H), 1.53 – 1.45 (m, 1H), 1.15 – 1.03 (m, 4H), 0.98 (t, *J* = 7.1 Hz, 3H, CH$_2$C$\underline{H}_3$), 0.88 – 0.78 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.3 ($CO_2H$), 159.5 (1-C), 124.5 (6-C), 123.4 (8a-C), 114.3 (7-C), 110.6 (8-C), 64.2 (3-C), 57.4 (4-C), 42.8 (C$\underline{H}_2$CH$_3$), 41.2, 30.1, 29.1, 26.14, 26.07, 26.03, 13.1 (CH$_2$C$\underline{H}_3$). HRMS *m/z* calcd for $C_{16}H_{22}N_2NaO_3^+$ $[M+Na]^+$: 313.1523; found 313.1519.

***cis*-3-Cyclohexyl-2-ethyl-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (*cis*-8r)** was prepared according to General procedure 2 from *N*-(cyclohexylmethylene)ethanamine. Yield 17 mg (12%), contains 8% of *trans*-diastereomer, colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 2.6, 1.6 Hz, 1H, 6-H), 6.97 (dd, *J* = 3.9, 1.6 Hz, 1H, 7-H), 6.24 (dd, *J* = 3.9, 2.6 Hz, 1H, 8-H), 5.03 (d, *J* = 4.1 Hz, 1H, 4-H), 4.43 (dq, *J* = 14.1, 7.1 Hz, 1H, C$\underline{H}_2$CH$_3$), 3.90 (t, *J* = 4.1 Hz, 1H, 3-H), 2.93 (dq, *J* = 14.1, 7.1 Hz, 1H, C$\underline{H}_2$CH$_3$), 1.76 – 1.66 (m, 3H, 1', 2', 6'-H), 1.59 – 1.55 (m, 2H, 2', 6'-H), 1.27 (t, *J* = 7.1 Hz, 3H, CH$_2$C$\underline{H}_3$), 1.24 – 0.93 (m, 6H, 3', 4', 5'-H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.4 ($CO_2H$), 160.2 (1-C), 124.9 (6-C), 124.4 (8a-C), 114.7 (7-C), 110.5 (8-C), 62.9 (3-C), 60.0 (4-C), 43.7 (C$\underline{H}_2$CH$_3$), 41.3 (1'-C), 32.7 (6'-C), 28.2 (2'-C), 26.8 (5'-C), 26.4 (3'-C), 25.9 (4'-C), 13.9 (CH$_2$C$\underline{H}_3$). HRMS *m/z* $[M+Na]^+$ calcd for $C_{16}H_{22}N_2NaO_3^+$ $[M+Na]^+$: 313.1523; found 313.1536.

***trans*-Methyl 2-(4-methoxybenzyl)-3-(1-(methylsulfonyl)piperidin-4-yl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylate (*trans*-8s)** was prepared according to General

procedure 3 from 1-(4-methoxyphenyl)-*N*-((1-(methylsulfonyl)piperidin-4-yl)methylene)methanamine. Eluent: DCM–$Me_2CO$ (100:1 to 10:1). Yield 114 mg (48%), colorless solid; mp 260 – 261 °C (dec.). $^1$H NMR (400 MHz, $CDCl_3$-$d_6$) δ 7.18 (d, *J* = 8.6 Hz, 2H), 6.98 (dd, *J* = 3.9, 1.5 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.65 (dd, *J* = 2.6, 1.5 Hz, 1H), 6.30 (dd, *J* = 3.9, 2.6 Hz, 1H), 5.58 (d, *J* = 14.6 Hz, 1H), 4.69 (d, *J* = 1.3 Hz, 1H), 3.89 (ddt, *J* = 11.9, 4.5, 2.3 Hz, 1H), 3.82 – 3.75 (m, 2H), 3.78 (s, 3H), 3.27 (s, 3H), 2.74 (s, 3H), 2.54 (dt, *J* = 11.9, 2.5 Hz, 1H), 2.45 (dt, *J* = 11.9, 2.5 Hz, 1H), 1.84 (dt, *J* = 12.3, 2.7 Hz, 1H), 1.75 – 1.55 (m, 3H), 1.30 – 1.20 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.9, 159.5, 158.4, 130.3, 129.3, 124.3, 123.5, 114.3, 114.2, 111.2, 61.7, 57.2, 55.5, 53.1, 48.7, 46.13, 46.06, 39.4, 35.1, 29.2, 27.8. HRMS *m/z* calcd for $C_{23}H_{30}N_3O_6S^+$ $[M+H]^+$: 476.1850; found 476.1849.

***cis*-Methyl 2-(4-methoxybenzyl)-3-(1-(methylsulfonyl)piperidin-4-yl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylate (*cis*-8s)** was prepared according to General procedure 3 from 1-(4-methoxyphenyl)-*N*-((1-(methylsulfonyl)piperidin-4-yl)methylene)methanamine. Eluent: DCM–$Me_2CO$ (100:1 to 10:1). Yield 24 mg (10%), yellow amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$-$d_6$) δ 7.26 – 7.24 (m, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.01 (dd, *J* = 3.9, 1.5 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.28 (t, *J* = 3.3 Hz, 1H), 5.69 (d, *J* = 14.8 Hz, 1H), 4.81 (d, *J* = 3.8 Hz, 1H), 3.82 (s, 3H), 3.81 (s, 3H), 3.79 – 3.70 (m, 4H), 2.71 (s, 3H), 2.45 (ddt, *J* = 11.8, 8.8, 4.2 Hz, 2H), 1.70 (tt, *J* = 9.9, 5.1 Hz, 1H), 1.54 (q, *J* = 4.3 Hz, 2H), 1.46 (q, *J* = 4.4 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.9, 159.5, 158.9, 129.7, 129.1, 124.8, 124.0, 115.1, 114.5, 110.8, 60.5, 59.7, 55.5, 53.0, 49.9, 46.2, 38.3, 35.1, 30.6, 27.8. HRMS *m/z* calcd for $C_{23}H_{29}N_3NaO_6S^+$ $[M+Na]^+$: 498.1669; found 498,1676.

**Methyl 2'-isobutyl-1'-oxo-2',4'-dihydro-1'*H*-spiro[cyclohexane-1,3'-pyrrolo[1,2-*a*]pyrazine]-4'-carboxylate (8t)** was prepared according to General procedure 3 from N-cyclohexylidene-2-methylpropan-1-amine. Eluent: *n*-hexane–EtOAc (4:1 to 2:1). Yield 48 mg (30%), light brown oil. $^1$H NMR (400 MHz, $CDCl_3$-$d_6$) δ 6.92 (dd, *J* = 3.8, 1.6 Hz, 1H), 6.67 (dd, *J* = 2.6, 1.6 Hz, 1H), 6.25 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.16 (s, 1H), 3.73 (dd, *J* = 14.3, 8.8 Hz, 1H),

3.66 (s, 3H), 3.03 (dd, *J* = 14.3, 6.3 Hz, 1H), 1.96 – 1.60 (m, 8H), 1.53 (dt, *J* = 13.1, 3.7 Hz, 1H), 1.40 (tq, *J* = 12.8, 3.2 Hz, 1H), 1.27 (dtt, *J* = 12.7, 8.5, 3.9 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 6H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.7, 160.4, 124.7, 122.2, 113.8, 110.6, 62.3, 59.4, 52.8, 46.6, 34.0, 32.4, 30.6, 25.1, 23.1, 22.7, 20.5, 20.0. HRMS *m/z* calcd for $C_{18}H_{27}N_2O_3^+$ $[M+H]^+$: 319.2016; found 319.2023.

**1-Ethyl 4'-methyl 2'-butyl-1'-oxo-2',4'-dihydro-1'*H*-spiro[piperidine-4,3'-pyrrolo[1,2-*a*]pyrazine]-1,4'-dicarboxylate (8u)** was prepared according to General procedure 3 from ethyl 4-(butylimino)piperidine-1-carboxylate. Eluent: *n*-hexane–EtOAc (3:1 to 1:1). Yield 86 mg (44%), light brown amorphous solid. $^1$H NMR (400 MHz, $CDCl_3$-$d_6$) δ 6.94 (dd, *J* = 3.8, 1.5 Hz, 1H), 6.69 – 6.68 (m, 1H), 6.27 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.13 (s, 1H), 4.33 – 4.28 (m, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.09 – 4.02 (m, 1H), 3.76 – 3.69 (m, 1H), 3.67 (s, 3H), 3.30 – 3.18 (m, 2H), 2.95 – 2.87 (m, 1H), 2.18 (dt, *J* = 13.0, 4.8 Hz, 1H), 2.04 – 1.99 (m, 1H), 1.72 – 1.69 (m, 2H), 1.58 – 1.32 (m, 4H), 1.27 (t, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.1, 159.4, 155.5, 124.6, 122.5, 114.2, 111.0, 61.9, 60.4, 58.9, 53.0, 40.6, 40.3, 40.1, 33.7, 33.1, 31.4, 20.4, 14.8, 14.0. HRMS *m/z* calcd for $C_{20}H_{30}N_3O_5^+$ $[M+H]^+$: 392.2180; found 392.2182.

***cis*-3-(2-Methoxyphenyl)-1-oxo-2-(*p*-tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (*cis*-9a)** was prepared according to General procedure 4 from *N*-(2-methoxybenzylidene)-4-methylaniline. The resulting mixture was recrystallized from MeCN to afford pure *cis*-diastereomer. Yield 64 mg (34%); mp 276 – 277 °C (dec.). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.39 (br.s, 1H), 7.20 (ddd, *J* = 8.7, 7.2, 1.8 Hz, 1H), 7.12 – 7.09 (m, 3H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.90 (dd, *J* = 8.4, 1.1 Hz, 1H), 6.87 (dd, *J* = 3.8, 1.6 Hz, 1H), 6.84 (dd, *J* = 7.8 1.8 Hz, 1H), 6.78 (dt, *J* = 7.6, 1.1 Hz, 1H), 6.27 (dd, *J* = 3.8, 2.7 Hz, 1H), 5.90 (d, *J* = 4.9 Hz, 1H), 5.71 (d, *J* = 4.9 Hz, 1H), 3.54 (s, 3H), 2.25 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 167.5, 157.6, 159.7, 138.5, 135.8, 129.6, 129.0, 127.8, 126.9, 124.6, 124.0, 120.4, 113.6, 111.3, 109.8,

59.5, 57.2, 55.5, 20.5. HRMS *m/z* calcd for $C_{22}H_{20}N_2NaO_4^+$ $[M+Na]^+$: 399.1315; found 399.1329.

***trans/cis*-2,3-*bis*(4-Methoxyphenyl)-1-oxo-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (9b)** was prepared according to General procedure 4 from 4-methoxy-*N*-(4-methoxybenzylidene)aniline. Yield 143 mg (73%), as mixture of *trans/cis*-diastereomers (1:2.2), colorless solid.

Diastereomeric mixture was recrystallized from MeCN to afford pure *cis*-diastereomer (***cis*-9b**); yield 75 mg (38%), colorless solid; mp 221 – 223 °C (dec.). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.67 (br.s, 1H), 7.28 (dd, *J* = 2.7, 1.6 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 6.89 – 6.86 (m, 5H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.28 (dd, *J* = 3.8, 2.7 Hz, 1H), 5.77 (d, *J* = 4.8 Hz, 1H), 5.24 (d, *J* = 4.8 Hz, 1H), 3.72 (s, 3H), 3.68 (s, 3H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 167.5, 159.1, 157.7, 157.3, 133.7, 129.1, 128.6, 127.8, 125.0, 124.6, 113.9, 113.8, 113.6, 109.8, 64.8, 59.8, 55.2, 55.0. HRMS *m/z* calcd for $C_{22}H_{20}N_2NaO_5^+$ $[M+Na]^+$: 415.1264; found 415.1284.

***trans/cis*-1-Oxo-3-(thiophen-3-yl)-2-(*p*-tolyl)-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (9c)** was prepared according to General procedure 4 from 4-methyl-*N*-(thiophen-3-ylmethylene)aniline. Yield 91 mg (52%), as mixture of *trans/cis*-diastereomers (9:1), yellow solid.

Diastereomeric mixture was recrystallized from MeCN to afford pure *trans*-diastereomer (***trans*-9c**); yield of 37 mg (21%); yellowish solid; mp 239 – 240 °C (dec.). $^1$H NMR (400 MHz, acetone-$d_6$) δ 7.42 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.24 (dd, *J* = 2.7, 1.4 Hz, 1H), 7.15 (s, 4H), 7.00 (dd, *J* = 2.7, 1.6 Hz, 1H), 6.87 (dd, *J* = 3.8, 1.6 Hz, 1H), 6.84 (dd, *J* = 5.1, 1.4 Hz, 1H), 6.24 (dd, *J* = 3.8, 2.6 Hz, 1H), 5.77 (d, *J* = 1.8 Hz, 1H), 5.45 (d, *J* = 1.8 Hz, 1H), 2.30 (s, 3H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ 170.2, 158.3, 141.2, 140.3, 136.9, 130.1, 127.9, 127.4, 126.9, 125.84, 125.80, 124.0, 114.4, 110.7, 63.2, 62.8, 21.1. HRMS *m/z* calcd for $C_{19}H_{16}N_2NaO_3S^+$ $[M+Na]^+$: 375.0774; found 375.0771.

***trans/cis*-2-(4-Chlorophenyl)-1-oxo-3-phenyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-4-carboxylic acid (9d)** was prepared according to General procedure 4 from *N*-benzylidene-4-chloroaniline. Yield 93 mg (51%), as mixture of *trans/cis*-diastereomers (1:2.5), colorless solid.

Diastereomeric mixture was recrystallized from MeCN to afford pure *cis*-diastereomer (***cis*-9d**); yield 27 mg (14%); colorless solid; mp 249 – 250 °C (dec.). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.75 (br.s, 1H), 7.38 (d, $J$ = 8.7 Hz, 2H), 7.29 (t, $J$ = 2.1 Hz, 1H), 7.27 – 7.23 (m, 3H), 7.19 (d, $J$ = 8.8 Hz, 2H), 7.03 – 7.00 (m, 2H), 6.94 (dd, $J$ = 3.9, 1.6 Hz, 1H), 6.30 (dd, $J$ = 3.8, 2.7 Hz, 1H), 5.81 (d, $J$ = 4.9 Hz, 1H), 5.44 (d, $J$ = 4.9 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 167.4, 157.2, 139.7, 135.7, 130.9, 129.0, 128.63, 128.56, 128.51, 127.8, 125.3, 124.2, 114.1, 110.1, 64.7, 59.7. HRMS *m/z* calcd for $C_{20}H_{16}ClN_2O_3^+$ $[M+H]^+$: 367.0844, found 367.0831.

***trans/cis*-3-(4-Chlorophenyl)-1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-4-carboxylic acid (15a)** was prepared according to General procedure 5 from 4-chlorobenzaldehyde. Yield 55 mg (63%), as mixture of diastereomers (4:1), yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ (signals of major diastereomer) 7.29 – 7.18 (m, 2H), 7.16 – 7.11 (m, 2H), 7.09 (d, $J$ = 4.1 Hz, 1H), 6.89 (s, 1H), 6.31 (t, $J$ = 3.2 Hz, 1H), 6.01 (m, 1H), 5.14 (d, $J$ = 2.9 Hz, 1H); (observed signals of minor diastereomer) 7.37 – 7.32 (m, 2H), 7.18 (d, $J$ = 3.9 Hz, 1H), 6.98 (d, $J$ = 2.4 Hz, 1H), 6.38 (t, $J$ = 3.3 Hz, 1H), 5.92 (d, $J$ = 3.7 Hz, 1H), 5.08 (d, $J$ = 3.7 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ (signals of major diastereomer) 170.2, 158.8, 135.5, 134.1, 129.4, 127.4, 127.0, 119.4, 118.7, 112.4, 79.2, 59.9; (observed signals of minor diastereomer) 131.8, 131.7, 129.2, 127.5, 119.5. HRMS *m/z* calcd for $C_{14}H_9ClNO_4^-$ $[M–H]^-$: 290.0226, found 290.0240.

After standing of $CDCl_3$ solution of diastereomeric mixture for 12 hours at ambient temperature the precipitate has formed. It was filtered, dried *in vacuo* to give individual major diastereomer; yield 10 mg (11%), colorless solid; mp 179 – 181 °C (dec.). $^1$H NMR (400 MHz, DMSO-$d_6$) δ 13.25 (br.s, 1H), 7.52 (s, 4H), 7.31 (dd, $J$ = 2.6, 1.5 Hz, 1H), 7.04 (dd, $J$ = 4.0, 1.5 Hz, 1H), 6.36 (dd, $J$ = 4.0, 2.6 Hz, 1H), 6.20 (d, $J$ = 3.8 Hz, 1H), 5.47 (d, $J$ = 3.8 Hz, 1H). $^{13}$C NMR (100 MHz,

DMSO-$d_6$) δ 167.6, 157.4, 133.8, 133.1, 128.3, 127.9, 126.1, 119.0, 116.6, 110.9, 77.9, 59.6. HRMS *m/z* calcd for $C_{14}H_9ClNO_4^-$ [M–H]$^-$: 290.0226, found 290.0215.

**3-(4-(Methoxycarbonyl)phenyl)-1-oxo-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-4-carboxylic acid (15b)** was prepared according to General procedure 5 from methyl 4-formylbenzoate. Yield 63 mg (66%), as mixture of diastereomers (2.7:1), yellow oil. $^1$H NMR (400 MHz, acetone-$d_6$) δ (signals of major diastereomer) 7.99 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.16 (dd, *J* = 2.7, 1.5 Hz, 1H), 6.96 (dd, *J* = 4.0, 1.5 Hz, 1H), 6.29 – 6.27 (m, 2H), 5.78 (d, *J* = 2.5 Hz, 1H), 3.86 (s, 3H); observed signals of minor diastereomer: 8.08 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.25 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.07 (dd, 4.0, 1.5 Hz, 1H), 6.38 (dd, *J* = 4.0, 2.6 Hz, 1H), 5.56 (d, *J* = 3.7 Hz, 1H), 5.35 (br.s, COOH+$H_2O$), 3.91 (s, 3H). $^{13}$C NMR (100 MHz, acetone-$d_6$) δ (signals of major diastereomer) 168.1, 165.5, 157.4, 141.9, 129.5, 129.2, 126.1, 125.9, 119.2, 116.8, 110.6, 78.7, 59.0, 51.4; observed signals of minor diastereomer: 166.6, 165.8, 139.9, 130.4, 130.3, 126.2, 125.3, 120.6, 116.6, 110.8, 78.4, 59.9. HRMS *m/z* calcd for $C_{16}H_{12}NO_6^-$ [M–H]$^-$: 314.0670, found 314.0649.

**1-Oxo-3-(3-(trifluoromethyl)phenyl)-3,4-dihydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine-4-carboxylic acid (15c)** was prepared according to General procedure 5 from 3-(trifluoromethyl)benzaldehyde. Yield 76 mg (72%), as mixture of diastereomers (2.5:1), yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) δ (signals of major diastereomer) 7.62 (d, *J* = 7.6 Hz, 1H), 7.54 – 7.44 (m, 3H), 7.19 (dd, *J* = 4.0, 1.3 Hz, 1H), 6.94 – 6.91 (m, 1H), 6.47 (br.s, COOH+$H_2O$), 6.39 (dd, *J* = 4.0, 2.6 Hz, 1H), 6.11 (d, *J* = 3.1 Hz, 1H), 5.18 (d, *J* = 3.1 Hz, 1H); observed signals of minor diastereomer: 7.76 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.57 (t, *J* = 7.7 Hz, 1H), 7.28 – 7.26 (m, 1H), 7.00 (t, *J* = 1.9 Hz, 1H), 6.05 (d, *J* = 3.8 Hz, 1H), 5.14 (d, *J* = 3.8 Hz, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.1, 158.2, 136.6, 130.0, 129.7, 129.5, 126.7, 126.5 (q, *J* = 3.9 Hz), 123.7 (q, *J* = 272.7 Hz), 123.0 (q, *J* = 3.8 Hz), 119.7, 118.8, 112.6, 79.1, 59.9. HRMS *m/z* calcd for $C_{15}H_9F_3NO_4^-$ [M–H]$^-$: 324.0489, found 324.0465.

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### Notes

The authors declare no competing financial interest.

## ASSOCIATED CONTENT

### Supporting Information

X-ray crystallographic information for compounds *trans*-**8a**, *cis*-**8a**, *trans*-**8f**, *cis*-**9b**, *trans*-**9c**, *cis*-**9d** and copies of $^{1}$H and $^{13}$C NMR spectra for compounds **1o**, **8a-u**, **9a-d**, **15a-c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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