

Synthesis of Annelated Azaheterocycles Containing a 5-Carbamoylpyrazin-3-one Fragment by a Modification of the Four-Component Ugi Reaction

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A convenient synthesis of novel imidazole- and pyrrole-fused 1-oxo-1,2,3,4-tetrahydropyrazine heterocyclic structures by a novel modification of the four-component Ugi condensation is described. The usefulness and versatility of the developed approach for the synthesis of variously substituted com-

pounds is demonstrated and the scope and limitations of the chemistry involved are discussed.

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Introduction

The four-component Ugi reaction (Ugi-4CR) between an aldehyde, an amine, an isocyanide and a carboxylic acid has emerged as a powerful tool for rapid identification and optimization of lead compounds in drug discovery.^[1] One important modification of this reaction is the use of bifunctional reagents. Thus, modified syntheses using bifunctional keto acids (or formyl acids), amines and isonitriles as starting materials have been reported.^[2] For example, reaction of ω -keto acids^[2a] or aldehydes^[2d] with the corresponding isonitriles and amines led to β -lactams. A series of 2,3-dihydro-1*H*-isoindol-3-ones was prepared from 2-formyl^[2f] or 2-acetylbenzoic acids.^[2a] Using 1,8-naphthaldehydic acid, 2-formylphenoxyacetic acid and 2'-formylphenoxy-2-benzoic acid as the bifunctional reagents in Ugi coupling, a series of rare six-, seven- and eight-membered heterocyclic rings was obtained.^[2f] Recently, Marcaccini et. al reported a synthetic approach to novel *S,N*-heterocycles, starting from the corresponding thiocarboxylic ω -keto- or ω -formyl acids.^[2g,2h] Recent developments in the isocyanide-based multicomponent synthesis of heterocycles are reviewed by Zhu.^[3]

As a further modification of this useful synthetic methodology, we report an Ugi-type reaction of azaheterocyclic reagents bearing a (2-oxoethylamino)acetic acid fragment with isonitriles and primary amines. The reaction leads to

novel annelated heterocyclic systems containing the 5-carbamoylpyrazin-3-one fragment (Figure 1). Specifically, two series of novel imidazo[1,5-*a*]pyrazin-8-ones (structure **A**) and 6,7-dihydrofuro- and 6,7-dihydrothieno[2',3':4,5]pyrrolo[1,2-*a*]pyrazin-8(5*H*)-ones (structure **B**) were obtained. Heteroaryl-fused pyrazin-3-one fragments are present in a number of natural and synthetic physiologically active agents. Among them are antineoplastic and antibacterial alkaloids longamide, longamide B (structures **Ia,b**) and phakellstatins (**IIa,b**) isolated from marine organisms *Agelas* genus, *Homaxinella* sp. and *Phakellia mauritiana*,^[4] antitrombotic agent **III**^[5] and potential antiprotozoal drug **IV**^[6] (Figure 1). These examples have prompted us to explore synthetic routes to the mentioned target molecular scaffolds, which can serve as a fertile source of bioactive molecules.

Results

As first example of our approach, we describe the synthesis of 6,7-dihydro-5*H*-imidazo[1,5-*a*]pyrazin-8-one compounds **6** (Scheme 1). A solution of the dicarboxylate **1** in 1,4-dioxane was treated with bromoacetone under phase-transfer conditions, in the presence of K₂CO₃ and 18-crown-6, to afford the keto diester **2** in 60% yield. The key bifunctional keto acid **3** was then prepared using reaction of **2** with 1.5% methanolic KOH at 20 °C for 72 h. LCMS analysis of the crude reaction mixture revealed the presence of the desired acid **3** ($\approx$ 70%) as well as a small amount of isomeric acid ($\approx$ 5%) and the corresponding dicarboxylic acid ($\approx$ 25%). The observed difference in hydrolytic stability of the methyl carboxylate groups can be explained, in our opinion, by nucleophilic attack of the oxygen atom in enol form of compound **2** on the neighbouring carbonyl

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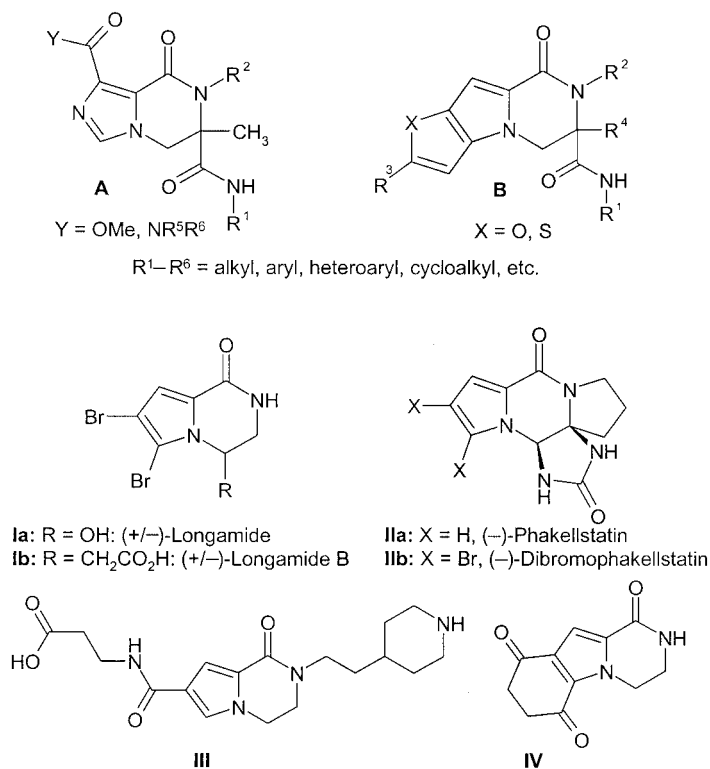
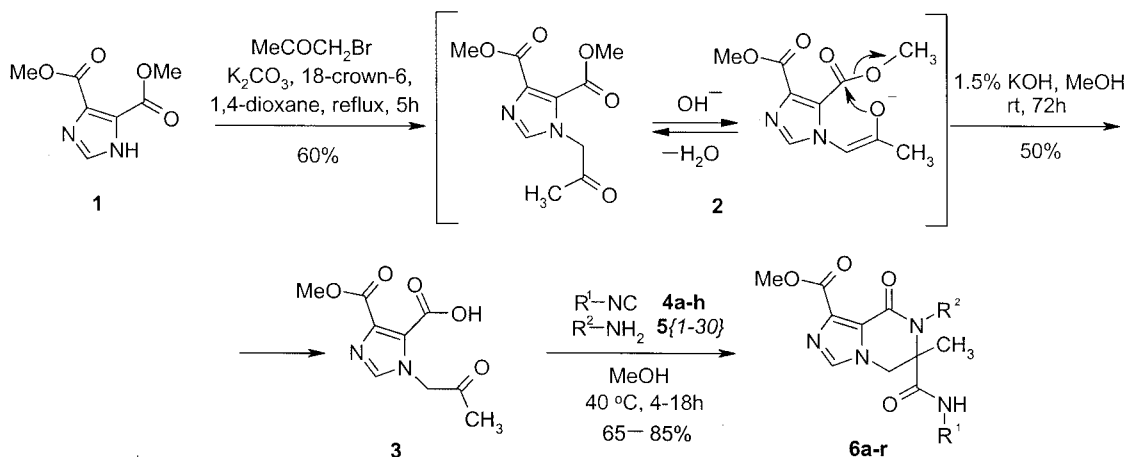


Figure 1. Structures obtained in this work.

Scheme 1. Synthesis of imidazo[1,5-*a*]pyrazin-8-ones **6a-r**.

carbon atom. Such intermolecular interaction weakens the ester bond of the 5-carboxylate group and thus allows its selective hydrolysis. The desired product **3** was isolated in 50% yield.

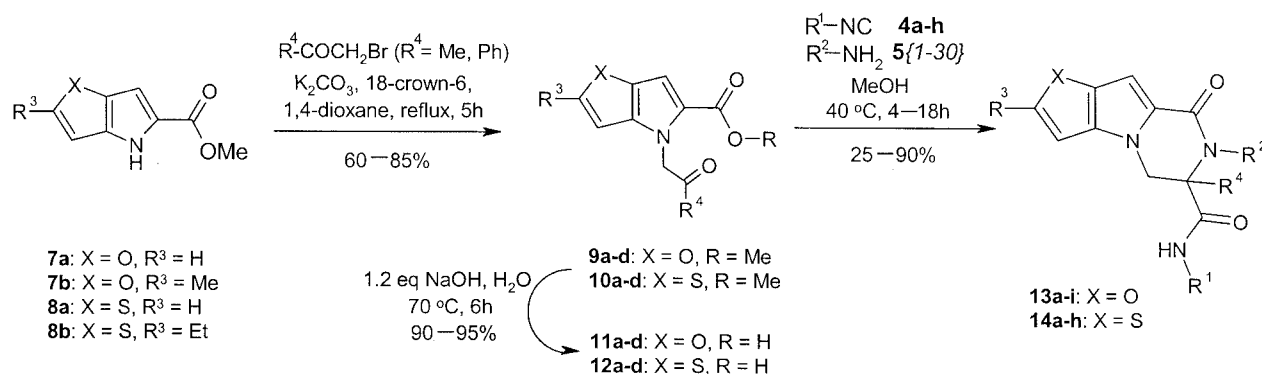
We have found that when keto acid **3** was treated with the isocyanide **4** and the primary amine **5** in methanol at 40 °C, conversion into 6,7-dihydro-5*H*-imidazo[1,5-*a*]pyrazin-8-ones **6a-r** (Table 1) proceeded smoothly and without any indication of major side reactions (yields 65–85%). In particular, in most cases there was no indication of attack upon the ester group, which can be used for introduction of additional complexity to the obtained scaffold.

To demonstrate the versatility of the developed Ugi-type condensation, we additionally synthesized two small sets of 6,7-dihydrofuro- and 6,7-dihydrothieno[2',3':4,5]pyrrolo[1,2-*a*]pyrazin-8(5*H*)-ones, which were not previously described (Scheme 2). Solutions of 4*H*-furo- and 4*H*-thieno[3,2-*b*]pyrrole derivatives **7a,b** and **8a,b** in 1,4-dioxane were alkylated with chloroacetone or bromoacetophenone under phase-transfer conditions, in the presence of K₂CO₃ and 18-crown-6, to afford the keto esters **9a-d** and **10a-d** in good yields (60–85%). The bifunctional reagents, **11a-d** and **12a-d**, were then prepared in 90–95% yields using mild alkali hydrolysis of **9a-d** and **10a-d**. The keto acids **11a-d**

Table 1. Structures and yields of compounds **6a–r**.

Compound	R ¹ /reagent ^[a]	R ² /reagent ^[a]	Yield [%]
6a	cyclopentyl/ 4a	3-chlorobenzyl/ 5 {1}	69
6b	cycloheptyl/ 4b	cyclopropyl/ 5 {2}	75
6c	cycloheptyl/ 4b	(2-thien-2-yl)ethyl/ 5 {3}	71
6d	cyclohexyl/ 4c	4-methoxybenzyl/ 5 {4}	78
6e	cyclohexyl/ 4c	Me/ 5 {5}	85
6f	cycloheptyl/ 4b	3-methoxybenzyl/ 5 {6}	65
6g	cycloheptyl/ 4b	2-ethoxybenzyl/ 5 {7}	65
6h	cycloheptyl/ 4b	2-methylbenzyl/ 5 {8}	78
6i	cycloheptyl/ 4b	3-methylbenzyl/ 5 {9}	72
6j	cycloheptyl/ 4b	3-methoxypropyl/ 5 {10}	65
6k	cyclopentyl/ 4a	<i>i</i> Pr/ 5 {11}	76
6l	cycloheptyl/ 4b	2-chlorobenzyl/ 5 {12}	70
6m	cycloheptyl/ 4b	4-chlorobenzyl/ 5 {13}	80
6n	cycloheptyl/ 4b	(4-chlorophenyl)ethyl/ 5 {14}	66
6o	cycloheptyl/ 4b	phenylpropyl/ 5 {15}	70
6p	cycloheptyl/ 4b	4-fluorobenzyl/ 5 {16}	79
6q	cycloheptyl/ 4b	(cyclohex-1-en-1-yl)ethyl/ 5 {17}	65
6r	cycloheptyl/ 4b	(4-ethoxyphenyl)ethyl/ 5 {18}	69

[a] Number of the corresponding isocyanide or amine on Scheme 1.

Scheme 2. Synthesis of 6,7-dihydrofuro- and 6,7-dihydrothieno[2',3':4,5]pyrrolo[1,2-a]pyrazin-8(5H)-ones **13a–i** and **14a–h**.

and **12a–d** were then treated with the isocyanides **4** and primary amines **5** in methanol at 40 °C to yield two small libraries of the desired products **13a–i** and **14a–h** (Table 2) belonging to furo- and thieno-series, respectively (yield 25–90%).

For imidazo[1,5-*a*]pyrazin-8-ones **6a–r**, isolated yields in the described reactions were often in excess of 60% and sometimes better than 80%. However, many 6,7-dihydrofuro- and 6,7-dihydrothieno[2',3':4,5]pyrrolo[1,2-*a*]pyrazin-8(5H)-ones (**13a–i** and **14a–h**, respectively) were obtained in low to moderate yields (25–50%), and this fact limits the applicability of the developed approach for these heterocyclic chemotypes. The reaction products **6a–r**, **13a–i** and **14a–h** usually precipitated from the reaction mixtures after the reaction was cooled to room temperature. The precipitates could be recrystallized from diethyl ether or purified by flash column chromatography on silica gel. All compounds were obtained as racemic mixtures of enantiomers.

The assignment of all structures was made on the basis of ¹H, ¹³C NMR and high-resolution mass-spectroscopy data; satisfactory analytical data were obtained for all synthesized compounds. In many cases, pure crystalline substances could be obtained, thus allowing firm stereochemi-

cal assignments to be made to the individual compounds through X-ray crystallography. For instance, the structure of **13a** was unambiguously established as *N*-cyclohexyl-7-isopropyl-6-methyl-8-oxo-5,6,7,8-tetrahydrofuro[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide by single-crystal X-ray analysis (Figure 2). Single crystals of compounds suitable for X-ray analysis were grown from diethyl ether.

Discussion

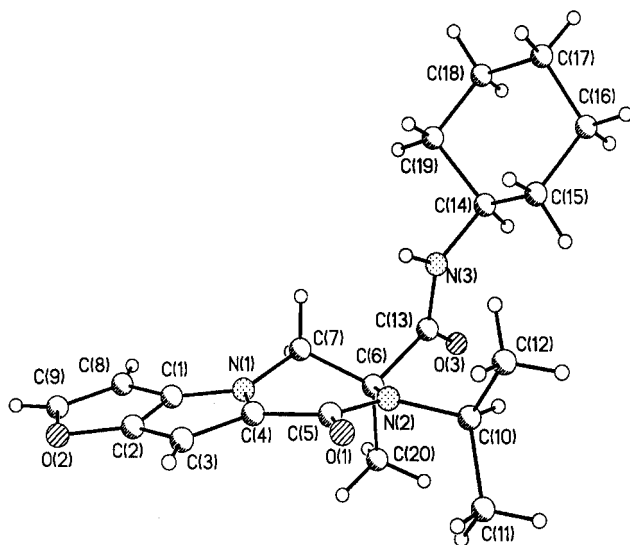
The reported synthetic approaches to heteroaryl-fused pyrazinones are typically tedious multistep procedures incompatible with the high-throughput combinatorial protocol.^[7,8] In one reported example of a combinatorial approach to 6,7-dihydro-5H-imidazo[1,5-*a*]pyrazin-8-ones, assembly of the core heterocyclic moiety occurs at the sixth step of the synthetic sequence.^[9] The method developed in this work dramatically reduces the number of synthetic stages leading to the target molecular scaffold.

The Ugi-4CR reaction developed in this work presumably follows the same course as the classical Ugi condensation with an intermediate imine being attacked by the isocy-

Table 2. Structures and yields of compounds **13a–i** and **14a–h**.

Compound	X	R ¹ /reagent ^[a]	R ² /reagent ^[a]	R ³	R ⁴	Yield [%]
13a	O	cyclohexyl/ 4c	<i>i</i> Pr/ 5 {11}	H	Me	43
13b	O	cyclohexyl/ 4c	3-fluorobenzyl/ 5 {19}	H	Ph	28
13c	O	cyclohexyl/ 4c	3-fluorobenzyl/ 5 {19}	Me	Ph	27
13d	O	cyclohexyl/ 4c	(pyridin-3-yl)methyl/ 5 {20}	Me	Me	63
13e	O	cyclooctyl/ 4d	(thien-2-yl)methyl/ 5 {21}	Me	Me	66
13f	O	3-methylbutyl/ 4e	2-methoxyethyl/ 5 {22}	H	Me	40
13g	O	(tetrahydrofuran-2-yl)methyl/ 4f	4-chlorobenzyl/ 5 {13}	H	Me	48
13h	O	cycloheptyl/ 4b	Bn/ 5 {23}	Me	Ph	36
13i	O	cycloheptyl/ 4b	Pr/ 5 {24}	H	Ph	27
14a	S	cycloheptyl/ 4b	2-furylmethyl/ 5 {25}	Et	Me	90
14b	S	cyclohexyl/ 4c	3-bromobenzyl/ 5 {26}	H	Ph	34
14c	S	cycloheptyl/ 4b	Pr 5 {24}	H	Ph	25
14d	S	cycloheptyl/ 4b	Pr 5 {24}	Et	Ph	28
14e	S	4-methylcyclohexyl/ 4g	(pyrrolidin-1-yl)ethyl 5 {27}	Et	Me	63
14f	S	cyclopentyl/ 4a	1-benzylpiperidin-4-yl 5 {28}	H	Me	65
14g	S	2-methylcyclohexyl/ 4h	3-fluorophenyl 5 {29}	H	Me	40
14h	S	cyclohexyl/ 4c	(1,3-benzodioxol-5-yl)methyl 5 {30}	Et	Ph	39

[a] Number of the corresponding isocyanide or amine on Scheme 3.

Figure 2. ORTEP plot for compound **13a**.

anide to give a nitrilium intermediate, which then undergoes intramolecular cyclization.^[1] Similar conditions were suitable for the reaction of a range of different primary amines and isonitriles with the keto acids **3**, **11** and **12**. With respect to amine component, various aliphatic and aromatic primary amines, such as substituted anilines, benzylamines and their heteroaryl analogs, linear and branched aliphatic amines and nitrogen-containing compounds, were tolerated without any limitations. A restriction is the limited number of commercially or synthetically available isonitriles. In this work, we used eight different isonitriles **4a–h** available from commercial sources. The process does, however, appear to be impeded by steric congestion, with the sterically hindered substrates (for example, when R⁴ = phenyl) undergoing slow and incomplete conversion to the final products.

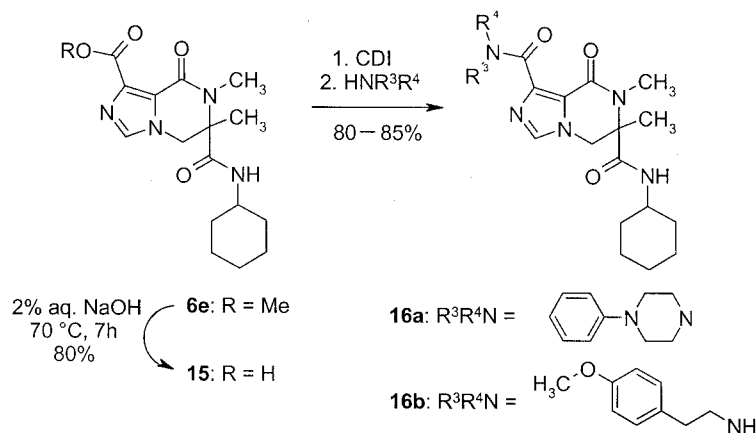
The ester functionality can be used for introduction of additional complexity to the obtained heterocyclic scaffolds

(Scheme 3). Thus, a representative methyl carboxylate **6e** was hydrolyzed under mild alkali conditions to smoothly afford the acid **15** (yield 80%). The latter was then converted into the amides **16a,b** using *N,N'*-carbonyldiimidazole (CDI)-promoted coupling with two different amines. The reaction proceeded in dimethylformamide via reactive imidazolide intermediates which were used in the reaction with amines without purification. Due to relatively mild reaction conditions (75–80 °C, 8 h), easy separation procedures and high yields (80–85%), the described reaction scheme can also be used in high-throughput combinatorial format. The amide formation mediated by strong coupling agents, such as SOCl₂ or POCl₃, was less successful in this case: The desired products were obtained in 30–45% yields.

The synthesized compounds represent examples of β -turn mimics^[10,11] with an inherent potential for combinatorial exploration of functional diversity. Reverse β -turns are common secondary structures in biologically active peptides or proteins that often play an important role in their interactions with receptors, enzymes, or antibodies. Such peptide–protein or protein–protein interactions can be mimicked by small molecules bearing similar structural features. Syntheses of a putative peptide β -turn mimetic based on piperazinone fragment were reported.^[12]

Conclusions

In this work, we have shown that novel heteroaryl-fused pyrazinones can be efficiently prepared by a novel modification of four-component Ugi reaction of heterocyclic bifunctional keto acids, isonitriles and amines. Considering the availability of initial reactants, convenient synthesis and isolation of products, this route provides a new valuable entry to novel heterocycle-fused analogs of biologically active pyrazinones. Compounds synthesized in this work constitute interesting examples of conformationally rigid cyclic peptidomimetics, which are the subject of increasing interest as

Scheme 3. Introduction of additional complexity to **6e**.

potential new small-molecule therapeutics. Biological testing of the obtained compounds is currently in progress.

Experimental Section

^1H and ^{13}C NMR spectra were recorded with Bruker DPX-300 spectrometer (300.13 MHz for ^1H NMR and 75.46 for ^{13}C NMR) in $[\text{D}_6]\text{DMSO}$ using TMS as an internal standard. LCMS spectra were recorded with PE SCIEX API 150EX liquid chromatograph equipped with a UV detector (λ_{max} 215 and 254 nm) and using a C_{18} column (100 $\times$ 4 mm). Elution started with water and ended with acetonitrile/water (95:5, v/v) and used a linear gradient at a flow rate of 0.15 mL/min and an analysis cycle time of 25 min. High-resolution mass spectra have been recorded using electrospray ionization time-of-flight reflectron experiments (ESI-TOF) on Agilent ESI-TOF mass spectrometer. Samples were electrosprayed into the TOF reflectron analyzer at an ESI voltage of 4000 V and a flow rate of 200 microliters per minute. Melting points were measured with a Buchi B-520 melting point apparatus and were not corrected. IR spectra were recorded with Specord M80 spectrometer in KBr. All solvents and reagents were obtained from Acros Organics, Aldrich or ChemDiv and used without purification.

General Procedure for Preparation of Keto Esters 2, 9a–d or 10a–d: A mixture of the dicarboxylate **1** or the carboxylates **7a,b** and **8a,b** (100 mmol), α -halo ketone (100 mmol), K_2CO_3 (16.56 g, 120 mmol), and 18-crown-6 phase-transfer catalyst (200 mg) in 1,4-dioxane (100 mL) was stirred at reflux for 7 h. The reaction mixture was cooled, diluted with toluene and washed with water until the extract was neutral, after which the organic layer was dried (anhydrous Na_2SO_4) and concentrated in vacuo. The desired product was chromatographed on silica gel (eluent CH_2Cl_2) to afford the corresponding keto ester **2**, **9a–d** or **10a–d** in 60–85% yield. Satisfactory analytical data were obtained for all the synthesized compounds, for example:

Dimethyl 1-(2-Oxopropyl)-1H-imidazole-4,5-dicarboxylate (2): ^1H NMR: δ = 2.25–2.31 (br. s, 3 H, CH_3), 3.53 (s, 3 H, CH_3), 3.71 (s, 3 H, CH_3), 6.89 (s, 1 H, ArH) ppm. HRMS: m/z 240.2154; calcd. 240.2132 [M^+].

Methyl 2-Methyl-4-(2-oxopropyl)-4H-furo[3,2-*b*]pyrrole-5-carboxylate (9b): M. p. 95–97 °C. IR $\tilde{\nu}$ = 1670 (CO), 1720 (CO) cm^{-1} . ^1H NMR: δ = 2.12 (s, 3 H, CH_3), 2.38–2.39 (br. s, 3 H, CH_3), 3.74 (s, 3 H, CH_3), 5.04–5.07 (br. s, 2 H, CH_2), 6.19 (s, 1 H, ArH), 6.65 (s, 1 H, ArH) ppm. HRMS: m/z 236.2405; calcd. 236.24981 [M^+].

Methyl 2-Ethyl-4-(2-oxopropyl)-4H-thieno[3,2-*b*]pyrrole-5-carboxylate (10a): M. p. 111–112 °C. IR $\tilde{\nu}$ = 1675 (CO), 1715 (CO) cm^{-1} . ^1H NMR: δ = 1.30–1.33 (t, J = 8.4 Hz, 3 H, CH_3), 2.10–2.13 (s, 3 H, CH_3), 2.83–2.86 (q, J = 8.4 Hz, 2 H, CH_2), 3.74–3.77 (s, 3 H, CH_3), 5.13–5.16 (s, 2 H, CH_2), 6.78 (s, 1 H, ArH), 7.05 (s, 1 H, ArH) ppm. HRMS: m/z 266.3321; calcd. 266.3342 [M^+].

4-Methoxycarbonyl-1-(2-oxopropyl)-1H-imidazole-5-carboxylic Acid (3):

Aqueous solution of KOH (1.5%, 100 mL) was added to a solution of the diester **2** (12.0 g, 50 mmol) in methanol (150 mL). The reaction mixture was stirred at room temp. for 72 h, then concentrated under reduced pressure to remove methanol. Water (150 mL) was added, and the mixture was acidified by addition of 1% aqueous HCl until pH 3 was reached. The formed precipitate was filtered off, washed with water (3 $\times$ 150 mL) and dried with Na_2SO_4 . Recrystallization from ethanol gave pure **3** as a white solid (5.66 g, 50%). ^1H NMR: δ = 2.30 (s, 3 H, CH_3), 3.57 (s, 3 H, CH_3), 6.74 (s, 1 H, ArH), 9.86–10.14 (br. s, 1 H, OH) ppm. ^{13}C NMR: δ = 28.21, 49.08, 51.48, 134.22, 138.18, 145.88, 156.65, 166.36, 168.87 ppm. HRMS: m/z 226.2003; calcd. 226.1861 [M^+].

General Procedure for Preparation of Keto Acids 11a–d and 12a–d:

A solution of NaOH (4.8 g, 120 mmol) in water (30 mL) was added to a solution of keto ester **9a–d** or **10a–d** (100 mmol) in methanol (100 mL). The reaction mixture was stirred at 70 °C for 6 h then cooled to room temp., and concentrated under reduced pressure to remove methanol. Water (10 mL) was added, and the mixture was acidified by addition of 1% aqueous HCl until pH 3 was reached. The formed precipitate was filtered off, washed with water (3 $\times$ 50 mL) and dried with Na_2SO_4 to give **11a–d** and **12a–d** in 90–95% yield. Satisfactory analytical data were obtained for all compounds, for example:

4-(2-Oxopropyl)-4H-furo[3,2-*b*]pyrrole-5-carboxylic Acid (11c): M. p. 168–169 °C. IR $\tilde{\nu}$ = 1640 (CO), 1725 (CO), 2200–3200 (OH) cm^{-1} . ^1H NMR: δ = 2.09 (s, 3 H, CH_3), 5.11–5.14 (s, 2 H, CH_2), 6.57 (d, J = 6.8 Hz, 1 H, ArH), 6.71 (s, 1 H, ArH), 7.55 (d, J = 6.8 Hz, 1 H, ArH), 11.94–11.98 (br. s, 1 H, OH) ppm. HRMS: m/z 208.1951; calcd. 208.1932 [M^+].

4-(2-Oxopropyl)-4H-thieno[3,2-*b*]pyrrole-5-carboxylic Acid (12d): M. p. 168–169 °C. IR $\tilde{\nu}$ = 1680 (CO), 1720 (CO), 2800–3300 (OH) cm^{-1} . ^1H NMR: δ = 2.12 (s, 3 H, CH_3), 5.24–5.26 (s, 2 H, CH_2), 7.04 (d, J = 6.2 Hz, 1 H, ArH), 7.11 (s, 1 H, ArH), 7.31–7.33 (d, J = 6.2 Hz, 1 H, ArH) ppm. HRMS: m/z 224.2551; calcd. 224.2566 [M^+].

General Procedure for the Synthesis of 6,7-Dihydro-5H-imidazo[1,5-*a*]pyrazin-8-ones 6a–r, 6,7-Dihydrofuro[2',3':4,5]pyrrolo[1,2-*a*]pyr-

azin-8(5H)-ones 13a–i and 6,7-Dihydrothieno[2',3':4,5]pyrrolo[1,2-*a*]pyrazin-8(5H)-ones 14a–h: The equimolar amounts of keto acid, isocyanide, and amine were dissolved in methanol to a concentration of 1 M in each component. The reaction mixture was stirred at 40 °C for 4–18 h. The reaction was followed by TLC (5% MeOH in CH₂Cl₂). On completion, the reaction mixture was cooled to room temp., the formed precipitate was filtered off and purified by recrystallization from diethyl ether or by chromatography on silica gel, eluting with a gradient of 0–10% MeOH in CH₂Cl₂.

Methyl 7-(3-Chlorobenzyl)-6-[(cyclopentylamino)carbonyl]-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6a): Yield 69%. ¹H NMR: δ = 1.13–1.81 (m, 8 H, cyclopentane), 1.49 (s, 3 H, CH₃), 3.81 (s, 3 H, CH₃), 3.81–3.83 (m, 1 H, CH), 4.11 (d, J = 6.9 Hz, 1 H, CH₂), 4.22 (d, J = 6.8 Hz, 1 H, CH₂), 4.9 (d, J = 6.9 Hz, 1 H, CH₂), 5.27 (d, J = 6.8 Hz, 1 H, CH₂), 7.15 (m, 4 H, ArH), 7.41 (d, J = 6.0 Hz, 1 H, NH), 7.68 (s, 1 H, ArH) ppm. ¹³C NMR: δ = 20.33, 23.46, 23.92, 31.26, 31.82, 45.58, 50.73, 51.13, 51.77, 64.80, 123.51, 125.30, 2 × 126.44, 129.98, 133.01, 134.18, 136.34, 142.27, 157.94, 162.80, 169.22 ppm. HRMS: m/z found: 444.1641; calcd. 444.9220 [M⁺].

Methyl 6-[(Cycloheptylamino)carbonyl]-7-cyclopropyl-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6b): Yield 75%. ¹H NMR: δ = 0.7–0.88 (m, 4 H, cyclopropane), 1.2–1.71 (m, 12 H, cycloheptane), 1.67 (s, 3 H, CH₃), 2.46–2.55 (br. s, 1 H, CH), 3.58–3.7 (m, 1 H, CH), 3.8 (s, 3 H, CH₃), 4.08 (d, J = 6.7 Hz, 1 H, CH₂), 4.73 (d, J = 6.7 Hz, 1 H, CH₂), 7.31 (br. s, 1 H, NH), 7.63 (s, 1 H, ArH) ppm. ¹³C NMR: δ = 7.8, 8.89, 20.32, 23.62, 23.97, 25.54, 26.32, 27.45, 27.85, 2 × 33.80, 50.62, 51.12, 51.59, 65.18, 124.65, 133.63, 135.84, 158.00, 162.81, 169.16 ppm. HRMS: m/z found: 388.2184; calcd. 388.4706 [M⁺].

Methyl 6-[(Cycloheptylamino)carbonyl]-6-methyl-8-oxo-7-(2-thien-2-ylethyl)-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6c): Yield 71%. ¹H NMR: δ = 1.23–1.62 (m, 12 H, cycloheptane), 1.52 (s, 3 H, CH₃), 3.11 (t, J = 4.4 Hz, CH₂), 3.3–3.45 (m, 1 H, CH), 3.6–3.72 (m, 1 H, CH), 3.81 (s, 3 H, CH₃), 4.06 (d, J = 6.8 Hz, 1 H, CH₂), 4.76 (d, J = 6.8 Hz, 1 H, CH₂), 6.85 (d, J = 7.2 Hz, 1 H, ArH), 6.9 (d+d, J = 7.4 Hz, 1 H, ArH), 7.15 (d, J = 7.2 Hz, 1 H, ArH), 7.51 (d, J = 6.2 Hz, 1 H, NH), 7.62 (s, 1 H, ArH) ppm. ¹³C NMR: δ = 19.72, 2 × 23.46, 27.13, 27.77, 28.82, 33.18, 33.81, 44.43, 50.10, 50.83, 51.69, 64.10, 123.01, 123.55, 124.83, 126.62, 134.04, 135.89, 140.80, 156.77, 162.51, 168.26 ppm. HRMS: m/z found: 458.2061; calcd. 458.5840 [M⁺].

Methyl 6-[(Cyclohexylamino)carbonyl]-7-(4-methoxybenzyl)-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6d): Yield 78%. ¹H NMR: δ = 1.0–1.68 (m, 10 H, cyclohexane), 1.5 (s, 3 H, CH₃), 3.39–3.42 (m, 1 H, CH), 3.7 (s, 3 H, CH₃), 3.8 (s, 3 H, CH₃), 4.05 (d, J = 6.8 Hz, 1 H, CH₂), 4.28 (d, J = 6.6 Hz, 1 H, CH₂), 4.87 (d, J = 6.8 Hz, 1 H, CH₂), 5.21 (d, J = 6.6 Hz, 1 H, CH₂), 6.8 (d, J = 7.8 Hz, 2 H, ArH), 7.12 (t, J = 7.0 Hz, 2 H, ArH), 7.22 (br. s, 1 H, NH), 7.62 (s, 1 H, ArH) ppm. ¹³C NMR: δ = 7.8, 8.89, 20.32, 23.62, 23.67, 25.54, 27.45, 27.55, 2 × 33.80, 50.62, 51.12, 51.50, 65.18, 124.65, 133.63, 135.84, 158.00, 162.81, 169.16 ppm. HRMS: m/z found: 454.5260; calcd. 454.5305 [M⁺].

Methyl 6-[(Cyclohexylamino)carbonyl]-6,7-dimethyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6e): Yield 85%. ¹H NMR: δ = 1.1–1.83 (m, 10 H, cyclohexane), 1.53 (s, 3 H, CH₃), 3.05 (s, 1 H, CH₃), 3.46–3.51 (m, 1 H, CH), 3.80 (s, 3 H, CH₃), 4.11 (d, J = 6.8 Hz, 1 H, CH₂), 4.71 (d, J = 6.8 Hz, 1 H, CH₂), 7.52 (d, J = 6.2 Hz, 1 H, NH), 7.61 (s, 1 H, ArH) ppm. ¹³C NMR: δ = 21.01, 23.65, 24.63, 25.59, 27.48, 27.44, 2 × 34.10, 51.60, 52.14, 52.98, 65.43, 125.64, 134.69, 135.98, 159.03, 162.89, 168.66 ppm. HRMS: m/z found: 348.4015; calcd. 348.4052 [M⁺].

Methyl 6-[(Cycloheptylamino)carbonyl]-7-(3-methoxybenzyl)-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6f): Yield 60%. ¹H NMR: δ = 1.12–1.7 (m, 12 H, cycloheptane), 1.56 (s, 3 H, CH₃), 3.5–3.61 (m, 1 H, CH), 3.7 (s, 3 H, CH₃), 3.8 (s, 3 H, CH₃), 4.07 (d, J = 6.7 Hz, 1 H, CH₂), 4.27 (d, J = 6.8 Hz, 1 H, CH₂), 4.83 (d, J = 6.7 Hz, 1 H, CH₂), 5.22 (d, J = 6.8 Hz, 1 H, CH₂), 6.7 (d, J = 6.3 Hz, 1 H, NH), 6.84 (s+d, 2 H, ArH), 7.24 (d+d, J = 7.6 Hz, 2 H, ArH), 7.62 (s, 1 H, ArH) ppm. ¹³C NMR: δ = 7.8, 9.01, 18.58, 22.77, 24.61, 25.02, 25.77, 27.41, 27.58, 2 × 33.85, 50.68, 52.02, 52.13, 64.99, 124.61, 133.64, 135.87, 157.88, 162.87, 169.16 ppm. HRMS: m/z found: 468.5527; calcd. 468.5576 [M⁺].

Methyl 6-[(Cycloheptylamino)carbonyl]-7-(2-ethoxybenzyl)-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6g): Yield 65%. ¹H NMR: δ = 1.2–1.8 (m, 12 H, cycloheptane), 1.54 (s, 6 H, 2CH₃), 3.5–3.61 (m, 1 H, CH), 3.71 (s, 3 H, CH₃), 4.1 (m, 3 H, CH, CH₂), 4.4 (d, J = 6.8 Hz, 1 H, CH₂), 4.90 (d, J = 6.7 Hz, 1 H, CH₂), 5.12 (d, J = 6.8 Hz, 1 H, CH₂), 6.8 (d+d, J = 7.8 Hz, 2 H, ArH), 7.13 (t, 2 H, ArH), 6.8 (d, J = 6.3 Hz, 1 H, NH), 7.24 (s, 1 H, ArH) ppm. ¹³C NMR: δ = 7.9, 9.11, 10.66, 18.55, 21.33, 24.01, 25.77, 26.12, 27.56, 28.43, 2 × 33.87, 51.03, 53.22, 54.27, 64.94, 124.67, 134.11, 134.89, 157.84, 162.85, 168.98 ppm. HRMS: m/z found: 482.5791; calcd. 482.5847 [M⁺].

Methyl 6-[(Cycloheptylamino)carbonyl]-6-methyl-7-(2-methylbenzyl)-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6h): Yield 78%. ¹H NMR: δ = 1.27–1.66 (m, 12 H, cycloheptane), 1.50 (s, 3 H, CH₃), 2.32 (s, 3 H, CH₃), 3.58–3.67 (m, 1 H, CH), 3.8 (s, 3 H, CH₃), 4.1 (d, J = 6.8 Hz, 1 H, CH₂), 4.2 (d, J = 6.6 Hz, 1 H, CH₂), 4.88 (d, J = 6.8 Hz, 1 H, CH₂), 5.27 (d, J = 6.6 Hz, 1 H, CH₂), 7.0–7.21 (m, 4 H, ArH), 7.5 (d, J = 6.2 Hz, 1 H, NH), 7.7 (s, 1 H, ArH) ppm. ¹³C NMR: δ = 7.7, 10.11, 19.59, 22.13, 24.63, 25.72, 25.95, 27.54, 27.59, 2 × 33.76, 51.04, 52.54, 52.75, 65.04, 125.65, 133.61, 135.71, 157.32, 162.23, 168.21 ppm. HRMS: m/z found: 452.5539; calcd. 452.5582 [M⁺].

Methyl 6-[(Cycloheptylamino)carbonyl]-6-methyl-7-(3-methylbenzyl)-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6i): Yield 72%. ¹H NMR: δ = 1.2–1.61 (m, 12 H, cycloheptane), 1.51 (s, 3 H, CH₃), 2.31 (s, 3 H, CH₃), 3.51–3.65 (m, 1 H, CH), 3.8 (s, 3 H, CH₃), 4.06 (d, J = 6.8 Hz, 1 H, CH₂), 4.25 (d, J = 6.8 Hz, 1 H, CH₂), 4.84 (d, J = 6.8 Hz, 1 H, CH₂), 5.27 (d, J = 6.8 Hz, 1 H, CH₂), 7.0 (d, J = 6.0 Hz, 1 H, NH), 7.08–7.2 (m, 4 H, ArH), 7.67 (s, 1 H, ArH) ppm. ¹³C NMR: δ = 7.8, 9.65, 20.32, 22.19, 24.43, 24.21, 25.91, 27.58, 28.34, 2 × 33.26, 52.14, 52.99, 53.43, 65.14, 124.21, 134.22, 135.73, 157.31, 164.32, 168.28 ppm. HRMS: m/z found: 452.5538; calcd. 452.5582 [M⁺].

Methyl 6-[(Cycloheptylamino)carbonyl]-7-(3-methoxypropyl)-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6j): Yield 65%. ¹H NMR: δ = 1.2–1.71 (m, 12 H, cycloheptane), 1.52 (s, 3 H, CH₃), 1.8–2.0 (m, 2 H, CH₂), 3.22 (s, 3 H, CH₃), 3.3–3.5 (m, 3 H, CH₂), 3.5–3.67 (m, 2 H, CH, CH₂), 3.8 (s, 3 H, CH₃), 4.08 (d, J = 6.8 Hz, 1 H, CH₂), 4.78 (d, J = 6.8 Hz, 1 H, CH₂), 7.44 (d, J = 5.8 Hz, 1 H, NH), 7.6 (s, 1 H, ArH) ppm. ¹³C NMR: δ = 8.1, 9.64, 23.11, 24.65, 25.11, 26.03, 27.78, 29.33, 3 × 33.72, 37.65, 52.44, 52.65, 53.48, 58.76, 65.15, 71.43, 158.01, 164.36, 168.76 ppm. HRMS: m/z 420.5095; calcd. 420.5130 [M⁺].

Methyl 6-[(Cyclopentylamino)carbonyl]-7-isopropyl-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6k): Yield 76%. ¹H NMR: δ = 1.12–2.0 (m, 8 H, cyclopentane), 1.4 (s, 3 H, CH₃), 1.5 (s, 3 H, CH₃), 1.6 (s, 3 H, CH₃), 3.12–3.3 (m, 1 H, CH), 3.8 (s, 3 H, CH₃), 3.9–4.02 (m, 1 H, CH), 4.2 (d, J = 7.0 Hz, 1 H, CH₂), 4.5 (d, J = 7.0 Hz, 1 H, CH₂), 7.58 (s, 4 H, ArH), 7.9 (d, J = 6.2 Hz, 1 H, NH) ppm. ¹³C NMR: δ = 2 × 19.43, 23.43, 24.59,

32.01, 33.21, 45.58, 51.13, 52.43, 53.01, 64.81, 159.11, 163.99, 169.66 ppm. HRMS: m/z 362.4287; calcd. 362.4323 [M^+].

Methyl 7-(2-Chlorobenzyl)-6-[(cycloheptylamino)carbonyl]-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6l): Yield 70%. ^1H NMR: δ = 1.24–1.63 (m, 12 H, cycloheptane), 1.5 (s, 3 H, CH_3), 3.61–3.7 (m, 1 H, CH), 3.81 (s, 3 H, CH_3), 4.2 (d, J = 6.9 Hz, 1 H, CH_2), 4.29 (d, J = 6.8 Hz, 1 H, CH_2), 4.94 (d, J = 6.9 Hz, 1 H, CH_2), 5.33 (d, J = 6.8 Hz, 1 H, CH_2), 7.12–7.3 (m, 4 H, ArH), 7.44–7.53 (br. s, 1 H, NH), 7.7 (s, 1 H, ArH) ppm. ^{13}C NMR: δ = 7.9, 9.65, 22.19, 24.46, 24.28, 25.34, 27.57, 28.34, 2 $\times$ 33.28, 52.04, 52.91, 53.43, 65.19, 124.28, 134.43, 135.54, 158.21, 164.35, 168.88 ppm. HRMS: m/z 472.9711; calcd. 472.9761 [M^+].

Methyl 7-(4-Chlorobenzyl)-6-[(cycloheptylamino)carbonyl]-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6m): Yield 80%. ^1H NMR: δ = 1.21–1.75 (m, 12 H, cycloheptane), 1.51 (s, 3 H, CH_3), 3.53–3.7 (m, 1 H, CH), 3.85 (s, 3 H, CH_3), 4.1 (d, J = 6.7 Hz, 1 H, CH_2), 4.21 (d, J = 6.8 Hz, 1 H, CH_2), 4.88 (d, J = 6.7 Hz, 1 H, CH_2), 5.31 (d, J = 6.8 Hz, 1 H, CH_2), 7.21 (m, 4 H, ArH), 7.42 (d, J = 6.2 Hz, 1 H, NH), 7.69 (s, 1 H, ArH) ppm. ^{13}C NMR: δ = 7.8, 10.34, 22.21, 25.21, 25.78, 25.99, 27.37, 29.01, 2 $\times$ 33.24, 52.15, 53.03, 54.63, 65.19, 124.28, 134.41, 135.22, 158.98, 164.21, 168.23 ppm. HRMS: m/z 472.9719; calcd. 472.9761 [M^+].

Methyl 7-[2-(4-Chlorophenyl)ethyl]-6-[(cycloheptylamino)carbonyl]-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6n): Yield 66%. ^1H NMR: δ = 1.27–1.77 (m, 12 H, cycloheptane), 1.51 (s, 3 H, CH_3), 2.8–3.0 (t, J = 7.6 Hz, 1 H, CH_2), 3.21–3.3 (q, J = 7.6 Hz, 1 H, CH_2), 3.57–3.72 (m, 1 H, CH), 3.8–3.85 (m, 1 H, CH), 3.85 (s, 3 H, CH_3), 4.06 (d, J = 7.0 Hz, 1 H, CH_2), 4.76 (d, J = 7.0 Hz, 1 H, CH_2), 7.22 (m, 4 H, ArH), 7.42 (br. s, 1 H, NH), 7.67 (s, 1 H, ArH) ppm. ^{13}C NMR: δ = 8.1, 9.87, 22.27, 25.28, 25.78, 26.13, 28.43, 28.59, 28.98, 2 $\times$ 33.25, 52.15, 53.13, 54.67, 65.24, 124.11, 133.85, 134.13, 157.48, 164.23, 169.43 ppm. HRMS: m/z 486.9980; calcd. 487.0032 [M^+].

Methyl 6-[(Cycloheptylamino)carbonyl]-6-methyl-8-oxo-7-(3-phenylpropyl)-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6o): Yield 70%. ^1H NMR: δ = 1.25–1.76 (m, 12 H, cycloheptane), 1.53 (s, 3 H, CH_3), 1.8–2.0 (m+m, 2 H, CH_2), 2.62 (t, J = 7.4 Hz, 2 H, CH_2), 3.18–3.28 (m, 1 H, CH_2), 3.52–3.74 (m, 2 H, CH, CH_2), 3.81 (s, 3 H, CH_3), 4.02 (d, J = 6.8 Hz, 1 H, CH_2), 4.72 (d, J = 6.8 Hz, 1 H, CH_2), 7.1–7.27 (m, 5 H, ArH), 7.4 (d, J = 6.3 Hz, 1 H, NH), 7.63 (s, 1 H, ArH) ppm. ^{13}C NMR: δ = 7.7, 9.21, 21.66, 24.12, 25.13, 25.54, 26.54, 27.42, 28.52, 29.12, 2 $\times$ 34.01, 52.35, 53.13, 54.62, 65.55, 124.87, 134.06, 134.98, 156.87, 164.04, 169.21 ppm. HRMS: m/z 466.5803; calcd. 466.5853 [M^+].

Methyl 6-[(Cycloheptylamino)carbonyl]-7-(4-fluorobenzyl)-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6p): Yield 79%. ^1H NMR: δ = 1.22–1.7 (m, 12 H, cycloheptane), 1.5 (s, 3 H, CH_3), 3.51–3.67 (m, 1 H, CH), 3.82 (s, 3 H, CH_3), 4.08 (d, J = 6.8 Hz, 1 H, CH_2), 4.20 (d, J = 6.9 Hz, 1 H, CH_2), 4.89 (d, J = 6.8 Hz, 1 H, CH_2), 5.3 (d, J = 6.9 Hz, 1 H, CH_2), 7.0 (dd, J = 7.6 Hz, 2 H, ArH), 7.28–7.39 [m(F), 2 H, ArH], 7.41 (d, J = 6.0 Hz, 1 H, NH), 7.68 (s, 1 H, ArH) ppm. ^{13}C NMR: δ = 7.9, 9.43, 22.21, 24.33, 25.41, 25.99, 27.27, 28.77, 2 $\times$ 33.28, 53.21, 54.13, 54.98, 64.32, 125.06, 134.41, 135.22, 158.98, 165.11, 169.14 ppm. HRMS: m/z 456.5170; calcd. 456.5215 [M^+].

Methyl 6-[(Cycloheptylamino)carbonyl]-7-(2-cyclohex-1-en-1-ylethyl)-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6q): Yield 65%. ^1H NMR: δ = 1.21–1.73 (m, 12 H, cycloheptane), 1.21–1.73 (m, 4 H, cyclohexene), 1.53 (s, 3 H, CH_3), 2.04

(m, 2 H, CH_2), 2.1–2.26 (m, 4 H, cyclohexene), 3.13–3.26 (m, 1 H, CH_2), 3.6–3.8 (m, 2 H, CH, CH_2), 3.8 (s, 3 H, CH_3), 4.05 (d, J = 6.9 Hz, 1 H, CH_2), 4.72 (d, J = 6.9 Hz, 1 H, CH_2), 5.4 (s, 1 H, CH), 7.37 (d, J = 6.2 Hz, 1 H, NH), 7.64 (s, 1 H, ArH) ppm. ^{13}C NMR: δ = 8.1, 9.64, 22.63, 23.11, 24.65, 25.11, 25.32, 26.13, 27.78, 28.43, 29.11, 29.76, 3 $\times$ 33.32, 37.55, 52.49, 53.48, 58.76, 65.15, 71.43, 158.01, 164.36, 168.88 ppm. HRMS: m/z 456.5858; calcd. 456.5901 [M^+].

Methyl 6-[(Cycloheptylamino)carbonyl]-7-[2-(4-ethoxyphenyl)ethyl]-6-methyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylate (6r): Yield 69%. ^1H NMR: δ = 1.3–1.65 (m, 12 H, cycloheptane), 1.45 (t, J = 8.4 Hz, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 2.8–3.0 (m, 2 H, CH_2), 3.21–3.29 (m, 1 H, CH_2), 3.59–3.71 (m, 1 H, CH), 3.86 (s, 3 H, CH_3), 3.9–4.03 (m, 4 H, CH, CH_2), 4.77 (d, J = 6.8 Hz, 1 H, CH_2), 6.82 (d, J = 6.8 Hz, 2 H, ArH), 7.11 (d, J = 7.2 Hz, 2 H, ArH), 7.41 (br. s, 1 H, NH), 7.64 (s, 1 H, ArH) ppm. ^{13}C NMR: δ = 7.8, 9.88, 10.66, 18.59, 22.43, 24.11, 25.47, 26.11, 27.59, 28.55, 29.97, 2 $\times$ 32.88, 51.03, 53.22, 54.27, 64.55, 124.69, 134.76, 135.32, 156.87, 162.84, 168.35 ppm. HRMS: m/z 496.6071; calcd. 496.6118 [M^+].

***N*-Cyclohexyl-7-isopropyl-6-methyl-8-oxo-5,6,7,8-tetrahydrofuro-[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (13a):** Yield 43%. ^1H NMR: δ = 1.41 (s, 9 H, 3 CH_3), 1.0–2.0 (m, 10 H, cyclohexane), 3.1–3.21 (m, 1 H, CH), 3.54–3.71 (m, 1 H, CH), 4.01 (d, J = 7.0 Hz, 1 H, CH_2), 4.43 (d, J = 7.0 Hz, 1 H, CH_2), 6.51 (d, J = 6.8 Hz, 2 H, ArH), 7.50 (s, 1 H, ArH), 7.92 (d, J = 6.1 Hz, 1 H, NH) ppm. ^{13}C NMR: δ = 2 $\times$ 21.32, 23.43, 24.59, 32.31, 33.21, 45.32, 51.18, 52.43, 64.81, 116.32, 122.31, 143.54, 163.99, 169.66 ppm. HRMS: m/z 357.1671; calcd. 357.4565 [M^+].

***N*-Cyclohexyl-7-(3-fluorobenzyl)-8-oxo-6-phenyl-5,6,7,8-tetrahydrofuro[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (13b):** Yield 28%. ^1H NMR: δ = 0.8–1.7 (m, 10 H, cyclohexane), 3.4–3.6 (m, 1 H, CH), 3.7–3.8 (d, J = 6.9 Hz, 1 H, CH_2), 4.7–4.8 (d, J = 6.9 Hz, 1 H, CH_2), 5.0–5.17 (m, 2 H, CH_2), 6.3–6.47 (m, 1 H, ArH), 6.5–6.63 (m, 3 H, ArH), 6.7–6.81 (m, 1 H, ArH), 6.9–7.08 (m, 1 H, ArH), 7.15–7.31 (m, 5 H, ArH), 7.45–7.58 (s+d, J = 6.0 Hz, 2 H, ArH, NH) ppm. ^{13}C NMR: δ = 7.9, 9.43, 24.33, 25.41, 25.99, 27.43, 28.72, 2 $\times$ 33.21, 53.21, 54.73, 64.32, 119.43, 122.32, 125.06, 126.76, 127.33, 133.65, 134.41, 135.22, 144.31, 164.87, 169.54 ppm. HRMS: m/z 485.2181; calcd. 485.5632 [M^+].

***N*-Cyclohexyl-7-(3-fluorobenzyl)-2-methyl-8-oxo-6-phenyl-5,6,7,8-tetrahydrofuro[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (13c):** Yield 27%. ^1H NMR: δ = 0.85–1.84 (m, 10 H, cyclohexane), 2.36 (s, 3 H, CH_3), 3.51–3.58 (m, 1 H, CH), 3.8 (d, J = 6.8 Hz, 1 H, CH_2), 4.68 (d, J = 6.8 Hz, 1 H, CH_2), 4.87–5.11 (d+d, J = 6.9 Hz, 2 H, CH_2), 6.1 (s, 1 H, ArH), 2.51 (s, 1 H, ArH), 6.51 (t, J = 6.7 Hz, 2 H, ArH), 6.7–6.8 (t, J = 6.7 Hz, 1 H, ArH), 7.0–7.1 (q, J = 7.2 Hz, 1 H, ArH), 7.17–7.31 (m, 6 H, ArH) ppm. ^{13}C NMR: δ = 7.87, 13.43, 24.13, 25.54, 26.19, 27.43, 28.72, 2 $\times$ 34.08, 54.01, 54.73, 64.32, 120.21, 122.37, 125.45, 126.33, 127.21, 134.27, 134.99, 135.54, 144.32, 164.78, 168.36 ppm. HRMS: m/z 499.2181; calcd. 499.5903 [M^+].

***N*-Cyclohexyl-2,6-dimethyl-8-oxo-7-(pyridin-3-ylmethyl)-5,6,7,8-tetrahydrofuro[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (13d):** Yield 63%. ^1H NMR: δ = 0.8–1.65 (m, 10 H, cyclohexane), 1.4 (s, 3 H, CH_3), 2.32–2.39 (s, 3 H, CH_3), 3.31–3.42 (q, J = 7.4 Hz, 1 H, CH), 3.9 (d, J = 6.7 Hz, 1 H, CH_2), 4.24 (d, J = 6.8 Hz, 1 H, CH_2), 4.61 (d, J = 6.7 Hz, 1 H, CH_2), 5.16 (d, J = 6.8 Hz, 1 H, CH_2), 6.1 (s, 1 H, ArH), 6.5 (s, 1 H, ArH), 7.1–7.3 (m, 2 H, ArH), 7.58–7.61 (d, J = 6.4 Hz, 1 H, NH), 8.35 (s, 1 H, ArH), 8.49 (s, 1 H, ArH) ppm. ^{13}C NMR: δ = 7.9, 13.87, 23.49, 25.51, 33.02, 34.79, 45.65, 52.21, 54.31, 64.81, 116.32, 119.43, 120.65, 122.31, 124.06, 124.98,

133.33, 144.14, 163.32, 169.61 ppm. HRMS: m/z 420.2230; calcd. 420.5158 [M^+].

***N*-Cyclooctyl-2,6-dimethyl-8-oxo-7-(thien-2-ylmethyl)-5,6,7,8-tetrahydrofuro[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (13e):** Yield 66%. ^1H NMR: δ = 1.1–1.57 (m, 14 H, cyclooctane), 1.58 (s, 3 H, CH_3), 2.4 (s, 3 H, CH_3), 3.51–3.2 (m, 1 H, CH), 3.8 (d, J = 6.6 Hz, 1 H, CH_2), 4.55 (d, J = 6.9 Hz, 1 H, CH_2), 4.66 (d, J = 6.9 Hz, 1 H, CH_2), 5.07 (d, J = 6.9 Hz, 1 H, CH_2), 6.1 (s, 1 H, ArH), 6.49 (d, J = 7.3 Hz, 1 H, ArH), 6.53 (s, 1 H, ArH), 6.8 (t, J = 7.4 Hz, 1 H, ArH), 7.06 (d, J = 7.4 Hz, 1 H, ArH), 7.22 (d, J = 5.9 Hz, 1 H, NH) ppm. ^{13}C NMR: δ = 7.9, 14.13, 23.43, 24.22, 25.59, 27.21, 33.12, 34.76, 46.05, 54.26, 54.91, 64.83, 116.33, 119.43, 120.65, 122.31, 124.06, 124.98, 133.33, 163.32, 168.43 ppm. HRMS: m/z 453.2157; calcd. 453.6081 [M^+].

7-(2-Methoxyethyl)-6-methyl-*N*-(3-methylbutyl)-8-oxo-5,6,7,8-tetrahydrofuro[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (13f): Yield 40%. ^1H NMR: δ = 0.6 (s, 3 H, CH_3), 0.8 (s, 3 H, CH_3), 1.11–1.3 (m, 3 H, CH_2), 2.9–3.1 (m, 2 H, CH_2), 3.2 (s, 3 H, CH_3), 3.5–3.6 (m, 3 H, CH_2), 1.7–1.81 (m, 1 H, CH), 3.9 (d, J = 7.0 Hz, 1 H, CH_2), 4.55 (d, J = 7.0 Hz, 1 H, CH_2), 6.49 (d, J = 7.4 Hz, 2 H, ArH), 7.4 (s, 2 H, ArH, NH) ppm. ^{13}C NMR: δ = 19.11, 23.13, 24.59, 25.65, 32.31, 33.21, 45.30, 47.76, 51.18, 52.43, 54.58, 64.81, 122.31, 143.54, 154.65, 163.99, 169.64 ppm. HRMS: m/z 361.2079; calcd. 361.4447 [M^+].

7-(4-Chlorobenzyl)-6-methyl-8-oxo-*N*-(tetrahydrofuran-2-ylmethyl)-5,6,7,8-tetrahydrofuro[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (13g): Yield 48%. ^1H NMR: δ = 1.0–1.7 (m, 6 H, tetrahydrofuran), 1.5 (s, 3 H, CH_3), 3.0–3.2 (m, 1 H, CH), 3.5–3.7 (m, 1 H, CH_2), 4.0–4.2 (m, 1 H, CH_2), 4.66 (d, J = 6.8 Hz, 1 H, CH_2), 5.5 (d, J = 6.8 Hz, 1 H, CH_2), 6.55 (d, J = 7.2 Hz, 2 H, ArH), 7.09–7.36 (m, 4 H, ArH), 7.5 (s, 1 H, ArH), 7.7–7.9 (m, 1 H, NH) ppm. ^{13}C NMR: δ = 7.8, 14.27, 23.49, 33.12, 34.39, 53.11, 54.31, 64.81, 116.38, 119.43, 121.61, 122.31, 124.06, 124.44, 133.6, 134.54, 144.61, 163.38, 168.22 ppm. HRMS: m/z 441.1524; calcd. 441.9184 [M^+].

7-Benzyl-*N*-cycloheptyl-2-methyl-8-oxo-6-phenyl-5,6,7,8-tetrahydrofuro[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (13h): Yield 36%. ^1H NMR: δ = 1.0–1.7 (m, 12 H, cycloheptane), 2.35 (s, 3 H, CH_3), 1.6–1.72 (m, 1 H, CH), 4.1 (d, J = 6.8 Hz, 1 H, CH_2), 4.58 (d, J = 6.7 Hz, 1 H, CH_2), 4.81 (d, J = 6.8 Hz, 1 H, CH_2), 4.92 (d, J = 6.7 Hz, 1 H, CH_2), 6.1 (s, 1 H, ArH), 6.57 (s, 1 H, ArH), 6.8–7.32 (m, 11 H, ArH, NH) ppm. ^{13}C NMR: δ = 7.89, 13.41, 24.13, 25.54, 26.01, 26.19, 27.41, 28.43, 29.41, 2 $\times$ 33.58, 54.11, 55.21, 64.37, 121.43, 122.39, 124.33, 126.04, 127.21, 133.22, 134.55, 135.53, 144.39, 165.12, 168.87 ppm. HRMS: m/z 495.2592; calcd. 495.6270 [M^+].

***N*-Cycloheptyl-8-oxo-6-phenyl-7-propyl-5,6,7,8-tetrahydrofuro[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (13i):** Yield 27%. ^1H NMR: δ = 0.59 (s, 3 H, CH_3), 1.1–1.65 (m, 14 H, cycloheptane, CH_2), 2.58–2.7 (m, 1 H, CH), 3.38–3.5 (m, 1 H, CH_2), 3.68–3.8 (m, 1 H, CH_2), 4.55–4.73 (d, J = 7.0 Hz, 1 H, CH_2), 4.83–5.04 (d, J = 7.0 Hz, 1 H, CH_2), 6.37–6.6 (d, J = 7.4 Hz, 2 H, ArH), 7.1 (d, J = 7.2 Hz, 1 H, NH), 7.25–7.77 (m, 5 H, ArH), 7.45 (s, 1 H, ArH) ppm. ^{13}C NMR: δ = 7.87, 21.49, 24.13, 25.23, 26.61, 26.99, 27.41, 28.46, 29.49, 2 $\times$ 34.12, 54.58, 55.11, 64.65, 128.21, 134.76, 134.99, 136.43, 145.12, 164.07, 168.81 ppm. HRMS: m/z 433.2435; calcd. 433.5553 [M^+].

***N*-Cycloheptyl-2-ethyl-7-(2-furylmethyl)-6-methyl-8-oxo-5,6,7,8-tetrahydrothieno[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (14a):** Yield 90%. ^1H NMR: δ = 1.2–1.5 (m, 12 H, cyclooctane), 1.21–1.25 (t, J = 8.4 Hz, 3 H, CH_3), 1.6 (s, 3 H, CH_3), 2.73–2.9 (q,

J = 7.9 Hz, 2 H, CH_2), 3.47–3.51 (m, 1 H, CH), 4.0 (d, J = 6.7 Hz, 1 H, CH_2), 4.7 (d, J = 6.9 Hz, 1 H, CH_2), 4.55 (d, J = 6.7 Hz, 1 H, CH_2), 4.82 (d, J = 6.9 Hz, 1 H, CH_2), 6.3 (d, J = 7.3 Hz, 2 H, ArH), 6.6–6.71 (s, 2 H, ArH), 6.85 (s, 1 H, ArH), 7.35–7.41 (s, 1 H, NH) ppm. ^{13}C NMR: δ = 7.8, 16.13, 20.31, 23.33, 24.82, 25.55, 27.20, 33.10, 34.33, 46.05, 54.26, 54.91, 64.54, 114.54, 119.43, 120.88, 122.31, 124.06, 124.98, 134.36, 164.31, 168.21 ppm. HRMS: m/z 453.2157; calcd. 453.6081 [M^+].

7-(3-Bromobenzyl)-*N*-cyclohexyl-8-oxo-6-phenyl-5,6,7,8-tetrahydrothieno[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (14b): Yield 34%. ^1H NMR: δ = 0.7–1.9 (m, 10 H, cyclohexane), 3.41–3.58 (m, 1 H, CH), 3.67–3.78 (d, J = 6.4 Hz, 1 H, CH_2), 4.8–4.92 (d, J = 6.8 Hz, 1 H, CH_2), 5.12–5.19 (d+d, J = 6.8 Hz, 1 H, CH_2), 5.2–5.3 (d, J = 6.8 Hz, 1 H, CH_2), 6.8–6.82 (d, J = 6.8 Hz, 1 H, ArH), 5.84 (s, 1 H, ArH), 6.87–7.1 (m, 3 H, ArH), 7.18–7.38 (m, 7 H, ArH), 7.52–7.61 (d, J = 6.2 Hz, 1 H, NH) ppm. ^{13}C NMR: δ = 7.87, 24.13, 25.54, 26.19, 27.43, 28.72, 2 $\times$ 34.08, 54.01, 54.73, 64.32, 120.21, 122.37, 125.45, 126.33, 127.21, 134.27, 134.99, 135.54, 144.32, 164.78, 168.36 ppm. HRMS: m/z 562.1150; calcd. 562.5334 [M^+].

***N*-Cycloheptyl-8-oxo-6-phenyl-7-propyl-5,6,7,8-tetrahydrothieno[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (14c):** Yield 25%. ^1H NMR: δ = 0.56–0.7 (t, J = 8.4 Hz, 3 H, CH_3), 1.1–1.8 (m, 14 H, cycloheptane, CH_2), 2.6–2.75 (m, 1 H, CH_2), 3.4–3.52 (m, 1 H, CH_2), 3.73–3.84 (m, 1 H, CH), 4.62–4.8 (d, J = 7.0 Hz, 1 H, CH_2), 5.07–5.18 (d, J = 7.0 Hz, 1 H, CH_2), 6.88 (s, 1 H, ArH), 7.9–8.0 (d, J = 7.4 Hz, 1 H, ArH), 7.1–7.19 (d, J = 5.9 Hz, 1 H, NH), 7.2–7.28 (d, J = 7.2 Hz, 1 H, ArH), 7.38–7.53 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 7.89, 22.19, 24.17, 25.28, 26.44, 27.43, 27.41, 28.46, 29.49, 2 $\times$ 33.21, 54.59, 56.43, 64.65, 128.21, 134.04, 134.43, 136.43, 145.12, 166.32, 169.21 ppm. HRMS: m/z 449.2206; calcd. 449.6199 [M^+].

***N*-Cycloheptyl-2-ethyl-8-oxo-6-phenyl-7-propyl-5,6,7,8-tetrahydrothieno[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (14d):** Yield 28%. ^1H NMR: δ = 0.58–0.70 (t, J = 5.5 Hz, 3 H, CH_3), 1.15–1.7 (m, 14 H, cycloheptane, CH_2), 1.25–1.28 (t, J = 8.6 Hz, 3 H, CH_3), 2.6–2.8 (m, 1 H, CH_2), 2.82–2.9 (q, J = 7.8 Hz, 2 H, CH_2), 3.3–3.52 (m, 1 H, CH_2), 3.72–3.9 (m, 1 H, CH), 4.6–4.79 (d, J = 6.9 Hz, 1 H, CH_2), 5.06–5.17 (d, J = 6.9 Hz, 1 H, CH_2), 6.6 (s, 1 H, ArH), 6.8 (s, 1 H, ArH), 7.0–7.1 (d, J = 6.4 Hz, 1 H, NH), 7.3–7.5 (m, 5 H, ArH) ppm. ^{13}C NMR: δ = 7.85, 20.32, 22.11, 25.07, 25.28, 26.48, 28.23, 28.98, 29.11, 29.49, 2 $\times$ 33.77, 54.51, 56.48, 64.15, 129.11, 134.77, 135.13, 136.43, 145.17, 165.72, 168.51 ppm. HRMS: m/z 477.2528; calcd. 477.6741 [M^+].

2-Ethyl-6-methyl-*N*-(4-methylcyclohexyl)-8-oxo-7-(2-pyrrolidin-1-ylethyl)-5,6,7,8-tetrahydrothieno[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (14e): Yield 63%. ^1H NMR: δ = 0.77–0.82 (t, J = 8.7 Hz, 3 H, CH_3), 1.25–1.30 (t, J = 7.6 Hz, 3 H, CH_3), 1.45 (br. s, 3 H, CH_3), 0.77–1.8 (m, 13 H, cyclohexane, pyrrolidine), 2.4–2.62 (m, 2 H, CH_2), 2.65–3.0 (m, 6 H, 3 CH_2), 3.3–3.52 (m, 2 H, CH_2), 3.8–4.0 (m, 2 H, 2 CH), 4.7 (d, J = 6.8 Hz, 1 H, CH_2), 6.68 (s, 1 H, ArH), 6.73 (s, 1 H, ArH), 7.8 (d, J = 6.6 Hz, 1 H, NH) ppm. ^{13}C NMR: δ = 19.11, 14.22, 20.54, 23.13, 24.59, 25.65, 26.74, 32.31, 34.51, 45.30, 47.75, 51.10, 52.43, 64.18, 122.37, 143.59, 153.61, 163.99, 168.24 ppm. HRMS: m/z 470.2795; calcd. 470.6824 [M^+].

7-(1-Benzylpiperidin-4-yl)-*N*-cyclopentyl-6-methyl-8-oxo-5,6,7,8-tetrahydrothieno[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (14f): Yield 65%. ^1H NMR: δ = 1.4 (s, 3 H, CH_3), 1.3–2.22 (m, 13 H, cyclopentane, piperidine), 2.7–2.94 (m, 4 H, 2 CH_2), 3.3–3.5 (d+d, J = 6.4 Hz, 2 H, CH_2), 4.0–4.11 (q, J = 6.6 Hz, 1 H, CH), 4.13–4.2 (d, J = 7.0 Hz, 1 H, CH_2), 1.4–1.5 (d, J = 7.0 Hz, 1 H,

CH₂), 6.9 (s, 1 H, ArH), 6.93–7.0 (d, J = 7.4 Hz, 1 H, ArH), 7.15–7.21 (m, 6 H, ArH), 8.13 (d, J = 4.9 Hz, 1 H, NH) ppm. ¹³C NMR: δ = 7.83, 22.11, 25.07, 25.29, 26.36, 28.27, 28.99, 30.43, 31.48, 2 × 34.15, 54.51, 56.48, 62.43, 119.54, 130.33, 134.77, 135.19, 138.42, 145.17, 165.78, 169.51 ppm. HRMS: m/z 490.2482; calcd. 490.6728 [M⁺].

7-(3-Fluorophenyl)-6-methyl-N-(2-methylcyclohexyl)-8-oxo-5,6,7,8-tetrahydrothieno[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (14g): Yield 40%. ¹H NMR: δ = 0.54 (s, 3 H, CH₃), 1.28 (s, 3 H, CH₃), 0.8–1.79 (m, 8 H, cyclohexane), 3.0–3.18 (m, 2 H, 2CH), 4.32–4.4 (d, J = 6.5 Hz, 1 H, CH₂), 5.0–5.07 (d, J = 6.9 Hz, 1 H, CH₂), 6.7–7.4 (m, 7 H, ArH), 7.57–7.7 (t, J = 6.2 Hz, 1 H, NH) ppm. ¹³C NMR: δ = 7.86, 25.07, 25.28, 28.23, 28.98, 29.11, 29.49, 34.77, 54.51, 57.42, 64.15, 122.21, 133.20, 136.33, 137.73, 145.17, 166.22, 168.51 ppm. HRMS: m/z 439.1797; calcd. 439.5561 [M⁺].

7-(1,3-Benzodioxol-5-ylmethyl)-N-cyclohexyl-2-ethyl-8-oxo-6-phenyl-5,6,7,8-tetrahydrothieno[2',3':4,5]pyrrolo[1,2-*a*]pyrazine-6-carboxamide (14h): Yield 39%. ¹H NMR: δ = 1.28–1.32 (t, J = 8.6 Hz, 3 H, CH₃), 0.8–1.7 (m, 10 H, cyclohexane), 2.8–3.0 (q, J = 6.6 Hz, 2 H, CH₂), 3.4–3.53 (m, 1 H, CH), 3.9–4.07 (m, 1 H, CH), 4.67–4.8 (m, 1 H, CH), 4.6–4.77 (d, J = 6.9 Hz, 1 H, CH₂), 5.05–5.18 (d, J = 6.9 Hz, 1 H, CH₂), 5.88 (d, J = 8.0 Hz, 2 H, CH₂, 1,3-benzodioxolyl), 6.12 (d, J = 8.0 Hz, 1 H, ArH, 1,3-benzodioxolyl), 6.46 (d, J = 8.0 Hz, 2 H, ArH, 1,3-benzodioxolyl), 6.65 (s, 1 H, ArH), 6.88 (s, 1 H, ArH), 7.0–7.15 (m, 1 H, NH), 7.2–7.39 (m, 5 H, ArH) ppm. ¹³C NMR: δ = 7.71, 14.33, 24.01, 24.28, 25.99, 26.19, 27.43, 28.21, 2 × 34.18, 52.71, 54.01, 54.83, 66.12, 121.29, 122.37, 125.45, 126.33, 128.43, 134.27, 135.09, 136.34, 146.12, 164.77, 169.31 ppm. HRMS: m/z 555.2257; calcd. 555.7015 [M⁺].

6-[(Cyclohexylamino)carbonyl]-6,7-dimethyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1-carboxylic Acid (15): To a solution of ester **6e** (696 mg, 2 mmol) in methanol (15 mL) was added a 2% aqueous solution of NaOH (10 mL). The reaction mixture was stirred at 70 °C for 7 h, then cooled to room temp. and concentrated under reduced pressure to remove methanol. Water (15 mL) was added, and the mixture was acidified by addition of 1% aqueous HCl until pH 3 was reached. The formed precipitate was filtered off, washed with water (3 × 50 mL) and dried with Na₂SO₄ to give **15** as a white solid (536 mg, 80%). Yield 80%. ¹H NMR: δ = 1.0–1.5 (m, 10 H, cyclohexane), 1.62 (s, 3 H, CH₃), 3.03 (s, 3 H, CH₃), 3.41–3.58 (m, 1 H, CH), 4.3 (d, J = 6.8 Hz, 1 H, CH₂), 4.8 (d, J = 6.8 Hz, 1 H, CH₂), 7.88 (s, 1 H, ArH), 7.9 (d, J = 6.2 Hz, 1 H, NH), 14.63 (s, 1 H, OH) ppm. ¹³C NMR: δ = 19.46, 24.50, 24.61, 24.99, 29.10, 31.81, 31.89, 48.81, 50.03, 64.89, 123.22, 135.14, 137.98, 159.95, 161.25, 167.63 ppm. HRMS: m/z 334.1712; calcd. 334.3781 [M⁺].

General Procedure for Preparation of Amides 16a,b: 1,1'-Carbonyldiimidazole (178 mg, 1.1 mmol) was added portionwise to a solution of the acid **15** (334 mg, 1 mmol) in DMF (2 mL). The resulting mixture was stirred at room temperature for 10 min and then at 80–90 °C for 3 h to accomplish the conversion of initial acid into the corresponding imidazolide intermediate. The mixture was cooled to room temperature and DMF was added until the total volume was equal to 4 mL. A portion of this solution (2 mL) was added to a solution of amine HNR³R⁴ (1 mmol) in dry DMF (500 μ L), and the reaction mixture was stirred at 75–80 °C for 8 h and then cooled to room temperature. Water (2 mL) was added, the formed precipitate was filtered off and recrystallized from diethyl ether to afford pure carboxamide **16a** or **16b**.

N-Cyclohexyl-6,7-dimethyl-8-oxo-1-[(4-phenylpiperazin-1-yl)carbonyl]-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-6-carboxamide (16a): Yield 85%. ¹H NMR: δ = 1.1–1.8 (m, 10 H, cyclohexane), 1.61 (s,

3 H, CH₃), 2.91 (s, 3 H, CH₃), 3.0–3.33 (m, 6 H, 3CH₂), 3.4–3.54 (m, 1 H, CH), 3.8–3.91 (m, 2 H, CH₂), 4.17 (d, J = 6.9 Hz, 1 H, CH₂), 4.72 (d, J = 6.9 Hz, 1 H, CH₂), 6.75 (t, J = 6.8 Hz, 1 H, ArH), 6.88 (d, J = 7.4 Hz, 2 H, ArH), 7.22 (t, J = 7.0 Hz, 2 H, ArH), 7.68 (d, J = 6.2 Hz, 1 H, NH), 7.71 (s, 1 H, ArH) ppm. ¹³C NMR: δ = 19.92, 24.54, 24.64, 25.06, 28.09, 31.91, 45.73, 48.06, 48.51, 48.62, 50.19, 64.13, 2 × 115.86, 119.25, 119.61, 2 × 128.81, 128.91, 136.38, 137.52, 150.75, 158.17, 163.09, 168.64 ppm. HRMS: m/z 478.2772; calcd. 478.5993 [M⁺].

N⁶-Cyclohexyl-N¹-[2-(4-methoxyphenyl)ethyl]-6,7-dimethyl-8-oxo-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-1,6-dicarboxamide (16b): Yield 80%. ¹H NMR: δ = 1.1–1.35 (m, 5 H, cyclohexane), 1.58 (s, 3 H, CH₃), 1.59–1.76 (m, 5 H, cyclohexane), 3.01 (s, 3 H, CH₃), 3.45–3.57 (m, 1 H, CH), 4.25 (d, J = 6.8 Hz, 1 H, CH₂), 4.4–4.52 (m, 2 H, CH₂), 4.84–4.95 (m, 1 H, CH₂), 6.8 (d, J = 6.8 Hz, 1 H, ArH), 7.24 (d, J = 7.2 Hz, 1 H, ArH), 7.86 (s, 1 H, ArH), 7.92 (d, J = 6.0 Hz, 1 H, NH), 10.86 (br. s, 1 H, NH) ppm. ¹³C NMR: δ = 19.79, 24.52, 24.63, 25.01, 29.03, 31.83, 31.92, 48.58, 50.07, 54.98, 64.04, 2 × 113.73, 121.17, 2 × 128.54, 131.14, 136.68, 138.05, 158.18, 159.96, 160.22, 168.19 ppm. HRMS: m/z 467.2445; calcd. 467.5729 [M⁺].

Crystallographic Data for 13a: Tetragonal single crystal [0.55 × 0.10 × 0.10 mm³, space group *I*₄/a, unit cell constants a = 20.669(5) Å, b = 20.669(5) Å, c = 18.394(7) Å, α = 90°, β = 90°, γ = 90°, V = 7859(4) Å³, Z = 16, D_x = 1.263 Mg/m³]. Cell parameters were retrieved using SMART software and refined using SAINT on all observed reflections. Data reduction was performed with SAINT, and the structures were solved by the direct method using the SHELXS-97 program incorporated in SHELXTL-PC V 5.10 and refined by the least-squares method on F^2 . The final R indices are R_1 = 0.0509, wR_2 = 0.1221.

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- [1] a) I. Ugi, S. Lohberger, R. Karl, in: *Comprehensive Organic Synthesis*, vol. 2 (Eds.: B. M. Trost, L. Flemming, C. Heathcock), Pergamon, Oxford, **1996**, pp. 1083–1109; b) A. Domling, I. Ugi, *Angew. Chem.* **2000**, 39, 3168–3210.
- [2] a) K. M. Short, A. M. M. Mjalli, *Tetrahedron Lett.* **1997**, 38, 359–362; b) K. Paulvannan, *Tetrahedron Lett.* **1999**, 40, 1851–1854; c) V. Hulme, M.-P. Cherrier, *Tetrahedron Lett.* **1999**, 40, 5295–5299; d) J. Zhang, A. Jacobson, J. R. Rusche, W. Herlihy, *J. Org. Chem.* **1999**, 64, 1074–1076; e) D. Lee, J. K. Sello, S. L. Schreiber, *Org. Lett.* **2000**, 2, 709–712; f) S. V. Ley, S. J. Taylor, *Bioorg. Med. Chem. Lett.* **2002**, 12, 1813–1816; g) S. Marcaccini, R. Pepino, T. Torroba, D. Miguel, M. Garcia-Valverde, *Tetrahedron Lett.* **2002**, 43, 8591–8593; h) S. Marcaccini, D. Miguel, T. Torroba, M. Garcia-Valverde, *J. Org. Chem.* **2003**, 68, 3315–3318.
- [3] J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144.
- [4] a) F. Cafieri, E. Fattorusso, O. Tagliatela-Scafati, *J. Nat. Prod.* **1998**, 61, 122–125; b) K. Poullennec, D. Romo, *J. Am. Chem. Soc.* **2003**, 125, 6344–6345.
- [5] B. C. Askew, R. A. Bednar, B. Bednar, D. A. Claremon, J. J. Cook, C. J. McIntyre, C. A. Hunt, R. J. Gould, R. J. Lynch,

- J. J. Lynch Jr., S. L. Gaul, M. T. Stranieri, G. R. Sitko, M. A. Holahan, J. D. Glass, T. Hamill, L. M. Gorham, T. Prueksaritanont, J. J. Baldwin, G. D. Hartman, *J. Med. Chem.* **1997**, *40*, 1779–1788.
- [6] R. A. Tapia, Y. Prieto, F. Pautet, M. Domard, M.-E. Sarciron, N. Walchshofer, H. Fillion, *Eur. J. Org. Chem.* **2002**, *23*, 4005–4010.
- [7] D. R. Sliskovic, in: *Comprehensive Heterocyclic Chemistry, II* (Eds.: A. R. Katritzky, C. W. Rees, E. F. Scriven), Pergamon, Oxford, **1996**, *9*, pp. 345.
- [8] P. K. Bridson, R. V. Iyengar, *Heterocycles* **1995**, *41*, 1271–1274.
- [9] A. Gopalsamy, M. Shi, *Org. Lett.* **2003**, *5*, 3907–3909.
- [10] J. T. Randolph, D. A. DeGoey, *Curr. Top. Med. Chem.* **2004**, *4*, 1079–1095.
- [11] R. M. Jones, P. D. Boatman, G. Semple, Y. J. Shin, S. Y. Tamura, *Curr. Opin. Pharmacol.* **2003**, *3*, 530–543.
- [12] A. Golebiowski, J. Jozwik, S. R. Klopfenstein, A.-O. Colson, A. L. Grieb, A. F. Russell, V. L. Rastogi, C. F. Diven, D. E. Portlock, J. J. Chen, *J. Comb. Chem.* **2002**, *4*, 584–590.

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