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Multicomponent Assembly of Diverse Pyrazin-2(1*H*)-one Chemotypes

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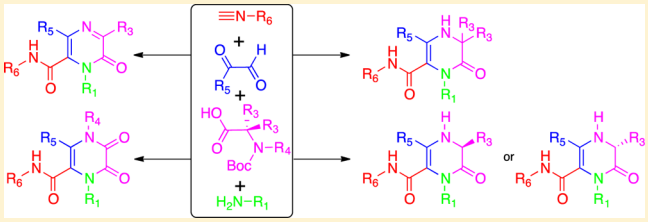
Supporting Information

ABSTRACT: An expedient and concise Ugi-based approach for the rapid assembly of pyrazin-2(1*H*)-one-based frameworks has been developed. This convergent approach encompasses skeletal, functional and stereochemical diversity, exhibiting an unusually high bond-forming efficiency as well as high structure and step economies. The method involves the use of readily available commercial reagents and is an example of the reconciliation of structural complexity with operational simplicity in a time- and cost-effective manner.



INTRODUCTION

Owing to their prolific bioactivity, pyrazines − and particularly their 2-oxo-derivatives [pyrazin-2(1*H*)-ones] − are recognized as valuable scaffolds in drug discovery.[1] These chemotypes, which are featured in natural products,[2] bioactive compounds[3] and in several therapeutic agents (Figure 1),[1] have proven to be particularly versatile for scaffolding strategies.[4] In addition to the bioactivity issue, the reactivity of the 2-azadiene system of the pyrazin-2(1*H*)-one core provides elegant access to diverse molecular architectures.[5] While pyridazin-2(1*H*)-ones appear frequently in bioactive molecules, synthetic methodologies targeting this structural platform are somewhat limited.[6]

The early synthesis of these systems involved the condensation of α-diketones with α-aminoamides,[6] an approach that has very limited scope and generally produces mixtures of regioisomers. Incisive work by Hoornaert,[7] three decades ago, unveiled the most widely employed preparative entry to pyrazin-2(1*H*)-ones, wherein an α-aminonitrile is treated with HX and oxalyl halide to afford N-1,C-6-disubstituted-3,5-dihalopyrazin-2(1*H*)-ones. The different reactivities of the halogens on the heterocycle enables the sequential functionalization of these positions,[8] usually employing metal-catalyzed cross-coupling reactions.[9] Despite its versatility and efficiency, Hoornaert's method has intrinsic limitations[7] [e.g., it requires strongly acidic conditions that are not compatible with sensitive functional groups, it involves the manipulation of hazardous cyanide sources, requires prolonged reaction times and the reaction outcome is influenced by the electronic and steric effects of substituents]. Furthermore, the subsequent decoration of the heterocyclic core often involves multiple steps, involving the use of expensive reagents, additives and metallic catalysts. In a similar fashion, the synthetic methods targeting functionalized 3,4-dihydropyrazin-2(1*H*)-ones remain clearly insufficient.[10] Therefore, the development of integrated approaches to enable the straightforward assembly of pyrazin-2(1*H*)-one chemotypes remains a methodological challenge.

Within the framework of a project aimed at the concise assembly of privileged scaffolds, we considered the feasibility of an isocyanide-based multicomponent approach to deliver highly substituted pyrazin-2(1*H*)-ones (**7**). The Ugi-based approach to 2,5-diketopiperazines is an established method,[11] but very few reports have described MCR-based methods to access pyrazin-2(1*H*)-ones.[12] Despite their efficiency, existing methods have limited scope and reduced flexibility in that they do not allow the assembly of diverse pyrazin-2(1*H*)-one-based scaffolds. The pathway proposed here, which follows the Ugi/Deprotect/Cyclize (UDC)[13] strategy, is shown in Scheme 1. We envisaged that the Ugi four-component reaction (U-4CR)[14] employing glyoxals (**1**) and N-Boc protected amino acids (**4**) as key bifunctional precursors would afford Ugi adducts **5**. Subsequent cleavage of the protecting group and cyclization would furnish 3,4-dihydropyrazin-2(1*H*)-ones (**6**) that could be easily aromatized to provide the target structures **7**. Herein, we report an integrated step- and structure-economic *de novo* U-4CR-based procedure that enables the straightforward assembly of different chemotypes derived from the pyrazin-2(1*H*)-one scaffold in a time- and cost-effective manner.

RESULTS AND DISCUSSION

The feasibility of the proposed sequence relies heavily on the chemoselectivity of the U-4CR employing glyoxals (**1**) as well

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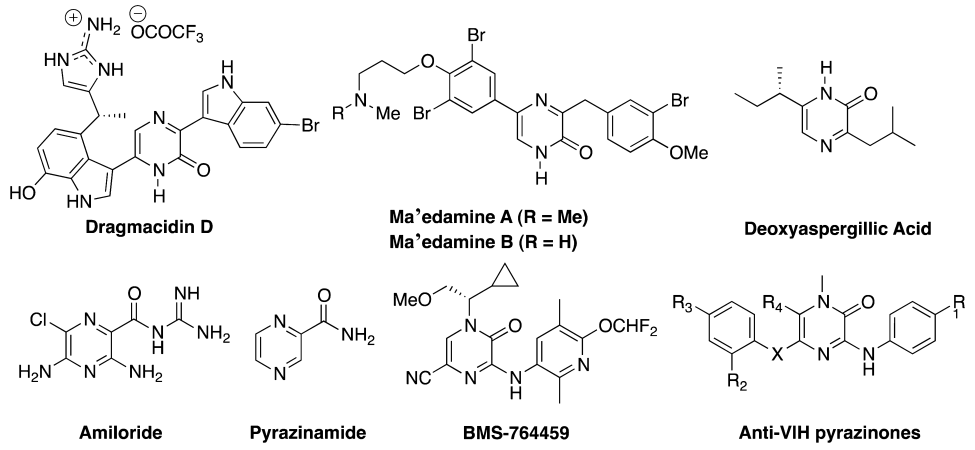
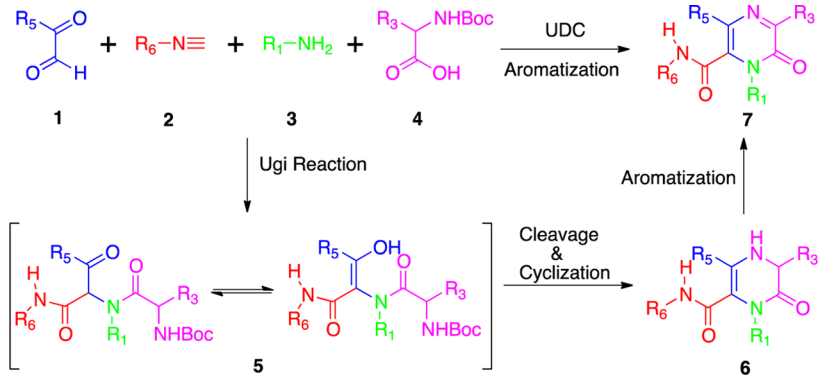
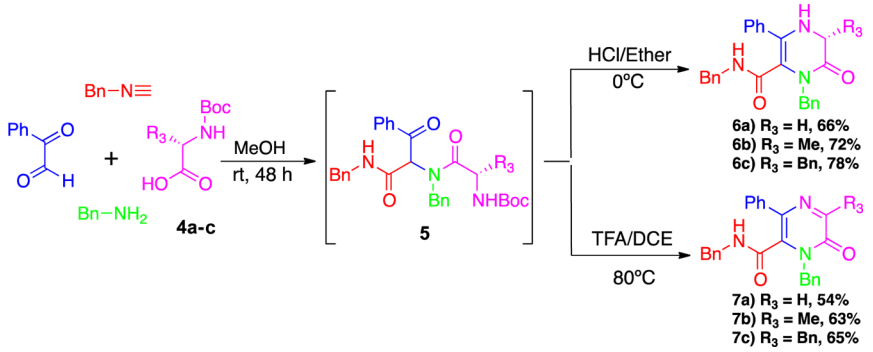


Figure 1. Representative alkaloids, drugs and bioactive compounds derived from the pyrazine scaffold.

Scheme 1. Proposed synthetic route to pyrazin-2(1*H*)-ones



Scheme 2. Ugi-based assembly of pyrazin-2(1*H*)-ones and their 3,4-dihydro-analogues



as the reactivity profile of the Ugi adducts **5**. Phenylglyoxal (**1a**), benzylisonitrile (**2a**), benzylamine (**3a**) and a set of N-Boc protected amino acids (**4a–c**) were selected as model substrates (Scheme 2). Equimolar amounts of these substrates were submitted to the standard U-4CR conditions, in methanol at room temperature for 48 h. Excellent chemoselectivity was observed, thus confirming the low reactivity of the ketone moiety of the phenylglyoxal during U-4CR. This process gave Ugi adducts **5** satisfactorily and the reaction behavior did not seem to be sensitive to the increasing steric hindrance present in the amino acid partner (**4a–c**, R_3 = H, Me, Bn). Inspection of reagents and conditions to cleave the Boc group in the adducts **5** confirmed the feasibility of the proposed pathway in a shorter sequence, while simultaneously revealing remarkable facets of this chemistry that highlight its scope and versatility in terms of the rapid generation of molecular diversity (Scheme 2).

Among the reagents evaluated, TFA-mediated cleavage (30% TFA/DCE at 80 °C, 2 h) under aerobic conditions proved to be particularly attractive, directly affording target pyrazin-2(1*H*)-ones **7** in satisfactory yields (Scheme 2). Under these conditions 3,4-dihydropyrazin-2(1*H*)-ones (**6**) undergo an oxidative aromatization, thus avoiding the use of oxidants or catalytic dehydrogenation. The search for alternative cleavage conditions revealed that 3,4-dihydropyrazin-2(1*H*)-ones (**6**) could be satisfactorily obtained by treatment of compounds **5** with 2N HCl/ether (0 °C, 0.5 h) or H_3PO_4 (room temperature). We next turned to the U-4CR-based one-pot assembly of pyrazinone derivatives **6** or **7**. After monitoring the Ugi reaction and judging it complete, the solvent was

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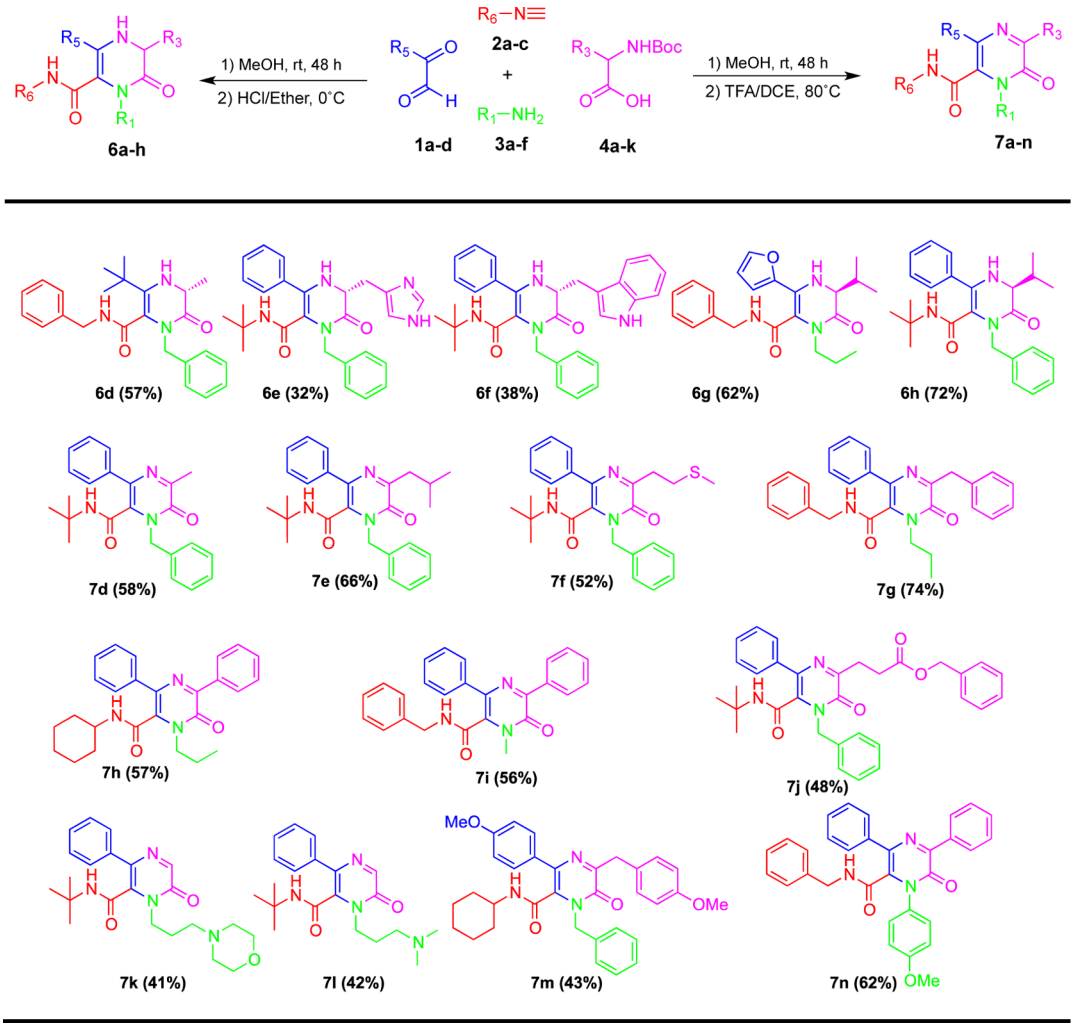
Scheme 3. Ugi-Based Assembly of pyrazin-2(1*H*)-one derivatives (6 and 7)



evaporated and the crude adduct **5** was treated with either TFA in DCE or HCl/ether (Scheme 2). Gratifyingly, both methods delivered pyrazin-2(1*H*)-ones **7** or 3,4-dihydropyrazin-2(1*H*)-ones (**6**) with satisfactory overall yields.

Once the feasibility of the proposed pathway had been validated, the scope and robustness of this five-step one-pot *de novo* pyrazin-2(1*H*)-one synthesis was evaluated (Scheme 3) by considering a diverse range of commercially available glyoxals (**1**), isocyanides (**2**), amines (**3**) and either racemic or enantiopure N-Boc protected amino acids (**4**). Although the primary aim of this work was the development of a general and robust high-throughput synthetic method to assemble diversely decorated pyrazin-2(1*H*)-ones (**7**), we decided to briefly evaluate the synthesis of some representative enantiopure 3,4-dihydropyrazin-2(1*H*)-ones (**6**).

The results in Scheme 3 enable a preliminary assessment of the exploratory power of this conceptual and experimentally simple strategy. Two remarkable features of the methodology reported here concern its outstanding bond-forming efficiency and step economy, which allow compounds **6** and **7** to be assembled in a one-pot process that involves the formation of four or five new bonds, respectively. It can be seen that this approach enables the rapid *de novo* assembly of pyrazin-2(1*H*)-ones (**7**) and their 3,4-dihydro analogues (**6**), while allowing the incorporation of highly diverse residues at variable positions (R_1, R_3, R_5, R_6) of the heterocyclic core (Scheme 3). The yields obtained range from 32 to 78%, with reported values referred to the overall yield of the three (or four) synthetic steps involved (U-4CR, deprotection, cyclization, aromatization), thus indicating excellent yields for each simple step. The method proved to be broadly successful with all variable components (**1**–**4**). Excellent reactivity profiles were found for tested N-Boc protected amino acids, the success of which enables the introduction of significant structural and stereochemical diversity (Scheme 3). A similar fashion was observed for the amine partner (including alkyl, aryl and heterocyclic derivatives). Different aryl and heteroaryl fragments, as well the bulky neighboring *tert*-butyl group or cyclopropyl residue, are successfully introduced at position 5 through the glyoxal precursor (**1**), while the sequence fails when using pyruvaldehyde, which does not conserve the chemoselectivity profile exhibited by its hindered analogues during the U-4CR. It is apparent from the results in Scheme 3 that the process is highly successful not only to introduce functional diversity but also stereochemical diversity at position 3 of the heterocyclic scaffold. Thus, the use of enantiopure N-Boc amino acids (**4**) successfully afforded enantiomerically pure 3,4-dihydropyrazin-2(1*H*)-ones (**6**). It was verified that **6** were isolated in good yields and also without racemization at the stereocenter (ee >95%), as determined by chiral HPLC analysis. It should be

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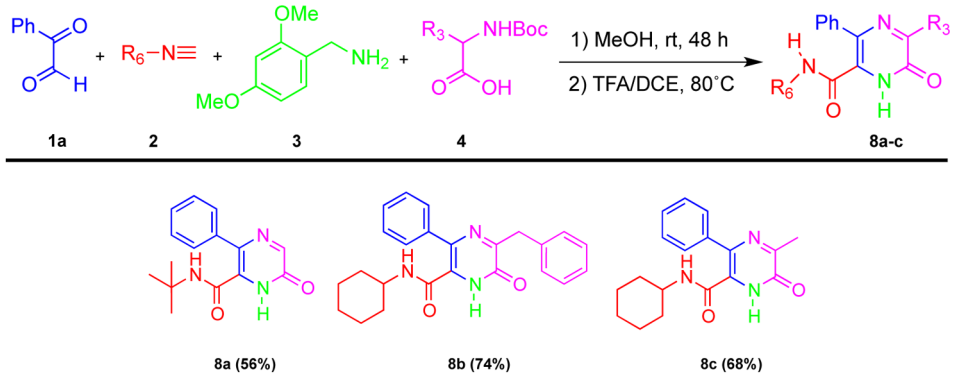
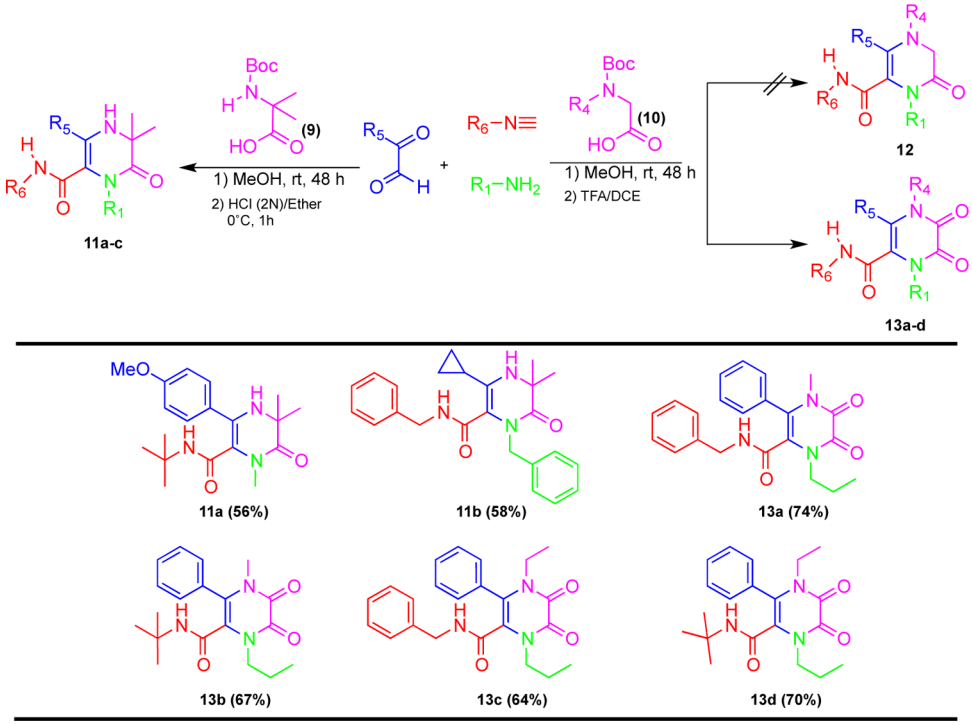
Scheme 4. Ugi-Based assembly of pyrazin-2(1*H*)-ones unsubstituted at position 1



Scheme 5. Ugi-based assembly of pyrazine derivatives 11 and 13



pointed that while 3,4-dihydropyrazin-2(1*H*)-ones (**6**) are stable at the solid state, they spontaneously aromatize on standing in solution (e.g., $CDCl_3$, DMSO-d_6 or MeOH) for more than 72h. Accordingly, chiral HPLC determinations were performed employing freshly prepared 3,4-dihydropyrazin-2(1*H*)-one solutions.

In an effort to broaden the exploratory power of the method, the assembly of pyrazin-2(1*H*)-ones unsubstituted at position 1 of the heterocyclic backbone (**8**) was assessed (Scheme 4). Although several authors have reported successful U-4CR with ammonia,[15] our attempts with model reagents failed. The use of 2,4-dimethoxy-benzylamine as an ammonia surrogate during the U-4CR (Scheme 4), enabled us to overcome this drawback. It was anticipated that the acidic conditions required for the deprotection-cyclization-aromatization sequence would promote concomitant cleavage of the 2,4-dimethoxybenzyl residue, directly affording **8**. The viability of the proposed pathway was evaluated for phenylglyoxal, some representative amino acids and isocyanides. It was found that the one-pot sequence performed quite well, successfully delivering the desired pyrazin-2(1*H*)-ones (**8**) in yields in the range 56−74%.

To further evaluate the generality of the newly developed strategy, its effectiveness in the assembly of novel chemotypes derived from the 3,4-dihydropyrazin-2(1*H*)-one scaffold was assessed (Scheme 5). We particularly focused on the assembly of 3,3-disubstituted-3,4-dihydropyrazin-2(1*H*)-ones (**11**) and 4-substituted-3,4-dihydropyrazin-2(1*H*)-ones (**12**). With this aim in mind glycine Boc derivatives **9** and **10a−b** were submitted to U-4CR conditions and subsequently deprotected (Scheme 5). These substrates showed different reactivity profiles.

For example, the sterically hindered substrate **9** exhibited remarkable performance during the UDC sequence, thus enabling the straightforward assembly of hitherto unknown 3,3-dimethyl-3,4-dihydropyrazin-2(1*H*)-ones (**11**). As can be seen (Scheme 5), the transformations retain the efficiency and excellent scope previously observed. In sharp contrast to the results described above, the analytical and spectroscopic data

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obtained for compounds isolated from the UDC-based sequence employing glycine derivatives **10** (Scheme 5) revealed that the products obtained were not the desired **12**, but rather 4-alkyl-pyrazin-2,3-diones (**13**). The structural assignment within the series (see Supporting Information) was complemented by X-ray crystallography data obtained on a monocrystal of one representative compound (Compound **13d**).[16]

Analysis of the Ugi adduct intermediate for compound **13d** corroborated the performance of U-4CR, confirming that compounds **13** are produced during the deprotection-cyclization sequence. The evaluation of milder methods to cleave the protecting group afforded pyrazin-2,3-diones **13** irrespective of the reagent or conditions employed, thus evidencing the robustness of the pathway delivering these structures. Although it is premature to put forward a mechanistic proposal, the previously experienced tendency to aromatize of **6** strongly supports the occurrence of an oxidative pathway mediated by highly reactive 2(1*H*)pyrazinoium salts. A preliminary exploration of the transformation revealed the efficiency, broad scope and robustness of the identified pyrazin-2,3-(1*H*,4*H*)-dione synthesis, which afforded compounds **13** in satisfactory yields (64−74%). To the best of our knowledge, the pathway reported herein constitutes the first direct preparative method for the straightforward assembly of diversely decorated pyrazin-2,3-(1*H*,4*H*)-diones.

In summary, we report a U-4CR-based approach that provides an integrated and straightforward entry to several chemotypes derived from the pyrazin-2(1*H*)-one scaffold. This convergent and versatile method, which exhibits an unusually high bond-forming efficiency as well as structure and step economies, presents broad substrate scope and excellent functionality tolerance. This approach enables the rapid assembly of diverse pyrazin-2(1*H*)-one-based frameworks encompassing skeletal, functional and stereochemical diversity. In addition, the method involves the use of readily available commercial reagents and operationally simple synthetic protocols and does not require advanced intermediates, anhydrous solvents or transition metal catalysts. This approach therefore exemplifies the reconciliation of structural complexity and operational simplicity in an environmentally friendly and time- and cost-effective manner.

EXPERIMENTAL SECTION

Commercially available starting materials and reagents were purchased and used without further purification from freshly opened containers. Polystyrene-supported *p*-toluenesulfonic acid was purchased from commercial sources. All solvents were purified and dried by standard methods. Organic extracts were dried with anhydrous Na_2SO_4. The reactions were monitored by TLC and purified compounds each showed a single spot. Unless stated otherwise, UV light and/or iodine vapor were used for the detection of compounds. The synthesis and purification of all compounds were accomplished using the equipment routinely available in organic chemistry laboratories. Most of the preparative experiments were performed in coated vials on an organic synthesizer with orbital stirring. Purification of isolated products was carried out by column chromatography. Compounds were routinely characterized by spectroscopic and analytical methods. Melting points were determined on a melting point apparatus and are uncorrected. The chemical structures of the obtained compounds were characterized by nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C) and high-resolution mass spectra (HRMS). Unless otherwise quoted, NMR spectra were recorded in $CDCl_3$. Chemical shifts are given as δ values against tetramethylsilane as internal standard and J values are given in Hz. The enantiomeric excesses were determined by chiral-phase HPLC analysis employing freshly prepared 3,4-dihydropyrazin-2(1*H*)-one solutions.

General procedure for the one-pot synthesis of 3,4-dihydropyrazin-2(1*H*)-ones 6 and pyrazin-2(1*H*)-ones 7. A mixture of the glyoxal derivative (1.0 mmol), the amine (1.0 mmol), the isocyanide and the protected aminoacid (1.0 mmol) in MeOH (3 mL) was submitted to orbital stirring at room temperature for 48 h. After completion of the reaction, CH_2Cl_2 (3 mL) and PS-*p*-TsOH (2.0 mmol) were added. The reaction mixture was submitted to orbital stirring at room temperature until complete consumption of the unreacted isocyanide (30−60 min). The polystyrene-supported reagent was filtered off and successively washed [3 times (5 mL)] with MeOH, AcOEt and CH_2Cl_2. Evaporation of the solvents from the filtrate afforded a residue, which was treated with HCl 2N in ether (and stirred at room temperature for 1h) to afford **6** or 30% TFA in DCE (and heated to 80 °C for 1h) to afford **7**. The solution was then treated with saturated $NaHCO_3$. After extraction with ethyl acetate, the organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to afford an oily residue that was purified by chromatographic methods on silica gel using hexane/AcOEt mixtures.

General procedure for the one-pot synthesis of pyrazin-2(1*H*)-ones 8. A mixture of the glyoxal derivative (1.0 mmol), 2,4-dimethoxybenzylamine (1.0 mmol), the isocyanide and the protected aminoacid (1.0 mmol) in MeOH (3 mL) was submitted to orbital stirring at room temperature for 48 h. After completion of the reaction, CH_2Cl_2 (3 mL) and PS-*p*-TsOH (2.0 mmol) were added. The reaction mixture was submitted to orbital stirring at room temperature until complete consumption of the unreacted isocyanide (30−60 min). The polystyrene-supported reagent was filtered off and successively washed [3 times (5 mL)] with MeOH, AcOEt and CH_2Cl_2. Evaporation of the solvents from the filtrate afforded a residue, which was treated with 30% TFA in DCE (10 mL) and heated to 80 °C for 2h. The solution was then treated with saturated $NaHCO_3$. After extraction with ethyl acetate, the organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to afford an oily residue that was purified by chromatographic methods on silica gel using hexane/AcOEt mixtures.

*N,1-dibenzyl-6-oxo-3-phenyl-1,4,5,6-tetrahydropyrazine-2-carboxamide (**6a**).* yield 66%, 262.8 mg, white powder (EtOH, mp 158−160 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.60 (d, J = 7.5 Hz, 2H), 7.50 − 7.09 (m, 11H), 6.86 (dd, J = 6.7, 2.8 Hz, 2H), 6.26 (t, J = 5.4 Hz, 1H), 5.28 (d, J = 15.0 Hz, 1H), 5.17 (s, 1H), 4.67 (d, J = 20.8 Hz, 1H), 4.55 − 4.39 (m, 1H), 4.30 (dd, J = 14.9, 6.2 Hz, 1H), 4.21 − 4.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 167.4, 164.9, 161.0, 137.0, 135.7, 135.2, 131.1, 129.8, 129.0, 128.7, 128.6, 128.2, 128.1, 127.6, 127.2, 127.1, 61.6, 48.4, 43.8; HRMS (CI) m/z calcd. for $C_{25}H_{23}N_3O_2$ $[M+H]^+$: 398.1869, found: 398.1856.

*(R)-N,1-dibenzyl-5-methyl-6-oxo-3-phenyl-1,4,5,6-tetrahydropyrazine-2-carboxamide (**6b**).* yield 72%, 297.2 mg, pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.56 (d, J = 6.3 Hz, 2H), 7.43 − 7.11 (m, 13H), 6.86 − 6.73 (m, 1H), 6.04 (t, J = 5.9 Hz, 1H), 5.15 (dd, J = 20.1, 1.8 Hz, 1H), 4.35 − 4.22 (m, 1H), 4.15 − 4.03 (m, 2H), 3.95 (d, J = 15.2 Hz, 1H), 1.65 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 170.0, 165.0, 160.9, 136.3, 135.3, 130.9, 129.0, 128.9, 128.8, 128.6, 128.1, 128.0, 127.7, 127.6, 127.3, 127.1, 62.2, 48.1, 43.9, 20.4; HRMS (CI) m/z calcd. for $C_{26}H_{25}N_3O_2$ $[M+H]^+$: 412.2025, found: 412.2007.

*(R)-N,1,5-tribenzyl-6-oxo-3-phenyl-1,4,5,6-tetrahydropyrazine-2-carboxa-mide (**6c**).* yield 78%, 380.7 mg, pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.77 − 7.64 (m, 1H), 7.65 − 7.48 (m, 2H), 7.41 − 7.29 (m, 5H), 7.23 (dtd, J = 10.6, 7.6, 4.9 Hz, 6H), 7.10 − 6.92 (m, 4H), 6.93 − 6.80 (m, 1H), 6.61 − 6.45 (m, 1H), 5.79 (t, J = 5.8 Hz, 1H), 5.15 (d, J = 4.2 Hz, 1H), 5.02 − 4.84 (m, 2H), 4.61 (ddd, J = 6.6, 4.3, 1.9 Hz, 1H), 4.21 (d, J = 5.8 Hz, 2H), 3.78 − 3.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 168.4, 164.9, 159.8, 138.4, 137.0, 135.3, 131.0, 130.3, 129.2, 128.9, 128.7, 128.5, 128.3, 128.0, 127.9, 127.6, 127.3, 127.1, 126.6, 126.2, 62.7, 48.4, 43.8, 38.3; HRMS (CI) m/z calcd. for $C_{32}H_{29}N_3O_2$ $[M+H]^+$: 488.2338, found: 488.2363.

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*(R)-N,1-dibenzyl-3-(tert-butyl)-5-methyl-6-oxo-1,4,5,6-tetrahydropyrazine-2-carboxamide (**6d**).* yield 57%, 223.6 mg, white powder (EtOH, mp 147−149 °C); ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm): 7.46 − 7.05 (m, 10H), 5.87 (s, 1H), 5.12 (d, J = 14.7 Hz, 1H), 4.63 (s, 1H), 4.35 − 4.18 (m, 3H), 4.18 − 3.99 (m, 1H), 1.74 − 1.51 (m, 3H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.3, 171.3, 165.9, 137.2, 135.7, 128.9, 128.8, 128.3, 128.2, 127.9, 127.8, 60.4, 57.1, 49.1, 43.9, 39.3, 28.1, 18.0. HRMS (ESI- FIA-TOF) m/z calcd. for $C_{24}H_{29}N_3O_2$ $[M+H]^+$: 392.2333, found: 392.2337.

*(R)-5-((1H-imidazol-4-yl)methyl)-1-benzyl-N-(tert-butyl)-6-oxo-3-phenyl-1,4,5,6-tetrahydropyrazine-2-carboxamide (**6e**).* yield 32%, 142.2 mg, white powder (EtOH, mp 223−224 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): δ 7.65 − 7.52 (m, 2H), 7.52 − 7.27 (m, 8H), 7.23 − 7.12 (m, 2H), 6.92 (s, 1H), 5.22 (d, J = 15.1 Hz, 1H), 5.06 (s, 1H), 4.96 (s, 1H), 4.44 (td, J = 5.7, 1.7 Hz, 1H), 4.29 (d, J = 15.1 Hz, 1H), 3.51 (dd, J = 5.7, 3.7 Hz, 2H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.6, 163.1, 162.1, 135.9, 135.4, 134.4, 131.2, 129.1, 129.0, 128.2, 128.0, 127.1, 125.8, 62.9, 61.9, 52.2, 49.4, 28.2; HRMS (CI) m/z calcd. for $C_{26}H_{29}N_5O_2$ $[M+H]^+$: 444.2400, found: 444.2393.

*(R)-5-((1H-indol-3-yl)methyl)-1-benzyl-N-(tert-butyl)-6-oxo-3-phenyl-1,4,5,6-tetrahydropyrazine-2-carboxamide (**6f**).* yield 38%, 187.6 mg, white powder (EtOH, mp 289−290 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.64 − 7.28 (m, 8H), 7.24 − 7.06 (m, 3H), 7.04 − 6.90 (m, 1H), 6.67 (dd, J = 8.5, 6.9 Hz, 2H), 6.44 (d, J = 7.6 Hz, 2H), 5.56 (d, J = 15.4 Hz, 1H), 4.41 (dd, J = 5.5, 1.6 Hz, 1H), 4.16 (s, 1H), 3.89 (d, J = 15.5 Hz, 1H), 3.38 (dd, J = 15.9, 1.6 Hz, 1H), 3.26 (dd, J = 15.9, 5.4 Hz, 1H), 1.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 170.1, 168.0, 138.6, 136.0, 135.5, 133.0, 129.3, 128.3, 128.2, 126.9, 126.9, 126.7, 124.7, 122.8, 120.1, 118.8, 111.2, 109.2, 67.6, 57.1, 54.5, 51.0, 47.4, 28.0; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{31}H_{32}N_4O_2$ $[M+H]^+$: 493.2604, found: 493.2609.

*(S)-N-benzyl-3-(furan-2-yl)-5-isopropyl-6-oxo-1-propyl-1,4,5,6-tetrahydro-pyrazine-2-carboxamide (**6g**).* yield 62%, 236.9 mg, white powder, (EtOH, mp 139−140 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.47 (d, J = 1.7 Hz, 1H), 7.35 − 7.19 (m, 2H), 7.19 − 7.01 (m, 3H), 6.60 − 6.33 (m, 2H), 5.19 (s, 1H), 4.39 (qd, J = 14.8, 5.7 Hz, 2H), 4.11 (brs, 1H), 3.90 − 3.75 (m, 1H), 2.94 (ddd, J = 14.0, 8.7, 5.7 Hz, 1H), 2.76 (ddq, J = 9.8, 6.8, 3.5, 3.1 Hz, 1H), 1.70 − 1.40 (m, 3H), 1.18 (d, J = 6.9 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.0, 165.3, 150.9, 150.8, 144.0, 137.2, 128.7, 127.7, 127.3, 112.6, 112.1, 65.6, 62.1, 47.6, 43.9, 29.8, 19.9, 16.8, 11.2; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{22}H_{27}N_3O_3$ $[M+H]^+$: 382.2125, found: 382.2121.

*(S)-1-benzyl-N-(tert-butyl)-5-isopropyl-6-oxo-3-phenyl-1,4,5,6-tetrahydro-pyrazine-2-carboxamide (**6h**).* yield 72%, 308.3 mg, white powder (EtOH, mp 124−125 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.76 − 7.65 (m, 2H), 7.48 − 7.23 (m, 8H), 5.34 (d, J = 14.9 Hz, 1H), 5.06 (s, 1H), 4.97 (s, 1H), 4.18 (d, J = 15.0 Hz, 1H), 4.08 (s, 1H), 2.90 − 2.75 (m, 1H), 1.26 (d, J = 6.9 Hz, 3H), 1.09 (s, 9H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 168.8, 164.1, 160.3, 136.4, 136.0, 130.66, 129.0, 128.7, 128.3, 128.0, 127.1, 65.8, 62.7, 48.7, 30.0, 28.3, 20.0, 16.9; HRMS (ESI-FIA-TOF) m/z: Calcd. for $C_{25}H_{31}N_3O_2$ $[M+Na]^+$: 428.2308, found: 428.2286.

*N,1-dibenzyl-6-oxo-3-phenyl-1,6-dihydropyrazine-2-carboxamide (**7a**).* yield 54%, 213.9 mg, white powder (EtOH, mp 188−190 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.20 (s, 1H), 7.60 − 7.46 (m, 2H), 7.43 − 7.30 (m, 3H), 7.26 (s, 5H), 7.23 − 7.00 (m, 3H), 6.74 − 6.33 (m, 2H), 5.70 (t, J = 5.4 Hz, 1H), 5.42 (s, 2H), 4.05 (d, J = 5.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.4, 154.6, 149.4, 135.8, 135.4, 132.6, 131.9, 129.7, 129.3, 128.7, 128.6, 128.6, 128.1, 128.0, 127.9, 127.8, 125.8, 47.2, 44.2; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{25}H_{21}N_3O_2$ $[M+H]^+$: 396.1707, found: 396.1692.

*N,1-dibenzyl-5-methyl-6-oxo-3-phenyl-1,6-dihydropyrazine-2-carboxamide (**7b**).* yield 63%, 257.8 mg, white powder (EtOH, mp 184 − 185 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.63 − 7.46 (m, 2H), 7.43 − 7.33 (m, 3H), 7.32 − 7.21 (m, 5H), 7.21 − 7.00 (m, 3H), 6.64 − 6.44 (m, 2H), 5.50 (s, 2H), 5.35 (t, J = 5.6 Hz, 1H), 4.05 (d, J = 5.4 Hz, 2H), 2.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.8, 158.9, 154.8, 136.3, 136.2, 135.5, 131.3, 130.3, 128.7, 128.6, 128.6, 128.4, 128.3, 128.2, 127.9, 127.7, 124.3, 47.5, 44.2, 21.5; HRMS (EI) m/z calcd. for $C_{26}H_{23}N_3O_2$ $[M]^+$: 409.1790, found: 409.1791.

*N,1,5-tribenzyl-6-oxo-3-phenyl-1,6-dihydropyrazine-2-carboxamide (**7c**).* yield 65%, 315.4 mg, white powder (EtOH, mp 166 − 167 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.42 − 7.33 (m, 2H), 7.31 − 7.23 (m, 2H), 7.23 − 6.81 (m, 14H), 6.44 − 6.24 (m, 2H), 5.29 (s, 2H), 5.14 (t, J = 5.4 Hz, 1H), 4.08 (s, 2H), 3.87 (d, J = 5.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.7, 159.6, 154.3, 137.0, 136.2, 136.1, 135.5, 131.2, 130.6, 129.7, 129.4, 128.6, 128.6, 128.40, 128.3, 128.1, 127.9, 127.7, 126.6, 125.2, 124.4, 47.6, 44.2, 40.5; HRMS (EI) m/z calcd. for $C_{32}H_{27}N_3O_2$ $[M]^+$: 485.2103, found: 485.2101.

*1-benzyl-N-(tert-butyl)-5-methyl-6-oxo-3-phenyl-1,6-dihydropyrazine-2-carboxamide (**7d**).* yield 58%, 217.6 mg, white powder (EtOH, mp 191 − 192 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.66 − 7.49 (m, 2H), 7.47 − 7.18 (m, 8H), 5.47 (s, 2H), 4.97 (s, 1H), 2.56 (s, 3H), 0.92 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.0, 158.6, 155.1, 136.8, 136.1, 131.6, 131.3, 128.8, 128.6, 128.4, 128.1, 128.0, 127.9, 52.6, 48.1, 27.9, 21.6; HRMS (EI) m/z calcd. for $C_{23}H_{25}N_3O_2$ $[M]^+$: 375.1947, found: 375.1949.

*1-benzyl-N-(tert-butyl)-5-isobutyl-6-oxo-3-phenyl-1,6-dihydropyrazine-2-carboxamide (**7e**).* yield 66%, 275.4 mg, white powder (EtOH, mp 144 − 145 °C); ^{1}H NMR (300 MHz, Chloroform-d) δ (ppm): 7.64 − 7.52 (m, 2H), 7.48 − 7.14 (m, 8H), 5.47 (s, 2H), 5.01 (s, 1H), 2.82 (dd, J = 7.0, 5.2 Hz, 2H), 2.32 (dt, J = 13.5, 6.8 Hz, 1H), 1.06 − 0.98 (m, 6H), 0.93 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.9, 160.6, 154.8, 136.6, 136.0, 131.2, 130.9, 128.8, 128.6, 128.5, 128.3, 127.8, 127.6, 52.4, 47.8, 42.6, 27.7, 26.7, 22.7; HRMS (EI) m/z calcd. for $C_{26}H_{31}N_3O_2$ $[M]^+$: 417.2416, found: 417.2415.

*1-benzyl-N-(tert-butyl)-5-(2-(methylthio)ethyl)-6-oxo-3-phenyl-1,6-dihydro-pyra-zine-2-carboxamide (**7f**).* yield 52%, 240.8 mg, white powder (EtOH, mp 120 − 121 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.65 − 7.54 (m, 2H), 7.47 − 7.16 (m, 8H), 5.47 (s, 2H), 5.02 (s, 1H), 3.24 (dd, J = 7.6, 6.7 Hz, 2H), 2.98 (dd, J = 7.8, 7.0 Hz, 2H), 2.18 (s, 3H), 0.93 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.8, 158.7, 154.5, 136.4, 135.8, 131.6, 130.9, 128.6, 128.5, 128.4, 128.3, 127.7, 127.6, 52.4, 47.9, 33.4, 30.6, 27.6, 15.3; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{25}H_{29}N_3O_2S$ $[M+H]^+$: 436.2053, found: 436.2057.

*N,5-dibenzyl-6-oxo-3-phenyl-1-propyl-1,6-dihydropyrazine-2-carboxamide (**7g**).* yield 74%, 315.5 mg, white powder (EtOH, mp 140 − 142 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.69 − 7.50 (m, 2H), 7.51 − 7.33 (m, 5H), 7.33 − 7.04 (m, 6H), 6.87 − 6.71 (m, 2H), 5.90 (t, J = 5.7 Hz, 1H), 4.28 (d, J = 5.5 Hz, 2H), 4.18 (s, 2H), 4.06 − 3.72 (m, 2H), 1.97 − 1.54 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.8, 159.1, 154.1, 137.1, 136.4, 135.9, 131.4, 130.8, 129.5, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 127.8, 126.5, 48.4, 44.4, 40.2, 22.2, 11.3; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{28}H_{27}N_3O_2$ $[M+H]^+$: 438.2176, found: 438.2176.

*N-cyclohexyl-6-oxo-3,5-diphenyl-1-propyl-1,6-dihydropyrazine-2-carboxamide (**7h**).* yield 57%, 237.2 mg, white powder (EtOH, mp 230 − 232 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.31 − 8.13 (m, 2H), 7.55 − 7.38 (m, 2H), 7.34 − 7.13 (m, 6H), 5.41 (d, J = 8.4 Hz, 1H), 3.97 − 3.77 (m, 2H), 3.73 − 3.47 (m, 1H), 1.83 − 1.57 (m, 2H), 1.55 − 0.95 (m, 8H), 0.83 (t, J = 7.4 Hz, 3H), 0.76 − 0.54 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.9, 153.8, 151.9, 136.5, 135.7, 132.2, 130.1, 129.3, 128.4, 128.3, 128.3, 128.0, 124.5, 48.9, 48.6, 31.9, 25.1, 24.4, 22.2, 11.4; HRMS (EI) m/z calcd. for $C_{26}H_{29}N_3O_2$ $[M]^+$: 416.2333, found: 416. 2336.

*N-benzyl-1-methyl-6-oxo-3,5-diphenyl-1,6-dihydropyrazine-2-carboxamide (**7i**).* yield 56%, 221.3 mg, white powder (EtOH, mp 223 − 224 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.34 (dt, J = 7.1, 2.2 Hz, 2H), 7.61 (qd, J = 4.7, 4.2, 2.7 Hz, 2H), 7.38 (dqd, J = 6.5, 4.3, 1.7 Hz, 6H), 7.29 − 7.11 (m, 3H), 6.86 (dq, J = 6.8, 4.2, 3.6 Hz, 2H), 6.19 (t, J = 5.7 Hz, 1H), 4.32 (d, J = 5.6 Hz, 2H), 3.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.8, 154.1, 151.9, 136.3, 136.0, 135.5, 131.7, 131.1, 130.3, 129.2, 128.7, 128.6, 128.4, 128.1, 128.0,

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127.8, 127.8, 44.2, 33.3; HRMS (EI) m/z calcd. for $C_{25}H_{21}N_3O_2$ $[M]^+$: 395.1634, found: 395.1638.

*Benzyl 3-(4-benzyl-5-(tert-butylcarbamoyl)-3-oxo-6-phenyl-3,4-dihydro-pyrazin-2-yl)propanoate (**7j**).* yield 48%, 251.6 mg, pale yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.64 − 7.48 (m, 2H), 7.45 − 7.15 (m, 13H), 5.46 (s, 2H), 5.12 (s, 2H), 5.03 (s, 1H), 3.29 (t, J = 6.8 Hz, 2H), 2.89 (t, J = 6.8 Hz, 2H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 172.9, 160.9, 158.3, 154.4, 136.4, 136.0, 135.8, 131.4, 130.7, 128.6, 128.5, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 66.2, 52.4, 47.9, 30.0, 28.4, 27.7; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{32}H_{33}N_3O_4$ $[M+H]^+$: 524.2544, found: 524.2540.

*N-(tert-butyl)-1-(3-morpholinopropyl)-6-oxo-3-phenyl-1,6-dihydropyrazine-2-carboxamide (**7k**).* yield 41%, 163.7 mg, white powder (EtOH, mp 178 − 179 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.20 (s, 1H), 7.61 − 7.50 (m, 2H), 7.50 − 7.28 (m, 3H), 6.37 (s, 1H), 4.16 (d, J = 6.8 Hz, 2H), 3.67 − 3.29 (m, 2H), 3.18 (t, J = 7.6 Hz, 2H), 2.89 (s, 4H), 2.36 (t, J = 7.4 Hz, 2H), 1.51 − 1.22 (m, 2H), 1.13 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.6, 154.9, 148.3, 135.9, 133.1, 132.7, 128.6, 128.5, 128.5, 63.7, 54.8, 52.8, 51.8, 42.9, 27.7, 23.3; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{22}H_{30}N_4O_3$ $[M+H]^+$: 399.2391, found: 399.2386.

*N-(tert-butyl)-1-(3-(dimethylamino)propyl)-6-oxo-3-phenyl-1,6-dihydro-pyrazine-2-carboxamide (**7l**).* yield 42%, 149.8 mg, white powder (EtOH, mp 149 − 151 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.21 (s, 1H), 7.67 − 7.50 (m, 2H), 7.50 − 7.29 (m, 3H), 5.73 (s, 1H), 4.16 − 3.97 (m, 2H), 2.45 (t, J = 6.9 Hz, 2H), 2.27 (s, 6H), 2.15 − 1.92 (m, 2H), 1.17 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.6, 154.7, 148.5, 136.0, 133.6, 131.8, 128.5, 128.4, 128.3, 56.8, 52.7, 45.2, 45.0, 27.9, 26.2; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{20}H_{28}N_4O_2$ $[M+H]^+$: 357.2285, found: 357.2280.

*N-benzyl-1-(4-methoxyphenyl)-6-oxo-3,5-diphenyl-1,6-dihydro-pyrazine-2-carbo-xamide (**7m**).* yield 43%, 302.7 mg, white powder (EtOH, mp 214 − 216 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.51 − 8.35 (m, 2H), 7.80 − 7.65 (m, 2H), 7.52 − 7.29 (m, 6H), 7.23 − 7.04 (m, 5H), 6.98 − 6.82 (m, 2H), 6.72 − 6.60 (m, 2H), 6.21 (t, J = 5.8 Hz, 1H), 4.01 (d, J = 5.7 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.0, 160.0, 154.1, 152.9, 136.3, 135.4, 132.0, 130.4, 129.3, 129.0, 128.9, 128.7, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.6, 127.5, 114.5, 55.4, 43.7; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{31}H_{25}N_3O_3$ $[M+H]^+$: 488.1969, found: 488.1978.

*1-benzyl-N-cyclohexyl-5-(4-methoxybenzyl)-3-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrazine-2-carboxamide (**7n**).* yield 62%, 231.4 mg, white powder (EtOH, mp 137 − 139 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.33 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 6.3 Hz, 5H), 6.80 − 6.61 (m, 4H), 5.26 (s, 2H), 4.87 (d, J = 8.1 Hz, 1H), 4.00 (s, 2H), 3.64 (s, 3H), 3.61 (s, 3H), 3.42 − 3.27 (m, 1H), 1.35 − 0.63 (m, 8H), 0.52 − 0.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.1, 159.8, 159.5, 158.3, 154.3, 136.1, 130.8, 130.5, 130.4, 129.6, 129.2, 128.8, 128.5, 128.0, 127.7, 113.9, 113.8, 55.4, 55.2, 48.6, 47.6, 39.5, 31.4, 25.1, 24.1; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{33}H_{35}N_3O_4$ $[M+H]^+$: 538.2700, found: 538.2695.

*N-(tert-butyl)-6-oxo-3-phenyl-1,6-dihydropyrazine-2-carboxamide (**8a**).* yield 56%, 152.4 mg, white powder (EtOH, mp 246 − 247 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 10.19 (s, 1H), 8.15 (s, 1H), 7.61 − 7.19 (m, 5H), 5.43 (s, 1H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.0, 154.6, 151.3, 135.6, 133.4, 129.8, 129.7, 129.3, 126.9, 52.3, 27.9; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{15}H_{17}N_3O_2$ $[M+H]^+$: 272.1394, found: 272.1385.

*5-benzyl-N-cyclohexyl-6-oxo-3-phenyl-1,6-dihydropyrazine-2-carboxamide (**8b**).* yield 74%, 278.8 mg, white powder (EtOH, mp 215 − 216 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 9.99 (s, 1H), 7.59 − 7.38 (m, 7H), 7.36 − 7.14 (m, 3H), 5.58 (d, J = 7.7 Hz, 1H), 4.21 (s, 2H), 3.82 − 3.65 (m, 1H), 1.73 − 1.56 (m, 1H), 1.56 − 1.13 (m, 6H), 1.12 − 0.96 (m, 1H), 0.94 − 0.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.9, 159.2, 154.0, 136.6, 136.0, 132.8, 129.7, 129.6, 129.5, 129.3, 128.4, 126.6, 124.9, 48.8, 39.5, 31.9, 25.1, 23.9; HRMS (EI) m/z calcd. for $C_{24}H_{25}N_3O_2$ $[M]^+$: 387.1947, found: 387.1944.

*N-cyclohexyl-5-methyl-6-oxo-3-phenyl-1,6-dihydropyrazine-2-carboxamide (**8c**).* yield 68%, 230.8 mg, white powder (EtOH, mp 244 − 245 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 10.02 (s, 1H), 7.68 − 7.32 (m, 5H), 5.59 (d, J = 7.8 Hz, 1H), 3.97 − 3.56 (m, 1H), 2.55 (s, 3H), 1.79 − 0.90 (m, 8H), 0.77 (dtd, J = 13.6, 10.1, 3.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.4, 159.2, 154.5, 136.0, 132.7, 129.8, 129.6, 129.4, 124.5, 48.8, 31.9, 25.1, 23.9, 20.6; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{18}H_{21}N_3O_2$ $[M+H]^+$: 312.1707, found: 312.1710.

General procedure for the one-pot synthesis of pyrazin-2(1*H*)-ones 11. A mixture of the glyoxal derivative (1.0 mmol), the amine (1.0 mmol), the isocyanide and the protected aminoacid (1.0 mmol) in MeOH (3 mL) was submitted to orbital stirring at room temperature for 48 h. After completion of the reaction, CH_2Cl_2 (3 mL) and PS-*p*-TsOH (2.0 mmol) were added. The reaction mixture was submitted to orbital stirring at room temperature until complete consumption of the unreacted isocyanide (30−60 min). The polystyrene-supported reagent was filtered off and successively washed [3 times (5 mL)] with MeOH, AcOEt and CH_2Cl_2. Evaporation of the solvents from the filtrate afforded a residue, which was treated with HCl (2N) in ether and stirred at room temperature for 2h. The solution was then treated with saturated $NaHCO_3$. After extraction with ethyl acetate, the organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to afford an oily residue that was purified by chromatographic methods on silica gel using hexane/AcOEt mixtures.

*N-(tert-butyl)-3-(4-methoxyphenyl)-1,5,5-trimethyl-6-oxo-1,4,5,6-tetrahy-dropyrazine-2-carboxamide (**11a**).* yield 56%, 206.2 mg, white powder (EtOH, mp 118 − 120 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.35 − 7.28 (m, 2H), 7.26 (s, 1H), 6.92 − 6.83 (m, 2H), 5.11 (s, 1H), 3.81 (s, 3H), 3.21 (s, 3H), 1.68 (s, 6H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.5, 162.1, 159.8, 129.8, 128.2, 123.6, 113.5, 59.3, 55.4, 51.9, 31.1, 28.1, 27.5, 23.3; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{19}H_{27}N_3O_3$ $[M+Na]^+$: 368.1945, found: 368.1948.

*N,1-dibenzyl-3-cyclopropyl-5,5-dimethyl-6-oxo-1,4,5,6-tetrahy-dropyrazine-2-carboxamide (**11b**).* yield 58%, 218.6 mg, white powder (EtOH mp 84 − 85 °C), Yield: 56%. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.36 − 7.04 (m, 11H), 5.81 (d, J = 5.8 Hz, 1H), 4.86 (s, 2H), 4.38 (d, J = 5.8 Hz, 2H), 1.72 (td, J = 6.6, 6.0, 2.7 Hz, 1H), 1.62 − 1.53 (m, 1H), 1.47 (s, 7H), 0.63 − 0.57 (m, 1H), 0.57 − 0.51 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 169.9, 162.7, 155.7, 137.3, 137.0, 130.2, 128.8, 128.7, 128.5, 128.3, 128.1, 127.8, 127.8, 127.5, 127.1, 127.1, 59.1, 46.5, 44.0, 28.2, 28.1, 23.6, 13.0, 6.7. HRMS (ESI) m/z calcd. for $C_{24}H_{27}N_3O_2$ $[M+H]^+$: 390.2176, found: 390.2178.

General procedure for the one-pot synthesis of pyrazin-2(1*H*)-ones 13. A mixture of the glyoxal derivative (1.0 mmol), the amine (1.0 mmol), the isocyanide and the protected aminoacid (1.0 mmol) in MeOH (3 mL) was submitted to orbital stirring at room temperature for 48 h. After completion of the reaction, CH_2Cl_2 (3 mL) and PS-*p*-TsOH (2.0 mmol) were added. The reaction mixture was submitted to orbital stirring at room temperature until complete consumption of the unreacted isocyanide (30−60 min). The polystyrene-supported reagent was filtered off and successively washed [3 times (5 mL)] with MeOH, AcOEt and CH_2Cl_2. Evaporation of the solvents from the filtrate afforded a residue, which was treated with 30% TFA in DCE (10 mL) and heated to 80 °C for 1h. The solution was then treated with saturated $NaHCO_3$. After extraction with ethyl acetate, the organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to afford an oily residue that was purified by chromatographic methods on silica gel using hexane/AcOEt mixtures.

*N-benzyl-4-methyl-5,6-dioxo-3-phenyl-1-propyl-1,4,5,6-tetrahy-dropyrazine-2-carboxamide (**13a**).* yield 74%, 279.8 mg, white powder (EtOH mp 128 − 129 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.60 − 7.30 (m, 6H), 7.22 − 7.07 (m, 4H), 6.95 − 6.80 (m, 1H), 4.26 − 4.11 (m, 2H), 3.78 − 3.53 (m, 2H), 3.04 (s, 3H), 1.94 − 1.56 (m, 2H), 0.98 − 0.75 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.1, 155.7, 154.4, 136.9, 130.7, 130.5, 129.8, 129.0, 128.5, 127.8, 127.3, 123.8, 120.4, 48.2, 43.8, 33.6, 21.8, 11.2; HRMS (CI) m/z calcd. for $C_{22}H_{23}N_3O_3$ $[M+H]^+$: 378.1812, found: 378.1816.

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*N-(tert-butyl)-4-methyl-5,6-dioxo-3-phenyl-1-propyl-1,4,5,6-tetrahydropyra-zine-2-carboxamide (**13b**).* yield 67%, 230.6 mg, white powder (EtOH mp 241 − 243 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.49 (s, 5H), 5.83 (s, 1H), 3.94 − 3.69 (m, 2H), 3.11 (s, 3H), 1.92 − 1.67 (m, 2H), 1.01 (s, 9H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.1, 155.4, 154.3, 130.9, 130.8, 129.7, 128.8, 123.6, 121.2, 51.8, 48.6, 33.6, 27.6, 21.7, 11.3; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{19}H_{25}N_3O_3$ $[M+H]^+$: 344.1969, found: 344.1970.

*N-benzyl-4-ethyl-5,6-dioxo-3-phenyl-1-propyl-1,4,5,6-tetrahydro-pyrazine-2-carboxamide (**13c**).* yield 64%, 250.8 mg, white powder (EtOH mp 198 − 199 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.51 − 7.35 (m, 5H), 7.24 − 7.14 (m, 3H), 6.92 − 6.67 (m, 2H), 6.07 (t, J = 6.0 Hz, 1H), 4.12 (d, J = 4.3 Hz, 2H), 3.88 − 3.68 (m, 2H), 3.63 (q, J = 7.0 Hz, 2H), 1.89 − 1.64 (m, 2H), 1.03 (t, J = 7.0 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.2, 155.1, 154.7, 137.0, 130.8, 130.2, 129.8, 128.8, 128.4, 127.9, 127.3, 123.2, 120.7, 48.2, 43.8, 40.9, 21.8, 13.2, 11.2; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{23}H_{25}N_3O_3$ $[M+H]^+$: 392.1969, found: 392.1971.

*N-(tert-butyl)-4-ethyl-5,6-dioxo-3-phenyl-1-propyl-1,4,5,6-tetra-hydropyra-zine-2-carboxamide (**13d**).* yield 70%, 250.7 mg, colorless crystals (EtOH mp 267 − 269 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.49 (s, 3H), 7.26 (s, 2H), 5.67 (s, 1H), 3.90 − 3.75 (m, 2H), 3.67 (q, J = 7.1 Hz, 2H), 1.90 − 1.70 (m, 2H), 1.13 − 0.86 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 160.4, 155.1, 154.2, 131.4, 130.9, 129.9, 128.9, 123.1, 121.0, 52.1, 48.7, 41.2, 27.9, 22.0, 13.5, 11.6; HRMS (ESI-FIA-TOF) m/z calcd. for $C_{20}H_{28}N_3O_3$ $[M]^+$: 358.2125, found: 358.2121.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all compounds and crystallographic information files (CIF) of compound **13d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) The Supporting Information contains the crystallographic information files (CIF) of compound **13d**. Additional information can be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC 906542).