Synthesis and Characterization of Novel Methyl (3)5-(N-Boc-piperidinyl)-1H-pyrazole-4-carboxylates

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Abstract: Series of methyl 3- and 5-(N-Boc-piperidinyl)-1H-pyrazole-4-carboxylates were developed and regioselectively synthesized as novel heterocyclic amino acids in their N-Boc protected ester form for achiral and chiral building blocks. In the first stage of the synthesis, piperidine-4-carboxylic and (R)- and (S)-piperidine-3-carboxylic acids were converted to the corresponding β-keto esters, which were then treated with N,N-dimethylformamide dimethyl acetal. The subsequent reaction of β-enamine diketones with various N-mono-substituted hydrazines afforded the target 5-(N-Boc-piperidinyl)-1H-pyrazole-4-carboxylates as major products, and tautomeric NH-pyrazoles prepared from hydrazine hydrate were further N-alkylated with alkyl halides to give 3-(N-Boc-piperidinyl)-1H-pyrazole-4-carboxylates. The structures of the novel heterocyclic compounds were confirmed by 1H-, 13C-, and 15N-NMR spectroscopy and HRMS investigation.

Keywords: heterocyclic amino acids; pyrazoles; piperidines; β-keto esters; enamines; hydrazines; building blocks

1. Introduction

Heterocyclic amino acids are becoming very important in modern drug discovery [1–5]. For instance, (R)-piperidine-3-carboxylic acid (DL-nipeptic acid) is one of the most potent inhibitors of neuronal and glial γ-aminobutyric acid (GABA) uptake in vitro [6]. (S)-Pyrrolidinyl-2-carboxylic acid (L-proline) has been found to act as an agonist of the glycine receptor and of both the N-methyl-D-aspartate (NMDA) and non-NMDA ionotropic glutamate receptors [7].

Heterocyclic amino acids are also important scaffolds and building blocks for the preparation of heterocyclic systems, hybrids, and peptides [8–11]. For example, L-proline has been used as a scaffold in the preparation of pyrrolizidine [12–14], pyrrolo[1,2-c][1,3]oxazole [15], pyrrolo[2,1-c][1,4]benzodiazepine [16], and benzof[b]pyrrolo[1,2-a][1,4]diazepine derivatives [17], while nipectic and isonipecotic acids have given derivatives of heterospirocyclic 3-amino-2H-azirines [18,19]. Moreover, L-proline is a building block for N-(3-mercapto-2-d-methylpropanoyl)-L-proline, named captopril, which is used to regulate blood pressure [20]. D-Nipectic acid, a building block for (R)-1-[4,4-bis-(3-methyl-2-thienyl)-3-butenyl]-3-piperidine carboxylic acid, named (R)-tiagabine, which amplifies neurotransmission of GABA, the predominant inhibitory neurotransmitter in the brain [21–23]. New derivatives of nipectic acid, guvacin, and homo-β-proline are very potent and selective analogs of GABA uptake inhibitors [24–26].

The heterocyclic tripeptide Gly-Pro-Glu I, containing an L-proline residue, is a neuroprotective compound for the control of neurodegenerative processes such as Parkinson’s
disease [27,28], while a proline peptidomimetic, faldaprevir II, was used as an experimental drug to treat hepatitis (Figure 1) [29–31]. The synthetically prepared derivative of the tripeptide (pyro)Glu-His-Pro(NH$_2$) III has specific activity as a hypothalamic gland thyrotropin-releasing hormone [32]. Many aromatic heterocyclic amino acids, such as [5-amino-4-(tert-butoxycarbonyl)thiophen-2-yl]acetic acid, provide synthetic peptides, including enantiopure cyclic tetraamide IV [33], which are similar to compounds in marine plants that exhibit resistance to infection or antitumor effects [34].

![Figure 1. Examples of biologically active peptides derived from heterocyclic amino acids: Gly-Pro-Glu I, faldaprevir II, (pyro)Glu-His-Pro(NH$_2$) III, cyclic tetraamide IV, and VPC00628 V.](image)

Heterocyclic amino acids have been applied widely as building blocks for the preparation of DNA-encoded chemical libraries, including heterocyclic hybrid and peptide compounds [35–39]. In general, a DNA-encoded library of target component molecules should have a high degree of structural and functional diversity, taking into account diversity-oriented synthesis (DOS) [40]. For example, a highly specific and potent p38α kinase tripeptide-type inhibitor (VPC00628) V containing the residue of 3-amino-1-phenyl-1H-pyrazole-4-carboxylic acid has been identified directly from a multimillion-membered DNA-encoded molecule library that was prepared using high-fidelity yoctoReactor (yR) technology [41].

We recently reported an efficient protocol for synthesizing highly functionalized amino acid building blocks by combining pyrazole, indazole, and indole carboxylates with N-Boc-3-iodoazetidine [42]. Moreover, we synthesized 4-(N-Boc-cycloaminyl)-1,3-thiazole- and 4-(N-Boc-cycloaminyl)-1,3-selenazole-5-carboxylates as novel heterocyclic chiral amino acid-like derivatives [43,44]. Herein, we report the efficient synthesis of 3(5)-(N-Boc-piperidiny1)-1H-pyrazole-4-carboxylic acids as heterocyclic amino acid-like derivatives for novel achiral and chiral building blocks from piperidine-4-carboxylic and (R)- and (S)-piperidine-3-carboxylic acids.

2. Results and Discussion

Numerous methods for forming pyrazole ring systems have been developed. The most common synthetic method for the production of pyrazoles is the condensation of the corresponding hydrazine derivative, which acts as a double nitrogen nucleophile, with three carbon units containing compounds such as 1,3-dicarbonyl and 2,3-unsaturated carbonyl, or enamine [45–47]. Rosa et al. [48] developed a simple and efficient method for preparing both regioisomers of 4,5-substituted N-phenylpyrazoles from β-enamino diketones and phenylhydrazine, and the regiochemistry of the reaction was protic or aprotic solvent depen-
dent. A patent [49] was obtained for the synthesis of 4-(piperidin-4-yl)-N-phenylpyrazole derivatives from β-enamino diketones with 4-fluoro- and 4-methoxyphenylhydrazines.

Our strategy for the synthesis of methyl 3(5)-(N-Boc-piperidinyl)-1H-pyrazole-4-carboxylates according to the enamine method is described in Schemes 1 and 2, and Figure 2. The synthetic sequence started with preparing β-keto esters 2a–c by treating N-Boc protected piperidine acids 1a–c with 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum’s acid) in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) and 4-dimethylaminopyridine (DMAP), and further methanolysis of Meldrum’s acid adduct [50,51]. Compounds 2a–c were treated with N,N-dimethylformamide dimethyl acetal (DMF·DMA) to obtain β-enamino diketones 3a–c [49].

Scheme 1. Synthesis of starting β-enamino diketones 3a–c.

In the next step, we investigated the formation of 3(5)-substituted-1H-pyrazoles 5 and 6 via the key intermediates 4 and 4′ (Scheme 2). Optimization of the coupling reaction conditions was undertaken, choosing 3a and phenylhydrazine as a model system (Table 1). An investigation of the reaction course and regioselectivity was carried out in various solvents, and the LC/MS and 1H-NMR spectral data of the crude reaction mixture of intermediate compound 4a and products 5a, 6a were analyzed after 1 and 18 h (Table 1). EtOH was used as a polar protic (Table 1, entry 1), ACN as a polar aprotic (Table 1, entry 2), and CCl₄ as a nonpolar solvent (Table 1, entry 3). As a result, the reaction in EtOH provided high regioselectivity (99.5%) and good yield (78%) of 5a and just traces of its regioisomer 6a (Table 1, entry 1). Similarly, the reaction in ACN resulted in 5a as the main product (75%), and 6a was obtained with a 3% yield (Table 1, entry 2). The poorest yield and regioselectivity
were observed when the reaction mixture was stirred in CCl$_4$. In this case, 5a formed as a major product with 54% yield, and regioisomer 6a was obtained with 9% yield (Table 1, entry 3). During optimization of the reaction conditions in different solvents, $^1$H-NMR analysis of the crude reaction mixture after 1 h also showed the formation of intermediate compound 4a, which was successfully isolated for structure elucidation. The regioisomer 6a formed as a minor isomer via intermediate 4′a which resulted from the nucleophilic attack of a secondary amino group of phenylhydrazine on β-enamino diketone 3a.

![Figure 2. Synthesized compounds 5a-o.](image)

**Table 1.** Solvent effect on the formation of compounds 4a, 5a, and 6a.

| Entry | Solvent * | t (h) | 4a/5a/6a ** | t (h) | 4a/5a/6a ** | 5a, Yield (%) *** |
|-------|-----------|-------|-------------|-------|-------------|------------------|
| 1     | EtOH      | 1     | 52.4/46.8/0.8 | 18 | 0/99.5/0.5 | 78 |
| 2     | ACN       | 1     | 27.6/68.2/4.2 | 18 | 0/95.2/4.8 | 75 |
| 3     | CCl$_4$   | 1     | 58.3/27.5/14.2 | 18 | 18.3/67.9/13.8 | 54 |

* All reaction mixtures were stirred at room temperature. ** Ratio was determined by $^1$H-NMR spectral data from crude sample. *** After purification by column chromatography.

In the case of intermediate compound 4a, the key information for structure elucidation was obtained from the $^{15}$N-NMR data. In the $^1$H-$^{15}$N HMBC spectrum of 4a, the $^{15}$N shift of δ −241.2 ppm was assigned to nitrogen N$_a$, due to the correlation with the neighboring protons 2′(6′)-H (δ 6.81 ppm) from the phenyl moiety (Figure 3). The $^1$H-$^{15}$N HSQC experiment indicated that proton N$_a$-H (δ 6.24 ppm) had one-bond connectivity with the aforementioned nitrogen N$_a$ at δ −241.2 ppm, while proton N$_b$-H (δ 11.72 ppm) generated a cross peak with nitrogen N$_b$ at δ −275.1 ppm. The formation of compound 4a was also confirmed by a NOESY experiment, which exhibited NOEs between the 2′(6′)-H protons at δ 6.81 ppm and the enamine proton at δ 8.28 ppm. However, the configuration of the (2E or 2Z)-isomer of compound 4a is not yet known.

Discrimination between regioisomeric compounds 5a and 6a was based on data from $^1$H-$^{13}$C HMBC, $^1$H-$^{15}$N HMBC, and $^1$H-$^1$H NOESY experiments (Figure 3). The $^1$H-$^{15}$N HMBC experiment of the major regioisomer 5a revealed three-bond correlations between the piperidine 4′-H proton at δ 3.10 ppm and the phenyl group 2′(6′)-H protons.
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at δ 7.34 ppm, with the pyrazole N-1 “pyrrole-like” nitrogen at δ –160.3 ppm [52,53]. The 1H-1H NOESY spectrum of 5a exhibited NOEs between the phenyl group 2′(6′)-H protons and the 4′-H proton from the piperidine moiety.

The second regioisomer 6a was easily identified by utilizing a similar approach. The minor regioisomer 6a exhibited a strong three-bond connectivity between the piperidine proton 4′-H (δ 3.43 ppm) and the pyrazole N-2 “pyridine-like” nitrogen at δ –81.5 ppm, while the phenyl group protons 2′(6′)-H (δ 7.68 ppm) showed three-bond connectivity with the pyrazole N-1 “pyrrole-like” nitrogen at δ –165.7 ppm. Moreover, the pyrazole 5-H proton in the 1H-13C HMBC spectrum showed a three-bond connectivity with the phenyl group C-1′′ carbon at δ 139.3 ppm. Finally, confirmation of these regiochemical assignments was obtained from the 1H-1H NOESY 6a spectrum, showing only the NOEs between the phenyl group 2′(6′)-H protons and the pyrazole 5-H proton (δ 8.34 ppm).

The optimal conditions for the regioselective synthesis of methyl 5-(N-Boc-piperidinyl)-1H-pyrazole-4-carboxylate 5a were applied to the synthesis of other pyrazoles to evaluate the scope of the methodology (Figure 2). β-Enamino diketone 3a was coupled with different phenylhydrazines to give corresponding products 5b–h with fair to good yields. No obvious effect of the phenylhydrazine substituent on the reaction yield was observed. A reaction of β-enameino diketone 3a with methylhydrazine provided a corresponding tert-butyl 4-[4-(methoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]piperidine-1-carboxylate 5i with a 51% yield. To our delight, the reactions of chiral β-enameino diketones 3b, c with phenyl-, (4-methylphenyl)- or [3-(trifluoromethyl)phenyl]hydrazines formed products 5j–o, also with good yields. While analyzing the LC/MS and 1H-NMR spectral data of crude cyclization reaction mixtures, the formation of the regioisomeric 6b–o was observed at trace amounts. The structure of compounds 5b–o was determined by analogous NMR spectroscopy experiments as described above.

Next, having β-enameino diketone 3a, we also performed a cyclocondensation reaction with hydrazine hydrate under the conditions described above, and the formation of...
tautomeric 3(5)-substituted NH-pyrazole 7 was established by NMR analysis (Scheme 3, Figure 4).

Scheme 3. Two tautomers, 7a and 7b, of 3(5)-substituted NH-pyrazole (7) and regioisomers 5i, 6i, and compound 8.

Figure 4. Relevant $^1$H-$^1$C HMBC, $^1$H-$^1$5N HMBC, and $^1$H-$^1$H NOESY correlations and $^1$H-NMR (italics), $^{13}$C-NMR, and $^{15}$N-NMR (bold) chemical shifts of compound 7 (tautomeric equilibrium of 7a and 7b) and regioisomers 5i, 6i in CDCl$_3$ (25 °C).

The prototropic tautomerism of NH-pyrazoles is well documented in many scientific studies, including with the use of multinuclear dynamic NMR spectroscopy [54–56]. In general, the annular tautomerism of 3(5)-1H-pyrazoles in solution under normal conditions is a very rapid process on the NMR time scale, and the determination of tautomeric ratios can usually be achieved only at low temperatures [57]. We carried out NMR studies of compound 7 at 25 °C in a diluted CDCl$_3$ solution (Figure 4). The $^1$H-NMR spectrum of compound 7 revealed a narrow singlet of the pyrazole ring proton resonating at $\delta$ 7.96 [3(5)-H] and two singlets for methyl ester and Boc moiety protons in the area of $\delta$ 3.83 (OCH$_3$) and 1.47 [C(CH$_3$)$_3$] ppm, respectively. The $^{13}$C-NMR spectrum provided important information; as expected, the characteristic signal of the pyrazole C-4 carbon at $\delta$ 110.1 ppm remained sharp, while the other two signals of pyrazole ring carbons 3(5)-C resonated at $\delta$ 138.7 and 153.6 ppm and appeared broadened. It is known that the broadening of NMR spectral lines very often reflects dynamic structural transformations of molecules in solution [58]. Therefore, the observed broadness of relevant C-3 and C-5 pyrazole carbon signals is due to the coalescence of individual signals to average signals, indicating tautomeric equilibrium of 7 (7a and 7b). In addition, the pyrazole NH proton ($\delta$ 11.52 ppm) exhibited NOEs not only with the pyrazole ring proton at 7.96 ppm but also with the 3$'$-H piperidine protons at 1.70 ppm, which is only possible in the case of annular tautomerism 7.
It was not possible to obtain relevant information for the nitrogen atoms of the pyrazole ring N-1 and N-2 from the $^{15}$N-NMR spectral data since $^1$H,$^{15}$N HSQC and HMBC experiments showed no direct or long-range correlations with appropriate protons.

Tautomeric compound 7 was alkylated with alkyl iodides (Scheme 3). It is known that N-alkylation of asymmetrically ring-substituted 1H-pyrazoles generally results in the formation of a mixture of regioisomeric N-substituted products [59]. Treatment of compound 7 with methyl iodide in the presence of KOH in DMF gave an inseparable mixture of regioisomers 5i and 6i in a ratio of about 1:5 and a total yield of 74%. However, alkylation of 1H-pyrazole-4-carboxylate 7 with ethyl iodide under analogous conditions afforded compound 8 as the sole product with a good 87% yield.

Discrimination of regioisomeric compounds 5i and 6i were based on $^1$H-$^{13}$C HMBC, $^1$H-$^{15}$N HMBC, and $^1$H-$^1$H NOESY spectral data (Figure 4). In the $^1$H-$^{15}$N HMBC spectra of minor regioisomer 5i, a $^{15}$N shift of $\delta -178.3$ ppm was assigned to the “pyrrole-like” nitrogen N-1 due to the correlation of this signal with a piperidine ring proton 4$^\prime$-H ($\delta 3.54$ ppm). The $^1$H-$^{13}$C HMBC experiment exhibited a three-bond correlation of the 1-CH$_3$ protons with a pyrazole quaternary carbon C-5 at $\delta 148.7$ ppm. Moreover, the $^1$H-$^1$H NOESY spectrum of 5i exhibited NOEs between the methyl group protons (1-CH$_3$) at 3.92 ppm and the piperidine proton 4$^\prime$-H at $\delta 3.54$ ppm. In the $^1$H-$^{15}$N HMBC spectra of the major regioisomer 6i, an appropriate correlation between the piperidine ring proton 4$^\prime$-H ($\delta 3.36$ ppm) and the “pyridine-like” pyrazole N-2 nitrogen which resonated at $\delta -77.3$ ppm could be observed. The $^1$H-$^{13}$C HMBC spectral data of compound 6i provided a strong three-bond correlation of 1-CH$_3$ protons with pyrazole protonated carbon C-5 at $\delta 134.6$ ppm. Finally, the regiochemistry of compound 6i was confirmed by a NOESY experiment, which exhibited NOEs between the 1-CH$_3$ protons and pyrazole proton 5-H ($\delta 7.78$ ppm). The structure of compound 8 was determined by analogous NMR spectroscopy experiments as described above.

After the successful synthesis of 3(5)-(N-Boc-piperidinyl)-1H-pyrazole-4-carboxylates, we further prepared several pyrazole carboxylic acids (Scheme 4). In particular, achiral pyrazole-4-carboxylic acid 9a was prepared from the corresponding ester 5a under the basic conditions (2N NaOH, methanol, reflux). The same hydrolysis conditions were applied to the production of chiral pyrazole-4-carboxylic acids (R)-9b and (S)-9c from esters 5j and 5k, respectively.

Pyrazole carboxylic acid amides, including anilides, have been known to play an important role in agrochemical research as fungicides [60,61]. Pyrazole-4-carboxylic acids 9a–c were used to obtain new anilide compounds (Scheme 4). First, 9a reacted with aniline in the presence of EDC·HCl, DMAP, and dichloromethane to give pyrazole anilide 10a. Moreover, chiral pyrazole anilide (R)-10b (100% ee) was obtained from carboxylic acid 9b, while the corresponding chiral anilide (S)-10c (96% ee) was synthesized from carboxylic acid 9c. The enantiomeric purity of prepared anilides 10b,c was evaluated by chiral HPLC analysis. As an example, HPLC analysis of enantiomeric samples of anilides 10b,c is shown in Figure 5.

**Figure 5.** Chiral HPLC analysis of (a) anilide 10b and (b) anilide 10c. Conditions: CHIRAL ART Amylose-SA (100 × 4.6 mm I.D.; S-3 µm; chiral selector amylose tris(3,5-dimethylphenylcarbamate); YMC); mobile phase: ACN/(H$_2$O + 0.1% HCOOH (30:70→70:30 in 10 min); T = 36 °C; flow rate 1.0 mL/min.
3. Materials and Methods

3.1. General Information

All starting materials were purchased from commercial suppliers and were used as received. Flash column chromatography was performed on Silica Gel 60 Å (230–400 µm, Merck KGaA, Darmstadt, Germany). Thin-layer chromatography was carried out on Silica Gel plates (Merck Kieselgel 60 F254) and visualized by UV light (254 nm). Melting points were determined on a Büchi M-565 melting point apparatus and were uncorrected. The IR spectra were recorded on a Bruker Vertex 70v FT-IR spectrometer (Bruker Optik GmbH, Ettlingen, Germany) using neat samples and are reported in the frequency of absorption (cm⁻¹). Mass spectra were obtained on a Shimadzu LCMS-2020 (ESI⁺) spectrometer (Shimadzu Corporation, Kyoto, Japan). High-resolution mass spectra were measured on Bruker MicrOTOF-Q III (ESI⁺) apparatus (Bruker Daltonik GmbH, Bremen, Germany). Optical rotation data were recorded on a UniPol L SCHMIDT+HAENSCH polarimeter (concentration of compound (g/100 mL) was included in calculations automatically (Windaus-Labortechnik GmbH & Co. KG, Clausthal-Zellerfeld, Germany). HPLC analysis was carried out on Shimadzu LC-2030C apparatus with CHIRAL ART Amylose-SA (100 x 4.6 mm I.D.; S-3 µm; chiral selector amylose tris(3,5-dimethylphenylcarbamate); YMC, Shimadzu USA Manufacturing, Inc., Canby, OR, USA). The ¹H, ¹³C-, and ¹⁵N-NMR spectra were recorded in CDCl₃ solutions at 25 °C on a Bruker Avance III 700 (700 MHz for ¹H, 176 MHz for ¹³C, 71 MHz for ¹⁵N, Bruker BioSpin AG, Fallanden, Switzerland) spectrometer equipped with a 5 mm TCI ¹H,¹³C/¹⁵N/D z-gradient cryoprobe, and a Bruker Avance III 400 (400 MHz for ¹H, 101 MHz for ¹³C, 40 MHz for ¹⁵N, (Bruker BioSpin AG)
spectrometer using a 5 mm directly detecting BBO probe. The chemical shifts (δ) expressed in ppm, were relative to tetramethylsilane (TMS). The 13N-NMR spectra were referenced to neat, external nitromethane (coaxial capillary). Full and unambiguous assignment of the 1H-, 13C- and 15N-NMR resonances was achieved using a combination of standard NMR spectroscopic techniques [62] such as DEPT, COSY, gs-HSQC, gs-HMBC, NOESY and 1,1-ADEQUATE experiments [63]. 1H-, 13C-, and 1H-15N HMBD NMR spectra, and HRMS data of all new compounds are provided in Supplementary Materials as Figures S1–S99.

3.2. Synthesis of tert-Butyl 3- and 4-[(2)-3-(Dimethylamino)-2-(methoxycarbonyl)prop-2-enoyl]piperidine-1-carboxylates (3a–c)

To a solution of the corresponding l-tert-butoxycarbonyl)piperidinecarboxylic acid (1a–c) (4 g, 17.4 mmol) in DCM (24 mL) cooled to 0 °C temperature Meldrum’s acid (2.77 g, 19.2 mmol) was added followed by DMAP (4.26 g, 34.9 mmol). Then EDC-HCl (51 mg, 9%) treated with phenylhydrazine (160 mg, 1.5 mmol). The reaction mixture was stirred at r.t. for 18 h. After removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (acetone/hexane, 1:7, v/v) to yield compounds 3a (441 mg, 78%) and 3b (17 mg, 3%). Method II. The reaction of compound 3a (500 mg, 1.5 mmol) with phenylhydrazine (160 mg, 1.5 mmol) in ACN (15 mL), was carried out as described in Method I, and the resulted residue was purified by gradient flash chromatography on silica gel (acetone/n-hexane, 1:15 → 1:7, v/v) to provide compound 5a (424 mg, 75%) and 6a (17 mg, 3%). Method III. The reaction of compound 3a (500 mg, 1.5 mmol) with phenylhydrazine (160 mg, 1.5 mmol) in CCL4 (15 mL) was carried out as described in Method I, and the resulted residue was purified by gradient flash chromatography on silica gel (acetone/n-hexane, 1:15 → 1:7, v/v) to yield compounds 4a (79 mg, 14%), 5a (305 mg, 54%) and 6a (51 mg, 9%).

3.3. Synthesis Procedure for the Preparation of Compounds 4a, 5a, and 6a

Method I. Compound 3a (500 mg, 1.5 mmol) was dissolved in EtOH (15 mL) and treated with phenylhydrazine (160 mg, 1.5 mmol). The reaction mixture was stirred at r.t. for 18 h. After removal of the solvent in vacuo, the residue was purified by flash chromatography (SiO2, eluent: acetone/n-hexane, 1:7, v/v) to provide compound 5a (441 mg, 78%).

Method II. The reaction of compound 3a (500 mg, 1.5 mmol) with phenylhydrazine (160 mg, 1.5 mmol) in ACN (15 mL), was carried out and purified as described in Method I and afforded compounds 5a (424 mg, 75%) and 6a (17 mg, 3%).

Method III. The reaction of compound 3a (500 mg, 1.5 mmol) with phenylhydrazine (160 mg, 1.5 mmol) in CCL4 (15 mL) was carried out as described in Method I, and the resulted residue was purified by gradient flash chromatography on silica gel (acetone/n-hexane, 1:15 → 1:7, v/v) to yield compounds 4a (79 mg, 14%), 5a (305 mg, 54%) and 6a (51 mg, 9%).

3.3.1. tert-Butyl 4-[(2E(Z)-2-(methoxycarbonyl)-3-(2-phenylhydrazinyl)prop-2-enoyl]piperidine-1-carboxylate (4a)

Yellowish oil. 1H-NMR (700 MHz, CDCl3): δ 1.46 (s, 9H, C(CH3)3), 1.53–1.60 (m, 2H, Pip 3,5-H), 1.75–1.83 (m, 2H, Pip 3,5-H), 2.76–2.87 (m, 2H, Pip 2,6-H), 3.70 (tt, J = 11.7 Hz, 3.5 Hz, 1H, Pip 4-H), 3.73 (s, 3H, OCH3), 4.06–4.26 (m, 2H, Pip 2,6-H), 6.24 (s, 1H, N(CH3)H), 6.81 (d, J = 8.1 Hz, 2H, Ph 2',6'-H), 6.99 (t, J = 7.4 Hz, 1H, Ph 4'-H), 7.28 (t, J = 7.8 Hz, 2H, Ph 3',5'-H), 8.28 (d, J = 10.8 Hz, 1H, 3E(Z)-H), 11.76 (d, J = 10.8 Hz, 1H, N(CH3)H). 13C-NMR (176 MHz, CDCl3): δ 28.5 (2 × CH2, Pip 3,5-C and C(CH3)3), 43.8 (2 × CH2, Pip 2,6-C), 45.5 (Pip 4-C), 51.1 (OCH3), 79.3 (C(CH3)3), 99.2 (2E(Z)-C), 113.6 (2 × CH, Ph 2',6'-C), 122.4 (Ph 4'-C), 129.5 (2 × CH, Ph 3',5'-C), 146.3 (Ph 1'-C), 154.8 (COOC(CH3)3), 162.4 (3E(Z)-C), 166.6 (COOCH3), 203.5 (C=O). 15N-NMR (71 MHz, CDCl3): δ = −275.1 (N(CH3)H), −241.2 (N(CH3)H). IR (FT-IR, νmax, cm−1): 3438(N-H), 2928, 1717 (C=O), 1690 (C=O), 1242, 767. MS m/z (%): 402 ([M − H]−, 95%). HRMS (ESI+) for C21H20N3NaO5 ([M + Na]+) calcd 426.1999, found 426.2001.
3.3.2. tert-Butyl  
4-[4-(methoxycarbonyl)-1-phenyl-1H-pyrazol-5-yl]piperidine-1-carboxylate (5a)  
Yellowish crystals, mp 151–153 °C.  
$^{1}$H-NMR (700 MHz, CDCl$_3$): $\delta$ 1.46 (s, 9H, C(CH$_3$)$_3$), 1.53–1.61 (m, 2H, Pip 3,5-H), 2.28 (qd, $J_1$ = 12.7 Hz, 4.5 Hz, 2H, Pip 3,5-H), 2.49–2.69 (m, 2H, Pip 2,6-H), 3.10 (tt, $J_2$ = 12.4 Hz, 3.6 Hz, 1H, Pip 4-H), 3.84 (s, 3H, OCH$_3$), 4.02–4.27 (m, 2H, Pip 2,6-H), 7.31–7.37 (m, 2H, Ph 2,6-H), 7.47–7.54 (m, 2H, Ph 3,5-H), 8.03 (s, 1H, Pyr 3-H).  
$^{13}$C-NMR (176 MHz, CDCl$_3$): $\delta$ 28.4 (C(CH$_3$)$_3$), 28.6 (2 $\times$ CH$_2$, Pip 5,5-C), 35.1 (Pip 4-C), 44.1 (2 $\times$ CH$_2$, Pip 2,6-C), 51.2 (OCH$_3$), 79.4 (C(CH$_3$)$_3$), 111.7 (Pyr 4-C), 126.6 (2 $\times$ CH, Ph 2,6-C), 129.3 (2 $\times$ CH, Ph 3,5-C), 129.4 (Ph 4-C), 139.2 (Ph 1-C), 143.2 (Pyr 3-C), 149.8 (Pyr 5-C), 154.7 (COOC(CH$_3$)$_3$), 163.5 (COOCH$_3$).  
$^{15}$N-NMR (71 MHz, CDCl$_3$): $\delta$ −294.5 (N-Boc), −160.3 (Pyr N-1), −76.0 (Pyr N-2). IR (FT-IR, $\nu_{max}$, cm$^{-1}$): 2979, 1712 (C=O), 1674 (C=O), 1255, 765. MS $m/z$ (%): 386 ([M + H]$^+$, 99%). HRMS (ESI$^+$) for C$_{21}$H$_{27}$N$_3$NaO$_4$ ([M + Na]$^+$) calc 408.1894, found 408.1894.

3.3.3. tert-Butyl  
4-[4-(methoxycarbonyl)-1-phenyl-3-yl]piperidine-1-carboxylate (6a)  
Brownish crystals, mp 134–136 °C.  
$^{1}$H-NMR (700 MHz, CDCl$_3$): $\delta$ 1.47 (s, 9H, C(CH$_3$)$_3$), 1.83 (qd, $J_1$ = 12.2 Hz, 4.2 Hz, 2H, Pip 3,5-H), 1.93–2.01 (m, 2H, Pip 3,5-H), 2.83–2.97 (m, 2H, Pip 2,6-H), 3.43 (tt, $J_2$ = 11.6 Hz, 3.7 Hz, 1H, Pip 4-H), 3.85 (s, 3H, OCH$_3$), 4.12–4.29 (m, 2H, Pip 2,6-H), 7.30–7.35 (m, 1H, Ph 4-H), 7.43–7.49 (m, 2H, Ph 3,5-H), 7.65–7.70 (m, 2H, Ph 2,6-H), 8.34 (s, 1H, Pyr 5-H).  
$^{13}$C-NMR (176 MHz, CDCl$_3$): $\delta$ 28.6 (C(CH$_3$)$_3$), 31.0 (2 $\times$ CH$_2$, Pip 3,5-C), 35.0 (Pip 4-C), 44.0 (2 $\times$ CH$_2$, Pip 2,6-C), 51.4 (OCH$_3$), 79.4 (C(CH$_3$)$_3$), 112.8 (Pyr 4-C), 119.5 (2 $\times$ CH, Ph 2,6-C), 127.3 (Ph 4-C), 129.7 (2 $\times$ CH, Ph 3,5-C), 131.2 (Pyr 5-C), 139.3 (Ph 1-C), 155.0 (COOC(CH$_3$)$_3$), 159.0 (Pyr 3-C), 163.8 (COOCH$_3$).  
$^{15}$N-NMR (71 MHz, CDCl$_3$): $\delta$ −292.6 (N-Boc), −165.7 (Pyr N-1), −81.5 (Pyr N-2). IR (FT-IR, $\nu_{max}$, cm$^{-1}$): 2949, 1708 (C=O), 1692 (C=O), 1537, 753. MS $m/z$ (%): 386 ([M + H]$^+$, 95%). HRMS (ESI$^+$) for C$_{21}$H$_{27}$N$_3$NaO$_4$ ([M + Na]$^+$) calc 408.1894, found 408.1894.

3.4. Synthesis of tert-Butyl 4-[4-(methoxycarbonyl)-1H-pyrazol-5-yl]piperidine-1-carboxylates (5b–o)  
Compounds 5b–o were obtained from β-enamino diketones 3a–c (500 mg, 1.5 mmol) and appropriate hydrazines (1.5 mmol) in EtOH (15 mL) by the procedure which was used for the preparation of compound 5a (Method I).

3.4.1. tert-Butyl  
4-[4-(methoxycarbonyl)-1-(4-methylphenyl)-1H-pyrazol-5-yl]piperidine-1-carboxylate (5b)  
Compound 3a was coupled with p-tolylhydrazine hydrochloride. The obtained residue was purified by column chromatography (SiO$_2$, eluent: acetone/n-hexane, 1:7, v/v) to provide compound 5b as yellowish crystals. Yield 411 mg (70%), mp 133–135 °C.  
$^{1}$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.49–1.61 (m, 2H, Pip 3,5-H), 2.23 (qd, $J_1$ = 12.6 Hz, 4.3 Hz, 2H, Pip 3,5-H), 2.44 (s, 3H, CH$_3$), 2.49–2.72 (m, 2H, Pip 2,6-H), 3.10 (tt, $J_2$ = 12.4 Hz, 3.6 Hz, 1H, Pip 4-H), 3.83 (s, 3H, OCH$_3$), 4.00–4.29 (m, 2H, Pip 2,6-H), 7.17–7.23 (m, 2H, Ph 2,6-H), 7.27–7.32 (m, 2H, Ph 3,5-H), 8.00 (s, 1H, Pyr 3-H).  
$^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$ 21.4 (CH$_3$), 28.6 (C(CH$_3$)$_3$), 28.9 (2 $\times$ CH$_2$, Pip 3,5-C), 35.3 (Pip 4-C), 44.4 (2 $\times$ CH$_2$, Pip 2,6-C), 51.4 (OCH$_3$), 79.6 (C(CH$_3$)$_3$), 111.5 (Pyr 4-C), 126.5 (2 $\times$ CH, Ph 2,6-C), 130.0 (2 $\times$ CH, Ph 3,5-C), 137.0 (Ph 1-C), 139.7 (Ph 4-C), 142.9 (Pyr 3-C), 150.1 (Pyr 5-C), 155.0 (COOC(CH$_3$)$_3$), 163.8 (COOCH$_3$).  
$^{15}$N-NMR (41 MHz, CDCl$_3$): $\delta$ −294.5 (N-Boc), −160.6 (Pyr N-1), −75.8 (Pyr N-2). IR (FT-IR, $\nu_{max}$, cm$^{-1}$): 2980, 1703 (C=O), 1688 (C=O), 1255, 779. MS $m/z$ (%): 400 ([M + H]$^+$, 99%). HRMS (ESI$^+$) for C$_{22}$H$_{29}$N$_3$NaO$_4$ ([M + Na]$^+$) calc 422.2050, found 422.2051.

3.4.2. tert-Butyl  
4-[4-(methoxycarbonyl)-1-(3-methylphenyl)-1H-pyrazol-5-yl]piperidine-1-carboxylate (5c)  
Compound 3a was coupled with m-tolylhydrazine hydrochloride. The obtained residue was purified by column chromatography (SiO$_2$, eluent: acetone/n-hexane, 1:9, v/v) to provide compound 5c as white crystals. Yield 310 mg (53%), mp 123–124 °C.
NMR (400 MHz, CDCl₃): δ 1.45 (s, 9H, C(CH₃)₃), 1.51−1.60 (m, 2H, Pip 3,5-H), 2.26 (qd, J = 12.7 Hz, 4.4 Hz, 2H, Pip 3,5-H), 2.42 (s, 3H, CH₃), 2.50−2.71 (m, 2H, Pip 2,6-H), 3.08 (tt, J = 12.4 Hz, 3.6 Hz, 1H, Pip 4-H), 3.83 (s, 3H, OCH₃), 4.04−4.26 (m, 2H, Pip 2,6-H), 7.10 (d, J = 7.9 Hz, 1H, Ph 6-H), 7.16 (s, 1H, Ph 2-H), 7.30 (d, J = 8.0 Hz, 1H, Ph 4-H), 7.37 (t, J = 7.7 Hz, 1H, Ph 5-H), 8.01 (s, 1H, Pyr 3-H). ¹³C NMR (101 MHz, CDCl₃): δ 21.4 (CH₃), 28.6 (C(CH₃)₂), 28.8 (2 × CH₂, Pip 3,5-C), 35.3 (Pip 4-C), 44.3 (2 × CH₂, Pip 2,6-C), 51.4 (OCH₃), 79.6 (C(CH₃)₃), 111.8 (Pyr 4-C), 123.6 (Ph 6-C), 127.4 (Ph 2-C), 129.1 (Ph 5-C), 130.3 (Ph 4-C), 139.4 (Ph 1-C), 139.8 (Ph 3-C), 142.9 (Pyr 3-C), 150.0 (Pyr 5-C), 155.0 (COOC(CH₃)₃), 163.8 (COOCH₃). ¹⁵N NMR (41 MHz, CDCl₃): δ −159.9 (Pyr N-1), −76.2 (Pyr N-2). IR (FT-IR, νmax, cm⁻¹): 2979, 1703 (C=O), 1688 (C=O), 1243, 779. MS m/z (%): 404 ([M + H⁺], 100%). HRMS (ESI⁺) for C₂₂H₂₉N₅NaO₄ ([M + Na⁺] calcd 422.2050, found 422.2050.

3.4.3. tert-Butyl

4-(1-(3-fluorophenyl)-4-(methoxycarbonyl)-1H-pyrazol-5-yl)piperidine-1-carboxylate (5d)

Compound 5a was coupled with (3-fluorophenyl)hydrazine hydrochloride. The obtained residue was purified by column chromatography (SiO₂, eluent: acetone/n-hexane, 1:8, v/v) to provide compound 5d as yellowish crystals. Yield 433 mg (73%), mp 134–136 °C.

¹¹H NMR (400 MHz, CDCl₃): δ 1.45 (s, 9H, C(CH₃)₃), 1.51−1.64 (m, 2H, Pip 3,5-H), 2.27 (qd, J = 12.7 Hz, 4.4 Hz, 2H, Pip 3,5-H), 2.49−2.72 (m, 2H, Pip 2,6-H), 3.08 (tt, J = 12.3 Hz, 3.6 Hz, 1H, Pip 4-H), 3.83 (s, 3H, OCH₃), 3.96−4.32 (m, 2H, Pip 2,6-H), 7.05−7.17 (m, 2H, Ph 2,6-H), 7.19−7.25 (m, 1H, Ph 4-H), 7.43−7.53 (m, 1H, Ph 5-H), 8.02 (s, 1H, Pyr 3-H).

¹³C NMR (101 MHz, CDCl₃): δ 28.6 (C(CH₃)₃), 28.8 (2 × CH₂, Pip 3,5-C), 35.3 (Pip 4-C), 44.3 (2 × CH₂, Pip 2,6-C), 51.5 (OCH₃), 79.7 (C(CH₃)₃), 112.3 (Pyr 4-C), 114.6 (d, J = 23.8 Hz, Ph 2-C), 116.8 (d, J = 20.9 Hz, Ph 4-C), 122.5 (d, J = 3.3 Hz, Ph 6-C), 130.7 (d, J = 9.0 Hz, Ph 5-C), 140.7 (d, J = 9.7 Hz, Ph 1-C), 143.3 (Pyr 3-C), 150.1 (Pyr 5-C), 154.9 (COOC(CH₃)₃), 162.8 (d, J = 249.7 Hz, Ph 3-C), 163.5 (COOCH₃). ¹⁵N NMR (41 MHz, CDCl₃): δ −161.2 (Pyr N-1), −74.5 (Pyr N-2). IR (FT-IR, νmax, cm⁻¹): 2980, 1711 (C=O), 1674 (C=O), 1243, 867. MS m/z (%): 404 ([M + H⁺], 99%). HRMS (ESI⁺) for C₂₂H₂₉N₅NaO₄ ([M + Na⁺] calcd 426.1800, found 426.1799.

3.4.4. tert-Butyl

4-[1-(3-fluorophenyl)-4-(methoxycarbonyl)-1H-pyrazol-5-yl]piperidine-1-carboxylate (5e)

Compound 5a was coupled with (2-fluorophenyl)hydrazine hydrochloride. The obtained residue was purified by column chromatography (SiO₂, eluent: acetone/n-hexane, 1:8, v/v) to provide compound 5e as yellowish crystals. Yield 367 mg (62%), mp 114–116 °C.

¹¹H NMR (400 MHz, CDCl₃): δ 1.43 (s, 9H, C(CH₃)₃), 1.48−1.58 (m, 1H, Pip 3-H), 1.60−1.76 (m, 1H, Pip 5-H), 2.03−2.30 (m, 2H, Pip 3,5-H), 2.44−2.71 (m, 2H, Pip 2,6-H), 2.88−3.05 (m, 1H, Pip 4-H), 3.83 (s, 3H, OCH₃), 3.95−4.29 (m, 2H, Pip 2,6-H), 7.22−7.32 (m, 2H, Ph 3,6-H), 7.34−7.42 (m, 1H, Ph 5-H), 7.47−7.55 (m, 1H, Ph 4-H), 8.06 (s, 1H, Pyr 3-H).

¹³C NMR (101 MHz, CDCl₃): δ 28.6 (C(CH₃)₃) and 2 × CH₂, Pip 3,5-C), 35.6 (Pip 4-C), 44.1 (2 × CH₂, Pip 2,6-C), 51.4 (OCH₃), 78.3 (C(CH₃)₃), 111.8 (Pyr 4-C), 116.9 (d, J = 19.6 Hz, Ph 3-C), 125.0 (d, J = 4.0 Hz, Ph 6-C), 127.4 (d, J = 12.6 Hz, Ph 1-C), 129.7 (Ph 5-C), 131.8 (d, J = 7.7 Hz, Ph 4-C), 143.7 (Pyr 3-C), 151.4 (Pyr 5-C), 154.9 (COOC(CH₃)₃), 157.5 (d, J = 252.5 Hz, Ph 2-C), 163.6 (COOCH₃). ¹⁵N NMR (41 MHz, CDCl₃): δ −292.8 (N-Boc), −172.7 (Pyr N-1), −73.8 (Pyr N-2). IR (FT-IR, νmax, cm⁻¹): 2980, 1716 (C=O), 1682 (C=O), 1275, 770. MS m/z (%): 404 ([M + H⁺], 96%). HRMS (ESI⁺) for C₂₁H₂₈FN₃NaO₄ ([M + Na⁺] calcd 426.1800, found 426.1800.

3.4.5. tert-Butyl

4-[4-(methoxycarbonyl)-1-(4-methoxyphenyl)-1H-pyrazol-5-yl]piperidine-1-carboxylate (5f)

Compound 5a was coupled with (4-methoxyphenyl)hydrazine hydrochloride. The obtained residue was purified by column chromatography (SiO₂, eluent: acetone/n-hexane, 1:8, v/v) to provide compound 5f as orange crystals. Yield 366 mg (60%), mp 151–153 °C.

¹¹H NMR (400 MHz, CDCl₃): δ 1.44 (s, 9H, C(CH₃)₃), 1.48−1.59 (m, 2H, Pip 3,5-H), 2.20 (qd, J = 12.7 Hz, 5.1 Hz, 2H, Pip 3,5-H), 2.49−2.73 (m, 2H, Pip 2,6-H), 3.09 (tt, J = 12.4 Hz,
3.6 Hz, 1H, Pip 4-H), 3.83 (s, 3H, COOCH3), 3.87 (s, 3H, OCH3), 3.99–4.30 (m, 2H, Pip 2,6-H), 6.98 (d, J = 8.8 Hz, 2H, Ph 3,5-H), 7.23 (d, J = 8.8 Hz, 2H, Ph 2,6-H), 7.99 (s, 1H, Pyr 3-H). 13C-NMR (101 MHz, CDCl3): δ 28.6 (C(CH3)2), 28.9 (2 × CH2, Pip 3,5-C), 35.3 (Pip 4-C), 44.2 (2 × CH2, Pip 2,6-C), 51.4 (COOC(CH3)2), 55.7 (OCH3), 79.6 (C(CH3)3), 111.6 (Pyr 4-C), 114.5 (2 × CH, Ph 3,5-C), 128.0 (2 × CH, Ph 2,6-C), 132.4 (Ph 1-C), 142.7 (Pyr 3-C), 150.2 (Pyr 5-C), 154.9 (COOC(CH3)2), 160.3 (Ph 4-C), 163.8 (COOC(CH3)). 15N-NMR (41 MHz, CDCl3): δ −161.4 (Pyr N-1), −75.4 (Pyr N-2). IR (FT-IR, ηmax cm⁻¹): 2981, 1715 (C=O), 1682 (C=O), 1245, 780. MS m/z (%): 416 [M+H]+, 100%. HRMS (ESI⁺) for C22H29N3NaO5 ([M+Na]+) calcd 438.1999, found 438.2000.

3.4.6. tert-Butyl 4-[4-(methoxycarbonyl)-1-(3-methoxyphenyl)-1H-pyrazol-5-yl]piperidine-1-carboxylate (5g)

Compound 3a was coupled with (3-methoxyphenyl)hydrazine hydrochloride. The obtained residue was purified by column chromatography (SiO2 eluent: acetone/n-hexane, 1:9, v/v) to provide compound 5g as yellowish crystals. Yield 330 mg (54%), mp 69–71 °C. 1H-NMR (400 MHz, CDCl3): δ 1.45 (s, 9H, C(CH3)3), 1.50–1.61 (m, 2H, Pip 3,5-H), 2.27 (qd, J = 12.7 Hz, 4.3 Hz, 2H, Pip 3,5-H), 2.51–2.71 (m, 2H, Pip 2,6-H), 3.11 (tt, J = 12.4 Hz, 3.7 Hz, 1H, Pip 4-H), 3.83 (s, 6H, OCH3 and COOCH3), 3.99–4.29 (m, 2H, Pip 2,6-H), 6.85–6.93 (m, 2H, Ph 2,4-H), 7.00–7.06 (m, 1H, Ph 6-H), 7.35–7.43 (m, 1H, Ph 5-H), 8.01 (s, 1H, Pyr 3-H), 13C-NMR (101 MHz, CDCl3): δ 28.6 (C(CH3)2), 28.8 (2 × CH2, Pip 3,5-C), 35.3 (Pip 4-C), 44.3 (2 × CH2, Pip 2,6-C), 51.4 (COOC(CH3)2), 55.7 (OCH3), 79.6 (C(CH3)3), 112.0 (Pyr 4-C), 112.5 (Ph 2-C), 115.5 (Ph 4-C), 118.8 (Ph 6-C), 130.1 (Ph 5-C), 140.4 (Ph 1-C), 143.0 (Pyr 3-C), 150.0 (Pyr 5-C), 155.0 (COOC(CH3)2), 160.4 (Ph 3-C), 163.7 (COOC(CH3)). IR (FT-IR, ηmax cm⁻¹): 2979, 1702 (C=O), 1686 (C=O), 1109, 778. MS m/z (%): 400 ([M + H]+, 100%). HRMS (ESI⁺) for C22H29N3NaO5 ([M + Na]+) calcd 438.1999, found 438.2000.

3.4.7. tert-Butyl 4-[4-(methoxycarbonyl)-1-[3-(trifluoromethyl)phenyl]-1H-pyrazol-5-yl]piperidine-1-carboxylate (5h)

Compound 3a was coupled with [3-(trifluoromethyl)phenyl]hydrazine hydrochloride. The obtained residue was purified by column chromatography (SiO2 eluent: acetone/n-hexane, 1:5, v/v) to provide compound 5h as yellowish crystals. Yield 506 mg (76%), mp 113–115 °C. 1H-NMR (700 MHz, CDCl3): δ 1.46 (s, 9H, C(CH3)3), 1.55–1.62 (m, 2H, Pip 3,5-H), 2.24–2.37 (m, 2H, Pip 3,5-H), 2.50–2.70 (m, 2H, Pip 2,6-H), 3.05 (tt, J = 12.3 Hz, 3.6 Hz, 1H, Pip 4-H), 3.86 (s, 3H, OCH3), 4.06–4.29 (m, 2H, Pip 2,6-H), 7.54–7.57 (m, 1H, Ph 6-H), 7.65 (br s, 1H, Ph 2-H), 7.68 (tt, J = 7.9 Hz, 1H, Ph 5-H), 7.79 (br s, 1H, Ph 4-H), 8.06 (s, 1H, Pyr 3-H). 13C-NMR (176 MHz, CDCl3): δ 28.4 (C(CH3)2), 28.8 (2 × CH2, Pip 3,5-C), 35.4 (Pip 4-C), 44.1 (2 × CH2, Pip 2,6-C), 51.4 (OCH3), 79.6 (C(CH3)3), 112.5 (Pyr 4-C), 123.3 (q, J = 271.5 Hz, CF3), 123.7 (q, J = 3.7 Hz, Ph 2-C), 126.2 (q, J = 3.7 Hz, Ph 4-C), 129.7 (Ph 3-C), 130.1 (Ph 6-C), 132.1 (q, J = 33.3 Hz, Ph 3-C), 139.8 (Ph 1-C), 143.5 (Pyr 3-C), 150.1 (Pyr 5-C), 154.8 (COOC(CH3)2), 163.3 (COOC(CH3)). 15N-NMR (71 MHz, CDCl3): δ −294.7 (N-Boc), −163.3 (Pyr N-1), −76.0 (Pyr N-2). IR (FT-IR, ηmax cm⁻¹): 2980, 1714 (C=O), 1686 (C=O), 1169, 1062. MS m/z (%): 354 ([M–Boc + H]+), 454 ([M + H]+), 99%. HRMS (ESI⁺) for C22H22F3N3NaO4 ([M + Na]+) calcd 476.1768, found 476.1768.

3.4.8. tert-Butyl 4-[4-(methoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]piperidine-1-carboxylate (5i)

Compound 3a was coupled with methylhydrazine. The obtained residue was purified by column chromatography (SiO2 eluent: acetone/n-hexane, 1:3, v/v) to provide compound 5i as white crystals. Yield 242 mg (51%), mp 147–149 °C. 1H NMR (400 MHz, CDCl3): δ 1.48 (s, 9H, C(CH3)3), 1.59–1.70 (m, 2H, Pip 3,5-H), 2.15 (qd, J = 12.7 Hz, 4.4 Hz, 2H, Pip 3,5-H), 2.68–2.89 (m, 2H, Pip 2,6-H), 3.53 (tt, J = 12.6 Hz, 3.7 Hz, 1H, Pip 4-H), 3.79 (s, 3H, OCH3), 3.90 (s, 3H, CH3), 4.10–4.44 (m, 2H, Pip 2,6-H), 7.81 (s, 1H, Pyr 3-H). 13C NMR (101 MHz, CDCl3): δ 28.6 (C(CH3)3), 28.6 (2 × CH2, Pip 3,5-C), 34.2 (Pip 4-C), 38.7 (CH3), 44.5 (2 × CH2, Pip 2,6-C), 51.2 (OCH3), 79.8 (C(CH3)3), 111.3 (Pyr 4-C), 141.5 (Pyr 3-C), 148.8 (Pyr 5-C), 154.9 (COOC(CH3)2), 164.0 (COOC(CH3)). 15N NMR (41 MHz, CDCl3): δ −293.2
(N-Boc), −176.9 (Pyr N-1), −75.1 (Pyr N-2). IR (FT-IR, $\nu_{\text{max}}$, cm$^{-1}$): 2980, 1705 (C=O), 1688 (C=O), 1234, 779. MS $m/z$ (%): 324 ([M + H]$^+$, 100%). HRMS (ESI$^+$) for C$_{16}$H$_{25}$N$_3$NaO$_4$ ([M + Na]$^+$) calc 346.1737, found 346.1737.

3.4.9. tert-Butyl

(3R)-3-[4-(methoxycarbonyl)-1-phenyl-1H-pyrazol-5-yl]piperidine-1-carboxylate (5j)

Compound 3b was coupled with phenylhydrazine. The obtained residue was purified by column chromatography (SiO$_2$, eluent: acetonitrile/n-hexane, 1:7, v/v) to provide compound 5j as a brownish oil. Yield 379 mg (67%), $[\alpha]_D^{20} = 6.4$ (c 1.12, MeOH). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.40 (s, 10H, C(CH$_3$)$_2$ and Pip 5-H), 1.63–1.78 (m, 2H, Pip 4,5-H), 2.46 (qd, $J = 13.1$ Hz, 1H, Pip 4-H), 2.74–2.87 (m, 1H, Pip 6-H), 2.88–3.01 (1H, Pip 3-H), 3.54–3.69 (m, 1H, Pip 2-H), 3.86 (s, 3H, OCH$_3$), 3.92–4.17 (m, 2H, Pip 2,6-H), 7.36–7.42 (m, 2H, Ph 2,6-H), 7.48–7.54 (m, 3H, Ph 3,4,5-H), 8.05 (s, 1H, Pyr 3-H). $^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$ 25.3 (Pip 5-C), 27.4 (Pip 4-C), 28.5 (C(CH$_3$)$_3$), 36.0 (Pip 3-C), 43.7 (Pip 6-C), 46.1 (Pip 2-C), 51.5 (OCH$_3$), 79.6 (C(CH$_3$)$_3$), 112.3 (Pyr 4-C), 126.5 (2 × CH, Ph 2,6-C), 129.4 (Ph 4-C), 129.5 (2 × CH, Ph 3,5-C), 139.0 (Ph 1-C), 143.3 (Pyr 3-C), 148.1 (Pyr 5-C), 154.8 (COO(C(CH$_3$)$_3$)), 163.9 (COOCH$_3$). $^{15}$N-NMR (41 MHz, CDCl$_3$): $\delta$ −159.4 (Pyr N-1), −76.1 (Pyr N-2). IR (FT-IR, $\nu_{\text{max}}$, cm$^{-1}$): 2975, 1716 (C=O), 1687 (C=O), 1261, 1099, 757. MS $m/z$ (%): 286 ([M-Boc+H]$^+$), 386 ([M + H]$^+$), 95%. HRMS (ESI$^+$) for C$_{21}$H$_{27}$N$_3$NaO$_4$ ([M + Na]$^+$) calc 408.1894, found 408.1893.

3.4.10. tert-Butyl

(3S)-3-[4-(methoxycarbonyl)-1-phenyl-1H-pyrazol-5-yl]piperidine-1-carboxylate (5k)

Compound 3c was coupled with phenylhydrazine. The obtained residue was purified by column chromatography (SiO$_2$, eluent: acetonitrile/n-hexane, 1:11, v/v) to provide compound 5k as a brownish oil. Yield 436 mg (77%), $[\alpha]_D^{20} = −6.4$ (c 0.73, MeOH). $^1$H-NMR (400 MHz, CDCl$_3$): 1.40 (s, 10H, C(CH$_3$)$_2$ and Pip 5-H), 1.60–1.80 (m, 2H, Pip 4,5-H), 2.46 (qd, $J = 13.3$ Hz, 1H, Pip 4-H), 2.80 (s, 1H, Pip 6-H), 2.94 (s, 1H, Pip 3-H), 3.48–3.79 (m, 1H, Pip 2-H), 3.86 (s, 3H, OCH$_3$), 3.91–4.30 (m, 2H, Pip 2,6-H), 7.32–7.46 (m, 2H, Ph 2,6-H), 7.46–7.56 (m, 3H, Ph 3,4,5-H), 8.05 (s, 1H, Pyr 3-H). $^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$ 25.3 (Pip 5-C), 27.4 (Pip 4-C), 28.5 (C(CH$_3$)$_3$), 36.0 (Pip 3-C), 44.0 (Pip 6-C), 46.0 (Pip 2-C), 51.5 (OCH$_3$), 79.6 (C(CH$_3$)$_3$), 112.3 (Pyr 4-C), 126.5 (2 × CH, Ph 2,6-C), 129.4 (Ph 4-C), 129.5 (2 × CH, Ph 3,5-C), 139.1 (Ph 1-C), 143.3 (Pyr 3-C), 148.1 (Pyr 5-C), 154.7 (COO(C(CH$_3$)$_3$)), 163.9 (COOCH$_3$) IR (FT-IR, $\nu_{\text{max}}$, cm$^{-1}$): 2975, 1717 (C=O), 1684 (C=O), 1408, 1259, 757. MS $m/z$ (%): 386 ([M + H]$^+$), 96%. HRMS (ESI$^+$) for C$_{21}$H$_{27}$N$_3$NaO$_4$ ([M + Na]$^+$) calc 408.1894, found 408.1892.

3.4.11. tert-Butyl

(3R)-3-[4-(methoxycarbonyl)-1-(4-methylphenyl)-1H-pyrazol-5-yl]piperidine-1-carboxylate (5l)

Compound 3b was coupled with p-tolylhydrazine hydrochloride. The obtained residue was purified by column chromatography (SiO$_2$, eluent: acetonitrile/n-hexane, 1:7, v/v) to provide compound 5l as a brownish oil. Yield 458 mg (77%), $[\alpha]_D^{20} = 4.1$ (c 0.62, MeOH). $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 1.40 (s, 10H, C(CH$_3$)$_2$ and Pip 5-H), 1.61–1.74 (m, 2H, Pip 4,5-H), 2.43 (s, 4H, Pip 4-H and CH$_3$), 2.79 (s, 1H, Pip 6-H), 2.93 (s, 1H, Pip 3-H), 3.48–3.72 (m, 1H, Pip 2-H), 3.85 (s, 3H, OCH$_3$), 3.90–4.18 (m, 2H, Pip 2,6-H), 7.22–7.33 (m, 4H, Ph 2,3,5,6-H), 8.03 (s, 1H, Pyr 3-H). $^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$ 21.4 (CH$_3$), 25.3 (Pip 5-C), 27.4 (Pip 4-C), 28.5 (C(CH$_3$)$_3$), 36.0 (Pip 3-C), 43.9 (Pip 6-C), 45.8 (Pip 2-C), 51.5 (OCH$_3$), 79.5 (C(CH$_3$)$_3$), 112.1 (Pyr 4-C), 126.3 (2 × CH, Ph 2,6-C), 130.0 (2 × CH, Ph 3,5-C), 136.6 (Ph 1-C), 139.6 (Ph 4-C), 143.1 (Pyr 3-C), 148.1 (Pyr 5-C), 154.7 (COO(C(CH$_3$)$_3$)), 164.0 (COOCH$_3$). $^{15}$N-NMR (41 MHz, CDCl$_3$): $\delta$ −157.9 (Pyr N-1), −76.4 (Pyr N-2). IR (FT-IR, $\nu_{\text{max}}$, cm$^{-1}$): 2976, 1710 (C=O), 1692 (C=O), 1148, 824. MS $m/z$ (%): 300 ([M-Boc + H]$^+$), 400 ([M + H]$^+$), 97%. HRMS (ESI$^+$) for C$_{22}$H$_{29}$N$_3$NaO$_4$ ([M + Na]$^+$) calc 422.2050, found 422.2052.
3.4.12. tert-Butyl (3S)-3-[4-(methoxycarbonyl)-1-(4-methylphenyl)-1H-pyrazol-5-yl]piperidine-1-carboxylate (5m)

Compound 3c was coupled with p-tolylhydrazine hydrochloride. The obtained residue was purified by column chromatography (SiO₂, eluent: acetone/n-hexane, 1:9, v/v) to provide compound 5m as brownish oil. Yield 475 mg (81%), [α]D₂⁰ = −4.3 (c 0.86, MeOH).

1H-NMR (400 MHz, CDCl₃): δ 1.40 (s, 10H, C(CH₃)₂ and Pip 5-H), 1.61–1.77 (m, 2H, Pip 4,5-H), 2.43 (s, 4H, Pip 4-H and CH₂), 2.79 (s, 1H, Pip 6-H), 2.93 (s, 1H, Pip 3-H), 3.48–3.76 (m, 1H, Pip 2-H), 3.85 (s, 3H, OCH₃), 3.90–4.26 (m, 2H, Pip 2,6-H), 7.21–7.32 (m, 4H, Ph 2,3,5,6-H), 8.03 (s, 1H, Pyr 3-H). 13C-NMR (101 MHz, CDCl₃): δ 21.4 (CH₃), 25.3 (Pip 5-C), 27.4 (Pip 4-C), 28.5 (C(CH₃)₂), 36.1 (Pip 3-C), 43.5 (Pip 6-C), 46.4 (Pip 2-C), 51.5 (OCH₃), 79.5 (C(CH₃)₂), 112.1 (Pyr 4-C), 126.3 (2 × CH, Ph 2,6-C), 130.0 (2 × CH, Ph 3,5-C), 136.6 (Ph 1-C), 139.6 (Ph 4-C), 143.1 (Pyr 3-C), 148.1 (Pyr 5-C), 154.7 (COOC(CH₃)₂), 164.0 (COOCH₃).

IR (FT-IR, νmax, cm⁻¹): 2930, 1714 (C=O), 1688 (C=O), 1261, 822. MS m/z (%): 400 ([M + H]⁺, 95%). HRMS (ESI⁺) for C₂₂H₂₉N₃NaO₄ ([M + Na]⁺) calcd 422.2050, found 422.2051.

3.4.13. tert-Butyl (3R)-3-[4-(methoxycarbonyl)-1-[3-(trifluoromethyl)phenyl]-1H-pyrazol-5-yl]piperidine-1-carboxylate (5n)

Compound 3b was coupled with [3-(trifluoromethyl)phenyl]hydrazine hydrochloride. The obtained residue was purified by column chromatography (SiO₂, eluent: acetone/n-hexane, 1:5, v/v) to provide compound 5n as brownish oil. Yield 526 mg (79%), [α]D₂⁰ = 9.9 (c 1.31, MeOH).

1H-NMR (700 MHz, CDCl₃): δ 1.39 (br s, 10H, C(CH₃)₂ and Pip 5-H), 1.68–1.77 (m, 2H, Pip 4,5-H), 2.50 (qd, J = 12.9 Hz, 3.9 Hz, 1H, Pip 4-H), 2.72–3.00 (m, 2H, Pip 3,6-H), 3.52–3.75 (m, 1H, Pip 2-H), 3.87 (s, 3H, OCH₃), 3.90–4.21 (m, 2H, Pip 2,6-H), 7.52–7.69 (m, 2H, Ph 5,6-H), 7.71 (br s, 1H, Ph 2-H), 7.73–7.82 (m, 1H, Pyr 4-H), 8.07 (s, 1H, Pyr 3-H). 13C-NMR (176 MHz, CDCl₃): δ 25.2 (Pip 5-C), 27.3 (Pip 4-C), 28.3 (C(CH₃)₂), 35.9 (Pip 3-C), 43.9 (Pip 6-C), 45.7 (Pip 2-C), 51.5 (OCH₃), 79.6 (C(CH₃)₂), 112.8 (Pyr 4-C), 123.3 (q, J = 272.4 Hz, CF₃), 123.5 (Ph 2-C), 126.1 (Ph 4-C), 129.4 (Ph 5-C), 130.0 (Ph 6-C), 132.2 (Ph 3-C), 139.3 (Ph 1-C), 143.7 (Pyr 3-C), 148.1 (Pyr 5-C), 154.7 (COOC(CH₃)₂), 163.5 (COOCH₃).

15N-NMR (41 MHz, CDCl₃): δ −162.0 (Pyr N-1), −76.1 (Pyr N-2). IR (FT-IR, νmax, cm⁻¹): 2951, 1717 (C=O), 1688 (C=O), 1130, 1098. MS m/z (%): 354 ([M-Boc + H]^⁺), 454 ([M + H]^⁺), 96%. HRMS (ESI⁺) for C₂₂H₂₆F₃N₃NaO₄ ([M + Na]⁺) calcd 476.1768, found 476.1769.

3.4.14. tert-Butyl (3S)-3-[4-(methoxycarbonyl)-1-[3-(trifluoromethyl)phenyl]-1H-pyrazol-5-yl]piperidine-1-carboxylate (5o)

Compound 3c was coupled with [3-(trifluoromethyl)phenyl]hydrazine hydrochloride. The obtained residue was purified by column chromatography (SiO₂, eluent: acetone/n-hexane, 1:11, v/v) to provide compound 5o as brownish oil. Yield 420 mg (63%), [α]D₂⁰ = −9.8 (c 0.85, MeOH).

1H-NMR (700 MHz, CDCl₃): δ 1.39 (br s, 10H, C(CH₃)₂ and Pip 5-H), 1.68–1.77 (m, 2H, Pip 4,5-H), 2.50 (qd, J = 12.9 Hz, 3.9 Hz, 1H, Pip 4-H), 2.72–3.00 (m, 2H, Pip 3,6-H), 3.52–3.75 (m, 1H, Pip 2-H), 3.87 (s, 3H, OCH₃), 3.90–4.21 (m, 2H, Pip 2,6-H), 7.52–7.69 (m, 2H, Ph 5,6-H), 7.71 (br s, 1H, Ph 2-H), 7.73–7.82 (m, 1H, Pyr 4-H), 8.08 (s, 1H, Pyr 3-H). 13C-NMR (176 MHz, CDCl₃): δ 25.2 (Pip 5-C), 27.3 (Pip 4-C), 28.3 (C(CH₃)₂), 35.9 (Pip 3-C), 43.9 (Pip 6-C), 45.7 (Pip 2-C), 51.5 (OCH₃), 79.6 (C(CH₃)₂), 112.8 (Pyr 4-C), 123.3 (q, J = 272.4 Hz, CF₃), 123.5 (Ph 2-C), 126.1 (Ph 4-C), 129.4 (Ph 5-C), 130.0 (Ph 6-C), 132.2 (Ph 3-C), 139.3 (Ph 1-C), 143.7 (Pyr 3-C), 148.1 (Pyr 5-C), 154.7 (COOC(CH₃)₂), 163.5 (COOCH₃).

3.5. Synthesis of tert-Butyl 4-[4-(methoxycarbonyl)-1H-pyrazolyl]piperidine-1-carboxylate (7)

Compound 3a (500 mg, 1.5 mmol) was dissolved in EtOH (15 mL) and treated with 55% hydrazine hydrate solution (74 mg, 1.5 mmol). Reaction mixture was stirred at r.t. for 18 h. After removal of the solvent in vacuo, the residue was purified by flash column chromatography (SiO₂, eluent: acetone/n-hexane, 1:7, v/v) to provide compound 7 as white crystals.
Yield 272 mg (60%), mp 128–130 °C. 1H-NMR (700 MHz, CDCl₃): δ 1.47 (s, 9H, C(CH₃)₃), 1.64–1.78 (m, 2H, Pip 3,5-H), 1.92–1.99 (m, 2H, Pip 3,5-H), 2.77–2.95 (m, 2H, Pip 2,6-H), 3.53 (t, J = 12.0 Hz, 1H, Pip 4-H), 3.83 (s, 3H, OCH₃), 4.10–4.36 (m, 2H, Pip 2,6-H), 7.96 (s, 1H, Pyr 3(5)-H), 11.52 (s, 1H, Pyr NH). 13C-NMR (176 MHz, CDCl₃): δ 28.5 (C(CH₃)₃), 30.8 (2 × CH₂, Pip 3,5-C), 33.8 (Pip 4-C), 44.2 (2 × CH₂, Pip 2,6-C), 51.2 (OCH₃), 79.8 (CH(CH₃)₂), 110.1 (Pyr 4-C), 138.7 and 153.6 (Pyr 3(5)-C), 154.9 (COOC(CH₃)₃), 164.1 (COOCH₃). 15N-NMR (71 MHz, CDCl₃): δ = −292.7 (N-Boc). IR (FT-IR, νmax cm⁻¹): 3208 (N-H), 2980 (N-H), 1655 (C=O), 1434, 1165, 763. MS m/z (%): 210 ([M-Boc + H⁺]), 308 ([M − H⁻]), 97%. HRMS (ESI⁺) for C₁₇H₂₅N₃NaO₄ ([M + Na⁺]) calc 332.1581, found 332.1581.

3.6. Synthesis of tert-Butyl 4-[4-(methoxycarbonyl)-1H-pyrazolyl]-1-piperidine-1-carboxylates (5i, 6i, 8)

A solution of compound 7 (100 mg, 0.3 mmol), KOH (27 mg, 0.5 mmol), and alkyl iodide (1 mmol) in DMF (0.75 mL) was stirred at r.t. for 4 h. The reaction mixture was diluted with EtOAc (10 mL), washed with H₂O (2 × 15 mL) and brine (15 mL). The organic layer was dried with anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using an eluent—Hex/Me₂CO in the appropriate ratio.

3.6.1. tert-Butyl

4-[4-(methoxycarbonyl)-1-methyl-1H-pyrazol-3-yl]piperidine-1-carboxylic acid (6i) and tert-Butyl 4-[4-(methoxycarbonyl)-1-methyl-1H-pyrazol-5-yl]piperidine-1-carboxylate (5i)

Compound 7 was coupled with iodomethane. The obtained residue was purified by column chromatography (SiO₂, eluent: acetone/n-hexane, 1:4, v/v) to provide an inseparable mixture of regioisomers 6i:5i (5:1) as white crystals. Yield 77 mg (74%). 1H-NMR (700 MHz, CDCl₃) (two isomers are seen in the spectra ratio ~ 5:1 (6i:5i)): δ 1.44 (s, 9H, C(CH₃)₃), 1.47 (s, 9H, C(CH₃)₃), 1.59–1.76 (m, 2H, Pip 3,5-H), 1.82–1.95 (m, 2H, Pip 2,6-H, 6i and 5i), 2.14 (q, J = 12.7 Hz, 4.5 Hz, 2H, Pip 3,5-H, 5i), 2.69–2.95 (m, 2H, Pip 2,6-H, 6i and 5i), 3.36 (t, J = 11.8 Hz, 3.6 Hz, 1H, Pip 4-H, 6i), 3.54 (t, J = 12.6 Hz, 1H, Pip 4-H, 5i), 3.79 (s, 3H, OCH₃, 6i), 3.80 (s, 3H, OCH₃, 5i), 3.85 (s, 3H, CH₃, 6i), 3.92 (s, 3H, CH₃, 5i), 4.03–4.34 (m, 2H, Pip 2,6-H, 6i and 5i), 7.78 (s, 1H, Pyr 5-H, 6i), 7.82 (s, 1H, Pyr 3-H, 5i), 100%). HRMS (ESI⁺) for C₁₇H₂₅N₃NaO₄ ([M + Na⁺] calc 332.1581, found 332.1581.)

3.6.2. tert-Butyl

4-[1-ethyl-4-(methoxycarbonyl)-1H-pyrazol-3-yl]piperidine-1-carboxylate (8)

Compound 7 was coupled with iodoethane. The obtained residue was purified by column chromatography (SiO₂, eluent: acetone/n-hexane, 1:5, v/v) to provide compound 8 as white crystals, yield 95 mg (87%), mp 77–78 °C. 1H-NMR (700 MHz, CDCl₃): δ 1.43–1.50 (m, 12H, C(CH₃)₂ and CH₂CH₃), 1.72 (q, J = 12.5 Hz, 4.1 Hz, 2H, Pip 3,5-H), 1.85–1.93 (m, 2H, Pip 2,6-H), 2.80–2.90 (m, 2H, Pip 2,6-H), 3.37 (t, J = 11.8 Hz, 3.6 Hz, 1H, Pip 4-H), 3.79 (s, 3H, OCH₃), 4.08–4.23 (m, 4H, Pip 2,6-H and CH₂CH₃), 7.82 (s, 1H, Pyr 5-H). 13C-NMR (176 MHz, CDCl₃): δ 15.2 (CH₂CH₃), 28.6 (C(CH₃)₂), 31.1 (2 × CH₂, Pip 3,5-C), 34.9 (Pip 4-C), 44.4 (2 × CH₂, Pip 2,6-C), 47.3 (CH₂CH₃), 51.3 (OCH₃), 79.9 (CH(CH₃)₂), 110.5 (Pyr 4-C), 133.1 (Pyr 5-C), 155.2 (COOC(CH₃)₃), 157.8 (Pyr 3-C), 163.9 (COOCH₃). 15N-NMR (71 MHz, CDCl₃): δ = −168.7 (Pyr N-1), −82.9 (Pyr N-2). IR (FT-IR, νmax cm⁻¹): 2980, 1715 (C=O), 1678 (C=O), 1219, 768. MS m/z (%): 338 ([M + H⁺]), 99%). HRMS (ESI⁺) for C₁₇H₂₇N₃NaO₄ ([M + Na⁺]) calc 360.1894, found 360.1894.
3.7. Synthesis of 5-[1-(tert-Butoxycarbonyl)piperidinyl]-1H-pyrazole-4-carboxylic acids (9a-c)

Corresponding ester (5a, 5j, 5k) (300 mg, 0.78 mmol) was dissolved in MeOH (0.1 mM) and treated with 2 N NaOH (4 equiv). The solution was stirred under reflux for 5 h. After removal of the solvent in vacuo, the residue was dissolved in water (15 mL), washed with EtOAc (2 × 15 mL), acidified with 1 M HSO₃H (pH = 1), and washed with EtOAc (2 × 15 mL). The extracts were combined and dried over sodium sulfate, filtered, and concentrated to dryness to give desired compounds which were directly used in the next step without further purification.

3.7.1. 5-[1-(tert-Butoxycarbonyl)piperidin-4-yl]-1-phenyl-1H-pyrazole-4-carboxylic Acid (9a)

Brownish crystals, yield 240 mg (83%), mp 190–192 °C. ¹H-NMR (400 MHz, CDCl₃): δ 1.46 (s, 9H, C(CH₂)₃), 1.52–1.70 (m, 2H, Pip 3,5-H), 2.26 (qd, J = 12.7 Hz, 4.3 Hz, 2H, Pip 3,5-H), 2.48–2.76 (m, 2H, Pip 2,6-H), 3.12 (tt, J = 12.5 Hz, 3.6 Hz, 1H, Pip 4-H), 3.97–4.30 (m, 2H, Pip 2,6-H), 7.31–7.38 (m, 2H, Ph 2,6-C), 7.47–7.57 (m, 3H, Ph 3,4,5-C), 8.09 (s, 1H, Pyr N-1), 9.39 (br s, 1H, OH). ¹³C-NMR (101 MHz, CDCl₃): δ 28.6 (C(CH₂)₃), 28.8 (2 × CH₂, Pip 3,5-C), 35.4 (Pip 4-C), 44.3 (2 × CH₂, Pip 2,6-C), 79.8 (C(CH₂)₃), 111.5 (Pyr 4-C), 126.8 (2 × CH, Pip 2,6-C), 129.5 (2 × CH, Ph 3,5-C), 129.7 (Pyr 4-C), 139.3 (Ph 1-C), 140.5 (Ph 3-C), 140.8 (Pyr 5-C), 141.3 (COOC(CH₂)₃), 163.8 (COOH). ¹⁵N-NMR (41 MHz, CDCl₃): δ −159.6 (Pyr N-1), −73.1 (Pyr N-2). IR (FT-IR, ν max, cm⁻¹): 2930, 1686 (C=O), 1412, 1147, 764. MS m/z (%): 370 ([M − H]⁻, 95%). HRMS (ESI⁺) for C₂₀H₂₅N₃NaO₄ ([M + Na]⁺) calcd 394.1737, found 394.1738.

3.7.2. 5-[(3R)-1-(tert-Butoxycarbonyl)piperidin-3-yl]-1-phenyl-1H-pyrazole-4-carboxylic Acid (9b)

Brownish crystals, yield 254 mg (88%), mp 86–88 °C, [α]D²⁰ = 10.4 (c 1.10, MeOH). ¹H-NMR (400 MHz, CDCl₃): δ 1.41 (s, 10H, C(CH₂)₃ and Pip 5-H), 1.60–1.80 (m, 2H, Pip 4,5-H), 2.38–2.52 (m, 1H, Pip 4-H), 2.64–2.86 (m, 1H, Pip 6-H), 2.86–3.13 (m, 1H, Pip 3-H), 3.45–3.75 (m, 1H, Pip 2-H), 3.87–4.23 (m, 2H, Pip 2,6-H), 7.36–7.44 (m, 2H, Ph 2,6-H), 7.49–7.57 (m, 3H, Ph 3,4,5-C), 8.15 (s, 1H, Pyr 3-H). ¹³C-NMR (101 MHz, CDCl₃): δ 25.2 (Pip 5-C), 27.4 (Pip 4-C), 28.5 (C(CH₂)₃), 36.1 (Pip 3-C), 43.5 (Pip 6-C), 46.3 (Pip 2-C), 79.7 (C(CH₂)₃), 111.8 (Pyr 4-C), 126.8 (2 × CH, Pip 2,6-C), 129.5 (2 × CH, Ph 3,4,5-C), 138.9 (Ph 1-C), 141.4 (Pip 3-C), 148.8 (Pyr 5-C), 154.7 (COOC(CH₂)₃), 168.3 (COOH). ¹⁵N-NMR (41 MHz, CDCl₃): δ −158.1 (Pyr N-1), −75.8 (Pyr N-2). IR (FT-IR, ν max, cm⁻¹): 2930, 1689, 1412, 1147, 764. MS m/z (%): 370 ([M − H]⁻, 97%). HRMS (ESI⁺) for C₂₀H₂₅N₃NaO₄ ([M + Na]⁺) calcd 394.1737, found 394.1738.

3.7.3. 5-[(3S)-1-(tert-Butoxycarbonyl)piperidin-3-yl]-1-phenyl-1H-pyrazole-4-carboxylic Acid (9c)

Yellowish crystals, yield 243 mg (84%), mp 88–90 °C, [α]D²⁰ = −10.5 (c 1.0, MeOH). ¹H-NMR (400 MHz, CDCl₃): δ 1.41 (s, 10H, C(CH₂)₃ and Pip 5-H), 1.62–1.78 (m, 2H, Pip 4,5-H), 2.45 (qd, J = 12.7 Hz, 7.3 Hz, 1H, Pip 4-H), 2.68–2.87 (m, 1H, Pip 6-H), 2.92–3.08 (m, 1H, Pip 3-H), 3.46–3.67 (m, 1H, Pip 2-H), 3.87–4.21 (m, 2H, Pip 2,6-H), 7.36–7.45 (m, 2H, Ph 2,6-H), 7.47–7.57 (m, 3H, Ph 3,4,5-C), 8.15 (s, 1H, Pyr 3-H). ¹³C-NMR (101 MHz, CDCl₃): δ 25.2 (Pip 5-C), 27.4 (Pip 4-C), 28.5 (C(CH₂)₃), 36.1 (Pip 3-C), 43.5 (Pip 6-C), 46.3 (Pip 2-C), 79.7 (C(CH₂)₃), 111.7 (Pyr 4-C), 126.5 (2 × CH, Pip 2,6-C), 129.6 (2 × CH, Ph 3,4,5-C), 138.9 (Ph 1-C), 141.4 (Pyr 3-C), 148.9 (Pyr 5-C), 154.7 (COOC(CH₂)₃), 168.3 (COOH). IR (FT-IR, ν max, cm⁻¹): 2930, 1689 (C=O), 1412, 1148, 765. MS m/z (%): 370 ([M − H]⁻, 97%). HRMS (ESI⁺) for C₂₀H₂₅N₃NaO₄ ([M + Na]⁺) calcd 394.1737, found 394.1739.

3.8. Synthesis of tert-Butyl 3- and 4-[4-[(Phenylcarbamoyl)-1H-pyrazol-5-yl]piperidine-1-carboxylates (10a–c)

To a solution of the appropriate pyrazole-4-carboxylic acids (9a–c) (200 mg, 0.54 mmol) and DMAP (7 mg, 0.05 mmol) in DCM (0.1 mM) cooled to 0 °C temperature EDC·HCl (114 mg, 0.59 mmol) and aniline (50 mg, 0.54 mmol) were added. The reaction mixture was
left at r.t. for 48 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography using an eluent—Hex/Me₂CO (6:1, v/v).

3.8.1. tert-Butyl
4-[1-phenyl-4-(phenylcarbamoyle)-1H-pyrazol-5-yl]piperidine-1-carboxylate (10a)

White crystals, yield 192 mg (80%), mp 187–189 °C. ¹H-NMR (400 MHz, CDCl₃): δ 1.42 (s, 9H, C(CH₃)₃), 1.55–1.76 (m, 2H, Pip 3,5-H), 2.18–2.33 (m, 2H, Pip 3,5-H), 2.43–2.71 (m, 2H, Pip 2,6-H), 3.15 (tt, J = 12.4 Hz, 3.5 Hz, 1H, Pip 4-H), 3.99–4.24 (m, 2H, Pip 2,6-H), 7.10–7.18 (m, 1H, NHPh 4-H), 7.33–7.39 (m, 4H, NHPh 3,5-H and NPh 2,6-H), 7.48–7.54 (m, 3H, NPh 3,4,5-H), 7.54–7.61 (m, 2H, NHPh 2,6-H), 7.67 (s, 1H, NH), 7.90 (s, 1H, Pyr 3-H).

¹C-NMR (101 MHz, CDCl₃): δ 28.6 (C(CH₃)₃), 29.6 (2 × CH₂, Pip 3,5-C), 35.4 (Pip 4-C), 44.3 (2 × CH₂, Pip 2,6-C), 79.6 (C(CH₃)₃), 116.0 (Pyr 4-C), 120.5 (2 × CH, NHPh 2,6-C), 124.6 (NHPh 4-C), 126.8 (2 × CH, NHPh 2,6-C), 129.2 (2 × CH, NHPh 3,5-C), 129.5 (2 × CH, NPh 3,5-C), 129.7 (NPh 4-C), 138.0 (NHPh 1-C), 138.9 (Pyr 3-C), 139.6 (NPh 1-C), 149.2 (Pyr 5-C), 154.9 (COOC(CH₃)₃), 161.8 (CONH).

13N-NMR (41 MHz, CDCl₃): δ −252.4 (NH), −159.8 (Pyr N-1), −76.7 (Pyr N-2). IR (FT-IR, νmax, cm⁻¹): 3390, 1671 (C=O), 1435, 748. MS m/z (%): 347 ([M-Boc + H]⁺, 99%). HRMS (ESI⁺) for C₂₉H₃₀N₄NaO₃ ([M + Na]⁺) calcd 469.2220, found 469.2220.

3.8.2. tert-Butyl
(3R)-3-[1-phenyl-4-(phenylcarbamoyle)-1H-pyrazol-5-yl]piperidine-1-carboxylate (10b)

White crystals, yield 197 mg (82%), mp 199–201 °C, [α]D²⁰ = −20.1 (c 0.87, MeOH).

¹H-NMR (400 MHz, CDCl₃): δ 1.40 (s, 10H, C(CH₃)₃ and Pip 5-H), 1.57–1.70 (m, 1H, Pip 5-H), 1.70–1.83 (m, 1H, Pip 5-H), 2.48 (qd, J = 12.9 Hz, 4.0 Hz, 1H, Pip 4-H), 2.69–3.05 (m, 2H, Pip 3,6-H), 3.49–3.81 (m, 1H, Pip 2-H), 3.88–4.24 (m, 2H, Pip 2,6-H), 7.10–7.18 (m, 1H, NHPh 4-H), 7.33–7.45 (m, 4H, NHPh 3,5-H and NPh 2,6-H), 7.46–7.59 (m, 5H, NHPh 2,6-H and NPh 3,4,5-H), 7.72 (s, 1H, NH), 7.92 (s, 1H, Pyr 3-H).

¹C-NMR (101 MHz, CDCl₃): δ 25.2 (Pip 5-C), 27.9 (Pip 4-C), 28.5 (C(CH₃)₃), 36.3 (Pip 3-C), 43.8 (Pip 6-C), 46.6 (Pip 2-C), 79.5 (C(CH₃)₃), 116.5 (Pyr 4-C), 120.6 (2 × CH, NHPh 2,6-C), 124.7 (NHPh 4-C), 126.5 (2 × CH, NPh 2,6-C), 129.3 (2 × CH, NHPh 3,5-C), 129.5 (3 × CH, NPh 3,4,5-C), 137.9 (NHPh 1-C), 139.1 (NPh 1-C), 139.3 (Pyr 3-C), 147.0 (Pyr 5-C), 154.8 (COOC(CH₃)₃), 161.8 (CONH).

15N-NMR (41 MHz, CDCl₃): δ −252.5 (NH), −158.7 (Pyr N-1), −77.1 (Pyr N-2). IR (FT-IR, νmax, cm⁻¹): 3400 (N-H), 1677 (C=O), 1405, 1137, 751. MS m/z (%): 447 ([M + H]⁺, 96%). HRMS (ESI⁺) for C₂₉H₃₀N₄NaO₃ ([M + Na]⁺) calcd 469.2220, found 469.2220. The enantiomeric excess was determined by HPLC with a CHIRAL ART Amylose-SA column, tR = 6.5 min (100%), ee = 100%.

3.8.3. tert-Butyl
(3S)-3-[1-phenyl-4-(phenylcarbamoyle)-1H-pyrazol-5-yl]piperidine-1-carboxylate (10c)

White crystals, yield 161 mg (67%), mp 199–201 °C, [α]D²⁰ = 19.9 (c 0.70, MeOH).

¹H-NMR (400 MHz, CDCl₃): δ 1.39 (s, 10H, C(CH₃)₃ and Pip 5-H), 1.57–1.67 (m, 1H, Pip 5-H), 1.71–1.80 (m, 1H, Pip 4-H), 2.48 (qd, J = 12.8 Hz, 1.8 Hz, 1H, Pip 4-H), 2.69–3.02 (m, 2H, Pip 3,6-H), 3.45–3.83 (m, 1H, Pip 2-H), 3.88–4.20 (m, 2H, Pip 2,6-H), 7.10–7.18 (m, 1H, NHPh 4-H), 7.33–7.44 (m, 4H, NHPh 3,5-H and NPh 2,6-H), 7.46–7.61 (m, 5H, NHPh 2,6-H and NPh 3,4,5-H), 7.75 (s, 1H, NH), 7.92 (s, 1H, Pyr 3-H).

¹C-NMR (101 MHz, CDCl₃): δ 25.2 (Pip 5-C), 27.9 (Pip 4-C), 28.5 (C(CH₃)₃), 36.3 (Pip 3-C), 43.9 (Pip 6-C), 46.6 (Pip 2-C), 79.5 (C(CH₃)₃), 116.5 (Pyr 4-C), 120.6 (2 × CH, NHPh 2,6-C), 124.6 (NHPh 4-C), 126.5 (2 × CH, NPh 2,6-C), 129.3 (2 × CH, NHPh 3,5-C), 129.5 (3 × CH, NPh 3,4,5-C), 137.9 (NHPh 1-C), 139.1 (NPh 1-C), 139.3 (Pyr 3-C), 147.0 (Pyr 5-C), 154.8 (COOC(CH₃)₃), 161.8 (CONH).

15N-NMR (41 MHz, CDCl₃): δ −252.4 (NH), −158.6 (Pyr N-1), −77.0 (Pyr N-2). IR (FT-IR, νmax, cm⁻¹): 3402 (N-H), 1677 (C=O), 1405, 1137, 751. MS m/z (%): 347 ([M-Boc + H]⁺), 447 ([M + H]⁺, 99%). HRMS (ESI⁺) for C₂₉H₃₀N₄NaO₃ ([M + Na]⁺) calcd 469.2220, found 469.2220. The enantiomeric excess was determined by HPLC with a CHIRAL ART Amylose-SA column, tR = 6.5 min (1.8% minor enantiomer), tR = 9.2 min (98.2% major enantiomer), ee = 96%.
4. Conclusions

In summary, we developed a new regioselective process for synthesizing 3- or 5-\((\text{N-Boc-piperidinyl})\)-1H-pyrazole-4-carboxylates as achiral and chiral heterocyclic building blocks. Regioselective synthesis of targeted building blocks was obtained starting from piperidine-4-carboxylic and (R)- and (S)-piperidine-3-carboxylic acids conversion to the corresponding \(\beta\)-enamino diketones via formation of intermediate \(\beta\)-keto esters. Further investigation of the reaction of \(\beta\)-enamino diketones with various aryl and alkyl hydrazines in various solvents at room temperature proved the regioselective formation of 5-\((\text{N-Boc-piperidinyl})\)-1H-pyrazole-4-carboxylates in ethanol compared to polar aprotic or nonprotic solvents. Regioisomeric 3-\((\text{N-Boc-piperidinyl})\)-1H-pyrazole-4-carboxylates were obtained by treating \(\beta\)-enamino diketones with hydrazine hydrate and subsequent alkylolation of tautomeric 3(5)-substituted NH-pyrazole with alkylhalides. Furthermore, we demonstrated that 5-\((\text{N-Boc-piperidinyl})\)-1H-pyrazole-4-carboxylates can be successfully applied to the synthesis of tert-butyl 3- and 4-[4-(phenylcarbamoyl)-1H-pyrazol-5-yl]piperidine-1-carboxylates by basic hydrolysis and the subsequent reaction of obtained carboxylic acids with aniline in the presence of EDC·HCl and DMAP. The structures of all synthesized compounds were confirmed by detailed NMR spectroscopy and HRMS investigations.

Supplementary Materials: The following are available online. Figure S1: \(^1\)H-NMR (700 MHz, CDCl\(_3\)) spectrum of compound 4a, Figure S2: \(^1\)C-NMR (176 MHz, CDCl\(_3\)) spectrum of compound 4a, Figure S3: \(^1\)H,\(^1\)N HMBC (71 MHz, CDCl\(_3\)) spectrum of compound 4a, Figure S4: HRMS (ESI-TOF) of compound 4a, Figure S5: \(^1\)H-NMR (700 MHz, CDCl\(_3\)) spectrum of compound 5a, Figure S6: \(^1\)C-NMR (176 MHz, CDCl\(_3\)) spectrum of compound 5a, Figure S7: \(^1\)H,\(^1\)N HMBC (71 MHz, CDCl\(_3\)) spectrum of compound 5a, Figure S8: HRMS (ESI-TOF) of compound 5a, Figure S9: \(^1\)H-NMR (700 MHz, CDCl\(_3\)) spectrum of compound 6a, Figure S10: \(^1\)C-NMR (176 MHz, CDCl\(_3\)) spectrum of compound 6a, Figure S11: \(^1\)H,\(^1\)N HMBC (71 MHz, CDCl\(_3\)) spectrum of compound 6a, Figure S12: HRMS (ESI-TOF) of compound 6a, Figure S13: \(^1\)H-NMR (400 MHz, CDCl\(_3\)) spectrum of compound 5b, Figure S14: \(^1\)C-NMR (101 MHz, CDCl\(_3\)) spectrum of compound 5b, Figure S15: \(^1\)H,\(^1\)N HMBC (41 MHz, CDCl\(_3\)) spectrum of compound 5b, Figure S16: HRMS (ESI-TOF) of compound 5b, Figure S17: \(^1\)H-NMR (400 MHz, CDCl\(_3\)) spectrum of compound 5c, Figure S18: \(^1\)C-NMR (176 MHz, CDCl\(_3\)) spectrum of compound 5c, Figure S19: \(^1\)N-NMR (41 MHz, CDCl\(_3\)) spectrum of compound 5c, Figure S20: HRMS (ESI-TOF) of compound 5c, Figure S21: \(^1\)H-NMR (400 MHz, CDCl\(_3\)) spectrum of compound 5d, Figure S22: \(^1\)C-NMR (101 MHz, CDCl\(_3\)) spectrum of compound 5d, Figure S23: \(^1\)H-\(^1\)N HMBC (41 MHz, CDCl\(_3\)) spectrum of compound 5d, Figure S24: HRMS (ESI-TOF) of compound 5d, Figure S25: \(^1\)H-NMR (400 MHz, CDCl\(_3\)) spectrum of compound 5e, Figure S26: \(^1\)C-NMR (101 MHz, CDCl\(_3\)) spectrum of compound 5e, Figure S27: \(^1\)H,\(^1\)N HMBC (41 MHz, CDCl\(_3\)) spectrum of compound 5e, Figure S28: HRMS (ESI-TOF) of compound 5e, Figure S29: \(^1\)H-NMR (400 MHz, CDCl\(_3\)) spectrum of compound 5f, Figure S30: \(^1\)C-NMR (176 MHz, CDCl\(_3\)) spectrum of compound 5f, Figure S31: \(^1\)N-NMR (41 MHz, CDCl\(_3\)) spectrum of compound 5f, Figure S32: HRMS (ESI-TOF) of compound 5f, Figure S33: \(^1\)H-NMR (400 MHz, CDCl\(_3\)) spectrum of compound 5g, Figure S34: \(^1\)C-NMR (101 MHz, CDCl\(_3\)) spectrum of compound 5g, Figure S35: HRMS (ESI-TOF) of compound 5g, Figure S36: \(^1\)H-NMR (700 MHz, CDCl\(_3\)) spectrum of compound 5h, Figure S37: \(^1\)C-NMR (176 MHz, CDCl\(_3\)) spectrum of compound 5h, Figure S38: \(^1\)H,\(^1\)N HMBC (71 MHz, CDCl\(_3\)) spectrum of compound 5h, Figure S39: HRMS (ESI-TOF) of compound 5h, Figure S40: \(^1\)H-NMR (400 MHz, CDCl\(_3\)) spectrum of compound 5i, Figure S41: \(^1\)C-NMR (101 MHz, CDCl\(_3\)) spectrum of compound 5i, Figure S42: \(^1\)H,\(^1\)N HMBC (41 MHz, CDCl\(_3\)) spectrum of compound 5i, Figure S43: HRMS (ESI-TOF) of compound 5i, Figure S44: \(^1\)H-NMR (400 MHz, CDCl\(_3\)) spectrum of compound 5j, Figure S45: \(^1\)C-NMR (101 MHz, CDCl\(_3\)) spectrum of compound 5j, Figure S46: \(^1\)H,\(^1\)N HMBC (41 MHz, CDCl\(_3\)) spectrum of compound 5j, Figure S47: HRMS (ESI-TOF) of compound 5j, Figure S48: \(^1\)H-NMR (400 MHz, CDCl\(_3\)) spectrum of compound 5k, Figure S49: \(^1\)C-NMR (101 MHz, CDCl\(_3\)) spectrum of compound 5k, Figure S50: HRMS (ESI-TOF) of compound 5k, Figure S51: \(^1\)H-NMR (400 MHz, CDCl\(_3\)) spectrum of compound 5l, Figure S52: \(^1\)C-NMR (101 MHz, CDCl\(_3\)) spectrum of compound 5l, Figure S53: \(^1\)H,\(^1\)N HMBC (41 MHz, CDCl\(_3\)) spectrum of compound 5l, Figure S54: HRMS (ESI-TOF) of compound 5l, Figure S55: \(^1\)H-NMR (400 MHz, CDCl\(_3\)) spectrum of compound 5m, Figure S56: \(^1\)C-NMR (101 MHz, CDCl\(_3\)) spectrum of compound 5m, Figure S57: HRMS (ESI-TOF) of compound 5m, Figure S58: \(^1\)H-NMR (700 MHz, CDCl\(_3\)) spectrum of compound 5n, Figure S59: \(^1\)C-NMR
(176 MHz, CDCl₃) spectrum of compound 5n, Figure S60: ¹H,¹³C HMBC (41 MHz, CDCl₃) spectrum of compound 5n, Figure S61: HRMS (ESI-TOF) of compound 5n, Figure S62: ¹H-NMR (700 MHz, CDCl₃) spectrum of compound 5o, Figure S63: ¹³C-NMR (176 MHz, CDCl₃) spectrum of compound 5o, Figure S64: HRMS (ESI-TOF) of compound 5o, Figure S65: ¹H-NMR (700 MHz, CDCl₃) spectrum of compound 7, Figure S66: ¹³C-NMR (176 MHz, CDCl₃) spectrum of compound 7, Figure S67: ¹H-¹H NOESY (CDCl₃) spectrum of compound 7, Figure S68: HRMS (ESI-TOF) of compound 7, Figure S69: ¹H-NMR (700 MHz, CDCl₃) spectrum of compounds 6i and 5i, Figure S70: ¹³C-NMR (176 MHz, CDCl₃) spectrum of compounds 6i and 5i, Figure S71: ¹H,¹³C HMBC (71 MHz, CDCl₃) spectrum of compounds 6i and 5i, Figure S72: HRMS (ESI-TOF) of compound 6i and 5i, Figure S73: ¹H-NMR (700 MHz, CDCl₃) spectrum of compound 8, Figure S74: ¹³C-NMR (176 MHz, CDCl₃) spectrum of compound 8, Figure S75: ¹H,¹⁵N HMBC (71 MHz, CDCl₃) spectrum of compound 8, Figure S76: HRMS (ESI-TOF) of compound 8, Figure S77: ¹H-NMR (400 MHz, CDCl₃) spectrum of compound 9a, Figure S78: ¹³C-NMR (101 MHz, CDCl₃) spectrum of compound 9a, Figure S79: ¹H,¹⁵N HMBC (41 MHz, CDCl₃) spectrum of compound 9a, Figure S80: HRMS (ESI-TOF) of compound 9a, Figure S81: ¹H-NMR (400 MHz, CDCl₃) spectrum of compound 9b, Figure S82: ¹³C-NMR (101 MHz, CDCl₃) spectrum of compound 9b, Figure S83: ¹H,¹³C HMBC (41 MHz, CDCl₃) spectrum of compound 9b, Figure S84: HRMS (ESI-TOF) of compound 9b, Figure S85: ¹H-NMR (400 MHz, CDCl₃) spectrum of compound 9c, Figure S86: ¹³C-NMR (101 MHz, CDCl₃) spectrum of compound 9c, Figure S87: HRMS (ESI-TOF) of compound 9c, Figure S88: ¹H-NMR (400 MHz, CDCl₃) spectrum of compound 10a, Figure S89: ¹³C-NMR (101 MHz, CDCl₃) spectrum of compound 10a, Figure S90: ¹H,¹⁵N HMBC (41 MHz, CDCl₃) spectrum of compound 10a, Figure S91: HRMS (ESI-TOF) of compound 10a, Figure S92: ¹H-NMR (400 MHz, CDCl₃) spectrum of compound 10b, Figure S93: ¹³C-NMR (101 MHz, CDCl₃) spectrum of compound 10b, Figure S94: ¹H,¹⁵N HMBC (41 MHz, CDCl₃) spectrum of compound 10b, Figure S95: HRMS (ESI-TOF) of compound 10b, Figure S96: ¹H-NMR (400 MHz, CDCl₃) spectrum of compound 10c, Figure S97: ¹³C-NMR (101 MHz, CDCl₃) spectrum of compound 10c, Figure S98: ¹H,¹⁵N HMBC (41 MHz, CDCl₃) spectrum of compound 10c, Figure S99: HRMS (ESI-TOF) of compound 10c.

Author Contributions: Conceptualization, F.A.S. and A.Š.; methodology, N.K.; validation, N.K., G.M. and G.R.; formal analysis, A.B., G.R. and M.D.; investigation, G.M., V.M. and M.D.; data curation, V.M.; writing—original draft preparation, A.Š., A.B., E.A. and G.M.; writing—review and editing, N.K. and V.K.; visualization A.B., A.Š. and E.A.; resources, F.A.S., supervision, A.Š. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Vipergen ApS (Copenhagen, Denmark).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding authors.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are not available from the authors.

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