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Synthesis and Rotational Isomerism of 1-Substituted Methyl (*S*)-[5-(2-Nitrophenyl)-1*H*-pyrazole-4-carbonyl]alaninates

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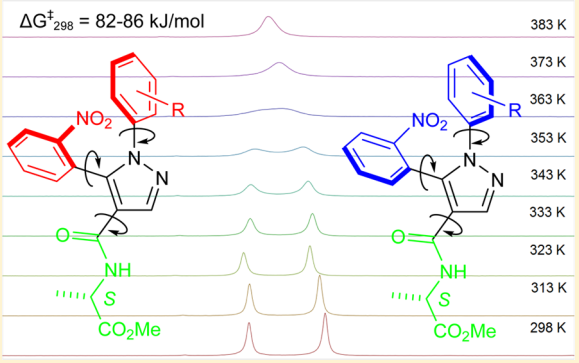
Supporting Information

ABSTRACT: Seven title compounds **12a–g** and the (*S*)-prolinate analogue **13** were prepared in five steps from 2-nitrobenzoic acid (**7**). Reduction of the nitro group followed by derivatization of the so formed anilines **14** gave the *N*-alkyl-(**15a–c**), *N*-acyl-(**16a,b** and **19**), and *N*-vinyl derivative **20**. NMR spectra of (*S*)-alanine and (*S*)-proline derived compounds **12**, **13**, **14–16**, **19**, and **20** exhibited two sets of signals corresponding to pairs of conformational diastereomers. The free energy barriers of rotation, $\Delta G^{\ddagger}_{298}$ = 82–86 kJ mol^{-1}, were determined by ^{1}H NMR for **12a**, **12d**, **12f**, and **12g** and evaluated by DFT calculations.



1. INTRODUCTION

Various heterocyclic systems are important scaffolds, which found a widespread use and application as building blocks, reagents, and ligands in synthetic and medicinal chemistry, (organo)catalysis, and material science.[1]

An important new approach to drug discovery involves the application of protein epitope mimetic (PEM) technology. The *β*-hairpin is an especially interesting naturally occurring scaffold used by many proteins for biomolecular recognition and thus is an attractive tool for mimetic design. Within this context, a variety of bi- and tricyclic systems can be envisaged as hairpin mimetics, such as D-Pro-L-Pro (**A**), azabicycloalkane amino acids **B**, 4,6-disubstituted dibenzo[*b*,*d*]furans and 9*H*-xanthenes **C**, and 2-(2′-(aminomethyl)-[1,1′-biphenyl]-2-yl)acetic acid (**D**). The last one is a particularly interesting PEM molecule and secondary structure stabilizing template. Though quite flexible at first glance, it is conformationally constrained due to the restricted rotation around the C–C bond connecting the aryl residues (Figure 1).[2,3]

Rotational isomerism describes the phenomenon of rotation about a single bond in a molecule.[4] Atropisomerism, described first by Christie and Kenner in 1922,[5] is a type of rotational (conformational) axial chirality-associated isomerism in which the isomers can be isolated.[6] As defined arbitrarily by Ōki, the condition for the existence of atropisomerism is, that one of the isolated isomers has a half-life time of at least 1000 s. Accordingly, the minimum free energy barrier should be 109.6 kJ mol^{-1} at 350 K.[7] From initial 'academic curiosity', axial chirality has recently been recognized as a fundamental basis for many reagents and catalysts in asymmetric synthesis[8] and as a decisive factor in pharmacological properties of bioactive compounds.[9] Nowadays, the majority of known axially chiral compounds are based on carbocyclic biaryls (e.g. BINAP,

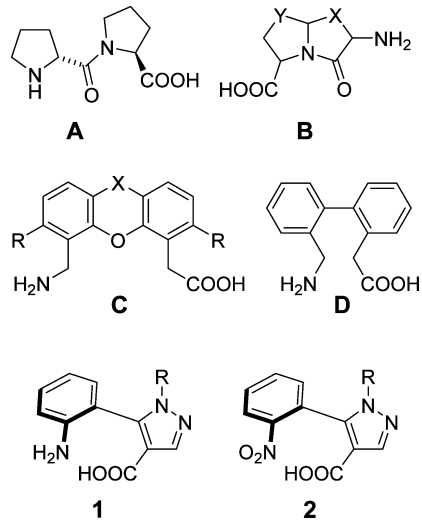


Figure 1. Examples of known PEM templates (hairpin mimetics) **A–D**,[2,3] potential PEM template **1**, and its nitro-masked precursor **2**.

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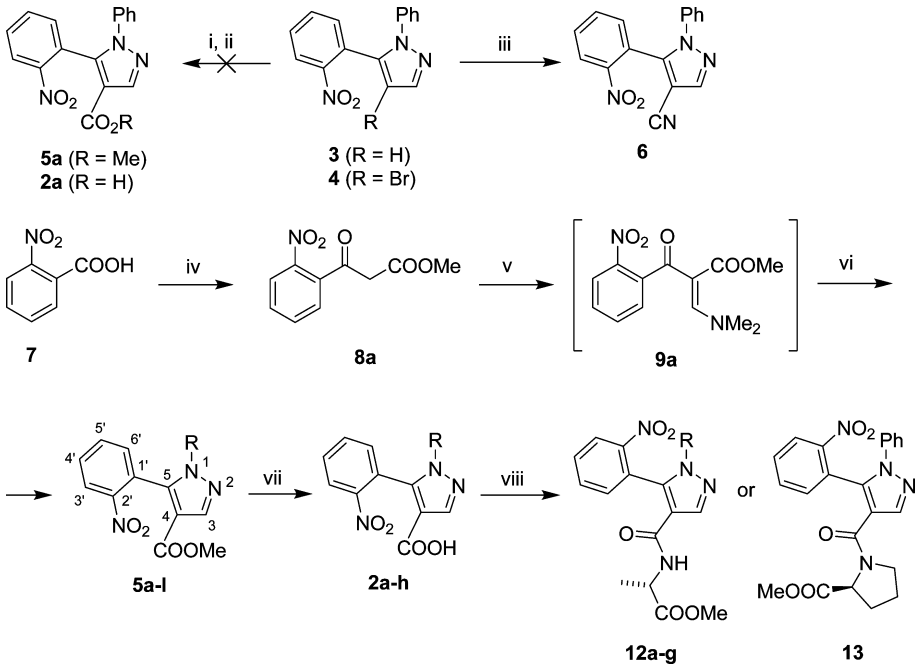
Scheme 1



[a]Reaction conditions: (i) BuLi, THF, − 78 °C; (ii) $ClCO_2Me$ or CO_2, −78 → 20 °C; (iii) KCN, NaI, CuI, toluene, reflux; (iv) CDI, THF, r.t., then $MeO_2CCH_2CO_2K$, $MgCl_2$, 60 °C; (v) DMFDMA, toluene, reflux; (vi) $RNHNH_2$·HCl (**10a−l**), *n*-PrOH or *n*-BuOH, reflux; (vii) 2 M NaOH, MeOH, 35 °C; (viii) CDI, MeCN, r.t., then (*S*)-AlaOMe·HCl (**11a**) or (*S*)-ProOMe·HCl (**11b**), NMM.

QINAP, BINOL, etc.),[8] whereas the field of hetarene-based analogues is somewhat less explored.[10]

Recently, we published a simple synthesis and some further transformations of 1-substituted 5-(2-aminophenyl)-1-phenyl-1*H*-pyrazoles.[11] In extension, we thought that 5-(2-aminophenyl)-1-phenyl-1*H*-pyrazole-4-carboxylic acid (**1**), available from the nitro-masked precursor **2**, might be an interesting axially chiral PEM template (cf. Figure 1). Additional motivation for this research was based on the literature search (SciFinder Scholar), which revealed that the majority of known 1,5-diaryl-1*H*-pyrazole-4-carboxamides were biologically active. For example, they are potent central nicotinic acetylcholine receptor antagonists[12] useful in treating small cell lung cancer,[13−16] they act as CB1[17] and histamine H3 receptor antagonists,[18] as cannabinoid receptor modulators,[19] as inhibitors of NHE-1,[20] and as fungicides.[21] Consequently, the above reasons triggered our decision to synthesize some derivatives of **1** and **2** to study their rotational isomerism. Herein, we report the synthesis and rotational isomerism of derivatives of **1** and **2** including experimental determination of rotation barriers by NMR spectroscopy.

2. RESULTS AND DISCUSSION

Starting compounds **3** and **4** were prepared in two steps from 2-nitroacetophenone following the literature procedure.[11] Attempted preparation of the key-intermediates **2a** and **5a** via lithiation/carboxylation of **3** and **4** failed, whereas Cu-catalyzed cyanation of **4** gave the cyano compound **6** in only 18% yield (Scheme 1, Table 1). Therefore, another synthetic approach was explored. Masamune-Claisen condensation of 2-nitrobenzoic acid (**7**), followed by treatment of the *β*-keto ester **8a** with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA), and cyclization of the intermediate enaminone **9a** with monosubstituted hydrazines **10a−l** in refluxing 1-propanol or 1-butanol gave the desired pyrazole derivatives **5a−l** in 24−98% yields over two steps. These were then hydrolyzed with 2 M NaOH in methanol at 35 °C and the carboxylic acids **2a−h** were finally coupled with L-AlaOMe (**11a**) and L-ProOMe (**11b**) to give the corresponding amides **12a−g** and **13** in 54−87% yields (Scheme 1, Table 1).

Table 1. Experimental Data for Compounds 2a−h, 5a−l, 12a−g, and 13

		yield (%)			
compound	R	**2**	**5**	**12**	**13**
2a, 5a, 10a, 12a, 13	Ph	96	48	72	54
2b, 5b, 10b, 12b	cyclohexyl	97	98	72	–
2c, 5c, 10c, 12c	*tert*-butyl	100	26	71	–
2d, 5d, 10d, 12d	2-pyridyl	84	40	75	–
2e, 5e, 10e, 12e	2-chlorophenyl	92	77	87	–
2f, 5f, 10f, 12f	2,4,6-trichlorophenyl	53	84	69	–
2g, 5g, 10g, 12g	4-methoxyphenyl	96	82	85	–
2h, 5h, 10h	2-bromophenyl	45	72	–	–
5i, 10i	Me	–	58	–	–
5j, 10j	2,2,2-trifluoroethyl	–	63	–	–
5k, 10k	CH_2CO_2Et	–	24	–	–
5l, 10l	6-phenylpyridazin-3-yl	–	85	–	–

To our great delight (although quite expectedly), the ^1H and ^{13}C NMR spectra of compounds **12** and **13** exhibited two sets of signals in a ratio of ∼1:1. This was in agreement with the proposed formation of a mixture of conformational diastereomers, presumably due to slow rotation around the C(5)−C(1′) bond (Figure 2). Unfortunately, attempts to separate the conformational diastereomers of **12** and **13** by preparative (CC, MPLC) and analytical (TLC, HPLC) chromatographic techniques failed.

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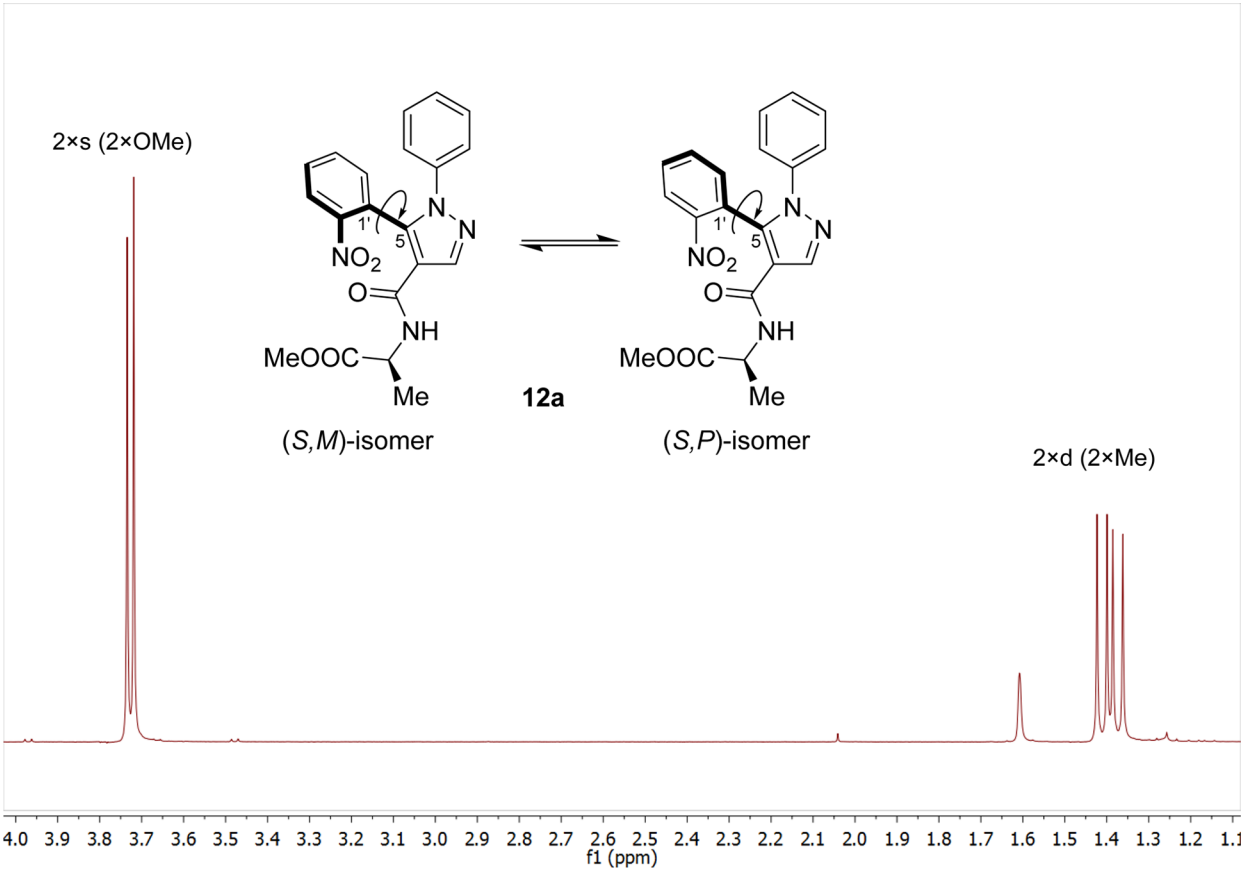
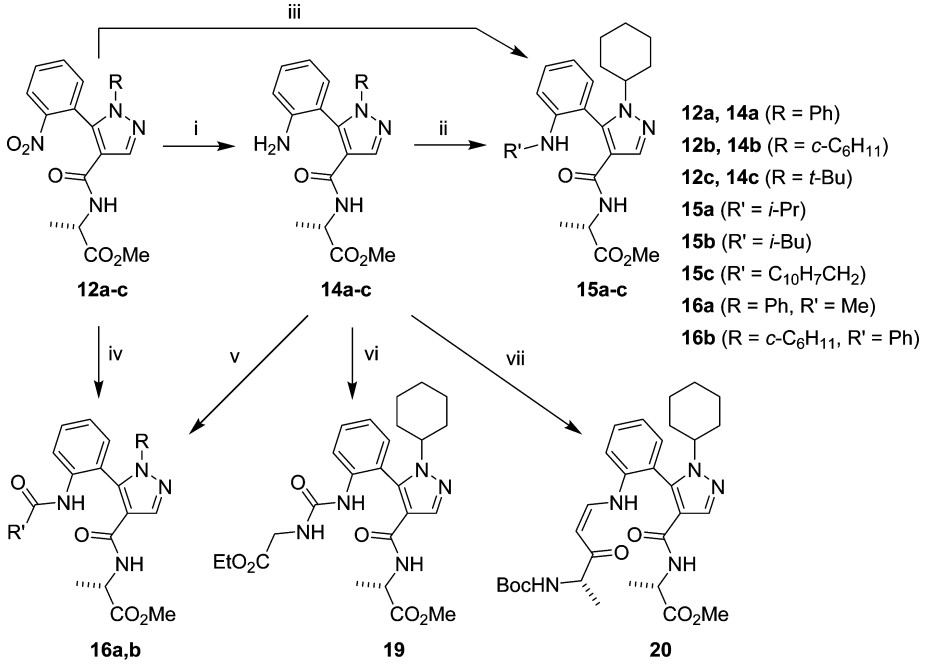


Figure 2. Partial ^{1}H NMR spectrum of compound **12a** ($CDCl_3$, 300 MHz) exhibiting two sets of signals corresponding to the (*S,M*)-isomer and the (*S,P*)-isomer.

Scheme 2



[a]Reaction conditions: (i) H_2, Pd−C, MeOH, r.t.; (ii) 2-naphthaldehyde, EtOH, r.t., then $NaBH_4$, MeOH, r.t.; (iii) H_2, Pd−C, MeOH, acetone or isobutyraldehyde, r.t.; (iv) H_2, Pd−C, AcOH, Ac_2O, r.t.; (v) PhCOCl, pyridine, 0 °C → r.t.; (vi) OCN−CH_2CO_2Et (**17**), CH_2Cl_2, r.t.; (vii) *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate (**18**), CH_2Cl_2, 0 °C → r.t.

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Our inability to separate the conformational diastereomers by chromatography was explainable at best by isomerization around the chiral axis being slow on the NMR chemical shift time scale, yet too fast for preparative separation. We then decided to carry out reduction of the nitro group followed by derivatization of the so formed aniline. We hoped that increased steric hindrance by bulky N-substituents in addition to possible intramolecular hydrogen bonding between the NH and C═O groups might slow down rotation around the C(5)−C(1′) bond. Catalytic hydrogenation of nitro compounds **12a−c** in the presence of Pd−C in methanol furnished the corresponding anilines **14a−c** in 71−87% yields, whereas reductive alkylation of **12b** with acetone and isobutyraldehyde furnished the *N*-alkylated anilines **15a** and **15b** in 59% and 61% yield, respectively (Scheme 2, Table 2). Reductive alkylation of **14b** with 2-naphthaldehyde and $NaBH_4$ gave **15c** in 36% yield. Next, catalytic hydrogenation of **12a** in a mixture of acetic acid and acetic anhydride gave the acetylamino derivative **16a** in 75% yield, whereas benzoylation of the aniline **14b** afforded the N-benzoyl analogue **16b** in 72% yield. Addition of **14b** to ethyl isocyanatoacetate (**17**) and to *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate (**18**)[22] led to the corresponding urea-(**19**) and enaminone derivative **20**. NMR spectra of the products **14−16**, **19**, and **20** exhibited two sets of signals, however, we were again not able to separate the isomers (Scheme 2, Table 2).

Table 2. Experimental Data for Compounds 14−16, 19, and 20

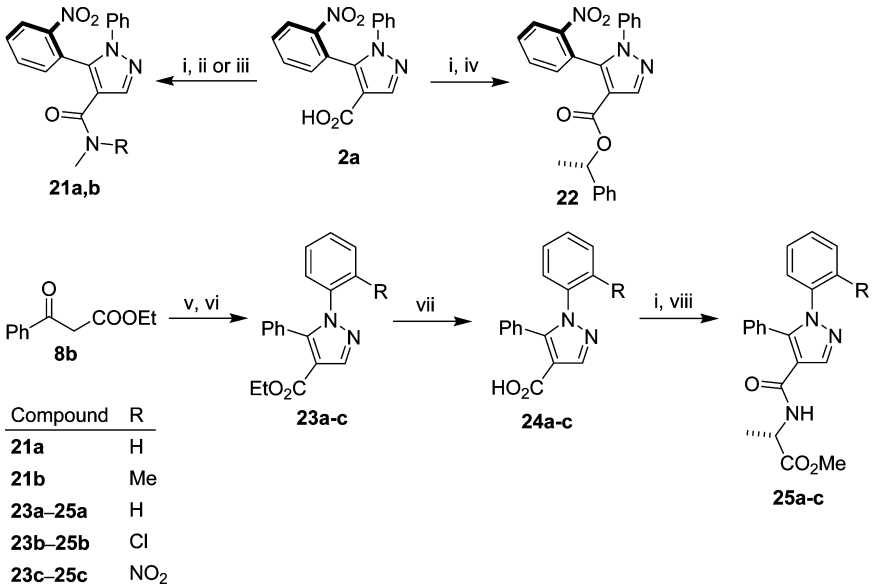
compd.	R	R′	yield (%)
14a	Ph	[a]	72
14b	*c*-C_6H_{11}	[a]	87
14c	*t*-butyl	[a]	71
15a	[a]	*i*-Pr	59
15b	[a]	*i*-Bu	61
15c	[a]	2-$C_{10}H_7CH_2$	36
16a	Ph	Me	75
16b	*c*-C_6H_{11}	Ph	72
19	[a]	[a]	72
20	[a]	[a]	74

[a]Not applicable.

Although existence of two conformational diastereomers in solution due to slow rotation of the nonsymmetrical 2-nitrophenyl group seemed obvious, also slow rotation of substituents at positions N(1) and C(4), as well as *cis*/*trans*-isomerization of the carboxamido group had to be taken into account. To clarify this issue, some more derivatives with different substitution pattern were synthesized. *N*-Methyl carboxamides **21a,b** and the (*S*)-1-phenylethyl ester **22** were obtained by coupling of **2a** with the corresponding nucleophiles, while (*S*)-1-aryl-5-phenyl-1*H*-pyrazole-4-carbonyl)alaninates **25a−c** were synthesized from ethyl benzoylacetate (**8b**) following standard synthetic protocol (Scheme 3, cf. Scheme 1). NMR spectra of compounds **21a,b**, **23a−c**, **24a−c** devoid of a chiral center and NMR spectra of (*S*)-alaninates **25a−c** with symmetrical phenyl group at position 5 and a chiral center at the side chain exhibited single sets of signals. Diastereotopicity of nuclei was observed only in NMR spectra of (*S*)-1-phenylethyl ester **22** with a nonsymmetrical nitrophenyl group at position 5 and a chiral center at the side chain. This indicated, that anisochronicity of nuclei resulted only from the combination of chiral center and chiral axis due to slow rotation of the 5-nitrophenyl group, whereas other aforementioned isomerisations were not relevant in this respect (Scheme 3).

3. Structure Determination. The structures of novel compounds **2a−h**, **5a−l**, **12a−g**, **13**, **14a−c**, **15a−c**, **16a,b**, **19**, **20**, **21a,b**, **22**, **23b,c**, **24b,c**, and **25a−c** were determined by spectroscopic methods (IR, ^1H and ^{13}C NMR, and MS) and by elemental analyses for C, H, and N. Compounds **2c**, **2d**, **2g**, **5h**, **5k**, **13**, **14c**, **15b**, **16b**, **19**, **20**, **22**, **23b,c**, and **24b,c** were not

Scheme 3



[a]Reaction conditions: (i) CDI, MeCN, r.t.; (ii) add $MeNH_2$·HCl, NMM, r.t.; (iii) add 2 M Me_2NH in MeOH, r.t.; (iv) add (*S*)-1-phenylethanol, r.t.; (v) DMFDMA, toluene, reflux; (vi) $RNHNH_2$·HCl (**10a,e**) or 2-$O_2NC_6H_5NHNH_2$·HCl (**10m**), *n*-PrOH, reflux; (vii) 2 M NaOH, MeOH, 35 °C; (viii) add (*S*)-AlaOMe·HCl (**11a**), NMM.

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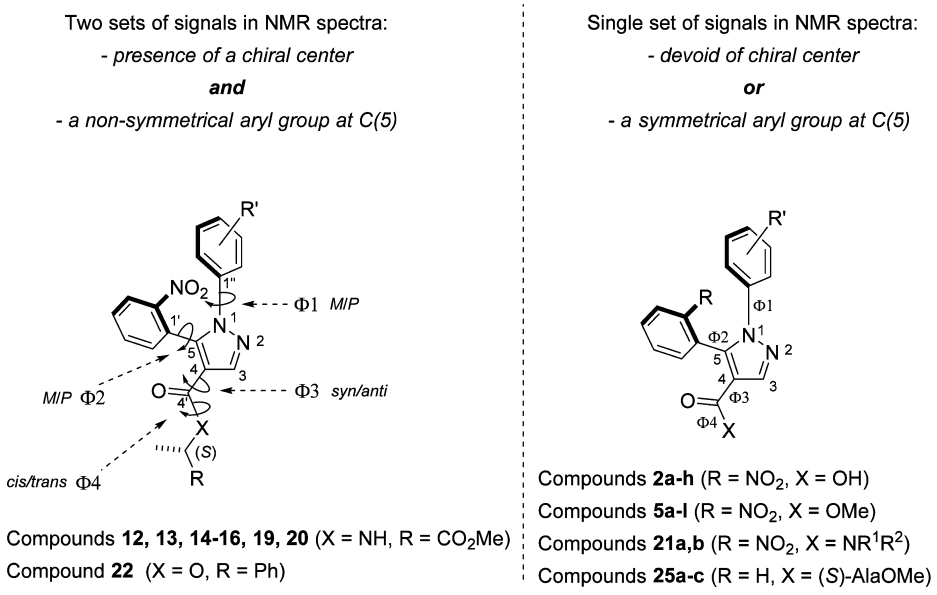

Figure 3. Conformational isomerism and torsion angles Φ1−Φ4 in compounds **5**, **12**, **14**−**16**, **19**−**22**, and **25**.

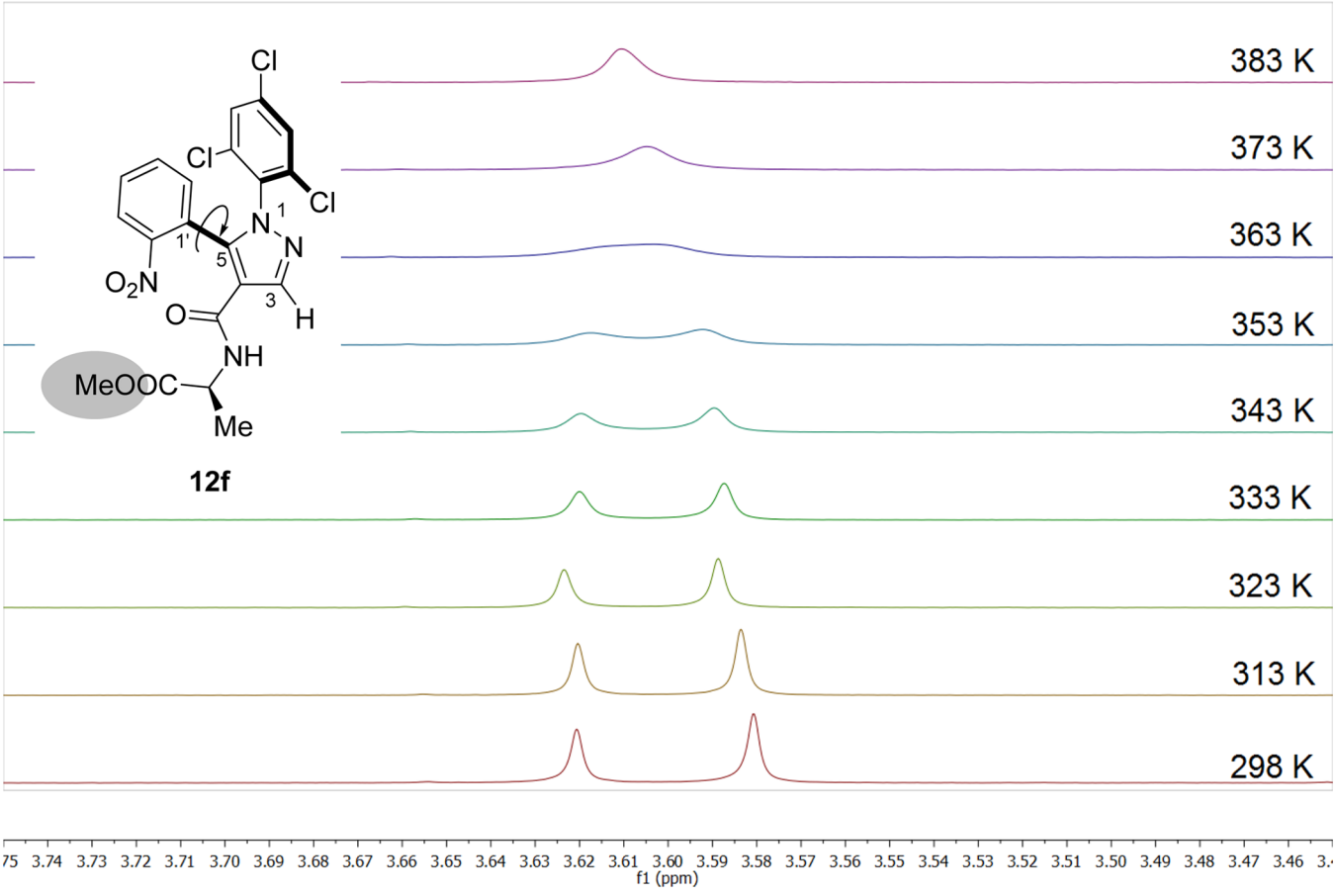

Figure 4. Partial ^{1}H NMR spectrum of **12f** (DMSO-d_6, 300 MHz) at 298−383 K showing the singlets for the OMe group. The coalescence temperature (T_c) is around 365 K.

obtained in analytically pure form. Their identities were confirmed by ^{13}C NMR and/or EI-HRMS.

The structures of compounds **4**, **6**, **5e**, **5f**, and **25b** were determined by X-ray diffraction, which unambiguously confirmed axial chirality of these compounds.[23] Unfortunately, the crystal structures were not compliant with structural requirements for β-turn minetics.[2f,g] Crystal structures of compounds **4**, **6**, **5e**, **5f**, and **25b** are depicted in the Supporting Information.

Rotational isomerism of compounds **5**, **12**, **13**, **14**−**16**, and **19**−**25** in solution was studied by NMR. In $CDCl_3$ and DMSO-d_6 solution, all pyrazole derivatives **5**, **12**, **13**, **14**−**16**, and **19**−

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Table 3. Selected Thermodynamic Parameters for Compounds 12a, 12d, 12f, and 12g Determined by ^{1}H NMR in DMSO-d_6 Using CTM and CLA Approach

		compound			
entry	parameter	**12a**	**12d**	**12f**	**12g**
1	$\Delta\nu_0$ (s^{-1})[a]	11.8	3.1	10.5	12.0
2	k_c (s^{-1})	26.1	6.91	23.3	26.6
3	T_c (K)[b]	423	375	365	431
4	$\Delta G^{\ddagger}_c$ (kJ/mol)[c]	93.3	95.1	80.2	94.8
5	$\Delta G^{\ddagger}_c$ (kJ/mol)[d]	93.4	91.1	80.3	95.0
6	E_a (kJ/mol)[b]	70.8	51.1	96.0	62.8
7	$\Delta H^{\ddagger}$ (kJ/mol)[e]	67.8	48.2	93.0	59.8
8	$\Delta S^{\ddagger}$ (J/mol K)[e]	−0.88	−1.65	0.50	−1.18
9	$\Delta G^{\ddagger}_{298}$ (kJ/mol)[b]	85.9	82.3	82.7	84.2
10	k_{298} (s^{-1})[b]	5.5×10^{-3}	2.31×10^{-2}	1.97×10^{-2}	1.08×10^{-2}

[a] $\Delta\nu_0$ is chemical shift difference for OMe of each diastereomer in DMSO-d_6 at 298 K. [b] Obtained from k_c and plot of ln k against 1000/T. [c] From $\Delta G^{\ddagger}_c = 19.1 \times 10^{-3} \cdot T_c \cdot (9.97 + \log T_c - \log|\Delta\nu_0|)$. [d] From $\Delta G^{\ddagger}_T = RT \cdot (23.76 + \ln T - \ln k)$. [e] Obtained from plot of $\ln(k/T)$ against $1000/T$.

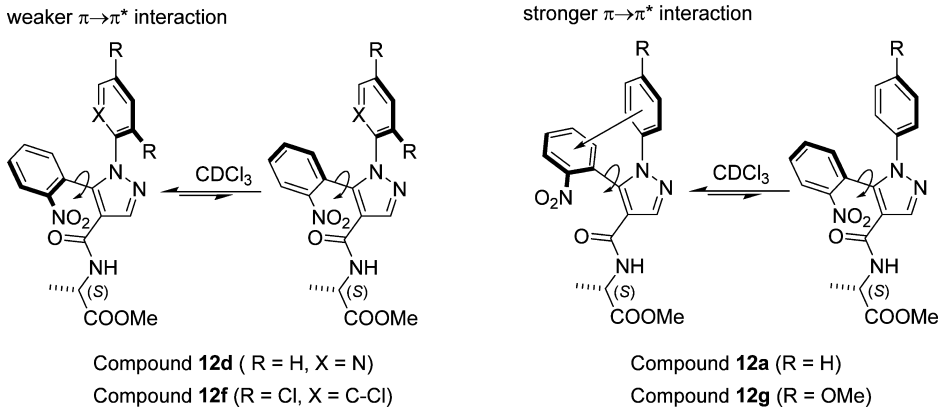

Figure 5. Comparison of $\pi \rightarrow \pi^*$ interactions in compounds **12d**, **12f** and **12a**, **12g**.

25 with at least one nonsymmetrical substituent exist as interconverting mixtures of conformational isomers, due to rotation around the following single bonds (Figure 3): N(1)−C(1″) bond (torsion angle Φ1), C(5)−C(1′) bond (torsion angle Φ2), C(4)−C(4′) bond (torsion angle Φ3), and the amide or ester bond (torsion angle Φ4). Single sets of signals in the NMR spectra of compounds **2**, **5**, **21**, **23**, and **24** devoid of a stereogenic center are in agreement with conformational enantiomers and isochronous enantiotopic nuclei (Figure 3, right). Accordingly, introduction of a chiral center at the side chain in compounds **12**, **13**, **14**−**16**, **19**, **20**, **22**, and **25** should induce diastereotopicity to nuclei. However, anisochronicity of diastereotopic nuclei was observed only for compounds **12**, **13**, **14**−**16**, **19**, **20**, and **22** with a nonsymmetrical 2-nitropenyl group at position 5 (Figure 3, left), whereas in compounds **25a**−**c** with a symmetrical phenyl group at position 5 the nuclei remained isochronous (Figure 3, right). In the presence of a chiral center in compounds **25a**−**c**, isochrony of nuclei is explainable by fast rotation around Φ1, Φ3, and Φ4. This clearly leads to the conclusion that diastereotopicity of nuclei in compounds **12**, **13**, **14**−**16**, **19**, **20**, and **22** is induced by a combination of a chiral center at the side chain and chiral axis formed by slow rotation around Φ2. On the other hand, rotation around the other bonds is faster and, hence, does not induce diastereotopicity (Figure 3).

4. Experimental Determination of Rotational Barrier through ^{1}H NMR Data. The ^{1}H NMR spectra of compounds **12a**, **12d**, **12f**, and **12g** were measured in DMSO-d_6 at different temperatures ranging from 298 to 393 K. The singlet for OMe group was chosen as the reference signal. The coalescence of signals was not reached for **12a** and **12g**, while the signals for **12d** and **12f** coalesced at ∼375 K and ∼365 K, respectively. ^{1}H NMR spectrum of compound **12f** in region 3.45−3.75 ppm is depicted in Figure 4.[23]

On the basis of the above temperature dependent ^{1}H NMR data, the experimental free energy of activation for rotation at the temperature of coalescence, $\Delta G^{\ddagger}_c$, was determined for compounds **12a**, **12d**, **12f**, and **12g** using coalescence temperature method (CTM).[24−27] The rates of rotation at T_c were determined using the equation for symmetrical exchange, $k_c = \pi \cdot \Delta\nu_0/2^{1/2}$, whereas the $\Delta G^{\ddagger}_c$ values were determined from the modified Eyring equation.[25] The results are summarized in Table 3 (Entries 1−4).[23] Next, thermodynamic parameters for the above compounds were determined by the complete line shape analysis method (CLA).[24,25,27] The rates of isomerization were determined from the modified Eyring equations for the intermediate and fast exchange.[28] The coalescence temperature (T_c), free energy of activation for rotation, $\Delta G^{\ddagger}_c$, and activation energy for rotation (isomerization), E_a, were determined from Arrhenius plot of ln k against $1000/T$.[29] Since the relative proportion of the two rotamers was close to 1:1, the $\Delta G^{\ddagger}_c$ was determined from the modified Eyring equation for equally populated rotamers.[30,31] The $\Delta H^{\ddagger}$ and the $\Delta S^{\ddagger}$, were determined from Arrhenius plot of $\ln(k/T)$ against $1000/T$. The results are summarized in Table 3 (Entries 5−10).[23] The experimental free energy barriers of rotation at 298 K for compounds **12a**, **12d**, **12f**, and **12g**, $\Delta G^{\ddagger}_{298}$ = 82.3−85.9 kJ mol^{-1} (Table 3, Entry 9), were below the arbitrary limit, $\Delta G^{\ddagger}_{300}$ > 93.5 kJ mol^{-1}, defined by Ōki.[7]

^{1}H NMR data and thermodynamic parameters obtained by CLA approach (cf. Table 3) reveal, that compounds **12d** and **12f** exhibit slightly lower free energy of activation for rotation, $\Delta G^{\ddagger}_{298}$ = 82.3 and 82.7 kJ mol^{-1} at 298 K which is reflected in lower coalescence

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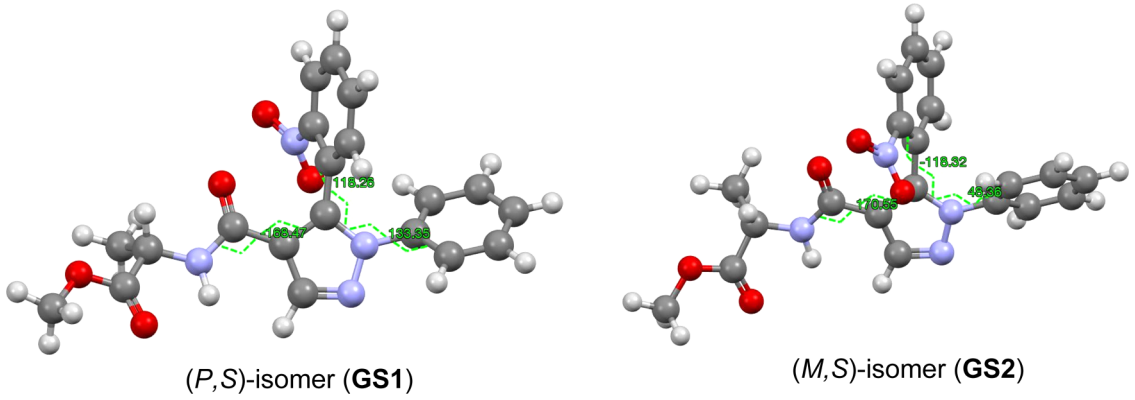

Figure 6. GS1-global minimum (left) and GS2-local minimum (right) conformations of **12a**.

temperature, T_c = 375 and 365 K (cf. Table 3). Accordingly, isomerization of **12d** and **12f** ($k_{298} \sim 0.02$ s^{-1}) is faster than isomerization of **12a** and **12g** ($k_{298} \leq 0.01$ s^{-1}). This difference is explainable by the $\pi \rightarrow \pi^*$ interactions between the aromatic rings. Higher energy barrier of rotation in compounds **12a** and **12g** is in agreement with stronger $\pi \rightarrow \pi^*$ interactions between electron-poor 2-nitrophenyl group and electron-rich N-aryl groups. On the other hand, such $\pi \rightarrow \pi^*$ interactions are weaker in compounds **12d** and **12f** bearing electron-poor N-aryl groups (Figure 5).

5. Computational Determination of Rotational Barrier and Modes of Rotation. Finally, the observations on the conformational equilibrium were corroborated by quantum mechanical calculations at the B3LYP/6-311G and B3LYP/6-311+G(d,p) level of theory in the gas phase by means of the Gaussian 09 software.[32] The stationary points at the potential energy surface (PES) were determined and the structure was characterized as minima or transition state based on the number of imaginary frequencies (0 or 1). Pyrazole ring represented the rigid part, while the aryl substituents and the amide moiety exhibited conformational freedom. Torsion angles Φ1, Φ2, Φ3, and Φ4 used to follow energetic changes induced by rotations are defined on Figure 3. PES, obtained at the B3LYP/6-311G level of theory, revealed the (*P*,*S*)-conformer as the GS1-global minimum with the lowest energy and the (*M*,*S*)-conformer as the GS2-local minimum, optimized with the B3LYP/6-311+G(d,p) level of theory, which is marginally (0.33 kJ/mol) higher in energy in the gas phase. This result is in excellent agreement with the experimental value, ΔG_{298} = 0.30 kJ/mol, determined by ^{1}H NMR from the 53:47 ratio of conformational diastereomers of **12a** in $CDCl_3$ at 298 K. The PES scan also revealed four possible transition state conformations. TS1 and TS2 correspond to the conversion of [GS1] ↔ [TS1] ↔ [GS2] ↔ [TS2] ↔ [GS1] via rotation around Φ1 and Φ2. They are of the same geometry and energy ΔE is located 97.1 kJ/mol above the GS1. TS3 and TS4 were found during simultaneous rotation of the nitrophenyl substituent (Φ2) and the amide side chain (Φ3). The respective energies (ΔE) of TS3 and TS4, 109.3, and 91.9 kJ/mol, indicated that TS4 was 17.4 kJ/mol more stable than TS3. Finally, TS5 and TS6 were identified upon 360° scan of the amide bond dihedral (Φ4) in the GS1-global minimum conformation. The sum of three bond angles around the amide nitrogen (an index of sp^3 character)[33] in TS5 and TS6 was 339.7° and 334.6°, respectively. This indicated strong sp^3 character on the amide nitrogen in allocated transition states TS5 and TS6. The evaluated amide bond rotational barrier for the compound **12a** (ΔE = 75.6 kJ/mol) was in the range of expectancy according to the literature data.[34] The fully optimized ground-state structures (GS1 and GS2) of **12a** at B3LYP/6-311+G(d,p) level are shown in Figure 6. Total and relative energies for **12a** obtained by DFT calculations are given in Table 4. The PES scans (obtained at the B3LYP/6-311G level of theory) and geometries of transition states TS1−TS6 (optimized at the B3LYP/6-311+G(d,p) level of theory) are given in the Supporting Information.

Thus, evaluation of the conformational freedom in derivative **12a** by DFT method demonstrated that the rotational barrier of nitrophenyl ring is for ΔE = 17.4 kJ/mol higher in energy than that of the resonance stabilized amide bond. The obtained data support conformational change form [GS1] to [GS2] via TS4 with ΔG_{298} = 102.4 kJ/mol rotational barrier that is in fair agreement with the experimental value.

Table 4. Total Energies and Relative Energies Obtained by DFT Calculation for Compound 12a

	B3LYP/6−311+G(d,p)		
	E_{ZPE} (a.u.)[a]	ΔE (kJ/mol)	ΔG (kJ/mol)
GS1-global minimum	−1368.02465	0	
GS2-local minimum	−1368.02453	0.33[b]	0.32[b]
TS1	−1367.98766	97.1	104.2
TS2	−1367.98766	97.1	104.2
TS3	−1367.98303	109.3	119.1
TS4	−1367.98966	91.9	102.4
TS5	−1367.99265	84.0	86.5
TS6	−1367.99629	74.5	75.6

[a]Zero-point energy corrected values (EZPE) of B3LYP/6-311+G(d,p). [b]A 53:47 ratio of conformational diastereomers of **12a** in $CDCl_3$ at 298 K corresponds to energy difference, ΔG_{298} = 0.30 kJ/mol.

6. CONCLUSION

In summary, methyl (1-substituted-5-(2-nitrophenyl)-1*H*-pyrazole-4-carbonyl)-L-alaninates **12a−g** and their 5-(2-aminophenyl) analogues **14−16**, **19**, and **20** were prepared as potential PEM templates in 4−6 steps from 2-nitrobenzoic acid (**7**). NMR spectra of compounds **12**, **13**, **14−16**, **19**, and **20** exhibit two sets of signals, which are due to slow rotation of 2-nitrophenyl group. The axial chirality of these compounds was additionally confirmed by their crystal structures. The experimental free energy of rotation at T_c and at 350 K was determined by ^{1}H NMR for compounds **12a**, **12d**, **12f**, and **12g**. Our inability to separate the isomers is explainable by the experimental value for free energy of rotation, $\Delta G^{\ddagger}_{298}$ = 82−86 kJ mol^{-1}, which is below the arbitrary limit, $\Delta G^{\ddagger}_{300}$ > 93.5 kJ mol^{-1}, defined by Ōki.[7] Evaluation of the conformational freedom in derivative **12a** by DFT method was in agreement with the experimental data indicating that rotational barrier of nitrophenyl ring was higher in energy than that of resonance stabilized amide bond. The experimental and computational results also suggest that rotation of the nitrophenyl group (atropisomerization) occurs in a molecular gear-type process through simultaneous rotation of the 1-aryl, 5-(2-nitrophenyl), and 4-carboxamido group. In terms of PEM, title compounds are too rigid to be good mimics; however, increased flexibility

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induced by replacement of the amino and carboxy groups with aminomethyl and carboxymethyl groups could make the template **1** a better β-turn mimic.

7. EXPERIMENTAL SECTION

7.1. General Methods. Melting points were determined on a Kofler micro hot stage and on an automated melting point system. The NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 using TMS as the internal standard on a 300 or 500 MHz instrument at 300 and 500 MHz for ^{1}H and at 75.5 and 126 MHz for ^{13}C nucleus, respectively. Optical rotations were measured on polarimeter using 1 mL cell with a 10 cm path lenghth. Mass spectra were recorded on TOF LC/MS spectrometer and IR spectra on a FTIR ATR spectrophotometer. Microanalyses were performed by combustion analysis on a CHN analyzer. Catalytic hydrogenations were carried out on a hydrogenation apparatus (500 mL), always at room temperature under 4 bar of H_2. Column chromatography (CC), flash column chromatography (FC), and dry-vacuum flash chromatography (DVFC) were performed on silica gel (particle size 35−70 μm). 2-Nitrobenzoic acid (**7**), CDI, potassium monomethyl malonate, DMFDMA, hydrazine derivatives **10a−l**, (*S*)-α-amino acid esters hydrochlorides **11a,b**, isobutyraldehyde, IBCF, and ethyl isocyanatoacetate (**17**) are commercially available. 4-Bromo-5-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole (**4**)[11] and *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)-carbamate (**18**)[22] were prepared according to the literature procedures.

The temperature dependent NMR data were acquired on 300 MHz NMR spectrometer equipped with 5 mm 1*H*/19F/X PFG ATB Broadband Probe at 298 K. ^{1}H spectra were obtained with a 5000 Hz sweep width, 3.7 s acquisition time, 9.0 μs (90°) pulse width, 15 s delay time and 16 scans. Chemical shifts were referenced to the residual solvent signal of DMSO-d_6 at δ_H 2.50 ppm. Temperature-dependent measurements were carried out between 313 and 393 K with steps of 10 K.

7.2. 5-(2-Nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (6). A 10 mL Schlenk flask was charged with 4-bromo-5-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole (**4**)[11] (1.72 g, 5 mmol), NaI (150 mg, 1 mmol), CuI (95 mg, 0.5 mmol), and KCN (390 mg, 6 mmol), the flask was evacuated, and filled with argon. Anhydrous toluene (5 mL) and *N*,*N*-dimethylethylenediamine (0.54 mL, 5 mmol) were added, the mixture was refluxed under argon for 24 h, and cooled to room temperature. Aqueous ammonia (25%, 10 mL) was added and the product was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over anh. sodium sulfate, filtered, and the filtrate was evaporated in vacuo. The residue was purified by DVFC (silica gel, EtOAc−hexanes, 1:1). Fractions containing the product were combined and evaporated in vacuo. The residue was further purified by MPLC (silica gel, EtOAc−hexanes, 1:2). Fractions containing the product were combined and evaporated in vacuo to give **6**. Yield: 255 mg (18%) of yellowish crystals; mp 131−134 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (2H, dd, J = 8.2, 1.4 Hz); 7.28−7.34 (3H, m); 7.58 (1H, dd, J = 7.6, 1.4 Hz); 7.69 (1H, td, J = 8.2, 1.4 Hz); 7.79 (1H, td, J = 7.6, 1.1 Hz); 8.08 (1H, s); 8.11 (1H, dd, J = 8.2, 1.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 94.7, 112.8, 122.4, 124.3, 124.6, 125.6, 129.1, 129.4, 131.7, 132.6, 134.1, 137.9, 142.6, 143.9. m/z (ESI) = 291 (MH^+). m/z (HRMS) Found: 291.0876 (MH^+). $C_{16}H_{11}N_4O_2$ requires: m/z = 291.0877. (Found: C 65.82, H 3.28, N 18.87. $C_{16}H_{10}N_4O_2 \cdot 1/8H_2O$ requires: C 65.69, H 3.53, N 19.15.); ν_{max} (ATR) 3130, 2232 (CN), 1524, 1496, 1347, 759, 691 cm^{-1}.

7.3. Synthesis of Methyl 3-(2-nitrophenyl)-3-oxopropanoate (8a). CDI (1.79 g, 11 mmol) was added to a solution of 2-nitrobenzoic acid (**7**) (1.68 g, 10 mmol) in acetonitrile (25 mL) and the mixture was stirred at r.t. for 1 h. Then, a solid well homogenized mixture of powdered anh. $MgCl_2$ (0.95 g, 10 mmol) and potassium monomethyl malonate (2.34 g, 15 mmol) was added, and the mixture was stirred at 70 °C for 90 h. Volatile components were evaporated in vacuo, the residue was taken up in EtOAc (50 mL), and the so formed suspension washed with 1 M $NaHSO_4$ (3 × 50 mL), saturated aq. $NaHCO_3$ (3 × 50 mL), and brine (70 mL). The organic phase was dried for 20 min over anh. Na_2SO_4, filtered, and the filtrate was evaporated in vacuo to give **8a**. Yield: 1.58 g (70%) of yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.73 (3H, s); 3.90 (2H, s); 7.53 (1H, dd, J = 7.5, 1.3 Hz); 7.65 (1H, ddd, J = 8.1, 7.5, 1.2 Hz); 7.78 (1H, td, J = 7.5, 1.3 Hz); 8.18 (1H, dd, J = 8.1, 1.2 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 48.7, 52.5, 124.3, 128.1, 131.0, 134.6, 136.7, 145.3, 167.1, 194.6. m/z (ESI) = 224 (MH^+). m/z (HRMS) Found: 224.0556 (MH^+). $C_{10}H_{10}NO_5$ requires: m/z = 224.0565. ν_{max} (ATR) 2955, 1740 (C═O), 1526, 1437, 1345, 1203, 987, 699 cm^{-1}.

7.4. General Procedure for the Synthesis of 1-Substituted Methyl 5-(2-nitrophenyl)-1*H*-pyrazole-4-carboxylates 5a−l. A mixture of **8a** (0.67 g, 3 mmol), anh. toluene (10 mL), and DMFDMA (0.5 mL, 3.3 mmol) was stirred under reflux for 4 h and volatile components were evaporated in vacuo to give the crude enaminone **9** as a brown oily residue. The residue was dissolved in 1-propanol (10 mL) or 1-butanol (10 mL), hydrazine derivative **10a−l** (3.6 mmol) and 37% hydrochloric acid (6 drops) were added, and the mixture was stirred under reflux for 3−32 h. Volatile components were evaporated in vacuo and the residue was purified by FC (EtOAc/hexanes). Fractions containing the product were combined and evaporated in vacuo to give the crude products **5a−l**. The solid products **5a−f,i,j,l** were suspended in Et_2O or *i*-Pr_2O (15 mL), the suspensions were stirred at r.t. for 1 h, and the precipitates were collected by filtration and washed with Et_2O or *i*-Pr_2O (2 × 5 mL) to give the purified compounds **5a−f,i,j,l**. The oily products **5g,h,k** were purified by CC (EtOAc/hexanes). Fractions containing the product were combined and evaporated in vacuo to give the crude products **5g,h,k**.

7.4.1. Methyl 5-(2-nitrophenyl)-1-phenyl-1H-pyrazole-4-carboxylate (5a). Prepared from **8a** (1.08 g, 4.8 mmol), DMFDMA (0.75 mL, 5 mmol), and phenylhydrazine hydrochloride **10a** (0.84 g, 5.8 mmol) in 1-propanol, reflux for 4 h, FC (EtOAc/hexanes, 1:2), trituration with Et_2O. Yield: 744 mg (48%) of white crystals; mp 124−126 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (3H, s), 7.18−7.22 (1H, m), 7.26−7.33 (5H, m), 7.53−7.60 (2H, m), 8.11−8.16 (1H, m), 8.18 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.4, 113.5, 124.6, 125.0, 128.5, 129.1, 130.5, 132.6, 133.0, 138.6, 141.6, 142.2, 142.2, 149.1, 162.9. m/z (ESI) = 324 (MH^+). m/z (HRMS) Found: 324.0984 (MH^+). $C_{17}H_{14}N_3O_4$ requires: m/z = 324.0984. (Found: C, 63.07; H, 3.84; N, 13.04. $C_{17}H_{13}N_3O_4$ requires: C, 63.16; H, 4.05; N, 13.00.); ν_{max} (ATR) 3123, 2953, 1712 (C═O), 1528, 1503, 1351, 1239, 773 cm^{-1}.

7.4.2. Methyl 1-cyclohexyl-5-(2-nitrophenyl)-1H-pyrazole-4-carboxylate (5b). Prepared from **8a** (1.58 g, 7.1 mmol), DMFDMA (1.2 mL, 8 mmol), and cyclohexylhydrazine hydrochloride **10b** (1.20 g, 8 mmol) in 1-propanol, reflux for 14 h, FC (EtOAc), trituration with Et_2O. Yield: 1.43 g (63%) of yellowish crystals; mp 167−169 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10−1.30 (3H, m); 1.64 (1H, br d, J = 12.4 Hz); 1.79−2.09 (6H, m); 3.62 (3H, s); 3.70 (1H, tt, J = 11.5, 4.1 Hz); 7.34 (1H, dd, J = 7.5, 1.6 Hz); 7.70 (1H, td, J = 7.8, 1.6 Hz); 7.76 (1H, td, J = 7.5, 1.4 Hz); 8.00 (1H, s); 8.23 (1H, dd, J = 8.1, 1.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.1, 25.5, 25.5, 32.5, 33.3, 51.3, 59.3, 111.9, 125.0, 125.2, 130.8, 132.0, 133.4, 140.9, 140.9, 149.2, 163.3. m/z (ESI) = 330 (MH^+). m/z (HRMS) Found: 330.1450 (MH^+). $C_{17}H_{20}N_3O_4$ requires: m/z = 330.1448. (Found: C, 62.01; H, 5.65; N, 12.65. $C_{17}H_{19}N_3O_4$ requires: C, 62.00; H, 5.81; N, 12.76.); ν_{max} (ATR) 2939, 2860, 1710 (C═O), 1523, 1349, 1214, 782 cm^{-1}.

7.4.3. Methyl 1-tert-butyl-5-(2-nitrophenyl)-1H-pyrazole-4-carboxylate (5c). Prepared from **8a** (0.67 g, 3 mmol), DMFDMA (0.5 mL, 3.3 mmol), and *tert*-butylhydrazine hydrochloride **10c** (0.47 g, 3.8 mmol) in 1-butanol, reflux for 32 h, FC (EtOAc/hexanes, 1:1), trituration with *i*-Pr_2O. Yield: 0.26 g (26%) of yellowish crystals; mp 106−108 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (9H, s, *t*-Bu), 3.59 (3H, s), 7.40 (1H, dd, J = 7.4, 1.7 Hz), 7.66 (1H, td, J = 7.8, 1.7 Hz), 7.71 (1H, td, J = 7.5, 1.5 Hz), 7.96 (1H, s), 8.24 (1H, dd, J = 8.0, 1.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 30.7, 51.2, 63.2, 113.2, 125.0, 128.2, 130.5, 132.6, 133.0, 139.7, 141.1, 148.4, 163.3. m/z (ESI) = 304 (MH^+). m/z (HRMS) Found: 304.1294 (MH^+). $C_{15}H_{18}N_3O_4$ requires: m/z = 304.1292. (Found: C, 59.70; H, 5.56; N, 13.77. $C_{15}H_{17}N_3O_4$ requires: C, 59.40; H, 5.65; N, 13.85.); ν_{max} (ATR) 2986, 2952, 1707 (C═O), 1519, 1341, 1213, 1149, 1020, 758 cm^{-1}.

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*7.4.4. Methyl 5-(2-nitrophenyl)-1-(2-pyridyl)-1H-pyrazole-4-carboxylate (**5d**).* Prepared from **8a** (0.67 g, 3 mmol), DMFDMA (0.5 mL, 3.3 mmol), 2-hydrazinopyridine **10d** (0.41 g, 3.8 mmol), and 37% hydrochloric acid (6 drops) in 1-butanol, reflux for 24 h, FC (EtOAc/hexanes, 1:1), trituration with *i*-Pr_2O. Yield: 0.38 g (40%) of yellowish crystals; mp 137−139 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (3H, s); 7.11 (1H, ddd, J = 7.4, 4.9, 1.1 Hz); 7.36 (1H, dd, J = 7.3, 1.7 Hz); 7.60 (1H, td, J = 7.5, 1.7 Hz); 7.64 (1H, td, J = 7.5, 1.6 Hz); 7.76 (1H, ddd, J = 8.3, 7.4, 1.9 Hz); 7.86 (1H, dt, J = 8.2, 1.0 Hz); 8.00 (1H, ddd, J = 4.8, 1.8, 0.8 Hz); 8.20 (1H, s); 8.25 (1H, dd, J = 8.0, 1.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.6, 115.0, 116.6, 122.6, 124.5, 127.1, 129.9, 132.3, 133.0, 138.7, 142.4, 142.6, 147.7, 148.4, 151.7, 162.9. m/z (ESI) = 325 (MH^+). m/z (HRMS) Found: 325.0933 (MH^+). $C_{16}H_{13}N_4O_4$ requires: m/z = 325.0931. (Found: C, 59.29; H, 3.42; N, 17.40. $C_{16}H_{12}N_4O_4$ requires: C, 59.26; H, 3.73; N, 17.28.); ν_{max} (ATR) 3122, 2950, 1707 (C═O), 1517, 1345, 1290, 1240, 781, 759 cm^{-1}.

*7.4.5. Methyl 1-(2-chlorophenyl)-5-(2-nitrophenyl)-1H-pyrazole-4-carboxylate (**5e**).* Prepared from **8a** (2.23 g, 10 mmol), DMFDMA (1.5 mL, 10 mmol), and 2-chlorophenylhydrazine hydrochloride **10e** (1.97 g, 11 mmol) in 1-propanol, reflux for 24 h, DVFC (EtOAc/hexanes, 1:2), trituration with Et_2O. Yield: 2.75 g (77%) of white crystals; mp 113−117 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (3H, s); 7.20 (1H, td, J = 7.7, 0.9 Hz); 7.31 (1H, td, J = 7.9, 1.4 Hz); 7.35 (2H, dd, J = 7.8, 1.1 Hz); 7.45 (1H, dd, J = 8.0, 0.6 Hz); 7.50−7.57 (2H, m); 8.06−8.11 (1H, m); 8.22 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.5, 113.1, 124.1, 124.6, 127.7, 129.6, 130.3, 130.6, 131.1, 132.1, 132.2, 133.0, 136.2, 142.3, 143.5, 148.8, 162.9. m/z (ESI) = 358, 360 (MH^+). m/z (HRMS) Found: 358.0589 (MH^+). $C_{17}H_{13}ClN_3O_4$ requires: m/z = 358.0589. (Found: C, 57.13; H, 3.29; N, 11.64. $C_{17}H_{12}ClN_3O_4$ requires: C, 57.07, H, 3.38, N, 11.75.); ν_{max} (ATR) 2950, 1712 (C═O), 1522, 1498, 1346, 1237, 1136, 758 cm^{-1}.

*7.4.6. Methyl 5-(2-nitrophenyl)-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carboxylate (**5f**).* Prepared from **8a** (2.23 g, 10 mmol), DMFDMA (1.5 mL, 10 mmol), 2,4,6-trichlorophenylhydrazine **10f** (2.33 g, 11 mmol), and 37% aq. HCl (0.7 mL) in 1-propanol, reflux for 24 h, DVFC (EtOAc/hexanes, 1:1), trituration with *i*-Pr_2O. Yield: 3.57 g (84%) of white crystals; mp 175−177 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.72 (3H, s); 7.31 (1H, d, J = 2.2 Hz); 7.33 (1H, dd, J = 7.5, 1.8 Hz); 7.44 (1H, d, J = 2.2 Hz); 7.54 (1H, td, J = 7.5, 1.6 Hz); 7.58 (1H, td, J = 7.8, 1.8 Hz); 8.20 (1H, dd, J = 7.9, 1.6 Hz); 8.28 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.7, 114.6, 123.1, 125.6, 128.8, 129.2, 131.1, 131.3, 133.1, 133.3, 135.5, 136.2, 137.0, 143.3, 143.8, 148.4, 162.9. m/z (ESI) = 426, 428, 430 (MH^+). m/z (HRMS) Found: 425.9810 (MH^+). $C_{17}H_{11}Cl_3N_3O_4$ requires: m/z = 425.9810. (Found: C, 47.89; H, 2.34; N, 9.73. $C_{17}H_{10}Cl_3N_3O_4$ requires: C, 47.86, H, 2.36, N, 9.85.); ν_{max} (ATR) 3094, 1709 (C═O), 1530, 1352, 1230, 957, 807, 757 cm^{-1}.

*7.4.7. Methyl 1-(4-methoxyphenyl)-5-(2-nitrophenyl)-1H-pyrazole-4-carboxylate (**5g**).* Prepared from **8a** (0.67 g, 3 mmol), DMFDMA (0.5 mL, 3.3 mmol), and 4-methoxyphenylhydrazine hydrochloride **10g** (0.63 g, 3.6 mmol) in 1-butanol, reflux for 16 h, FC (EtOAc/hexanes, 1:2). Yield: 0.868 g (82%) of brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.68 (3H, s); 3.76 (3H, s); 6.77−6.81 (2H, m); 7.19−7.23 (3H, m); 7.54−7.58 (2H, m); 8.10−8.13 (1H, m); 8.15 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.4, 55.4, 113.2, 114.2, 124.6, 125.0, 126.4, 130.4, 131.7, 132.7, 133.0, 141.6, 141.9, 149.0, 159.4, 163.0. m/z (ESI) = 354 (MH^+). m/z (HRMS) Found: 354.1098 (MH^+). $C_{18}H_{16}N_3O_5$ requires: m/z = 354.1084. ν_{max} (ATR) 2953, 1711 (C═O), 1512, 1348, 1228, 1135, 1016, 834, 808, 781, 752 cm^{-1}.

*7.4.8. Methyl 1-(2-bromophenyl)-5-(2-nitrophenyl)-1H-pyrazole-4-carboxylate (**5h**).* Prepared from **8a** (446 mg, 2 mmol), DMFDMA (0.3 mL, 2 mmol), 2-bromophenylhydrazine **10h** (492 mg, 2.2 mmol), and 37% aq. HCl (4 drops) in 1-propanol, reflux for 24 h, DVFC (EtOAc/hexanes, 1:2). Yield: 80 mg (72%) of brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.70 (3H, s); 7.23−7.27 (2H, m); 7.33−7.37 (1H, m); 7.39−7.44 (1H, m); 7.51−7.58 (2H, m); 7.62−7.67 (1H, m); 8.07−8.11 (1H, m); 8.23 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.5, 113.2, 122.1, 124.1, 124.6, 128.4, 129.6, 130.7, 131.3, 132.2, 133.1, 133.6, 137.9, 142.2, 143.3, 148.9, 163.0. m/z (ESI) = 402, 404 (MH^+). m/z (HRMS) Found: 402.0082 (MH^+). $C_{17}H_{13}BrN_3O_4$ requires: m/z = 402.0084. ν_{max} (ATR) 2951, 1711 (C═O), 1525, 1497, 1436, 1347, 1232, 1137, 755, 730 cm^{-1}.

*7.4.9. Methyl 1-methyl-5-(2-nitrophenyl)-1H-pyrazole-4-carboxylate (**5i**).* Prepared from **8a** (0.67 g, 3 mmol), DMFDMA (0.5 mL, 3.3 mmol), methylhydrazine **10i** (0.17 g, 3.8 mmol), and 37% hydrochloric acid (6 drops) in 1-propanol, reflux for 4 h, FC (EtOAc/hexanes, 3:1), trituration with *i*-Pr_2O. Yield: 0.45 g (58%) of yellowish crystals; mp 114−116 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.63 (3H, s); 3.72 (3H, s, 1-Me); 7.40 (1H, dd, J = 7.5, 1.5 Hz, 6′-H); 7.70 (1H, td, J = 7.8, 1.5 Hz, 5′-H); 7.77 (1H, td, J = 7.6, 1.3 Hz, 4′-H); 7.97 (1H, s); 8.23 (1H, dd, J = 8.1, 1.3 Hz, 3′-H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 37.4, 51.3, 112.9, 124.8, 125.0, 130.9, 132.2, 133.5, 140.9, 142.0, 148.9, 163.1. m/z (ESI) = 262 (MH^+). m/z (HRMS) Found: 262.0825 (MH^+). $C_{12}H_{12}N_3O_4$ requires: m/z = 262.0822. (Found: C, 55.15; H, 4.03; N, 16.03. $C_{12}H_{11}N_3O_4$ requires: C, 55.17; H, 4.24; N, 16.09.); ν_{max} (ATR) 2951, 1707 (C═O), 1529, 1355, 1215, 757 cm^{-1}.

*7.4.10. Methyl 5-(2-nitrophenyl)-1-(2,2,2-trifluoroethyl)-1H-pyrazole-4-carboxylate (**5j**).* Prepared from **8a** (0.67 g, 3 mmol), DMFDMA (0.5 mL, 3.3 mmol), 2,2,2-trifluoroethylhydrazine **10j** (0.43 g, 3.8 mmol), and 37% hydrochloric acid (6 drops) in 1-butanol, reflux for 4 h, FC (EtOAc/hexanes, 1:1), trituration with *i*-Pr_2O. Yield: 0.67 g (63%) of yellowish crystals; mp 106−108 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.64 (3H, s); 4.41 and 4.70 (2H, 2 sextets, 1:1, J = 16.2 Hz); 7.25 (1H, br d, J = 7.4 Hz); 7.75 (1H, td, J = 7.8, 1.6 Hz); 7.80 (1H, td, J = 7.5, 1.5 Hz); 8.08 (1H, s); 8.26 (1H, dd, J = 8.1, 1.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 50.9 (q, J = 35.6 Hz), 51.6, 114.3, 122.6 (q, J = 280 Hz), 123.4, 125.2, 131.6, 132.8, 133.7, 142.4, 143.7, 148.8, 162.5. m/z (ESI) = 330 (MH^+). m/z (HRMS) Found: 330.0694 (MH^+). $C_{13}H_{11}F_3N_3O_4$ requires: m/z = 330.0696. (Found: C, 47.71; H, 2.84; N, 12.56. $C_{13}H_{10}F_3N_3O_4$ requires: C, 47.43; H, 3.06; N, 12.76.); ν_{max} (ATR) 2972, 1702 (C═O), 1526, 1237, 1214, 1158, 785 cm^{-1}.

*7.4.11. Methyl 1-(2-ethoxy-2-oxoethyl)-5-(2-nitrophenyl)-1H-pyrazole-4-carboxylate (**5k**).* Prepared from **8a** (0.67 g, 3 mmol), DMFDMA (0.5 mL, 3.3 mmol), and ethyl 2-hydrazinoacetate hydrochloride **10k** (0.59 g, 3.8 mmol) in 1-butanol, reflux for 4 h, FC (EtOAc/hexanes, 1:1). Yield: 0.23 g (24%) of yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (3H, t, J = 7.1 Hz); 3.64 (3H, s); 4.17 and 4.23 (2H, 2dq, 1:1, J = 10.8, 7.1 Hz); 4.56 and 4.93 (2H, 2d, 1:1, J = 17.4 Hz); 7.50 (1H, dd, J = 7.2, 1.8 Hz); 7.70 (1H, td, J = 7.6, 1.7 Hz); 7.73 (1H, td, J = 7.5, 1.5 Hz); 8.04 (1H, s); 8.21 (1H, dd, J = 7.9, 1.6 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 51.5, 51.6, 62.3, 113.6, 124.0, 124.9, 131.2, 132.6, 133.4, 141.8, 142.8, 149.0, 162.9, 167.3. m/z (ESI) = 334 (MH^+). m/z (HRMS) Found: 334.1030 (MH^+). $C_{15}H_{16}N_3O_6$ requires: m/z = 334.1034. ν_{max} (ATR) 2954, 1746 (C═O), 1712 (C═O), 1528, 1349, 1214, 1022, 783 cm^{-1}.

*7.4.12. Methyl 5-(2-nitrophenyl)-1-(6-phenylpyridazin-3-yl)-1H-pyrazole-4-carboxylate (**5l**).* Prepared from **8a** (0.67 g, 3 mmol), DMFDMA (0.5 mL, 3.3 mmol), 3-hydrazino-6-phenylpyridazine **10l** (0.80 g, 3.8 mmol), and 37% hydrochloric acid (6 drops) in 1-butanol, reflux for 24 h, FC (EtOAc/hexanes, 1:1), trituration with *i*-Pr_2O. Yield: 1.02 g (85%) of brownish crystals; mp 181−184 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (3H, s); 7.45−7.49 (3H, m); 7.50 (1H, br dd, J = 7.6, 1.5 Hz); 7.64 (1H, td, J = 8.2, 1.5 Hz); 7.71 (1H, td, J = 7.5, 1.3 Hz); 7.92−7.96 (2H, m); 7.96 (1H, d, J = 9.2 Hz); 8.21 (1H, d, J = 9.2 Hz); 8.27 (1H, s); 8.28 (1H, br dd, J = 8.4, 1.1 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 51.7, 115.8, 121.6, 125.0, 126.4, 126.7, 127.3, 129.2, 130.4, 130.4, 132.4, 133.4, 135.4, 142.9, 143.5, 147.8, 154.4, 159.0, 162.6. m/z (ESI) = 402 (MH^+). m/z (HRMS) Found: 402.1197 (MH^+). $C_{21}H_{16}N_5O_4$ requires: m/z = 402.1197. (Found: C, 62.98; H, 3.50; N, 17.33. $C_{21}H_{15}N_5O_4$ requires: C, 62.84; H, 3.77; N, 17.45.); ν_{max} (ATR) 2952, 1716 (C═O), 1535, 1350, 1244, 1131, 781, 740, 684 cm^{-1}.

7.5. General Procedure for the Synthesis of 1-Substituted 5-(2-Nitrophenyl)-1*H*-pyrazole-4-carboxylic acids 2a−l. A mixture of the ester **5** (2.7 mmol), methanol (30 mL), and 2 M aq. NaOH (5.9 mL, 11.8 mmol) was stirred at 50 °C for 24 h. Methanol was evaporated in vacuo (40 mbar, 40 °C) and the aqueous solution was

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acidified with 1 M aq. HCl to pH ~ 1. The precipitate was collected by filtration and washed with water (2 × 5 mL) to give **2a**–**g**.

*7.5.1. 5-(2-Nitrophenyl)-1-phenyl-1H-pyrazole-4-carboxylic acid (**2a**).* Prepared from **5a** (3.23 g, 10 mmol). Yield: 2.977 g (96%) of white crystals; mp 210–213 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19–7.24 (1H, m); 7.25–7.32 (5H, m); 7.53–7.60 (2H, m); 8.09–8.15 (1H, m); 8.20 (1H, s); 9.86 (1H, br s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 113.0, 124.6, 124.8, 125.0, 128.6, 129.1, 130.6, 132.7, 133.1, 138.5, 142.5, 142.9, 148.7, 167.8. *m/z* (ESI) = 310 (MH^+). *m/z* (HRMS) Found: 310.0829 (MH^+). $C_{16}H_{12}N_3O_4$ requires: *m/z* = 310.0828. (Found: C, 61.71; H, 3.64; N, 13.34. $C_{16}H_{11}N_3O_4$ requires: C, 62.14; H, 3.58; N, 13.59.); ν_{max} (ATR) 3412, 2876, 1672 (C═O), 1532, 1501, 1356, 783 cm^{-1}.

*7.5.2. 1-Cyclohexyl-5-(2-nitrophenyl)-1H-pyrazole-4-carboxylic acid (**2b**).* Prepared from **5b** (0.90 g, 2.7 mmol). Yield: 0.66 g (78%) of white crystals; mp 235–238 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.07–1.19 (3H, m); 1.56 (1H, br s); 1.67–1.99 (6H, m); 3.73 (1H, qt, *J* = 11.5, 4.0 Hz); 7.59 and 7.60 (1H, 2dd, 1;1, *J* = 7.6, 1.2 Hz); 7.80 and 7.84 (1H, 2td, *J* = 8.1 and 1.4 Hz); 7.88 and 7.90 (1H, 2td, td, *J* = 7.5, 1.2 Hz); 7.92 and 7.99 (1H, 2s, 1:1); 8.23 and 8.26 (1H, 2dd, *J* = 8.2, 1.3 Hz); 12.18 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ 24.7, 24.7, 32.2, 32.5, 58.1, 112.0, 124.2, 124.7, 131.1, 132.1, 133.8, 140.4, 148.7, 163.4. *m/z* (ESI) = 316 (MH^+). *m/z* (HRMS) Found: 316.1294 (MH^+). $C_{16}H_{18}N_3O_4$ requires: *m/z* = 316.1292. (Found: C, 59.90; H, 5.28; N, 13.08. $C_{16}H_{17}N_3O_4 \cdot 1/4H_2O$ requires: C, 60.09; H, 5.52; N, 13.14.); ν_{max} (ATR) 2941, 2857, 1666 (C═O), 1531, 1346, 1224, 779, 695 cm^{-1}.

*7.5.3. 1-tert-Butyl-5-(2-nitrophenyl)-1H-pyrazole-4-carboxylic acid (**2c**).* Prepared from **5c** (0.53 g, 1.7 mmol). Yield: 0.51 g (100%) of white crystals; mp 191–194 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.39 (9H, s); 7.62 (1H, dd, *J* = 7.5, 1.6 Hz); 7.77 (1H, td, *J* = 7.8, 1.6 Hz); 7.82 (1H, td, *J* = 7.5, 1.4 Hz); 7.90 (1H, s); 8.22 (1H, dd, *J* = 8.2, 1.32 Hz); 12.07 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ 30.2, 62.6, 113.4, 124.7, 127.3, 130.9, 132.9, 133.4, 139.4, 140.5, 148.0, 163.4. *m/z* (ESI) = 290 (MH^+). *m/z* (HRMS) Found: 290.1136 (MH^+). $C_{14}H_{16}N_3O_4$ requires: *m/z* = 290.1135. (Found: C, 58.15; H, 5.14; N, 14.27. $C_{14}H_{15}N_3O_4$ requires: C, 58.13; H, 5.23; N, 14.53.); ν_{max} (ATR) 3459, 2989, 1694 (C═O), 1521, 1354, 1231, 77 cm^{-1}.

*7.5.4. 5-(2-Nitrophenyl)-1-(2-pyridyl)-1H-pyrazole-4-carboxylic acid (**2d**).* Prepared from **5d** (1.55 g, 4.8 mmol). Yield: 1.30 g (84%) of white crystals; mp 175–177 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.28 (1H, ddd, *J* = 7.4, 4.9, 1.1 Hz); 7.44 (1H, dd, *J* = 7.1, 2.0 Hz); 7.70 (1H, td, *J* = 7.5, 1.9 Hz); 7.72 (1H, td, *J* = 7.4, 1.7 Hz); 7.85 (1H, dt, *J* = 8.3, 1.0 Hz); 7.97 (1H, ddd, *J* = 8.9, 7.5, 1.9 Hz); 8.02 (1H, ddd, *J* = 4.8, 1.8, 0.8 Hz); 8.24 (1H, dd, *J* = 7.1, 2.0 Hz); 8.28 (1H, s); 12.60 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ 115.5, 116.8, 123.1, 124.2, 126.5, 130.3, 132.3, 133.5, 139.5, 141.7, 142.6, 147.6, 147.9, 151.1, 163.2. *m/z* (ESI) = 311 (MH^+). *m/z* (HRMS) Found: 311.0775 (MH^+). $C_{15}H_{11}N_4O_4$ requires: *m/z* = 311.0775. (Found: C, 57.78; H, 3.21; N, 17.89. $C_{15}H_{10}N_4O_4$ requires: C, 58.07; H, 3.25; N, 18.06.); ν_{max} (ATR) 2926, 1725 (C═O), 1529, 1435, 1349, 1238, 790, 774 cm^{-1}.

*7.5.5. 1-(2-Chlorophenyl)-5-(2-nitrophenyl)-1H-pyrazole-4-carboxylic acid (**2e**).* Prepared from **5e** (1.79 g, 5 mmol). Yield: 1.58 g (92%) of brownish crystals; mp 217–229 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.19 (1H, td, *J* = 7.7, 1.4 Hz); 7.27–7.38 (3H, m); 7.41–7.47 (1H, m); 7.47–7.53 (2H, m); 8.01–8.07 (1H, m); 8.23 (1H, s). ^{13}C NMR (126 MHz, DMSO-d_6) δ 113.9, 124.3, 124.5, 127.6, 129.5, 130.3, 130.4, 131.0, 132.1, 132.1, 133.0, 136.3, 142.8, 143.3, 148.7, 164.2. *m/z* (ESI) = 344, 346 (MH^+). *m/z* (HRMS) Found: 344.0433 (MH^+). $C_{16}H_{11}ClN_3O_4$ requires: *m/z* = 344.0433. (Found: C, 56.19; H, 2.80; N, 12.26. $C_{16}H_{10}ClN_3O_4$ requires: C, 55.91; H, 2.93; N, 12.23.); ν_{max} (ATR) 2865, 1709 (C═O), 1526, 1504, 1229, 1206, 1144, 777, 761 cm^{-1}.

*7.5.6. 5-(2-Nitrophenyl)-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carboxylic acid (**2f**).* Prepared from **5f** (2.13 g, 5 mmol). Yield: 1.1 g (53%) of white crystals; mp 210–216 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.30 (1H, dd, *J* = 7.2, 1.8 Hz); 7.68–7.77 (2H, m); 7.83 (1H, d, *J* = 2.3 Hz); 8.00 (1H, d, *J* = 2.3 Hz); 8.23 (1H, dd, *J* = 7.9, 1.7 Hz); 8.32 (1H, s); 12.75 (1H, br s). ^{13}C NMR (126 MHz, DMSO-d_6) δ 114.8, 122.1, 125.3, 129.0, 129.1, 130.9, 131.6, 132.6, 133.7, 133.7, 135.4, 136.2, 142.8, 143.1, 147.6, 163.0. *m/z* (ESI) = 412, 414, 416 (MH^+). *m/z* (HRMS) Found: 411.9653 (MH^+). $C_{16}H_9Cl_3N_3O_4$ requires: *m/z* = 411.9653. (Found: C, 46.34; H, 1.90; N, 10.10. $C_{16}H_8Cl_3N_3O_4$ requires: C, 46.57; H, 1.59; N, 10.18.); ν_{max} (ATR) 2872, 1681 (C═O), 1533, 1498, 1479, 1350, 1298, 856, 777 cm^{-1}.

*7.5.7. 1-(4-Methoxyphenyl)-5-(2-nitrophenyl)-1H-pyrazole-4-carboxylic acid (**2g**).* Prepared from **5g** (707 mg, 2 mmol). Yield: 651 mg (96%) of brown crystals; mp 115–120 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (3H, s); 6.76–6.80 (2H, m); 7.17–7.20 (2H, m); 7.21–7.23 (1H, m); 7.53–7.58 (2H, m); 8.08–8.12 (1H, m); 8.17 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 55.4, 113.2, 114.2, 124.7, 125.0, 126.5, 130.3, 131.7, 132.8, 133.0, 142.0, 142.5, 148.8, 159.4, 166.0. *m/z* (ESI) = 340 (MH^+). *m/z* (HRMS) Found: 340.0938 (MH^+). $C_{17}H_{14}N_3O_5$ requires: *m/z* = 340.0928. ν_{max} (ATR) 2929, 1703 (C═O), 1513, 1441, 1350, 1301, 1240, 836, 767 cm^{-1}.

*7.5.8. 1-(2-Bromophenyl)-5-(2-nitrophenyl)-1H-pyrazole-4-carboxylic acid (**2h**).* Prepared from **5h** (402 mg, 1 mmol). Yield: 174 mg (45%) of white crystals; mp 224–227 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.30 (1H, br s, 1H of Ar); 7.38 (3H, dq, *J* = 7.3, 3.7 Hz); 7.65 (1H, td, *J* = 7.8, 1.6 Hz); 7.70 (1H, td, *J* = 7.6, 1.4 Hz); 7.78 (1H, dd, *J* = 5.9, 3.4 Hz); 8.14 (1H, dd, *J* = 8.1, 1.3 Hz); 8.21 (1H, s); 12.61 (1H, br s). ^{13}C NMR (126 MHz, DMSO-d_6) δ 114.8, 122.1, 125.3, 129.0, 129.1, 130.9, 131.6, 132.6, 133.7, 133.7, 135.4, 136.2, 142.8, 143.1, 147.6, 163.0. *m/z* (ESI) = 388, 390 (MH^+). *m/z* (HRMS) Found: 387.9921 (MH^+). $C_{16}H_{11}BrN_3O_4$ requires: *m/z* = 387.9927. (Found: C, 49.74; H, 2.69; N, 10.67. $C_{16}H_{10}BrN_3O_4$ requires: C, 49.51; H, 2.60; N, 10.83.); ν_{max} (ATR) 2867, 1707 (C═O), 1525, 1502, 1350, 1228, 1207, 1145, 775, 760 cm^{-1}.

7.6. General Procedure for the Synthesis of Methyl (*S*)-(5-(2-nitrophenyl)-1-substituted-1*H*-pyrazole-4-carbonyl)alaninates 12a–g and Methyl (*S*)-(5-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonyl)prolinate (13). CDI (0.34 g, 2.1 mmol) was added to a solution of carboxylic acid **2a**–**g** (2 mmol) in anh. MeCN (10 mL) and the mixture was stirred at r.t. for 2 h. Then, *N*-methylmorpholine (0.22 mL) and (*S*)-amino ester hydrochloride **11a**,**b** (2.2 mmol) were added and stirring at r.t. was continued for 40 h. Volatile components were evaporated in vacuo, the residue was taken up in EtOAc (30 mL), and washed with 1 M HCl (3 × 20 mL), aq. $NaHCO_3$ (2 × 20 mL), and brine (20 mL). The organic phases were combined, dried over anh. Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. The residue was purified by DVFC (silica gel, EtOAc–hexanes) or MPLC (silica gel, EtOAc–hexanes). Fractions containing the product were combined and evaporated in vacuo to give **12a**–**g** and **13**.

*7.6.1. Methyl (S)-(5-(2-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbonyl)alaninate (**12a**).* Prepared from **2a** (0.618 g, 2 mmol) and methyl (*S*)-alaninate hydrochloride (**11a**) (0.31 g, 2.2 mmol), DVFC (EtOAc–hexanes, 1:1). Yield: 0.567 g (72%) of white crystals; mp 178–179 °C; $[\alpha]_D^{22}$ − 72.0 (*c* = 1.00, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 and 1.41 (3H, 2d, 1:1, *J* = 7.1 Hz); 3.72 and 3.73 (3H, 2s, 1:1); 4.64 and 4.65 (1H, 2 quintets, 1:1, *J* = 7.2 Hz); 6.29 and 6.31 (1H, 2d, 1:1, *J* = 7.9 Hz); 7.20–7.33 (6H, m); 7.51–7.62 (2H, m); 8.03 and 8.06 (1H, 2s, 1:1); 8.07–8.14 (1H, m). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.7, 18.8, 47.8, 47.9, 52.5, 52.5, 116.5, 116.6, 124.7, 124.8, 125.0, 125.1, 125.1, 125.1, 125.1, 128.4, 128.4, 129.1, 129.1, 130.4, 130.5, 132.9, 132.9, 133.0, 133.1, 138.7, 138.7, 138.8, 139.2, 140.1, 140.4, 149.1, 161.3, 161.4, 173.4, 173.5. *m/z* (ESI) = 395 (MH^+). *m/z* (HRMS) Found: 395.1354 (MH^+). $C_{20}H_{19}N_4O_5$ requires: *m/z* = 395.1355. (Found: C, 60.78; H, 4.65; N, 14.12. $C_{20}H_{18}N_4O_5$ requires: C, 60.91; H, 4.60; N, 14.21.); ν_{max} (ATR) 3341, 1745 (C═O), 1627 (C═O), 1565, 1526, 1503, 1353, 1295, 1169, 770 cm^{-1}.

*7.6.2. Methyl (S)-1-cyclohexyl-(5-(2-nitrophenyl)-1H-pyrazole-4-carbonyl)alaninate (**12b**).* Prepared from **2b** (0.631 g, 2 mmol) and methyl (*S*)-alaninate hydrochloride (**11a**) (0.307 g, 2.2 mmol), DVFC (EtOAc–hexanes, 2:1). Yield: 0.575 g (72%) of white crystals; mp 196–198 °C; $[\alpha]_D^{22}$ − 57.8 (*c* = 0.50, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10–1.30 (3H, m), 1.33 and 1.36 (3H, 2d, 1:1, *J* = 7.1 Hz);

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1.63 (1H, br d, J = 12.5 Hz); 1.80−1.89 (3H, m); 1.90−2.06 (3H, m); 3.66 (1H, tt, J = 11.8, 4.0 Hz); 3.70 and 3.71 (3H, 2s, 1:1); 4.58 and 4.60 (1H, 2 quintets, 1:1, J = 7.2 Hz); 6.17 and 6.20 (1H, 2d, 1:1, J = 7.3 Hz); 7.37 and 7.39 (1H, 2 dd, 1:1, J = 7.5, 1.5 Hz); 7.69 and 7.70 (1H, 2 td, 1:1, J = 7.9, 1.5 Hz); 7.74 and 7.76 (1H, 2 td, 1:1, J = 7.5, 1.5 Hz); 7.85 and 7.88 (1H, 2s, 1:1); 8.20 and 8.21 (1H, 2 dd, 1:1, J = 8.1, 1.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.8, 18.9, 25.1, 25.1, 25.5, 25.6, 32.5, 33.4, 47.7, 47.8, 52.6, 52.6, 59.1, 59.1, 114.9, 115.0, 125.0, 125.1, 125.2, 125.2, 130.8, 130.9, 132.3, 132.3, 133.4, 133.4, 137.5, 137.8, 139.2, 139.5, 149.2, 149.2, 161.7, 161.7, 173.6, 173.7. m/z (ESI) = 401 (MH^+). m/z (HRMS) Found: 401.1819 (MH^+). $C_{20}H_{25}N_4O_5$ requires: m/z = 401.1822. (Found: C, 60.04; H, 5.98; N, 13.93. $C_{20}H_{24}N_4O_5$ requires: C, 59.99; H, 6.04; N, 13.99.); ν_{max} (ATR) 3319, 2939, 2857, 1714 (C═O), 1622 (C═O), 1524, 1348, 1214, 782, 766 cm^{-1}.

*7.6.3. Methyl (S)-1-tert-butyl-(5-(2-nitrophenyl)-1H-pyrazole-4-carbonyl)alaninate (**12c**).* Prepared from **2c** (0.579 g, 2 mmol) and methyl (*S*)-alaninate hydrochloride (**11a**) (0.31 g, 2.2 mmol), DVFC (EtOAc−hexanes, 2:1). Yield: 0.532 g (71%) of white crystals; mp 154−156 °C; $[\alpha]_D^{22}$ − 48.3 (c = 0.80, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 and 1.31 (3H, 2d, J = 7.1 Hz, 1:1); 1.45 (9H, s); 3.67 and 3.68 (3H, 2s, 1:1); 4.53 and 4.54 (1H, 2 quintets, J = 7.2 Hz), 6.12 and 6.16 (1H, 2br d, 1:1, J = 7.3 Hz); 7.42 and 7.44 (1H, 2dd, 1:1, J = 7.5, 1.6 Hz); 7.64 and 7.66 (1H, 2td, 1:1, J = 7.7, 1.6 Hz); 7.68 and 7.70 (1H, 2td, 1:1, J = 7.5, 1.4 Hz); 7.81 and 7.83 (1H, 2s, 1:1); 8.19 and 8.20 (1H, 2dd, J = 8.0, 1.4 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.8, 18.9, 30.7, 30.7, 47.7, 47.7, 52.5, 52.6, 63.1, 63.1, 116.4, 116.5, 125.0, 125.0, 128.0, 128.1, 130.6, 130.7, 132.8, 132.9, 132.9, 133.0, 136.4, 136.7, 139.0, 139.4, 148.7, 148.7, 161.8, 161.8, 173.6, 173.7. m/z (ESI) = 375 (MH^+). m/z (HRMS) Found: 375.1658 (MH^+). $C_{18}H_{23}N_4O_5$ requires: m/z = 375.1663. (Found: C, 58.52; H, 5.83; N, 14.43. $C_{18}H_{22}N_4O_5$ requires: C, 57.75; H, 5.92; N, 14.96.); ν_{max} (ATR) 3308, 2984, 1751 (C═O), 1627 (C═O), 1520, 1341, 1201, 1147, 757 cm^{-1}.

*7.6.4. Methyl (S)-(5-(2-nitrophenyl)-1-(2-pyridyl)-1H-pyrazole-4-carbonyl)alaninate (**12d**).* Prepared from **2d** (0.621 g, 2 mmol) and methyl (*S*)-alaninate hydrochloride (**11a**) (0.31 g, 2.2 mmol), DVFC (EtOAc−hexanes, 4:1). Yield: 0.593 g (75%) of white crystals; mp 144−146 °C; $[\alpha]_D^{22}$ − 37.5 (c = 0.60, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 and 1.33 (3H, 2d, 1:1 J = 7.1 Hz); 3.67 and 3.70 (3H, 2s, 1:1); 4.60 and 4.61 (1H, 2 quintets, 1:1, J = 7.1 Hz); 6.18 and 6.25 (1H, 2d, 1:1, J = 7.2 Hz); 7.09 (1H, ddd, J = 7.4, 4.9, 1.0 Hz); 7.41 and 7.43 (1H, 2dd, 1:1, J = 7.4, 2.0 Hz); 7.63 and 7.64 (1H, 2td, 1:1, J = 7.5, 2.0 Hz); 7.65 and 7.68 (1H, 2td, 1:1, J = 7.5, 1.5 Hz); 7.74 (1H, dddd, J = 8.2, 7.3, 1.8, 0.9 Hz); 7.86 (1H, dd, J = 8.2, 1.1 Hz); 7.98 (1H, ddd, J = 4.9, 1.8, 0.9 Hz); 8.13 and 8.16 (1H, 2s, 1:1); 8.24 (1H, dt, J = 8.3, 1.9 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.6, 18.8, 48.0, 48.0, 52.6, 52.6, 116.3, 116.4, 118.7, 118.8, 122.4, 122.4, 124.5, 124.5, 126.6, 126.9, 130.2, 130.3, 132.4, 132.6, 133.1, 133.3, 138.7, 138.7, 139.2, 139.7, 140.4, 140.9, 147.5, 147.5, 149.0, 149.1, 151.8, 151.8, 161.4, 161.5, 173.2, 173.4. m/z (ESI) = 396 (MH^+). m/z (HRMS) Found: 396.1298 (MH^+). $C_{19}H_{18}N_5O_5$ requires: m/z = 396.1302. (Found: C, 57.72; H, 4.33; N, 17.71. $C_{19}H_{17}N_5O_5$ requires: C, 57.72; H, 4.33; N, 17.71.); ν_{max} (ATR) 3341, 2947, 1753 (C═O), 1620 (C═O), 1562, 1519, 1476, 1349, 792, 759 cm^{-1}.

*7.6.5. Methyl (S)-1-(2-chlorophenyl)-5-(2-nitrophenyl)-1H-pyrazole-4-carbonyl)alaninate (**12e**).* Prepared from **2e** (0.687 g, 2 mmol) and methyl (*S*)-alaninate hydrochloride (**11a**) (0.307 g, 2.2 mmol), DVFC (EtOAc−hexanes, 1:2). Yield: 747 mg (87%) of white crystals; mp 135−138 °C; $[\alpha]_D^{22}$ − 57.7 (c = 1.05, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 and 1.42 (3H, 2d, 1:1 J = 7.1 Hz); 3.72 and 3.74 (3H, 2s, 1:1); 4.65 and 4.65 (1H, 2 quintets, 1:1, J = 7.2 Hz); 6.35 and 6.37 (1H, 2d, 1:1, J = 7.3 Hz); 7.20 and 7.21 (1H, 2t, 1:1, J = 7.7 Hz); 7.29−7.36 and 7.29−7.36 (2H, 2m, 1:1); 7.37−7.45 and 7.37−7.45 (2H, 2m, 1:1); 7.48−7.59 and 7.48−7.59 (2H, 2m, 1:1); 8.05 and 8.07 (1H, 2t, 1:1, J = 2.1 Hz); 8.09 and 8.11 (1H, 2s, 1:1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.7, 18.8, 47.8, 47.9, 52.5, 52.6, 116.1, 116.1, 124.0, 124.1, 124.6, 124.6, 127.6, 127.6, 129.6, 129.6, 130.3, 130.3, 130.6, 130.7, 131.0, 131.0, 132.2, 132.2, 132.3, 132.4, 133.0, 133.1, 136.2, 136.2, 139.1, 139.4, 141.8, 142.1, 148.8, 148.8, 161.2, 161.3, 173.4, 173.5. m/z (ESI) = 429, 431 (MH^+). m/z (HRMS) Found: 429.0958 (MH^+). $C_{20}H_{18}ClN_4O_5$ requires: m/z = 429.0960. (Found: C, 56.04; H, 3.78; N, 13.24. $C_{20}H_{17}ClN_4O_5$ requires: C, 56.02; H, 4.00; N, 13.07.); ν_{max} (ATR) 3324, 1738 (C═O), 1625 (C═O), 1566, 1524, 1501, 1352, 763 cm^{-1}.

*7.6.6. Methyl (S)-(5-(2-nitrophenyl)-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonyl)alaninate (**12f**).* Prepared from **2f** (825 mg, 2 mmol) and methyl (*S*)-alaninate hydrochloride (**11a**) (0.307 g, 2.2 mmol), DVFC (EtOAc−hexanes, 1:1). Yield: 687 mg (69%) of white crystals; mp 186−190 °C; $[\alpha]_D^{22}$ − 36.0 (c = 0.50, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 and 1.42 (3H, 2d, 1:1, J = 7.4 Hz); 3.73 and 3.73 (3H, 2s, 1:1); 4.64 and 4.65 (1H, 2 quintets, 1:1, J = 7.1 Hz); 6.45 and 6.48 (1H, 2d, 1:1, J = 7.3 Hz); 7.31 and 7.32 (1H, 2d, 1:1, J = 2.4 Hz); 7.37−7.43 and 7.37−7.43 (2H, 2m, 1:1); 7.52−7.61 and 7.52−7.61 (2H, 2m, 1:1); 8.12−8.17 and 8.12−8.17 (1H, 2m, 1:1); 8.17 and 8.18 (1H, 2s, 1:1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.7, 18.7, 48.0, 48.1, 52.6, 52.6, 117.9, 118.0, 122.9, 123.0, 125.5, 125.5, 128.6, 128.7, 129.0, 129.0, 131.0, 131.1, 131.5, 131.7, 133.0, 133.1, 133.2, 133.2, 135.5, 135.5, 135.9, 136.0, 136.8, 136.8, 140.1, 140.5, 141.7, 141.9, 148.4, 148.4, 161.2, 161.2, 173.3, 173.5. m/z (ESI) = 497, 499, 501 (MH^+). m/z (HRMS) Found: 497.0177 (MH^+). $C_{20}H_{16}Cl_3N_4O_5$ requires: m/z = 497.0181. (Found: C, 48.25; H, 2.93; N, 11.15. $C_{20}H_{15}Cl_3N_4O_5$ requires: C, 48.26; H, 3.04; N 11.26.); ν_{max} (ATR) 3344, 3065, 2951, 1720 (C═O), 1650 (C═O), 1618, 1572, 1555, 1530, 1498, 1477, 1436, 1376, 1350, 1296, 1260, 1231, 1156, 1117, 1044, 1009, 986, 959, 928, 885, 868, 854, 832, 822, 807, 784, 761, 749, 732, 708, 668, 652, 639, 614 cm^{-1}.

*7.6.7. Methyl (S)-(1-(4-methoxyphenyl)-5-(2-nitrophenyl)-1H-pyrazole-4-carbonyl)alaninate (**12g**).* Prepared from **2g** (0.679 g, 2 mmol) and methyl (*S*)-alaninate hydrochloride (**11a**) (0.307 g, 2.2 mmol), DVFC (EtOAc−hexanes, 1:2). Yield: 720 mg (85%) of brownish crystals; mp 127−131 °C; $[\alpha]_D^{22}$ − 52.4 (c = 0.50, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 and 1.40 (3H, 2d, 1:1, J = 7.2 Hz); 3.71 and 3.73 (3H, 2s, 1:1); 3.76 (3H, s); 4.64 and 4.64 (1H, 2 quintets, 1:1, J = 7.2 Hz); 6.35 and 6.39 (1H, 2d, 1:1, J = 7.4 Hz); 6.76−6.80 and 6.76−6.80 (2H, 2m, 1:1); 7.16−7.20 and 7.16−7.20 (2H, 2m, 1:1); 7.25−7.31 and 7.25−7.31 (1H, 2m, 1:1); 7.52−7.61 and 7.52−7.61 (2H, 2m, 1:1); 8.01 and 8.04 (1H, 2s, 1:1); 8.08−8.11 and 8.08−8.11 (1H, 2m, 1:1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.6, 18.7, 47.8, 47.8, 52.5, 52.5, 55.4, 55.4, 114.2, 114.2, 116.0, 116.1, 124.6, 124.7, 125.0, 125.1, 126.5, 126.5, 130.3, 130.4, 131.7, 131.7, 132.9, 132.9, 133.0, 133.1, 138.5, 138.8, 140.1, 140.5, 149.0, 149.0, 159.4, 159.4, 161.4, 161.5, 173.4, 173.6. m/z (ESI) = 425 (MH^+). m/z (HRMS) Found: 425.1456 (MH^+). $C_{21}H_{21}N_4O_6$ requires: m/z = 425.1456. (Found: C, 59.37; H, 4.68; N, 12.96. $C_{21}H_{20}N_4O_6$ requires: C, 59.43; H, 4.75; N, 13.20.); ν_{max} (ATR) 3339, 1758 (C═O), 1626 (C═O), 1514, 1254, 837, 753 cm^{-1}.

*7.6.8. Methyl (S)-(5-(2-nitrophenyl)-1-phenyl-1H-pyrazole-4-carbonyl)prolinate (**13**).* Prepared from **2a** (0.618 g, 2 mmol) and methyl (*S*)-prolinate hydrochloride (**11b**) (0.306 g, 2.2 mmol), FC (EtOAc/hexanes, 1:1). Yield: 0.450 g (54%) of greenish oil; $[\alpha]_D^{22}$− 76.1 (c = 1.15, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86−2.01 (2H, m); 2.05−2.31 (2H, m); 3.46−3.90 (2H, m); 3.67 (3H, s); 4.50−4.62 (1H, m); 7.19−7.25 (2H, m); 7.26−7.32 (3H, m); 7.37−7.46 (1H, m); 7.48−7.64 (2H, m); 7.94−8.06 (2H, m and 3-H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 25.3, 25.4, 29.1, 29.2, 48.8, 49.3, 52.2, 52.2, 59.0, 59.2, 117.4, 117.7, 124.6, 124.7, 125.0, 125.0, 125.0, 125.0, 128.3, 128.3, 129.1, 129.1, 130.2, 130.2, 133.0, 133.2, 133.3, 133.4, 138.6, 138.7, 139.2, 139.6, 140.0, 140.1, 148.5, 148.6, 162.5, 162.6, 172.4, 172.6. m/z (ESI) = 421 (MH^+). m/z (HRMS) Found: 421.1506 (MH^+). $C_{22}H_{21}N_4O_5$ requires: m/z = 421.1506. ν_{max} (NaCl) 2966, 1742 (C═O), 1620 (C═O), 1528, 1500, 1351, 1198, 770, 694 cm^{-1}.

7.7. General Procedure for the Preparation of Methyl 1-Substituted (*S*)-(5-(2-Aminophenyl)-1*H*-pyrazole-4-carbonyl)-alaninates 14a−d. A mixture of nitro compound **12** (1 mmol), MeOH (50 mL), and 10% Pd−C (40 mg) was hydrogenated under 3 bar of H_2 at r.t. for 4 h. The catalyst was removed by filtration through a glass-sintered funnel and the filtrate was evaporated in vacuo. The residue was purified by DVFC (silica gel, EtOAc−hexanes). Fractions

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containing the product were combined and evaporated in vacuo to give **14**.

*7.7.1. Methyl (S)-(5-(2-aminophenyl)-1-phenyl-1H-pyrazole-4-carbonyl)alaninate (**14a**).* Prepared from **12a** (0.394 g, 1 mmol). Yield: 0.346 g (95%) of brown oil; $[\alpha]_D^{22}$+13.6 (c = 1.10, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 and 1.26 (3H, 2d, 1:1, J = 7.1 Hz); 3.65 and 3.68 (3H, 2s, 1:1); 3.92 (2H, br s); 4.61 (1H, quintet, J = 7.2 Hz); 6.01 and 6.38 (1H, 2d, 1:1, J = 7.2 Hz); 6.71−6.85 (2H, m); 6.92 and 6.97 (1H, dd, J = 1.6, 7.7 Hz); 7.21−7.36 (6H, m); 8.25 and 8.26 (1H, 2s, 1:1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.2, 18.2, 47.8, 47.9, 52.3, 52.3, 113.4, 113.6, 115.9, 116.3, 118.0, 118.0, 119.0, 119.1, 124.2, 124.2, 127.9, 127.9, 128.9, 128.9, 131.00, 131.1, 131.6, 131.6, 138.5, 138.5, 139.1, 139.1, 142.0, 142.1, 145.3, 145.6, 161.9, 161.9, 173.0, 173.2. m/z (ESI) = 365 (MH^+). m/z (HRMS) Found: 365.1629 (MH^+). $C_{20}H_{21}N_4O_3$ requires: m/z = 365.1614. ν_{max} (ATR) 3344, 1741 (C═O), 1646 (C═O), 1545, 1499, 1212, 760 cm^{-1}. The hydrochloride salt of **14a** was obtained in the following way. The free amine **14a** (0.267 g, 0.7 mmol) was dissolved in EtOAc (15 mL), 2 M HCl−EtOAc (1 mL, 2 mmol) was added, and the mixture was stirred at r.t. for 16 h. The precipitate was collected by filtration and washed with EtOAc (5 mL) to give **14a**·HCl. Yield: 0.060 g (21%) of white solid; mp 130−136 °C; $[\alpha]_D^{22}$ − 13.3 (c = 0.15, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.35 and 1.40 (3H, 2d, 1:1, J = 7.2 Hz); 3.58 and 3.66 (3H, s); 4.48 (1H, quintet J = 7.2 Hz); 6.87−6.93 (1H, m); 6.97−7.10 (1H, m); 7.26−7.57 (7H, m); 8.40 and 8.47 (1H, 2s, 1:1); 8.93 and 9.02 (1H, 2br s, 1:1). ^{13}C NMR (126 MHz, DMSO-d_6) δ 16.9, 16.9, 47.9, 48.0, 52.0, 52.1, 116.9, 117.0, 125.5, 125.5, 125.7, 125.7, 128.2, 128.2, 128.8, 128.8, 130.7, 130.8, 132.3, 132.3, 138.8, 138.8, 140.0, 140.1, 163.2, 163.3, 172.6, 172.8. m/z (ESI) = 365 (MH^+). m/z (HRMS) Found: 365.1608 (MH^+). $C_{20}H_{21}N_4O_3$ requires: m/z = 365.1614. (Found: C, 60.55; H, 5.18; N, 13.46. $C_{20}H_{21}ClN_4O_3$ requires: C, 59.92; H, 5.28; N, 13.98.); ν_{max} (ATR) 3446, 1739 (C═O), 1630 (C═O), 1500, 1458, 1218, 766 cm^{-1}.

*7.7.2. Methyl (S)-(5-(2-aminophenyl)-1-cyclohexyl-1H-pyrazole-4-carbonyl)alaninate (**14b**).* Prepared from **12b** (0.400 g, 1 mmol), FC (EtOAc/hexanes, 1:3). Yield: 0.323 g (87%) of white crystals; mp 141−146 °C; $[\alpha]_D^{22}$ + 28.2 (c = 0.50, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): 1.14−1.26 and 1.14−1.26 (3H, 2m, 1:1); 1.17 and 1.21 (3H, 2d, 1:1, J = 7.1 Hz); 1.60−1.67 and 1.60−1.67 (1H, 2m, 1:1); 1.78−1.89 and 1.78−1.89 (4H, 2m, 1:1); 1.89−2.03 and 1.89−2.03 (2H, 2m, 1:1); 3.64 and 3.66 (3H, 2s, 1:1); 3.72 (2H, br s); 3.52−3.68 and 3.70−3.86 (1H, 2m, 1:1); 4.57 and 4.57 (1H, 2 quintets, 1:1, J = 7.1 Hz); 6.08 and 6.12 (1H, 2d, 1:1, J = 7.4 Hz); 6.83−6.95 (2H, 2m, 1:1); 7.07 and 7.12 (1H, 2dd, 1:1, J = 7.6, 1.6 Hz); 7.33−7.38 and 7.33−7.38 (1H, 2m, 1:1); 8.11 and 8.12 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.3, 18.3, 25.0, 25.0, 25.4, 25.4, 32.8, 33.2, 47.7, 47.7, 52.3, 52.3, 58.3, 58.3, 113.1, 113.2, 115.7, 115.7, 115.9, 116.3, 119.0, 119.0, 130.6, 130.7, 131.6, 131.6, 137.6, 137.6, 140.7, 140.8, 145.4, 145.6, 162.2, 162.2, 173.2, 173.3. m/z (ESI) = 371 (MH^+). m/z (HRMS) Found: 371.2075 (MH^+). $C_{20}H_{27}N_4O_3$ requires: m/z = 371.2078. (Found: C, 63.39; H, 7.29; N, 14.71. $C_{20}H_{26}N_4O_3$·1/2H_2O requires: C, 63.31; H, 7.17; N, 14.77.); ν_{max} (ATR) 3394, 2928, 2857, 1747 (C═O), 1653 (C═O), 1629, 1543, 1201, 1141, 828, 751 cm^{-1}.

*7.7.3. Methyl (S)-(5-(2-aminophenyl)-1-tert-butyl-1H-pyrazole-4-carbonyl)alaninate (**14c**).* Prepared from **12c** (0.374 g, 1 mmol), FC (EtOAc/hexanes, 1:3). Yield: 0.140 g (39%) of yellow solid, mp 162−164 °C; $[\alpha]_D^{22}$ + 12.1 (c = 1.00, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 and 1.12 (3H, 2d, 1:1, J = 7.2 Hz); 1.50 (9 H, br s); 3.62 and 3.65 (3H, 2s, 1:1); 3.68 and 3.75 (2H, 2d, 1:1, J = 5.2 Hz); 4.50 and 4.54 (1H, d, J = 8.0 and 7.2 Hz); 5.82 and 5.87 (1H, 2d, 1:1, J = 7.2 Hz); 6.78−6.86 and 6.86−6.93 (1H, 2m, 1:1); 7.13 (1H, d, J = 7.6 Hz); 7.20 (1H, d, J = 9.0 Hz); 7.33 and 7.35 (1H, 2m, 1:1); 8.08 (1H, br s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.1, 18.1, 30.3, 30.3, 47.6, 47.7, 52.2, 52.2, 62.5, 62.5, 115.7, 115.8, 116.1, 116.3, 117.6, 117.7, 118.6, 118.6, 131.2, 131.3, 131.5, 131.6, 137.6, 137.6, 139.6, 139.7, 145.4, 145.6, 162.2, 162.2, 173.1, 173.3. m/z (ESI) = 345 (MH^+). m/z (HRMS) Found: 345.1918 (MH^+). $C_{18}H_{25}N_4O_3$ requires: m/z = 345.1921. ν_{max} (ATR) 3403, 3332, 2924, 1748 (C═O), 1637 (C═O), 1537, 1455, 1196, 1144, 752 cm^{-1}.

7.8. Synthesis of Methyl (*S*)-{1-cyclohexyl-5-[2-(alkylamino)-phenyl]-1*H*-pyrazole-4-carbonyl}alaninates 15a,b. A mixture of nitro compound **12b** (400 mg, 1 mmol), MeOH (30 mL), acetone (20 mL, excess) or isobutyraldehyde (128 μL, 1.4 mmol), 2 M aq. HCl (1 drop, ∼20 mg), and 10% Pd−C (40 mg) was hydrogenated under 4 bar of H_2 at r.t. for 8 h. The catalyst was removed by filtration through a glass-sintered funnel and the filtrate was evaporated in vacuo. The residue was purified by DVFC (EtOAc/hexanes, 1:2). Fractions containing the product were combined and evaporated in vacuo to give **15a,b**.

*7.8.1. Methyl (S)-{1-cyclohexyl-5-[2-(isopropylamino)phenyl]-1H-pyrazole-4-carbonyl}-alaninate (**15a**).* Prepared from **12b** (400 mg, 1 mmol) and acetone (20 mL, excess). Yield: 0.242 g (59%) of white solid; mp 118−121 °C; $[\alpha]_D^{22}$ + 16.6 (c = 0.85, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 and 1.11 (6H, 2d, 1:1, J = 7.2 Hz); 1.14 and 1.15 (3H, 2d, 1:1, J = 7.2 Hz); 1.17−1.26 and 1.17−1.26 (3H, 2m, 1:1); 1.59−1.65 and 1.59−1.65 (1H, 2m, 1:1); 1.75−1.84 and 1.75−1.84 (4H, 2m, 1:1); 1.85−1.95 and 1.85−1.95 (1H, 2m, 1:1); 1.96−2.05 and 1.96−2.05 (1H, 2m, 1:1); 3.21 and 3.21 (1H, 2 br s, 1:1); 3.61 and 3.62 (3H, 2s, 1:1); 3.63−3.72 and 3.63−3.72 (2H, 2m, 1:1); 4.53 and 4.53 (1H, 2 quintets, 1:1, J = 7.3 Hz); 6.01 and 6.06 (1H, 2d, 1:1, J = 7.3 Hz); 6.76−6.84 and 6.76−6.84 (2H, 2m, 1:1); 7.03 and 7.09 (1H, 2 dd, 1:1, J = 7.6, 1.7 Hz); 7.39−7.44 and 7.39−7.44 (1H, m); 8.14 and 8.14 (1H, 2s, 1:1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.4, 18.4, 22.6, 22.7, 23.0, 23.0, 25.1, 25.1, 25.5, 25.5, 25.5, 25.5, 32.9, 33.0, 33.4, 33.4, 43.9, 44.0, 47.8, 47.9, 52.3, 52.4, 58.3, 58.4, 111.8, 112.0, 112.7, 112.7, 115.8, 115.9, 117.1, 117.3, 131.0, 131.1, 132.0, 132.0, 137.5, 137.6, 141.3, 141.3, 145.9, 146.1, 162.2, 162.2, 173.1, 173.2. m/z (ESI) = 413 (MH^+). m/z (HRMS) Found: 413.2543 (MH^+). $C_{23}H_{33}N_4O_3$ requires: m/z = 413.2547. (Found: C, 67.02; H, 8.11; N, 13.61. $C_{23}H_{32}N_4O_3$ requires: C, 66.96; H, 7.82; N, 13.58.); ν_{max} (ATR) 3394, 3320, 2931, 2857, 1744 (C═O), 1652 (C═O), 1540, 1514, 1170, 747 cm^{-1}.

*7.8.2. Methyl (S)-{1-cyclohexyl-5-[2-(isobutylamino)phenyl]-1H-pyrazole-4-carbonyl}-alaninate (**15b**).* Prepared from **12b** (400 mg, 1 mmol) and isobutyraldehyde (128 μL, 1.4 mmol). Yield: 0.260 g (61%) of white solid; mp 107−110 °C; $[\alpha]_D^{22}$ + 17.6 (c = 0.50, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 and 0.81 (6H, 2d, 1:1, J = 6.8 Hz); 1.09 and 1.11 (3H, 2d, 1:1, J = 5.3 Hz); 1.12−1.22 and 1.12−1.22 (3H, 2m, 1:1); 1.54−1.61 and 1.54−1.61 (1H, 2m, 1:1); 1.68−1.83 and 1.68−1.83 (5H, 2m, 1:1); 1.84−2.02 and 1.84−2.02 (2H, 2m, 1:1); 2.82−2.92 and 2.82−2.92 (2H, 2m, 1:1); 3.48−3.56 and 3.48−3.56 (1H, 2 br s, 1:1); 3.57 and 3.57 (3H, 2s, 1:1); 3.63−3.73 and 3.63−3.73 (1H, 2m, 1:1); 4.48 and 4.49 (1H, 2 quintets, 1:1, J = 7.2 Hz); 5.98 and 6.05 (1H, 2d, 1:1, J = 7.3 Hz); 6.70−6.83 and 6.70−6.83 (2H, 2m, 1:1); 6.99 and 7.05 (1H, 2 dd, 1:1, J = 7.6, 1.7 Hz); 7.34−7.40 and 7.34−7.40 (1H, m); 8.09 and 8.09 (1H, 2s, 1:1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.2, 18.4, 20.2, 20.3, 20.3, 20.3, 25.0, 25.0, 25.4, 25.4, 25.4, 25.4, 27.8, 27.8, 32.8, 32.8, 33.3, 33.3, 47.7, 47.7, 51.2, 51.2, 52.2, 52.2, 58.2, 58.2, 111.0, 111.3, 112.4, 112.4, 115.7, 115.8, 117.1, 117.2, 130.6, 130.7, 131.9, 131.9, 137.4, 137.5, 141.0, 141.0, 146.8, 147.0, 162.0, 162.0, 172.9, 173.0. m/z (ESI) = 427 (MH^+). m/z (HRMS) Found: 427.2697 (MH^+). $C_{24}H_{35}N_4O_3$ requires: m/z = 427.2704. (Found: C, 66.65; H, 8.03; N, 12.81. $C_{24}H_{34}N_4O_3$·1/3H_2O requires: C, 66.64; H, 8.08; N, 12.95.); ν_{max} (ATR) 3399, 3321, 2932, 2854, 1747 (C═O), 1652 (C═O), 1509, 1201, 1168, 734 cm^{-1}.

7.9. Synthesis of Methyl (1-cyclohexyl-5-{2-[(naphthalen-1-yl)methyl]amino}-phenyl)-1*H*-pyrazole-4-carbonyl)-L-alaninate (15c). A mixture of amino compound **14b** (370 mg, 1 mmol), EtOH (10 mL) and 2-naphthaldehyde (156 mg, 1 mmol) was stirred at r.t. for 120 h. The solvent was evaporated and the resulting imine was dissolved in MeOH (10 mL) and $NaBH_4$ (50 mg, 1.3 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. Volatile components were evaporated in vacuo, the residue was taken up in Et_2O (100 mL), and washed with aq. $NaHCO_3$ (50 mL). The organic phases were combined, dried over anh. Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. The residue was purified by CC (silica gel, EtOAc−hexanes, 1:1). Fractions containing the product were combined and evaporated in vacuo to give **15c**. Yield: 184 mg

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(36%) of white crystals; mp 135−138 °C; $[\alpha]_D^{22}$ + 3.3 (*c* = 0.60, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 and 1.18 (3H, 2d, 1:1, *J* = 7.1 Hz); 1.20−1.31 and 1.20−1.31 (3H, 2m, 1:1); 1.61−1.68 and 1.61−1.68 (1H, 2m, 1:1); 1.78−2.08 and 1.78−2.08 (6H, 2m, 1:1); 3.56 and 3.63 (3H, 2s, 1:1); 3.74−3.83 and 3.74−3.83 (1H, 2m, 1:1); 4.14 and 4.17 (1H, 2t, 1:1, *J* = 5.8 Hz); 4.49 and 4.52 (2H, 2d, 1:1, *J* = 5.1 Hz); 4.55 and 4.59 (1H, 2 quintets, 1:1, *J* = 7.2 Hz); 5.99 and 6.08 (1H, 2d, 1:1, *J* = 7.2 Hz); 6.79 and 6.81 (1H, 2d, 1:1, *J* = 9.3 Hz); 6.85 and 6.88 (1H, 2t, 1:1, *J* = 6.4 Hz); 7.09 and 7.15 (1H, 2dd, 1:1, *J* = 7.5, 1.6 Hz); 7.31−7.38 and 7.31−7.38 (2H, 2m, 1:1); 7.42−7.49 and 7.42−7.49 (2H, 2m, 1:1); 7.68 and 7.70 (1H, 2s, 1:1); 7.75 and 7.75 (1H, 2 br d, 1:1, *J* = 7.6 Hz); 7.78 and 7.78 (1H, 2dd, 1:1, *J* = 8.5, 2.8 Hz); 7.81 and 7.81 (1H, 2 br d, 1:1, *J* = 7.9 Hz); 8.15 and 8.15 (1H, 2s, 1:1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.2, 18.4, 25.0, 25.4, 25.5, 25.5, 33.0, 33.3, 47.7, 47.8, 47.8, 47.8, 52.2, 52.3, 58.3, 58.3, 111.7, 111.9, 112.9, 113.0, 115.8, 115.9, 117.8, 117.9, 125.0, 125.1, 125.5, 125.6, 125.8, 125.9, 126.2, 126.3, 127.6, 127.6, 127.7, 127.7, 128.5, 128.5, 130.6, 130.7, 131.9, 131.9, 132.7, 132.8, 133.4, 133.4, 136.1, 136.2, 137.4, 137.4, 141.0, 141.1, 146.3, 146.6, 162.0, 162.1, 173.0, 173.1. *m*/*z* (ESI) = 511 (MH^+). *m*/*z* (HRMS) Found: 511.2701 (MH^+). $C_{31}H_{35}N_4O_3$ requires: *m*/*z* = 511.2704. (Found: C, 73.23; H, 6.58; N, 10.98. $C_{31}H_{34}N_4O_3$ requires: C, 72.92; H, 6.71; N, 10.97.); ν_{max} (ATR) 3387, 3342, 2933, 2856, 1747 (C═O), 1643 (C═O), 1505, 826, 747 cm^{-1}.

7.10. Synthesis of Methyl (*S*)-(5-(2-acetylaminophenyl)-1-phenyl-1*H*-pyrazole-4-carbonyl)alaninate (16a). A mixture of nitro compound **12a** (0.197 g, 0.5 mmol), AcOH (10 mL), Ac_2O (5 mL), and 10% Pd−C (20 mg) was hydrogenated under 3 bar of H_2 at r.t. for 4 h. Then, hydrogenation was stopped, MeOH (10 mL) was added, and the mixture was left at r.t. for 2 h to solvolize excess Ac_2O. The catalyst was removed by filtration through a glass-sintered funnel and the filtrate was evaporated in vacuo. The residue was purified by FC (EtOAc/hexanes, 1:1). Fractions containing the product were combined and evaporated in vacuo to give **16a**. Yield: 0.153 g (75%) of yellowish solid; mp 86−91 °C; $[\alpha]_D^{22}$ − 19.4 (*c* = 0.20, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 and 1.38 (3H, 2d, 1:1, *J* = 7.2 Hz); 2.02 and 2.03 (3H, 2s, 1:1); 3.74 and 3.76 (3H, 2s, 1:1); 4.63 and 4.65 (1H, 2 quintets, 1:1, *J* = 7.2 Hz); 6.29 and 6.56 (1H, 2d, 1:1, *J* = 7.0 Hz); 6.96 (1H, br t, *J* = 6.4 Hz); 7.08 (1H, br q, *J* = 7.9 Hz); 7.14−7.21 (1H, m); 7.22−7.34 (4H, m); 7.39−7.46 (1H, m); 7.73 and 7.79 (1H, 2 br d, *J* = 8.0 Hz); 8.10 (1H, br s); 8.62 and 8.86 (1H, 2s, 1:1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.0, 18.2, 23.8, 24.0, 48.1, 48.3, 52.6, 52.7, 117.6, 117.8, 123.1, 123.9, 124.7, 124.8, 125.5, 125.9, 126.0, 126.7, 128.0, 128.0, 129.0, 129.0, 130.7, 130.8, 131.3, 131.4, 137.1, 137.2, 138.9, 138.9, 139.3, 139.7, 139.7, 140.1, 163.2, 163.3, 169.1, 169.3, 173.2, 173.6. *m*/*z* (ESI) = 407 (MH^+). *m*/*z* (HRMS) Found: 407.1723 (MH^+). $C_{22}H_{23}N_4O_4$ requires: *m*/*z* = 407.1719. (Found: C, 64.09; H, 5.22; N, 13.07. $C_{22}H_{22}N_4O_4 \cdot 1/3AcOH$ requires: C, 63.84; H, 5.52; N, 13.14.); ν_{max} (KBr) 3467, 1741 (C═O), 1639 (C═O), 1586, 1500, 1390, 1307, 764 cm^{-1}.

7.11. Synthesis of Methyl (*S*)-[5-(2-benzamidophenyl)-1-cyclohexyl-1*H*-pyrazole-4-carbonyl]alaninate (16b). Benzoyl chloride (64 μL, 0.55 mmol) was added to a cold (0 °C) solution of aniline **14b** (185 mg, 0.5 mmol) in anh. pyridine (10 mL) and the mixture was stirred at r.t. for 24 h. Volatile components were evaporated in vacuo and the residue was purified by DVFC (silica gel, EtOAc/hexanes, 1:2). Fractions containing the product were combined and evaporated in vacuo to give **16b**. Yield: 0.170 g (72%) of white crystals; mp 77−83 °C; $[\alpha]_D^{22}$+6.8 (*c* = 3.8, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09−1.24 and 1.09−1.24 (3H, 2m, 1:1); 1.35 and 1.38 (3H, 2d, 1:1, *J* = 7.2 Hz); 1.51−1.64 and 1.51−1.64 (2H, 2m, 1:1); 1.65−1.72 and 1.65−1.72 (1H, 2m, 1:1); 1.74−1.87 and 1.74−1.87 (2H, 2m, 1:1); 1.91−2.04 and 1.91−2.04 (2H, 2m, 1:1); 3.69 and 3.74 (3H, 2s, 1:1); 3.75−3.84 and 3.75−3.84 (1H, 2m, 1:1); 4.62 and 4.65 (1H, 2 quintets, 1:1, *J* = 7.2 Hz); 6.23 and 6.27 (1H, 2d, 1:1, *J* = 7.2 Hz); 7.22−7.25 and 7.22−7.25 (1H, 2m, 1:1); 7.31−7.36 and 7.31−7.36 (1H, 2m, 1:1); 7.37−7.43 and 7.37−7.43 (2H, 2m, 1:1); 7.46−7.50 and 7.46−7.50 (1H, 2m, 1:1); 7.57−7.62 and 7.57−7.62 (1H, 2m, 1:1); 7.69−7.76 and 7.69−7.76 (2H, 2m, 1:1); 7.93 and 7.96 (1H, 2s, 1:1); 8.10 and 8.19 (1H, 2 br d, 1:1, *J* = 8.1 Hz); 9.14 and 9.27 (1H, 2s, 1:1).^{13}C NMR (126 MHz, $CDCl_3$) δ 18.4, 18.5, 25.1, 25.1, 25.4, 25.4, 25.5, 25.5, 33.1, 33.1, 33.2, 33.3, 48.2, 48.3, 52.7, 52.8, 58.6, 58.6, 115.9, 115.9, 122.1, 123.0, 125.3, 126.1, 125.3, 125.7, 127.3, 127.3, 127.3, 127.3, 128.7, 128.7, 128.8, 128.8, 130.4, 130.5, 131.2, 131.2, 131.9, 132.0, 134.2, 134.4, 137.6, 137.7, 138.4, 138.6, 139.0, 139.1, 163.5, 163.5, 165.6, 165.8, 173.4, 173.5. *m*/*z* (ESI) = 475 (MH^+). *m*/*z* (HRMS) Found: 475.2333 (MH^+). $C_{27}H_{31}N_4O_4$ requires: *m*/*z* = 475.2340. (Found: C, 68.09; H, 6.52; N, 11.58. $C_{27}H_{30}N_4O_4$ requires: C, 68.34; H, 6.37; N, 11.81); ν_{max} (ATR) 3272, 2932, 2856, 1743 (C═O), 1637 (C═O), 1508, 1205, 760, 707 cm^{-1}.

7.12. Synthesis of Methyl (*S*)-(1-cyclohexyl-5-{2-[3-(2-ethoxy-2-oxoethyl)ureido]-phenyl}-1*H*-pyrazole-4-carbonyl)-alaninate (19). Ethyl isocyanatoacetate (**17**) (400 μL, 3.6 mmol) was added to a solution of aniline **14b** (185 mg, 0.5 mmol) in anh. dichloromethane (10 mL) and the mixture was stirred at r.t. for 24 h. Volatile components were evaporated in vacuo to give **19**. Yield: 0.180 g (72%) of white crystals; $[\alpha]_D^{22}$ − 5.2 (*c* = 0.95, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96−1.13 and 0.96−1.13 (3H, 2m, 1:1); 1.18 and 1.18 (3H, 2d, 1:1, *J* = 7.1 Hz); 1.26 and 1.29 (3H, 2d, 1:1, *J* = 7.1 Hz); 1.50−1.57 and 1.50−1.57 (1H, 2m, 1:1); 1.57−1.74 and 1.57−1.74 (4H, 2m, 1:1); 1.76−1.89 and 1.76−1.89 (2H, 2m, 1:1); 3.50−3.57 and 3.50−3.57 (1H, 2m, 1:1); 3.58 and 3.58 (3H, 2s, 1:1); 3.77 and 3.80 (2H, 2d, 1:1, *J* = 5.5 Hz); 4.08 and 4.08 (2H, 2q, 1:1, *J* = 7.1 Hz); 4.34 and 4.35 (1H, 2 quintets, 1:1, *J* = 7.2 Hz); 7.07 and 7.09 (1H, 2t, 1:1, *J* = 6.0 Hz); 7.04−7.09 and 7.04−7.09 (2H, 2m, 1:1); 7.36−7.42 and 7.36−7.42 (1H, 2m, 1:1); 7.51 and 7.60 (1H, 2s, 1:1); 7.89−7.92 and 7.89−7.92 (1H, 2m, 1:1); 7.92 and 8.09 (1H, 2d, 1:1, *J* = 7.2 Hz); 8.14 and 8.16 (1H, 2s, 1:1). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.1, 14.1, 17.0, 17.1, 24.9, 24.9, 32.0, 32.2, 32.9, 33.0, 41.2, 41.2, 47.3, 47.4, 51.8, 51.8, 57.3, 57.3, 60.3, 60.3, 115.8, 115.9, 120.3, 120.5, 122.0, 122.0, 122.3, 122.4, 129.5, 129.6, 130.7, 131.1, 138.2, 138.4, 138.4, 138.5, 139.4, 139.6, 155.3, 155.3, 161.7, 161.8, 170.6, 170.7, 173.1, 173.2. *m*/*z* (ESI) = 500 (MH^+). *m*/*z* (HRMS) Found: 500.2498 (MH^+). $C_{25}H_{34}N_5O_6$ requires: *m*/*z* = 500.2504. ν_{max} (ATR) 3401, 3319, 2933, 2858, 1747 (C═O), 1704 (C═O), 1633 (C═O), 1586, 1542, 1197, 767 cm^{-1}.

7.13. Synthesis of Methyl (*S*)-{5-[2-({(*S*,*Z*)-4-[(*tert*-butoxycarbonyl)amino]-3-oxopent-1-en-1-yl}amino)phenyl]-1-cyclohexyl-1*H*-pyrazole-4-carbonyl}alaninate (20). A solution of aniline **14b** (370 mg, 1 mmol) in anh. dichloromethane (5 mL) was added to a cold (0 °C) solution of *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate (**18**) in anh. dichloromethane (5 mL) and the mixture was stirred at r.t. for 16 h. Volatile components were evaporated in vacuo and the residue was purified by CC (silica gel, EtOAc/hexanes, 3:2). Fractions containing the product were combined and evaporated in vacuo to give **20**. Yield: 0.420 g (74%) of white crystals; mp 91−95 °C; $[\alpha]_D^{22}$ + 20.4 (*c* = 1.05, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.07−1.24 and 1.07−1.24 (3H, 2m, 1:1, 3H of C_6H_{11}); 1.26 and 1.26 (3H, 2d, 1:1, *J* = 7.0 Hz); 1.27 and 1.30 (3H, 2d, 1:1, *J* = 7.1 Hz); 1.45 and 1.45 (9H, 2s, 1:1); 1.59−1.66 and 1.59−1.66 (1H, 2m, 1:1); 1.72−1.88 and 1.72−1.88 (4H, 2m, 1:1); 1.90−2.06 and 1.90−2.06 (2H, 2m, 1:1); 3.60−3.67 and 3.60−3.67 (1H, 2m, 1:1); 3.67 and 3.69 (3H, 2s, 1:1); 4.24 and 4.24 (1H, 2 quintets, 1:1, *J* = 7.0 Hz); 4.59 and 4.62 (1H, 2 quintets, 1:1, *J* = 7.0 Hz); 5.29 and 5.30 (1H, 2d, 1:1, *J* = 7.8 Hz); 5.41 and 5.44 (1H, 2d, 1:1, *J* = 7.2 Hz); 6.08 and 6.08 (1H, 2d, 1:1, *J* = 5.5 Hz); 7.21−7.35 and 7.21−7.35 (4H, 2m, 1:1); 7.53−7.59 and 7.53−7.59 (1H, 2m, 1:1); 8.12 and 8.15 (1H, 2s, 1:1); 11.04 and 11.07 (1H, 2d, 1:1, *J* = 8.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.8, 18.8, 19.4, 19.6, 25.1, 25.1, 25.5, 25.5, 25.6, 25.6, 28.5, 28.5, 32.5, 32.5, 33.4, 33.4, 47.9, 47.9, 52.5, 52.5, 53.8, 54.0, 58.7, 58.8, 79.4, 79.4, 95.4, 95.7, 115.1, 115.4, 116.3, 116.4, 118.3, 118.5, 123.9, 124.0, 131.5, 131.7, 131.7, 131.8, 137.1, 137.4, 139.7, 139.9, 139.8, 140.1, 143.3, 143.9, 155.3, 155.4, 161.9, 162.0, 173.5, 173.5, 198.4, 198.6. *m*/*z* (ESI) = 568 (MH^+). *m*/*z* (HRMS) Found: 568.3122 (MH^+). $C_{30}H_{42}N_5O_6$ requires: *m*/*z* = 568.3130. (Found: C, 63.22; H, 7.44; N, 12.28. $C_{30}H_{41}N_5O_6$ requires: C, 63.47; H, 7.28; N, 12.34.); ν_{max} (ATR) 3304, 2932, 2857, 1720 (C═O), 1627 (C═O), 1585, 1454, 1278, 1161, 753 cm^{-1}.

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7.14. Synthesis of *N*-Methyl 5-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carboxamides 21a,b. CDI (0.17 g, 1.05 mmol) was added to a solution of carboxylic acid **2a** (1 mmol) in anh. MeCN (5 mL) and the mixture was stirred at r.t. for 2 h. Then amine (2 mmol) was added and stirring at r.t. was continued for 40 h. Volatile components were evaporated in vacuo and the residue was purified by DVFC (silica gel, EtOAc–hexanes). Fractions containing the product were combined and evaporated in vacuo to give **21**.

*7.14.1. N-Methyl-5-(2-nitrophenyl)-1-phenyl-1H-pyrazole-4-carboxamide (**21a**).* Prepared from **2a** (310 mg, 1 mmol) and $MeNH_2$ (2 M in MeOH, 1 mL, 2 mmol), DVFC (EtOAc/hexanes, 1:2). Yield: 0.138 g (43%) of white solid; mp 214–216 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.82 (3H, d, J = 4.8 Hz); 5.95 (1H, br q, J = 3.9 Hz); 7.25–7.31 (6H, m); 7.52–7.58 (2H, m); 7.93 (1H, s); 8.08–8.12 (1H, m). ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.2, 116.8, 124.6, 125.0, 125.2, 128.3, 129.1, 130.3, 132.9, 133.0, 138.5, 138.7, 140.2, 149.1, 162.7. m/z (ESI) = 323 (MH^+). m/z (HRMS) Found: 323.1139 (MH^+). $C_{17}H_{15}N_4O_3$ requires: m/z = 323.1139. (Found: C, 63.39; H, 4.30; N, 17.15. $C_{17}H_{14}N_4O_3$ requires: C, 63.35; H, 4.38; N, 17.38.); ν_{max} (ATR) 3306, 3098, 1621 (C=O), 1573, 1525, 1501, 1342, 961, 767 cm^{-1}.

*7.14.2. N,N-Dimethyl-5-(2-nitrophenyl)-1-phenyl-1H-pyrazole-4-carboxamide (**21b**).* Prepared from **2a** (310 mg, 1 mmol) and Me_2NH (2 M in MeOH, 1 mL, 2 mmol), DVFC (EtOAc/hexanes, 1:3). Yield: 0.172 g (51%) of white solid; mp 159–163 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.96 and 3.08 (6H, 2 br s, 1:1); 7.20–7.25 (2H, m), 7.27–7.32 (3H, m); 7.46 (1H, dd, J = 7.6, 1.5 Hz); 7.54 (1H, td, J = 7.8, 1.6 Hz); 7.60 (1H, td, J = 7.5, 1.4 Hz); 7.86 (1H, s); 7.99 (1H, dd, J = 8.1, 1.3 Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.3, 39.0, 117.6, 124.7, 124.8, 124.9, 128.2, 129.1, 130.3, 133.1, 133.1, 138.7, 138.8, 139.2, 148.8, 164.4. m/z (ESI) = 337 (MH^+). m/z (HRMS) Found: 337.1294 (MH^+). $C_{18}H_{17}N_4O_3$ requires: m/z = 337.1295. (Found: C, 63.85; H, 4.76; N, 16.11. $C_{18}H_{16}N_4O_3 \cdot 1/8H_2O$ requires: C, 63.85; H, 4.84; N, 16.55.); ν_{max} (ATR) 2926, 1619 (C=O), 1525, 1498, 1345, 774, 763 cm^{-1}.

7.15. Synthesis of (*S*)-1-Phenylethyl 5-(2-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carboxylate (22). Carboxylic acid **2a** (155 mg, 0.5 mmol) was dissolved in thionyl chloride (4 mL), the mixture was heated under reflux for 4 h, and the volatile components were evaporated in vacuo. The residue was dissolved in anh. CH_2Cl_2 (5 mL), (*S*)-(−)-1-phenylethanol (60 μL, 0.5 mmol) was added, and stirring at r.t. was continued for 24 h. The reaction mixture was concentrated in vacuo and the residue was purified by DVFC (silica gel, EtOAc/hexanes, 1:3). Fractions containing the product were combined and evaporated in vacuo to give **22**. Yield: 77 mg (37%) of colorless oil; $[\alpha]_D^{22}$ + 66.0 (c = 0.15, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.42 and 1.43 (3H, 2d, 53:47, J = 6.6 Hz); 5.87 and 5.92 (1H, 2q, 47:53, J = 6.7 Hz); 6.99–7.04 and 6.99–7.04 (1H, 2m); 7.18–7.33 and 7.18–7.33 (10H, 2m); 7.51–7.59 and 7.51–7.59 (2H, 2m); 8.08–8.15 and 8.08–8.15 (1H, 2m); 8.22 and 8.23 (1H, 2s, 46:54). ^{13}C NMR (126 MHz, $CDCl_3$) δ ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.8, 22.1, 72.3, 72.5, 124.7, 124.7, 125.0, 125.0, 125.0, 125.0, 125.9, 125.9, 125.9, 125.9, 127.7, 127.8, 128.3, 128.3, 128.4, 128.4, 128.5, 128.5, 129.1, 129.1, 129.1, 129.1, 130.4, 130.4, 132.6, 132.8, 133.0, 133.0, 138.7, 138.7, 141.2, 141.4, 142.3, 142.6, 161.6, 161.7. m/z (ESI) = 414 (MH^+). m/z (HRMS) Found: 414.1444 (MH^+). $C_{24}H_{20}N_3O_4$ requires: m/z = 414.1448. ν_{max} (ATR) 2929, 1708 (C=O), 1525, 1498, 1347, 1223, 1135, 1007, 960, 754, 693 cm^{-1}.

7.16. General Procedure for the Synthesis of 1-Substituted Ethyl 5-phenyl-1*H*-pyrazole-4-carboxylates 23a–c. A mixture of **8b** (0.96 g, 5 mmol), anh. toluene (15 mL), and DMFDMA (0.8 mL, 5.3 mmol) was stirred under reflux for 4 h and volatile components were evaporated in vacuo. The residue was dissolved in 1-butanol (15 mL), hydrazine derivative **10a,e,m** (5.5 mmol) and 37% hydrochloric acid (11 drops) were added, and the mixture was stirred under reflux for 16 h. Volatile components were evaporated in vacuo and the residue was purified by FC (EtOAc/hexanes). Fractions containing the product were combined and evaporated in vacuo to give the crude products **23a–c**.

*7.16.1. Ethyl 1,5-diphenyl-1H-pyrazole-4-carboxylate (**23a**).* Prepared from **8b** (0.96 g, 5 mmol), DMFDMA (0.8 mL, 5.3 mmol), and phenylhydrazine hydrochloride **10a** (0.80 g, 5.5 mmol), FC (EtOAc/hexanes, 1:2). Yield: 1.32 g (90%) of brownish crystals. Physical and spectral data of pyrazole **23a** were in agreement with the literature data.[35]

*7.16.2. Ethyl 1-(2-chlorophenyl)-5-phenyl-1H-pyrazole-4-carboxylate (**23b**).* Prepared from **8b** (0.96 g, 5 mmol), DMFDMA (0.8 mL, 5.3 mmol), and 2-chlorophenylhydrazine hydrochloride **10e** (0.98 g, 5.5 mmol), FC (EtOAc/hexanes, 1:2). Yield: 1.50 g (92%) of brownish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (3H, t, J = 7.1 Hz); 4.22 (2H, q, J = 7.1 Hz); 7.22–7.33 (8H, m); 7.36–7.41 (1H, m), 8.23 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 60.2, 113.1, 127.3, 127.7, 128.1, 129.2, 130.0, 130.2, 130.3, 130.6, 132.4, 137.0, 142.7, 147.5, 162.9. m/z (ESI) = 327, 329 (MH^+). m/z (HRMS) Found: 327.0890 (MH^+). $C_{18}H_{16}ClN_2O_2$ requires: m/z = 327.0895. ν_{max} (ATR) 3063, 2981, 1708 (C=O), 1555, 1499, 1444, 1224, 1127, 760, 695 cm^{-1}.

*7.16.3. Ethyl 1-(2-nitrophenyl)-5-phenyl-1H-pyrazole-4-carboxylate (**23c**).* Prepared from **8b** (0.96 g, 5 mmol), DMFDMA (0.8 mL, 5.3 mmol), 2-nitrophenylhydrazine hydrochloride **10m** (0.84 g, 5.5 mmol), and 37% aq. HCl (11 drops), FC (EtOAc/hexanes, 1:2). Yield: 1.32 g (78%) of brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (3H, t, J = 7.1 Hz); 4.23 (2H, q, J = 7.1 Hz); 7.24 (1H, dd, J = 7.6, 1.7 Hz); 7.28–7.37 (5H, m); 7.48–7.56 (2H, m); 7.91 (1H, dd, J = 7.8, 1.8 Hz); 8.20 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 60.3, 114.1, 125.2, 127.6, 128.1, 129.5, 129.7, 129.7, 130.4, 132.7, 133.2, 143.5, 145.9, 146.8, 162.6. m/z (ESI) = 338 (MH^+). m/z (HRMS) Found: 338.1143 (MH^+). $C_{18}H_{16}N_3O_4$ requires: m/z = 338.1135. ν_{max} (ATR) 3386, 2987, 2781, 1714 (C=O), 1524, 1451, 1350, 782, 771, 749, 65 cm^{-1}.

7.17. General Procedure for the Synthesis of 1-Substituted 5-Phenyl-1*H*-pyrazole-4-carboxylic acids 24a–c. A mixture of the ester **23** (3 mmol), methanol (30 mL), and 2 M aq. NaOH (6.6 mL, 13.2 mmol) was stirred at 50 °C for 24 h. Methanol was evaporated in vacuo (40 mbar, 40 °C) and the aqueous solution was acidified with 1 M aq. HCl to pH ~ 1 and the product **24** was either collected by filtration and washed with water (2 × 5 mL) or taken up in EtOAc (50 mL) when oily acid was formed. The organic phase was dried for 20 min over anh. Na_2SO_4, filtered, and the filtrate was evaporated in vacuo to give **24a–c**.

*7.17.1. 1,5-Diphenyl-1H-pyrazole-4-carboxylic acid (**24a**).* Prepared from **23a** (877 mg, 3 mmol). Yield: 753 mg (95%) of brownish crystals. Physical and spectral data of carboxylic acid **24a** were in agreement with the literature data.[36]

*7.17.2. 1-(2-Chlorophenyl)-5-phenyl-1H-pyrazole-4-carboxylic acid (**24b**).* Prepared from **23b** (980 mg, 3 mmol). Yield: 788 mg (88%) of brownish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.33 (8H, m); 7.38 (1H, dd, J = 8.1, 1.4 Hz); 8.26 (1H, s); 8.83 (1H, br s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 112.1, 127.3, 127.6, 127.8, 129.3, 129.9, 130.1, 130.3, 130.7, 132.3, 136.7, 143.5, 148.1, 168.1. m/z (ESI) = 299, 301 (MH^+). m/z (HRMS) Found: 299.0583 (MH^+). $C_{16}H_{12}ClN_2O_2$ requires: m/z = 299.0582. ν_{max} (ATR) 2914, 1721 (C=O), 1550, 1502, 1224, 1202, 1137, 778, 763, 696 cm^{-1}.

*7.17.3. 1-(2-Nitrophenyl)-5-phenyl-1H-pyrazole-4-carboxylic acid (**24c**).* Prepared from **23c** (1.01 g, 3 mmol). Yield: 751 mg (81%) of brownish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (1H, dd, J = 7.5, 1.7 Hz); 7.25–7.32 (4H, m); 7.33–7.38 (1H, m); 7.48–7.56 (2H, m); 7.91 (1H, dd, J = 7.7, 1.8 Hz); 8.24 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 113.0, 125.2, 127.1, 128.2, 129.7, 129.7, 129.9, 130.3, 132.5, 133.3, 144.2, 145.7, 147.6, 167.9. m/z (ESI) = 310 (MH^+). m/z (HRMS) Found: 310.0826 (MH^+). $C_{16}H_{12}N_3O_4$ requires: m/z = 310.0822. ν_{max} (ATR) 3065, 1681 (C=O), 1530, 1500, 1349, 1243, 778, 726, 695 cm^{-1}.

7.18. General Procedure for the Synthesis of Methyl 1-Substituted (*S*)-(5-Phenyl-1*H*-pyrazole-4-carbonyl)alaninates 25a–c. CDI (0.34 g, 2.1 mmol) was added to a solution of carboxylic acid **24a–c** (2 mmol) in anh. MeCN (10 mL) and the mixture was stirred at r.t. for 2 h. Then, *N*-methylmorpholine (0.22 mL) and L-alanine methyl ester hydrochloride (**11a**) (0.31 g, 2.2 mmol) were added and stirring at r.t. was continued for 40 h. Volatile components were evaporated in vacuo, the residue was taken up in EtOAc (30 mL),

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and washed with 1 M HCl (3 × 20 mL), aq. $NaHCO_3$ (2 × 20 mL), and brine (20 mL). The organic phases were combined, dried over anh. Na_2SO_4, filtered, and the filtrate was evaporated in vacuo. The residue was purified by DVFC (silica gel, EtOAc–hexanes). Fractions containing the product were combined and evaporated in vacuo to give **25a–c**.

*7.18.1. Methyl (S)-(1,5-diphenyl-1H-pyrazole-4-carbonyl)-alaninate (**25a**).* Prepared from **24a** (0.529 g, 2 mmol) and methyl (*S*)-alaninate hydrochloride (**11a**) (0.31 g, 2.2 mmol), DVFC (EtOAc–hexanes, 1:1). Yield: 0.538 g (77%) of white crystals; mp 109–111 °C; $[\alpha]_D^{22}$ − 18.0 (*c* = 0.50, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (3H, d, *J* = 7.2 Hz); 3.68 (3H, s); 4.64 (1H, quintet, *J* = 7.2 Hz); 5.94 (1H, d, *J* = 7.3 Hz); 7.18–7.22 (2H, m); 7.25–7.30 (3H, m); 7.33–7.37 (2H, m); 7.41–7.48 (3H, m); 8.20 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.3, 47.9, 52.4, 117.3, 125.1, 127.9, 128.7, 128.8, 129.1, 129.8, 130.4, 139.1, 141.5, 141.8, 162.0, 173.2. *m*/*z* (ESI) = 350 (MH^+). *m*/*z* (HRMS) Found: 350.1513 (MH^+). $C_{20}H_{20}N_3O_3$ requires: *m*/*z* = 350.1499. (Found: C, 68.79; H, 5.41; N, 11.95. $C_{20}H_{19}N_3O_3$ requires: C, 68.75; H, 5.48; N, 12.03.); ν_{max} (ATR) 3307, 1732 (C=O), 1636 (C=O), 1561, 1496, 1386, 1304, 1224, 762, 695 cm^{-1}.

*7.18.2. Methyl (S)-(1-(2-chlorophenyl)-5-phenyl-1H-pyrazole-4-carbonyl)alaninate (**25b**).* Prepared from **24b** (0.597 g, 2 mmol) and methyl (*S*)-alaninate hydrochloride (**11a**) (0.31 g, 2.2 mmol), DVFC (EtOAc–hexanes, 1:2). Yield: 0.537 g (70%) of brownish oil; $[\alpha]_D^{22}$ − 15.6 (*c* = 2.0, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (3H, d, *J* = 7.1 Hz); 3.68 (3H, s); 4.65 (1H, quintet, *J* = 7.2 Hz); 6.01 (1H, d, *J* = 7.3 Hz); 7.22–7.26 (1H, m); 7.28–7.40 (8H, m); 8.23 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.3, 47.9, 52.4, 116.4, 127.3, 127.8, 128.7, 129.8, 130.0, 130.1, 130.2, 130.7, 132.5, 136.8, 141.7, 143.9, 161.9, 173.2. *m*/*z* (ESI) = 384, 386 (MH^+). *m*/*z* (HRMS) Found: 384.1118 (MH^+). $C_{20}H_{19}ClN_3O_3$ requires: *m*/*z* = 384.1119. (Found: C, 60.64; H, 4.48; N, 13.98. $C_{20}H_{18}N_4O_5$ requires: C, 60.91; H, 4.60; N, 14.21.); ν_{max} (ATR) 3315, 2952, 1740 (C=O), 1644 (C=O), 1557, 1518, 1498, 1488, 1446, 1207, 1166, 912, 762, 727, 696 cm^{-1}.

*7.18.3. Methyl (S)-(1-(2-nitrophenyl)-5-phenyl-1H-pyrazole-4-carbonyl)alaninate (**25c**).* Prepared from **24c** (0.619 g, 2 mmol) and methyl (*S*)-alaninate hydrochloride (**11a**) (0.31 g, 2.2 mmol), DVFC (EtOAc–hexanes, 1:2). Yield: 0.426 g (54%) of brownish crystals; mp 154–159 °C; $[\alpha]_D^{22}$ − 9.0 (*c* = 0.50, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (3H, d, *J* = 7.1 Hz); 3.69 (3H, s); 4.65 (1H, quintet, *J* = 7.2 Hz); 6.01 (1H, d, *J* = 7.2 Hz); 7.23 (1H, dd, *J* = 7.3, 2.0 Hz); 7.36–7.46 (5H, m); 7.52 (2H, pd, *J* = 7.6, 1.7 Hz); 7.91 (1H, dd, *J* = 7.8, 1.8 Hz); 8.19 (1H, s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.4, 48.0, 52.4, 117.4, 125.2, 127.3, 129.1, 129.6, 129.7, 130.2, 130.3, 132.5, 133.2, 142.5, 143.3, 145.9, 161.5, 173.1. *m*/*z* (ESI) = 395 (MH^+). *m*/*z* (HRMS) Found: 395.1345 (MH^+). $C_{20}H_{19}N_4O_5$ requires: *m*/*z* = 395.1350. (Found: C, 60.64; H, 4.48; N, 13.98. $C_{20}H_{18}N_4O_5$ requires: C, 60.91; H, 4.60; N, 14.21.); ν_{max} (ATR) 3301, 1733 (C=O), 1635 (C=O), 1563, 1536, 1361, 1303, 766, 748, 698 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02467.

Crystal data. (CIF)

Copies of the NMR spectra, X-ray diffraction data, DNMR spectra, computational details, additional tables and figures. (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*, 5th ed.; Wiley-Blackwell, 2010; Chapters 30–33, pp 587–664.

(2) (a) Vagner, J.; Qu, H.; Hruby, V. J. *Curr. Opin. Chem. Biol.* **2008**, *12*, 292–296. (b) Robinson, J. A.; DeMarco, S.; Gombert, F.; Moehle, K.; Obrecht, D. *Drug Discovery Today* **2008**, *13*, 944–951. (c) Robinson, J. A. *Acc. Chem. Res.* **2008**, *41*, 1278–1288. (d) Hanessian, S.; Auzzas, L. *Acc. Chem. Res.* **2008**, *41*, 1241–1251. (e) Wells, J. A.; McClendon, C. L. *Nature* **2007**, *450*, 1001–1009. (f) Hutchinson, E. G.; Thornton, J. M. *Protein Sci.* **1994**, *3*, 2207–2216. (g) Gallo, E. A.; Gellman, S. H. *J. Am. Chem. Soc.* **1993**, *115*, 9774–9788.

(3) (a) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789–12854. (b) Halab, L.; Gosselin, F.; Lubell, W. D. *Biopolymers* **2000**, *55*, 101–122. (c) Cluzeau, J.; Lubell, W. D. *Biopolymers* **2005**, *80*, 98–150.

(4) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereoisomers in Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; pp 49–70.

(5) Christie, G. H.; Kenner, J. *J. Chem. Soc., Trans.* **1922**, *121*, 614–620.

(6) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *14–5. Biphenyls. Atropisomerism in Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; pp 1142–1155.

(7) Ōki, M. Recent Advances in Atropisomerism. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, N. L., Wilen, S. H., Eds.; John Wiley and Sons: New York, 1983; Vol. *14*, pp 1–81.

(8) (a) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, *1992*, 503–517. (b) McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809–3844. (c) Bringmann, G.; Price Mortimer, A.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384–5427.

(9) Bringmann, G.; Günther, C.; Ochse, M.; Schupp, O.; Tasler, S. In *Biaryls in Nature in Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Eds.; Springer: Vienna, 2001; Vol. *82*, pp 1–249.

(10) Alkorta, I.; Elguero, J.; Roussel, C.; Vanthuyne, N.; Piras, P. *Adv. Heterocycl. Chem.* **2012**, *105*, 1–188.

(11) Janjić, M.; Prebil, R.; Grošelj, U.; Kralj, D.; Malavašič, Č.; Golobič, A.; Stare, K.; Dahmann, G.; Stanovnik, B.; Svete, J. *Helv. Chim. Acta* **2011**, *94*, 1703–1717.

(12) Peng, Y.; Zhang, Q.; Snyder, G. L.; Zhu, H.; Yao, W.; Tomesch, J.; Papke, R. L.; O'Callaghan, J. P.; Welsh, W. J.; Wennogle, L. P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4825–4830.

(13) Udagawa, S.; Yamamoto, M.; Aoki, T.; Oosumi, K.; Hayashi, K. WO 2014069554.

(14) Peng, Y.; Wennogle, L. P.; Zhang, Q.; Tomesch, J. WO 2012178057.

(15) Li, P.; Peng, Y.i; Tomesch, J.; Wennogle, L. P.; Zhang, Q. WO 2012178112.

(16) Peng, Y.; Wennogle, L.; Zhang, Q.; Tomesch, J. WO 2012177263.

(17) Menozzi, G.; Fossa, P.; Cichero, E.; Spallarossa, A.; Ranise, A.; Mosti, L. *Eur. J. Med. Chem.* **2008**, *43*, 2627–2638.

(18) Bailey, N.; Bamford, M. J.; Dean, D. K.; Pickering, P. L.; Wilson, D. M.; Witherington, J. WO 2005058837.

(19) Pendri, A.; Gerritz, S.; Dodd, D. S.; Sun, C. US 20050080087.

(20) Hamanaka, E. S.; Guzman-Perez, A.; Ruggeri, R. B.; Wester, R. T.; Mularski, C. J. WO 9943663.

(21) Pepin, R.; Schmitz, C.; Lacroix, G. B.; Dellis, P.; Veyrat, C. EP 360701.

(22) Šenica, L.; Grošelj, U.; Kasunič, M.; Kočar, D.; Stanovnik, B.; Svete, J. *Eur. J. Org. Chem.* **2014**, *2014*, 3067–3071.

(23) For details, see Supporting Information.

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J. Org. Chem. 2016, 81, 146–161

(24) Sandström, J. In *Dynamic NMR Spectroscopy*; Academic Press: London, 1982; pp 93−123, 151−176.
(25) Hesse, M.; Meier, H.; Zeeh, B. In *Spektroskopische Methoden in der Organische Chemie*; Georg Thieme Verlag: Stuttgart, 1995; pp 98−100.
(26) Kemp, W. In *NMR in Chemistry: A Multinuclear Introduction*; Macmillan Education Ltd.: London, U.K., 1986; pp 158−168.
(27) Friebolin, H. In *Basic One- and Two-Dimensional NMR Spectroscopy*; Wiley-VCH: Weinheim, 2005; pp 309−314, and references cited therein.
(28) Gasparro, F. P.; Kolodny, N. H. *J. Chem. Educ.* **1977**, *54*, 258−261.
(29) Levine, R. D. In *Molecular Reaction Dynamics*; Cambridge University Press: Cambridge, 2005; pp 1−568.
(30) (a) Frank, J. H.; Powder-Georger, Y. L.; Ramsewak, R. S.; Reynolds, W. F. *Molecules* **2012**, *17*, 7914−7926. (b) Zimmer, K. D.; Shoemaker, R.; Ruminski, R. R. *Inorg. Chim. Acta* **2006**, *359*, 1478−1484.
(31) Shanan-Atidi, H.; Bar-Eli, K. H. *J. Phys. Chem.* **1970**, *74*, 961−963.
(32) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision D.01; Gaussian, Inc.: Wallingford, CT, 2013.
(33) (a) Yamada, S. In *Sterically Hindered Twisted Amides in The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; John Wiley and Sons: New York, 2000; pp 215−246. (b) Kirby, A. J.; Komarov, I. V.; Wothers, P. D.; Feeder, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 785−786.
(34) For examples, see: (a) Skorupska, E. A.; Nazarski, R. B.; Ciechanska, M.; Jozwiak, A.; Klys, A. *Tetrahedron* **2013**, *69*, 8147−8154. (b) Olsen, R. A.; Liu, L.; Ghaderi, N.; Johns, A.; Hatcher, M. E.; Mueller, L. J. *J. Am. Chem. Soc.* **2003**, *125*, 10125−10132.
(35) Chandrakantha, B.; Isloor, A. M.; Sridharan, K.; Philip, R.; Shetty, P.; Padaki, M. *Arabian J. Chem.* **2013**, *6*, 97−102.
(36) Kasımoğulları, R.; Arslan, B. S. *J. Heterocycl. Chem.* **2010**, *47*, 1040−1048.

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