Pergamon

Tetrahedron 58 (2002) 1595–1605

TETRAHEDRON

Synthesis of 1-hydroxypyrazole glycine derivatives

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Received 15 October 2001; accepted 3 January 2002

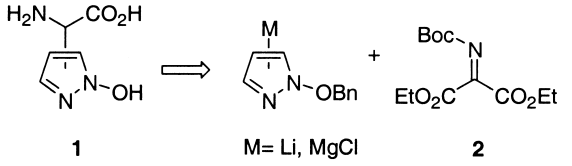
Abstract—A series of novel α-amino acids containing the 1-hydroxypyrazole ring has been prepared by addition of organomagnesium or organolithium intermediates to diethyl *N*-Boc-iminomalonate as an electrophilic glycine equivalent. Electrophiles, aryl and heteroaryl substituents were introduced in the pyrazole ring. © 2002 Published by Elsevier Science Ltd.

1. Introduction

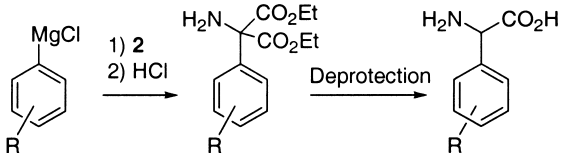
The synthesis of new and structurally diverse unnatural amino acids is a continuous challenge for organic chemists.[1,2] Non-proteinogenic amino acids play a key role in the drug discovery process. Their incorporation in peptides and proteins often increases metabolic stability and generates unusual secondary structures. Furthermore, aromatic and heteroaromatic glycine derivatives have found valuable applications as antagonists of the glutamate receptors in the central nervous system,[3] in β-lactam antibiotics[4,5] or in glycopeptide antibiotics such as vancomycin.[6]

Herein, we report the synthesis of a novel class of 1-hydroxypyrazole α-amino acids **1**. 1-Hydroxypyrazoles can be regarded as analogues of both weak carboxylic acids and phenols, due to the presence of the relatively acidic *N*-hydroxy functionality (pK_a 6.3).[7] Our group is currently investigating this hypothesis. 1-Hydroxypyrazoles have so far been used to replace the phenol group in Tamoxiphen analogues,[8] or to mimic the action of the distal carboxylic acid of (*S*)-Glu.[9] Extensive methodology for regioselective metalation and functionalization of the ring, allowing the introduction of electrophiles, aryl, heteroaryl and acyl groups have been developed in recent years.[10–12] We now wish to report the application of this chemistry to the preparation of functionalized heteroaromatic amino acids. In our strategy the key step for the introduction of the glycine functionality is the addition of lithium and magnesium 1-benzyloxypyrazole derivatives to diethyl *N*-Boc iminomalonate **2** (Scheme 1).

We recently demonstrated the utility of this stable and reactive electrophilic glycine equivalent for the preparation of functionalized arylglycines.[13] The reaction with various arylmagnesium reagents afforded arylaminomalonates in good yields after mild deprotection of the *N*-Boc group (Scheme 2). The corresponding amino acids were obtained after acidic or basic hydrolysis, followed by decarboxylation.



Scheme 1.



Scheme 2.

2. Results and discussion

2.1. 1-Hydroxypyrazolylglycines 6 and 10

We first investigated the preparation of the amino acid **6**, introducing the glycine functionality at C-5 of **3** (Scheme 3). Lithiation of 1-benzyloxypyrazole **3** with *n*-BuLi at −78°C,[11] followed by addition of 1.1 equiv. of imine **2**, afforded the expected intermediate **4** in 92% yield. The addition of the organolithium compound occurred selectively at the imine carbon and no competing addition at the ester or the carbamate group was observed. The first attempt to remove all the protecting groups (ethyl, benzyl and *N*-Boc) in one step by refluxing **4** in conc HCl or HBr, gave complex, inseparable mixtures. Therefore, the benzyl

Keywords: arylglycine; amino acid; 1-hydroxypyrazole; imino malonate.

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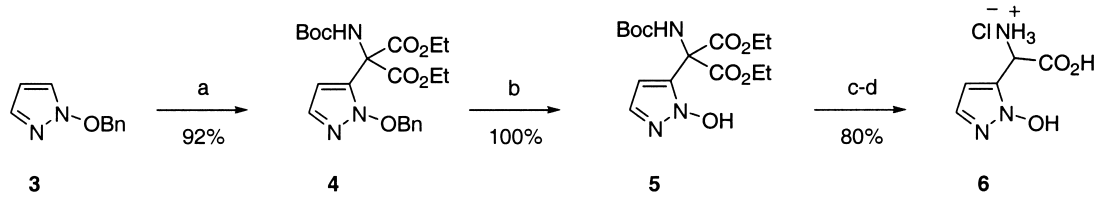
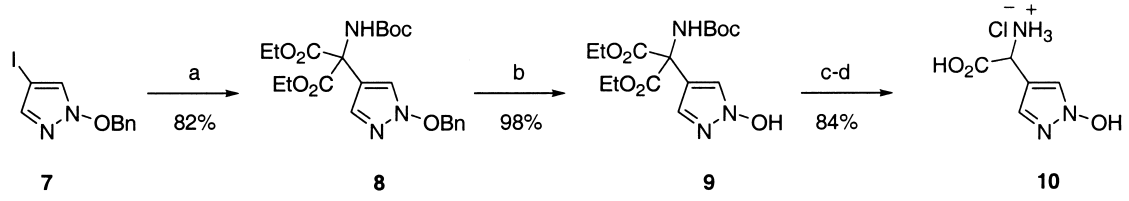
0040–4020/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4020(02)00021-2



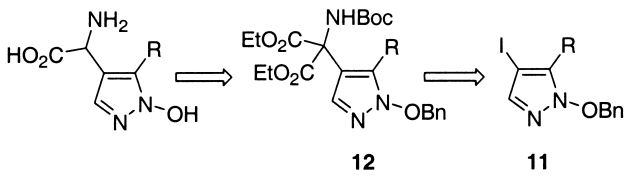
Scheme 3. *Reagents and conditions*: (a) *n*-BuLi, THF, −78°C, 5 min; then **2**, −78°C, 1 h; (b) H_2 (1 atm), 10% Pd/C, MeOH, 0°C, 30 min; (c) LiOH, THF/H_2O, rt, 12 h; (d) 2N HCl, 60°C, 30 min.



Scheme 4. *Reagents and conditions*: (a) *i*-PrMgCl, THF, 0°C, 30 min, then cooling to −78°C, imine **2**, 3 h; (b) H_2 (1 atm), 10% Pd/C, MeOH, 0°C, 30 min; (c) LiOH, THF, rt, 4 h; (d) 2N HCl, 60°C, 30 min.

group was first removed by mild hydrogenolysis (10% Pd/C at 0°C)[11] to produce the free *N*-hydroxy derivative **5** in quantitative yield. The liberation of the amino acid functionality was then attempted by standard acidic or basic hydrolysis of the diethyl malonate followed by decarboxylation,[14] and removal of the *N*-Boc group.[15] Refluxing the intermediate **5** in 6N HCl for 12 h gave a mixture of the expected product **6** and the partially deprotected diethyl aminomalonate. All attempts to drive the hydrolysis of the ester to completion by increasing reaction time and concentration of the acid, only led to progressive decomposition of the thermally sensitive final product. Instead basic hydrolysis was attempted. 1-Hydroxypyrazole **5** was treated with LiOH in THF–water to hydrolyze the esters. Subsequent stirring in 2N HCl at 60°C for 30 min gave decarboxylation and deprotection of the amino functionality. The pure crystalline **6** was so obtained in 80%.

A similar strategy was employed for the preparation of regioisomer **10** introducing the glycine functionality at C-4 (Scheme 4). Treatment of 1-benzyloxy-4-iodopyrazole **7** with *i*-PrMgCl at 0°C generated a 4-pyrazolylmagnesium chloride intermediate by halogen–metal exchange.[10] Low temperature addition of **2** gave the expected adduct **8** in 82% yield, as the sole product. The final deprotection of the debenzylated intermediate **9** was attempted both by acidic and basic hydrolysis. Even though the target amino acid **10** could be obtained by acidic treatment (6N HCl for 12 h), cumbersome purification by ion exchange was required. On the other hand, basic hydrolysis (2N LiOH) followed by mild acidic *N*-Boc deprotection and decarboxylation (2N HCl), gave the pure crystalline **10** in 84% yield by simple evaporation to dryness.



Scheme 5. R=aryl, heteroaryl, electrophiles.

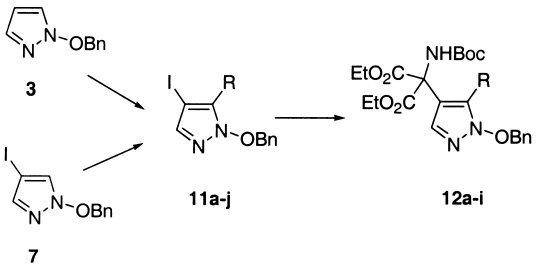
2.2. 5-Substituted 1-hydroxypyrazolylglycines (14)

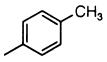
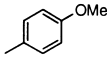
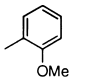
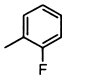
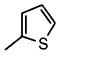
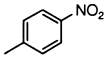
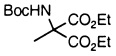
With these results in hand, we focused on the synthesis of 5-substituted 1-hydroxypyrazole glycine derivatives (Scheme 5). The strategy involves the preparation of **11** as the key intermediate, where aryl, heteroaryl and electrophiles would be introduced at C-5. Halogen–metal exchange, followed by addition of the imine **2**, would afford the amino acid precursor **12**.

Aryl and heteroaryl substituents were introduced at C-5 by Pd(0) catalyzed Negishi cross-coupling from 1-benzyloxypyrazole **3** and commercially available aryliodides.[12] Iodination of the crude products with ICl gave 5-aryl-4-iodopyrazoles **11a–f** in 54–92% overall yields (Table 1, entries 1–6). Electrophiles were also introduced in the 5-position affording **11g–j** (Table 1, entries 7–10). When **7** was treated with the hard base[16] LDA at −78°C, selective deprotonation at C-5 occurred without any competing halogen–metal exchange at C-4.[17] Quenching with electrophiles gave adducts **11g–i** in good yields. When **2** was used as electrophile, **11j** was generated in 54% yield.

The glycine functionality was then introduced at C-4. Halogen–metal exchange was previously performed with *i*-PrMgCl from **7**, generating the positionally stable 4-magnesium intermediate, since the corresponding 4-lithium intermediate has proved to be very unstable.[10] Recently it was observed that this instability is considerably reduced when substituents are present at C-5, allowing the successful use of the more reactive organolithium intermediate.[18,19] Treatment of **11a** with *i*-PrMgCl at 0°C, followed by addition of imine **2**, afforded **12a** in 54% yield. The yield increased to 78% when the halogen–metal exchange was performed with *n*-BuLi. Therefore, the latter protocol was used to prepare compounds **12a–i**. The synthesis of **12f** proved to be more troublesome due to the presence of the sensitive nitro group. The reaction of **11f**

Table 1. Synthesis of intermediates **12a–i**



Entry	R	11	Yield (%)	12[a]	Yield (%)
1		**11a**[b]	73	**12a**	78
2		**11b**[b]	92	**12b**	75
3		**11c**[b]	81	**12c**	70
4		**11d**[b]	75	**12d**	69
5		**11e**[b]	81	**12e**	81
6		**11f**[b]	54	**12f**[c]	72
7	CH_3	**11g**[d]	94	**12g**	84
8	SCH_3	**11h**[d]	73	**12h**	75
9	Cl	**11i**[d]	98	**12i**	83
10		**11j**[d]	54		

[a] *Reagents and conditions*: *n*-BuLi, −78°C then imine **2**.
[b] Isolated yields based on the starting material **3**. *Reagents and conditions*: *n*-BuLi, −78°C, 10 min; $ZnCl_2$ rt; RI, $Pd(P\ Ph_3)_4$, DMF, 80°C, 2 h; ICl, CH_2Cl_2, rt.
[c] *Reagents and conditions*: PhLi, −105°C, then imine **2**.
[d] Isolated yields based on the starting material **7**. *Reagents and conditions*: LDA, −78°C, 5 min, then electrophile.

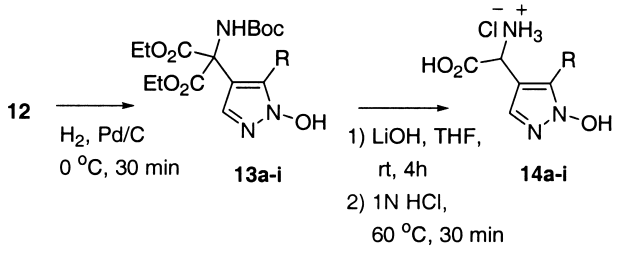
with both *i*-PrMgCl and *n*-BuLi gave rise to a complex mixture of products. This problem could be overcome by the use of PhLi at −105°C, providing the desired product **12f** in 72% yield (Table 1, entry 6).[20,21]

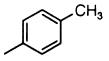
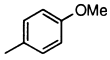
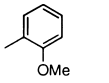
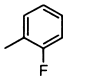
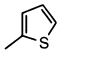
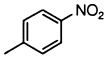
Deprotection of **12a–i** was performed in two steps (Table 2). The benzyl group was first removed by hydrogenolysis to afford 1-hydroxypyrazole derivatives **13a–i** in essentially quantitative yields. These conditions were not applicable to derivative **12f**, since reduction of the nitro group took place during debenzylation. Basic hydrolysis and decarboxylation of 1-hydroxypyrazoles **13a–e** and **13g–i** were accomplished following the above mentioned methodology, to provide the pure final amino acids **14a–e** and **14g–i** in good yields (Table 2, entries 1–5 and 7–9). Compound **14f** was obtained in 94% yield by refluxing **12f** in 12N HCl for 12 h. Analytically pure **14f** precipitated upon cooling of the reaction mixture.

2.3. 4-Substituted 1-hydroxypyrazolylglycines (18)

Several 4-substituted hydroxypyrazole glycines were prepared by introducing aryl groups at C-4. Two different

Table 2. Synthesis of 1-hydroxypyrazole amino acids **14a–i**

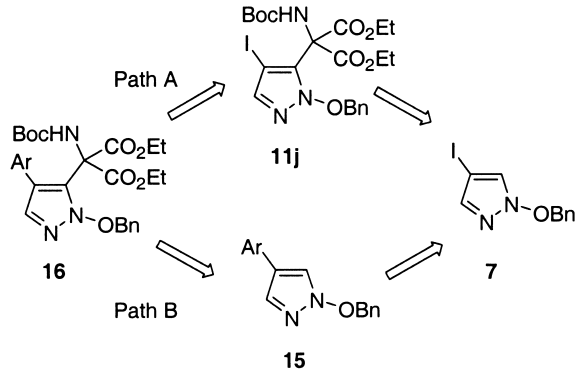


Entry	R	13	Yield (%)	14	Yield (%)
1		**13a**	99	**14a**	96
2		**13b**	100	**14b**	96
3		**13c**	98	**14c**	86
4		**13d**	99	**14d**	83
5		**13e**	98	**14e**	89
6		**13f**	–	**14f**[a]	94
7	CH_3	**13g**	97	**14g**	81
8	SCH_3	**13h**	92	**14h**	89
9	Cl	**13i**	95	**14i**	84

[a] Product obtained directly from **12f**. See Section 4.

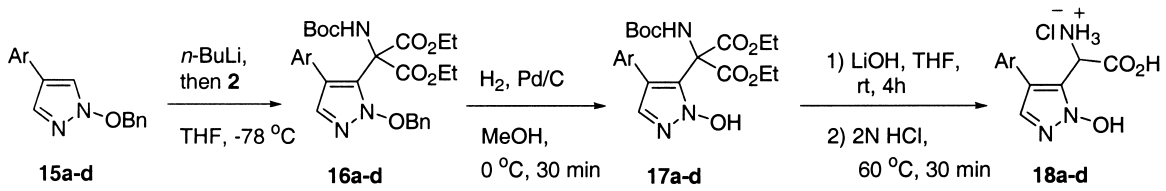
approaches could be envisaged for the synthesis of this class of compounds (Scheme 6). The more convergent path A involves the previously prepared **11j** as the key intermediate (Scheme 6). Therefore, we attempted to introduce aryl substituents by Pd(0) catalysed Suzuki cross-coupling[22,23] between aryl boronic acids and **11j**. Unfortunately, the desired products could be obtained only in very low yields. Extensive decomposition of the starting material was observed by increasing temperature and reaction time, indicating the thermal instability of **11j**. All attempts to improve this preliminary result by changing solvent, base or catalyst were unsuccessful, and the strategy was therefore abandoned.

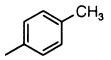
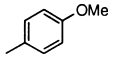
An alternative strategy involves the synthesis of 4-aryl-1-benzyloxypyrazole **15** followed by introduction of the



Scheme 6.

Table 3. Synthesis of 1-hydroxypyrazole glycine **18a–d**



Entry	Ar	16	Yield (%)	17	Yield (%)	18	Yield (%)
1		**16a**	69	**17a**	99	**18a**	87
2		**16b**	75	**17b**	100	**18b**	80
3		**16c**	69	**17c**	99	**18c**	97
4		**16d**	65	**17d**	98	**18d**	74

glycine moiety at C-5 (Path B, Scheme 6). Intermediates **15a–d** were generated by Negishi cross-coupling from **7** and aryliodides as previously reported.[10,19] Deprotonation at C-5 with *n*-BuLi followed by addition of the imine **2** gave the desired products **16a–d** in 65–75% yields (Table 3). These intermediates were debenzylated in quantitative yields prior to the final deprotection. Acidic treatment of 1-hydroxypyrazole derivative **17a** (6N HCl for 12 h), gave the pure diethyl aminomalonate derivative as the only product. No traces of the desired amino acid were detected by NMR even after prolonged refluxing in conc HCl or HBr. However, the target amino acids **18a–d** could be obtained in 74–94% yields by basic hydrolysis–acidification–decarboxylation.

3. Conclusions

In summary, we have presented the synthesis of a new class of α-heteroaryl glycines based on the addition of lithium and magnesium 1-benzyloxypyrazole intermediates to an electrophilic glycine equivalent. This reaction was successfully combined with selective functionalisation of the 1-hydroxypyrazole ring giving access to a broad range of *N*-Boc heteroaryl malonic esters. The corresponding substituted 1-hydroxypyrazole amino acids could be obtained after deprotection–decarboxylation under mild conditions.

4. Experimental

4.1. General

All reactions involving air-sensitive reagents were performed under N_2 using syringe-septum cap technique. All glassware was flamed-dried prior to use. Flash chromatography (FC) was performed using silica Merck 60 (230–460 mesh). ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) were recorded on a Varian instrument using TMS as internal standard. Melting points are uncorrected. HRMS was performed on a Micromass LCT instrument. IR were performed on a Equinox55 instrument in 0.3% KBr. All solvents and reagents were of analytical grade purchased from Aldrich or Fluka and used without further purification. *N*-Boc iminomalonate **2** was prepared as previously described.[13] THF was distilled from Na/benzophenone ketyl under N_2. DMF was dried and stored over 3 Å molecular sieves. 1 M solutions of $ZnCl_2$ were prepared by flame drying the zinc salt under vacuum before dissolving it in dry THF. *n*-BuLi[24] and *i*-PrMgCl[25] solutions were titrated prior to use. $Pd(PPh_3)_4$ was prepared as previously described.[26]

4.1.1. Diethyl 2-(1-benzyloxypyrazol-5-yl)-2-*tert*-butoxycarbonylamino-malonate (4). To a stirred solution of **3** (1 mmol) in THF (10 mL) at −78°C, was added dropwise 1.6 M *n*-BuLi in hexane (0.75 mL, 1.1 mmol) over 2 min. After 5 min, a solution of imine **2** (300 mg, 1.1 mmol) in THF (1 mL) was added, and the mixture was stirred for 1 h at −78°C, before quenching cold with water. The reaction was allowed to warm to rt, NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3×15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford the crude product. FC (petroleum ether/EtOAc 6:1→4:1) gave **4** (412 mg, 92%) as a colorless oil. R_f 0.2 (petroleum ether/EtOAc 5:1). IR (KBr) 3421, 2981, 1751, 1726, 1482, 1368, 1256, 1203, 1162, 1023 cm^{-}.[1] ^{1}H NMR ($CDCl_3$) δ 7.44–7.34 (m, 5H), 7.26 (d, J=2.4 Hz, 1H), 6.70 (d, J=2.4 Hz, 1H), 6.16 (br s, 1H), 5.24 (s, 2H), 4.29–4.11 (m, 4H), 1.37 (s, 9H), 1.17 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 165.3, 153.5, 133.1, 132.1, 130.8, 129.7, 129.2, 128.5, 106.7, 80.7, 79.9, 63.2, 62.8, 27.9, 13.5. HRMS $[M+H]^+$ calcd for $C_{22}H_{30}N_3O_7$: 448.2084. Found: 448.2065.

4.1.2. Diethyl 2-*tert*-butoxycarbonylamino-2-(1-hydroxypyrazol-5-yl)-malonate (5). Compound **4** (447 mg, 1 mmol), 10% Pd/C (65 mg) in MeOH (8 mL), were vigorously stirred under hydrogen (1 atm) at 0°C for 30 min. Filtration through celite, washing with MeOH and evaporation of the solvent gave the crude product as a pale yellow oil that crystallized on standing. FC (petroleum ether/EtOAc 1:1→1:2) gave **5** as colorless crystals (357 mg, 100%). Mp 97–98°C (petroleum ether/Et_2O). R_f

0.22 (petroleum ether/EtOAc 1:1). IR (KBr) 3419, 2981, 1752, 1718, 1475, 1368, 1256, 1203, 1162, 1024 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.12 (d, J=2.4 Hz, 1H), 6.66 (br d, J=2.4 Hz, 1H), 6.46 (br s, 1H, NH), 4.38–4.18 (m, 4H), 1.36 (s, 9H), 1.24 (t, J=7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 165.2, 153.9, 131.4, 130.4, 106.1, 80.9, 63.4, 62.9, 27.9, 13.6. Anal. calcd for $C_{15}H_{23}N_3O_7$: C, 50.42; H, 6.49; N, 11.76. Found: C, 50.61; H, 6.38; N 11.51.

4.1.3. Hydrochloride salt of amino-(1-hydroxypyrazol-5-yl)-acetic acid (6). To a solution of **5** (357 mg, 1 mmol) in THF (4 mL) was added a 2.5 M aqueous solution of LiOH (3.5 mL, 9 mmol). The mixture was vigorously stirred at rt for 12 h. The solution was cooled to 0°C and 1 M HCl was added dropwise until pH 2. The mixture was extracted with EtOAc (3×20 mL), the combined organic layers were washed with brine (10 mL), filtered and evaporated to dryness. The residue was stirred in 2 M HCl (3 mL) at 60°C for 30 min. After evaporation to dryness **6** (155 mg, 80%) was obtained as a pale yellow oil that slowly crystallized under vacuum. The crystals were triturated twice with Et_2O and dried under vacuum. Mp decomposition above 130°C. IR (KBr) 3205, 3164, 2885, 2622, 1729, 1489, 1236 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.91 (br s, 3H), 7.19 (d, J=2.4 Hz, 1H), 6.34 (d, J=2.4 Hz, 1H), 5.21 (br q, J=5.0 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 160.9, 124.7, 120.5, 97.4, 39.7. HRMS $[M-HCl-H]^-$ calcd for $C_5H_6N_3O_3$: 156.0409. Found: 156.0460.

4.1.4. Diethyl 2-(1-benzyloxypyrazol-4-yl)-2-*tert*-butoxycarbonylamino-malonate (8). To a stirred solution of **7** (300 mg, 1 mmol) in THF (10 mL) at 0°C, was added dropwise 2.0 M *i*-PrMgCl in THF (0.6 mL, 1.2 mmol). After stirring at 0°C for 30 min, the mixture was cooled to −78°C and a solution of the imine **2** (300 mg, 1.1 mmol) in THF (1 mL) was added. Stirring was continued at −78°C for 3 h before quenching cold with water. The reaction mixture was allowed to warm to rt, NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3×15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. FC (petroleum ether/EtOAc 5:1→3:1) afforded **8** (366 mg, 82%) as a colorless oil. R_f 0.19 (petroleum ether/EtOAc 4:1). IR (KBr) 3431, 2980, 1744, 1719, 1368, 1269, 1165 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.38–7.32 (m, 7H), 6.26 (br s, 1H), 5.26 (s, 2H), 4.30–4.19 (m, 2H), 4.14 (dq, J=10.7, 7.1 Hz, 2H), 1.40 (s, 9H), 1.19 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 167.0, 153.9, 133.7, 132.1, 129.5, 129.1, 128.6, 123.0, 115.0, 80.6, 80.5, 63.3, 62.7, 27.9, 13.6. HRMS $[M+H]^+$ calcd for $C_{22}H_{30}N_3O_7$: 448.2084. Found: 448.2072.

4.1.5. Diethyl 2-*tert*-butoxycarbonylamino-2-(1-hydroxypyrazol-4-yl)-malonate (9). Compound **7** (447 mg, 1 mmol), 10% Pd/C (65 mg) in MeOH (8 mL), were vigorously stirred under hydrogen (1 atm) at 0°C for 30 min. Filtration through celite, washing with MeOH and evaporation of the solvent gave the crude product as a pale yellow oil that crystallized on standing. FC (petroleum ether/EtOAc 1:1→1:2) gave **9** as colorless crystals (349 mg, 98%). Mp 134–135°C (Et_2O/petroleum ether). R_f 0.22 (petroleum ether/EtOAc 1:1). IR (KBr) 3250, 2984, 1749, 1676, 1407, 1266, 1211 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.58 (d, J=0.9 Hz, 1H), 7.24 (d, J=0.9 Hz, 1H), 6.31 (br s, 1H), 4.29 (m, 2H), 4.21 (dq, J=10.5, 7.2 Hz, 2H), 1.41 (s, 9H), 1.24 (t, J=7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.9, 153.9, 130.5, 122.5, 114.9, 80.7, 63.5, 62.9, 27.9, 13.7. Anal. calcd for $C_{15}H_{23}N_3O_7$: C, 50.42; H, 6.49; N, 11.76. Found: C, 50.67; H, 6.37; N 11.75.

4.1.6. Hydrochloride salt of amino-(1-hydroxypyrazol-4-yl)-acetic acid (10). To a solution of **9** (357 mg, 1 mmol) in THF (4 mL) was added a 2.5 M aqueous solution of LiOH (3.5 mL, 9 mmol). The mixture was vigorously stirred at rt for 4 h. The solution was cooled to 0°C and 1 M HCl was added dropwise until pH 2. The mixture was extracted with EtOAc (3×20 mL), the combined organic layers were washed with brine (10 mL), filtered and evaporated to dryness. The residue was stirred in 2 M HCl (3 mL) at 60°C for 30 min. After evaporation of HCl, **10** (161 mg, 84%) was obtained as a colorless oil that slowly crystallized. The crystals were triturated with Et_2O and dried under vacuum. Mp>190°C. IR (KBr) 3029, 2935, 2612, 1743, 1497, 1285, 1219 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.77 (br s, 3H), 7.68 (d, J=1.0 Hz, 1H), 7.24 (d, J=1.0 Hz, 1H), 4.96 (br q, J=5.0 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 169.8, 131.3, 122.8, 111.2, 48.0. HRMS $[M-HCl-H]^-$ calcd for $C_5H_6N_3O_3$: 156.0409. Found: 156.0469.

4.2. General procedure for the preparation of 11a–f

To a stirred solution of **3** (174 mg, 1 mmol) in THF (8 mL) at −78°C, was added dropwise 1.6 M *n*-BuLi in hexane (0.68 mL, 1.1 mmol) over 2 min. After 5 min, a 1 M solution of $ZnCl_2$ in THF (1.5 mL, 1.5 mmol) was added. The solution was allowed to warm to rt, the aryl halide (1.5 mmol) and $Pd(PPh_3)_4$ (2 mol%) in DMF (4 mL) were added. The mixture was heated to 80°C for 2 h before quenching with sat. aq. NH_4Cl (10 mL). Water (5 mL) was added and the mixture was extracted with Et_2O (3×15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford the crude product, which was iodinated without further purification.

The crude 5-aryl-1-benzyloxypyrazole was dissolved in CH_2Cl_2 (10 mL), K_2CO_3 (357 mg, 2.2 mmol) and ICl (276 mg, 2 mmol) were added. After stirring at rt for 1 h, 1 M aq. Na_2SO_3 was added to destroy the excess of ICl. The mixture was extracted with CH_2Cl_2 (3×20 mL), dried over Na_2SO_4, filtered and evaporated to dryness. Purification of the residue by FC (petroleum ether/EtOAc) gave the title compound.

4.2.1. 1-Benzyloxy-4-iodo-5-(4-tolyl)-pyrazole (11a). From 4-iodotoluene. FC (petroleum ether/EtOAc 6:1). Yield 73%. Pale yellow oil. R_f 0.26 (petroleum ether/EtOAc 5:1). ^1H NMR ($CDCl_3$) δ 7.41 (s, 1H), 7.30–7.24 (m, 2H), 7.22–7.16 (m, 5H), 7.04–7.01 (m, 2H), 5.66 (s, 2H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 139.2, 138.5, 136.8, 132.9, 129.7, 129.6, 129.2, 129.0, 128.5, 124.1, 80.6, 55.9, 21.4. Anal. calcd for $C_{17}H_{15}N_2OI$: C, 52.33; H, 3.87; N 7.18. Found: C, 52.07; H, 3.62; N 7.16.

4.2.2. 1-Benzyloxy-4-iodo-5-(4-methoxyphenyl)-pyrazole (11b). From 4-iodoanisole. FC (petroleum ether/EtOAc 5:1). Yield 92%. Pale yellow oil. R_f 0.48 (petroleum ether/EtOAc 4:1). ^1H NMR ($CDCl_3$) δ 7.40 (s, 1H), 7.32 (br d,

J=8.9 Hz, 2H), 7.21 (m, 3H), 7.03 (m 2H), 6.92 (br d, J=8.9 Hz, 2H), 5.06 (s, 2H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 160.0, 138.3, 136.5, 132.8, 131.0, 129.8, 129.1, 128.4, 119.2, 113.6, 80.4, 55.7, 55.1. Anal. calcd for $C_{17}H_{15}N_2OI$: C, 50.26; H, 3.72; N 6.90. Found: C, 50.47; H, 3.72; N 6.80.

4.2.3. 1-Benzyloxy-4-iodo-5-(2-methoxyphenyl)-pyrazole (11c). From 2-iodoanisole. FC (petroleum ether/EtOAc 5:1). Yield 81%. Pale yellow oil. R_f 0.24 (petroleum ether/EtOAc 5:1). ^{1}H NMR ($CDCl_3$) δ 7.43 (s, 1H), 7.14 (m, 1H), 7.23 (m, 3H), 6.90 (m, 5H), 5.12 (s, 2H), 3.74 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 157.3, 137.9, 134.9, 133.3, 132.1, 131.2, 129.5, 128.9, 128.4, 120.3, 116.2, 110.0, 80.3, 58.1, 55.4. Anal. calcd for $C_{17}H_{15}N_2OI$: C, 50.26; H, 3.72; N 6.90. Found: C, 50.14; H, 3.68; N 6.86.

4.2.4. 1-Benzyloxy-5-(2-fluorophenyl)-4-iodo-pyrazole (11d). From 2-iodofluorobenzene. FC (petroleum ether/EtOAc 5:1). Yield 75%. Pale yellow oil. R_f 0.24 (petroleum ether/EtOAc 5:1). ^{1}H NMR ($CDCl_3$) δ 7.47 (s, 1H), 7.41 (m, 1H), 7.28 (m, 1H), 7.20–7.09 (m, 4H), 7.05 (dd, J=7.2, 2.0 Hz, 1H), 6.99 (m, 2H), 5.17 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 159.7 (d, J=250 Hz), 138.5, 132.9, 132.6, 132.3 (d, J=2.3 Hz), 131.5 (d, J=8.3 Hz), 129.7, 129.2, 128.5, 123.9 (d, J=3.7 Hz), 115.9 (d, J=21 Hz), 115.4 (d, J=15 Hz), 80.5, 57.9. Anal. calcd for $C_{16}H_{12}FIN_2O$: C, 48.75; H, 3.07; N 7.11. Found: C, 48.54; H, 2.93; N 7.17.

4.2.5. 1-Benzyloxy-4-iodo-5-(thien-2-yl)-pyrazole (11e). From 2-iodothiophene. FC (petroleum ether/EtOAc 8:1→6:1). Yield 81%. Pale yellow oil. R_f 0.52 (petroleum ether/EtOAc 5:1). ^{1}H NMR ($CDCl_3$) δ 7.56 (dd, J=3.7, 1.0 Hz, 1H), 7.42 (dd, J=5.1, 1.0 Hz, 1H), 7.40 (s, 1H), 7.26 (m, 5H), 7.08 (dd, J=5.1, 3.7 Hz, 1H), 5.19 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 139.0, 132.7, 131.2, 129.9, 129.3, 128.9, 128.5, 127.6, 127.0, 126.9, 80.7, 55.7. Anal. calcd for $C_{17}H_{15}N_2OI$: C, 43.99; H, 2.90; N 7.33. Found: C, 43.79; H, 2.76; N 7.19.

4.2.6. 1-Benzyloxy-4-iodo-5-(4-nitrophenyl)-pyrazole (11f). From 4-iodonitrobenzene. FC (petroleum ether/EtOAc 5:1). Yield 54%. Yellow crystals. Mp 120–121°C (petroleum ether/EtOAc). R_f 0.41 (petroleum ether/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 8.16 (m, 2H), 7.49 (s, 1H), 7.41 (m, 2H), 7.25 (m, 1H), 7.11 (m, 2H), 6.87 (m, 2H), 5.14 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 147.4, 139.0, 135.1, 133.2, 132.2, 130.4, 129.9, 129.5, 128.4, 123.1, 80.8, 56.6. Anal. calcd for $C_{16}H_{12}N_3O_3I$: C, 45.63; H, 2.87; N 9.98. Found: C, 45.83; H, 2.95; N 9.83.

4.3. General procedure for the synthesis of 11g–j

To a stirred solution of **7** (300 mg, 1 mmol) in THF (8 mL) at −78°C, was added dropwise a solution of freshly prepared LDA (1.3 mmol) in THF. After 5 min, the electrophile was added and stirring was continued at −78°C for 1 h. The solution was then allowed to warm to rt, sat. aq. NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. Purification by FC (petroleum ether/EtOAc) afforded the title compound.

4.3.1. 1-Benzyloxy-4-iodo-5-methylpyrazole (11g). Using iodomethane as electrophile. FC (petroleum ether/EtOAc 5:1). Yield 94 %. Colorless crystals. Mp 73–74°C (petroleum ether/EtOAc). R_f 0.42 (petroleum ether/EtOAc 5:1). ^{1}H NMR ($CDCl_3$) δ 7.38 (m, 3H), 7.29 (s, 1H), 7.27 (m, 2H), 5.25 (s, 2H), 1.87 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 137.4, 134.4, 133.5, 130.1, 129.6, 128.7, 80.2, 55.7, 9.7. Anal. calcd for $C_{11}H_{11}IN_2O$: C, 42.06; H, 3.53; N 8.92. Found: C, 42.20; H, 3.27; N 8.79.

4.3.2. 1-Benzyloxy-4-iodo-5-methylsulfanylpyrazole (11h). Using dimethyldisulfide as electrophile. FC (petroleum ether/EtOAc 7:1). Yield 73%. Colorless crystals. Mp 46–48°C (petroleum ether/EtOAc). R_f 0.21 (petroleum ether/EtOAc 8:1). ^{1}H NMR ($CDCl_3$) δ 7.40 (m, 5H), 7.39 (s, 1H), 5.31 (s, 2H), 2.23 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 138.3, 133.2, 131.7, 130.1, 129.5, 128.7, 81.1, 65.7, 18.1. Anal. calcd for $C_{11}H_{11}IN_2OS$: C, 38.16; H, 3.20; N 8.09. Found: C, 38.41; H, 2.97; N 8.03.

4.3.3. 1-Benzyloxy-5-chloro-4-iodopyrazole (11i). Using hexachloroethane as electrophile. FC (petroleum ether/EtOAc 7:1). Yield 98%. Colorless crystals. Mp 69–70°C. R_f 0.52 (petroleum ether/EtOAc 5:1). ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 5H), 7.37 (s, 1H), 5.27 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 138.1, 132.6, 130.1, 129.7, 128.7, 125.4, 81.2, 56.2. Anal. calcd for $C_{10}H_8ClIN_2O$: C, 35.90; H, 2.41; N 8.37. Found: C, 36.17; H, 2.32; N 8.09.

4.3.4. Diethyl 2-(1-benzyloxy-4-iodopyrazol-5-yl)-2-*tert*-butoxycarbonylamino-malonate (11j). Using **2** as electrophile. FC (petroleum ether/EtOAc 7:1). Yield 54%. Colorless crystals. Mp 92–93°C. R_f 0.47 (petroleum ether/EtOAc 5:1). ^{1}H NMR ($CDCl_3$) δ 7.50 (m, 2H), 7.39 (s, 1H), 7.38 (m, 3H), 6.04 (br s, 1H), 5.36 (s, 2H), 4.18 (dq, J=10.7, 7.1 Hz, 2H), 4.04 (m, 2H), 1.44 (s, 9H), 1.16 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 165.9, 153.9, 138.8, 133.9, 133.3, 130.5, 130.4, 129.4, 128.6, 80.6, 80.3, 63.5, 63.4, 27.9, 13.3. Anal. calcd for $C_{22}H_{28}IN_3O_7$: C, 46.08; H, 4.92; N 7.33. Found: C, 46.31; H, 4.73; N 7.36.

4.4. General method for the synthesis of derivatives 12a–e and 12g–i

To a stirred solution of **11a–e** and **11g–i** (1 mmol) in THF (10 mL) at −78°C, was added dropwise 1.6 M *n*-BuLi in hexane (0.75 mL, 1.2 mmol) over 2 min. After 10 min, a solution of imine **2** (300 mg, 1.1 mmol) in THF (1 mL) was added, and the mixture was stirred for −78°C for 1 h, before quenching with water. The reaction was allowed to warm to rt, NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3×15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford the crude product. Purification of the residue by FC (petroleum ether/EtOAc) gave the title compound.

4.4.1. Diethyl 2-[1-benzyloxy-5-(4-tolyl)-pyrazol-4-yl]-2-*tert*-butoxycarbonylamino-malonate (12a). From **11a**. FC (petroleum ether/EtOAc 6:1→4:1). Yield 78%. Colorless crystals. Mp 82–83°C. R_f 0.25 (petroleum ether/EtOAc 4:1). IR (KBr) 3287, 2978, 1768, 1749, 1719, 1500, 1262, 1198, 1170 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 1H), 7.27 (m, 1H), 7.18 (m, 2H), 7.12 (d, J=7.9 Hz, 2H), 6.94 (d,

J=7.2 Hz, 2H), 5.88 (s, 1H), 5.05 (s, 2H), 4.14 (m, 2H), 3.98 (dq, J=10.7, 7.1 Hz, 2H), 2.39 (s, 3H), 1.30 (s, 9H), 1.16 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 167.1, 153.3, 138.7, 134.5, 133.4, 130.4, 129.8, 129.0, 128.5, 128.4, 122.3, 113.0, 80.1 63.7, 62.7, 27.9, 21.3, 13.7, one signal missing. Anal. calcd for $C_{29}H_{35}N_3O_7$: C, 64.79; H, 6.56; N 7.82. Found: C, 64.84; H, 6.61; N 7.83.

4.4.2. Diethyl 2-[1-benzyloxy-5-(4-methoxyphenyl)-pyrazol-4-yl]-2-*tert*-butoxycarbonylamino-malonate (12b). From **11b**. FC (petroleum ether/EtOAc 4:1). Yield 75%. Colorless crystals. Mp 94–96°C. R_f 0.13 (petroleum ether/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 7.86 (s, 1H), 7.28 (m, 1H), 7.19 (m, 2H), 6.96 (m, 4H), 6.84 (m, 2H), 5.90 (s, 1H), 5.06 (s, 2H), 4.16 (m, 2H), 4.01 (dq, J=10.7, 7.1 Hz, 2H), 3.85 (s, 3H), 1.32 (s, 9H), 1.18 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 167.1, 159.9, 153.3, 134.5, 134.4, 133.3, 131.8, 129.8, 128.9, 128.4, 119.7, 113.3, 112.6, 80.1, 80.0, 63.7, 62.6, 55.2, 27.9, 13.62. Anal. calcd for $C_{29}H_{35}N_3O_8$: C, 62.92; H, 6.37; N 7.59. Found: C, 62.68; H, 6.30; N 7.46.

4.4.3. Diethyl 2-[1-benzyloxy-5-(2-methoxyphenyl)-pyrazol-4-yl]-2-*tert*-butoxycarbonylamino-malonate (12c). From **11c**. FC (petroleum ether/EtOAc 4:1). Yield 70%. Colorless crystals. Mp 99–100°C. R_f 0.13 (petroleum ether/EtOAc 4:1→3:1). ^{1}H NMR ($CDCl_3$) δ 7.83 (s, 1H), 7.41 (m, 1H), 7.24 (m, 3H), 6.93 (m, 5H), 5.94 (br s, 1H), 5.17 (d, J=10.2 Hz, 1H), 4.99 (d, J=10.2 Hz, 1H), 4.31–4.00 (m, 3H), 3.88 (m, 1H), 3.70 (s, 3H), 1.31 (s, 9H), 1.24 (t, J=7.1 Hz, 3H), 1.14 (t, J=7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 166.8, 166.5, 157.15, 153.3, 133.7, 133.3, 132.2, 130.7, 130.3, 129.3, 128.6, 126.1, 119.9, 116.2, 113.2, 110.1, 80.0, 79.4, 63.5, 63.2, 62.0, 54.8, 27.7, 13.4, 13.4. Anal. calcd for $C_{29}H_{35}N_3O_8$: C, 62.92; H, 6.37; N 7.59. Found: C, 62.82; H, 6.27; N 7.56.

4.4.4. Diethyl 2-[1-benzyloxy-5-(2-fluorophenyl)-pyrazol-4-yl]-2-*tert*-butoxycarbonylamino-malonate (12d). From **11d**. FC (petroleum ether/EtOAc 4:1→2:1). Yield 69%. Pale yellow crystals. Mp 140–142°C. R_f 0.13 (petroleum ether/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 7.94 (s, 1H), 7.40 (m, 1H), 7.28 (tt, J=7.3, 1.3 Hz, 1H), 7.19 (m, 2H), 7.08 (m, 2H), 6.96 (m, 3H), 5.93 (br s, 1H), 5.21 (d, J=9.7 Hz, 1H), 5.04 (d, J=9.7 Hz, 1H), 4.21 (m, 2H), 4.10 (m, 2H), 1.28 (s, 9H), 1.21 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.9, 166.7, 160.1 (d, J=250 Hz), 153.4, 134.7, 133.3, 132.8, 131.2 (d, J=7.0 Hz), 129.7, 129.0, 128.5, 128.0, 123.7 (d, J=3.6 Hz), 116.0 (d, J=13.7 Hz), 115.3 (d, J=21.5 Hz), 113.7, 80.2, 80.0, 63.6, 62.8, 62.6, 27.9, 13.6. Anal. calcd for $C_{28}H_{32}FN_3O_7$: C, 62.10; H, 5.96; N 7.76. Found: C, 62.34; H, 5.97; N 7.55.

4.4.5. Diethyl 2-[1-benzyloxy-5-(thien-2-yl)-pyrazol-4-yl]-2-*tert*-butoxycarbonylamino-malonate (12e). From **11e**. FC (petroleum ether/EtOAc 4:1). Yield 81%. Colorless crystals. Mp 104–106°C. R_f 0.20 (petroleum ether/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 7.89 (s, 1H), 7.45 (dd, J=5.1, 1.1 Hz, 1H), 7.31–7.21 (m, 3H), 7.05 (m, 2H), 7.02 (dd, J=5.1, 3.6 Hz, 1H), 6.81 (dd, J=3.6, 1.0 Hz, 1H), 6.01 (br s, 1H), 5.15 (s, 2H), 4.19 (m, 2H), 4.05 (dq, J=10.7, 7.1 Hz, 2H), 1.36 (s, 9H), 1.19 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.9, 153.5, 134.7, 133.2, 131.0, 129.8, 129.1, 128.5, 127.7, 126.7, 126.4, 114.6, 80.6, 80.1, 63.8, 62.8, 28.1, 13.7, one signal missing. Anal. calcd for $C_{26}H_{31}N_3O_7S$: C, 58.96; H, 5.90; N 7.93. Found: C, 58.67; H, 5.97; N 7.71.

4.4.6. Diethyl 2-(1-benzyloxy-5-methylpyrazol-4-yl)-2-*tert*-butoxycarbonylamino-malonate (12g). From **11g**. FC (petroleum ether/EtOAc 4:1). Yield 84%. Colorless oil. R_f 0.20 (petroleum ether/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 7.53 (s, 1H), 7.35 (m, 3H), 7.28 (m, 2H), 6.18 (br s, 1H), 5.25 (s, 2H), 4.27 (m, 2H), 4.18 (dq, J=10.7, 7.1 Hz, 2H), 1.95 (s, 3H), 1.42 (s, 9H), 1.24 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 167.1, 153.6, 133.7, 132.7, 131.4, 129.9, 129.3, 128.5, 80.4, 79.9, 64.0, 62.6, 28.0, 13.7, 9.3, one signal missing. Anal. calcd for $C_{23}H_{31}N_3O_7$: C, 59.86; H, 6.77; N 9.10. Found: C, 60.12; H, 6.76; N 9.18.

4.4.7. Diethyl 2-(1-benzyloxy-5-methylsulfanylpyrazol-4-yl)-2-*tert*-butoxycarbonylamino-malonate (12h). From **11h**. FC (petroleum ether/EtOAc 4:1). Yield 75%. Colorless crystals. Mp 42–43°C. R_f 0.24 (petroleum ether/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 7.84 (s, 1H), 7.46 (m, 2H), 7.38 (m, 2H), 6.34 (br s, 1H), 5.34 (s, 2H), 4.33 (m, 2H), 4.25 (dq, J=10.7, 7.1 Hz, 2H), 2.20 (s, 3H), 1.40 (s, 9H), 1.26 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.7, 153.7, 134.5, 133.5, 129.9, 129.3, 128.6, 126.2, 81.0, 80.9, 63.9, 62.8, 28.1, 18.2, 13.7, one signal missing. Anal. calcd for $C_{23}H_{31}N_3O_7S$: C, 55.97; H, 6.33; N 8.51. Found: C, 56.27; H, 6.07; N 8.79.

4.4.8. Diethyl 2-(1-benzyloxy-5-chloropyrazol-4-yl)-2-*tert*-butoxycarbonylamino-malonate (12i). From **11i**. FC (petroleum ether/EtOAc 4:1). Yield 83%. Colorless oil. R_f 0.26 (petroleum ether/EtOAc 4:1). ^{1}H NMR ($CDCl_3$) δ 7.85 (s, 1H), 7.37 (m, 5H), 6.24 (br s, 1H), 5.27 (s, 2H), 4.29 (m, 2H), 4.21 (dq, J=10.7, 7.1 Hz, 2H), 1.40 (s, 9H), 1.25 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.1, 153.7, 143.5, 132.8, 129.9, 129.4, 128.6, 119.8, 111.2, 80.7, 80.4, 63.2, 62.9, 27.9, 13.6. Anal. calcd for $C_{22}H_{28}ClN_3O_7$: C, 54.83; H, 5.86; N 8.72. Found: C, 54.60; H, 5.57; N 8.58.

4.4.9. Diethyl 2-[1-benzyloxy-5-(4-nitrophenyl)-pyrazol-4-yl]-2-*tert*-butoxycarbonylamino-malonate (12f). To a stirred solution of **11f** (421 mg, 1 mmol) in THF (10 mL) at −105°C, was added dropwise 1.6 M PhLi in cyclohexane/ether 70:30 (0.75 mL, 1.2 mmol), keeping the internal temperature below −102°C. The dark green solution was stirred for 30 min at −105°C. A solution of **2** (382 mg, 1.4 mmol) in THF (1 mL) was slowly added. Stirring was continued for 2 h at −105°C before quenching cold with NH_4Cl (1 mL). The reaction mixture was allowed to warm to rt, NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3×15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. FC (petroleum ether/EtOAc 3:1→ 2:1) gave **12f** (409 mg, 72%) as pale yellow crystals: mp 112–113°C (petroleum ether/EtOAc). R_f 0.45 (petroleum ether/EtOAc 2:1). ^{1}H NMR ($CDCl_3$) δ 8.08 (m, 2H), 7.94 (s, 1H), 7.30 (m, 1H), 7.15 (m, 2H), 7.06 (m, 2H), 6.82 (m, 2H), 5.79 (s br, 1H), 5.12 (s, 2H), 4.27–4.17 (m, 2H), 4.09 (dq, J=10.7, 7.1 Hz, 2H), 1.23 (s, 9H), 1.20 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.8, 153.1, 147.5, 134.9, 134.5, 132.9, 132.7, 131.5, 129.9, 129.3, 128.5, 122.4, 113.0, 80.2, 80.0, 63.5, 62.9, 27.8, 13.6. Anal. calcd for $C_{28}H_{32}N_4O_9$: C, 59.15; H, 5.67; N 9.85. Found: C, 59.36; H, 5.45; N 9.81.

4.5. General method for the synthesis of 16a–e

To a stirred solution of **15a–d** (1 mmol) in THF (10 mL) at −78°C, was added dropwise 1.6 M *n*-BuLi in hexane (0.75 mL, 1.2 mmol) over 2 min. After 5 min, a solution of imine **2** (382 mg, 1.4 mmol) in THF (1 mL) was added, and the mixture was stirred at −78°C for 3 h, before quenching cold with water. The reaction was allowed to warm to rt, NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3×15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford the crude product. Purification of the residue by FC (petroleum ether/EtOAc) gave the title compound.

4.5.1. Diethyl 2-[1-benzyloxy-4-(4-tolyl)-pyrazol-5-yl]-2-*tert*-butoxycarbonylamino-malonate (16a). From **15a**. FC (petroleum ether/EtOAc 6:1→4:1). Yield 69%. Colorless crystals. Mp 111–113°C (petroleum ether/EtOAc). R_f 0.25 (petroleum ether/EtOAc 4:1). IR (KBr) 3401, 2971, 1760, 1733, 1722, 1481, 1301, 1272, 1160 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.52 (m, 2H), 7.41 (m, 3H), 7.32 (d, J=7.8 Hz, 2H), 7.29 (s, 1H), 7.17 (d, J=7.8 Hz, 2H), 6.10 (br s, 1H), 5.38 (s, 2H), 3.91 (dq, J=10.7, 7.1 Hz, 2H), 3.65 (m, 2H), 2.35 (s, 3H), 1.44 (s, 9H), 0.98 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 165.9, 153.9, 136.7, 133.4, 132.6, 129.9, 129.4, 129.1, 128.8, 128.5, 126.2, 120.6, 80.2, 80.0, 64.3, 63.0, 28.0, 20.9, 13.3, one signal missing. Anal. calcd for $C_{29}H_{35}N_3O_7$: C, 64.79; H, 6.56; N 7.82. Found: C, 65.09; H, 6.65; N 7.77.

4.5.2. Diethyl 2-[1-benzyloxy-4-(4-methoxyphenyl)-pyrazol-5-yl]-2-*tert*-butoxycarbonylamino-malonate (16b). From **15b**. FC (petroleum ether/EtOAc 6:1→4:1). Yield 75%. Pale yellow oil. R_f 0.17 (petroleum ether/EtOAc 5:1). ^1H NMR ($CDCl_3$) δ 7.53 (m, 2H), 7.40 (m, 5H), 7.27 (s, 1H), 6.90 (m, 2H), 6.12 (s, 1H), 5.37 (s, 2H), 3.92 (dq, J=10.7, 7.1 Hz, 2H), 3.82 (s, 3H), 3.68 (m, 2H), 1.45 (s, 9H), 1.00 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 165.9, 158.9, 153.9, 133.4, 132.7, 130.7, 129.9, 129.2, 128.6, 126.2, 125.3, 120.4, 113.6, 80.3, 80.1, 63.4, 63.1, 55.2, 28.1, 13.4. HRMS $[M+H]^+$ calcd for $C_{29}H_{36}N_3O_8$: 554.2502. Found: 554.2491.

4.5.3. Diethyl 2-[1-benzyloxy-4-(2-fluorophenyl)-pyrazol-5-yl]-2-*tert*-butoxycarbonylamino-malonate (16c). From **15c**. FC (petroleum ether/EtOAc 5:1→2:1). Yield 69%. Colorless crystals. Mp 115–116°C (petroleum ether/EtOAc). R_f 0.21 (petroleum ether/EtOAc 5:1). ^1H NMR ($CDCl_3$) δ 7.52 (m, 3H), 7.41 (m, 3H), 7.35 (d, J=1.3 Hz, 1H), 7.29 (m, 1H), 7.12 (m, 2H), 6.05 (br s, 1H), 5.41 (s, 2H), 3.95 (dq, J=10.7, 7.1 Hz, 2H), 3.73 (m, 2H), 1.40 (s, 9H), 1.05 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 165.8, 160.2 (d, J=247 Hz), 153.7, 133.5, 133.4, 132.8 (d, J=65.9 Hz), 129.8, 129.1, 128.9 (d, J=7.6 Hz), 128.6, 127.0, 123.5 (d, J=3.7 Hz), 120.1 (d, J=14.4 Hz), 115.3 (d, J=22.0 Hz), 113.3, 80.3, 79.9, 64.3, 63.1, 28.0, 13.3. Anal. calcd for $C_{28}H_{32}FN_3O_7$: C, 62.10; H, 5.96; N 7.76. Found: C, 62.17; H, 5.96; N 7.59.

4.5.4. Diethyl 2-[1-benzyloxy-4-(thien-2-yl)-pyrazol-5-yl]-2-*tert*-butoxycarbonylamino-malonate (16d). From **15d**. FC (petroleum ether/EtOAc 5:1→4:1). Yield 65%. Colorless crystals. Mp 140°C (petroleum ether/EtOAc). R_f 0.25 (petroleum ether/EtOAc 5:1). ^1H NMR ($CDCl_3$) δ 7.52 (m, 2H), 7.41 (m, 3H), 7.38 (s, 1H), 7.25 (dd, J=5.1, 1.0 Hz, 1H), 7.16 (br s, 1H), 7.03 (dd, J=5.1, 3.5 Hz, 1H), 6.14 (br s, 1H, NH), 5.37 (s, 2H), 3.99 (dq, J=10.6, 7.1 Hz, 2H), 3.73 (m, 2H), 1.46 (s, 9H), 1.01 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 165.8, 154.0, 133.6, 133.3, 133.1, 130.1, 129.2, 128.6, 127.5, 127.2, 125.3, 113.7, 80.3, 80.3, 64.1, 63.3, 28.1, 13.4, one signal missing. Anal. calcd for $C_{26}H_{31}N_3O_7S$: C, 58.96; H, 5.90; N 7.93. Found: C, 59.03; H, 5.98; N 7.88.

4.6. General method for the hydrogenolysis of the benzyl group. Synthesis of 13a–e, 13g–i and 17a–d

Compounds **12a–e**, **12g–i** and **16a–d** (1 mmol), 10% Pd/C (65 mg) in MeOH (8 mL), were vigorously stirred under hydrogen (1 atm) at 0°C for 45 min. Filtration through celite, washing with MeOH and evaporation of the solvent gave the crude product. The pure products were obtained after filtration by flash chromatography (petroleum ether/EtOAc).

4.6.1. Diethyl 2-*tert*-butoxycarbonylamino-2-[1-hydroxy-5-(4-tolyl)-pyrazol-4-yl]-malonate (13a). From **12a**. FC (petroleum ether/EtOAc 3:1→1:1). Yield 99%. Colorless crystals. Mp decomposition above 160°C. R_f 0.2 (petroleum ether/EtOAc 2:1). IR (KBr) 3405, 2981, 1763, 1747, 1722, 1474, 1256, 1203, 1165, 1024, 1024 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.72 (s, 1H), 7.26 (s, 4H), 5.98 (s, 1H), 4.16 (m, 2H), 3.98 (dq, J=10.7, 7.1 Hz, 2H), 2.42 (s, 3H), 1.31 (s, 9H), 1.17 (t, J=1.2 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 167.0, 153.4, 139.1, 133.3, 132.7, 130.5, 128.8, 124.5, 112.5, 80.0, 63.6, 62.7, 27.9, 21.3, 13.6. Anal. calcd for $C_{22}H_{29}N_3O_7$: C, 59.05; H, 6.53; N, 9.39. Found: C, 58.76; H, 6.36; N 9.43.

4.6.2. Diethyl 2-*tert*-butoxycarbonylamino-2-[1-hydroxy-5-(4-methoxyphenyl)-pyrazol-4-yl]-malonate (13b). From **12b**. FC (petroleum ether/EtOAc 2:1→1:2). Yield 100%. Colorless crystals. Mp 148–149°C. R_f 0.30 (petroleum ether/EtOAc 1:1) ^1H NMR ($CDCl_3$) δ 7.70 (s, 1H), 7.29 (d, J=8.8 Hz, 2H), 6.97 (d, J=8.8 Hz, 2H), 6.02 (s, 1H), 4.18 (br dq, J=10.7, 7.1 Hz, 2H), 4.00 (dq, J=10.7, 7.1 Hz, 2H), 3.86 (s, 3H), 1.31 (s, 9H), 1.17 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 167.0, 160.2, 153.5, 133.3, 132.7, 131.9, 119.5, 113.5, 112.5, 80.1, 63.6, 62.7, 55.2, 28.0, 13.6. Anal. calcd for $C_{22}H_{29}N_3O_8$: C, 57.01; H, 6.31; N 9.07. Found: C, 57.10; H, 6.13; N 9.01.

4.6.3. Diethyl 2-*tert*-butoxycarbonylamino-2-[1-hydroxy-5-(2-methoxyphenyl)-pyrazol-4-yl]-malonate (13c). From **12c**. FC (petroleum ether/EtOAc 2:1→2:1). Yield 98%. Colorless crystals. Mp 147–148°C. R_f 0.32 (petroleum ether/EtOAc 1:1). ^1H NMR ($CDCl_3$) δ 7.65 (s, 1H), 7.43 (dd, J=7.5, 1.7 Hz, 1H), 7.24 (d, J=7.3 Hz, 1H), 7.03 (dt, J=7.5, 0.7 Hz, 1H), 6.96 (d, J=8.3 Hz, 1H), 6.02 (s, 1H), 4.10 (m, 3H), 3.88 (m, 1H), 3.78 (s, 3H), 1.31 (s, 9H), 1.17 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.7, 166.4, 157.3, 153.4, 132.2, 132.1, 130.9, 129.9, 120.1, 116.1, 113.0, 110.5, 80.0, 63.6, 62.4, 62.2, 55.1, 27.9, 13.6. Anal. calcd for $C_{22}H_{29}N_3O_8$: C, 57.01; H, 6.31; N 9.07. Found: C, 56.84; H, 6.16; N 8.85.

4.6.4. Diethyl 2-*tert*-butoxycarbonylamino-2-[5-(2-fluorophenyl)-1-hydroxy-pyrazol-4-yl]-malonate (13d). From **12d**. FC (petroleum ether/EtOAc 2:1→1:1). Yield 100%. Colorless crystals. Mp 154–155°C. R_f 0.46 (petroleum ether/EtOAc 1:1). ^{1}H NMR ($CDCl_3$) δ 7.79 (s, 1H), 7.46 (m, 1H), 7.34 (br dt, J=7.5, 1.5 Hz, 1H), 7.23 (dt, J=7.5, 1.0 Hz, 1H), 7.16 (t, 1H), 5.99 (s, 1H), 4.20 (m, 2H), 4.05 (m, 1H), 1.27 (s, 9H), 1.19 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.6, 160.3 (d, J=250 Hz), 153.4, 132.9, 132.8 (d, J=1.9 Hz), 131.4, 127.6, 123.8 (d, J=3.6 Hz), 115.9, 115.4 (d, J=21 Hz), 113.5, 80.0, 63.6, 62.7, 27.9, 13.6. Anal. calcd for $C_{21}H_{26}FN_3O_7$: C, 55.87; H, 5.81; N 9.31. Found: C, 56.14; H, 5.84; N 9.31.

4.6.5. Diethyl 2-*tert*-butoxycarbonylamino-2-[1-hydroxy-5-(thien-2-yl)-pyrazol-4-yl]-malonate (13e). From **12e**. FC (petroleum ether/EtOAc 2:1→1:1). Yield 98%. Colorless crystals. Mp decomposition abobe 69°C. R_f 0.55 (petroleum ether/EtOAc 1:1). ^{1}H NMR ($CDCl_3$) δ 7.79 (s, 1H), 7.52 (dd, J=5.1, 1.2 Hz, 1H), 7.18 (dd, J=3.6, 1.2 Hz, 1H), 7.12 (dd, J=5.1, 3.6 Hz, 1H), 6.1 (s, 1H), 4.20 (dq, J=10.7, 7.1 Hz, 2H), 4.05 (dq, J=10.7, 7.1 Hz, 2H), 1.59 (s, 9H), 1.20 (t, J=1.2 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.7, 153.6, 132.8, 131.1, 128.6, 127.2, 126.7, 126.2, 114.2, 80.0, 63.6, 62.8, 27.9, 13.6, one signal missing. Anal. calcd for $C_{19}H_{25}N_3O_7S$: C, 51.93; H, 5.73; N, 9.56. Found: C, 52.18; H, 5.73; N 9.28.

4.6.6. Diethyl 2-*tert*-butoxycarbonylamino-2-(1-hydroxy-5-methylpyrazol-4-yl)-malonate (13g). From **12g**. Yield 97%. Colorless crystals. Mp 108–110°C. ^{1}H NMR ($CDCl_3$) δ 7.42 (s, 1H), 6.27 (s, 1H), 4.31 (br dq, J=10.7, 7.1 Hz, 2H), 4.22 (dq, J=10.7, 7.1 Hz, 2H), 2.31 (s, 3H), 1.41 (s, 9H), 1.26 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 167.0, 153.8, 130.5, 130.4, 112.1, 80.6, 64.1, 62.7, 28.0, 13.8, 9.6. Anal. calcd for $C_{16}H_{25}N_3O_7$: C, 51.74; H, 6.78; N 11.31. Found: C, 52.03; H, 6.84; N 11.24.

4.6.7. Diethyl 2-*tert*-butoxycarbonylamino-2-(1-hydroxy-5-methylsulfanylpyrazol-4-yl)-malonate (13h). From **12h**. Yield 92%. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.76 (s, 1H), 6.43 (s, 1H), 4.34 (dq, J=10.7, 7.1 Hz, 2H), 4.22 (dq, J=10.7, 7.1 Hz, 2H), 2.35 (s, 3H), 1.38 (s, 9H), 1.26 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.6, 153.7, 132.4, 126.3, 118.0, 80.4, 63.8, 62.8, 28.0, 17.5, 13.6. HRMS $[M+H]^+$ calcd for $C_{16}H_{26}N_3O_7S$: 404.1491. Found: 404.1503.

4.6.8. Diethyl 2-*tert*-butoxycarbonylamino-2-(5-chloro-1-hydroxypyrazol-4-yl)-malonate (13i). From **12i**. Yield 95%. Colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.74 (s, 1H), 6.37 (s, 1H), 4.28 (m, 4H), 1.40 (s, 9H), 1.26 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 166.0, 153.6, 132.9, 120.6, 111.2, 80.5, 62.9, 60.3, 27.8, 13.5. HRMS $[M+H]^+$ calcd for $C_{15}H_{23}ClN_3O_7$: 392.1224. Found: 392.1246.

4.6.9. Diethyl 2-*tert*-butoxycarbonylamino-2-[1-hydroxy-4-(4-tolyl)-pyrazol-5-yl]-malonate (17a). From **16a**. FC (petroleum ether/EtOAc 3:1→1:1). Yield 99%. Colorless crystals. Mp 150°C. R_f 0.37 (petroleum ether/EtOAc 1:1). IR (KBr) 3364, 2983, 1758, 1725, 1675, 1498, 1290, 1202, 1160 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.29 (s, 1H), 7.15 (m, 4H), 6.74 (br s, 1H), 4.10 (dq, J=10.7, 7.1 Hz, 2H), 3.66 (br dq, J=10.7, 7.1 Hz, 2H), 2.35 (s, 3H), 1.50 (s, 9H), 1.07 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 164.9, 156.8, 136.7, 130.7, 129.9, 128.9, 128.4, 126.2, 120.4, 82.5, 63.8, 63.5, 27.9, 20.9, 13.2. Anal. calcd for $C_{22}H_{29}N_3O_7$: C, 59.05; H, 6.53; N, 9.39. Found: C, 58.81; H, 6.37; N 9.25.

4.6.10. Diethyl 2-*tert*-butoxycarbonylamino-2-[1-hydroxy-4-(4-methoxyphenyl)-pyrazol-5-yl]-malonate (17b). From **16b**. FC (petroleum ether/EtOAc 2:1→1:2). Yield 96 %. Off-white crystals (petroleum ether/EtOAc). Mp 149–150°C. R_f 0.27 (petroleum ether/EtOAc 2:1). ^{1}H NMR ($CDCl_3$) δ 11.53 (br s, 1H), 7.27 (s, 1H), 7.18 (d, J=8.7 Hz, 2H), 6.90 (d, J=8.7 Hz, 2H), 6.74 (s, 1H), 4.10 (dq, J=10.7, 7.1 Hz, 2H), 3.81 (s, 3H), 3.71 (dq, J=10.7, 7.1 Hz, 2H), 1.49 (s, 9H), 1.09 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 165.0, 158.8, 156.9, 130.8, 129.8, 126.2, 125.4, 120.1, 113.8, 82.6, 64.0, 63.6, 55.2, 28.0, 13.4. Anal. calcd for $C_{22}H_{29}N_3O_8$: C, 57.01; H, 6.31; N 9.07. Found: C, 56.93; H, 6.12; N 9.26.

4.6.11. Diethyl 2-*tert*-butoxycarbonylamino-2-[4-(2-fluorophenyl)-1-hydroxypyrazol-5-yl]-malonate (17c). From **16c**. FC (petroleum ether/EtOAc 2:1 (1:1). Yield 99%. Colorless crystals. Mp decomposition above 180°C. R_f 0.40 (petroleum ether/EtOAc 1:1). ^{1}H NMR ($CDCl_3$) δ 7.34 (d, J=1.4 Hz, 1H), 7.32–7.08 (m, 4H), 6.71 (s, 1H), 4.10 (dq, J=10.7, 7.1 Hz, 2H), 3.69 (dq, J=10.7, 7.1 Hz, 2H), 1.49 (s, 9H), 1.11 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 164.7, 159.7 (d, J=248 Hz), 156.9, 132.0 (d, J=2.5 Hz), 131.6 (d, J=2.8 Hz), 129.3 (d, J=7.9 Hz), 127.1, 123.9 (d, J=3.7 Hz), 120.5 (d, J=16 Hz), 115.6 (d, J=22 Hz), 113.3, 82.7, 64.04, 63.5, 28.1, 13.3. Anal. calcd for $C_{21}H_{26}FN_3O_7$: C, 55.87; H, 5.81; N 9.31. Found: C, 55.91; H, 5.74; N 9.21.

4.6.12. Diethyl 2-*tert*-butoxycarbonylamino-2-[1-hydroxy-4-(thien-2-yl)-pyrazol-5-yl]-malonate (17d). From **16d**. FC (petroleum ether/EtOAc 2:1→1:1). Yield 98 %. Pale yellow crystals. Mp 150°C. R_f 0.31 (petroleum ether/EtOAc 2:1). ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 1H), 7.24 (dd, J=5.2, 1.1 Hz, 1H), 7.00 (dd, J=5.2, 3.5 Hz, 1H), 6.80 (dd, J=3.5, 1.1 Hz, 1H), 6.70 (s, 1H), 4.17 (dq, J=10.7, 7.1 Hz, 2H), 3.83 (dq, J=10.7, 7.1 Hz, 2H), 1.48 (s, 9H), 1.13 (t, J=7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ 164.7, 156.9, 133.6, 131.7, 127.4, 127.1, 126.4, 125.3, 113.1, 82.7, 64.1, 63.5, 28.0, 13.4. Anal. calcd for $C_{19}H_{25}N_3O_7S$: C, 51.93; H, 5.73; N, 9.56. Found: C, 51.82; H, 5.64; N 9.51.

4.7. General method for the deprotection of the amino acid functionality. Synthesis of 14a–e, 14g–i and 18a–d

To a solution of **13a–e**, **13g–i**, **17a–d** (0.5 mmol) in THF (4 mL) was added a 2.5 M aq. LiOH (3.5 mL, 9 mmol). The mixture was vigorously stirred at rt for 4 h in case of compounds **13a–e** and **13g–i**, and at 50°C for 12 h in case of compounds **17a–d**. The solution was cooled to 0°C and 1 M HCl was added dropwise until pH 2. The mixture was extracted with EtOAc (3×20 mL), the combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and evaporated to dryness. Decarboxylation and *N*-Boc deprotection were accomplished by stirring the residue in 2 M HCl at 60°C for 30 min. The hydrochloride salts were obtained after removal of the HCl

under reduced pressure (unless otherwise stated). Where possible, the crystals were triturated with Et_2O.

4.7.1. Hydrochloride salt of amino-[1-hydroxy-5-(4-tolyl)-pyrazol-4-yl]-acetic acid (14a). From **13a**. Precipitation of the product occurred by cooling the solution to rt. The precipitate was filtered and washed with cold water. Yield 96%. Colorless crystals. Mp decomposition above 180°C. ^{1}H NMR (DMSO-d_6) δ 8.84 (br s, 3H), 7.56 (d, J=8.0 Hz, 2H), 7.46 (s, 1H), 7.36 (d, J=8.0 Hz, 2H), 4.62 (br s, 1H), 2.38 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 170.8, 139.8, 135.5, 131.1, 130.7, 130.4, 125.0, 110.4, 48.4, 21.9. HRMS [M−HCl–H]$^-$ calcd for $C_{12}H_{12}N_3O_3$: 246.0879. Found: 246.0915.

4.7.2. Hydrochloride salt of amino-[1-hydroxy-5-(4-methoxyphenyl)-pyrazol-4-yl]-acetic acid (14b). From **13b**. Yield 96%. Colorless crystals (MeOH/EtOAc). Mp decomposition above 175°C. ^{1}H NMR (DMSO-d_6) δ 8.71 (br s, 3H), 7.58 (d, J=8.8 Hz, 2H), 7.43 (s, 1H), 7.12 (d, J=8.8 Hz, 2H), 4.54 (br s, 1H), 3.83 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 170.8, 160.9, 135.3, 132.1, 131.0, 119.9, 115.3, 110.1, 56.3, 48.5. HRMS [M−HCl–H]$^-$ calcd for $C_{12}H_{12}N_3O_4$: 262.0828. Found: 262.0856.

4.7.3. Hydrochloride salt of amino-[1-hydroxy-5-(2-methoxyphenyl)-pyrazol-4-yl]-acetic acid (14c). From **13c**. Yield 86%. Colorless crystals (MeOH/EtOAc). Mp>200°C. ^{1}H NMR (DMSO-d_6) δ 8.70 (br s, 3H), 7.50–7.40 (m, 2H), 7.40 (s, 1H), 7.15 (d, J=8.8 Hz, 1H), 7.06 (dt, J=7.4, 0.8 Hz, 1H), 4.50 (q, J=5.1 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (CD_3OD) δ 170.8, 158.9, 134.2, 133.4, 132.9, 131.3, 121.9, 116.5, 112.8, 111.6, 56.2, 49.5. HRMS [M−HCl–H]$^-$ calcd for $C_{12}H_{12}N_3O_4$: 262.0828. Found: 262.0859.

4.7.4. Hydrochloride salt of amino-[5-(2-fluorophenyl)-1-hydroxypyrazol-4-yl]-acetic acid (14d). From **13d**. Yield 83%. Pale green crystals. Mp decomposition above 177°C. ^{1}H NMR (DMSO-d_6) δ 8.86 (br d, J=4.7 Hz, 3H), 7.69–7.55 (m, 2H), 7.50 (s, 1H), 7.43–7.35 (m, 2H), 4.54 (br q, J=5.1 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 170.5, 160.7 (d, J=250 Hz), 133.3, 133.1 (d, J=8.0 Hz), 131.4, 130.0, 125.7 (d, J=3.5 Hz), 117.1 (d, J=21 Hz), 115.8 (d, J=15 Hz), 111.5, 47.5. HRMS [M−HCl–H]$^-$ calcd for $C_{11}H_9FN_3O_3$: 250.0628. Found: 250.0658.

4.7.5. Hydrochloride salt of amino-[1-hydroxy-5-(thien-2-yl)-pyrazol-4-yl]-acetic acid (14e). From **13e**. Yield 89%. Thick oil that slowly crystallized on standing. Colorless crystals (MeOH/EtOAc). Mp decomposition above 185°C. ^{1}H NMR (DMSO-d_6) δ 8.92 (br s, 3H), 7.87 (dd, J=5.1, 1.1 Hz, 1H), 7.63 (dd, J=3.7, 1.1 Hz, 1H), 7.53 (s, 1H), 7.29 (dd, J=5.1, 3.7 Hz, 1H), 4.91 (br q, J=4.8 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 169.7, 154.4, 130.4, 129.3, 128.7, 127.7, 126.8, 109.7, 47.6. Anal. calcd for $C_9H_9N_3O_3S$. HCl: C, 39.21; H, 3.66; N, 15.24. Found: C, 39.97; H, 3.97; N 14.41.

4.7.6. Hydrochloride salt of amino-[1-hydroxy-5-(4-nitrophenyl)-pyrazol-4-yl]-acetic acid (14f). 12f (284 mg, 0.5 mmol) was refluxed in 6N HCl (4 mL) for 12 h. The solution was cooled to rt, and the precipitate so formed was filtered washing with ice cold water. Pale green crystals (147 mg, 94%). Recrystallization (MeOH/EtOAc) gave colorless crystals. Mp>190°C. ^{1}H NMR (DMSO-d_6) δ 8.76 (br s, 3H), 8.41 (d, J=8.8 Hz, 2H), 7.94 (d, J=8.8 Hz, 2H), 7.54 (s, 1H), 4.78 (s, 1H). ^{13}C NMR (CD_3OD) δ 170.5, 149.9, 134.7, 134.4, 132.3, 131.7, 125.1, 111.7, 54.8. HRMS [M−HCl–H]$^-$ calcd for $C_{11}H_9N_4O_5$: 227.0573. Found: 227.0598.

4.7.7. Hydrochloride salt of amino-(1-hydroxy-5-methylpyrazol-4-yl)-acetic acid (14g). From **13g**. The crude product was triturated twice with Et_2O, to afford pale yellow sticky crystals. The product was very hygroscopic and turned quickly into a wax in contact with air. Yield 81%. ^{1}H NMR (DMSO-d_6) δ 8.76 (br s, 3H), 7.17 (s, 1H), 4.89 (br s, 1H), 2.20 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 169.9, 131.2, 130.1, 108.4, 47.5, 8.3. HRMS [M−HCl–H]$^-$ calcd for $C_6H_8N_3O_3$: 170.0566: Found: 170.0637.

4.7.8. Hydrochloride salt of amino-(1-hydroxy-5-methylsulfanylpyrazol-4-yl)-acetic acid (14h). From **13h**. The crude product was triturated twice with Et_2O, to afford off-white crystals. Yield 89%. Mp decomposition above 170°C. ^{1}H NMR (DMSO-d_6) δ 8.74 (br s, 3H), 7.39 (s, 1H), 4.89 (s, 1H), 2.36 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 169.5, 130.4, 127.6, 115.2, 47.8, 18.0. HRMS [M−HCl–H]$^-$ calcd for $C_6H_8N_3O_3S$: 202.0286. Found: 202.0318.

4.7.9. Hydrochloride salt of amino-(5-chloro-1-hydroxypyrazol-4-yl)-acetic acid (14i). From **13i**. The crude product was triturated twice with Et_2O, to afford colorless crystals. Yield 84%. The product was very hygroscopic and turned quickly into a wax in contact with air. ^{1}H NMR (DMSO-d_6) δ 8.83 (br s, 3H), 7.46 (s, 1H), 4.89 (br q, J=5.1 Hz, 1H). ^{13}C NMR (DMSO-d_6) δ 168.8, 131.2, 120.2, 108.4, 46.9. HRMS [M−HCl–H]$^-$ calcd for $C_5H_5ClN_3O_3$: 190.0020. Found: 190.0075.

4.7.10. Hydrochloride salt of amino-[1-hydroxy-4-(4-tolyl)-pyrazol-5-yl]-acetic acid (18a). From **17a**. Yield 87%. Pale yellow crystals were obtained after removal of HCl and trituration with Et_2O. Mp decomposition above 160°C. ^{1}H NMR (DMSO-d_6) δ 8.99 (br s, 3H), 7.41 (s, 1H), 7.37 (d, J=8.1 Hz, 2H), 7.25 (d, J=8.1 Hz, 2H), 5.21 (s, 1H), 2.33 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 167.3, 136.6, 130.3, 129.6, 128.9, 128.0, 124.1, 121.0, 45.8, 20.7. HRMS [M−HCl–H]$^-$ calcd for $C_{12}H_{12}N_3O_3$: 246.0879. Found: 246.0911.

4.7.11. Hydrochloride salt of amino-[1-hydroxy-4-(4-methoxyphenyl)-pyrazol-5-yl]-acetic acid (18b). From **17b**. Yield 80%. Pale yellow crystals were obtained after evaporation of HCl and trituration with Et_2O. Mp decomposition above 158°C. ^{1}H NMR (CD_3OD) δ 7.39 (d, J=8.5 Hz, 2H), 7.35 (s, 1H), 7.01 (d, J=8.5 Hz, 2H), 5.34 (s, 1H), 3.81 (s, 3H). ^{13}C NMR (CD_3OD) δ 166.9, 159.6, 130.5, 129.3, 123.6, 123.1, 121.8, 114.2, 54.4, 46.1. HRMS [M−HCl–H]$^-$ calcd for $C_{12}H_{12}N_3O_4$: 262.0828. Found: 262.0860.

4.7.12. Hydrochloride salt of amino-[4-(2-fluorophenyl)-1-hydroxypyrazol-5-yl]-acetic acid (18c). From **17c**. Yield 97%. Pale yellow crystals were obtained after evaporation

of HCl and trituration with Et_2O. Mp decomposition above 155°C. ^{1}H NMR (DMSO-d_6) δ 8.95 (br s, 3H), 7.53 (dt, J=7.7, 1.7 Hz, 1H), 7.41 (m, 2H), 7.29 (m, 2H), 5.15 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 167.2, 159.4 (d, J=245 Hz), 131.9 (d, J=3.5 Hz), 131.3 (d, J=2.8 Hz), 129.7 (d, J=8.0 Hz), 125.6, 125.0 (d, J=3.4 Hz), 119.3 (d, J=14.8 Hz), 116.1 (d, J=22 Hz), 114.2, 46.1. HRMS $[M-HCl-H]^-$ calcd for $C_{11}H_9FN_3O_3$: 250.0628. Found: 250.0658.

4.7.13. Hydrochloride salt of amino-[1-hydroxy-4-(thien-2-yl)-pyrazol-5-yl]-acetic acid (18d). From **17d**. Yield 74%. The product was obtained after removal of the HCl as a pale yelllow thick oil. ^{1}H NMR (CD_3OD) δ 7.44 (d, J=4.9 Hz, 1H), 7.41 (s, 1H), 7.19 (d, J=3.3 Hz, 1H), 7.12 (dd, J=4.9, 3.3 Hz, 1H), 5.44 (s, 1H). ^{13}C NMR (DMSO-d_6) δ 168.0, 133.5, 132.3, 129.2, 127.2, 126.9, 124.8, 116.5, 47.5. The product was only 95% pure according to NMR.

Acknowledgements

This work was supported by Leo Pharmaceuticals, Copenhagen, Denmark and the Danish Natural Science Research Council. We also thanks Dr N. Rastrup-Andersen and Mr J. Henriksen of the Analytical Department of Leo Pharmaceuticals for performing HRMS and IR analysis.

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