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Novel 5-substituted 1-pyrazolol analogues of ibotenic acid: Synthesis and pharmacology at glutamate receptors

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Abstract—5-Substituted 1-pyrazolol analogues of ibotenic acid have been synthesized and pharmacologically characterized on ionotropic and metabotropic glutamate receptors (iGluRs and mGluRs). The syntheses involved introduction of bromide, alkyls, phenyl and arylalkyls in the 5-position of 1-benzyloxypyrazole leading to 5-substituted (*RS*)-2-amino-(1-hydroxy-4-pyrazolyl)acetic acids (**5a**–**l**). The pharmacological activities of the synthesized analogues ranged from the 5-cyclopropylmethyl analogue (**5f**) with weak but selective affinity for NMDA receptors (IC_{50} = 35 μM), over the 5-*n*-propyl analogue (**5c**), which was a selective mGluR2 agonist (EC_{50} = 72 μM), to the 5-cyclohexylmethyl analogue (**5g**), which was a selective mGluR2 antagonist (K_i = 32 μM), and the 5-phenylethyl analogue (**5j**), which was a weak but apparently selective mGluR1 antagonist (K_i = 230 μM). This series of compounds afforded GluR ligands with a broad spectrum of pharmacological profiles, and showing potential for development of new compounds with subtype-selective activities at various GluRs.

1. Introduction

(*S*)-Glutamic acid (Glu) is the main excitatory neurotransmitter in the central nervous system and is involved in many important physiological and pathophysiological functions.[1–4] The action of Glu is mediated by activation of two groups of receptors, the ionotropic and metabotropic Glu receptors (iGluRs and mGluRs).

The iGluR family is divided according to the agonists that were originally identified to activate the receptors selectively.[2] The compounds are *N*-methyl-D-aspartic acid (NMDA), (*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid ((*S*)-AMPA) and kainic acid (KA).[2]

The eight mGluRs are separated into three groups according to protein sequence homology and signal transduction pathways, Group I (mGluR1 and mGluR5), Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7 and mGluR8).[4]

Several heterocyclic amino acids, which are mimicking Glu structurally and pharmacologically, have been isolated from nature or synthesized in the laboratory. Ibotenic acid ((*RS*)-2-amino-(3-hydroxy-5-isoxazolyl)acetic acid, Ibo) isolated from *Amanita muscaria* and the synthetic analogue (*S*)-AMPA both contain a 3-isoxazolol moiety, which is acidic and mimics the distal carboxyl group in Glu (Fig. 1).[5–8]

The 1-pyrazolols **1**–**4** are analogues of Ibo and (*S*)-AMPA and have shown interesting pharmacological activity at both iGluRs and mGluRs (Fig. 1).[8,9]

Compounds **1** and **3** are equipotent agonists and compound **2** is a partial agonist at mGluR2 receptors, whereas **1** is a weak agonist and **2** and **3** weak antagonists at NMDA receptor subtypes.[9] Based on these results, four groups of derivatives were selected in order to gain further knowledge of the structure–activity relationship of the compounds: the bromo analogue (**5a**), the alkyl analogues (**5b**–**e**), the more bulky alkyl analogues (**5f**, **g**) and the phenylalkyl analogues (**5h**–**l**) (Fig. 2).

Keywords: Synthesis; Pyrazole; 1-Pyrazolol; Ibotenic acid; Amino acids; Ionotropic and metabotropic glutamate receptor ligands.
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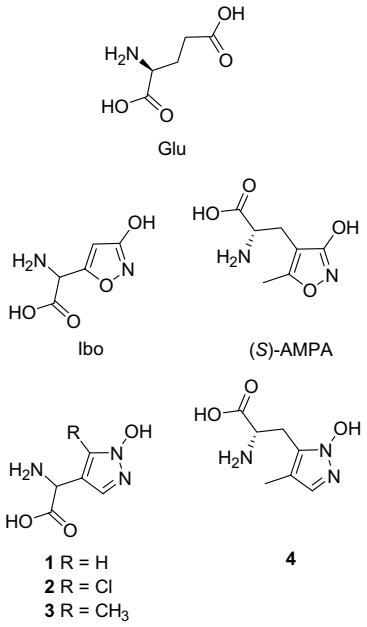


Figure 1. Structures of Glu, Ibo, (*S*)-AMPA, three 1-pyrazolol analogues of Ibo (**1**–**3**) and the 1-pyrazolol analogue of AMPA (**4**).

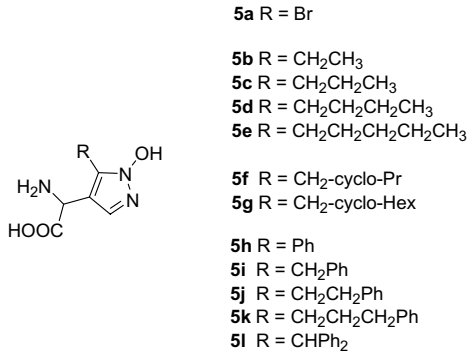
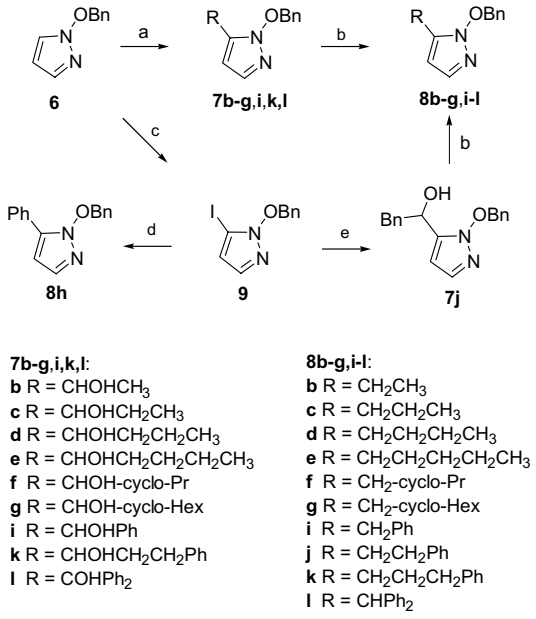


Figure 2. Structures of new 1-pyrazolol analogues (**5a**–**l**).

2. Chemistry

The 5-position of 1-benzyloxypyrazole (**6**) has been metallated with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and *n*-BuLi and reacted with a variety of electrophiles, such as D_2O, MeI, DMF, C_2Cl_6, CBr_4, Br_2 and I_2.[10] We took advantage of this reactivity and synthesized a variety of alcohols **7b**–**g**, **i**, **k**–**l** using *n*-BuLi (Scheme 1). The use of TMEDA resulted in lower yields of alcohols. The alcohols were reduced by ionic hydrogenation[11,12] to the alkyls **8b**–**g**, **i**–**l** using trifluoroacetic acid and triethylsilane. The synthesis of phenylethylalcohol (**7j**) posed problems due to polymerization of phenylacetaldehyde. Therefore, the 5-iodo compound (**9**) was prepared and treated with *i*-PrMgCl and phenylacetaldehyde to give alcohol **7j**. The phenyl **8h** was obtained in high yields using standard Suzuki conditions (Scheme 1 and Table 1).

Iodination of the 4-position of compounds **8b**–**l** was achieved in high yields using iodine monochloride under neutral conditions (Scheme 2).[13] The dihalogenated compound (**10a**) was synthesized from **9** or **8a** using



Scheme 1. Reagents: (a) *n*-BuLi, aldehyde or ketone, THF; (b) Et_3SiH, TFA, CH_2Cl_2; (c) *n*-BuLi, I_2, THF; (d) $PhB(OH)_2$, $PdCl_2(PPh_3)_2$, K_2CO_3 (aq), DMF; (e) *i*-PrMgCl, $PhCH_2CHO$, THF (yields in Table 1).

LDA/tetrabromomethane or iodine monochloride, respectively (Scheme 2 and Table 1).

Derivatization of the 4-position of 1-benzyloxypyrazole can be achieved using an iodine–magnesium exchange reaction of 4-iodo compound, **9**, followed by addition of an electrophile (Scheme 3).[13,14] Recurrent problems were encountered concerning storage of the ketimine, 2-(*N*-*tert*-butoxycarbonylimino)malonic acid diethyl ester, used previously for the synthesis of amino acids **1**–**3**,[15,16] and the purification of the resulting protected amino acids. Therefore, the aldimine, (*N*-*tert*-butoxycarbonylimino)acetic acid ethyl ester (**11**), was used instead. The aldimine, **11**, was prepared from α-bromoglycine using a scavenger amine, morpholinomethyl-polystyrene.[17] The freshly prepared aldimine, **11**, was kept in solution and added to the reactors with the magnesium halides of compounds **9** and **10a**–**l**. The protected amino acids, **12** and **13a**–**l**, were achieved in moderate yields (Scheme 3 and Table 1).

For compounds **12** and **13a**–**e**, **g**–**l**, the deprotection was performed in two steps using basic hydrolysis and acidic treatment to generate the amino acids **5a**–**e**, **g**–**l** and **2**. The amino acids were obtained as zwitterions after adjustment of pH. In the case of the cyclopropylmethyl analogue (**5f**), which was unstable upon hydrogen bromide treatment, a previously described three-step deprotection[16] was employed starting with **13f** (Scheme 3 and Table 1).

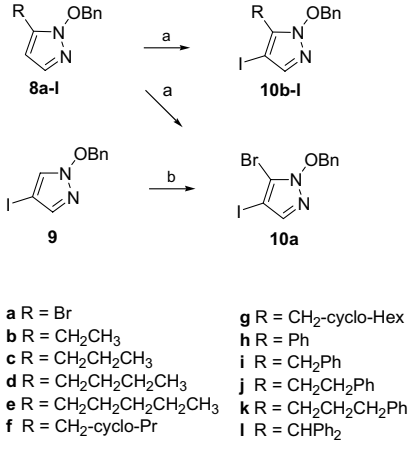
3. pK_a values

The pK_a values of 1-pyrazolol and derivatives **5b**, **e** and **g** were determined by potentiometric titration (Table 2).

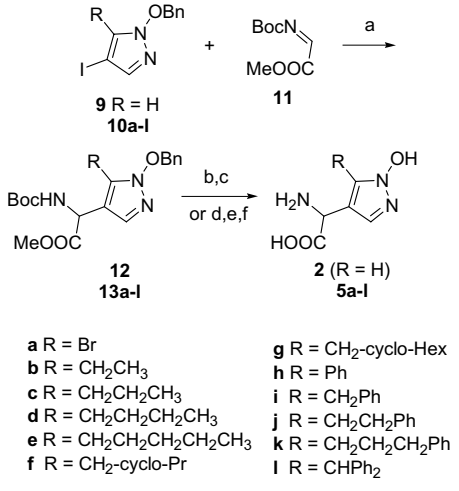
Table 1. Isolated yields (%) of intermediates and amino acids **2** and **5a–l**[a]

Compound.	Substituent in 5-position	Alcohol	Substituent (halogen, alkyl, aryl)	Iodide[b]	Protected amino acid	Deprotected amino acid 1. LiOH[b]/2. HBr
2	Hydrogen	—	—	—	42	98/35
5a	Bromine	—	81[c]	21	33	99/66
5b	Ethyl	90	69	98	64	86/58
5c	Propyl	88	29	97	44	83/50
5d	Butyl	85	69	100	48	100/36
5e	Pentyl	80	73	100	46	100/41
5f	Cyclopropylmethyl	84	65	100	48	69/100/89[d]
5g	Cyclohexylmethyl	83	70	100	51	100/15
5h	Phenyl	—	78[e]	97	74	88/60
5i	Benzyl	76	77	97	60	98/54
5j	Phenylethyl	57[d]	71	96	49	76/49
5k	Phenylpropyl	63	65	99	43	80/25
5l	Benzhydryl	77	46	97	46	74/60

[a] Reactions described in Schemes 1–3.
[b] Crude yields.
[c] From 1-benzyloxypyrazole (**6**).
[d] Used other protocol: 1. Pd/C/H_2, 69%, 2. LiOH, 100% (crude yield), 3. HCl, 89%.
[e] From 1-benzyloxy-5-iodo-pyrazole (**9**).



Scheme 2. Reagents: (a) I–Cl, K_2CO_3, $CHCl_3$; (b) LDA, CBr_4, THF (yields in Table 1).



Scheme 3. Reagents: (a) *i*-PrMgCl, THF, then **11**, THF; (b) LiOH (aq), THF; (c) HBr (aq). For **13f–5f**; (d) H_2, Pd/C, MeOH; (e) LiOH (aq), THF; (f) HCl (aq) (yields in Table 1).

Table 2. pK_a Values of heterocyclic hydroxy moieties and amino groups determined by potentiometric titration[a]

	OH	NH_2
1-Pyrazolol	6.1 (6.3)[b]	—
3-Isoxazolol[c]	5.85	—
Ibo[d]	5.04	8.16
5b (Ethyl)	6.0	9.6
5e (Pentyl)	6.2	9.5
5g (Cyclohexylmethyl)	6.1	9.4
4, 1-pyrazolol-AMPA[e]	5.89	9.81
AMPA[f]	5.12	10.09

[a] Due to the low pK_a values of the carboxyl group, the determinations of these values were not reliable.
[b] Ref. 20.
[c] Ref. 18.
[d] Ref. 19.
[e] Ref. 8.
[f] Ref. 21.

The pK_a values of 1-pyrazolol and 3-isoxazolol[18] were found to be of equal magnitude. With the presence of the amino acid moiety in Ibo,[19] the pK_a value of 3-isoxazolol was lowered by almost one unit, whereas for the 1-pyrazolol analogues **5b**, **e** and **g**, the pK_a value was retained. Interestingly, the pK_a value of the amino group was approximately one and a half unit higher in compounds **5b**, **e** and **g** as compared to Ibo[19]. Based on the determined pK_a values of **5b**, **e** and **g**, all the 1-pyrazolol analogues (**5a–l**) are expected to be fully ionized at physiological pH.

4. Pharmacology

All compounds were pharmacologically characterized at native iGluRs on rat cortical membranes using [^{3}H]AMPA, [^{3}H]KA and [^{3}H]CGP39653 binding assays representing AMPA, KA and NMDA receptors, respectively (Table 3). The bromo and ethyl compounds (**5a**, **b**) showed weak affinity for NMDA receptors and were approximately equipotent with the chloro and methyl

Table 3. Receptor binding affinities at native iGluRs on rat cortical membranes and pharmacological activities at cloned mGluRs expressed in CHO cells[a,b]

	AMPA [^{3}H]AMPA IC_{50} (μM)	KA [^{3}H]KA IC_{50} (μM)	NMDA [^{3}H]CGP-39653 K_i (μM)	EC_{50} (μM) or K_i (μM)		
				mGluR1a	mGluR2	mGluR4a
Glu	0.34[c]	0.38[c]	0.20[d]	13[e]	4.4[e]	13[e]
Ibo	>100[f]	22[f]	5.3[f]	43[e]	110[e]	>1000[e]
1 (H)	>100[g]	>100[g]	39[g,h]	85[g]	230[g]	24[g]
2 (Chloro)	47[g]	>100[g]	64[g,i]	>1000[g]	51 (67%)[g,j]	>1000[g]
3 (Methyl)	>100[g]	>100[g]	56[g,i]	>1000[g]	100[g]	>1000[g]
5a (Bromo)	>100	>100	25 [4.60 ± 0.02]	>1000	170 (43%)[j] [3.82 ± 0.15]	>1000
5b (Ethyl)	>100	>100	32 [4.50 ± 0.05]	>1000	57 [4.25 ± 0.05]	>1000
5c (Propyl)	>100	>100	>100	>1000	72 [4.17 ± 0.09]	>1000
5d (Butyl)	>100	>100	>100	>1000	>1000	>1000
5e (Pentyl)	>100	>100	>100	>1000	>1000	>1000
5f (Cyclopropylmethyl)	>100	>100	35 [4.47 ± 0.04]	>1000	>1000	>1000
5g (Cyclohexylmethyl)	>100	>100	>100	>1000	**32** [4.50 ± 0.03]	>1000
5h (Phenyl)	>100	>100	>100	>1000	**180** [3.75 ± 0.03]	>1000
5i (Benzyl)	>100	>100	67 [4.18 ± 0.03]	>1000	**120** [3.93 ± 0.08]	>1000
5j (Phenylethyl)	>100	>100	>100	**230** [3.71 ± 0.16]	>1000	>1000
5k (Phenylpropyl)	>100	>100	54 [4.27 ± 0.02]	**260** [3.59 ± 0.01]	**67** [4.19 ± 0.06]	>1000
5l (Benzhydryl)	>100	47 [4.33 ± 0.06]	>100	>1000	>1000	>1000

[a] iGluRs: data are given as means of at least three to four independent experiments and the numbers in brackets indicate [pIC_{50} ± SEM] or [pK_i ± SEM].
[b] mGluRs: antagonist activity in bold. Data are given as means of at least three independent experiments and the numbers in brackets indicate [pEC_{50} ± SEM] or [pK_i ± SEM].
[c] Ref. 22.
[d] Ref. 9.
[e] Ref. 23.
[f] Ref. 24.
[g] Ref. 9.
[h] Agonist in functional assay see Ref. 9.
[i] Antagonist in functional assay see Ref. 9.
[j] Partial agonist, X% of max. response.

compounds (**2**, **3**). The cyclopropylmethyl analogue, **5f**, showed similar affinity, whereas the *n*-propyl analogue (**5c**) showed no affinity. Compounds containing larger substituents generally resulted in inactive compounds at NMDA receptors, except for the benzyl (**5i**) and phenylpropyl compounds (**5l**), which retained low affinity. No affinity for AMPA and KA receptors was observed for any of the compounds except for the diphenylmethyl compound, **5l**, which displayed weak affinity for KA receptors (Table 3).

The compounds (**5a**–**l**) were tested functionally at mGluR1a, mGluR2 and mGluR4a representing Group I, II and III receptors, respectively. All compounds were inactive at mGluR1 except for compounds **5j** and **5k**, which turned out to be weak antagonists. At mGluR2, the bromo compound, **5a**, was a partial agonist, which was also observed with the chloro compound, **2**. The ethyl and propyl compounds (**5b**, **c**) were agonists at mGluR2 and with activities comparable to those of the unsubstituted analogue (**1**) and the methyl analogue (**3**).

The butyl, pentyl, cyclopropylmethyl substituted compounds (**5d**–**f**) were all inactive at mGluR2 both as agonist and antagonists (at 1 mM). The more bulky cyclohexylmethyl compound, **5g**, turned out to be an antagonist with a K_i value of 32 μM. The phenyl and benzyl compounds (**5h**, **i**) were also antagonists at mGluR2. The bulky phenylethyl and diphenylmethyl analogues (**5j** and **l**) had no activity at mGluR2, whereas the phenylpropyl compound (**5k**) turned out to be an antagonist almost as potent as compound **5g** (cyclohexylmethyl).

5. Conclusion

New methods were developed for introduction of alkyl substituents in the 5-position of protected 1-pyrazolols. Reaction of 5-metallated 1-benzyloxypyrazole with aldehydes and ketones gave the corresponding alcohols, which were reduced to the respective alkanes using triethylsilane and trifluoroacetic acid. Subsequent iodination using iodine monochloride to obtain 4-iodinated pyrazoles followed by metal–halogen exchange and reaction with aldimine **11** afforded protected amino acids. Deprotection in two steps gave the desired amino acids (**5a**–**l**) in zwitterionic form.

The pK_a determination of three of the pyrazole analogues (**5b**, **e**, **g**) gave pK_a values of the 1-pyrazolol moiety ranging from 6.0 to 6.2 as compared to a pK_a value of 5.04 of the 3-isoxazolol moiety in Ibo. This illustrates the potential of using the 1-pyrazolol moiety for bioisosteric replacement of the distal carboxyl group of Glu. Notably, the pK_a values of the ammonium groups of the 1-pyrazolol amino acids were approximately 1.5 unit

higher compared to Ibo. This may be explained by the stronger inductive effect of the neighbouring oxygen in the isoxazole ring, compared to the more distant and less electronegative nitrogen in the pyrazole ring. An analogous effect can be seen in morpholine ($pK_a = 8.7$) compared to piperidine ($pK_a = 11.2$).[25] However, all of the compounds are primarily tri-ionized at physiological pH and the determined pK_a values determined for **5b**, **e** and **g** show very little variation. Therefore, the observed differences in pharmacology cannot be explained by differences in pK_a values.

The pharmacological characterization of the 1-pyrazolol compounds at iGluRs and mGluRs showed a remarkable variation of pharmacological profiles. Compounds containing small substituents, bromide (**5a**), ethyl (**5b**) or cyclopropylmethyl (**5f**), showed weak affinities for NMDA receptors, whereas most other analogues were without affinity for the NMDA site. Compound **5f** was the only analogue with affinity for the NMDA receptor site showing no activity at any of the mGluRs. Although weak NMDA receptor affinities were observed for the benzyl (**5i**) and phenylpropyl (**5k**) analogues, the phenyl (**5h**) and phenylethyl (**5j**) analogues were found to be inactive ($IC_{50} > 100$ μM).

The most intriguing results were related to the activities observed at mGluRs. In contrast to the unsubstituted analogue **1**, all of the substituted analogues (**2**, **3** and **5a**–**l**) were inactive at mGluR4. Similarly, most analogues were inactive at mGluR1. However, the phenylethyl (**5j**) and the phenylpropyl analogues (**5k**) were antagonists at mGluR1. This means that compound **5j** was a weak but selective antagonist at mGluR1. Notably, the activities at mGluR2 showed remarkable variations. The ethyl- (**5b**) and propyl-substituted (**5c**) compounds were agonists with EC_{50} values below 100 μM, and **5c** was thus a selective mGluR2 agonist. The compounds containing extended alkyls, butyl (**5d**) and pentyl (**5e**), and the cyclopropylmethyl (**5f**) analogue showed no activity at mGluRs, whereas the bulky and lipophilic cyclohexylmethyl (**5g**), phenyl (**5h**), benzyl (**5i**) and phenylpropyl (**5k**) analogues were antagonists with K_i values in the range of 32–180 μM. The cyclohexylmethyl (**5g**) and phenylpropyl (**5k**) analogues showed the highest potencies. Compound **5g** only inhibited mGluR2 and was thus a selective mGluR2 antagonist. When comparing mGluR activity with iGluR activity, it is important to note that mGluR activity generally is 10- to 50-fold lower than iGluR activity as seen for Glu itself (Table 3). Thus, the observed mGluR activities in the range 30–230 μM are indicative of selectivity when comparing with iGluR data.

The results for the mGluR2 agonists indicate limited space for agonist molecules. We have previously hypothesized that interaction of the substituent of 5-substituted pyrazol analogues with Gly296 in mGluR2 reduces the efficacy of the compounds.[9] The ligand binding domain is formed like a venus fly-trap that closes around the ligand resulting in receptor activation. Reduced domain closure due to steric clash between the substituent and Gly296 leads to reduced activation of the receptor. Current data confirm this hypothesis since the degree of activation decreases in the substituent series Me > Cl > Br > Ph.

Clearly, this series of compounds shows potential for development of ligands with multiple activities at the various GluR sites, especially the mGluRs, some analogues being selective agonists and some being selective antagonists.

6. Experimentals

6.1. Chemistry

All materials were obtained from commercial suppliers and used without further purification unless otherwise stated. 1-Benzyloxypyrazole was prepared as previously described.[10] *i*-PrMgCl and *n*-BuLi were titrated prior to use.[26,27] THF was distilled from Na/benzophenone under N_2. All air-sensitive reactions were carried out under N_2. Melting points were measured in open capillary tubes by normal oil bath method or an OptiMelt MPA100 apparatus (SRS) and are all uncorrected. Compounds were visualized on TLC (silica gel 60 F254 plates) using UV light, $FeCl_3$ or $KMnO_4$. Flash chromatography (FC) was performed on a glass column (silica gel 60, 0.040–0.063 mm), a FlashMaster™ Personal one column (FP) (ISOLUTE^R SPE Columns) or a FlashMaster™ (F) (ISOLUTE^R SPE Columns) apparatus. Preparative HPLC was performed on an XTerra Prep MS C_{18} column (10 × 300 mm, 10 μm) equipped with an XTerra guard column (10 × 10 mm) connected to a Jasco 880 pump (flow = 10 mL/min), a Rheodyne 7125 injector, a 5 mL loop, a TSP UV100 spectrophotometer (210 nm) and a Hitachi D-2000 Chromato-Integrator.

^1H, ^{13}C and APT NMR spectra were recorded on a 300/75 MHz Varian (Gemini) instrument or on a 500/125 MHz Bruker Avance DRX500 instrument. TMS was used as internal reference for ^1H NMR spectra and $CDCl_3$ was used as internal reference standard for ^{13}C NMR spectra. Elemental analyses were carried out at the Analytical Research Department, H. Lundbeck A/S, Denmark.

Accurate mass determination (HRMS) was performed on a Micromass Q-Tof mass spectrometer (MeOH, 8.74 μL min^{-1}) in electrospray (ES) mode. GCMS analyses were performed using electron ionization. Analytical LCMS data were obtained on a PE Sciex API 150EX instrument equipped with atmospheric pressure photo ionization and a Shimadzu LC-10ADvp system. Column: 30 × 4.6 mm Waters Symmetry C18 column with 3.5 μm particle size; Solventsystem: A = water/trifluoroacetic acid (100:0.05) and B = water/acetonitrile/trifluoroacetic acid (5:95:0.035); Method: Linear gradient elution with 90% A to 100% B in 10 min and with a flow rate of 2 mL/min. Purity was determined by integration of the UV (254 nm) and ELSD trace by using a Shimadzu SPD-10Advp UV detector and a Sedere Sedex 55 ELSD detector. The retention times (T_R) are expressed in minutes.

The pK_a values were measured potentiometrically using a Sirius GLpKa Auto-titrator and the data were analyzed with Sirius pKaLOGP software (version 5.2). Multiple runs were performed using MeOH/H_2O mixtures. The derived pK_a values were extrapolated to zero organic solvent using Yasuda–Shedlovsky plots.[28,29] The samples were run from low pH to high pH using first HCl (aq) to obtain a pH of 2 and then titrated with KOH (aq).

6.1.1. (*RS*)-2-Amino-(1-hydroxy-4-pyrazolyl)acetic acid (2). Compound **12** (90 mg, 0.25 mmol) was dissolved in THF (0.4 mL) and 2.5 M LiOH (aq) (0.2 mL, 0.5 mmol) was added. The reaction mixture was left stirring for 4 h at rt, then cooled to 0 °C and pH adjusted to ~1 using 1 M HCl (aq). The mixture was extracted using EtOAc (3×), and the combined organic phases were washed with brine, dried using $MgSO_4$ and concentrated in vacuo yielding crude (*RS*)-2-(1-benzyloxy-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid as a foamy oil (85 mg). ^{1}H NMR ($CDCl_3$) δ 1.37 and 1.45 (2× br s, 9H), 5.06–5.44 (m, α-CH, NH, CH_2, 4H), 7.09–7.33 (m, phenyl, H-3, H-5, 7H), 10.23 (br s, COOH, 1H). 48% HBr (aq) (1.1 mL) was added to (*RS*)-2-(1-benzyloxy-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonyl-amino)acetic acid (69 mg, 0.2 mmol). The mixture was left stirring overnight at rt and concentrated in vacuo. The oil was dissolved in 70% EtOH (aq) (1.5 mL) and treated with propylene oxide (0.4 mL) to give **2** as the zwitterion (11 mg, 35%). Mp decomp. >178 °C. ^{1}H NMR (DMSO-d_6) δ 4.13 (s, α-CH, 1H), 7.09 (br s, H-3, 1H), 7.41 (br s, H-5, 1H), 7.78 (br s, 1H). Anal. Calcd for $C_5H_7N_3O_3{\cdot}1/3H_2O$: C, 36.81; H, 4.74; N, 25.76. Found: C, 36.62; H, 4.61; N, 25.45.

6.1.2. (*RS*)-2-Amino-(5-bromo-1-hydroxy-4-pyrazolyl) acetic acid (5a). The title compound was prepared according to the procedure described for **2** starting with **13a** (81 mg, 0.18 mmol). Treatment with LiOH gave crude (*RS*)-2-(1-benzyloxy-5-bromo-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid (77 mg, 99%). HBr treatment of 69 mg of this intermediate gave **5a** as the zwitterion (25 mg, 66%). Mp decomp. >220 °C. ^{1}H NMR (DMSO-d_6) 3.95 (s, α-CH, 1H), 7.22 (s, H-3, 1H), 7.90 (br s, 2H). Anal. Calcd for $C_5H_6BrN_3O_3{\cdot}2/3H_2O$: C, 24.21; H, 2.98; N, 16.94. Found: C, 24.07; H, 3.01; N, 16.60.

6.1.3. (*RS*)-2-Amino-(5-ethyl-1-hydroxy-4-pyrazolyl)acetic acid (5b). The title compound was prepared according to the procedure described for **2** starting with **13b** (147 mg, 0.38 mmol). Treatment with LiOH gave crude (*RS*)-2-(1-benzyloxy-5-ethyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid (122 mg, 86%). HBr treatment of 107 mg of this intermediate gave **5b** which was isolated as the zwitterion (31 mg, 58%). Mp decomp. >182 °C. ^{1}H NMR (DMSO-d_6) δ 1.11 (t, J = 8 Hz, CH_3, 3H), peak hidden under DMSO (CH_2), 4.02 (s, α-CH, 1H), 7.00 (s, H-3, 1H). ^{1}H NMR (D_2O) δ 1.17 (t, J = 8 Hz, CH_3, 3H), 2.64–2.73 (m, CH_2, 2H), 4.75 (s, α-CH, 1H), 7.20 (s, H-3, 1H). Anal. Calcd for $C_7H_{11}N_3O_3{\cdot}1/6H_2O$: C, 44.68; H, 6.07; N, 22.33. Found: C, 44.55; H, 6.35; N, 22.21.

6.1.4. (*RS*)-2-Amino-(1-hydroxy-5-propyl-4-pyrazolyl) acetic acid (5c). The title compound was prepared according to the procedure described for **2** starting with **13c** (258 mg, 0.64 mmol). Treatment with LiOH gave crude (*RS*)-2-(1-benzyloxy-5-propyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid (206 mg, 83%) and further treatment with HBr gave **5c** isolated as the zwitterion (53 mg, 50%). Mp decomp >182 °C. ^{1}H NMR (DMSO-d_6) δ 0.91 (t, J = 7 Hz, CH_3, 3H), 1.54–1.58 (m, CH_2, 2H), 2.59–2.65 (m, peak partly hidden under DMSO, CH_2), 4.04 (s, α-CH, 1H), 7.03 (s, H-3, 1H). Anal. Calcd for $C_8H_{13}N_3O_3{\cdot}1/2H_2O$: C, 46.15; H, 6.78; N, 20.18. Found: C, 46.27; H, 6.40; N, 19.94.

6.1.5. (*RS*)-2-Amino-(1-benzyloxy-5-butyl-4-pyrazolyl) acetic acid (5d). The title compound was prepared according to the procedure described for **2** starting with **13d** (462 mg, 1.11 mmol). Treatment with LiOH gave crude (*RS*)-2-(1-benzyloxy-5-butyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid (447 mg, 100%). Further treatment with HBr gave **5d** but instead of isolating the zwitterion using propylene oxide, the pH was adjusted to 3–4 with 4 M NaOH (aq) followed by HPLC (15 mM AcOH (aq)) purification and recrystallization (H_2O) (85 mg, 36%). Mp decomp. >188 °C. ^{1}H NMR (DMSO-d_6) δ 0.89 (t, J = 8 Hz, CH_3, 3H), 1.30–1.34 (m, CH_2, 2H), 1.49–1.53 (m, CH_2, 2H), 2.50–2.55 (m, peak below DMSO, CH in CH_2, 1H), 2.60–2.65 (m, CH in CH_2, 1H), 4.05 (s, α-CH, 1H), 7.02 (s, H-3, 1H). Anal. Calcd for $C_9H_{15}N_3O_3{\cdot}1/4H_2O$: C, 49.65; H, 7.17; N, 19.30. Found: C, 49.59; H, 7.40; N, 19.35.

6.1.6. (*RS*)-2-Amino-(1-hydroxy-5-pentyl-4-pyrazolyl) acetic acid (5e). The title compound was prepared according to the procedure described for **5d** starting with **13e** (545 mg, 1.26 mmol). Treatment with LiOH gave crude (*RS*)-2-(1-benzyloxy-5-pentyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid (526 mg, 100%). Further treatment with HBr, pH adjustment with NaOH (aq), HPLC purification (5% MeOH in 15 mM AcOH (aq)) and recrystallization (H_2O) gave **5e** (117 mg, 41%). Mp decomp. >183 °C. ^{1}H NMR (DMSO-d_6) δ 0.88 (t, J = 8 Hz, CH_3, 3H), 1.30–1.31 (m, 2× CH_2, 4 H), 1.53–1.55 (m, CH_2, 2H), 2.54 (m, below DMSO, CH in CH_2aryl, 1H), 2.60–2.65 (m, CH in CH_2aryl, 1H), 4.04 (s, α-CH, 1H), 7.02 (s, H-3, 1H). Anal. Calcd for $C_{10}H_{17}N_3O_3{\cdot}1/3H_2O$: C, 51.49; H, 7.63; N, 18.01. Found: C, 51.75; H, 7.66; N, 18.12.

6.1.7. (*RS*)-2-Amino-(5-cyclopropylmethyl-1-hydroxy-4-pyrazolyl)acetic acid (5f). Compound **13f** (475 mg, 1.1 mmol) was dissolved in MeOH (5 mL). Pd/C (68 mg) was added and the reaction mixture was hydrogenated (Schmidlin NM hydrogen generator) at 0 °C for 1 h. The mixture was filtered and concentrated in vacuo giving 2-(*N*-*tert*-butoxycarbonylamino)-2-(5-cyclopropylmethyl-1-hydroxy-4-pyrazolyl)acetic acid methyl ester (257 mg, 69%). ^{1}H NMR ($CDCl_3$) δ 0.29–0.31 (m, CH_2, 2H), 0.49 (br d, J = 8 Hz, CH_2, 2H), 1.02–1.07 (m, CH, 1H), 1.42 (s, *t*-bu, 9H), 2.67 (br d, J = 7 Hz, CH_2, 2H), 3.73 (s, CH_3, 3H), 5.23–5.25 (m, α-CH and NH, 2H), 7.05 (s, H-3, 1H). ^{13}C NMR ($CDCl_3$) δ 4.8 (CH_2), 9.9 (CH), 27.5 (CH_2), 28.4 (CH_3), 49.2 (CH),

52.8 (CH_3), 80.5 (C), 112.4 (C), 129.0 (CH), 134.4 (C), 155.0 (C), 171.7 (C). 2-(*N*-*tert*-Butoxycarbonylamino)-2-(5-cyclopropylmethyl-1-hydroxy-4-pyrazolyl)acetic acid methyl ester (230 mg, 0.71 mmol) was dissolved in THF (0.6 mL) and 2.5 M LiOH (aq) (0.57 mL, 1.41 mmol) was added. The reaction mixture was left stirring for 4 h at rt, then cooled to 0 °C and pH adjusted to ~2 using 1 M HCl (aq). The mixture was extracted using EtOAc (3×), filtered through Na_2SO_4 (Isolute SPE column) and concentrated in vacuo yielding crude 2-(*N*-*tert*-butoxycarbonylamino)-2-(5-cyclopropylmethyl-1-hydroxy-4-pyrazolyl)acetic acid in quantitative yield. The compound was finally deprotected using 2 M HCl (aq) (3.5 mL) under rt overnight. The mixture was concentrated in vacuo and titrated several times with dry Et_2O giving **5f** as the HCl salt (157 mg, 89%). Mp decomp. >176 °C. ^{1}H NMR (D_2O) δ 0.29 (br d, J = 4 Hz, CH_2, 2H), 0.53 (br d, J = 8 Hz, CH_2, 2H), 1.04–1.06 (m, CH, 1H), 2.63–2.77 (m, CH_2, 2H) 5.18 (s, α-CH, 1H), 7.37 (s, H-3, 1H). Anal. Calcd for $C_9H_{13}N_3O_3{\cdot}HCl{\cdot}1/3H_2O$: C, 42.61; H, 5.83; N, 16.56. Found: C, 42.48; H, 6.02; N, 16.49.

6.1.8. (*RS*)-2-Amino-(5-cyclohexylmethyl-1-hydroxy-4-pyrazolyl)acetic acid (5g). The title compound was prepared according to the procedure described for **5d** starting with **13g** (667 mg, 1.46 mmol). Treatment with LiOH gave crude (*RS*)-2-(1-benzyloxy-5-cyclohexylmethyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid (646 mg, 100%). Further treatment with HBr, pH adjustment with NaOH (aq), HPLC (10% MeOH in 15 mM AcOH (aq)) purification and recrystallization (H_2O) gave **5g** (58 mg, 15%). Mp decomp. >210 °C. ^{1}H NMR (DMSO-d_6) δ 0.96 (br s, 2H), 1.12–1.14 (m, 3H), 1.16–1.63 (m, 6H), 2.43 (dd, J = 7, 15 Hz, CH in CH_2, 1H), 2.57 (dd, J = 7, 14 Hz, CH in CH_2, 1H), 4.04 (s, α-CH, 1H), 7.03 (s, H-3, 1H). Anal. Calcd for $C_{12}H_{19}N_3O_3{\cdot}1/3H_2O$: C, 55.58; H, 7.64; N, 16.20. Found: C, 55.48; H, 7.56; N, 16.04.

6.1.9. (*RS*)-2-Amino-(1-hydroxy-5-phenyl-4-pyrazolyl) acetic acid (5h). The title compound was prepared according to the procedure described for **2** starting with **13h** (106 mg, 0.24 mmol). Treatment with LiOH gave crude (*RS*)-2-(1-benzyloxy-5-phenyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid (91 mg, 88%). HBr treatment of 82 mg of this intermediate gave **5h** as the zwitterion (27 mg, 60%). Mp decomp. >199 °C. ^{1}H NMR (DMSO-d_6) δ 3.99 (s, α-CH, 1H), 7.29 (s, H-3, 1H), 7.45 (t, J = 7 Hz, 1H), 7.51 (t, J = 8 Hz, 2H), 7.90 (d and br s, J = 8 Hz, 3H). Anal. Calcd for $C_{11}H_{11}N_3O_3{\cdot}1/2H_2O$: C, 54.54; H, 4.99; N, 17.35. Found: C, 54.83; H, 5.00; N, 17.01.

6.1.10. (*RS*)-2-Amino-(5-benzyl-1-hydroxy-4-pyrazolyl) acetic acid (5i). The title compound was prepared according to the procedure described for **2** starting with **13i** (193 mg, 0.43 mmol). Treatment with LiOH gave crude (*RS*)-2-(5-benzyl-1-benzyloxy-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid (184 mg, 98%). HBr treatment of 159 mg of this intermediate gave **5i** as the zwitterion (49 mg, 54%). Mp decomp. >162 °C. ^{1}H NMR (DMSO-d_6) δ 3.97 (d, J_{AB} = 15 Hz, CH in CH_2, 1H), 4.10 (s, α-CH, 1H), 4.12 (d, J_{AB} = 15 Hz, CH in CH_2, 1H), 7.10 (s, H-3, 1H), 7.17–7.29 (m, 5H), 7.87 (br s, 2H). Anal. Calcd for $C_{12}H_{13}N_3O_3{\cdot}1H_2O$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.28; H, 5.79; N, 17.47.

6.1.11. (*RS*)-2-Amino-(1-hydroxy-5-phenylethyl-4-pyrazolyl)acetic acid (5j). The title compound was prepared according to the procedure described for **2** starting with **13j** (150 mg, 0.32 mmol). Treatment with LiOH gave crude (*RS*)-2-(1-benzyloxy-5-phenylethyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid (95 mg, 76%) and further treatment with HBr gave **5j** isolated as the zwitterion (27 mg, 49%). Mp decomp. >166 °C. ^{1}H NMR (DMSO-d_6) δ 2.80–2.91 (m, 2× CH_2, 4H), 4.11 (s, α-CH, 1H), 7.05 (s, H-3, 1H), 7.19–7.84 (m, 5H). Anal. Calcd for $C_{13}H_{15}N_3O_3{\cdot}1H_2O$: C, 55.91; H, 6.13; N, 15.05. Found: C, 56.11; H, 6.42; N, 14.69.

6.1.12. (*RS*)-2-Amino-[1-hydroxy-5-(3-phenylpropyl)-4-pyrazolyl]acetic acid (5k). The title compound was prepared according to the procedure described for **2** starting with **13k** (219 mg, 0.46 mmol). Treatment with LiOH gave crude (*RS*)-2-(1-benzyloxy-5-(3-phenylpropyl)-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid (171 mg, 80%) and further treatment with HBr gave **5k** isolated as the zwitterion (25 mg, 25%). Mp decomp. >162 °C. ^{1}H NMR (DMSO-d_6) δ 1.87–1.90 (m, CH_2, 2H), 2.54–2.70 (m, 2× CH_2, 4H), 4.03 (s, α-CH, 1H), 7.04 (s, H-3, 1H), 7.17–7.29 (m, 5H). Anal. Calcd for $C_{14}H_{17}N_3O_3{\cdot}2/3H_2O$: C, 58.53; H, 6.43; N, 14.63. Found: C, 58.83; H, 6.39; N, 14.38.

6.1.13. (*RS*)-2-Amino-(5-benzhydryl-1-hydroxy-4-pyrazolyl)acetic acid (5l). The title compound was prepared according to the procedure described for **2** starting with **13l** (246 mg, 0.47 mmol). Treatment with LiOH gave crude (*RS*)-2-(1-benzyloxy-5-benzhydryl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid (178 mg, 74%) and further treatment with HBr gave **5l** isolated as the zwitterion (67 mg, 60%). Mp decomp. >175 °C. ^{1}H NMR (DMSO-d_6) δ 3.72 (s, α-CH, 1H), 5.95 (s, $CHPh_2$, 1H), 7.14–7.31 (m, H-3 and 2× Ph, 11H). Anal. Calcd for $C_{18}H_{17}N_3O_3.1H_2O$: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.01; H, 5.69; N, 12.10.

6.1.14. 1-(1-Benzyloxy-5-pyrazolyl)ethanol (7b). 1-Benzyloxypyrazole (390 mg, 2.2 mmol) in THF (10 mL) was cooled to −78 °C and *n*-BuLi in hexanes (1.68 M, 2 mL, 3.4 mmol) was added over 5 min. The mixture was left stirring for 5 min at −78 °C before CH_3CHO (0.2 mL, 158 mg, 3.6 mmol) was added. The mixture was left stirring at −78 °C for 1 h and then warmed to rt over 3 h and left at rt for 1 h. Satd NH_4Cl (aq) was added followed by additional water. The mixture was extracted using EtOAc (3×). The organic phases were pooled, washed with brine, dried using $MgSO_4$ and concentrated in vacuo. FC (F, petroleum ether/EtOAc) gave **7b** (440 mg, 90%) as a clear oil. TLC (petroleum ether/EtOAc 3:1) R_f 0.14. ^{1}H NMR ($CDCl_3$) δ 1.29 (d, J = 7 Hz, CH_3, 3H), 2.55 (br s, OH, 1H), 4.59 (q, J = 7 Hz, CHOH, 1H), 5.29 (s, CH_2, 2H), 6.04 (d, J = 2 Hz, H-4, 1H), 7.19 (d, J = 2 Hz, H-3, 1H),

7.27–7.37 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 21.8 (CH_3), 60.4 (CH), 80.1 (CH_2), 100.5 (CH), 128.8 (CH), 129.5 (CH), 130.1 (CH), 132.6 (C), 133.6 (C), 139.9 (C). LCMS *m*/*z* 219 ($M+H^+$); T_R = 1.98; purity (UV, ELSD): 87%, 98%. The reaction was also tried using TMEDA (1.1 equiv), *n*-BuLi (1.1 equiv) and CH_3CHO (5 equiv) and the conditions described in the literature but the reaction resulted in lower yields.[10]

6.1.15. 1-(1-Benzyloxy-5-pyrazolyl)propan-1-ol (7c). The title compound was prepared according to the procedure described for **7b** starting with 1-benzyloxypyrazole (1.00 g, 5.7 mmol). FC (F, petroleum ether/EtOAc) gave **7c** as a clear oil (1.18 g, 88%). TLC (petroleum ether/EtOAc 3:1) R_f 0.19. ^{1}H NMR ($CDCl_3$) δ 0.79 (t, J = 8 Hz, CH_3, 3H), 1.55 (m, CH, 1H), 1.68 (m, CH, 1H), 3.27 (br s, OH, 1H), 4.37 (t, J = 7 Hz, CHOH, 1H), 5.24 (d, J_{AB}=10 Hz, CH in CH_2, 1H), 5.25 (d, J_{AB} = 10 Hz, CH in CH_2, 1H), 6.02 (d, J = 2 Hz, H-4, 1H), 7.16 (d, J = 2 Hz, H-3, 1H), 7.27–7.32 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 9.8 (CH_3), 28.9 (CH_2), 65.5 (CH), 80.0 (CH_2), 100.8 (CH), 128.5 (CH), 129.2 (CH), 129.8 (CH), 132.4 (CH), 133.5 (C), 139.0 (C).

6.1.16. 1-(1-Benzyloxy-5-pyrazolyl)butan-1-ol (7d). The title compound was prepared according to the procedure described for **7b** starting with 1-benzyloxypyrazole (1.00 g, 5.7 mmol). FC (F, petroleum ether/EtOAc) gave **7d** as a clear oil (1.19 g, 85%). TLC (petroleum ether/EtOAc 2:1) R_f 0.29. ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7 Hz, CH_3, 3H), 1.20 (m, CH, 1H), 1.33 (m, CH, 1H), 1.49 (m, CH, 1H), 1.56 (br s, 1H, OH), 1.68 (m, CH, 1H), 4.38 (dd, J = 6, 8 Hz, CHOH, 1H), 5.33 (d, J_{AB} = 11 Hz, CH in CH_2, 1H), 5.37 (d, J_{AB} = 11 Hz, CH in CH_2, 1H), 6.03 (d, J = 2 Hz, H-4, 1H), 7.25–7.40 (m, phenyl, H-3, 6H). ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 18.9 (CH_2), 38.0 (CH_2), 64.4 (CH), 80.1 (CH_2), 100.8 (CH), 129.0 (CH), 129.7 (CH), 130.3 (CH), 133.0 (CH), 133.9 (C), 139.3 (C).

6.1.17. 1-(1-Benzyloxy-5-pyrazolyl)pentan-1-ol (7e). The title compound was prepared according to the procedure described for **7b** starting with 1-benzyloxypyrazole (1.00 g, 5.7 mmol). FC (F, petroleum ether/EtOAc) gave **7e** as a clear oil (1.19 g, 80%). TLC (petroleum ether/EtOAc 2:1) R_f 0.29. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7 Hz, CH_3, 3H), 1.10–1.35 (m, 2× CH_2, OH, 5H), 1.50–1.70 (2× m, CH_2, 2H), 4.36 (br t, J = 8 Hz, CHOH, 1H), 5.32 (d, J_{AB} = 11 Hz, CH in CH_2, 1H), 5.37 (d, J_{AB} = 11 Hz, CH in CH_2, 1H), 6.03 (d, J = 2 Hz, H-4, 1H), 7.25–7.40 (m, H-3, phenyl, 6H). ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 22.5 (CH_2), 27.8 (CH_2), 35.7 (CH_2), 64.7 (CH), 80.1 (CH_2), 100.8 (CH), 129.0 (CH), 129.7 (CH), 130.3 (CH), 132.9 (CH), 133.9 (C), 139.3 (C).

6.1.18. (1-Benzyloxy-5-pyrazolyl)cyclopropylmethanol (7f). The title compound was prepared according to the procedure described for **7b** starting with 1-benzyloxypyrazole (1.00 g, 5.7 mmol). FC (F, petroleum ether/EtOAc) gave **7f** as a clear oil (1.18 g, 84%). TLC (petroleum ether/EtOAc 2:1) R_f 0.22. ^{1}H NMR ($CDCl_3$) δ 0.09 (m, CH, 1H), 0.33 (m, CH, 1H), 0.46 (m, CH, 1H), 0.59 (m, CH, 1H), 1.18 (m, CH, 1H), 1.95 (br s, OH, 1H), 3.71 (d, J = 8 Hz, CHOH, 1H), 5.35 (s, CH_2, 2H), 6.14 (d, J = 2 Hz, H-4, 1H), 7.26–7.39 (m, phenyl, H-3, 6H). ^{13}C NMR ($CDCl_3$) δ 2.4 (CH_2), 3.65 (CH_2), 16.1 (CH), 68.8 (CH), 80.3 (CH_2), 101.4 (CH), 128.9 (CH), 129.6 (CH), 130.2 (CH), 132.8 (CH), 133.9 (C), 138.3 (C).

6.1.19. (1-Benzyloxy-5-pyrazolyl)cyclohexylmethanol (7g). The title compound was prepared according to the procedure described for **7b** starting with 1-benzyloxypyrazole (1.00 g, 5.7 mmol). FC (F, petroleum ether/EtOAc) gave **7g** as a clear oil (1.36 g, 83%). TLC (petroleum ether/EtOAc 2:1) R_f 0.32. ^{1}H NMR ($CDCl_3$) δ 0.78–0.84 (m, 1H), 0.89–0.97 (m, 1H), 1.03–1.19 (m, 3H), 1.31 (d, J = 13 Hz, 1H), 1.51–1.61 (m, 3H), 1.70 (d, J = 13 Hz, 1H), 1.93 (d, J = 13 Hz, 1H), 2.29 (d, J = 5 Hz, 1H), 4.21 (dd, J = 5, 8 Hz, CHOH), 5.25 (d, J_{AB} = 11 Hz, CH in CH_2, 1H), 5.29 (d, J_{AB} = 11 Hz, CH in CH_2, 1H), 6.02 (d, J = 2 Hz, H-4, 1H), 7.20 (d, J = 2 Hz, H-3, 1H), 7.28–7.37 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 25.7 (CH_2), 25.8 (CH_2), 26.3 (CH_2), 28.7 (CH_2), 28.9 (CH_2), 43.1 (CH), 69.3 (CH), 80.0 (CH_2), 101.3 (CH), 128.7 (CH), 129.3 (CH), 130.0 (CH), 132.7 (CH), 133.7 (C), 138.4 (C).

6.1.20. (1-Benzyloxy-5-pyrazolyl)phenylmethanol (7i). The title compound was prepared according to the procedure described for **7b** starting with 1-benzyloxypyrazole (1.00 g, 5.7 mmol). FC (F, petroleum ether/EtOAc) gave **7i** as a clear oil (1.21 g, 76%). TLC (petroleum ether/EtOAc 2:1) R_f 0.29. ^{1}H NMR ($CDCl_3$) δ 2.41 (br s, OH, 1H), 5.19 (d, J_{AB} = 10 Hz, CH in CH_2, 1H), 5.26 (d, J_{AB} = 10 Hz, CH in CH_2, 1H), 5.53 (s, CHOH, 1H), 5.85 (d, J = 2 Hz, H-4, 1H), 7.20 (d, J = 2 Hz, H-3, 1H), 7.21-7.40 (m, 2× Ph, 10H). ^{13}C NMR ($CDCl_3$) δ 67.1 (CH), 80.2 (CH_2), 102.6 (CH), 126.4 (CH), 128.2 (CH), 128.6 (CH), 128.9 (CH), 129.6 (CH), 130.2 (CH), 132.8 (CH), 133.7 (C), 138.7 (C), 140.7 (C). LCMS *m*/*z* 281 ($M+H^+$); T_R = 2.77; purity (UV, ELSD): 85%, 98%.

6.1.21. 1-(1-Benzyloxy-5-pyrazolyl)-2-phenylethanol (7j). 1-Benzyloxy-5-iodopyrazole (**9**) (743 mg, 2.5 mmol) in THF (10 mL) was cooled to 0 °C. *i*-PrMgCl (2.1 M, 1.4 mL, 3.0 mmol) was added to the solution dropwise. The mixture was warmed to rt and left stirring for 1 h. The mixture was cooled to 0 °C and freshly prepared phenylacetaldehyde[30] in THF (2 mL) was added whereupon the mixture turned from turbid to clear. The mixture was left for 1 h at rt, whereupon satd NH_4Cl (aq) was added followed by extraction using EtOAc (3×). The pooled organic phases were washed with brine and dried using $MgSO_4$. FC (FP, petroleum ether/EtOAc 2:1) gave **7j** as a clear oil (304 mg, 57%). TLC (petroleum ether/EtOAc 2:1) R_f 0.20. ^{1}H NMR ($CDCl_3$) δ 2.34 (s, OH, 1H), 2.80–2.95 (m, CH2, 2H), 4.66 (t, J = 6 Hz, CHOH, 1H), 5.07 (d, J_{AB} = 11 Hz, CH in CH_2, 1H), 5.20 (d, J_{AB} = 11 Hz, CH in CH_2, 1H), 6.05 (d, J = 2 Hz, H-4, 1H), 7.05–7.07 (m, 2H), 7.17–7.36 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 42.5 (CH_2), 65.6 (CH), 80.2 (CH_2), 101.3 (CH), 126.7 (CH), 128.4 (CH), 128.8 (CH), 129.5 (CH), 130.0 (CH), 132.7 (CH), 133.7 (C), 137.2 (C), 138.3 (C). The compound could also be

synthesized from 1-benzyloxypyrazole-5-carbaldehyde[10] (200 mg, 1 mmol) in THF followed by the addition of benzyl magnesium chloride in THF (2 M, 0.6 ml, 1.2 mmol) at 0 °C and left stirring for 150 min at rt. The reaction was worked-up according to the above-mentioned synthesis. FC (F, petroleum ether/EtOAc) gave **7j** as a clear oil (57 mg, 20%).

6.1.22. 1-(1-Benzyloxy-5-pyrazolyl)-3-phenylpropan-1-ol (7k). The title compound was prepared according to the procedure described for **7b** starting with 1-benzyloxypyrazole (1.00 g, 5.7 mmol). FC (F, petroleum ether/EtOAc) gave **7k** as a clear oil (1.12 g, 63%). TLC (petroleum ether/EtOAc 2:1) R_f 0.19. ^{1}H NMR ($CDCl_3$) δ 1.36 (d, J = 4 Hz, OH, 1H), 1.82–2.03 (2× m, CH_2, 2H), 2.50–2.68 (2× m, CH_2, 2H), 4.36 (m, CHOH, 1H), 5.26 (d, J_{AB} = 11 Hz, CH in CH_2, 1H), 5.35 (d, J_{AB} = 11 Hz, CH in CH_2, 1H), 6.04 (d, J = 2 Hz, H-4, 1H), 7.13–7.38 (m, 2× phenyl and H-3, 11H). ^{13}C NMR ($CDCl_3$) δ 31.8 (CH_2), 37.4 (CH_2), 63.9 (CH), 80.1 (CH_2), 100.9 (CH), 126.1, 128.6, 128.6, 129.0, 129.6, 130.3, 133.0, 133.8, 139.0, 141.3.

6.1.23. (1-Benzyloxy-5-pyrazolyl)diphenylmethanol (7l). The title compound was prepared according to the procedure described for **7b** starting with 1-benzyloxypyrazole (1.00 g, 5.7 mmol). FC (F, petroleum ether/EtOAc) gave **7l** as a white solid (1.56 g, 77%). TLC (petroleum ether/EtOAc 2:1) R_f 0.5. ^{1}H NMR ($CDCl_3$) δ 3.96 (s, OH, 1H), 4.91 (s, CH_2, 2H), 5.57 (d, J = 2 Hz, H-4, 1H), 6.93 (br d, J = 7 Hz, 2H), 7.19 (d, J = 2 Hz, H-3, 1H), 7.26–7.38 (m, 13H).

6.1.24. 1-Benzyloxy-5-bromopyrazole (8a). 1-Benzyloxypyrazole (1.05 g, 6.0 mmol) in THF (35 ml) was cooled to −78 °C. *n*-BuLi in hexanes (2 M, 3.2 mL, 6.4 mmol) was added to the solution. The mixture was left stirring at −78 °C for 15 min followed by the addition of solid CBr_4 (3.8 g, 11.5 mmol) in THF (7 ml). The mixture was left stirring at −78 °C for 1 h, whereupon satd NH_4Cl (aq) was added. The mixture was extracted using EtOAc (3×). The organic phases were pooled, washed with brine, dried using $MgSO_4$ and concentrated in vacuo. FC (FP, toluene/petroleum ether 0:1–1:1) gave **8a** as an oil (1.24 g, 81%). TLC (toluene/petroleum ether/EtOAc 4:4:1) R_f 0.5. The NMR data were consistent with the literature data.[10]

6.1.25. 1-Benzyloxy-5-ethylpyrazole (8b). Compound **7b** (1.16 g, 5.3 mmol) was dissolved in dry CH_2Cl_2 (15 mL). The mixture was put under N_2 and cooled to 0 °C. Triethylsilane (4.2 mL, 26.4 mmol) was added followed by the addition of trifluoroacetic acid (12 mL). The mixture was left refluxing at 50 °C overnight. The mixture was cooled to 0 °C and H_2O was added to the reaction mixture followed by extraction with Et_2O (3×). The pooled organic phases were washed with satd $NaHCO_3$ (aq) until a pH of ~7 was obtained. The organic phase was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. FC (4:4:1 toluene/petroleum ether/EtOAc) afforded **8b** as a yellow oil (745 mg, 69%). ^{1}H NMR ($CDCl_3$) δ 1.04 (t, J = 8 Hz, CH_3, 3H,), 2.28 (q, J = 8 Hz, CH_2, 2H), 5.27 (s, CH_2, 2 H), 5.86 (d, J = 2 Hz, H-4, 1H), 7.22 (d, J = 2 Hz, H-3, 1H), 7.29–7.37 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 12.5 (CH_3), 17.5 (CH_2), 79.9 (CH_2), 101.0 (CH), 128.7 (CH), 129.4 (CH), 130.1 (CH), 132.7 (CH), 134.1 (C), 138.4 (C). *m*/*z* (EI) 202 (7%), 185, 105, 91 (100%). HRMS *m*/*z* found: 225.1006 [M+Na$^+$]. Calcd for $C_{12}H_{14}N_2ONa$: 225.1004 [M+Na$^+$].

6.1.26. 1-Benzyloxy-5-propylpyrazole (8c). The title compound was prepared according to the procedure described for **8b** starting with **7c** (1.18 g, 5.1 mmol), but with modifications. After work up and chromatography (FC (F, petroleum ether/EtOAc)), NMR showed a 1:1 mixture of R–O–$COCF_3$ and product. The mixture was heated at 60 °C with MeOH overnight and concentrated in vacuo. FC (F, petroleum ether/EtOAc) gave **8c** as a clear oil (322 mg, 29%). TLC (petroleum ether/EtOAc 9:1) R_f 0.44. ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 8 Hz, CH_3, 3H), 1.39–1.46 (m, CH_2, 2H), 2.22 (t, J = 8 Hz, CH_2Ar, 2H), 5.24 (s, CH_2, 2H), 5.83 (d, J = 2 Hz, H-4, 1H), 7.19 (d, J = 2 Hz, H-3, 1H), 7.26–7.30 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 13.6 (CH_3), 21.3 (CH_2), 29.6 (CH_2), 79.6 (CH_2), 101.4 (CH), 128.5 (CH), 129.1 (CH), 129.8 (CH), 132.4 (CH), 133.9 (C), 136.5 (C). *m*/*z* (EI) 216 (7%), 199, 105, 91 (100%). HRMS *m*/*z* found: 239.1166 [M+Na$^+$]. Calcd for $C_{13}H_{16}N_2ONa$: 239.1160 [M+Na$^+$].

6.1.27. 1-Benzyloxy-5-butylpyrazole (8d). The title compound was prepared according to the procedure described for **8b** starting with **7d** (877 mg, 3.6 mmol). FC (petroleum ether/EtOAc 1:0–2:1) gave **8d** as a clear oil (569 mg, 69%). TLC (petroleum ether/EtOAc 2:1) R_f 0.6. ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 7 Hz, CH_3, 3H), 1.23 (m, CH_2, 2H), 1.37 (m, CH_2, 2H), 2.23 (t, J = 8 Hz, CH_2Ar, 2H), 5.25 (m, CH_2, 2H), 5.83 (d, J = 2 Hz, H-4, 1H), 7.20 (d, J = 2 Hz, H-3, 1H), 7.27–7.33 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 13.6 (CH_3), 22.2 (CH_2), 23.5 (Ar–CH_2), 30.1 (CH_2), 79.6 (CH_2), 101.4 (CH), 128.5 (CH), 129.1 (CH), 129.9 (CH), 132.5 (CH), 133.9 (C), 136.8 (C). *m*/*z* (EI) 230 (3%), 213, 171, 91 (100%). HRMS *m*/*z* found: 253.1325 [M+Na$^+$]. Calcd for $C_{14}H_{18}N_2ONa$: 253.1317 [M+Na$^+$].

6.1.28. 1-Benzyloxy-5-pentylpyrazole (8e). The title compound was prepared according to the procedure described for **8b** starting with **7e** (1.13 g, 4.3 mmol), but instead of using satd $NaHCO_3$ (aq), a 1:1 solution of concentrated NH_4OH and H_2O was used to adjust the pH to ~7. FC (petroleum ether/EtOAc 1:0–2:1) gave **8e** as a clear oil (775 mg, 73%). TLC (petroleum ether/EtOAc 2:1) R_f 0.6. ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7 Hz, CH_3, 3H), 1.16–1.26 (m, 2× CH_2, 4H), 1.36–1.42 (m, CH_2, 2H), 2.22 (t, J = 8 Hz, CH_2Ar, 2H), 5.25 (s, CH_2, 2H), 5.83 (d, J = 2 Hz, H-4, 1H), 7.19 (d, J = 2 Hz, H-3, 1H), 7.26–7.32 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3), 22.2 (CH_2), 23.7 (CH_2), 27.6 (CH_2), 31.2 (CH_2), 79.6 (CH_2), 101.3 (CH), 128.5 (CH), 129.1 (CH), 129.8 (CH), 132.4 (CH), 133.9 (C), 136.8 (C). *m*/*z* (EI) 244 (1%), 171, 105, 91 (100%). HRMS *m*/*z* found: 267.1465 [M+Na$^+$]. Calcd for $C_{15}H_{20}N_2ONa$: 267.1473 [M+Na$^+$].

6.1.29. 1-Benzyloxy-5-cyclopropylmethylpyrazole (8f). The title compound was prepared according to the procedure described for **8e** starting with **7f** (620 mg, 2.5 mmol). FC (petroleum ether/EtOAc 1:0–2:1) gave **8f** as a clear oil (377 mg, 66%). TLC (petroleum ether/EtOAc 2:1) R_f 0.6. ^{1}H NMR ($CDCl_3$) δ 0.11 (q, J = 5 Hz, CH_2, 2H), 0.53 (q, J = 5 Hz, CH_2, 2H), 0.84–0.91 (m, CH, 1H), 2.22 (d, J = 7 Hz, CH_2, 2H), 5.35 (s, CH_2, 2H), 6.07 (d, J = 1 Hz, H-4, 1H), 7.31 (d, H-3, J = 2 Hz, 1H), 7.35–7.44 (m, phenyl, 5H). TMS is hidden in spectra so used CH_2 in OBn as internal reference (5.35 in **8e**). ^{13}C NMR ($CDCl_3$) δ 4.6 (CH_2), 9.2 (CH), 28.8 (CH_2), 79.8 (CH_2), 101.7 (CH), 128.6 (CH), 129.2 (CH), 130.0 (CH), 132.6 (CH), 134.0 (C), 136.5 (C). *m/z* (EI) 228 (2%), 211, 171, 91 (100%). HRMS *m/z* found: 229.1347 [M+H$^+$]. Calcd for $C_{14}H_{17}N_2O$: 229.1341 [M+H$^+$].

6.1.30. 1-Benzyloxy-5-cyclohexylmethylpyrazole (8g). The title compound was prepared according to the procedure described for **8e** starting with **7g** (1.36 g, 4.76 mmol). FC (petroleum ether/EtOAc 1:0–2:1) gave **8g** as a clear oil (902 mg, 70%). TLC (petroleum ether/EtOAc 2:1) R_f 0.6. ^{1}H NMR ($CDCl_3$) δ 0.78–0.85 (m, 2H), 1.04–1.18 (m, 3H), 1.33 (m, 1H, CH), 1.58–1.65 (m, phenyl, 5H), 2.17 (d, J = 7 Hz, 2H), 5.26 (s, CH_2, 2H), 5.83 (d, J = 2 Hz, H-4), 7.20 (d, J = 2 Hz, H-3), 7.29–7.37 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 26.1 (CH_2), 26.3 (CH_2), 31.6 (CH_2), 33.0 (CH_2), 37.2 (CH), 79.7 (CH_2), 102.4 (CH), 128.6 (CH), 129.2 (CH), 129.9 (CH), 132.5 (CH), 134.1 (C), 135.4 (C). *m/z* (EI) 270 (2%), 253, 171, 91 (100%). HRMS *m/z* found: 271.1801 [M+H$^+$]. Calcd for $C_{17}H_{23}N_2O$: 271.1810 [M+H$^+$].

6.1.31. 1-Benzyloxy-5-phenylpyrazole (8h). 1-Benzyloxy-5-iodopyrazole (**9**) (305 mg, 1 mmol) was dissolved in DMF (2 mL) and purged with N_2 for 10 min. $PhB(OH)_2$ (244 mg, 2 mmol) and $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) were added. The reaction mixture was purged with N_2·K_2CO_3 (aq) (3 M, 0.67 mL, 2 mmol) was added and the mixture was left refluxing at 80 °C overnight under N_2. The reaction mixture was cooled to rt and H_2O (20 mL) was added. The reaction mixture was extracted with Et_2O (3×) and the organic phases pooled and washed with 20 mL of 2 M NaOH (2×). The organic phase was further washed with H_2O, brine, dried using $MgSO_4$ and concentrated in vacuo. FC (petroleum ether/toluene 1:0–1:1) gave **8h** as a clear oil (196 mg, 78%). TLC (petroleum ether/toluene/EtOAc 4:4:1) R_f 0.31. ^{1}H NMR ($CDCl_3$) δ 5.15 (s, CH_2, 2H), 6.26 (d, J = 2 Hz, H-4, 1H), 7.13–7.36 (m, 9H), 7.51–7.53 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 80.5 (CH_2), 102.8 (CH), 127.7, 128.3, 128.4, 128.5, 129.1, 129.9, 133.0 (CH), 133.2 (C), 136.1 (C). LCMS *m/z* 251 (M+H$^+$); T_R = 3.39; purity (UV, ELSD): 97%, 99%.

6.1.32. 5-Benzyl-1-benzyloxypyrazole (8i). The title compound was prepared according to the procedure described for **8b** starting with **7i** (400 mg, 1.43 mmol). FC (FP, petroleum ether/toluene/EtOAc 1:1:0–4:4:1) gave **8i** as a clear oil (290 mg, 77%). TLC (petroleum ether/toluene/EtOAc 4:4:1) R_f 0.17. ^{1}H NMR ($CDCl_3$) δ 3.55 (s, CH_2, 2H), 5.15 (s, CH_2, 2H), 5.74 (d, J = 2 Hz, H-4, 1H), 7.00 (d, J = 7 Hz, phenyl, 2H), 7.15–7.35 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 30.3 (CH_2), 79.7 (CH_2), 102.8 (CH), 126.6 (CH), 128.5 (CH), 128.6 (CH), 128.6 (CH), 129.2 (CH), 130.0 (CH), 132.6 (CH), 133.8 (C), 135.4 (C), 137.5 (C).

6.1.33. 1-Benzyloxy-5-phenylethylpyrazole (8j). The title compound was prepared according to the procedure described for **8b** starting with **7j** (304 mg, 1.0 mmol). FC (petroleum ether/EtOAc 1:0–2:1) gave **8j** as a clear oil (204 mg, 71%). TLC (petroleum ether/EtOAc 2:1) R_f 0.28. ^{1}H NMR ($CDCl_3$) δ 2.54 (t, J = 8 Hz, CH_2, 2H), 2.66 (t, J = 8 Hz, CH_2, 2H), 5.18 (s, CH_2, 2H), 5.81 (s, H-4, 1H), 7.03–7.04 (m, 2H), 7.16–7.33 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 25.8 (CH_2), 34.3 (CH_2), 79.7 (CH_2), 101.8 (CH), 126.2 (CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 129.3 (CH), 130.0 (CH), 132.6 (CH), 134.0 (C), 135.9 (C), 140.7 (C). *m/z* (EI) 278 (6%), 261, 105, 91 (100%). HRMS *m/z* found: 301.1328 [M+Na$^+$]. Calcd for $C_{18}H_{18}N_2ONa$: 301.1317 [M+Na$^+$].

6.1.34. 1-Benzyloxy-5-(3-phenylpropyl)pyrazole (8k). The title compound was prepared according to the procedure described for **8b** starting with **7k** (1.12 g, 3.6 mmol). FC (F, petroleum ether/EtOAc) gave **8k** as a clear oil (682 mg, 65%). TLC (petroleum ether/EtOAc 9:1) R_f 0.19. ^{1}H NMR ($CDCl_3$) δ 1.73 (quintet, J = 8 Hz, $CH_2CH_2CH_2$, 2H), 2.25 (t, J = 8 Hz, CH_2, 2H), 2.51 (t, J = 8 Hz, CH_2, 2H), 5.22 (s, CH_2, 2H), 5.85 (br s, H-4, 1H), 7.10 (d, J = 8 Hz, 2H), 7.16–7.24 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 23.5 (CH_2), 29.6 (CH_2), 35.3 (CH_2), 79.8 (CH_2), 101.6 (CH), 126.0 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 129.3 (CH), 130.0 (CH), 132.7 (CH), 133.9 (C), 136.5 (C), 141.6 (C). *m/z* (EI) 292 (1%), 188, 171, 91 (100%). HRMS *m/z* found: 315.1486 [M+Na$^+$]. Calcd for $C_{19}H_{20}N_2ONa$: 315.1473 [M+Na$^+$].

6.1.35. 5-Benzhydryl-1-benzyloxypyrazole (8l). The title compound was prepared according to the procedure described for **8b** starting with **7l** (1.56 g, 4.4 mmol). FC (F, petroleum ether/EtOAc) gave **8l** as a clear oil (680 mg, 46%). TLC (petroleum ether/EtOAc 4:1) R_f 0.44. ^{1}H NMR ($CDCl_3$) δ 5.00 (s, CH_2, 2H), 5.20 (s, CH, 1H), 5.66 (d, J = 2 Hz, H-4, 1H), 6.98–7.00 (m, 4H), 7.13–7.14 (m, 2H), 7.20–7.28 (m, 7H), 7.31–7.39 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 47.1 (CH), 79.7 (CH_2), 104.3 (CH), 127.0 (CH), 128.6 (CH), 128.8 (CH), 129.4 (CH), 130.2 (CH), 132.5 (CH), 133.8 (C), 138.6 (C), 141.4 (C).

6.1.36. 1-Benzyloxy-5-iodopyrazole (9). 1-Benzyloxypyrazole (1.16 g, 6.7 mmol) in THF (35 ml) was cooled to −78 °C. *n*-BuLi in hexanes (2 M, 4.3 mL, 8.6 mmol) was added to the solution. The mixture was left stirring at −78 °C for 10 min followed by the addition of solid I_2 under positive flow of N_2. The mixture was left stirring at −78 °C for 45 min, whereupon 5% $Na_2S_2O_3$ (aq) (25 mL) was added. The mixture was extracted using EtOAc (3×). The organic phases were pooled, washed with brine, dried using $MgSO_4$ and concentrated in vacuo. FC (FP, toluene/petroleum ether 1:1) yielded the compound as a clear oil (1.77 g, 89%). TLC (toluene/petroleum ether 1:1) R_f 0.4. The NMR data were consistent with the literature data.[10]

6.1.37. 1-Benzyloxy-5-bromo-4-iodopyrazole (10a). Compound **8a** (500 mg, 2 mmol) was dissolved in $CHCl_3$ (6 mL) and K_2CO_3 (312 mg, 2.2 mmol) was added followed by the addition of ICl (385 mg, 2.4 mmol) in $CHCl_3$ (2 mL). The reaction mixture was left stirring overnight at rt. The reaction mixture was quenched with 1 M Na_2SO_3 (aq) followed by extraction with CH_2Cl_2 (3×). The organic phases were combined, washed with brine, dried with $MgSO_4$ and concentrated in vacuo. FC (toluene/petroleum ether 1:1) yielded **10a** (156 mg, 21%). TLC (toluene/petroleum ether 1:1) R_f 0.33. ^{1}H NMR ($CDCl_3$) δ 5.27 (s, CH_2, 2H), 7.35–7.40 (m, phenyl, H-3, 6H). ^{13}C NMR ($CDCl_3$) δ 60.9 (C), 81.4 (CH_2), 113.3 (C), 128.8 (CH), 129.7 (CH), 130.1 (CH), 132.7 (C), 139.1 (CH). Other method: LDA (1.3 mmol) in THF (5 mL) was freshly prepared from *n*-BuLi (2 M, 2.65 mL, 1.3 mmol) and *i*-Pr_2NH (127 mg, 1.3 mmol) in THF (5 mL) at −78 °C under N_2 and left stirring at rt for 30 min. LDA (1.3 mmol) in THF (5 mL) was added to 1-benzyloxy-4-iodopyrazole[13] (300 mg, 1 mmol) in THF (5 mL) over 1 min at −78 °C. The mixture was left stirring at −78 °C for 5 min. CBr_4 (408 mg, 1.2 mmol) in THF (1 mL) was added over 1 min and the mixture was left at −78 °C for 1 h. The reaction mixture was quenched with satd NH_4Cl (aq) at −78 °C, warmed to rt and worked-up according to the procedure described for **7b**, although with Et_2O as organic solvent. FC (FP, cyclohexane/toluene 1:0–18:1) yielded **10a** (107 mg, 28%). TLC (cyclohexane/toluene 1:1) R_f 0.30. The NMR data were consistent with the above-mentioned data.

6.1.38. 1-Benzyloxy-5-ethyl-4-iodopyrazole (10b). Compound **8b** (400 mg, 2 mmol) was dissolved in $CHCl_3$ (6 mL). Addition of K_2CO_3 (400 mg, 2.8 mmol) was followed by the addition of ICl (480 mg, 3 mmol) in $CHCl_3$ (2 mL). The reaction mixture was left stirring overnight at rt. The reaction mixture was quenched with 1 M Na_2SO_3 (aq) followed by extraction with CH_2Cl_2 (3×). The organic phases were combined, washed with brine, dried with $MgSO_4$ and concentrated in vacuo yielding crude **10b** as a clear oil (634 mg). TLC (petroleum ether/EtOAc 9:1) R_f 0.38. ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 8 Hz, CH_3, 3H), 2.36 (q, J = 8 Hz, CH_2, 2H), 5.26 (s, CH_2, 2H), 7.28–7.36 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 12.5 (CH_3), 17.8 (CH_2), 54.8 (C), 80.1 (CH_2), 128.7 (CH), 129.4 (CH), 129.9 (CH), 133.4 (C), 137.4 (CH), 138.6 (C).

6.1.39. 1-Benzyloxy-4-iodo-5-propylpyrazole (10c). The title compound was prepared according to the procedure described for **10b** starting with **8c** (322 mg, 1.5 mmol) and gave crude **10c** (493 mg). TLC (toluene/petroleum ether/EtOAc 4:4:1) R_f 0.45. ^{1}H NMR ($CDCl_3$) δ 0.84 (t, J = 7 Hz, CH_3, 3H), 1.40–1.47 (m, CH_2, 2H), 2.32 (t, J = 8 Hz, CH_2Ar, 2H), 5.25 (s, CH_2, 2H), 7.28–7.36 (m, phenyl, H-3, 6H). ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 21.4 (CH_2), 26.1 (CH_2), 55.6 (C), 79.6 (CH_2), 128.7 (CH), 129.4 (CH), 129.8 (CH), 133.6 (C), 137.5 (CH). C-5 is missing, but must be covered under the signal of 137.5.

6.1.40. 1-Benzyloxy-5-butyl-4-iodopyrazole (10d). The title compound was prepared according to the procedure described for **10b** starting with **8d** (541 mg, 2.4 mmol) and gave crude **10d** (835 mg). TLC (toluene/petroleum ether/EtOAc 4:4:1) R_f 0.47. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 8 Hz, CH_3, 3H), 1.24 (sextet, J = 7 Hz, $CH_2C\underline{H}_2CH_3$, 2H), 1.35 (quintet, J = 8 Hz, $CH_2C\underline{H}_2CH_2$, 2H), 2.33 (t, J = 8 Hz, $ArCH_2$, 2H), 5.25 (s, CH_2, 2H), 7.27–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 22.3 (CH_2), 24.0 (CH_2), 30.0 (CH_2), 55.5 (C), 80.0 (CH_2), 128.7 (CH), 129.4 (CH), 129.9 (CH), 133.6 (C), 137.5 (CH), 137.7 (C). *m/z* (EI) 356 (3%), 339, 297, 212, 91 (100%). HRMS *m/z* found: 379.0305 [M+Na$^+$]. Calcd for $C_{14}H_{17}IN_2O$-Na: 379.0283 [M+Na$^+$].

6.1.41. 1-Benzyloxy-4-iodo-5-pentylpyrazole (10e). The title compound was prepared according to the procedure described for **10b** starting with **8e** (642 mg, 2.6 mmol) and gave crude **10e** (977 mg). TLC (toluene/petroleum ether/EtOAc 4:4:1) R_f 0.5. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7 Hz, CH_3, 3H), 1.20–1.28 (m, 2× CH_2, 4H), 1.38 (quintet, J = 8 Hz, $ArCH_2CH_2CH_2$, 2H), 2.32 (t, J = 8 Hz, $ArCH_2$, 2H), 5.25 (s, CH_2, 2H), 7.24–7.35 (m, phenyl, H-3, 6H). ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 22.2 (CH_2), 24.1 (CH_2), 27.5 (CH_2), 31.2 (CH_2), 55.4 (C), 80.0 (CH_2), 128.7 (CH), 129.4 (CH), 129.8 (CH), 133.5 (C), 137.4 (CH), 137.7 (C). *m/z* (EI) 370 (1%), 353, 297, 226, 91 (100%). HRMS *m/z* found: 371.0609 [M+H$^+$]. Calcd for $C_{15}H_{20}IN_2O$: 371.0620 [M+H$^+$].

6.1.42. 1-Benzyloxy-5-cyclopropylmethyl-4-iodopyrazole (10f). The title compound was prepared according to the procedure described for **10b** starting with **8f** (338 mg, 1.5 mmol) and gave crude **10f** (532 mg). TLC (toluene/petroleum ether/EtOAc 4:4:1) R_f 0.4. ^{1}H NMR ($CDCl_3$) δ 0.19 (q, J = 5 Hz, CH_2, 2H) 0.39–0.42 (m, CH_2, 2H), 0.97–0.93 (m, CH, 1H), 2.28 (d, J = 7 Hz, CH_2CH, 2H), 5.28 (s, CH_2, 2H), 7.25–7.34 (m, phenyl, H-3, 6H). ^{13}C NMR ($CDCl_3$) δ 4.8 (CH_2), 9.8 (CH), 28.7 (CH_2), 55.6 (C), 80.2 (CH_2), 128.8 (CH), 129.4 (CH), 129.8 (CH), 133.5 (C), 137.5 (C), 137.6 (CH).

6.1.43. 1-Benzyloxy-5-cyclohexylmethyl-4-iodopyrazole (10g). The title compound was prepared according to the procedure described for **10b** starting with **8g** (374 mg, 1.4 mmol) and gave crude **10g** (555 mg). TLC (toluene/petroleum ether/EtOAc 4:4:1) R_f 0.5. ^{1}H NMR ($CDCl_3$) δ 0.89–0.96 (m, 2H), 1.09–1.18 (m, 3H), 1.54–1.66 (m, 6H), 2.21 (d, J = 7 Hz, $ArCH_2$, 2H), 5.26 (s, CH_2, 2H), 7.25–7.39 (m, phenyl, H-3, 6H). ^{13}C NMR ($CDCl_3$) δ 26.1 (CH_2), 26.3 (CH_2), 31.7 (CH_2), 33.1 (CH_2), 37.4 (CH), 56.6 (C), 80.1 (CH_2), 128.8 (CH), 129.5 (CH), 129.9 (CH), 133.7 (C), 136.8 (C), 137.6 (CH).

6.1.44. 1-Benzyloxy-4-iodo-5-phenylpyrazole (10h). The title compound was prepared according to the procedure described for **10b** starting with **8h** (373 mg, 1.5 mmol) and gave crude **10h** (543 mg). TLC (toluene/petroleum ether/EtOAc 4:4:1) R_f 0.5. ^{1}H NMR ($CDCl_3$) δ 5.07 (s, CH_2, 2H), 6.97–6.98 (m, 2H), 7.16–7.19 (m, 2H), 7.25–7.28 (m, 1H), 7.35–7.38 (m, 5H), 7.42 (s, H-3, 1H). ^{13}C

NMR ($CDCl_3$) δ 56.2 (C), 80.8 (CH_2), 127.1 (C), 128.3 (CH), 128.5 (CH), 129.1 (CH), 129.3 (CH), 129.8 (CH), 129.9 (CH), 132.9 (C), 136.9 (C), 138.6 (CH). LCMS *m/z* 377 ($M+H^+$); $T_R = 3.66$; purity (UV, ELSD): 90%, 99%.

6.1.45. 5-Benzyl-1-benzyloxy-4-iodopyrazole (10i). The title compound was prepared according to the procedure described for **10b** starting with **8i** (265 mg, 1 mmol) and gave crude **10i** (379 mg). TLC (toluene/petroleum ether/EtOAc 4:4:1) R_f 0.5. ^1H NMR ($CDCl_3$) δ 3.74 (s, CH_2, 2H), 5.02 (s, CH_2, 2H), 7.10–7.34 (m, 11H). ^{13}C NMR ($CDCl_3$) δ 30.1 (CH_2), 56.9 (C), 80.2 (CH_2), 126.8 (CH), 128.4 (CH), 128.7 (CH), 128.7 (CH), 129.4 (CH), 129.8 (CH), 133.3 (C), 136.2 (C), 136.8 (C), 137.6 (CH). *m/z* (EI) 390 (11%), 373, 91 (100%). HRMS *m/z* found: 391.0298 [$M+H^+$]. Calcd for $C_{17}H_{16}IN_2O$: 391.0307 [$M+H^+$].

6.1.46. 1-Benzyloxy-4-iodo-5-phenylethylpyrazole (10j). The title compound was prepared according to the procedure described for **10b** starting with **8j** (209 mg, 0.75 mmol) and gave crude **10j** (293 mg). TLC (toluene/petroleum ether/EtOAc 4:4:1) R_f 0.4. ^1H NMR ($CDCl_3$) δ 2.62–2.69 (m, 2× CH_2, 4H), 5.10 (s, CH_2, 2H), 7.07–7.08 (m, 2H), 7.16–7.36 (m, 9H). ^{13}C NMR ($CDCl_3$) δ 26.5 (CH_2), 33.9 (CH_2), 55.8 (C), 80.1 (CH_2), 126.4 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 129.5 (CH), 129.9 (CH), 133.6 (C), 136.5 (C), 137.6 (CH), 140.5 (C).

6.1.47. 1-Benzyloxy-4-iodo-5-(3-phenyl-propyl)pyrazole (10k). The title compound was prepared according to the procedure described for **10b** starting with **8k** (663 mg, 2.3 mmol) and gave crude **10e** (939 mg). TLC (toluene/petroleum ether/EtOAc 4:4:1) R_f 0.4. ^1H NMR ($CDCl_3$) δ 1.63 (quintet, $J = 8$ Hz, $CH_2CH_2CH_2$, 2H), 2.25 (t, $J = 8$ Hz, CH_2, 2H), 2.44 (t, $J = 8$ Hz, CH_2, 2H), 5.10 (s, CH_2, 2H), 7.05 (d, $J = 7$ Hz, 2H), 7.08–7.09 (m, 3H), 7.14–7.22 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 23.8 (CH_2), 29.2 (CH_2), 35.3 (CH_2), 55.5 (C), 80.1 (CH_2), 126.0 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 129.4 (CH), 129.9 (CH), 133.4 (C), 137.3 (C), 137.5 (CH), 141.3 (C). *m/z* (EI) 418 (2%), 314, 297, 105, 91 (100%). HRMS *m/z* found: 441.0450 [$M+Na^+$]. Calcd for $C_{19}H_{19}IN_2ONa$: 441.0440 [$M+Na^+$].

6.1.48. 5-Benzhydryl-1-benzyloxy-4-iodopyrazole (10l). The title compound was prepared according to the procedure described for **10b** starting with **8l** (628 mg, 1.8 mmol) and gave crude **10l** (832 mg). TLC (toluene/petroleum ether/EtOAc 4:4:1) R_f 0.47. ^1H NMR ($CDCl_3$) δ 4.80 (s, CH_2, 2H), 5.73 (CH), 7.06–7.34 (m, 16H). ^{13}C NMR ($CDCl_3$) δ 47.1 (CH), 56.9 (C), 79.6 (CH_2), 127.1 (CH), 128.6 (CH), 128.7 (CH), 129.2 (CH), 129.4 (CH), 129.7 (CH), 133.3 (C), 137.1 (C), 138.6 (CH), 139.3 (C).

6.1.49. 2-(*N*-*tert*-Butoxycarbonylimino)acetic acid methyl ester (11). The title compound was prepared according to Nakamura et al.[17] with modifications. Morpholinomethyl-polystyrene (1.25 g, 3.6 mmol/g, 4.5 mmol) was placed in a 20 mL syringe with filter and washed with CH_2Cl_2 (2×) and THF (2×). The resin was dried under vacuum at rt. A freshly prepared solution of 2-bromo-2-(*N*-*tert*-butoxycarbonylamino)acetic acid methyl ester[31] (800 mg, 3.0 mmol) in THF (10 mL) under argon was sucked into the syringe containing M-PS. The slurry was shaken for 30 min at rt. The solution was pressed out in a dry flask flushed with argon. The syringe was washed with dry THF (2 mL) leading to a total volume of 12.5 mL.

The concentration of the solution was determined by taking out 1 mL of the solution and adding this to a dry flask containing MeOH (1 mL). Concentration of the mixture gave the α-methoxy compound, 2-(*N*-*tert*-butoxycarbonylamino)-2-methoxyacetic acid methyl ester (37 mg), leading to a calculated concentration of the solution (0.17 M, overall yield 71%). The yields of subsequent reactions were in the range of 69–79%.

6.1.50. (*RS*)-2-(1-Benzyloxy-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid methyl ester (12). 1-Benzyloxy-4-iodo-pyrazole (**9**) (582 mg, 1.94 mmol) was dissolved in THF and cooled to 0 °C. *i*-PrMgCl (1.2 mL, 2.4 mmol, 1.24, 2 M) was added over 1 min. The mixture was left stirring for 30 min at 0 °C and then cooled to −78 °C. The imine **11** (11.5 mL, 0.17 M, 1.96 mmol) in THF was added slowly. The mixture turned from turbid to clear yellow. The mixture was slowly warmed from −78 °C to rt over several hours. Satd NH_4Cl (aq) was added followed by extraction using EtOAc (3×). The pooled organic phases were washed with brine and dried using $MgSO_4$. FC (F, petroleum ether/EtOAc) gave **12** (291 mg, 42%). TLC (petroleum ether/EtOAc 3:1) R_f 0.25. ^1H NMR ($CDCl_3$) δ 1.43 (s, *t*-bu, 9H), 3.69 (s, CH_3, 3H), 5.22–5.24 (m, CH_2, α-CH, 3H), 5.45 (br d, $J = 8$ Hz, NH, 1H), 7.03 (s, H-5 or H-3, 1H), 7.26–7.36 (m, H-3 or H-5, phenyl, 6H). ^{13}C NMR ($CDCl_3$) δ 25.4 (CH_3), 49.6 (CH), 52.8 (CH_3), 80.4 (C), 80.8 (CH_2), 115.1 (C), 121.7 (CH), 128.8 (CH), 129.4 (CH), 129.8 (CH), 131.8 (CH), 133.6 (C), 155.0 (C), 171.3 (C).

6.1.51. (*RS*)-2-(1-Benzyloxy-5-bromo-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid methyl ester (13a). The title compound was prepared according to the procedure described for **12** starting with **10a** (242 mg, 0.64 mmol). FC (F, petroleum ether/EtOAc) and recrystallization (petroleum ether/EtOAc) gave white crystalline **13a** (92 mg, 33%, recovered 42 mg of a mixture of **8a** and **10a**). Mp 137.5–137.5 °C. TLC (petroleum ether/EtOAc 2:1) R_f 0.4. ^1H NMR ($CDCl_3$) δ 1.44 (s, *t*-bu, 9H), 3.73 (s, CH_3, 3H), 5.22–5.39 (m, α-CH, CH_2, NH, 4H), 7.34 (s, H-3, 1H), 7.37–7.40 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 28.4 (C), 49.5 (CH), 52.9 (CH_3), 80.5 (C), 81.3 (CH_2), 107.2 (C), 115.5 (C), 128.7 (CH), 129.7 (CH), 130.1 (CH), 132.8 (C.), 132.9 (CH), 154.8 (C), 170.6 (C).

6.1.52. (*RS*)-2-(1-Benzyloxy-5-ethyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid methyl ester (13b). The title compound was prepared according to the procedure described for **12** starting with **10b** (194 mg, 0.59 mmol). FC (F, petroleum ether/EtOAc) gave **13b**

(147 mg, 64%, recovered 24 mg of **8b**). TLC (petroleum ether/EtOAc 2:1) R_f 0.19. ^{1}H NMR ($CDCl_3$) δ 1.04 (t, J = 8 Hz, CH_3, 3H), 1.44 (s, *t*-bu, 9H), 2.42 (q, J = 7 Hz, CH_2, 2H), 3.72 (s, CH_3, 3H), 5.15–5.30 (m, α-CH, NH, CH_2, 4H), 7.18 (br s, H-3), 7.28–7.38 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 13.2 (CH_3), 16.4 (CH_2), 28.4 (CH_3), 49.2 (CH), 52.7 (CH_3), 80.1 (CH_2), 80.3 (C), 111.7 (C), 128.7 (CH), 129.4 (CH), 129.9 (CH), 130.8 (CH), 133.7 (C), 136.6 (C), 154.9 (C), 171.6 (C).

6.1.53. (*RS*)-2-(1-Benzyloxy-5-propyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid methyl ester (13c). The title compound was prepared according to the procedure described for **12** starting with **10c** (493 mg, 1.44 mmol). FC (F, petroleum ether/EtOAc) gave **13c** (258 mg, 44%, recovered 153 mg of **8c**). TLC (petroleum ether/EtOAc 2:1) R_f 0.4. ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 8 Hz, CH_3, 3H), 1.43–1.47 (m and br s, *t*-bu and CH_2, 11H), 2.36 (t, J = 7 Hz, CH_2, 2H), 3.71 (s, CH_3, 3H), 5.14–5.32 (m, α-CH, NH, CH_2, 4H), 7.19 (br s, H-3, 1H), 7.28–7.37 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 13.8 (CH_3), 21.9 (CH_2), 24.7 (CH_2), 28.3 (CH_3), 49.2 (CH), 52.5 (CH_3), 79.9 (CH_2), 80.1 (C), 112.0 (C), 128.7 (CH), 129.3 (CH), 129.8 (CH), 130.8 (CH), 133.7 (C), 135.2 (C), 154.9 (C), 171.6 (C).

6.1.54. (*RS*)-2-(1-Benzyloxy-5-butyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid methyl ester (13d). The title compound was prepared according to the procedure described for **12** starting with **10d** (358 mg, 1.01 mmol). FC (F, petroleum ether/EtOAc) gave **13c** (201 mg, 48%, recovered 114 mg of **8d**). TLC (petroleum ether/EtOAc 2:1) R_f 0.4. ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 9 Hz, CH_3, 3H), 1.25–1.29 (m, CH_2, 2H), 1.38–1.43 (m, CH_2, 2H), 1.43 (s, *t*-bu, 9H), 2.34–3.38 (m, CH_2, 2H), 3.71 (s, CH_3, 3H), 5.14–5.32 (m, α-CH, NH, CH_2, 4H), 7.19 (br s, H-3, 1H), 7.28–7.37 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 22.4 (CH_2), 28.3, 28.3, 30.6, 49.2 (CH), 52.5 (CH_3), 79.9 (CH_2), 79.9 (C), 111.8 (C), 128.6 (CH), 129.3 (CH), 129.8 (CH), 130.8 (CH), 133.7 (C), 135.4 (C), 154.8 (C), 171.6 (C).

6.1.55. (*RS*)-2-(1-Benzyloxy-5-pentyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid methyl ester (13e). The title compound was prepared according to the procedure described for **12** starting with **10e** (301 mg, 0.81 mmol). FC (F, petroleum ether/EtOAc) gave **13c** (163 mg, 46%, recovered 106 mg of **8e**). TLC (petroleum ether/EtOAc 2:1) R_f 0.27. ^{1}H NMR ($CDCl_3$) δ 0.85 (t, J = 7 Hz, CH_3, 3H), 1.21–1.28 (m, 2× CH_2, 4H), 1.43 (br s, *t*-bu and CH_2, 11H), 2.36 (t, J = 8 Hz, $ArCH_2$, 2H), 3.69 (s, CH_3, 3H), 5.16 (br d, J = 7 Hz, NH or α-CH), 5.25 (s, CH_2, 2H), 5.48 (br d, J = 7 Hz, NH or α-CH), 7.19–7.35 (m, phenyl and H-3, 6H). ^{13}C NMR ($CDCl_3$) δ 13.7 (CH_3), 22.1 (CH_2), 22.6 (CH_2), 28.0 (CH_2 or CH_3), 28.1 (CH_2 or CH_3), 31.3 (CH_2), 49.0 (CH), 52.3 (CH_3), 79.7 (CH_2), 79.7 (C), 111.7 (C), 128.5 (CH), 129.1 (CH), 129.6 (CH), 130.7 (C), 133.5 (CH), 135.2 (C), 154.7 (C), 171.4 (C).

6.1.56. (*RS*)-2-(1-Benzyloxy-5-cyclopropylmethyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid methyl ester (13f). The title compound was prepared according to the procedure described for **12** starting with **10f** (508 mg, 1.43 mmol). FC (F, petroleum ether/EtOAc) gave **13f** (289 mg, 48%, recovered 151 mg of **8f**). TLC (petroleum ether/EtOAc 2:1) R_f 0.37. ^{1}H NMR ($CDCl_3$) δ 0.17 (br t, J = 6 Hz, CH_2, 2H), 0.43 (br d, J = 9 Hz, CH_2, 2H), 0.87–0.89 (m, CH, 1H), 1.43 (s, *t*-bu, 9H), 2.31 (br d, J = 8 Hz, CH_2, 2H), 3.71 (s, CH_3, 3H), 5.18–5.42 (m, CH_2, α-CH and NH, 4H), 7.21 (s, H-3, 1H), 7.27–7.32 (m, phenyl, 5H). ^{13}C NMR ($CDCl_3$) δ 4.8 (CH_2), 9.7 (CH), 27.3 (CH_2), 28.2 (CH_3), 49.1 (CH), 52.4 (CH_3), 79.9 (CH_2 and C), 111.9 (C), 128.5 (CH), 129.2 (CH), 129.6 (CH), 130.8 (CH), 133.5 (C), 134.7 (C), 154.8 (C), 171.5 (C).

6.1.57. (*RS*)-2-(1-Benzyloxy-5-cyclohexylmethyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid methyl ester (13g). The title compound was prepared according to the procedure described for **12** starting with **10g** (562 mg, 1.42 mmol). FC (F, petroleum ether/EtOAc) gave **13g** (333 mg, 51%, recovered 173 mg of **8g**). TLC (petroleum ether/EtOAc 2:1) R_f 0.39. ^{1}H NMR ($CDCl_3$) δ 0.83–0.91 (m, 2H), 1.09–1.15 (m, 3H), 1.43 (s, *t*-bu, 9H), 1.50–1.63 (m, 6H), 2.24 (d, J = 7 Hz, CH_2, 2H), 3.70 (s, CH_3, 3H), 5.13–5.39 (m, α-CH, NH, CH_2, 4H), 7.20 (s, H-3, 1H), 7.27–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 26.0 (CH_2), 26.1 (CH_2), 28.2 (CH_3), 30.1 (CH_2), 32.7 (CH_2), 32.9 (CH_2), 37.2 (CH), 49.0 (CH), 52.3 (CH_3), 79.7 (CH_2), 79.8 (C), 112.3 (C), 128.5 (CH), 129.2 (CH), 129.6 (CH), 130.6 (CH), 133.6 (C), 134.1 (C), 154.7 (C), 171.5 (C).

6.1.58. (*RS*)-2-(1-Benzyloxy-5-phenyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid methyl ester (13h). The title compound was prepared according to the procedure described for **12** starting with **10h** (266 mg, 0.71 mmol). FC (F, petroleum ether/EtOAc) gave **13h** (229 mg, 74%, recovered 45 mg of **8h**). TLC (petroleum ether/EtOAc 2:1) R_f 0.22. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, *t*-bu, 9H), 3.66 (s, CH_3, 3H), 5.07–5.27 (m, α-CH, NH, CH_2, 4H), 6.97 (d, J = 7 Hz, 2H), 7.17 (t, J = 8Hz, 2H), 7.25–7.40 (m, 7H). ^{13}C NMR ($CDCl_3$) δ 28.3 (CH_3), 49.3 (CH), 52.6 (CH_3), 80.2 (C), 80.6 (CH_2), 112.9 (C), 126.7, 128.4, 128.5, 129.0, 129.2, 129.7, 129.9, 131.4 (CH), 133.0, 135.2, 154.8 (C), 171.6 (C).

6.1.59. (*RS*)-2-(5-Benzyl-1-benzyloxy-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid methyl ester (13i). The title compound was prepared according to the procedure described for **12** starting with **10i** (379 mg, 0.97 mmol). FC (F, petroleum ether/EtOAc) gave **13i** (264 mg, 60%, recovered 64 mg of **8i**). TLC (petroleum ether/EtOAc 2:1) R_f 0.21. ^{1}H NMR ($CDCl_3$) δ 1.41 (s, *t*-bu, 9H), 3.63 (s, CH_3, 3H), 3.80 (s, CH_2, 2H), 5.02-5.22 (m, α-CH, NH, CH_2, 4H), 7.07–7.36 (m, 11H). ^{13}C NMR ($CDCl_3$) δ 28.3 (CH_3), 28.7 (CH_2), 49.3 (CH), 52.6 (CH_3), 80.1 (CH_2), 80.2 (C), 112.8 (C), 126.8 (CH), 128.4 (CH), 128.7 (CH), 129.4 (CH), 129.9 (CH), 131.3 (CH), 133.4 (C), 133.5 (C), 137.3 (C), 154.8 (C), 171.4 (C).

6.1.60. (*RS*)-2-(1-Benzyloxy-5-phenylethyl-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid methyl ester (13j). The title compound was prepared according to the

procedure described for **12** starting with **10j** (274 mg, 0.68 mmol). FC (F, petroleum ether/EtOAc) gave **13j** (155 mg, 49%, recovered 89 mg of **8j**). TLC (petroleum ether/EtOAc 2:1) R_f 0.3. ^{1}H NMR ($CDCl_3$) δ 1.43 (s, *t*-bu, 9H), 2.67–2.73 (m, 2× CH_2, 4H), 3.71 (s, CH_3, 3H), 5.09–5.18 (m, α-CH, NH, CH_2, 4H), 7.07–7.36 (m, 11H). ^{13}C NMR ($CDCl_3$) δ 25.2 (CH_2), 28.4 (CH_3), 34.5 (CH_2), 49.3 (CH), 52.6 (CH_3), 80.0 (CH_2), 80.2 (C), 112.2 (C), 126.4 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 129.4 (CH), 129.8 (CH), 131.1 (CH), 133.7 (C), 134.4 (C), 140.6 (C), 154.9 (C), 171.5 (C).

6.1.61. (*RS*)-[1-Benzyloxy-5-(3-phenylpropyl)-4-pyrazolyl]-*tert*-butoxycarbonylamino)acetic acid methyl ester (13k). The title compound was prepared according to the procedure described for **12** starting with **10k** (447 mg, 1.07 mmol). FC (F, petroleum ether/EtOAc) gave **13k** (219 mg, 43%, recovered 150 mg of **8k**). TLC (petroleum ether/EtOAc 2:1) R_f 0.34. ^{1}H NMR ($CDCl_3$) δ 1.43 (s, *t*-bu, 9H), 1.77 (br quintet, $J = 8$ Hz, $CH_2CH_2CH_2$, 2H), 2.38 (br t, $J = 7$ Hz, CH_2, 2H), 2.44 (t, $J = 8$ Hz, CH_2, 2H), 3.69 (s, CH_3, 3H), 5.13–5.29 (m, α-CH, NH and CH_2, 4H), 7.12–7.26 (m, 11H). ^{13}C NMR ($CDCl_3$) δ 22.4 (CH_2), 28.3 (CH_3), 29.9 (CH_2), 35.5 (CH_2), 49.2 (CH), 52.6 (CH_3), 80.0 (CH_2), 80.2 (C), 112.1 (C), 126.0 (CH), 128.4 (CH, 128.3989), 128.4 (CH, 128.4496), 128.7 (CH), 129.3 (CH), 129.8 (CH), 130.9 (CH), 133.5 (C), 135.0 (C), 141.4 (C), 154.9 (C), 171.5 (C).

6.1.62. (*RS*)-2-(5-Benzhydryl-1-benzyloxy-4-pyrazolyl)-2-(*N*-*tert*-butoxycarbonylamino)acetic acid methyl ester (13l). The title compound was prepared according to the procedure described for **12** starting with **13l** (470 mg, 1.01 mmol). FC (F, petroleum ether/EtOAc) gave **13l** (246 mg, 46%). TLC (petroleum ether/EtOAc 2:1) R_f 0.26. ^{1}H NMR ($CDCl_3$) δ 1.38 (s, *t*-bu, 9H), 3.59 (s, CH_3, 3H), 4.71–4.92 (m, NH, CH_2, α-CH, 4H), 5.80 (s, $CHPh_2$, 1H), 7.04–7.28 (m, 16H). ^{13}C NMR ($CDCl_3$) δ 28.3 (CH_3), 46.3 (CH), 49.0 (CH), 52.4 (CH_3), 79.5 (CH_2), 80.0 (C), 112.9 (C), 127.2 (CH), 128.6 (CH), 128.7 (CH), 129.0 (CH), 129.1 (CH), 129.3 (CH), 129.7 (CH), 131.7 (CH), 133.4 (C), 135.6 (C), 139.4 (C), 139.7 (C), 154.5 (C), 171.6 (C).

6.2. Pharmacology

6.2.1. iGluR receptor binding. Rat brain membrane preparations used in the receptor binding experiments for iGluRs were prepared according to the method described by Ransom and Stec.[32] Affinities for native AMPA, KA and NMDA receptors were determined using 5 nM [^{3}H]AMPA[33], 5 nM [^{3}H]KA[34] and 2 nM [^{3}H]CGP39653[35], respectively, with some modifications.[24]

6.2.2. mGluR activity. Chinese hamster ovary (CHO) cell lines stably expressing rat mGluR1a, mGluR2 and mGluR4a were prepared as previously described.[9,36–38] Measurement of intracellular Ca^{2+} levels and cyclic AMP formation: pharmacological activity at mGluR1a was assessed by measurement of intracellular Ca^{2+} levels as previously described.[39] Pharmacological activity at mGluR2 and mGluR4a was assessed by measuring intracellular cAMP levels as previously described.[9,40]

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