Novel σ_1 Receptor Ligands by Oxa-Pictet–Spengler Reaction of Pyrazolylethanol

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Abstract: The oxa-Pictet–Spengler reaction of 2-(1-phenylpyrazol-5-yl)ethanol required the weak acid pyridinium *p*-toluenesulfonate to provide pyrano[4,3-*c*]pyrazoles with additional functional groups in the side chain. These functional groups allow the introduction of various amino substituents into the side chain in position 4. In receptor binding studies the aminoethyl-substituted pyranopyrazoles revealed higher σ_1 receptor affinities and σ_1/σ_2 selectivities than the shorter aminomethyl homologues. The pyranopyrazole bearing the phenylpiperidine substituent (K_i = 0.99 nM) represents the most potent and that bearing the piperidine substituent the most selective (σ_1/σ_2 = 180) σ_1 ligands of this series of compounds.

Keywords: σ_1 receptor ligands, oxa-Pictet–Spengler reaction, annulated pyrazoles, pyrazolylethanol, structure affinity relationships

Introduction

The unique class of σ receptors is subdivided into σ_1 and σ_2 receptors. The σ_1 receptor is expressed in the periphery and in the central nervous system (CNS). In particular, high amounts are found in regions involved in memory, emotion, as well as sensoric and motor functions.[1,2] Due to their involvement in different neurological processes, σ_1 receptors represent an attractive target for the development of novel drugs for CNS diseases, including depression, schizophrenia, anxiety, cocaine addiction, neuropathic pain, as well as some neurodegenerative disorders (e.g., Alzheimer's disease, Parkinson's disease).[3–6] Despite the fact that the σ_2 receptor is less well characterized than the σ_1 subtype, it represents a promising target for the tumor therapy.[7]

Development of Novel σ_1 Receptor Ligands with Pyranopyrazole Substructure

Indazole derivatives of type 1 (Figure 1) were described as potent and selective σ_1 receptor antagonists with high analgesic activity in the capsaicin model of neuropathic pain. For example, 4-phenylpiperidine derivative **1a** (NR_2 = 4-phenylpiperidin-1-yl, Y = Me) shows high σ_1 receptor affinity and selectivity [K_i (σ_1) = 7.0 nM, K_i (σ_2) = 39.7 nM] combined with analgesic activity in the late phase of the capsaicin assay (neuropathic pain model).[8–11] The pyranopyrazole derivatives **2** were also shown to represent very potent and selective σ_1 receptor ligands [e.g., **2a**: R = Bn, K_i (σ_1) = 1.7 nM, K_i (σ_2) = 773 nM].[12] The structural combination of the potent σ_1 receptor ligands **1** and **2** led to the aminoalkyl-substituted pyranopyrazoles **3** and **4**, which are the topic of this article.

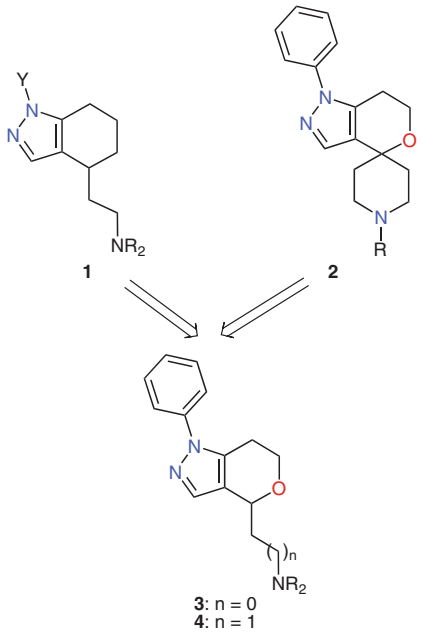

Figure 1

The bicyclic framework of **3** and **4** should be established by an oxa-Pictet–Spengler reaction of a pyrazolylethanol derivative. Late stage diversification should be achieved by introduction of various amino substituents at the very end of the synthesis.

The synthesis of tetrahydroisoquinolines by condensation of 2-phenylethylamines with carbonyl compounds (aldehydes, ketones) is termed the Pictet–Spengler reaction. Isochromanes as structural analogues of tetrahydroisoquinolines are prepared by the same strategy employing 2-phenylethanol derivatives instead of 2-phenylethylamines. This oxygen version of the Pictet–Spengler reaction was termed the 'oxa-Pictet–Spengler reaction' for the first time in 1992.[13] Several examples of inter- and intramolecular oxa-Pictet–Spengler reactions have been reported including the synthesis of optically active isochromanes. Moreover, electron-rich heteroarylethanol

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derivatives (e.g., thiophene, indole, furan, pyrrole derivatives) were extensively employed to produce annulated pyran derivatives by the oxa-Pictet–Spengler reaction.[14–17] However, only a few examples using pyrazole as an electron-rich, nucleophilic aromatic system have been reported in the literature.[15,18]

Synthesis

The synthesis of the pyranopyrazole framework started with pyrazolylethanol **6**, which was prepared by treatment of lithiated pyrazole **5** with ethylene sulfate and subsequent hydrolysis of the sulfuric acid monoester.[18] At first the oxa-Pictet–Spengler reaction of **6** and bromoacetaldehyde dimethyl acetal was performed with the Lewis acid boron trifluoride–diethyl ether complex (2 equiv) at 0 °C (Scheme 1). After a reaction time of seven hours the mixed acetal **7** was isolated in 77% yield. Heating the reaction mixture to reflux provided the pyranopyrazole **8** in 6% yield. Similar results were obtained with catalytic amounts of boron trifluoride–diethyl ether complex or *p*-toluenesulfonic acid. We assume that protonation of the pyrazole ring leads to the reduced electron density in the *N*-heterocycle inhibiting the intramolecular electrophilic substitution. Therefore the weaker acid catalyst pyridinium *p*-toluenesulfonate (PPTS) was employed for the oxa-Pictet–Spengler reaction. Heating pyrazolylethanol **6** and bromoacetaldehyde dimethyl acetal with five equivalents of pyridinium *p*-toluenesulfonate in acetonitrile led to the pyranopyrazole **8** in 34% yield. Variation of the reaction time, reaction temperature, and stoichiometry of the components did not improve the yield of **8**, presumably due to decomposition of bromoacetaldehyde dimethyl acetal and/or the bromomethyl derivative **8**.

S_N2 Substitution of bromomethyl derivative **8** with various secondary amines afforded the aminomethyl-substituted pyranopyrazoles **3a**–**g**. Since tertiary amines usually give higher σ_1 receptor affinities than secondary amines, tertiary amines were synthesized preferably. In particular, amino groups were selected that showed promising σ_1 receptor affinities in other types of ligands (e.g., the 4-phenylpiperidin-1-yl group in **1a**).

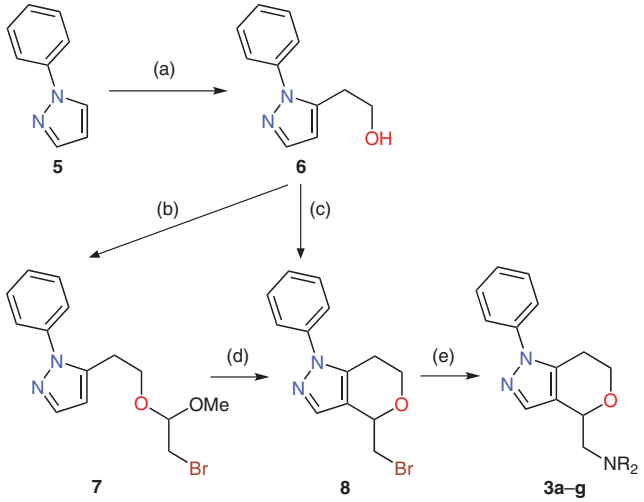
The homologous aminoethyl derivatives **4**, which are very similar to the lead compounds **1** and **2**, should be prepared

Biographical Sketches

Torsten Schläger studied pharmacy at the Albert-Ludwigs-Universität of Freiburg (Germany) and received Approbation as a Pharmacist in 2004. Then he moved to the Westfälische Wilhems-Universität of Münster (Germany). In 2008 he obtained his Ph.D. in the field of pharmaceutical and medicinal chemistry under the supervision of Prof. Wünsch. Currently he is working at Beiersdorf AG in Hamburg (Germany).

After studying Pharmacy at the Westfälische Wilhelms-Universität in Münster (Germany), **Dirk Schepmann** received Approbation as a Pharmacist in 1999. He did his Ph.D. in pharmaceutical and medicinal chemistry at the University of Münster (Germany) with Prof. Dr. Dr. h.c. Gottfried Blaschke in 2003. Then he joined the group of Prof. Dr. Bernhard Wünsch where he is now working as lecturer. His main areas of research are the pharmacological testing of new promising drug candidates, the development of receptor binding assays, and the study of structure-affinity relationships at various receptors in the central nervous system, including σ, NMDA, and opioid receptors.

Bernhard Wünsch studied pharmacy at the Ludwig-Maximilians-Universität of Munich (Germany) and obtained Approbation as a Pharmacist in 1984. His Ph.D. was carried out in pharmaceutical and medicinal chemistry under the supervision of Prof. Dr. Dr. h.c. Fritz Eiden in Munich. After receiving Habilitation in Pharmaceutical Chemistry in 1993, he was appointed to a C3-professor for Pharmaceutical Chemistry at Albert-Ludwigs-Universität Freiburg, and in 2002 to a C4-professor at Westfälische Wilhelms-Universität Münster (Germany). His main research interest lies in the development of novel ligands for various receptors in the central nervous system, namely for σ receptors, opioid receptors, and different binding sites at NMDA receptors. A particular feature of his research is the relationship between the three-dimensional structure of ligands (stereochemistry) and their interaction with receptor proteins.



Compd	NR_2	Yield (%)
3a	pyrrolidin-1-yl	48
3b	piperidin-1-yl	58
3c	4-phenylpiperidin-1-yl	41
3d	morpholin-4-yl	58
3e	4-methylpiperazin-1-yl	40
3f	4-phenylpiperazin-1-yl	67
3g	dimethylamino	22

Scheme 1 *Reagents and conditions*: (a) 1. *n*-BuLi, THF, –78 °C, 1.5 h, 2. ethylene sulfate, THF, –78 °C, 1 h, then r.t., 2 h, 3. H_2SO_4, H_2O, 100 °C, 16 h, 38%; (b) $BrCH_2CH(OMe)_2$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, –50 °C, then 0 °C, 7 h, 77%; (c) $BrCH_2CH(OMe)_2$, PPTS, MeCN, reflux, 74 h, 34%; (d) $BF_3{\cdot}OEt_2$, CH_2Cl_2, reflux 24 h, 6%; (e) HNR_2, MeCN, K_2CO_3, reflux, 25–47 h, 41–67%; **3g**: 6 d reflux, 22%.

according to the same strategy. However, all attempts to synthesize the chloroethyl homologue of **8** by an oxa-Pictet–Spengler reaction of pyrazolylethanol **6** with 3-chloropropanal diethyl acetal failed to give the desired product; alkylation of the pyrazole N-atom by the alkyl halide could be the reason for this failure. In order to avoid pyrazole alkylation, acrolein dimethyl acetal was employed instead of the 3-chloropropanal acetal. However, heating **6** with acrolein dimethyl acetal in acetonitrile with pyridinium *p*-toluenesulfonate did not lead to the desired pyran derivative.

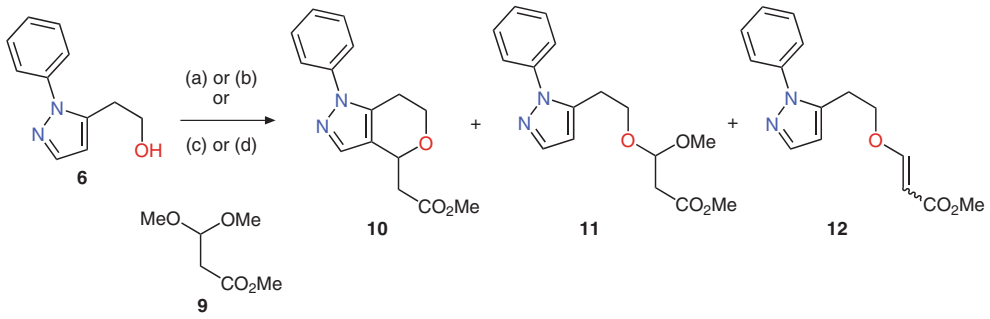
Next, the propionic acid ester **9** was used as a C_3 building block for the oxa-Pictet–Spengler reaction with **6** (Scheme 2). Heating a solution of **6** and pyridinium *p*-toluenesulfonate in acetonitrile to reflux provided a 1:1 mixture of the desired pyranopyrazole **10** and the elimination product **12** in a total yield of 35%. Heating the same compounds in a less polar solvent mixture (toluene–CH_2Cl_2, 1:1) gave exclusively the elimination product **12** (49% yield). Irradiation of an acetonitrile solution with microwaves (140 °C) produced a 3:1 mixture of **10** and **12** in 58% yield. As shown for the reaction of **6** with bromoacetaldehyde acetal (Scheme 1), the transformation of **6** with **9** stopped at the mixed acetal **11** when using boron trifluoride–diethyl ether complex.

In order to reduce the amount of side products and to increase the yield of the oxa-Pictet–Spengler product, 3-(benzyloxy)propanal (**14**)[19] was used as the C_3 building block (Scheme 3). Aldehyde **14** was obtained by oxidation of 3-(benzyloxy)propanol (**13**) with Dess–Martin periodinane (DMP).[20] The oxa-Pictet–Spengler reaction of the aldehyde **14** with pyrazolylethanol **6** provided only low yields (28%) of the pyranopyrazole **16**, which was accompanied by benzyl alcohol resulting from β-elimination from **14**. After conversion of aldehyde **14** into the dimethyl acetal **15**, the β-elimination of benzyl alcohol was considerably reduced leading to an increased yield (43%) of the desired pyranopyrazole **16**.

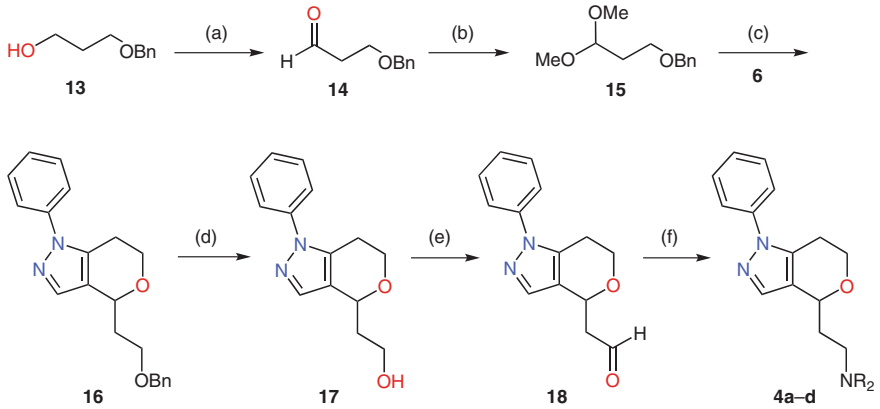
Hydrogenolytic removal of the *O*-benzyl protective group of **16** and subsequent oxidation of primary alcohol **17** with Dess–Martin periodinane[20] led to the aldehyde **18**, which allowed the introduction of various amino moieties upon reductive amination with sodium triacetoxyborohydride.[21] In particular, amino moieties were selected which displayed promising σ_1 affinities in the series of aminomethyl derivatives **3**.

Receptor Affinity

The results of the σ_1 and σ_2 receptor affinities of aminoalkyl-substituted pyranopyrazoles compared with those of lead compounds and reference compounds are given in Table 1. The potent and σ_1 selective radioligand [^{3}H]-(+)-pentazocine and membrane preparations from guinea pig brain were used in the σ_1 assay. Constant amounts of the receptor preparation and the radioligand were incubated in competition experiments with increasing concentrations of the test compounds. The nonspecific binding was



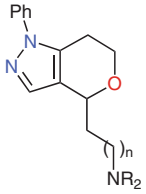
Scheme 2 *Reagents and conditions*: (a) method A: $(MeO)_2CHCH_2CO_2Me$, PPTS, MeCN, reflux, 45 h, **10** and **12** (35%, ratio **10/12**, 1:1); (b) method B: $(MeO)_2CHCH_2CO_2Me$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, reflux, 122 h, **11** (33%); (c) method C: $(MeO)_2CHCH_2CO_2Me$, PPTS, toluene–CH_2Cl_2 (1:1), reflux, 120 h, **12** (49%); (d) method D: $(MeO)_2CHCH_2CO_2Me$, PPTS, MeCN, microwave irradiation, **10** and **12** (58%, ratio **10/12**, 3:1).



Compd	NR_2	Yield (%)
4a	piperidin-1-yl	57
4b	4-phenylpiperidin-1-yl	75
4c	4-phenylpiperazin-1-yl	80
4d	dimethylamino	71

Scheme 3 *Reagents and conditions*: (a) DMP, CH_2Cl_2, 15 °C, 3 h, 81%; (b) MeOH, $HC(OMe)_3$, PTSA, r.t., 1 h, 98%; (c) **6**, PPTS, MeCN, reflux, 23 h, 43%; (d) H_2, balloon, Pd/C, MeOH, r.t., 7 h, 89%; (e) DMP, CH_2Cl_2, 15 °C, 1.5 h, 95%; (f) HNR_2, $NaBH(OAc)_3$, DCE, r.t., 15–17 h, 57–80%.

Table 1 σ_1 and σ_2 Receptor Affinities of Aminoalkyl-Substituted Pyranopyrazoles Compared with those of Lead Compounds and Reference Compounds



Compd	NR_2	n	σ_1 $K_i \pm$ SEM (nM)	σ_2 $K_i \pm$ SEM (nM)	Selectivity σ_1/σ_2
1a[8]	–[a]		7.0	39.7	5.7
2a[12]	–[a]		1.71 ± 0.08	773	452
3a	pyrrolidin-1-yl	0	59 ± 11	322	5.5
3b	piperidin-1-yl	0	10 ± 1.2	453	45
3c	4-phenylpiperidin-1-yl	0	1.6 ± 0.41	8.3 ± 2.7	5
3d	morpholin-4-yl	0	169 ± 40	>1 μM	>6
3e	4-methylpiperazin-1-yl	0	219 ± 7.2	>1 μM	>24
3f	4-phenylpiperazin-1-yl	0	42 ± 3.3	210 ± 54	5
3g	NMe_2	0	>1 μM	>1 μM	–
4a	piperidin-1-yl	1	3.0 ± 0.72	536	180
4b	4-phenylpiperidin-1-yl	1	0.99 ± 0.07	15 ± 3.0	15
4c	4-phenylpiperazin-1-yl	1	2.9 ± 0.43	431	149
4d	NMe_2	1	24 ± 2.0	IC_{50} > 1 μM	>42
(+)-pentazocine			4.2 ± 1.1	–	–
haloperidol			3.9 ± 1.5	78 ± 2.3	20
di-*o*-tolylguanidine			61 ± 18	42 ± 15	0.7
progesterone			660 ± 115	–	–

[a] Compound **1a**: NR_2 = 4-phenylpiperidin-1-yl, Y = Me; compound **2a**: R = Bn (Figure 1).

determined in the presence of a large excess of non-tritiated (+)-pentazocine.[22–24] In the σ_2 assay rat liver membrane preparations were used as receptor material and [^{3}H]-di-*o*-tolylguanidine served as radioligand. Since di-*o*-tolylguanidine also interacts with σ_1 receptors, (+)-pentazocine was added to mask σ_1 receptors in the competition experiments.[22–24]

Whereas the aminomethyl derivative **3g** with a small dimethylamino group did not show significant interaction with σ_1 receptors, the corresponding pyrrolidine **3a** and piperidine **3b** represent moderate σ_1 receptor ligands. The highest σ_1 affinity was observed for amines with an additional phenyl substituent, as demonstrated for the phenylpiperidine derivative **3c** (K_i = 1.6 nM). The same trend was observed for the homologous aminoethyl derivatives **4**. However, the σ_1 affinity of all aminoethyl derivatives **4** (n = 1) is always higher than the σ_1 affinity of the corresponding aminomethyl derivatives **3** (n = 0). It should be noted that even the dimethylamine derivative **4d** reveals very high σ_1 receptor affinity. The most potent σ_1 ligand of this series is the phenylpiperidine derivative **4b** with a K_i value of 0.99 nM. Thus, **4b** is among the most potent σ_1 ligands known.

The pyranopyrazole derivatives show lower σ_2 than σ_1 affinities. Generally, the σ_1/σ_2 selectivities of the aminoethyl derivatives **4** are higher than the σ_1/σ_2 selectivities of the corresponding aminomethyl derivatives **3**, which is due to the higher σ_1 affinities of **4**. [compare σ_1/σ_2 selectivity of **3b** (45-fold) and **4a** (180-fold)]. A rather low σ_1/σ_2 selectivity was found for the phenylpiperidines **3c** (5-fold) and **4b** (15-fold) interacting not only with the σ_1 receptor, but also with the σ_2 receptor protein.

The aminoalkyl-substituted derivatives **3** and **4** reveal lower σ_1 receptor affinities compared with the parent spirocyclic pyranopyrazoles **2**. It can be concluded that a distance of two methylene moieties as found for compounds **1**, **2**, and **4** between the basic amino group and the pyranopyrazole ring system is optimal for high σ_1 binding, whereas only one methylene moiety as in compounds **3** is less favorable for interacting with σ_1 receptors. A conformational restriction of the aminoethyl side chain in a spirocyclic system (e.g., **2**) further increases σ_1 affinity.

Conclusion

The oxa-Pictet–Spengler reaction of pyrazolylethanol **6** using strong acids (e.g., $BF_3{\cdot}OEt_2$, PTSA) did not provide pyranopyrazoles due to protonation and deactivation of the pyrazole system. With the weak acidic catalyst pyridinium *p*-toluenesulfonate, pyranopyrazoles **8** and **16** were formed, which bear additional substituents in their side chain allowing further derivatization. Introduction of amino substituents in the side chain led to potent and selective σ_1 ligands. Generally, the aminoethyl derivatives **4** with the same amine–pyranopyrazole distance as in the spirocyclic lead compounds **2**, are more potent than the shorter aminomethyl homologues **3**.

Unless otherwise stated, moisture sensitive reactions were conducted under dry N_2. THF was dried with Na/benzophenone and was freshly distilled before use. TLC: Silica gel 60 F_{254} plates (Merck). Flash chromatography (FC): Silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column, eluent, fraction size and R_f value. Melting point: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. MS: MAT GCQ (Thermo-Finnigan); EI = electron impact, ESI = electrospray ionization. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Mercury-400BB spectrometer (Varian); relative to TMS; coupling constants are given with 0.5 Hz resolution; the assignments of ^{13}C and ^{1}H NMR signals were supported by 2D NMR techniques. Elemental analysis: CHN-Rapid Analysator (Fons-Heraeus).

2-Bromoacetaldehyde Methyl 2-(1-Phenylpyrazol-5-yl)ethyl Acetal (7)

Under N_2, bromoacetaldehyde dimethyl acetal (157 μL, 1.33 mmol) and $BF_3{\cdot}OEt_2$ (68 μL, 0.54 mmol) were successively added to a soln of alcohol **6** (50 mg, 0.27 mmol) in CH_2Cl_2 (4 mL) at –50 °C. After warming up to 0 °C the soln was stirred for 7 h. Sat. $NaHCO_3$ soln and H_2O were added and the mixture was extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried (K_2CO_3), the solvent was evaporated in vacuo and the residue (138 mg) was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 7:3 + 1% Me_2NEt, 20 mL, R_f = 0.31) to give a pale-yellow oil; yield: 68 mg (77%).

IR (neat): 2925 (C–H_{aliph}), 1598, 1501 (C=C), 1120, 1068 (C–O), 764, 695 cm^{-1} (C–H).

^{1}H NMR ($CDCl_3$): δ = 2.91 (t, *J* = 6.8 Hz, 2 H, ArCH_2CH$_2$O), 3.20 (s, 3 H, OCH_3), 3.17–3.25 (m, 2 H, BrCH_2CH), 3.57–3.66 (m, 1 H, ArCH$_2$CH_2O), 3.77–3.78 (m, 1 H, ArCH$_2$CH_2O), 4.49 (t, *J* = 5.5 Hz, 1 H, BrCH$_2$C*H*), 6.25 (d, *J* = 1.6 Hz, 1 H, H4$_{pyrazole}$), 7.28–7.43 (m, 5 H, CH_{Ph}), 7.52 (d, *J* = 1.6 Hz, 1 H, H3$_{pyrazole}$).

MS (ESI): *m*/*z* [^{79}Br-M] calcd for $C_{14}H_{17}BrN_2O_2$: 325.2; found: *m*/*z* (%) = 325 [^{79}Br-M$^+$, 26], 327 [^{81}Br-M$^+$, 26].

4-(Bromomethyl)-1-phenyl-1,4,6,7-tetrahydropyrano[4,3-*c*]-pyrazole (8)

Bromoacetaldehyde dimethyl acetal (942 μL, 7.97 mmol) and PPTS (6.7 g, 26.6 mmol) were successively added to a soln of alcohol **6** (1.0 g, 5.31 mmol) in MeCN (35 mL). The mixture was heated to reflux for 74 h. Then the solvent was removed in vacuo, the residue was dissolved in CH_2Cl_2 and H_2O, the aqueous layer was separated and extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried (K_2CO_3) and concentrated in vacuo, and the residue (945 mg) was purified by flash chromatography (6 cm, *n*-hexane–EtOAc, 8:2, 40 mL, R_f = 0.29) to give a pale-yellow solid; yield: 529 mg (34%); mp 110 °C.

IR (neat): 3049 (C–H_{arom}), 2977, 2935 (C–H_{aliph}), 2855 (C–H), 1596, 1503 (C=C), 1089, 1069 (C–O), 763, 964 cm^{-1} (C–H).

^{1}H NMR ($CDCl_3$): δ = 2.68–2.77 (m, 1 H, ArCH_2CH$_2$O), 2.99–3.09 (m, 1 H, ArCH_2CH$_2$O), 3.57 (dd, *J* = 11.0, 7.4 Hz, 1 H, CHCH_2Br), 3.70 (dd, *J* = 10.8, 4.1 Hz, 1 H, CHCH_2Br), 3.76 (ddd, *J* = 11.5, 9.6, 3.7 Hz, 1 H, ArCH$_2$CH_2O), 4.23 (ddd, *J* = 11.4, 5.4, 3.0 Hz, 1 H, ArCH$_2$CH_2O), 4.98 (dd, *J* = 7.2, 4.1 Hz, 1 H, C*H*CH$_2$Br), 7.37 (t, *J* = 7.0 Hz, 1 H, *p*-CH_{Ph}), 7.42–7.53 (m, 4 H, CH_{Ph}), 7.60 (s, 1 H, H3$_{pyrazole}$).

MS (ESI): *m*/*z* [^{79}Br-M] calcd for: $C_{13}H_{13}BrN_2O$: 293.2; found: *m*/*z* (%) = 293 [^{79}Br-M$^+$, 45], 295 [^{81}Br-M$^+$, 37], 316 [^{79}Br-M + Na$^+$, 53], 318 [^{81}Br-M + Na$^+$, 47], 609 [2 ^{79}Br-M + Na$^+$, 100].

1-Phenyl-4-(pyrrolidin-1-ylmethyl)-1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazole (3a); Typical Procedure

K_2CO_3 (377 mg, 2.73 mmol) and freshly distilled pyrrolidine (56.0 μL, 0.68 mmol) were successively added to a soln of bromomethyl derivative **8** (100 mg, 0.34 mmol) in MeCN (5 mL). The mixture was heated to reflux for 29 h. It was then filtered, the solvent was removed in vacuo, and the residue (94 mg) was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 5:5 + 1% Me_2NEt, 20 mL, R_f = 0.06) to give a colorless solid; yield: 46 mg (48%); mp 89 °C.

IR (neat): 3061 (C–H_{arom}), 2961, 2929 (C–H_{aliph}), 2854 (C–H), 1598, 1504 (C=C), 1090 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 1.72–1.83 (m, 4 H, pyrrolidine 3-CH_2, 4-CH_2), 2.55–2.64 [m, 5 H, pyrrolidine 2-CH_2, 5-CH_2 (4 H), ArC$H_2$$CH_2O$ (1 H)], 2.73 (dd, *J* = 12.7, 3.3 Hz, 1 H, CHCH_2N), 2.82 (dd, *J* = 12.9, 9.0 Hz, 1 H, CHCH_2N), 2.98 (dddd, *J* = 15.8, 10.0, 5.6, 1.6 Hz, 1 H, ArC$H_2$$CH_2O$), 3.61 (ddd, *J* = 11.2, 10.3, 3.7 Hz, 1 H, ArCH_2CH_2O), 4.09 (ddd, *J* = 11.4, 5.6, 2.3 Hz, 1 H, ArCH_2CH_2O), 4.77–4.84 (m, 1 H, C*H*CH_2N), 7.27 (t, *J* = 7.2 Hz, 1 H, *p*-CH_{Ph}), 7.35–7.44 (m, 4 H, CH_{Ph}), 7.46 (s, 1 H, $H3_{pyrazole}$).

^{13}C NMR ($CDCl_3$): δ = 23.8 (2 C, pyrrolidine 3-CH_2, 4-CH_2), 25.1 (1 C, Ar*C*$H_2$$CH_2O$), 55.1 (2 C, pyrrolidine 2-CH_2, 5-CH_2), 61.6 (1 C, CH*C*H_2N), 63.5 (1 C, ArCH_2*C*H_2O), 72.5 (1 C, *C*HCH_2N), 77.4 (1 C, 4-$C_{pyrazole}$), 122.9 (2 C, *o*-CH_{Ph}), 127.2 (1 C, *p*-CH_{Ph}), 129.5 (2 C, *m*-CH_{Ph}), 136.1 (1 C, C_{Ph} quat), 136.2 (1 C, 3-$CH_{pyrazole}$), 139.8 (1 C, 5-$C_{pyrazole}$).

MS (ESI): *m*/*z* [M] calcd for $C_{17}H_{21}N_3O$: 283.4; found: *m*/*z* (%) = 284 [MH^+, 100], 589 [2 M + Na^+, 13].

Anal. Calcd for $C_{17}H_{21}N_3O$ (283.4): C, 72.1; H, 7.47; N, 14.8. Found: C, 71.6; H, 7.49; N, 14.5.

1-Phenyl-4-(piperidin-1-ylmethyl)-1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazole (3b)

Following the typical procedure for **3a** using K_2CO_3 (302 mg, 2.18 mmol), freshly distilled piperidine (81 μL, 0.81 mmol), and **8** (80 mg, 0.27 mmol) in MeCN (5 mL) with heating to reflux for 42 h gave a residue (89 mg) which was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 5:5 + 1% Me_2NEt, 20 mL, R_f = 0.11) to give a colorless solid; yield: 47 mg (58%); mp 91 °C.

IR (neat): 3059 (C–H_{arom}), 2930 (C–H_{aliph}), 2850 (C–H), 1599, 1504 (C=C), 1091 (C–O), 758, 693 cm^{-1} (C–H).

^1H NMR ($CDCl_3$): δ = 1.38–1.45 (m, 2 H, piperidine 4-CH_2), 1.52–1.63 (m, 4 H, piperidine 3-CH_2, 5-CH_2), 2.40–2.69 [m, 7 H, piperidine 2-CH_2, 6-CH_2 (4 H), ArC$H_2$$CH_2O$ (1 H), CHCH_2N (2 H)], 2.98 (dddd, *J* = 15.8, 10.1, 5.6, 1.6 Hz, 1 H, ArC$H_2$$CH_2O$), 3.61 (ddd, *J* = 11.3, 10.2, 3.9 Hz, 1 H, ArCH_2CH_2O), 4.97 (ddd, *J* = 11.5, 5.7, 2.2 Hz, 1 H, ArCH_2CH_2O), 4.78–4.84 (m, 1 H, C*H*CH_2N), 7.25 (t, *J* = 7.0 Hz, 1 H, CH_{Ph}), 7.35–7.48 (m, 4 H, CH_{Ph}), 7.51 (s, 1 H, $H3_{pyrazole}$).

^{13}C NMR ($CDCl_3$): δ = 24.5 (1 C, piperidine 4-CH_2), 25.1 (1 C, Ar*C*$H_2$$CH_2O$), 26.1 (2 C, piperidine 3-CH_2, 5-CH_2), 55.5 (2 C, piperidine 2-CH_2, 6-CH_2), 63.6 (1 C, ArCH_2*C*H_2O), 64.5 (1 C, CH*C*H_2N), 71.2 (1 C, *C*HCH_2N), 77.4 (1 C, 4-$C_{pyrazole}$), 122.8 (2 C, *o*-CH_{Ph}), 127.2 (1 C, *p*-CH_{Ph}), 129.5 (2 C, *m*-CH_{Ph}), 136.0 (1 C, C_{Ph} quat), 136.5 (1 C, 3-$CH_{pyrazole}$), 139.8 (1 C, 5-$C_{pyrazole}$).

MS (ESI): *m*/*z* [M] calcd for $C_{18}H_{23}N_3O$: 297.4; found: *m*/*z* (%) = 298 [MH^+, 100], 617 [2 M + Na^+, 15].

Anal. Calcd for $C_{18}H_{23}N_3O$ (297.4): C, 72.7; H, 7.80; N, 14.1. Found: C, 72.5; H, 7.80; N, 13.8.

1-Phenyl-4-(4-phenylpiperidin-1-ylmethyl)-1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazole (3c)

Following the typical procedure for **3a** using K_2CO_3 (302 mg, 2.18 mmol), 4-phenylpiperidine (132 mg, 0.82 mmol), and **8** (80 mg, 0.27 mmol) in MeCN (5 mL) with heating to reflux for 25 h gave a residue (190 mg) which was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 5:5 + 1% Me_2NEt, 20 mL, R_f = 0.25) to give a colorless resin; yield: 41 mg (41%).

IR (neat): 3058, 3026 (C–H_{arom}), 2932 (C–H_{aliph}), 2847 (C–H), 1598, 1504 (C=C), 1091 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 1.82–1.98 (m, 4 H, piperidine 3-CH_2, 5-CH_2), 2.19–2.30 (m, 2 H, piperidine 2-CH_2, 6-CH_2), 2.50–2.59 (m, 1 H, piperidine 4-CH), 2.65–2.73 [m, 2 H, ArC$H_2$$CH_2O$ (1 H), CHCH_2N (1 H)], 2.81 (dd, *J* = 13.3, 8.2 Hz, 1 H, CHCH_2N), 3.07 (dddd, *J* = 15.8, 10.2, 5.6, 1.5 Hz, 1 H, ArC$H_2$$CH_2O$), 3.22 (br t, *J* = 10.0 Hz, 2 H, piperidine 2-CH_2, 6-CH_2), 3.70 (ddd, *J* = 11.3, 10.2, 3.9 Hz, 1 H, ArCH_2CH_2O), 4.27 (ddd, *J* = 11.5, 5.7, 2.2 Hz, 1 H, ArCH_2CH_2O), 4.91–4.97 (m, 1 H, C*H*CH_2N), 7.20 (t, *J* = 7.0 Hz, 1 H, *p*-CH_{Ph}), 7.25–7.38 (m, 5 H, CH_{Ph}), 7.43–7.56 (m, 4 H, CH_{Ph}), 7.60 (s, 1 H, $CH_{pyrazole}$).

^{13}C NMR ($CDCl_3$): δ = 25.1 (1 C, Ar*C*$H_2$$CH_2O$), 33.7 (2 C, piperidine 3-CH_2, 5-CH_2), 42.9 (1 C, piperidine 4-CH), 55.1, 55.6 (1 C, piperidine 2-CH_2, 6-CH_2), 63.6 (1 C, ArCH_2*C*H_2O), 64.3 (1 C, CH*C*H_2N), 71.3 (1 C, *C*HCH_2N), 77.5 (1 C, 4-$C_{pyrazole}$), 119.4 (1 C, $C_{4\text{-}Ph}$ quat), 112.9 (2 C, *o*-CH_{Ph}), 126.4 (1 C, *p*-$CH_{4\text{-}Ph}$), 127.1 (2 C, *o*-$CH_{4\text{-}Ph}$), 127.2 (1 C, *p*-CH_{Ph}), 128.7 (2 C, *m*-$CH_{4\text{-}Ph}$), 129.5 (2 C, *m*-CH_{Ph}), 136.1 (1 C, C_{Ph} quat), 136.4 (1 C, 3-$CH_{pyrazole}$), 139.8 (1 C, 5-$C_{pyrazole}$).

MS (ESI): *m*/*z* [M] calcd for $C_{24}H_{27}N_3O$: 373.5; found: *m*/*z* (%) = 374 [MH^+, 100], 769 [2 M + Na^+, 47].

Anal. Calcd for $C_{24}H_{27}N_3O$ (373.5): C, 77.2; H, 7.29; N, 11.3. Found: C, 77.0; H, 7.34; N, 11.1.

4-(Morpholin-4-ylmethyl)-1-phenyl-1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazole (3d)

Following the typical procedure for **3a** using K_2CO_3 (377 mg, 2.73 mmol), morpholine (59.7 μL, 0.68 mmol), and **8** (100 mg, 0.34 mmol) in MeCN (5 mL) with heating to reflux for 47 h gave a residue (105 mg) which was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 2:8, 20 mL, R_f = 0.06) to give a colorless solid; yield: 59 mg (58%); mp 115 °C.

IR (neat): 3061 (C–H_{arom}), 2967, 2918 (C–H_{aliph}), 2850 (C–H), 1599, 1505 (C=C), 1114, 1087 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 2.48–2.73 [m, 7 H, morpholine 2-CH_2, 6-CH_2 (4 H), ArC$H_2$$CH_2O$ (1 H), CHCH_2N (2 H)], 2.99 (dddd, *J* = 15.8, 10.2, 5.7, 1.7 Hz, 1 H, ArC$H_2$$CH_2O$), 3.61 (ddd, *J* = 11.4, 10.4, 3.7 Hz, 1 H, ArCH_2CH_2O), 3.68–3.77 (m, 4 H, morpholine 3-CH_2, 5-CH_2), 4.18 (ddd, *J* = 11.4, 5.7, 2.2 Hz, 1 H, ArCH_2CH_2O), 4.81–4.89 (m, 1 H, C*H*CH_2N), 7.28 (t, *J* = 7.2 Hz, 1 H, *p*-CH_{Ph}), 7.35–7.49 (m, 4 H, CH_{Ph}), 7.51 (s, 1 H, $H3_{pyrazole}$).

^{13}C NMR ($CDCl_3$): δ = 25.4 (1 C, Ar$CH_2$$CH_2O$), 54.9 (2 C, morpholine 2-CH_2, 6-CH_2), 64.0 (1 C, ArCH_2*C*H_2O), 64.5 (1 C, CH*C*H_2N), 67.5 (2 C, morpholine 3-CH_2, 5-CH_2), 71.2 (1 C, *C*HCH_2N), 77.8 (1 C, 4-$C_{pyrazole}$), 123.2 (2 C, *o*-CH_{Ph}), 127.6 (1 C, *p*-CH_{Ph}), 129.8 (2 C, *m*-CH_{Ph}), 136.4 (1 C, C_{Ph} quat), 136.6 (1 C, 3-$CH_{pyrazole}$), 140.0 (1 C, 5-$C_{pyrazole}$).

MS (ESI): *m*/*z* [M] calcd for $C_{17}H_{21}N_3O_2$: 299.4; found: *m*/*z* (%) = 300 [MH^+, 100], 621 [2 M + Na^+, 43].

Anal. Calcd for $C_{17}H_{21}N_3O_2$ (299.4): C, 68.2; H, 7.07; N, 14.0. Found: C, 68.3; H, 7.06; N, 13.9.

4-(4-Methylpiperazin-1-ylmethyl)-1-phenyl-1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazole (3e)

Following the typical procedure for **3a** using K_2CO_3 (377 mg, 2.73 mmol), 1-methylpiperazine (113.5 μL, 1.02 mmol), and **8** (100 mg, 0.34 mmol) in MeCN (5 mL) with heating and stirring under reflux for 42 h gave a residue (109 mg) which was purified by flash chromatography (3 cm, h = 18 cm, EtOAc + 5% Me_2NEt, R_f = 0.14) to give a colorless solid; yield: 42 mg (40%); mp 66 °C.

IR (neat): 2923 (C–H_{aliph}), 2851 (C–H), 1599, 1505 (C=C), 1093 (C–O), 759, 694 (C–H) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.28 (s, 3 H, piperazine CH_3), 2.43–2.75 [m, 11 H, piperazine 2-CH_2, 3-CH_2, 5-CH_2, 6-CH_2 (8 H), CHCH_2N (2 H), ArC$H_2$$CH_2$O (1 H)], 2.98 (dddd, *J* = 15.7, 10.0, 5.7, 1.6 Hz, 1 H, ArC$H_2$$CH_2$O), 3.61 (dd, *J* = 11.2, 10.1, 3.7 Hz, 1 H, ArCH_2CH_2O), 4.17 (ddd, *J* = 11.4, 5.5, 2.0 Hz, 1 H, ArCH_2CH_2O), 4.80–4.87 (m, 1 H, C*H*CH_2N), 7.27 (t, *J* = 7.2 Hz, 1 H, *p*-CH_{Ph}), 7.35–7.48 (m, 4 H, CH_{Ph}), 7.50 (s, 1 H, $H3_{pyrazole}$).

^{13}C NMR ($CDCl_3$): δ = 25.1 (1 C, Ar*C*$H_2$$CH_2$O), 46.1 (1 C, piperazine CH_3), 53.7, 55.1 (2 C each, piperazine 2-CH_2, 3-CH_2, 5-CH_2, 6-CH_2), 63.56 (1 C, ArCH_2*C*H_2O), 63.59 (1 C, CH*C*H_2N), 71.2 (1 C, *C*HCH_2N), 77.5 (1 C, 4-$C_{pyrazole}$), 122.9 (2 C, *o*-CH_{Ph}), 127.3 (1 C, *p*-CH_{Ph}), 129.5 (2 C, *m*-CH_{Ph}), 136.0 (1 C, C_{Ph} quat), 136.4 (1 C, 3-$CH_{pyrazole}$), 139.7 (1 C, 5-$C_{pyrazole}$).

MS (ESI): *m*/*z* [M] calcd for $C_{18}H_{24}N_4O$: 312.4; found: *m*/*z* (%) = 313 [MH^+, 100], 647 [2 M + Na^+, 13].

Anal. Calcd for $C_{18}H_{24}N_4O$ (312.4): C, 69.2; H, 7.74; N, 17.9. Found: C, 69.2; H, 7.79; N, 17.4.

1-Phenyl-4-(4-phenylpiperazin-1-ylmethyl)-1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazole (3f)

Following the typical procedure for **3a** using K_2CO_3 (302 mg, 2.18 mmol), 1-phenylpiperazine (125 μL, 0.82 mmol), and **8** (80 mg, 0.27 mmol) in MeCN (5 mL) with heating to reflux for 41 h gave a residue (135 mg) which was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 5:5 + 1% Me_2NEt, 20 mL, R_f = 0.18) to give a colorless solid; yield: 68 mg (67%); mp 151 °C.

IR (neat): 3062 (C–H_{arom}), 2944 (C–H_{aliph}), 2852 (C–H), 1596, 1500 (C=C), 1098 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 2.63–2.84 [m, 7 H, ArC$H_2$$CH_2$O (1 H), CHC$H_2$N (2 H), piperazine 3-$CH_2$, 5-$CH_2$ (4 H)], 3.06 (dddd, *J* = 15.8, 10.1, 5.8, 1.5 Hz, 1 H, ArC$H_2$$CH_2$O), 3.25–3.33 (m, 4 H, piperazine 2-CH_2, 6-CH_2), 3.70 (ddd, *J* = 11.2, 10.2, 3.6 Hz, 1 H, ArCH_2CH_2O), 4.28 (ddd, *J* = 11.4, 5.5, 2.0 Hz, 1 H, ArCH_2CH_2O), 4.90–5.00 (m, 1 H, C*H*CH_2N), 6.84 (t, *J* = 7.2 Hz, 1 H, *p*-$CH_{4\text{-}Ph}$), 6.95 (d, *J* = 8.0 Hz, 2 H, *o*-$CH_{4\text{-}Ph}$), 7.22–7.30 (m, 2 H, *m*-$CH_{4\text{-}Ph}$), 7.34 (t, *J* = 7.1 Hz, 1 H, *p*-$CH_{4\text{-}Ph}$), 7.41–7.55 (m, 4 H, CH_{Ph}), 7.59 (s, 1 H, $H3_{pyrazole}$).

^{13}C NMR ($CDCl_3$): δ = 25.1 (1 C, Ar*C*$H_2$$CH_2$O), 49.3 (2 C, piperazine 2-CH_2, 6-CH_2), 54.2 (2 C, piperazine 3-CH_2, 5-CH_2), 63.7 (1 C, ArCH_2*C*H_2O), 63.8 (1 C, CH*C*H_2N), 71.2 (1 C, *C*HCH_2N), 77.4 (1 C, 4-$C_{pyrazole}$), 116.3 (2 C, *o*-$CH_{4\text{-}Ph}$), 119.2 (1 C, $C_{4\text{-}Ph}$, quat), 119.9 (1 C, *p*-$CH_{4\text{-}Ph}$), 122.9 (2 C, *o*-CH_{Ph}), 127.3 (1 C, *p*-CH_{Ph}), 129.4 (2 C, *m*-$CH_{4\text{-}Ph}$), 129.5 (2 C, *m*-CH_{Ph}), 136.1 (1 C, C_{Ph} quat), 136.4 (1 C, 3-$CH_{pyrazole}$), 139.7 (1 C, 5-$C_{pyrazole}$).

MS (ESI): *m*/*z* [M] calcd for $C_{23}H_{26}N_4O$: 374.5; found: *m*/*z* (%) = 375 [MH^+, 100], 771 [2 M + Na^+, 43].

Anal. Calcd for $C_{23}H_{26}N_4O$ (374.5): C, 73.8; H, 7.00; N, 15.0. Found: C, 73.6; H, 7.08; N, 14.6.

***N*,*N*-Dimethyl-1-(1-phenyl-1,4,6,7-tetrahydropyrano[4,3-*c*]-pyrazol-4-yl)methanamine (3g)**

Following the typical procedure for **3a** using K_2CO_3 (377 mg, 2.73 mmol), 2 M Me_2NH in THF (1.7 mL, 3.40 mmol, 6 ×, every 24 h), and **8** (100 mg, 0.34 mmol) in MeCN (5 mL) with heating to reflux for 6 d gave a residue (95 mg) which was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 1:1 + 2% Me_2NEt, 20 mL, R_f = 0.08) to give a colorless solid; yield: 19 mg (22%); mp 103 °C.

IR (neat): 3056 (C–H_{arom}), 2972, 2952 (C–H_{aliph}), 2858, 2822 (C–H), 1599, 1505 (C=C), 1087 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 2.39 [s, 6 H, N$(CH_3)_2$], 2.57 [dd, *J* = 13.3, 3.5 Hz, 1 H, CHCH_2N$(CH_3)_2$], 2.65–2.74 [m, 2 H, CHCH_2N$(CH_3)_2$ (1 H), ArC$H_2$$CH_2$O (1 H)], 3.06 (dddd, *J* = 15.8, 10.1, 5.7, 1.6 Hz, 1 H, ArC$H_2$$CH_2$O), 3.70 (ddd, *J* = 11.3, 10.1, 3.6 Hz, 1 H, ArCH_2CH_2O), 4.25 (ddd, *J* = 11.5, 5.8, 2.2 Hz, 1 H, ArCH_2CH_2O), 4.80–4.88 [m, 1 H, C*H*CH_2N$(CH_3)_2$], 7.34 (t, *J* = 7.0 Hz, 1 H, *p*-CH_{Ph}), 7.42–7.55 [m, 5 H, CH_{Ph} (4 H), $H3_{pyrazole}$ (1 H)].

^{13}C NMR ($CDCl_3$): δ = 25.1 (1 C, Ar*C*$H_2$$CH_2$O), 46.4 [2 C, N$(CH_3)_2$], 63.6 (1 C, Ar$CH_2$*C*$H_2$O), 64.8 [1 C, CH*C*$H_2N(CH_3)_2$], 71.5 [1 C, *C*HC$H_2N(CH_3)_2$], 77.5 (1 C, 4-$C_{pyrazole}$), 122.9 (2 C, *o*-$CH_{Ph}$), 127.3 (1 C, *p*-$CH_{Ph}$), 129.5 (2 C, *m*-$CH_{Ph}$), 136.08 (1 C, C_{Ph} quat), 136.11 (1 C, 3-$CH_{pyrazole}$), 139.8 (1 C, 5-$C_{pyrazole}$).

MS (ESI): *m*/*z* [M] calcd for $C_{15}H_{19}N_3O$: 257.3; found: *m*/*z* (%) = 258 [MH^+, 100], 537 [2 M + Na^+, 5].

Anal. Calcd for $C_{15}H_{19}N_3O$ (257.3): C, 70.0; H, 7.44; N, 16.3. Found: C, 70.2; H, 7.62; N, 15.6.

Methyl (1-Phenyl-1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazol-4-yl)acetate (10), Methyl 3-Methoxy-3-[2-(1-phenylpyrazol-5-yl)ethoxy]propanoate (11), and Methyl 3-[2-(1-Phenylpyrazol-5-yl)ethoxy]acrylate (12)

Method A: Methyl 3,3-dimethoxypropanoate (**9**, 72 μL, 0.51 mmol) and PPTS (534 mg, 2.12 mmol) were successively added to a soln of alcohol **6** (80 mg, 0.42 mmol) in MeCN (5 mL) and the mixture was heated to reflux for 45 h; Additional ester **9** (2 equiv) was added after 15 h and 30 h. The solvent was removed in vacuo, the residue was dissolved in H_2O and the aqueous layer was extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried (K_2CO_3), filtered, and concentrated in vacuo, and the residue (282 mg) was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 7:3, 20 mL) to give **10** and **12** as a colorless oil; yield: 40 mg (35%); ratio **10**/**12** 1:1; R_f = 0.17.

Method B: Methyl 3,3-dimethoxypropanoate (**9**, 75 μL, 0.53 mmol) and $BF_3{\cdot}OEt_2$ (135 μL, 1.06 mmol) were successively added to a soln of the alcohol **6** (50 mg, 0.27 mmol) in CH_2Cl_2 (5 mL). The mixture was heated to reflux for 122 h; additional ester **9** (2 equiv) was added after 2 d and 4 d. Then 2 M NaOH (~5 mL) and H_2O were added and the mixture was extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried (K_2CO_3), filtered, and concentrated in vacuo, and the residue (209 mg) was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 7:3, 20 mL) to give mixed acetal **11** as a colorless oil; yield: 27 mg (33%); R_f = 0.14.

Method C: Methyl 3,3-dimethoxypropanoate (**9**, 75 μL, 0.53 mmol) and PPTS (334 mg, 1.33 mmol) were successively added to a soln of alcohol **6** (50 mg, 0.27 mmol) in toluene–CH_2Cl_2 (1:1, 6 mL) and the mixture was heated to reflux for 120 h; additional ester **9** (2 equiv) was added after 2 d and 4 d. Then, H_2O was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried (K_2CO_3), filtered, and concentrated in vacuo, and the residue (191 mg) was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 8:2, 20 mL) to give acrylate **12** as a colorless oil; yield: 36 mg (49%); R_f = 0.40 (*n*-hexane–EtOAc, 5:5).

Method D: A soln of alcohol **6** (50 mg, 0.27 mmol), methyl 3,3-dimethoxypropanoate (**9**, 113 μL, 0.80 mmol), and PPTS (334 mg, 1.33 mmol) in MeCN (5 mL) was reacted under microwave irradiation (180 W, 5 bar, 140 °C, 5–60–5 min); additional ester **9** (2 equiv) was added after 20 min and 40 min. The mixture was concentrated in vacuo, the residue was dissolved in H_2O and extracted

with CH_2Cl_2 (3 ×). The organic layer was dried (K_2CO_3), filtered, and concentrated in vacuo, and the residue (205 mg) was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 7:3, 20 mL); to give **10** and **12** as a colorless oil; yield: 43 mg (58%); ratio **10**/**12** 3:1; R_f = 0.17.

Compound 10

IR (neat): 2951 (C–H_{aliph}), 1735 (C=O), 1598, 1502 (C=C), 1134 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 2.67–2.73 (m, 1 H, OCH_2CH_2Ar), 2.79–2.82 (m, 2 H, $CHCH_2CO_2CH_3$), 2.98–3.09 (m, 1 H, OCH_2CH_2Ar), 3.68–3.78 [m, 4 H, OCH_2CH_2Ar (1 H), CO_2CH_3 (3 H)], 4.15–4.20 (m, 1 H, OCH_2CH_2Ar), 5.08–5.11 (m, 1 H, $CHCH_2CO_2CH_3$), 7.35–7.55 (m, 5 H, CH_{Ph}), 7.63 (s, 1 H, $H3_{pyrazole}$).

MS (ESI): *m*/*z* [M] calcd for $C_{15}H_{16}N_2O_3$: 272.3; found: *m*/*z* (%) = 273 [MH^+, 9], 567 [2 M + Na^+].

Compound 11

IR (neat): 2950 (C–H_{aliph}), 2833 (C–H), 1735 (C=O), 1598, 1502 (C=C), 1117, 1062 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 2.63 (d, *J* = 5.5 Hz, 2 H, $H_3CCO_2CH_2CH$), 2.97 (t, *J* = 6.9 Hz, 2 H, OCH_2CH_2Ar), 3.27 (s, 3 H, OCH_3), 3.65–3.74 [m, 4 H, CO_2CH_3 (3 H), OCH_2CH_2Ar (1 H)], 3.78–3.88 (m, 1 H, OCH_2CH_2Ar), 4.89 (t, *J* = 5.9 Hz, 1 H, $H_3CO_2CH_2CH$), 6.30 (d, *J* = 2.0 Hz, 1 H, $H4_{pyrazole}$), 7.38–7.53 (m, 5 H, CH_{Ph}), 7.62 (d, *J* = 2.0 Hz, 1 H, $H3_{pyrazole}$).

MS (ESI): *m*/*z* [M] calcd for $C_{16}H_{20}N_2O_4$: 304.4: *m*/*z* (%) = 305 [MH^+, 36], 631 [2 M + Na^+, 100].

Compound 12

IR (neat): 2951 (C–H_{aliph}), 1707 (C=O), 1598, 1502 cm^{-1} (C=C).

^1H NMR ($CDCl_3$): δ = 3.10 (t, *J* = 6.7 Hz, 2 H, OCH_2CH_2Ar), 3.69 (s, 3 H, CO_2CH_3), 4.01 (t, *J* = 6.7 Hz, 2 H, OCH_2CH_2Ar), 5.17 (d, *J* = 12.9 Hz, 1 H, $OCH=CHCO_2CH_3$), 6.29 (d, *J* = 2.0 Hz, 1 H, $H4_{pyrazole}$), 7.35–7.55 [m, 6 H, $OCH=CHCO_2CH_3$ (1 H), CH_{Ph} (5 H)], 7.63 (d, *J* = 2.0 Hz, 1 H, $H3_{pyrazole}$).

MS (ESI): *m*/*z* [M] calcd for $C_{15}H_{16}N_2O_3$: 272.3; found: *m*/*z* (%) = 273 [MH^+, 9], 567 [2 M + Na^+].

3-(Benzyloxy)propanal (14)[19]

DMP (11.5 g, 27.1 mmol) was added to a cold (0 °C) soln of alcohol **13** (3.0 g, 18.0 mmol) in CH_2Cl_2 (70 mL). The mixture was warmed to 15 °C and stirred at 15 °C for 3 h. Then sat. $NaHCO_3$ soln and H_2O were added. The mixture was extracted with CH_2Cl_2 (3 ×), the organic layers were dried (K_2CO_3) and concentrated in vacuo, and the residue (3.4 g) was purified by flash chromatography (8 cm, *n*-hexane–EtOAc, 9:1, 100 mL, R_f = 0.13) to give a colorless solid; yield: 2.4 g (81%).

IR (neat): 3030 (C–H_{arom}), 2862 (C–H_{aliph}), 1722 (C=O), 1091 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 2.70 (td, *J* = 6.1, 2.0 Hz, 2 H, $O=CHCH_2CH_2O$), 3.82 (t, *J* = 6.1 Hz, 2 H, $O=CHCH_2CH_2O$), 4.54 (s, 2 H, CH_2OCH_2Ph), 7.29–7.38 (m, 5 H, CH_{Ph}), 9.80 (t, *J* = 1.8 Hz, 1 H, $O=CHCH_2CH_2O$).

MS (ESI): *m*/*z* [M] calcd for $C_{10}H_{12}O_2$: 164.2; found: *m*/*z* (%) = 165 [MH^+, 100].

3-(Benzyloxy)propanal Dimethyl Acetal (15)

A soln of aldehyde **14** (2.4 g, 14.6 mmol), trimethyl orthoformate (2.4 mL, 21.9 mmol), and PTSA (139 mg, 0.73 mmol) in MeOH (50 mL) was stirred at r.t. for 1 h. After addition of sat. $NaHCO_3$ soln (~5 mL) and H_2O, the mixture was extracted with CH_2Cl_2 (3 ×). The organic layer was dried (K_2CO_3) and the solvent was evaporated in vacuo to give a colorless solid; yield: 3.0 g (98%).

IR (neat): 3031 (C–H_{arom}), 2933 (C–H_{aliph}), 1097, 1050 cm^{-1} (C–O).

^1H NMR (DMSO-d_6): δ = 1.75–1.80 [m, 2 H, $(H_3CO)_2CHCH_2CH_2O$], 3.20 [s, 6 H, $(H_3CO)_2CHCH_2$], 3.43 [t, *J* = 6.5 Hz, 2 H, $(H_3CO)_2CHCH_2CH_2O$], 4.43 (s, 2 H, OCH_2Ph), 4.46 [t, *J* = 5.7 Hz, 1 H, $(H_3CO)_2CHCH_2$], 7.22–7.37 (m, 5 H, CH_{Ph}).

MS (ESI): *m*/*z* [M] calcd for $C_{12}H_{18}O_3$: 210.3; found: *m*/*z* (%) = 210 [M^+, 71], 228 [M + NH_4^+, 74], 233 [M + Na^+, 23], 443 [2 M + Na^+, 100].

4-[2-(Benzyloxy)ethyl]-1-phenyl-1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazole (16)

Acetal **15** (838 mg, 3.98 mmol), PPTS (3.3 g, 13.3 mmol), and Na_2SO_4 (1 g) were successively added to a soln of the alcohol **6** (500 mg, 2.66 mmol) in MeCN (30 mL) and the mixture was heated to reflux for 23 h. It was filtered, the solvent was removed in vacuo, the residue was dissolved in H_2O, and the aqueous layer was extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried (K_2CO_3) and concentrated in vacuo, and the residue (550 mg) was purified by flash chromatography (6 cm, *n*-hexane–EtOAc, 8:2, 65 mL, R_f = 0.15) to give a colorless solid; yield: 382 mg (43%); mp 78 °C.

IR (neat): 3030 (C–H_{arom}), 2922 (C–H_{aliph}), 2857 (C–H), 1599, 1504 (C=C), 1089 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 2.03 (dtd, *J* = 14.4, 8.8, 5.5 Hz, 1 H, $CHCH_2CH_2OBn$), 2.20 (dtd, *J* = 14.4, 7.2, 3.7 Hz, 1 H, $CHCH_2CH_2OBn$), 2.69 (br d, *J* = 15.8 Hz, 1 H, $ArCH_2CH_2O$), 3.02 (dddd, *J* = 15.8, 9.9, 5.8, 1.7 Hz, 1 H, $ArCH_2CH_2O$), 3.61–3.70 (m, 2 H, $CHCH_2CH_2OBn$), 3.77 (ddd, *J* = 11.2, 9.6, 3.3 Hz, 1 H, $ArCH_2CH_2O$), 4.17 (ddd, *J* = 11.4, 5.7, 2.8 Hz, 1 H, $ArCH_2CH_2O$), 4.56 (d, *J* = 12.8 Hz, 1 H, OCH_2Ph), 4.58 (d, *J* = 12.8 Hz, 1 H, OCH_2Ph), 4.89 (ddd, *J* = 5.3, 3.7, 1.7 Hz, 1 H, $CHCH_2CH_2OBn$), 7.25–7.39 (m, 5 H, CH_{Ph}), 7.42–7.55 [m, 6 H, CH_{Ph} (5 H), $H3_{pyrazole}$ (1 H)].

MS (ESI): *m*/*z* [M] calcd for $C_{21}H_{22}N_2O_2$: 334.4; found: *m*/*z* (%) = 335 [MH^+, 100], 357 [M + Na^+, 14], 668 [2 M, 60], 691 [2 M + Na^+, 97].

2-(1-Phenyl-1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazol-4-yl)ethanol (17)

A mixture of **16** (400 mg, 1.20 mmol), 10% Pd/C (120 mg), and MeOH (16 mL) was stirred under a H_2 atmosphere (balloon) at r.t. for 7 h. The catalyst was removed by filtration, the solvent was evaporated in vacuo and the residue (286 mg) was purified by flash chromatography (4 cm, *n*-hexane–EtOAc, 3:7, 30 mL, R_f = 0.15) to give a colorless solid; yield: 260 mg (89%); mp 73 °C.

IR (neat): 3412 (O–H), 3062 (C–H_{arom}), 2922 (C–H_{aliph}), 2859 (C–H), 1598, 1505 (C=C), 1049 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 1.95 (dtd, *J* = 14.1, 8.6, 5.6 Hz, 1 H, HCH_2CH_2OH), 2.13 (dtd, *J* = 14.3, 5.5, 3.3 Hz, 1 H, $CHCH_2CH_2OH$), 2.54 (t, *J* = 5.2 Hz, 1 H, $CHCH_2CH_2OH$), 2.62 (ddd, *J* = 16.0, 3.7, 1.8 Hz, 1 H, $ArCH_2CH_2O$), 3.03 (dddd, *J* = 16.0, 10.6, 5.8, 1.8 Hz, 1 H, $ArCH_2CH_2O$), 3.61 (ddd, *J* = 11.3, 10.6, 3.7 Hz, 1 H, $ArCH_2CH_2O$), 3.88 (q, *J* = 5.1 Hz, 2 H, $CHCH_2CH_2OH$), 4.18 (ddd, *J* = 11.4, 5.8, 1.9 Hz, 1 H, $ArCH_2CH_2O$), 4.90 (ddd, *J* = 5.3, 3.3, 1.8 Hz, 1 H, $CHCH_2CH_2OH$), 7.26–7.31 (m, 1 H, *p*-CH_{Ph}), 7.40–7.46 [m, 5 H, CH_{Ph} (4 H), $H3_{pyrazole}$ (1 H)].

MS (ESI): *m*/*z* [M] calcd for $C_{14}H_{16}N_2O_2$: 244.3; found: *m*/*z* (%) = 245 [MH^+, 100], 511 [2 M + Na^+, 6].

2-(1-Phenyl-1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazol-4-yl)acetaldehyde (18)

At 0 °C, DMP (391 mg, 0.92 mmol) was added to a soln of alcohol **17** (150 mg, 0.61 mmol) in CH_2Cl_2 (7 mL). The mixture was stirred

at 15 °C for 1.5 h. After addition of sat. $NaHCO_3$ soln (~4 mL) and H_2O, the mixture was extracted with CH_2Cl_2 (3 ×). The organic layer was dried (K_2CO_3) and concentrated in vacuo, and the residue (172 mg) was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 5:5, 20 mL, R_f = 0.25) to give a pale yellow oil; yield: 140 mg (95%).

IR (neat): 3063 (C–H_{arom}), 2918 (C–H_{aliph}), 2858 (C–H), 1719 (C=O), 1598, 1503 (C=C), 1066 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 2.70 (ddd, *J* = 15.9, 3.6, 2.1 Hz, 1 H, ArC*H*$_2$CH$_2$O), 2.89 (dd, *J* = 6.0, 2.1 Hz, 2 H, CHC*H*$_2$CHO), 3.06 (dddd, *J* = 16.0, 10.2, 5.9, 1.7 Hz, 1 H, ArC*H*$_2$CH$_2$O), 3.71 (ddd, *J* = 11.4, 10.3, 3.7 Hz, 1 H, ArCH$_2$C*H*$_2$O), 4.21 (ddd, *J* = 11.4, 5.8, 2.2 Hz, 1 H, ArCH$_2$C*H*$_2$O), 5.25 (tt, *J* = 6.1, 1.4 Hz, 1 H, C*H*CH$_2$CHO), 7.32–7.37 (m, 1 H, *p*-CH_{Ph}), 7.44–7.52 [m, 5 H, CH_{Ph} (4 H), $H3_{pyrazole}$ (1 H)], 9.87 (t, *J* = 2.1 Hz, 1 H, CHCH$_2$C*H*O).

MS (ESI): *m*/*z* [M] calcd for $C_{14}H_{14}N_2O_2$: 242.3; found: *m*/*z* (%) = 243 [MH^+, 6], 275 [MH^+ + MeOH, 28], 297 [M + MeOH + Na^+, 32], 570 [2 M + MeOH + Na^+, 100], 572 [2 MH + MeOH + Na^+, 29].

1-Phenyl-4-[2-(piperidin-1-yl)ethyl]-1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazole (4a); Typical Procedure

A mixture of the aldehyde **18** (140 mg, 0.58 mmol), freshly distilled piperidine (57 μL, 0.58 mmol), Na[BH(OAc)$_3$] (184 mg, 0.87 mmol), and DCE (4 mL) was stirred at r.t. for 16 h. Sat. $NaHCO_3$ soln (~5 mL) and H_2O were added. The aqueous layer was extracted with CH_2Cl_2 (3 ×). The organic layer was dried (K_2CO_3) and concentrated in vacuo, and the residue (218 mg) was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 7:3 + 2% Me_2NEt, 20 mL, R_f = 0.09) to give a colorless oil; yield: 103 mg (57%).

IR (neat): 3062 (C–H_{arom}), 2930 (C–H_{aliph}), 2851 (C–H), 1599, 1504 (C=C), 1092 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 1.40–1.48 (m, 2 H, piperidine 4-CH$_2$), 1.56–1.64 (m, 4 H, piperidine 3-CH$_2$, 5-CH$_2$), 1.91–2.00 (m, 1 H, CHC*H*$_2$CH$_2$N), 2.01–2.10 (m, 1 H, CHC*H*$_2$CH$_2$N), 2.43 (br s, 4 H, piperidine 2-CH$_2$, 6-CH$_2$), 2.52–2.58 (m, 2 H, CHCH$_2$C*H*$_2$N), 2.68 (br d, *J* = 15.8 Hz, 1 H, ArC*H*$_2$CH$_2$O), 3.02 (dddd, *J* = 15.8, 9.8, 5.6, 1.7 Hz, 1 H, ArC*H*$_2$CH$_2$O), 3.66 (ddd, *J* = 11.5, 10.0, 3.8 Hz, 1 H, ArCH$_2$C*H*$_2$O), 4.17 (ddd, *J* = 11.3, 5.7, 2.5 Hz, 1 H, ArCH$_2$C*H*$_2$O), 4.75 (ddd, *J* = 5.5, 3.8, 1.9 Hz, 1 H, C*H*CH$_2$CH$_2$N), 7.32 (tt, *J* = 7.2, 1.6 Hz, 1 H, *p*-CH_{Ph}), 7.43–7.53 [m, 5 H, CH_{Ph} (4 H), $H3_{pyrazole}$ (1 H)].

MS (ESI): *m*/*z* [M] calcd for $C_{19}H_{25}N_3O$: 311.4; found: *m*/*z* (%) = 312 [MH^+, 100], 645 [2 M + Na^+, 23].

Anal. Calcd for $C_{19}H_{25}N_3O$ (311.4): C, 73.3; H, 8.09; N, 13.5. Found: C, 72.8; H, 8.21; N, 13.5.

1-Phenyl-4-[2-(4-phenylpiperidin-1-yl)ethyl]-1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazole (4b)

Following the typical procedure for **4a** using aldehyde **18** (85 mg, 0.35 mmol), 4-phenylpiperidine (57 mg, 0.35 mmol), Na[BH(OAc)$_3$] (112 mg, 0.53 mmol), and DCE (3 mL) at r.t. for 17 h gave a residue (219 mg) which was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 7:3 + 2% Me_2NEt, 20 mL, R_f = 0.11) to give a colorless solid; yield: 102 mg (75%); mp 70 °C.

IR (neat): 3027 (C–H_{arom}), 2929 (C–H_{aliph}), 2849 (C–H), 1599, 1504 (C=C), 1092 (C–O), 757, 696 cm^{-1} (C–H).

^1H NMR ($CDCl_3$): δ = 1.75–1.81 (m, 4 H, piperidine 3-CH$_2$, 5-CH$_2$), 1.92–2.11 [m, 4 H, piperidine 2-CH$_2$, 6-CH$_2$ (2 H), CHC*H*$_2$CH$_2$N (2 H)], 2.40–2.49 (m, 1 H, piperidine 4-CH), 2.54–2.60 (m, 2 H, CHCH$_2$C*H*$_2$N), 2.62 (br d, *J* = 15.8 Hz, 1 H, ArC*H*$_2$CH$_2$O), 2.97 (dddd, *J* = 15.7, 9.9, 5.6, 1.5 Hz, 1 H, ArC*H*$_2$CH$_2$O), 3.05 (br d, *J* = 11.3 Hz, 2 H, piperidine 2-CH$_2$, 6-CH$_2$), 3.62 (ddd, *J* = 11.3, 10.0, 3.7 Hz, 1 H, ArCH$_2$C*H*$_2$O), 4.13 (ddd, *J* = 11.4, 5.7, 2.5 Hz, 1 H, ArCH$_2$C*H*$_2$O), 4.72 (ddd, *J* = 5.4, 3.8, 1.8 Hz, 1 H, C*H*CH$_2$CH$_2$N), 7.10–7.29 [m, 6 H, CH_{Ph} (5 H), $H3_{pyrazole}$ (1 H)], 7.37–7.48 (m, 5 H, CH_{Ph}).

MS (ESI): *m*/*z* [M] calcd for $C_{25}H_{29}N_3O$: 387.5: *m*/*z* (%) = 388 [MH^+, 100].

Anal. Calcd for $C_{25}H_{29}N_3O$ (387.5): C, 77.5; H, 7.54; N, 10.8. Found: C, 77.2; H, 7.59; N, 10.7.

1-Phenyl-4-[2-(4-phenylpiperazin-1-yl)ethyl]-1,4,6,7-tetrahydropyrano[4,3-*c*]pyrazole (4c)

Following the typical procedure for **4a** using aldehyde **18** (92 mg, 0.38 mmol), 1-phenylpiperazine (58 μL, 0.38 mmol), Na[BH(OAc)$_3$] (121 mg, 0.57 mmol), and DCE (3 mL) at r.t. for 17 h gave a residue (212 mg) which was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 7:3 + 2% Me_2NEt, 20 mL, R_f = 0.14) to give a colorless oil; yield: 118 mg (80%).

IR (neat): 3059 (C–H_{arom}), 2949 (C–H_{aliph}), 2818 (C–H), 1598, 1502 (C=C), 1092 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 1.96–2.15 (m, 2 H, CHC*H*$_2$CH$_2$N), 2.63–2.73 [m, 7 H, piperazine 3-CH$_2$, 5-CH$_2$ (4 H), CHCH$_2$C*H*$_2$N (2 H), ArC*H*$_2$CH$_2$O (1 H)], 3.04 (dddd, *J* = 15.7, 9.9, 5.7, 1.7 Hz, 1 H, ArC*H*$_2$CH$_2$O), 3.23 (t, *J* = 5.1 Hz, 4 H, piperazine 2-CH$_2$, 6-CH$_2$), 3.68 (ddd, *J* = 11.4, 9.9, 3.8 Hz, 1 H, ArCH$_2$C*H*$_2$O), 4.19 (ddd, *J* = 11.4, 5.7, 2.4 Hz, 1 H, ArCH$_2$C*H*$_2$O), 4.80 (ddd, *J* = 5.2, 3.7, 1.9 Hz, 1 H, C*H*CH$_2$CH$_2$N), 6.85 (tt, *J* = 7.2, 1.0 Hz, 1 H, *p*-$CH_{4\text{-}Ph}$), 6.94 (dd, *J* = 8.7, 1.1 Hz, 2 H, *o*-$CH_{4\text{-}Ph}$), 7.24–7.29 (m, 2 H, *m*-$CH_{4\text{-}Ph}$), 7.33 (tt, *J* = 7.2, 1.6 Hz, 1 H, *p*-CH_{Ph}), 7.44–7.54 [m, 5 H, CH_{Ph} (4 H), $H3_{pyrazole}$ (1 H)].

MS (ESI): *m*/*z* [M] calcd for $C_{24}H_{28}N_4O$: 388.5; found: *m*/*z* (%) = 389 [MH^+, 100], 411 [M + Na^+, 6], 799 [2 M + Na^+, 35].

Anal. Calcd for $C_{24}H_{28}N_4O$ (388.5): C, 74.2; H, 7.26; N, 14.4. Found: C, 73.8; H, 7.29; N, 14.3.

N,*N*-Dimethyl-2-(1-phenyl-1,4,6,7-tetrahydropyrano[4,3-*c*]-pyrazol-4-yl)ethanamine (4d)

Following the typical procedure for **4a** using aldehyde **18** (60 mg, 0.25 mmol), 2 M Me_2NH in THF (124 μL, 0.25 mmol), Na[BH(OAc)$_3$] (79 mg, 0.37 mmol), and DCE (1 mL) at r.t. for 15 h gave a residue (79 mg) which was purified by flash chromatography (3 cm, *n*-hexane–EtOAc, 5:5+2% Me_2NEt, 20 mL, R_f = 0.09) to give a colorless oil; yield: 48 mg (71%).

IR (neat): 3047 (C–H_{arom}), 2941 (C–H_{aliph}), 2856, 2816 (C–H), 1599, 1504 (C=C), 1092 cm^{-1} (C–O).

^1H NMR ($CDCl_3$): δ = 1.88–1.98 [m, 1 H, CHC*H*$_2$CH$_2$N(CH$_3$)$_2$], 2.00–2.09 [m, 1 H, CHC*H*$_2$CH$_2$N(CH$_3$)$_2$], 2.29 [s, 6 H, N(CH$_3$)$_2$], 2.45–2.58 [m, 2 H, CHCH$_2$C*H*$_2$N(CH$_3$)$_2$], 2.68 (br d, *J* = 15.8 Hz, 1 H, ArC*H*$_2$CH$_2$O), 3.03 (dddd, *J* = 15.8, 10.0, 5.7, 1.8 Hz, 1 H, ArC*H*$_2$CH$_2$O), 3.67 (ddd, *J* = 11.4, 10.0, 3.8 Hz, 1 H, ArCH$_2$C*H*$_2$O), 4.18 (ddd, *J* = 11.4, 5.7, 2.4 Hz, 1 H, ArCH$_2$C*H*$_2$O), 4.77 [ddd, *J* = 8.4, 3.7, 1.8 Hz, 1 H, *H*CH$_2$CH$_2$N(CH$_3$)$_2$], 7.33 (tt, *J* = 7.2, 1.6 Hz, 1 H, *p*-CH_{Ph}), 7.43–7.53 [m, 5 H, CH_{Ph} (4 H), $H3_{pyrazole}$ (1 H)].

MS (ESI): *m*/*z* [M] calcd for $C_{16}H_{21}N_3O$: 271.4; found: *m*/*z* (%) = 272 [MH^+, 100], 294 [M + Na^+, 9], 565 [2 M + Na^+, 93].

Anal. Calcd for $C_{16}H_{21}N_3O$ (271.4): C, 70.8; H, 7.80; N, 15.5. Found: C, 70.3; H, 7.97; N, 15.0.

Receptor Binding Studies

The σ_1 and σ_2 receptor affinities were recorded as described in the literature.[22–24]

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