Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry 12 (2004) 4511–4532
Bioorganic & Medicinal Chemistry

Inhibitors of the glycine transporter type-2 (GlyT-2): synthesis and biological activity of benzoylpiperidine derivatives

Ronald L. Wolin,* Alejandro Santillán, Jr., Liu Tang, Charles Huang, Xiaoxia Jiang and Timothy W. Lovenberg

Johnson & Johnson Pharmaceutical Research and Development, LLC, 3210 Merryfield Row, San Diego, CA 92121, USA

Received 23 March 2004; accepted 24 May 2004
Available online 6 July 2004

Abstract—A series of benzoylpiperidine analogs related to **4a** was prepared, and their ability to inhibit the uptake of [^{14}C]-glycine in COS7 cells transfected with human glycine transporter type-2 (GlyT-2) was evaluated. Small structural changes to the benzoylpiperidine region of the molecule led to a significant decrease in GlyT-2 inhibitory activity. In contrast, the distal aryl ring was more tolerant to functional group modifications and could accommodate a variety of substitutes at the C-2 or C-3 positions. Comparable activities to **4a** were obtained by replacing the anilino nitrogen with an ether linkage **27** or by exchanging the isopropoxy ether moiety with an isopropyl amino group **15**. A distinct preference for a 2-carbon tether ($n = 1$) was observed relative to the corresponding 3-carbon homolog ($n = 2$).

1. Introduction

The two primary inhibitory neurotransmitters in the central nervous system (CNS) are γ-aminobutyric acid (GABA) and glycine. Currently, there are two known glycine transporters expressed in the central nervous system; GlyT-1 and GlyT-2.[1] Separate genes encode each transporter and these proteins can be pharmacologically distinguished by their sensitivity to sarcosine (*N*-methylglycine).[2] Both the rat and human GlyT-2 transporters have been cloned and share ~93% sequence homology at the amino acid level.[3] Moreover, detailed binding studies have been conducted using ^{3}H-strychnine, which provides evidence that glycine is the major inhibitory amino acid operating in the brainstem and spinal cord of vertebrates, and exerts its effects post-synaptically at the strychnine-sensitive glycinergic receptor.[4,5] Thus, when glycine binds to its specific receptor it induces the opening of a ligand-gated chloride channel which in turn causes an increase in chloride ion (Cl^-) conductance along the post-synaptic membrane. This process leads to a hyperpolarized state in the post-synaptic neuron and ultimately raises the threshold for neuronal firing. Furthermore, the physiological effects of glycine are regulated by an efficient glycine transporter system that allows for the re-uptake of glycine back into the pre-synaptic neuron.[6] As a result, compounds that display an ability for inhibiting the re-uptake of glycine should also accentuate the post-synaptic inhibitory activity of the glycinergic receptor, and as such, may be useful for the treatment of certain CNS conditions such as tinnitus,[7] spasticity[8] and neuropathic pain.[9]

A high-throughput-screening (HTS) campaign of our in-house library identified **4a** as a compelling hit-to-lead candidate for inhibiting the uptake of [^{14}C]-Glycine into COS7 cells transfected with the human GlyT-2 transporter. Related compounds containing a cyclic tether, which are present in analogs such as Mazapertine[10] (**1**), the piperidine derivative **2** and the homopiperazine derivative **3** were all devoid of GlyT-2 activity. Moreover, **4a** possessed excellent selectivity for the GlyT-2 isoform, as evidenced by its lack of affinity for the GlyT-1 transporter which exhibited an $IC_{50} > 10{,}000$ nM. Based in part on these findings, we initiated a chemistry effort aimed at improving the potency of **4a** as a GlyT-2 antagonist (Fig. 1).[11] The compounds prepared in this study probed modifications to each of the three regions present in the parent compound **4a**; the distal aryl ring (Fig. 2), the tether (Fig. 3), and the benzoylpiperidine moiety (Figs. 4 and 5).

* Corresponding author. Fax: +1-858-784-3116; e-mail: rwolin@prdus.jnj.com

0968-0896/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2004.05.044

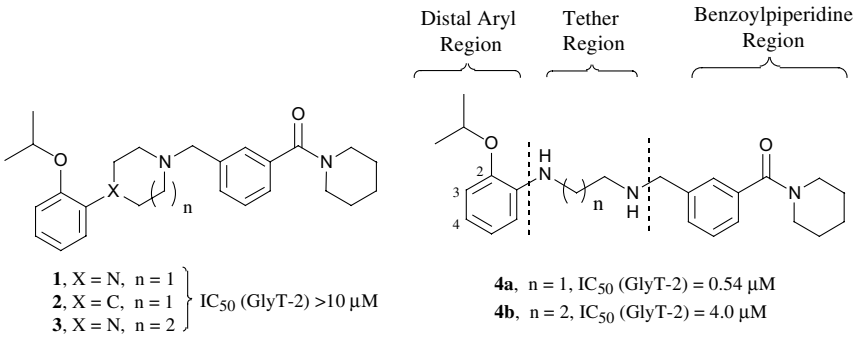
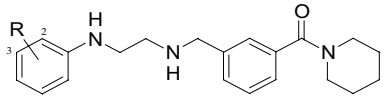
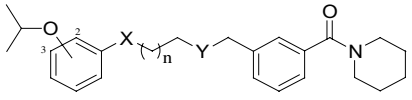


Figure 1.



Compd	R	Compd	R
5	3-$OCH(CH_3)_2$	**15**	2-$NHCH(CH_3)_2$
6	2-OC_5H_9	**16**	2-$NHSO_2CH_3$
7	3-OCH_3	**17**	2-NHCONHPh
8	2-OC_5H_{11}	**18**	2-$NHCONHCH_2Ph$
9	2-OCH_3	**19**	2-Br
10	2-OPh	**20**	2-Cl
11	2-OH	**21**	3-Br
12	H	**22**	3-Cl
13	2-NO_2	**23**	2-$CH(CH_3)_2$
14	2-NH_2	**24**	2-(3-Thienyl)
		25	2-(Ph-2-OCH_3)

Figure 2. Distal aryl ring variations.

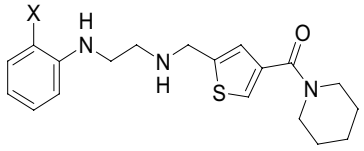


Compd	O-*i*Pr	X	n	Y
26	2	NH	1	NCH_3
27	2	NCH_3	1	NH
28	2	NCH_3	1	NCH_3
29	3	NH	1	NCH_3
30	3	NCH_3	1	NCH_3
31	2	O	1	NH
32	2	O	2	NH
33	3	O	1	NH
34	2	CH_2	1	NH
35	2	S	1	NH

Figure 3. Tether variations.

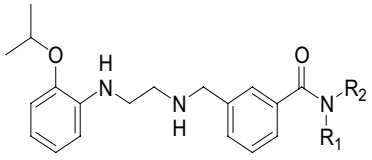
2. Chemistry

Two synthetic routes were employed for assembling analogs related to **4** and are outlined in Scheme 1. Treatment of 2-nitrophenol **45** with isopropyl iodide in the presence of potassium carbonate in DMF provided the corresponding isopropyl ether **46**. Exposure of **46** to hydrogen in the presence of Pd/C catalyst in EtOH afforded aniline **47**, which subsequently was alkylated



Compd	X
36	$OCH(CH_3)_2$
37	NO_2
38	NH_2
39	$NHCH(CH_3)_2$

Figure 4. Thiophene analogs.

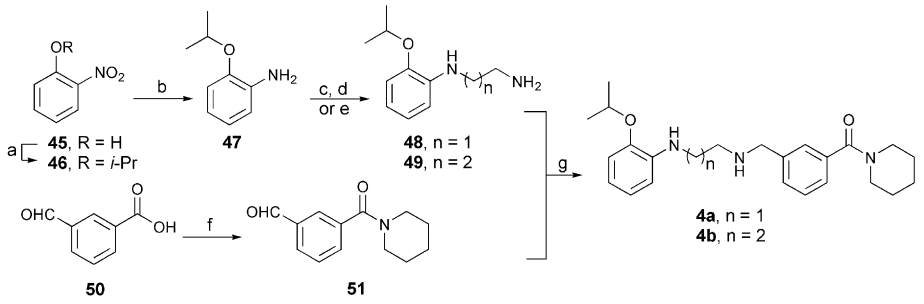


Compd	R_1	R_2
40		Homopiperidine
41		Pyrrolidine
42	Ethyl	Ethyl
43		Morpholine
44		4-Hydroxypiperidine

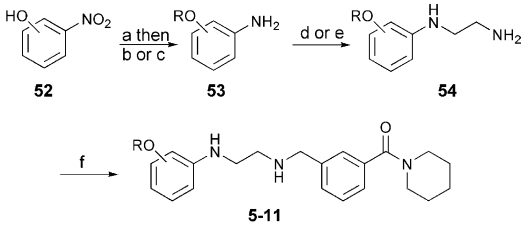
Figure 5. Amide variations.

with 2-chloroethylamine in refluxing isopropanol to provide **48**. Alternatively, treatment of **47** with oxazolidinone in refluxing ethylene glycol dimethyl ether (DME) also provided **48**.[12] Alkylation of **47** with 3-chloropropylamine afforded the homologated analog **49**. Carbodiimide mediated coupling[13] between 3-formyl benzoic acid (**50**) and piperidine furnished adduct **51**. Treatment of **51** with amines **48** and **49** under reductive amination conditions provided **4a** and **4b**, respectively.[14]

Our initial structure–activity studies focused on the distal aryl ring of **4a** (Fig. 1) and were designed to evaluate the nature and position of substituents attached to the aromatic ring. Toward that goal, an array of analogs was assembled that varied the position, steric, and lipophilic properties of the aryl substituent. Thus,



Scheme 1. Reagents: (a) isopropyl iodide, K_2CO_3, DMF; (b) H_2, 10% Pd/C, EtOH; (c) 2-choloroethylamine, *i*-PrOH, reflux; (d) 3-chloropropylamine, *i*-PrOH; (e) **47**–HCl salt, oxazolidinone, ethylene gylcol dimethylether; (f) piperidine, EDCI, HOBT, DMF; (g) $Na(OAc)_3BH$, 1,2-dichloroethane.



Scheme 2. Reagents: (a) R–Br, K_2CO_3, DMF; (b) $Na_2S_2O_4$, THF–H_2O; (c) H_2, 10% Pd/C, EtOH; (d) HCl salt, oxazolidinone, ethylene glycol dimethylether; (e) 2-chloroethylamine, *i*-PrOH; (f) **51**, $Na(OAc)_3BH$, 1,2-dichloroethane.

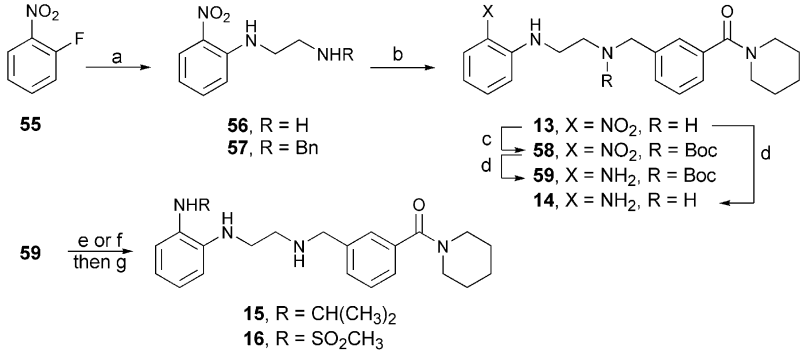
nitrophenol **52** was converted to aniline **53** utilizing the two-step sequence outlined in Scheme 2.[15] Subsequent conversion of **53** to the ethylenediamine analogs **5**–**12** was achieved in an identical manner to that described for **4a** and **4b**. The unsubstituted analog **12** was obtained using this route with aniline as the starting material.

The substituted anilino derivatives **13**–**16** were obtained as outlined in Scheme 3. Accordingly, treatment of 2-fluoronitrobenzene (**55**) with either ethylenediamine or monobenzyl ethylenediamine furnished **56** or **57**, respectively.[16] Further treatment of **56** with aldehyde **51** under reductive amination conditions provided **13**. Reduction of **13** under hydrogenation conditions furnished aniline **14**. Alternatively, selective protection of the benzylic nitrogen provided the *N*-Boc intermediate **58**, which was reduced to aniline **59** after exposure to hydrogen in the presence of Pd/C catalyst. Alkylation of **59** using isopropyl iodide in DMF containing K_2CO_3 followed by removal of the *N*-Boc group provided **15**. In a similar fashion, sulfonlylation of **59** and subsequent deprotection afforded **16**.

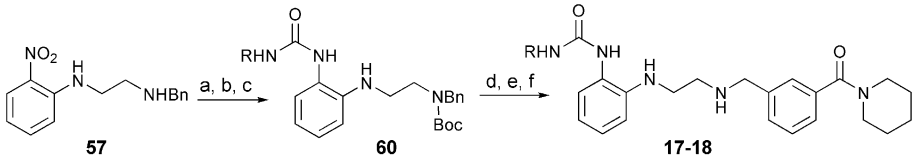
The urea derivatives **17** and **18** were assembled as outlined in Scheme 4 utilizing the aforementioned intermediate **57**. The more basic amine was protected using Boc anhydride. Subsequent reduction of the nitro group and urea formation using the appropriate isocyanate furnished **60**. Removal of both the Boc and benzyl protecting groups furnished the primary amine, which was treated with aldehyde **51** under reductive amination conditions to yield the targeted compounds **17**–**18**.

Halogenated analogs **19**–**22** were obtained beginning from commercially available anilines **61** as depicted in Scheme 5.[15] As was discussed previously, alkylation of **61** with 2-chloroethylamine gave diamine **62**, which was subsequently treated with aldehyde **51** to yield the target compounds **19**–**22**.

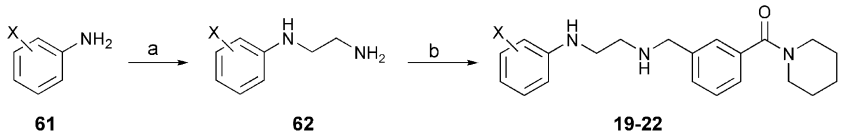
Our efforts also investigated the replacement of the C-2 alkoxy with a carbon substituent. The synthesis of the deoxygenated analog **23** followed the identical route utilized for the halogen substituted analogs depicted in Scheme 5. The synthesis of **23** utilized the commercially available 2-isopropylaniline (**61**, X = 2-$CH(CH_3)_2$). The introduction of the 2-thienyl and 2-methoxyphenyl



Scheme 3. Reagents: (a) ethylenediamine or *N*-benzylethylenediamine, CH_3CN; (b) **51**, $Na(OAc)_3BH$, 1,2-dichloroethane; (c) $(Boc)_2O$, CH_2Cl_2; (d) H_2, Pd/C, EtOH; (e) isopropyl iodide, K_2CO_3, DMF; (f) R–SO_2Cl, Et_3N, CH_2Cl_2; (g) CF_3CO_2H, CH_2Cl_2.



Scheme 4. Reagents: (a) $(Boc)_2O$, CH_2Cl_2; (b) H_2, Pd/C, EtOH, 1 atm; (c) R–NCO, Et_3N, CH_2Cl_2; (d) CF_3CO_2H, CH_2Cl_2; (e) H_2, Pd/C, EtOAc–HOAc (5:1, v/v) 50 psi; (f) **51**, $Na(OAc)_3BH$, 1,2-dichloroethane.



Scheme 5. Reagents: (a) 2-chloroethylamine, *i*-PrOH, reflux; (b) **51**, $Na(OAc)_3BH$, 1,2-dichloroethane.

moieties was accomplished via Suzuki coupling[17] between arylbromide **19** and the requisite boronic acid to furnish adducts **24** and **25**, respectively, as seen in Scheme 6.

We also probed the importance of the chain length and the nature of the heteroatom(s) present in the tether joining the two aryl segments in **4a** by the synthesis of compounds **26**–**35** (Schemes 7–10). Our initial studies aimed to identify what effect, if any, hydrogen bonding has on biological activity. To address the importance of these interactions the nitrogen atoms present in the tether region of **4a** were successively alkylated (Scheme 7). Exposure of **4a** to iodomethane in the presence of K_2CO_3 led to the methylation at the more reactive benzylic nitrogen to afford **26**. Alternatively, **4a** was converted to the *N*-Boc derivative **63**, which was subsequently treated with NaH and MeI to provided **64**. Removal of the Boc protecting group with TFA gave **27**. The synthesis of **28** was achieved by methylating **27** employing the conditions utilized to generate **26**. The synthesis of the analogous 3-isopropoxy targets, **29** and **30**, were obtained in a similar manner and are summarized in Scheme 7.

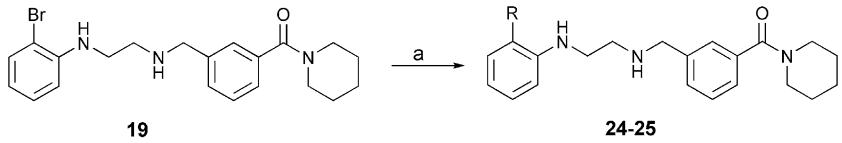
The synthesis of **31**, which replaces the anilino nitrogen with an oxygen is shown in Scheme 8. This route involved initial alkylation of **65** with *N*-*t*-Boc-ethanolamine under Mitsunobu[18] conditions to provide adduct **66**. Removal of the *N*-Boc group and subsequent treatment with **51** under reductive amination conditions afforded the ether derivative **31**. Alternatively, treatment of 2-(isopropoxy)phenol **66** with K_2CO_3 in DMF followed by the addition of *N*-(3-bromopropyl)phthalimide provided **67**. Hydrolysis of the phthalimide moiety with hydrazine and subsequent treatment with **51** under reductive amination conditions gave the propylamine analog **32**. Interestingly, when the alkylation of **65** was attempted with *N*-(2-bromoethyl)phthalimide using the same set of conditions as above, elimination to the vinyl phthalimide resulted, and no alkylation of **65**.

The 3-isopropoxy analog **33** was prepared starting from resorcinol monobenzoate **69** as outlined in Scheme 9. Alkylation of **68** under Mitsunobu conditions followed by Boc deprotection furnished the desired amine **69**. Addition of aldehyde **51** to **69** in the presence of $Na(OAc)_3BH$ provided **70**, which was hydrolyzed to phenol **71** and alkylated with 2-iodopropane furnishing the target compound **33**.

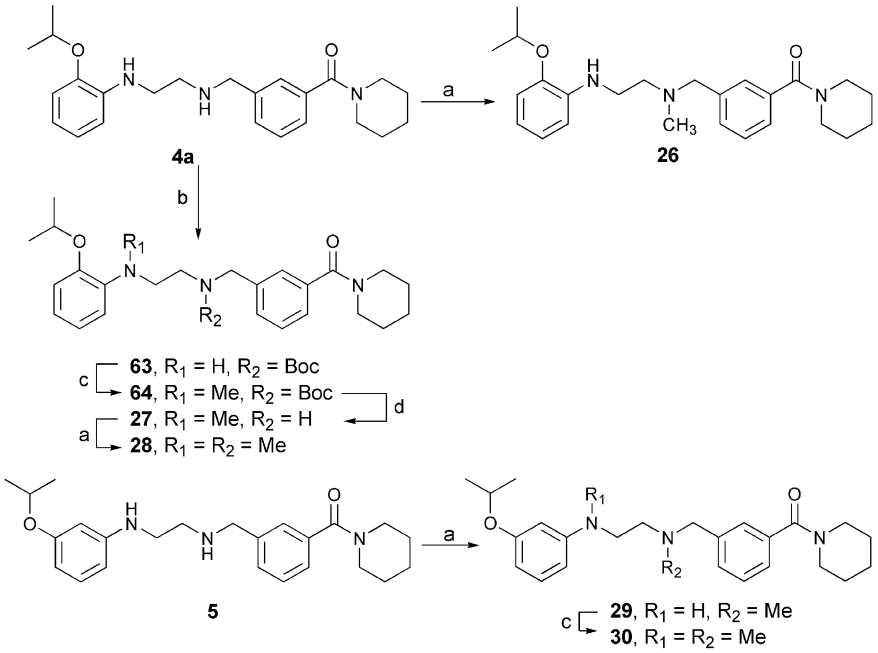
The carbon isostere **34** was prepared as shown in Scheme 10. Treatment of 3-(2-hydroxyphenyl)propionic acid (**72**) with K_2CO_3 and 2-iodopropane provided the bis-isopropyl adduct **73**. Subjecting **73** to methanolic ammonia gave rise to the corresponding amide **74**, which was reduced with $LiAlH_4$ to amine **75**. Reductive amination with **51** gave the carbon congener **34**.

Replacement of the anilino nitrogen of **4a** with sulfur was accomplished as outlined in Scheme 11. Sequential alkylation of thiophenol **76** with *N*-(2-bromoethyl)phthalimide and 2-iodopropane produced **77**. Removal of the phthalimide moiety with hydrazine and subjecting the resulting amine with **51** under reductive amination conditions provided the sulfur isostere **34**.

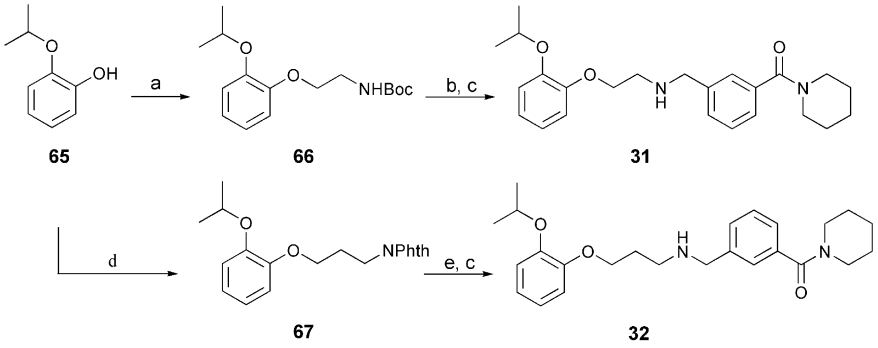
Our studies also investigated replacements for the benzoyl moiety by replacing it with thiophene bioisosteres as outlined in Scheme 12. Carbodiimide mediated coupling between **78** and piperidine produced the thiophene-2-carboxaldehyde **79**, which upon exposure to **48** under reductive amination conditions afforded the thiophene isostere **36**. The aniline derivatives **38** and **39** were



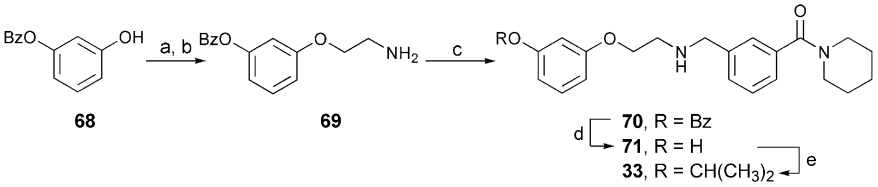
Scheme 6. Reagents: (a) Ar–$B(OH)_2$, $Pd(PPh_3)_4$, EtOH–toluene (1:4), Na_2CO_3.



Scheme 7. Reagents: (a) MeI, K_2CO_3, DMF; (b) $(Boc)_2O$, CH_2Cl_2; (c) MeI, NaH, DMF; (d) CF_3CO_2H, CH_2Cl_2.



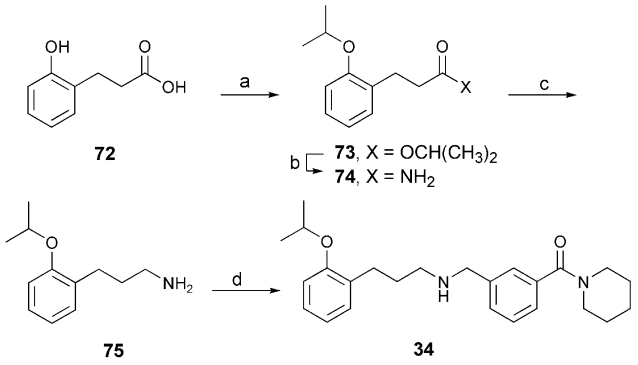
Scheme 8. Reagents: (a) *N*-*t*-Boc-ethanolamine, DBAD, Ph_3P, THF; (b) CF_3CO_2H, CH_2Cl_2; (c) **51**, $Na(OAc)_3BH$, 1,2-dichloroethane; (d) *N*-(3-bromopropyl)phthalimide, K_2CO_3, DMF; (e) NH_2NH_2, EtOH.



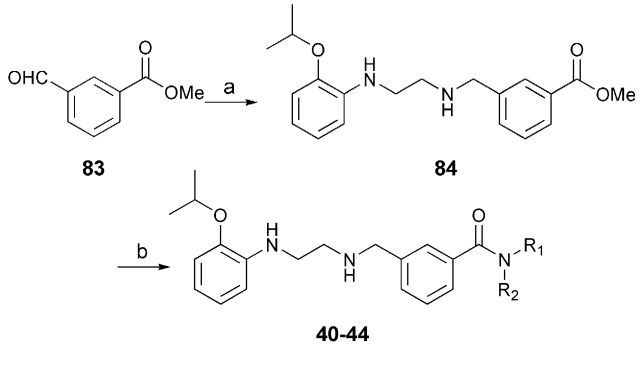
Scheme 9. Reagents: (a) *N*-*t*-Boc-ethanolamine, DBAD, Ph_3P, THF; (b) CF_3CO_2H, CH_2Cl_2; (c) **51**, $Na(OAc)_3BH$, 1,2-dichloroethane; (d) NaOH, THF–H_2O; (e) 2-iodopropane, K_2CO_3, DMF.

accessed by treatment of **79** with amine **56** to provide **37**. Reduction of **37** under hydrogenation conditions furnished aniline **38**. Alternatively, protection of the benzylic nitrogen and reduction of the nitro group gave aniline **81**, which was alkylated with 2-iodopropane to afford compound **82**. Removal of the *N*-Boc group in **82** afforded the desired isostere **39**.

Lastly, a series of compounds designed to probe the importance of the piperidine amide in **4a** were synthesized and their preparation is outlined in Scheme 13. Thus, reductive amination of methyl(3-formyl benzoic acid) (**83**) with **48** provided ester **84**. Further treatment of **84** with a series of amines under Weinreb and coworkers conditions[19] furnished amides **40**–**44**.



Scheme 10. Reagents: (a) 2-iodopropane, K_2CO_3, DMF; (b) NH_3–MeOH; (c) LAH, THF; (d) **51**, $Na(OAc)_3BH$, 1,2-dichloroethane.

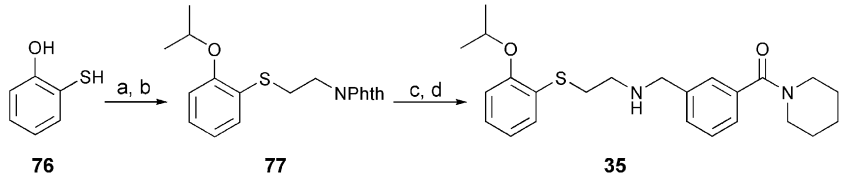


Scheme 13. Reagents: (a) **48**, $Na(OAc)_3BH$, 1,2-dichloroethane; (b) R_1 R_2–NH, $AlMe_3$, toluene.

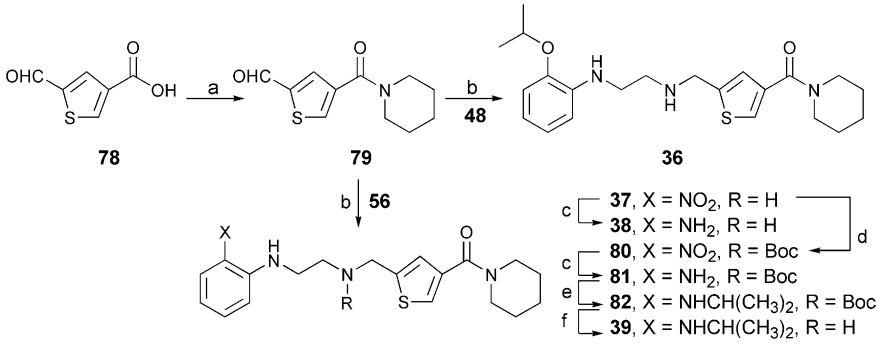
3. Results and discussion

GlyT-2 inhibitory activity was determined by the ability of compounds to inhibit the uptake of [^{14}C]-glycine in COS-7 cells transfected with the human glycine transporter-2 (GlyT-2).[20] As the data in Table 1 indicates, replacement of the isopropyl ether moiety at the C-2 position with cyclopentyl **6**, 2-pentanyl **8**, methyl **9**, or phenyl unit **10** afforded compounds that were 2.5–3.5-fold less potent than **4a**. Relocating the isopropoxy group **5** or the methoxy substituent **7** to the C-3 position was well tolerated and only resulted in a 2-fold decrease in potency. The absence of activity (IC_{50}'s $> 10\,\mu M$) for the phenol derivative **11** clearly indicates that an ether moiety is important for retaining biological activity. Replacing the C-2 ether moiety with a methylsulfonamide **16**, phenyl urea **17**, or a benzyl urea **17** revealed that a nonbasic nitrogen was important for maintaining biological activity. However, as a group, these analogs were 6-fold less potent than **4a**. Similar to the results observed for phenol **11**, the unsubstituted aniline **14** was also devoid of activity. Within the halogenated series of derivatives, the C-2 bromo **19**, and C-2 chloro **20** analogs were equivalent in activity (IC_{50}'s = 1.0 and 1.2 μM, respectively) and only slightly less potent than **4a**. The C-3 halogen analogs (**21** and **22**) were also equipotent, but 6-fold less active than **4a**. The C-2 carbon-linked analogs containing either an isopropyl or thienyl substituent **23** and **24**, respectively, displayed moderate GlyT-2 inhibitory activity, however, the methoxyphenyl analog **25** was devoid of activity.

The results for modifications carried out to the tether are provided in Table 2. Direct comparison of **4a** and **4b** clearly show that inclusion of the 2-carbon tether is preferred relative to the 3-carbon tether by 10-fold. Focusing on the *N*-methylated analogs (**26**–**30**) it is apparent that methylation of the benzylic nitrogen de-

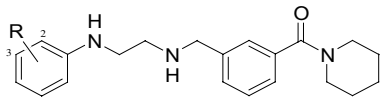


Scheme 11. Reagents: (a) *N*-(2-bromoethyl)phthalimide, K_2CO_3, DMF; (b) 2-iodopropane, K_2CO_3, DMF; (c) NH_2NH_2, EtOH; (d) **51**, $Na(OAc)_3BH$, 1,2-dichloroethane.



Scheme 12. Reagents: (a) piperidine, EDCI, HOBT, DMF; (b) $Na(OAc)_3BH$, 1,2-dichloroethane; (c) H_2, Pd/C, EtOH; (d) $(Boc)_2O$, Et_3N, CH_2Cl_2; (e) 2-iodopropane, K_2CO_3, DMF; (f) HCl–dioxane, CH_2Cl_2.

Table 1. GlyT-2 antagonist activity for substituted aryl ring derivatives



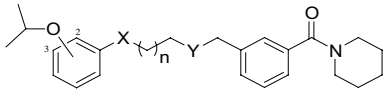
Compound	R	IC_{50} (μM)	Compound	R	IC_{50} (μM)
4a	2-$OCH(CH_3)_2$	0.54[a]	**15**	2-$NHCH(CH_3)_2$	0.63a
5	3-$OCH(CH_3)_2$	1.00	**16**	2-$NHSO_2Ph$	3.10
6	2-OC_5H_9	1.20	**17**	2-NHCONHPh	3.00
7	3-OCH_3	0.80	**18**	2-$NHCONHCH_2Ph$	3.00
8	2-OC_5H_{11}	3.16	**19**	2-Br	1.00
9	2-OCH_3	2.50	**20**	2-CI	1.20
10	2-OPh	3.00	**21**	3-Br	3.00
11	2-OH	>10	**22**	3-CI	3.00
12	H	>10	**23**	2-$CH(CH_3)_2$	2.50
13	2-NO_2	5.00	**24**	2-(3-Thienyl)	0.95
14	2-NH_2	>10	**25**	2-(Ph-2-OCH_3)	>10

[a] Compounds **4a** and **15** had IC_{50}'s >10,000 nM at the GlyT-1 transporter.

stroys biological activity when the isopropoxy unit is attached at the C-2 position. In contrast, methylation of the anilino nitrogen leads to a decrease in potency, but it is not completely abolished. Interestingly, methylation of the benzylic nitrogen does not significantly affect GlyT-2 inhibitory activity when the isopropoxy unit is appended to the C-3 position (i.e., compounds **29** and **30**). Additionally, in comparing compounds **4a** and **5**, it is apparent that the length of the tether plays a greater role in GlyT-2 inhibition than does the location of the isopropoxy substituent. The carbon **34** and sulfur **35** analogs maintained moderate activity while lacking the ability to serve as a hydrogen bond donor. Interestingly, the two oxygen isosteres **31** and **32** displayed an almost identical profile to the nitrogen analogs **4a** and **4b**, with **31** being equivalent in potency to the lead **4a**.

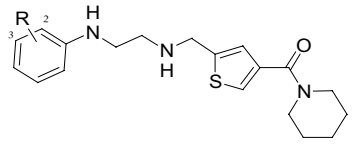
The data from Table 3 indicate that greater diversity within this series can be achieved by replacing the benzene ring with a thiophene bioisostere, but this transformation does not lead to an improvement in GlyT-2 inhibitory activity.

Table 2. GlyT-2 antagonist activity for tether modified derivatives



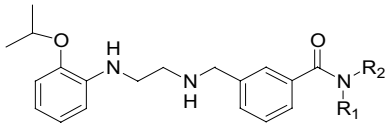
Compound	O-*i*-Pr	X	*n*	Y	ICF_{50} (μM)
4a	2	NH	1	NH	0.54
4b	2	NH	2	NH	4.00
5	3	NH	1	NH	1.00
26	2	NH	1	NCH_3	>10
27	2	NCH_3	1	NH	3.54
28	2	NCH_3	1	NCH_3	>10
29	3	NH	1	NCH_3	1.60
30	3	NCH_3	1	NCH_3	1.60
31	2	0	1	NH	0.40
32	2	0	2	NH	3.00
33	2	0	1	NH	1.60
34	2	CH_2	1	NH	3.98
35	2	S	1	NH	1.60

Table 3. GlyT-2 antagonist activity for the thiophene derivatives



Compound	X	IC_{50} (μM)
36	2-$OCH(CH_3)_2$	3.1
37	$2NO_2$	>10
38	$2NH_2$	>10
39	2-$NHCH(CH_3)_2$	3.1

Table 4. GlyT-2 antagonist activity for various amide derivatives



Compound	R_1	R_2	IC_{50} (μM)
4a	Piperidine	Piperidine	0.54
40	Homopiperidine	Homopiperidine	1.80
41	Pyrrolidine	Pyrrolidine	3.00
42	Ethyl	Ethyl	10.0
43	Morpholine	Morpholine	10.0
44	4-Hydroxypiperidine	4-Hydroxypiperidine	10.0

Lastly, the amide congeners included in Table 4 reveal the highly sensitive nature of this region to minor structural changes. Only the homologous ring-expanded and ring-contracted analogs (**40** and **41**, respectively) displayed measurable GlyT-2 inhibitory activity. The *N*,*N*-diethyl **42**, morpholino **43**, and 4-hydroxypiperidine **44** analogs were essentially inactive as GlyT-2 inhibitors.

4. Conclusion

A study aimed at improving the GlyT-2 inhibitory activity of **4a** was undertaken. Two compounds, **15** and **31**, were identified as having potency equal to the initial

lead **4a**. However, the benzoylpiperidine region (Fig. 1) was unable to tolerate minor structural modifications without a concomitant loss of activity. On the other hand, the distal aromatic and tether region were able to accommodate moderate alterations. The most potent compounds resulting from this study, **4a**, **15**, and **31**, were more than 20-fold selective for the GlyT-2 transporter over the GlyT-1 transporter. While these studies did not lead to an overall improvement in GlyT-2 inhibitory activity, we were able to demonstrate that moderately potent and highly selective ligands could be developed for this transporter.

5. Experimental

5.1. General

NMR spectra were obtained on either a Bruker model DPX400 (400 MHz) or DPX500 (500 MHz) spectrometer. The format of the ^{1}H NMR data below is: chemical shift in ppm down field of the tetramethylsilane reference (multiplicity, coupling constant J in Hz, integration). Mass spectra were obtained on an Agilent series 1100 MSD using electrospray ionization (ESI) in either positive or negative mode as indicated. The 'mass calculated' for a molecular formula is the monoisotopic mass of the compound. Flash column chromatography was accomplished using the ISCO Foxy 200 system and one of the following commercially available, prepacked columns: Biotage 40S (SiO_2; 40 g), Biotage 40M (SiO_2; 90 g), Biotage 40L (SiO_2; 120 g), Biotage 65M (SiO_2; 300 g), or ISCO Redisep (SiO_2; 10, 12, 35, 40, or 120 g). Preparative TLC was accomplished using PLC plates (20 × 20 cm silica gel 60 F_{254}, 0.5 mm).

5.2. (3-{[2-(2-Isopropoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (4a)

To a solution of 2-nitrophenol (0.14 g, 1.0 mmol) in DMF (2 mL) was added K_2CO_3 (0.69 g, 5.0 mmol), and the resulting suspension was stirred for 15 min. 2-Iodopropane (0.34 g, 2.0 mmol) was added. The reaction mixture was stirred at 25 °C overnight, then was diluted with ethyl acetate (EtOAc, 20 mL), and washed with H_2O (10 mL), 1 N NaOH (2 × 20 mL), satd $NaHCO_3$ (2 × 20 mL) and then brine (20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a yellow oil (0.141 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 1.5, 8.0 Hz, 1H), 7.48 (dt, J = 1.6, 8.7 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 6.98 (t, J = 8.2 Hz, 1H), 4.67 (hp, J = 6.1 Hz, 1H), 1.39 (d, J = 6.1 Hz, 6H).

5.2.1. B. 2-Isopropoxy-phenylamine. To a solution of 1-isopropoxy-2-nitro-benzene (10 g, 55 mmol) in THF (100 mL) was added a solution of sodium hydrosulfite (48 g, 280 mmol) in H_2O (200 mL). The reaction mixture was stirred at 25 °C for 1 h then at 55 °C for 2 h. The mixture was treated with 1 N HCl (50 mL), followed by 1 N NaOH (50 mL) to neutralize the solution, and then was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (CH_2Cl_2) to provide a tan oil (2.2 g, 26%). MS (ESI): mass calculated for $C_9H_{13}NO$, 151.10; m/z found, 152.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81–6.68 (m, 4H), 4.52 (hp, J = 6.1 Hz, 1H), 3.64 (br s, 2H), 1.35 (d, J = 6.1 Hz, 6H).

5.2.2. C. N^1-(2-Isopropoxy-phenyl)-ethane-1,2-diamine. To a solution of 2-isopropoxy-phenylamine (2.18 g, 14.4 mmol) in isopropanol (20 mL) was added 2-chloroethylamine hydrochloride (2.3 g, 20 mmol), and the mixture was stirred at 85 °C for 24 h. Triethylamine (1.46 g, 14.4 mmol) was added, and the resulting mixture was stirred at 85 °C for 24 h. The reaction mixture was made basic using 1 N NaOH (40 mL), and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (1:10:150 $NH_4OH/CH_3OH/CH_2Cl_2$, then with 10% CH_3OH/CH_2Cl_2) to give a brown oil (0.59 g, 21%). MS (ESI): mass calculated for $C_{11}H_{18}N_2O$, 194.14; m/z found, 195.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (dt, J = 7.6, 1.4 Hz, 1H), 6.77 (dd, J = 8.0, 1.4 Hz, 1H), 6.65–6.61 (m, 2H), 4.52 (hp, J = 6.1 Hz, 1H), 3.22 (t, J = 5.8 Hz, 2H), 2.94 (t, J = 6.0 Hz, 2H), 1.61 (br s, 2H), 1.35 (d, J = 6.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 139.2, 121.2, 116.4, 112.5, 110.2, 70.6, 46.5, 41.2, 22.3.

5.2.3. D. 3-(Piperidine-1-carbonyl)-benzaldehyde. To a solution of 3-formyl-benzoic acid (2.0 g, 13 mmol) in DMF (130 mL) was added piperidine (1.25 g, 14.7 mmol), and the resulting solution was stirred at 25 °C for 15 min. The solution was treated with HOBt (2.7 g, 20 mmol) and EDCI (3.8 g, 20 mmol), and the reaction mixture was stirred at 25 °C for 18 h. The mixture was partitioned with H_2O (250 mL) and EtOAc (300 mL), and the organic layer was washed with 1 M NaOH (100 mL), 1 M HCl (100 mL) then brine (100 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a colorless oil (2.21 g, 76%). MS (ESI): mass calculated for $C_{13}H_{15}NO_2$, 217.11; m/z found, 218.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.94–7.90 (m, 2H), 7.68–7.57 (m, 2H), 3.73 (br s, 2H), 3.34 (br s, 2H), 1.70–1.54 (m, 6H).

5.2.4. E. (3-{[2-(2-Isopropoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. To a solution of N^1-(2-isopropoxy-phenyl)-ethane-1,2-diamine (0.228 g, 1.17 mmol) in 1,2-dichloroethane (2.8 mL) was added a solution of 3-(piperidine-1-carbonyl)-benzaldehyde (0.213 g, 0.980 mmol), and the mixture was stirred at 25 °C for 15 min. The mixture was treated with $NaBH(OAc)_3$ (0.311 g, 1.47 mmol), and the resulting suspension was stirred at 25 °C for 5 h. The suspension was partitioned with 1 M NaOH (25 mL) and EtOAc

(50 mL), and the organic layer was washed with brine (25 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (0–5% CH_3OH/CH_2Cl_2) to provide the desired product as a colorless oil (0.256 g, 66%). MS (ESI): mass calculated for $C_{24}H_{33}N_3O_2$, 395.26; m/z found, 396.3 $[M+H]^+$, 418.3 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.23 (m, 4H), 6.85–6.76 (m, 2H), 6.65–6.60 (m, 2H), 4.51 (hp, $J = 6.1$ Hz, 1H), 3.84 (s, 3H), 3.69 (br s, 2H), 3.31 (br s, 2H), 3.27 (t, $J = 5.9$ Hz, 2H), 2.91 (t, $J = 6.0$ Hz, 2H), 1.66–1.49 (br m, 6H), 1.35 (d, $J = 6.1$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 145.0, 140.4, 139.3, 136.6, 129.0, 128.4, 126.4, 125.3, 121.2, 116.4, 112.5, 110.3, 53.2, 48.7, 48.1, 43.3, 43.0, 26.5, 25.6, 24.5, 22.3.

5.3. (3{[3-(2-Isopropoxy-phenylamino)-propylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (4b)

5.3.1. A. N^1-(2-Isopropoxy-phenyl)-propane-1,3-diamine. To a solution of 2-isopropoxy-phenylamine (0.50 g, 3.3 mmol) in isopropanol (7 mL) was added Et_3N (0.67 g, 6.6 mmol) and 3-chloropropylamine hydrochloride (0.515 g, 3.96 mmol). The reaction mixture was heated to 50 °C for 24 h, then to 90 °C for 24 h. The mixture was treated with saturated $NaHCO_3$ (20 mL), EtOAc (40 mL) and H_2O (20 mL), and then the aqueous layer was back-extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (50–100% EtOAc/hexanes) to provide an amber oil (0.10 g, 15%). MS (ESI): mass calculated for $C_{12}H_{20}N_2O$, 208.16; m/z found, 209.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.85–6.81 (m, 1H), 6.77–6.60 (m, 1H), 6.66–6.60 (m, 2H), 4.51 (hp, $J = 6.1$ Hz, 1H), 3.27 (t, $J = 6.6$ Hz, 2H), 3.10 (t, $J = 7.0$ Hz, 2H), 2.06 (p, $J = 6.7$ Hz, 2H), 1.34 (d, $J = 6.1$ Hz, 6H).

5.3.2. B. (3-{[3-(2-Isopropoxy-phenylamino)-propylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. The title compound was prepared similarly to **4a**, steps D and E, substituting N^1-(2-isopropoxy-phenyl)-propane-1,3-diamine for N^1-(2-isopropoxy-phenyl)-ethane-1,2-diamine in step E. MS (ESI): mass calculated for $C_{25}H_{35}N_3O_2$, 409.27; m/z found, 410.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.32 (m, 3H), 7.26–7.22 (m, 1H), 6.87–6.82 (m, 1H), 6.78–6.76 (m, 1H), 6.64–6.60 (m, 2H), 4.54–4.45 (m, 1H), 3.84 (br s, 2H), 3.71 (br s, 2H), 3.32 (br s, 2H), 3.21 (t, $J = 6.7$ Hz, 2H), 2.78 (t, $J = 6.8$ Hz, 2H), 1.90–1.84 (m, 2H), 1.67 (br s, 4H), 1.51 (br s, 2H), 1.33 (d, $J = 6.1$ Hz, 6H).

5.4. (3-{[2-(3-Isopropoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (5)

The title compound was prepared similarly to **4a**, steps C–E, substituting 3-isopropoxyphenylamine for 2-isopropoxyphenylamine in step C.

5.4.1. A. N^1-(3-Isopropoxy-phenyl)-ethane-1,2-diamine. MS (ESI): mass calculated for $C_{11}H_{18}N_2O$, 194.14; m/z found, 195.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (t, $J = 8.1$ Hz, 1H), 6.27–6.19 (m, 2H), 6.19 (br s, 1H), 4.51 (hp, $J = 6.1$ Hz, 1H), 3.41–3.22 (m, 6H), 2.93 (br s, 2H), 1.31 (d, $J = 6.1$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 149.3, 129.8, 105.8, 104.4, 100.8, 69.5, 44.8, 40.1, 21.9.

5.4.2. B. (3-{[2-(3-Isopropoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. MS (ESI): mass calculated for $C_{24}H_{33}N_3O_2$, 395.26; m/z found, 396.4 $[M+H]^+$, 418.4 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.23 (m, 4H), 7.03 (t, $J = 8.0$ Hz, 1H), 4.49 (hp, $J = 6.1$ Hz, 1H), 3.80 (s, 2H), 3.69 (br s, 2H), 3.30 (br s, 2H), 3.18 (t, $J = 5.5$ Hz, 2H), 2.85 (t, $J = 5.5$ Hz, 2H), 1.65–1.45 (m, 6H), 1.30 (d, $J = 6.0$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 158.9, 149.7, 140.4, 136.4, 129.7, 128.9, 128.3, 126.2, 125.1, 105.8, 104.2, 100.6, 69.3, 53.1, 48.6, 47.8, 43.2, 42.9, 26.4, 25.4, 24.4, 22.0.

5.5. (3-{[2-(2-Cyclopentyloxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (6)

The title compound was prepared similarly to **4a**, steps A–E substituting iodocyclopentane for 2-iodopropane in step A.

5.5.1. A. 1-Cyclopentyloxy-2-nitro-benzene. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, $J = 8.7$, 1.7 Hz, 1H), 7.50–7.46 (m, 1H), 7.08–7.06 (m, 1H), 6.99–6.94 (m, 1H), 4.92–4.88 (m, 1H), 1.94–1.90 (m, 4H), 1.87–1.81 (m, 2H), 1.65–1.62 (m, 2H).

5.5.2. B. 2-Cyclopentyloxy-phenylamine. To a solution of 1-cyclopentyloxy-2-nitro-benzene (5.0 g, 24 mmol) in ethanol (EtOH, 95 mL) was added Pd on carbon (Pd/C; 10 wt %, 5.14 g), and the resulting suspension was stirred under H_2 (50 psi) at 25 °C for 6 h. The suspension was filtered (Celite®), and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography (5–10% EtOAc/hexanes) to provide the desired product (3.6 g, 84%). MS (ESI): mass calculated for $C_{11}H_{15}NO$, 177.12; m/z found, 178.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.80–6.68 (m, 4H), 4.80–4.76 (m, 1H), 1.94–1.85 (m, 4H), 1.83–1.73 (m, 2H), 1.68–1.58 (m, 2H).

5.5.3. C. N^1-(2-Cyclopentyloxy-phenyl)-ethane-1,2-diamine. ^1H NMR (400 MHz, $CDCl_3$) δ 6.82 (dt, $J = 7.6$, 1.3 Hz, 1H), 6.76–6.74 (m, 1H), 6.66–6.61 (m, 2H), 4.78–4.74 (m, 1H), 3.38 (br s, 2H), 3.29 (t, $J = 5.7$ Hz, 2H), 3.06–2.91 (m, 2H), 1.96–1.87 (m, 4H), 1.86–1.75 (m, 2H), 1.69–1.55 (m, 2H).

5.5.4. D. (3-{[2-(2-Cyclopentyloxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. MS (ESI): mass calculated for $C_{26}H_{35}N_3O_2$, 421.27, m/z found, 422.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ

7.41–7.39 (m, 1H), 7.35–7.32 (m, 2H), 7.26–7.24 (m, 1H), 6.83 (dt, $J = 7.6$, 1.4 Hz, 1H), 6.76 (dd, $J = 7.6$, 1.2 Hz, 1H), 6.65–6.61 (m, 2H), 4.80–4.75 (m, 1H), 3.85 (s, 2H), 3.70 (br s, 2H), 3.32 (br s, 2H), 3.27 (t, $J = 5.8$ Hz, 2H), 2.92 (t, $J = 5.8$ Hz, 2H), 1.96–1.73 (m, 7H), 1.67–1.57 (m, 6H), 1.50 (br s, 2H).

5.6. (3{[2-(3-Methoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (7)

The title compound was prepared similarly to **4a**, steps C–E, substituting 3-methoxy-phenylamine for 2-isopropoxy-phenylamine in step C.

5.6.1. A. N^1-(3-Methoxy-phenyl)-ethane-1,2-diamine. MS (ESI): mass calculated for $C_9H_{14}N_2O$, 166.11; m/z found, 167.1 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6, HCl salt) δ 8.18 (br s, 2H), 7.00–6.96 (m, 1H), 6.22–6.15 (m, 3H), 5.93 (br s, 1H), 3.67 (s, 3H), 3.35–3.26 (m, 2H), 5.93 (br s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.4, 149.4, 129.7, 105.4, 101.9, 98.0, 54.7, 25.5.

5.6.2. B. (3-{[2-(3-Methoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. MS (ESI): mass calculated for $C_{22}H_{29}N_3O_2$, 367.23, m/z found, 368.3 $[M+H]^+$, 390.3 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.23 (m, 4H), 7.06 (t, $J = 8.1$ Hz, 1H), 6.25 (dt, $J = 8.0$, 2.2 Hz, 2H), 6.18 (t, $J = 2.2$ Hz, 1H), 2.10 (s, 2H), 3.75 (s, 3H), 3.69 (br s, 2H), 3.31 (br s, 2H), 3.21 (t, $J = 5.6$ Hz, 2H), 2.89 (t, $J = 5.9$ Hz, 2H), 1.66 (br s, 4H), 1.49 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 160.7, 149.7, 140.1, 136.6, 129.9, 129.0, 128.4, 126.4, 125.4, 106.0, 102.5, 98.8, 55.0, 53.1, 48.7, 47.8, 43.1, 26.4, 25.5, 24.5.

5.7. [3-({[2-(1-Ethyl-propoxy)-phenylamino]-ethylamino}-methyl)-phenyl]-piperidin-1-yl-methanone (8)

The title compound was prepared similarly to **4a**, steps A–E substituting 3-iodopentane for 2-iodopropane in step A.

5.7.1. A. 1-(1-Ethyl-propoxy)-2-nitro-benzene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, $J = 5.1$, 1.7 Hz, 1H), 7.50–7.46 (m, 1H), 7.08–7.06 (m, 1H), 6.99–6.94 (m, 1H), 4.92–4.88 (m, 1H), 1.94–1.90 (m, 4H), 1.87–1.81 (m, 2H), 1.65–1.62 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 133.6, 125.4, 119.6, 115.5, 81.3, 32.7, 23.8.

5.7.2. B. 2-(1-Ethyl-propoxy)-phenylamine. MS (ESI): mass calculated for $C_{11}H_{17}NO$, 179.13, m/z found, 180.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78–6.66 (m, 4H), 4.12 (p, $J = 5.8$ Hz, 1H), 3.55 (br s, 2H), 1.73–1.66 (m, 4H), 0.96 (t, $J = 7.5$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 137.1, 120.8, 118.3, 115.2, 113.2, 80.5, 26.1, 9.6.

5.7.3. C. N^1-[2-(1-Ethyl-propoxy)-phenyl]-ethane-1,2-diamine. MS (ESI): mass calculated for $C_{13}H_{22}N_2O$, 222.17; m/z found, 223.3 $[M+H]^+$.

5.7.4. D. [3-({2-[2-(1-Ethyl-propoxy)-phenylamino]-ethylamino}-methyl)-phenyl]-piperidin-1-yl-methanone. MS (ESI): mass calculated for $C_{26}H_{37}N_3O_2$, 423.29, m/z found, 424.5 $[M+H]^+$, 446.5 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.39 (m, 1H), 7.34–7.31 (m, 2H), 7.26–7.24 (m, 1H), 6.85–6.81 (m, 1H), 6.76–6.74 (m, 1H), 6.64–6.60 (m, 2H), 4.12 (p, $J = 5.8$ Hz, 1H), 3.85 (br s, 2H), 3.70 (br s, 2H), 3.30–3.27 (m, 4H), 2.92 0.96 (t, $J = 5.9$ Hz, 2H), 1.73–1.66 (m, 8H), 1.49 (br s, 2H), 0.95 (t, $J = 7.4$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 145.5, 140.3, 139.2, 136.6, 129.0, 128.4, 126.4, 125.3, 121.0, 116.3, 112.2, 110.2, 80.6, 53.2, 48.7, 48.0, 43.2, 43.1, 26.4, 26.1, 25.6, 24.5, 9.6.

5.8. (3-{[2-(2-Methoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (9)

The title compound was prepared similarly to **4a**, steps C–E, substituting 2-methoxy-phenylamine for 2-isopropoxy-phenylamine in step C.

5.8.1. A. N^1-(2-Methoxy-phenyl)-ethane-1,2-diamine. MS (ESI): mass calculated for $C_9H_{14}N_2O$, 166.11, m/z found, 167.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br s, 2H), 6.83–6.76 (m, 2H), 6.62–6.56 (m, 2H), 5.19 (br t, $J = 4.3$ Hz, 1H), 3.76 (s, 3H), 3.37–3.32 (br t, $J = 4.9$, 4.6 Hz, 2H), 2.95 (t, $J = 4.8$ Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.6, 137.3, 121.0, 116.2, 110.0, 109.2, 55.3, 37.7.

5.8.2. B. (3-{[2-(2-Methoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. MS (ESI): mass calculated for $C_{22}H_{29}N_3O_2$, 367.23; m/z found, 368.3 $[M+H]^+$, 390.2 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 3H), 7.26–7.23 (m, 1H), 6.85 (dt, $J = 7.6$, 1.3 Hz, 1H), 6.75 (dd, $J = 7.9$, 1.3 Hz, 1H), 6.65 (dt, $J = 7.6$, 1.4 Hz, 1H), 6.61 (d, $J = 7.8$ Hz, 2H), 3.85–3.81 (m, 5H), 3.69 (br s, 2H), 3.31 (br s, 2H), 3.26 (t, $J = 5.8$ Hz, 2H), 2.91 (t, $J = 6.0$ Hz, 2H), 1.65 (br s, 4H), 1.49 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 146.8, 140.2, 138.1, 136.5, 129.0, 128.3, 126.3, 125.3, 121.1, 116.4, 109.8, 109.3, 55.3, 53.1, 48.6, 47.9, 43.1, 43.0, 26.4, 25.5, 24.4.

5.9. (3-{[2-(2-Phenoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (10)

The title compound was prepared similarly to **4a**, steps C–E substituting 2-phenoxy-phenylamine for 2-isopropoxy-phenylamine in step C.

5.9.1. A. N^1-(2-Phenoxy-phenyl)-ethane-1,2-diamine. MS (ESI): mass calculated for $C_{14}H_{16}N_2O$, 228.13; m/z

found, 229.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (br s, 1H), 7.28–6.67 (m, 9H), 3.55–3.15 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 137.7, 129.6, 124.5, 123.1, 118.7, 118.6, 118.0, 112.7, 41.5, 39.0.

5.9.2. B. (3-{[2-(2-Phenoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. MS (ESI): mass calculated for $C_{27}H_{31}N_3O_2$, 429.24; m/z found, 430.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.22 (m, 6H), 7.05–6.95 (m, 4H), 6.84 (dd, $J = 7.8$, 1.4 Hz, 1H), 6.75 (dd, $J = 8.0$, 1.4 Hz, 1H), 6.64 (dt, $J = 7.8$, 1.4 Hz, 1H), 4.54 (br s, 1H), 3.76 (s, 2H), 3.69 (br s, 2H), 3.39–3.25 (m, containing a t, $J = 5.8$ Hz, 4H), 2.85 (t, $J = 6.0$ Hz, 2H), 1.85 (br s, 1H), 1.65 (br s, 4H), 1.48 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 157.5, 143.1, 141.7, 140.5, 140.5, 136.6, 136.5, 129.6, 128.9, 128.4, 127.7, 126.3, 125.6, 125.3, 124.9, 122.6, 119.3, 117.3, 116.7, 111.6, 64.5, 53.1, 48.7, 47.9, 43.1, 26.4, 25.5, 24.5.

5.10. (3{[2-(2-Hydroxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (11)

The title compound was prepared similarly to **4a**, steps C–E, substituting 2-aminophenol for 2-isopropoxy-phenylamine in Step C.

5.10.1. A. 2-(2-Amino-ethylamino)-phenol. MS (ESI): mass calculated for $C_8H_{12}N_2O$, 152.09; m/z found, 153.1 $[M+H]^+$. ^1H NMR (400 MHz, D_2O) δ 6.77–6.71 (m, 2H), 6.64–6.57 (m, 2H), 3.31 (t, $J = 6.1$ Hz, 2H), 3.05 (t, $J = 6.0$ Hz, 2H). ^1H NMR (400 MHz, DMSO-d_6) δ 9.35 (br s, 1H), 8.21 (br s, 2H), 6.72 (dd, $J = 7.7$, 1.3 Hz, 1H), 6.63 (dt, $J = 7.7$, 1.3 Hz, 1H), 6.55 (dd, $J = 7.8$, 1.3 Hz, 1H), 6.44 (dt, $J = 7.5$, 1.4 Hz, 1H). ^{13}C NMR (100 MHz, D_2O) δ 144.5, 136.3, 121.7, 119.3, 115.3, 112.8, 41.0, 38.8.

5.10.2. B. (3-{[2-(2-Hydroxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. MS (ESI): mass calculated for $C_{21}H_{27}N_3O_2$, 353.21; m/z found, 354.1 $[M+H]^+$, 376.1 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.21 (m, 4H), 6.74–6.70 (m, 1H), 6.62–6.50 (m, 3H), 3.79 (s, 3H), 3.69 (br s, 2H), 3.28 (br s, 2H), 3.21 (t, $J = 5.3$ Hz, 2H), 2.82 (t, $J = 5.5$ Hz, 2H), 1.64 (br s, 4H), 1.45 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 145.3, 139.6, 137.4, 136.2, 129.5, 128.4, 126.7, 125.4, 120.3, 117.9, 114.8, 112.5, 52.9, 48.7, 47.7, 43.9, 43.2, 26.4, 25.5, 24.4.

5.11. {3-[(2-Phenylamino-ethylamino)-methyl]-phenyl}-piperidin-1-yl-methanone (12)

The title compound was prepared similarly to **4a**, steps D and E, substituting N^1-phenylethane-1,2-diamine for N^1-(2-isopropoxy-phenyl)-ethane-1,2-diamine in step E. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 3H), 7.26–7.25 (m, 1H), 7.19–7.14 (m, 2H), 6.70 (t, $J = 7.4$ Hz, 1H), 6.63 (d, $J = 7.7$ Hz, 2H), 3.85 (s, 2H), 3.70 (br s, 2H), 3.31 (br s, 2H), 3.25 (t, $J = 5.7$ Hz, 2H), 2.93 (t, $J = 5.7$ Hz, 2H), 1.67 (br s, 4H), 1.50 (br s, 2H), 1.26 (br s, 2H).

5.12. (3-{[2-(2-Nitro-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (13)

5.12.1. A. N^1-(2-Nitro-phenyl)-ethane-1,2-diamine. To a mixture of ethylenediamine (1.05 g, 17.5 mmol) and K_2CO_3 (2.44 g, 17.7 mmol) in anhydrous CH_3CN (300 mL) heated to 70 °C, a solution of *o*-fluoronitrobenzene (1.25 g, 8.87 mmol) in CH_3CN (50 mL) was added drop wise over 2 h. The resulting suspension was stirred at 70 °C for 1 h, and then allowed to cool to 25 °C and stirred for 18 h. The suspension was filtered, and the filtrate was concentrated under reduced pressure. The crude residue was partitioned between water (200 mL) and CH_2Cl_2 (200 mL), and the organic layer was washed with water (2×200 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a bright yellow semisolid (1.5 g, 78%). MS (ESI): mass calculated for $C_8H_{11}N_3O_2$, 181.09; m/z found, 182.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (br s, 1H), 8.17 (dd, $J = 8.6$, 1.6 Hz, 1H), 7.46–7.41 (m, 1H), 6.86 (dd, $J = 8.7$, 0.82 Hz, 1H), 6.63–6.62 (m, 1H), 3.39 (q, $J = 5.7$ Hz, 2H), 3.06 (t, $J = 5.7$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.8, 45.7, 113.4, 115.3, 127.1, 136.2, 145.6 ppm.

5.12.2. B. (3-{[2-(2-Nitro-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. The title compound was prepared similarly to **4a**, steps D and E, substituting N^1-(2-nitro-phenyl)-ethane-1,2-diamine for N^1-(2-isoproxy-phenyl)-ethane-1,2-diamine in step E, yielding a bright yellow semisolid (2.18 g, 89%). MS (ESI): mass calculated for $C_{21}H_{26}N_4O_3$, 282.20; m/z found, 283.2 $[M+H]^+$, 405.2 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (br s, 1H), 8.15 (dd, $J = 8.6$, 1.6 Hz, 1H), 7.44–7.33 (m, 4H), 7.29–7.25 (m, 1H), 6.83 (dd, $J = 8.6$, 0.7 Hz, 1H), 6.64–6.60 (m, 1H), 3.87 (s, 2H), 3.70 (br s, 2H), 3.38 (q, $J = 5.8$ Hz, 2H), 3.33 (br s, 2H), 3.06 (t, $J = 5.8$ Hz, 2H), 1.67 (br s, 4H), 1.50 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 145.4, 140.5, 136.7, 136.2, 131.9, 129.0, 128.5, 126.8, 126.4, 125.4, 115.2, 113.9, 53.5, 48.8, 47.3, 43.1, 42.6, 26.5, 25.6, 24.6.

5.13. (3-{[2-(2-Amino-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (14)

To a solution of (3-{[2-(2-nitro-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (0.060 g, 0.16 mmol) in EtOH (1.6 mL) was added cyclohexadiene (0.55 mL) followed by Pd/C (10 wt %, 0.02 g), and the resulting suspension was heated to 100 °C for 45 min. The suspension was filtered (Celite®), and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography (0–5% CH_3OH/CH_2Cl_2) to provide the product as a colorless oil (0.034 g, 61%). MS (ESI): mass calculated for

$C_{21}H_{28}N_4O$, 352.23; m/z found, 353.2 $[M+H]^+$, 375.2 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 3H), 7.26–7.24 (m, 1H), 6.80 (d t, $J = 5.4$, 1.9 Hz, 1H), 6.72–6.64 (m, 3H), 3.84 (br s, 2H), 3.70 (br s, 2H), 3.32 (br s, 2H), 3.21 (t, $J = 5.7$ Hz, 2H), 2.94 (t, $J = 5.7$ Hz, 2H), 1.67 (br s, 4H), 1.50 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 140.7, 137.7, 136.7, 134.6, 129.1, 128.4, 126.5, 125.3, 120.5, 118.7, 116.3, 112.0, 53.3, 48.1, 43.8, 29.7, 26.5, 24.6 ppm.

5.14. (3-{[2-(2-Isopropylamino-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (15)

5.14.1. A. [2-(2-Nitro-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester. To a solution of (3-{[2-(2-nitro-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (2.18 g, 5.70 mmol) in CH_2Cl_2 (25 mL) was added a solution of di-*tert*-butyl-dicarbonate (1.24 g, 5.68 mmol) in CH_2Cl_2 (32 mL), and the resulting solution was stirred at 25 °C for 2 h. The solvent was removed in vacuo, and the residue was partitioned between water (100 mL) and EtOAc (100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (0–8% CH_3OH/CH_2Cl_2) to provide a bright yellow semisolid (2.36 g, 86%). MS (ESI): mass calculated for $C_{26}H_{34}N_4O_5$, 482.25; m/z found, 483.2 $[M+H]^+$, 505.2 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 8.09 (d, $J = 8.5$ Hz, 1H), 7.44–7.27 (m, 5H), 6.88–6.83 (m, 1H), 6.61 (t, $J = 7.6$ Hz, 1H), 4.50–4.54 (m, 2H), 3.68–3.30 (m, 8H), 1.65 (br s, 4H), 1.48 (br s, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 156.0, 145.6, 139.0, 137.2, 136.5, 132.2, 129.0, 128.3, 126.9, 126.4, 126.0, 115.7, 114.0, 80.8, 51.6, 50.3, 49.0, 46.1, 45.6, 43.3, 41.5, 28.6, 26.7, 25.9, 24.8.

5.14.2. B. [2-(2-Amino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester. The title intermediate was prepared analogously to compound **14**, substituting [2-(2-nitro-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester for (3-{[2-(2-nitro-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone, yielding a tan semisolid (1.4 g, 62%). MS (ESI): mass calculated for $C_{26}H_{36}N_4O_3$, 452.28; m/z found, 453.3 $[M+H]^+$, 475.2 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (br s, 1H), 8.09 (d, $J = 8.5$ Hz, 1H), 7.44–7.27 (m, 5H), 6.88–6.83 (m, 1H), 6.61 (t, $J = 7.6$ Hz, 1H), 4.54–4.50 (m, 2H), 3.68–3.30 (m, 8H), 1.65 (br s, 4H), 1.48 (br s, 11H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 156.0, 145.6, 139.0, 137.2, 136.5, 132.2, 129.0, 128.3, 126.9, 126.4, 126.0, 115.7, 114.0, 80.8, 51.6, 50.3, 49.0, 46.1, 45.6, 43.3, 41.5, 28.6, 26.7, 25.9, 24.8.

5.14.3. C. [2-(2-Isopropylamino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester. To a solution of [2-(2-amino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester (0.060 g, 0.133 mmol) in DMF (1.3 mL) was added K_2CO_3 (0.092 g, 0.67 mmol). 2-Iodopropane (0.112 g, 0.66 mmol) was added to the resulting suspension, and the mixture was stirred at 50 °C for 6 h. The reaction mixture was partitioned with CH_2Cl_2 (30 mL) and 1 N NaOH (30 mL), and the organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (0–5% CH_3OH/CH_2Cl_2) to provide a colorless oil (0.032 g, 49%). MS (ESI): mass calculated for $C_{29}H_{42}N_4O_3$, 494.33; m/z found, 495.3 $[M+H]^+$, 517.3 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.32 (m, 1H), 7.28–7.24 (m, 4H), 6.77–6.53 (m, 4H), 4.51–4.46 (m, 2H), 3.69 (br s, 2H), 3.58 (br s, 2H), 3.42 (br s, 1H), 3.28 (br s, 2H), 3.23 (t, $J = 6.0$ Hz, 2H), 1.66 (br s, 4H), 1.51–1.44 (m, 11H), 1.22 (d, $J = 6.3$ Hz, 6H).

5.14.4. D. (3-{[2-(2-Isopropylamino-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. To a solution of [2-(2-isopropylamino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester (0.026 g, 0.053 mmol) in CH_2Cl_2 (0.53 mL) was added 1 M HCl in dioxane (0.10 mL), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was partitioned with 1 M NaOH (20 mL) and CH_2Cl_2 (20 mL), and the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the desired product as a white solid (0.020 g, 96%). MS (ESI): mass calculated for $C_{24}H_{34}NO$, 394.27; m/z found, 395.2 $[M+H]^+$, 417.3 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.32 (m, 3H), 7.27–7.24 (m, 1H), 6.80–6.73 (m, 2H), 6.69–6.66 (m, 2H), 3.85 (s, 2H), 3.70 (br s, 2H), 3.58 (hp, $J = 6.3$ Hz, 1H), 3.32 (br s, 2H), 3.21 (t, $J = 5.8$ Hz, 2H), 2.94 (t, $J = 5.8$ Hz, 2H), 1.67 (br s, 4H), 1.50 (br s, 2H), 1.23 (d, $J = 6.3$ Hz, 6H).

5.15. *N*-(2-{2-[3-(Piperidine-1-carbonyl)-benzylamino]-ethylamino}-phenyl)-methanesulfonamide (16)

5.15.1. A. [2-(2-Methanesulfonylamino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester. To a solution of [2-(2-amino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester (example **13**, step B; 0.10 g, 0.22 mmol) in CH_2Cl_2 (4 mL) was added Et_3N (0.033 g, 0.33 mmol) and methanesulfonyl chloride (0.028 g, 0.24 mmol), and the resulting mixture was stirred at 25 °C for 17 h. The reaction mixture was treated with satd NH_4Cl (10 mL), H_2O (10 mL) and CH_2Cl_2 (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by preparative TLC (30% acetone/hexanes) to provide the desired product (0.060 g, 51%). MS (ESI): mass calculated for $C_{27}H_{38}N_4O_5S$, 530.26; m/z found, 531.2 $[M+H]^+$.

5.15.2. B. *N*-(2-{2-[3-(Piperidine-1-carbonyl)-benzylamino]-ethylamino}-phenyl)-methanesulfonamide. The title compound was prepared analogously to compound

15, step D, substituting [2-(2-methanesulfonyl-amino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester for [2-(2-isopropylamino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester, yielding the desired sulfonamide (0.020 g, 42%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (br s, 1H), 7.33–7.28 (m, 2H), 7.20–7.13 (m, 3H), 6.68–6.64 (m, 2H), 3.84 (s, 2H), 3.74–3.71 (m, 2H), 3.31 (br s, 2H), 3.23 (t, $J = 5.5$ Hz, 2H), 3.02 (s, 3H), 2.88 (t, $J = 5.5$ Hz, 2H), 1.67–1.50 (m, 6H).

5.16. 1-Phenyl-3-(2-{2-[3-(piperidine-1-carbonyl)-benzyl-amino]-ethylamino}-phenyl)-urea (17)

5.16.1. A. *N*-Benzyl-*N*′-(2-nitro-phenyl)-ethane-1,2-diamine. The title intermediate was prepared analogously to compound, example **13**, step A, substituting N^1-benzyl-ethane-1,2-diamine for ethylenediamine. MS (ESI): mass calculated for $C_{15}H_{17}N_3O_2$, 271.13; m/z found, 272.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (br s, 1H), 8.20 (dd, $J = 1.5$, 8.6 Hz, 1H), 7.48–7.25 (m, 6H), 6.85 (d, $J = 8.5$ Hz, 1H), 6.65 (t, $J = 8.3$ Hz, 1H), 3.88 (s, 2H), 3.43 (dd, $J = 5.5$, 11.4 Hz, 2H), 3.02 (t, $J = 6.0$ Hz, 2H).

5.16.2. B. 1-[2-(2-Benzylamino-ethylamino)-phenyl]-3-phenyl-urea. Substitution of *N*-benzyl-*N*′-(2-nitro-phenyl)-ethane-1,2-diamine for (3-{[2-(2-nitro-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone as done for compound **15**, step A, gave benzyl-[2-(2-nitro-phenylamino)-ethyl]-carbamic acid *tert*-butyl ester, the nitro group of which was reduced as for compound **6**, step B, to provide [2-(2-amino-phenylamino)-ethyl]-benzyl-carbamic acid *tert*-butyl ester. Substitution of the ester and phenylisocyanate for [2-(2-amino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester and methanesulfonylchloride in the procedure of example **14**, step A, gave benzyl-{2-[2-(3-phenyl-ureido)-phenylamino]-ethyl}-carbamic acid *tert*-butyl ester, which was converted to the title intermediate as done for compound **15**, step D. MS (ESI): mass calculated for $C_{22}H_{24}N_4O$, 360.20; m/z found, 361.2 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05–7.24 (m, 1H), 6.94–6.90 (m, $J = 7.3$ Hz, 1H), 6.66–6.62 (m, 3H), 6.29 (br s, 1H), 4.53 (br s, 1H), 3.65 (s, 2H), 3.12 (t, $J = 5.7$ Hz, 2H), 2.80–2.75 (m, 2H).

5.16.3. C. 1-[2-(2-Amino-ethylamino)-phenyl]-3-phenyl-urea. The title intermediate was prepared similarly to compound **6**, step B, substituting 1-[2-(2-benzylamino-ethylamino)-phenyl]-3-phenyl-urea for 1-cyclopentyl-oxy-2-nitro-benzene. MS (ESI): mass calculated for $C_{15}H_{18}N_4O$, 370.15; m/z found, 371.1 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13–7.35 (m, 6H), 7.03–6.99 (m, 1H), 6.78–6.69 (m, 2H), 3.20–3.10 (m, 2H), 2.90–2.85 (m, 2H), 2.00–2.40 (br m, 3H).

5.16.4. D. 1-Phenyl-3-(2-{2-[3-(piperidine-1-carbonyl)-benzylamino]-ethylamino}-phenyl)-urea. The title compound was prepared similarly to **4a**, steps D and E, substituting 1-[2-(2-amino-ethylamino)-phenyl]-3-phenyl-urea for N^1-(2-isoproxy-phenyl)-ethane-1,2-diamine in step E. MS (ESI): mass calculated for $C_{28}H_{33}N_5O_2$, 471.26; m/z found, 472.2 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br s, 1H), 7.48–7.11 (m, 9H), 7.05–6.95 (m, 1H), 6.92–6.85 (m, 1H), 6.64 (dt, $J = 7.6$, 1.0 Hz, 1H), 6.53 (d, $J = 7.2$ Hz, 1H), 3.73 (s, 2H), 3.65 (br s, 2H), 3.28 (br s, 2H), 3.08 (dd, $J = 5.6$, 5.0 Hz, 2H), 2.80 (dd, $J = 5.5$, 5.1 Hz, 2H), 2.60–2.40 (br m, 2H), 1.60 (br s, 4H), 1.44 (br s, 2H).

5.17. 1-Benzyl-3-(2-{2-[3-(piperidine-1-carbonyl)-benzyl-amino]-ethylamino}-phenyl)-urea (18)

5.17.1. A. 1-[2-(2-Amino-ethylamino)-phenyl]-3-benzyl-urea. Substitution of *N*-(2-benzylamino-ethyl)-benzene-1,2-diamine and benzylisocyanate for [2-(2-amino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester and methanesulfonylchloride as for compound **16**, step A, provided benzyl-{2-[2-(3-benzyl-ureido)-phenylamino]-ethyl}-carbamic acid *tert*-butyl ester. Analogous deprotection conditions as for compound **15**, step D, gave 1-benzyl-3-[2-(2-benzyl-amino-ethylamino)-phenyl]-urea. The benzylamine intermediate was then converted to the title intermediate by its substitution for 1-cyclopentyloxy-2-nitro-benzene in the procedure for compound **6**, step B. ^{1}H NMR (400 MHz, CD_3OD) δ 7.35–7.30 (m, 3H), 7.28–7.08 (m, 4H), 6.80–6.76 (m, 1H), 6.74–6.68 (m, 1H), 4.38 (s, 2H), 3.49 (t, $J = 5.6$ Hz, 2H), 3.11 (t, $J = 5.9$ Hz, 2H).

5.17.2. B. 1-Benzyl-3-(2-{2-[3-(piperidine-1-carbonyl)-benzylamino]-ethylamino}-phenyl)-urea. The title compound was prepared similarly to **4a**, steps D and E substituting 1-[2-(2-amino-ethylamino)-phenyl]-3-benzyl-urea for N^1-(2-isoproxy-phenyl)-ethane-1,2-diamine in step E. MS (ESI): mass calculated for $C_{29}H_{35}N_5O_2$, 485.28, m/z found, 486.3 $[M+H]^+$. ^{1}H NMR (400 MHz, CD_3OD) δ 7.43–7.11 (m, 11H), 6.75 (d, $J = 7.6$ Hz, 1H), 6.67 (dt, $J = 7.6$, 1.1 Hz, 1H), 4.32 (s, 2H), 3.84 (s, 2H), 3.64 (br s, 2H), 4.06 (t, $J = 5.8$ Hz, 2H), 3.02 (t, $J = 5.8$ Hz, 2H), 1.75–1.45 (m, 4H), 1.47 (br s, 2H).

5.18. (3-{[2-(2-Bromo-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (19)

The title compound was prepared similarly to **4a**, steps C–E, substituting 2-bromo-phenylamine for 2-isopropoxy-phenylamine in step C.

5.18.1. A. N^1-(2-Bromo-phenyl)-ethane-1,2-diamine. MS (ESI): mass calculated for $C_8H_{11}BrN_2$, 214.01; m/z found, 215.0 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, $J = 7.8$, 1.5 Hz, 1H), 7.18 (dt, $J = 7.4$, 1.5 Hz, 1H), 6.67 (dd, $J = 8.1$, 1.3 Hz, 1H), 6.58 (dt, $J = 8.0$, 1.4 Hz, 1H), 3.28 (t, $J = 5.7$ Hz, 2H), 3.04 (br s, 3H), 2.95 (t, $J = 5.9$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 132.5, 128.7, 117.7, 111.4, 108.8, 41.2, 37.4.

5.18.2. B. (3-{[2-(2-Bromo-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. MS (ESI): mass calculated for $C_{21}H_{26}BrN_3O$, 415.13; m/z found, 416.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.38 (m, 4H), 7.35–7.32 (m, 1H), 7.27–7.24 (m, 1H), 6.63–6.61 (m 1H), 6.55 (t, $J = 7.5$ Hz, 1H), 4.85 (br s, 1H), 3.84 (br s, 2H), 3.69 (br s, 2H), 3.31–3.23 (m, 4H), 2.94–2.92 (m, 2H), 1.83–1.48 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 145.1, 140.5, 136.6, 132.3, 128.9, 128.4, 126.3, 125.3, 117.6, 111.3, 109.8, 53.0, 48.7, 47.5, 43.1, 26.4, 25.5, 24.5.

5.19. (3-{[2-(2-Chloro-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (20)

The title compound was prepared analogously to compound **21**, substituting 2-chloroaniline for 3-bromoaniline. MS (ESI): mass calculated for $C_{26}H_{23}ClN_3O$, 371.18; m/z found, 372.2 $[M+H]^+$. ^1H NMR (400 MHz, $CHCl_3$) δ 7.40–7.10 (m, 6H), 6.91 (dd, $J = 8.0$, 1.3 Hz, 1H), 6.84 (dt, $J = 7.8$, 1.3 Hz, 1H), 6.66–6.59 (m, 2H), 4.82 (br s, 1H), 3.85 (s, 2H), 3.66 (br s, 2H), 3.40–3.25 (m, 4H), 2.93 (t, $J = 5.6$ Hz, 2H), 1.74–1.49 (m, 8H).

5.20. (3{[2-(3-Bromo-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (21)

To a solution of 3-bromoaniline (0.50 g, 2.9 mmol) in diethyl ether (Et_2O, 5 mL) was added 4 M HCl in dioxane (1 mL), and the mixture was stirred at 25 °C for 1 h. Solvent was removed under reduced pressure, and the resulting HCl salt was dissolved in 2-(2-methoxy-ethoxyl)ethanol (2 mL). 2-Oxazolidinone (0.429 g, 4.93 mmol) was added, and the reaction mixture was heated to 180 °C for 24 h. The collected crude solid was purified by column chromatography (0–10% (1% NH_4OH in MeOH)/CH_2Cl_2) to provide N^1-(3-bromo-phenyl)-ethane-1,2-diamine (0.10 g, 16%). 3-(Piperidine-1-carbonyl)-benzaldehyde (example **1**, step D; 0.091 g, 0.42 mmol) was added to a solution of the phenyl-diamine in 1,2-dichloroethane (10 mL), and the reaction mixture was stirred at 25 °C for 15 min. The mixture was treated with $NaBH(OAc)_3$ (0.128 g, 0.604 mmol), and the resulting suspension was stirred at 25 °C for 18 h. The suspension was partitioned with saturated NH_4Cl (20 mL) and CH_2Cl_2 (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (2–10% CH_3OH/CH_2Cl_2) and then by preparative TLC (10% CH_3OH/CH_2Cl_2) to provide the desired product (0.060 g, 34%). MS (ESI): mass calculated for $C_{21}H_{26}BrN_3O$, 415.13; m/z found, 416.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.26 (m, 3H), 7.21–7.16 (m, 1H), 6.93 (t, $J = 8.0$ Hz, 1H), 6.74–6.71 (m, 1H), 6.67 (t, $J = 2.0$ Hz, 1H), 6.47–6.44 (m, 1H), 4.23 (br s, 1H), 3.75 (s, 2H), 3.64 (br s, 2H), 3.25 (br s, 2H), 3.10 (t, $J = 5.6$ Hz, 2H), 2.83–2.80 (m, 2H), 1.60–1.43 (m, 6H).

5.21. (3-{[2-(3-Chloro-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (22)

The title compound was prepared analogously to compound **21**, substituting 3-chloroaniline for 3-bromoaniline. MS (ESI): mass calculated for $C_{21}H_{26}ClN_3O$, 371.9; m/z found, 372.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (br s, 3H), 7.19 (br s, 1H), 6.98 (br t, $J = 7.9$ Hz, 1H), 6.57 (d, $J = 7.6$ Hz, 1H), 6.51 (br s, 1H), 6.41 (d, $J = 7.7$ Hz, 1H), 3.76 (br s, 2H), 3.63 (br s, 2H), 3.24 (br s, 2H), 3.11 (br s, 2H), 1.60–1.43 (m, 6H).

5.22. (3-{[2-(2-Isopropyl-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (23)

The title compound was prepared similarly to **4a**, steps C–E substituting 2-isopropyl-phenylamine for 2-isopropoxy-phenylamine in step C.

5.22.1. A. N^1-(2-Isopropyl-phenyl)-ethane-1,2-diamine. MS (ESI): mass calculated for $C_{11}H_{18}N_2$, 178.15; m/z found, 179.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, $J = 7.6$, 1.4 Hz, 1H), 7.09 (dt, $J = 7.7$, 1.4 Hz, 1H), 6.73 (dt, $J = 7.5$, 1.0 Hz, 1H), 6.64 (d, $J = 8.0$ Hz, 1H), 3.25 (t, $J = 5.5$ Hz, 2H), 2.99 (t, $J = 6.0$ Hz, 2H), 2.94 (hp, $J = 6.7$ Hz, 1H), 1.24 (d, $J = 6.7$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 132.6, 126.6, 125.0, 117.5, 110.5, 45.8, 40.7, 27.0, 22.3.

5.22.2. B. (3-{[2-(2-Isopropyl-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. MS (ESI): mass calculated for $C_{24}H_{33}N_3O$, 379.26; m/z found, 380.3 $[M+H]^+$, 402 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 3H), 7.26–7.24 (m, 1H), 7.15–7.08 (m, 2H), 6.73 (dt, $J = 7.5$, 1.0 Hz, 1H), 6.63 (dd, $J = 7.8$, 1.0 Hz, 1H), 3.84 (s, 2H), 3.69 (br s, 2H), 3.30–3.23 (m, containing a t at 3.25, $J = 5.4$ Hz, 4H), 2.97–2.89 (m, 3H), 1.66 (br s, 4H), 1.48 (br s, 2H), 1.26 (d, $J = 6.8$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 140.4, 136.6, 132.5, 128.9, 128.4, 126.6, 126.4, 125.3, 124.9, 117.2, 110.5, 53.0, 48.7, 47.8, 43.3, 27.1, 26.5, 25.6, 24.5, 22.3.

5.23. Piperidin-1-yl-(3-{[2-(2-thiophen-3-yl-phenylamino)-ethylamino]-methyl}-phenyl)-methanone (24)

Piperidin-1-yl-(3-{[2-(2-thiophen-3-yl-phenylamino)-ethylamino]-methyl}-phenyl)-methanone

To a solution of (3-{[2-(2-bromo-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (0.06 g, 0.144 mmol) and 3-thiopheneboronic acid (0.037 g, 0.246 mmol) in 2 M Na_2CO_3/EtOH/toluene (1:1:4, 6 mL) was added $Pd(PPh_3)_4$ (0.014 g, 0.0123 mmol) and the resulting solution was stirred to reflux for 16 h. The solution was treated with EtOAc (20 mmL), aqueous saturated $NaHCO_3$ (20 mL) and the aqueous layer was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brined, dried ($MgSO_4$),

filtered, and the solvent was removed under reduced pressure. The crude residue was purified by preparative TLC (10% MeOH/CH_2Cl_2) to provide the desired product 0.0168 g (28%) as a tan oil. MS (ESI): mass calculated for $C_{25}H_{29}N_3OS$, 419.20; m/z found, 420.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.16 (m, 10H), 6.76–6.69 (m, 2H), 3.79 (br s, 2H), 3.70 (br s, 2H), 3.30–3.24 (m, 4H), 2.88 (t, $J = 6.0$ Hz, 2H), 1.66–1.48 (br m, 6H).

5.24. (3-{[3-(2-Isopropoxy-phenoxy)-propylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (25)

The title compound was prepared similarly to compound **24**, substituting 2-methoxybenzeneboronic acid for 3-thiopheneboronic acid.

5.24.1. A. 2-[3-(2-Isopropoxy-phenoxy)-propyl]-isoindole-1,3-dione. The crude residue was purified by column chromatography (5–20% EtOAc/hex) to provide the desire product 0.956 g (87%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.82 (m, 2H), 7.73–7.69 (m, 2H), 6.93–6.86 (m, 4H), 4.46 (hp, $J = 6.1$ Hz, 1H), 4.06 (t, $J = 6.2$ Hz, 2H), 3.92 (t, $J = 7.1$ Hz, 2H), 2.20 (p, $J = 6.4$ Hz, 2H), 1.33 (d, $J = 6.1$ Hz, 6H).

5.24.2. B. 3-(2-Isopropoxy-phenoxy)-propylamine. The resulting residue was purified by column chromatography (20–50% EtOAc/hex) to provide the desired product 0.267 g (45%). MS (electrospray): exact mass calculated for $C_{12}H_{19}NO_2$, 209.29, m/z found, 210.2, $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 6.91–6.83 (m, 4H), 4.46 (hp, $J = 6.1$ Hz, 1H), 4.07 (t, $J = 5.9$ Hz, 2H), 2.97 (t, $J = 6.5$ Hz, 2H), 1.99 (p, $J = 6.2$ Hz, 2H), 1.32 (d, $J = 6.1$ Hz, 6H).

5.24.3. C. (3-{[3-(2-Isopropoxy-phenoxy)-propylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. MS (electrospray): exact mass calculated for $C_{25}H_{34}N_2O_3$, 410.26, m/z found, 411.4, $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.38 (m, 2H), 7.33 (t, $J = 7.5$ Hz, 1H), 7.27–7.25 (m, 1H), 6.95–6.85 (m, 4H), 4.45 (hp, $J = 6.1$ Hz, 1H), 4.08 (t, $J = 6.0$ Hz, 2H), 3.87 (br s, 2H), 3.69 (br s, 2H), 3.31 (br s, 2H), 2.87 (t, $J = 6.6$ Hz, 2H), 2.06–2.00 (m, 2H), 1.65 (br s, 4H), 1.48 (br s, 2H), 1.31 (d, $J = 6.1$ Hz, 6H).

5.25. [3-({[2-(2-Isopropoxy-phenylamino)-ethyl]-methyl-amino}-methyl)-phenyl]-piperidin-1-yl-methanone (26)

To a solution of (3-{[2-(2-isopropoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (0.032 g, 0.081 mmol) in DMF (0.8 mL) was added K_2CO_3 (0.022 g, 0.16 mmol) and iodomethane (0.03 g, 0.2 mmol), and the resulting suspension was stirred at 25 °C for 45 min. The suspension was partitioned with EtOAc (20 mL) and H_2O (20 mL), and the organic layer was washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by preparative TLC (2% CH_3OH/CH_2Cl_2) to provide a colorless oil (0.015 g, 47%). MS (ESI): mass calculated for $C_{26}H_{35}N_3O_2$, 409.27; m/z found, 410.5 $[M+H]^+$, 432.4 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, $J = 7.6$ Hz, 1H), 7.36–7.31 (m, 2H), 7.27–7.25 (m, 1H), 6.84 (dt, $J = 7.8$, 1.3 Hz, 1H), 6.78 (dt, $J = 7.8$, 1.3 Hz, 1H), 6.63 (dt, $J = 7.8$, 1.6 Hz, 1H), 6.58 (dt, $J = 7.8$, 1.6 Hz, 1H), 4.53 (hp, $J = 6.1$ Hz, 1H), 3.70 (br s, 2H), 3.60 (br s, 2H), 3.31 (br s, 2H), 3.20 (t, $J = 6.1$ Hz, 2H), 2.73 (t, $J = 6.1$ Hz, 2H), 2.20 (s, 3H), 1.62–1.46 (m, 6H), 1.37 (d, $J = 6.1$ Hz, 6H).

5.26. [(3-({2-[(2-Isopropoxy-phenyl)-methyl-amino]-ethyl-amino}-methyl)-phenyl]-piperidin-1-yl-methanone (27)

5.26.1. A. [2-(2-Isopropoxy-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester. To a solution of (3-{[2-(2-isopropoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (0.133 g, 0.336 mmol) in CH_2Cl_2 (3.5 mL) was added di-*tert*-butyl dicarbonate (0.073 g, 0.33 mmol), and the resulting solution was stirred at 25 °C for 45 min. The solvent was removed under reduced pressure, and the crude residue was purified by column chromatography (0–5% CH_3OH/CH_2Cl_2) to provide a colorless oil (0.144 g, 86%). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.32 (m, 1H), 7.28–7.22 (m, 4H), 6.83–6.76 (m, 2H), 6.64–6.57 (m, 2H), 4.55–4.45 (m, 3H), 3.68 (br s, 2H), 3.50 (br s, 1H), 3.37 (br s, 1H), 3.31–3.26 (m, 5H), 1.66–1.62 (m, 6H), 1.50 (br s, 9H), 1.34 (d, $J = 6.1$ Hz, 6H).

5.26.2. B. {2-[(2-Isopropoxy-phenyl)-methyl-amino]-ethyl}-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester. To a solution of [2-(2-isopropoxy-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester (0.077 g, 0.16 mmol) in DMF (1.6 mL) cooled to 0 °C was added NaH (0.062 g, 1.6 mmol), and the resulting suspension was allowed to warm to 25 °C over 30 min. The suspension was cooled to 0 °C, and iodomethane (0.22 g, 1.6 mmol) was added. This suspension was allowed to warm to 25 °C over 4 h and then was partitioned with EtOAc (25 mL) and H_2O (25 mL). The aqueous layer was back-extracted with EtOAc (25 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% CH_3OH/CH_2Cl_2) to provide a colorless oil (0.028 g, 35%). MS (ESI): mass calculated for $C_{30}H_{43}N_3O_4$, 509.33; m/z found, 510.5 $[M+H]^+$.

5.26.3. C. [3-({2-[(2-Isopropoxy-phenyl)-methyl-amino]-ethylamino}-methyl)-phenyl]-piperidin-1-yl-methanone. The title compound was prepared analogously to compound **15**, step D, substituting {2-[(2-isopropoxy-phenyl)-methyl-amino]-ethyl}-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester for [2-(2-isopropylamino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester. MS (ESI):

mass calculated for $C_{25}H_{35}N_3O_2$, 409.27; m/z found, 410.4 $[M+H]^+$, 432.4 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.33 (m, 4H), 7.06–7.00 (m, 2H), 6.93–6.88 (m, 2H), 4.55 (hp, $J = 6.0$ Hz, 1H), 4.02 (s, 2H), 3.69 (br s, 2H), 3.31 (br s, 2H), 3.19 (t, $J = 5.9$ Hz, 2H), 2.90 (t, $J = 5.9$ Hz, 2H), 2.70 (s, 3H), 1.66 (br s, 4H), 1.49 (br s, 2H), 1.29 (d, $J = 6.0$ Hz, 6H).

5.27. {3-[({2-[(2-Isopropoxy-phenyl)-methyl-amino]-ethyl}-methyl-amino)-methyl]-phenyl}-piperidin-1-yl-methanone (28)

MS (ESI): mass calculated for $C_{26}H_{37}N_3O_2$, 323.29; m/z found, 324.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, $J = 5.9$, 3.3 Hz, 1H), 7.53 (dd, $J = 5.9$, 3.3 Hz, 1H), 7.30–7.33 (m, 2H), 6.93–6.82 (m, 4H), 4.59 (hp, $J = 6.1$ Hz, 1H), 3.70 (br s, 2H), 3.52 (s, 2H), 3.31 (br s, 2H), 3.25 (t, $J = 7.3$ Hz, 2H), 2.80 (s, 3H), 2.63 (t, $J = 7.3$ Hz, 2H), 2.19 (s, 3H), 1.67 (br s, 6H), 1.35 (d, $J = 6.1$ Hz, 6H).

5.28. [3-({[2-(3-Isopropoxy-phenylamino)-ethyl]-methyl-amino}-methyl)-phenyl]-piperidin-1-yl-methanone (29)

To a solution of (3-{[2-(3-isopropoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (0.048 g, 0.12 mmol) in CH_3CN (10 mL) was added a solution of formaldehyde (0.0029 g, 0.097 mmol) in CH_3CN (5 mL), followed by sodium cyanoborohydride (0.006 g, 0.1 mmol) and acetic acid (two drops), and the resulting solution was stirred at 25 °C for 15 h. The solution was treated with aqueous satd $NaHCO_3$ (20 mL), H_2O (20 mL) and EtOAc (30 mL). The aqueous layer was back-extracted with EtOAc (3×40 mL), and the combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% CH_3OH/CH_2Cl_2) to provide a tan oil (0.0063 g, 13%). MS (ESI): mass calculated for $C_{25}H_{35}N_3O_2$, 409.27; m/z found, 410.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.26 (m, 4H), 7.04 (t, $J = 8.0$ Hz, 1H), 6.26–6.16 (m, 3H), 4.15 (hp, $J = 6.0$ Hz, 1H), 3.71–3.61 (m, 4H), 3.31–3.20 (m, 4H), 2.72 (br s, 2H), 2.26 (br s, 2H), 1.66–1.50 (m, 8H), 1.32 (d, $J = 6.0$ Hz, 6H).

5.29. {3-[({2-[(3-Isopropoxy-phenyl)-methyl-amino]-ethyl}-methyl-amino)-methyl]-phenyl}-piperidin-1-yl-methanone (30)

To a solution of (3-{[2-(3-isopropoxy-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (0.048 g, 0.12 mmol) in CH_3CN (10 mL) was added a solution of formaldehyde (0.040 g, 1.3 mmol) in CH_3CN (5 mL), sodium cyanoborohydride (0.080 g, 1.3 mmol) and acetic acid (two drops), and the resulting solution was stirred at 25 °C for 15 h. The reaction mixture was treated with aqueous saturated $NaHCO_3$ (20 mL), H_2O (20 mL) and EtOAc (30 mL). The aqueous layer was back-extracted with EtOAc (3×40 mL), and the combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and filtered. The filtrate was concentrated under reduced pressure. The crude residue was purified by preparative TLC (5% CH_3OH/CH_2Cl_2) to provide a tan oil (8.7 mg, 18%). MS (ESI): mass calculated for $C_{26}H_{37}N_3O_2$, 423.29; m/z found, 424.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.26 (m, 4H), 7.08 (t, $J = 8.1$ Hz, 1H), 6.29–6.21 (m, 3H), 4.52 (hp, $J = 6.0$ Hz, 1H), 3.70–3.31 (br m, 8 H), 2.92 (br s, 3H), 2.68 (br s, 2H), 2.33 (br s, 3H), 1.67–1.50 (br m, 8H), 1.32 (d, $J = 6.0$ Hz, 6H).

5.30. (3-{[2-(2-Isopropoxy-phenoxy)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (31)

5.30.1. A. [2-(2-Isopropoxy-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester. To a solution of 2-isopropoxy-phenol (0.50 g, 3.3 mmol) in THF (5 mL) was added a suspension of polymer-supported PPh_3 (2.2 g) and (2-hydroxy-ethyl)-carbamic acid *tert*-butyl ester (0.53 g, 3.3 mmol) in THF (2 mL). The mixture was cooled to 0 °C, treated with di-*tert*-butylazodicarboxylate (1.1 g, 4.9 mmol), and then allowed to warm to 25 °C over 18 h. The resulting mixture was filtered (Celite®), and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography (520% EtOAc/hexanes) to provide the desired product (0.75 g, 78%). ^1H NMR (400 MHz, $CDCl_3$) δ 6.97–6.88 (m, 4H), 4.49 (hp, $J = 6.1$ Hz, 1H), 4.06 (t, $J = 5.1$ Hz, 2H), 3.50–3.46 (m, 2H), 1.45 (s, 9H), 1.37 (d, $J = 6.1$ Hz, 6H).

5.30.2. B. (3-{[2-(2-Isopropoxy-phenoxy)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. Substitution of [2-(2-isopropoxy-phenoxy)-ethyl]-carbamic acid *tert*-butyl ester for [2-(2-isopropylamino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester in compound **15**, step D, provided 2-(2-isopropoxy-phenoxy)-ethylamine. Using the procedure similar to **4a**, steps D and E, the amine intermediate was then converted to the title compound by its substitution for 2-isopropoxy-phenyl-ethane-1,2-diamine in step E. MS (ESI): mass calculated for $C_{24}H_{32}N_2O_3$, 396.24; m/z found, 397.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.34 (m, 3H), 7.28–7.26 (m, 1H), 6.96–6.89 (m, 4H), 4.47 (hp, $J = 6.1$ Hz, 1H), 4.13 (t, $J = 5.04$ Hz, 2H), 3.91 (br s, 2H), 3.70 (br s, 2H), 3.34 (br s, 2H), 3.03 (t, $J = 5.0$ Hz, 2H), 1.67 (br s, 4H), 1.51 (br s, 2H), 2.63 (d, $J = 6.1$ Hz, 6H).

5.31. (3-{[3-(2-Isopropoxy-phenoxy)-propylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (32)

5.31.1. A. 2-[3-(2-Isopropoxy-phenoxy)-propyl]-isoindole-1,3-dione. To a solution of 2-isopropoxy-phenol (0.50 g, 3.3 mmol) in DMF (5 mL) was added K_2CO_3 (2.3 g, 17 mmol), and the resulting suspension was stirred at 25 °C for 15 min. A solution of 2-(3-bromo-propyl)-isoindole-1,3-dione (0.97 g, 3.6 mmol) in DMF (2 mL) was added, and the reaction mixture was heated to 80 °C for

18 h. The mixture was filtered, and the filtrate was diluted with 1:1 Et_2O/EtOAc (100 mL), washed with H_2O (2×20 mL) then brine (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (5–20% EtOAc/hexanes) to provide the desire product (0.956 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.82 (m, 2H), 7.73–7.69 (m, 2H), 6.93–6.86 (m, 4H), 4.46 (hp, $J = 6.1$ Hz, 1H), 4.06 (t, $J = 6.2$ Hz, 2H), 3.92 (t, $J = 7.1$ Hz, 2H), 2.20 (p, $J = 6.4$ Hz, 2H), 1.33 (d, $J = 6.1$ Hz, 6H).

5.31.2. B. 3-(2-Isopropoxy-phenoxy)-propylamine. To a solution of 2-[3-(2-isopropoxy-phenoxy)-propyl]-isoindole-1,3-dione in EtOH (6 mL) was added hydrazine (0.448 g, 14.0 mmol), and the reaction mixture was heated to 50 °C for 30 min. The solvent was removed under reduced pressure, and the crude residue was partitioned between CH_2Cl_2 (50 mL) and H_2O (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by column chromatography (20–50% EtOAc/hexanes) to provide the desired product (0.267 g, 45%). MS (ESI): mass calculated for $C_{12}H_{19}NO_2$, 209.29; m/z found, 210.2 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91–6.83 (m, 4H), 4.46 (hp, $J = 6.1$ Hz, 1H), 4.07 (t, $J = 5.9$ Hz, 2H), 2.97 (t, $J = 6.5$ Hz, 2H), 1.99 (p, $J = 6.2$ Hz, 2H), 1.32 (d, $J = 6.1$ Hz, 6H).

5.31.3. C. (3-{[3-(2-Isopropoxy-phenoxy)-propylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. The title compound was prepared similarly to **4a** steps D and Esubstituting 3-(2-isopropoxy-phenoxy)-propylamine for N^1-(2-isopropoxy-phenyl)-ethane-1,2-diamine. MS (ESI): mass calculated for $C_{25}H_{34}N_2O_3$, 410.26; m/z found, 411.4 $[M+H]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.38 (m, 2H), 7.33 (t, $J = 7.5$ Hz, 1H), 7.27–7.25 (m, 1H), 6.95–6.85 (m, 4H), 4.45 (hp, $J = 6.1$ Hz, 1H), 4.08 (t, $J = 6.0$ Hz, 2H), 3.87 (br s, 2H), 3.69 (br s, 2H), 3.31 (br s, 2H), 2.87 (t, $J = 6.6$ Hz, 2H), 2.06–2.00 (m, 2H), 1.65 (br s, 4H), 1.48 (br s, 2H), 1.31 (d, $J = 6.1$ Hz, 6H).

5.32. (3-{[3-(2-Isopropoxy-phenyl)-propylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (33)

5.32.1. A. 3-(2-Isopropoxy-phenyl)-propionic acid isopropyl ester. To a solution of 3-(2-hydroxy-phenyl)-propionic acid (0.94 g, 5.7 mmol) in DMF (11.3 mL) was added K_2CO_3 (3.9 g, 28.3 mmol) and 2-iodopropane (1.9 g, 11.3 mmol) and the resulting suspension was stirred at 25 °C for 15 h. The suspension was partitioned with EtOAc (75 mL) and H_2O (50 mL) and the organic layer was washed with 1 M NaOH (2×50 mL), brine (50 mL), dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure. The crude oil was purified by column chromatography (0–30% EtOAc–hexanes) to provide the desired product 0.51 g (36%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.12 (m, 2H), 6.85–6.81 (m, 2H), 4.99 (hp, $J = 6.3$ Hz, 1H), 4.56 (hp, $J = 6.1$ Hz, 1H), 2.91 (t, $J = 7.8$ Hz, 2H), 2.57 (t, $J = 7.8$ Hz, 2H), 1.34 (d, $J = 6.1$ Hz, 6H), 1.20 (d, $J = 6.3$ Hz, 6H).

5.32.2. B. 3-(2-Isopropoxy-phenyl)-propionamide. To a solution of 3-(2-isopropoxy-phenyl)-propionic acid isopropyl ester (0.19 g, 0.8 mmol) in methanol (6.0 mL) in a sealed tube cooled to −78 °C was bubbled nitrogen for 5 min. The solution was sealed and allowed to warm to 25 °C and stirred for 24 h. The solution was cooled to −78 °C, uncapped, transferred to a flask and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (0–15% MeOH–CH_2Cl_2) to provide the desired product 0.10 g (69%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.15 (m, 2H), 6.88–6.84 (m, 2H), 5.47 (br s, 1H), 5.27 (br s, 1H), 4.58 (hp, $J = 6.1$ Hz, 1H), 2.94 (t, $J = 7.7$ Hz, 2H), 2.57 (t, $J = 7.7$ Hz, 2H), 1.35 (d, $J = 6.0$ Hz, 6H).

5.32.3. C. 3-(2-Isopropoxy-phenyl)-propylamine. To a solution of 3-(2-isopropoxy-phenyl)-propionamide (0.07 g, 0.34 mmol) in THF (6.8 mL) was added lithium aluminum hydride (0.05 g, 1.35 mmol) and the resulting suspension was stirred at reflux for 2 h. The suspension was cooled to 0 °C and treated sequentially with H_2O (0.10 mL), 10% NaOH (0.10 mL) and H_2O (0.15 mL). The resulting solid was filtered and washed with EtOAc (50 mL), and the organic layer dried (Na_2SO_4), filtered, and the solvent was removed under reduced pressure to provide the desired product 0.05 g (65%) as a colorless oil. MS (electrospray): exact mass calculated for $C_{12}H_{19}NO$, 193.15, m/z found, 194.2 $[M+H]^+$.

5.32.4. D. (3-{[3-(2-Isopropoxy-phenyl)-propylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. MS (electrospray): exact mass calculated for $C_{25}H_{34}N_2O_2$, 394.26, m/z found, 395.3 $[M+H]^+$, 417.3 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 3H), 7.27–7.24 (m, 1H), 7.15–7.10 (m, 2H), 6.86–6.82 (m, 2H), 4.53 (hp, $J = 6.1$ Hz, 1H), 3.81 (s, 2H), 3.70 (br s, 2H), 3.32 (br s, 2H), 2.68–2.62 (m, 4H), 1.85–1.77 (m, 2H), 1.67 (br s, 4H), 1.50 (br s, 2H), 1.32 (d, $J = 6.1$ Hz, 6H).

5.33. (3-{[3-(2-Isopropoxy-phenyl)-propylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (34)

5.33.1. A. 3-(2-Isopropoxy-phenyl)-propionic acid isopropyl ester. To a solution of 3-(2-hydroxy-phenyl)-propionic acid (0.94 g, 5.7 mmol) in DMF (11.3 mL) was added K_2CO_3 (3.9 g, 28 mmol) and 2-iodopropane (1.9 g, 11 mmol), and the resulting suspension was stirred at 25 °C for 15 h. The suspension was partitioned with EtOAc (75 mL) and H_2O (50 mL), and the organic layer was washed with 1 M NaOH (2×50 mL) then brine (50 mL), dried (Na_2SO_4), and filtered. The filtrate

was concentrated under reduced pressure yielding a crude oil, which was purified by column chromatography (0–30% EtOAc/hexanes) to provide a colorless oil (0.51 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.12 (m, 2H), 6.85–6.81 (m, 2H), 4.99 (hp, $J = 6.3$ Hz, 1H), 4.56 (hp, $J = 6.1$ Hz, 1H), 2.91 (t, $J = 7.8$ Hz, 2H), 2.57 (t, $J = 7.8$ Hz, 2H), 1.34 (d, $J = 6.1$ Hz, 6H), 1.20 (d, $J = 6.3$ Hz, 6H).

5.33.2. B. 3-(2-Isopropoxy-phenyl)-propionamide. Ammonia gas was bubbled through a −78 °C solution of 3-(2-isopropoxy-phenyl)-propionic acid isopropyl ester (0.19 g, 0.76 mmol) in CH_3OH (6.0 mL) for 5 min. The reaction tube was sealed, and the solution was allowed to warm to 25 °C, and stirred for 24 h. The solution was then cooled to −78 °C, and the tube was unsealed. The solution was concentrated under reduced pressure. The crude residue was purified by column chromatography (0–15% CH_3OH/CH_2Cl_2) to provide a white solid (0.10 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.15 (m, 2H), 6.88–6.84 (m, 2H), 5.47 (br s, 1H), 5.27 (br s, 1H), 4.58 (hp, $J = 6.1$ Hz, 1H), 2.94 (t, $J = 7.7$ Hz, 2H), 2.57 (t, $J = 7.7$ Hz, 2H), 1.35 (d, $J = 6.0$ Hz, 6H).

5.33.3. C. 3-(2-Isopropoxy-phenyl)-propylamine. To a solution of 3-(2-isopropoxy-phenyl)-propionamide (0.070 g, 0.34 mmol) in THF (6.8 mL) was added lithium aluminum hydride (0.051 g, 1.34 mmol), and the resulting suspension was stirred at reflux for 2 h. The suspension was cooled to 0 °C and treated sequentially with H_2O (0.10 mL), 10% NaOH (0.10 mL) and H_2O (0.15 mL). The resulting solid was filtered off and washed with EtOAc (50 mL). The combined filtrates were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a colorless oil (0.050 g, 65%). MS (ESI): mass calculated for $C_{12}H_{19}NO$, 193.15; m/z found, 194.2 $[M+H]^+$.

5.33.4. D. (3-{[3-(2-Isopropoxy-phenyl)-propylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. The title compound was prepared similarly to **4a**, steps D and E, substituting 3-(2-isopropoxy-phenyl)-propylamine for N^1-(2-isopropoxy-phenyl)-ethane-1,2-diamine in step E. MS (ESI): mass calculated for $C_{25}H_{34}N_2O_2$, 394.26; m/z found, 395.3 $[M+H]^+$, 417.3 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 3H), 7.27–7.24 (m, 1H), 7.15–7.10 (m, 2H), 6.86–6.82 (m, 2H), 4.53 (hp, $J = 6.1$ Hz, 1H), 3.81 (s, 2H), 3.70 (br s, 2H), 3.32 (br s, 2H), 2.68–2.62 (m, 4H), 1.85–1.77 (m, 2H), 1.67 (br s, 4H), 1.50 (br s, 2H), 1.32 (d, $J = 6.1$ Hz, 6H).

5.34. (3-{[2-(2-Isopropoxy-phenylsulfanyl)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone (35)

5.34.1. A. 2-[2-(2-Hydroxy-phenylsulfanyl)-ethyl]-isoindole-1,3-dione. To a solution of 2-mercaptophenol (1.0 g, 7.9 mmol) in DMF (80 mL) was added 2-(2-bromo-ethyl)-isoindole-1,3-dione (1.8 g, 7.1 mmol) followed by K_2CO_3 (1.1 g, 7.9 mmol), and the suspension was stirred at 25 °C for 2 h. The suspension was then diluted with H_2O (200 mL), and the resulting mixture was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with H_2O (2 × 100 mL), dried (Na_2SO_4) and filtered, and the filtrate was concentrated under reduced pressure. The crude oil was purified by column chromatography (0–30% EtOAc/hexanes) to provide a light yellow solid (1.8 g, 76%). MS (ESI): mass calculated for $C_{16}H_{13}NO_3$ S, 299.06; m/z found, 432.4 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, $J = 5.4$, 3.0 Hz, 2H), 7.73 (dd, $J = 5.4$, 3.0 Hz, 2H), 7.56 (d, $J = 8.0$ Hz, 1H), 7.26–7.21 (m, 1H), 7.00 (s, 1H), 6.95 (dd, $J = 7.9$, 1.3 Hz, 1H), 6.88 (dt, $J = 7.9$, 1.3 Hz, 1H), 3.90 (t, $J = 6.2$ Hz, 2H), 3.05 (t, $J = 6.2$ Hz, 2H).

5.34.2. B. 2-[2-(2-Isopropoxy-phenylsulfanyl)-ethyl]-isoindole-1,3-dione. The title intermediate was prepared similarly to **4a**, step A, substituting 2-[2-(2-hydroxy-phenylsulfanyl)-ethyl]-isoindole-1,3-dione for 2-nitrophenol. MS (ESI): mass calculated for $C_{19}H_{19}NO_3S$, 341.11; m/z found, 342.2 $[M+H]^+$, 364.1 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, $J = 5.6$, 3.1 Hz, 2H), 7.70 (dd, $J = 5.6$, 3.1 Hz, 2H), 7.53 (dd, $J = 7.8$, 1.7 Hz, 1H), 7.14–7.09 (m, 1H), 6.89–6.81 (m, 2H), 4.58 (hp, $J = 6.0$ Hz, 1H), 3.91 (t, $J = 7.3$ Hz, 2H), 3.21 (t, $J = 7.3$ Hz, 2H), 1.38 (d, $J = 6.0$ Hz, 6H).

5.34.3. C. 2-(2-Isopropoxy-phenylsulfanyl)-ethylamine. The title intermediate was prepared analogously to compound **32**, step B, substituting 2-[2-(2-isopropoxy-phenylsulfanyl)-ethyl]-isoindole-1,3-dione for 2-[3-(2-isopropoxy-phenoxy)-propyl]-isoindole-1,3-dione. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, $J = 7.6$, 1.5 Hz, 1H), 7.15 (dt, $J = 7.6$, 1.5 Hz, 1H), 6.90–6.84 (m, 2H), 4.57 (hp, $J = 6.2$ Hz, 1H), 2.96 (t, $J = 5.9$ Hz, 2H), 2.86 (t, $J = 5.9$ Hz, 2H), 1.52 (br s, 2H), 1.37 (d, $J = 6.2$ Hz, 6H).

5.34.4. D. (3-{[2-(2-Isopropoxy-phenylsulfanyl)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. The title compound was prepared similarly to **4a**, steps D and E, substituting 2-(2-isopropoxy-phenylsulfanyl)-ethylamine for N^1-(2-isopropoxy-phenyl)-ethane-1,2-diamine in step D. MS (ESI): mass calculated for $C_{24}H_{32}N_2O_2S$, 412.22; m/z found, 413.2 $[M+H]^+$, 435.2 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 5H), 7.15 (dt, $J = 7.7$, 1.5 Hz, 1H), 6.89–6.84 (m, 2H), 4.57 (hp, $J = 6.2$ Hz, 1H), 3.80 (s, 2H), 3.70 (br s, 2H), 3.31 (br s, 2H), 3.06 (t, $J = 6.4$ Hz, 2H), 2.84 (t, $J = 6.4$ Hz, 2H), 1.94 (br s, 1H), 1.66 (br s, 4H), 1.49 (br s, 2H), 1.36 (d, $J = 6.2$ Hz, 6H).

5.35. (5-{[2-(2-Isopropoxy-phenylamino)-ethylamino]-methyl}-thiophen-3-yl)-piperidin-1-yl-methanone (36)

5.35.1. A. 4-(Piperidine-1-carbonyl)-thiophene-2-carbaldehyde. The title intermediate was prepared similarly to **4a**, step D, substituting 5-formyl-thiophene-3-carboxylic

acid for 3-formyl-benzoic acid. MS (ESI): mass calculated for $C_{11}H_{13}NO_2S$, 223.29; m/z found, 224.0 $[M+H]^+$, 246.0 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) 9.92 (s, 1H), 7.83 (s, 1H), 7.83 (s, 1H), 3.68 (br s, 2H), 3.50 (br s, 2H), 1.71 (br s, 4H), 1.63 (br s, 2H).

5.35.2. B. (5-{[2-(2-Isopropoxy-phenylamino)-ethylamino]-methyl}-thiophen-3-yl)-piperidin-1-yl-methanone. The title compound was prepared similarly to **4a**, step E, substituting 4-(piperidine-1-carbonyl)-thiophene-2-carbaldehyde for 3-(piperidine-1-carbonyl)-benzaldehyde. MS (ESI): mass calculated for $C_{22}H_{31}N_3O_2S$, 401.21; m/z found, 402.2 $[M+H]^+$, 424.2 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, $J = 1.4$ Hz, 1H), 6.97 (d, $J = 1.4$ Hz, 1H), 6.84 (dt, $J = 7.8$, 1.3 Hz, 1H), 6.78 (dd, $J = 8.4$, 1.1 Hz, 1H), 6.65–6.60 (m, 2H), 4.62 (br s, 1H), 4.52 (hp, $J = 6.2$ Hz, 1H), 3.99 (s, 2H), 3.56 (br s, 4H), 3.25 (t, $J = 5.7$ Hz, 2H), 2.94 (t, $J = 5.7$ Hz, 2H), 1.66 (br s, 3H), 1.57 (br s, 3H), 1.36 (d, $J = 6.2$ Hz, 6H).

5.36. *N*,*N*-Diethyl-3-{[2-(2-isopropoxy-phenylamino)-ethylamino]-methyl}-benzamide (37)

5.36.1. A. 3-{[2-(2-Isopropoxy-phenylamino)-ethylamino]-methyl}-benzoic acid methyl ester. To a solution of N^1-(2-isopropoxy-phenyl)-ethane-1,2-diamine (0.432 g, 2.22 mmol) and 3-formyl-benzoic acid methyl ester (0.0328 g, 2.0 mmol) in 1,2-dichloroethane (22 mL) was added sodium triacetoxyborohydride (0.636 g, 3 mmol) and the resulting suspension was stirred at 25 °C for 2 h. The solution was partitioned with EtOAc (50 mL), H_2O (20 mL) and 1 N NaOH (30 mL) and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (5–10% MeOH/CH_2Cl_2) to provide the desire product 0.32 g (46.8%) as an orange oil. MS (electrospray): exact mass calculated for $C_{20}H_{26}N_2O_3$, 342.19, m/z found, 343.2, $[M+H]^+$, 365.2, $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.92 (apparent d, $J = 7.7$ Hz, 1H), 7.56 (apparent d, $J = 7.7$ Hz, 1H), 7.39 (t, $J = 7.7$ Hz, 1H), 6.76–6.82 (m, 2H), 6.61–6.65 (m, 2H), 4.51 (hp, $J = 6.0$ Hz, 1H), 3.90 (s, 3H), 3.88 (s, 2H), 3.27 (t, $J = 5.8$ Hz, 2H), 2.91 (t, $J = 6.0$ Hz, 2H), 1.34 (d, $J = 6.0$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 145.0, 140.7, 139.3, 132.661, 130.2, 129.4, 128.4, 128.3, 121.2, 116.4, 112.6, 110.3, 53.2, 52.0, 48.1, 43.4, 39.2, 23.3, 22.3.

5.36.2. B. *N*,*N*-Diethyl-3-{[2-(2-isopropoxy-phenylamino)-ethylamino]-methyl}-benzamide. To a solution of diethylamine (0.064 g, 0.876 mmol) in toluene (1 mL) was added trimethylaluminum (2 M in hexane, 0.0438 mL, 0.876 mmol) and the solution was stirred at 25 °C for 5 min. The solution was treated with a solution of 3-{[2-(2-isopropoxy-phenylamino)-ethylamino]-methyl}-benzoic acid methyl ester (0.05 g, 0.146 mmol) in toluene (1 mL) and the reaction mixture was stirred at 70 °C for 18 h. The reaction mixture was partitioned with H_2O (10 mL) and EtOAc (20 mL) and the organic layer was washed with 1 N NaOH (10 mL), brine (10 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude residue was purified by preparative TLC (10% MeOH/CH_2Cl_2) to provide the desired product 0.083 g (15%) as a tan oil. MS (electrospray): exact mass calculated for $C_{23}H_{33}N_3O_2$, 383.26, m/z found, 384.3, $[M+H]^+$, 406.3, $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (br d, $J = 7.5$ Hz, 1H), 7.35–7.31 (m, 2H), 7.24 (br d, $J = 7.6$ Hz, 1H), 6.83 (dt, $J = 7.6$, 1.3 Hz, 1H), 6.78–6.76 (m, 1H), 6.65–6.61 (m, 2H), 4.52 (hp, $J = 6.1$ Hz, 1H), 3.85 (s, 3H), 3.53 (br s, 2H), 3.28 (t, $J = 5.9$ Hz, 2H), 3.23 (br s, 2H), 2.92 (t, $J = 6.0$ Hz, 2H), 1.34 (d, $J = 6.1$ Hz, 6H), 1.25–1.01 (br m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 145.0, 140.0, 139.2, 137.4, 128.9, 128.5, 126.1, 124.9, 121.2, 116.5, 112.6, 110.3, 70.6, 53.2, 48.0, 43.1, 39.2, 22.3, 14.2, 12.9.

5.37. 5-{[2-(2-Amino-phenylamino)-ethylamino]-methyl}-thiophen-3-yl)-piperidin-1-yl-methanone (38)

5.37.1. A. (5-{[2-(2-Nitro-phenylamino)-ethylamino]-methyl}-thiophen-3-yl)-piperidin-1-yl-methanone. The title intermediate was prepared similarly to **4a**, step E, using 4-(piperidine-1-carbonyl)-thiophene-2-carbaldehyde and N^1-(2-nitro-phenyl)-ethane-1,2-diamine. MS (ESI): mass calculated for $C_{19}H_{24}N_4O_3S$, 388.49; m/z found, 389.1 $[M+H]^+$, 411.1 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (br s, 1H), 8.17 (dd, $J = 8.6$, 1.5 Hz, 1H), 7.45–7.41 (m, 1H), 7.34 (d, $J = 1.2$ Hz, 1H), 7.01 (d, $J = 1.2$ Hz, 1H), 6.58 (d, $J = 7.8$ Hz, 1H), 6.67–6.62 (m, 1H), 4.04 (s, 2H), 3.57 (br s, 4H), 3.42 (dd, $J = 6.0$, 5.5 Hz, 1H), 3.03 (t, $J = 6.0$ Hz, 2H), 1.67 (br s, 4H), 1.60 (br s, 2H).

5.37.2. B. [2-(2-Nitro-phenylamino)-ethyl]-[4-(piperidine-1-carbonyl)-thiophen-2-yl-methyl]-carbamic acid *tert*-butyl ester. The title intermediate was prepared analogously to compound **15**, step A, substituting (5-{[2-(2-nitro-phenylamino)-ethylamino]-methyl}-thiophen-3-yl)-piperidin-1-yl-methanone for (3-{[2-(2-nitro-phenylamino)-ethylamino]-methyl}-phenyl)-piperidin-1-yl-methanone. ^1H NMR (400 MHz, $CDCl_3$) δ 8.21–8.11 (m, 2H), 7.44 (t, $J = 7.6$ Hz, 1H), 7.35 (d, $J = 1.0$ Hz, 1H), 7.02–6.84 (m, 2H), 6.66 (t, $J = 7.7$ Hz, 1H), 4.59–4.55 (m, 2H), 3.62–3.44 (m, 8H), 1.08 (br s, 4H), 1.58 (br s, 2H), 1.52 (br s, 9H).

5.37.3. C. [2-(2-Amino-phenylamino)-ethyl]-[4-(piperidine-1-carbonyl)-thiophen-2-yl-methyl]-carbamic acid *tert*-butyl ester. The title intermediate was prepared analogously to compound **15**, step B, substituting [2-(2-nitro-phenylamino)-ethyl]-[4-(piperidine-1-carbonyl)-thiophen-2-yl-methyl]-carbamic acid *tert*-butyl ester for [2-(2-nitro-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (br s, 1H), 6.90 (br s, 1H), 6.78–6.74 (m, 1H), 6.68–6.55 (m, 3H), 4.57–4.49 (m,

2H), 3.68–3.39 (m, 6H), 3.25 (br s, 2H), 1.65 (br s, 2H), 1.55 (br s, 4H), 1.50 (br s, 9H).

5.37.4. D. (5-{[2-(2-Amino-phenylamino)-ethylamino]-methyl}-thiophen-3-yl)-piperidin-1-yl-methanone. The title compound was prepared analogously to compound **15**, step D, substituting [2-(2-amino-phenylamino)-ethyl]-[4-(piperidine-1-carbonyl)-thiophen-2-yl-methyl]-carbamic acid *tert*-butyl ester for [2-(2-isopropylamino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, $J = 1.5$ Hz, 1H), 6.99 (d, $J = 1.5$ Hz, 1H), 6.82–6.77 (m, 1H), 6.72–6.64 (m, 3H), 3.98 (s, 2H), 3.50 (br s, 4H), 3.21 (t, $J = 5.7$ Hz, 2H), 2.96 (t, $J = 5.7$ Hz, 2H), 1.67 (br s, 2H), 1.58 (br s, 4H).

5.38. (5-{[2-(2-Isopropylamino-phenylamino)-ethyl-amino]-methyl}-thiophen-3-yl)-piperidin-1-yl-methanone (39)

The title compound was prepared analogously to compound **15**, steps C and D, substituting [2-(2-amino-phenylamino)-ethyl]-[4-(piperidine-1-carbonyl)-thiophen-2-yl-methyl]-carbamic acid *tert*-butyl ester (example **35**, step C) for [2-(2-amino-phenylamino)-ethyl]-[3-(piperidine-1-carbonyl)-benzyl]-carbamic acid *tert*-butyl ester in step C.

5.38.1. A. [2-(2-Isopropylamino-phenylamino)-ethyl]-[4-(piperidine-1-carbonyl)-thiophen-2-yl-methyl]-carbamic acid *tert*-butyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, $J = 1.5$ Hz, 1H), 6.97 (br s, 1H), 6.77–6.57 (m, 4H), 4.50–4.54 (m, 2H), 3.43–3.62 (s, 8H), 3.25 (t, $J = 6.1$ Hz, 2H), 1.66 (br s, 2H), 1.57 (br s, 4H), 1.51 (br s, 9H), 1.22 (d, $J = 6.1$ Hz, 6H).

5.38.2. B. (5-{[2-(2-Isopropylamino-phenylamino)-ethyl-amino]-methyl}-thiophen-3-yl)-piperidin-1-yl-methanone. MS (ESI): mass calculated for $C_{22}H_{32}N_4OS$, 400.58; m/z found, 401.2 $[M+H]^+$, 423.2 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, $J = 1.5$ Hz, 1H), 6.99 (br s, 1H), 6.80–6.73 (m, 2H), 6.69–6.66 (m, 2H), 4.01 (s, 2H), 3.66–3.48 (m, 5H), 3.21–3.18 (m, 2H), 2.99–2.96 (m, 2H), 1.68 (br s, 2H), 1.59 (br s, 4H), 1.25 (d, $J = 6.2$ Hz, 6H).

5.39. Azepan-1-yl-(3-{[2-(2-isopropoxy-phenylamino)-ethylamino]-methyl}-phenyl)-methanone (40)

The title compound was prepared analogously to compound **42**, substituting azepane for diethylamine in step B. MS (ESI): mass calculated for $C_{25}H_{35}N_3O_2$, 409.27; m/z found, 410.3 $[M+H]^+$, 432.3 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (br d, $J = 7.6$ Hz, 1H), 7.35–7.31 (m, 2H), 7.25 (br d, $J = 7.6$ Hz, 1H), 6.83 (dt, $J = 7.7$, 1.3 Hz, 1H), 6.78–6.76 (m, 1H), 6.65–6.61 (m, 2H), 4.52 (hp, $J = 6.1$ Hz, 1H), 3.86 (s, 2H), 3.66 (t, $J = 5.9$ Hz, 2H), 3.35–3.28 (m, 4H), 2.93 (t, $J = 6.0$ Hz, 2H), 1.85–1.80 (m, 2H), 1.64–1.58 (m, 6H), 1.35 (d, $J = 6.0$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 145.0, 139.6, 137.4, 128.9, 128.5, 126.3, 125.2, 121.2, 116.5, 112.6, 110.3, 70.6, 53.1, 49.7, 47.9, 46.3, 43.0, 29.5, 27.3, 26.5, 22.3.

5.40. (3-{[2-(2-Isopropoxy-phenylamino)-ethylamino]-methyl}-phenyl)-pyrrolidin-1-yl-methanone (41)

The title compound was prepared analogously to compound **42**, substituting pyrrolidine for diethylamine in step B. MS (ESI): mass calculated for $C_{23}H_{31}N_3O_2$, 381.2; m/z found, 382.3 $[M+H]^+$, 404.3 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (br s, 1H), 7.43 (d, $J = 7.3$ Hz, 1H), 7.39–7.31 (m, 2H), 6.83 (dt, $J = 7.6$, 1.3 Hz, 2H), 6.78–6.76 (m, 2H), 6.65–6.61 (m, 2H), 4.52 (hp, $J = 6.0$ Hz, 1H), 3.88 (s, 3H), 3.62 (t, $J = 6.9$ Hz, 2H), 3.93 (t, $J = 6.7$ Hz, 2H), 3.33 (t, $J = 6.0$ Hz, 2H), 2.95 (t, $J = 6.0$ Hz, 2H), 1.96–1.83 (br m, 4H), 3.45 (d, $J = 6.0$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 145.0, 139.0, 137.4, 129.9, 128.5, 127.1, 126.1, 121.2, 116.6, 112.6, 110.3, 70.6, 52.9, 49.6, 47.6, 46.2, 42.6, 26.3, 24.4, 22.3.

5.41. *N*,*N*-Diethyl-3-{[2-(2-isopropoxy-phenylamino)-ethylamino]-methyl}-benzamide (42)

5.41.1. A. 3-{[2-(2-Isopropoxy-phenylamino)-ethylamino]-methyl}-benzoic acid methyl ester. To a solution of N^1-(2-isopropoxy-phenyl)-ethane-1,2-diamine (example **1**, step C; 0.432 g, 2.22 mmol) and 3-formyl-benzoic acid methyl ester (0.33 g, 2.0 mmol) in 1,2-dichloroethane (22 mL) was added sodium triacetoxyborohydride (0.6 g, 3 mmol), and the resulting suspension was stirred at 25 °C for 2 h. The resulting solution was partitioned with EtOAc (50 mL), H_2O (20 mL) and 1 N NaOH (30 mL), and the aqueous layer was back-extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (5–10% CH_3OH/CH_2Cl_2) to provide an orange oil (0.32 g, 46%). MS (ESI): mass calculated for $C_{20}H_{26}N_2O_3$, 342.19; m/z found, 343.2 $[M+H]^+$, 365.2 $[M+Na]^+$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.91–7.94 (m, 1H), 7.57–7.55 (m, 1H), 7.39 (t, $J = 7.7$ Hz, 1H), 6.76–6.82 (m, 2H), 6.61–6.65 (m, 2H), 4.51 (hp, $J = 6.0$ Hz, 1H), 3.90 (s, 3H), 3.88 (s, 2H), 3.27 (t, $J = 5.8$ Hz, 2H), 2.91 (t, $J = 6.0$ Hz, 2H), 1.34 (d, $J = 6.0$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 145.0, 140.7, 139.3, 132.661, 130.2, 129.4, 128.4, 128.3, 121.2, 116.4, 112.6, 110.3, 53.2, 52.0, 48.1, 43.4, 39.2, 23.3, 22.3.

5.41.2. B. *N*,*N*-Diethyl-3-{[2-(2-isopropoxy-phenylamino)-ethylamino]-methyl}-benzamide. To a solution of diethylamine (0.064 g, 0.88 mmol) in toluene (1 mL) was added trimethylaluminum (2.0 M in hexane, 0.044 mL, 0.88 mmol), and the resulting solution was stirred at 25 °C for 5 min. A solution of 3-{[2-(2-isopropoxy-phenylamino)-ethylamino]-methyl}-benzoic acid methyl ester

(0.05 g, 0.146 mmol) in toluene (1 mL) was added, and the reaction mixture was stirred at 70 °C for 18 h. The mixture was partitioned with H_2O (10 mL) and EtOAc (20 mL). The organic layer was washed with 1 N NaOH (10 mL) then brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by preparative TLC (10% CH_3OH/CH_2Cl_2) to provide a tan oil (0.083 g, 15%). MS (ESI): mass calculated for $C_{23}H_{33}N_3O_2$, 383.26; m/z found, 384.3 $[M+H]^+$, 406.3 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (br d, $J = 7.5$ Hz, 1H), 7.35–7.31 (m, 2H), 7.24 (br d, $J = 7.6$ Hz, 1H), 6.83 (dt, $J = 7.6$, 1.3 Hz, 1H), 6.78–6.76 (m, 1H), 6.65–6.61 (m, 2H), 4.52 (hp, $J = 6.1$ Hz, 1H), 3.85 (s, 3H), 3.53 (br s, 2H), 3.28 (t, $J = 5.9$ Hz, 2H), 3.23 (br s, 2H), 2.92 (t, $J = 6.0$ Hz, 2H), 1.34 (d, $J = 6.1$ Hz, 6H), 1.25–1.01 (br m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 145.0, 140.0, 139.2, 137.4, 128.9, 128.5, 126.1, 124.9, 121.2, 116.5, 112.6, 110.3, 70.6, 53.2, 48.0, 43.1, 39.2, 22.3, 14.2, 12.9.

5.42. (3-{[2-(2-Isopropoxy-phenylamino)-ethylamino]-methyl}-phenyl)- morpholin-4-yl-methanone (43)

The title compound was prepared analogously to compound **42**, substituting morpholine for diethylamine in step B. MS (ESI): mass calculated for $C_{23}H_{31}N_3O_3$, 397.24; m/z found, 398.3 $[M+H]^+$, 420.3 $[M+Na]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45–7.26 (m, 4), 6.83 (dt, $J = 7.7$, 1.4 Hz, 1H), 6.77 (d, $J = 7.7$ Hz, 1H), 6.66–6.62 (m, 2H), 4.52 (hp, $J = 6.0$ Hz, 1H), 3.86 (s, 2H), 3.75–3.42 (br m, 8H), 3.29 (t, $J = 5.9$ Hz, 2H), 2.93 (t, $J = 5.9$ Hz, 2H), 1.35 (d, $J = 6.0$ Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 145.0, 140.2, 139.2, 135.4, 129.7, 128.6, 126.8, 125.8, 121.2, 116.6, 112.6, 110.3, 70.6, 66.9, 53.1, 48.0, 43.1, 22.3.

5.43. (4-Hydroxy-piperidin-1-yl)-(3-{[2-(2-isopropoxy-phenylamino)-ethylamino]-methyl}-phenyl)-methanone (44)

5.43.1. A. 3-(4-Hydroxy-piperidine-1-carbonyl)-benzaldehyde. The title intermediate was prepared similarly to **4a**, step D, substituting piperidin-4-ol for piperidine. MS (ESI): mass calculated for $C_{13}H_{15}NO_3$, 233.11; m/z found, 234.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.95–7.91 (m, 2H), 7.68 (d, $J = 7.5$ Hz, 1H), 7.60 (t, $J = 7.5$ Hz, 1H), 4.19 (br s, 1H), 4.04–4.10 (m, 1H), 3.65 (br s, 1H), 3.49 (br s, 1H), 3.47 (br s, 1H), 2.00–1.54 (m, 5H).

5.43.2. B. (4-Hydroxy-piperidin-1-yl)-(3-{[2-(2-isopropoxy-phenylamino)-ethylamino]-methyl}-phenyl)-methanone. The title compound was prepared similarly to **4a**, steps A–C, and E, substituting 3-(4-hydroxy-piperidine-1-carbonyl)-benzaldehyde for 3-(piperidine-1-carbonyl)-benzaldehyde in step E. MS (ESI): mass calculated for $C_{24}H_{33}N_3O_3$, 411.25; m/z found, 412.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.24 (m, 3H), 7.18–7.16 (m, 1H), 6.79–6.75 (m, 1H), 6.72–6.70 (m, 1H), 6.59–6.55 (m, 2H), 4.45 (hp, $J = 6.1$ Hz, 1H), 4.11 (br s, 1H), 3.90–3.84 (m, 1H), 3.80 (s, 2H), 3.50 (br s, 1H), 3.26–3.23 (m, 3H), 3.09 (br s, 1H), 2.89–2.86 (m, 2H), 1.89–1.72 (m, 2H), 1.53–1.40 (m, 2H), 1.28 (d, $J = 6.1$ Hz, 6H).

Acknowledgements

The authors would like to thank Dr. Jiejun Wu for his assistance in obtaining spectroscopic data. We also would like to acknowledge Dr. Bernhard Meurers and Dr. Adrienne Dubin for insightful discussions.

References and notes

1. (a) Guastella, J.; Brecha, N.; Weigman, C.; Lester, H.; Davidson, N. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 7189; (b) Liu, Q.-R.; López-Corcuera, B.; Mandiyan, S.; Nelson, H.; Nelson, N. *J. Biol. Chem.* **1993**, *268*, 22802; (c) López-Corcuera, B.; Martínez-Maza, R.; Nuñez, E.; Rouz, M.; Supplisson, S.; Aragón, C. *J. Neurochem.* **1998**, *71*, 2211; (d) Aragón, C.; López-Corcuera, B. *Eur. J. Pharm* **2003**, *479*, 249.
2. (a) Grenningloh, G.; Rienitz, A.; Schmitt, B.; Methfessel, C.; Zensen, M.; Beyreuther, K.; Gundelfinger, E. D.; Betz, H. *Nature* **1987**, *328*, 215; (b) Young, A. B.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1973**, *70*, 2832; (c) Zarbin, M. A.; Wamsley, J. K.; Kuhar, M. J. *J. Neurosci.* **1981**, *1*, 532; (d) Probst, A.; Cortes, R.; Palacios, J. M. *Neuroscience* **1986**, *17*, 11.
3. (a) Gallagher, M. J.; Burgess, L. H.; Brunden, K. R. *Mol. Brain Res.* **1999**, *70*, 101; (b) Evans, J.; Herdon, H.; Cairns, W.; O'Brien, E.; Chapman, C.; Terret, J.; Gloger, I. *FEBS Lett.* **1999**, *463*, 301.
4. (a) Zafra, F.; Aragón, C.; Olivares, L.; Danbolt, N. C.; Gimenez, C.; Storm-Mathisen, J. *J. Neurosci.* **1995**, *15*, 3952; (b) Luque, J. M.; Nelson, N.; Richards, J. G. *Neuroscience* **1995**, *64*, 525; (c) Jursky, F.; Nelson, N. *J. Neurochem.* **1995**, *64*, 1026.
5. Krnjevic, K. *Phys. Rev.* **1974**, *54*, 418.
6. Inhibition of the glycine re-uptake process is analogous to the mechanism by which selective serotonin reuptake inhibitors (SSRI's) operate.
7. Friauf, E.; Aragón, C.; Lohrke, S.; Westenfelder, B.; Zafra, F. *J. Comp. Neurol.* **1999**, *412*, 17.
8. (a) Simpson, R. K.; Gondo, M.; Robertson, C. S.; Goodman, J. C. *Neurochem. Res.* **1996**, *21*, 1221; (b) Caulfield, W. L.; Collie, I. T.; Dickins, R. S.; Epemolu, O.; McGuire, R.; Hill, D. R.; McVey, G.; Morphy, J. R.; Rankovic, Z.; Sundaram, H. *J. Med. Chem.* **2001**, *44*, 2679.
9. Huang, W.; Simpson, R. K. *Neurologic. Res.* **2000**, *22*, 160.
10. (a) Reitz, A. B.; Baxter, E. W.; Codd, E. E.; Davis, C. B.; Jordan, A. D.; Maryanoff, B. E.; Maryonoff, C. A.; McDonnell, M. E.; Powell, E. T.; Renzi, M. J.; Schott, M. R.; Scott, M. K.; Shank, R. P.; Vaught, J. L. *J. Med. Chem.* **1998**, *41*, 1997; (b) Reitz, A. B. International patent publication, WO 93/04682.
11. Examples of other GlyT-2 medicinal chemistry programs: (a) Ho, K. K.; Appell, K. C.; Baldwin, J. J.; Bohnstedt, A. C.; Dong, G.; Guo, T.; Horlick, R.; Islam, K. R.; Kultgen, S. G.; Masterson, C. M.; McDonald, E.;

McMillan, K.; Morphy, J. R.; Rankovic, Z.; Sundaram, H.; Webb, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 545; (b) Isaac, M.; Abdelmalik, S.; Da Silva, K.; Arora, J.; MacLean, N.; Hung, B.; McCallum *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1371; (c) Caufield, W. L.; Collie, I. T.; Dickins, R. S.; Epemolu, O.; McGuire, R.; Hill, D. R.; McVey, G.; Morphy, R.; Rankovic, Z.; Sundaram, H. *J. Med. Chem.* **2001**, *44*, 2679.

12. (a) Poindexter, G. S.; Owens, D. A.; Dolan, P. L.; Woo, E. *J. Org. Chem.* **1992**, *57*, 6257; (b) Kesten, S. R.; Heffner, T. G.; Johnson, S. J.; Pugsley, T. A.; Wright, J. L.; Wise, L. D. *J. Med. Chem.* **1999**, *42*, 3718.
13. Sheehan, J. C.; Cruichshank, P. A.; Boshart, G. L. *J. Org. Chem.* **1961**, *26*, 2525.
14. Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryonoff, C. A.; Shah, D. *J. Org. Chem.* **1996**, *61*, 3849.
15. Commercially available anilines: *o*-anisole, 2-phenoxy aniline, and 2-hydroxy aniline.
16. Linsker, F.; Evans, R. L. *J. Org. Chem.* **1945**, *10*, 283.
17. Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, *3*, 207.
18. Mitsunobu, O. *Synthesis* **1981**, *1*, 1–28.
19. Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4174.
20. Lovenberg, T. W.; Roland, B. L.; Wilson, S. J.; Xiaoxia, J.; Pyati, J.; Huvar, A.; Jackson, M. R.; Erlander, M. G. *Mol. Pharm.* **1999**, *55*, 1101.