Supporting Information for

Solid Phase Synthesis of Aspartic Peptidase Inhibitors: 3-Alkoyx-4-Aryl Piperidines

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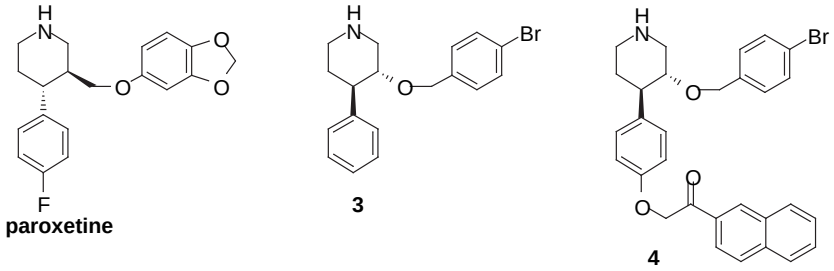
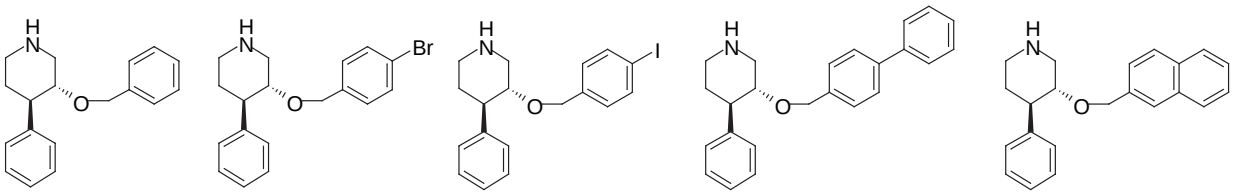


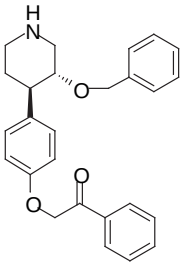
Figure 2. Comparison of paroxetine with piperidines 3 & 4

Table 1. Compounds 16a-d synthesized with respective crude yields

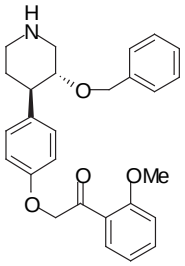


16a (95%) **16b** (81%) **16c** (77%) **16d** (98%) **16d** (88%)

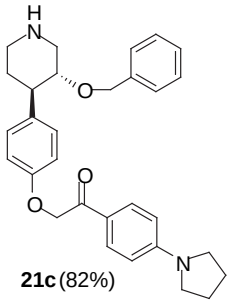
Table 2. Compounds 21a-l synthesized with respective crude yields



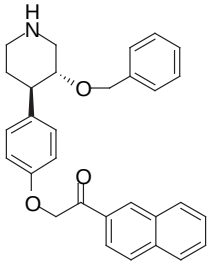
21a (80%)



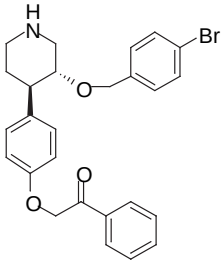
21b (75%)



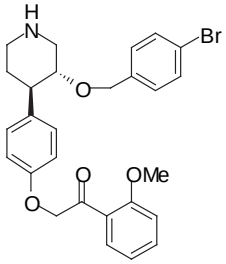
21c (82%)



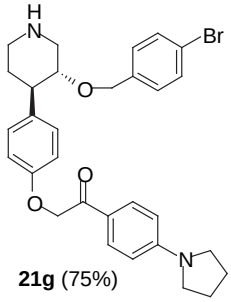
21d (68%)



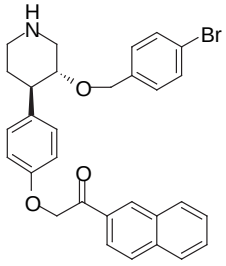
21e (57%)



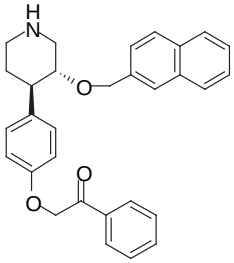
21f (57%)



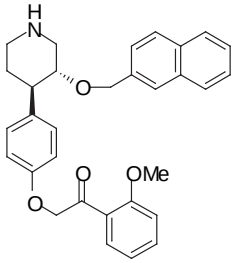
21g (75%)



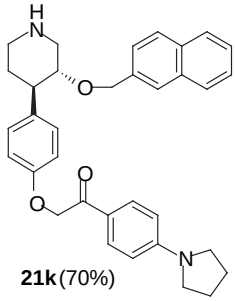
21h (64%)



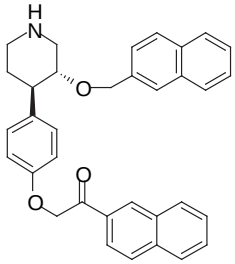
21i (68%)



21j (65%)

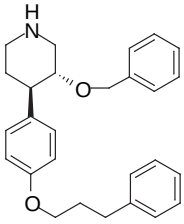


21k (70%)

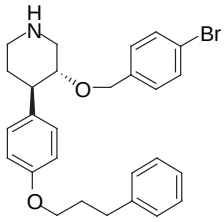


21l (62%)

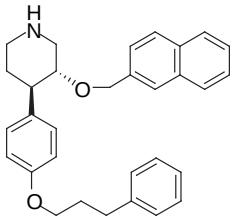
Table 3. Compounds 26a-f synthesized with respective crude yields



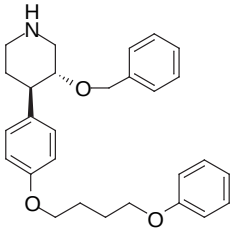
26a (65%)



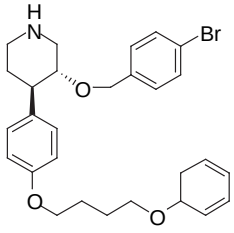
26b (58%)



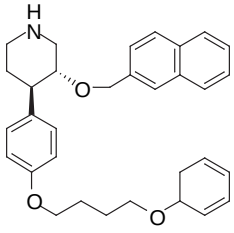
26c (58%)



26d (67%)



26e (55%)



26f (54%)

Experimentals

A. General

All reactions were carried out under an atmosphere of argon using flame or oven dried glassware. All combinatorial reactions run in parallel were carried out in teflon capped vials and mixed on agitated using a Labquake shaker. A Buchi rotary evaporator equipped with a water condenser, a dry ice trap, and a water aspirator was used for the concentrated *in vacuo* steps. Tetrahydrofuran (THF) was distilled from Na/benzophenone. Dichloromethane (DCM) was distilled from calcium hydride. Merrifield resin was purchased from Nova Biochem. P-TBD resin was purchased from Fluka. All other solvents and reagents were purchased from Aldrich and used without further purification.

^{1}H NMR spectra to determine % conversion following cleavage of solid phase resin products of the subsequent reaction were taken on a 300 MHz Bruker Aspect 3000 system at ambient temperature. HPLC analysis to determine % conversion following cleavage of solid phase reactions and determine purity of final products cleaved from solid phase resin was performed on a HP1000 Series HPLC equipped with a diode array detector. Electrospray ionization time of flight mass spectra (ESI-MS) was performed on Micromass LCT Mass Spectrometer (Beverly, MA).

B. Procedures

***(R, R)*-3-hydroxy-4-phenyl-piperidine hydrochloride (9).** To **7a** (1.1g, 4.0 mmol) was added 4N HCl-dioxane (15 mL). The reaction was monitored by TLC and after complete consumption of starting material the reaction was concentrated *in vacuo*. Tituration with Et_2O afforded **9** subsequently attached to resin **12** without further purification.

***(R, R)*-3-hydroxy-4-(4-hydroxy-phenyl)-piperidine-hydrochloride (10).** To **7b** (0.20 g, 0.68 mmol) was added 4N HCl-dioxane (3.0 mL). The reaction was monitored by TLC and after complete consumption of starting material the reaction was concentrated *in vacuo*. Tituration with Et_2O afforded **10** subsequently attached to resin **12** without further purification.

***(R, R)*-4-(4-allyloxy-phenyl)-3-hydroxy-piperidine-hydrochloride (11).** To **8** (0.57 g, 1.7 mmol) was added 4N HCl-dioxane (10 mL). The reaction was monitored by TLC and after complete consumption of starting material the reaction was concentrated *in vacuo*. Tituration with Et_2O afforded **11** subsequently attached to resin **12** without further purification.

Alkylation of Merrifield Resin (12). To a stirred suspension of NaH (0.2 g of a 95% suspension, 7.9 mmol) in DMF (5 mL) at 0° C was added m-amidophenol. After stirring for 1 hr at 0° C, to the reaction was added Merrifield resin (1.34 g, 1.48 meq/g, 2.0 mmol) and nBu_4NI (0.07g, 2.0 mmol). The reaction was allowed to warm to room temperature and stirrred. The reaction mixture was filtered and washed with DMF, CH_2Cl_2, MeOH, DMF, and CH_2Cl_2 to afford 1.49g of **12** (1.48 meq/g) as a brown resin.

Attachment of 9 to resin (14). To a stirred suspension of **12** (0.85 g, 1.2 mmol) in THF (10 mL) at -10° C was added BF_3-OEt_2 (1.6 mL, 12.6 mmol). Following stirring for 20 min, *t*BuONO (1.5 mL, 12.6 mmol) was added to the reaction mixture. The suspension was stirred at -10° C for 2 hr. The reaction mixture was filtered and washed with cold CH_2Cl_2 and DMF to afford a bright red resin. To a stirred suspension of this resin in CH_2Cl_2 (10 mL) at -10° C was added **9** and TEA (0.33 mL, 4.0 mmol) in CH_2Cl_2:DMF (8 mL, 2:1). The reaction was stirred at -10° C for 10 min and allowed to stir 2 hr at rt. The reaction mixture was filtered and washed with CH_2Cl_2, DMF, and CH_2Cl_2 to afford 1.05 g of **14** (1.44 meq/g) as an orange resin.

Alkylation of 3,4-hydroxy-phenyl piperidine resin (15). To a suspension of **14** (0.075 g, 0.11 mmol) in THF (2 mL) was added KOtBu (1.1 mL, 1.1 mmol). The suspension were agitated for 15 minutes whereupon the benzyl bromide derivative (30 eq, 3.3 mmol) and nBu_4NI (2 eq, 0.22) were added. The reactions were allowed mix overnight at 50° C overnight on a labquake mixer. The reaction mixtures were filtered and washed with DMF, CH_2Cl_2, MeOH, DMF, and CH_2Cl_2 to afford **15** as an orange resin.

Attachment of 11 to resin (17). To a stirred suspension of **12** (0.60 g, 0.89 mmol) in THF (8 mL) at -10° C was added BF_3-OEt_2 (1.1 mL, 8.9 mmol). Following stirring for 20 min, *t*BuONO (1.1 mL, 8.9 mmol) was added to the reaction mixture. The suspension was stirred at -10° C for 2 hr. The reaction mixture was filtered and washed with cold CH_2Cl_2 and DMF to afford a bright red resin. To a stirred suspension of this resin in CH_2Cl_2 (8 mL) at -10° C was added **11** and TEA (0.14 mL, 1.7 mmol) in CH_2Cl_2 (8 mL). The reaction was stirred at -10° C for 10 min and allowed to stir 2 hr at rt. The reaction mixture was filtered and washed with CH_2Cl_2, DMF, and CH_2Cl_2 to afford 0.65 g of **17** (1.18 meq/g) as a red resin.

Alkylation of 3,4-hydroxy-alloxyphenol piperidine resin (18). To a suspension of **17** (0.11 g, 0.13 mmol) in THF (2 mL) was added KOtBu (1.6 mL, 1.6 mmol). The suspension were agitated for 15 minutes whereupon the benzyl bromide derivative (30 eq, 4.8 mmol) and nBu_4NI (2 eq, 0.32) were

added. The reactions were allowed mix overnight at 50° C on a labquake mixer. The reaction mixtures were filtered and washed with DMF, CH_2Cl_2, MeOH, DMF, and CH_2Cl_2 to afford **18** as a dark red resin.

Allyl removal from 3,4-hydroxymethylarene-alloxyphenol piperidine resin (19). To a suspension of **18** (0.14 g, 0.17 mmol) in DCM (10 mL) was added $Pd(PPh_3)_4$ (0.464 g, 0.40 mmol). The reactions were allowed to stir for 15 minutes then morpholine (0.70 mL, 8.0 mmol) was added. After stirring for 1 hr the reactions mixtures were filtered and washed with DCM, MeOH, DCM to afford **19** as a dark red resin

Alkylation of 3,4-hydroxybenzyl-phenol piperidine resin (20). To **19** (0.030 g, 0.04 mmol) and Cs_2CO_3 (0.22 g, 0.67 mmol) was added $CHCl_3$:MeOH (2 mL, 2:1 ratio). The suspensions were agitated for 15 minutes whereupon the 2'bromoacetophenone derivative (40 eq, 1.8 mmol) was added. The reactions were allowed mix overnight at 35° C on a labquake mixer. The reaction mixtures were filtered and washed with DMF, CH_2Cl_2, MeOH, DMF, and CH_2Cl_2 to afford **20** as dark rust colored resin.

Attachment of 10 to resin (23). To a stirred suspension of **12** (0.20 g, 0.30 mmol) in THF (4 mL) at -10° C was added BF_3-OEt_2 (0.38 mL, 3.0 mmol). Following stirring for 20 min, *t*BuONO (0.35 mL, 3.0 mmol) was added to the reaction mixture. The suspension was stirred at -10° C for 2 hr. The reaction mixture was filtered and washed with cold CH_2Cl_2 and DMF to afford a bright red resin. To a stirred suspension of this resin in CH_2Cl_2 (4 mL) at -10° C was added **10** (0.16 g, 0.40 mmol) and TEA (0.049 mL, 0.59 mmol) in CH_2Cl_2:DMF (8 mL, 2:1). The reaction was stirred at -10° C for 10 min and allowed to stir 2 hr at rt. The reaction mixture was filtered and washed with CH_2Cl_2, DMF, and CH_2Cl_2 to afford 0.22 g of **22** (1.25 meq/g) as a dark purple resin.

Alkylation of 3,4-hydroxy-phenol piperidine resin (23). To **22** (0.10 g, 0.12 mmol) and Cs_2CO_3 (0.73 g, 1.8 mmol) was added $CHCl_3$:MeOH (2 mL, 2:1 ratio). The suspensions were agitated for 15 minutes whereupon the alkyl bromide derivatives (20 eq, 2.4 mmol) were added. The reactions were allowed mix overnight at 35° C on a labquake mixer. The reaction mixtures were filtered and washed with DMF, CH_2Cl_2, MeOH, DMF, and CH_2Cl_2 to afford **23** as a dark reddish-purple resin.

Alkylation of 3,4-hydroxy-phenyl-etherpiperidine resin (24). To a suspension of **23** (0.03 g, 0.04 mmol) in THF (2 mL) was added KOtBu (0.44 mL, 0.44 mmol). The suspensions were agitated for 15 minutes whereupon the benzyl bromide derivative (30 eq, 1.32 mmol) and nBu_4NI (3 eq, 0.13) was

added. The reactions were allowed mix overnight at 50° C on a labquake mixer. The reaction mixtures were filtered and washed with DMF, CH_2Cl_2, MeOH, DMF, and CH_2Cl_2 to afford **24** as a dark red resin.

Cleavage of Final Products from Triazene Linker (16a-e, 21a-l or 26a-e).

To a teflon capped vial was added 25-30 mgs of resin (**15**, **20**, or **25**) and a 10% TFA/ DCM solution (1.5 mL). The vial is then capped and agitated for 5 mins. The resin was then filtered and the filtrate collected. The resin was washed with a 10% TFA/ DCM solution (3 x 1 mL) and the subsequent filtrates collected. The combined filtrates were concentrated *in vacuo* to afford the final 8-12 mgs of the final solid phase products (**16**, **22**, or **26**) as pale yellow solid.

Purification of Final Products via Solid Phase Extraction (SPE).

To a teflon capped vial was added 125 mgs (2.6 mmol/g) of Polymer-bound 1,5,7-triazabicyclo[4.4.0]dec-5-ene (P-TBD). The resin was swollen in 2 mL DCM for 2 mins, then approx. 4 mgs of the final reaction product (**21a-l**) and 4 mL DCM was added to the vial. The vial was then capped and agitated for 1 min. The resin was then filtered and the filtrate collected. The resin is washed with DCM and the subsequent filtrate collected. The combined filtrates are concentrated *in vacuo* to afford approx. 4 mgs of the final solid phase product **21a-l.**

Representative purification: