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Review

Synthesis of pharmaceutically active compounds containing a disubstituted piperidine framework

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Abstract—The synthesis of pharmaceutically active compounds bearing a disubstituted piperidine framework is reviewed. Due to their frequent occurrence in pharmaceutical research, functionalized piperidines and the synthetic methodologies used for their preparation are of considerable topical interest. The present review focuses on the synthetic pathways used for the preparation of disubstituted piperidines and also briefly covers the activity and/or usage of the same.

Contents

1. Introduction

The *N*-heterocyclic piperidine ring is a frequently encountered molecular fragment in natural products and pharmaceutically active compounds. During a fairly recent 10-year period, several thousand piperidine compounds have been mentioned in clinical and preclinical studies.[1] Accordingly, the preparation of functionalized piperidines has been extensively studied, synthetic methods leading to multifunctionalized and chiral derivatives being of particular interest at present.[2–7] This review focuses on the synthesis of a specific subclass of functionalized piperidines, namely disubstituted piperidines bearing pharmaceutical activity. This particular class of compounds is highly varying regarding both the synthetic methods used for their preparation as well as their structure and function. The references have been drawn from the electronic version of the Drug Data Report (MDL/ISIS database) which includes data from the years 1988 through 2006. Excluded are piperidones, unsaturated *N*-heterocycles, amidines and bicyclic compounds.

Keywords: Synthesis; Disubstituted piperidines; Heterocyclic compounds; Pharmaceutical activity.
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The chapters are ordered according to substitution pattern of the compounds presented, the activity and/or usage of which are also briefly mentioned.

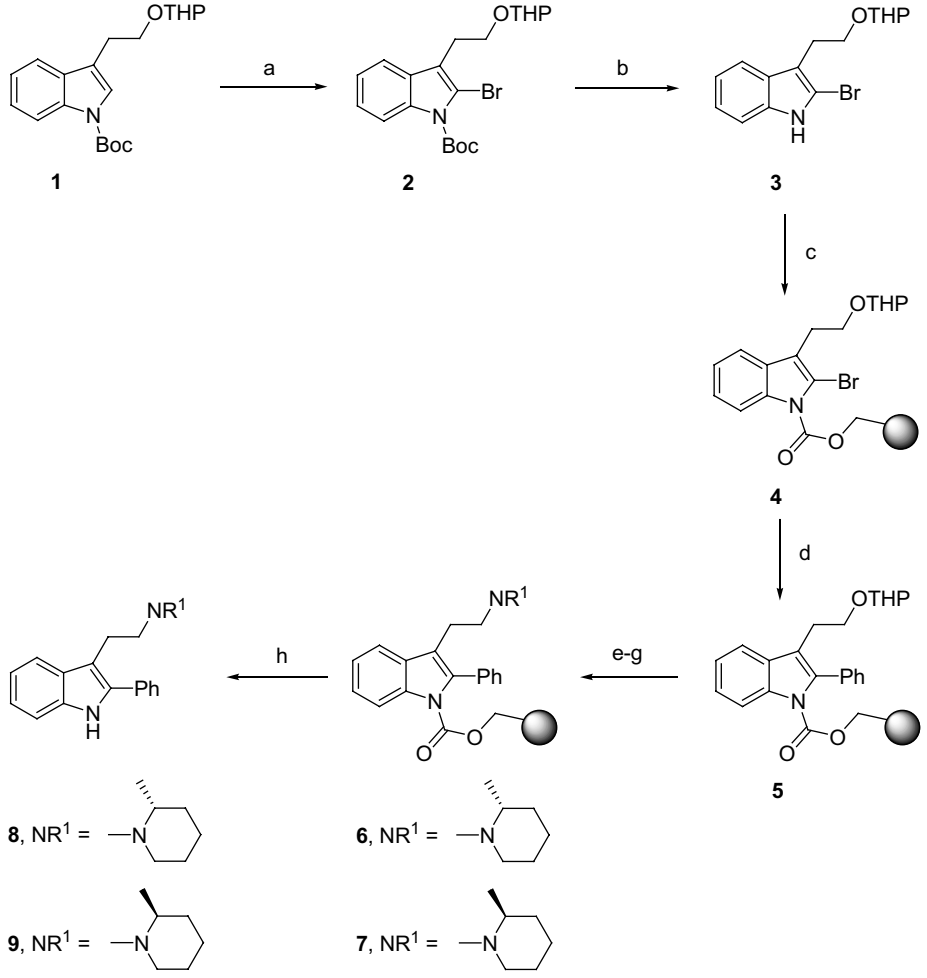
2. Conclusion

As shown in the present review, a wide variety of synthetic strategies are being used for the preparation of pharmaceutically active disubstituted piperidines with a range of potential applications. Many of the synthetic pathways described here are rather complex including numerous reaction steps. Methods often used in the preparation of piperidines, such as reduction of pyridines and cyclization of linear chains, are represented. However, many of the pathways described utilize starting materials already incorporating the desired piperidine moiety. The preparation of pharmaceutically active compounds of this kind remains a major challenge in synthetic organic chemistry. Due to the demand for improved selectivity and reduction of side effects of potential drugs in pharmaceutical research, compounds with increasing molecular complexity, including those containing a disubstituted piperidine framework, are likely to be designed even in the future.

3. Synthesis of pharmaceutically active disubstituted piperidines

3.1. Compounds containing the 1,2-disubstituted piperidine framework

Stevenson et al.[8] have described a solid-phase synthetic route to a number of 2-aryl tryptamines having h5-HT_{2A} receptor antagonistic activity. This highly interesting series contained two compounds (**8** and **9**) embodying a 1,2-disubstituted piperidine moiety. The solid-phase methodology employed in the preparation of this pair of compounds commenced with the making of the resin-bound intermediate **4** in three steps (Scheme 1).[9] Bromination of the tryphtol derivative **1** in the indole 2-position by lithiation with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) followed by treatment with $BrCF_2CF_2Br$ gave **2**. Compound **2** was further converted to the free 2-bromoindole **3** by removal of the Boc group using sodium methoxide.



Scheme 1. Solid-phase synthetic route described by Stevenson et al. for the preparation of compounds **8** and **9**. Reagents and conditions: (a) LiTMP, THF, −78 °C, then $BrCF_2CF_2Br$; (b) NaOMe, MeOH, 20 °C; (c) Wang resin, KHMDS, toluene, −78 → 20 °C, 30 min; (d) $Pd(PPh_3)_4$, $PhSnR_3$, THF, 70 °C; (e) PPTS, 10% EtOH/DCE; (f) Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine; (g) HNR^1, DCE; (h) AcOH, 110 °C.

The resin-bound 2-bromoindole **4** was finally obtained by loading of **3** onto the *p*-nitrophenylcarbonate derivative of the Wang resin. Reaction of the resin-bound intermediate **4** with phenyl stannane proceeded with good conversion rates. Subsequent removal of the THP group from **5** afforded the resin-bound alcohol, which was activated as the corresponding triflate and treated with a nucleophilic amine giving compounds **6** and **7**. Finally, treatment with hot acetic acid in order to cleave off the resin followed by purification with ion exchange chromatography gave the desired products **8** and **9**.

3.2. Compounds containing the 1,3-disubstituted piperidine framework

In the mid 1990s, Hoekstra et al.[10] conducted a study on fibrinogen C-terminal γ-chain related β-turn peptide mimetics containing a nipecotic acid scaffold. This led to the finding of the prototypical fibrinogen receptor (GPIIb/IIIa) antagonist RWJ-50042 (**10**, Fig. 1). Attempts on developing more potent candidates were then pursued by solid-phase parallel synthesis of analogues of **10** producing several promising molecules and culminating in the discovery of RWJ-53308 (**15**).[11,12] The fibrinogen receptor antagonist series and related compounds have also been claimed in a series of patent applications.[13–16]

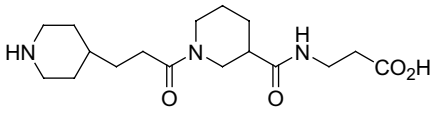


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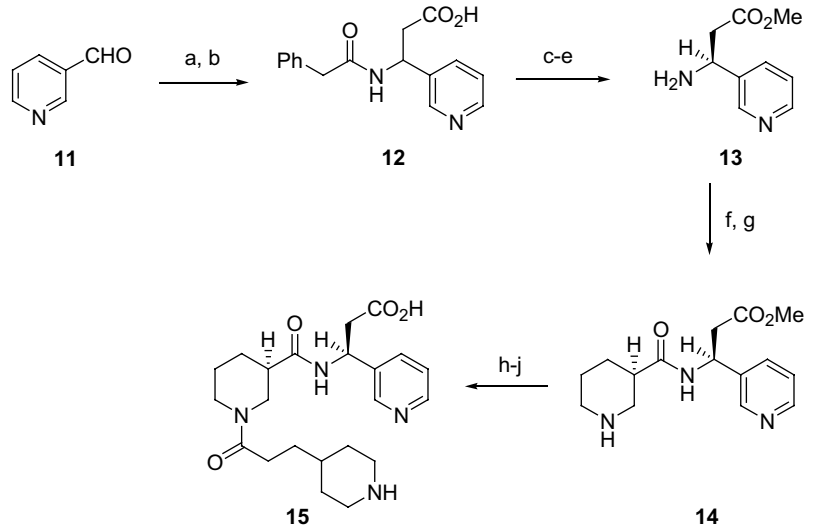
Figure 1. Structure of GPIIb/IIIa antagonist RWJ-50042 (**10**) developed by Hoekstra et al.

Preparation of this potent, orally active GPIIb/IIIa antagonist started off by a modified Knoevenagel condensation of aldehyde **11** with malonic acid/ammonia which gave the corresponding racemic β-amino acid (Scheme 2). Separation of the β-amino acid enantiomers was achieved by conversion to the corresponding phenylacetamide **12**, followed by resolution of **12** with penicillin amidase. HBTU (2-[1*H*-benzotriazol-1-yl]-1,1,3,3-tetramethyluronium hexafluorophosphate) activation of *N*-Boc-(*R*)-nipecotic acid, addition of β-amino ester **13** and Boc removal with hydrochloric acid then yielded the secondary amine **14**. Yet another HBTU activation, this time of *N*-Boc-4-piperidinepropanoic acid, provided the tertiary amide. Subsequent purification, saponification and removal of the Boc group finally gave the product **15** for in vivo studies.

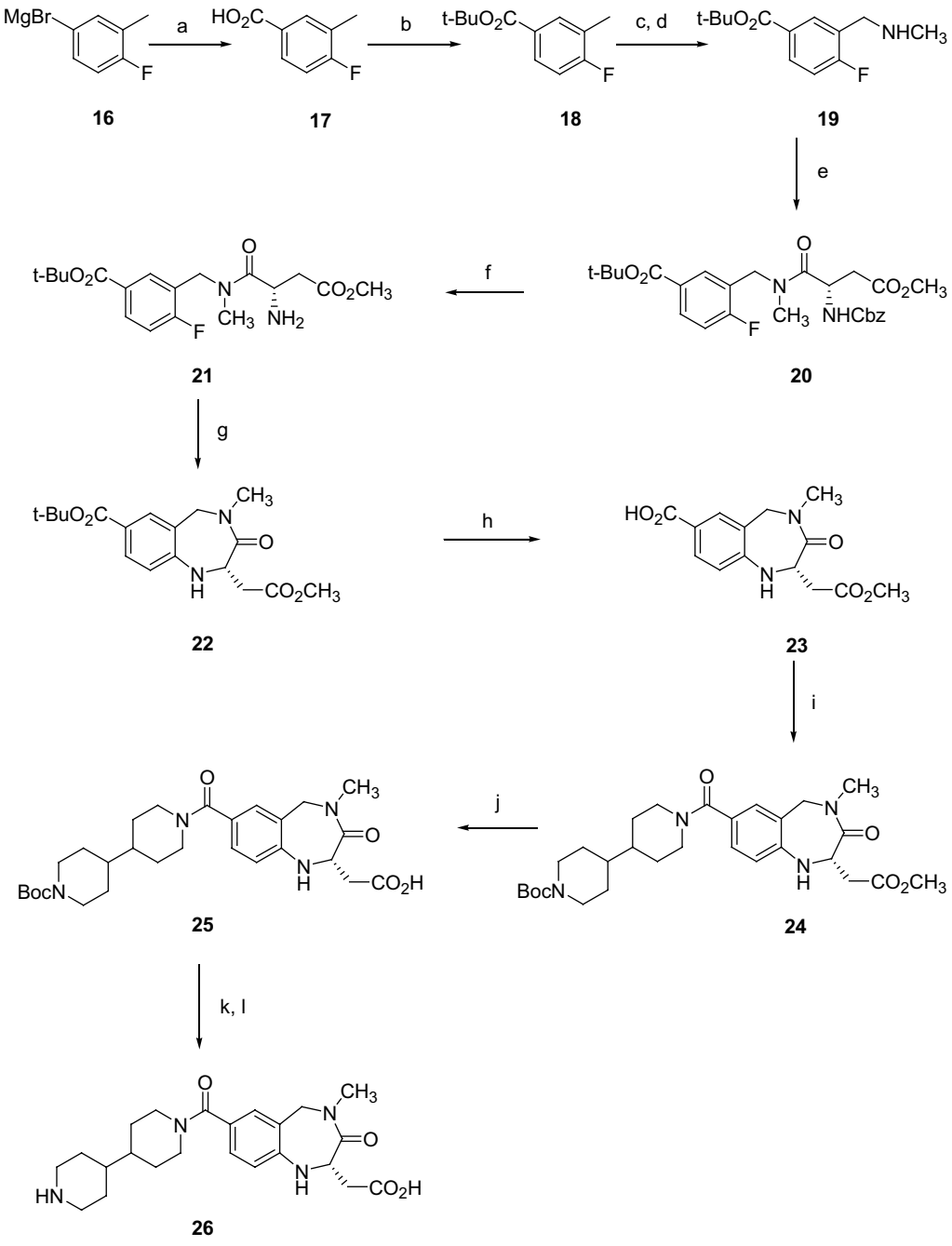
3.3. Compounds containing the 1,4-disubstituted piperidine framework

The preparation of a highly potent, selective and orally active fibrinogen receptor antagonist SB 214857 (**26**) containing a 1,4-disubstituted piperidine moiety has been reported by Miller et al.[17] The enantiospecific synthesis of **26** from a derivative of L-aspartic acid commenced by carboxylation of commercially available 4-fluoro-3-methylphenylmagnesium bromide (**16**) providing 4-fluoro-3-methylbenzoic acid (**17**) in 77% yield (Scheme 3). Compound **17** was then esterified with isobutylene in the presence of catalytic trifluoromethanesulfonic acid giving *tert*-butyl ester **18** in 94% yield. Amine **19** was obtained from **18** in 70% overall yield by benzylic bromination with NBS followed by reaction of the crude benzyl bromide with excess 40% aqueous methylamine. The amino group in **19** was acylated with *N*-CbZ-L-aspartic acid β-methyl ester in the presence of DCC and HOBt affording the amide **20** (86% yield), while subsequent hydrogenolysis of



11 **12** **13** **14** **15**

Scheme 2. Preparation of the potent, orally active fibrinogen antagonist RWJ-53308 (**15**) according to Hoekstra and coworkers. Reagents and conditions: (a) malonic acid, NH_4OAc, EtOH, reflux; (b) $PhCH_2COCl$, Et_3N, aq acetone; (c) penicillin amidase, pH 7.5; (d) 6 N HCl (aq); (e) 4 N HCl/1,4-dioxane/MeOH; (f) *N*-Boc-(*R*)-nipecotic acid, HBTU, HOBT, NMM, MeCN; (g) 4 N HCl/1,4-dioxane; (h) *N*-Boc-4-piperidinepropanoic acid, HBTU, HOBT, NMM, MeCN; (i) LiOH, aq THF; (j) 4 N HCl/1,4-dioxane.



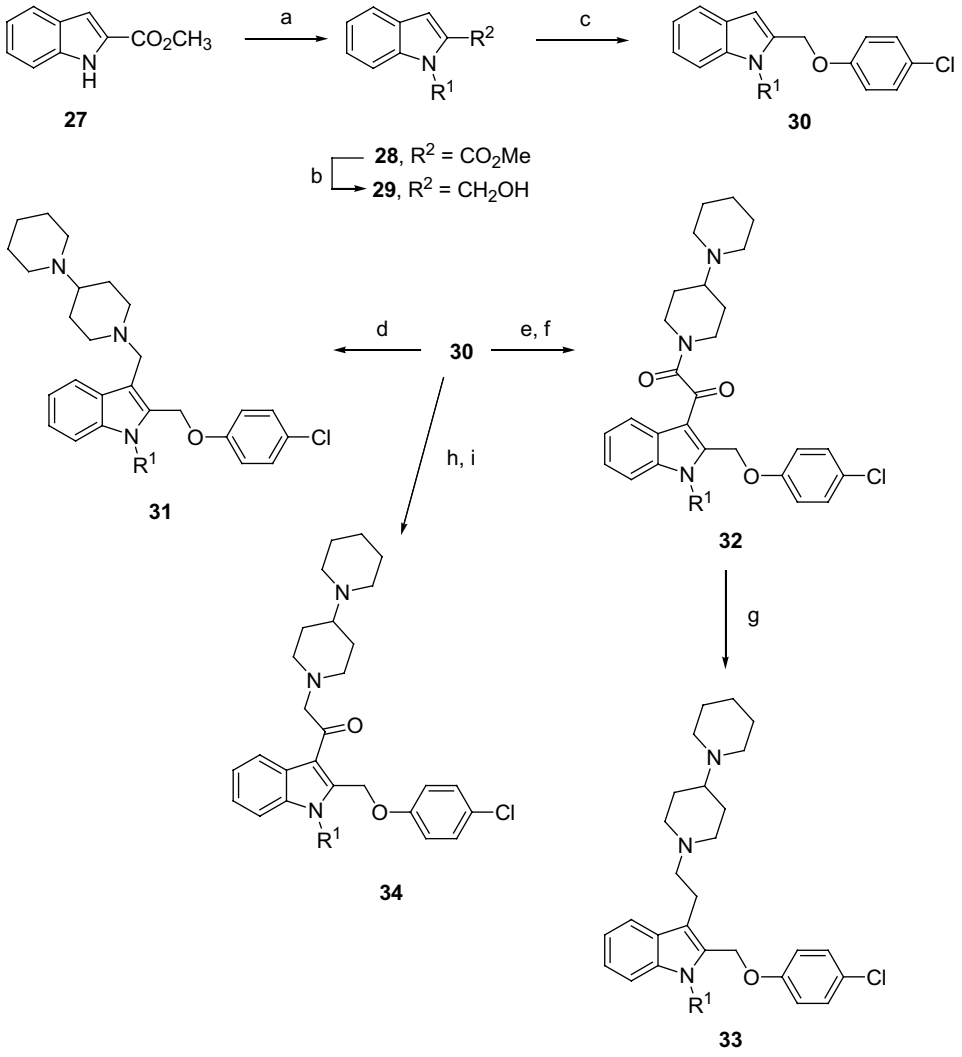
Scheme 3. Synthetic strategy for the preparation of SB 214857 (**26**) by Miller and coworkers. Reagents and conditions: (a) CO_2, THF; (b) isobutylene, 5 mol% TfOH, Et_2O, sealed pressure bottle, −78 °C to room temperature; (c) NBS, $(PhCO)_2O_2$, CCl_4, reflux; (d) 40% aq CH_3NH_2, THF; (e) Cbz-L-Asp-β-methyl ester, DCC, HOBt·H_2O, DMF; (f) H_2, 10% Pd/C, MeOH; (g) 0.1 M **21** in anhydrous DMSO, 125 °C; (h) 1:1 TFA/CH_2Cl_2, anisole; (i) 1-Boc-4,4′-bipiperidine, EDC, $(i\text{-Pr})_2NEt$, DMF; (j) 2.0 N NaOH, 1:1 MeOH/THF, then AcOH; (k) 4 M HCl in dioxane, $CHCl_3$, then neutralization of excess reagent with 1.0 N KOH in EtOH to give **26**·HCl; (l) precipitation from aqueous solution at pH 6.8.

the Cbz protecting group under standard conditions gave the cyclization precursor **21** in 98% yield. The desired cyclization product **22** was then obtained in 47% yield (>99:1 *S*/*R*) by warming a solution of **21** in DMSO for 18 h. Deprotection of the *tert*-butyl ester **22** with trifluoroacetic acid in the presence of anisole gave carboxylic acid **23** (yield 95%), followed by coupling of **23** with 1-Boc-4,4′-bipiperidine in the presence of EDC which afforded the fully protected SB 214857 (**24**) in 94% yield. Finally, saponification to afford carboxylic acid **25** and subsequent removal of the Boc group gave zwitterionic SB 214857 (**26**) in good overall yield. The preparation of a myriad of other platelet aggregation inhibitors carrying the 1,4-disubstituted piperidine framework has been reported in both scientific articles[18–20] and claimed in patent applications[21–31] during the past two decades.

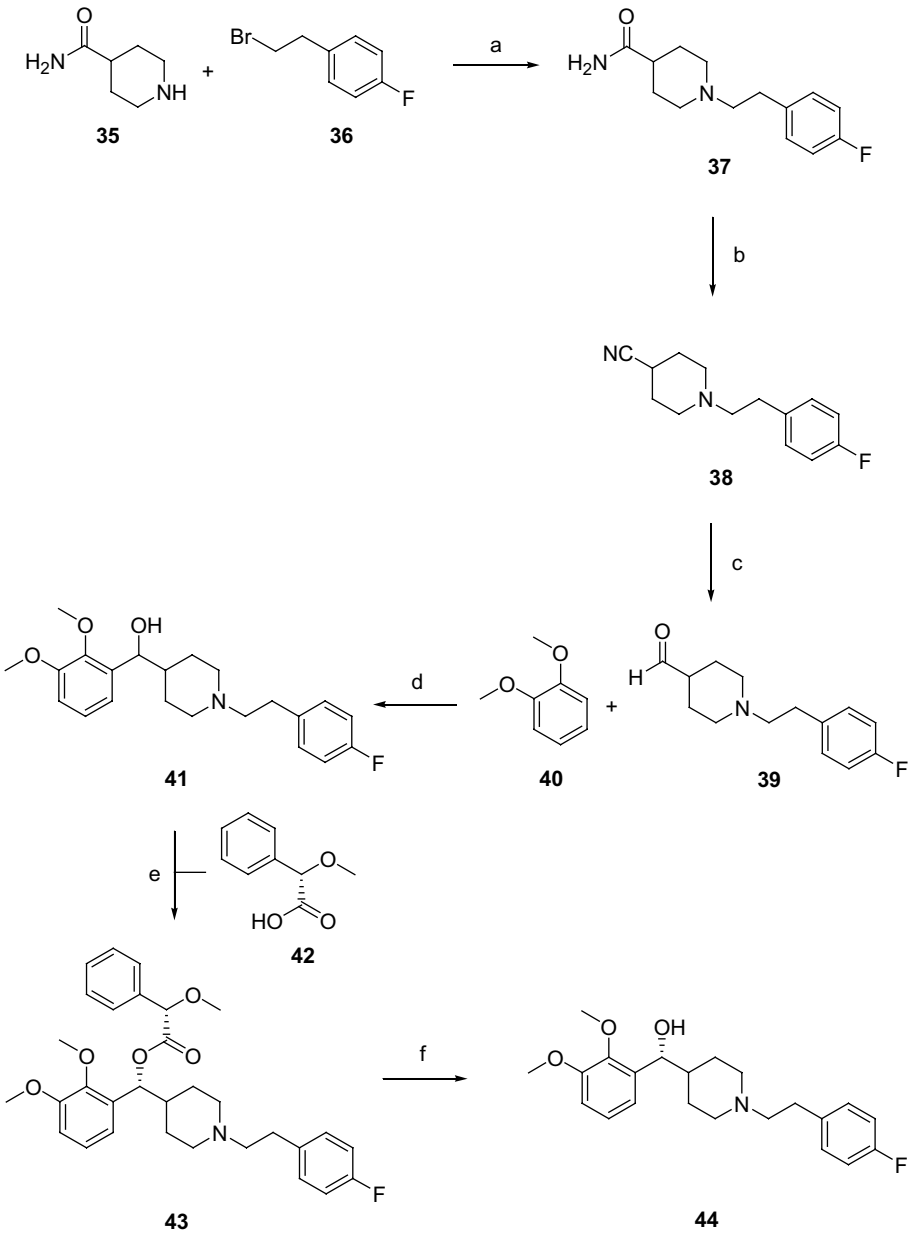
Another type of pharmaceutically active compounds containing the 1,4-disubstituted piperidine moiety has

been reported by Hipskind and coworkers.[32] This series of potent NPY Y-1 antagonists was prepared as illustrated in Scheme 4. Deprotonation and subsequent alkylation of **27** with sodium hydride and the appropriate alkyl halide, respectively, gave compound **28**. Treatment of **28** with lithium aluminium hydride to evoke reduction followed by nucleophilic aromatic substitution of a fluorobenzene yielded **30**. The aryloxy group could also be incorporated via Mitsunobu reaction of **29** and the appropriate phenol. A subsequent Mannich reaction of **30** gave compounds **31**. Intermediate **30** could also be reacted with oxalyl chloride followed by treatment with amine to yield derivatives **32**. These in turn could be further reduced with borane–dimethyl sulfide producing compounds **33** in reasonable yield. Alternatively, **30** could be treated with bromoacetyl bromide and powdered lithium carbonate under ultrasound conditions followed by treatment with the appropriate amine. This afforded compounds **34** in modest quantities.

In 1998, Sorbera et al.[33] reported the synthetic pathway towards 5-HT_{2A} antagonist MDL-100907 (**44**, Scheme 5). This antipsychotic agent containing a 1,4-disubstituted piperidine moiety may be prepared in several different ways.[34,35] One of the possible routes, illustrated in Scheme 5 below, was claimed by Carr and coworkers[34] in a patent application in 1991. The synthesis commenced by condensation of the piperidine-4-carboxamide **35** with 2-(4-fluorophenyl)ethyl bromide (**36**) yielding 1-[2-(4-fluorophenyl)ethyl]piperidine-4-carboxamide (**37**). The amide was further converted to the corresponding nitrile (**38**) by reaction with refluxing $POCl_3$ and the reduction of **38** with diisobutyl aluminium hydride then gave the aldehyde **39**. A subsequent condensation with 1,2-dimethoxybenzene (**40**) using BuLi afforded racemic MDL-100907 (**41**), which was esterified with (*S*)-2-methoxy-2-phenylacetic acid (**42**) to give a mixture of diastereoisomers separable by column chromatography. The pure diastereoisomer **43** was finally saponified with K_2CO_3 to yield the desired compound **44**.



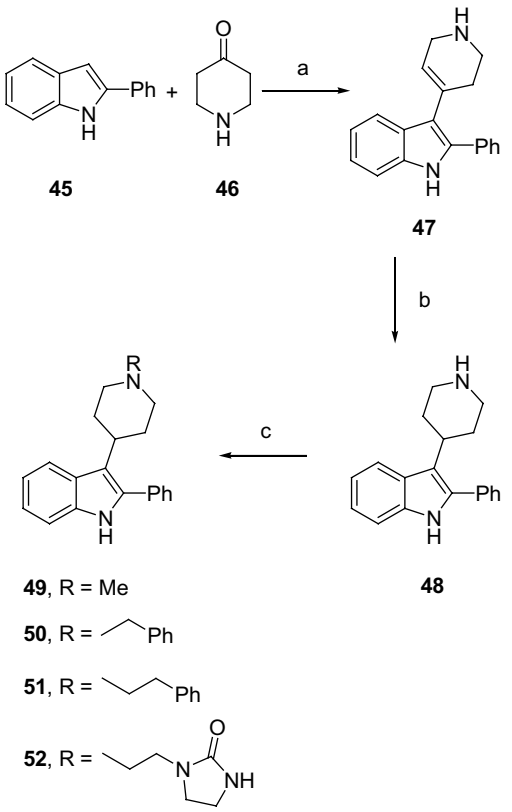
Scheme 4. Synthesis of **33** and **34** by Hipskind et al. Reagents and conditions: (a) NaH, R^1I or R^1Br, DMF, 0 °C to room temperature; (b) LAH, THF, 0 °C to room temperature; (c) NaH, ArF, DMF, 80 °C; (d) amine, paraformaldehyde, concentrated aqueous HCl, NaOAc, EtOAc; (e) oxalyl chloride, diethyl ether; (f) amine, THF; (g) borane–dimethyl sulfide complex, THF; (h) bromoacetyl bromide, Li_2CO_3, diethyl ether; (i) amine, THF.



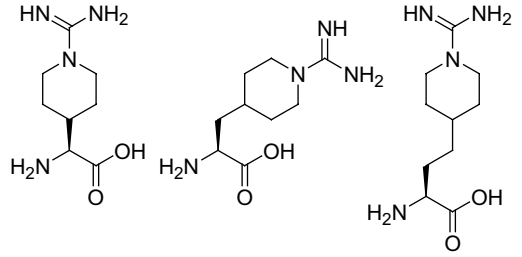
Scheme 5. Preparation of MDL-100907 (**44**) according to Carr et al. Reagents and conditions: (a) K_2CO_3, DMF; (b) $POCl_3$, reflux; (c) DIBAL–H, THF; (d) BuLi, THF; (e) DCC, DMAP, $CHCl_3$, reflux, then column chromatography; (f) K_2CO_3, methanol/water.

Rowley et al.[36–38] have described the synthesis of a series of another type of serotonin receptor h5-HT_{2A} antagonists containing a 1,4-piperidine framework. These piperidinyl derivatives (**49**–**52**) were prepared in three steps from 2-phenyl indole (**45**, Scheme 6). The synthetic strategy began with the reaction of 4-piperidone **46** with the indole **45**, which gave tetrahydropyridine **47** in 78% yield. Reduction of **47** afforded piperidine **48** (75% yield), the alkylation of which provided the desired compounds **49**–**52** in moderate to high yields. This series of h5-HT_{2A} receptor antagonists also included examples containing the 1,3-disubstituted or the 3,4-disubstituted piperidine moieties.

The preparation of robust and metabolically stable neurotensin (NT) peptide analogues containing a 1,4-disubstituted piperidine framework has been reported by Achilefu et al.[39] These compounds may be used as tissue-specific diagnostic or cytotoxic drugs in the management of NT receptor positive tumours. Commercially available amino acid mimics were used to stabilize the scissile amide bonds (**53**–**55**, Fig. 2). The preparation of tridecapeptide NT with these amino acids incorporated succeeded using an automated solid-phase peptide synthesis (standard Fmoc strategy). A radiometal chelator (DTPA) for nuclear imaging or fluorescein (FITC) for optical imaging was also incorporated in the peptide analogues. The reactive DTPA intermediate, tri-*tert*-butyl DTPA, was conjugated to the N-terminus of NT peptide analogue by the same process used to assemble the peptide. TFA-mediated cleavage of the peptide from the solid-phase resin, together with removal of side-



Scheme 6. Synthesis of h5-HT_{2A} receptor antagonists (**49–52**) according to Rowley et al. Reagents and conditions: (a) $AcOH/H_3PO_4$, 100 °C; (b) ammonium formate, 10% Pd/C, MeOH, reflux; (c) RBr (or MeI), K_2CO_3, DMF, room temperature.



53, Gly(PipAm) **54**, Ala(PipAm) **55**, hAla(PipAm)

Figure 2. Structures and abbreviations of amino acid mimics containing the 1,4-disubstituted piperidine framework and used by Achilefu et al. for the preparation of NT peptide analogues.

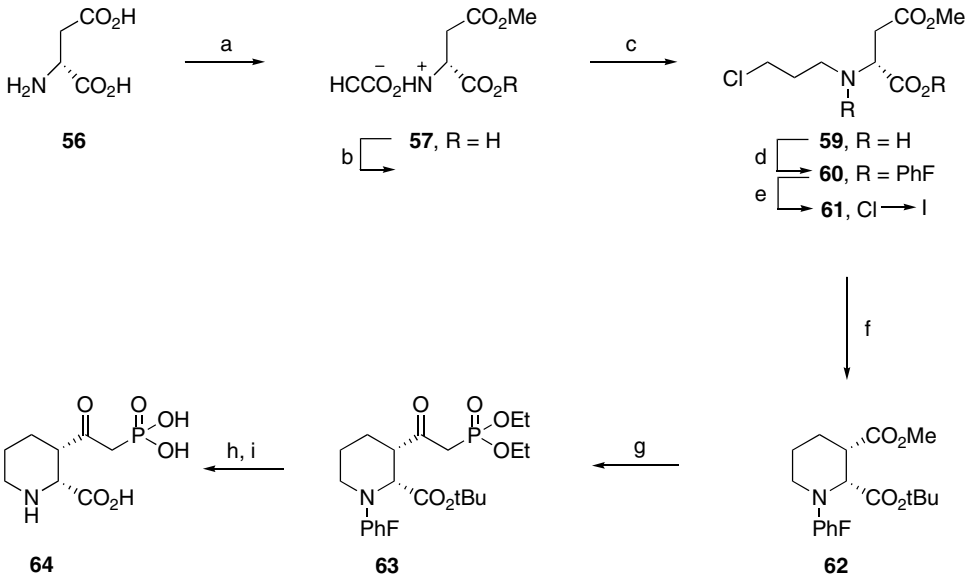
chain protecting groups, gave the desired products. The FITC derivatives were synthesized by solution-phase reaction, that is, HPLC-purified NT peptide analogues were reacted with fluorescein isothiocyanate. The synthesis of these compounds has also been claimed in a patent application.[40]

3.4. Compounds containing the 2,3-disubstituted piperidine framework

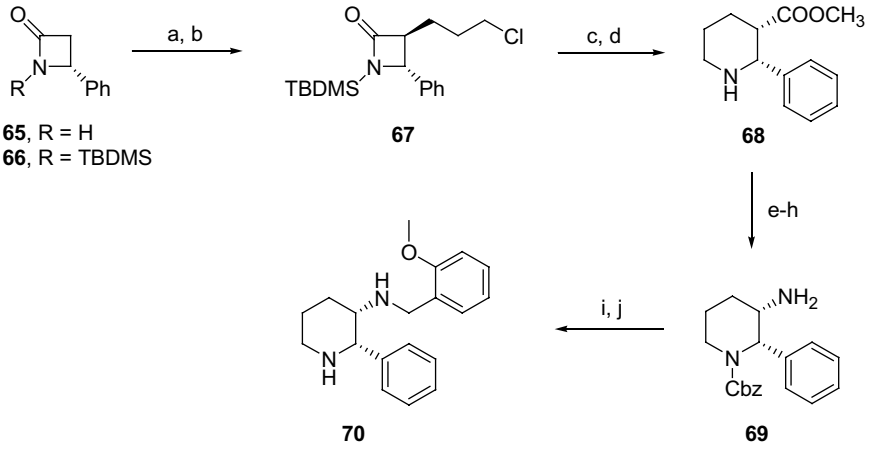
The preparation of a competitive, glutamate antagonist of the NMDA receptor complex containing a 2,3-disubstituted piperidine framework has been reported by Whitten et al.[41,42] The synthetic strategy used in the preparation of this conformationally restricted compound (3*S*)-phosphonoacetyl-(2*R*)-piperidinecarboxylic acid (**64**) was initiated by using (*R*)-aspartic acid (**56**) as a chiral template (Scheme 7). Selective functionalization of the α- and β-carboxylic acid groups of **56** was achieved in two steps: methylation of the distal group by treatment with methanol giving **57** followed by transesterification with *tert*-butyl acetate and perchloric acid leading to **58**. Subsequent N-alkylation with chlorobromopropane gave **59** in 55% yield, the N-protection of which with phenylfluorenyl provided **60** in 85% yield. Quantitative conversion of **60** to the corresponding iodide **61** was achieved using Finkelstein conditions. Cyclization of **61** by warming the corresponding enolate then gave piperidine **62** in 65% yield. The desired *cis* enolate was formed in LDA at −78 °C using 2,6-diisopropylphenol as the proton source and warming the mixture to −35 °C during the course of several hours. By treatment of **62** with lithium methyl diethylphosphonate at −78 °C, the chiral β-ketophosphonate **63** was obtained in 66% yield. Finally, a two-step deprotection of **63** gave the desired product **64** in 52% yield.

In 1992, Desai et al.[43] described the synthesis of the potent substance P antagonist (+)-(2*S*,3*S*)-2-methoxybenzyl-2-phenylpiperidin-3-yl-amine or CP-99,994 (**70**, Scheme 8). The enantiospecific synthesis strategy commenced with N-protection of (−)-(4*R*)-4-phenyl-2-azetidinone (**65**) to give **66** in 99% yield. A subsequent highly stereospecific alkylation with 1-bromo-3-chloropropane provided the *trans* product **67** in 78% yield, after which a two-step sequence gave compound **68** (78% from **67**): simultaneous removal of TBDMS and hydrolysis of the β-lactam **67** affording the corresponding aminomethyl ester, followed by cyclization of the crude product to give the 2,3-disubstituted piperidine **68**. Next, the carbomethoxy group was converted into an amino group via four steps: (i) N-protection, (ii) conversion of carbomethoxy group to carboxamide, (iii) oxidation of carboxamide to an *N*-Boc group through Hoffmann degradation and (iv) cleavage of the Boc group to yield **69** in 44% from **68**. Finally, reductive amination of **69** with *o*-methoxybenzaldehyde and cleavage of the Cbz group gave the desired product **70** (83%, isolated as dihydrochloride salt). Numerous 2,3-disubstituted piperidine derivatives possessing tachykinin receptor antagonistic activity have been claimed in patent applications during the past two decades by Desai et al.[44,45] and others at Pfizer Inc.,[46–54] as well as other pharmaceutical companies.[55–66]

The synthetic strategy used for the preparation of another substance P antagonist containing the 2,3-disubstituted piperidine framework has been reported by Harrison et al.[67] Synthesis of the racemic mixture of the desired compound **76** was first described, after which the stereoisomer (+)-(2*S*,3*S*)-**76** having the highest binding affinity for the hNK_1 receptor was selectively prepared. The preparation commenced by reduction of the keto lactam **71** using sodium borohydride to provide the hydroxyl-lactam **72** with high selectivity (>10:1 *cis*/*trans*, Scheme 9). A subsequent reduction of the lactam



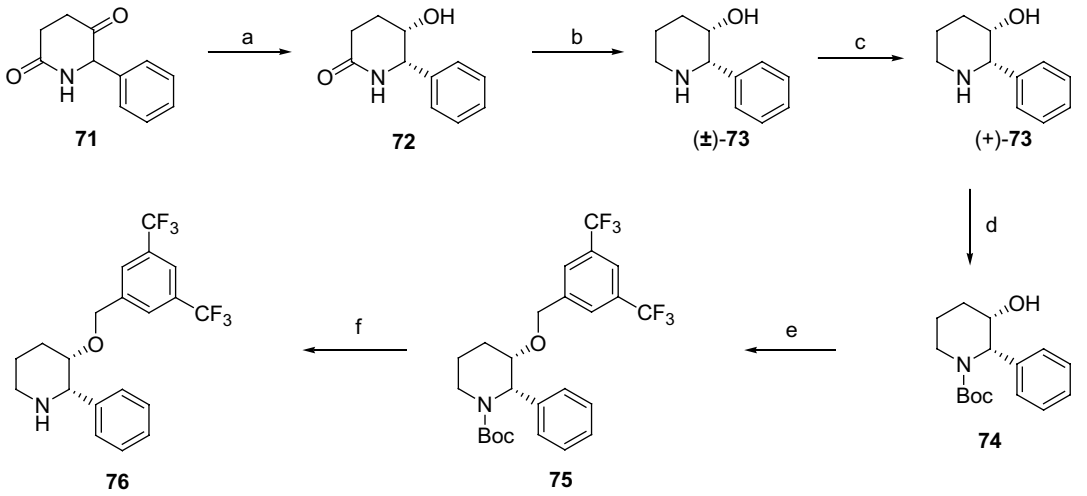
Scheme 7. Preparation of (3*S*)-phosphonoacetyl-(2*R*)-piperidinecarboxylic acid (**64**) according to Whitten et al. Reagents: (a) MeOH, $SOCl_2$; (b) $CH_3CO_2C(CH_3)_3$, $HClO_4$; (c) $Br(CH_2)_3Cl$, $NaHCO_3$; (d) PhFBr, $Pb(NO_3)_2$, $NEt(i\text{-}Pr)_2$; (e) NaI; (f) LDA, 2,6-diisopropylphenol; (g) $LiCH_2PO(OCH_2CH_3)_2$; (h) TFA, TMSI; (i) propylene oxide, MeOH.



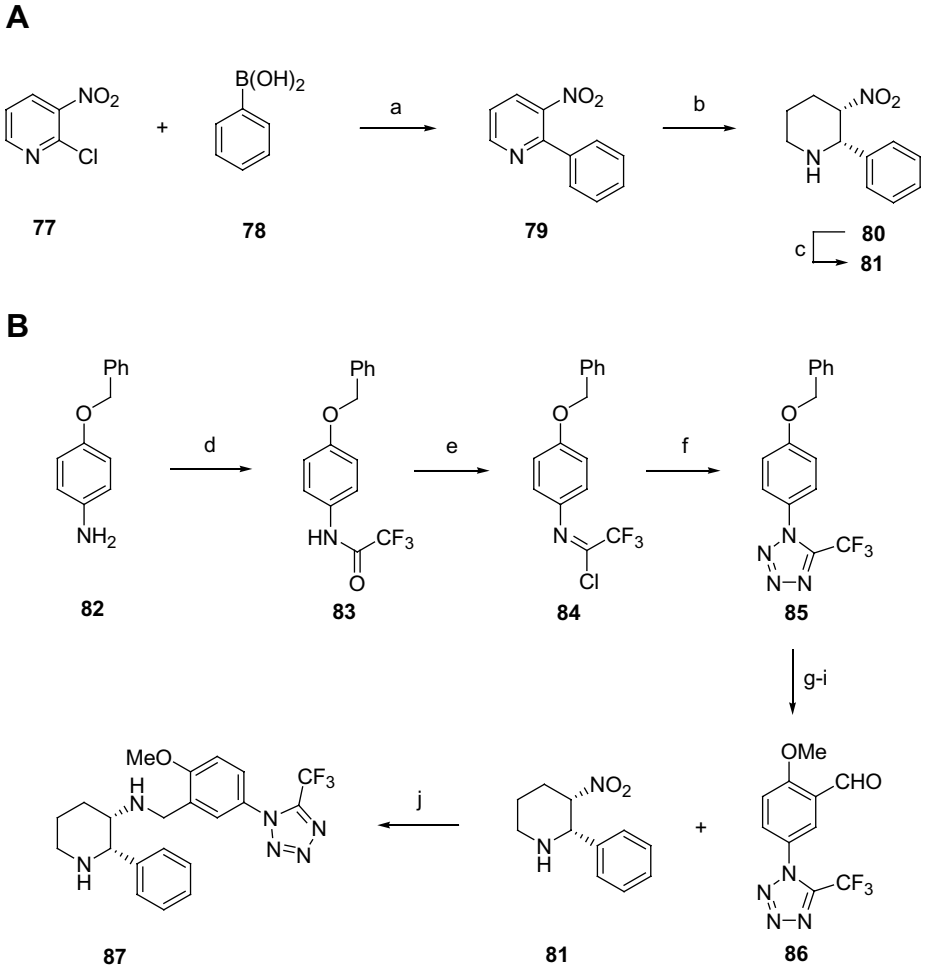
Scheme 8. Synthesis of CP-99,994 (**70**) according to Desai et al. Reagents and conditions: (a) TBDMS–Cl, Et_3N, 25 °C; (b) $LiEt_2N$, −50 °C, $Br(CH_2)_3Cl$, THF; (c) MeOH, 5% H_2SO_4, reflux, 1 h; (d) NaI, $NaHCO_3$, DMF, 100 °C, 15 min; (e) Cbz–Cl, Et_3N, CH_2Cl_2, 25 °C, 18 h; (f) Me_3Al, NH_4Cl, 50 °C; (g) LTA, *t*-BuOH, reflux, 3–5 h; (h) EtOAc–HCl, 25 °C, 2–4 h; (i) 2-(MeO)PhCHO, $NaBH_3CN$; (j) Pd/C, NH_4OCOH–Et_2O–HCl.

carbonyl using borane (76% yield) and resolution of the enantiomeric mixture of **73** with dibenzoyl tartaric acid gave the enantiomeric benzyl ethers (+)-(2*S*,3*S*)-**73** and (−)-(2*R*,3*R*)-**73**. Treatment of (+)-**73** with di-*tert*-butyl dicarbonate giving carbamate **74** (99% yield) followed by O-alkylation with 3,5-bis(trifluoromethyl)benzyl bromide yielded compound **75** in 82%. Removal of the nitrogen protecting group then gave the substance P antagonist (2*S*,3*S*)-3-(3,5-dimethylbenzyloxy)-2-phenylpiperidine (**76**, 99% yield) also called L-733,060. Harrison and coworkers have also reported the synthesis of other piperidine compounds similar to the one described here possessing substance P antagonistic activity.[68–72]

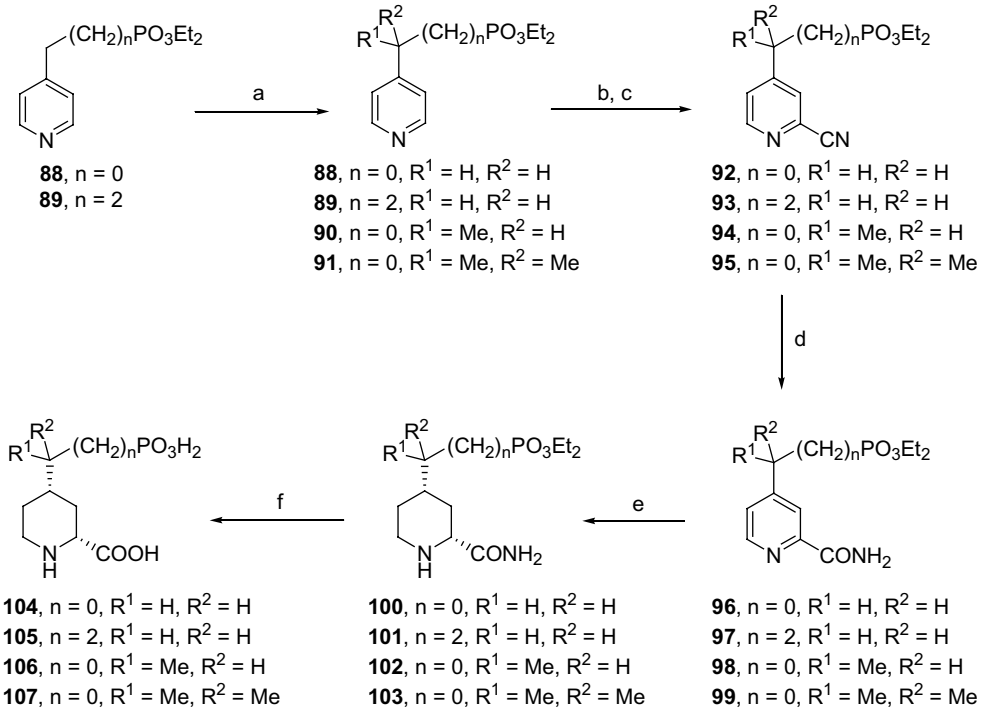
The discovery of the substance P antagonistic activity of CP-99,994 (**70**) presented above has also led to another series of compounds possessing similar pharmaceutical activity. Preparation of an exceptionally potent member of this family of tetrazole substance P antagonists was reported by Armour et al. (Scheme 10).[73] The compound GR205171 (**87**) was a follow-up to the earlier findings of the same researchers on the high potency of the tetrazolyl-substituted analogues.[74] The synthesis started with the preparation of **81** in three steps (A, Scheme 10). Commercially available 2-chloro-3-nitropyridine (**77**) and phenylboric acid (**78**) were catalytically coupled giving nitro-pyridine **79** in 99% yield. The nitro-pyridine **79** was hydrogenated with Pearlman's catalyst under acidic conditions to give the *cis*-diamine **80** in 75% yield. The desired homochiral diamine **81** was obtained in 76% yield (97% ee) by resolution with di-*p*-toluoyl-L-tartaric acid. The tetrazole moiety was then incorporated as shown by route B in



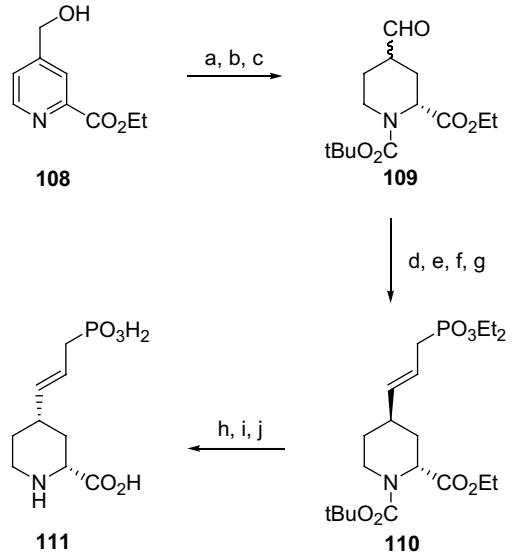
Scheme 9. Synthetic strategy for the preparation of L-733,060 (**76**) by Harrison et al. Reagents and conditions: (a) $NaBH_4$, MeOH, −20 °C; (b) BH_3·THF, reflux, then *p*-TsOH; (c) Na_2CO_3, (−)-dibenzoyl tartaric acid; (d) di-*tert*-butyl dicarbonate, CH_2Cl_2; (e) NaH, DMF, 3,5-bis(trifluoromethyl)benzyl bromide; (f) trifluoroacetic acid.



Scheme 10. Preparation of tetrazole substance P receptor antagonist GR205171 (**87**) according to Armour et al. Reagents and conditions: (A) a—2 N Na_2CO_3 (aq), dimethoxyethane, $Pd(PPh_3)_4$, reflux; b—H_2, PdOH/C, EtOH, cHCl; c—di-*p*-toluoyl-L-tartaric acid, EtOH, H_2O; (B) d—CF_3COCl; e—resin-supported PPh_3, CCl_4; f—NaN_3, AcOH, 70 °C, 4 h; g—H_2, 10% Pd/C, EtOH; h—hexamethylenetetraamine, AcOH; i—MeI, K_2CO_3, DMF; j—$NaBH(OAc)_3$.



Scheme 11. Synthesis of 4-(phosphonoalkyl)-2-piperidinecarboxylic acids **104**–**107** according to Hutchison and coworkers. Reagents: (a) MeI, LDA/THF/HMPA (**90**) or NaH in DMF/THF (**91**); (b) MCPBA, CH_2Cl_2; (c) TMSCN, TEA; (d) concd H_2SO_4; (e) H_2, PtO_2, HOAc; (f) 6 N HCl.

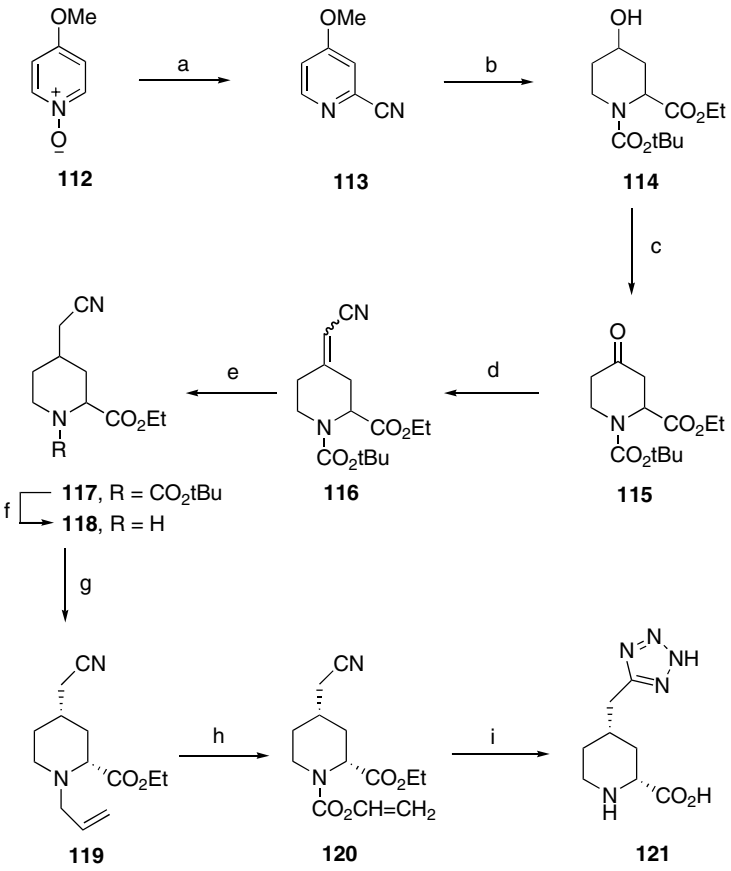


Scheme 12. Synthesis of 4-(phosphonoalkenyl)-2-piperidinecarboxylic acid **111** according to Hutchison et al. Reagents: (a) H_2, PtO_2, HOAc; (b) $(t\text{-BuOCO})_2O$, TEA; (c) PCC, CH_2Cl_2; (d) $Ph_3P{=}CHCHO$; (e) $NaBH_4$; (f) NBS, Ph_3P; (g) $(EtO)_3P$; (h) TFA; (i) LiOEt; (j) 6 N HCl.

Scheme 10. The synthesis commenced by acetylation of **82**, followed by conversion of the trifluoroacetamide **83** into the imino-chloride **84** (93% yield) using resin-supported triphenylphosphine and carbon tetrachloride. Cyclization with sodium azide and acetic acid yielded the tetrazole **85** in 69%. Using standard methods, this tetrazole was converted to benzaldehyde **86** which was further reacted with the homochiral diamine **81** by reductive amination to give the final product **87** in fairly good yield. Similar tetrazolyl-substituted analogues have also been claimed by Armour and coworkers in a series of patent applications.[75–77]

3.5. Compounds containing the 2,4-disubstituted piperidine framework

Hutchison et al.[78] have described the preparation of a series of 4-(phosphonoalkyl)- and 4-(phosphonoalkenyl)-2-piperidinecarboxylic acids showing potent and selective NMDA receptor antagonist activity in biological testing. The most notable NMDA antagonistic activity was shown by the *cis* phosphonates **104** (CGS 19755, Scheme 11) and **111** (Scheme 12). The disubstituted 4-(phosphonoalkyl)-2-piperidinecarboxylic acids **104**–**107** (Scheme 11) were synthesized starting from 4-picolyl chloride or 4-(3-chloropropyl)pyridine which were treated with the sodium salt of diethyl phosphate in toluene to afford the corresponding 4-[(diethylphosphono)alkyl]pyridines **88**–**89** in moderate to very good yields. The 4-[(diethylphosphono)alkyl]pyridines **90**–**91** were prepared by alkylation of **88** with methyl iodide. Using MCPBA, these pyridines were then converted to their corresponding *N*-oxides in excellent yields. Conversion of the *N*-oxides to 2-cyanopyridine derivatives **92**–**95** was then achieved in moderate to excellent yields by heating the *N*-oxides with a mixture of trimethylsilyl cyanide and Et_3N. The amides **96**–**99** were obtained in moderate to very good yields by selective hydrolysis of the nitriles **92**–**95** with concentrated H_2SO_4. Hydrogenation of the amides **96**–**99** with Adams' catalyst followed by neutralization with Na_2CO_3 in CH_2Cl_2 yielded the *cis*-piperidinecarboxamides **100**–**103**, which were di-

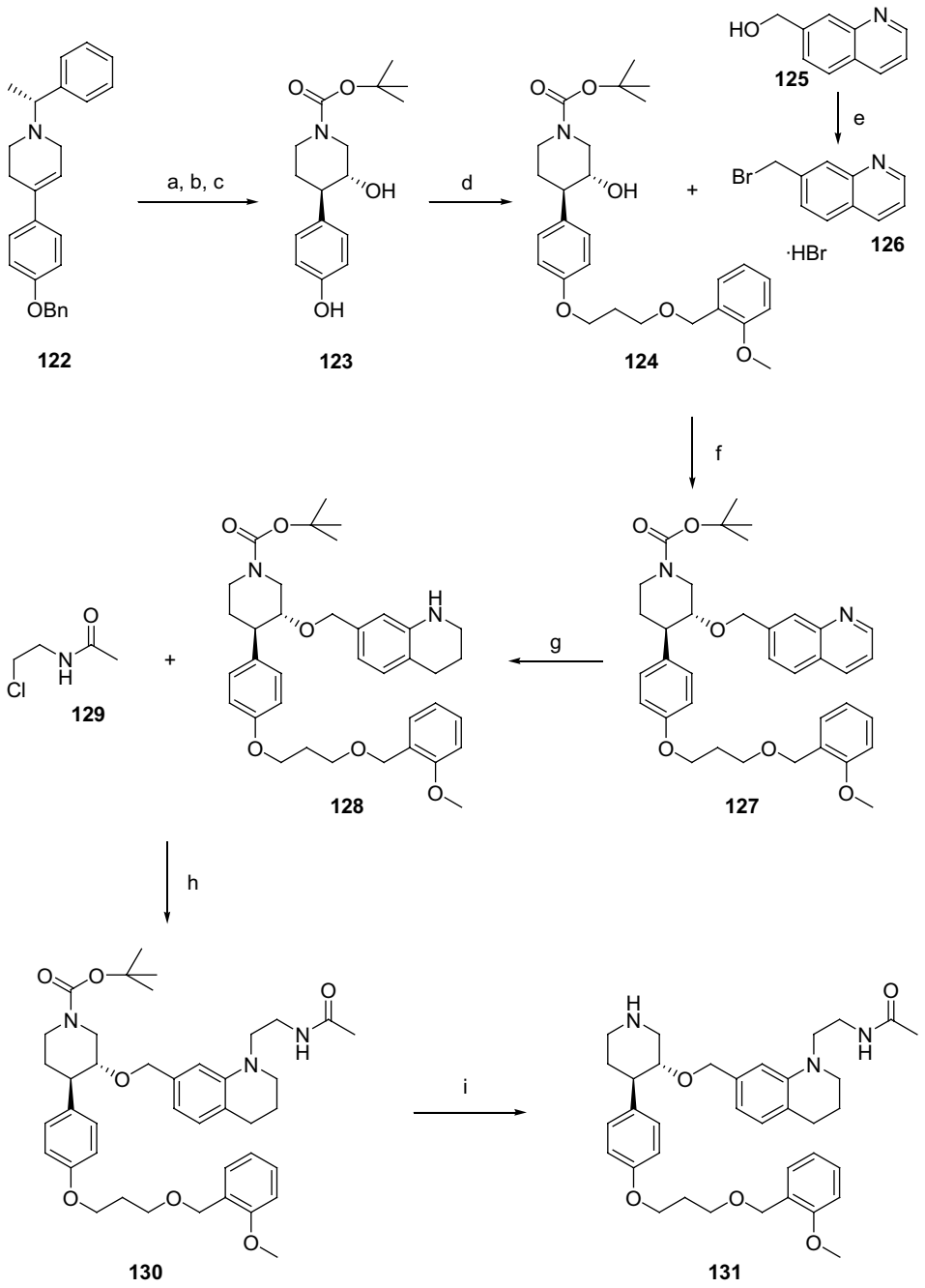


Scheme 13. Synthetic pathway employed by Ornstein et al. Reagents and conditions: (a) TMSCN, Me_2NCOCl, CH_2Cl_2, room temperature; (b) i—48% HBr, reflux; ii—EtOH, HCl, reflux; iii—H_2, 5% Rh/Al_2O_3, EtOH, 100 °C, 1000 psi; iv—di-*tert*-butyl dicarbonate, *i*-Pr_2Net, CH_2Cl_2, EtOH, room temperature; (c) PCC, 4 Å molecular sieves, CH_2Cl_2, room temperature; (d) $(EtO)_2P(O)CH_2CN$, NaH, THF, room temperature; (e) H_2, 5% Pd/C, EtOH, room temperature, 60 psi; (f) TFA, CH_2Cl_2, room temperature; (g) $NaHCO_3$, DMSO, allyl bromide; (h) vinyl chloroformate, proton sponge, $ClCH_2CH_2Cl$, reflux; (i) i—*n*-Bu_3SnN_3, 80 °C; ii—6 N HCl, reflux.

rectly hydrolysed in refluxing 6 N HCl to afford the desired 4-(phosphonoalkyl)-2-piperidinecarboxylic acids **104**–**107**.

The preparation of the 4-(phosphonoalkenyl)-2-piperidinecarboxylic acid **111** (Scheme 12)[78] was initiated by conversion of 4-(hydroxymethyl)pyridine to the corresponding 2-carbethoxy derivative **108** in a four-step sequence without isolation of the intermediates: protection of the alcohol with *tert*-butyldimethylsilyl chloride, *N*-oxide formation with MCPBA, nitrile formation using TMSCN in Et_3N and nitrile/protecting group hydrolysis with NaOEt in EtOH followed by 6 N HCl treatment (overall yield 59%). The piperidine derivative of **108** was then obtained by hydrogenation with Adams' catalyst followed by protection of the nitrogen with di-*tert*-butyl carbonate and oxidation with pyridinium chlorochromate providing the aldehyde **109** in 36% yield. The aldehyde was further reacted with (formylmethylene)triphenylphosphorane, giving the corresponding α,β-unsaturated aldehyde, which was again reduced with $NaBH_4$ to yield the corresponding allylic alcohol. Conversion of the allylic alcohol to allylic bromide with NBS and Ph_3P and the subsequent treatment with $(EtO)_3P$ afforded the diethyl phosphonate ester **110** in 17% overall yield. Finally, removal of the protecting group with trifluoroacetic acid, equilibration with LiOEt in EtOH to give the *cis* isomer and hydrolysis with HCl afforded 4-(phosphonoalkenyl)-2-piperidinecarboxylic acid **111** in 48% overall yield. In addition to the *cis* phosphonates presented here, Hutchison and coworkers also reported the preparation of the 2,4-disubstituted *trans* isomer of **111** as well as some α,β-unsaturated phosphonic acids.[78] Furthermore, similar heterophosphonic acid derivatives of 2-piperidine showing potent and selective NMDA receptor antagonist activity in mammals have been claimed by both Hutchison et al. and others in patent applications.[79,80]

The synthesis of another series of potent and selective NMDA receptor antagonists containing the 2,4-disubstituted piperidine framework was reported by Ornstein and coworkers.[81] The work was a follow-up to the preparation of a series of 3- and 4-(phosphonoalkyl)pyridine- and piperidine-2-carboxylic acids similar or identical to the ones described by Hutchison and coworkers (vide supra).[82] The synthetic strategy for the preparation of the most potent compound of this series of *cis*-4-(tetrazolylalkyl)piperidine-2-carboxylic acids, namely (±)-(2*SR*,4*RS*)-4-(1*H*-tetrazol-5-ylmethyl)piperidine (LY233053, (±)-**121**), is presented in Scheme 13. Treatment of the commercially available



Scheme 14. Synthesis of prototypic piperidine renin inhibitor **131** according to Märki et al. Reagents and conditions: (a) i—BH_3·THF (1 M), THF, 1 h, room temperature; ii—NaOH (aq), H_2O_2 (aq), 45 °C, 3 h, 50% as crystalline pure diastereomer; (b) H_2/Pd/C, MeOH, room temperature, 15 h; (c) di-*tert*-butyldicarbonate, Et_3N, MeOH, −10 to 0 °C, 3 h, 96% (two steps), 98.8–100% ee; (d) 1-(3-chloro-propoxymethyl)-2-methoxy-benzene, potassium carbonate, DMF, 66 h, 120 °C, 80%; (e) HBr, AcOH, 1 h, 75 °C, 97%; (f) NaH, DMF, 24 h, room temperature, 94%; (g) $NaBH_4$, $NiCl_2$, MeOH, 1 h, 0 °C, 1 h, room temperature, 91%; (h) Na_2CO_3, MeCN, KI, 16 h, reflux, 90%; (i) $ZnBr_2$, dichloroethane, 2 h, 50 °C, 71%.

4-methoxypyridine *N*-oxide **112** with cyanotrimethylsilane and *N*,*N*-dimethylcarbamoyl chloride afforded the 2-cyanopyridine **113**. Subsequent dealkylation of the methyl ether and hydrolysis of the nitrile was achieved by treatment with aqueous HBr under reflux conditions to give the corresponding hydroxy acid. Esterification of this hydroxy acid with ethanolic HCl followed by hydrogenation and Boc-protection gave the alcohol **114** in 40% yield. The alcohol was then oxidized with pyridinium chlorochromate and powdered 4 Å molecular sieves to give the corresponding ketone **115** in 96% yield. Treatment of ketone **115** with the sodium salt of diethyl (cyanomethyl)phosphonate provided compound **116** in 88% yield. Hydrogenation of cyanomethylidene **116** gave the cyanomethyl compound **117** in 96% yield (85:15 mixture of the *cis* and *trans* isomers). The *cis* and *trans* isomers were then separated by conversion to the *N*-allylpiperidine **119**. This was accomplished by removal of the *tert*-butyl carbamate protecting group giving **118**, followed by treatment with allyl bromide

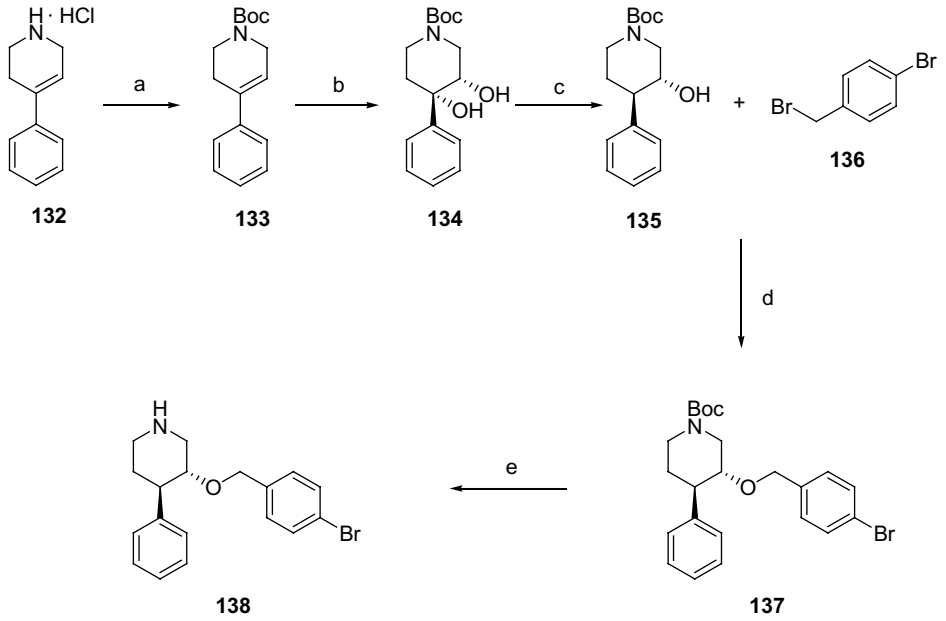
to afford the *cis* isomer **119** in 62% yield (and the *trans* isomer in 9% yield). Continuing conversion of **119** to the corresponding vinyl carbamate **120** (85% yield) by treatment with vinyl chloroformate and 1,8-bis(dimethylamino)naphthalene, and the subsequent treatment of **120** with azidotri-*n*-butylstannane and aqueous HCl finally gave the desired amino acid **121** in 69% yield. Ornstein et al. later reported the resolution of compound **121**, also concluding that the NMDA receptor antagonism resides with the isomer (−)-**121** (LY235723).[83] These compounds, and several derivatives thereof, have also been claimed in two patent applications.[84,85]

3.6. Compounds containing the 3,4-disubstituted piperidine framework

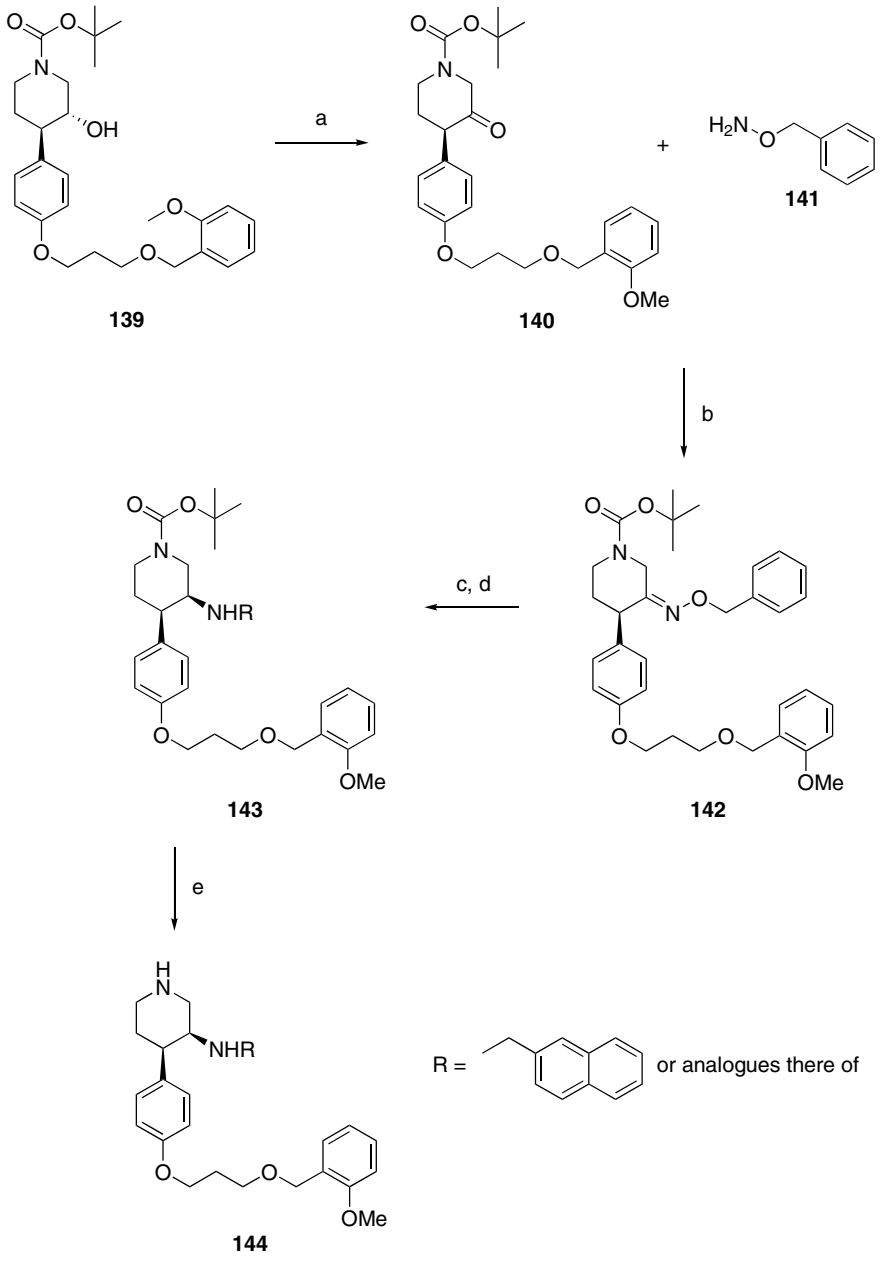
Märki et al.[86] have reported the synthesis of a series of piperidine renin inhibitors having potential benefits in the treatment of chronic renal failure patients. By inhibiting the renin-angiotensin system (RAS), these non-peptidomimetic compounds produce an antihypertensive effect. This effect is, however, produced without the drawbacks observed with peptidomimetic compounds, as well as without the side effects observed with ACE inhibitors and angiotensin II receptor antagonists. Two drug candidate compounds were identified as a result of synthetic optimization in two structural series.[87,88] The synthetic strategy used for the preparation of one of these candidates (**131**) is shown in Scheme 14. The 3,4-disubstituted piperidine compound **131** has an acetylaminoethyl substituent attached to the tetrahydroquinoline *N*-function which fits into the non-substrate S3 sub-pocket. A number of renin inhibitors of this kind have also been claimed in patent applications.[89,90]

As a follow-up to the work by Märki and coworkers,[86] Bursavich et al.[91] reported the preparation of two new 3,4-disubstituted piperidine inhibitors of aspartic peptidases. The synthetic route leading to one of these compounds, piperidine **138**, is shown in Scheme 15. The synthesis started by N-protection of 4-phenyl-1,2,3,6-tetrahydropyridine (**132**) with Boc_2O providing compound **133** in 92% yield. Sharpless asymmetric dihydroxylation then gave the diol **134** in 95% yield, which was subsequently reduced with Raney nickel to give **135** (84% yield, >95% ee). The hydroxyl group of **135** was alkylated with NaH and *p*-bromobenzyl bromide **136** providing the Boc-protected piperidine **137** in 77% yield. Finally, removal of the Boc group with HCl–dioxane gave the desired piperidine **138** which could be directly used in enzyme assays.

Cody and coworkers[92,93] have also developed a new series of potent *cis*-disubstituted amino-aryl-piperidine-type renin inhibitors. By utilizing one of the compounds from the series reported by Märki et al.[86] as a starting point, compounds such as piperidine **144** were discovered (Scheme 16). Compound **144** is characterized by a *cis*-orientation of the two stereocentres on the amino-aryl-piperidine framework, as well as the incorporation of a secondary amine in place of the exocyclic oxygen of the inhibitors described above. The optimized synthetic route for the preparation of **144** began with the synthesis of **139** according to methods reported by Märki et al.[86] and Bursavich et al.[91] Alcohol **139** was then converted to ketone **140** by PCC oxidation in 34% yield, followed by formation of the benzyloxime **141** to provide compound **142** (85% yield). Hydrogenation with Raney nickel gave the corresponding primary amine in 78% yield, and the subsequent acylation/alkylation in the presence of triethylamine then afforded products such as **143** (80% yield). Finally, removal of the *tert*-Boc group with zinc bromide gave the secondary amine **144** in 60% yield.



Scheme 15. Preparation of piperidine inhibitor **138** of aspartic peptidases according to Bursavich et al. Reagents and conditions: (a) Boc_2O, TEA, DMAP, CH_3CN, 8 h; (b) AD-mix-α, $CH_3SO_2NH_2$, *t*-BuOH/H_2O, 12 h; (c) Raney-Ni, EtOH, reflux, 2 h; (d) NaH, DMF, 12 h; (e) HCl/dioxane.



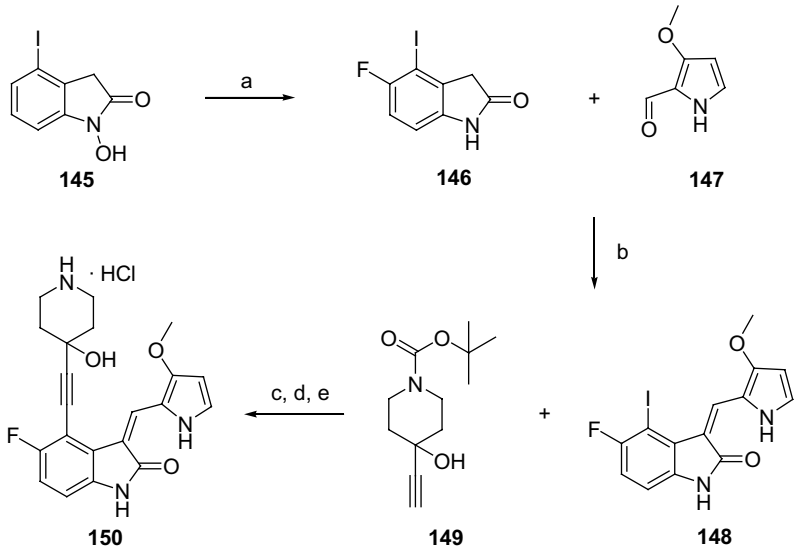
Scheme 16. Synthetic pathway by Cody et al. Reagents and conditions: (a) PCC, Celite, sieves; (b) pyridine, room temperature; (c) H_2/RaNi, MeOH, room temperature; (d) R–X, Et_3N, DCM, room temperature; (e) $ZnBr_2$, 1,2-dichloroethane, 50 °C.

3.7. Compounds containing the 4,4-disubstituted piperidine framework

The preparation of a series of oxindole-type inhibitors of CDK2 with varying alkynyl moieties at their C-4 position has been described by Luk et al.[94–96] One of the potent inhibitor structures (**150**) of this series, the preparation of which is described in Scheme 17, contained a 4,4-disubstituted piperidinyl substituent at its C-4 position. The synthesis of **150** was initiated by treating compound **145** with DAST affording the indolone **146**. Intermediate **148** was then obtained by coupling **146** with 3-methoxy-2-pyrrole carboxaldehyde (**147**). Finally, the desired hydrochloride salt of (*Z*)-1,3-dihydro-5-fluoro-4-[(4-hydroxypiperidin-4-yl)-ethynyl]-3-[(3-methoxy-*1H*-pyrrol-2-yl)methylene]-2*H*-indol-2-one (**150**) was prepared in three steps: Pd(0)-mediated coupling of **148** with *N*-Boc-4-hydroxy-4-ethynyl piperidine (**149**), cleavage of the Boc group and mixing of the free base with a hydrochloric acid solution.

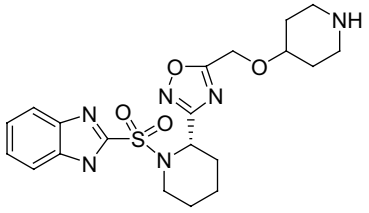
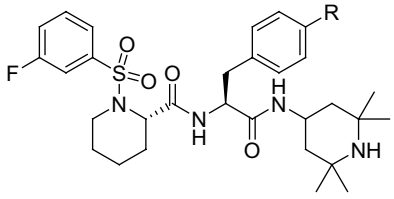
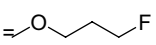
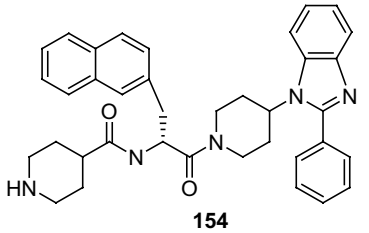
3.8. Summary of compounds reported in the patent literature only

A very high percentage of the information on the synthesis of pharmaceutically active compounds containing a disubstituted piperidine framework appears in the patent literature. Due to the free on-line patent databases, this material should be readily available to most researchers. Compounds of interest appearing only in



Scheme 17. Synthesis of the small molecule CDK2 inhibitor **150** according to Luk et al. Reagents and conditions: (a) DAST, CH_2Cl_2, −25 °C; (b) 1% piperidine in isopropanol; (c) $Pd(Ph_3P)_4$, CuI cat, Et_3N, DMF, 80 °C; (d) $C_2HO_2F_3$, CH_2Cl_2, H_2O; (e) MeOH, 4 N HCl in dioxane.

Table 1. Pharmaceutically active compounds containing a disubstituted piperidine framework reported only in the patent literature

Molecular structure	Piperidine framework	Activity/usage	Ref.
 **151**	1,2-Disubstituted	Neurotrophic factor, treatment of neurological disorders	97
 **152**, R =  **153**, R = 	1,2-Disubstituted	Neurotrophic agents, antiparkinsonian	98
 **154**	1,4-Disubstituted	Growth hormone releasing peptide mimetic, treatment of osteoporosis	99

(*continued on next page*)

Table 1 (*continued*)

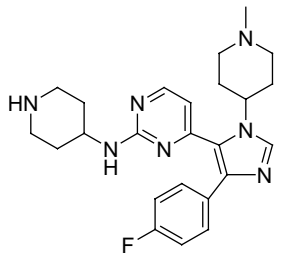
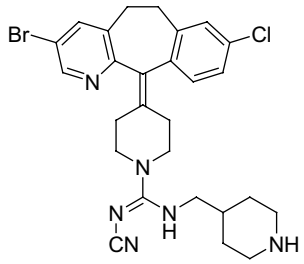
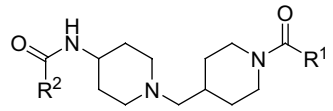
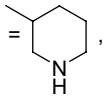
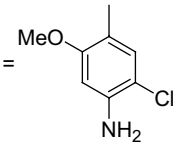
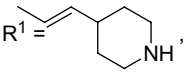
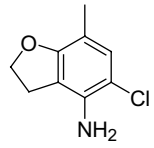
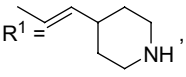
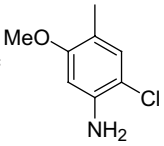
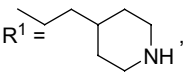
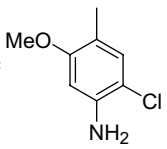
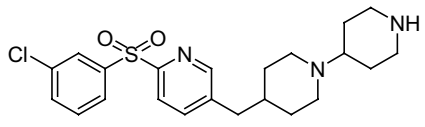
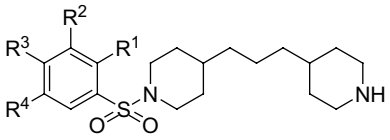
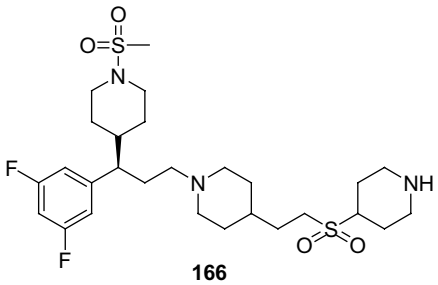
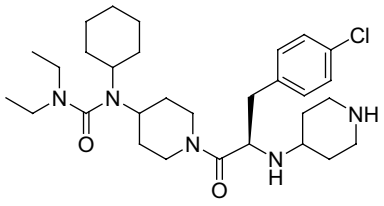
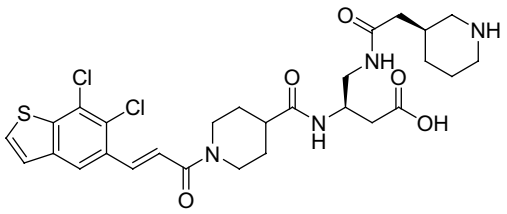
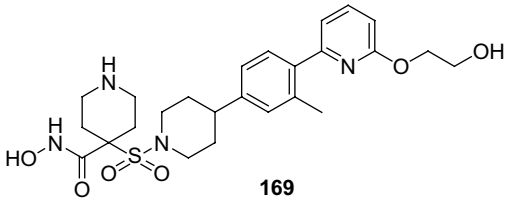
Molecular structure	Piperidine framework	Activity/usage	Ref.
 **155**	1,4-Disubstituted	Cytokine inhibitor, antiinflammatory	100
 **156**	1,4-Disubstituted	Farnesyl-protein transferase inhibitor, antineoplastic	101
 **157**, R^1 =  , R^2 = 			
158, R^1 =  , R^2 = 	1,4-Disubstituted	Serotonin 4 receptor agonist, stimulant and peristaltic	102, 103
159, R^1 =  , R^2 = 			
160, R^1 =  , R^2 = 			
 **161**	1,4-Disubstituted	Muscarinic antagonist, treatment of cognitive disorders	104

Table 1 (*continued*)

Molecular structure	Piperidine framework	Activity/usage	Ref.
 **162**, R^1 = Me, R^2 = H, R^3 = H, R^4 = Me **163**, R^1 = H, R^2 = Cl, R^3 = Me, R^4 = Cl **164**, R^1 = OMe, R^2 = H, R^3 = H, R^4 = OMe **165**, R^1 = Me, R^2 = H, R^3 = H, R^4 = Cl	1,4-Disubstituted	Antibacterial	105
 **166**	1,4-Disubstituted	Modulator of chemokine receptor activity, for example, antiasthmatic	106
 **167**	1,4-Disubstituted	Antidiabetic, antiobesity, etc.	107
 **168**	1,4-Disubstituted	VLA-1 integrin antagonist, agent for chronic obstructive pulmonary disease	108
 **169**	1,4-Disubstituted and 4,4-disubstituted	Metalloprotease inhibitor, for example, antiarthritic and wound healing agent	109

(*continued on next page*)

Table 1 (*continued*)

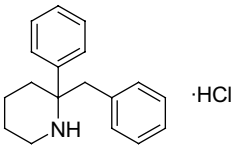
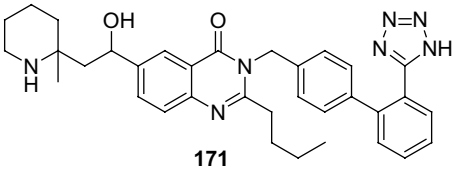
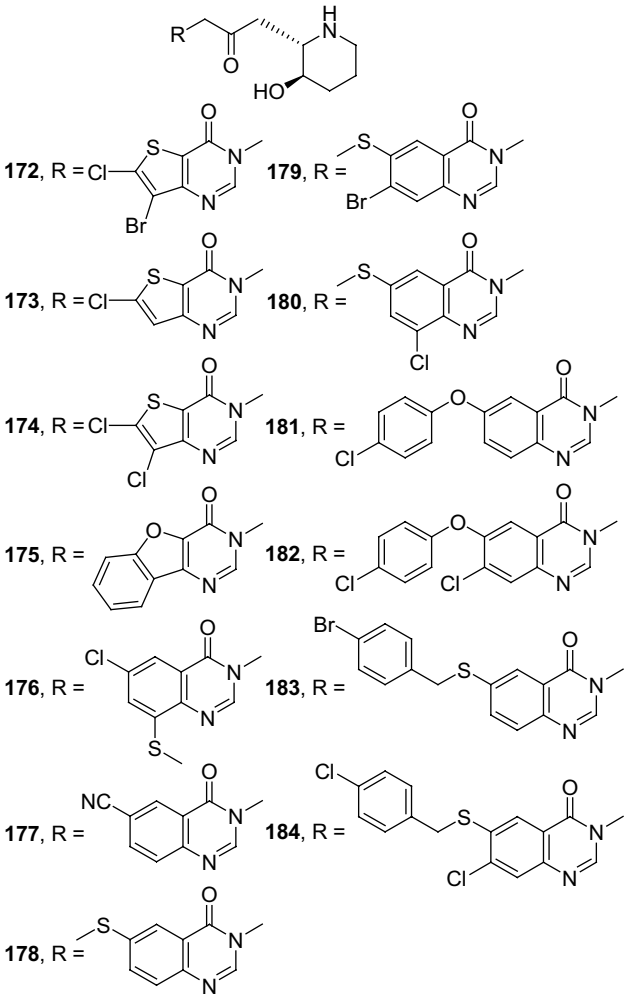
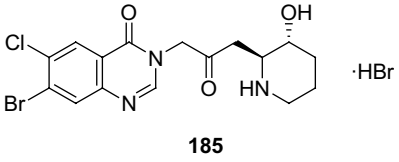
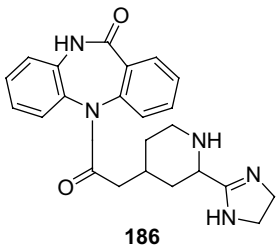
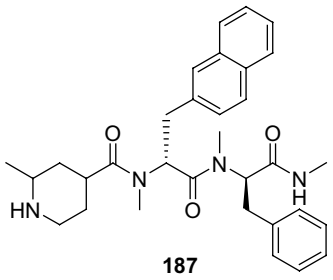
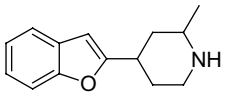
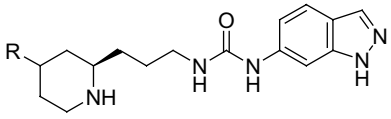
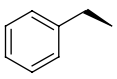
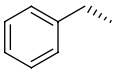
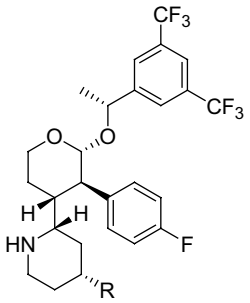
Molecular structure	Piperidine framework	Activity/usage	Ref.
 **170**	2,2-Disubstituted	NMDA receptor antagonist, treatment of neurological disorders	110
 **171**	2,2-Disubstituted	Angiotensin II AT1 antagonist, antihypertensive	111
 **172**, **173**, **174**, **175**, **176**, **177**, **178**, **179**, **180**, **181**, **182**, **183**, **184**	2,3-Disubstituted	Anticoccidial agents	112, 113
 **185**	2,3-Disubstituted	Antifibrotic agent, for example, anticoccidial	114–120

Table 1 (*continued*)

Molecular structure	Piperidine framework	Activity/usage	Ref.
 **186**	2,4-Disubstituted	Antimuscarinic, treatment of gastrointestinal disorders	121
 **187**	2,4-Disubstituted	Growth hormone release promoting agent	122
 **188**	2,4-Disubstituted	Serotonin reuptake inhibitor, antidepressant	123
 **189**, R =  **190**, R = 	2,4-Disubstituted	Modulators of chemokine receptor activity, antiallergic and antiasthmatic	124
 **191**, R = OH **192**, R = OMe	2,4-Disubstituted	Tachykinin NK-1 receptor antagonists, for example, anxiolytic and antiemetic	125

(*continued on next page*)

Table 1 (*continued*)

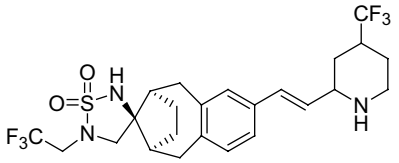
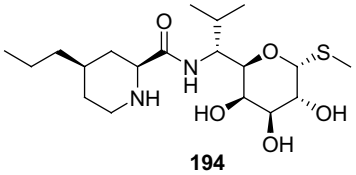
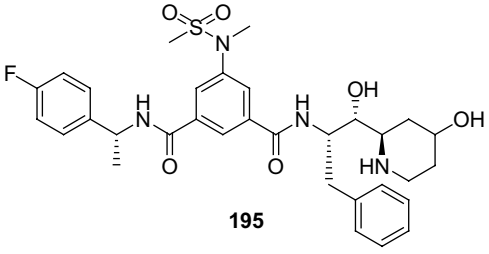
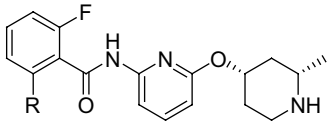
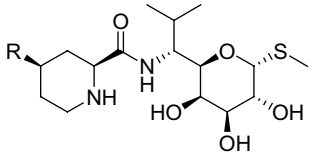
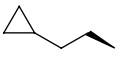
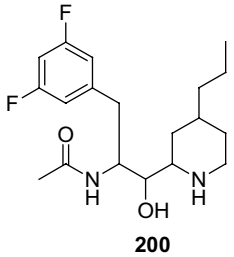
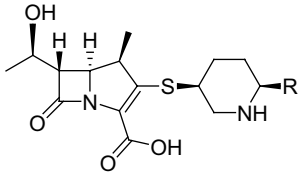
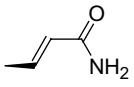
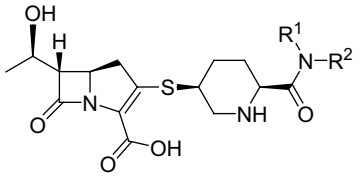
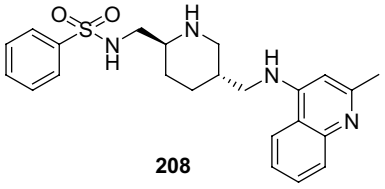
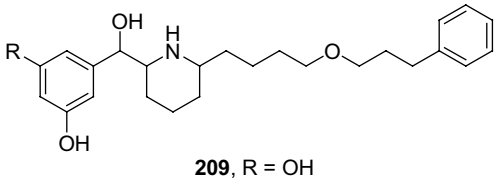
Molecular structure	Piperidine framework	Activity/usage	Ref.
 **193**	2,4-Disubstituted	γ-Secretase inhibitor, treatment of Alzheimer's disease	126
 **194**	2,4-Disubstituted	Antimicrobial agent	127
 **195**	2,4-Disubstituted	β-Secretase inhibitor, treatment of Alzheimer's disease	128
 **196**, R = F **197**, R = Cl	2,4-Disubstituted	5-HT_{1F} agonist, treatment of migrane	129
 **198**, R =  **199**, R = 	2,4-Disubstituted	Antimicrobial agent	127–130
 **200**	2,4-Disubstituted	Ethanolcyclicamine aspartyl protease inhibitor, treatment of amyloidosis	131

Table 1 (*continued*)

Molecular structure	Piperidine framework	Activity/usage	Ref.
 **201**, R =  **202**, R =  **203**, R =  **204**, R = 	2,5-Disubstituted	Antibacterial activity	132
 **205**, R^1 = Me, R^2 = Me **206**, R^1 = H, R^2 = H **207**, R^1 = H, R^2 = Me	2,5-Disubstituted	Antibacterial activity	132
 **208**	2,5-Disubstituted	Ligand for NPY Y-5 receptor, antiobesity	133
 **209**, R = OH **210**, R = CH_2OH	2,6-Disubstituted	β2-Adrenoreceptor agonist, bronchodilator	134

(*continued on next page*)

Table 1 (*continued*)

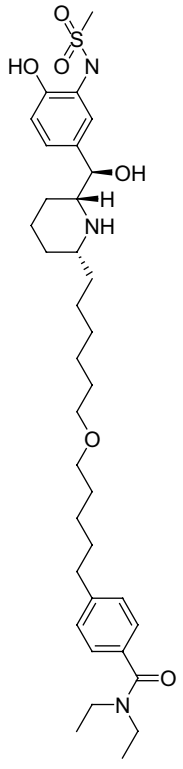
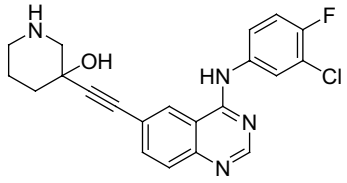
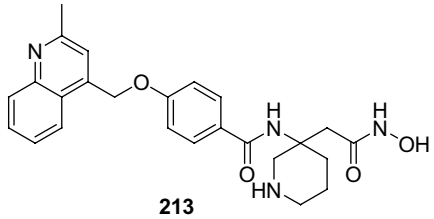
Molecular structure	Piperidine framework	Activity/usage	Ref.
 **211**	2,6-Disubstituted	β2-Adrenoreceptor agonist, bronchodilator	134
 **212**	3,3-Disubstituted	Anticancer agent	135
 **213**	3,3-Disubstituted	β-Amino acid derivative, matrix metalloprotease and TNF-α inhibitor	136

Table 1 (*continued*)

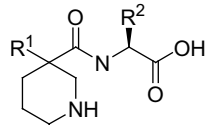
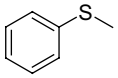
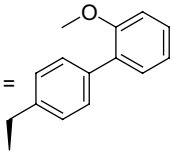
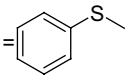
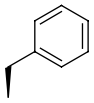
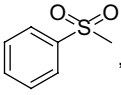
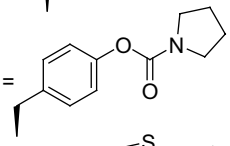
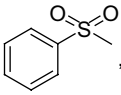
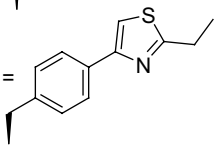
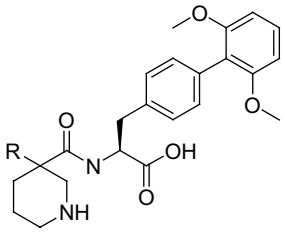
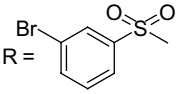
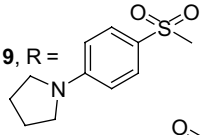
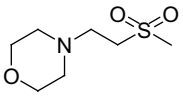
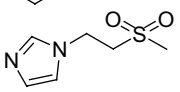
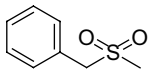
Molecular structure	Piperidine framework	Activity/usage	Ref.
 **214**, R^1 =  , R^2 = 			
215, R^1 =  , R^2 = 	3,3-Disubstituted	Cell adhesion inhibitors, treatment of, for example, asthma and Alzheimer's disease	137
216, R^1 =  , R^2 = 			
217, R^1 =  , R^2 = 			
 **218**, R = 			
219, R = 	3,3-Disubstituted	Cell adhesion inhibitors, treatment of, for example, asthma and Alzheimer's disease	137
220, R = 			
221, R = 			
222, R = 			

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Table 1 (*continued*)

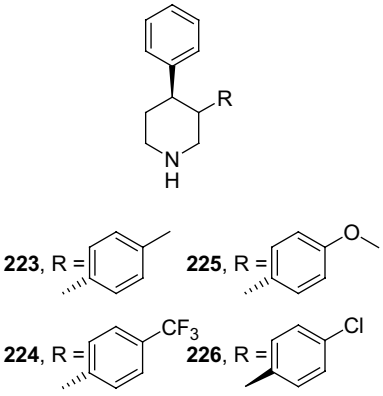
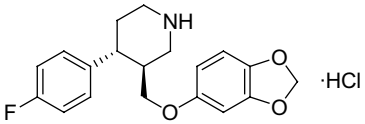
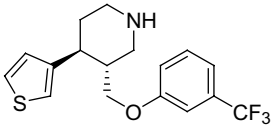
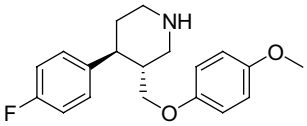
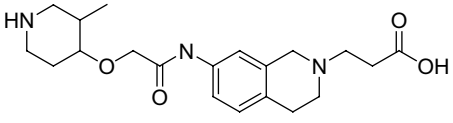
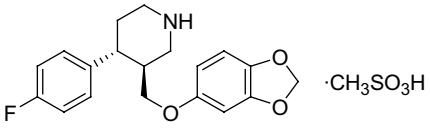
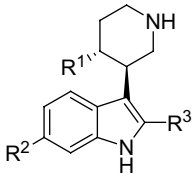
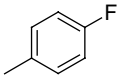
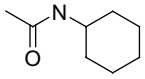
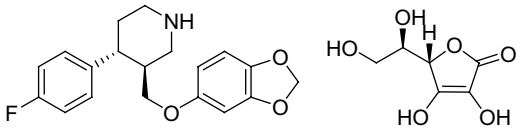
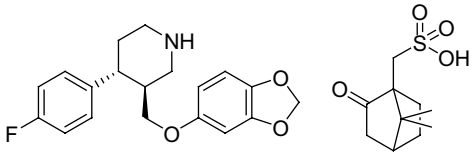
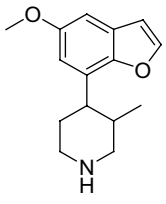
Molecular structure	Piperidine framework	Activity/usage	Ref.
 **223**, R = **225**, R = **224**, R = **226**, R =	3,4-Disubstituted	Antidepressant	138
 **227**	3,4-Disubstituted	Serotonin reuptake inhibitor, anxiolytic and antidepressant	139–152
 **228**	3,4-Disubstituted	Treatment of, for example, migraine and epilepsy	153
 **229**	3,4-Disubstituted	Serotonin reuptake inhibitor, antidepressant	154
 **230**	3,4-Disubstituted	Fibrinogen receptor antagonist, platelet antiagregatory	155
 **231**	3,4-Disubstituted	Serotonin reuptake inhibitor, antidepressant	156

Table 1 (*continued*)

Molecular structure	Piperidine framework	Activity/usage	Ref.
 **232**, R^1 = F, R^2 = H, R^3 = Ph **234**, R^1 = F, R^2 = H, R^3 =  **235**, R^1 = F, R^2 = F, R^3 =  **236**, R^1 = F, R^2 = F, R^3 =  **237**, R^1 = OH, R^2 = H, R^3 = Ph **238**, R^1 = F, R^2 = F, R^3 = Ph	3,4-Disubstituted	5-HT_{2A} antagonist, antipsychotic	157
 **239**	3,4-Disubstituted	Serotonin reuptake inhibitor, antidepressant	158
 **240**	3,4-Disubstituted	Serotonin reuptake inhibitor, antidepressant	159
 **241**	3,4-Disubstituted	5-HT_{1C} agonist, antidepressant and antiobesity	160

(*continued on next page*)

Table 1 (*continued*)

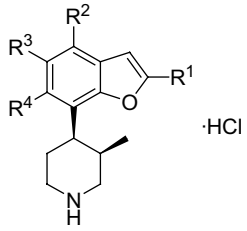
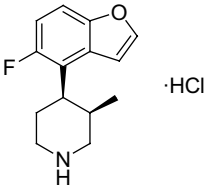
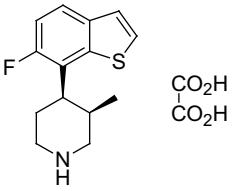
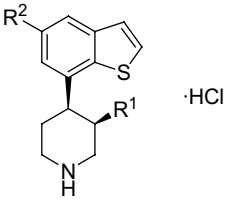
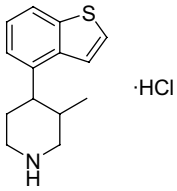
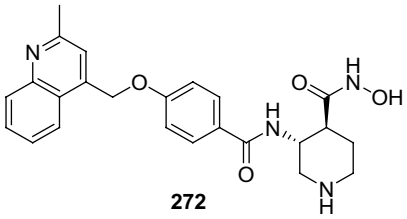
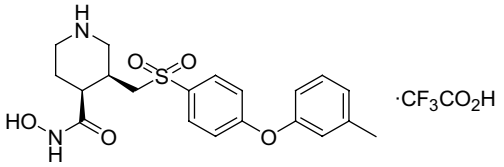
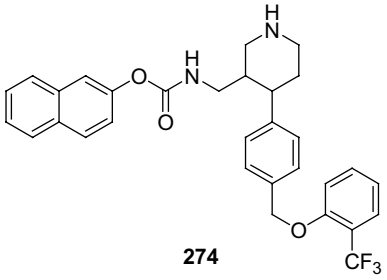
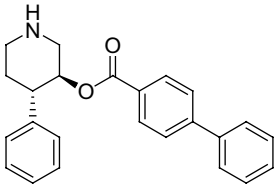
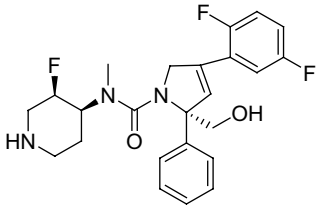
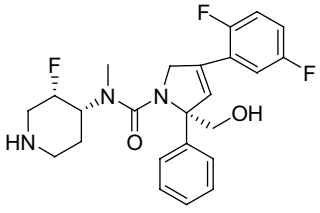
Molecular structure	Piperidine framework	Activity/usage	Ref.
 ·HCl **242**, R^1 = H, R^2 = H, R^3 = CF_3, R^4 = H **243**, R^1 = H, R^2 = H, R^3 = F, R^4 = H **244**, R^1 = H, R^2 = H, R^3 = Cl, R^4 = H **245**, R^1 = H, R^2 = F, R^3 = H, R^4 = F **246**, R^1 = Me, R^2 = H, R^3 = H, R^4 = H **247**, R^1 = H, R^2 = H, R^3 = H, R^4 = F	3,4-Disubstituted	5-HT_{1C} agonist, antidepressant and antiobesity	160
 ·HCl **248**	3,4-Disubstituted	5-HT_{1C} agonist, antidepressant and antiobesity	160
 CO_2H CO_2H **249**	3,4-Disubstituted	5-HT_{1C} agonist, antidepressant and antiobesity	161
 ·HCl **250**, R^1 = Et, R^2 = H **260**, R^1 = Me, R^2 = F **270**, R^1 = Me, R^2 = H	3,4-Disubstituted	5-HT_{1C} agonist, antidepressant and antiobesity	161
 ·HCl **271**	3,4-Disubstituted	5-HT_{1C} agonist, antidepressant and antiobesity	161

Table 1 (*continued*)

Molecular structure	Piperidine framework	Activity/usage	Ref.
 **272**	3,4-Disubstituted	β-Amino acid derivative, matrix metalloprotease and TNF-α inhibitor	162
 **273**	3,4-Disubstituted	Matrix metalloprotease and TNF-α inhibitor, antiarthritic	163
 **274**	3,4-Disubstituted	Aspartic proteinase inhibitor, treatment of, for example, Alzheimer's disease	164
 **275**	3,4-Disubstituted	β-Secretase inhibitor, treatment of Alzheimer's disease	165
 **276**	3,4-Disubstituted	Mitotic kinesin inhibitor, treatment of cancer	166, 167
 **277**	3,4-Disubstituted	Mitotic kinesin inhibitor, treatment of cancer	166, 167

(*continued on next page*)

Table 1 (*continued*)

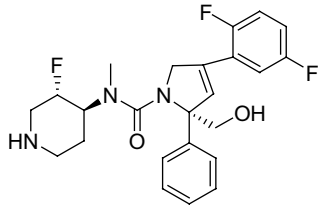
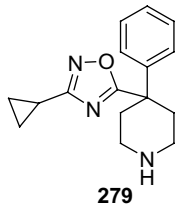
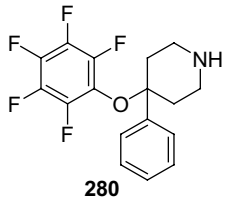
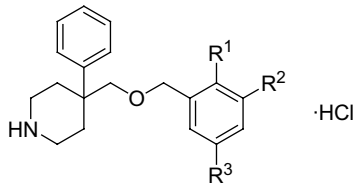
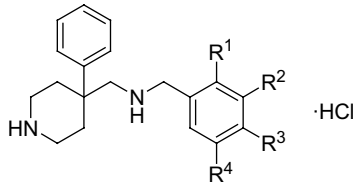
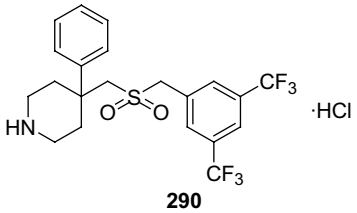
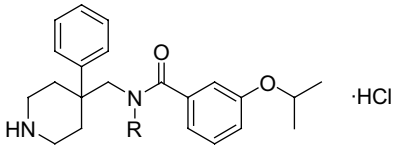
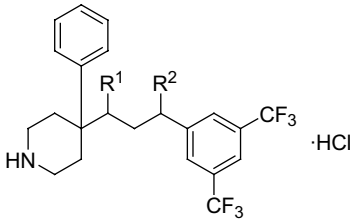
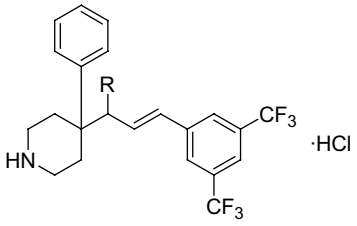
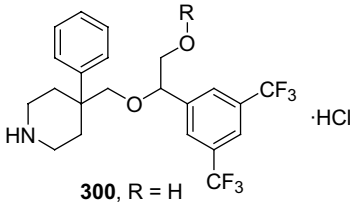
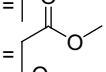
Molecular structure	Piperidine framework	Activity/usage	Ref.
 **278**	3,4-Disubstituted	Mitotic kinesin inhibitor, treatment of cancer	166, 167
 **279**	4,4-Disubstituted	Analgesic and antipsychotic	168
 **280**	4,4-Disubstituted	Analgesic, antidepressant, anticonvulsant and antihypertensive	169
 **281**, R^1 = H, R^2 = CF_3, R^3 = CF_3 **282**, R^1 = CF_3, R^2 = H, R^3 = H **283**, R^1 = H, R^2 = H, R^3 = H **284**, R^1 = H, R^2 = *t*-Bu, R^3 = Cl **285**, R^1 = H, R^2 = Cl, R^3 = Cl **286**, R^1 = H, R^2 = CF_3, R^3 = H	4,4-Disubstituted	Tachykinin antagonists, treatment of, for example, pain and inflammation	170
 **287**, R^1 = OMe, R^2 = H, R^3 = H **288**, R^1 = H, R^2 = CF_3, R^3 = CF_3 **289**, R^1 = H, R^2 = Cl, R^3 = Cl	4,4-Disubstituted	Tachykinin antagonists, treatment of, for example, pain and inflammation	171

Table 1 (*continued*)

Molecular structure	Piperidine framework	Activity/usage	Ref.
 **290**	4,4-Disubstituted	Tachykinin antagonists, treatment of, for example, pain and inflammation	171
 **291**, R = H **292**, R = Me	4,4-Disubstituted	Tachykinin antagonists, treatment of, for example, pain and inflammation	171
 **293**, R^1 = O, R^2 = H **294**, R^1 = OMe, R^2 = H **295**, R^1 = OH, R^2 = H **296**, R^1 = H, R^2 = O **297**, R^1 = H, R^2 = OH	4,4-Disubstituted	Tachykinin antagonists, treatment of, for example, pain and inflammation	172
 **298**, R = OMe **299**, R = OH	4,4-Disubstituted	Tachykinin antagonists, treatment of, for example, pain and inflammation	172
 **300**, R = H **301**, R = Me **302**, R = Et **303**, R =  **304**, R =  **305**, R = 	4,4-Disubstituted	Tachykinin antagonists, treatment of, for example, pain and inflammation	173

(*continued on next page*)

Table 1 (*continued*)

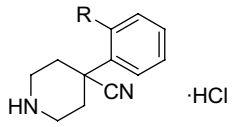
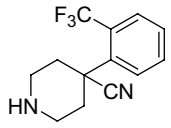
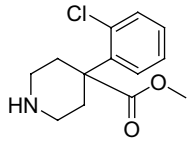
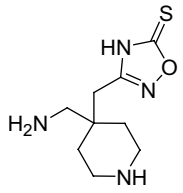
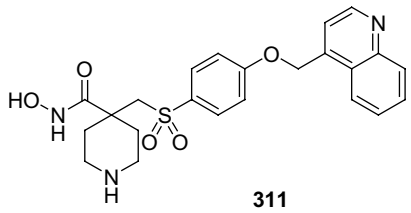
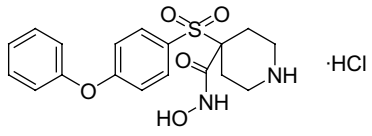
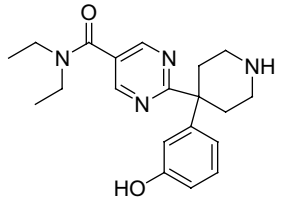
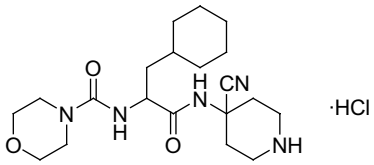
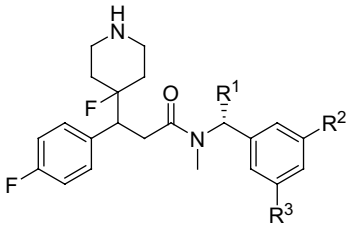
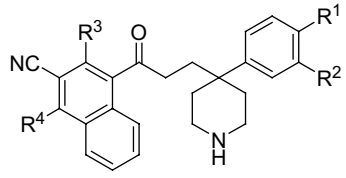
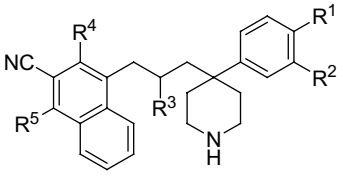
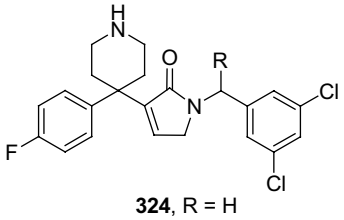
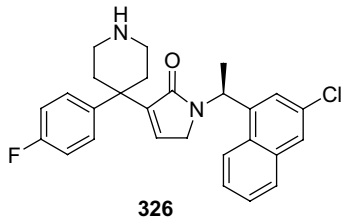
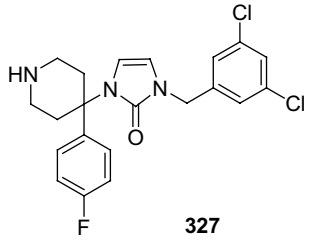
Molecular structure	Piperidine framework	Activity/usage	Ref.
 **306**, R = Me **307**, R = Cl	4,4-Disubstituted	α-1a Adrenergic receptor antagonists, agent for prostate disorders	174
 **308**	4,4-Disubstituted	α-1a Adrenergic receptor antagonist, agent for prostate disorders	174
 **309**	4,4-Disubstituted	α-1a Adrenergic receptor antagonist, agent for prostate disorders	174
 **310**	4,4-Disubstituted	Treatment of, for example, epilepsy, anxiety and inflammatory diseases	175
 **311**	4,4-Disubstituted	Matrix metalloproteinase inhibitor, antiarthritic	176
 **312**	4,4-Disubstituted	Metalloprotease inhibitor, antineoplastic and antiangiogenic	177
 **313**	4,4-Disubstituted	Agent for neurogenic pain	178

Table 1 (*continued*)

Molecular structure	Piperidine framework	Activity/usage	Ref.
 **314**	4,4-Disubstituted	Reversible inhibitor of cysteine proteases, treatment of autoimmune diseases	179
 **315**, R^1 = Me, R^2 = CF_3, R^3 = CF_3 **316**, R^1 = H, R^2 = Br, R^3 = Br **317**, R^1 = H, R^2 = CF_3, R^3 = CF_3	4,4-Disubstituted	Tachykinin and/or serotonin reuptake inhibitors, anxiolytic and antidepressant	180
 **318**, R^1 = Cl, R^2 = Cl, R^3 = OMe, R^4 = OMe **319**, R^1 = F, R^2 = H, R^3 = H, R^4 = H **320**, R^1 = F, R^2 = H, R^3 = Et, R^4 = H	4,4-Disubstituted	NK_1 receptor antagonists and selective serotonin reuptake inhibitors, antidepressant	181
 **321**, R^1 = Cl, R^2 = Cl, R^3 = H, R^4 = H, R^5 = H **322**, R^1 = F, R^2 = H, R^3 = H, R^4 = OMe, R^5 = OMe **323**, R^1 = F, R^2 = H, R^3 = Me, R^4 = OMe, R^5 = OMe	4,4-Disubstituted	NK_1 receptor antagonists and selective serotonin reuptake inhibitors, antidepressant	182
 **324**, R = H **325**, R = Me	4,4-Disubstituted	Tachykinin and/or serotonin reuptake inhibitors, anxiolytic and antidepressant	183

(*continued on next page*)

Table 1 (*continued*)

Molecular structure	Piperidine framework	Activity/usage	Ref.
 **326**	4,4-Disubstituted	Tachykinin and/or serotonin reuptake inhibitors, anxiolytic and antidepressant	183
 **327**	4,4-Disubstituted	Tachykinin and/or serotonin reuptake inhibitors, anxiolytic and antidepressant	184

the patent literature have been collected in Table 1 providing also references to the original source in which the information on the preparative procedures can be retrieved.

Acknowledgements

Financial support from the Academy of Finland (project number 203283) and the Magnus Ehrnrooth foundation is gratefully acknowledged. The authors thank CSC, the Finnish IT center for science, for providing the rights to use the Drug Data Report (MDL/ISIS database) and Dr. Hiroshi Nakamura (Pfizer) for his kind assistance in obtaining some of the patent literature. S.K. also wishes to thank Ms. Susanna Repo and Ms. Anita Forss for their help with the literature search.

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5. Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693–3712.
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