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Generation of 3-Piperidine(methan)amines and Cyclic 3-Piperidine-methanamines as Potential Substance P Antagonists

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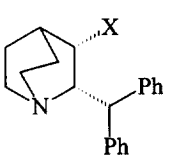
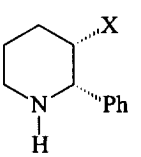
Abstract: A general method is described for the synthesis of 3-piperidine(methan)amines and their cyclic analogues. The 3,5-dichloro-2*H*-1,4-oxazin-2-ones **6** and 3-aryl substituted analogues are reacted with acetylenic dienophiles yielding pyridines. Further catalytic hydrogenation and functional group transformation (**1**) or substitution (**2-3**) with ring closure reactions (**4**) followed by hydrogenation provided the 2,3,5-*cis* substituted piperidines **1-3** and a *cis* substituted [3,4-*c*]pyrrolopiperidine **4**. These compounds have recently raised great interest due to their Substance P antagonist profiles.

INTRODUCTION

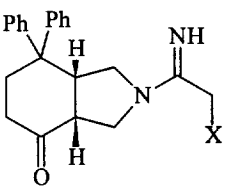
Numerous 3-piperidine(methan)amines and [3,4-*c*]pyrrolopiperidine compounds have recently raised great interest due to their Substance P (SP) antagonist profiles. SP is a member of the tachykinin peptide family[1] and the pharmacological actions of the mammalian tachykinin SP are implicated in pain control[2] and in the pathogenesis of a variety of inflammatory diseases, migraine[3], rheumatoid arthritis[4], asthma[5] and nausea. An initial lead compound in this field, CP-96,345, was discovered as a result of an extensive chemical synthetic program[6]. Molecular modifications of this compound led to CP-99,994[7], one of the most potent SP antagonists yet known. Since the disclosure of the first non-peptide SP antagonist CP-96,345, numerous reports of antagonists encompassing a variety of structure types have appeared in the literature, e.g. CP-99,994, RP 67,580[8], RPR 100893[9] and GR203040.[10]



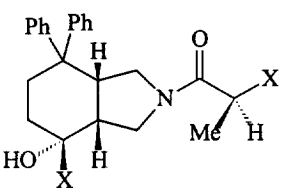
CP-96,345
(X= $NHCH_2$-2-MeOPh)



CP-99,994 (X= $NHCH_2$-2-MeOPh)
GR203040
(X= $NHCH_2$-(2-MeO-5-tetrazol-1-yl)Ph)

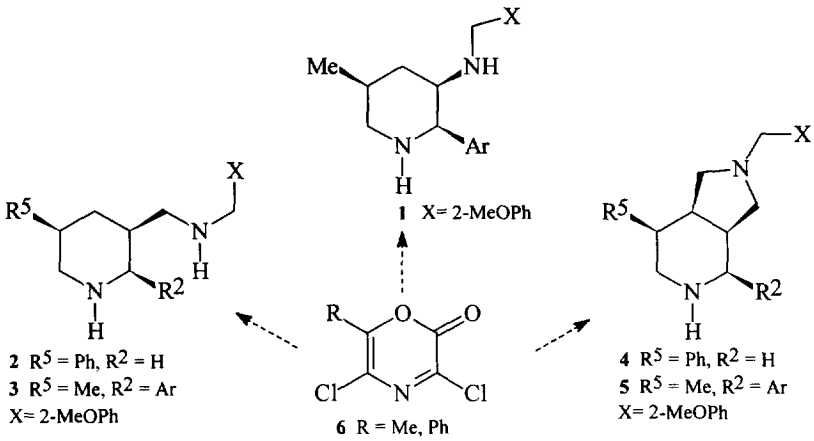


RP 67,580
(X= 2-MeOPh)



RPR 100893
(X= 2-MeOPh)

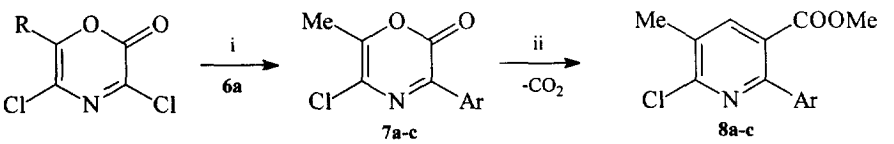
In this paper we deal with a synthetic approach to 2,3,5-*cis*-substituted piperidines **1-3** and the *cis*-substituted [3,4-*c*]pyrrolopiperidines **4-5** via oxazinones **6** shown in scheme 1.



Scheme 1

RESULTS AND DISCUSSION

Our approach to the 2,3,5-*cis*-substituted piperidines **1** is summarized in scheme 2. The 3,5-dichloro-6-methyl-oxazin-2-one **6a** was prepared from the corresponding α-hydroxynitrile[11] and then arylated in the 3-position. The 3-arylated oxazinones[12] **7a-c** were reacted with methyl propiolate yielding the 6-chloro-2,3,5-tri-substituted pyridines **8a-c**.[13]



6a R = Me
6b R = Ph

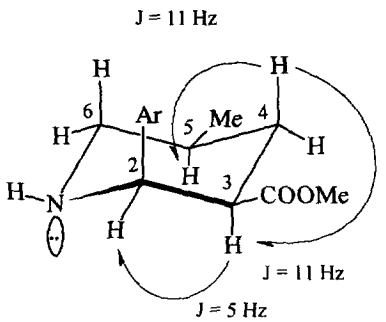
7a : Ar = 4-MeOPh
7b : Ar = Ph
7c : Ar = 3,4-MeOPh

8a : Ar = 4-MeOPh
8b : Ar = Ph
8c : Ar = 3,4-MeOPh

i **7a**: 1 eq. **6a**, 4 eq. anisole, 4 eq. $AlCl_3$, CH_2Cl_2, 2h, rt; **7b**: 1 eq. **6a**, 4 eq. $AlCl_3$, benzene, 12h, rt; **7c**: 1 eq. **6a**, 4 eq. veratrole. 4 eq. $AlCl_3$, CH_2Cl_2, 2h, rt; ii) 3 eq. methyl propiolate, toluene, 80 °C, 4h

Scheme 2

Catalytic hydrogenation of these compounds in acetic acid with 15 % (w/w) platinum oxide and 10 % (w/w) Pd/C as catalysts yielded the 2,3,5-*cis*-substituted piperidines **9a-c** with an "all-cis" configuration.[14] This configuration can be deduced from the coupling pattern in the ^1H NMR spectrum. The axial H-4 proton in e.g. **9c** shows an axial-axial coupling (12.5 Hz) with the protons in 3- and 5-position, while the coupling (5 Hz) between H-3 and H-2 indicates an axial position of the 2-aryl group.

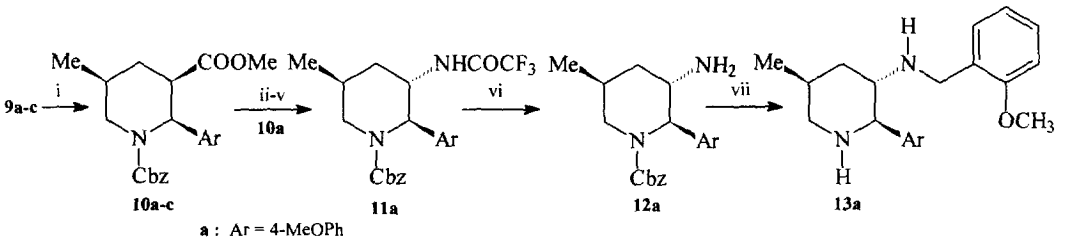


9a : Ar = 4-MeOPh
9b : Ar = Ph
9c : Ar = 3,4-MeOPh

NMR-data:

δ (ppm)	m	J(Hz)	
0.95	d	CH_3-H-5ax: 6.5	5-CH_3
1.74	m		H-5ax
1.81	ddd	gem: 11	H-4ax
		H-4ax-H-5ax: 11	
		H-4ax-H-3ax: 11	
2.11	ddd	gem: 11	H-4eq
		H-4eq-H-3ax: 5	
		H-4eq-H-5ax: 5	
2.39	dd	gem: 12, H-6ax-H-5ax: 9	H-6ax
2.77	dd	gem:12, H-6eq-H-5ax: 3.5	H-6eq
3.08	ddd	H-3ax-H-4ax: 11	H-3ax
		H-3ax-H-2eq: 5	
		H-3ax-H-4eq: 5	
4.51	d	H-3ax-H-2eq: 5	H-2eq

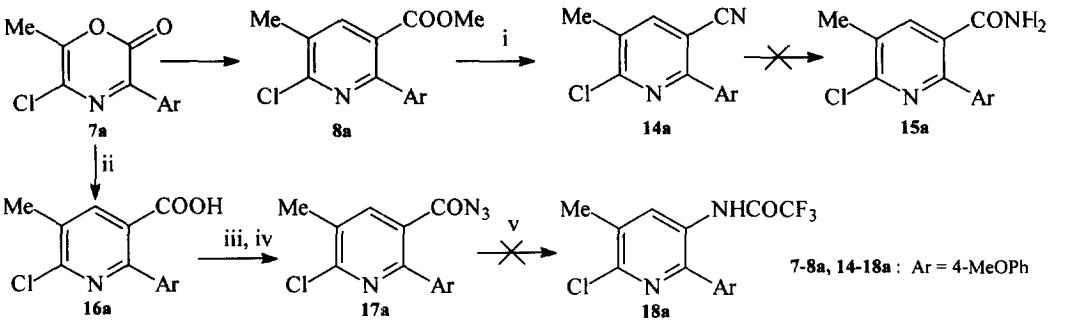
Protection of the piperidine nitrogen of **9a-c** with benzyl chloroformate yielded compounds **10a-c** (scheme 3). Subsequent hydrolysis of the methyl ester of **9a** with lithium hydroxide followed by reaction with thionyl chloride and sodium azide, yielded the corresponding acyl azide. This acyl azide underwent a Curtius rearrangement in the presence of trifluoroacetic acid providing the trifluoroacetamide **11a**. However NMR analysis showed epimerisation at the C-3 atom, probably due to the LiOH treatment. The axial H-4 proton shows an axial-axial coupling (11 Hz) with the H-3 proton, an axial-equatorial coupling with the H-5 proton, while the coupling (9 Hz) between H-2 and H-3 indicates the *trans* relationship between the 2-aryl and the 3-amino group. Deprotection of the trifluoroacetamide derivative in a mixture of methanol/water and potassium carbonate provided the amine **12a**. Reductive amination of the amine with 2-methoxybenzaldehyde was done with hydrogen and Pd/C as catalyst. Simultaneous deprotection of the piperidine-*N*-atom led to the *N*-[(2-methoxyphenyl)methyl]-3-piperidinamine **13a**.



i) 1.2 eq. BnOCOCl, 2 eq. K_2CO_3, CH_3CN, -20 °C, 2h; ii) 5 eq. LiOH, H_2O/MeOH (1:5), rt, 24h; iii) 3 eq. $SOCl_2$, toluene, 80 °C, 8h; iv) 2 eq. NaN_3, H_2O/CH_2Cl_2, Bu_4NBr, 0 °C, 2h; *v*) 2 eq. CF_3COOH, CH_2Cl_2, reflux, 6h; vi) 2 eq. K_2CO_3, H_2O/MeOH (1:1), rt, 60h; vii) 1eq. 2-MeO-benzaldehyde, MeOH, cat. CH_3COOH, H_2, Pd/C, 1 atm, rt

Scheme 3

To avoid epimerisation, functional group transformation was performed at the pyridine stage before reduction (scheme 4). Conversion of the ester group of **8a** into amide with dimethylaluminum amide (*in situ* generated from trimethylaluminum and ammonium chloride) did not yield the amide but the corresponding nitrile **14a**. Hydrolysis of this nitrile required extreme conditions providing the amide **15a** in very low yield.

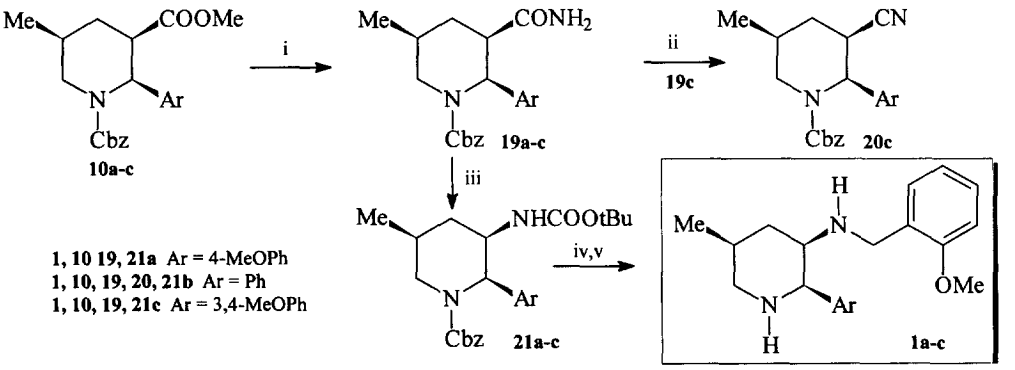


i) 5 eq. Me_2AlNH_2, benzene, 50 °C, 48h; ii) HC≡CCOOH, 80 °C, 12h; iii) 3 eq. $SOCl_2$, toluene, 80 °C, 4h; iv) 4 eq. NaN_3, toluene, 80 °C, 8h; v) 2 eq. CF_3COOH, CH_2Cl_2, reflux, 40h

Scheme 4

Formation of the acyl azide **17a** by conversion of the pyridine carboxylic acid **16a** -generated from **7a** and propiolic acid- into the corresponding acid chloride, followed by reaction with azide was successful. However reflux of **17a** with trifluoroacetic acid (to catalyse the conversion and to intercept the intermediate isocyanate) in dichloromethane did not provide the corresponding trifluoroacetamide **18a**.

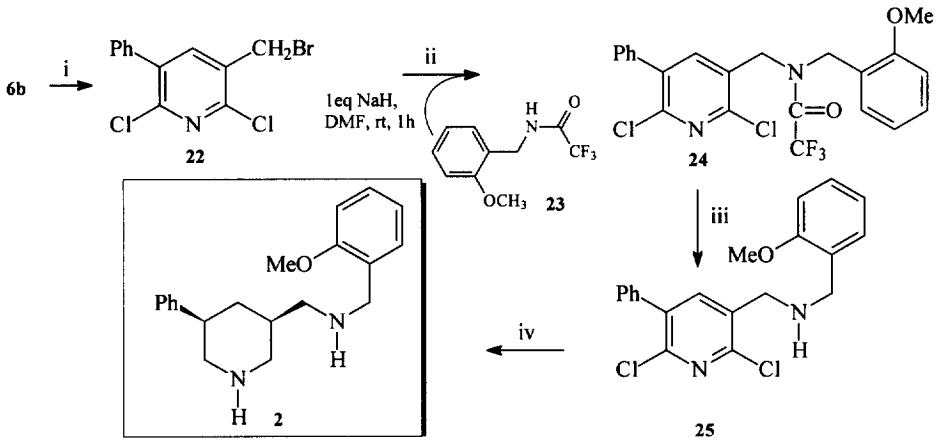
In an alternative way we could realize the functional group transformation at the piperidine stage without epimerisation (scheme 5). The protected piperidine carboxylates **10a-c** were treated with dimethylaluminum amide[15] to provide easily the amides **19a-c**. With **19c** and hydroxy(tosyloxy)iodobenzene (HTIB)[16] as Hofmann reagent the nitrile **20c** was obtained instead of the amine. The rearrangement of **19a-c** with lead(IV)acetate[17] in refluxing *t*-butanol yielded the *t*-butoxycarbonyl protected amines **21a-c**. Deprotection of the amino group with hydrogen chloride in ethyl acetate, followed by reductive amination and simultaneous deprotection of the piperidine-*N*-atom with hydrogen and palladium on carbon, afforded the expected 2,3,5-substituted piperidinamines **1a-c**. The *cis*-configuration was confirmed by NMR analysis: the axial H-4 proton shows an axial-axial coupling (7.5 Hz) with the H-3 and H-5 protons, while the coupling (4 Hz) between H-3 and H-2 indicates an axial position of the aryl group in 2-position.



i) 5 eq. NH_4Cl, 5 eq. $AlMe_3$ (2M solution in hexanes), CH_2Cl_2, reflux, 16h; ii) 1 eq. HTIB, CH_3CN, reflux, 2h; iii) 2×1 eq. $Pb(OAc)_4$, *t*-BuOH, reflux, 1.5h; iv) HCl, EtOAc, rt, 5 min; v) 1 eq. 2-MeO-benzaldehyde, MeOH, cat. CH_3COOH, H_2, Pd/C, 1 atm, rt

Scheme 5

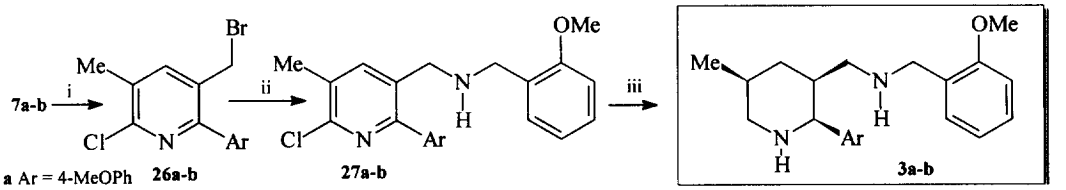
The synthesis of the 3,5-disubstituted piperidine **2** started from the bromomethyl substituted pyridine **22** generated by the cycloaddition-elimination reaction of the oxazinone **6b** with propargyl bromide[13] (scheme 6). Treatment of compound **22** with 2-methoxybenzylamine yielded the tertiairy amine rather than the desired secundary amine **25**. This problem was solved by reacting **22** with the sodium salt of the amide **23**, obtained by treatment of 2-methoxybenzylamine with ethyl trifluoroacetate[18,19]. Reflux of an ethanol solution of the generated trifluoroacetamide **24** in the presence of a catalytic amount of sodium hydroxide yielded the desired compound **25** quantitatively. The compound **25** was selectively reduced to the desired product **2** in the presence of a mixture of catalysts consisting of 10 % (w/w) palladium on carbon and 20 % (w/w) platinum oxide hydrate. The hydrogenolysis of the C-Cl bonds and the reduction of the pyridine ring were carried out simultaneously. Structure of the compound **2** was confirmed by spectral data and elemental analysis.



i) propargyl bromide, 80% solution in toluene, 80 °C, 12h; ii) 1 eq. **23**, rt, 1h; iii) EtOH, NaOH (cat.), reflux, 1.5h; iv) H_2, Pd/C (10 %w/w), $PtO_2.xH_2O$ (20%w/w), CH_3COOH, 1atm, rt

Scheme 6

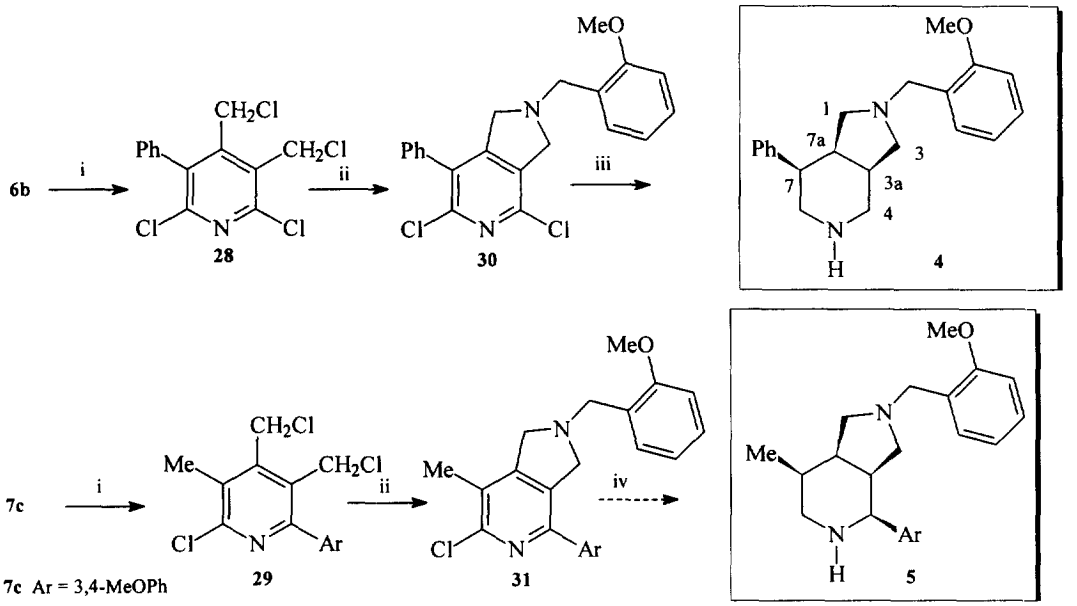
In a similar way the 3-piperidinemethanamines **3a-b** were obtained from the 3-functionalized oxazinones **7a-b** in a cycloaddition-elimination reaction with propargyl bromide[13] yielding the regioselectively substituted pyridines **26a-b** (scheme 7). Nucleophilic substitution of the bromomethyl group with an excess of 2-methoxybenzylamine led to the 3-aminopyridines **27a-b** which could be converted with Adam's catalyst under atmospheric pressure of hydrogen into the 2,3,5-*cis*-substituted piperidines **3a-b**.



i) propargyl bromide (80% sol. in toluene), 80 °C, 2h; ii) 4 eq. 2-MeO-benzylamine, EtOH, reflux, 4h; iii) H_2, $PtO_2.xH_2O$, CH_3COOH, 1 atm, rt

Scheme 7

The desired [*N*-(2-methoxyphenyl)methyl]pyrrolo[3,4-*c*]piperidines **4** and **5** were approached by a Diels-Alder reaction of 2*H*-1,4-oxazin-2-ones **6b** and **7c** (scheme 8) with 1,4-dichloro-2-butyne yielding the 3,4-bis(chloromethyl)-pyridines **28** and **29**. The latter were reacted with 2-methoxybenzylamine to form the pyrrolopyridines **30** and **31**. However the desired pyrrolopiperidine **4** could be obtained only in poor yield by reduction of **30** with palladium and platinum oxide. The coupling constants between the H-3a-H-4 and H-3a-H-3 protons at one hand and between H-7a-H-7 and H-7a-H-1 at the other hand confirm the *cis* relationship. The hydrogenolysis of the benzylic bonds is a competing side reaction and moreover the dihydropyrrole rings are easily oxidized to pyrrole rings by air. The reduction of **31** with platinum oxide yielded a complex mixture. The pyrrolopiperidine **5** could only be detected mass spectroscopically. Even reduction with ruthenium dioxide -a catalyst used to avoid epimerisation- did not yield the expected product[20].



i) 1,4-dichloro-2-butyne, 80 °C, 10d; ii) 1.1 eq 2-MeO-benzylamine, 2.2 eq K_2CO_3, THF, reflux, 6h; iii) H_2, Pd/C (10 % (w/w)), $PtO_2.xH_2O$ (20 % (w/w)), 2 eq K_2CO_3, CH_3COOH, 1 atm, rt; iv) H_2, $PtO_2.xH_2O$ (20% (w/w)), 1.2 eq K_2CO_3, CH_3COOH, 1atm, rt or H_2, RuO_2, (2% (w/w)), MeOH/CH_3COOH, 70 atm, 90 °C

Scheme 8

CONCLUSION

By functionalisation of the 3- or 6-position of the 3,5-dichloro-2*H*-oxazin-2-ones **6a-b**, a wide variety of regioselectively substituted pyridines can be obtained after cycloaddition-elimination reaction with various dienophiles. Further functional group transformation (compound **1**), substitution reactions (compounds **2** and **3**) or ring closure reactions (compound **4**) followed by catalytic hydrogenation with hydrogen and palladium and/or platinum oxide provided the desired *cis*-multisubstituted piperidines **1-4**, a wide series of potential non-peptide Substance P antagonists.

EXPERIMENTAL SECTION

Infrared spectra were recorded on a Perkin-Elmer 297 grating IR spectrophotometer and a Perkin-Elmer 1720 Fourier Transform spectrometer. ^{1}H NMR spectra and the ^{13}C NMR spectra were recorded on a Bruker WM 250 or on a Bruker AMX 400 instrument. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to TMS or to the deuterated solvent as an internal reference. Mass spectra were run by using a Kratos MS50TC instrument and a DS90 data system. For the chromatography analytical TLC plates (Alugram SilG/UV_{254}) and 70-230 mesh silica gel 60 (E.M.Merck) were used. Melting points were taken using a Reichert-Jung Thermovar apparatus and an electrothermal IA 9000 digital melting point apparatus and are uncorrected. Microanalyses were performed by Janssen Pharmaceutica on a Carlo Erba elemental analyser type 1106.

The 3,5-dichloro-6-functionalized-2*H*-1,4-oxazin-2-ones **6a-b** used for the preparation of compounds **1-5** were synthesized according to the procedures described in the literature[1]. Synthesis and spectroscopic data of 3-aryl substituted 2*H*-1,4-oxazin-2-ones **7a-b** are described previously[12].

5-chloro-3-(3,4-dimethoxyphenyl)-6-methyl-2*H*-1,4-oxazin-2-one (7c)

A mixture of the 3,5-dichloro-6-methyl-2*H*-1,4-oxazin-2-one **6a** (0.01 mol) and 4.0 equivalents aluminum chloride in 100 ml dichloromethane was stirred at room temperature for 15 minutes, then 4.0 equivalents veratrole were added. After stirring for 15 hours the reaction mixture was poured into 200 ml of ice water and extracted with chloroform (3×200 ml). The combined extracts were dried over magnesium sulfate. Evaporation of the solvent gave the crude product which was purified by column chromatography (SiO_2; 5 % EtOAc/$CHCl_3$) and recrystallized from a dichloromethane/hexanes mixture.

Yield: 91 %; m.p.: 167 °C (CH_2Cl_2/hexanes); IR (KBr) cm^{-1}: 1730 (s), 1600 (s); ^{1}H NMR ($CDCl_3$): 2.41 (s, 3H, 6-CH_3), 3.98 and 3.99 (2×s, 6H, 2×OCH_3), 6.92 (d, ^3J = 9 Hz, 1H, PhH-5), 7.89 (d, ^4J = 2 Hz, 1H, PhH-2), 8.15 (d×d, ^3J = 9 Hz, ^4J = 2 Hz, 1H, PhH-6); ^{13}C NMR ($CDCl_3$): 17.0 (CH_3), 56.0 (OCH_3), 56.0 (OCH_3), 110.5 (PhC-5), 123.6 (PhC-6), 125.0 (PhC-2), 125.6 (C-5), 125.8 (PhC-1), 145.6 (C-3), 147.1 (C-6), 148.3 (PhC-3), 152.3 (PhC-4), 153.0 (C-2); m/z: 281 (95), 253 (100); exact mass for $C_{13}H_{12}ClNO_4$: 281.0452; found: 281.0465.

2-aryl-6-chloro-5-methyl-3-pyridinecarboxylates (8a-c). General procedure:

The oxazinone **7a-c** (0.01 mol) was dissolved in a solution of methyl propiolate (0.03 mol) in dry toluene (5 ml) and stirred at 80 °C under N_2-atmosphere until the starting compound had disappeared (TLC-control). After removal of the excess methyl propiolate and toluene, the pyridines were purified by column chromatography (SiO_2; $CHCl_3$/EtOAc).

methyl 6-chloro-2-(4-methoxyphenyl)-5-methyl-3-pyridinecarboxylate (8a)

Yield: 88 %; m.p.: 76 °C (CH_2Cl_2/hexanes); IR (KBr) cm^{-1} : 1732 (s), 1022 and 1256 (m); ^{1}H NMR ($CDCl_3$): 2.43 (s, 3H, 5-CH_3), 3.73 (s, 3H, 3-$COOCH_3$), 3.84 (s, 3H, OCH_3), 6.94 (d, ^3J = 8.5 Hz, 2H, PhH-3,5), 7.49 (d, ^3J =8.5 Hz, 2H, PhH-2,6), 7.91 (s, 1H, pyH-4); ^{13}C NMR ($CDCl_3$): 18.9 (CH_3), 52.3 ($COO\underline{C}H_3$), 55.2 (OCH_3), 113.6 (PhC-3), 125.0 (C-3), 129.9 (C-5), 130.0 (PhC-2), 130.9 (PhC-1), 140.8 (C-4), 152.8 (C-6), 156.6 (C-2), 160.3 (PhC-4), 168.0 ($\underline{C}OOCH_3$); m/z: 291 (100), 260 (28), 217 (9); exact mass for $C_{15}H_{14}ClNO_3$: 291.0662; found: 291.0663.

methyl 6-chloro-5-methyl-2-phenyl-3-pyridinecarboxylate (8b)

Yield: 92 %; m.p.: 98-100 °C (CH_2Cl_2/hexanes); IR (KBr) cm^{-1}: 1724 (s), 701 (m); ^{1}H NMR ($CDCl_3$): 2.44 (s, 3H, 5-CH_3), 3.68 (s, 3H, 3-$COOCH_3$), 7.38-7.44 (m, 3H, PhH-2,4,6), 7.47-7.55 (m, 2H, PhH-3,5), 7.91 (s, 1H, pyH-4); ^{13}C NMR ($CDCl_3$): 19.0 (CH_3), 52.3 ($COO\underline{C}H_3$), 125.5 (C-3), 128.1 (PhC-2), 128.6 (PhC-3), 128.9 (PhC-4), 130.7 (C-5), 138.6 (PhC-1), 140.9 (C-4), 153.0 (C-6), 156.8 (C-2), 167.7 ($\underline{C}OOCH_3$); m/z: 261 (24), 246 (100); exact mass for $C_{14}H_{12}ClNO_2$: 261.0556; found: 261.0572; anal cald for $C_{14}H_{12}ClNO_2$: C 64.25, H 4.62, N 5.32; found C 64.28, H 4.62, N 5.26.

methyl 6-chloro-2-(3,4-dimethoxyphenyl)-5-methyl-3-pyridinecarboxylate (8c)

Yield: 90 %; oil; IR (NaCl) cm^{-1}: 1724 (s); ^1H NMR ($CDCl_3$): 2.45 (s, 3H, 5-CH_3), 3.73 (s, 3H, 3-$COOCH_3$), 3.93 and 3.94 (2×s, 6H, 2×OCH_3), 6.89 (d, ^3J = 8 Hz, 1H, PhH-5), 7.06 (d×d, ^3J = 8 Hz, ^4J = 2 Hz, 1H, PhH-6), 7.15 (d, ^4J = 2 Hz, 1H, PhH-2), 7.89 (s, 1H, pyH-4); ^{13}C NMR ($CDCl_3$): 18.9 (CH_3), 52.3 ($COO\underline{C}H_3$), 55.8 (OCH_3), 55.8 (OCH_3), 110.5 (PhC-5), 111.7 (PhC-2), 121.4 (PhC-6), 125.3 (C-3), 129.9 (PhC-1), 131.0 (C-5), 140.6 (C-4), 148.6 (PhC-4), 149.8 (PhC-3), 152.5 (C-6), 155.9 (C-2), 168.0 ($\underline{C}OOCH_3$); m/z: 321 (100), 306 (25), 290 (8); exact mass for $C_{16}H_{16}ClNO_4$: 321.0768; found: 321.0766.

methyl 2-aryl-5-methyl-3-piperidinecarboxylates (9b-c). General procedure:

To a solution of 5 mmol methyl 2-aryl-6-chloro-5-methyl-3-pyridinecarboxylate **8b-c** in 20 ml acetic acid, 5.5 mmol K_2CO_3, 15 % (w/w) Pd/C and 10 % (w/w) $PtO_2.xH_2O$ was added. After absorption of 4 equivalents of hydrogen, the catalysts were filtered and washed with acetic acid (150 ml) and dichloromethane (150 ml). The residues were evaporated and 100 ml H_2O was added. Dropwise adding of ammonium hydroxide (28 % NH_3 in H_2O) to pH=10 was followed by extraction with dichloromethane (3×100 ml). The collected organic layers were dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (Al_2O_3; $CHCl_3$/ MeOH).

methyl 5-methyl-2-phenyl-3-piperidinecarboxylate (9b)

Yield: 86 %; oil; IR (NaCl) cm^{-1}: 3328 (br), 1732 (s); ^1H NMR ($CDCl_3$): 0.92 (d, 3H, J(CH_3-H5ax) = 6.5 Hz, CH_3), 1.78 (m, 2H, H4ax + H5ax), 2.22 (d×d×d, J(H4ax-H4eq) = 11 Hz, J(H4eq-H3ax) = 5 Hz, J(H4eq-H5ax) = 5 Hz, 1H, H4eq), 2.40 (d×d, J(H6ax-H6eq) = 12 Hz, J(H6ax-H5ax) = 9 Hz, 1H, H6ax), 2.77 (d×d, J(H6ax-H6eq) = 12 Hz, J(H6eq-H5ax) = 3.5 Hz, 1H, H6eq), 3.12 (d×d×d, J(H4ax-H3ax) = 11 Hz, J(H2eq-H3ax) = 5 Hz, J(H4eq-H3ax) = 5 Hz, 1H, H3ax), 3.52 (s, 3H, 3-$COO\underline{C}H_3$), 4.54 (d, J(H2eq-H3ax) = 5Hz, 1H, H2eq), 7.29 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$): 18.6 (CH_3), 30.3 (C-4), 30.6 (C-5), 43.8 (C-3), 47.4 (C-6), 50.9 ($COO\underline{C}H_3$), 55.8 (C-2), 126.3 (PhC-4), 127.6 (PhC-2), 127.7 (PhC-3), 140.2 (PhC-1), 173.2 (CO); m/z: 233 (9), 174 (17), 146 (100); exact mass for $C_{14}H_{19}NO_2$: 233.1416; found: 233.1421.

methyl 2-(3,4-dimethoxyphenyl)-5-methyl-3-piperidinecarboxylate (9c)

Yield: 92 %; oil; IR (NaCl) cm^{-1}: 3340 (br), 1731 (s); ^1H NMR ($CDCl_3$): 0.95 (d, J(CH_3-H5ax) = 6.5 Hz, 3H, CH_3), 1.74 (m, 1H, H5ax), 1.81 (d×d×d, J(H4ax-H4eq) = 11 Hz, J(H4ax-H3ax) = 11 Hz, J(H4ax-H5ax) = 11 Hz, 1H, H4ax), 2.11 (d×d×d, J(H4ax-H4eq) = 11 Hz, J(H4eq-H3ax) = 5 Hz, J(H4eq-H5ax) = 5 Hz, 1H, H4eq), 2.39 (d×d, J(H6ax-H6eq) = 12 Hz, J(H6ax-H5ax) = 9 Hz, 1H, H6ax), 2.77 (d×d, J(H6ax-H6eq) = 12 Hz, J(H6eq-H5ax) = 3.5 Hz, 1H, H6eq), 3.08 (d×d×d, J(H4ax-H3ax) = 11 Hz, J(H2eq-H3ax) = 5 Hz, J(H4eq-H3ax) = 5 Hz, 1H, H3ax), 3.57 (s, 3H, 3-$COOCH_3$), 3.87 and 3.89 (2s, 6H, 2×OCH_3), 4.51 (d, J(H2eq-H3ax) = 5Hz, 1H, H2eq), 6.78 (d, ^3J = 8 Hz, 1H, PhH-5), 6.89 (d×d, ^3J = 8 Hz, ^4J = 2 Hz, 1H, PhH-6), 6.98 (d, ^4J = 2 Hz, 1H, PhH-2); ^{13}C NMR ($CDCl_3$): 18.9 (CH_3), 30.8 (C-4), 30.8 (C-5), 44.4 (C-3), 47.6 (C-6), 51.2 ($COO\underline{C}H_3$), 55.5 and 55.8 (2×OCH_3), 55.8 (C-2), 110.4 (PhC-5), 111.4 (PhC-2), 119.6 (PhC-6), 132.9 (PhC-1), 147.5 (PhC-4), 148.5 (PhC-3), 173.6 (CO); m/z: 293 (10), 262 (27), 165 (100); exact mass for $C_{16}H_{23}NO_4$: 293.1627; found: 293.1622.

methyl 2-aryl-5-methyl-1-[(phenylmethoxy)carbonyl]-3-piperidinecarboxylates (10a-c). General procedure:

Under nitrogen atmosphere 5.5 mmol benzyl chloroformate in 5 ml acetonitrile was added dropwise (-20 °C) to a suspension of 5 mmol methyl 2-aryl-5-methyl-3-piperidinecarboxylate **9b-c** or crude **9a** and 12 mmol K_2CO_3 in 20 ml dry acetonitrile. After reaction for one hour at -20 °C, the reaction mixture was brought to room temperature and 100 ml CH_2Cl_2 and 50 ml H_2O was added. The organic layer was washed with H_2O (2×20ml), 10 % HCl/H_2O (20ml), H_2O (20 ml) and a saturated NaCl solution (20 ml). The organic layer was dried on $MgSO_4$, evaporated and purified by column chromatography (SiO_2; $CHCl_3$/EtOAc) yielding the *N*-protected piperidinecarboxylates .

NMR analysis shows double signals due to the amide function (two rotamers). By raising the temperature the separated signals coalesce and become single sharp signals. In the experimental part the absorptions of the two signals are reproduced.

methyl 2-(4-methoxyphenyl)-5-methyl-1-[(phenylmethoxy)carbonyl]-3-piperidinecarboxylate (10a)

Yield: 89 %; oil; IR (NaCl) cm^{-1}: 1734 (s), 1698 (s); ^1H NMR ($CDCl_3$): 0.91 and 0.94 (2×d, $J(CH_3$-H5ax) = 6 Hz, 3H, 5-CH_3), 1.70 (m, broad, 1H, H5ax), 1.7 (d×d×d, J(H4ax-H4eq) = 12.5 Hz, J(H4ax-H3ax) = 12.5 Hz, J(H4ax-H5ax) = 12.5 Hz, 1H, H4ax), 2.10 (m, broad, 1H, H4eq), 2.37 (d×d, J(H6ax-H6eq) = 12.5 Hz, J(H6ax-H5ax) = 12.5 Hz, 1H, H6ax), 2.98 (d×d×d, J(H4ax-H3ax) = 12.5 Hz, J(H2eq-H3ax) = 5 Hz, J(H4eq-H3ax) = 5 Hz, 1H, H3ax), 3.59 (s, 3H, 3-$COOCH_3$), 3.77 (s, OCH_3), 3.88 and 4.03 (2×d, broad, J(H6ax-H6eq) = 12.5 Hz, 1H, H6eq), 5.16 and 5.27 (2×d, J = 13 Hz, 1H, 1-$COOC\underline{H}_2Ph$), 5.18 (s, J = 13 Hz, 1H, 1-$COOC\underline{H}_2Ph$), 5.83 and 5.99 (d, J(H2eq-H3ax) = 5Hz, 1H, H2eq), 6.76 and 6.80 (d, ^3J = 8 Hz, PhH-3,5), 7.10 and 7.20 (d, ^3J = 8 Hz, PhH-2,6), 7.34 (m, 5H, $COOCH_2Ph$); ^{13}C NMR ($CDCl_3$): 18.7 (CH_3), 30.0 and 30.3 (C-4), 30.8 and 31.2 (C-5), 44.2 and 45.1 (C-3), 46.2 (C-6), 51.7 ($COO\underline{C}H_3$), 53.5 and 53.9 (C-2), 55.1 (OCH_3), 67.3 ($O\underline{C}H_2Ph$), 113.7 (PhC-3), 127.8 (CH_2PhC-4), 127.9 (CH_2PhC-2), 128.4 (CH_2PhC-3), 128.9 and 129.1 (PhC-2), 130.1 (PhC-1), 136.8 (CH_2PhC-1), 158.6 (PhC-4), 155.2 and 155.5 ($\underline{C}OOCH_2Ph$), 172.7 and 172.9 ($\underline{C}OOCH_3$); m/z: 397 (1), 306 (9), 262 (100), 91 (76); exact mass for $C_{23}H_{27}NO_5$: 397.1889; found: 397.1893.

methyl 5-methyl-2-phenyl-1-[(phenylmethoxy)carbonyl]-3-piperidinecarboxylate (10b)

Yield: 94 %; oil; IR (NaCl) cm^{-1}: 1735 (s), 1694 (s); ^1H NMR ($CDCl_3$): 0.88 and 0.92 (2×d, $J(CH_3$-H5ax) = 6 Hz, 3H, 5-CH_3), 1.65-1.74 (m, broad, 1H, H5ax), 2.10 (d×d×d, J(H4ax-H4eq) = 12.5 Hz, J(H4ax-H3ax) = 12.5 Hz, J(H4ax-H5ax) = 12.5 Hz, 1H, H4ax), 2.34 (m, broad, 1H, H4eq), 2.62 (d×d, J(H6ax-H6eq) = 12.5 Hz, J(H6ax-H5ax) = 12.5 Hz, 1H, H6ax), 2.98 (d×d×d, J(H4ax-H3ax) = 12.5 Hz, J(H2eq-H3ax) = 5 Hz, J(H4eq-H3ax) = 5 Hz, 1H, H3ax), 3.58 (s, 3H, 3-$COOC\underline{H}_3$), 3.90 and 4.08 (2×d, J(H6ax-H6eq) = 12 Hz, J(H6eq-H5ax) = 3.5 Hz, 1H, H6eq), 5.16 and 5.28 (2×d, J = 13 Hz, 2H, 1-$COOC\underline{H}_2Ph$), 5.89 and 6.04 (2×d, J(H2eq-H3ax) = 5Hz, 1H, H2eq), 7.02-7.48 (m, 10H, PhH + 1-$COOCH_2PhH$) ; ^{13}C NMR ($CDCl_3$): 18.7 (CH_3), 29.9 and 30.2 (C-4), 30.8 and 31.2 (C-5), 44.0 and 44.9 (C-3), 46.3 (C-6), 51.7 ($COO\underline{C}H_3$), 53.8 and 54.3 (C-2), 67.3 ($O\underline{C}H_2Ph$), 127.1 (PhC-4), 127.2 (PhC-2), 127.6 (PhC-3), 127.7 (CH_2PhC-4), 127.8 (CH_2PhC-2), 127.9 (CH_2PhC-3), 138.0 (CH_2PhC-1), 138.1 (PhC-1), 155.1 and 155.4 ($\underline{C}OOCH_2Ph$), 172.6 and 172.8 ($\underline{C}OOCH_3$); m/z: 367 (1), 276 (6), 232 (55), 91 (100); exact mass for $C_{22}H_{25}NO_4$: 367.1784; found: 367.1786.

methyl 2-(3,4-dimethoxyphenyl)-5-methyl-1-[(phenylmethoxy)carbonyl]-3-piperidinecarboxylate (10c)

Yield: 97 %; oil; IR (NaCl) cm^{-1}: 1734 (s), 1699 (s); ^1H NMR ($CDCl_3$): 0.93 and 0.95 (2×d, $J(CH_3$-H5ax) = 6 Hz, 3H, 5-CH_3), 1.60-1.86 (m, broad, 2H, H5ax + H4ax), 2.10 (m, broad, 1H, H4eq), 2.38 (d×d, J(H6ax-H6eq) = 12.5 Hz, J(H6ax-H5ax) = 12.5 Hz, 1H, H6ax), 3.00 (m, broad, 1H, H3ax), 3.60 (s, 3H, 3-$COOCH_3$), 3.63 and 3.78 (2×s, 3H, 3-OCH_3), 3.84 (s, 3H, 4-OCH_3), 3.90 and 4.04 (2×d, broad, J(H6ax-H6eq) = 12 Hz, 1H, H6eq), 5.63 and 5.79 (2×d, J = 13 Hz, 2H,1-$COOC\underline{H}_2Ph$), 5.84 and 5.99 (2×d, J(H2eq-H3ax) = 5Hz, 1H, H2eq), 6.62-6.86 (m, 3H, PhH), 7.25-7.40 (m, 5H, 1-$COOCH_2PhH$) ; ^{13}C NMR ($CDCl_3$): 18.7 (CH_3), 30.1 and 30.4 (C-4), 30.8 and 31.2 (C-5), 44.1 and 45.0 (C-3), 47.2 (C-6), 51.7 ($COO\underline{C}H_3$), 53.6 and 54.0 (C-2), 55.7 and 55.7 (2×OCH_3), 67.2 ($O\underline{C}H_2Ph$), 110.8 (PhC-5), 111.5 and 111.7 (PhC-2), 119.7 and 119.8 (PhC-6), 127.7 (CH_2PhC-4), 127.9 (CH_2PhC-2), 128.4 (CH_2PhC-3), 130.6 and 130.79 (PhC-1), 136.7 (CH_2PhC-1), 148.1 (PhC-4), 148.9 (PhC-3), 155.0 and 155.5 ($\underline{C}OOCH_2Ph$), 172.7 and 172.9 ($\underline{C}OOCH_3$); m/z: 427 (7), 336 (6), 292 (100), 91 (61); exact mass for $C_{24}H_{29}NO_6$: 427.1995; found: 427.1987.

2-(4-methoxyphenyl)-5-methyl-1-[(phenylmethoxy)carbonyl]-*N*-trifluoroacetyl-3-piperidinamine (11a)

To 8 mmol of compound **10a** in 30 ml MeOH/H_2O (5:1) 40 mmol LiOH.H_2O was added. The reaction mixture was stirred at room temperature for 24 hours. After evaporation, 50 ml of 2*N* HCl and 50 ml CH_2Cl_2 was added . The organic layer was separated and the H_2O layer was extracted with CH_2Cl_2 (2×50 ml). The organic layer was dried on $MgSO_4$, filtered and evaporated. The obtained carboxylic acid derivative was dissolved in 30 ml dry CH_2Cl_2 and 16 mmol $SOCl_2$ and 9.6 mmol NEt_3 was added. After stirring for 8 hours at 80 °C, 50 ml water was added. The H_2O layer was extracted with CH_2Cl_2 (2×50 ml) and the organic layer was dried, filtered and evaporated. The residue was dissolved in 30ml CH_2Cl_2. and cooled down. A solution of 16 mmol NaN_3 in 5 ml water and 20 mg Bu_4NBr was added and the reaction mixture was stirred for 2 hours at 0 °C. The organic layer was separated and dried on $MgSO_4$, filtered

and 2 ml of dry CF_3COOH was added and the reaction mixture was refluxed for 6 hours. After reflux 30 ml water was added and the organic layer was washed with a saturated $NaHCO_3$ solution (2×20 ml). Drying on $MgSO_4$ and evaporating yielded the 2-(4-methoxyphenyl)-5-methyl-1-[(phenylmethoxy)carbonyl]-*N*-trifluoracetyl-3-piperidinamine **11a**.

Yield: 36 %; oil; IR (NaCl) cm^{-1}: 3430 and 3306 (br), 1698 (s), 1400-1100 (m); m/z: 451 (82), 407 (36), 338 (67), 253 (100), 209 (41), 91 (61).

2-(4-methoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]-5-methyl-3-piperidinamine (13a)

A solution of 2 mmol **11a** and 4 mmol K_2CO_3 in 15 ml MeOH/H_2O (1:1) was strirred for 60 hours at room temperature. After evaporating and adding 50 ml water and 100 ml CH_2Cl_2, the organic layer was extracted with CH_2Cl_2 (2×100 ml). The collected organic layers were dried on $MgSO_4$, filtered and evaporated. The crude 3-piperidinamine **12a** was dissolved in 20 ml methanol and 1 ml acetic acid; 2 mmol 2-methoxybenzaldehyde and 0.15 g Pd/C (10 % Pd) was added. After absorption of 2 equivalents of hydrogen gas the catalyst was filtered and washed with acetic acid (150 ml) and CH_2Cl_2 (150 ml). The solvents were evaporated and 50 ml water was added. The solution was brought to pH=10 by adding NH_4OH and extracted with CH_2Cl_2 (3×100 ml). The collected organic layers were dried on $MgSO_4$, filtered and evaporated. Purifying via column chromatography (Al_2O_3; $CHCl_3$/MeOH) yielded the 2-(4-methoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]-5-methyl-3-piperidinamine **13a**.

Yield: 82 %; m.p. (oxalate salt): 209 °C ((*i*-Pr)$_2$O, *i*-PrOH); IR (KBr) cm^{-1}: 3327 (br), 1243 and 1033 (m); ^{1}H NMR ($CDCl_3$): 1.15 (d, J(CH_3-H5ax) = 7 Hz, 3H, 5-CH_3), 1.53 (d×d×d, J(H4ax-H4eq) = 13 Hz, J(H4ax-H3ax) = 11 Hz, J(H4ax-H5eq) = 5 Hz, 1H, H4ax), 2.0-2.1 (m, broad, 2H, H4eq + H5eq), 2.73 (d×d×d, J(H4ax-H3ax) = 11 Hz, J(H2eq-H3ax) = 9 Hz, J(H4eq-H3ax) = 3.5 Hz, 1H, H3ax), 2.81 (d×d×d, J(H6ax-H6eq) = 11.5 Hz, J(H6eq-H5eq) = 2 Hz, J(H6eq-H4eq) = 2Hz, 1H, H6eq), 2.98 (d×d, J(H6ax-H6eq) = 11.5 Hz, J(H6ax-H5eq) = 3 Hz, 1H, H6ax), 3.35 (d, J(H2ax-H3ax) = 9 Hz, 1H, H2ax), 3.49 (s, 3H, 2-OCH_3), 3.49 and 3.71 (2×d, J = 13 Hz, 2H, NCH_2), 3.79 (s, 3H, 4-OCH_3), 6.71 (d, ^3J = 8 Hz, 1H, NCH_2PhH-3), 6.82 (d, ^3J = 8.5 Hz, 2H, PhH-3,5), 6.83 (d×d, ^3J = 8 Hz, 1H, NCH_2PhH-5), 7.02 (d, ^3J = 8 Hz, 1H, NCH_2PhH-6), 7.17 (d×d, ^3J = 8 Hz, 1H, NCH_2PhH-4), 7.21 (d, ^3J = 8.5 Hz, 2H, PhH-2,6); ^{13}C NMR ($CDCl_3$): 17.9 (CH_3), 28.4 (C-5), 36.4 (C-4), 46.2 (C-6), 52.0 (NCH_2), 53.9 (C-3), 54.5 (4-OCH_3), 55.0 (2-OCH_3), 67.1 (C-2), 109.7 (NCH_2PhC-3), 113.6 (PhC-3), 119.9 (NCH_2PhC-5), 127.8 (NCH_2PhC-1), 127.9 (NCH_2PhC-4), 128.8 (PhC-2), 129.7 (NCH_2PhC-6), 134.4 (PhC-1), 157.4 (NCH_2PhC-2), 158.8 (PhC-4); m/z: 340 (14), 219 (18), 205 (13), 190 (100), 136 (39); exact mass for $C_{21}H_{28}N_2O_2$: 340.2151; found: 340.2153; anal cald for $C_{21}H_{28}N_2O_2.C_2H_2O_4.H_2O$: C 61.59, H 7.19, N 6.25; found C 62.00, H 6.87, N 6.22.

2-aryl-5-methyl-1-[(phenylmethoxy)carbonyl]-3-piperidinecarboxamides (19a-c). General procedure:

To a suspension of 25 mmol NH_4Cl in 26 ml CH_2Cl_2 at -5 °C 12.5 ml of a 2 M solution $AlMe_3$ in hexanes was slowly added. After 1 hour stirring at room temperature a solution of 5 mmol methyl 5-methyl-1-[(phenylmethoxy)carbonyl]-2-aryl-3-piperidinecarboxylate **10a-c** in 10 ml CH_2Cl_2 was added and the solution was refluxed for 16 hours. After cooling down 100 ml 5 % HCl solution was carefully added. The H_2O layer was extracted with CH_2Cl_2 (3×100ml) and the collected organic layers were dried on $MgSO_4$. Evaporating of the solvent and column chromatography (SiO_2; EtOAc) yielded the amides **19a-c**.

2-(4-methoxyphenyl)-5-methyl-1-[(phenylmethoxy)carbonyl]-3-piperidinecarboxamide (19a)

Yield: 79 %; m.p.: 175-177 °C (EtOAc); IR (KBr) cm^{-1}: 3404, 3354, 3309 and 3256 (br), 1680 and 1663 (s); ^{1}H NMR ($CDCl_3$): 0.91 and 0.97 (d, J(CH_3-H5ax) = 6 Hz, 3H, 5-CH_3), 1.70 (m, 1H, H5ax), 1.76 (d×d×d, J(H4ax-H4eq) = 12.5 Hz, J(H4ax-H3ax) = 12.5 Hz, J(H4ax-H5ax) = 12.5 Hz, 1H, H4ax), 2.01 (m, broad, 1H, H4eq), 2.37 (d×d, J(H6ax-H6eq) = 12.5 Hz, J(H6ax-H5ax) = 12.5 Hz, 1H, H6ax), 2.84 (d×d×d, J(H4ax-H3ax) = 12.5 Hz, J(H2eq-H3ax) = 5.5 Hz, J(H4eq-H3ax) = 4.5 Hz, 1H, H3ax), 3.78 (s, 3H, OCH_3), 3.88 and 4.06 (d, broad, J(H6ax-H6eq) = 12.5 Hz, 1H, H6eq), 5.12 and 5.23 (2×d, J = 12.5, 1H, 1-COOC$\underline{H_2}$Ph), 5.16 (s, 1H, 1-COOC$\underline{H_2}$Ph), 5.73 and 5.86 (d, J(H2eq-H3ax) = 5.5 Hz, 1H, H2eq), 6.77 and 6.80 (d, ^3J = 8 Hz, 2H, NCH_2PhH-3,5), 7.18 and 7.30 (d, ^3J = 8 Hz, 2H, NCH_2PhH-4,6), 7.30-7.40

(m, 5H, 1-$COOCH_2PhH$); ^{13}C NMR ($CDCl_3$): 18.8 (CH_3), 30.3 (C-4), 31.0 and 31.3 (C-5), 45.0 (C-3), 46.1 and 46.4 (C-6), 54.2 and 54.4 (C-2), 55.1 (OCH_3), 67.4 ($O\underline{C}H_2Ph$), 113.8 (PhC-3), 127.7 (CH_2PhC-4), 128.0 (CH_2PhC-2), 128.5 (CH_2PhC-3), 129.3 and 129.6 (PhC-2), 129.5 (PhC-1), 136.6 and 136.7 (CH_2PhC-1), 158.7 (PhC-4), 155.2 and 155.6 ($\underline{C}OOCH_2Ph$), 174.2 ($\underline{C}ONH_2$); m/z: 382 (2), 247 (91), 91 (100); exact mass for $C_{22}H_{26}N_2O_4$: 382.1892; found: 382.1886.

5-methyl-2-phenyl-1-[(phenylmethoxy)carbonyl]-3-piperidinecarboxamide (19b)

Yield: 82 %; oil; IR (NaCl) cm^{-1}: 3409, 3354, 3308 and 3212 (br), 1680 and 1665 (s); ^1H NMR ($CDCl_3$): 0.90 and 0.97 (d, $J(CH_3$-H5ax) = 6 Hz, 3H, 5-CH_3), 1.72 (m, 2H, H4ax + H5ax), 1.97-2.07 (m, broad, 1H, H4eq), 2.37 and 2.41 (d×d, J(H6ax-H6eq) = 12.5 Hz, J(H6ax-H5ax) = 12.5 Hz, 1H, H6ax), 2.88 (d×d×d, J(H4ax-H3ax) = 12.5 Hz, J(H2eq-H3ax) = 5.5 Hz, J(H4eq-H3ax) = 4.5 Hz, 1H, H3ax), 3.90 and 4.08 (d, broad, J(H6ax-H6eq) = 12.5 Hz, 1H, H6eq), 5.12 and 5.21 (2×d, J = 12.5, 2H, 1-$COOC\underline{H}_2Ph$), 5.79 and 5.90 (d, J(H2eq-H3ax) = 5.5 Hz, 1H, H2eq), 7.20-7.40 (m, 10H, 2-PhH + 1-$COOCH_2PhH$); ^{13}C NMR ($CDCl_3$): 18.8 and 18.9 (CH_3), 30.3 (C-4), 31.0 and 31.4 (C-5), 45.0 (C-3), 46.4 and 46.6 (C-6), 54.7 and 54.9 (C-2), 67.5 ($O\underline{C}H_2Ph$), 127.5 (PhC-4), 127.7 (CH_2PhC-4), 128.0 (CH_2PhC-2), 128.1 (PhC-2), 128.5 (CH_2PhC-3), 128.6 (PhC-3), 136.7 (PhC-1), 137.4 and 137.8 (CH_2PhC-1), 155.3 and 155.8 ($\underline{C}OOCH_2Ph$), 173.9 and 174.0 ($\underline{C}ONH_2$); m/z: 352 (1), 217 (75), 91 (100); exact mass for $C_{21}H_{24}N_2O_3$: 352.1787; found: 352.1791.

2-(3,4-dimethoxyphenyl)-5-methyl-1-[(phenylmethoxy)carbonyl]-3-piperidinecarboxamide (19c)

Yield: 89 %; oil; IR (NaCl) cm^{-1}: 3348 and 3199 (br), 1675 (s); ^1H NMR ($CDCl_3$): 0.90 and 0.93 (2×d, $J(CH_3$-H5ax) = 6 Hz, 3H, 5-CH_3), 1.67 (m, br, 1H, H5ax), 1.75 (d×d×d, J(H4ax-H4eq) = 12.5 Hz, J(H4ax-H3ax) = 12.5 Hz, J(H4ax-H5ax) = 12.5 Hz, 1H, H4ax), 1.98 (m, broad, 1H, H4eq), 2.38 (d×d, J(H6ax-H6eq) = 12.5 Hz, J(H6ax-H5ax) = 12.5 Hz, 1H, H6ax), 2.84 (m, br, 1H, H3ax), 3.60 and 3.71 (2×s, 3H, 3-OCH_3), 3.79 (s, 3H,4-OCH_3), 3.90 and 4.05 (d, broad, J(H6ax-H6eq) = 12.5 Hz, 1H, H6eq), 5.07 and 5.24 (2×d, J = 13 Hz, 2H, 1-$COOC\underline{H}_2Ph$), 5.79 and 5.93 (2×d, J(H2eq-H3ax) = 5 Hz, 1H, H2eq), 5.29 and 6.56 (2×s, br, 2H, 3-$CONH_2$), 6.66-7.00 (m, 3H, PhH), 7.18-7.44 (m, 5H, 1-$COOCH_2PhH$); ^{13}C NMR ($CDCl_3$): 18.5 (CH_3), 30.2 (C-4), 30.6 and 31.0 (C-5), 44.7 (C-3), 46.0 and 46.1 (C-6), 54.1 and 54.4 (C-2), 55.4 and 55.4 (2×OCH_3), 67.0 ($O\underline{C}H_2Ph$), 110.7 (PhC-5), 111.8 (PhC-2), 119.7 and 120.2 (PhC-6), 127.3 (CH_2PhC-4), 127.7 (CH_2PhC-2), 128.2 (CH_2PhC-3), 129.5 and 130.1 (PhC-1), 136.5 (CH_2PhC-1), 147.9 (PhC-4), 148.6 (PhC-3), 154.9 and 155.4 ($\underline{C}OOCH_2Ph$), 174.6 ($\underline{C}ONH_2$); m/z: 412 (4), 277 (100), 91 (84); exact mass for $C_{23}H_{28}N_2O_5$: 412.1998; found: 412.2001.

2-(3,4-dimethoxyphenyl)-5-methyl-1-[(phenylmethoxy)carbonyl]-3-piperidinecarbonitrile (20c)

To a solution of 4 mmol hydroxy(tosyloxy)iodobenzene in 30 ml dry acetonitrile at 65 °C a solution of 4 mmol **19c** in 10 ml dry acetonitrile was added over 5 min. The reaction mixture was refluxed for 6 hours and 50 ml water and 100 ml CH_2Cl_2 was added. The organic layer was separated and extracted with CH_2Cl_2 (2×100 ml). The collected organic layers were dried on $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (Al_2O_3; $CHCl_3$).

Yield: 77 %; oil; IR (NaCl) cm^{-1}: 2253 (s), 1698 (s); ^1H NMR ($CDCl_3$): 0.93 (d, $J(CH_3$-H5ax) = 6 Hz, 3H, 5-CH_3), 1.71 (m, 1H, H5ax), 1.83 (d×d×d, J(H4ax-H4eq) = 12 Hz, J(H4ax-H3ax) = 12 Hz, J(H4ax-H5ax) = 12 Hz, 1H, H4ax), 2.09 (d×d×d, J(H4ax-H4eq) = 12 Hz, J(H4eq-H3ax) = 5 Hz, J(H4eq-H5ax) = 12 Hz, 1H, H4eq), 2.51 (d×d, J(H6ax-H6eq) = 13.5 Hz, J(H6ax-H5ax) = 11.5 Hz, 1H, H6ax), 3.17 (d×d×d, J(H4ax-H3ax) = 12 Hz, J(H2eq-H3ax) = 5 Hz, J(H4eq-H3ax) = 5 Hz, 1H, H3ax), 3.77 (s, br, 3H, 3-OCH_3), 3.89 (s, 3H, 4-OCH_3), 4.01 (d, broad, J(H6ax-H6eq) = 13.5 Hz, 1H, H6eq), 5.1-5.3 (m, 2H, 1-$COOC\underline{H}_2Ph$), 5.72 (d, J(H2eq-H3ax) = 5 Hz, 1H, H2eq), 6.83 (d, ^3J= 8 Hz, 1H, NCH_2PhH-5), 6.93 (br, 1H, NCH_2PhH-2), 7.06 (d, ^3J= 8 Hz, 2H, NCH_2PhH-6), 7.34 (m, 5H, 1-$COOCH_2PhH$); ^{13}C NMR ($CDCl_3$): 18.3 (CH_3), 30.6 (C-5), 31.0 (C-3), 31.8 (C-4), 45.9 (C-6), 52.9 (C-2), 55.7 and 55.7 (2×OCH_3), 67.6 ($O\underline{C}H_2Ph$), 110.8 (PhC-5), 111.4 (PhC-2), 119.8 (PhC-6), 119.9 (C≡N), 127.9 (CH_2PhC-2), 128.1 (CH_2PhC-4), 128.4 (PhC-1), 128.5 (CH_2PhC-3), 136.2 (CH_2PhC-1), 148.6 (PhC-4), 149.1 (PhC-3), 155.0 ($\underline{C}OOCH_2Ph$); m/z: 394 (11), 303 (19), 259 (93), 91 (100); exact mass for $C_{23}H_{26}N_2O_4$: 394.1892; found: 394.1887.

2-aryl-*N*-(*t*-butoxycarbonyl)-5-methyl-1-[(phenylmethoxy)carbonyl]-3-piperidinamines (21a-c). General procedure:

To a solution of 5 mmol of compounds **19a-c** in 40 ml dry *t*-BuOH at 50 °C, 5.2 mmol lead(IV)acetate was added and the reaction mixture was refluxed for 30 minutes. During 1 hour 5.2 mmol lead(IV)acetate was added in small portions. The reaction mixture was then poured into 100 ml cold 1*N* HCl solution. The water layer was extracted with ethyl acetate (3×100ml) and the collected organic layers were washed with water (50 ml), 5 % NaOH solution (50 ml), water and a saturated NaCl solution. After drying on $MgSO_4$ and evaporation, the pure product was obtained via column chromatography (Al_2O_3; $CHCl_3$).

***N*-(*t*-butoxycarbonyl)-2-(4-methoxyphenyl)-5-methyl-1-[(phenylmethoxy)carbonyl]-3-piperidinamine (21a)**

Yield: 72 %; m.p.: 170-172 °C; IR (KBr) cm^{-1}: 3430 and 3306 (br), 1702 and 1673 (s); ^1H NMR ($CDCl_3$): 1.00 (d, $J(CH_3\text{-}H5ax)$ = 6 Hz, 3H, 5-CH_3), 1.25-1.40 (m, br, 1H, H5ax), 1.41 (s, 9H, 3-NHCOO-*t*-C_4H_9), 1.88 (m, br, 2H, H4ax + H4eq), 2.78 (d×d, J(H6ax-H6eq) = 12 Hz, J(H6ax-H5ax) = 12 Hz, 1H, H6ax), 3.79 (s, br, 3H, 4-OCH_3), 4.08 (m, br, 1H, H3ax), 4.20 (m, 1H, broad, H6eq), 5.03 and 5.15 (2×d, J = 13 Hz, 2H, 1-COOC$\underline{H}_2$Ph), 5.45 (m, 1H, br, H2eq), 6.85 (d, 2H, ^3J = 8 Hz, PhH-3,5), 7.1-7.4 (m, 7H, 1-$COOCH_2$PhH + PhH-4,6); ^{13}C NMR ($CDCl_3$): 18.8 (5-CH_3), 28.4 (CH_3), 30.6 (C-5), 35.1 (C-4), 47.3 (C-6), 50.0 (C-3), 55.2 (OCH_3), 56.0 (C-2), 67.3 (O$\underline{C}H_2$Ph), 79.6 (COO$\underline{C}(CH_3)_3$), 114.0 (PhC-3), 127.8 (CH_2PhC-2), 128.4 (CH_2PhC-4), 128.4 (CH_2PhC-3), 130.4 (PhC-1), 130.4 (PhC-2), 136.9 (CH_2PhC-1), 159.2 (PhC-4), 154.9 ($\underline{C}OOCH_2$Ph), 155.7 (COO$\underline{C}(CH_3)_3$); m/z: 337 (25), 202 (10), 91 (100).

***N*-(*t*-butoxycarbonyl)-5-methyl-2-phenyl-1-[(phenylmethoxy)carbonyl]-3-piperidineamine (21b)**

Yield: 78 %; oil; IR (NaCl) cm^{-1}: 3408 and 3348 (br), 1686 (s); ^1H NMR ($CDCl_3$): 1.02 and 1.08 (2×d, $J(CH_3\text{-}H5ax)$ = 6 Hz, 3H, 5-CH_3), 1.3-1.4 (m, br, 1H, H5ax), 1.45 (s, 9H, 3-NHCOO-*t*-C_4H_9), 1.88 (m, br, 2H, H4ax + H4eq), 3.01 (d×d, J(H6ax-H6eq) = 12 Hz, J(H6ax-H5ax) = 12 Hz, 1H, H6ax), 3.98 (m, br, 1H, H3ax), 4.03 (m, broad, 1H, H6eq), 5.23 (s, br, 2H, 1-COOC$\underline{H}_2$Ph), 5.72 and 5.84 (d, J(H2eq-H3ax) = 5.5 Hz, 1H, H2eq), 7.3-7.7 (m, 10H, PhH + 1-$COOCH_2$PhH); m/z: 425 (1), 351 (42), 307 (86), 91 (100); exact mass for $C_{25}H_{32}N_2O_4$: 424.2362; found: 424.2362.

***N*-(*t*-butoxycarbonyl)-2-(3,4-dimethoxyphenyl)-5-methyl-1-[(phenylmethoxy)carbonyl]-3-piperidineamine (21c)**

Yield: 82 %; oil; IR (NaCl) cm^{-1}: 3439 and 3347 (br), 1701 (s); ^1H NMR ($CDCl_3$): 1.00 and 1.08 (2×d, $J(CH_3\text{-}H5ax)$ = 6 Hz, 3H, 5-CH_3), 1.3-1.4 (m, br, 1H, H5ax), 1.43 (s, 9H, 3-NHCOO-*t*-C_4H_9), 1.89 (m, br, 2H, H4ax + H4eq), 2.78 (d×d, J(H6ax-H6eq) = 12 Hz, J(H6ax-H5ax) = 12 Hz, 1H, H6ax), 3.69 (s, br, 3H, 3-OCH_3), 3.88 (s, 3H, 4-OCH_3), 4.05 (m, br, 1H, H3ax), 4.20 (m, broad, 1H, H6eq), 4.9-5.2 (m, br, 2H, 1-COOC$\underline{H}_2$Ph), 6.6-7.0 (m, 3H, PhH), 7.1-7.4 (m, 5H, 1-$COOCH_2$PhH); ^{13}C NMR ($CDCl_3$): 18.9 and 19.3 (5-CH_3), 28.3 (CH_3), 29.9 and 30.3 (C-5), 34.5 and 34.9 (C-4), 47.4 and 48.6 (C-6), 49.0 and 49.8 (C-3), 55.8 and 55.8 (2×OCH_3), 56.0 and 56.2 (C-2), 67.2 and 67.3 (O$\underline{C}H_2$Ph), 79.5 (COO$\underline{C}(CH_3)_3$), 111.0 and 112.0 (PhC-5), 113.0 and 113.4 (PhC-2), 120.5 (PhC-6), 127.8 and 127.9 (CH_2PhC-2), 128.2 (CH_2PhC-4), 128.3 (CH_2PhC-3), 131.0 (PhC-1), 136.5 and 136.6 (CH_2PhC-1), 147.6 (PhC-4), 148.5 (PhC-3), 154.8 ($\underline{C}OOCH_2$Ph), 155.7 (COO$\underline{C}(CH_3)_3$); m/z: 485 (1), 429 (7); 367 (4), 57 (100).

2-aryl-5-methyl-3- *N*-[(2-methoxyphenyl)methyl]-piperidinamine (1a-c). General procedure:

Four mmol **21a-c** was dissolved in 20 ml ethyl acetate and dry HCl gas was bubbled through the solution during 5 minutes. The reaction mixture was poured into 100 ml NH_4OH solution and extracted with CH_2Cl_2 (3×100 ml). The collected organic layers were dried on $MgSO_4$, filtered and evaporated. The obtained 3-piperidinamines were dissolved in 20 ml methanol and 1 ml acetic acid then 4 mmol 2-methoxybenzaldehyde and 0.3 g Pd/C was added. After absorption of 2 equivalents hydrogen gas, the catalyst was filtered and washed with acetic acid (150 ml) and CH_2Cl_2 (150 ml). The solvents were evaporated and H_2O (50 ml) was added. Dropwise adding of ammonium hydroxide (28 % NH_3 in H_2O) to pH=10 was followed by extraction with CH_2Cl_2 (3×100 ml). The collected organic layers were dried on $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (Al_2O_3; $CHCl_3$/MeOH).

2-(4-methoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]-5-methyl-3-piperidinamine (1a)

Yield: 75 %; m.p. (HCl-salt): 231 °C (*i*-Pr_2O/EtOH); IR (KBr) cm^{-1}: 3323 (br), 1033 and 1245 (m); ^1H NMR ($CDCl_3$): 1.13 (d, *J*(CH_3-H5ax) = 6.5 Hz, 3H, 5-CH_3), 1.73 (d×d×d, *J*(H4ax-H4eq) = 13.5 Hz, *J*(H4ax-H3ax) = 7.5 Hz, *J*(H4ax-H5ax) = 7.5 Hz, 1H, H4ax), 1.88 (d×d×d, *J*(H4ax-H4eq) = 13.5 Hz, *J*(H4eq-H3ax) = 4 Hz, *J*(H4eq-H5ax) = 4 Hz, 1H, H4eq), 1.90 (m, broad, 1H, H5ax), 2.74 (d×d, *J*(H6ax-H6eq) = 12.5 Hz, *J*(H6ax-H5ax) = 6.5 Hz, 1H, H6ax), 2.91 (d×d, *J*(H6ax-H6eq) = 12.5 Hz, *J*(H6eq-H5ax) = 4.5 Hz, 1H, H6eq), 3.10 (d×d×d, *J*(H4ax-H3ax) = 7.5 Hz, *J*(H2eq-H3ax) = 4 Hz, *J*(H4eq-H3ax) = 4 Hz, 1H, H3ax), 3.60 (s, 3H, OCH_3), 3.62 and 3.73 (2×d, *J* = 13.5, 2H, N-C<u>H</u>$_2$Ph), 3.78 (s, 3H, NCH_2Ph-OC<u>H</u>$_3$), 4.14 (d, *J*(H3ax-H2eq) = 4 Hz, 1H, H2eq), 6.74 (d, 1H, ^3J = 8 Hz, CH_2PhH-3), 6.83 (d×d, 1H, ^3J = 8 Hz, CH_2PhH-5), 6.85 (d, ^3J = 9 Hz, 2H, PhH-3,5), 7.10 (d, ^3J = 8 Hz, 1H, CH_2PhH-6), 7.15 (d×d, ^3J = 8 Hz, 1H, CH_2PhH-4), 7.39 (d, ^3J = 9 Hz, 2H, PhH-4,6); ^{13}C NMR ($CDCl_3$): 19.6 (5-CH_3), 28.9 (C-5), 34.7 (C-4), 46.7 (C-6), 49.7 (N<u>C</u>H_2PhOCH$_3$), 55.0 (NCH_2PhO<u>C</u>H$_3$), 55.2 (OCH_3), 56.0 (C-3), 60.3 (C-2), 110.2 (NCH_2PhC-3), 113.8 (PhC-3), 120.3 (NCH_2PhC-5), 127.9 (NCH_2PhC-4), 128.7 (NCH_2PhC-1), 129.3 (PhC-2), 129.5 (NCH_2PhC-6), 132.1 (PhC-1), 157.6 (NCH_2PhC-2), 158.7 (PhC-4); m/z: 340 (3), 219 (12), 190 (84), 121 (100); exact mass for $C_{21}H_{28}N_2O_2$: 340.2151; found: 340.2154; anal cald for $C_{21}H_{28}N_2O_2$.2HCl: C 61.02, H 7.31, N 6.78; found C 60.68, H 7.33, N 6.61.

***N*-[(2-methoxyphenyl)methyl]-5-methyl-2-phenyl-3-piperidinamine (1b)**

Yield: 68 %; oil; IR (NaCl) cm^{-1} : 3328 (br), 1242 and 1023 (m); ^1H NMR ($CDCl_3$): 1.18 (d, *J*(CH_3-H5ax) = 6.5 Hz, 3H, 5-CH_3), 1.83 (d×d×d, *J*(H4ax-H4eq) = 13.5 Hz, *J*(H4ax-H3ax) = 7.5 Hz, *J*(H4ax-H5ax) = 7.5 Hz, 1H, H4ax), 1.88 (d×d×d, *J*(H4ax-H4eq) = 13.5 Hz, *J*(H4eq-H3ax) = 4 Hz, *J*(H4eq-H5ax) = 4 Hz, 1H, H4eq), 1.90 (m, broad, 1H, H5ax), 2.38 (br, 1H, NH), 2.74 (d×d, *J*(H6ax-H6eq) = 12.5 Hz, *J*(H6ax-H5ax) = 6.5 Hz, 1H, H6ax), 2.91 (d×d, *J*(H6ax-H6eq) = 12.5 Hz, *J*(H6eq-H5ax) = 4.5 Hz, 1H, H6eq), 3.10 (d×d×d, *J*(H4ax-H3ax) = 7.5 Hz, *J*(H2eq-H3ax) = 4 Hz, *J*(H4eq-H3ax) = 4 Hz, 1H, H3ax), 3.60 (s, 3H, 2-OCH_3), 3.62 and 3.73 (2×d, *J* = 13.5, 2H, N-C<u>H</u>$_2$Ph), 4.14 (d, *J*(H3ax-H2eq) = 4 Hz, 1H, H2eq), 6.74 (d, ^3J = 8 Hz, 1H, CH_2PhH-3), 6.82 (d×d, ^3J = 8 Hz, 1H, CH_2PhH-5), 7.12-7.41 (m, 7H, CH_2PhH-4,6 + 2-PhH); ^{13}C NMR ($CDCl_3$): 18.8 (5-CH_3), 28.2 (C-5), 34.3 (C-4), 48.8 (C-6), 50.7 (N<u>C</u>H_2Ph), 54.7 (NCH_2PhO<u>C</u>H$_3$), 55.9 (C-3), 61.5 (C-2), 109.9 (CH_2PhH-3), 120.3 (CH_2PhC-5), 126.5 (PhC-4), 127.6 (CH_2PhC-4), 127.8 (PhC-2), 128.0 (PhC-3), 128.4 (CH_2PhC-1), 128.5 (CH_2PhC-6), 141.4 (PhC-1), 157.5 (CH_2PhC-2); m/z: 310 (5), 190 (100), 121 (57), 91 (47); exact mass for $C_{20}H_{26}N_2O$: 310.2045; found: 310.2044.

2-(3,4-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]-5-methyl-3-piperidinamine (1c)

Yield: 88 %; oil; IR (NaCl) cm^{-1}: 3325 (br), 2931(s), 1029 and 1243 (m); ^1H NMR ($CDCl_3$): 1.16 (d, *J*(CH_3-H5ax) = 7 Hz, 3H, 5-CH_3), 1.72-1.88 (m, 2H, H4ax + H4eq), 2.12 (m, br, 1H, H5ax), 2.35 (m, br, 1H, NH), 2.76 (d×d, *J*(H6ax-H6eq) = 13 Hz, *J*(H6ax-H5ax) = 7 Hz, 1H, H6ax), 2.88 (d×d, *J*(H6ax-H6eq) = 13 Hz, *J*(H6eq-H5ax) = 4.5 Hz, 1H, H6eq), 3.05 (d×d×d, *J*(H4ax-H3ax) = 7 Hz, *J*(H2eq-H3ax) = 4.5 Hz, *J*(H4eq-H3ax) = 4 Hz, 1H, H3ax), 3.58 (s, 3H, CH_2Ph-2-OC<u>H</u>$_3$), 3.60 and 3.70 (2×d, *J* = 13, 3-NH-C<u>H</u>$_2$Ph), 3.84 and 3.86 (2×s, 6H, 3,4-OCH_3), 4.05 (d, *J*(H3ax-H2eq) = 4 Hz, 1H, H2eq), 6.72 (d, 1H, ^3J = 8 Hz, 2-CH_2PhH-3), 6.83 (d, ^3J = 8 Hz, 1H, PhH-5), 6.85 (tr, ^3J = 8 Hz, 1H, CH_2PhH-5), 7.06 (d, ^4J = 2 Hz, PhH-2), 7.10 (d×d, ^3J = 8 Hz, ^4J = 2 Hz, 1H, CH_2PhH-6), 7.11 (d×d, ^3J = 8 Hz, ^4J = 2 Hz, 1H, PhH-6), 7.18 (tr×d, ^3J = 8 Hz, ^{4}J = 2 Hz, 1H, CH_2PhH-4); ^{13}C NMR ($CDCl_3$): 19.8 (5-CH_3), 28.6 (C-5), 34.2 (C-4), 46.7 (C-6), 50.8 (N<u>C</u>H_2PhOCH$_3$), 54.8 (NCH_2PhO<u>C</u>H$_3$), 55.8 (OCH_3), 55.8 (C-3), 61.0 (C-2), 109.9 (NCH_2PhC-3), 110.9 (PhC-5), 111.2 (PhC-2), 119.6 (PhC-6), 120.1 (NCH_2PhC-5), 127.9 (NCH_2PhC-4), 128.5 (NCH_2PhC-1), 129.5 (NCH_2PhC-6), 133.7 (PhC-1), 147.8 (PhC-3), 148.8 (PhC-4), 157.5 (NCH_2PhC-2); m/z: 370 (5), 235 (19), 190 (100), 121 (70); exact mass for $C_{22}H_{30}N_2O_3$: 370.2256; found: 370.2237.

3-bromomethyl-2,6-dichloro-5-phenylpyridine (22)

The oxazinone **6b** (0.01 mol) was refluxed in a commercially available 80 % (w/w) solution of propargyl bromide in toluene (4.5 g, 3.4 ml). After reaction, the solvent was distilled off and column chromatography followed by recrystallisation gave the corresponding pyridine **22**.

Yield: 92 %; m.p.: 97-100 °C (CH_2Cl_2/hexanes); IR (KBr) cm^{-1} : 2835 (m), 700 (m); ^1H NMR ($CDCl_3$): 4.57 (s, 2H, CH_2Br), 7.46 (m, 5H, PhH), 7.78 (s, 1H, pyH-4); ^{13}C NMR ($CDCl_3$): 27.9 (CH_2), 128.5 (PhC-4), 128.9 (PhC-3), 129.2 (PhC-2), 131.2 (C-3), 135.6 (PhC-1), 136.5 (C-5), 142.6 (C-4), 148.0 (C-2), 148.0 (C-6); m/z: 315 (12), 236 (100), 201 (9); exact mass for $C_{12}H_8BrCl_2N$: 314.9218; found: 314.9219.

***N*-[(2-methoxyphenyl)methyl]-trifluoroacetamide (23)**

Ethyl trifluoroacetate (9.2 mmol) was dissolved in 10 ml dry diethylether and stirred at 0 °C for 10 minutes. 2-Methoxybenzylamine (8.8 mmol) was added and the reaction mixture was stirred at the same temperature for one hour. After removal of the solvent, the residues were purified by fast column chromatography (SiO_2; $CHCl_3$) and a yellow crystalline compound was obtained. Yield: 98 %; m.p.: 68-69 °C (CH_2Cl_2/hexanes).

2,6-dichloro-3-[*N*-(2-methoxyphenyl)methyl]methylamino-5-phenylpyridine (25)

To a suspension of 80 % sodium hydride (2.8 mmol) in 2 ml dimethylformamide (DMF) a solution of 2-methoxybenzyl trifluoroacetamide **23** (2.8 mmol) in 5 ml of DMF was added dropwise at room temperature. When hydrogen evolution stopped, 3-bromomethyl-2,6-dichloro-5-phenylpyridine **22** (2.8 mmol) in 5 ml of DMF was added and the colour of the mixture changed from yellow to red. The reaction mixture was stirred at the same temperature overnight. The solvent was removed and the residue was subjected to column chromatography (SiO_2) and eluted with 20 % hexane in chloroform. Crude product **24** was refluxed for 1.5 hours in ethanol in the presence of a catalytic amount of sodium hydroxide yielding **25** quantitatively.

Yield: 69 %; oil; IR (NaCl) cm^{-1}: 3336 (br), 1602 (s); ^1H NMR ($CDCl_3$): 2.65 (s, 1H, NH), 3.72 (s, 3H, OCH_3), 3.80 (s, 2H, NCH_2Ph), 3.87 (s, 2H, $PyCH_2N$), 7.88 (s, 1H, pyH-4), 6.75-7.27 (m, 4H, NCH_2PhH), 7.35-7.50 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$): 48.8 (NCH_2Ph), 48.8 ($PyCH_2N$), 55.4 (OCH_3), 110.2 (NCH_2PhC-3), 120.2 (NCH_2PhC-4), 127.2 (NCH_2PhC-1), 128.0 (NCH_2PhC-6), 128.1 (PhC-3), 128.8 (NCH_2PhC-5), 129.0 (PhC-2), 130.0 (PhC-4), 133.4 (C-3), 135.6 (C-5), 136.3 (PhC-1), 141.5 (C-4), 146.0 (C-2), 147.6 (C-6), 157.5 (NCH_2PhC-2); m/z: 372 (7), 371 (14), 341 (4), 251 (52), 91 (100); exact mass for $C_{20}H_{18}Cl_2N_2O$:372.0796; found: 372.0760.

***N*-[(2-methoxyphenyl)methyl]-5-phenyl-3-piperidinemethanamine dihydrochloride (2)**

A mixture of compound **25** 1.0 g (2.7 mmol) and 0.74 g (5.4 mmol) K_2CO_3 in 25 ml of acetic acid was stirred under nitrogen atmosphere in the presenc of a mixture of catalysts (10 % (w/w) Pd/C; 20 % (w/w) $PtO_2.xH_2O$) for two days. The reaction mixture was diluted with water and filtered. The filtrate was neutralized with 5 % K_2CO_3 aqueous solution and extracted with chloroform (3×50 ml). The extract was dried over $MgSO_4$ and evaporated under reduced pressure. The residues were subjected to column chromatography (Al_2O_3) and eluted with 10 % methanol in chloroform. The product was converted into a hydrochloride salt by treating with a 6*N* HCl/isopropanol solution and further purified by recrystallisation in absolute ethanol.

Yield: 57 %; m.p.: 268-269 °C; ^1H NMR ($CDCl_3$): 1.55 (d×d×d, *J*(H4ax-H4eq) = 11 Hz, *J*(H4ax-H3ax) = 12 Hz, *J*(H4ax-H5ax) = 12 Hz, 1H, H4ax), 2.08 (d, *J*(H4ax-H4eq) = 11 Hz, 1H, H4eq), 2.55 (d×d×d×d, *J*(H3ax-H2ax) = 12 Hz, *J*(H3ax-H4ax) = 12 Hz, *J*(H3ax-H4eq) = 2 Hz, *J*(H3ax-H2eq) = 2 Hz, 1H, H3ax), 2.75 (d×d×d, *J*(H2ax-H2eq) = 11 Hz, *J*(H2ax-H1ax) = 12 Hz, *J*(H2ax-H3ax) = 12 Hz, 1H, H2ax), 2.83 (m, 1H, CCH_2N), 2.93 (m, 1H, CCH_2N), 2.95 (d×d×d, *J*(H6ax-H6eq) = 11 Hz, *J*(H6ax-H5ax) = 12 Hz, *J*(H6ax-H1ax) = 12 Hz, 1H, H6ax), 3.12 (d×d×d×d, *J*(H5ax-H4ax) = 12 Hz, *J*(H6ax-H5ax) = 12 Hz, *J*(H5ax-H4eq) = 2 Hz, *J*(H5ax-H6eq) = 2 Hz, 1H, H5ax), 3.27 (d, *J*(H6ax-H6eq) = 11 Hz, 1H, H6eq), 3.51 (d, *J*(H2ax-H2eq) = 11 Hz, 1H, H2eq), 3.83 (s, 3H, OCH_3), 4.10 (s, 2H, NCH_2Ph), 7.00-7.24 (m, 5H, NCH_2PhH), 7.28-7.55 (m, 5H, PhH), 9.38 (s, 2H, $=NH_2^+$, side chain), 9.64 (m, br, 1H, H1ax), 9.82 (d, br, *J*(H1ax-H1eq) = 9 Hz, 1H, H1eq); ^{13}C NMR ($CDCl_3$): 33.7 (C-4), 36.6 (C-3), 38.3 (C-5), 44.8 (C-6), 45.2 ($PyCH_2N$), 47.2 (C-2), 48.8 (NCH_2Ph), 55.6 (OCH_3), 111.1 (NCH_2PhC-3), 119.4 (NCH_2PhC-5), 120.3 (NCH_2PhC-1), 127.0 (PhC-3), 127.2 (NCH_2PhC-4), 128.7 (PhC-2), 130.8 (NCH_2PhC-6), 131.7 (PhC-4), 141.3 (PhC-1), 157.6 (NCH_2PhC-2); m/z: 310 (10), 189 (16), 173 (52), 160 (20), 121 (100), 91 (83); exact mass for $C_{20}H_{26}N_2O$: 310.2045; found: 310.2039; anal cald for $C_{20}H_{26}N_2O.2HCl$: C 62.66, H 7.36, N 7.31; found C 62.26, H 7.69, N 7.23.

2-aryl-3-bromomethyl-6-chloro-5-methylpyridine (26a-b). General procedure:

The oxazinones **7a-b** (0.01 mol) were dissolved in a commercially available solution of 80 % (w/w) propargyl bromide in toluene and stirred at 80 °C under nitrogen atmosphere untill the starting product had disappeared (TLC control). Toluene and excess of dienophile were evaporated under reduced pressure and the residue was purified by column chromatography (SiO_2; $CHCl_3$/EtOAc).

3-bromomethyl-6-chloro-2-(4-methoxyphenyl)-5-methylpyridine (26a)

Yield: 96 %; m.p.: 132-134 °C (CH_2Cl_2/hexanes); IR (KBr) cm^{-1}: 1608 (s), 1065 and 1249 (m); ^1H NMR ($CDCl_3$): 2.40 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.45 (s, 2H, CH_2Br), 6.98 (d, 2H, ^3J = 8.5 Hz, PhH-3,5), 7.58 (d, 2H, ^3J = 8.5 Hz, PhH-2,6), 7.66 (s, 1H, pyH-4); ^{13}C NMR ($CDCl_3$): 19.0 (CH_3), 30.4 (CH_2), 55.3 (OCH_3), 113.9 (PhC-3), 129.8 (C-5), 130.1 (PhC-2), 130.2 (C-3), 131.0 (PhC-1), 142.0 (C-4), 150.7 (C-6), 155.7 (C-2), 160.1 (PhC-4); m/z: 325 (7), 246 (100), 231 (26); exact mass for $C_{14}H_{13}BrClNO$: 324.9869; found: 324.9865.

3-bromomethyl-6-chloro-5-methyl-2-phenylpyridine (26b)

Yield: 88 %; m.p.: 72 °C (CH_2Cl_2/hexanes); IR (KBr) cm^{-1}: 3052 (m), 701 (m); ^1H NMR ($CDCl_3$): 2.38 (s, 3H, CH_3), 4.41 (s, 2H, CH_2Br), 7.39-7.49 (m, 3H, PhH), 7.54-7.63 (m, 2H, PhH), 7.66 (s, 1H, pyH-4); ^{13}C NMR ($CDCl_3$): 19.0 (CH_3), 29.9 (CH_2), 128.3 (PhC-2), 128.6 (PhC-3), 128.7 (PhC-4), 130.0 (C-3), 131.5 (C-5), 137.6 (PhC-1), 142.1 (C-4), 150.7 (C-6), 155.8 (C-2); m/z: 295 (5), 216 (100); exact mass for $C_{13}H_{11}BrClN$: 294.9764; found: 294.9767.

2-aryl-6-chloro-[*N*-(2-methoxyphenyl)methyl]-5-methyl-3-pyridinemethanamine (27a-b)

The pyridine **26a-b** was dissolved in EtOH an 4 equivalents 2-methoxybenzylamine were added. The reaction mixture was refluxed until all starting material had disappeared (4h). The solvent was evaporated and the residue was purified by column chromatography yielding **27a-b**.

6-chloro-2-(4-methoxyphenyl)-[*N*-(2-methoxyphenyl)methyl]-5-methyl-3-pyridinemethanamine (27a)

Yield: 88 %; oil; IR (NaCl) cm^{-1}: 3336 (br), 1033 and 1249 (m); ^1H NMR ($CDCl_3$): 2.40 (s, 3H, CH_3), 3.74 (s, 2H, $PyrCH_2NHC\underline{H}_2Ar$), 3.78 (s, 3H, 2-$OC\underline{H}_3$), 3.81 (s, 2H, $PyrC\underline{H}_2NHCH_2Ar$), 3.83 (s, 3H, 4-$OCH_3$), 6.80 (d, ^3J = 8 Hz, 1H, $NHCH_2PhH$-3), 6.84 (d×d, ^3J = 8 Hz, 1H, $NHCH_2PhH$-5), 6.88 (d, ^3J = 8.5 Hz, 2H, PhH-3,5), 7.13 (d, ^3J = 8 Hz, 1H, $NHCH_2PhH$-6), 7.21 (d×d, ^3J = 8 Hz, 1H, $NHCH_2PhH$-4), 7.42 (d, ^3J = 8.5Hz, 2H, PhH-2,6), 7.86 (s, 1H, pyH-4); ^{13}C NMR ($CDCl_3$): 19.0 (CH_3), 48.1 ($PyrCH_2NH\underline{C}H_2Ar$), 48.5 ($Pyr\underline{C}H_2NHCH_2Ar$), 55.2 ($OCH_3$), 55.2 ($OCH_3$), 110.2 ($NHCH_2PhC$-3), 113.6 (PhC-3), 120.4 ($NHCH_2PhC$-5), 125.8 ($NHCH_2PhC$-1), 128.8 ($NHCH_2PhC$-6), 130.0 ($NHCH_2PhC$-4), 130.0 (C-5), 130.2 (PhC-1), 130.3 (PhC-2), 130.8 (C-3), 141.2 (C-4), 149.5 (C-6), 156.1 (C-2), 157.5 ($NHCH_2PhC$-2), 159.7 (PhC-4) ; m/z: 382 (3), 261 (42), 136 (100); exact mass for $C_{22}H_{23}ClN_2O_2$: 382.1448; found: 382.1428.

6-chloro-[*N*-(2-methoxyphenyl)methyl]-5-methyl-2-phenyl-3-pyridinemethanamine (27b)

Yield: 85 %; oil; IR (NaCl) cm^{-1}: 3332 (br), 1029 and 1243 (m); ^1H NMR ($CDCl_3$): 2.38 (s, 3H, CH_3), 3.70 (s, 2H, $PyCH_2NHC\underline{H}_2Ar$), 3.72 (s, 2H, $PyC\underline{H}_2NHCH_2Ar$), 3.75 (s, 3H, OCH_3), 6.80 (d, ^3J = 8Hz, 1H, $NHCH_2PhH$-3), 6.83 (d×d, ^3J = 7.5 Hz, 1H, $NHCH_2PhH$-5), 7.09 (d×d, ^3J = 7.5 Hz, ^4J = 2 Hz, 1H, $NHCH_2PhH$-6), 7.19 (d×d×d, ^3J(H3-H4) = 8 Hz, ^{3}J (H4-H5) = 7.5 Hz, ^4J = 2 Hz, 1H, $NHCH_2PhH$-4), 7.31-7.39 (m, 3H, Ph-H), 7.46-7.53 (m, 2H, Ph-H), 7.74 (s, 1H, pyH-4); ^{13}C NMR ($CDCl_3$): 19.0 (CH_3), 48.8 ($PyCH_2NH\underline{C}H_2Ar$), 49.2 ($Py\underline{C}H_2NHCH_2Ar$), 55.1 ($OCH_3$), 110.2 ($NHCH_2PhC$-3), 120.3 ($NHCH_2PhC$-5), 127.8 ($NHCH_2PhC$-1), 128.0 (PhC-2), 128.1 ($NHCH_2PhC$-6), 128.3 ($NHCH_2PhC$-4), 128.9 (PhC-3), 129.7 (PhC-4), 130.6 (C-5), 132.4 (C-3), 138.5 (PhC-1), 140.9 (C-4), 149.0 (C-6), 156.1 (C-2), 157.5 ($NHCH_2PhC$-2); m/z: 352 (4), 231 (63), 136 (79), 91 (100); exact mass for $C_{21}H_{21}ClN_2O$: 352.1342; found: 352.1337.

2-aryl-*N*-[(2-methoxyphenyl)methyl]-5-methyl-3-piperidinemethanamine (3a-b). General procedure:

Five mmol of **27a-b** was dissolved in 30 ml acetic acid and 0.2 g $PtO_2.xH_2O$ was added. After absorption of 5 equivalents hydrogen gas the catalyst was filtered off and the residue was washed with acetic acid (150 ml) and CH_2Cl_2 (150 ml). The solvents were evaporated and 100 ml water was added. After adding of ammonium hydroxide (28 % NH_3

in H_2O) to pH=10 the solution was extracted with CH_2Cl_2 (3×100 ml). The collected organic layers were dried on $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (Al_2O_3; $CHCl_3$/MeOH) yielding **3a-b**.

2-(4-methoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]-5-methyl-3-piperidinemethanamine (3a)

Yield: 78 %; m.p. (dihydrochloride.ethanolate (1:1).monohydrate): 165 °C (EtOH); IR (NaCl) cm^{-1}: 3326 (br), 1245 and 1034 (m); ^1H NMR ($CDCl_3$): 1.00 (d, J(CH_3-H5ax) = 6.5 Hz, 3H, 5-CH_3), 1.43 (d×d×d, J(H4ax-H4eq) = 13 Hz, J(H4ax-H3ax) = 9 Hz, J(H4ax-H5ax) = 9 Hz, 1H, H4ax), 1.82 (d×d×d, J(H4ax-H4eq) = 13 Hz, J(H4eq-H3ax) = 5 Hz, J(H4eq-H5ax) = 5 Hz, 1H, H4eq), 1.85 (m, 1H, H5ax), 2.30 (m, 1H, H3ax), 2.40 (m, 2H, pipC$\underline{H}_2$N), 2.68 (d×d, J(H6ax-H6eq) = 12 Hz, J(CH6ax-H5ax) = 8.5 Hz, 1H, H6ax), 2.81 (d×d, J(H6ax-H6eq) = 12 Hz, J(CH6eq-H5ax) = 4 Hz, 1H, H6eq), 3.58 (d, J = 13, 1H, pipCH_2NC$\underline{H}_2$Ph), 3.67 (d, J = 13, 1H, pipCH_2NC$\underline{H}_2$Ph), 3.75 (s, 3H, NCH_2Ph-OC$\underline{H}_3$), 3.80 (s, 3H, 4-OCH_3), 4.13 (d, J(H3ax-H2eq) = 3.5 Hz, 1H, H2eq), 6.75-7.35 (m, 8H, Ar-H); ^{13}C NMR ($CDCl_3$): 19.7 (CH_3), 30.8 (C-5), 33.9 (C-4), 39.9 (C-3), 48.5 (C-6), 49.0 (pip$\underline{C}H_2$NHCH_2Ph), 52.1 (NH$\underline{C}H_2$Ph), 55.1 (OCH_3), 55.1 (OCH_3), 58.6 (C-2), 110.0 (NHCH_2PhC-3), 113.6 (PhC-3), 120.2 (NHCH_2PhC-5), 127.9 (NHCH_2PhC-4), 128.3 (NHCH_2PhC-1), 129.6 (NHCH_2PhC-6), 129.9 (PhC-2), 134.1 (PhC-1), 157.5 (NHCH_2PhC-2), 158.5 (PhC-4); m/z: 354 (16), 233 (18), 218 (54), 204 (61), 121 (100); exact mass for $C_{22}H_{30}N_2O_2$: 354.2307; found: 354.2316; anal cald for $C_{22}H_{30}N_2O_2.2HCl.H_2O.C_2H_6O$: exact C 58.75, H 8.22, N 5.71, found C 58.49, H 8.37, N 5.54.

***N*-[(2-methoxyphenyl)methyl]-5-methyl-2-phenyl-3-piperidinemethanamine (3b)**

Yield: 86 %; m.p. (hydrochloride salt): 181 °C (CCl_4); IR (NaCl) cm^{-1} : 3327 (br), 2922 (m); ^1H NMR ($CDCl_3$): 0.99 (d, J(CH_3-H5ax) = 6.5 Hz, 3H, 5-CH_3), 1.44 (d×d×d, J(H4ax-H4eq) = 13 Hz, J(H4ax-H3ax) = 9 Hz, J(H4ax-H5ax) = 9 Hz, 1H, H4ax), 1.70 (m, 1H, H5ax), 1.81 (d×d×d, J(H4ax-H4eq) = 13 Hz, J(H4eq-H3ax) = 5 Hz, J(H4eq-H5ax) = 5 Hz, 1H, H4eq), 2.26 (m, 1H, H3ax), 2.39 (m, 2H, pipC$\underline{H}_2$N), 2.68 (d×d, J(H6ax-H6eq) = 12 Hz, J(CH6ax-H5ax) = 8.5 Hz, 1H, H6ax), 2.78 (d×d, J(H6ax-H6eq) = 12 Hz, J(CH6eq-H5ax) = 4 Hz, 1H, H6eq), 3.55 (d, J = 13 Hz, 1H, pipNC$\underline{H}_2$Ph), 3.62 (d, J = 13Hz, 1H, NC$\underline{H}_2$Ph), 3.72 (s, 3H, 2-OCH_3), 4.07 (d, J(H3ax-H2eq) = 5 Hz, 1H, H2eq), 6.76 (d, ^3J = 8 Hz, 1H, NCH_2PhH-3), 6.82 (d×d, ^3J = 7.5 Hz, 1H, NCH_2PhH-5), 7.04 (d×d, ^3J = 7.5 Hz, ^4J = 2 Hz, 1H, NCH_2PhH-6), 7.16 (d×d×d, ^3J = 7.5 Hz, ^3J = 8 Hz, ^4J = 2 Hz, 1H, NCH_2PhH-4), 7.2-7.4 (m, 5-H, 2-Ph-H); ^{13}C NMR ($CDCl_3$): 19.7 (CH_3), 30.9 (C-5), 34.0 (C-4), 40.0 (C-3), 49.0 (C-6), 49.1 (pip$\underline{C}H_2$NHCH_2Ph), 52.0 (pipCH_2NH$\underline{C}H_2$Ph), 55.0 (OCH_3), 59.6 (C-2), 109.9 (NHCH_2PhC-3), 120.2 (NHCH_2PhC-5), 126.6 (PhC-4), 127.8 (NHCH_2PhC-4), 128.4 (NHCH_2PhC-1), 128.1 (PhC-2), 128.5 (PhC-3), 129.4 (NHCH_2PhC-6), 142.9 (PhC-1), 157.3 (NHCH_2PhC-2); m/z: 324 (1), 203 (10), 188 (17), 174 (32), 121 (100); exact mass for $C_{21}H_{28}N_2O$: 324.2202; found: 324.2209; anal cald for $C_{21}H_{28}N_2O.2HCl.2H_2O$: exact C 58.31, H 7.93, N 6.48; found C 58.58, H 7.57, N 6.32.

2-[*N*-(2-methoxyphenyl)methyl]-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine (30-31). General procedure:

The pyridine **29** was prepared from the oxazinone **7c** by a procedure described previously for the preparation of **28** from **6b**[21].

6-chloro-3,4-bis(chloromethyl)-2-(3,4-dimethoxyphenyl)-5-methylpyridine (29)

Yield: 87 %; m.p.: 161 °C (CH_2Cl_2); IR (KBr) cm^{-1}: 2937 (m), 720 and 697 (m); ^1H NMR ($CDCl_3$): 2.55 (s, 3H, CH_3), 3.95 and 3.96 (2×s, 6H, 2×OCH_3), 4.69 (s, 2H, 3-CH_2Cl), 4.83 (s, 2H, 4-CH_2Cl), 6.97 (d, ^3J = 8 Hz, 1H, PhH-5), 7.23 (d, ^4J = 2 Hz, 1H, PhH-2), 7.25 (d×d, ^3J = 8 Hz, ^4J = 2 Hz, 1H, PhH-6); ^{13}C NMR ($CDCl_3$): 15.6 (CH_3), 38.3 (4-CH_2), 40.8 (5-CH_2), 55.9 (OCH_3), 55.9 (OCH_3), 111.0 (PhC-5), 112.1 (PhC-2), 121.6 (PhC-6), 127.9 (C-5), 130.5 (C-3), 130.7 (PhC-1), 147.1 (C-4), 148.7 (PhC-4), 149.7 (PhC-3), 152.2 (C-2), 157.5 (C-6); m/z: 359 (100), 324 (65), 293 (39); exact mass for $C_{16}H_{16}Cl_3NO_2$: 359.0247; found: 359.0247.

2-[*N*-(2-methoxyphenyl)methyl]-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridines (30-31)

A mixture of **28** or **29** (2.0 mmol), K_2CO_3 (4.4 mmol) and 2-methoxybenzylamine (2.2 mmol) in THF (30ml) was refluxed under nitrogen atmosphere for 3 hours. Upon cooling, the solvent was removed by evaporation. Water was

added and the mixture was extracted with chloroform (3×100 ml). The extract was dried over $MgSO_4$, evaporated and the residue was purified by column chromatography (SiO_2; 2 % EtOAc/ $CHCl_3$) yielding **30** and **31**.

4,6-dichloro-2-[*N*-(2-methoxyphenyl)methyl]-7-phenyl-2,3-dihydro-1*H*-pyrrolo[3,4-c]pyridine (30)

Yield: 76 %; oil; IR (NaCl) cm^{-1}: 1588 (s); ^1H NMR ($CDCl_3$): 3.78 (s, 3H, OCH_3), 3.90 (s, 2H, 3-H), 3.90 (s, 2H, N-CH_2-Ar), 4.07 (s, 2H, 1-H), 6.84-7.26 (m, 4H, NCH_2PhH), 7.23-7.41 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$): 52.9 (N$\underline{C}H_2$Ph), 55.2 (OCH_3), 56.6 (C-3), 58.9 (C-1), 110.3 (NCH_2PhC-3), 120.3 (NCH_2PhC-5), 125.2 (NCH_2PhC-1), 128.4 (NCH_2PhC-4), 128.4 (PhC-3), 128.6 (PhC-2), 128.6 (PhC-4), 130.1 (NCH_2PhC-6), 130.6 (C-3a), 131.4 (PhC-1), 134.2 (C-7), 142.0 (C-7a), 148.9 (C-6), 154.2 (C-4), 157.2 (NCH_2PhC-2); m/z: 384 (5), 353 (2), 263 (41), 121 (85); exact mass for $C_{21}H_{18}Cl_2N_2O$: 384.0796; found: 384.0691 (unstable).

2,3-dihydro-6-chloro-4-(3,4-dimethoxyphenyl)-2-[*N*-(2-methoxyphenyl)methyl]-7-methyl-1*H*-pyrrolo[3,4-c]pyridine (31)

Yield: 78 %; m.p.: 134-136 °C (CH_2Cl_2/hexanes); IR (KBr) cm^{-1}: 1588 (s); ^1H NMR ($CDCl_3$): 2.23 (s, 3H, CH_3), 3.82, 3.88 and 3.91 (3×s, 9H, 3×OCH_3), 3.95 (s, 4H, H-3 + N$\underline{C}H_2$Ph), 4.17 (s, 2H, H-1), 6.8-7.4 (m, 7H, NCH_2PhH + PhH); ^{13}C NMR ($CDCl_3$): 53.2 (N$\underline{C}H_2$Ph), 55.3 (OCH_3), 55.7 (OCH_3), 55.7 (OCH_3), 57.5 (C-3), 58.6 (C-1), 110.4 (NCH_2PhC-3), 110.8 (PhC-5), 111.1 (PhC-2), 120.4 (NCH_2PhC-5), 120.5 (PhC-6), 124.2 (NCH_2PhC-1), 126.1 (C-7), 128.4 (NCH_2PhC-6), 130.1 (NCH_2PhC-4), 130.8 (PhC-1), 132.0 (C-3a), 148.8 (C-7a), 149.0 (PhC-4), 149.5 (PhC-3), 152.8 (C-6), 157.3 (C-4), 157.3 (NCH_2PhC-2); m/z: 424 (20), 303 (74), 121 (100); exact mass for $C_{24}H_{25}ClN_2O_3$: 424.1554; found: 424.1526

2-[*N*-(2-methoxyphenyl)methyl]-7-phenyl-tetrahydro-1*H*-pyrrolo[3,4-c]piperidine (4)

A mixture of compound **30** (1.0 g, 2.6 mmol) and K_2CO_3 (0.72 g, 5.4 mmol) in 25 ml acetic acid was stirred under nitrogen atmosphere in the presence of a mixture of catalysts (10 % Pd/C, 100 mg; $PtO_2x.H_2O$, 200 mg) for six days. The same workup procedure as for **3a-b** was followed.

Yield: 22 %; oil; ^1H NMR ($CDCl_3$): 1.80 (br, NH), 2.26 (d×d, ^2J = 10 Hz, ^3J(H1-H(7a)eq) = 10 Hz, 2H, H-1), 2.35 (m, 1H, H(3a)ax), 2.43 (d, ^2J = 10 Hz, 1H, H-3), 2.65 (m, 1H, H(7a)eq), 2.78 (d×d, ^2J = 10 Hz, J(H3-H(3a)ax) = 5 Hz, 1H, H-3), 2.82 (d×d, ^2J = 12 Hz, J(H4ax-H(3a)ax) = 12 Hz, 1H, H4ax), 2.88 (d×d, ^2J = 10 Hz, J(H1-H(7a)eq) = 8 Hz, 1H, H-1), 2.96 (d×d, ^2J = 12 Hz, J(H6ax-H7ax) = 12 Hz, 1H, H6ax), 3.08 (d×d, ^2J = 12 Hz, J(H4eq-H(3a)ax) = 6 Hz, 1H, H4eq), 3.15 (d×d, ^2J = 12 Hz, J(H6eq-H7ax) = 5 Hz, 1H, H6eq), 3.33 (d×d×d, J(H7ax-H6ax) = 12 Hz, J(H7ax-H6eq) = 5 Hz, J(H7ax-H(7a)eq) = 5 Hz, 1H, H7ax), 3.78 (s, 3H, OCH_3), 3.80 (s, 2H, N$\underline{C}H_2$Ph), 6.80-7.10 (m, 4H, N$\underline{C}H_2$PhH), 7.08-7.31 (m, 5H, PhH); ^{13}C NMR ($CDCl_3$): 38.0 (C-3), 41.7 (C-5), 42.3 (C-4), 45.1 (C-6), 47.6 (C-2), 51.7 (C-1), 54.4 (N$\underline{C}H_2$Ph), 55.2 (OCH_3), 57.5 (C-3), 110.1 (NCH_2PhC-3), 120.1 (NCH_2PhC-1), 120.3 (NCH_2PhC-5), 126.1 (NCH_2PhC-4), 128.4 (NCH_2PhC-5), 127.0 (PhC-2), 128.3 (PhC-3), 129.8 (PhC-4), 142.5 (PhC-1), 157.2 (NCH_2PhC-2); m/z: 322 (26), 321 (4), 215 (12), 201 (39), 121 (99), 91 (100); exact mass for $C_{21}H_{26}N_2O$: 322.2045; found: 322.2043

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