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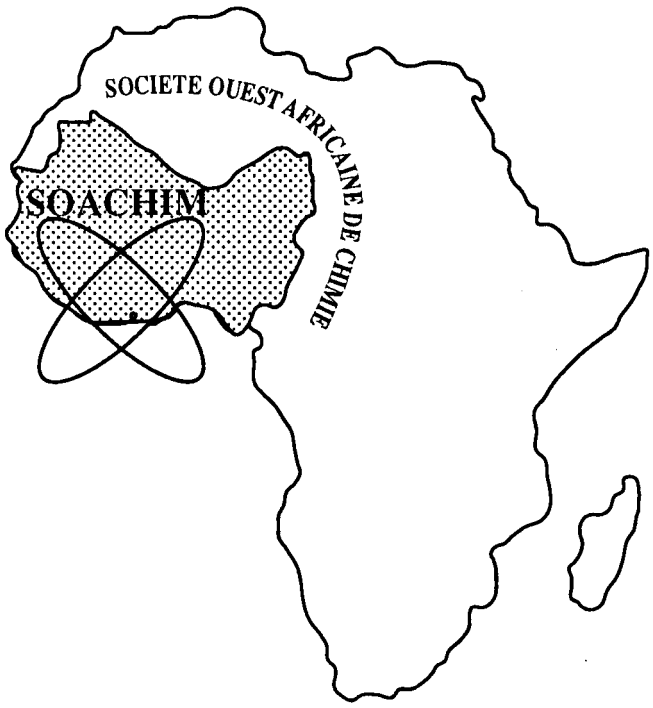

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Synthesis of *N*-Substituted piperidines from piperidone

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Abstract : A reductive amination reaction between *N*-boc-piperidin-4-one and 3,4-dichloroaniline was successfully employed for the synthesis of the *N*-(3,4-dichloropheny)-*N*-(2-phenoxylethyl) piperidin-4-amine. The synthesis of a small set of derivatives of this promising scaffold modified on the piperidine nitrogen is also reported. Three-carbon modified derivatives were synthesized using a simple aza-Michael reaction with acrylonitrile and *tert*-butyl acrylate, whereas two-carbon elongation products were obtained by alkylation with bromoacetonitrile, 2-iodoethanol and 2-chloro-*N*, *N*-dimethylethylamines.

Key words:Piperidine, Reductive amination, Hydrogenation, Nucleophilic substitution, Aza-Michael reaction.

Synthèse de pipéridines N-substituées dérivées de la pipéridone

Résumé: Une réaction d'amination réductrice entre la*N*-Boc-pipéridin-4-one et la 3,4-dichloroaniline a été employée avec succès pour la synthèse de la*N*-(3,4-dichloropheny)-*N*-(2-phenoxylethyl) piperidin-4-amine **1**. La synthèse d'un ensemble de petites molécules dérivées de ce composé prometteur modifié sur l'azote de la pipéridine est aussi rapportée. Des dérivés modifiés à trois carbones ont été synthétisés avec une réaction de type d'aza-Michael simple utilisant l'acrylonitrile et l'acrylate de *tert*-butyle, tandis que des produits d'allongement à deux carbones ont été obtenus par alkylation avec le bromoacétonitrile, le 2-iodoéthanol et la 2-chloro-*N*, *N*-diméthyléthylamine.

Mots clés: Pipéridine, Amination réductrice, Hydrogénation, Substitution nucléophile, Réaction Aza-Michael.

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1. Introduction

The 4-arylaminopiperidine is a structural moiety located in many alkaloids [1-8] and pharmaceutical products such as Fentanyl and structurally related analgesic opioids or H1-antihistamines agents such as Bamipine [9-15] and Neurokinin 1 (NK1) receptor antagonists [16-18]. Studies have shown that compounds with piperidine ring [19] have selectivity for NK1 receptor over NK2, NK3, opioid and 5-HT receptors.

There is more than one ligand-binding domain on the NK 1 receptor for the non-peptide antagonists, and these binding domains can be found in various places. The main ligand binding site is in the hydrophobic core between the loops and the outer segments of transmembrane domains 3–7 (TM3–TM7) [20].

The routes research [21-23] are being pursued for the discovery of new antidepressants with less side effects, a faster onset of action and a better rate of response.

In the process of searching for new small molecules interacting with the central nervous system, we have identified the *N*-(3,4-dichloropheny)-*N*-(2-phenoxylethyl)piperidin-4-amine (Figure 1) as a promising scaffold. We report herein the synthesis of a new derivatives with as potential antidepressants NK1 antagonists [24-28].

2. Methodology

To improve the interaction of parent compound **1**within the binding site of the NK1 receptor, we chose to add functional groups such as alcohol, amine or carboxylic acid groups on the nitrogen atom of the piperidine nucleus through a two- or three-carbon linker. Alternatively, the coupling of phenylalanine to 1 by a direct amide bond or a diamino linker allowed to design new compounds with an additional polar functional group and a hydrophobic phenyl ring to fill the hydrophobic space.

3. Results and discussions

The key compound **1** has been synthesized through a four-step process according to the Scheme 1. Thus, reductive amination [29-32] of *N*-boc-piperidin-4-one **2** with 3,4-dichloroaniline **3**in $(CH_2Cl)_2$, gave compound **4** in 72% yield. Acylation of the sodium salt of **4** with phenoxyacetyl chloride in DMF at 0 °C furnished compound **5** (72%). Reduction [33-35] of the amide **5** with diborane in THF gave the product **6** (99%). Final deprotection [36, 37] of **6**usingtrifluoroacetic acid at room temperature provided compound **1** (98%) (**Figure2**).

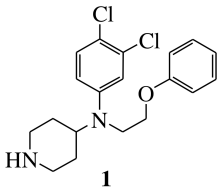

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Figure 1: Compound **1**

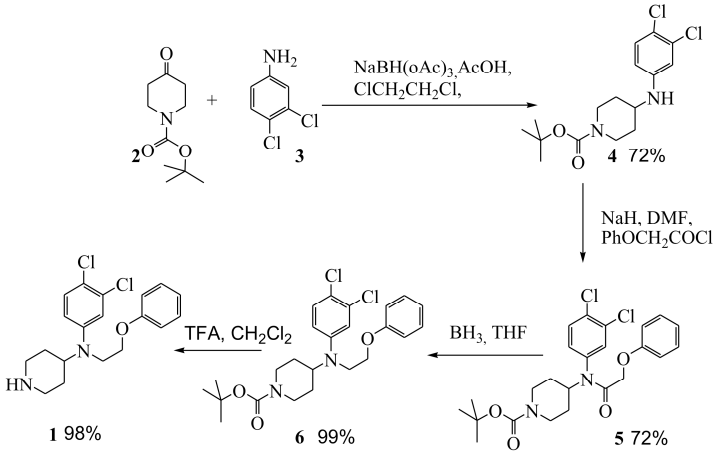

Figure 2: Synthesis of compound **1**

A pharmaco-modulation has been achieved on the parent molecule **1** taking into profit the nucleophilicity of the piperidine nitrogen leading to compounds (**7**-**14**) with good yield. Thus, the aza-Michael addition of **1** with *tert*-butyl acrylate followed by deprotection with trifluoroacetic acid gave compound **7** (79%). In a similar manner, addition of **1**to acrylonitrile followed by catalytic hydrogenation [38, 39] using Raney nickel as catalyst delivered the compound **8** (81%) (**Figure3**). The coupling agents (DCC, EDCI etc.) give poor yields or choice the mixed of ethyl chloroformate.

The coupling reaction of a phenylalanine residue directly or through a three-carbon linker was next envisioned. The synthesis of **10** required the formation of a simple peptide bond between acid **7** and phenylalanine. However, attempts to perform this reaction did not meet any success in spite of the use of several methods previously described in the literature [40-45]. We therefore turned to an alkylation process using the 3-bromopropionamide **9** easily available in high yield through acylation of (*R*, *S*)-phenylalanine *t*-butyl ester with 3-bromopropionyl chloride. Thus condensation of **1** with bromoamide**9** using Triton B [46-48] followed by deprotection of the ester function with trifluoroacetic acid gave, after recrystallization, **10** (78%). The amide bond formation between the *N*-protected phenylalanine and **1,** followed by amine function deprotection using TFA provided compound **11** (86%) (**Figure4**).

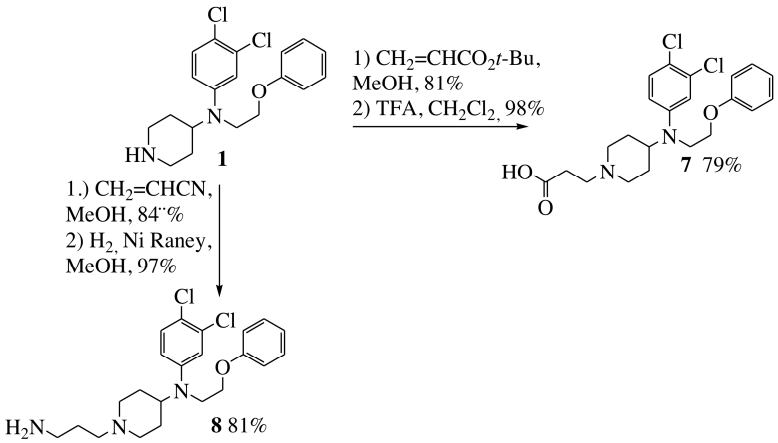

Figure 3: synthesis of compound**7** and **8**

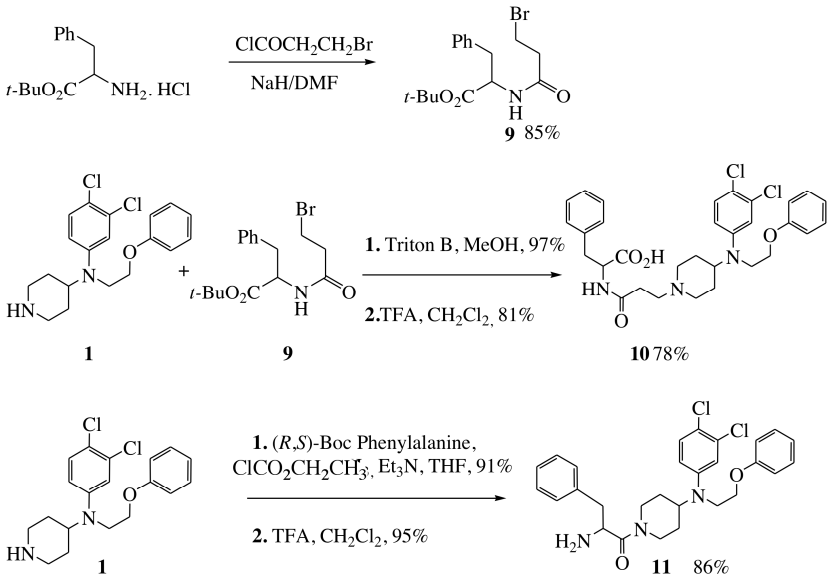

Figure 4: synthesis of compound **10** and **11**

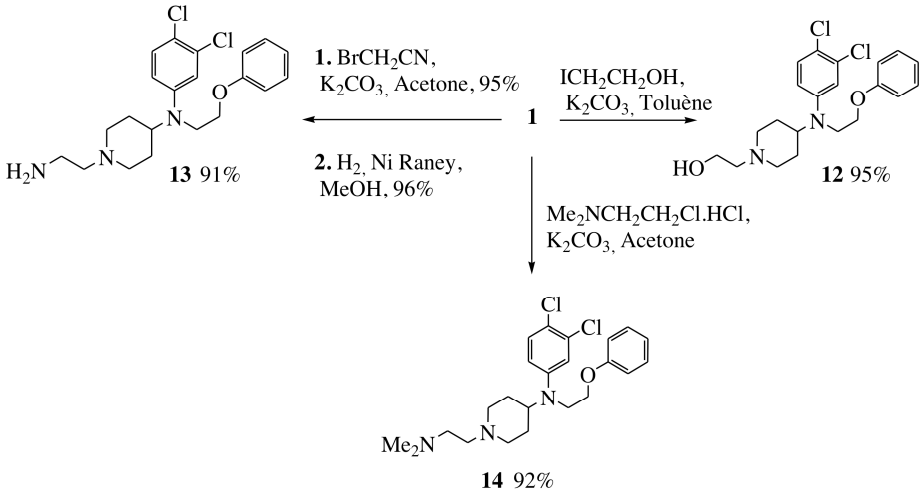

Figure 5: synthesis of compound **12-14**

Two-carbon linkers were introduced on the piperidine nitrogen using alkylation reaction with bromoacetonitrile, 2-iodoethanol and 2-chloro-*N*,*N*-dimethylethylamine to give respectively compounds **12** (95%), **13** (91%) and **14** (92%)(**Figure 5**).

4. Conclusion

In this study, we have prepared a small set of new nitrogen heterocycles displaying the *N*-(3,4-dichloropheny)-*N*-(2-phenoxylethyl) piperidin-4-amine scaffold using a flexible chemistry.
Seven new derivatives were prepared in good yield. Biological evaluation of these compounds is currently under investigation in our laboratory and will be described in due course.

Experimental section

The ^{1}H and ^{13}C spectra were recorded in $CDCl_3$ at ambient temperature on a Bruker AMX 300 spectrometer. Some products secured by DEPT 135, HMQC and HMBC experiments. Chemical shifts are given in δ (ppm) and coupling constants J (Hz) relative to TMS as internal standard; multiplicities were recorded as s (singlet), d (doublet), dd (double doublet), t (triplet), dt (double triple), q (quartet) or m (multiplet). Reactions involving anhydrous conditions were conducted in dry glassware under a nitrogen atmosphere. The infrared spectra have been recorded on a spectrometer Perkin-Elmer 842 (reference: polystyrene). The melting point have been measured on a Tottoli S Bucchi device. The microanalysis has been done on a Perkin-Elmer 2400-CMN apparatus. GC/MS conditions: Analyses were performed using a 5890 gas chromatogram connected to a G 1019 A mass spectrometer (both from Hewlett Packard) operating in the electro spray ionization mode (ESI).

tert-Butyl 4-(3,4-dichlorophenylamino)piperidine-1-carboxylate (4).

A solution of 3,4-dichloro aniline (3.25 g, 20 mmol) in 1,2-dichloroethane (100 mL) containing *t*-butyl-4-oxo-1-piperidine carboxylate (4 g, 20 mmol), sodium triacetoxyborohydride (6.3 g, 30 mmol) and acetic acid (1.71 mL, 30 mmol) was stirred for 24 h at 20 °C. 1N NaOH (50 mL, 50 mmol) and 50 mL of ethyl acetate were added. The phases were separated and the aqueous layer was extracted with ethyl acetate (3x25 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by crystallization (ether petroleum / ethyl acetate (8/2)).Yield: 4.99 g (72%). Mp = 157°C. IR cm^{-1}: 3337(NH); 1727.32 (CO carbamate). MS (ESI) m/z: 346.0[M+H] $^{+}$. ^{1}H NMR($CDCl_3$, 250MHz): 1.42 (s, 9H, $C(CH_3)_3$); 1.56 - 1.82 (m, 4H, $2xCH_2$); 2.65 (m, 1H, CH); .28-3.38 (m, 4H, $2xCH_2$); 4.10 (br s, 1H, NH); 6.35 - 7.20 (m, 3HAr). ^{13}C NMR($CDCl_3$, 62.5MHz) □: 28.50 (3 x CH_3, $C(CH_3)_3$); 32.20 (2 x CH_2); 42.70 (2 x CH_2); 50.20 (CH); 79.80 (C, $C(CH_3)_3$; 113.00 CHAr; 114.10 CHAr; 119.70 C; 130.70 CHAr; 132.90 C; 146.40C; 155.10 (CO carbamate).

tert-Butyl 4-(*N*-(3,4-dichlorophenyl)-2-phenoxyacetamido) piperidine-1-carboxylate (5).

To an ice-cooled suspension of sodium hydride (60% in mineral oil, 0.522g, 13.05 mmol) in DMF (10 mL) was added dropwise a solution of compound **4** (3.0 g, 8.7 mmol), in DMF (15 mL). After stiring 1 hour phenoxyacethylchloride (3 mL, 21.75 mmol) was added. The reaction mixture was stirred for additionnal hours at 0 °C, and the temperature was raised to room temperature. 10 mL

water was carrefully added. The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over $MgSO_4$, and concentrated in vacuum. The crude product was purified by crystallisation (ether petroleum / ethyl acetate (8/2)). Yield: 3.02 g (72%). Mp = 170 °C. IR cm^{-1}:1727.5 (CO carbamate); 1693.33 (CO amide). MS (ESI) m/z: 479.5 $[M+H]^+$; 496.5 $[M+NH_4]^+$. ^1H NMR($CDCl_3$, 250MHz): 1.42 (s, 9H, $C(CH_3)_3$); 1.50 - 1.75 (m, 4H, 2xCH_2); 3.30 – 3.40 (m, 4H, 2xCH_2); 3.65 (m, 1H, CH); 4.30 (s, 2H, CH_2); 6.70 - 7.60 (m, 8HAr). ^{13}C NMR ($CDCl_3$, 62.5MHz): 27.70 (3 x CH_3, $C(CH_3)_3$); 29.60 (2x CH_2); 42.30(2x CH_2); 52.60 CH; 66.30 CH_2; 79.20 (C, $C(CH_3)_3$); 114.00 (2xCHAr); 121.00 C; 128. 70 CHAr; 128.80 (2xCHAr); 130.60 CHAr; 131.20;CHAr; 132.90CHAr; 133.20 C;135.80 C; 153.80 C; 157.00(CO amide); 166.50 (CO carbamate).

tert-Butyl 4-((3,4-dichlorophenyl) (2-phenoxyethyl)amino)piperidine-1-carboxylate(6).

A solution of compound **5** (1.0 g, 2.08 mmol) in THF (10mL) was added BH_3 (1M in THF) (0.45 g 5.2 mmol) at 0°C. The reaction mixture was stirred for 2h at 20 °C, filtered, and then concentrated in vacuum. The residual is taken in 20 mL of ethyl acetate, washed successively with a saturated solution of NaCl (2x10 mL) and water (2x10 mL). The organic phase was dried over $MgSO_4$ filtered and concentrated under reduced pressure. The residue was purified by column chromatography (ether petroleum / ethyl acetate (8/2)). Yield: 0.96g (99%). IR cm^{-1}: 1727.35 (CO carbamate). MS (ESI) m/z: 466.0 $[M+H]^+$. Rf: 0.4 (ether petroleum / ethyl acetate (80/20)).^1H NMR ($CDCl_3$, 250MHz): 1.42 (s, 9H, $C(CH_3)_3$); 1.56 - 1.82 (m, 4H, 2xCH_2); 2.65 (m, 1H, CH); 3.30 – 3.40 (m, 4H, 2xCH_2); 3.67 (t, J = 6.39 Hz, 2H, CH_2); 4.00 (t, 2H, J = 6.39 Hz, CH_2); 6.70 - 7.60 (m, 8HAr). ^{13}C NMR ($CDCl_3$, 62.5MHz): 27.73 (3 x CH_3, $C(CH_3)_3$); 30.13 (2x CH_2); 44.05 (2x CH_2); 44.78 CH_2; 56.99 CH; 66.35 CH_2; 80.14 (C, $C(CH_3)_3$); 114.99 (2xCHAr); 115.46 CHAr; 121.45 CHAr; 122.67 C; 129.67 CHAr; 129.88 (2x CHAr); 129.95 CHAr; 134.30 C; 147.16 C; 155.01 C; 159.04 (CO carbamate).

4-(3,4-Dichlorophenyl)amino-_N_-(2-phenoxylethyl)piperidine(1).

A solution of compound **6** (0.272g 0.584 mmol) in CH_2Cl_2 (1 mL) under argon containing trifluoroacetique acid (1mL 12.85 mmol) was stirred for 2h at 20 °C. After concentration in vacuum, the residual is taken in 5 mL of ethyl acetate then neutralized by $NaHCO_3$ (5%). The aqueous layer was extracted with ethyl acetate (4x5mL). The combined organic phases were dried over $MgSO_4$ filtered and concentrated under reduced pressure. The residue was purified by column chromatography (dichloromethane / methanol (90/10) + 5% of triethylamine). Yield: 0.210g (98%). IR cm^{-1}: 3333 (NH). MS (ESI) m/z: 366.0 $[M+H]^+$. Rf: 0.3 (dichloromethane / methanol (90/10) + 5% of triethylamine).^1H NMR ($CDCl_3$, 250MHz): 1.60 - 1.90 (m, 4H, 2xCH_2); 2.00 (broad s, 1H, NH); 2.65 - 2.80 (m, 3H, CH, CH_2); 3.20 - 3.33 (m, 2H, CH_2); 3.65 (t, 2H, J = 6.39 Hz, CH_2); 4.17 (t, 2H, J = 6.39 Hz, CH_2); 6.60 - 7.50 (m, 8HAr). ^{13}C NMR ($CDCl_3$, 62.5MHz): 31.43 (2x CH_2); 44.82 CH_2; 46.82 (2x CH_2); 56.93 CH; 66.35 CH_2; 113.15 CHAr; 114.86 (2xCHAr); 121.84 C; 128.67 CHAr; 128.86 (2xCHAr); 130.60 CHAr; 131.22 CHAr; 135.32 C; 150.17 C; 160.88 C. Anal. Calcd for ($C_{19}H_{22}Cl_2N_2O$): C, 62.47; H, 6.07; N, 7.67. Found: C, 62.24; H, 6.03; N, 7.68.

3-(4-(_N_-(3,4-Dichlorophenyl)-_N_-(2-phenoxyethyl)amino)piperidin-1-yl)propanoic acid (7).

A solution of Compound **1** (0.335g, 0.917 mmol) in methanol (5mL) under argon pressure containing _t_-butyl acrylat (0.294g 2.29 mmol) was stirred for 4 h at 20 °C. The MeOH was concentrated in vacuum. The residue was purified by column chromatography (ethyl acetate). Yield: 0.365g (81%). IR cm^{-1}: 1730.01 (CO ester). MS (ESI) m/z: 494.5 $(M+H)^+$Rf: 0.35 (ethyl acetate).^1H NMR ($CDCl_3$, 250MHz): 1.45 (s,9H, C $(CH_3)_3$); 1.70-1.85 (m, 4H, 2xCH_2); 2.00 - 2.20 (m, 2H, CH_2); 2.40 (t, 2H, J =7.03Hz, CH_2); 2.70 (t, 2H, J = 7.03 Hz, CH_2); 2.95 - 3.10 (m, 2H, CH_2); 3.45 - 3.55 (m,1H, CH); 3.60 (t, 2H, J = 6.39Hz, CH_2); 4.16 (t, 2H, J = 6.39Hz, CH_2); 6.60 - 7.40 (m, 8HAr). ^{13}C NMR($CDCl_3$, 62.5MHz): 28.54 (3 x CH_3, $C(CH_3)_3$);30.04 (2xCH_2); 34.24 CH_2; 44.74 CH_2; 53.48 (2xCH_2); 54.01 CH_2; 56.68 CH; 56.90 CH_2; 80.14 (C, $C(CH_3)_3$); 113.16 CHAr; 114.87 (2xCHAr); 115.00CHAr; 119.92 (2xC); 121.46 CHAr; 129.93 (2xCHAr); 130.93 CHAr; 148.45 C;158.96 C; 172.31 (CO ester). The deprotection of protected derivative (0.296g, 0.599mmol) is typical procedure for the preparation of products **1**: The residue was purified by crystallization (petroleum ether / ethyl acetate / ethylic ether (4/4/2)). Yield: 0.256g (98%). IR cm^{-1}: 3399.1 (acid OH); 1689.05 (acid CO). MS (ESI) m/z: 438.5 $[M+H]^+$. Mp = 118°C. ^1H NMR (CD_3OD, 250MHz): 1.95 - 2.20 (m, 4H, 2xCH_2); 2.50 - 2.70 (m, 3H, CH, CH_2);2.90 - 3.10 (m, 2H, CH_2); 2.95 - 3.10 (m, 2H, CH_2); 3.15 -

3.25 (m, 2H, CH_2); 3.50 - 3.57 (m, 2H , CH_2); 3.75 - 4.10 (m, 2H, CH_2); 6.80 - 7.35 (m, 8HAr). ^{13}C NMR(CD_3OD 62.5MHz): 27.28 (2xCH_2); 42.50 (2xCH_2); 50.87 (2xCH_2); 52.34 CH_2; 53.59 CH_2; 64.81 CH_2; 111.81 CHAr; 112.66 CHAr; 115.91 (2xCHAr); 119.24 (2xC); 119.47 CHAr; 129.22 (2xCHAr); 130.35CHAr; 131.42 C; 146.83 C; 156.96 (acid CO). Anal. Calcd for: ($C_{22}H_{26}Cl_2N_2O_3$): C, 60.42; H, 5.99; N, 5.68. Found: C, 60.39, H, 6.0; N, 5.66.

1-(3-Aminopropyl)-*N*-(3,4-dichlorophenyl)-*N*-(2-phenoxyethyl)piperidin-4-amine (8).

A solution of compound **1** (0.390g, 1.068 mmol) in methanol (5 mL) was added acrylonitrile (0.141g, 2.67 mmol). After being stirred at room temperature for 12h, the formed solid was filtered (0.377g, 84%).IR cm^{-1}: 2248.38 (CN). Mp = 122°C, MS (ESI) m/z:419.5 [M+H] $^+$Rf: 0.3 (ethylacetate). ^{1}H NMR($CDCl_3$, 250MHz): 1.75 - 1.90 (m, 4H, 2xCH_2); 2.15 - 2.30 (m, 2H, CH_2); 2.50 (t, 2H, *J* = 7.05Hz, CH_2); 2.70 (t, 2H, *J* = 7.05 Hz, CH_2); 2.95 - 3.10 (m, 2H, CH_2); 3.45 - 3.55 (m,1H, CH); 3.60 (t, 2H, *J* = 6.39Hz, CH_2); 4.17 (t, 2H, *J* = 6.39Hz, CH_2); 6.60 - 7.30 (m, 8HAr). ^{13}C NMR($CDCl_3$, 62.5MHz): 16.59 CH_2; 29.90 (2xCH_2); 44.75 (2xCH_2); 53.32 CH_2; 53.66 CH_2; 56.51 CH; 66.68 CH_2; 113.26 **C**N; 114.85 (2xCHAr); 115.10 CHAr; 119.17 C; 120.06 CHAr; 121.5CHAr; 129.95 (2xCHAr); 130.97 CHAr; 133.38 C;148.27 C; 158.83 C. A solution of methanol (50 mL) was purged with ammoniac for about 20mn. The derivative nitrile (0.224g 0.535 mmol) and 10% (0.058 mmol) of nickel Raney previously washed with methanol were added successively. The reaction mixture was stirred under pressure of hydrogen overnight at room temperature. After filtration on celite, then concentration in vacuum, the residual is taken in 5 mL of ethyl acetate then neutralized by HCl (5%) (2x5mL).The aqueous phase are united and treated with $NaHCO_3$ (5%) (3x5mL).The resulting mixture was extracted with ethyl acetate (4 x 5 mL). The combined organic phases were dried over $MgSO_4$ filtered and concentrated in vacuum. The crude product was purified by column chromatography (dichloromethane / methanol (90/10) + 5% of triethylamine). Yield: 0.220g (97%). IR cm^{-1}: 3450.10 (NH_2). MS (ESI) m/z:423.05 $(M+H)^+$; 462.0 $(M+K)^+$. Rf: 0.3 (dichloromethane / methanol (90/10) + 5% of triethylamine). ^{1}H NMR ($CDCl_3$, 250MHz): 1.61 (broad s, 2H, NH_2); 1.72 - 1.9 (m, 4H, 2xCH_2); 1.95 - 2.10 (m, 2H, CH_2); 2.4 0(t, 2H, *J* = 7.05 Hz, CH_2); 2.70 (t, 2H, *J* = 7.05 Hz, CH_2); 2.72 - 2.85 (m, 2H, CH_2); 2.95 - 3.10 (m, 2H, CH_2); 3.45 - 3 .55 (m, 1H, CH); 3.60 (t, 2H, *J* = 6.39 Hz, CH_2); 4.00 (t, 2H, *J* = 6.39 Hz, CH_2); 6.6 - 7.3 (m, 8HAr). ^{13}C NMR($CDCl_3$ 62.5MHz) 30.04 CH_2; 31.18 (2xCH_2); 41.19 (2xCH_2); 44.71 CH_2; 53.86 CH_2; 56.74 CH_2; 56.79 CH; 66.33 CH_2; 114.85 (2xCHAr); 115.10 CHAr; 119.55 C; 121.44CHAr; 129.95(2xCHAr); 130.35CHAr; 130.90 CHAr;146.14 C; 131.42 C; 156.62 C. Anal. Calcd for: ($C_{22}H_{29}Cl_2N_3O$): C, 62.56; H, 6.92; N, 9.95. Found: C, 62.55; H, 6.91; N, 9.96.

***tert*-Butyl 2-(3-bromopropanamido)-3-phenylpropanate (9)**.

To an ice-cooled suspension of sodium hydride (60% in mineral oil, 0.452g 11.29 mmol) in DMF (10 mL) was added dropwise a solution of salt of (*R*, *S*)- *tert*-Butoxycarbonyl Phenylalanine (1 g 4.5 mmol) in DMF (5 mL). After 30 min of stirring under argon pressure, 3-bromopropionyl chloride (1.138 mL 11.29 mmol) was added. The reaction mixture was stirred for 12h at 20°C. 10 mL water was carrefully added. The resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic phases were dried over $MgSO_4$ filtered and concentrated under reduced pressure. The crude product was purified chromatography (dichloromethane / methanol (90/10)). Yield (1.362g, 85%). IR cm^{-1}: 3324.7 (NH); 1733.65 (CO ester); 1681.38 (CO amide). MS (ESI) m/z:357.0 [M+H] $^+$; 378.0 $[M + Na]^+$; Rf : 0.3 (dichloromethane / methanol (90/10)). ^{1}H NMR($CDCl_3$, 250MHz): 1.35 (s, 9H, $C(CH_3)_3$); 2.69 - 3.07 (m, 2H, CH_2); 3.58 (t, 2H, *J* = 6.7Hz, CH_2); 3.75 (t, 2H, *J* = 6.7 Hz, CH_2); 4.78 (m, 1H, CH); 6.82 - 7.45 (m, 5HAr); 8.12 (d broad, 1H, NH). ^{13}C NMR(CDCl3 62.5MHz): (two conformeres): 26.30 - 27.60 (3xCH_3, $C(CH_3)_3$); 28.60 - 29.70 CH_2; 37.90 - 38.40 CH_2; 39.30 - 39.50 CH_2; 53.90 - 54.20 CH; 83.20 (C, $C(CH_3)_3$); 126.30 CHAr; 127.30 - 127.90 (2x CHAr); 128.40 - 128.60 (2xCHAr); 136.30 - 136.40 C; 170.40 - 171.30 C; 174.20-174.40 C.

2-(3-(4-(*N*-(3,4-Dichlorophenyl)-*N*-(2-phenoxyethyl)amino)piperidin-1-yl)propanamido)-3-phenyl propanoic acid (10).

A solution of compound **1** (0.3 g 0.821 mmol) in methanol (5 mL) containing Triton B (*N*, *N*, *N*-Trimethyl-1-phenylmethanaminium hydroxide) (0.216 mL 1.232 mmol) was stirred for 30 min. Compound **9** (0.438 mL 1.232 mmol) is added, the reaction is heated under reflux for 6h. The reaction mixture is cooled and then concentrated in vacuum.

The residual is taken in 10 mL of ethyl acetate then washed to water (4x5mL). The aqueous layer was extracted with ethyl acetate (4x5mL). The combined organic phases were dried over $MgSO_4$ filtered and concentrated under reduced pressure. The crude product was purified by chromatography (dichloromethane / methanol (95/5) + triethylamine 5%). Yield: 0.510g (97%). IR cm^{-1}: 3342.25 (NH); 1731.41 (CO ester); 1659.86 (CO amide). MS (ESI) m/z: 641.0 $[M+H]^+$. Rf: 0.25 (dichloromethane / methanol (90/10) + triethylamine 5%). ^1H NMR ($CDCl_3$, 250MHz): 1.42 (s, 9H, $C(CH_3)_3$); 1.62 - 1.70 (m, 2H, CH_2); 1.91 - 2.02 (m, 4H, 2xCH_2); 2.33 - 2.75 (m, 6H, 3xCH_2); 3.02 - 3.25 (m, 2H, CH_2); 3.42 - 3.63 (m, 3H, CH, CH_2); 3.92 (t, 2H, J = 6.87Hz, CH_2); 4.72 - 4.94 (m, 1H, CH); 6.64 - 7.45 (m, 13HAr); 9.52 (d broad, 1H, NH). ^{13}C NMR ($CDCl_3$, 62.5MHz) : 26.10 (3 x CH_3, $C(CH_3)_3$); 27.30 CH_2; 32.40 CH_2; 40.40 (2x CH_2); 46.70 (2x CH_2); 55.10 CH_2; 55.7 CH_2; 55.90 CH; 58.60 CH; 68.50 CH_2; 84.70 (C, $C(CH_3)_3$); 114.20 CHAr; 115.30 (3xCHAr); 115.90 C; 117.10 C; 122.10 CHAr; 123.70 CHAr; 129.40 (2xCHAr); 130.80 (2xCHAr); 132.20 (2xCHAr); 133.20CHAr; 139.40 C; 150.80 C; 161.30 C; 173.40 C; 174.40 C. The deprotection of protected derivative (0.350g, 0.546 mmol) is typical procedure for the preparation of products **1**: The crude product was purified by precipitation (petroleum ether / ethylic ether/ ethyl acetate (3/2/1)), filtered and dried to give a white powder. The power is crystallized in a pentane / ethyl acetate (1/5). Yield: 0.250g (81%). IR cm^{-1}: 3200 - 3500 (acid OH + NH); 1721.41 (acid CO); 1683.31 (CO amide). MS (ESI) m/z: 585.5 $[M+H]^+$. Mp = 150°C.^1H NMR($CDCl_3$,250MHz): 1.63 - 1.72 (m, 2H, CH_2); 1.92 - 2.10 (m, 4H, 2xCH_2); 2.29 - 2.68 (m, 6H, 3xCH_2); 3.12 - 3.19 (m, 2H, CH_2); 3.39 - 3.63 (m, 3H, CH, CH_2); 3.91 (t, 2H, J = 6.87Hz, CH_2); 4.69 - 4.91 (m, 1H, CH); 6.58 - 7.45 (m, 13HAr); 9.55 (d broad, 1H, NH); 10.5 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$, 62.5MHz): 29.40 CH_2; 32.80 CH_2; 38.20 CH_2; 44.60 CH_2; 52.70 (2xCH_2); 52.90 CH_2; 54.40 CH_2; 55.30 CH; 55.80 CH; 66.90 CH_2; 113.90 CHAr; 114.70 CHAr; 115.20 (2xCHAr); 116.00 C; 118.10 C; 121.60 CHAr; 126.70 CHAr; 128.60 (2xCHAr); 130.20 (2xCHAr); 130.40 (2xCHAr); 131.32 CHAr; 137.70C; 147.10 C; 157.20 C; 169.40 C; 174.10 C. Anal. Calcd for: ($C_{31}H_{35}Cl_2N_3O_4$): C, 63.70; H, 6.04; N, 7.19. Found: C, 63.69; H, 6.05; N, 7.20.

1-(4-(*N*-(3,4-Dichlorophenyl)-*N*-(2-phenoxyethyl)amino)piperidin-1-yl)-2-amino-3-phenylpropan-1-one (11)

A solution of *N-tert*-Butoxycarbonyl-phenylanaline (0.2 g, 0.803 mmol) in THF (8 mL) containing triethylamine (0.125 mL 0.905 mmol) was added ethyl chloroformate (0.079 mL, 0.8294 mmol) at -10°C. After 45 min of stirring under argon atmosphere, compound **1** (0.33g, 0.903 mmol) was added. The reaction mixture was stirred for 12h at 20°C, and then concentrated in vacuum. The residual is taken in 10 mL of ethyl acetate then washed to water (2x5mL). The phases were separated and the aqueous layer is extracted with ethyl acetate (4x5mL). The combined organic phases were dried over $MgSO_4$ filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate / petroleum ether (7/3)). Yield: 0.450g (91%). IR cm^{-1}: 3302.27 (NH); 1737.65 (CO carbamate); 1681.38 (CO amide). MS (ESI) m/z: 612.5 $[M+H]^+$. Rf: 0.3 (ethyl acetate / petroleum ether (7/3). ^1H NMR ($CDCl_3$, 250MHz): 1.45 (m, 13H, $C(CH_3)_3$), CH_2, CH_2); 2.35 - 2.48 (m, 1H, C**H**(H)); 2.94 - 3.45 (m, 4H, 2xCH_2); 3.52 - 3.99 (m, 5H, 2xCH_2, C**H**(H)); 4.69 - 4.91 (m, 1H, CH); 5.41 - 5.50 (m, 1H,CH); 6.54 - 7.45 (m, 13HAr, NH). ^{13}C NMR ($CDCl_3$, 62.5MHz) (two conformers): 28.80 (3xCH_3, $C(CH_3)_3$); 29.40 - 29.50 (2xCH_2); 40.70 - 41.20 CH_2; 42.00 - 42.20 (2xCH_2); 45.30 - 45.90 CH_2; 51.00 - 51.50 CH; 56.40 - 56.70 CH; 65.70 - 66.10 CH_2; 83.20 $C(CH_3)_3$; 113.30 - 113.60 CHAr; 114.70 - 114.80 (2xCHAr); 115.30 - 115.60 (2xCHAr); 121.50 C, 126.50 - 126.60 CHAr; 127.80 - 127.9 (2xCHAr); 128.70 - 128.80 (2xCHAr); 129.40 - 129.50 (2xCHAr), 131.00 CHAr; 135.60 C; 138.90 - 139.10 C; 150.80C; 157.55 C; 160.80 - 160.90 C; 172.50 - 172.60 C. The deprotection of protected derivative (0.400g, 0.653mmol) is typical procedure for the preparation of products **1**: The crude product was purified by chromatography (dichloromethane / methanol (8/2) + 5% triethylamine). Yield: 0.320g (95%). IR cm^{-1}: 3373.04(NH); 1693.73 (CO amide). MS (ESI) m/z: 513.0 $[M+H]^+$; 552.5 $(M+K)^+$. ^1H NMR($CDCl_3$,250MHz): 1.21 - 1.85 (m, 4H, 2xCH_2); 2.46 - 2.56 (m, 1H, C***H***(H)); 2.92 - 3.15 (m, 5H,C***H***(H), CH_2, NH_2); 3.21 - 3.42 (m, 1H, C***H***(H)); 3.45 - 3.99 (m, 5H, C***H***(H), 2xCH_2); 4.15 - 4.25 (m, 1H, CH); 4.75 - 4.80 (m, 1H, CH); 6.56 - 7.41 (m, 13HAr). ^{13}C NMR (d^6DMSO, 80°C, 62.5MHz): 29.80 (2xCH_2); 42.40 (2xCH_2); 44.50 (2xCH_2); 52.00 CH; 56.00 CH; 66.90 CH_2; 113.40 CHAr; 114.70 (2x CHAr); 115.20 (2xCHAr); 120.10C; 121.50 CHAr; 127.50 (2xCHAr); 128.90 (2xCHAr); 129.90 CHAr; 130.00 CHAr; 131.00 CHAr; 135.50C; 138.80C; 148.80 C; 159.00 C; 160.80 C. Anal. Calcd for: ($C_{28}H_{31}Cl_2N_3O_2$): C, 65.62; H, 6.10; N, 8.20. Found: C, 65.70, H, 6.07, N, 8.19.

2-(4-(*N*-(3,4-dichlorophenyl)-*N*-(2-phenoxyethyl)amino)piperidin-1-yl)ethanol(12).

A solution of compound **1** (0.215g, 0.588 mmol) in toluene (5 mL) was added K_2CO_3 (0.121g, 0.882 mmol). After 30 min of stirring under argon atmosphere, 2-iodo-ethanol (0.095g, 1.176 mmol) was added. The reaction mixture was stirred for 4h at toluene reflux, and then concentrated in vacuum. The mixture is taken in 5 mL of ethyl acetate then washed to water. The aqueous phase is extracted with ethyl acetate (4x5mL). The combined organic phases were dried over $MgSO_4$ filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dichloromethane / methanol (90/10)). Yield: 0.230g (95%). IR cm^{-1}: 3417.37 (OH). MS (ESI) m/z: 410.0 [M+H] $^+$Rf: 0.3 (dichloromethane / methanol (90/10)).^{1}H NMR($CDCl_3$, 250MHz): 1.75 - 1.90 (m, 4H, 2xCH_2); 2.10 - 2.23 (m, 2H, CH_2); 2.50 (t, 2H, *J* = 7.05Hz, CH_2); 3.00 - 3.20 (m, 3H, CH_2, OH); 3.50 - 3.70 (m, 5H, CH, 2xCH_2); 4.00 (t, 2H, *J* = 6.39Hz, CH2); 6.60 - 7.30 (m, 8HAr). ^{13}C NMR($CDCl_3$, 62.5MHz) : 29.99 (2xCH_2); 44.76 (2x CH_2); 53.58 CH_2; 56.64 CH; 58.45 CH_2; 59.64 CH_2; 66.27 CH_2; 113.26 CHAr; 114.84 (2xCHAr); 115.06CHAr; 120.05 C; 121.50 CHAr; 129.96 (2xCHAr); 130.92 CHAr; 133.38 C;148.28 C; 158.82 C. Anal. Calcd for: ($C_{21}H_{26}Cl_2N_2O_2$): C, 61.62; H, 6.40; N, 6.84. Found: C, 61.61, H, 6.40; N, 6.85.

1-(2-Aminoethyl)-*N*-(3,4-dichlorophenyl)-*N*-(2-phenoxyethyl)piperidin-4-amine (13).

A solution of compound **1** (0.50g 1.369 mmol) in acetone (5 mL) containing K_2CO_3 (0.283g 2.05 mmol), bromoacetonitrile (0.328g 2.738 mmol) and (0.456g, 2.738mmol) of potassium iodide was stirred for 6h at acetone reflux. After evaporation, the residue is taken in 5 mL of ethyl acetate then washed to water. The aqueous phase is extracted with ethyl acetate (4x5mL). The combined organic phases were dried over $MgSO_4$ filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate (9/1)). Yield: 0.526g (95%). IR cm^{-1}: 2232.01 (CN). MS (ESI) m/z:405.0 [M+H] $^+$. Mp = 110°C.Rf: 0.4 (ethyl acetate). ^{1}H NMR($CDCl_3$,250MHz): 1.7 - 1.8 (m, 4H, 2xCH_2); 2.30 - 2.50 (m, 2H, CH_2); 2.70 - 2.85 (m, 2H, CH_2); 3.34 (m, 1H, CH); 3.40 (s, 2H, CH_2); 3.50 (t, 2H, *J* = 6.39Hz, CH_2); 3.90 (t, 2H, *J* = 6.39Hz, CH_2); 6.50 - 7.30 (m, 8HAr). ^{13}C NMR($CDCl_3$, 62.5MHz): 29.67 (2xCH_2); 44.80 CH_2; 46.54 CH_2; 52.48 (2xCH_2); 55.79 CH; 66.24 CH_2; 113.20 CHAr; 113.90 **C**N; 114.84 (2xCHAr); 115.06CHAr; 120.26 C; 121.56 CHAr; 129.99 (2xCHAr); 131.03 CHAr; 133.44 C; 148.26 C; 158.82 C. The hydrogenation of the nitrile derivative (0.500g, 1.24mmol) is typical procedure for the preparation of products **8**. The crude product was purified by column chromatography (dichloromethane / methanol (90/10) + 5% of triethylamine). Yield: 0.485g (96%). IR cm^{-1}: 3450.10 (NH_2). MS (ESI) m/z: 409.0 $[M+H]^+$; 448.0 $[M+K]^+$. Rf: 0.3 (dichloromethane / methanol (90/10) + 5% of triethylamine).^{1}H NMR($CDCl_3$,250MHz): 1.77 - 1.90 (m, 4H, 2xCH_2); 2.14 (m, 2H, CH_2); 2.56 - 2.63 (m, 2H, CH_2); 2.96 - 3.01 (m, 4H, 2xCH_2); (t, 2H, *J* = 7.05 Hz, CH_2); 3.49 (m, 1H, CH); 3.613.98 (t, 2H, *J* = 7.05 Hz, CH_2); 5.63 (broad s, 2H, NH_2); 6.60 - 7.28 (m, 8HAr). ^{13}C NMR (CDCl3, 62.5MHz): 30.04 (2xCH_2); 39.40 (2xCH_2); 44.81 CH_2; 46.10 CH_2; 54.90 CH_2; 55.78 CH; 67.80 CH_2; 114.50 CHAr; 116.10 (2xCHAr); 116.30 CHAr; 121.10 C; 122.70CHAr; 131.20(2xCHAr); 132.20 CHAr; 134.60 C; 149.60 C; 160.10 C. Anal. Calcd for: ($C_{22}H_{29}Cl_2N_3O$): C, 61.77; H, 6.66; N, 10.29. Found: C, 61.78, H, 6.66, N, 10.30.

***N*-(3,4-Dichlorophenyl)-1-(2-(dimethylamino)ethyl)-*N*-(2-phenoxyethyl)piperidin-4-amine (14)**.

A solution of compound **1**(0.350g, 0.958 mmol) in acetone (5 mL) containing 2-chloro-*N*, *N*-dimethy-ethylamine-hydrochlorure (0.276g, 19.14 mmol), and K_2CO_3 (0.793g 57.42 mmol) was stirred for 6h at acetone reflux. The reaction mixture is cooled, and then concentrated in vacuum. The crude product was taken in 5 mL of ethyl acetate then washed through water. The aqueous layer is extracted with ethyl acetate (4x5mL). The combined organic phases were dried over $MgSO_4$ filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (dichloromethane / methanol (90/10) + 5% of triethylamine). Yield: 0.385g (92%). IR cm^{-1}: 2942.72 ($N(CH_3)_2$). MS (ESI) m/z: 436.5 [M+H] $^+$Rf: 0.3 (dichloromethane / methanol (90/10) + 5% of triethylamine).^{1}H NMR($CDCl_3$, 250MHz): 1.70 - 1.90 (m, 4H, 2xCH_2); 2.10 - 2.25 (m, 2H, CH_2); 2.40 (s, 6H, N (CH_3)$_2$; 2.60 (m, 4H, 2xCH_2); 3.00 - 3.20 (m, 2H, CH_2); 3.45 - 3.70 (m, 3H, CH, CH_2); 4.00 (t, 2H, *J* = 6.39Hz, CH_2); 6.60 - 7.40 (m, 8HAr). ^{13}C NMR ($CDCl_3$, 62.5MHz) : 29.86 (2xCH_2); 44.74 (2x CH_2); 45.72 N(CH_3)$_2$; 54.14 CH_2; 56.03 CH_2; 56.63 CH; 56.9 CH_2; 66.37 CH_2; 113.20 CHAr; 114.84 (2xCHAr); 115.06CHAr; 119.47 CHAr; 119.93 C; 129.91 (2xCHAr); 130.92

CHAr; 133.35 C; 148.36 C; 158.85 C. Anal. Calcd for: ($C_{23}H_{31}Cl_2N_3O$): C, 63.30; H, 7.16; N, 9.63. Found: C, 63.21, H, 7.12; N, 9.60.

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6. References

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