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Mimicking of Ergot Alkaloids and Synthetic Piperidine Drugs by 2,5-Substituted Piperidines Derived from *Cis* and *Trans* Ethyl 1-Benzyl-6-Cyano-3-Piperidinecarboxylate.

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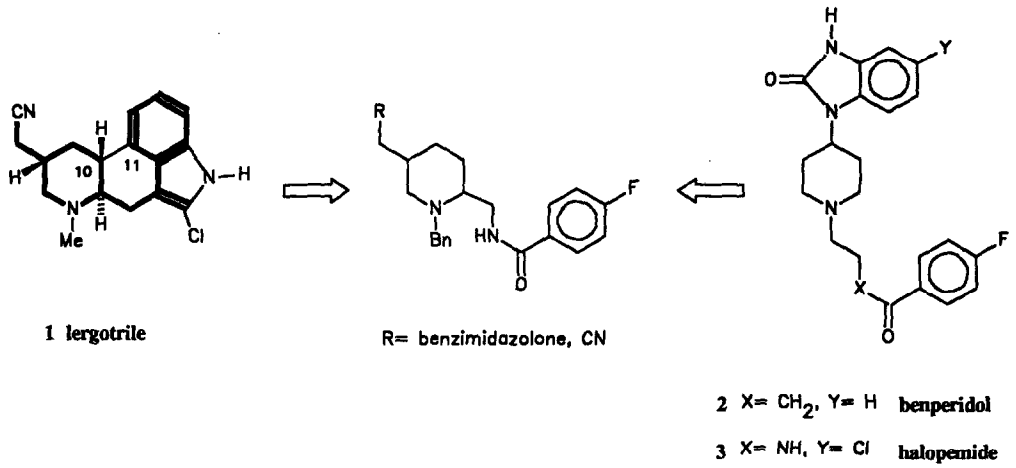
Abstract: *This report describes the synthesis of pharmacologically interesting 2,5-substituted piperidines from cis and trans ethyl 1-benzyl-6-cyano-3-piperidinecarboxylate 4. Reduction and p-fluorobenzoylation of 4 led to the primary alcohols 7. The alcohols were transformed into the tosylates 11 which were used in nucleophilic substitution reactions. An oxidation-reductive amination route proceeding via the aldehydes 17 also was investigated. Finally a novel synthesis was developed for the 3,6-diazabicyclo[3.2.2]nonanes.*

INTRODUCTION

Alkaloids like morphine, reserpine and LSD all have a piperidine moiety in their structure. Efforts to mimic the pharmacological activities of these compounds have therefore led to the synthesis of a large number of 1,4-substituted piperidines. In contrast to most natural alkaloids these molecules are achiral and are characterized by a great conformational freedom which results in an enhanced receptor affinity. In many natural alkaloids the piperidine moiety not only has a 1,4- but also a 2,5-substitution pattern. The 2,5-substituted piperidines combine the conformational flexibility of the 1,4-piperidine side chains with the chiral orientation of the alkaloid substituents and hence can be expected to possess pharmacological activity.

Recently we developed a new approach to the 2,5-substituted piperidines.[1] This proceeded via a regioselective oxidation of 3-substituted piperidines with $Hg(OAc)_2$. The resulting 6-iminium ions were trapped *in situ* with cyanide to give the 5-substituted 2-piperidinecarbonitriles. These proved to be useful tools in the synthesis of 2,5-substituted piperidines and polycyclic derivatives thereof.[2,3] This report describes the preparation of specific 2,5-substituted piperidines from *cis* and *trans* ethyl 1-benzyl-6-cyano-3-piperidinecarboxylate. The target compounds were selected on the basis of their homology with several known 1,4-substituted piperidines and/or ergot alkaloids showing potent pharmacological activity.

The 2,5-substituted piperidines described here can be considered as modified ergot alkaloids (Scheme 1). Disconnection of the 10-11 linkage between the piperidine and phenyl rings of lergotrile **1**[4] and replacement of the indole moiety with a nearly isosteric benzoyl group leads to the 2,5-substituted piperidine indicated by the bold substructure. N-insertion completes the transformation into the target piperidine compounds. The 1,4-substituted piperidines of the butyrophenone type (*e.g.* benperidol **2**[5]) also served as templates (Scheme 1). The substituents were shifted to the 2- and 5-position in such a way that the distance between the piperidine-N and the functional groups was kept constant. As in halopemide **3**[6] the α-carbonyl methylene of the butyrophenone chain was replaced by a NH-group.

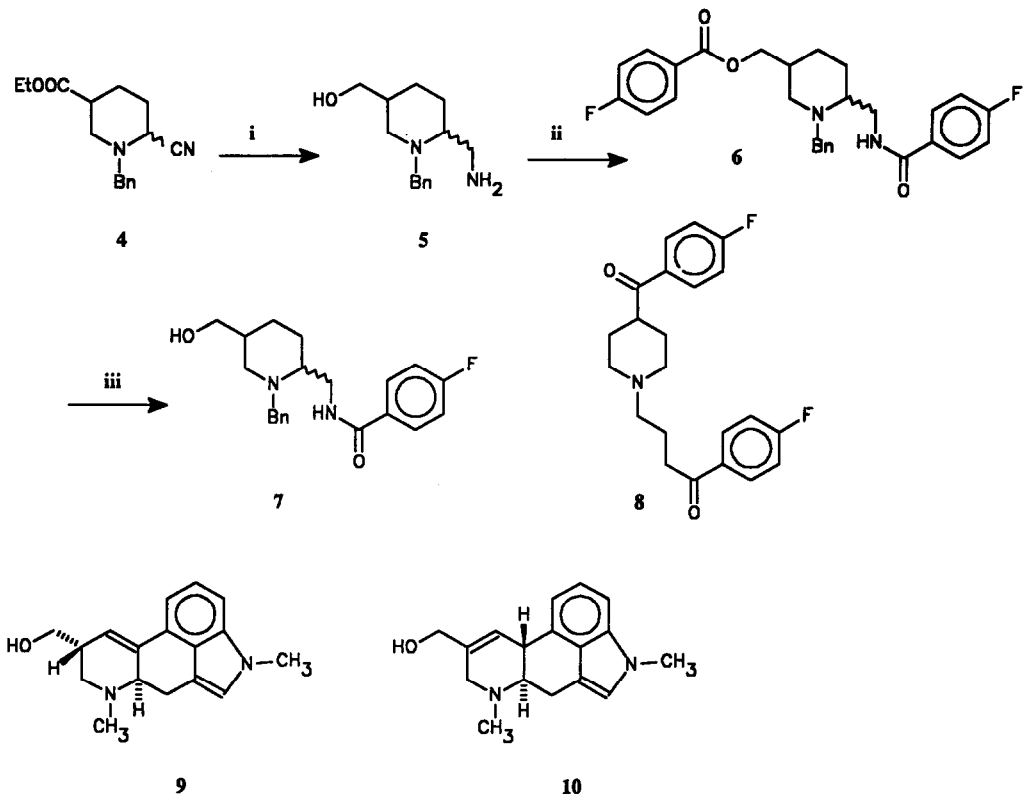


Scheme 1

RESULTS AND DISCUSSION

In order to introduce the group in 2-position we tried to selectively reduce the nitrile function in ethyl 1-benzyl-6-cyano-3-piperidinecarboxylate **4** (mixture of diastereoisomers).[1] However, hydrogenation with Adam's catalyst (acetic acid or methanol) or Raney-Ni (methanol) led to decyanation instead of reduction of the nitrile function. In polar medium the α-aminonitrile is in equilibrium with an iminium ion[1] which is reduced to the corresponding amine. On treatment with a half molar quantity of $LiAlH_4$ the nitrile group was left intact but the ester function was reduced to an alcohol. Finally, both the nitrile and the ester function were reduced by reaction with an excess of $LiAlH_4$ (Scheme 2). The resulting polar amino alcohol **5** was not isolated, but was used as such in the next step of the reaction sequence. Addition of an equimolar amount of 4-fluorobenzoyl chloride in CH_2Cl_2 at 0°C or in CH_3CN at -20°C[7] invariably led to a mixture of *N*- and *O*-benzoylation products. Addition of an excess gave the *N,O*-di-(4-fluorobenzoyl) derivatives **6**. At this stage it was possible to separate the *cis* and *trans* isomers by column chromatography. All further reactions were performed on the pure diastereoisomers.

The ^1H NMR data for the *trans* product **6b** reveal an equatorial orientation of both the 2- and the 5-substituents (Figure 1b). The axial H-6 appears as a triplet ($^2J_{6a6e}$= $^3J_{6a5a}$= 10.5 Hz). The proton H-4a shows a quartet-multiplet pattern ($^2J_{4a4e}$= $^3J_{4a3a}$= $^3J_{4a5a}$= 10 Hz). The high J-values for the coupling between H-6a and H-5a and between H-4a and H-5a indicate the *trans* diaxial disposition of these protons. For H-2a a doublet-quartet coupling pattern is observed ($^3J_{2a3a}$= 10.5 Hz), again corresponding to a *trans* diaxial orientation of H-2a and H-3a. For the *cis* isomer **6a**, the proton H-6a appears as a doublet of doublets ($^2J_{6a6e}$= 12.5 Hz, $^3J_{6a5a}$= 9 Hz). This means that the 5-substituent is mainly equatorial and the 2-substituent mainly axial (Figure 1a). Apparently, the steric interaction with the equatorial *N*-benzyl group forces the 2-substituent into an axial position.



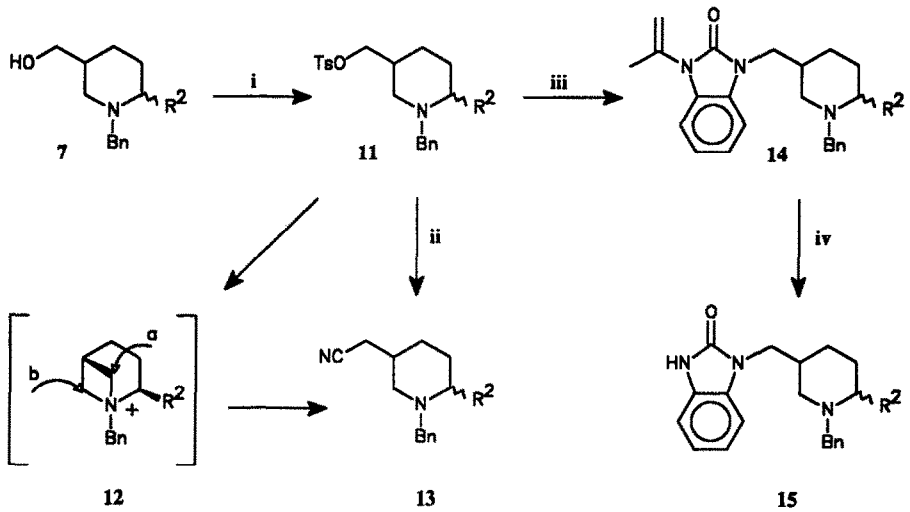
i: $LiAlH_4$, THF, reflux; ii: 4-FC_6H_4COCl, NEt_3, CH_2Cl_2, 0°C; iii: KOt-Bu, MeOH, r.t.

Scheme 2

Fig. 1

Transesterification of the esters **6** with KOt-Bu in methanol yielded the alcohols **7**. Whereas esters **6** are analogues of the neuroleptic lenperone **8**[8]; the alcohols **7** contain the hydroxymethyl group of the hallucinogenic ergot alkaloids lysergol **9** and elymoclavine **10**.[9]

Transformation of the alcohols **7** into the tosylates **11** (TsCl, pyridine) proceeded without difficulty (Scheme 3). Reaction of the tosylates with cyanide in acetonitrile under phase transfer catalysis afforded the cyanomethyl derivatives **13**. Under these conditions epimerisation occurs at C-5. This can be explained by the formation of an azetidinium ion **12**[10]. The cyanide can attack the bridged intermediate from two sides to give the *cis* product **13a** (route a) and the *trans* product **13b** (route b). When starting from the *cis* isomer **11a** the *cis* product **13a** was formed predominantly (*cis-trans* ratio 4/1) and from the *trans* isomer **11b** mainly the *trans* product **13b** was isolated (*cis-trans* ratio 1/2). The different product ratios show that the normal S_N2 reaction competes with the azetidinium pathway. The 5-cyanomethyl derivatives **13** resemble the anti-Parkinson ergot alkaloid lergotrile **1**.[4] Attempts to transform the nitrile group into a 4-fluoroacetophenone derivative by way of a Grignard reaction failed, probably due to the electrostatic repulsion between the 4-fluorophenylmagnesium bromide and the amide anion produced on the side chain in 2-position.



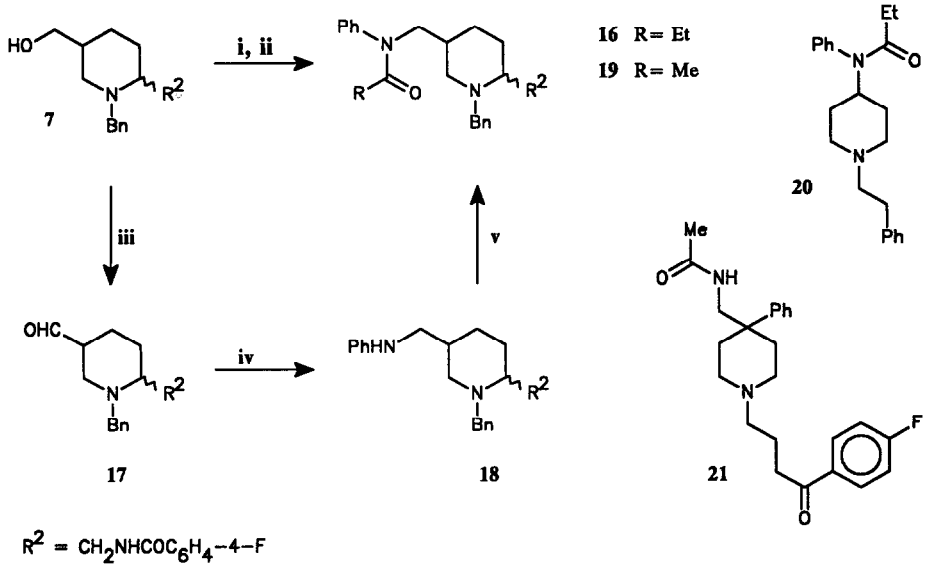
R^2 = $CH_2NHCOC_6H_4$–4–F

i: TsCl, C_5H_5N, 0°C; ii: KCN, $Bu_4N^+Br^-$, CH_3CN, reflux; iii: 1-(2-propenyl)benzimidazolone, KOt-Bu, 18-crown-6-ether, PhMe, 70°C; iv: conc. HCl, MeOH-H_2O, reflux.

Scheme 3

To introduce the benzimidazolone moiety of the piperidine drugs benperidol **3**[5] and halopemide **4**[6], the tosylates **11** were made to react with the anion of 1-(2-propenyl)benzimidazolone.[11] With toluene as solvent, the desired substitution occurred without observed epimerisation. This can be ascribed to the apolar nature of the solvent which disfavors the formation of the charged azetidinium ion **12**. Acid promoted cleavage of the enamine protecting group[11] in **14** gave the 5-[(1,3-dihydro-2-oxobenzimidazol-3-yl)methyl]piperidines **15**.

Reaction of the anion derived from *N*-phenylpropionamide with the tosylate **11a** afforded compound **16a** in low yield (19%) (Scheme 4). To increase the yield of compounds **16** an alternative reaction sequence was investigated. Oxidation of the alcohols **7** with pyridine-SO_3, NEt_3 and DMSO[12] led to the corresponding aldehydes **17**. Under the reaction conditions partial epimerisation occurred at the C-5 aldehyde centre. Because of its instability the aldehyde was not isolated, but was used directly in the next step. Reductive amination with aniline in the presence of $NaCNBH_3$ gave the amines **18** in good yield as a mixture of the diastereoisomers (66% from **7a**, ratio 54/12; 60% from **7b**, ratio 14/46). Acetylation or propionylation finally afforded the target molecules **16a** and **19a-b**. The substituents in these molecules are a combination of the 1- and 4-substituents in the analgetic fentanyl **20**[13] and the antiemetic aceperone **21**.[14]

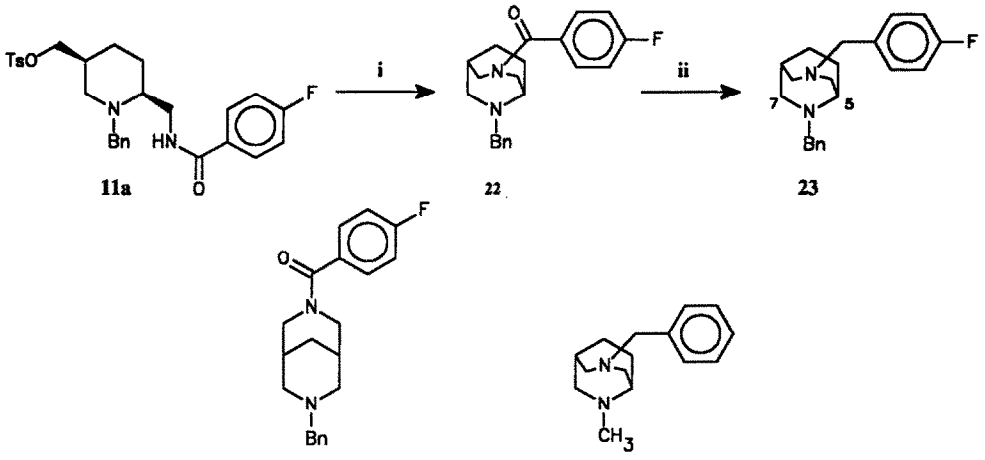


i: TsCl, C_5H_5N, 0°C; ii: $C_6H_5NHCOEt$, KOt-Bu, 18-crown-6-ether, PhMe, 70°C; iii: $C_5H_5N.SO_3$, NEt_3, DMSO, r.t.; iv: $C_6H_5NH_2$, $NaCNBH_3$, MeOH, pH 6, r.t. then reflux; v: CH_3COCl or EtCOCl, NEt_3, CH_2Cl_2, 0°C.

Scheme 4

For *cis* compound **11a**, the combination of a good leaving group in the 5-position and a potential nucleophilic entity in the 2-position stimulated us to investigate the possibilities for the formation of bridged 2,5-substituted piperidine systems. Until now only one synthetic route to the 3,6-diazabicyclo[3.2.2]nonanes has been reported.[15] Some quinolone derivatives of this skeleton show bactericide activity.[16] Abstraction of the secondary amide H-atom in **11a** with NaH in THF followed by intramolecular substitution of the tosylate group yielded the desired product **22** in moderate yield (38%). Increasing the nucleophilic capacities of the anion through cation solvation with DMF was not successful (23% yield). *In situ* exchange of the tosylate by iodide (KI in THF) clearly enhanced the leaving group properties raising the yield of **22** to 73%. This product shows great similarity with the 7-benzyl-3-(4-fluorobenzoyl)-3,7-diazabicyclo[3.3.1]nonane **24**

which was patented for its antiarrhythmic properties.[17] $LiAlH_4$ reduction of **22** gave the 3-(4-fluorobenzyl) derivative **23**. According to a molecular model, the piperidine ring adopts a twisted boat conformation. This boat form retains a large degree of conformational freedom due to the three-atom bridge forming part of two seven-membered rings. Comparison of the ^{13}C NMR data of the 3-(4-fluorobenzyl)-6-benzyl compound **23** with the reported[15] 3-benzyl-6-methyl analogue **25**, indicates an upfield shift for C-5 (57.2→54.4 ppm) but not for C-7. This shift is caused by the additional phenyl group and implies a gauche conformation for (C-5)-N-CH_2-Ph and an anti conformation for (C-7)-N-CH_2-Ph.



i: KI, NaH, THF, reflux; ii: $LiAlH_4$, THF, reflux.

Scheme 5

We can conclude that the diastereomeric ethyl 1-benzyl-6-cyano-3-piperidinecarboxylates **4** form an excellent starting material for the preparation of pharmacologically interesting 2,5-substituted piperidines. Furthermore, a new synthetic route to the bridged 3,6-diazabicyclo[3.2.2]nonanes is presented.

EXPERIMENTAL

All m.p.s are uncorrected. IR spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Perkin-Elmer 297 grating IR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AMX 400 and WM 250 instruments operating at 400 and 250 MHz for ^1H and 100 and 63 MHz for ^{13}C measurements. The ^1H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane as an internal reference. *J* values are recorded in Hz. Mass spectra were run on a Kratos MS50 instrument; the ion source temperature was 150-250°C as required. Exact mass measurements were performed at a resolution of 10.000. Analytical and preparative thin layer chromatography was performed using Merck silica gel 60 PF-224. Column chromatography was carried out using 70-230 mesh silica gel 60 (E. M. Merck).

Ethyl 1-benzyl-6-cyano-3-piperidinecarboxylate (4)

This compound has been described previously.[1] A prolonged reaction time and thorough extraction on work-up increased the yield from 67% to 77%.

A mixture of ethyl 1-benzyl-3-piperidinecarboxylate (14.34 g, 0.058 mol) and mercuric acetate (92.51 g, 0.290 mol) in aq. acetic acid (1.4 l, 2.5%) was stirred at 90°C for 6 h. The mixture then was cooled in an ice bath and KCN (37.39 g, 0.581 mol) dissolved in aq. acetic acid (pH 5) was added under vigorous stirring. The reaction mixture was stirred at room temp. for 1 h and made alkaline with K_2CO_3. The aqueous phase was further extracted with CH_2Cl_2 (5 x 300 ml) and the combined extracts were filtered, dried ($MgSO_4$) and evaporated. The residue was chromatographed over silica gel (15:85 EtOAc-hexane) to afford a mixture of epimers **4a** and **4b** as a yellow oil (55:45, total yield: 12.23 g, 77.4%).

[1-Benzyl-2-[(4-fluorobenzoyl)aminomethyl]-5-piperidinyl]methyl 4-fluorobenzoate (6)

To a stirred and cooled (0°C) solution of 4 (5.05 g, 0.019 mol) in dry THF was added $LiAlH_4$ (3.52 g, 0.093 mol). The mixture then was refluxed for 1.5 h and allowed to come to room temp. The excess hydride was destroyed by dropwise addition of ice water until hydrogen evolution ceased. The precipitate was filtered off and the mixture was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated. The residue was dissolved in CH_2Cl_2 and then NEt_3 (1.88 g, 0.019 mol) and *p*-fluorobenzoyl chloride (5.89 g, 0.037 mol) were added dropwise at 0°C. After the mixture had been stirred at room temp. for 30 min a second portion of NEt_3 (1.88 g, 0.019 mol) and *p*-fluorobenzoyl chloride (2.95 g, 0.019 mol) was added. The mixture was stirred for another 30 min and washed with water. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified over a silica column (gradient elution 15:85→30:70 EtOAc-CH_2Cl_2) to afford **6a** (3.55 g, 40%) and **6b** (2.77 g, 31%).

ν_{max} (NaCl)/cm^{-1} 3700-3100 (NH), 3070, 3030 (ArH), 2940, 2860 (CH_2), 2800 (NCH_2), 1720 (COO), 1645, 1545 (NCO), 1600, 1500, 850, 765, 700 (ArH); m/z 476 (M -2H)$^+$, 387 (M -Bn)$^+$, 326 (M -$CH_2NHCOC_6H_4F$)$^+$, 123 (FC_6H_4CO)$^+$, 91 (C_7H_7)$^+$ [Found (M -$CH_2NHCOC_6H_4F$)$^+$, 326.1556. $C_{20}H_{21}NO_2F$ requires 326.1557].

6a: m.p. (EtOAc-hexane) 120°C; δ_H (400 MHz; $CDCl_3$) 1.63 (2H, m, H-3ax, H-4ax), 1.79 (1H, m, H-4eq), 1.89 (1H, m, H-3eq), 2.23 (1H, m, H-5ax), 2.63 (1H, dm, *J* 12.5 Hz, H-6eq), 2.82 (1H, m, H-2eq), 2.87 (1H, dd, *J* 12.5, 8 Hz, H-6ax), 3.49 (2H, m, *CH*$_2$NHCO), 3.61, 3.98 (2H, d, *J* 13 Hz, N*CH*$_2$Ph), 4.25 (1H, dd, *J* 11, 6.5 Hz, CH_2COO), 4.33 (1H, dd, *J* 11, 7 Hz, CH_2COO), 6.63 (1H, br s, NHCO), 7.09 (2H, t, *J* 8.5 Hz, H-3', H-5' $NCOC_6H_4F$), 7.12 (2H, t, *J* 8.5 Hz, H-3', H-5' $OCOC_6H_4F$), 7.25 (5H, m, CH_2*Ph*), 7.73 (2H, dd, *J* 8.5, 5.5 Hz, H-2', H-6' $NCOC_6H_4F$), 7.96 (2H, dd, *J* 8.5, 5.5 Hz, H-2', H-6' $OCOC_6H_4F$); δ_C (63 MHz; $CDCl_3$) 23.5 (C-3), 24.0 (C-4), 31.6 (C-5), 39.7 (*CH*$_2$NCO), 50.6 (C-6), 56.8 (C-2), 58.2 (N*CH*$_2$Ph), 66.5 (*CH*$_2$OCO), 115.4, 126.3, 127.1, 128.4, 128.5, 129.1, 130.7, 132.0 (C-Ar), 139.2 (C-1' CH_2Ph), 164.6 (C-4' $NCOC_6H_4F$), 165.4 (COO), 165.7 (C-4' $OCOC_6H_4F$),

166.4 (NCO); Anal. Calcd. for $C_{28}H_{28}F_2N_2O_3$: C, 70.28; H, 5.90; N, 5.85. Found: C, 70.46; H, 5.91; N, 5.82.

6b: m.p. (EtOAc-hexane) 106°C; δ_H (250 MHz; $CDCl_3$) 1.10-1.35 (1H, m, H-4ax), 1.60-2.15 (5H, m, H-3, H-4eq, H-5ax, H-6ax), 2.63 (1H, dq, *J* 10.5, 3.5 Hz, H-2ax), 3.12 (1H, dm, *J* 10.5 Hz, H-6eq), 3.35, 4.09 (2H, d, *J* 13.5 Hz, N*CH*$_2$Ph), 3.69 (2H, dd, *J* 4, 3.5 Hz, *CH*$_2$NHCO), 4.03 (1H, dd, *J* 11, 6.5 Hz, CH_2COO), 4.16 (1H, dd, *J* 11, 5.5 Hz, CH*CH*$_2$COO), 6.80 (1H, br s, NH), 7.06 (2H, t, *J* 8.5 Hz, H-2', H-6' $NCOC_6H_4F$), 7.09 (2H, t, *J* 8.5 Hz, H-2', H-6' $OCOC_6H_4F$), 7.30 (5H, m, CH_2*Ph*), 7.75 (2H, dd, *J* 8.5, 5.5 Hz, H-3', H-5' $NCOC_6H_4F$), 7.92 (2H, dd, *J* 8.5, 5.5 Hz, H-3', H-5' $OCOC_6H_4F$); δ_C (63 MHz; $CDCl_3$) 27.1 (C-4), 28.8 (C-3), 35.4 (C-5), 41.6 (*CH*$_2$NHCO), 55.8 (C-6), 57.1 (N*CH*$_2$Ph), 59.8 (C-2), 67.3 (*CH*$_2$OCO), 115.4, 126.3, 127.2, 128.5, 128.6, 129.1, 130.6, 132.0 (C-Ar), 138.2 (C-1' CH_2Ph), 164.6 (C-4' $NCOC_6H_4F$), 165.3 (COO), 165.7 (C-4' $OCOC_6H_4F$), 166.5 (NCO); Anal. Calcd. for $C_{28}H_{28}F_2N_2O_3$: C, 70.28; H, 5.90; N, 5.85. Found: C, 70.63; H, 5.94; N, 5.78.

***N*-[(1-Benzyl-5-hydroxymethyl-2-piperidinyl)methyl]-4-fluorobenzamide (7)**

To a solution of **6a** (5.84 g, 0.012 mol) in methanol (100 ml) was added a catalytic amount of KOt-Bu and the mixture was stirred at room temp. under N_2 for 16 h. The solvent was evaporated and the residue dissolved in CH_2Cl_2. The organic phase was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (silica, 6:94 MeOH-CH_2Cl_2) to give **7a** as an oil (3.97 g, 91%). **6b** (3.54 g, 0.007 mol) was treated likewise to give **7b** (2.07 g, 79%).

ν_{max} (NaCl)/cm^{-1} 3700-3100 (OH and NH), 2930, 2860 (CH_2), 2800 (NCH_2), 1645, 1550 (NCO), 1600, 1500, 850, 765, 700 (ArH); m/z 356 $(M)^+$, 354 $(M-2H)^+$, 265 $(M-Bn)^+$, 204 $(M-CH_2NHCOC_6H_4F)^+$, 123 $(FC_6H_4CO)^+$, 91 $(C_7H_7)^+$ [Found M^+, 356.1847. $C_{21}H_{25}N_2O_2F$ requires 356.1900].

7a: δ_H (250 MHz; C_6D_6) 1.20-1.63 (5H, m, H-3, H-4, H-5ax), 2.10 (1H, br s, OH), 2.35-2.50 (1H, m, H-2eq), 2.40 (1H, dd, *J* 13, 3.5 Hz, H-6eq), 2.56 (1H, dd, *J* 13, 8.5 Hz, H-6ax), 3.27, 3.32 (2H, dd, *J* 11, 6 Hz, *CH*$_2$OH), 3.34, 3.65 (2H, d, *J* 13.5 Hz, N*CH*$_2$Ph), 3.43 (2H, t, *J* 5.5 Hz, *CH*$_2$NHCO), 6.38 (1H, br t, NHCO), 6.78 (2H, t, *J* 8.5 Hz, H-3', H-5' C_6H_4F), 7.05-7.25 (5H, m, CH_2*Ph*), 7.53 (2H, dd, *J* 8.5, 5 Hz, H-2', H-6' C_6H_4F); δ_C (63 MHz; $CDCl_3$) 23.7 (C-3), 24.1 (C-4), 34.2 (C-5), 39.5 (*CH*$_2$NHCO), 51.4 (C-6), 56.4 (C-2), 58.3 (N*CH*$_2$Ph), 65.8 (CH_2OH), 115.3, 127.1, 128.4, 128.5, 129.1, 130.6 (C-Ar), 139.3 (C-1' CH_2Ph), 164.4 (C-4' C_6H_4F), 166.5 (CON).

7b: δ_H (250 MHz; $CDCl_3$) 1.04 (1H, qd, *J* 12, 4 Hz, H-4ax), 1.60-1.80 (3H, m, H-3eq, H-4eq, H-5ax), 1.62 (1H, m, H-3ax), 1.88 (1H, t, *J* 11 Hz, H-6ax), 2.41 (1H, br s, OH), 2.52 (1H, dq, *J* 11, 3, H-2ax), 3.09 (1H, dm, *J* 11 Hz, H-6eq), 3.30, 4.03 (2H, d, *J* 14 Hz, N*CH*$_2$Ph), 3.35, 3.42 (2H, dd, *J* 11, 5.5 Hz, CH_2OH), 3.63 (2H, t, *J* 4 Hz, *CH*$_2$NHCO), 6.82 (1H, br s, NHCO), 7.08 (2H, t, *J* 8.5 Hz, H-3', H-5' C_6H_4F), 7.27 (5H, m, CH_2*Ph*), 7.72 (2H, dd, *J* 8.5, 5 Hz, H-2', H-6' C_6H_4F); δ_C (63 MHz; $CDCl_3$) 27.0 (C-4), 29.1 (C-3), 38.5 (C-5), 41.7 (*CH*$_2$NHCO), 56.4 (C-6), 57.5 (N*CH*$_2$Ph), 59.8 (C-2), 65.9 (CH_2OH), 115.4, 127.2, 128.5, 129.1, 130.6 (C-Ar), 138.4 (C-1' CH_2Ph), 164.6 (d, C-4' C_6H_4F), 166.6 (NCO).

***N*-[[1-Benzyl-5-[(4-methylphenyl)sulfonyloxymethyl]-2-piperidinyl]methyl]-4-fluorobenzamide (11)**

To a stirred and cooled (0°C) solution of **7a** (2.56 g, 7.2 mmol) in dry pyridine was added tosyl chloride (2.75 g, 14.4 mmol). The solution was stirred at 0°C under N_2 for 16 h. The pyridine was evaporated at room temp. under reduced pressure and the residue was chromatographed over silica gel (15:85 EtOAc-CH_2Cl_2) to give **11a** as an oil (2.88 g, 79%). **7b** (1.97 g, 5.53 mmol) was treated in the same way to give **11b** (1.47 g, 52%).

ν_{max} (NaCl)/cm^{-1} 3700-3100 (NH), 3090, 3060, 3030 (ArH), 2940, 2870 (CH_2), 2810 (NCH_2), 1650, 1545 (NCO), 1370 (SO_3), 850, 770, 700 (ArH); m/z 508 $(M-2H)^+$, 358 $(M-CH_2NHCOC_6H_4F)^+$, 123 $(FC_6H_4CO)^+$, 91 $(C_7H_7)^+$ [Found $(M-CH_2NHCOC_6H_4F)^+$, 358.1466. $C_{20}H_{24}NO_3S$ requires 358.1477].

11a: δ_H (400 MHz; $CDCl_3$) 1.36-1.52 (2H, m, H-3, H-4), 1.62 (1H, m, H-4eq), 1.77 (1H, dq, *J* 4.5, 9 Hz, H-3eq), 2.05 (1H, m, H-5eq), 2.43 (3H, s, CH_3), 2.57 (1H, dd, *J* 12.5, 2.5 Hz, H-6eq), 2.68 (1H, dd, *J* 12.5, 8 Hz, H-6ax), 2.73 (1H, quin, *J* 5 Hz, H-2eq), 3.47 (1H, m, CH_2NCO), 3.58, 3.86 (2H, d, *J* 13 Hz,

N*CH*$_2$Ph), 3.90 (1H, dd, *J* 9.5, 6 Hz, *CH*$_2$OTs), 3.97 (1H, dd, *J* 9.5, 6 Hz, *CH*$_2$OTs), 6.58 (1H, br s, NHCO), 7.10 (2H, t, *J* 8.5 Hz, H-3', H-5' NCOC$_6$H$_4$F), 7.23-7.30 (7H, m, H-Ar), 7.68-7.75 (4H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) 21.6 (CH_3), 23.2, 23.4 (C-3, C-4), 31.9 (C-5), 39.4 (*CH*$_2$NHCO), 50.5 (C-6), 56.3 (C-2), 58.3 (N*CH*$_2$Ph), 72.0 (*CH*$_2$OTs), 115.5, 127.3, 127.8, 128.5, 128.6, 129.2, 129.9, 130.7 (C-Ar), 132.9 (C-1' SO$_2$C$_6$H$_4$Me), 139.2 (C-1' CH$_2$*Ph*), 144.9 (C-4' SO$_2$C$_6$H$_4$Me), 164.6 (d, C-4' C$_6$H$_4$F), 166.4 (NCO).

11b: δ_H (400 MHz; $CDCl_3$) 1.04 (1H, qd, *J* 11.5, 4 Hz, H-4ax), 1.57 (1H, m, H-3ax) 1.73 (1H, m, H-4eq), 1.84 (1H, t, *J* 11 Hz, H-6ax), 1.92 (1H, m, H-5ax), 2.43 (3H, s, CH_3), 2.50 (1H, dd, *J* 15, 3 Hz, H-2ax), 2.95 (1H, d, *J* 10.5 Hz, H-6eq), 3.28, 3.98 (2H, d, *J* 12 Hz, N*CH*$_2$Ph), 3.60 (1H, m, CH$_2$NCO), 3.73 (1H, dd, *J* 9, 5.5 Hz, *CH*$_2$OTs), 3.78 (1H, dd, *J* 9.5, 5.5 Hz, *CH*$_2$OTs), 6.62 (1H, br s, NHCO), 7.08 (2H, t, *J* 8.5 Hz, H-3', H-5' NCOC$_6$H$_4$F), 7.23 (3H, m, H-Ar), 7.28 (4H, m, H-Ar), 7.67 (4H, m, H-Ar); δ_C (100 MHz; $CDCl_3$) 21.7 (CH_3), 26.6 (C-4), 28.7 (C-3), 35.6 (C-5), 41.6 (*CH*$_2$NHCO), 55.5 (C-6), 57.4 (N*CH*$_2$Ph), 59.5 (C-2), 72.6 (*CH*$_2$OTs), 115.5, 127.3, 127.9, 128.4, 128.6, 129.2, 129.9, 130.6 (C-Ar), 132.8 (C-1' SO$_2$C$_6$H$_4$Me), 138.5 (C-1' CH$_2$*Ph*), 144.8 (C-4' SO$_2$C$_6$H$_4$Me), 163.7 (d, C-4' C$_6$H$_4$F), 166.5 (NCO).

***N*-[(1-Benzyl-5-cyanomethyl-2-piperidinyl)methyl]-4-fluorobenzamide (13)**

To a solution of **11a** (1.000 g, 2 mmol) in dry acetonitrile was added KCN (0.511 g, 8 mmol) and a catalytic amount of $Bu_4N^+Br^-$. The mixture was refluxed under N_2 for 24 h, water was added and the product was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica, 1:4 EtOAc-CH_2Cl_2) to afford **13a** (0.450 g, 63%) and **13b** as oils (0.116 g, 16%). **11b** (295 mg, 6 mmol) was treated in the same way to afford **13a** (20 mg, 10%) and **13b** (50 mg, 25%).

ν_{max} (NaCl)/cm^{-1} 3600-3100 (NH), 3070, 3030 (ArH), 2940, 2860 (CH_2), 2800 (NCH_2), 2240 (CN), 1650, 1540 (NCO), 1600, 1505, 850, 765, 700 (ArH); m/z 213 (M -CH$_2$NHCOC$_6$H$_4$F)$^+$, 123 (FC$_6$H$_4$CO)$^+$, 91 (C_7H_7)$^+$ [Found (M -CH$_2$NHCOC$_6$H$_4$F)$^+$, 213.1396. $C_{14}H_{17}N_2$ requires 213.1392].

13a: δ_H (250 MHz; $CDCl_3$) 1.48-2.00 (4H, m, H-3, H-4), 2.10 (1H, m, H-5ax), 2.32 (2H, m, CH_2CN), 2.65 (1H, dd, *J* 12.5, 4 Hz, H-6eq), 2.75 (1H, dd, *J* 12.5, 8 Hz, H-6ax), 2.77 (1H, m, H-2eq), 3.49 (1H, dt, *J* 13.5, 5.5 Hz, *CH*$_2$NHCO), 3.60 (1H, ddd, *J* 13.5, 7, 4.5 Hz, *CH*$_2$NHCO), 3.66, 3.92 (2H, d, *J* 13.5 Hz, N*CH*$_2$Ph), 6.52 (1H, br t, NHCO), 7.10 (2H, dd, *J* 8.5 Hz, H-3', H-5' NCOC$_6$H$_4$F), 7.30 (5H, m, CH$_2$*Ph*), 7.69 (2H, dd, *J* 8.5, 5 Hz, H-2', H-6' NCOC$_6$H$_4$F); δ_C (63 MHz; $CDCl_3$) 20.6 (*CH*$_2$CN), 23.5 (C-3), 26.1, (C-4), 29.8 (C-5), 38.9 (*CH*$_2$NHCO), 52.6 (C-6), 56.5 (C-2), 58.2 (N*CH*$_2$Ph) 118.4 (CN), 115.2, 127.1, 128.3, 128.4, 129.1, 130.6 (C-Ar), 139.2 (C-1' CH$_2$Ph), 164.5 (d, C-4' C$_6$H$_4$F), 166.3 (NCO).

13b: δ_H (250 MHz; $CDCl_3$) 1.10-1.30 and 1.87-1.97 (2H and 3H, m, H-3, H-4, H-5ax), 1.98 (1H, t, *J* 11 Hz, H-6ax), 2.17 (1H, dd, *J* 16, 6 Hz, CH$_2$CN), 2.24 (1H, dd, *J* 16, 6 Hz, CH$_2$CN), 2.53 (1H, dq, *J* 11, 4 Hz, H-2ax), 2.88 (1H, dd, *J* 8.5, 2 Hz, H-6eq), 3.31, 4.03 (2H, d, *J* 13.5 Hz, N*CH*$_2$Ph), 3.63 (2H, m, *CH*$_2$NHCO), 6.59 (1H, br s, NHCO), 7.07 (2H, t, *J* 8.5 Hz, H-3', H-5' NCOC$_6$H$_4$F), 7.28 (5H, m, CH$_2$*Ph*), 7.72 (2H, dd, *J* 8.5, 5 Hz, H-2', H-6' NCOC$_6$H$_4$F); δ_C (63 MHz; $CDCl_3$) 21.6 (*CH*$_2$CN), 28.8 (C-4), 29.5 (C-3), 32.5 (C-5), 41.4 (*CH*$_2$NHCO), 57.2, 57.6 (C-6, N*CH*$_2$Ph), 59.2 (C-2), 117.8 (CN), 115.3, 127.1, 128.2, 128.5, 129.0, 130.5 (C-Ar), 138.3 (C-1' CH$_2$Ph), 164.5 (d, C-4' C$_6$H$_4$F), 166.3 (NCO).

***N*-[[1-Benzyl-5-[[1,3-dihydro-2-oxo-1-(2-propenyl)benzimidazol-3-yl]methyl]-2-piperidinyl]methyl]-4-fluorobenzamide (14)**

To a solution of **11a** (308 mg, 6 mmol) in dry toluene was added 1,3-dihydro-1-(2-propenyl)-2-benzimidazolone (126 mg, 7 mmol), KOt-Bu (162 mg, 15 mmol) and a catalytic amount of 18-crown-6-ether. The mixture was stirred at 70°C under N_2 for 24 h, water was added and the aqueous phase was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent evaporated. The residue was

chromatographed over a silica column (2:3 EtOAc-CH_2Cl_2) to give **14a** as an oil (212 mg, 69%). **11b** (296 mg, 6 mmol) was treated in the same manner to give **14b** (149 mg, 50%) (silica, 1:1 EtOAc-CH_2Cl_2).

ν_{max} (NaCl)/cm^{-1} 3700-3000 (NH), 3070, 3030 (ArH), 2930, 2860 (CH_2), 2800, 2760 (NCH_2), 1705 (NCON), 1655, 1545 (NCO), 1600, 1580, 1500, 850, 760, 735, 695 (ArH); m/z 510 $(M-2H)^+$, 360 $(M-CH_2NHCOC_6H_4F)^+$, 123 $(FC_6H_4CO)^+$, 91 $(C_7H_7)^+$ [Found $(M-CH_2NHCOC_6H_4F)^+$, 360.2072. $C_{23}H_{26}N_3O$ requires 360.2076].

14a: δ_H (250 MHz; $CDCl_3$) 1.28 (1H, m, H-4ax), 1.53 (1H, tm, *J* 9 Hz, H-3ax), 1.62-1.95 (2H, m, H-3eq, H-4eq), 2.22 (3H, s, CH_3), 2.28-2.45 (1H, m, H-5ax), 2.55 (1H, dm, *J* 12 Hz, H-6eq), 2.70-2.90 (2H, m, H-2eq, H-6ax), 3.55-3.63 (2H, m, CH_2NHCO), 3.58, 3.88 (2H, d, *J* 13.5 Hz, NCH_2Ph), 3.76, 3.89 (2H, dd, *J* 14, 7.5 Hz, NCONCH_2), 5.20 (1H, s, CH_2=C), 5.36 (1H, d, *J* 1.5 Hz, CH_2=C), 6.80 (1H, br s, NHCO), 6.98 and 7.05-7.30 (1H and 10H, m, H-Ar), 7.70 (2H, dd, *J* 8.5, 5 Hz, H-3', H-5' C_6H_4F); δ_C (63 MHz; $CDCl_3$) 19.9 (CH_3), 23.3 (C-3), 24.7 (C-4), 31.2 (C-5), 39.4 (CH_2NHCO), 43.7 (CH_2NCON), 51.1 (C-6), 56.1 (C-2), 58.1 (NCH_2Ph), 112.7 (CH_2=C), 107.6, 108.9, 115.1, 121.1, 121.4, 126.9, 128.2, 128.5, 128.7, 129.8, 129.2, 130.6, 137.8 (C=CH_2 and C-Ar), 139.0 (C-1' CH_2Ph), 152.8 (NCON), 164.4 (d, C-4' C_6H_4F), 166.3 (CONH).

14b: δ_H (250 MHz; $CDCl_3$) 1.23 (1H, ddm, *J* 16, 12 Hz, H-4ax), 1.59 (1H, dq, *J* 10.5, 3 Hz, H-3ax), 1.65-1.85 (2H, m, H-3eq, H-4eq), 2.03 (1H, t, *J* 10.5 Hz, H-6ax), 2.09 (1H, m, H-5ax), 2.17 (3H, s, CH_3), 2.58 (1H, ddm, *J* 11, 3 Hz, H-2ax), 2.95 (1H, dt, *J* 10.5, 2 Hz, H-6eq), 3.30, 3.97 (2H, d, *J* 13 Hz, NCH_2Ph), 3.52 (2H, m, CH_2NHCO), 3.58 (2H, m, NCONCH_2), 5.13, 5.82 (2H, s, CH_2=C), 6.67 (1H, br s, NHCO), 6.94, 7.05-7.15, 7.15-7.30 (1H, 5H, 5H, m, H-Ar), 7.72 (2H, dd, *J* 8.5, 5 Hz, H-2', H-6' C_6H_4F); δ_C (63 MHz; $CDCl_3$) 19.9 (CH_3), 28.3 (C-4), 28.8 (C-3), 35.3 (C-5), 41.6 (CH_2NH), 44.5 (NCONCH_2), 56.8, 57.3 (C-6, NCH_2Ph), 59.4 (C-2), 112.7 (CH_2=C), 107.6, 108.9, 115.3, 121.1, 121.3, 126.9, 128.3, 128.5, 128.7, 129.8, 129.0, 130.5, 137.9 (CH_2=C and C-Ar), 138.1 (C-1' CH_2Ph), 152.8 (NCON), 164.5 (d, C-4' C_6H_4F), 166.3 (CON).

N-[[1-Benzyl-5-[(1,3-dihydro-2-oxobenzimidazol-3-yl)methyl]-2-piperidinyl]methyl]-4-fluorobenzamide (15)

14a (788 mg, 1.5 mmol) was dissolved in MeOH-H_2O (1:1, 20 ml) and conc. HCl (6 ml) was added. The mixture was refluxed for 1 h and allowed to come to room temp. The solution was made alkaline with aq. NaOH and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and purified by column chromatography (silica, EtOAc) to give **15a** as white crystals (400 mg, 55%). **14b** (400 mg, 0.8 mmol) was treated in the same manner to give **15b** (140 mg, 38%).

ν_{max} (NaCl)/cm^{-1} 3700-3100 (NH), 3070, 3040 (ArH), 2940, 2860 (CH_2), 2800 (NCH_2), 1700 (NCON), 1645, 1550 (NCO), 850, 760, 735, 700 (ArH); m/z 472 $(M)^+$, 320 $(M-CH_2NHCOC_6H_4F)^+$, 123 $(FC_6H_4CO)^+$, 91 $(C_7H_7)^+$ [Found $(M-CH_2NHCOC_6H_4F)^+$, 320.1755. $C_{20}H_{22}N_3O$ requires 320.1763].

15a: m.p. (EtOAc) 182°C; δ_H (400 MHz; DMSO-d_6) 1.42-1.58 (2H, m, H-3ax, H-4ax), 1.70 (2H, m, H-3eq, H-4eq), 2.21 (m, 1H, H-5ax), 2.46 (1H, dd, *J* 12, 3 Hz, H-6eq), 2.63 (1H, dd, *J* 12, 9 Hz, H-6ax), 2.87 (1H, m, H-2eq), 3.51 (1H, dt, *J* 12, 7 Hz, CH_2NHCO), 3.61 (1H, dt, *J* 12, 5 Hz, CH_2NHCO), 3.65, 3.83 (2H, d, *J* 14 Hz, NCH_2Ph), 3.67 (1H, dd, *J* 14, 7 Hz, NCONCH_2), 3.79 (1H, dd, *J* 14, 8, NCONCH_2), 6.98, 7.10-7.30 (4H and 7H, m, H-Ar), 7.90 (2H, m, H-2', H-6' C_6H_4F), 8.15 (1H, m, NHCO), 10.70 (1H, s, NCONH); δ_C (100 MHz; DMSO-d_6) 23.9 (C-4), 24.4 (C-3), 32.8 (C-5), 37.6 (CH_2NHCO), 43.2 (NCONCH_2), 50.8 (C-6), 56.7 (C-2), 58.0 (NCH_2Ph), 107.3, 108.6, 114.7, 120.2, 120.4, 126.3, 127.8, 128.0, 128.1, 129.4, 130.3, 130.8 (C-Ar), 139.3 (C-1' CH_2Ph), 154.6 (NCON), 163.8 (d, C-4' C_6H_4F), 165.4 (NCO); Anal. Calcd. for $C_{28}H_{29}FN_4O_2$: C, 71.17; H, 6.19; N, 11.86. Found: C, 70.86; H, 6.12; N, 11.79.

15b: m.p. (MeOH-CH_2Cl_2) 110°C; δ_H (400 MHz; DMSO-d_6) 1.05 (1H, m, H-4ax), 1.35 (1H, m, H-3ax), 1.66 (1H, dm, *J* 12 Hz, H-4eq), 1.79 (1H, dm, *J* 11 Hz, H-3eq), 1.87 (1H, t, *J* 11 Hz, H-6ax), 1.99 (1H, m, H-5ax), 2.43 (1H, m, H-2ax), 2.72 (1H, d, *J* 11 Hz, H-6eq), 3.29, 4.03 (2H, d, *J* 13 Hz, NCH_2Ph), 3.50, 3.60 (2H, m, CH_2NHCO), 3.55 (1H, dd, *J* 14, 7 Hz, NCONCH_2), 3.62 (1H, dd, *J* 14, 6 Hz,

NCONCH$_2$), 6.90-7.10, 7.10-7.40 (H-Ar), 7.90 (2H, m, H-2', H-6' C$_6$H$_4$F), 8.40 (1H, s, NHCO), 9.75 (1H, s, NCONH); δ_C (100 MHz; DMSO-*d*$_6$) 27.5 (C-4), 28.5 (C-3), 34.5 (C-5), 41.9 (*CH*$_2$NHCO), 43.4 (NCON*CH*$_2$), 55.7, 56.8, 60.1 (C-2, N*CH*$_2$Ph, C-6), 107.8, 108.6, 115.1, 120.3, 120.6, 126.6, 127.9, 128.0, 128.7, 129.8, 130.5, 131.0 (C-Ar), 139.0 (C-1' CH$_2$Ph), 154.3 (NCON), 163.8 (d, C-4' C$_6$H$_4$F), 165.3 (CON); Anal. Calcd. for C$_{28}$H$_{29}$FN$_4$O$_2$: C, 71.17; H, 6.19; N, 11.86. Found: C, 70.78; H, 6.11; N, 11.70.

***N*-[[1-Benzyl-5-[(*N*-phenyl)aminomethyl]-2-piperidinyl]methyl]-4-fluorobenzamide (18)**

To a solution of **7a** (370 mg, 1.0 mmol) and NEt$_3$ (2 ml) in dry DMSO (3 ml) was added dropwise a solution of SO$_3$-pyridine (827 mg, 5.2 mmol) in dry DMSO. The mixture was stirred at room temp. under N$_2$ for 1 h. Ice water was added and the solution was extracted with CH$_2$Cl$_2$. The organic phase was washed with water (5x10 ml), dried (MgSO$_4$) and evaporated. The residue (**17a,b**) was dissolved in methanol and aniline (194 mg, 2.1 mmol) and NaCNBH$_3$ (131 mg, 2.1 mmol) were added. The reaction mixture was brought to pH 6 with 2N HCl, stirred at room temp. under N$_2$ for 15 min and refluxed for 30 min. The reaction was quenched with 2N HCl and the mixture was stirred at room temp. for 5 min. It was then made alkaline with aq. K$_2$CO$_3$ and extracted with CH$_2$Cl$_2$. The organic phase was dried (MgSO$_4$) and evaporated. The residue was chromatographed over a silica column (gradient elution, 1:4→2:3 EtOAc-CH$_2$Cl$_2$) to give **18a** (242 mg, 54%) and **18b** (55 mg, 12%) as oils. **7b** (1.049 mg, 3.0 mmol) was treated likewise to give **18a** (172 mg, 14%) and **18b** (580 mg, 46%).

17a,b: ν_{max} (NaCl)/cm^{-1} 3500, 3200 (NH), 3090, 3070, 3030 (ArH), 2940, 2860 (CH$_2$), 2820, 2740 (NCH$_2$), 1725 (CHO), 1645, 1545 (NCO), 1605, 1505, 850, 735, 700 (ArH); δ_H (250 MHz, CDCl$_3$) 3.40, 4.00 (2H, d, *J* 13 Hz, N*CH*$_2$Ph), 7.05 (2H, t, *J* 8.5 Hz, H-3', H-5' C$_6$H$_4$F), 7.30 (5H, m, CH$_2$*Ph*), 7.70 (2H, m, H-2', H-6' C$_6$H$_4$F), 9.50, 9.55 (1H, s, CHO); δ_C (250 MHz, CDCl$_3$) 21.3, 22.8, 24.7, 27.2 (C-3, C-4), 40.3, 40.4 (*CH*$_2$NCO), 45.4, 47.5 (C-5), 49.6, 50.7 (C-6), 57.2, 57.7 (N*CH*$_2$Ph), 57.8, 58.9 (C-2), 115.0, 126.9, 128.0, 128.1, 128.2, 129.0, 130.4 (C-Ar), 138.4, 138.6 (C-1' CH$_2$Ph), 163.9 (d, C-4' C$_6$H$_4$F), 166.2 (NCO), 202.6, 203.5 (CHO).

18: ν_{max} (NaCl)/cm^{-1} 3500-3100 (NH), 3090, 3070, 3030 (ArH), 2940, 2860 (CH$_2$), 2800 (NCH$_2$), 1650, 1550 (NCO), 1600, 1500, 850, 735, 700 (ArH); m/z 431 (M)$^+$, 279 (M -CH$_2$NHCOC$_6$H$_4$F)$^+$, 134 [Bn(Me)N=CH$_2$]$^+$, 123 (FC$_6$H$_4$CO)$^+$, 91 (C$_7$H$_7$)$^+$ [Found: M$^+$, 431.2370. C$_{27}$H$_{30}$N$_3$OF requires M, 431.2373].

18a: δ_H (400 MHz; CDCl$_3$) 1.51 (1H, m, H-4ax), 1.62 (1H, m, H-3ax), 1.74-1.90 (2H, m, H-3eq, H-4eq), 2.02 (1H, m, H-5ax), 2.62 (1H, dd, *J* 12, 3 Hz, H-6eq), 2.76 (1H, dd, *J* 12, 8 Hz, H-6ax), 2.78 (1H, m, H-2eq), 3.04 (1H, dd, *J* 12, 6 Hz, *CH*$_2$NHPh), 3.13 (1H, dd, *J* 12, 7.5 Hz, *CH*$_2$NHPh), 3.48-3.63 (2H, m, *CH*$_2$NHCO), 3.60, 3.94 (2H, d, *J* 13.5 Hz, N*CH*$_2$Ph), 6.55 (2H, d, *J* 8 Hz, H-2', H-6' NPh), 6.70 (2H, t, *J* 8 Hz, NHCO, H-4' NPh), 7.09 (2H, t, *J* 8 Hz, H-3', H-5' C$_6$H$_4$F), 7.17 (2H, t, *J* 8 Hz, H-3', H-5' NPh), 7.30 (5H, m, NCH$_2$*Ph*), 7.72 (2H, dd, *J* 8.5, 5 Hz, H-2', H-6' C$_6$H$_4$F); δ_C (100 MHz; CDCl$_3$) 23.6 (C-3), 25.5 (C-4), 31.5 (C-5), 39.6 (*CH*$_2$NHCO), 46.7 (*CH*$_2$NPh), 51.9 (C-6), 56.5 (C-2), 58.1 (N*CH*$_2$Ph), 112.6, 115.4, 117.2, 127.2, 128.4, 128.5, 129.1, 130.7 (C-Ar), 139.6 (C-1' CH$_2$Ph), 148.2 (C-1' NPh), 164.6 (d, C-4' C$_6$H$_4$F), 166.3 (NCO).

18b: δ_H (400 MHz; CDCl$_3$) 1.07 (1H, qd, *J* 11.5, 4 Hz, H-4ax), 1.61 (1H, qd, *J* 11, 4 Hz, H-3ax), 1.74 (1H, dq, *J* 11, 3.5 Hz, H-3eq), 1.77-1.92 (2H, m, H-5ax, H-4eq), 1.88 (1H, t, *J* 10 Hz, H-6ax), 2.54 (1H, dq, *J* 11, 3 Hz, H-2ax), 2.90 (2H, m, *CH*$_2$NHPh), 3.06 (1H, d, *J* 10 Hz, H-6eq), 3.31, 4.00 (2H, d, *J* 13.5 Hz, N*CH*$_2$Ph), 3.63 (2H, m, *CH*$_2$NHCO), 6.53 (2H, d, *J* 8 Hz, H-2', H-6' NPh), 6.67 (2H, t, *J* 8 Hz, NHCO, H-4' NPh), 7.08 (2H, t, *J* 8.5 Hz, H-3', H-5' C$_6$H$_4$F), 7.14 (2H, dd, *J* 8.5, 8 Hz, H-3', H-5' NPh), 7.28 (5H, m, CH$_2$*Ph*), 7.70 (2H, dd, *J* 8.5, 5 Hz, H-2', H-6' C$_6$H$_4$F); δ_C (100 MHz; CDCl$_3$) 28.8 (C-4), 29.2 (C-3), 35.9 (C-5), 41.7 (*CH*$_2$NHCO), 47.9 (*CH*$_2$NHPh), 57.4, 57.6 (N*CH*$_2$Ph, C-6), 59.6 (C-2), 112.6, 115.4, 117.2, 127.1, 128.4, 128.5, 129.1, 130.6 (C-Ar), 138.5 (C-1' CH$_2$Ph), 148.2 (C-1' NPh), 164.7 (d, C-4' C$_6$H$_4$F), 166.5 (NCO).

***N*-[[1-Benzyl-5-[(*N*-acetyl,*N*-phenyl)aminomethyl]-2-piperidinyl]methyl]-4-fluorobenzamide (19)**
To a stirred and cooled (0°C) solution of **18a** (200 mg, 0.46 mmol) and NEt_3 (94 mg, 1.0 mmol) in CH_2Cl_2 was added acetyl chloride (73 mg, 0.93 mmol). After stirring at 0°C under N_2 for 45 min, 1N NaOH was added. The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated. The residue was purified over silica gel (7:3 EtOAc-CH_2Cl_2) yielding **19a** as an oil (213 mg, 97%). **18b** (528 mg, 1.2 mmol) was treated likewise yielding **19b** (449 mg, 78%) (silica, EtOAc).
ν_{max} (NaCl)/cm^{-1} 3700-3000 (ArH), 3070, 3030 (ArH), 2930, 2850 (CH_2), 2800 (NCH_2), 1650, 1545 (NCO), 1600, 1500, 850, 700, 735 (ArH); m/z 321 (M -$CH_2NHCOC_6H_4F$)$^+$, 123 (FC_6H_4CO)$^+$, 91 (C_7H_7)$^+$ [Found (M -$CH_2NHCOC_6H_4F$)$^+$, 321.1970. $C_{21}H_{25}N_2O$ requires 321.1967].
19a: δ_H (400 MHz; $CDCl_3$) 1.43 (1H, m, H-4ax), 1.56 (1H, m, H-4eq), 1.65 (1H, m, H-3eq), 1.73 (1H, m, H-3ax), 1.77 (3H, s, CH_3), 1.84 (1H, m, H-5ax), 2.47 (1H, dd, *J* 10.5, 3 Hz, H-6eq), 2.63 (1H, dd, *J* 10.5, 8 Hz, H-6ax), 2.73 (1H, quin, *J* 5 Hz, H-2eq), 3.51 (2H, m, *CH_2*NHCO), 3.52, 3.87 (2H, d, *J* 13 Hz, N*CH_2*Ph), 3.59 (1H, dd, *J* 13.5, 6.5 Hz, *CH_2*NPh), 3.81 (1H, dd, *J* 13.5, 8.5 Hz, *CH_2*NPh), 5.26 (1H, br s, NHCO), 6.97 (2H, dd, *J* 7, 1.5 Hz, H-2', H-6' NPh) ,7.09 (2H, t, *J* 8 Hz, H-3', H-5' C_6H_4F), 7.23 (5H, m, CH_2*Ph*), 7.25-7.38 (3H, m, H-3', H-4', H-5' NPh), 7.78 (2H, dd, *J* 8, 5.5 Hz, H-2', H-6' C_6H_4F); δ_C (100 MHz; $CDCl_3$) 22.8 (CH_3), 23.7 (C-3), 24.9 (C-4), 39.6 (*CH_2*NHCO), 51.1, 51.3 (*CH_2*NPh, C-6), 56.6 (C-2), 58.3 (N*CH_2*Ph), 115.3, 127.1, 127.7, 128.4, 128.7, 129.3, 129.6, 130.8 (C-Ar C_6H_4F), 139.3 (C-1' CH_2Ph), 143.0 (C-1' NPh), 164.5 (d, C-4' C_6H_4F), 166.4 (NCOPh), 170.5 (PhNCO).
19b: δ_H (400 MHz; $CDCl_3$) 1.09 (1H, qd, *J* 11.5, 9.5 Hz, H-4ax), 1.58 (1H, m, H-3ax), 1.72 (3H, s, CH_3), 1.65-1.85 (4H, m, H-3eq, H-4eq, H-5ax, H-6ax), 2.52 (1H, m, H-2ax), 2.94 (1H, d, *J* 9.5 Hz, H-6eq), 3.22, 4.05 (2H, d, *J* 13.5 Hz, N*CH_2*Ph), 3.47 (1H, dd, *J* 13, 5.5 Hz, *CH_2*NPh), 3.60 (1H, dd, *J* 13, 7.5 Hz, *CH_2*NPh), 3.64 (2H, m, *CH_2*NHCO), 6.78 (1H, br s, NHCO), 6.92 (2H, dd, *J* 8, 2 Hz, H-2', H-6' NPh), 7.17 (2H, t, *J* 8 Hz, H-3', H-5' C_6H_4F), 7.20-7.40 (8H, m, CH_2*Ph*, H-3', H-4', H-5' NPh), 7.73 (2H, dd, *J* 8, 5.5 Hz, H-3', H-5' C_6H_4F); δ_C (100 MHz; $CDCl_3$) 22.6 (CH_3), 28.3 (C-4), 29.2 (C-3), 34.6 (C-5), 41.7 (*CH_2*NHCO), 52.3, 56.6 (*CH_2*NPh, C-6), 57.1 (N*CH_2*Ph), 59.7 (C-2), 115.4, 127.1, 127.6, 127.7, 128.4, 128.6, 129.1, 129.6, 130.6 (C-Ar), 138.6 (C-1' CH_2Ph), 143.2 (C-1' NPh), 164.5 (d, C-4' C_6H_4F), 166.5 (NCO), 170.5 (PhNCO).

***N*-[[1-Benzyl-5-[(*N*-phenyl,*N*-propionyl)aminomethyl]-2-piperidinyl]methyl]-4-fluorobenzamide (16a)**
a) To a solution of **11a** (625 mg, 1.2 mmol) in dry toluene was added *N*-phenylpropionamide (183 mg, 1.2 mmol), KOt-Bu (230 mg, 2.5 mmol) and a catalytic amount of 18-crown-6-ether. After the mixture had been stirred at 70°C under N_2 for 24 h, water was added and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$) and evaporated. The residue was purified over silica gel (1:9 EtOAc-CH_2Cl_2) to afford **16a** as an oil (100 mg, 17%).
b) Compound **18a** was treated with propionyl chloride in an analogous way as described for the preparation of **19** to give **16a** as an oil (89 %).
ν_{max} (NaCl)/cm^{-1} 3700, 3000 (NH), 3070, 3030 (ArH), 2930, 2850 (CH_2), 2800 (NCH_2), 1650, 1545 (NCO), 1600, 1500, 850, 735, 700 (ArH); m/z 487 (M)$^+$, 485 (M -2H)$^+$, 408 (485 -Ph), 430 (M -CO -Et)$^+$, 335 (M -$CH_2NHCOC_6H_4F$)$^+$, 123 (FC_6H_4CO)$^+$, 91 (C_7H_7)$^+$ [Found (M -$CH_2NHCOC_6H_4F$)$^+$, 335.2123. $C_{22}H_{27}N_2O$ requires 335.2123].
16a: δ_H (250 MHz; $CDCl_3$) 1.02 (3H, t, *J* 7 Hz, CH_3), 1.30-1.95 (5H, m, H-3, H-4, H-5ax), 1.88 (2H, q, *J* 7 Hz, $NCOCH_2$), 2.48 (1H, dd, *J* 13, 3.5, H-6eq), 2.66 (1H, dd, *J* 13, 8 Hz, H-6ax), 2.75 (1H, quin, *J* 5.5 Hz, H-2eq), 3.51-3.57 (2H, m, *CH_2*NHCO), 3.53, 3.88 (2H, d, *J* 13.5 Hz, N*CH_2*Ph), 3.59 (1H, dd, *J* 13.5, 6.5 Hz, *CH_2*NPh), 3.84 (1H, dd, *J* 13.5, 8.5 Hz, *CH_2*NPh), 6.88 (1H, br s, NHCO), 7.00 (2H, dd, *J* 6, 1.5 Hz, H-3', H-5' NPh), 7.10 (2H, t, *J* 8 Hz, H-3', H-5' C_6H_4F), 7.20-7.40 (8H, m, CH_2*Ph*, H-2', H-4', H-6' NPh), 7.82 (2H, dd, *J* 8, 5 Hz, H-2', H-6' C_6H_4F); δ_C (63 MHz; $CDCl_3$) 9.5 (CH_3), 23.7 (C-3), 24.9 (C-4), 27.7 (*CH_2*NCO), 30.7 (C-5), 39.5 (*CH_2*NHCO), 51.2 (C-6, *CH_2*NPh), 56.6 (C-2), 58.3

(N*CH*$_2$Ph), 115.3, 127.0, 127.6, 127.9, 128.2, 128.6, 129.3, 129.5, 130.7 (C-Ar), 139.3 (C-1' CH_2Ph), 142.6 (C-1' NPh), 163.8 (d, C-4' C_6H_4F), 166.3 (NCO), 173.8 (PhNCO).

6-Benzyl-3-(4-fluorobenzoyl)-3,6-diazabicyclo[3.2.2]nonane (22)

A mixture of **11a** (652 mg, 1.3 mmol), KI (318 mg, 1.9 mmol) and NaH (61 mg, 2.6 mmol) in dry THF was refluxed under N_2 for 6 h. Water was added and the aqueous solution was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was purified by column chromatography (silica, 2:3 EtOAc-$CHCl_3$) to give **22** as white crystals (316 mg, 73%).
m.p. (EtOAc-hexane) 79°C; ν_{max} (NaCl)/cm^{-1} 3050, 3030 (ArH), 2920, 2870 (CH_2), 2800 (NCH_2), 1635 (CO), 1600, 850, 735, 695 (ArH); m/z 338 $(M)^+$, 247 $(M\text{ -Bn})^+$, 215 $(M\text{ -}FC_6H_4CO)^+$, 91 $(C_7H_7)^+$ [Found M^+, 338.1790. $C_{21}H_{23}N_2OF$ requires 338.1794].
δ_C (100 MHz; $CDCl_3$) 21.8, 22.8 (C-8, C-9), 31.5 (C-1), 54.5, 55.3, 60.8 (C-2, C-4, C-5, C-7, NCH_2Ph), 115.5, 127.3, 128.4, 128.9, 129.2, 133.2 (C-Ar), 163.2 (d, C-4' C_6H_4F), 171.0 (NCO).

6-Benzyl-3-(4-fluorobenzyl)-3,6-diazabicyclo[3.2.2]nonane (23)

$LiAlH_4$ (70 mg, 1.84 mmol) was added to a solution of **22** (124 mg, 0.37 mmol) in dry THF and the mixture was refluxed for 30 min under N_2. Water was added and the solution was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica, EtOAc) to give **23** as an oil (77mg, 65%).
ν_{max} (NaCl)/cm^{-1} 3090, 3070, 3030, 1600, 825, 725, 690 (ArH); m/z 324 $(M)^+$, 233 $(M\text{ -Bn})^+$, 215 $(M\text{ -}FC_6H_4CH_2)^+$, 152 $[FC_6H_4CH_2(Me)N{=}CH_2]^+$, 109 $(FC_6H_4CH_2)^+$, 91 $(C_7H_7)^+$ [Found M^+, 324.2000. $C_{21}H_{25}N_2F$ requires 324.2001].
δ_H (400 MHz; $CDCl_3$) 1.60 (1H, m, H-8), 1.88 (3H, m, H-8, H-9), 1.93 (1H, m, H-1), 2.60 (2H, m, H-4), 2.48 (1H, dm, *J* 11 Hz, H-2 or H-7), 2.83 (4H, m, H-5, H-2, H-7), 3.48, 3.54 (2H, d, *J* 13 Hz, N*CH*$_2$$C_6H_4F$), 3.70, 3.76 (2H, d, *J* 13 Hz, N*CH*$_2$Ph), 6.97 (2H, t, *J* 8.5 Hz, H-2', H-6' C_6H_4F), 7.30 (7H, m, Ph); δ_C (100 MHz; $CDCl_3$) 22.9 (C-8), 24.7 (C-9), 31.8 (C-1), 54.4 (C-5), 56.7 (C-2 or C-7), 58.9 (C-4), 60.9 (N*CH*$_2$Ph), 61.6 (N*CH*$_2$$C_6H_4F$), 61.8 (C-2 or C-7), 114.9, 126.6, 128.1, 128.6, 130.0 (C-Ar), 140.1 (C-1' Ph), 161.9 (d, C-4' C_6H_4F).

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