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Synthesis of 2,5-Substituted Piperidines: Transposition of 1,4-Substitution Pattern for the Analgesic Drug R6582.

Nicole P. Baens, Frans Compernolle*, Suzanne M. Toppet and Georges J. Hoornaert

Laboratorium voor Organische Synthese, K U Leuven, Celestijnenlaan 200F, B-3001 Leuven (Belgium)

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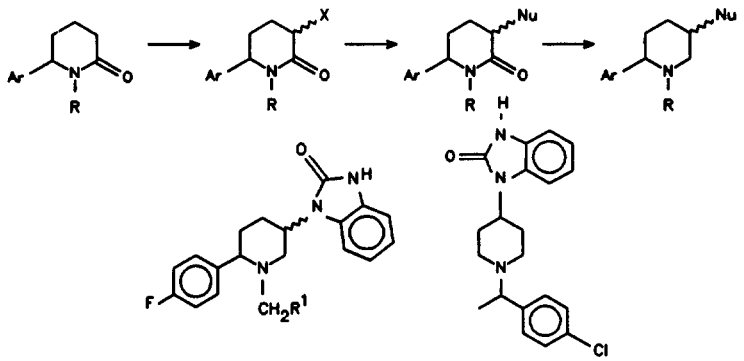
Abstract *This report describes the synthesis of cis 5-(1,3-dihydro-2-oxo-2H-benzimidazol-1-yl)-2-p-fluorophenyl-1-methylpiperidine (1a) and the analogous cis and trans 1-benzylpiperidines 2a,b Key steps in the synthesis were the α-chlorination of the lactams 5 and 6 (1-methyl-and 1-benzyl-6-p-fluorophenyl-2-piperidinone), and nucleophilic substitution of the resulting cis and trans 3-chloro lactams 8a,b and 9a,b ^{1}H NMR analysis for the epimeric 3,6-substituted lactam compounds revealed a preferred axial orientation for the 3-chloro substituent and an equatorial orientation for the 3-(oxobenzimidazolyl) group For the reduced compound, cis N-methyl piperidine 1a, a conformational equilibrium was observed This was shifted to the [2ax,5eq] form for the cis N-benzyl analogue 2a.*

INTRODUCTION

The 2,5-substituted piperidines can combine chiral properties of the rigid polycyclic alkaloids such as reserpine, LSD, morphine and the flexibility of the 1,4-substituted monocyclic piperidine drugs These combined properties could result in a more selective interaction with the complementary receptor site and, hence, a better pharmacological activity In our previous work relating to the synthesis of 2,5-substituted piperidines,[1-6] mainly two routes were followed. Regioselective oxidation of 3-substituted piperidines gave the corresponding 6-iminium ions which were trapped with cyanide [1-4] In the lactam approach,[5-6] the enolate anions were generated with LDA, and made to react with carbonyl electrophiles

A useful extension of the lactam strategy (Scheme 1) involves introduction of the pharmacophoric group as a nucleophilic entity through initial halogenation of the lactam anions; the sequence is concluded by reduction of the lactam carbonyl group In this context, the *cis* and *trans* 2,5-substituted piperidines **1a,b** and **2a,b** were chosen as target molecules. Their structures are derived from that of the analgesic drug compound **3** by transposition of the 1- and 4-substituents. The analgesic and narcotic potency of **3** exceeds that of the well-known mepiridine with a factor of *ca.* 2,000.[7] For recognition of the receptor site, the orientation of the modified 2- and 5-substituents and the conformational mobility of the piperidine ring are of crucial importance Therefore, particular attention is paid in this work to the assignment of configurations and preferred conformations for the piperidine compounds.

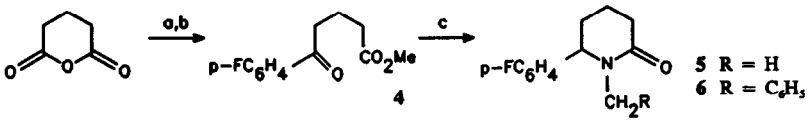


1a,b $R^1 = H$ **3 (R6582)**
2a,b $R^1 = C_6H_5$ [64440-2602]

Scheme 1

RESULTS AND DISCUSSION

The 6-aryl substituted lactams **5** and **6** were prepared from the 5-keto ester **4** *via* the reductive amination-cyclisation route depicted in Scheme 2. The 5-keto acid precursor of **4** was obtained by Friedel-Crafts acylation of fluorobenzene and glutaric anhydride.[8] The esterification to methyl ester **4** and the further conversion to lactams **5** and **6** were accomplished in excellent yield.



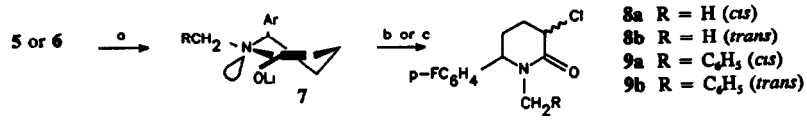
5 R = H
6 R = C_6H_5

a) C_6H_5F (1 2 eq), $AlCl_3$, CH_2Cl_2, 0°C, 78%, b) MeOH, C_6H_5Me, H_2SO_4, reflux, 91%, c) $MeNH_2$ HCl or $C_6H_5CH_2NH_2$, $NaCNBH_3$, MeOH, pH=6, reflux, 92 and 98%

Scheme 2

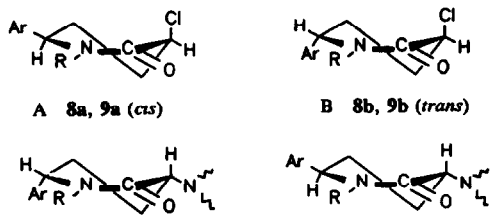
For α-chlorination of **5** and **6** (Scheme 3), the lactam anions **7** were generated with LDA in THF at -15°C. The solutions then were cooled to -100°C (for **5**) and -78°C (for **6**) and treated with benzenesulfonyl chloride as the chlorinating agent.[9] These procedures yielded 1:1 and 1:4 *cis*, *trans* mixtures **8a,b** (93%) and **9a,b** (96%). The isomers **8a** and **8b** were separated by column chromatography When chlorination of the N-methyl lactam **5** was carried out at -78°C, a mixture of **5**, **8a,b** and dichlorinated product was obtained (see below) In the ^1H NMR spectra of **8a**, **8b**, and **9a,b** (Table 1), the axial orientation of the α-chloro substituent is apparent from the Σ^3J values for H-3 Due to repulsion of the C=O and C-Cl dipoles, the orthogonal disposition is preferred to the parallel lining. This effect results in favoured conformations A for the *cis* compounds and B for the *trans* compounds (Fig 1) characterized, respectively, by Σ^3J values 13 5 Hz for H-6ax and 9 Hz for H-6eq (Table 1) The relative assignment of protons H-3 and H-6 was based on the large value measured for $^1J_{CHCl}$ (155 Hz) compared to $^1J_{CHAr}$ (143 Hz), in accordance with the reported incremental values.[10] Further support for this assignment came from

the ASIS (aromatic solvent induced shift)[11] measurements shown in Table 1, wich reveal values $\Delta\delta$ 0.4-0.7 for H-6 and the expected low values $\Delta\delta$ 0.1-0.3 for the α-proton H-3.



a) LDA, THF, -15°C, b) -100°C, $C_6H_5SO_2Cl$ (5 → 8, 93%), c) -78°C, $C_6H_5SO_2Cl$ (6 → 9, 96%)

Scheme 3



A **8a, 9a** (*cis*) B **8b, 9b** (*trans*)

C **10a, 11a, 12a, 13a** D **11b, 13b**

Fig.1 Preferred conformations for epimeric 3,6-substituted lactam compounds

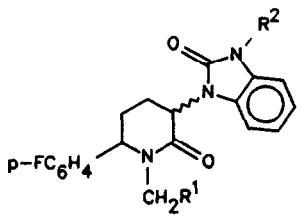
Table 1· Characteristic δ and Σ^3J values for protons H-3 and H-6 (or H-5 and H-2) in the ^1H NMR spectra of lactams **8-13** and piperidines **1a** and **2a,b**

Compound[A]	Solvent	H-3 δ	H-3 Σ^3J(Hz)	H-6 δ	H-6 Σ^3J(Hz)
8a(A)	$CDCl_3$	4 55[B]	9 5(t)	4 48[C]	13 5(dd)
	C_6D_6	4 35[D]	9 5(t)	3 8[D]	13 5(dd,8,5 5)
8b(B)	$CDCl_3$	4 53	8(t)	4 61	9(dd)
	C_6D_6	4 40[D]	8(t)	3 93[D]	9(dd,6,3)
9a(A)	$CDCl_3$	4 61		4 40	13.5(dd)
	C_6D_6	4 32	10(t)	3 92	13.5(dd,8,5 5)
9b(B)	$CDCl_3$	4 65	7 5(t)	4 55	9(dd)
	C_6D_6	4 37	7 5(t)	4 12	9(dd,6,3)
10a(C)	DMSO-d_6	5 05	18(dd,12,6)	4 80	6(dd,5,1)
11a(C)	$CDCl_3$	4 83	18(dd,12,6)	4 65	6(dd,5,1)
11b(D)	$CDCl_3$	5 23		4 55	15(dd,10,5)
12a(C)	DMSO-d_6	4 95	18(dd,12,6)	4 8	6(dd,5,1)
13a(C)	$CDCl_3$	5 17	18(dd,12,6)	4 78	7(dd,5,1)
13b(D)	$CDCl_3$	5 33	18(dd,12,6)	4 69	16(dd,11,5)
		H-5		H-2	
1a(mixt)[E]	$CDCl_3$-CD_3OD	4 75[F]	20(m)	3 30	broad
2a[2ax,5eq]	DMSO-d_6	4 58	28(m)	3 78	9(t,4 5)
2b[2eq,5eq]	DMSO-d_6	4 40	32(m)	3 40	13 5(dd,11,2 5)

A) see Fig 1 for preferred conformation, B) $^1J_{CHCl}$= 155 Hz, C) $^1J_{CHAr}$= 142 Hz, D) the corresponding C-atom was assigned by selective ^1H-^{13}C decoupling, E) conformational mixture, F) assigned by decoupling from the H-6 proton at δ 3 45 (dd, ^2J = 13Hz, $^3J_{6,5}$ = 3 5 Hz)

Substitution of the α-chloro lactams **8** and **9** (Scheme 4) was performed under phase transfer conditions with the anion derived from the N-protected reagent 1,3-dihydro-1-isopropenyl-2H-benzimidazol-2-one [12] However, prolonged reaction times were needed for complete reaction (6-7 days at 90°C) From the reaction of either pure *cis* or *trans* N-methyl lactam **8a** or **8b** (or the mixture **8a,b**), the same *cis* substituted product **10a** was obtained. This result was clarified when the epimerised reagent **8b** was detected by t l.c. as an intermediate in the conversion of *cis* compound **8a** to **10a**. In contrast, reaction of the N-benzyl compounds occurred without apparent epimerisation From the 1.4 *cis*, *trans* mixture **9a,b** the *trans* and *cis* products **11b** and **11a** were formed in a 3 7 ratio (60% yield) This ratio roughly corresponds to that expected for an S_N2 inversion.

Both the epimerisation **8a** → **8b**, and the dichlorination of **5** mentioned before, reflects the higher acidity of the N-methyl lactams **8a,b** compared to **9a,b** For the N-benzyl compounds, apparently anion formation is impeded by the increased steric interactions of the N-substituent in going from a planar amide to an sp^3 N-atom (see structure of the analogous anion **7**)



10a R^1 = H, R^2 = -CMe=CH_2 (*cis*)
11a R^1 = C_6H_5, R^2 = -CMe=CH_2 (*cis*)
11b R^1 = C_6H_5, R^2 = -CMe=CH_2 (*trans*)
12a R^1 = R^2 = H (*cis*)
13a R^1 = C_6H_5, R^2 = H (*cis*)
13b R^1 = C_6H_5, R^2 = H (*trans*)

	a	b	c
8a or **8b** or **8a,b**	→ **10a** (36%)	→ **12a** (80%)	→ **1a** (31%)
	a,d	b	c
9a,b	→ **11a** (58%)	→ **13a** (78%)	→ **2a** (57%)
	a,d	b	c
	→ **11b** (26%)	→ **13b** (75%)	→ **2b** (52%)

a) 1,3-dihydro-1-isopropenyl-2H-benzimidazol-2-one, KO*t*-Bu, Bu_4NHSO_4, C_6H_5Me, 90°C, b) 4M H_2SO_4 in H_2O-EtOH, reflux, c) BH_3 THF, THF, 55-65°C, d) chromatographic separation

Scheme 4

To remove the isopropenyl protecting group, the purified compounds **10a**, **11a** and **11b** were subjected to acid hydrolysis This afforded the corresponding benzimidazolone products **12a**, **13a** and **13b** (Scheme 4) In the ^1H NMR spectra of compounds **10-13** (Table 1), the preferred equatorial orientation of the benzimidazolone group is shown by the large Σ^3J values for H-3ax Consequently, the *cis* compounds **10a**, **11a**, **12a** and **13a** are characterized by small Σ^3J values for H-6eq, corresponding to the preferred [3eq,6ax] conformation C. For the *trans* compounds **11b** and **13b**, the [3eq,6eq] form D is apparent from the large Σ^3J values for both H-3ax and H-6ax

The final step in the synthesis of target compounds **1a**, **2a** and **2b** required reduction of the lactam carbonyl group This was accomplished by treatment of **12a**, **13a** and **13b** with BH_3 THF at 55-65°C (Scheme 4). In the ^1H NMR spectrum (Table 1) of **1a**, a conformational equilibrium was indicated by the low value (20 Hz) observed for $\Sigma(^3J_{5,4} + {}^3J_{5,6})$ Since proton H-5 is coupled to four vicinal protons, this value is consistent with a partial H-5eq orientation By contrast, the preferred orientations [2ax,5eq] and [2eq,5eq] were established for the 2- and 5-substituents of the N-benzyl compounds **2a** and **2b** This assignment was based on the high Σ^3J values found for the axial protons H-5 (28 and 32 Hz) and the characteristic coupling patterns observed for H-2eq (t, 4 5 Hz) and H-2ax (dd, 11 and 2 5 Hz) The

conformational differences between the *cis* compounds **1a** and **2a** can be attributed to steric interaction of the N-benzyl and 2-aryl groups.

In an extended set of receptor binding assays, including the target μ-opiate and kappa receptors, no appreciable binding affinity was observed for the piperidine compounds **1a**, **2a** and **2b**.

CONCLUSION

The synthesis of the target compounds **1a** and **2a,b** exemplifies a new approach to 2,5-substituted piperidines. The 2-substituent can be varied by using other 5-keto acids as precursors for the 6-substituted lactams. Subsequent α-chlorination of these lactams then allows for introduction of the 5-substituent as a nucleophilic entity.

The conformational mobility of the trisubstituted piperidine ring systems depends on various factors. For the 3,6-substituted lactams, the conformational preference is governed by the dipolar or steric interaction of the α-substituent. For the *trans* 2,5-substituted piperidine **2b**, the favourable [2eq,5eq] form prevails. The conformational equilibrium observed for *cis* N-methyl piperidine **1a** is shifted to the [2ax,5eq] form for the analogous N-benzyl compound

EXPERIMENTAL SECTION

IR spectra were recorded as thin films between NaCl plates or as solids in KBr pellets on a Perkin-Elmer 297 grating IR spectrofotometer. ^{1}H NMR spectra were recorded on a Varian EM-3940 90 MHz instrument, and ^{1}H and ^{13}C NMR spectra on a Bruker WM 250 instrument operating at 250 MHz for ^{1}H and 62.9 MHz for ^{13}C measurements The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to TMS as an internal standard. Mass spectra were run on a Kratos MS50 instrument and DS90 data system; 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).

***p*-Fluorophenyl-5-oxopentanoic acid**

To a stirred and cooled (0°C) mixture of $AlCl_3$ (39.3g, 0.30 mol) in 60 ml of anhydrous CH_2Cl_2 was added dropwise a solution of glutaric anhydride (15g, 0 13 mol) and fluorobenzene (14.9 ml, 0.16 mol) in 30 ml of anhydrous CH_2Cl_2 (N_2 atmoshere). After 5 h at 0°C, the reaction was worked up by addition of 100 ml of water and 20 ml of 35M HCl. The organic phase was separated and the aq. phase was extracted further with CH_2Cl_2. The organic phase was washed successively with cold 10M HCl (40 ml) and water (40 ml), then it was extracted with cold aq. Na_2CO_3 The aq phase was collected, acidified and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated to afford the crude acid (21.3g, 78%) as white crystals m p. (EtOAc-hexane) 142°C; ν_{Max} (KBr)/cm^{-1} 1705 (COOH), 1675 (CO), 1600, 1510, 840 (ArH); m/z 210 $(M)^+$, 192 $(M - H_2O)^+$, 164 $(M - H_2O - CO)^+$, 138 $(FC_6H_4C(OH)=CH_2)^+$, 123 $(FC_6H_4-CO)^+$, 95 $(FC_6H_4)^+$. δ_H (90 MHz; DMSO-d_6) 1.9 (2H, m, CH_2CH_2COOH), 2.3 (2H, t, ^3J 7.5 Hz, CH_2COOH), 3 1 (2H, t, ^3J 7 5 Hz, $COCH_2$), 7 3 (2H, t, ^3J 9 Hz, H-3', H-5' C_6H_4F), 8.1 (2H, dd, ^3J 9,6 Hz, H-2', H-6' C_6H_4F), 12 (1H, s, OH)

Methyl-5-*p*-fluorophenyl-5-oxopentanoate (4)

A mixture of *p*-fluorophenyl-5-oxopentanoic acid (1 00g, 4 8 mmol), 12 ml of MeOH and a catalytic amound of sulfuric acid in 20 ml of toluene was refluxed for 90 min. The solvent was evaporated, the residue was made alkaline with aq. Na_2CO_3 and the mixture extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica 3:97 EtOAc-$CHCl_3$) to give **4** as white crystals (1 00g, 93%) m.p (pentane) 44 5°C, ν_{Max} (KBr)/cm^{-1} 1740 ($COOCH_3$), 1685 (CO), 1600, 1510, 830 (ArH), m/z 225 $(M)^+$, 193 $(M - MeOH)^+$, 165 $(M - MeOH - CO)^+$, 138 $(FC_6H_4C(OH)=CH_2)^+$, 123 $(FC_6H_4CO)^+$, 95 $(FC_6H_4)^+$ δ_H (90 MHz;$CDCl_3$) 2.1 (2H, m, CH_2CH_2CO-OCH_3), 2 4 (2H, t, ^3J 7.5 Hz, CH_2COOCH_3), 3.1 (2H, t, ^3J 7 5 Hz, $COCH_2$), 3.7 (3H, s, CH_3), 7 2 (2H, t, ^3J 9 Hz, H-3', H-5', C_6H_4F), 8.1 (2H, dd, ^3J 9,6 Hz, H-2', H-6' C_6H_4F)

6-*p*-Fluorophenyl-1-methyl-2-piperidinone (5)

To a stirred solution of methylamine hydrochloride (3 5g, 52 mmol) in 70 ml of methanol (N_2 atmosphere) was added compound **4** (3.00g, 13 mmol) and $NaCNBH_3$ (2 0g, 31 mmol) The mixture was brought to pH 6 with HOAc, then it was refluxed for 6 h After evaporation, the residue was distributed between aq K_2CO_3 and CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica (gradient elution $CHCl_3$ → 3 7 EtOAc-$CHCl_3$) affording **5** as a yellow oil (2.47g, 92%) ν_{Max} (NaCl)/cm^{-1} 3450 (amine), 1640 (CO), 1610, 1510, 830 (ArH), m/z 207 $(M)^+$, 192 $(M - CH_3)^+$, 178 $(M - NCH_3)^+$, 150 $(M - CH_3NCO)^+$, 138 $(M - CH_2=CHCH_2CO)^+$, 136 $(M - CH_3CH_2CH_2CO)^+$, 122 $(FC_6H_4CH=CH_2)^+$, 112 $(M - FC_6H_4)^+$ [Found M^+ , 207 1049 $C_{12}H_{14}FNO$ requires M, 207 1059] δ_H (90 MHz;$CDCl_3$) 1.8-2.3 (4H, m, H-4, H-5), 2 5 (2H, t, ^3J 6 Hz, H-3), 2 8 (3H, s, CH_3), 4 6 (1H, t, ^3J 6 Hz, H-6), 7 1 (4H, s, ArH)

1-Benzyl-6-*p*-fluorophenyl-2-piperidinone (6)

In a procedure similar to that described for **5**, a solution prepared from benzylamine (5.6 ml, 52 mmol), 70 ml of methanol, **4** (3 00g, 13 mmol) and $NaCNBH_3$ (3.63g, 32 mmol) was adjusted to pH 6 with HOAc After reflux for 6 h, workup as described for **5** and chromatography over silica gel (gradient elution $CHCl_3$ → 3 7 EtOAc-$CHCl_3$) afforded **6** as a yellow oil (3 62g, 98%). ν_{Max} (NaCl)/cm^{-1} 3380 (amine), 1640 (CO), 1605, 1585, 1510, 830, 750, 700 (ArH), m/z 283 $(M)^+$, 214 $(M - CH_2=CHCH_2CO)^+$, 192 $(M - Bn)^+$, 178 $(M - NBn)^+$, 91 $(Bn)^+$ [Found M^+, 283 1367 $C_{18}H_{18}FNO$ requires M, 283 1372] δ_H (250 MHz,$CDCl_3$) 1 6-2 3 (2H, m, H-4, H-5), 2 6 (2H, t, ^3J 6 Hz, H-3), 3 3 (1H, d, ^2J 15 Hz, $CH_2C_6H_5$), 4 5 (1H, t, ^3J 4 5 Hz, H-6), 5 6 (1H, d, ^2J 15 Hz, $CH_2C_6H_5$), 7 2 (9H, m, ArH)

***Cis* and *trans* 3-chloro-6-*p*-fluorophenyl-1-methyl-2-piperidinone (8a and 8b)**

To a stirred and cooled (0°C) solution of diisopropylamine (0 73 ml, 5 2 mmol) in dry THF (15 ml) was added n-BuLi (1 6 M in hexane, 3.26 ml, 5 2 mmol) After 20 min the solution was cooled to -15°C, followed by dropwise addition of **5** (0 72g, 3 5 mmol) dissolved in dry THF (15 ml) The solution was stirred at -15°C for 30 min, cooled to -100°C, and treated dropwise with benzenesulfonyl chloride (1.1 ml, 8 7 mmol) After reaction at -100°C for 45 min, the mixture was allowed to come to room temp. The precipitate was filtered off and the mixture was distributed between water and CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated The residue was purified on silica gel (gradient elution $CHCl_3$ → 1.4 EtOAc-$CHCl_3$) to give the less polar *trans* isomer **8b** (0 37g, 46%) and the more polar *cis* isomer **8a**

(0 44g, 54%) (total yield 96%) ν_{Max} (NaCl)/cm^{-1} 1657 (CO), 1600, 1510, 840 (ArH); m/z 241 $(M)^+$, 223 $(M-H_2O)^+$, 206 $(M-Cl)^+$, 178 $(M-Cl-CO)^+$, 146 $(M-FC_6H_4)^+$, 136 $(FC_6H_4C{=}NCH_3)^+$, 122 $(FC_6H_4CH{=}CH_2)^+$ [Found M^+, 241.0670. $C_{12}H_{13}ClFNO$ requires M, 241.0668].

8a m p. (pentane-CH_2Cl_2) 79°C, δ_H (250 MHz,$CDCl_3$) 2.1-2.4 (4H, m, H-4, H-5), 2.76 (3H, s, CH_3), 4 48 (1H, dd, ^3J 8 5, 5 Hz, H-6ax), 4.55 (1H, t, ^3J 4.7 Hz, H-3eq), 7 2 (4H, m, ArH), δ_C ($CDCl_3$) 166.7 (C=O), 161.1 (C-4' C_6H_4F), 136.5 (C-1' C_6H_4F), 128 1 (C-2', C-6' C_6H_4F), 115.5 and 115 9 (C-3', C-5' C_6H_4F), 63 2 (C-6), 54.5 (C-3), 33.5 (CH_3), 28 3 (C-4,5)

8b: oil; δ_H (250 MHz;$CDCl_3$) 1.8 (1H, m, ΣJ 27 Hz) and 2 0 (1H, m, ΣJ 27 Hz) (H-4eq and H-5eq), 2 25 (1H, m, ΣJ 34 Hz) and 2 7 (1H, m, ΣJ 38 Hz) (H-4ax and H-5ax), 2.85 (3H, s, CH_3), 4 53 (1H, td, ^3J 4 Hz, ^4J 1 Hz, H-3eq), 4 61 (1H, dd, ^3J 6,3 Hz, H-6eq), 7 (4H, m, ArH), δ_C ($CDCl_3$) 166 5 (C=O), 161 8 (C-4' C_6H_4F), 135 7 (C-1' C_6H_4F), 128.6 (C-2', C-6' C_6H_4F), 115.4 (C-3', C-5' C_6H_4F), 62 3 (C-6), 54 3 (C-3), 34 5 (CH_3), 26 7 and 26.5 (C-4,5)

***Cis, trans* 1-benzyl-3-chloro-6-*p*-fluorophenyl-2-piperidinone (9a,b)**

In a procedure similar to that described for **8a** and **8b**, a solution of LDA in THF (15 ml) was prepared from n-BuLi (1 6M in hexane, 3 26 ml, 5 2 mmol) and diisopropylamine (0 73 ml, 5 2 mmol) To this solution was added at -15°C a solution of **6** (0 99g, 3 5 mmol) After being stirred for 30 min, the solution was cooled to -78°C and treated with benzenesulfonyl chloride (1 1 ml, 8 7 mmol) Workup as described for **8a** and **8b** and chromatography over silica (gradient elution $CHCl_3$ → 1 4 EtOAc-$CHCl_3$) afforded **9a,b** as a mixture of diastereoisomers (ratio of *cis/trans* isomers 20%/80%) (1 07g, 96%) ν_{Max} (NaCl)/cm^{-1} 1660 (CO), 1610, 1510, 760, 700, 840 (ArH), m/z 317 $(M)^+$, 282 $(M-Cl)^+$, 253 $(M-HCl-CO)^+$, 160 $(M-Cl-FC_6H_4CH{=}CH_2)^+$, 122 $(FC_6H_4CH{=}CH_2)^+$, 91 $(Bn)^+$ [Found M^+, 317 0983 $C_{18}H_{17}ClFNO$ requires M, 317 0981]

9a δ_H (250 MHz;$CDCl_3$) 1 9-2 3 (4H, m, H-4, H-5), 3 47 (1H, d, ^2J 15 Hz, $CH_2C_6H_5$), 4 4 (1H, dd, ^3J 8,6 Hz, H-6ax), 4 61 (1H, td, ^3J 5,5 Hz, ^4J 1 Hz, H-3eq), 5.41 (1H, d, ^2J 15 Hz, $CH_2C_6H_5$), 7-7.4 (9H, m, ArH), δ_C ($CDCl_3$) 59 8 (C-6), 54 8 (C-3), 47 7 ($CH_2C_6H_5$), 28.5 and 28 3 (C-4, C-5)

9b δ_H (250 MHz, $CDCl_3$) 1 75 (m), 2 0 (m), 2 30 (m) and 2 60 (m) (4H, H-4eq,ax, H-5eq,ax), 3.4 (1H, d, ^2J 15 Hz, $CH_2C_6H_5$), 4.55 (1H, dd, ^3J 6,3 Hz, H-6eq), 4 65 (1H, t, ^3J 3 7 Hz, H-3eq), 5 6 (1H, d, ^2J 15 Hz, $CH_2C_6H_5$), 7-7 4 (9H, m, ArH), δ_C ($CDCl_3$) 58 7 (C-6), 54 6 (C-3), 48 1 ($CH_2C_6H_5$), 26 5 and 26 2 (C-4, C-5)

***Cis* 3-(1,3-dihydro-3-methylethenyl-2-oxo-2H-benzimidazol-1-yl)-6-*p*-fluorophenyl-1-methyl-2-piperidinone (10a)**

To a solution of **8a,b** (1 00g, 4 1 mmol) and 1,3-dihydro-1-isopropenyl-2H-benzimidazol-2-one (1 31g, 7 5 mmol) in toluene (25 ml) was added KO*t*-Bu (0 84g, 7 5 mmol) and Bu_4NHSO_4 (0.41g, 1.2 mmol) The reaction mixture was stirred at 90°C under nitrogen for 7 days The solution was filtered, evaporated and the residue was dissolved in CH_2Cl_2 The solution was washed with water, dried over $MgSO_4$, and evaporated The residue was purified by column chromatography (silica, 1 4 EtOAc-$CHCl_3$) to afford **10a** (0 60g, 39%) as white crystals m p (hexane-EtOAc) 198°C, ν_{Max} (KBr)/cm^{-1} 1703 (NCON), 1654 (CON), 1605, 1610, 842, 733 (ArH), m/z 379 $(M)^+$, 206 $(M-R^{(3)})^+$, 205 $(M-R^{(3)}-H)^+$, 200 $(R^{(3)}CH{=}CH_2)^+$, 174 $(R^{(3)}H)^+$ [Found M^+, 379 1699 $C_{22}H_{22}FN_3O_2$ requires M, 379 1694] δ_H (250 MHz,DMSO-d_6) 1.7-2 6 (4H, m, H-4, H-5), 2 15 (3H, s, CH_3), 2.75 (3H, s, NCH_3), 4 8 (1H, d, Σ^3J 6 Hz, H-6eq), 5.05 (1H, dd,

^3J 12,6 Hz, H-3ax), 5.17 (1H, s) and 5.40 (1H, q, ^4J 1 Hz) (=CH_2), 7-7 35 (8H, m, ArH), 7.5 (2H, dd, ^3J 7 5,4.5 Hz, H-2', H-6', C_6H_4F); δ_C (DMSO-d_6) 166.6 (CON), 163.8 (C-4' C_6H_4F), 151.5 (NCON), 137.5 (C-1' C_6H_4F), 128.7, 121 2, 115.2, 113.0 and 108.4 (C-Ar and *C*=CH_2), 61.6 (C-6), 52.5 (C-3), 34 1 (NCH_3), 29.1 (C-5), 20.3 (C-4), 19.9 (CH_3)

***Cis* and *trans* 1-benzyl-3-(1,3-dihydro-3-methylethenyl-2-oxo-2H-benzimidazol-1-yl)-6-*p*-fluorophenyl-2-piperidinone (11a and 11b)**

In a procedure simular to that described for **10a**, compounds **9a,b** (1.00g, 3 2 mmol) were made to react with 1,3-dihydro-1-isopropenyl-2H-benzimidazol-2-one (0 63g, 3.6 mmol), KO*t*-Bu (0.81g, 7.2 mmol) and Bu_4NHSO_4 (0 31g, 0.9 mmol). The reaction mixture was stirred at 90°C under nitrogen for 6 days. Workup as described for **10a** and chromatography over silica gel (10:90 CH_3CN-$CHCl_3$) afforded the less polar *cis* isomer **11a** (0 85g, 58%) and the more polar *trans* isomer **11b** (0.38g, 26%) (total yield 84%).

11a oil, ν_{Max} (NaCl)/cm^{-1} 1711 (NCON), 1659 (CON), 1606, 1510, 842, 741, 702 (ArH); m/z 455 $(M)^+$, 281 $(M - R^{(3)})^+$, 253 $(M - R^{(3)} - CO)^+$, 200 $(R^{(3)}CH{=}CH_2)^+$, 174 $(R^{(3)}H)^+$, 91 $(Bn)^+$ [Found: M^+, 455.2007. $C_{28}H_{26}FN_3O_2$ requires M, 455 2007] δ_H (250 MHz;$CDCl_3$) 1.8-2 7 (4H, m, H-4, H-5), 2.26 (3H, s, CH_3), 3 45 (1H, d, ^2J 14 5 Hz, $CH_2C_6H_5$), 4.65 (1H, dd, ^3J 5,1 Hz, H-6eq), 4.83 (1H, dd, ^3J 12,6 Hz, H-3ax), 5 34 (1H, s) and 5 4 (1H, q, ^4J 1 Hz) (=CH_2), 5.65 (1H, d, ^2J 14.5 Hz, $CH_2C_6H_5$), 7.2 (11H, m, ArH), 7 5 (2H, dd, ^3J 7.5,4 5 Hz, H-3', H-5' C_6H_4F); δ_C ($CDCl_3$) 167 0 (CON), 160 5 (C-4' C_6H_4F), 152.7 (NCON), 138.1, 136 0, 129.7, 121.7, 116 1, 113 6, 109 5 and 107 7 (C-Ar and *C*=CH_2), 58.9 (C-6), 53.5 (C-3), 48.7 ($CH_2C_6H_5$), 30 3 (C-5), 20.9 (C-4), 20.2 (CH_3).

11b: m p (CH_2Cl_2-MeOH) 158°C, ν_{Max} NaCl/cm^{-1} 1704 (NCON), 1651 (NCO), 1605, 1500, 834, 742, 703 (ArH), m/z 455 $(M)^+$, 364 $(M - Bn)^+$, 200 $(R^{(3)}CH{=}CH_2)^+$, 175 $(R^{(3)}+2H)^+$, 91 $(Bn)^+$ [Found: M^+, 455.2014. $C_{28}H_{26}FN_3O_2$ requires M, 455 2007] δ_H (250 MHz,$CDCl_3$) 1 9-2.52 (4H, m, H-4, H-5), 2.27 (3H, s, CH_3), 3 51 (1H, d, ^2J 14 5 Hz, $CH_2C_6H_5$), 4 55 (1H, dd, ^3J 10,5 Hz, H-6ax), 5 23 (1H, dd, H-3ax), 5.25 (1H, s) and 5.40 (1H, q, ^4J 1 Hz) (C=CH_2), 5 46 (1H, d, ^2J 14.5 Hz, $CH_2C_6H_5$), 7 2 (13H, m, ArH).

***Cis* 3-(1,3-dihydro-2-oxo-2H-benzimidazol-1-yl)-6-*p*-fluorophenyl-1-methyl-2-piperidinone(12a)**

Compound **10a** (1.00g, 2 6 mmol) was dissolved in 20 ml 1:1 EtOH-H_2SO_4 (8M in water). The mixture was refluxed under nitrogen for 32 h The solution was made alkaline with aq. KOH and extracted with CH_2Cl_2 The combined extracts were dried, evaporated and chromatographed on a silica column (30·70 EtOAc-$CHCl_3$) to afford **12a** (0.73g, 80%) as a solid m p (hexane-EtOAc) 269°C, ν_{Max} (NaCl)/cm^{-1} 1709 (NCON), 1654 (NCO), 1600, 1510, 823, 760 (ArH); m/z 339 $(M)^+$, 206 $(M - R^{(3)})^+$, 177 $(M - R^{(3)}H - CO)^+$, $(M - R^{(3)}H - CO)^+$, 160 $(R^{(3)}CH{=}CH_2)^+$, 134 $(R^{(3)}H)^+$, 122 $(FC_6H_4CH{=}CH_2)^+$ [Found: M^+, 339 1382 $C_{19}H_{18}FN_3O_2$ requires M, 339.1382]. δ_H (250 MHz,DMSO-d_6) 1 7-2.65 (4H, m, H-4, H-5), 2 75 (3H, s, CH_3), 4.8 (1H, dd, ^3J 5,1 Hz, H-6eq), 4 95 (1H, dd, ^3J 12,6 Hz, H-3ax), 7 (4H, m, $ArH^{(3)}$), 7.2 (2H, m, H-2', H-6' C_6H_4F), 7.6 (2H, dd, ^3J 7.5,4.5 Hz, H-3', H-5' C_6H_4F), 7.7 (1H, s, NH); δ_C (DMSO-d_6) 166.8 (CON), 161 4 (C-4' C_6H_4F), 153.8 (NCON), 137 4 (C-1' C_6H_4F), 130 8, 128 4, 120.5, 120.3, 118.8, 115.0, 108.7 and 107 5 (C-Ar), 61 6 (C-6), 52 1 (C-3), 34.0 (CH_3), 29.1 (C-5), 20 5 (C-4)

***Cis* and *trans* 1-benzyl-3-(1,3-dihydro-2-oxo-2H-benzimidazol-1-yl)-6-*p*-fluorophenyl-2-piperidinone (13a and 13b)**

In procedures similar to that described for **12a**, compounds **11a** (1.00g, 2.2 mmol) and **11b** (1.00g, 2.2 mmol) were dissolved in 20 ml 1.1 EtOH-H_2SO_4 (8M in water) and the solutions were refluxed under nitrogen for 13.5 h. Workup as described for **12a** and purification by column chromatography on silica gel (gradient elution $CHCl_3$ → 1.1 EtOAc-$CHCl_3$) afforded **13a** (0.72g, 78%) and **13b** (0.69g, 75%)

13a. oil, ν_{Max} (NaCl)/cm^{-1} 1703 (NCON), 1655 (NCO), 1607, 1511, 820, 757 (ArH); m/z 415 $(M)^+$, 324 $(M\text{ -Bn})^+$, 310 $(M\text{ -NBn})^+$, 281 $(M\text{ -}R^{(3)}H)^+$, 253 $(M\text{ -}R^{(3)}H\text{ -CO})^+$, 160 $(R^{(3)}CH{=}CH_2)^+$, 106 $(HNBn)^+$, 91 $(Bn)^+$ [Found: M^+, 415.1700. $C_{25}H_{22}FN_3O_2$ requires M, 415 1694]. δ_H (250 MHz,$CDCl_3$) 1.7-2.5 (4H, m, H-4, H-5), 3.5 (1H, d, ^2J 15 Hz, $CH_2C_6H_5$), 4 78 (1H, dd, ^3J 6,1 Hz, H-6eq), 5.17 (1H, dd, ^3J 12,6 Hz, H-3ax), 5.36 (1H, d, ^2J 15 Hz, $CH_2C_6H_5$), 7-7.7 (13H, m, ArH), 10.87 (1H, s, NH); δ_C ($CDCl_3$) 167 1 (CON), 159.5 (C-4' C_6H_4F), 153 7 (NCON), 137.1, 129.2-127 0, 120.5, 115.0, 108.7 and 107 5 (C-Ar), 59.0 (C-6), 52.0 (C-3), 48.2 ($CH_2C_6H_5$), 29 1 (C-5), 20 3 (C-4).

13b: m p (hexane-MeOH) 247-248°C, ν_{Max} (NaCl)/cm^{-1} 1702 (NCON), 1646 (NCO), 1613, 1511, 820, 757 (ArH), m/z 415 $(M)^+$, 324 $(M\text{ -Bn})^+$, 281 $(M\text{ -}R^{(3)}H)^+$, 253 $(M\text{ -}R^{(3)}H\text{ -CO})^+$, 160 $(R^{(3)}CH{=}CH_2)^+$, 106 $(HNBn)^+$, 91 $(Bz)^+$ [Found: M^+, 415 1701 $C_{25}H_{22}FN_3O_2$ requires M, 415.1694] δ_H (250 MHz; $CDCl_3$) 2 3-2 65 (4H, m, H-4, H-5), 3.59 (1H, d, ^2J 15 Hz, $CH_2C_6H_5$), 4.69 (1H, dd, ^3J 11,5 Hz, H-6ax), 5.18 (1H, d, ^2J 15 Hz, $CH_2C_6H_5$), 5.33 (1H, dd, ^3J 12,6 Hz, H-3ax), 7 2 (13H, m, ArH); δ_C ($CDCl_3$) 167.6 (CON), 159.6 (C-4' C_6H_4F), 154 1 (NCON), 137 0, 130 1-126.9, 120.5, 115.3, 108 7 and 108 1 (C-Ar), 60 5 (C-6), 51 8 (C-3), 47 0 ($CH_2C_6H_5$), 31.1 (C-5), 24.4 (C-4)

***Cis* 5-(1,3-dihydro-2-oxo-2H-benzimidazol-1-yl)-2-*p*-fluorophenyl-1-methylpiperidine (1a)**

To a stirred solution of **12a** (0.25g, 0.70 mmol) in dry THF was added dropwise borane (1M in THF, 14.5 ml, 14 5 mmol). The mixture was heated at 65°C (N_2 atmosphere) for 14 h The reaction mixture was acidified with an excess of aq 2N HCl After being stirred for 1 h, the mixture was made alkaline with aq. K_2CO_3 and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica gel, EtOAc) affording **1a** (0.077g, 31%) as white crystals.

m.p (hexane-EtOAc) 220.5-220.9°C, ν_{Max} (KBr)/cm^{-1} 1694 (NCON), 1604, 1510, 834, 736 (ArH), m/z 325 $(M)^+$, 310 $(M\text{ -}CH_3)^+$, 230 $(M\text{ -}FC_6H_4)^+$, 191 $(M\text{ -}R^{(3)}H)^+$, 160 $(R^{(3)}CH{=}CH_2)^+$ [Found: M^+, 325.1574 $C_{19}H_{20}FN_3O$ requires M, 325 1590] δ_H (250 MHz,$CDCl_3$-CD_3OD) 1 8-2.5 (4H, m, H-3, H-4), 2 28 (3H, s, CH_3), 2.91 (1H, broad m, H-6), 3 37 (1H, broad m, H-2), 3 45 (1H, dd, ^3J 13,3.5 Hz, H-6), 4 75 (1H, m, Σ^3J 20 Hz, H-5), 7-8.2 (8H, m, ArH), 10 66 (1H, s, NH), δ_C (DMSO-d_6) 160.0 (C-4' C_6H_4F), 156.0 (NCON), 139.5 (C-1' C_6H_4F), 130.3, 129 2, 129 1, 128 2, 121.2, 115.5, 115 2, 111.5 and 109 5 (C-Ar), 66.4 (C-2), 54.5 (C-6), 49.6 (C-5), 43 0 (CH_3), 30.2 and 26 8 (C-3,4).

Anal Calcd for $C_{19}H_{20}FN_3O$: C, 70.13, H, 6 20; N, 12 91 Found. C, 69.80, H, 6 21; N, 12.63.

***Cis* and *trans* 1-benzyl-5-(1,3-dihydro-2-oxo-2H-benzimidazol-1-yl)-2-*p*-fluorophenyl piperidine (2a and 2b)**

To a stirred solution of **13a** or **13b** (0 25g, 0.60 mmol) in dry THF was added borane (1M in THF, 11 ml, 11 mmol). The mixture was heated at 50-60°C (N_2 atmosphere) for 13 h Workup as described for **1a** and purification by column chromatography (silica gel, gradient elution $CHCl_3$ → 1:1 EtOAc-$CHCl_3$) afforded **2a** (0 15g, 57%) or **2b** (0 14g, 52%)

2a oil, ν_{Max} (NaCl)/cm^{-1} 1695 (CO), 1604, 1500, 835, 734, 700 (ArH), m/z 401 $(M)^+$, 310 $(M\text{ -Bn})^+$, 267

(M -$R^{(5)}$H)$^+$, 176 (M -$R^{(5)}$H -Bn)$^+$, 160 ($R^{(5)}$CH=CH_2)$^+$, 109 ($FC_6H_4CH_2$)$^+$, 91 (Bn)$^+$ [Found: M$^+$, 401 1901 $C_{25}H_{24}FN_3O$ requires M, 401 1903] δ_H (250 MHz;DMSO-d_6) 1.7-2 4 (4H, m, H-3, H-4), 2.65 (1H, dd, ^2J 13 Hz, ^3J 5 Hz, H-6eq), 3.35 (1H, m, H-6ax), 3.78 (1H, d, ^2J 14 Hz, $CH_2C_6H_5$), 3.78 (1H, t, ^3J 4.5 Hz, H-2eq), 4.59 (1H, m, Σ^3J 28 Hz, H-5ax), 6.93 (3H, s, ArH), 7.29 (8H, m, ArH), 7.65 (2H, q, ArH), 10.79 (1H, s, NH); δ_C (DMSO-d_6) 159.1 (C-4' C_6H_4F), 153.9 (NCON), 138.7, 129.5-126 8, 120 1, 115 0, 108.7 (C-Ar), 59.8 (C-2), 57.9 (C-6), 48.5 (C-5), 47 1 ($CH_2C_6H_5$), 26.8 (C-3), 24.3 (C-4)
Anal Calcd for $C_{25}H_{24}FN_3O$· C, 74.79, H, 6.03; N, 10.47. Found· C, 74.51, H, 5.90; N, 10.20.
2b m.p. (CH_2Cl_2-MeOH) 283.5-284.2°C, ν_{Max} (KBr)/cm^{-1} 1698 (CO), 1606, 1509, 835, 757, 700 (ArH); m/z similar to that of compound **1b** [Found. M$^+$, 401.1900 $C_{25}H_{24}FN_3O$ requires M, 401.1903]. δ_H (250 MHz; DMSO-d_6) 1 7-1.95 (3H, m, H-3, H-4eq), 2 43 (1H, qd, ^2J and ^3J 13 Hz, ^3J 4 Hz, H-4ax), 2 84 (2H, m, H-6), 2 95 (1H, d, ^2J 12 5 Hz, $CH_2C_6H_5$), 3 40 (1H, dd, ^3J 11,2 5 Hz, H-2ax), 3.65 (1H, d, ^2J 12.5 Hz, $CH_2C_6H_5$), 4.4 (1H, m, Σ^3J 32 Hz, H-5ax), 6.8-7.8 (13H, m, ArH), 10.79 (1H, s, NH).
Anal Calcd for $C_{25}H_{24}FN_3O$ C, 74 79, H, 6 03, N, 10.47 Found C, 74 50, H, 5 90, N, 10.21.

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