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The synthesis and preliminary pharmacological evaluation of the racemic *cis* and *trans* 3-alkylfentanyl analogues

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Abstract: A general, five step method for the synthesis of 3-alkylfentanyl analogues (*i.e.*, *cis* and *trans* 3-alkyl-4-anilidopiperidines **6.1**–**6.6**) has been developed. The starting *N*-phenethyl-4-piperidone **1** was first converted into the cyclohexylimine derivative **2**, α-deprotonated with butyllithium and the resulting imine anion efficiently monoalkylated with primary and secondary alkyl halides. After mild acid hydrolysis, the obtained 3-alkyl-4-piperidones **3.1**–**3.6** were isolated in good yields (79–85 %), then condensed with aniline to form imines **4.1**–**4.6**. Subsequent reduction of the imines ($LiAlH_4$/THF) yielded *cis*/*trans* mixtures of 3-alkyl-4-anilinopiperidines **5.1**–**5.6**. Quantitative separation of the diastereoisomers by column chromatography of Al_2O_3 gave pure *cis* **5.1**–**5.6** (29–51 % yield) and *trans* **5.1**–**5.6** (19–27 % yield), with the *cis*/*trans* ratio in the range 7/3–6/4. The synthesis was concluded by *N*-acylation of the purified **5.1**–**5.6**, with propionyl chloride, to afford *cis* and *trans* 3-alkyl-4-anilidopiperidines **6.1**–**6.6** (≈ 95 % yield, as monooxalate salts). No enatioseparation was attempted at any stage. The relative *cis*/*trans* stereochemistry was provisionally assigned from the ^{1}H-NMR spectra. Of the twelve synthesized 3-alkylfentanyls, ten compounds (two known and eight novel derivatives, all as the monooxalate salts) were preliminarily tested as analgesics in rats, comparing the potency to fentanyl. Except for the known (±)-*cis*-3-Me fentanyl **6.1*cis***, (8 × fentanyl), and the novel (±)-*cis*-3-Et fentanyl **6.2*cis***, (1.5 × fentanyl), all of the others were less active than fentanyl or inactive. Some tentative conclusions on the structure-activity relationship (SAR) in this series of derivatives have been made.

INTRODUCTION

The exceptional opioid analgesic activity of 4-anilidopiperidines (general structure *I*, Scheme 1) has been well documented in the past forty years.[1] Clinically successful drugs,

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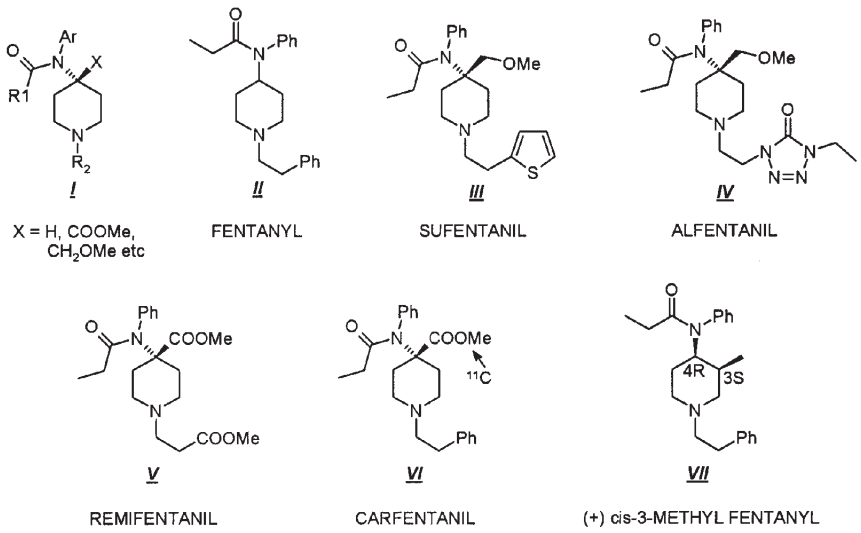
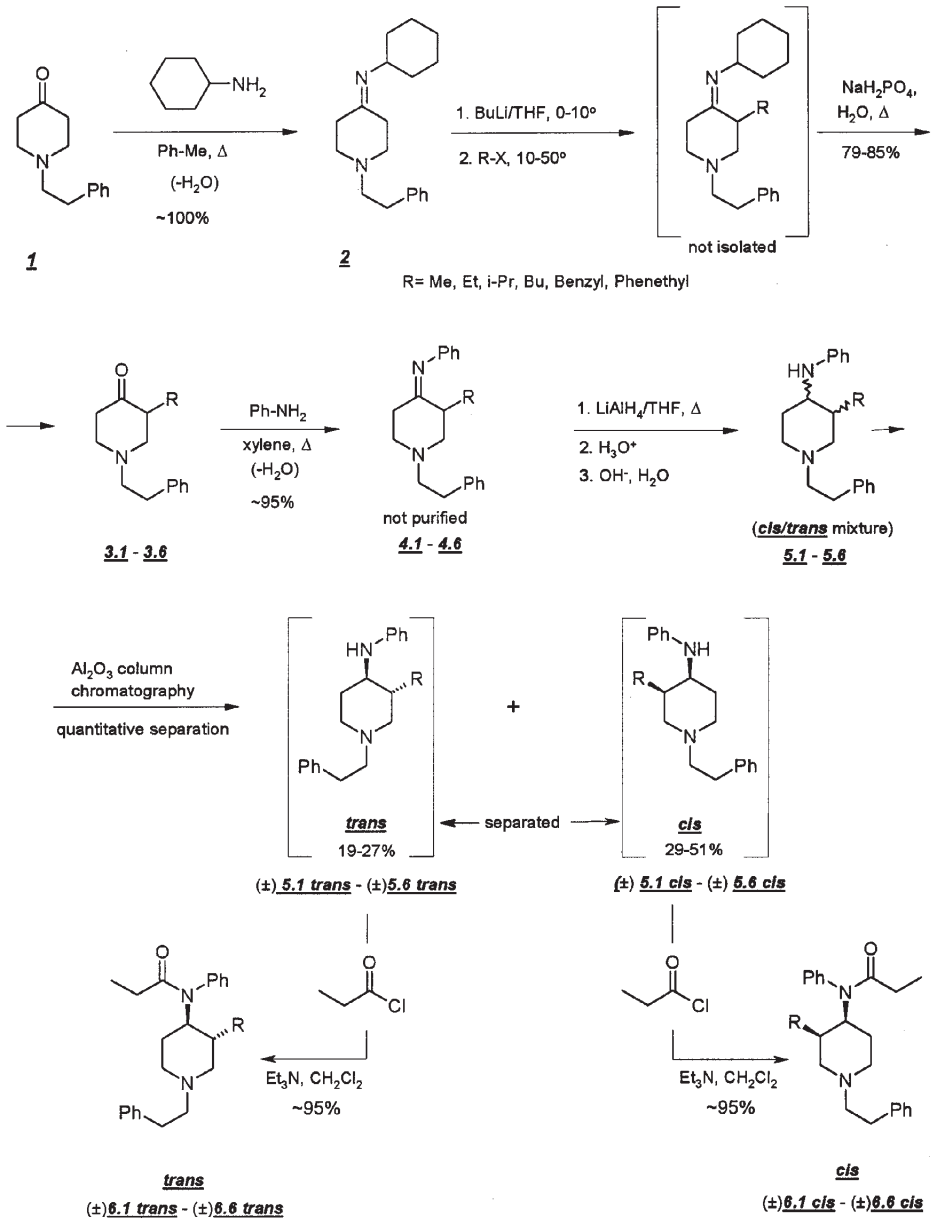


Scheme 1.

fentanyl *II*,[2] (a 50–100 times more potent analgesic in humans than morphine), sufentanil *III*,[2] (≈ 6 × fentanyl[3]), alfentanil *IV*,[2] (≈ 0.13 × fentanyl[4]) and remifentanil *V*,[2] (≈ 2.5–5 × fentanyl[5]) have been used extensively. Combined with various anesthetics, they have been employed in most of the major and minor surgeries, under the general anesthesia. Fentanyl and its derivatives are also widely used in conscious patients, to manage postoperative pain, in obstetrics and during various orthopedic interventions. Fentanyl transdermal patches (Duragesic®), with controlled drug release over several days, serve to control chronic cancer pain.[6] Carfentanil *VI* (≈ 20–30 × fentanyl[1a]) is a veterinary analgesic, used to sedate wild animals.[7] Numerous fentanyl analogues have been synthesized,[8] as potential candidates for novel drugs, in order to establish the structure-activity relationship (SAR) and to probe the opioid receptors. Isotopically labelled fentanyl derivatives have been employed in opioid receptor studies, both *in vitro* and *in vivo*. For example, positron emission tomography, (PET), with ^{11}C labelled carfentanyl, has been used in healthy volunteers to observe the opioid receptor distribution in the body organs and other receptor properties.[9]

Some thirty years ago it was disclosed that a methyl group introduced in the position 3 of the piperidine ring may dramatically enhance the activity, depending on the relative and the absolute stereochemistry.[10] Thus (+)-*cis*-3-Me fentanyl *VII* (≈19 × fentanyl) is *ca.* 100 times more potent as the (–)-enantiomer. The corresponding racemic *trans* isomer is approximately as active as fentanyl.[10b] Of the other 3-alkyl derivatives, only 3-Pr and 3-allyl analogues have been prepared up to the present[11] (Table II). Also, in an earlier work, 3-methoxycarbonyl fentanyl was synthesized.[8c]

These facts prompted us to prepare several novel 3-alkylfentanyl derivatives (general structure **6**, Scheme 2) and to establish the correlation between the structure (including stereochemistry) of the 3-alkyl group and the analgesic activity.



Scheme 2.

RESULTS AND DISCUSSION

The five step synthesis, starting from piperidone **1**, is outlined in Scheme 2. The requisite piperidones **3.1**–**3.6** were prepared by a modification of a general method for the

monoalkylation of carbonyl compounds *via* the imine or hydrazone derivatives.[12] Condensation of **1** and cyclohexylamine under azeotropic water separation gave imine **2**. The completion of the reaction was determined by IR spectroscopy (absence of the carbonyl band at ≈1710 cm^{-1}, presence of the imine band at ≈1665 cm^{-1}).

Deprotonation of **2** with butyllithium (THF, 10°) proceeded rapidly (like a titration) and quantitatively, yielding a bright, orange-red solution of the imine anion. No 1,2-addition reaction of butyllithium to the ketimine group was observed, as hydrolysis of the anion recovered only the starting piperidone **1**. The use of LDA instead of butyllithium was equally effective but offered no advantage in terms of the yields and purity of the products. The imine anion reacted rapidly with primary and secondary alkyl halides, MeI, EtI, *i*-PrI, BuBr and phenethyl bromide (PhenBr), to yield only the monoalkylated imine intermediates. Completion of the alkylation is observable visually, since the orange-red coloration of the anion changes to pale yellow. The imines are hydrolysed completely *in situ*, by the addition of an aqueous NaH_2PO_4 solution (pH ≈ 5–6), to afford good yields (79–85 %) of the corresponding 3-alkylpiperidones **3.1**–**3.6**. Only in the case of the 3-*i*-Pr derivative, the hydrolysis required lower pH (dil. HCl), apparently due to steric hindrance. Importantly, the obtained ketones were pure (≈ 95–98 %), containing neither polyalkylated products nor the starting piperidone **1** (0–3 %, acc to cap. GC and ^{1}H-NMR).

Conversion of piperidones **3.1**–**3.6** to the respective stereoisomeric 3-alkyl-4-anilinopiperidines **5.1**–**5.6** was effected in two steps, *via* the aromatic imine intermediates **4.1**–**4.6**. Similar procedures were applied earlier on some related systems.[13] The piperidones react with aniline (2 eq.) relatively slowly (12–36 h, depending on the steric hindrance), requiring boiling xylene and azeotropic water separation, as well as a Lewis acid catalyst (10 mol% of anh. $ZnCl_2$). In addition, the high sensitivity of the imines **4.1**–**4.6** to oxidative decomposition necessitates an inert atmosphere (Ar or N_2). Completion of the condensation was indicated by IR spectroscopy (disappearance of the carbonyl band at ≈1710 cm^{-1}, appearance of the imine band at ≈1660 cm^{-1}). Monitoring the reaction by TLC, GC or HPLC was not possible due to the rapid hydrolysis or decomposition of the imine.

The crude imines, together with the residual aniline, were then reduced using $LiAlH_4$ (4 eq. of H^-). The reduction was found to be sluggish in ether, but much faster in THF. Thus, it required ≈ 5–10 h to complete, depending on the steric hindrance of the imine. However, the reaction conditions had not been optimised with respect to the reaction time and the hydride mole ratio.

After the standard workup (excess hydride destruction with EtOAc and successive treatment with aqueous acid and alkali), the isolated residues consisted of *cis*/*trans* mixtures of the corresponding 3-alkyl-4-anilinopiperidine **5.1**–**5.6**, aniline and small amounts of the corresponding 3-alkylpiperidine-4-ol, (0–10 %, *cis*/*trans* mixture). The alcohols apparently originated from a partial hydrolysis of the imine, prior to reduction. After vacuum removal of the residual aniline and quantitative column chromatography separation on Al_2O_3, pure *cis*-**5.1**–**5.6** and *trans*-**5.1**–**5.6** diastereoisomers were obtained in all instances.

Yields of the pure 3-alkyl-4-anilinopiperidines ranged from 29–51 % for the *cis* isomers and from 19–27 % for the *trans* isomers, with the *cis*/*trans* ratio ≈ 7/3–6/4. Interestingly, the

diastereoisomers could not be separated by capillary GC nor on SiO_2 plates or columns, possibly due to a stronger, specific binding of the amines to silica as compared to alumina. The diastereoisomeric purity of **5.1**–**5.6** was determined to be ≈ 100 %, by ^{13}C-NMR and ^{1}H-NMR spectroscopy. The relative, *cis*/*trans* stereochemistry of the products was assigned from ^{1}H-NMR spectra of the corresponding 3-alkyl-4-anilidopiperidines **6.1**–**6.6**. Reduction procedures of imines **4.1**–**4.6** with some other reagents were examined briefly, following literature reports for related systems. Thus, reduction with $NaBH_3CN$ in MeOH or in a buffered methanolic solution[14] (citrate or acetate buffer, pH ≈ 5–6) produced very substantial amounts of the corresponding 3-alkylpiperidin-4-ol, due to the rapid hydrolysis of the imines by traces of moisture. Similarly, the alcohols predominated when reduction of the imines was attempted with a large excess of $NaBH_4$ in MeOH, EtOH or *i*-PrOH.[15] Catalytic hydrogenation[16] over 10 % Pd/C in MeOH, MeOH/buffer or EtOAc/AcOH, at 3–20 atm, was either exceedingly slow or led to hydrolysis and subsequent reduction to the alcohols.

Having prepared a total of 12 diastereoisomerically pure *cis* and *trans* anilinopiperidines **5.1**–**5.6**, the synthesis of the 3-alkylfentanyl analogues was completed by *N*-acylation of the secondary amino function, using propionyl chloride (2 eq.) in CH_2Cl_2. Despite the tertiary amino group in the piperidine ring serving as an HCl acceptor, it was found necessary to add extra base (0.5 eq. of Et_3N) to bring the reaction to completion. The obtained *cis* and *trans* anilidopiperidines **6.1**–**6.6**, where isolated and purified as the monooxalate salts, precipitated from *i*-PrOH, Et_2O, THF or EtOAc (> 95 % yields).

The relative, *cis*/*trans* stereochemistry was assigned by comparing the ^{1}H-NMR spectral data of *cis* and *trans* **6.1**–**6.6** to the published spectra[10b] of *cis*- and *trans*-3-Me fentanyl **6.1**, as represented in Table I. In the later instance, the absolute stereochemistry was determined by X-ray diffraction analysis. It was established that all of the prepared anilidopiperidines exhibit very specific ^{1}H-NMR signals of the C_4–H group in the piperidine ring. The signals possess a distinctive multiplicity and chemical shift, depending on the relative stereochemistry, Fig. 1. All the *cis* isomers, including *cis*-3-Me fentanyl **6.1*cis***, display a fully resolved doublet of triplets ($J_t \approx 4$ Hz, $J_d \approx 12$ Hz), except for **6.3*cis***, (3-*i*-Pr), which shows an apparent quintet. The chemical shifts, compared to the corresponding *trans* isomers, have uniformly lower values by ≈ 0.2 δ. The *trans* isomers show either triplets ($J_t \approx 11$–12 Hz), with additional partial splitting into doublets or fully resolved triplets of doublets as in the case of **6.5*trans*** compound (3-Phen, $J_d = 4$ Hz, $J_t = 11$ Hz). Thus, the relative stereochemistry of the synthesized fentanyl derivatives may be considered as being provisionally assigned with a considerable degree of certainty.

Ten of the synthesized compounds, all in the racemic form, were tested as opioid analgesics (*i.e.*, for antinociceptive activity) and compared with the potency to fentanyl. Those included two known compounds, *cis*-3-Me fentanyl **6.1*cis*** and *trans*-3-Me fentanyl **6.1*trans***, as well as eight novel derivatives: *cis*-3-Et fentanyl **6.2*cis***, *trans*-3-Et fentanyl **6.2*trans***, *cis*-3-*i*-Pr fentanyl **6.3*cis***, *cis*-3-Bu fentanyl **6.4*cis***, *trans*-3-Bu fentanyl **6.4*trans***, *cis*-3-Bn fentanyl **6.5*cis***, *trans*-3-Bn fentanyl **6.5*trans*** and *cis*-3-Phen fentanyl **6.6*cis***.

Wistar type rats (weighing 200–300 g) of both sexes were used in all the experiments. The analgesic (antinociceptive) activity was assessed by measuring the warm water in-

duced tail withdrawal reflex[17] after intraperitoneal administration of the oxalate salts of the tested compounds. Three doses of each compound were tested with 6–8 rats per dose and the obtained dose-response curves analysed using the linear regression statistical method. The ED_{50} values and the 95 % confidence limits were estimated from the dose-response curves using a standard statistical software.[18]

TABLE I. ^{1}H-NMR signals of the C_4–H group of *cis* and *trans* 3-alkyl-4-anilidopiperidines **6.1**–**6.6.** Chemical shift in ppm, coupling constants in Hz

No.	Compound	^{1}H-NMR (C_4–H signal)	No.	Compound	^{1}H-NMR (C_4–H signal)
1	**6.1** ***cis*** (3-Me)	4.41 (*dt*, J_t = 4.4, J_d = 12.6)[#]	7	**6.4** ***cis*** (3-Bu)	4.38 (*dt*, J_t = 4.5, J_d = 12.4)
2	**6.1** ***trans*** (3-Me)	4.58 (*t*, *J* = 11.4)[#]	8	**6.4** ***trans*** (3-Bu)	4.61 (*t*, *J* = 7.0)
3	**6.2** ***cis*** (3-Et)	4.40 (*dt*, J_t = 4.6, J_d = 12.4)	9	**6.5** ***cis*** (3-Bn)	4.49 (*dt*, J_t = 3.4, J_d = 12.4)
4	**6.2** ***trans*** (3-Et)	4.61 (*td*, J_d = 3, J_t = 12)	10	**6.5** ***trans*** (3-Bn)	4.75 (*t, J* = 10.0)
5	**6.3** ***cis*** (3-Pr)	4.60 (*quint*, *J* = 5.0)	11	**6.6** ***cis*** (3-Phen)	4.37 (*dt,* J_t = 4.6, J_d = 12.6)
6	**6.3** ***trans*** (3-Pr)	4.83 (*td*, J_d = 3.6, J_t = 12.0)	12	**6.5** ***trans*** (3-Phen)	4.64 (*td*, J_d = 4.0, J_t = 11.0)

[#] Lit. values[10b] for **6.1** ***cis***: 4.40 δ (*dt*, J_t = 5.0, J_d = 12.5); **6.1** ***trans***: 4.53 δ (*td*, J_d = 4.5, J_t = 12.5)

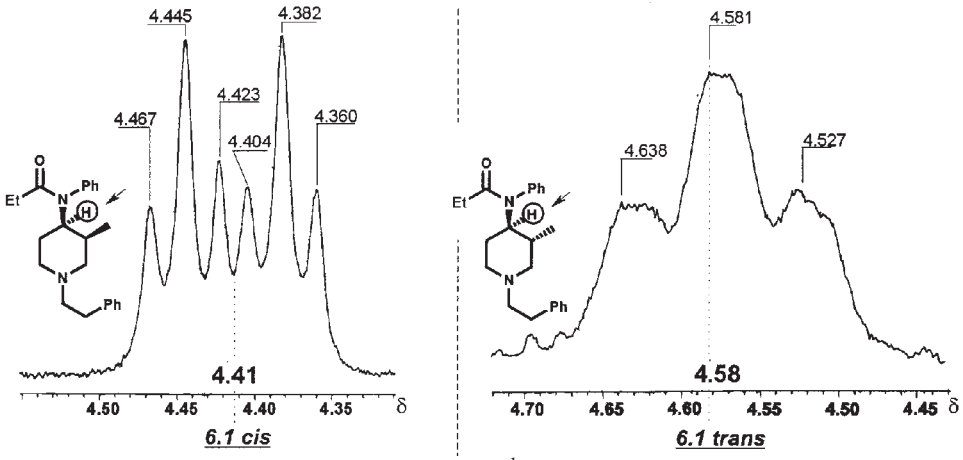


Fig. 1. Characteristic signals of the C_4–H proton in the ^{1}H-NMR spectra of *cis*-3-Me fentanyl **6.1*cis*** and *trans* 3-Me fentanyl **6.1*trans***. The signals are typical for all of the synthesized *cis*-and *trans*-3-alkylfentanyl analogues, respectively.

The absolute analgesic (antinociceptive) potencies, expressed as the ED_{50} value (dose that produced 50 % of the maximum possible antinociceptive effect), as well as the potencies relative to fentanyl are presented in Table II. For comparison, the literature values for

(±)-*cis*-3-Me fentanyl **6.1*cis*,** (±)-*trans*-3-Me fentanyl **6.1*trans***, (–)-*cis*-3-Me fentanyl, (+)-*cis*-3-Me fentanyl, (±)-*cis*-3-allyl fentanyl, (±)-*cis*-3-Pr fentanyl, (±)-*trans*-3-Pr fentanyl and morphine are also induded in Table II.

Based upon the preliminary results of the pharmacologic testing and in agreement with the published data, summarized in Table II, some tentative conclusions on the structure-activity relationship may be put forward.

– The presence of a substituent in position 3 of the piperidine ring generally decreases or completely inhibits the analgesic activity compared to fentanyl. Exceptions are the (+)-*cis*-3-Me analogue (≈ 19 × fentanyl) and (±)-*cis*-3-Et fentanyl **6.2*cis*** (≈ 1.5 × fentanyl). In the later instance, presumably, one of the enantiomers was much more active than the other.

– With increasing voluminosity of the alkyl group, the potency decreases rapidly. Thus (±)-*cis*-3-Pr fentanyl, (±)-*cis*-3-Bu fentanyl **6.4*cis***, and (±)-*cis*-3-Bn fentanyl **6.5*cis***, are 2, 16 and 126 times less potent than fentanyl, respectively. Derivatives which are even more bulky, (±)-*cis*-3-*i*-Pr fentanyl **6.3*cis***, and (±)-*cis*-3-Phen fentanyl **6.6*cis***, are inactive in doses up to 5 mg/kg.

– The relative *cis*/*trans* stereochemistry is important since the *cis* isomers are 1.5–6 times more active than the *trans* isomers.

– The absolute stereochemistry appears to be critical, judging from the fact that (+)-*cis*-3-Me fentanyl is about 100 times more active than the (–) enantiomer.

All of the tested compounds exhibited toxic effects characteristic for the μ selective opioid agonists, (such as morphine and fentanyl), including: Straub's tail, rigidity of the skeletal muscles, catalepsy, loss of the corneal and righting reflexes, impaired motoric coordination, and increased and/or decreased body temperature. All of the observed effects were fully antagonized by the nonselective opioid antagonist naloxone hydrochloride[19] (1 mg/kg), corroborating the hypothesis that the tested compounds are opioid agonists, most likely acting predominantly of μ opioid receptors. The detailed pharmacological results will be published elsewhere.

In conclusion, the presented synthetic method provides access to various 3-alkyl-4-anilidopiperidines **6.1**–**6.6**. The approach is relatively concise and efficient, except for the conversion of piperidones **3.1**–**3.6** to the anilinopiperidines **5.1**–**5.6** which is tedious and of low stereoselectivity, yielding *cis*/*trans* mixtures. However, as the diastereomeric mixtures are fully separable by simple column chromatography, the synthesis affords pure (±)-*cis* and (±)-*trans* 3-alkyl-4-anilidopiperidines **6.1**–**6.6**. The method may be useful, *inter alia*, to introduce isotopically labelled groups (^{13}C, ^{14}C, ^{11}C, ^{15}N), *via* the corresponding alkyl halides. In addition to simple alkyl groups, it is also possible to introduce some functional groups, compatible with the strongly basic imine anion (*e.g.*, amino, ether, ketal, carboxylate anion).[20]

Pharmacological results unambiguously show that all groups in the position 3 of the piperidine ring larger than methyl (and to a minimal extent ethyl), severely reduce the analgesic potency compared to fentanyl. It is likely that the steric factor alone, rather than the polarity and/or chemical reactivity, plays a crucial role in the pharmacological activity in

this series. Probably the more voluminous groups prevent the ligands from forming a sufficiently stable complex with the receptor, resulting in decreased analgesic activity.

TABLE II. Analgesic (antinociceptive) activities of 3-alkyl fentanyl analogues in the rat tail withdrawal test after intravenous (*iv*) and intraperitoneal (*ip*) administration (all the values differ considerably in humans)

No.	Compound	Route of administration	ED_{50}/(mg/kg)[A] (confidence limits)	Relative potency
1	Fentanyl	*iv*	0.011[B] (0.0095–0.0140)	1
		ip	0.0104[C] (0.006–0.018)	1
2	(±)-*cis*-3-Me Fentanyl **6.1*cis***	*iv*	0.0018[B,ref 10b] (0.0013–0.0024)	6.1
		ip	0.0013[C] (0.0012–0.0014)	8
3	(±)-*trans*-3-Me Fentanyl **6.1*trans***	*iv*	0.0094[B,ref 10b] (0.007–0.0127)	1.17
		ip	0.00525[C] (0.004–0.006)	1.98
4	(–)-*cis*-3-Me Fentanyl	*iv*	0.068[B,ref 10b] (0.051–0.091)	0.16
5	(+)-*cis*-3-Me Fentanyl	*iv*	0.00058[B,ref 10b] (0.00049–0.00068)	18.97
6	(±)-*cis*-3-Et Fentanyl **6.2*cis***	*ip*	0.0068[C] (0.0026–0.018)	1.49
7	(±)-*trans*-3-Et Fentanyl **6.2*trans***	*ip*	0.0116[C] (0.011–0.012)	0.9
8	(±)-*cis*-3-allyl Fentanyl	*iv*	0.08[B,D,ref 11]	0.138
9	(±)-*cis*-3-Pr Fentanyl	*iv*	0.02[B,D,ref 11]	0.55
10	(±)-*trans*-3-Pr Fentanyl	*iv*	0.04[B,D,ref 11]	0.275
11	(±)-*cis*-3-*i*-Pr Fentanyl **6.3*cis***	*ip*	no activity in doses up to 5 mg/kg[C]	–
12	(±)-*cis*-3-Bu Fentanyl **6.4*cis***	*ip*	0.162[C] (0.082–0.320)	0.064
13	(±)-*trans*-3-Bu Fentanyl **6.4*trans***	*ip*	0.348[C] (0.181–0.669)	0.03
14	(±)-*cis*-3-Bn Fentanyl **6.5*cis***	*ip*	1.31[C] (0.70–2.46)	0.0079
15	(±)-*trans*-3-Bn Fentanyl **6.5*trans***	*ip*	1.91[C] (0.39–9.4)	0.0054
16	(±)-*cis*-3-Phen Fentanyl **6.6*cis***	*ip*	no activity in doses up to 5 mg/kg[C]	–
17	Morphine	*iv*	3.14[B,D,ref 10b]	286

[A]ED_{50} values refer to the free bases of the tested compounds and are expressed in mg per kg of body weight; [B]Values reported in the literature; [C]Results obtained in our laboratories; [D]Confidence limits not reported

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer FT IR 1725X instrument, at 4 cm^{-1} resolution. ^{1}H-NMR and ^{13}C-NMR were recorded on a Varian Gemini spectrometer, at 200 MHz and 50 MHz, respectively, using $CDCl_3$ as the solvent and TMS as the internal standard. (In some ^{1}H-NMR spectra multiplet signals were insufficiently resolved for precise integration and the number of the corresponding hydrogens could not be determined. In those instances, only approximate multiplet intervals are reported). Coupling constants are given in Hz. Mass spectra were recorded on a Finnigan-Math instrument, model 8230, employing both the electron impact (70 eV) and chemical ionisation (with *i*-butane) technique. Gas chromatograms were obtained using a Varian 3400 instrument, on a nonpolar DB-5 column. MeOH, *i*-PrOH, Et_2O, THF, EtOAc, PhMe, hexane

and CH_2Cl_2 were of p.a. grade and purified further according to standard procedures. Absolute THF and Et_2O were prepared by distillation from benzophenone/sodium. Reagents were of p.a. grade and used as supplied (Aldrich Chemical Co., Merck Darmstadt Chemical Co. and Fluka Chemical Co.). Neutral Al_2O_3, activity II-III, Merck, Darmstadt was used for column chromatography while thin layer plates were coated with neutral Al_2O_3, HF_{254}, Merck, Darmstadt.

*1. N-[1-(2-Phenylethyl)piperidine-4-ylidene]cyclohexanamine (**2**)*

An apparatus equipped with a Dean and Stark adapter was purged with argon and charged with piperidone **1** (10.0 g, 49 mmol), cyclohexylamine (13.8 mL, 120 mmol), *p*-TsOH·H_2O (100 mg) and PhMe (100 mL). The mixture was stirred magnetically and heated under reflux, with continuous water separation, for 2 h, then cooled to ≈ 20 ºC under Ar and concentrated on a rotatory evaporator. The residual imine, dark viscous oil, is vacuum distilled (b.p. 165–170 ºC 0.1 torr). Yield: 13.52 g, ≈ 97 % (pale yellow viscous liquid). **2** hydrolyzes readily and is best kept under an Ar atmosphere. *IR*(cm^{-1}): 1665 (characteristic imine band).

*2. 3-Benzyl-1-phenethyl-piperidin-4-one (**3.5**)*

A typical procedure for the preparation of 3-alkyl piperidones **3.1**–**3.6** is illustrated on piperidone **3.5**. The method is directly applicable to all other 3-alkyl piperidones.

A three necked flask, equipped with a pressure equalizing dropping funnel, thermometer and a reflux condenser capped with a mineral oil bubbler was purged with Ar and charged with imine **2** dissolved in THF (5.0 g, 17.6 mmol/40 mL THF). Butyllithium (2.0 M in cyclohexane, ≈ 9.0 mL; 18.0 mmol) was injected into the dropping funnel and added dropwise, over 10 min, to the cooled (≈ 0 ºC) and stirred mixture. An intense yellow-orange coloration of the imine anion developed immediately. After additional stirring (15 min, ≈ 0 ºC), benzyl chloride (2.3 mL; 20 mmol/5 mL THF) was injected into the dropping funnel and then added dropwise (≈ 10 min, 0–5 ºC) to the reaction mixture. The reaction was mildly exothermic, LiCl precipitated and the yellow-orange coloration disappeared. The mixture was stirred for 1 h (≈ 20 ºC), then poured into aqueous $NaH_2PO_4·H_2O$ (5 g/50 mL water) and stirred for 30 min. The resulting emulsion was concentrated using a rotatory evaporator (≈ 50–60 ºC). The residue was extracted with CH_2Cl_2 (2 × 50 mL), the combined extracts dried (anh. K_2CO_3) and concentrated. Piperidone **3.5** was obtained as a yellow viscous oil. Yield: 4.80 g; 93 %. Purity (cap. GC): ≈ 96 %. Contamination with starting piperidone **1**: ≈ 1–2 %. The compound may be additionally purified on an Al_2O_3 column (30 g of alumina per 1 g of the substance) using hexane/EtOAc gradient (99:1, 98:2, *etc.*). *IR*/(cm^{-1}): 3422, 3082, 3058, 3024, 2965, 2950, 2928, 2904, 2858, 1709, 1667, 1600, 1495, 1476, 1453, 1424, 1376, 1362, 1335, 1279, 1250, 1219, 1166, 1139, 1080, 1050, 1029, 996, 889, 770, 749, 738, 723, 700; *^{1}H-NMR* (δ): 2.29–2.49 (*m*, 3H), 2.73–2.82 (*m*, 1H), 2.91–2.98 (*m*, 2H), 3.22 (*d*, *J* = 13.6, 1H), 3.40 (*d*, *J* = 12.0, 1H), 3.58–3.64 (*m*, 5H), 7.21–7.31 (*m*, $10H_{Ar}$). *^{13}C-NMR*/(ppm): 32.01, 32.63, 39.54, 49.88, 52.23, 56.98, 57.71, 124.88, 124.94, 127.13, 127.17, 127.38, 127.71, 138.18, 138.66, 208.74. *MS* (C.I.): 294 (M+1, 100).

The same procedure was used to prepare all the other piperidones **3**. The products were not purified by chromatography.

*3. (±)-3-Methyl-1-phenethyl-piperidin-4-one (**3.1**).*

From imine **2** (5.69 g, 20 mmol); Alkyl halide: MeI; Yield: 3.56 g; 82 %; Purity (cap. GC): 96 %. *IR*(cm^{-1}): 3085, 3062, 3027, 2964, 2932, 2806, 1716, 1603, 1496, 1472, 1455, 1418, 1378, 1358, 1329, 1220, 1187, 1139, 884, 751, 700; *^{1}H-NMR* (δ): 1.01 (*d*, *J* = 6.8, CH_3), 2.14 (*t*, *J* = 11.6, 1H), 2.30–2.49 (*m*, 2H), 2.53–2.73 (*m*, 4H), 2.77–2.88 (*m*, 2H), 3.12–3.22 (*m*, 2H), 7.15–7.37 (*m*, $5H_{Ar}$); *^{13}C-NMR*(ppm): 11.71, 33.87, 40.64, 44.00, 53.64, 58.90, 60.69, 125.97, 128.25, 128.49, 139.83, 210.56.

*4. (±)-3-Ethyl-1-phenethyl-piperidin-4-one (**3.2**).*

From imine **2** (5.69 g, 20 mmol); Alkyl halide: EtI; Yield: 3.93 g; 85 %; Purity (cap. GC): 95 %. *IR*(cm^{-1}): 3085, 3063, 3027, 2952, 2934, 1717, 1604, 1501, 1468, 1451, 1422, 1362, 1333, 1219, 1177, 1135, 1079, 1034, 887, 750, 698; *^{1}H-NMR* (δ): 0.89 (*t*, *J* = 6.8, CH_3), 1.23–1.33 (*m*, 1H), 1.74–1.90 (*m*, 1H), 2.19 (*t*, *J* = 10.8, 1H), 2.37–2.51 (*m*, 4H), 2.67–2.76 (*m*, 2H), 2.80–3.14 (*m*, 2H), 3.09–3.15 (*m*, 2H), 7.17–7.34 (*m*, $5H_{Ar}$); *^{13}C-NMR*(ppm): 11.18, 21.1, 33.89, 39.33, 51.11, 54.61, 61.35, 125.89, 128.01, 128.59, 139.87, 210.93.

*5. (±)-3-i-Propyl-1-phenethyl-piperidin-4-one (**3.3**).*

From imine **2** (5.69 g, 20 mmol); Alkyl halide: *i*-PrI; Yield: 3.88 g; 79 %; Purity (cap. GC): 95 %. *IR*(cm^{-1}): 3082, 3062, 3022, 2965, 2930, 1718, 1600, 1502, 1479, 1455, 1418, 1378, 1371, 1358, 1325, 1220, 1187, 1133, 747, 698; *^{1}H-NMR* (δ): 0.91 (*dd*, J_1 = 1.8, J_2 = 6.8, 2 CH_3), 1.55–1.85 (*m*, 1H), 2.22–2.26 (*m*, 2H), 2.46 (*t*, *J* = 6.2, 2H), 2.57–2.75 (*m*, 3H), 2.81–2.96 (*m*, 4H), 7.15–7.38 (*m*, 5H_{Ar}); *^{13}C-NMR*(ppm): 19.16, 20.67, 25.64, 33.90, 40.71, 53.66, 55.26, 56.17, 59.19, 125.94, 128.21, 128.47, 139.88, 210.71.

*6. (±)-3-Butyl-1-phenethyl-piperidin-4-one (**3.4**).*

From imine **2** (5.69 g, 20 mmol); Alkyl halide: BuBr; Yield 3.23 g; 83 %; Purity (cap. GC): 97 %. *IR*/(cm^{-1}): 3086, 3063, 3027, 2955, 2931, 2860, 1717, 1603, 1497, 1468, 1455, 1417, 1358, 1330, 1224, 1182, 1138, 1080, 1031, 887, 751, 700; *^{1}H-NMR* (δ): 0.89 (*t*, *J* = 7.0, CH_3), 1.21–1.36 (*m*, 5H), 1.71–1.92 (*m*, 1H), 2.24 (*t*, *J* = 10.8, 1H), 2.35–2.57 (*m*, 4H), 2.65–2.80 (*m*, 2H), 2.82–3.10 (*m*, 2H), 3.13–3.17 (*m*, 2H), 7.17–7.34 (*m*, 5H_{Ar}): *^{13}C-NMR*/(ppm): 13.86, 22.67, 26.88, 29.21, 34.00, 40.82, 49.58, 53.73, 58.94, 59.16, 126.08, 128.36, 128.62, 139.98, 210.85.

*7. (±)-1,3-Diphenethyl-piperidin-4-one (**3.6**).*

From imine **2**: 5.69 g, 20 mmol; Alkyl halide: PhenBr; Yield 3.92 g; 85 %; Purity (cap. GC): 94 %. *IR*(cm^{-1}): 3080, 3058, 3021, 2960, 2952, 2930, 2858, 1711, 1598, 1497, 1473, 1450, 1375, 1362, 1329, 1277, 1257, 1220, 1165, 1145, 1084, 1044, 1034, 999, 890, 771, 751, 740, 720, 701; *^{1}H-NMR* (δ): 2.13–2.42 (*m*, 5H); 2.66–2.78 (*m*, 1H); 2.84–2.95 (*m*, 2H); 3.31 (*d*, *J* = 12.5, 1H); 3.49 (*d*, *J* = 12.9; 1H); 3.61–3.68 (*m*, 5H); 7.22–7.32 (*m*, 10H_{Ar}); *^{13}C-NMR*(ppm): 32.21; 31.93; 33.02; 40.12; 51.08; 53.23; 56.14; 58.25; 124.69; 125.04; 127.11; 127.10; 127.79; 138.22; 138.97; 209.01.

*8. 3-Butyl-1-phenethyl-N-phenylpiperidin-4-amine (**5.4**).*

Typical procedure for the preparation of 3-alkyl-4-anilinopiperidines **5.1**–**5.6**, is illustrated on 3-butyl-4-anilinopiperidine (**5.4**). The method is directly applicable to all the other anilinopiperidines **5.1**–**5.6**.

A single necked flask equipped with a Dean and Stark adapter was purged with Ar and charged with piperidone **3.4** (3.0 g, 0.0116 mol), aniline (2.15 g, 2 eq.), anh. $ZnCl_2$ (0.16 g, 0.1 eq.) and xylene (100 mL). The mixture was stirred and refluxed for 36 h, under Ar, with azeotropic water separation, then cooled to ≈ 20 ºC and filtered under Ar. The filtrate was concentrated on a rotatory evaporator, using a moisture absorbing filter with 4A sieves, to prevent imine hydrolysis. The crude imine **4.4** was obtained as a dark-colored oil, containing residual aniline which was used directly in the next step. *IR* (cm^{-1}): 1660 (band characteristic of the imine group). A two necked flask equipped with a pressure-equalizing dropping funnel and a reflux condenser capped with a mineral oil bubbler (with gas inlet) was purged with Ar and charged with abs. THF (50 mL) and $LiAlH_4$ (0.44 g, 4 eq.). The mixture was stirred and heated to reflux, then imine **4.4** in THF (10 mL) was added dropwise, over 10 min (H_2 evolution). After 10 h (the Ar atmosphere was maintained), the mixture was cooled to ≈ 20 ºC, EtOAc (5 mL, 5 eq.) was added dropwise (H_2 evolution), followed by 10 % HCl (30 mL). The mixture was concentrated using a rotatory evaporator, the residue alkalized with 10 % NaOH to pH > 12, extracted (CH_2Cl_2, 3 × 50 mL), the combined extracts dried (anh. K_2CO_3) and concentrated. The excess aniline was removed under reduced pressure (0.5 mm Hg, 50 ºC, 30 min) and the residue chromatographed on an Al_2O_3 column (120 g of Al_2O_3) using hexane: EtOAc gradient: 99/1, 98/2, *etc*. The less polar *cis* isomer **5.4*cis*** eluted first followed by the *trans* isomer **5.4*trans***.

*8.1. (±)-**5.4*****cis***. Yield: 1.65 g, 42 % (pale yellow viscous oil). Purity (cap. GC) = 98 %. *IR*(cm^{-1}): 3410, 3085, 3055, 3026, 2952, 2929, 2858, 2803, 2767, 1601, 1503, 1467, 1455, 1434, 1376, 1317, 1255, 1205, 1180, 1156, 1128, 1104, 1076, 1030, 995, 749, 696; *^{1}H-NMR* (δ): 0.85 (*t*, *J* = 6.6, CH_3), 1.23–1.30 (*m*, 3 CH_2), 1.71–1.78 (*m*, 1H), 1.87–2.07 (*m*, 2H), 2.29–2.49 (*m*, 2H), 2.53–2.61 (*m*, 4H), 2.82 (*t*, *J* = 8.5, 2H), 3.61 (*q*, *J* = 4.8, 1H), 3.43–3.90 (*m*, 1H), 6.61 (*d*, *J* = 8.0, 2H_{Ar}), 6.70 (*t*, *J* = 7.0, 1H_{Ar}), 7.12–7.34 (*m*, 7H_{Ar}); *^{13}C-NMR*(ppm): 14.01, 23.03, 28.99, 31.32, 34.17, 34.66, 43.51, 52.32, 53.53, 59.11, 60.34, 112.81, 116.52, 125.69, 128,06, 128.40, 129.12, 140.16, 147.72, *MS* (C.I.): 245 (M–91.8), 337 (M+1, 100), 393 (M+57, 12).

*8.2. (±)-**5.4*****trans***. Yield: 1.00 g, 26 % (pale yellow viscous oil). Purity (cap. GC) = 98 %. *IR*(cm^{-1}): 3376, 3085, 3055, 3026, 2952, 2929, 2858, 1602, 1501, 1467, 1455, 1376, 1320, 1270, 1181, 1153, 1132, 1111, 1037, 1030, 992, 959, 868, 748, 696, *^{1}H-NMR* (δ): 0.87 (*t*, *J* = 6.6, CH_3), 1.10–1.44 (*m*, 3CH_2), 1.49–1.59 (*m*, 1H), 1.71–1.79 (*m*, 1H), 1.87 (*m*, 1H), 2.05–2.21 (*m*, 2H), 2.57–2.66 (*m*, 2H), 2.84 (*t*, *J* = 6.2, 2H), 2.93–3.15 (*m*, 3H), 3.42–3.80 (*m*, 1H), 6.58 (*d*, *J* = 8.0, 2H_{Ar}), 6.67 (*t*, *J* = 7.0, 1H_{Ar}), 7.10–7.34 (*m*, 7H_{Ar}). *^{13}C-NMR*(ppm): 13.91,

22.83, 29.08, 30.20, 32.27, 33.66, 42.30, 52.49, 54.71, 58.30, 60.43, 112.76, 116.60, 125.79, 128.16, 128.48, 129.07, 140.21, 147.66; (*MS* (C.I.): 245 (M–91, 10), 337 (M+1, 100), 393 (M+57, 10).

9. 3-Methyl-1-phenethyl-N-*phenylpiperidin-4-amine (**5.1**).*

From piperidone 3.1 (4.0 g, 0.0184 mol).

*9.1. (±)-**5.1*****cis***. Yield: 2.77 g, 51 % (pale yellow viscous oil). Purity (cap. GC) = 98 %. *IR*/(cm^{-1}): 3395, 3085, 3056, 3025, 2947, 1602, 1505, 1467, 1455, 1436, 1373, 1354, 1322, 1271, 1179, 1126, 1108, 1092, 1070, 1030, 992, 977, 867, 695; *^{1}H-NMR* (δ): 0.99 (*d*, *J* = 7.0, CH_3), 1.80 (*quint*, *J* = 4.6, CH_2), 2.12–2.30 (*m*, 1H), 2.48–2.68 (*m*, 6H), 2.81 (*t*, *J* = 8.4, 2H) 3.52–3.55 (*m*, 2H), 6.59–6.71 (*m*, $3H_{Ar}$), 7.13–7.33 (*m*, $7H_{Ar}$). *^{13}C-NMR*(ppm): 11.57, 29.00, 33.65, 40.26, 49.28, 50.10, 54.39, 60.64, 112.93, 116.74, 125.85, 128.22, 128.56, 129.18, 140.35, 147.17; *MS* (C.I.): 203 (M–91, 10), 295 (M+1, 100).

*9.2. (±)-**5.1*****trans***. Yield: 1.13 g, 21 % (pale yellow viscous oil). Purity (cap. GC) = 98 %. *IR*(cm^{-1}): 3395, 3085, 3055, 3025, 2947, 1602, 1505, 1466, 1455, 1437, 1371, 1354, 1322, 1272, 1181, 1126, 1107, 1090, 1070, 1030, 990, 977, 869, 695; *^{1}H-NMR* (δ): 1.01 (*d*, *J* = 6.6, CH_3), 1.37–1.50 (*m*, 1H), 1.58–1.76 (*m*, 1H), 1.86 (*t*, *J* = 10.8, 1H), 2.03–2.21 (*m*, 2H), 2.57 (*dd*, J_1 = 1.6, J_2 = 7.0, 1H), 2.62 (*d*, *J* = 4.6, 1H), 2.78–2.92 (*m*, 3H), 2.98–3.06 (*m*, 2H), 3.18–3.38 (*m*, 1H), 6.56–6.69 (*m*, $3H_{Ar}$), 7.12–7.33 (*m*, $7H_{Ar}$); *^{13}C-NMR*(ppm): 16.62, 32.59, 33.77, 37.84, 53.00, 56.52, 60.41, 60.91, 112.86, 116.74, 125.93, 128.29, 128.60, 129.20, 140.31, 147.82; *MS* (C.I.); 203 (M–91, 10) 295 (M+1, 100), 351 (M+57, 10).

10. 3-Ethyl-1-phenethyl-N-*phenylpiperidin-4-amine (**5.2**).*

From piperidone **3.2** (2.0 g, 0.00864 mol).

*10.1. (±)-**5.2*****cis***. Yield: 1.02 g, 38 % (pale yellow viscous oil). Purity (cap. GC) = 98 %. *IR*(cm^{-1}): 3418, 3084, 3053, 3025, 2956, 2874, 2803, 2768, 1601, 1504, 1467, 1455, 1433, 1373, 1316, 1253, 1180, 1124, 1100, 1075, 1046, 1030, 992, 748, 695, 506; *^{1}H-NMR* (δ): 0.89 (*t*, CH_3, *J* = 7.4), 1.39 (*quint*, CH_2, *J* = 7.4), 1.62–1.75 (*m*, 1H), 1.86–1.91 (*m*, 2H), 2.21–2.48 (*m*, 3H), 2.54–2.64 (*m*, 3H), 2.82 (*t*, *J* = 7.8, 2H), 3.57–3.70 (*m*, 2H), 6.59–6.70 (*m*, $3H_{Ar}$), 7.09–7.38 (*m*, $7H_{Ar}$); *^{13}C-NMR*(ppm): 11.57, 21.25, 29.00, 33.65, 40.26, 49.28, 50.10, 54.39, 60.64, 112.93, 116.74, 125.85, 128.22, 128.56, 129.18, 140.35, 147.17; *MS* (C.I.): 217 (M–91, 15), 309 (M+1, 100), 365 (M+57, 10).

*10.2. (±)-**5.2*****trans***. Yield: 0.71 g, 27 % (pale yellow viscous oil). Purity (cap. GC) = 98 %. *IR*(cm^{-1}): 3397, 3085, 3054, 3025, 2958, 2936, 2875, 2804, 2767, 1602, 1505, 1466, 1455, 1435, 1376, 1320, 1276, 1181, 1154, 1131, 1110, 1072, 1030, 748, 695; *^{1}H-NMR* (δ): 0.89 (*t*, CH_3, *J* = 7.4), 1.11–1.25 (*m*, 1H), 1.36–1.49 (*m*, 2H), 1.73–1.88 (*m*, 2H), 1.99–2.16 (*m*, 2H), 2.53–2.63 (*m*, 2H), 2.77–2.84 (*m*, 2H), 2.91–3.11 (*m*, 3H), 6.52–6.67 (*m*, $3H_{Ar}$), 7.10–7.32 (*m*, $7H_{Ar}$); *^{13}C-NMR*(ppm): 11.22, 23.13, 32.30, 33.61, 43.86, 52.55, 54.33, 57.79, 60.49, 112.67, 116.56, 125.87, 128.21, 128.52, 129.12, 140.18, 147.68; *MS* (C.I.): 217 (M–91, 15), 309 (M+1, 100), 365 (M+57, 10).

11. 3-i-Propyl-1-phenethyl-N-*phenylpiperidin-4-amine (**5.3**).*

From piperidone **3.3** (3.0 g, 0.0122 mol).

*11.1. (±)-**5.3*****cis***. Yield: 1.13 g, 29 % (pale yellow viscous oil). Purity (cap. GC) = 98 %. *IR*(cm^{-1}): 3425, 3053, 3025, 2953, 2870, 1601, 1505, 1469, 1455, 1430, 1383, 1365, 1350, 1314, 1249, 1214, 1179, 1147, 1104, 1085, 1030, 1011, 747, 693; *^{1}H-NMR* (δ): 0.89 (*d*, *J* = 6.0, CH_3), 0.95 (*d*, *J* = 6.2, CH_3), 1.53–1.73 (*m*, 3H), 1.94 (*qd*, J_q = 11.4, J_d = 2.2, 2H), 2.17 (*td*, J_d = 2.4, J_t = 12.8, 1H), 2.56–2.70 (*m*, 2H), 2.71–2.88 (*m*, 3H), 2.98–3.06 (*m*, 1H), 3.80 (broad. *s*, 2H), 6.58–6.70 (*m*, $3H_{Ar}$), 7.12–7.33 (*m*, $7H_{Ar}$); *^{13}C-NMR*(ppm): 20.34, 20.94, 27.33, 29.10, 33.67, 46.21, 46.30, 47.87, 52.89, 61.03, 112.78, 116.76, 126.03.

*11.2. (±)-**5.3*****trans***. Yield: 0.92 g, 23 % (pale yellow viscous oil). Purity (cap. GC): 98 %. *IR*/(cm^{-1}): 3392, 3053, 3025, 2955, 2871, 1602, 1505, 1466, 1454, 1434, 1369, 1353, 1318, 1283, 1233, 1181, 1154, 1137, 1123, 1071, 1031, 992, 749, 699; *^{1}H-NMR* (δ): 0.84 (*d*, *J* = 7.0, CH_3), 0.98 (*d*, *J* = 7.0, CH_3), 1.36–1.59 (*m*, 2H), 1.93 (*d*, *J* = 11.2, 1H), 2.04 (*d*, *J* = 10.4, 1H), 2.14–2.23 (*m*, 2H), 2.56–2.63 (*m*, 2H), 2.79–2.87 (*m*, 2H), 2.93–3.00 (*m*, 2H), 3.28 (*br. s*, 2H), 6.57–6.69 (*m*, $3H_{Ar}$), 7.12–7.34 (*m*, $7H_{Ar}$); *^{13}C-NMR* (ppm): 17.17, 20.94, 25.86, 32.54, 33.85, 47.30, 51.80, 52.75, 53.35, 60.89, 112.85, 116.80, 126.05, 128.40, 128.69, 129.36, 140.36, 147.64.

12. 3-Benzyl-1-phenethyl-N-*phenylpiperidin-4-amine (**5.5**).*

From piperidone **3.5** (2.0 g, 0.00681 mol).

*12.1. (±)-**5.5*****cis***. Yield: 1.02 g, 40 % (pale yellow viscous oil). Purity (cap. GC): 98 %. *IR*(cm^{-1}): 3401,

3084, 3059, 3025, 2942, 2859, 2802, 2767, 1602, 1504, 1468, 1454, 1434, 1372, 1314, 1288, 1255, 1179, 1154, 1120, 1071, 1030, 1004, 983, 910, 699, 506; *^{1}H-NMR* (δ): 1.73–1.88 (*m*, 3H), 2.28–2.82 (*m*, 10H), 3.45–3.60 (*m*, 1H), 3.67 (*br. s*, 1H), 6.58–6.74 (*m*, 3H$_{Ar}$), 7.00–7.34 (*m*, 12H$_{Ar}$); *^{13}C-NMR* (ppm): 28.72, 33.54, 40.49, 50.47, 50.68, 53.22, 54.20, 60.26, 113.29, 117.00, 125.58, 125.78, 128.01, 128.12, 128.53, 129.03, 129.12, 140.36, 140.55, 146.80; *MS* (C.I.): 280 (M–90, 25), 371 (M+1, 100), 427 (M+57, 20).

*12.2. (±)-**5.5*****trans***. Yield: 0.52 g, 0.21 % (pale yellow viscous oil). Purity (cap. GC): 98 %. *IR* (cm^{-1}): 3402, 3084, 3058, 3025, 2942, 2858, 2804, 2766, 1601, 1505, 1497, 1468, 1454, 1435, 1375, 1319, 1270, 1218, 1181, 1154, 1118, 1072, 1031, 748, 699; *^{1}H-NMR* (δ): 1.44 (*qt*, J_t = 1.6, J_q = 11.6, 1H), 1.84–1.92 (*m*, 2H), 2.13 (*qd*, J_d = 2.6, J_q = 11.2, 2H), 2.40–2.58 (*m*, 3H), 2.65–2.77 (*m*, 2H), 2.85–2.97 (*m*, 2H), 3.11 (*dd*, J_{d1} = 3, J_{d2} = 13.4, 2H), 3.35–3.55 (*br. s*, 1H), 6.58 (*d*, *J* = 8.6, 2H$_{Ar}$), 6.68 (*t*, *J* = 8.2, 1H$_{Ar}$), 7.08–7.38 (*m*, 12H$_{Ar}$); *^{13}C-NMR* (ppm): 32.10, 33.64, 37.29, 43.88, 52.30, 54.40, 57.83, 60.30, 113.00, 116.95, 125.83, 125.86, 128.16, 128.21, 128.54, 129.04, 129.22, 140.00, 140.24, 147.47; *MS* (C.I.): 279 (M–91, 30), 371 (M+1, 100), 428 (M+58, 20).

*13. 1,3-Diphenethyl-*N*-phenylpiperidin-4-amine (**5.6**).*

From piperidone **3.6** (2.0 g, 0.0065 mol).

*13.1 (±)-**5.6*****cis***. Yield: 0.78 g (31 %) (pale yellow viscous oil). Purity (cap. GC): 98 %. *IR* (cm^{-1}): 3402, 3084, 3058, 3025, 2945, 2858, 2804, 1604, 1514, 1501, 1465, 1442, 1381, 1330, 1277, 1220, 1182, 1150, 1122, 1062, 1030, 755, 700; *^{1}H-NMR* (δ): 1.33–1.69 (*m*), 1.86–1.97 (*m*), 2.05–2.18 (*m*), 2.35 (*s*, NH), 2.54–2.63 (*m*), 2.65–2.73 (*m*), 2.78–2.82 (*m*), 2.98–3.31 (*m*), 6.51–6.68 (*m*, 2H$_{Ar}$), 7.05–7.18 (*m*, 13H$_{Ar}$); *^{13}C-NMR* (ppm): 28.73, 33.18, 33.41, 37.74, 49.67, 50.14, 54.49, 60.22, 113.01, 116.84, 125.50, 125.81, 128.07, 128.11, 128.15, 128.47, 129.11, 140.09, 142.00, 147.01; *MS* (C.I.): 441 (M+57, 10 %), 385 (M+1, 100 %).

*13.2 (±)-**5.6*****trans***. Yield: 0.48 g (19 %) (pale yellow viscous oil). Purity (cap. GC): 98 %. *IR* (cm^{-1}): 3402, 3084, 3058, 3025, 2945, 2858, 2804, 1605, 1514, 1501, 1464, 1440, 1382, 1331, 1277, 1220, 1177, 1150, 1120, 1062, 1029, 748, 702; *^{1}H-NMR* (δ): 1.45–1.63 (*m*), 1.84–1.97 (*m*), 2.01–2.21 (*m*), 2.40 (*s*, NH), 2.55–2.64 (*m*), 2.65–2.73 (*m*), 2.78–2.82 (*m*), 3.00–3.31 (*m*), 6.51–6.68 (*m*, 2H$_{Ar}$), 7.05–7.18 (*m*, 13H$_{Ar}$): *^{13}C-NMR* (ppm): 29.05, 33.38, 33.49, 37.61, 49.70, 50.11, 54.55, 60.27, 113.09, 116.88, 125.48, 125.83, 128.06, 128.14, 128.19, 128.52, 129.06, 140.12, 142.08, 147.04; *MS* (C.I.): 441 (M+57, 14 %), 385 (M+1, 100 %).

*14. A typical procedure for the preparation of the 3-alkyl-4-anilidopiperidines **6.1**–**6.6**.*

This procedure is illustrated on compound (±)-**6.1*cis*** and it is directly applicable to all the other anilidopiperidines **6.1**–**6.6**. All the yields and the m.p.(dec.) values refer to the monooxalate salts. All the spectral data refer to the free bases.

*14.1. (±)-*cis-N-*(3-Methyl-1-phenethylpiperidin-4-yl)-*N*-phenylpropionamide* (**6.1*cis***). A three necked flask, equipped with a pressure-equalizing dropping funnel, reflux condenser capped with a mineral oil bubbler and a thermometer was flushed with Ar and charged with anilinopiperidine **5.1*cis*** (1.47 g; 5 mmol), Et_3N (0.35 mL; 2.5 mmol) and CH_2Cl_2 (15 mL). The mixture was cooled (–5–0 ºC), propionyl chloride (0.9 mL; 10 mmol/5 mL CH_2Cl_2) added dropwise over 5 min at 0–5 ºC and the stirring continued for 4 h at 20 ºC. The hydrochloride salts form a voluminous precipitate. Upon addition of MeOH (5 mL), the precipitate dissolved, the mixture was stirred for 10 min and then poured into aqueous K_2CO_3, (5 g/50 mL H_2O). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layers were dried (anh. K_2CO_3) and concentrated (rotatory evaporator). The residual oil was dissolved in dry *i*-PrOH (5 mL), added to anh. oxalic acid solution (0.55 g; 6.1 mmol/5 mL *i*-PrOH) and the mixture is left to crystallize at –20 ºC (12 h). The crystallized salt was filtered off, washed with ether and dried under vacuum (40 ºC, 2 h, 0.1 Torr). Yield: 2.07 g (94 %); m.p. (dec.): 162–163 ºC (Lit.[9b] 163–164 ºC). The purity of the free base (liberated from the oxalate salt), cap. GC > 99 %; pale yellow viscous oil.

Free base: *IR* (cm^{-1}): 3455, 3061, 3027, 2938, 2804, 2773, 1658, 1594, 1494, 1455, 1374, 1273, 1246, 1158, 1122, 1093, 1074, 1050, 1030, 1008, 985, 750, 701; *^{1}H-NMR* (δ): 1.10 (*t*, *J* = 7.6, CH_3), 1.11 (*d*, *J* = 7.0, CH_3), 1.21–1.31 (*m*, 1H), 1.44 (*td*, J_d = 4.2, J_t = 12.2, 1H), 1.94 (*q*, *J* = 7.2, CH_2), 2.06 (*dd*, J_1 = 3.2, J_2 = 11.6, 1H), 2.28 (*d*, *J* = 9.0, 1H), 2.40–2.58 (*m*, 2H), 2.66–2.82 (*m*, 5H), 4.41 (*dt*, J_t = 4.4, J_d = 12.6, C_4–H), 7.05–7.35 (*m*, 10H$_{Ar}$); *^{13}C-NMR* (ppm): 9.56, 13.88, 26.33, 28.93, 31.21, 33.61, 54.10, 57.46, 59.36, 60.25, 125.79, 127.89, 128.18, 128.67, 128.83, 129.00, 130.33, 130.69, 140.60, 174.33; *MS* (C.I.): 259 (M–91, 45), 351 (M+1, 100).

14.2. (±)-trans-N-*(3-Methyl-1-phenethylpiperidin-4-yl)*-N-*phenylpropionamide (**6.1trans**)*.

From (±)-**5.1*trans*** (1.0 g, 0.0034 mol); Yield: = 1.47 g, 98 %; m.p. (dec.): 157–158 ºC (Lit.[9b] 159–160 ºC). Free base: *IR* (cm^{-1}): 3061, 3025, 2940, 2801, 1658, 1594, 1495, 1455, 1372, 1279, 1241, 1160, 1093, 1070, 1053, 1030, 1014, 985, 751, 702; *^{1}H-NMR* (δ): 1.01 (*d*, J = 7.6, CH_3), 1.04 (*t*, J = 6.2, CH_3), 1.44 (*qd*, J_d = 3.2, J_q = 12.2, 1H), 1.69–1.77 (*m*, 2H), 1.96 (*q*, J = 7.4, CH_2), 2.12 (*td*, J_d = 2.4, J_t = 11.8, 1H), 2.47–2.55 (*m*, 2H), 2.71–2.77 (*m*, 2H), 2.95–3.01 (*m*, 2H), 4.58 (*t*, J_t = 11.4, C_4–H), 7.06–7.45 (*m*, 10 H_{Ar}); *^{13}C-NMR* (ppm): 9.69, 16.35, 28.44, 30.41, 33.70, 34.00, 53.11, 57.25, 60.34, 60.74, 125.98, 128.21, 128.32, 128.58, 129.38, 129.58, 130.98, 140.14, 174.24; *MS* (C.I.): 259 (M–91, 45), 351 (M+1, 100).

15.1. (±)-cis-N-*(3-Ethyl-1-phenethylpiperidin-4-yl)*-N-*phenylpropionamide (**6.2cis**)*.

From (±)-**5.2*cis***. (0.9 g, 0.0029 mol); Yield: 1.65 g, 95 %; m.p. (dec.): 142–144 ºC.

Free base: *IR* (cm^{-1}): 3061, 3026, 2958, 1657, 1595, 1495, 1454, 1374, 1273, 1246, 1158, 1125, 1092, 1056, 1032, 985, 751, 702; *^{1}H-NMR* (δ): 0.95 (*t*, J = 7.4, CH_3), 1.01 (*t*, J = 7.2, CH_3), 1.21–1.32 (*m*, 1H), 1.39 (*dd*, J_1 = 4.2, J_2 = 12, 1H), 1.52–1.64 (*m*, 2H), 1.94 (*q*, J = 7.2, CH_2), 2.04–2.14 (*m*, 2H), 2.38–2.60 (*m*, 3H), 2.67–2.81 (*m*, 3H), 3.02 (*dd*, J_1 = 2.4, J_2 = 11.8, 1H), 4.40 (*dt*, J_t = 4.6, J_d = 12.4, C_4–H), 7.05–7.36 (*m*, 10H_{Ar}); *^{13}C-NMR* (ppm): 9.53, 12.13, 18.74, 26.97, 28.99, 33.67, 38.15, 54.10, 58.19, 60.25, 125.74, 127.85, 128.16, 128.60, 128.80, 128.98, 130.13, 130.71, 140.50, 140.72, 174.39; *MS* (C.I.): 365 (M+1, 100).

15.2 (±)-trans-N-*(3-Ethyl-1-phenethylpiperidin-4-yl)*-N-*phenylpropionamide (**6.2trans**)*.

From (±)-**5.2*trans***. (0.5 g, 0.00162 mol). Yield: 0.74 g, 97 %; m.p. (dec.): 135–136 ºC.

Free base: *IR* (cm^{-1}): 3061, 3026, 2936, 2877, 1657, 1595, 1495, 1462, 1377, 1315, 1260, 1240, 1133, 1076, 1047, 744, 703; *^{1}H-NMR* (δ): 0.94 (*t*, J = 7.2, CH_3), 1.02 (*t*, J = 7.4, CH_3), 1.21–1.31 (*m*, 1H), 1.42–1.50 (*m*, 2H), 1.70–1.81 (*m*, 3H), 1.95 (*q*, J = 7.6, CH_2), 2.09 (*td*, J_d = 2.2, J_t = 12, 1H), 2.48–2.60 (*m*, 2H), 2.74 (*t*, J = 6.6, 2H), 2.99 (*d*, J = 11.2, 1H), 3.13 (*d*, J = 10, 1H), 4.61 (*td*, J_d = 3, J_t = 12, C_4–H), 7.06–7.42 (*m*, 10H_{Ar}); *^{13}C-NMR* (ppm): 9.56, 11.09, 22.83, 28.33, 30.32, 33.61, 40.30, 52.82, 55.44, 58.08, 60.45, 125.87, 128.11, 128.21, 128.47, 129.05, 129.33, 129.47, 130.95, 138.56, 140.03, 174.11; *MS* (C.I.): 273 (M–91, 30), 365 (M+1, 100), 407 (M+43, 20).

16.1 (±)-cis-N-*(3-isopropyl-1-phenethylpiperidin-4-yl)*-N-*phenylpropionamide (**6.3cis**)*.

From (±)-**5.3*cis***. (1.0 g, 0.0031 mol). Yield: 1.36 g, 94 %; m.p. (dec.): 122–124 ºC.

Free base: *IR* (cm^{-1}): 3061, 3030, 2951, 2944, 1652, 1595, 1540, 1495, 1461, 1455, 1397, 1382, 1259, 1181, 1141, 1130, 1074, 1050, 974, 940, 900, 751, 703; *^{1}H-NMR* (δ): 1.00 (*t*, J = 7.2, CH_3), 1.01 (*d*, J = 6.8, CH_3), 1.11 (*d*, J = 6.4, CH_3), 1.16–1.68 (*m*, 3H), 1.87–1.98 (*m*, CH_2), 2.00–2.11 (*m*, 2H), 2.14–2.24 (*m*, 2H), 2.35–2.57 (*m*, 2H), 2.67–2.76 (*m*, 2H), 4.60 (*quint*, J = 5.0, C_4–H), 7.04–7.43 (10H_{Ar}); *^{13}C-NMR* (ppm): 9.60, 20.92, 24.49, 26.06, 28.48, 29.08, 33.39, 42.39, 52.57, 54.00, 60.56, 125.90, 128.09, 128.27, 128.63, 129.02, 131.05, 140.43, 141.43, 174.75; *MS* (C.I.): 287 (M–91, 15), 379 (M+1, 100), 422 (M+44, 5).

16.2 (±)-trans-N-*(3-Isopropyl-1-phenethylpiperidin-4-yl)*-N-*phenylpropionamide (**6.3trans**)*.

From (±)-**5.3*trans***. (0.7 g, 0.0022 mol). Yield: 0.98 g, 95 %; m.p. (dec.): 115–117 ºC.

Free base: *IR* (cm^{-1}): 3060, 3028, 2956, 2938, 1652, 1595, 1541, 1495, 1463, 1455, 1391, 1372, 1255, 1181, 1142, 1125, 1071, 1049, 974, 943, 898, 752, 703; *^{1}H-=NMR* (δ): 0.98 (*d*, J = 6.8, CH_3), 1.01 (*d*, J = 6.8, CH_3), 1.02 (*t*, J = 7.4, CH_3), 1.15–1.33 (*m*, 1H), 1.48 (*td*, J_d = 4.0, J_t = 12.4, 2H), 1.70–1.82 (*m*, 2H), 1.91 (*q*, J = 5.2, CH_2), 1.97–2.16 (*m*, 2H), 2.46–2.62 (*m*, 2H), 2.64–2.80 (*m*, 2H), 2.88–3.04 (*m*, 2H), 4.83 (*td*, J_d = 3.6, J_t = 12.0, C_4–H), 7.04–7.43 (*m*, 10H_{Ar}); *^{13}C-NMR* (ppm): 9.64, 16.78, 21.00, 25.89, 28.39, 30.55, 33.72, 43.43, 53.00, 60.72, 125.88, 128.14, 128.25, 128.49, 129.27, 131.18, 138.61, 140.10, 174.02; *MS* (C.I.): 287 (M–91, 15), 379 (M+1, 100).

17.1. (±)-cis-N-*(3-Butyl-1-phenethylpiperidin-4-yl)*-N-*phenylpropionamide (**6.4cis**)*.

From (±)-**5.4*cis***: (1.5 g, 0.0045 mol). Yield: 2.08 g, 96 %; m.p. (dec.): 97–98 ºC).

Free base: *IR* (cm^{-1}): 3462, 3065, 3026, 2955, 2868, 2797, 1655, 1595, 1495, 1451, 1421, 1375, 1343, 1326, 1305, 1274, 1246, 1159, 1127, 1091, 1049, 1030, 768, 745, 704, 594, 507; *^{1}H-NMR* (δ): 0.92 (*t*, J = 7, CH_3), 1.01 (*t*, J = 7.6, CH_3), 1.21–1.49 (*m*), 1.97 (*q*, J = 6, CH_2), 2.04–2.15 (*m*), 2.43–2.61 (*m*), 2.66–2.78

(*m*), 2.93 (*t*, *J* = 2.5, 1H), 2.99 (*t*, *J* = 2.4, 1H), 4.38 (*dt*, J_d = 12.4, J_t = 4.5, C_4–H), 7.0–7.42 (*m*, 10H_{Ar}); ^{13}*C-NMR* (ppm): 9.52, 14.10, 22.90, 25.69, 27.01, 28.99, 30.06, 33.63, 36.49, 54.11, 55.01, 58.15, 60.16, 125.77, 127.85, 128.15, 128.61, 128.81, 128.96, 130.13, 130.71, 140.56, 140.78, 174.40; *MS* (C.I.): 393 (M+1, 100).

17.2. (±)-trans-N-*(3-Butyl-1-phenethylpiperidin-4-yl)*-N-*phenylpropionamide (**6.4trans**)*.

From (±)-**5.4*trans***: (0.8 g, 0.0024 mol). Yield: 1.13 g; 98 %; m.p. (dec.): 90–92 ºC.

Free base: *IR* (cm^{-1}): 3061, 3026, 2952, 2932, 1658, 1595, 1542, 1495, 1455, 1390, 1377, 1257, 1240, 1137, 1076, 746, 703; ^{1}*H-NMR* (δ): 0.94 (*t*, *J* = 7.0, CH_3), 1.03 (*t*, *J* = 7.4, CH_3), 1.16–1.55 (*m*, 7H), 1.77 (*t*, *J* = 11.0, 3H), 1.96 (*q*, *J* = 7.4, CH_2), 2.11 (*t*, *J* = 10.2, 1H), 2.48–2.60 (*m*, 2H), 2.70–2.78 (*m*, 2H), 2.99 (*d*, *J* = 11.2, 1H), 3.13 (*d*, *J* = 9.8, 1H), 4.61 (*t*, *J* = 7.0, C_4–H), 7.06–7.42 (*m*, 10H_{Ar}); ^{13}*C-NMR* (ppm): 9.64, 14.00, 22.94, 28.33, 28.90, 29.81, 30.35, 33.58, 38.84, 52.82, 55.57, 58.57, 60.43, 125.87, 126.11, 128.21, 128.47, 129.05, 129.27, 129.45, 130.91, 138.60, 140.03, 174.15; *MS* (C.I.): 302 (M–90, 80) 393 (M+1, 100) 436 (M+44, 80) 449 (M+57, 40).

18.1. (±)-cis-N-*(3-Benzyl-1-phenethylpiperidin-4-yl)*-N-*phenylpropionamide (**6.5cis**)*.

From (±)-**5.5*cis*** (0.90 g, 0.0024 mol). Yield: 1.18 g, 95 %; m.p. (dec.): 129–131 ºC.

Free base: *IR* (cm^{-1}): 3083, 3061, 3024, 2937, 2860, 1657, 1595, 1495, 1453, 1319, 1262, 1180, 1139, 1095, 1070, 1037, 903, 749, 734, 701;^{1}*H-NMR* (δ): 1.07 (*t*, *J* = 7.6, CH_3), 1.26–1.34 (*m*, 1H), 1.51 (*qd*, J_d = 4.2, J_q = 12.6, 1H), 2.00 (*q*, *J* = 6.0, CH_2), 1.94–2.09 (*m*, 2H), 2.25–2.40 (*m*, 1H), 2.42–2.52 (*m*, 1H), 2.55–2.67 (*m*, 3H), 2.73–2.88 (*m*, 4H), 4.49 (*dt*, J_t = 3.4, J_d = 12.4, C_4–H), 7.07–7.35 (*m*, 10H_{Ar}); ^{13}*C-NMR* (ppm): 9.64, 26.82, 28.95, 32.17, 33.43, 38.78, 53.68, 53.97, 58.19, 59.83, 125.45, 125.63, 127.81, 127.98, 128.52, 128.83, 128.96, 129.16, 129.98, 130.54, 140.49, 141.16, 174.39; *MS* (C.I.): 335 (M–91, 15), 427 (M+1, 100).

18.2. (±)-trans-N-*(3-Benzyl-1-phenethylpiperidin-4-yl)*-N-*phenylpropionamide (**6.5trans**)*.

From (±)-**5.5*trans*** (0.40 g, 0011 mol); Yield: 0.55 g, 97 %; m.p. (dec.): 125–126 ºC).

Free base: *IR* (cm^{-1}): 3085, 3061, 3026, 2937, 2860, 2804, 1658, 1595, 1495, 1453, 1315, 1259, 1177, 1137, 1092, 1073, 1032, 911, 749, 734, 701; ^{1}*H-NMR* (δ): 1.04 (*t*, *J* = 7.6, CH_3), 1.56 (*td*, J_d = 4.0, J_t = 12.4, 1H), 1.83 (*t*, *J* = 10.6, 2H), 1.99 (*q*, *J* = 7.6, CH_2), 2.12 (*td*, J_d = 1.6, J_t = 12.0, 1H), 2.34–2.51 (*m*, 4H), 2.53–2.69 (*m*, 2H), 2.78 (*dd*, J_1 = 2.2, J_2 = 10.2, 1H), 3.00 (*d*, *J* = 9.8, 1H), 3.24 (*dd*, J_1 = 2.2, J_2 = 14, 1H), 4.75 (*t*, *J* = 10.0, C_4–H), 7.04–7.45 (*m*, 15 H_{Ar}): ^{13}*C-NMR* (ppm): 9.67, 28.50, 30.65, 33.49, 36.82, 40.02, 52.69, 58.00, 58.41, 60.23, 125.90, 126.91, 128.25, 128.36, 128.49, 128.62, 129.43, 130.96, 138.76, 139.65, 139.99, 174.46; *MS* (C.I.): 335 (M–91, 10), 427 (M+1, 100).

19.1. (±)-cis-N-*(1,3-Diphenethylpiperidin-4-yl)*-N-*phenylpropionamide (**6.6cis**)*.

From (±)-**5.6*cis***: (0.60 g, 0.0016 mol); Yield: 0.80 g; 94 %; m.p. (dec.): 119–121 ºC.

Free base: *IR* (cm^{-1}): 3084, 3061, 3026, 2938, 2803, 2773, 1658, 1594, 1495, 1453, 1374, 1272, 1245, 1140, 1092, 1076, 1031, 1007, 749, 701; ^{1}*H-NMR* (δ): 1.00 (*t*, *J* = 7.2, CH_3), 1.22–1.35 (*m*), 1.37–1.50 (*m*), 1.70–1.81 (*m*), 1.90 (*q*, *J* = 7.4, CH_2), 1.00–2.12 (*m*), 2.13–2.18 (*m*), 2.43–2.62 (*m*), 2.66–2.81 (*m*), 2.94–2.98 (*m*), 3.00–3.04 (*m*), 4.37 (*dt*, J_t = 4.6, J_d = 12.6, C_4–H), 7.05–7.20 (*m*, 15H_{Ar}); ^{13}*C-NMR* (ppm): 9.57, 27.02, 27.75, 28.97, 33.63, 34.24, 36.70, 53.93, 55.08, 58.33, 59.91, 125.54, 125.77, 127.84, 128.19, 128.28, 128.34, 128.60, 128.84, 129.05, 130.09, 130.58, 140.54, 140.77, 142.26, 174.46; *MS* (C.I.): 441 (M+1,100).

19.2. (±)-trans-N-*(1,3-Diphenethylpiperidin-4-yl)*-N-*phenylpropionamide (**6.6trans**)*.

From (±)-**5.6*trans***: (0.40 g, 0.0010 mol); Yield: 0.43 g; 97 %. m.p. (dec.): 110–112 ºC.

Free base: *IR* (cm^{-1}): 3084, 3061, 3026, 2938, 2811, 1658, 1594, 1495, 1452, 1370, 1269, 1251, 1141, 1095, 1080, 1032, 1004, 749, 701; ^{1}*H-NMR* (δ): 1.00 (*t*, *J* = 7.6, CH_3), 1.25–1.41 (*m*), 1.49–1.80 (*m*), 1.90 (*q*, *J* = 8.0, CH_2), 2.04–2.19 (*m*), 2.48–2.63 (*m*), 2.68–2.80 (*m*), 2.94–3.00 (*m*), 3.22–3.28 (*m*), 4.64 (*td*, J_d = 4, J_t = 11, C_4–H), 7.05–7.20 (*m*, 15H_{Ar}); ^{13}*C-NMR* (ppm): 9.61, 25.93, 27.02, 30.67, 32.05, 33.69, 35.51, 52.17, 54.22, 57.83, 59.07, 125.51, 125.81, 127.79, 128.29, 128.30, 128.41, 128.66, 128.89, 129.05, 130.10, 130.61, 140.55, 140.81, 142.32, 174.51; *MS* (C.I.): 441 (M+1, 100).

ИЗВОД

СИНТЕЗА И ПРЕЛИМИНАРНИ ФАРМАКОЛОШКИ ТЕСТОВИ РЕЦЕМСКИХ *cis* И *trans* **3-**АЛКИЛ АНАЛОГА ФЕНТАНИЛА

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Развијен је општи метод за синтезу 3-алкил аналога фентанила (тј. *cis* и *trans* 3-алкил-4-анилидопиперидина **6.1**–**6.6**) у пет фаза. Полазни *N*-фенетил-4-пиперидон **1** прво је преведен у циклохексилиминског дериват **2**, α-депротонован бутиллитијумом, а постали иминског анјон ефикасно моноалкилован примарним и секундарним алкилхалогенидима. После благе киселе хидролизе, настали 3-алкил-4-пиперидони **3.1**–**3.6** изоловани су у добрим приносима (79–85 %), затим кондензовани са анилином до имина **4.1**–**4.6**. Редукцијом ових имина ($LiAlH_4$/THF) добијене су *cis*/*trans* смесе 3-алкил-4-анилинопиперидина **5.1**–**5.6**. Квантитативним хроматографским раздвајањем дијастереоизомера на стубу Al_2O_3 изоловани су чисти *cis* **5.1**–**5.6** (принос 29–51 %) и *trans* **5.1**–**5.6** (принос 19–27 %), где је *cis*/*trans* однос био у опсегу 7/3–6/4. Синтеза је завршена *N*-ациловањем пречишћених интермедијера **5.1**–**5.6** помоћу пропионил-хлорида, при чему су постали *cis* и *trans* 3-алкил-4-анилидопиперидини **6.1**–**6.6** (принос ≈ 95 **%,** као монооксалатне соли). Ни у једној фази није покушано раздвајање енантиомера. Релативна, *cis*/*trans*, стереохемија прелиминарно је одређена из ^{1}H-NMR спектра. Од дванаест синтетисаних 3-алкил-фентанила, десет једињења (два позната и осам нових, сва у облику моноокасалатних соли) прелиминарно су тестирана као аналгетици на пацовима, поредећи активност са фентанилом. Осим познатог (±)-*cis*-3-Me фентанила **6.1** ***cis*,** (8 × фентанил), и новог (±)-*cis*-3-Et фентанила **6.2** ***cis,*** (1,5 × фентанил), сви остали били су мање активни или неактивни. Изведени су одређени, прелиминарни закључци у вези односа структуре и активности у овој серији деривата.

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