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The synthesis and pharmacological evaluation of (±)-2,3-*seco*-fentanyl analogues*

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Abstract: An efficient, five-step synthetic approach to various acyclic 1,3-diamines has been developed and applied to the preparation of a novel class of open-chained fentanyl analogues. The acyclic derivatives **5.1**–**5.5** (all new compounds) were synthesized with the aim of estimating the significance of the piperidine ring for the opioid analgesic activity of anilido-piperidines. The starting β-keto-amide **1.1**, prepared by the aminolysis of methyl acetoacetate with methylphenethylamine, (93 % yield), was successively reacted with NaH and BuLi, to form the highly reactive α,γ-dienolate anion **1.1a**. Regio and chemoselective γ-alkylation of the dienolate with various primary and secondary alkyl halides furnished the β-keto-amides **1.2**–**1.5** (76–91 %). Reductive amination of the keto-amides **1.1**–**1.5** with aniline and Zn powder in acetic acid, *via* the enamine intermediates **2.1**–**2.5**, afforded the β-anilino amides 3.1–3.5 (74–85 %). After reductive deoxygenation of the tertiary amide group, using *in situ* generated diborane, the corresponding 1,3-diamines **4.1**–**4.5** were obtained (87–97 %). The synthesis of (±)-2,3-*seco*-fentanyls **5.1**–**5.5** was completed by *N*-acylation of the diamines **4.1**–**4.5** with propionyl chloride, followed by precipitation of the monooxalate salts (86–95 %). The parent compound, 2,3-*seco*-fentanyl **5.1**, was found to be a 40 times less potent narcotic analgesic than fentanyl but still 5–6 times more active than morphine in rats, while *i*-Pr derivative **5.3** was inactive. Apart from the pharmacological significance, the general procedure described herein may afford various functionalized, 1,3-diamines as potential complexing agents and building blocks for the synthesis of aza-crown ethers.

Keywords: open-chain fentanyl analogues, 1,3-diamines, opioid analgesics.

* Dedicated to Professor Živorad Čeković on the occasion of his 70th birthday.

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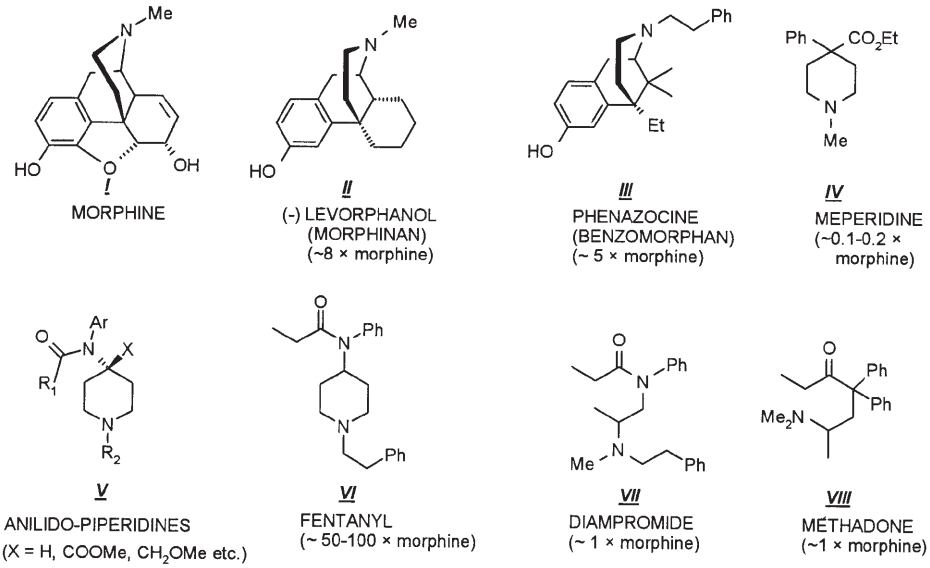
\# Serbian Chemical Society active member.

\+ Deceased on 11th October 2001.

INTRODUCTION

Analgesics are widely used to treat mild to severe pain of various origins.[1] They are generally divided into two broad groups: anti-inflammatory agents (steroid and non-steroid) and opioid analgesics acting upon the specific opioid receptors (μ, κ, δ) in the central nervous system and other tissues.[2] Morphine **I**,[3] a natural product and a major constituent of opium,[3] is certainly the best known representative of the later class, having been used to alleviate pain for millennia (originally as opium, then as the pure compound). However, its highly adverse effects, such as acute, life threating respiratory depression and chronic development of tolerance and addiction, led to efforts towards the synthesis of novel drugs with better pharmacological profiles.[4,5] Initially, the morphine molecule itself was modified *via* numerous partial syntheses, followed by the more complex total synthesis of various morphine-like compounds, generally known as opioids.[5] A number of novel classes of compounds, often structurally dissimilar to morphine, were found to possess high and clinically useful opioid analgesic activity. Those include[5] (Scheme 1) morphinans[3] (*e.g.*, levorphanol **II**),[3] benzomorphans[3] (*e.g.*, phenazocine **III**),[3] meperidines (*e.g.*, meperidine **IV**),[3] anilido-piperidines (gen. structure **V**, *e.g.*, fentanyl **VI**),[3,6] open-chain compounds (*e.g.*, diampromide **VII**,[3] methadone **VIII**),[3] synthetic opioid peptides[5] (related to the endogenous opioid peptides, natural ligands of opioid receptors) and many others.[5] Research efforts in the field of opioid analgesics and analgesia in general, continue unabated, as evidenced by the plethora of recent papers and patents.[7]



Scheme 1.

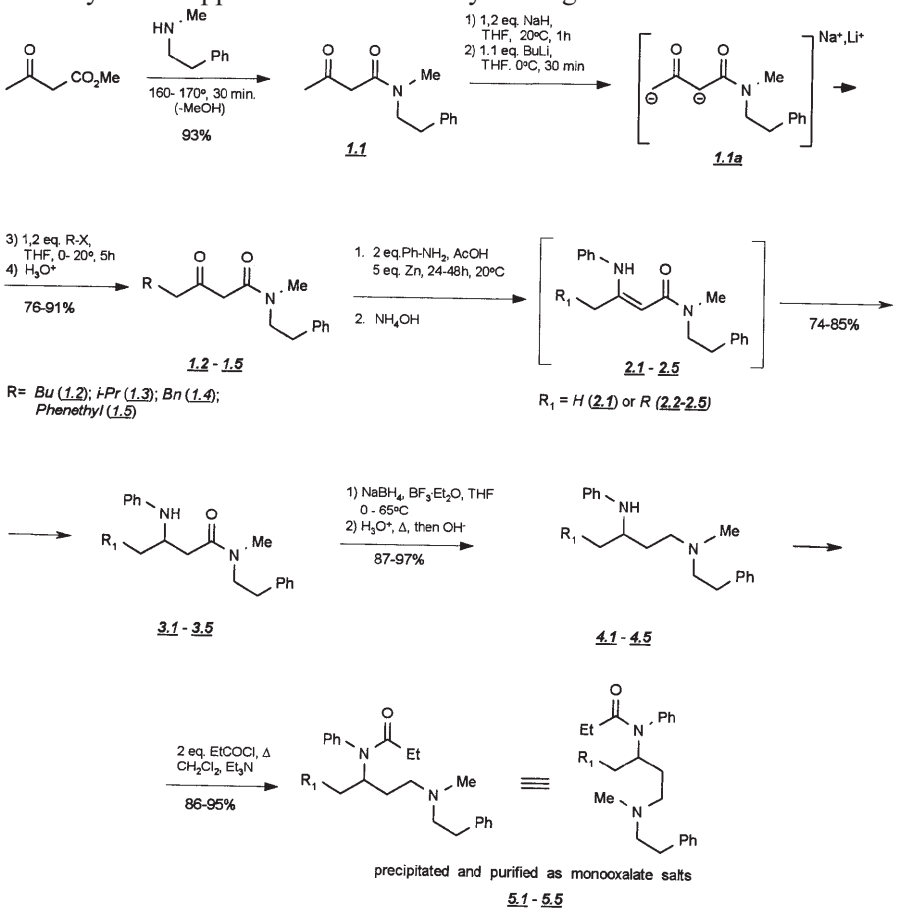
Except for the opioid peptides, the great majority of the synthetic opioids possess a piperidine (or rarely a pyrrolidine) ring and a basic nitrogen, known to be es-

sential for opioid activity.[5] Surprisingly, only a few open-chain derivatives, such as diampromide or methadone, have been synthesized. Although diampromide may be considered as an open-chain fentanyl analogue, structurally it is 1,2-diamine, unlike 1,3-diamines resulting from the scission of the pipeiridine ring.

In view of the fact that anilido-piperidines (fentanyl and its derivatives) are highly potent opioids (100–1000 × morphine), the synthesis of exact open-chain fentanyl analogues,[8] (2,3-*seco*-fentanyls) was envisaged in order to estimate the importance of the piperidine ring for opioid activity.

RESULTS AND DISCUSSION

The synthetic approach to *seco*-fentanyl analogues is outlined in Scheme 2.



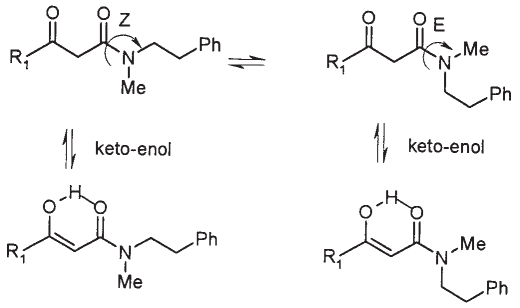
Scheme 2.

The starting keto-amide **1.1** was prepared by aminolysis of methyl acetoacetate with methylphenethylamine at ≈ 150 ºC. Esters of malonic acid and β-keto esters are known to undergo aminolysis much easier than simple esters, ei-

ther thermally or catalyzed by 4-dimethylaminopyridine (DMAP).[9] However, at lower temperatures (20–100 ºC), β-keto esters readily form stable conjugated enamines, especially in the presence of acid catalysts.[10] We also observed rapid enamine formation (by TLC and IR), when the aminolysis was attempted in various solvents (MeOH, *i*-PrOH, CH_2Cl, PhMe, xylene). On the contrary, the aminolysis proceeded smoothly in the absence of solvent, (≈2 eq. of methyl acetoacetate) at > 150 ºC and it was accelerated by the continuous removal of the formed MeOH. Further rate acceleration (2–3 times) was observed in the presence of basic catalyst (0.5 mol% MeONa). Thus, the keto-amide **1.1** was obtained within ≈ 15–20 min (93 % crude yield), while sterically more hindered amines, *N*-ethyl-2-phenethylamine and *N*,*N*-bis(2-phenylethyl)amine, required longer reaction times (60–120 min) and gave lower isolated yields (60–75 %). The latter two amides were not used further for the synthesis. In all instances, the formation of various side products was observed (≈5–25 % by TLC and GC). An alternative method to synthesize β-keto amides, by low temperature acylation of tertiary amide enolates, has been reported.[11] Although of considerable scope, it is operationally inconvenient and give slower yield (≈50 %).

In the next step, **1.1** was selectively γ-alkylated with various alkyl halides, to afford 4-alkyl keto amides **1.2**–**1.5**. The conversion was affected *via* the α,γ-enolate dianion **1.1a**, prepared by the literature procedure for bis-metalation of β-keto esters[12] and β-keto amides.[13] First, the α-monoenolate was generated using NaH (1.2 eq., THF, 30 ºC, 30 min), which was then reacted with BuLi (1.6 M, 1.05 eq., 0 ºC, 30 min), to form the orange-red dienolate **1.1a** solution. No addition products of BuLi (alcohols) were detected upon quenching with H_2O or MeOH. The dienolate **1.1a** is also thermally stable: after 5 h at 30 ºC, only the starting compound **1.1** was isolated after quenching. However, its high nucleophilicity permits its very rapid reaction with primary alkyl halides (chlorides, bromides, iodides) and *i*-PrI (15–30 min, 0–30 ºC, exothermal reaction), leading to colour discharge and the precipitation of the halide salts. The alkylation is exclusively γ-regioselective, with neither α-alkylated nor bis-alkylated products detected. It is also highly chemoselective (no significant side products were detected), affording the keto-amides **1.2**–**1.5** in 76–91 % yields, after purification. Significantly, *i*-PrI as alkylating agent gave no elimination product. Although it was found to be possible to a affect a consecutive α-alkylation, using excess of the alkylating reagent, (at ≈ 50 ºC), this possibility was not studied further. All the prepared keto-amides (**1.1**–**1.5**) exhibit distinct carbonyl bands in their IR spectra (1720, 1640 cm^{-1}), M+1 peaks (100 % in chemical ionisation MS) and were homogeneous by TLC and cap. GC (pyrity >95 %). The ^{1}H-NMR and ^{13}C-NMR spectra display extensive rotatory isomerism, as a result of constrained rotation around the (C=O)–N bond. The effect is significantly more pronounced compared to simple amides, since the β-keto group additionally rigi-

difies the system (Scheme 3). Almost all the signals in the ^{13}C-NMR spectra were doublets, separated by ≈0.5–2 ppm (see Experimental Section). In addition, the probable presence of enolic forms in low concentration could be inferred from the ^{1}H-NMR spectra (≈5.0 δ, *s*, vinyl H; ≈15 δ, *s*, enol OH).



Scheme 3.

Keto-amides **1.1**–**1.5** were converted into the corresponding β-anilino-amides **3.1**–**3.5** using aniline and Zn powder in acetic acid, according to a reductive amination procedure published earlier.[14] The optimal yields (74–85 % of the purified products) were obtained at ≈20 ºC after 24–48 h, while heating mainly gave stable conjugated enamines **2.1**–**2.5** and acetanilide.[15] The slow step in the process is enamine reduction, as enamine formation is rapid under the reaction conditions according to TLC and IR and they are readily isolatable. In the case of keto-amides **1.3** and **1.5**, complete reduction could not be achieved, due to steric hindrance (≈10–20 % of the corresponding enamines remained unreacted). After completion of the reduction (as evidenced by TLC and IR), the excess aniline was quantitatively converted into acetanilide by briefly heating the mixture (≈ 90 ºC, 1h). Under these conditions, the secondary amino group of the anilino-amides **3.1**–**3.5** did not undergo acetylation to any extent. After workup with aq. NH_4OH, to prevent precipitation of gelatinous $Zn(OH)_2$, the isolated products were precipitated as oxalate salts. An attempted direct reductive amination of keto-amide **1.1** with $NaBH_3CN$ (MeOH, solid NaH_2PO_4 or Et_3N/AcOH, pH 5–7), resulted in extensive reduction of the carbonyl group. However, preforming the enamine **2.1** (PhMe, cat. TsOH, aniline, water separation) and its reduction with $NaBH_3CN$, in two separate steps, cleanly furnished the β-anilino amide **3.1**. Spectral data confirmed the structures and purity: IR (carbonyl band at 1630 cm^{-1}), MS (CI, M+1 peaks 100 %), GC (purity > 95 %). However, rotatory isomerism in the ^{1}H-NMR and ^{13}C-NMR spectra was observed again, albeit to a lower extent. Thus, the observed ^{13}C-NMR signal separation of the rotatory isomers was ≈0.1–1 ppm (see Experimental).

The purified anilino-amides **3.1**–**3.5** were reductively deoxygenated to the diamines **4.1**–**4.5** using *in situ* generated diborane ($NaBH_4$, $BF_3{\cdot}Et_2O$, in THF) according to a known procedure for nitrile reduction.[16] We observed a rapid and quantitative reduction of the amide group (0.65 ºC, 2 h), with a BH_3 to amide mole

ratio of ≈4:1. A considerable excess of borane is necessary for complete reduction, as it forms a stable complex with the amino function of anilino-amides **3.1**–**3.5**. Similarly, the reduction products – diamines **4.1**–**4.5** – were obtained as stable complexes with at least two BH_3 molecules, requiring decomposition with boiling HCl. No side products were detected in the free bases (TLC, cap. GC, ^{1}H-NMR ^{13}C–NMR) (see Experimental). As expected evidence of rotatory isomerism was absent in the ^{1}H-NMR and ^{13}C-NMR spectra.

The synthesis of 2,3-*seco*-fentanyl analogues was completed by *N*-acylation of the diamines **4.1**–**4.5** with propionyl chloride in CH_2Cl_2. Although the molecules possess a tertiary amino function which binds the liberated HCl, the addition of ≈0.3 eq. of triethylamine was found necessary for quantitative acylation. The only detected contaminants were neutral compounds, formed by decomposition of the propionyl chloride under the reaction conditions. The anilides **5.1**–**5.5**, obtained in near quantitative yields, were purified as monooxalate salts. Spectral data of the free bases fully confirmed the proposed structures (see Experimental).

Two of the synthesised derivatives, **5.1** monooxalate (2,3-*seco*-fentanyl, the parent compound) and **5.3** monooxalate (*i*-Pr analogue), were tested pharmacologically for analgesic (antinociceptive) activity, using tail-immersion test in rats[17] and compared to fentanyl citrate as a standard. All three compounds were administered intraperitoneally. At least three doses of each compound were tested with 6–8 rats per dose. The dose-response curves were analysed using linear regression. The ED_{50} (dose effective upon 50 % of the tested animals) and 95 % confidence limits were estimated from the dose-response curve by using standard statistical software.[18] The present experiments revealed that **5.1** is about 40 times less potent than fentanyl with an ED_{50} (95 % confidence limits) values: 0.45 (0.19–1.03) mg/kg (**5.1** free base) and 0.0104 (0.006–0.018) mg/kg (fentanyl free base). Also, the ED_{99} of **5.1** exhibited significantly ($p < 0.05$) shorter duration of action (up to 30 min) in comparison to the equi-effective dose of fentanyl (up to 50 min). The antinociceptive effect of **5.1** was antagonized by the specific opioid antagonist, naloxone hydrochloride (0.025 mg/kg, s.c.), thus confirming the mechanism of action is indeed *via* the iopioid receptors. The other derivative, **5.3** monooxalate was found to be completely inactive.

The finding that a direct open-chained fentanyl analogue such as 2,3-*seco*-fentanyl is much less potent than fentanyl, generally suggests the influence of the steric factor upon the antinociceptive activity, and in particular, the significance of the piperidine ring as a pharmacophore. However, some acyclic systems may retain a very considerable analgesic potency (**5.1** is ≈5 times more potent than morphine in rats) indicating that a ring system (piperidine or other) is not essential for ligand-receptor binding. Rather, it seems that the piperidine ring, due to its relatively rigid conformation, serves mainly to enhance the ligand-receptor binding, amplifying the analgesic activity some 40 times.

Detailed pharmacological study of the open-chained fentanyl analogues will be published elsewhere.

Apart from the pharmacological significance, the synthetic approach disclosed in this paper may be applied to the synthesis of various 1,3-diamines as potential complexing agents and building blocks for the synthesis of aza-crown ethers. It is noteworthy that the synthesis could be readily extended, by several additional alkylation steps in the γ- and/or α-position of the keto-amides, thus permitting the construction of elaborate intermediates. A recent finding that the otherwise stable borane-amine complexes are quantitatively cleaved by a mild, catalytic process (MeOH, 10 % Pd/C or NaNi, r.t., 0.1–20 h) allows for the presence of acid-sensitive groups such as acetals, $–CO_2t$–Bu, –OMOM, –OTHP or OTBS.[19] Furthermore, aliphatic amines may be used in the reductive amination step, provided that the enamines are formed first, followed by $NaBH_3CH$ reduction.[6j]

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. (Insufficient resolution of some ^{1}H-NMR spectra precluded precise integration of the multiplets, hence the number of the corresponding hydrogens could not be determined. In these instances, only approximate multiplet intervals are reported). Mass spectra were recorded on a Finigan-Math instrument, model 8230, employing both the electron impact (70 eV) and chemical ionisation (with *i*-butane) techniques. Gas chromatograms were obtained on a Varian 3400 instrument with an FID detector, on a nonpolar DB-5 column (5 m). 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.). Dry flash chromatography was performed on SiO_2 12–26 μ or 10–18 μ, ICN Pharmaceutical. Magnetic stirring was used in all experiments.

1. N-*methyl-3-oxo*-N-*phenethylbutanamide* (**1.1**). A one necked, round bottomed flask fitted with a pressure equalizing dropping funnel to which a reflux condenser with a $CaCl_2$ drying tube was mounted was purged with Ar and the flask is charged with methyl acetoacetate (25.0 mL, 0.23 mol) and solid MeONa (0.1 g) while methyl-phenethyl amine (16.2 g, 0.12 mol) was added to the dropping funnel. The contents of the flask were stirred magnetically and heated to ≈160 ºC (oil bath), then the amine was added dropwise over 5 min. The rapid evolution of MeOH started immediately. The dropping funnel stopcock was closed after 5 min and the liberated MeOH was distilled into the dropping funnel through the side arm. After ceasation of the distillation (≈ 5 min), the reaction mixture was cooled (20 ºC), neutralized with solid NH_4Cl (200 mg), and the excess methyl acetoacetate removed (at ≈ 20 Torr). The residue was distilled. Yield: 24.4 g (93 %), pale yellow, viscous oil, b.p. 120–125 ºC/0.1 Torr; purity (cap. GC): 95 %. Further purification by dry flash chromatography (15 g SiO_2/1 g substance), using hexane/EtOAc gradient (95:5, 90:10, *etc*.), yields analytical sample; purity (cap. GC): 98 %.

IR (cm^{-1}): (characteristic bands) 1722, 1642. ^{13}*C-NMR* (ppm): [2 rotamers] 21.89, 30.03, 33.34, 33.47, 34.43, 36.49, 49.22, 49.76, 50.27, 52.09, 126.34, 126.85, 128.14, 128.45, 128.76, 137.90, 138.74, 166.43, 166.65, 202.44, 202.70. *MS (CI)*: 220 (M+1, 100 %).

A typical procedure for γ-alkylation of keto-amide **1.1** is illustrated for keto-amide **1.3**.

2. N*,5-dimetyl-3-oxo*-N-*phenethylhexanamide* (**1.3**). A round-bottomed flask (100 mL) was

fitted with a thermometer and pressure-equalizing dropping funnel connected to an oil bubblier through a septum. The system was purged with Ar and the flask charged with THF (40 mL) and NaH (60 %, 0.80 g, 11 mmol). A solution of keto-amide **1.1** (2.2 g, 10 mmol/5 mL THF) was added dropwise over 5 min, (H_2 evolution) and the stirring continued for 15 min at r.t. The homogeneous solution was cooled to 0 ºC, BuLi (2M/cyclohexane, 12.1 mmol, 6.1 mL) was injected into the dropping funnel and added dropwise over 10 min. The resulting orange-red solution was stirred for a further 15 min (0 ºC), then *i*-Prl (2.05 g, 12 mmol/5 mL THF) was injected into the dropping funnel and added over 10 min (0 ºC). The solution soon became colourless and a white precipitate formed (Nal). Stirring was continued for 1 h (≈20 ºC), the mixture was concentrated (rotatory evaporator), H_2O (50 mL) was added and the resulting emulsion extracted with CH_2Cl_2 (2 × 30 mL). After drying (anh. $MgSO_4$), filtration and solvent removal, the crude keto-amide **1.3** was obtained as a yellow-brown viscous oil, slightly contaminated with the starting keto-amide **1.1** and some impurities (GC purity ≈93 %). After dry flash chromatographic purification (≈40 g SiO_2), using a hexane/EtOAc gradient (95:5, 90:10, *etc*.), pure **1.3** was obtained as a pale yellow viscous oil. Yield: 2.0 g (76 %); purity (cap. GC) ≈99 %.

IR (cm^{-1}): (characteristic bands) 1722, 1642. ^{1}*H-NMR* (δ): [2 rotamers + enol form] 0.89 (*d*, *J* = 7.6, CH_3), 0.92 (*d*, *J* = 7.6, CH_3), 2.00–2.22 (*m*), 2.31 (*d*, *J* = 6.6), 2.41 (*J* = 6.8), 2.82–2.89 (*m*), 2.86 (*s*, *N*–CH_3), 2.98 (*s*, *N*–CH_3), 3.14 (*s*, CH_2), 3.48 (*t*, *J* = 6.8), 3.59 (*d*, *J* = 7.8), 3.62 (*d*, *J* = 9.0), 5.0–5.08 (*m*, enol form, vinyl H), 7.08–7.32 (*m*, $5H_{Ar}$), 14.75 (*d*, *J* = 32, enol OH). ^{13}*C-NMR* (ppm): [2 rotamers s] 21.74, 23.43, 23.48, 32.58, 32.86, 33.80, 35.77, 44.46, 48.03, 49.03, 49.10, 50.91, 51.39, 86.70, 125.68, 126.15, 127.82, 128.13, 128.17, 128.21, 137.56, 138.32, 166.09, 166.24, 171.26, 176.36, 176.82, 203.46, 203.67. *MS (CI)*: 262 (M+1, 100 %), 523 (2M+1, 60 %).

The above procedure was used to synthesize the keto-amides **1.2**, **1.4** and **1.5**.

3. N-*methyl-3-oxo*-N-*phenethyloctanamide* (**1.2**). Scale 15 mmol; yield: 3.75 g (91 %); pale yellow viscous oil; purity (cap. GC, not purified by chromatography): 96 %. Alkyl halide: butyl bromide.

IR (cm^{-1}): (characteristic bands) 1722, 1642. ^{1}*H-NMR* (δ):[2 rotamers + enol form] 0.84–0.92 (*m*), 1.22–1.35 (*m*), 1.44–1.62 (*m*), 2.42 (*t*, *J* = 7.4, CH_2), 2.52 (*t*, *J* = 7.2, CH_2), 2.81–2.93 (*m*), 2.87 (*s*, *N*–CH_3), 2.98 (*s*, *N*–CH_3), 3.16 (*s*, CH_2), 3.48 (*d*, *J* = 10.4, CH), 3.50 (*d*, *J* = 7.2, CH), 3.59 (*d*, *J* = 7.8), 3.62 (*d*, *J* = 9.0, CH), 5.0–5.08 (*m*, enolic form, vinyl H), 7.12–7.20 (*m*, $5H_{Ar}$). ^{13}C-NMR (ppm): [2 rotamers] 13.09, 21.59, 22.28, 25.37, 30.34, 30.47, 32.40, 32.67, 33.61, 35.59, 41.91, 47.35, 48.23, 48.93, 51.25, 85.55, 125.50, 125.95, 127.64, 127.95, 128.01, 128.07, 137.44, 138.15, 166.23, 166.32, 171.18, 203.75, 203.95. *MS(CI)*: 275 (M+1, 100 %), 551 (2M+1, 95 %).

4. N-*methyl-3-oxo*-N-*phenethyl-5-phenylpentanamide* (**1.4**). Scale: 10 mmol; yield: 2.69 g (87 %); pale yellow viscous oil; purity (cap. GC after chromatography): 99 %. Alkyl halide: benzyl chloride.

IR (cm^{-1}): (characteristic bands) 1722, 1642. ^{1}*H-NMR* (δ): [2 rotamers + enol form] 2.66–2.91 (*m*), 2.78 (*s*, *N*–CH_3), 2.95 (*s*, *N*–CH_3), 3.11 (*s*, CH_2), 3.40 (*t*, *J* = 7.0), 3.46 (*s*), 3.56 (*d*, *J* = 7.6), 3.59 (*d*, *J* = 9.0), 4.96 (*d*, *J* = 19, enol form, vinyl H), 7.06–7.36 (*m*, 10 H_{Ar}). ^{13}*C-NMR* (ppm): [2 rotamers] 28.83, 32.02, 32.68, 32.90, 33.77, 35.75, 43.45, 43.53, 47.87, 48.81, 49.11, 51.37, 86.32, 125.54, 125.79, 126.09, 126.25, 127.80, 127.84, 127.89, 128.23, 137.55, 138.93, 140.21, 166.05, 166.18, 203.05, 203.20. *MS (CI)*: 319 (M+1, 100 %), 619 (2M+1, 30 %).

5. N-*methyl-3-oxo*-N-*phenethyl-6-phenylhexanamide* (**1.5**). Scale: 10 mmol; yield: 2.65 g (82 %); pale yellow viscous oil; purity (cap. GC after chromatography): 99 %. Akyl halide: phenethyl bromide.

IR (cm^{-1}): (characteristic bands) 1722, 1642. ^{1}*H-NMR* (δ): [2 rotamers + enol form] 1.82–1.95 (*m*), 2.40–2.50 (*m*), 2.54–2.66 (*m*), 2.79–2.91 (*m*), 2.84 (*s*, *N*–CH_3), 2.97 (*s*, *N*–CH_3), 3.11 (*s*, CH_2), 3.46 (*t*, *J* = 7.0), 3.60 (*t*, *J* = 8.0), 5.01–5.08 (*br. d*, *J* = 14, enolic form, vinyl H), 7.05–7.38 (*m*, Ar). ^{13}*C-NMR* (ppm): [2 rotamers] 24.33, 32.65, 32.89, 33.80, 34.25, 34.54, 35.80, 41.42, 47.56, 48.55, 49.09, 51.40, 125.34, 125.77, 126.23, 127.80, 127.89, 128.25, 137.57, 138.34, 141.01, 166.19, 166.36, 203.63, 203.83. *MS (CI)*: 219 (M-104, 25 %), 324 (M+1, 100 %), 366 (M+43, 40 %), 647 (2M+1, 1 %).

The typical procedure for the synthesis of the anilino-amides **3.1**–**3.5** is illustrated for anilino-amide **3.3**.

6. N*,5-dimethyl*-N-*phenethyl-3-(phenylamino)hexanamide* (**3.3**). A single-necked, round-bottomed flask (25 mL) fitted with a reflux condenser was charged with the keto-amide **1.3** (1.31 g, 5.0 mmol), aniline (1.0 g, 11 mmol), activate Zn powder (2.0 g, 31 mmol) and AcOH (15 mL). The mixture was stirred (48 h at ≈20 ºC), then heated to ≈90 ºC (1 h), cooled and added slowly into NH_4OH (25 %, 40–50 mL, pH ≈ 10). After extraction (CH_2Cl_2, 2 × 30 mL), washing with H_2O (50 mL), drying (anh. K_2CO_3), filtration and solvent removal (rotatory evaporator), the crude product was obtained as a reddish-brown viscous oil. It was a mixture of enamine **2.3**, anilino-amide **3.3** and acetanilide with R_f values (eluent hexane/EtOAc 7:3): 0.60, 0.35 and 0.1, respectively. After dry flash chromatography (40 g SiO_2) with a hexane/EtOAc gradient (99:5, 90:10, *etc.*) pure anilino-amide **3.3** was obtained. Yield: 1.25 g, (74 g); pale yellow viscous oil, purity (cap. GC) ≈99 %.

IR (cm^{-1}): (characteristic bands): 3342, 1632, 1602. *^{1}H-NMR* (*δ*): [2 rotamers] 0.88 (*d*, *J* = 6.6, CH_3), 0.90 (*d*, *J* = 6.6, CH_3, 0.92 (*d*, *J* = 6.4, CH_3), 0.94 (*d*, *J* = 6.6, CH_3), 1.27–1.35 (*m*), 1.43–1.51 (*m*), 1.55–1.84 (*m*), 2.18 (*d*, *J* = 6.6), 2.30 (*d*, *J* = 4.4), 2.44 (*d*, *J* = 6.4), 2.50 (*d*, *J* = 4.4), 2.74–2.83 (*m*), 2.80 (*s*, *N*–CH_3), 2.92 (*s*, *N*–CH_3), 3.46 (*td*, J_d = 1.2, J_t = 8.2), 3.57 (*td*, J_d = 1.6, J_t = 8.0), 3.78–3.98 (*m*, CH_2), 6.56–6.70 (*m*, $3H_{Ar}$), 7.05–7.35 (*m*, $7H_{Ar}$). *^{13}C-NMR* (ppm): [2 rotamers] 21.93, 22.03, 23.05, 24.86, 24.92, 33.11, 33.51, 34.55, 36.01, 36.83, 37.46, 44.42, 48.25, 48.34, 49.53, 51.26, 113.06, 116.84, 126.16, 126.63, 128.31, 128.62, 128.68, 129.20, 137.99, 138.97, 147.41, 171.04, 171.22. *MS (CI)*: 339 (M+1, 100 %), 395 (M+57, 10 %).

The above procedure was used to synthesize the anilino-amides **3.1**, **3.2**, **3.4**, **3.5** except that the products were purified as oxalate salts (1.1 eq. of anh. oxalic acid in *i*-PrOH). The free bases were liberated at pH > 12 (10 % aq. NaOH).

7. N-*methyl*-N-*phenethyl-3-(phenylamino)butanamide* **3.1**. Scale: 15 mmol, yield: 3.78 g (85 %); pale yellow viscous oil, purity (cap. GC): 98 %.

IR (cm^{-1}): (characteristic bands): 3342, 1632, 1602. *^{1}H-NMR* (*δ*): [2 rotamers] 1.13 (*d*, *J* = 5.8, CH_3), 1.26 (*d*, 6.0, CH_3), 2.05–2.16 (*m*), 2.30–2.41 (*m*), 2.59 (*dd*, J_1 = 4.2, J_2 = 15.8), 2.75–2.86 (*m*), 2.81 (*s*, CH_3), 2.93 (*s*, CH_3), 3.46 (*t*, 7.4), 3.58 (*td*, J_d = 2, J_t = 7.2), 3.82–4.12 (*m*), 6.55–6.72 (*m*, $3H_{Ar}$), 7.05–7.37 (*m*, $7H_{Ar}$). *^{13}C-NMR* (ppm): [2 rotamers] 20.63, 20.72, 33.25, 33.56, 34.61, 36.09, 38.18, 38.97, 45.87, 49.02, 51.36, 113.39, 117.18, 126.23, 126.70, 128.40, 128.71, 129.22, 138.01, 138.97, 147.00, 170.93, 171.13. *MS (CI)*: 297 (M+1, 100 %), 311 (M+14, 10 %), 353 (M+57, 5 %).

8. N-*methyl*-N-*phenethyl-3-(phenylamino)octanamide* (**3.2**). Scale: 10 mmol, yield: 2.91 g (83 %), pale yellow viscous oil, purity (cap. GC), 98 %.

IR (cm^{-1}): (characteristic bands): 3342, 1632, 1602. *^{1}H-NMR* (*δ*): [2 rotamers] 0.84–0.87 (*m*), 1.26–1.62 (*m*), 2.09–2.20 (*m*), 2.28–2.59 (*m*), 2.73–2.82 (*m*), 2.79 (*s*, *N*–CH_3), 2.91 (*s*, CH_3), 3.41–3.48 (*m*), 3.52–3.60 (*m*), 3.72–3.87 (*m*), 6.55–6.69 (*m*, Ar), 7.07–7.32 (*m*, Ar). *^{13}C-NMR* (ppm): [2 rotamers] 13.93, 22.49, 26.04, 31.65, 33.25, 33.54, 34.62, 35.09, 36.09, 36.64, 37.20, 49.62, 50.38, 51.36, 113.18, 116.91, 126.19, 126.67, 128.37, 128.67, 129.20, 138.01, 139.01, 139.01, 147.46, 171.09, 171.25. *MS (CI)*: 353 (M+1, 100 %), 409 (M+57, 10 %).

9. N-*methyl*-N-*phenethyl-5-phenyl-3-(phenylamino)pentanamide* (**3.4**). Scale: 5.0 mmol, yield: 1.55 g, (80 %), pale yellow viscous oil, purity (cap. GC): 96 %

IR (cm^{-1}): (characteristic bands): 3342, 1632, 1602. *^{1}H-NMR* (*δ*): [2 rotamers] 1.63–1.84 (*m*), 1.89–2.02 (*m*), 2.23 (*dd*, J_1 = 4.0, J_2 = 9.8), 2.47 (*t*, *J* = 5.8), 2.69–2.80 (*m*), 2.74 (*s*, *N*–CH_3), 2.89 (*s*, *N*–CH_3), 3.40 (*t*, *J* = 7.2), 3.54 (*t*, *J* = 7.0, 3.69–3.89 (*m*), 3.91–4.18 (*m*), 6.52–6.69 (*m*, $3H_{Ar}$), 7.04–7.36 (*m*, $7H_{Ar}$). *^{13}C-NMR* (ppm): [2 rotamers] 32.70, 33.23, 33.54, 34.56, 36.05, 36.44, 36.58, 49.58, 49.98, 51.35, 113.38, 117.14, 125.74, 126.23, 126.72, 128.29, 128.40, 128.69, 129.25, 137.97, 138.94, 141.85, 147.39, 170.91, 171.11.

10. N-*methyl*-N-*phenethyl-6-phenyl-3-(phenylamino)hexanamide* (**3.5**). Scale: 5.0 mmol, yield: 1.56 g (78 %), pale yellow viscous oil, purity (cap. GC, after chromatography): 98 %.

IR (cm^{-1}): (characteristic bands): 33342, 1632, 1602. *^{1}H-NMR* (*δ*): [2 rotamers] 1.42–1.79 (*m*),

2.10 (*dd*, J_1 = 6.4, J_2 = 15.6), 2.29 (*dd*, J_1 = 5.2, J_2 = 15.6), 2.43 (*dd*, J_1 = 4.0, J_2 = 12.0), 2.54–2.62 (*m*), 2.66–2.80 (*m*), 2.74 (*s*, *N*–CH_3), 2.89 (*s*, *N*–CH_3), 3.40 (*t*, *J* = 7.6), 3.54 (*td*, J_d = 2, J_t = 7.2), 3.73–3.86 (*m*), 6.53–6.69 (*m*, Ar), 7.04–7.22 (*m*, Ar). *^{13}C-NMR* (ppm): [2 rotamers] 28.19, 33.23, 33.50, 34.56, 34.71, 35.60, 36.03, 36.64, 37.25, 49.60, 50.27, 51.33, 113.19, 117.02, 125.61, 126.19, 126.67, 128.18, 128.31, 128.65, 128.71, 129.22, 137.97, 138.96, 142.22, 147.37, 170.98, 171.18.

The typical procedure for the synthesis of the diamines **4.1**–**4.5** is illustrated for the diamine **4.3**.

11. N-*(5-methyl-1-(methyl(phenethyl)amino)hexan-3-yl)benzenamine* (**4.3**). A three-necked round-bottomed flask (100 mL) fitted with a thermometer, pressure-equalizing dropping funnel, and a reflux condenser connected to an oil bubbler through a septum. The system was purged with Ar and the flask charged with anh. THF (20 mL), a solution of **3.3** (1.0 g, 2.95 mmol/3 mL THF) and $NaBH_4$ (0.30 g, 7,8 mmol). As solution of $BF_3{\cdot}Et_2O$ (1.0 mL, 8.1 mmol/3 mL THF) was injected into the dropping funnel and added dropwise to the stirred mixture (10 min at –5 ºC), the stirring was continued for 1 h (< 0 ºC), then heated to reflux (1 h, ≈65 ºC). After cooling (≈20 ºC) the mixture was treated successively with H_2O (5 mL) and conc. HCl (10 mL, vigorous H_2 evolution!), followed by heating to reflux (30 min). After concentration (rotatory evaporator), the residue was dissolved in H_2O (5 mL) and alkalised (10 % NaOH, pH > 12). The liberated diamine **4.3** was extracted (CH_2Cl_2, 2 × 10 mL), dried (anh. K_2CO_3), filtered and the solvent removed. Yield: 0.86 g (90 %), pale yellow viscous oil. Purity (cap. GC): 97 %. This product was without purification for the nex step.

IR (cm^{-1}): (characteristic bands) 3393, 1602. *^{1}H-NMR* (δ): 0.88 (*d*, *J* = 6.6, CH_3), 0.93 (*d*, *J* = 6.8, CH_3), 1.30–1.46 (*m*), 1.63–1.72 (*m*), 2.39 (*s*, *N*–CH_3), 2.61–2.75 (*m*), 2.81–2.86 (*m*), 3.42–3.55 (*m*), 6.54–6.68 (*m*, 3HAr), 7.08–7.15 (*m*, 7HAr). *^{13}C-NMR* (ppm): 22.69, 24.79, 31.46, 32.92, 41.54, 44.60, 49.51, 54.16, 58.98, 112.67, 116.48, 126.13, 128.37, 128.58, 129.20, 139.38, 147.98. *MS (CI)*: 325 (M+1, 100 %), 381 (M+57, 20 %).

The above procedure was used to synthesize the diamines **4.1**, **4.2**, **4.4**, **4.5**.

12. N-*(4(methyl(phenethyl)amino)butan-2-yl)benzenamine* (**4.1**). Scale: 5.0 mmol, yield: 1.23 g (87 %), viscous oil, purity (cap. GC): 97 %.

IR (cm^{-1}): (characteristic bands) 3393, 1602. *^{1}H-NMR* (δ): 1.15 (*d*, *J* = 6.4, CH_3), 1.63 (*q*, *J* = 6.4, CH_2), 2.27 (*s*, *N*–CH_3), 2.48 (*t*, *J* = 6.8, CH_2), 2.53–2.62 (*m*, 1H), 2.70–2.80 (*m*, 3H), 3.49 (*pr.s.*, 1H), 4.03 (*pr.s.*, 1H), 6.53 (*d*, *J* = 7.6, 2 *o*-H_{Ar}), 6.63 (*t*, *J* = 7.2, 1 *p*-HAr). *^{13}C-NMR* (ppm): 20.67, 33.74, 34.03, 42.01, 47.43, 54.66, 58.58, 112.94, 116.54, 125.85, 128.25, 128.58, 129.11, 140.30, 147.71. *MS (CI)*: 191 (M-91, 25 %) 283 (M+1, 100 %).

13. N-*(1-(methyl(phenethyl)amino)octan-3-yl)benzenamine* (**4.2**). Scale: 5.0 mmol, yield: 1,59 g (94 %), viscous oil, purity (cap. GC): 96 %.

IR (cm^{-1}): (characteristic bands) 3393, 1602. *^{1}H-NMR* (δ): 0.87 (*t*, *J* = 7.0, CH_3), 1.28–1.37 (*m*), 1.44–1.52 (*m*), 1.55–1.62 (*m*), 1.72–1.78 (*m*), 2.29 (*s*, *N*–CH_3), 2.47–2.65 (*m*), 2.72–2.81 (*m*), 3.38 (*quint*, *J* = 6.1, CH), 6.51–6.67 ($3H_{Ar}$), 7.08–7.17 ($7H_{Ar}$). *^{13}C-NMR* (ppm): 13.95, 22.54, 25.53, 31.85, 33.69, 34.87, 41.98, 51.82, 54.58, 59.54, 112.78, 116.37, 125.90, 128.29, 128.61, 129.15, 140.33, 148.18. *MS (CI)*: 339 (M+1, 100 %), 395 (M+57, 20 %).

14. N-*(1-methyl(phenethyl)amino)-5-phenylpentan-3-yl)benzenamine* (**4.4**). Scale: 3.0 mmol, yield: 1.03 g (92 %), viscous oil, purity (cap. GC) 97 %.

IR (cm^{-1}): (characteristic bands) 3393, 1602. *^{1}H-NMR* (δ): 1.60–1.67 (*m*), 1.76–1.87 (*m*), 2.28 (*N*–CH_3), 2.47–2.81 (*m*), 3.40–3.45 (*m*), 6.48–6.67 (*m*, $3H_{Ar}$), 7.05–7.35 (*m*, $12H_{Ar}$). *^{13}C-NMR* (ppm): 31.79, 32.18, 33.61, 36.57, 41.87, 51.20, 54.45, 59.47, 112.81, 116.49, 125.69, 125.89, 128.25, 128.58, 129.12, 140.24, 141.96, 147.99. *MS (CI)*: 373 (M+1, 100 %) 429 (M+57, 15 %).

15. N-*(1-(methyl(phenethyl)amino)-6-phenylhexan-3yl)benzenamine* (**4.5**). Scale: 3.5 mmol, yield: 1.28 g (95 %), viscous oil, purity (cap. GC): 97 %.

IR (cm^{-1}): (characteristic bands) 3393, 1602. *^{1}H-NMR* (δ): 1.47–1.78 (*m*, 6H), 2.27 (*N*–CH_3), 2.47 (*t*, *J* = 7, CH_2), 2.53–2.59 (*m*, 4H), 2.70–2.79 (*m*, 1H), 3.34–3.46 (*m*, 1H), 3.80 (*pr. s*, 1H), 6.49–6.62 (*m*, $3H_{Ar}$), 7.07–7.29 (*m*, $12H_{Ar}$). *^{13}C-NMR* (ppm): 27.69, 31.75, 33.55, 34.41, 35.78, 41.89, 51.03, 54.50, 59.46, 112.79, 116.47, 125.68, 125.95, 128.23, 128.32, 128.63, 129.19, 140.17, 142.21, 148.09. *MS (CI)*: 387 (M+1, 100 %), 443 (M+57, 20 %).

The typical procedure for the synthesis of the anilido-amines **5.1**–**5.5** is illustrated by the anilido-amine **5.3**.

16. N-*(5-methyl-1-(methyl(phenethyl)amino)hexan-3-yl)*-N-*phenylpropionamide* (**5.3**). A three-necked round-bottomed flask (50 mL) fitted with a thermometer, pressure-equalizing dropping funnel, and a reflux condenser caped with a $CaCl_2$-drying tube, was purged with Ar and the flask charged with diamine **4.3** solution (0.70 g, 2.16 mmol/10 mL CH_2Cl_2) and Et_3N (0.14 mL, 1.0 mmol), while the propionyl chloride solution (≈0.45 mL, 5 mmol/2 mL CH_2Cl_2) was added to the droping funnel. The mixture was cooled (≈0 ºC) and the chloride solution added dropwise (≈10 min, ≈0 ºC). The stirring was continued (5 h, 0–20 ºC), whereupon the hydrochloride salt precipitate. MeOH (2 mL) was added (the precipitate dissolves) and after 30 min of stirring the mixture was poured into NH_4OH solution (25 %, 15 mL). The organic layer was washed with H_2O (2 × 15 mL), dried (anh. K_2CO_3), filtered and concentrated (rotatory evaporator, 80 ºC, 30 min). The remaining reddish viscous oil was dissolved in dry Et_2O (15 mL) and added dropwise, with stirring to an anh. oxalic acid solution (0.25 g, 2.8 mmol/3 mL Et_2O). After cooling (≈ 20 ºC, 12 h), the precipitated monooxalate salt was collected by filtration, washed with Et_2O (5 mL) and vacuum dried. Yield: 1.06 g (90 %), white powder, m.p. (dec.): 99–100 ºC. The free base was obtained by salt hydrolysis (10 %, NaOH, pH > 12) as a colourless oil. Purity (cap. GC) > 99 %. The spectral data refere to the free base.

IR (cm^{-1}): (characteristic bands): 1657, 1595. *^{1}H-NMR* (δ): 0.91 (*d*, *J* = 6.6, CH_3), 0.98 (*d*, *J* = 6.6, CH_3), 1.02 (*t*, *J* = 7.6, CH_3), 1.07–1.14 (*m*), 1.26–1.38 (*m*), 1.44–1.74 (*m*), 1.93 (*q*, *J* = 7.4, CH_2), 2.30 (*s*, *N*–CH_3), 2.48–2.66 (*m*), 2.73–2.82 (*m*), 4.90–5.05 (*m*, CH), 7.05–7.45 (10 H_{Ar}). *^{13}C-NMR* (ppm): 9.65, 22.55, 22.85, 24.86, 28.51, 31.43, 33.72, 42.20, 42.33, 51.23, 54.92, 59.72, 125.84, 128.03, 128.24, 128.58, 129.19, 130.02, 138.85, 140.37, 174.03. *MS (CI)*: 381 (M+1, 100 %).

The above procedure was used to synthesize the anilido-amines **5.1**, **5.2**, **5.4**, **5.5.**

17. N-*(4-(methyl(phenethyl)amino)butan-2-yl)*-N-*phenylpropionamide* (**5.1**). Scale: 4.0 mmol, yield (monooxalate salt): 1.62 g (95 %), white powder, m.p. (dec.): 115–117 ºC. Free base: colourless oil, purity (cap. GC): 97 %. The spectral data refer to the free base.

IR (cm^{-1}): (characteristic bands): 1657, 1595. *^{1}H-NMR* (δ): 1.02 (*t*, *J* = 7.4, CH_3), ≈1.02 (CH_3), 1.38–1.52 (*m*, 1H), 1.63–1.82 (*m*, 1H), 1.93 (*q*, *J* = 7.6, CH_2), 2.29 (*s*, *N*–CH_3), 2.42–2.65 (*m*, 4H), 2.72–2.82 (*m*, 2H), 4.92 (*quint*, *J* = 7.0, CH), 7.07–7.44 (*m*, 10 H_{Ar}). *^{13}C-NMR* (ppm): 9.29 (CH_3), 18.90 (CH_3), 28.12 (CH_2), 32.42 (CH_2), 33.34 (CH_2), 41.73 (CH_3), 48.38 (CH), 54.41 (CH_2), 59.31 (CH_2), [125.47, 127.74, 127.87, 128.00, 128.24, 128.84, CH_{Ar}], 138.58 (C_{Ar}), 140.00 (C_{Ar}), 173.04 (C=O). *MS (CI)*: 339 (M+1, 100 %).

18. N-*(1-(methyl(phenethyl)amino)octan-3-yl)*-N-*phenylpropionamide* (**5.2**). Scale: 3.5 mmol, yield (monooxalate salt): 1.55 g (91 %), white powder, m.p. (dec.): 111–114 ºC. Free base: colourless oil, purity (cap. GC): > 97 %. The spectral data refer to the free base.

IR (cm^{-1}): (characteristic bands): 1657, 1595. *^{1}H-NMR* (δ): 0.886 (*t*, *J* = 6.4, CH_3), 1.02 (*t*, *J* = 7.6, CH_3), 1.29–1.36 (*m*), 1.50–1.60 (*m*), 1.95 (*q*, *J* = 7.4, CH_2), 2.29 (*s*, CH_3), 2.48–2.62 (*m*), 2.72–2.82 (*m*), 4.74–4.88, 7.05–7.25 (*m*, 10H_{Ar}). *^{13}C-NMR* (ppm): 9.92, 13.59, 22.06, 25.92, 28.10, 30.75, 31.30, 32.83, 33.31, 41.76, 53.07, 54.46, 59.27, 125.39, 127.62, 127.80, 128.17, 128.80, 129.47, 138.69, 139.99, 173.54. *MS (CI)*: 395 (M+1, 100 %).

19. N-*(1-(methyl(phenethyl)amino)-5-phenylpentan-3-yl)*-N-*phenylpropionamide* (**5.4**). Scale: 2.5 mmol, yield (monooxalate salt): 1.16 g (89 %), white powder, m.p. (dec.): 103–105 ºC. Free base: colourless oil; purity (cap. GC): 97 %. The spectral data refer to the free base.

IR (cm^{-1}): (characteristic bands): 1657, 1595. *^{1}H-NMR* (δ): 1.05 (*t*, *J* = 7.4, CH_3), 1.55–1.79 (*m*, 4H), 1.99 (*q*, *J* = 7.8, CH_2), 2.28 (*s*, *N*–CH_3), 2.46–2.67 (*m*, 4H), 2.70–2.81 (*m*, 4H), 4.90–4.96 (*m*, CH), 7.13–7.43 (*m*, 15H_{Ar}). ^{13}*C-NMR* (ppm): 9.64, 28.48, 31.12, 33.01, 33.60, 35.09, 42.10, 53.40, 54.70, 59.59, 125.70, 125.76, 128.14, 128.51, 129.25, 129.76, 138.92, 140.29, 141.72, 174.13. *MS (CI)*: 337 (M-91, 20 %), 429 (M+1, 100 %).

20. N-*(1-(methyl(phenethyl)amino)-6-phenylhexan-3-yl)*-N-*phenylpropionamide* (**5.5**). Scale: 3.0 mmol, yield (monooxalate salt): 1.37 g (86 %), white powder, m.p. (dec.): 99–100 ºC. Free base: colourless oil, purity (cap. GC): 97 %. The spectral data refer to the free base.

IR (cm^{-1}): (characteristic bands): 1657, 1595. *^{1}H-NMR* (δ): 1.01 (*t*, *J* = 7.6, CH_3), 1.32–1.56 (*m*), 1.73 (*quint*, *J* = 7.2), 1.93 (*q*, *J* = 7.4, CH_2), 2.27 (*s*, *N*–CH_3), 2.44–2.66 (*m*), 2.70–2.80 (*m*), 4.78–4.95 (*m*, CH), 7.10–7.40 (*m*, $10H_{Ar}$). *^{13}C-NMR* (ppm): 9.67, 28.47, 31.20, 32.50, 33.64, 35.51, 42.15, 53.03, 54.81, 59.64, 125.63, 125.81, 127.99, 128.20, 128.44, 128.56, 129.82, 138.78, 140.36, 142.11, 174.14. *MS (CI)*: 443 (M+1, 100 %).

ИЗВОД

СИНТЕЗА И ФАРМАКОЛОШКО ИСПИТИВАЊЕ (±)-2,3-*seco*-АНАЛОГА ФЕНТАНИЛА

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Развијен је ефикасан поступак за добијање различитих ацикличних 1,3-диамина, у пет фаза, и примењен у синтези нове класе аналога фентанила отвореног низа. Деривати **5.1**–**5.5** (сви су нова једињења) синтетисани су са циљем да се процени утицај пиперидинског прстена на опиоидноаналгетичку активност анилидо-пиперидина. Полазни β-кето-амид **1.1**, добијен аминолизом метилацетоацетата метилфенетиламином (принос 93 %), био је сукцесивно третиран са NaH и BuLi, при чему је постао веома реактивни α,γ-диенолатни анјон **1.1a**. Регио- и хемоселективним γ-алкиловањем овог диенолата различитим примарним и секундарним алкил-халогенидима, добијени су β-кето-амиди **1.2**–**1.5** (принос 76–91 %). Редуктивним аминовањем кето-амида **1.1**–**1.5** помоћу Zn праха и сирћетне киселине, преко енаминских интермедијера **2.1**–**2.5**, постали су β-анилино-амиди **3.1**–**3.5** (принос 74–85 %). После редуктивне деоксигенације терцијене амидне функције, користећи *in situ* генерисани диборан, одговарајући 1,3-диамини **4.1**–**4.5** изоловани су у приносима **87**–**97** %. Синтеза (±)-2,3-*seco*-фентанила **5.1**–**5.5** завршена је *N*-ациловањем диамина **4.1**–**4.5** пропионил-хлоридом, а затим таложењем у облику монооксалатних соли (принос 86–95 %). Нађено је да је основно једињење, 2,3-*seco* фентанил **5.1**, 40 пута слабији наркотички аналгетик од фентанила, али још увек 5–6 пута активнији од морфина у пацова, док је *i*-Pr дериват **5.3** био неактиван. Осим фармаколошког значаја, општим поступком приказаним у овом раду, могу се синтетисати различити 1,3-диамини, укључујући и оне са функционалним групама. Ова једињења могу бити потенцијално значајна као комплексирајући агенси и као интермедијери у синтези аза-краун-етара.

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