Designing and Synthesis of Novel Amidated Fentanyl Analogs

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Dedicated to Prof. *Abdoljalil Mostashari* on the occasion of his 70th birthday

Some new amidated fentanyl (= *N*-[1-(2-phenylethyl)piperidin-4-yl]-*N*-phenylpropanamide) analogs with a 4-(*N*-phenylamido)piperidine scaffold and additional amide bonds have been designed and synthesized through *Ugi* four-component reaction (*Ugi*-4CR). Good-to-high yields, diversity-oriented synthesis, and possible applications in drug discovery are advantages of this approach.

Introduction. – Multicomponent reactions (MCRs) have attracted considerable interest owing to their exceptional synthetic efficiency [1]. Isocyanide-based MCRs (IMCRs) allow the synthesis of several different scaffolds [2]. The potential of isocyanides for the development of multicomponent reactions lies in the diversity of bond-forming processes available, their functional group tolerance, and the high levels of chemo-, regio-, and stereoselectivity often observed [3]. Therefore, the design of novel IMCRs has attracted great attention for the scientists working in areas such as drug discovery, organic synthesis, combinatorial chemistry, and material science [4]. Designing the *Ugi* four-component reactions (*Ugi*-4CRs) with new starting compounds for the construction of drugs or bioactive compounds is an interesting endeavor in organic synthesis [5]. Recently, this approach was used for the synthesis of 4-aminopiperidine-4-carboxylic acid derivatives and also for the preparation of the two drugs carfentanil and remifentanil [6].

There are some potent μ-opioid agonists which contain the 4-(phenylamino)piperidine scaffold [7], such as fentanyl [8], remifentanil [9], sufentanil [10], alfentanil [11], and carfentanil [12] (*Fig.*). Fentanyl is a synthetic μ-opioid, *ca.* 50–100 times more potent than morphine, and is characterized by a rapid onset of analgesia and a relatively short duration of action. Fentanyl is extensively used for anesthesia and analgesia in operating rooms and intensive care units. From its pharmacological action, it appeared to be capable of forming a complex with a stereospecific receptor postulated for analgesic action [13][14]. Meanwhile, some opioid drugs show in general poor bioavailability, mainly due to their inability to penetrate the blood–brain barrier and rapid degradation *in vivo* by several peptides [15]. To overcome these problems, diverse strategies such as using pseudo-peptides, incorporation of lipophilic moieties in the structure of the molecule, or insertion of natural opioid peptides have been adopted [16].

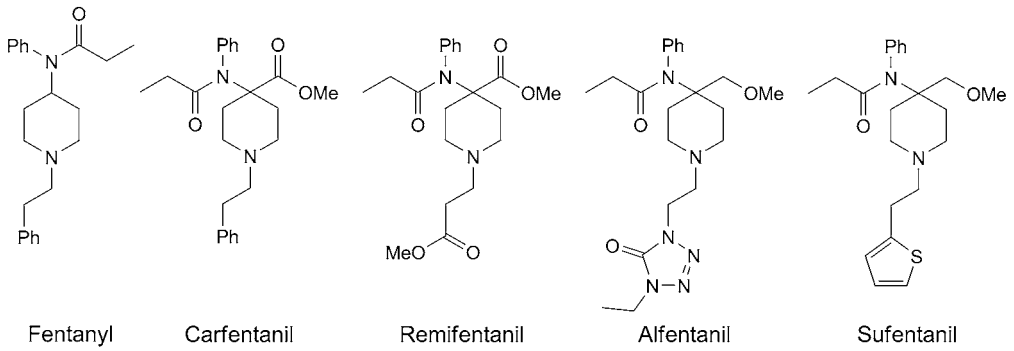

Figure. *Structures of opioid compounds with 4-aminopiperidine skeleton*

On the basis of these oberservation, we designed and synthesized novel compounds with insertion of suitable lipophilic scaffolds which contain the piperidine skeleton. Meanwhile, it was shown that the number of amide bonds in the structure of the drugs could affect the efficiency of the opioid drugs [17]. It seems that more amide groups are desired for efficient interaction with opioid receptors and to reduce presumably adverse side-effects. The importance of the piperidine skeleton in biological, synthetic, and material chemistry has inspired the development of numerous methods for their synthesis with control of activity [18]. With this in mind, we were attracted by the synthesis of novel fentanyl derivatives *via Ugi*-4CR by using a suitable COOH moiety.

In continuation of our recent research for the synthesis of novel compounds using the *Ugi*-4CR [19], here we report the synthesis of novel fentanyl analogs based on *Ugi*-4CR. Reaction of 4-Amino-1-(2-phenylethyl)piperidine with succinic anhydride and glutaric anhydride led to the known compounds **1a** and **1b** [20], respectively, with a COOH moiety. The reaction of benzaldehydes **2**, amines **3**, carboxylic acids **1a** and **1b**, and cyclohexyl isocyanide **4** at room temperature afforded novel amidated fentanyl analogs **5a**–**5k** (*Scheme*).

Results and Discussion. – We started our synthesis from the commercially available (2-phenylethyl)amine and methyl acrylate. The reaction sequence was: *a*) addition of (2-phenylethyl)amine to methyl acrylate, *b*) cyclization with NaH, *c*) ester hydrolysis and decarboxylation with 25% HCl [21a], *d*) formation of imine with aniline, *e*) reduction of the imine with $NaBH_4$ [21], *f*) reaction of the produced amine with succinic and glutaric anhydride [21b], to form the desired known carboxylic acid derivatives **1a** and **1b**, respectively. The reactions were found to proceed smoothly, and the products were purified by recrystallization. The overall yields for the synthesis of compounds **1a** and **1b** were 75%.

The feasibility of the *Ugi*-4CR was evaluated applying benzaldehyde (**2a**), 4-bromoaniline (**3c**), carboxylic acid **1a**, and cyclohexyl isocyanide (**4**; *Scheme*, *Table*). In accordance with literature procedures, MeOH was used as a solvent. Gratifyingly, after 24 h of stirring at room temperature, the desired product **5a** could be isolated in 85% yield. To extend the library of products and diversity of reactions, we expanded this reaction with different benzaldehyde derivatives **2**, amines, and two synthetic

Scheme. *Synthesis of Fentanyl Analogs through* Ugi-*4CR*

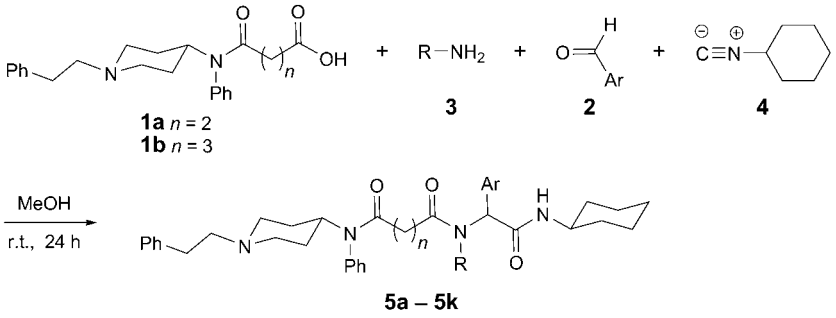

Table. *Synthesis of Novel Fentanyl Analogs* via Ugi-*4CR*[a])

Carboxylic acid	*n*	R	Ar	Product	Yield [%]
1a	2	4-Br–C_6H_4	Ph	**5a**	85
1a	2	2-I–C_6H_4	Ph	**5b**	95
1b	3	4-Br–C_6H_4	Ph	**5c**	77
1a	2	Ph	Ph	**5d**	80
1b	3	Ph	Ph	**5e**	78
1a	2	Bn	Ph	**5f**	73
1a	2	$PhCH_2CH_2$	Ph	**5g**	90
1a	2	Bn	4-MeO–C_6H_4	**5h**	72
1a	2	$PhCH_2CH_2$	4-MeO–C_6H_4	**5i**	63
1a	2	(Thiophen-2-yl)–CH_2CH_2	Ph	**5j**	96
1a	2	(Thiophen-2-yl)–CH_2CH_2	4-MeO–C_6H_4	**5k**	92

[a]) In all cases, cyclohexyl isocyanide (**4**) was used.

carboxylic acids. The structures of products **5a**–**5k** were verified by their IR, ^{1}H- and ^{13}C-NMR, and HR-MS data. For instance, in the ^{1}H-NMR spectrum of compound **5a**, there is a distinguished *singlet* for the CH of PhCH which resonated at δ(H) 6.27 ppm, and a *doublet* for the NH group at 6.50 ppm. The ^{13}C-NMR spectrum revealed three distinct peaks at δ(C) 168.5, 171.6, and 172.6 ppm for the amide C=O groups.

The synthesized novel fentanyl analogs with three amide bonds and lipophilic moieties probably have better flexibility and interactions with μ-receptors and also better permeability. The experiments are still being continued.

Conclusions. – We have developed an efficient procedure for the generation of amidated fentanyl derivatives. Good-to-excellent yields, high bond-forming efficiency, and tolerance of various groups toward the reaction conditions are advantages of this protocol. This method may have interesting implications on the construction of structurally diverse heterocyclic molecules and will find applications in combinatorial chemistry, diversity-oriented synthesis, and drug discovery. Studies toward this goal are in progress.

S. B. gratefully acknowledges the *Iran National Science Foundation* (*INSF*) for the financial support. We are also grateful to Prof. *R. Gleiter* for his invaluable comments.

Experimental Part

General. M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *ABB-FTLA* 2000 FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker* spectrometers; 500 or 300 (^1H), and 125 or 75 MHz (^{13}C); in (D_6)DMSO; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. HR-ESI-MS*: Mass-ESI-POS* (*Apex Qe-FT-ICR* instrument) spectrometer; in *m*/*z*.

2. *Synthesis of* **1a** *and* **1b**. *General Procedure:* Fentanyl intermediate, *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine, was prepared according to the known procedure [21a,d]. A mixture of *N*-phenyl-1-(2-phenylethyl)piperidin-4-amine (20 mmol) and succinic anhydride or glutaric anhydride (22 mmol) in $CHCl_3$ (100 ml) was stirred at r.t. overnight. The progress of the reaction was monitored by TLC (hexane/AcOEt 1:3). Then, the solvent was evaporated, and the resulting crude was crystallized from AcOEt/hexane to give pure products **1a** and **1b** [20], resp.

3. *Synthesis of* **5a**–**5k**. *General Procedure:* Aldehyde **2** (1 mmol) and amine **3** (1 mmol) were dissolved in MeOH (5 ml), and the mixture was stirred at r.t. for 30 min. Then, carboxylic acid **3** (1 mmol) was added, and stirring was continued for 15 min, followed by addition of cyclohexyl isocyanide (**4**; 1 mmol), and the mixture was stirred for 24 h. The progress of the reaction was monitored by TLC. Then, the solvent was evaporated, the resulting mixture was washed with sat. $NaHCO_3$ (30 ml), and the crude was crystallized from MeOH to give pure products **5a**–**5k**.

N^1*-(4-Bromophenyl)*-N^1*-[2-(cyclohexylamino)-2-oxo-1-phenylethyl]*-N^4*-phenyl*-N^4*-[1-(2-phenylethyl)piperidin-4-yl]butanediamide* (**5a**). Yield 637 mg (85%). White solid. M.p. 213–214°. IR (KBr): 3277, 3062, 2930, 2854, 1656, 1595. ^1H-NMR: 1.15–2.33 (*m*, 20 H); 2.51–2.55 (*m*, 2 H); 2.71–2.74 (*m*, 2 H); 3.01 (*d*, *J* = 10.4, 2 H); 3.82–3.92 (*m*, 1 H); 4.61–4.71 (*m*, 1 H); 6.27 (*s*, 1 H); 6.50 (*d*, *J* = 7.9, 1 H); 7.03–7.39 (*m*, 19 arom. H). ^{13}C-NMR: 25.0; 25.1; 25.7; 30.1; 30.5; 31.0; 32.8; 33.1; 33.8; 48.9; 52.5; 53.1; 53.2; 60.5; 64.2; 122.1; 126.1; 128.1; 128.2; 128.4; 128.5; 128.6; 129.4; 129.5; 130.4; 130.5; 130.6; 132.1; 134.8; 138.3; 139.1; 140.2; 168.5; 171.6; 172.6. HR-ESI-MS: 749.30645 ($[M+1]^+$, $C_{43}H_{50}{}^{79}BrN_4O_3^+$; calc. 749.30650). 751.30411 ($[M+1]^+$, $C_{43}H_{50}{}^{81}BrN_4O_3^+$; calc. 751.30416).

N^1*-[2-(Cyclohexylamino)-2-oxo-1-phenylethyl]*-N^1*-(4-iodophenyl)*-N^4*-phenyl*-N^4*-[1-(2-phenylethyl)-piperidin-4-yl]butanediamide* (**5b**). Yield 757 mg (95%). White solid. M.p. 81–82°. IR (KBr): 3444, 3060, 3028, 2931, 2855, 2806, 1733, 1653, 1594. ^1H-NMR: 1.13–2.31 (*m*, 19 H); 2.44–2.54 (*m*, 3 H); 2.71–2.74 (*m*, 2 H); 3.01 (*d*, *J* = 10.7, 2 H); 3.82–3.92 (*m*, 1 H); 4.62–4.74 (*m*, 1 H); 6.18 (*s*, 1 H); 6.56–6.57 (*d*, *J* = 7.9, 1 H); 6.90–7.48 (*m*, 17 arom. H); 7.59 (*d*, *J* = 8.0, 1 H); 7.88 (*d*, *J* = 8.0, 1 H). ^{13}C-NMR: 25.0; 25.2; 25.7; 30.5; 30.7; 31.1; 32.8; 33.0; 33.8; 49.0; 52.4; 53.1; 60.5; 64.9; 104.0; 126.0; 127.5; 128.2; 128.4; 128.5; 128.6; 129.2; 129.3; 129.5; 129.7; 130.3; 130.7; 131.8; 131.8; 132.9; 138.4; 139.7; 140.2; 142.1; 169.0; 171.7; 172.7. HR-ESI-MS: 797.29286 ($[M+1]^+$, $C_{43}H_{50}IN_4O_3^+$; calc. 797.29294).

N^1*-(4-Bromophenyl)*-N^1*-[2-(cyclohexylamino)-2-oxo-1-phenylethyl]*-N^5*-phenyl*-N^5*-[1-(2-phenylethyl)piperidin-4-yl]pentanediamide* (**5c**). Yield 588 mg (77%). White solid. M.p. 154–155°. IR (KBr): 3268, 3059, 2927, 2852, 2803, 1650, 1594, 1563. ^1H-NMR: 0.97–1.94 (*m*, 20 H); 2.13 (*t*, *J* = 11.4, 2 H); 2.50–2.53 (*m*, 2 H); 2.70–2.73 (*m*, 2 H); 2.98 (*d*, *J* = 10.4, 2 H); 3.74–3.83 (*m*, 1 H); 4.55–4.65 (*m*, 1 H); 5.64 (*d*, *J* = 6.9, 1 H); 6.06 (*s*, 1 H); 6.98–7.35 (*m*, 19 arom. H). ^{13}C-NMR: 21.1; 24.8; 24.9; 25.5; 30.6; 32.8; 32.8; 33.8; 34.1; 34.1; 48.8; 52.2; 53.1; 60.5; 64.3; 122.0; 126.0; 128.3; 128.4; 128.5; 128.6; 129.3; 130.3; 130.4; 131.9; 132.5; 134.6; 138.7; 139.0; 140.3; 168.6; 171.9; 172.7. HR-ESI-MS: 763.32081 ($[M+1]^+$, $C_{44}H_{52}{}^{79}BrN_4O_3^+$; calc. 763.32069). 765.31801 ($[M+1]^+$, $C_{44}H_{52}{}^{81}BrN_4O_3^+$; calc. 765.31789).

N^1*-[2-(Cyclohexylamino)-2-oxo-1-phenylethyl]*-N^1,N^4*-diphenyl*-N^4*-[1-(2-phenylethyl)piperidin-4-yl]butanediamide* (**5d**). Yield 537 mg (80%). White solid. M.p. 210–211°. IR (KBr): 3277, 3061, 3029, 2929, 2853, 2801, 1655, 1595, 1561. ^1H-NMR: 1.13–2.39 (*m*, 20 H); 2.52–2.56 (*m*, 2 H); 2.71–2.75 (*m*, 2 H); 3.02 (*d*, *J* = 9.6, 2 H); 3.80–3.90 (*m*, 1 H); 4.64–4.73 (*m*, 1 H); 6.30 (*s*, 1 H); 6.83 (*d*, *J* = 7.0, 1 H); 7.03–7.45 (*m*, 20 arom. H). ^{13}C-NMR: 25.1; 25.2; 25.6; 30.1; 30.5; 31.2; 32.8; 33.1; 33.7; 48.7; 48.8; 52.4; 53.1; 53.2; 60.5; 64.6; 126.1; 127.8; 127.9; 128.0; 128.1; 128.2; 128.4; 128.5; 128.6; 129.0; 129.3; 129.5; 130.4;

130.6; 130.7; 135.2; 138.4; 140.1; 168.7; 171.8; 172.9. HR-ESI-MS: 671.39531 ($[M+1]^+$, $C_{43}H_{51}N_4O_3^+$; calc. 671.39527).

N^1*-[2-(Cyclohexylamino)-2-oxo-1-phenylethyl]*-N^1,N^5*-diphenyl*-N^5*-[1-(2-phenylethyl)piperidin-4-yl]pentanediamide* (**5e**). Yield 534 mg (78%). White solid. M.p. 198–199°. IR (KBr): 3256, 3087, 3060, 2926, 2852, 1649, 1594. ^{1}H-NMR: 1.04–2.14 (*m*, 22 H); 2.50–2.53 (*m*, 2 H); 2.69–2.73 (*m*, 2 H); 2.97 (*d*, *J* = 11.2, 2 H); 3.76–3.86 (*m*, 1 H); 4.56–4.64 (*m*, 1 H); 5.79 (*d*, *J* = 7.8, 1 H); 6.01 (*s*, 1 H); 6.96–7.34 (*m*, 20 arom. H). ^{13}C-NMR: 21.2; 24.8; 24.9; 25.5; 30.5; 32.8; 32.9; 33.8; 34.1; 48.7; 52.1; 53.1; 60.5; 64.9; 126.0; 127.9; 128.2; 128.4; 128.6; 128.8; 129.3; 130.3; 130.4; 130.5; 130.6; 134.9; 138.7; 140.2; 140.3; 168.7; 172.0; 173.0. HR-ESI-MS: 685.41108 ($[M+1]^+$, $C_{44}H_{53}N_4O_3^+$; calc. 685.41106).

N^1*-[2-(Cyclohexylamino)-2-oxo-1-phenylethyl]*-N^4*-phenyl*-N^4*-[1-(2-phenylethyl)piperidin-4-yl]*-N^1*-(phenylmethyl)butanediamide* (**5f**). Yield 500 mg (73%). White solid. M.p. 185–186°. IR (KBr): 3286, 2930, 2855, 1652, 1497. ^{1}H-NMR: 1.21–2.16 (*m*, 19 H); 2.49–2.56 (*m*, 3 H); 2.71–2.75 (*m*, 2 H); 3.04 (*s*, 2 H); 3.85–3.95 (*m*, 1 H); 4.56 (*d*, *J* = 17.6, 1 H); 4.64–4.74 (*m*, 1 H); 4.94 (*d*, *J* = 17.6, 1 H); 6.34 (*s*, 1 H); 6.82 (*d*, *J* = 7.2, 1 H); 7.08–7.40 (*m*, 20 arom. H). ^{13}C-NMR: 25.1; 25.2; 25.8; 28.9; 30.4; 30.5; 31.7; 32.9; 33.2; 33.7; 48.7; 50.0; 52.5; 53.2; 53.1; 60.5; 62.6; 126.0; 126.1; 126.8; 128.0; 128.3; 128.4; 128.5; 128.6; 129.4; 129.6; 130.2; 130.3; 130.6; 135.6; 137.7; 138.2; 140.1; 168.4; 172.0; 174.6. HR-ESI-MS: 685.41127 ($[M+1]^+$, $C_{44}H_{53}N_4O_3^+$; calc. 685.41128).

N^1*-[2-(Cyclohexylamino)-2-oxo-1-phenylethyl]*-N^4*-phenyl*-N^1*-(2-phenylethyl)*-N^4*-[1-(2-phenylethyl)-piperidin-4-yl]butanediamide* (**5g**). Yield 629 mg (90%). White solid. M.p. 153–154°. IR (KBr): 3435, 3280, 3062, 3026, 2931, 2854, 1649, 1595, 1552, 1496. ^{1}H-NMR: 1.34–2.80 (*m*, 26 H); 3.01–3.05 (*m*, 2 H); 3.30–3.40 (*m*, 1 H); 3.78–3.92 (*m*, 2 H); 4.62–4.72 (*m*, 1 H); 6.41 (*s*, 1 H); 6.84 (*d*, *J* = 7.1, 1 H); 6.89–7.49 (*m*, 20 arom. H). ^{13}C-NMR: 25.2; 25.2; 25.7; 30.0; 30.5; 30.5; 31.9; 32.8; 33.0; 33.2; 33.7; 36.3; 48.2; 48.8; 52.6; 53.2; 60.5; 60.6; 126.0; 126.5; 128.1; 128.3; 128.4; 128.5; 128.6; 128.9; 129.0; 129.4; 129.6; 130.2; 130.5; 130.7; 136.3; 138.2; 140.1; 168.4; 172.0; 173.6. HR-ESI-MS: 699.42736 ($[M+1]^+$, $C_{45}H_{55}N_4O_3^+$; calc. 699.42743).

N^1*-[2-(Cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl]*-N^4*-phenyl*-N^4*-[1-(2-phenylethyl)piperidin-4-yl]*-N^1*-(phenylmethyl)butanediamide* (**5h**). Yield 515 mg (72%). White solid. M.p. 174–175°. IR (KBr): 3425, 3280, 3088, 3061, 3028, 3003, 2928, 2853, 2798, 2760, 1646, 1563, 1512, 1495. ^{1}H-NMR: 1.20–2.56 (*m*, 22 H); 2.71–2.74 (*m*, 2 H); 3.01–3.04 (*m*, 2 H); 3.72 (*s*, 3 H); 3.81–3.90 (*m*, 1 H); 4.53 (*d*, *J* = 17.6, 1 H); 4.63–4.72 (*m*, 1 H); 4.91 (*d*, *J* = 17.6, 1 H); 6.26 (*s*, 1 H); 6.71–6.75 (*m*, 3 H); 6.86 (*d*, *J* = 6.8, 1 H); 7.06–7.40 (*m*, 16 arom. H). ^{13}C-NMR: 25.1; 25.2; 25.7; 29.0; 30.5; 30.6; 31.6; 32.9; 33.2; 33.8; 48.7; 49.8; 52.6; 53.2; 55.2; 60.5; 62.1; 113.9; 114.0; 126.2; 126.1; 126.8; 127.7; 128.2; 128.4; 128.5; 128.6; 129.3; 129.5; 130.2; 130.6; 131.6; 137.8; 138.2; 140.2; 159.3; 168.6; 172.0; 174.5. HR-ESI-MS: 715.42140 ($[M+1]^+$, $C_{45}H_{55}N_4O_4^+$; calc. 715.42135).

N^1*-[2-(Cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl]*-N^4*-phenyl*-N^1*-(2-phenylethyl)*-N^4*-[1-(2-phenylethyl)piperidin-4-yl]butanediamide* (**5i**). Yield 460 mg (63%). White solid. M.p. 145–146°. IR (KBr): 3430, 3273, 3062, 3027, 2930, 2853, 2805, 1649, 1561, 1513, 1495. ^{1}H-NMR: 1.18–2.78 (*m*, 26 H); 3.02–3.05 (*m*, 2 H); 3.32–3.41 (*m*, 1 H); 3.75–3.81 (*m*, 2 H); 3.82 (*s*, 3 H); 4.63–4.72 (*m*, 1 H); 6.34 (*s*, 1 H); 6.81 (*d*, *J* = 8.4, 1 H); 6.87–7.43 (*m*, 19 arom. H). ^{13}C-NMR: 25.2; 25.8; 28.0; 30.3; 30.4; 31.8; 32.8; 33.0; 33.1; 33.6; 36.4; 48.0; 48.7; 52.5; 53.1; 55.3; 60.4; 61.0; 114.0; 114.1; 114.2; 126.1; 126.4; 128.3; 128.4; 128.5; 128.6; 129.4; 129.6; 130.2; 130.7; 131.6; 138.2; 138.3; 140.1; 159.5; 168.6; 172.0; 173.5. HR-ESI-MS: 729.43578 ($[M+1]^+$, $C_{46}H_{57}N_4O_4^+$; calc. 729.43555).

N^1*-[2-(Cyclohexylamino)-2-oxo-1-phenylethyl]*-N^4*-phenyl*-N^4*-[1-(2-phenylethyl)piperidin-4-yl]*-N^1*-[2-(thiophen-2-yl)ethyl]butanediamide* (**5j**). Yield 677 mg (96%). White solid. M.p. 172–173°. IR (KBr): 3432, 3271, 3081, 3060, 3029, 2929, 2851, 2814, 1652, 1596, 1559, 1494. ^{1}H-NMR: 1.34–2.74 (*m*, 26 H); 3.01–3.05 (*m*, 2 H); 3.38–3.47 (*m*, 1 H); 3.82–3.92 (*m*, 2 H); 4.62–4.72 (*m*, 1 H); 6.38 (*s*, 1 H); 6.54 (*d*, *J* = 3.2, 1 H); 6.83–7.47 (*m*, 18 arom. H). ^{13}C-NMR: 25.1; 25.2; 25.7; 27.9; 30.1; 30.4; 30.5; 31.8; 32.8; 32.9; 33.1; 33.7; 48.1; 48.8; 52.6; 53.1; 60.4; 61.6; 123.8; 125.2; 126.1; 126.9; 128.2; 128.4; 128.5; 128.6; 129.0; 129.4; 129.6; 130.2; 130.3; 130.7; 136.2; 138.2; 140.1; 140.2; 168.3; 172.0; 173.6. HR-ESI-MS: 705.38296 ($[M+1]^+$, $C_{43}H_{53}N_4O_3S^+$; calc. 705.38291).

N^1*-[2-(Cyclohexylamino)-1-(4-methoxyphenyl)-2-oxoethyl]*-N^4*-phenyl*-N^4*-[1-(2-phenylethyl)piperidin-4-yl]*-N^1*-[2-(thiophen-2-yl)ethyl]butanediamide* (**5k**). Yield 677 mg (92%). White solid. M.p. 150–151°. IR (KBr): 3290, 3064, 3028, 2930, 2853, 2804, 1647, 1513. ^{1}H-NMR: 1.16–2.74 (*m*, 26 H); 3.01–

3.05 (*m*, 2 H); 3.38–3.47 (*m*, 1 H); 3.80 (*s*, 3 H); 3.81–3.85 (*m*, 2 H); 4.62–4.72 (*m*, 1 H); 6.32 (*s*, 1 H); 6.57 (*d*, *J* = 3.0, 1 H); 6.78–7.43 (*m*, 17 arom. H). ^{13}C-NMR: 25.1; 25.2; 25.7; 27.9; 30.1; 30.4; 30.5; 31.8; 32.8; 32.9; 33.1; 33.7; 48.0; 48.8; 52.5; 53.1; 55.3; 60.4; 61.0; 114.1; 123.8; 125.2; 126.1; 126.9; 128.1; 128.4; 128.6; 129.4; 129.6; 130.2; 130.7; 131.5; 138.2; 140.1; 140.3; 159.5; 168.6; 172.0; 173.5. HR-ESI-MS: 735.39245 ($[M+1]^+$, $C_{44}H_{55}N_4O_4S^+$; calc. 735.39226).

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Received October 13, 2011