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Design, synthesis and molecular modelling of 1-amidinopiperidine thrombin inhibitors

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Design, synthesis and biochemical evaluation of a series of novel non-covalent thrombin inhibitors with a 1-amidinopiperidine moiety are presented. Replacement of the planar benzamidine group in azaphenylalanine derivatives with 1-amidinopiperidine resulted in lower activity but higher selectivity for this type of compounds. The binding conformation of inhibitors in the active site of thrombin was revealed by molecular modelling studies.

1. Introduction

In recent years, the development of small molecule, active site-directed thrombin inhibitors has led to a number of highly potent and selective compounds. Most compounds reported to date are either derivatives of the tripeptide sequence D-Phe-Pro-Arg or peptidomimetics such as NAPAP and argatroban. Usually they incorporate basic functional groups such as guanidine or amidine that interact with Asp189 at the bottom of the selectivity pocket of thrombin, together with lipophilic fragments that bind in the proximal and distal pockets (Rewinkel and Adang 1999; Steinmetzer et al. 2001; Gresele and Agneli 2002). The location of NAPAP in the active site of thrombin is illustrated in Fig. 1.

We prepared new peptidomimetic thrombin inhibitors with a 1-amidinopiperidine scaffold that are structurally related to the azaphenylalanine compounds already published, (Zega et al. 2001a, b; Obreza et al. 2004a, b). Based on this experience we retained the 2-naphthylsulfonyl moiety as a close to optimal group for the distal pocket (Obreza et al. 2004b), while we used a series of primary and secondary amines as synthons for the preparation of compounds that would bind optimally in the proximal pocket of thrombin. Instead of the planar benzene ring in the azaphenylalanine moiety of the previous molecules, we incorporated a saturated six-membered piperidine ring. A substituted piperidine ring, as a

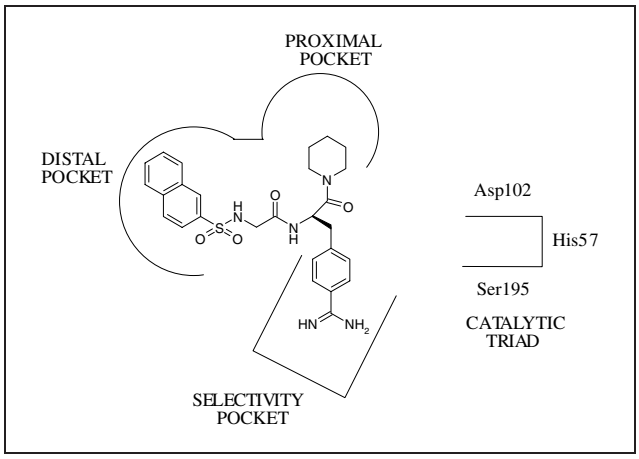
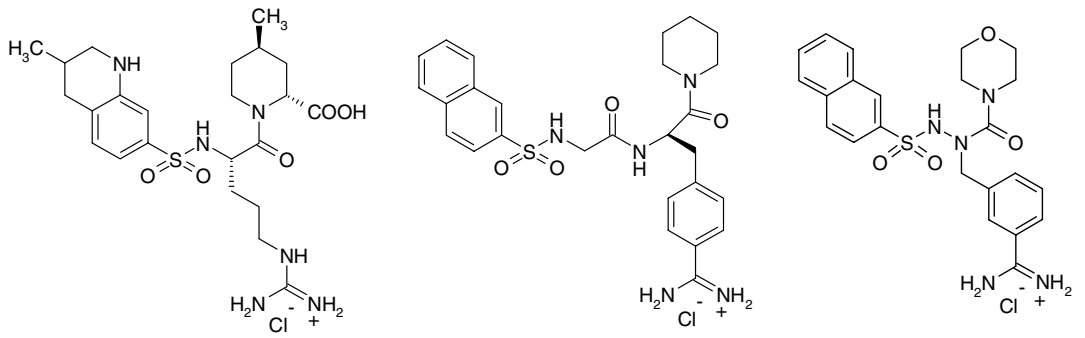
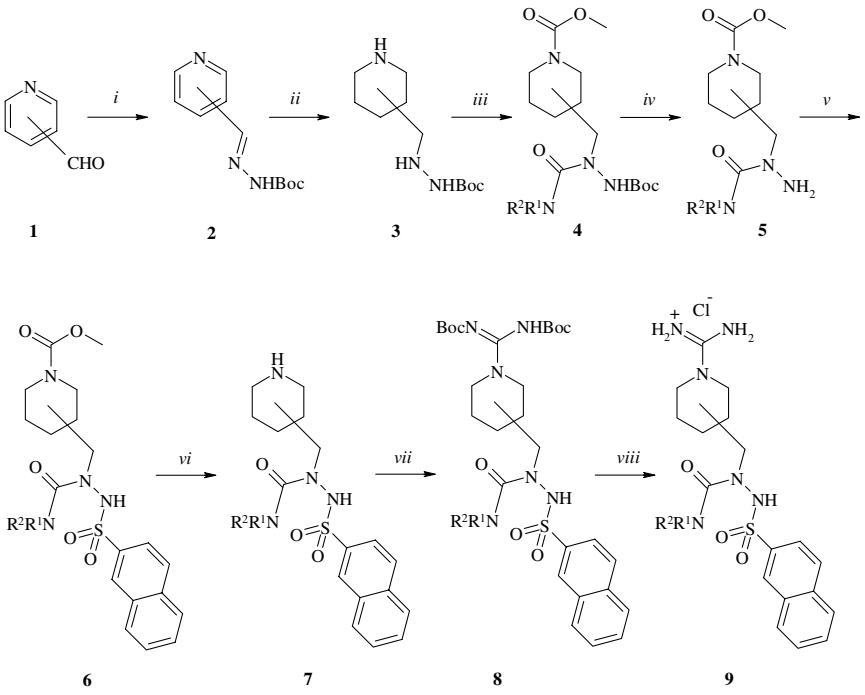


Fig. 1: Schematic illustration of NAPAP in the active site of thrombin



Argatroban **NAPAP** **10**

Scheme



(i) NH_2NH-Boc, EtOH, reflux; (ii) H_2/Pd/C, 50 °C, 50 bar, MeOH; (iii) 1. ClCOOMe, TEA, CH_2Cl_2; 2. triphosgene, TEA, HNR^1R^2, CH_2Cl_2; (iv) 1. CF_3COOH, CH_2Cl_2; 2. NaOH, H_2O; (v) naphthalene-2-sulfonyl chloride, DIEA, CH_2Cl_2; (vi) NaOH, H_2O, dioxane; (vii) BocNC(SMe)NHBoc, $HgCl_2$, TEA, EtOH; (viii) HCl, CH_2Cl_2

group for binding in the selectivity pocket, had already been used for preparing some potent thrombin inhibitors (Sanderson et al. 1998; Isaacs et al. 1998). From this structural modification we expected significant changes in activity and selectivity of amidinopiperidines. To explain these differences we prepared the new benzamidine derivative **10** according to the previously published procedure for this type of compounds (Zega et al. 2004), and performed docking experiments of compounds with morpholine as the part of the molecule that binds in the proximal pocket of thrombin.

In this paper we describe the synthesis, in vitro evaluation and molecular modelling of compounds incorporating these design principles.

2. Investigations, results and discussion

2.1. Synthesis of the compounds

The synthesis of **9a–n** is outlined in Scheme 1.

The condensation of nicotinaldehyde or isonicotinaldehyde with *tert*-butyl carbazate, followed by catalytic hydrogenation, yielded Boc-protected 2-piperidinylmethyl-1-hydrazinecarboxylates **3**. The secondary amino group in piperidine was selectively protected with methyl chloroformate and the compound was coupled with a series of primary and secondary amines, using triphosgene, to give compounds **4a**–**n**. The Boc-group was removed with trifluoroacetic acid in dichloromethane and the resulting semicarbazides reacted with naphthalene-2-sulfonyl chloride to give compounds **6a**–**n**. Methyl carbamate was hydrolysed in alkaline media to yield free piperidines **7a**–**n**. An amidine group was introduced by reaction with Boc-protected S-methylthiourea in the presence of mercury(II) chloride as catalyst followed by deprotection with gaseous hydrogen chloride in dichloromethane solution.

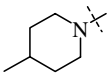
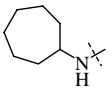
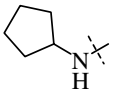
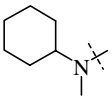
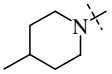
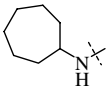
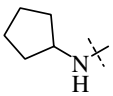
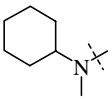
2.2. In vitro inhibitory activity of synthesized compounds against thrombin and trypsin

The activities of compounds **7a**–**m**, **9a**–**m** and **10** against thrombin and trypsin, measured *in vitro* and the results of clotting assays are presented in Tables 1 and 2. The 1-amidinopiperidine derivatives **9a**–**n** exhibit moderate inhibitory activity against thrombin and high selectivity against trypsin.

As expected, compounds **7a**–**n**, with the free secondary amino group in piperidine are virtually inactive since they cannot penetrate deep enough in the selectivity pocket of thrombin to interact with Asp 189. The replacement of the aromatic ring in the azaphenylalanine moiety by piperidine resulted in the loss of planarity in the ring, with a drop in activity by factors of 20 to 500, but increased selectivity of compounds, substituted on position 4 of piperidine ring. The same reduction in activity was observed in clotting assays. All the derivatives showed a significant increase especially in APTT and PT, while TT was less than 10 times higher compared with compound **10**. In all tests 4-substituted derivatives showed higher activity than the analogues with the side chain attached on the position 3 of piperidine ring. This result is quite the opposite as with benzamidines, where meta-substituted derivatives proved more active (Zega et al. 2001a, b).

The most important difference between thrombin and trypsin lies in amino acid residue 190 which is alanine in thrombin and serine in trypsin and the extra hydrophobic loop Tyr 47-Pro-Pro-Trp50 (Banner and Hardwary 1991). Thrombin thus has a more lipophilic and sterically larger selectivity pocket than trypsin. The additional hydroxyl group in serine is the main reason that the bulky, nonplanar 1-amidinopiperidine is more readily accommodated in

Table 1: Inhibitory activities of compounds 7 and 9 against thrombin and trypsin

Compd.	NR^1R^2	Position on aromatic ring	Ki (μM) thrombin	Ki (μM) trypsin	Selectivity
7a		3	>200	>200	
7b		4	19.1	>200	
7c		3	>200	>200	
7d		4	30.4	>200	
7e		3	>200	>200	
7f		4	33.2	>200	
7g		3	>200	>200	
7h		4	53.2	>200	
7i		3	>200	>200	
7j		4	46.1	>200	
7k		3	>200	>200	
7l		4	35.7	>200	
7m		3	>200	>200	
7n		4	18.8	>200	
9a		3	2.80	8.50	3.0
9b		4	0.47	38.8	83
9c		3	3.78	9.30	2.5
9d		4	0.35	>200	>570
9e		3	3.13	11.8	3.8
9f		4	0.50	65.8	130
9g		3	7.24	82.4	11
9h		4	1.10	80.8	74
9i		3	5.90	65.3	11
9j		4	1.22	>200	>170
9k		3	3.86	42.5	11
9l		4	0.47	106	230
9m		3	3.16	58.1	18
9n		4	0.45	>200	>450
Argatroban			0.011	>200	>18000
NAPAP			0.0075	0.347	47
10			0.017	0.31	18

the selectivity pocket of thrombin with the resulting increase in selectivity.

2.3. Molecular modelling

Flexible docking experiments followed by molecular dynamics relaxation of optimal binding positions were carried out in order to identify the possible binding modes of the synthesized inhibitors **9h** and **10** in both thrombin and trypsin active site. This information could provide a rationale for the lower potency of 1-amidinopiperidine thrombin inhibitors in comparison with inhibitors built on azaphenylalanine scaffold and furthermore explain improved selectivity of 1-amidinopiperidine thrombin inhibitors against trypsin. The binding energies of the docked inhibitors were calculated by empirical scoring function FlexX (F-score) that served as a scoring function that directed the docking calculations (Table 3).

Previously published work from this laboratory established that compounds possessing azaphenylalanine scaffold bind into thrombin in a similar matter as molecules of Argatroban/NAPAP family. These experimental results were the starting point for the evaluation of the obtained binding modes. Thus, the calculated poses for **10,** docked into thrombin active site, indicated that this compound's binding mode closely resembled the binding modes of experimentally determined azaphenylalanine thrombin inhibitors. The selected binding conformation of compound **10** that is compared in Fig. 2 with NAPAP binding conformation was ranked as the best docking solution.

The meta-substituted benzamidine moiety of inhibitor **10** is located deep into the S_1 pocket in the position that facilitates optimal strong contacts with Asp189. The crucial interactions with Asp189 virtually overlap with hydrogen bonding of the benzamidine fragment in experimental NAPAP/thrombin complex structure. Additionally one of the amidine nitrogens forms a hydrogen bond with Gly219 (2.91 Å) anchoring the benzamidine moiety even stronger into the S_1 pocket. Backbone oxygen of Gly216 residue interacts further with the nitrogen of the aza-functional

Table 2: Results of inhibitor testing with clotting assays

Compd.	TT IC_{200} (μM)	APTT IC_{200} (μM)	PT IC_{200} (μM)
9a	135.1	310.5	467.2
9b	57.6	197.9	276.8
9c	110.6	228.0	339.4
9d	26.3	111.8	167.3
9e	89.1	200.4	315.5
9f	44.7	158.5	216.0
9g	151.6	344.7	510.9
9h	47.2	168.3	237.7
9i	172.4	365.4	586.1
9j	38.1	118.6	151.8
9k	133.3	265.6	517.1
9l	32.1	112.0	171.0
9m	130.4	311.7	480.6
9n	27.3	94.2	153.7
Argatroban	2.3	0.16	1.3
NAPAP	1.6	0.24	0.87
10	6.3	1.2	5.3

TT = Thrombin time, APTT = Activated partial thromboplastin time, PT = Prothrombin time, IC_{200} = concentration of inhibitor, which prolonged clotting time for two times compared to the control clotting time without inhibitor

Table 3: Thrombin and trypsin binding energies for the selected binding conformations of 9h and 10 calculated by FlexX docking function (F-score) and RMS values between the binding conformation obtained by averaging molecular ensemble from molecular dynamics simulation

Compd.	Serine protease	F-score	Number of atoms	RMS
9h	Thrombin	−27.76	64	1.10
10		−35.99	59	1.05
9h	Tripsin	−10.77	64	0.85
10		−23.74	59	0.88

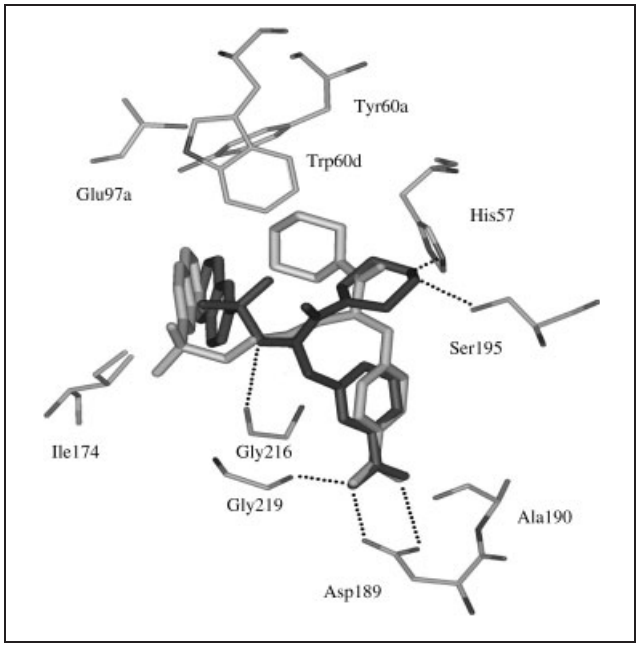


Fig. 2: Proposed conformation of a novel potent inhibitor built on azaphenylalanine scaffold **10** (black) docked into the thrombin acitve site. NAPAP binding conformation is shown in grey for comparison. Network of hydrogen bonds for **10** is also outlined

group. The morpholine moiety is placed into the S_2 pocket and its ring oxygen forms two strong hydrogen bonds, one with His57 and the other with Ser195. Finally the distal pocket of the active site is filled with naphthalene moiety, whose binding position is similar as in case of NAPAP. In Fig. 3 the binding conformation of 1-amidinopiperidine thrombin inhibitor **9h** is compared with the benzamidino derivative **10**.

The ground state conformation of 1-amidinopiperidine is a fully staggered conformation, shaped like a chair, and represents the conformation with a minimal torsional strain. Consequently the spatial orientation of amidine groups, attached on benzene or the ring nitrogen in piperidine, and their mode of binding in the active site of serine proteases could differ. However, our modelling procedure revealed that amidinopiperidine moiety of **9h** is located deep into the S_1 pocket forming a salt bridge interaction with Asp189 and the lengths of hydrogen bonds are almost identical as for inhibitor **10.** One of the **9h** amidine nitrogen forms a hydrogen bond with Gly219 thereby anchoring the benzamidine moiety even stronger into the S_1 pocket. The naphthalene moiety is placed in a distal pocket of the active site, however its position is slightly less favourable pointing out of the active site, thereby reducing the surface available for hydrophobic interaction. Sulfone oxygen of **9h** interacts with Gly216, but the position of aza-moiety does not enable the hydrogen bond formation with Gly216 seen previously for **10**. Hydrogen bond between oxygen of carbonyl of **9h** and hydroxy group of Ser195 can be formed due to the different overall placement, which is partially also a concequence of different position of the amidine moiety (position 4) in **9h** when compared with **10.** This amide position directs morpholine moiety deeper into the S_3 pocket, however in this position the ring oxygen cannot form additional interactions. Thus compound **9h** interacts through formation of 5 hydrogen bonds in comparison to 6 H-bonds found for the docked conformation of **10**. This information along with less favourable naphthalene position of **9h** could provide a possible explanation for the lower potency of **9h** in comparison with benzamidine derivatives.

Comparison of binding modes for **9h** with poses obtained for **10** in the trypsin active site revealed a noticeable difference, which could account for the superior selectivity of 1-amidinopiperidine thrombin inhibitors. Calculated binding modes of **10** form an optimal salt bridge with Asp189. As shown in Fig. 4, the benzamidine moiety of **10** is placed deep into S_1 pocket of the trypsin active site forming also hydrogen bonds with Gly219 and Ser190 and resembling the structure of the thrombin-ligand complex.

Furthermore the remaining two trypsin binding pockets are filled with naphthalene (S_3 pocket) and morpholine (S_2 pocket) moieties. On the other hand, in the case of 1-amidinopiperidine inhibitors, the docked position of amidinopiperidine moiety of **9h** does not enable optimal salt

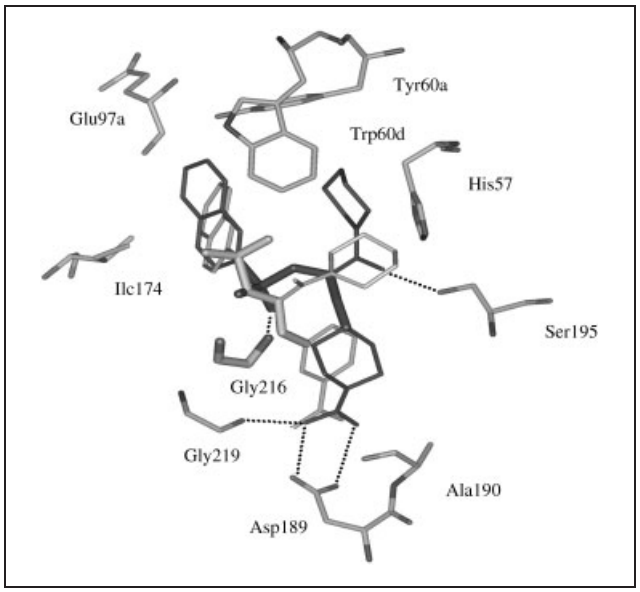


Fig. 3: Proposed binding mode for compound 1-amidinopiperidine thrombin inhibitor **9h** (black) in the thrombin active site. Binding conformation of **10** is shown in grey. Network of hydrogen bonds for **9h** is outlined

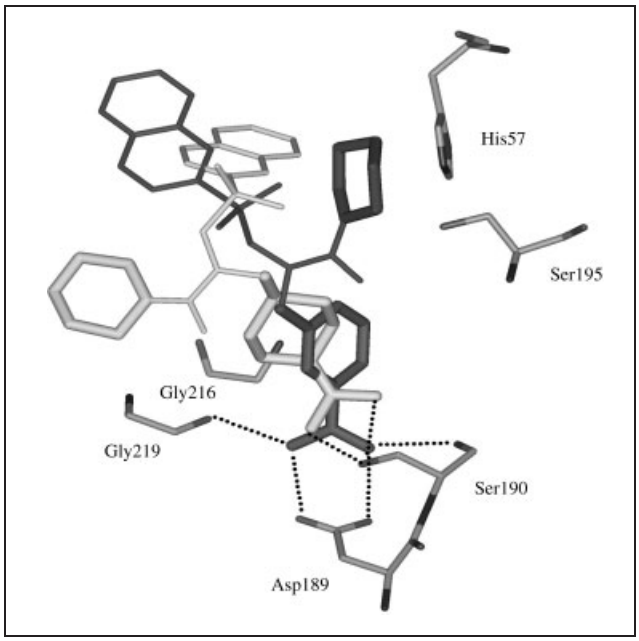


Fig. 4: Comparison of proposed binding conformations of **9h** (gray) and **10** (black) in trypsin active site

bridge interactions with Asp189. Hydrogen bonds with Gly219 and Ser190 that anchor the amidinopiperidine moiety in the S_1 pocket are still present, however, the overall binding mode indicates that much lower affinity is to be expected for **9h** as its morpholine moiety is also not placed into the S_2 pocket. Lack of salt bridge interaction with Asp 189 and unfavourable binding mode in case of compound **9h** both indicate lower affinity of **9h** in trypsin, providing an explanation for the observed improved selectivity of 1-amidinopiperidine thrombin inhibitors.

In conclusion, replacing the benzamidine group in azaphenylalanine derivatives by the nonplanar 1-amidinopiperidine moiety leads to compounds with lower inhibitory activity against thrombin, but with high selectivity against trypsin. The somehow disappointing results of *in vitro* testing were explained by molecular modelling experiments in which the proposed binding modes were calculated. Surprisingly, the results clearly showed the lack of certain interactions between our inhibitors and the active site of thrombin when compared with compound **10**. The presence of a nonplanar ring has an even greater effect on binding in the sterically restricted selectivity pocket of trypsin, thus leading to increased selectivity. This work proves that the use of saturated rings as a substitute for aromatic benzamidine is not appropriate in this series of compounds and further investigations are needed in search of a fragment that would combine the activity of benzamidines and selectivity of 1-amidinopiperidines. This work therefore constitutes an important step forward in the search for new peptidomimetic anticoagulants.

3. Experimental

All chemicals and solvents were supplied by Acros, Aldrich, Carlo Erba, Fluca, and Merck. Chromogenic substrates S-2238 (for thrombin) and S-2222 (for trypsin) were purchased from Chromogenix. ^{1}H NMR spectra were recorded on a Bruker avance DPX_{300} (300 MHz) spectrometer, using DMSO-d_6 and $CDCl_3$ as solvents and TMS as the internal standard. IR spectra were obtained on a Perkin Elmer 1600 FT-IR spectrometer. Mass spectra were measured on a VG-Analytical Autospec Q spectrometer. Elemental analyses were made on a Perkin Elmer 2400 CHN analyzer and the results were within the acceptable error range (less than 0.4%). Melting points were measured on a Koffler microscope and are uncorrected. TLC was performed on precoated sheets $60F_{254}$.

3.1. Determination of inhibition constants

A mixture of 50 µL of HBSA buffer (HBSA Buffer, pH 7.5, 1.191 g Hepes (Sigma, Deisenhofer, Germany), 4.387 g NaCl and 0.5 g bovine serum albumine (Sigma, Deisenhofer, Germany) in 500 mL of distilled water. 50 µL of inhibitor in water (final concentrations from 10 to 100 µM) and 50 µL of thrombin (0.5 NIH U/mL f.c.)) were incubated for 15 min at room temperature. The reaction was started with 50 µL of S-2238 (D-Phe-Pipecolyl-Arg-*p*-nitroanilide) (20 µM or 40 µM) and the absorbance of each sample at 405 nm (at 25 °C) was measured in triplicate every 10 s for a period of 15 min using a microtiter plate reader (Tecan Sunrise).

Thrombin activity was determined from the change in absorbance in the linear part of the velocity graph. Ki was calculated as $Ki = IC_{50}/(1 + S/Km)$. The Km for the substrate was determined under the test conditions with at least 6 substrate concentrations varying around Km and calculated with the non-linear regression programme Curve expert (Hilpert et al. 1994; Brandt et al. 1987; Cheng and Prusoff 1973).

The same procedure as outlined above (with chromogenic substrate S-2222 (N-Benzoyl-Ile-Glu-Gly-Arg-*p*-nitroanilide)) was used for measuring the inhibitory activity against trypsin.

3.2. Clotting assays

The inhibitors were also tested with clotting assays: thrombin time (BC-Thrombin), activated partial thromboplastin time (Pathromtin SL) and prothrombin time (Thromborel S, all reagents Dade Behring). One volume of inhibitor (50 µL) was added to nine volumes of normal pooled plasma (450 µL), incubated 5 min at 37 °C and then tested in an automatic coagulation timer (BCT, Dade Behring). Prolongation of the clotting times in relation to inhibitor concentration was registered. The results were expressed as the concentration of inhibitor, which prolonged clotting time for two times compared to the control clotting time with saline (IC_{200}).

3.3. Molecular modelling

Three-dimensional structures of the synthesized 1-amidinopiperidine thrombin inhibitors **9h** and inhibitor with azaphenylalanine scaffold **10** were generated with SPARTAN 5.0 software (Spartan 5.0, Wavefunction Inc., Irvine CA). After initial crude minimization with MMFF force field, structures were further minimized by a semi-empirical AM1 method. The X-ray structures of the potent non-covalent thrombin inhibitor NAPAP bound into the thrombin (1DWD) (Banner and Hardvary 1991) and trypsin (1PPC) (Bode et al. 1990) active site were obtained from the Protein Data Bank (PDB). FlexX molecular docking tool incorporated into Sybyl framework was used for the determination of the possible binding modes for both compounds (Sybil 7.0; Tripos Inc., St Louis, USA) Standard atom types of the Tripos force field were assigned to the imported optimised molecules and the amidine moiety was treated as positively charged. In both enzymes NAPAP was taken as a reference molecule and area inside 8Å around it was considered as an active site. Additionally, a sub-pocket was defined, comprising 5 Å around amino acid Asp 189. The default FlexX protonation pattern was modified as reported for 1DWD (Rarey et al. 1996), namely the alternative proton position for His57 was considered and the same protonation modification was introduced also into the trypsin active site. The increment construction algorithm utilised FlexX docking function to generate a population of 30 different binding poses for both inhibitors. Selected docked binding modes of inhibitors **9h** and **10** were then relaxed by molecular dynamic (MD) simulation in 1000 steps. The TRIPOS empirical force field was utilized and atomic partial charges were modelled according to the Gasteiger-Marsili method. 1fs integration time step was used and temperature was held constant at 300 K. Snapshots were saved every 5 steps of the simulation. From the obtained ensemble of 200 conformations an average structure was calculated that was subsequently compared with the initial docked conformations by all-atom superposition. All docking solutions were graphically inspected by using Insight and compared to experimentally determined structures of the ligand-enzyme complexes (Insight II, Accelrys Inc. San Diego)

3.4. Chemistry

3.4.1. *Tert-butyl 2-(3-pyridinylmethylidene)-1-hydrazinecarboxylate* (**2a**)

A mixture of 3.62 g (33.8 mmol) nicotinaldehyde and 4.65 g (35.2 mmol) *tert*-butyl-1-hydrazinecarboxylate in anhydrous ethanol (50 ml) was refluxed for 4 h. Approximately one half of solvent was evaporated in vacuo and the residue diluted with water. The resulting white solid was filtered and dried.
^{1}H NMR (DMSO-d_6): δ 1.48 (s, 9 H, $C(CH_3)_3$), 7.43 (q, 1 H, J = 12.6 Hz, Ar−H), 8,01 (m, 2 H, Ar−H), 8.55 (dd, 1 H, J_1 = 1.4 Hz, J_2 = 1.5 Hz. Ar−H), 8.74 (d, 1 H, J = 1.6 Hz, Ar−CH), 11.05 (s, 1 H, NH) ppm; MS (70 eV, EI): m/z (%): 222 (MH^+, 100); IR (KBr): 3175, 2974, 1736, 1598, 1551, 1426, 1367, 1268, 1149, 1055, 940, 864, 762, 710, 627 cm^{-1}; mp: 150−153 °C; yield: 90%.

3.4.2. *Tert-butyl 2-(4-pyridinylmethylidene)-1-hydrazinecarboxylate* (**2b**)

Isonicotinaldehyde (10.3 g, 96.3 mmol) and 12.7 g (96.3 mmol) *tert*-butylcarbazate were dissolved in 50 ml of anhydrous ethanol and refluxed for 5 h. Approximately 50% of the solvent was then removed *in vacuo* and the residue diluted with water. The resulting white solid was filtered and dried.
^{1}H NMR (DMSO-d_6): δ 1.48 (s, 9 H, $C(CH_3)_3$), 7.54 (d, 2 H, J = 5.8 Hz, Ar−H), 7.98 (s, 1 H, Ar−CH), 8.59 (d, 2 H, J = 5.7 Hz, Ar−H), 11.18 (s, 1 H, NH) ppm; MS (70 eV, EI): m/z (%): 222 (MH^+, 100); IR (KBr): 3472, 2982, 1725, 1571, 1368, 1280, 1151, 1055, 930, 864, 642 cm^{-1}; mp: 113−117 °C; Yield: 95%.

3.4.3. *Tert-butyl 2-(3-piperidinylmethyl)-1-hydrazinecarboxylate* (**3a**)

Tert-butyl 2-(3-pyridinylmethylidene)-1-hydrazinecarboxylate (**2a**, 6.70 g, 30.3 mmol) was dissolved in 50 ml of methanol and 2.00 g of 10% palladium on activated charcoal added to the solution with constant influx of argon. The reaction mixture was hydrogenated overnight at 50 °C and 50 bar. After the catalyst was removed, the solvent was evaporated under reduced pressure.
^{1}H NMR ($CDCl_3$): δ 1.05 (dq, 2 H, J_1 = 12.0 Hz, J_2 = 3.5 Hz, CH_2), 1.42 (m, 9 H, $C(CH_3)_3$), 1.62 (m, 2 H, CH_2), 1.78 (d, 1 H, J = 10.7 Hz, CH_2), 2,27 (t, 1 H, J = 11.5 Hz, CH_2), 2.56 (m, 3 H, CH, CH_2), 2.96 (d, 1 H, J = 12.0 Hz, CH_2), 3.10 (d, 1 H, J = 12.0 Hz, CH_2), 3.40 (s, 1 H, NH), 6.48 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 230 (MH^+, 100); IR (NaCl): 3314, 2921, 1684, 1552, 1475, 1299, 1136, 1021, 853 cm^{-1}; mp: 89−92 °C; yield: 99%.

3.4.4. *Tert-butyl 2-(4-piperidinylmethyl)-1-hydrazinecarboxylate* (**3b**)

Tert-butyl 2-(4-pyridinylmethylidene)-1-hydrazinecarboxylate (**2b**, 20.2 g, 91.3 mmol) was dissolved in 100 ml of methanol. 2.00 g of 10% palladium

on activated charcoal was added to the solution with constant influx of argon. The reaction mixture was hydrogenated overnight at 50 °C and 50 bar. After the catalyst was removed, the solvent was evaporated under reduced pressure.
^{1}H NMR (DMSO-d_6): δ 0.94 (dq, 2 H, $J_1 = 12.0$ Hz, $J_2 = 3.7$ Hz, CH_2), 1.43 (m, 11 H, $C(CH_3)_3$, CH_2), 1.61 (d, 2 H, J = 12.8 Hz, CH_2), 2.39 (dt, 2 H, $J_1 = 11.6$ Hz, $J_2 = 2.2$ Hz, CH_2), 2.88 (d, 2 H, J = 11.6 Hz, CH_2), 3.17 (s, 1 H, CH), 3,58 (s, 1 H, NH), 4.23 (s, 1 H, NH), 8.13 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 230 (MH^+, 100); IR (NaCl): 3307, 2914, 1701, 1542, 1475, 1366, 1289, 1141, 1018, 846 cm^{-1}; mp: 85–88 °C; yield: 96%.

3.4.5. Synthesis of compounds **4a**–**n***; general procedure*

Tert-butyl 2-(3-piperidinylmethyl)-1-hydrazinecarboxylate (**3a**, 10.2 mmol) or *tert*-butyl 2-(4-piperidinylmethyl)-1-hydrazinecarboxylate (**3b**) and triethylamine (3 ml) was dissolved in 45 ml of dichloromethane. Methylchloroformate (10.0 mmol) was added dropwise at 0 °C and the reaction mixture stirred on an icebath for 1 h. Triphosgene (4.11 mmol) was added, and after further stirring for 15 min at 0 °C, 2 ml (16.9 mmol) of the corresponding amine was added. The temperature of the reaction mixture was allowed to rise to room temperature. After a further hour of stirring, the solvent was evaporated under reduced pressure and the residue dissolved in 50 ml of ethylacetate. The reaction mixture was then extracted with 4 × 25 ml of 10% citric acid solution, 30 ml of saturated $NaHCO_3$ solution, followed by washing with 30 ml of demineralised water and 20 ml of saturated brine. The organic phase was dried over Na_2SO_4 and the solvent evaporated *in vacuo*.

3.4.5.1. Methyl 3-({2-(tert-butoxycarbonyl)-1-[(4-methyl-1-piperidinyl)carbonyl]hydrazino}methyl)-1-piperidinecarboxylate (**4a**)

^{1}H NMR ($CDCl_3$): δ 0,90 (d, 3 H, J = 6.4 Hz, CH_3), 1.15 (m, 5 H, CH, CH_2), 1.40 (s, 9 H, $C(CH_3)_3$), 1.55 (m, 4 H, CH_2), 1.77 (m, 1 H, CH), 1.99 (m, 2 H, CH_2), 2.63 (m, 2 H, CH_2), 3.32 (m, 2 H, CH_2), 3.69 (d, 1 H, J = 8.6 Hz, CH_2), 3.74 (s, 3 H, COO−CH_3), 3.83 (m, 2 H, CH_2), 4.15 (m, 1 H, CH_2), 6.57 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 413 (MH^+, 100); IR (NaCl): 3217, 2955, 1716, 1684, 1624, 1453, 1251, 1037, 816, 629 cm^{-1}; yield: 83%.

3.4.5.2. Methyl 4-({2-(tert-butoxycarbonyl)-1-[(4-methyl-1-piperidinyl)carbonyl]hydrazino}methyl)-1-piperidinecarboxylate (**4b**)

^{1}H NMR ($CDCl_3$): δ 0.96 (d, 3 H, J = 6.3 Hz, CH_3), 1.10–1.30 (m, 5 H, CH_2, CH), 1.48 (s, 9 H, $C(CH_3)_3$), 1.56–1.79 (m, 6 H, CH_2), 1.86 (m, 1 H, CH), 2.78 (q, 3 H, J = 12.4, CH_2), 3.13 (d, 1 H, J = 6.4 Hz, CH_2), 3.38–3.54 (m, 1 H, CH_2), 3.70 (s, 3 H, COO−CH_3), 3.89 (d, 1 H, J = 13.1 Hz, CH_2), 4.14 (q, 2 H, J = 7.0 Hz, CH_2), 6.54 (m, 1 H, NH) ppm; MS (FAB+): m/z (%): 413 (MH^+, 52), 126 (100); IR (NaCl): 3504, 3278, 2927, 2868, 1704, 1641, 1451, 1368, 1245, 1162, 970, 768 cm^{-1}; Yield: 75%.

3.4.5.3. Methyl 3-{[2-(tert-butoxycarbonyl)-1-(1-piperidinylcarbonyl) hydrazino]methyl}-1-piperidinecarboxylate (**4c**)

^{1}H NMR ($CDCl_3$): δ 1.24 (m, 2 H, CH_2), 1.47 (s, 9 H, $C(CH_3)_3$), 1.56 (m, 4 H, CH_2), 1.82 (m, 5 H, CH, CH_2), 2.02 (m, 2 H, CH_2), 3.08 (m, 2 H, CH_2), 3.32 (m, 2 H, CH_2), 3.43 (d, 1 H, J = 11.2 Hz, CH_2), 3.72 (s, 3 H, COO−CH_3), 3.89 (m, 2 H, CH_2), 4.11 (m, 1 H, CH_2), 6.93 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 399 (MH^+, 100); IR (NaCl): 3286, 2934, 1734, 1699, 1439, 1240, 1158, 1047 cm^{-1}; yield: 87%.

3.4.5.4. Methyl 4-{[2-(tert-butoxycarbonyl)-1-(1-piperidinylcarbonyl)hydrazino]methyl}-1-piperidinecarboxylate (**4d**)

^{1}H NMR ($CDCl_3$): δ 1.10–1.30 (m, 3 H, CH_2), 1.47 (s, 9 H, $C(CH_3)_3$), 1.49–1.79 (m, 7 H, CH_2), 1.86 (m, 1 H, CH), 2.76 (t, 2 H, J = 12.3 Hz, CH_2), 3.13 (d, 2 H, J = 6.5 Hz, CH_2), 3.34–3.46 (m, 4 H, CH_2), 3.70 (s, 3H, COO−CH_3), 4.14 (q, 2 H, J = 7.0 Hz, CH_2), 6.54 (m, 1 H, NH) ppm; MS (FAB+): m/z (%): 399 (MH^+, 96), 112 (100); IR (NaCl): 3281, 2934, 2855, 1703, 1638, 1449, 1252, 1163, 1028, 770 cm^{-1}; yield: 79%.

3.4.5.5. Methyl 3-{[1-(1-azepanylcarbonyl)-2-(tert-butoxycarbonyl)hydrazino]methyl}-1-piperidinecarboxylate (**4e**)

^{1}H NMR ($CDCl_3$): δ 1.31 (m, 4 H, CH_2), 1.43 (s, 9 H, $C(CH_3)_3$), 1.75 (m, 5 H, CH, CH_2), 1.91 (m, 2 H, CH_2), 2.06 (m, 2 H, CH_2), 3.14 (m, 2 H, CH_2), 3.68 (m, 7 H, CH_2), 3.78 (s, 3 H, COO−CH_3), 4.14 (m, 1 H, CH_2), 6.57 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 413 (MH^+, 41), 126 (100); IR (NaCl): 3281, 2932, 2857, 1734, 1437, 1241, 1156, 1047, 768 cm^{-1}; Yield: 83%.

3.4.5.6. Methyl 4-{[1-(1-azepanylcarbonyl)-2-(tert-butoxycarbonyl)hydrazino]methyl}-1-piperidinecarboxylate (**4f**)

^{1}H NMR ($CDCl_3$): δ 1.12–1.30 (m, 4 H, CH_2), 1.47 (s, 9 H, $C(CH_3)_3$), 1.74 (m, 7 H, CH_2, CH), 2.76 (m, 2 H, CH_2), 3.13 (m, 2 H, CH_2), 3.33–3.57 (m, 6 H, CH_2), 3.69 (s, 3 H, COO−CH_3), 4.13 (q, 2 H, J = 7.0 Hz, CH_2), 6.46 (m, 1 H, NH) ppm; MS (FAB+): m/z (%): 413 (MH^+, 22), 126 (100); IR (NaCl): 3276, 2930, 2856, 1703, 1639, 1451, 1278, 1161, 735 cm^{-1}; yield: 74%.

3.4.5.7. Methyl 3-{[2-(tert-butoxycarbonyl)-1-(4-morpholinylcarbonyl)hydrazino]methyl}-1-piperidinecarboxylate (**4g**)

^{1}H NMR ($CDCl_3$): δ 1.19 (m, 2 H, CH_2), 1.43 (s, 9 H, $C(CH_3)_3$), 1.65 (m, 2 H, CH_2), 1.81 (m, 1 H, CH), 1.91 (m, 2 H, CH_2), 2.06 (m, 2 H, CH_2), 3.14 (t, 4 H, J = 6.4 Hz, CH_2), 3.42 (t, 4 H, J = 6.4 Hz, CH_2), 3.65 (m, 1 H, CH_2), 3.78 (s, 3 H, COO−CH_3), 4.14 (m, 1 H, CH_2), 6.42 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 401 (MH^+, 100); IR (NaCl): 3247, 2984, 1732, 1549, 1446, 1237, 1087, 755, 652 cm^{-1}; yield: 86%.

3.4.5.8. Methyl 4-{[2-(tert-butoxycarbonyl)-1-(4-morpholinylcarbonyl)hydrazino]methyl}-1-piperidinecarboxylate (**4h**)

^{1}H NMR ($CDCl_3$): δ 1.06–1.29 (m, 3 H, CH_2), 1.48 (s, 9 H, $C(CH_3)_3$), 1.69–1.86 (m, 4 H, CH_2, CH), 2.77 (t, 2 H, J = 13.1 Hz, CH_2), 3.18–3.26 (m, 2 H, CH_2), 3.41 (m, 2 H, CH_2), 3.69 (s, 3 H, COO−CH_3), 3.66–3.75 (m, 4 H, CH_2), 4.13 (q, 2 H, J = 6.9 Hz, CH_2), 6.56 (m, 1 H, NH) ppm; MS (FAB+): m/z (%): 401 (MH^+, 32), 114 (100); IR (NaCl): 3290, 2977, 2928, 2856, 1703, 1641, 1452, 1368, 1251, 1161, 1117, 1021, 769 cm^{-1}; yield: 53%.

3.4.5.9. Methyl 3-({2-(tert-butoxycarbonyl)-1-[(cycloheptylamino)carbonyl]hydrazino}methyl)-1-piperidinecarboxylate (**4i**)

^{1}H NMR ($CDCl_3$): δ 1.10 (m, 2 H, CH_2), 1.26 (m, 4 H, CH_2), 1.44 (s, 9 H, $C(CH_3)_3$), 1.63–2.04 (m, 9 H, CH, CH_2), 2.32 (m, 4 H, CH_2), 2.86 (m, 1 H, CH), 3.57 (m, 1 H, CH_2), 3.74 (s, 3 H, COO−CH_3), 3.87 (m, 3 H, CH_2, NH), 4.12 (d, 1 H, J = 10.2 Hz, CH_2), 6.45 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 427 (MH^+, 52), 55 (100); IR (NaCl): 3245, 2967, 1649, 1537, 1428, 1221, 1034, 859, 625 cm^{-1}; yield: 73%.

3.4.5.10. Methyl 4-({2-(tert-butoxycarbonyl)-1-[(cycloheptylamino)carbonyl]hydrazino}methyl)-1-piperidinecarboxylate (**4j**)

^{1}H NMR ($CDCl_3$): δ 1.18–1.30 (m, 6 H, CH_2), 1.47 (s, 9 H, $C(CH_3)_3$), 1.49–1.93 (m, 9 H, CH, CH_2), 2.78 (m, 4 H, CH_2), 3.15 (m, 1 H, CH), 3.70 (s, 3 H, COO−CH_3), 3.87 (m, 3 H, CH_2, N−NH), 4.14 (q, 2 H, J = 7.1 Hz, CH_2), 6.45 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 427 (MH^+, 74), 93 (100); IR (NaCl): 3266, 2928, 1702, 1646, 1522, 1450, 1368, 1251, 1162, 968 cm^{-1}; yield: 62%.

3.4.5.11. Methyl 3-({2-(tert-butoxycarbonyl)-1-[(cyclopentylamino)carbonyl]hydrazino}methyl)-1-piperidinecarboxylate (**4k**)

^{1}H NMR ($CDCl_3$): δ 1.20–1.47 (m, 13 H, $C(CH_3)_3$, CH_2), 1.60 (m, 4 H, CH_2), 1.73 (m, 3 H, CH, CH_2), 2.62 (m, 2 H, CH, CH_2), 2.80 (m, 1 H, CH), 3.62 (s, 3 H, COO−CH_3), 3.75 (m, 1 H, CH_2), 4.02 (m, 2 H, CH_2), 6.00 (s, 1 H, CO−NH), 8.82 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 413 (MH^+, 100); IR (NaCl): 3276, 2936, 1700, 1522, 1438, 1242, 1160, 1047 cm^{-1}; yield: 85%.

3.4.5.12. Methyl 4-({2-(tert-butoxycarbonyl)-1-[(cyclopentylamino)carbonyl]hydrazino}methyl)-1-piperidinecarboxylate (**4l**)

^{1}H NMR ($CDCl_3$): δ 1.21 (m, 4 H, CH_2), 1.46 (s, 9 H, $C(CH_3)_3$), 1.53 (m, 4 H, CH_2), 1.71 (m, 3 H, CH_2, CH), 2.64 (m, 4 H, CH_2), 3.21 (m, 1 H, CH), 3.54 (m, 2 H, CH_2), 3.62 (s, 3 H, COO−CH_3), 3.71 (s, 1 H, NH), 4.12 (q, 2 H, J = 7.2 Hz, CH_2), 6.47 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 413 (MH^+, 85), 126 (100); IR (NaCl): 3254, 2984, 2961, 1705, 1584, 1403, 1264, 1210, 1047, 920, 836, 754, 642 cm^{-1}; yield: 38%.

3.4.5.13. Methyl 3-[(2-(tert-butoxycarbonyl)-1-{[cyclohexyl(methyl)amino]carbonyl}hydrazino)methyl]-1-piperidinecarboxylate (**4m**)

^{1}H NMR ($CDCl_3$): δ 1.09–1.56 (m, 19 H, $C(CH_3)_3$, CH_2), 1.77 (m, 7 H, CH, CH_2), 2.84 (s, 3 H, CH_3), 3.10 (m, 1 H, CH), 3.56 (m, 1 H, CH_2), 3.72 (s, 3 H, COO−CH_3), 3.90 (m, 2 H, CH_2), 4.14 (q, 1 H, J = 8.9 Hz, CH_2), 6.39 (m, 1 H, NH) ppm; MS (FAB+): m/z (%): 427 (MH^+, 42), 100 (100); IR (NaCl): 3108, 2980, 2867, 1725, 1642, 1506, 1446, 1368, 1319, 1254, 1159, 1044, 947, 868, 822, 744, 550 cm^{-1}; yield: 64%.

3.4.5.14. Methyl 4-[(2-(tert-butoxycarbonyl)-1-{[cyclohexyl(methyl)amino]carbonyl}hydrazino)methyl]-1-piperidinecarboxylate (**4n**)

^{1}H NMR ($CDCl_3$): δ 1.11–1.28 (m, 5 H, CH_2), 1.39–1.52 (m, 14 H, $C(CH_3)_3$, CH_2), 1.64–1.83 (m, 7 H, CH_2, CH), 2.80 (s, 3 H, CH_3), 3.12 (m, 1 H, CH), 3.40–3.58 (m, 1 H, CH_2), 3.70 (s, 3 H, COO−CH_3), 3.90 (m, 1 H, CH_2), 4.14 (q, 2 H, J = 7.1 Hz, CH_2), 6.48 (m, 1H, NH) ppm; MS (FAB+): m/z (%): 427 (MH^+, 64), 93 (100); IR (NaCl): 3284, 2931, 2856, 1704, 1640, 1450, 1368, 1251, 1161, 968, 768 cm^{-1}; yield: 71%.

*3.4.6. Synthesis of compounds **5a–n**; general procedure*

8.50 mmol of the corresponding compound **4** was dissolved in a mixture of 15 ml of dichloromethane and 20 ml of trifluoroacetic acid and stirred for 1 hour at room temperature. Dichloromethane and trifluoroacetic acid were removed under reduced pressure, and the residue dissolved in dichloromethane, extracted with 2×50 ml of saturated $NaHCO_3$ solution and washed with water and saturated brine. The organic phase was dried over Na_2SO_4. The solvent was removed in vacuo to yield pale yellow viscous liquids.

3.4.6.1. Methyl 3-({1-[(4-methyl-1-piperidinyl)carbonyl]hydrazino}methyl)-1-piperidinecarboxylate (**5a**)

^{1}H NMR (DMSO-d_6): δ 0.96 (d, 3 H, J = 6.2 Hz, CH_3), 1.25 (m, 2 H, CH_2), 1.48 (m, 3 H, CH, CH_2), 1.63 (m, 4 H, CH_2), 1.79 (m, 1 H, CH), 2.05 (m, 2 H, CH_2), 2.84 (m, 2 H, CH_2), 3.35 (m, 2 H, CH_2), 3.71 (d, 1 H, J = 8.1 Hz, CH_2), 3.76 (s, 3 H, COO−CH_3), 3.90 (m, 2 H, CH_2), 4.14 (m, 1 H, CH_2), 5.17 (s, 2 H, NH_2) ppm; MS (FAB+): m/z (%): 313 (MH^+, 76), 126 (100); IR (NaCl): 3116, 2924, 1682, 1441, 1241, 1145, 973, 770 cm^{-1}; yield: 67%.

3.4.6.2. Methyl 4-({1-[(4-methyl-1-piperidinyl)carbonyl]hydrazino}methyl)-1-piperidinecarboxylate (**5b**)

^{1}H NMR (DMSO-d_6): δ 0.88–1.12 (m, 6H, CH_2, CH, CH_3), 1.61 (t, 4H, J = 12.2 Hz, CH_2), 1.93 (m, 1 H, CH), 2.73–2.89 (m, 4 H, CH_2), 3.10 (d, 1 H, J = 7.1 Hz, CH_2), 3.19 (d, 1 H, J = 7.1 Hz, CH_2), 3.39 (q, 1 H, J = 7.0 Hz, CH_2), 3.58 (m, 5 H, COO−CH_3, CH_2), 3.79 (d, 1 H, J = 13.1 Hz, CH_2), 3.96 (m, 2 H, CH_2), 4.58 (m, 2 H, NH_2) ppm; MS (FAB+): m/z (%): 313 (MH^+, 56), 126 (100); IR (NaCl): 2926, 2869, 1698, 1449, 1414, 1247, 1200, 1138, 970, 769 cm^{-1}; yield: 90%.

3.4.6.3. Methyl 3-{[1-(1-piperidinylcarbonyl)hydrazino]methyl}-1-piperidinecarboxylate (**5c**)

^{1}H NMR (DMSO-d_6): δ 1.31 (m, 2 H, CH_2), 1.60 (m, 4 H, CH_2), 1.78 (m, 4 H, CH_2), 1.82–2.02 (m, 3 H, CH, CH_2), 2.88 (m, 2 H, CH_2), 3.07 (t, 2 H, J = 6.2 Hz, CH_2), 3.35 (d, 1 H, J = 7.0 Hz, CH_2), 3.66 (s, 3 H, COO−CH_3), 3.87 (d, 2 H, J = 9.2 Hz, CH_2), 4.02 (m, 1 H, CH_2), 5.31 (s, 2 H, NH_2) ppm; MS (FAB+): m/z (%): 399 (MH^+, 100); IR (NaCl): 3426, 2938, 1676, 1440, 1264, 1143, 1018, 856, 768 cm^{-1}; yield: 82%.

3.4.6.4. Methyl 4-{[1-(1-piperidinylcarbonyl)hydrazino]methyl}-1-piperidinecarboxylate (**5d**)

^{1}H NMR (DMSO-d_6): δ 0.97 (dq, 2 H, J_1 = 12.1 Hz, J_2 = 4.2 Hz, CH_2), 1.40–1.61 (m, 8 H, CH_2), 1.95 (m, 1 H, CH), 2.74 (t, 2 H, J = 11.2 Hz, CH_2), 3.00 (d, 1 H, J = 7.1 Hz, CH_2), 3.16–3.34 (m, 4 H, CH_2), 3.57 (m, 4 H, COO−CH_3, CH_2), 3.95 (d, 2 H, J = 12.3 Hz, CH_2), 4.62 (s, 2 H, NH_2) ppm; MS (FAB+): m/z (%): 299 (MH^+, 71), 112 (100); IR (NaCl): 3503, 2933, 2854, 1700, 1646, 1448, 1240, 1136, 970, 769 cm^{-1}; yield: 93%.

3.4.6.5. Methyl 3-{[1-(1-azepanylcarbonyl)hydrazino]methyl}-1-piperidinecarboxylate (**5e**)

^{1}H NMR (DMSO-d_6): δ 1.31 (m, 4 H, CH_2), 1.78 (m, 5 H, CH, CH_2), 1.88 (m, 2 H, CH_2), 1.99 (m, 2 H, CH_2), 3.13 (m, 2 H, CH_2), 3.61 (m, 7 H, CH_2), 3.77 (s, 3 H, COO−CH_3), 4.14 (d, 1 H, J = 10.3 Hz, CH_2), 5.13 (s, 2 H, NH_2) ppm; MS (FAB+): m/z (%):327 (MH^+, 90), 154 (100); IR (NaCl): 3442, 2936, 1676, 1434, 1265, 1156, 1097, 1012, 856, 767 cm^{-1}; yield: 91%.

3.4.6.6. Methyl 4-{[1-(1-azepanylcarbonyl)hydrazino]methyl}-1-piperidinecarboxylate (**5f**)

^{1}H NMR (DMSO-d_6): δ 0.94–1.12 (m, 2 H, CH_2), 1.48–1.74 (m, 10 H, CH_2), 1.94 (m, 1 H, CH), 2.74 (m, 2 H, CH_2), 2.98 (m, 2 H, CH_2), 3.31 (m, 3 H, CH_2), 3.57 (s, 3 H, COO−CH_3), 3.94 (d, 2 H, J = 11.7 Hz, CH_2), 4.18 (s, 1 H, CH_2), 4.56 (s, 2 H, NH_2) ppm; MS (FAB+): m/z (%): 313 (MH^+, 35), 126 (100); IR (NaCl): 3503, 2926, 2854, 1700, 1636, 1449, 1415, 1277, 969, 769 cm^{-1}; yield: 83%.

3.4.6.7. Methyl 3-{[1-(4-morpholinylcarbonyl)hydrazino]methyl}-1-piperidinecarboxylate (**5g**)

^{1}H NMR (DMSO-d_6): δ 1.24 (m, 2 H, CH_2), 1.73 (m, 4 H, CH_2), 1.85 (m, 1 H, CH), 1.94 (m, 2 H, CH_2), 2.21 (m, 2 H, CH_2), 3.09 (m, 4 H, CH_2), 3.51 (m, 4 H, CH_2), 3.72 (d, 1 H, J = 11.2 Hz, CH_2), 3.77 (s, 3 H, COO−CH_3), 4.09 (d, 1 H, J = 11.4 Hz, CH_2), 4.39 (s, 1 H, NH_2) ppm; MS (FAB+): m/z (%): 301 (MH^+, 73), 126 (100); IR (NaCl): 3306, 3114, 2974, 1672, 1446, 1168, 953, 847, 752 cm^{-1}; yield: 93%.

3.4.6.8. Methyl 4-{[1-(4-morpholinylcarbonyl)hydrazino]methyl}-1-piperidinecarboxylate (**5h**)

^{1}H NMR (DMSO-d_6): δ 0.91–1.08 (m, 2 H, CH_2), 1.57 (d, 2 H, J = 12.8 Hz, CH_2), 1.87 (m, 1 H, CH), 2.74 (m, 2 H, CH_2), 3.07–3.19 (m, 2 H, CH_2), 3.31 (m, 2 H, CH_2), 3.44 (m, 1 H, CH_2), 3.57 (m, 7 H, COO−CH_3, CH_2), 3.94 (d, 2 H, J = 11.8 Hz, CH_2), 4.35 (m, 1 H, CH_2), 4.56 (s, 2 H, NH_2) ppm; MS (FAB+): m/z (%): 301 (MH^+, 33), 114 (100); IR (NaCl): 3504, 3337, 2921, 2855, 1701, 1637, 1451, 1413, 1249, 1116, 1026, 769 cm^{-1}; yield: 90%.

3.4.6.9. Methyl 3-({1-[(cycloheptylamino)carbonyl]hydrazino}methyl)-1-piperidinecarboxylate (**5i**)

^{1}H NMR (DMSO-d_6): δ 1.18 (m, 6 H, CH_2), 1.78 (m, 5 H, CH, CH_2), 1.88 (m, 4 H, CH_2), 2.19 (m, 4 H, CH_2), 2.79 (m, 1 H, CH), 3.52 (d, 1 H, J = 10.3 Hz, CH_2), 3.70 (s, 3 H, COO−CH_3), 3.79 (m, 3 H, CH_2, NH), 4.06 (d, 1 H, J = 9.6 Hz, CH_2), 4.99 (s, 2 H, NH_2) ppm; MS (FAB+): m/z (%): 327 (MH^+, 100); IR (NaCl): 3312, 2985, 1726, 1640, 1443, 1181, 1025, 857, 820, 648, 552 cm^{-1}; yield: 92%.

3.4.6.10. Methyl 4-({1-[(cycloheptylamino)carbonyl]hydrazino}methyl)-1-piperidinecarboxylate (**5j**)

^{1}H NMR (DMSO-d_6): δ 1.00 (m, 2 H, CH_2), 1.40–1.65 (m, 12 H, CH_2), 1.74 (m, 2 H, CH_2), 1.86 (m, 1 H, CH), 2.74 (m, 3 H, CH_2), 3.01 (m, 1 H, CH), 3.58 (s, 3 H, COO−CH_3), 3.83 (m, 1 H, N−NH), 3.93 (d, 2 H, J = 10.6 Hz, CH_2), 4.36 (s, 1 H, CH_2), 4.56 (s, 2 H, NH_2) ppm; MS (FAB+): m/z (%): 327 (MH^+, 60), 93 (100); IR (NaCl): 3333, 2922, 2855, 1697, 1650, 1511, 1454, 1244, 964, 764 cm^{-1}; yield: 55%.

3.4.6.11. Methyl 3-({1-[(cyclopentylamino)carbonyl]hydrazino}methyl)-1-piperidinecarboxylate (**5k**)

^{1}H NMR (DMSO-d_6): δ 1.30 (m, 4 H, CH_2), 1.67 (m, 6 H, CH_2), 1.88 (m, 2 H, CH_2), 1.93 (m, 1 H, CH), 2.00 (d, 2 H, J = 11.6 Hz, CH_2), 2.41 (m, 1 H, CH), 3.02 (m, 1 H, CH_2), 3.52 (s, 1 H, CO−NH), 3.64 (s, 3 H, COO−CH_3), 3.73 (m, 1 H, CH_2), 3.87 (d, 2 H, J = 8.7 Hz, CH_2), 4.81 (s, 2 H, NH_2) ppm; MS (FAB+): m/z (%): 299 (MH^+, 100); IR (NaCl): 3276, 2936, 1700, 1522, 1438, 1242, 1160, 1047 cm^{-1}; yield: 54%.

3.4.6.12. Methyl 4-({1-[(cyclopentylamino)carbonyl]hydrazino}methyl)-1-piperidinecarboxylate (**5l**)

^{1}H NMR (DMSO-d_6): δ 1.21 (m, 6 H, CH_2), 1.55 (m, 4 H, CH_2), 1.83 (m, 1 H, CH), 2.66 (m, 4 H, CH_2), 3.21 (m, 1 H, CH), 3.64 (s, 3 H, COO−CH_3), 3.72 (s, 1 H, NH), 3.97 (d, 2 H, J = 12.0 Hz, CH_2), 4.14 (q, 2 H, J = 7.1 Hz, CH_2), 4.53 (s, 2 H, NH_2) ppm; MS (FAB+): m/z (%): 313 (MH^+, 100); IR (NaCl): 3306, 2945, 1735, 1563, 1403, 1245, 1005, 947, 811, 658 cm^{-1}; yield: 61%.

3.4.6.13. Methyl 3-[(1-{[cyclohexyl(methyl)amino]carbonyl}hydrazino)methyl]-1-piperidinecarboxylate (**5m**)

^{1}H NMR (DMSO-d_6): δ 1.13 (m, 6 H, CH_2), 1.45 (m, 4 H, CH_2), 1.73 (m, 5 H, CH, CH_2), 2.08 (m, 2 H, CH_2), 2.91 (s, 3 H, CH_3), 3.14 (m, 1 H, CH), 3.59 (m, 1 H, CH_2), 3.72 (s, 3 H, COO−CH_3), 3.97 (m, 2 H, CH_2), 4.21 (m, 1 H, CH_2), 5.16 (m, 2 H, NH_2) ppm; MS (FAB+): m/z (%): 327 (MH^+, 88), 126 (100); IR (NaCl): 3362, 1636, 1541, 1458, 1318, 1182, 1041, 937 cm^{-1}; yield: 83%.

3.4.6.14. Methyl 4-[(1-{[cyclohexyl(methyl)amino]carbonyl}hydrazino)methyl]-1-piperidinecarboxylate (**5n**)

^{1}H NMR (DMSO-d_6): δ 0.94–1.12 (m, 4 H, CH_2), 1.26 (q, 2 H, J = 12.4 Hz, CH_2), 1.42 (q, 2 H, J = 12.1 Hz, CH_2), 1.59 (m, 5 H, CH_2), 1.74 (d, 2 H, J = 12.7 Hz, CH_2), 1.95 (m, 1 H, CH), 2.62–2.74 (m, 4 H, CH, CH_3), 2.94 (d, 1 H, J = 7.1 Hz, CH_2), 3.17 (d, 1 H, J = 7.1 Hz, CH_2), 3.57 (s, 3 H, COO−CH_3), 3.93 (m, 2 H, CH_2), 4.19 (s, 1 H, CH_2), 4.56 (s, 2 H, NH_2) ppm; MS (FAB+): m/z (%): 327 (MH^+, 53), 83 (100); IR (NaCl): 3482, 3333, 2927, 2855, 1699, 1636, 1449, 1242, 969, 768 cm^{-1}; yield: 54%.

*3.4.7. Synthesis of compounds **6a–n**; general procedure*

The corresponding compound **5** (7.47 mmol) and 1.90 g (8.35 mmol) naphthalene-2-sulfonylchloride were dissolved in dichloromethane (25 ml). Triethylamine (2 ml) was added and the solution was stirred at room temperature for 3 days. The solvent was evaporated *in vacuo*, the residue dissolved in ethylacetate (50 ml) and extracted with 4×25 ml of 10% citric acid and 30 ml of saturated $NaHCO_3$ solution. The organic phase was washed with 30 ml of demineralised water and 30 ml of saturated brine, then dried over Na_2SO_4. Ethylacetate was evaporated *in vacuo* and a pale brown solid was left. Compounds **6a–n** were further purified by column chromatography (silicagel; dichloromethane : methanol 39 : 1).

3.4.7.1. Methyl 3-{[1-[(4-methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6a**)

^{1}H NMR (DMSO-d_6): δ 0,87 (d, 3 H, J = 6.1 Hz, CH_3), 1.18 (m, 2 H, CH_2), 1.37 (m, 3 H, CH, CH_2), 1.54 (m, 4 H, CH_2), 1.75 (m, 1 H, CH),

2.31–2.63 (m, 4 H, CH_2), 3.48 (m, 2 H, CH_2), 3.68 (m, 1 H, CH_2), 3.72 (s, 3 H, COO−CH_3), 3.87 (m, 2 H, CH_2), 4.13 (m, 1 H, CH_2), 7.63 (dqu, 2 H, $J_1 = 7.5$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.85 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.98 (d, 1 H, J = 7.6 Hz, Ar−H), 8.08 (d, 1 H, J = 8.4 Hz, Ar−H), 8.14 (d, 1 H, J = 7.6 Hz, Ar−H), 8.44 (s, 1 H, Ar−H), 9.37 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 503 (MH^+, 56), 55 (100); IR (KBr): 3434, 2927, 2852, 1668, 1438, 1239, 1166, 970, 751 cm^{-1}; mp: 91–95 °C; yield: 29%.

3.4.7.2. Methyl 4-{[1-[(4-methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6b**)

^{1}H NMR (DMSO-d_6): δ 0.46 (d, 3 H, J = 6.03 Hz, CH_3), 0.87–1.24 (m, 7 H, CH_2, CH), 1.48–1.70 (m, 4 H, CH_2), 1.94 (m, 1 H, CH), 2.70 (m, 4 H, CH_2), 2.91 (m, 2 H, CH_2), 3.56 (s, 3 H, COO−CH_3), 3.92 (d, 2 H, J = 10.3 Hz, CH_2), 7.69 (dqu, 2 H, $J_1 = 6.8$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.77 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.6$ Hz, Ar−H), 8.04 (d, 1 H, J = 7.7 Hz, Ar−H), 8.09 (d, 1 H, J = 8.7 Hz, Ar−H), 8.15 (d, 1 H, J = 7.7 Hz, Ar−H), 8.43 (s, 1 H, Ar−H), 9.45 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 503 (MH^+, 48), 93 (100); IR (KBr): 2926, 2855, 1801, 1699, 1448, 1242, 1166, 970 cm^{-1}; mp: 60–64 °C; yield: 17%.

3.4.7.3. Methyl 3-{[2-(2-naphthylsulfonyl)-1-(1-piperidinylcarbonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6c**)

^{1}H NMR (DMSO-d_6): δ 1.04 (m, 2 H, CH_2), 1.32 (m, 4 H, CH_2), 1.52 (m, 2 H, CH_2), 1.67 (m, 2 H, CH_2), 1.76–2.01 (m, 3 H, CH, CH_2), 2.88 (m, 2 H, CH_2), 3.02 (m, 2 H, CH_2), 3.46 (m, 1 H, CH_2), 3.71 (s, 3 H, COO−CH_3), 3.85 (d, 2 H, J = 11.6 Hz, CH_2), 4.01 (m, 1 H, CH_2), 7.62 (dqu, 2 H, $J_1 = 7.6$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.79 (dd, 1 H, $J_1 = 8.5$ Hz, $J_2 = 1.6$ Hz, Ar−H), 8.01 (d, 1 H, J = 7.6 Hz, Ar−H), 8.11 (d, 1 H, J = 8.5 Hz, Ar−H), 8.17 (d, 1 H, J = 7.5 Hz, Ar−H), 8.46 (s, 1 H, Ar−H), 9.53 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 499 (MH^+, 16), 112 (100); IR (KBr): 3411, 3023, 1693, 1435, 1240, 1167, 1075, 856, 750 cm^{-1}; mp: 76–85 °C; yield: 37%.

3.4.7.4. Methyl 4-{[2-(2-naphthylsulfonyl)-1-(1-piperidinylcarbonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6d**)

^{1}H NMR (DMSO-d_6): δ 0.85–1.05 (m, 6 H, CH_2), 1.24 (m, 2 H, CH_2), 1.54 (m, 2 H, CH_2), 1.89 (m, 1 H, CH), 2.66 (m, 2 H, CH_2), 2.89 (d, 2 H, J = 6.7 Hz, CH_2), 2.89 (m, 2 H, CH_2), 2.99 (m, 2 H, CH_2), 3.55 (s, 3 H, COO−CH_3), 3.90 (d, 2 H, J = 12.4 Hz, CH_2), 7.69 (dqu, 2 H, $J_1 = 7.5$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.77 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.8$ Hz, Ar−H), 8.04 (d, 1 H, J = 7.5 Hz, Ar−H), 8.10 (d, 1 H, J = 8.6 Hz, Ar−H), 8.16 (d, 1 H, J = 7.5 Hz, Ar−H), 8.43 (s, 1 H, Ar−H), 9.45 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 489 (MH^+, 10), 93 (100); IR (KBr): 3413, 3160, 2931, 2853, 1692, 1475, 1255, 1170, 1085, 914, 753, 697 cm^{-1}; mp: 72–77 °C; yield: 35%.

3.4.7.5. Methyl 3-{[1-(1-azepanylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6e**)

^{1}H NMR (DMSO-d_6): δ 1.26 (m, 4 H, CH_2), 1.71 (m, 4 H, CH_2), 1.81 (m, 1 H, CH), 1.92 (m, 2 H, CH_2), 2.17 (m, 2 H, CH_2), 2.83 (m, 2 H, CH_2), 3.46 (m, 1 H, CH_2), 3.70 (m, 9 H, CH_2, COO−CH_3), 4.10 (d, 1 H, J = 6.8 Hz, CH_2), 7.67 (dqu, 2 H, J_1= 7.8 Hz, $J_2 = 1.6$ Hz, Ar−H), 7.77 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.6$ Hz, Ar−H), 7.98 (d, 1 H, J = 8.3 Hz, Ar−H), 8.03 (d, 1 H, J = 8.7 Hz, Ar−H), 8.12 (d, 1 H, J = 7.8 Hz, Ar−H), 8.47 (s, 1 H, Ar−H), 9.41 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 503 (MH^+, 24), 126 (100); IR (KBr): 2933, 2857, 1693, 1434, 1383, 1239, 1167, 867 cm^{-1}; mp: 76–79 °C; yield: 39%.

3.4.7.6. Methyl 4-{[1-(1-azepanylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6f**)

^{1}H NMR (DMSO-d_6): δ 0.69 (m, 2 H, CH_2), 0.88–1.13 (m, 6 H, CH_2), 1.32 (m, 2 H, CH_2), 1.50–1.65 (m, 2 H, CH_2), 1.89 (m, 1 H, CH), 2.57–2.73 (m, 2 H, CH_2), 2.87 (m, 4 H, CH_2), 3.07 (m, 2 H, CH_2), 3.55 (s, 3 H, COO−CH_3), 3.90 (d, 2 H, J = 11.5 Hz, CH_2), 7.68 (dqu, 2 H, $J_1 = 5.9$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.79 (dd, 1 H, $J_1 = 6.9$ Hz, $J_2 = 1.6$ Hz, Ar−H), 8.02 (d, 1 H, J = 7.7 Hz, Ar−H), 8.09 (d, 1 H, J = 8.7 Hz, Ar−H), 8.15 (d, 1 H, J = 7.6 Hz, Ar−H), 8.44 (s, 1 H, Ar−H), 9.38 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 503 (MH^+, 19), 126 (100); IR (KBr): 3415, 1647, 1455, 1166, 872, 658 cm^{-1}; mp: 64–67 °C; yield: 13%.

3.4.7.7. Methyl 3-{[1-(4-morpholinylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6g**)

^{1}H NMR (DMSO-d_6): δ 1.22 (m, 2 H, CH_2), 1.59 (m, 2 H, CH_2), 1.83 (m, 1 H, CH), 1.90 (m, 2 H, CH_2), 2.13 (m, 2 H, CH_2), 3.22 (t, 4 H, J = 6.5 Hz, CH_2), 3.38 (t, 4 H, J = 6.4 Hz, CH_2), 3.59 (m, 1 H, CH_2), 3.78 (s, 3 H, COO−CH_3), 4.12 (d, 1 H, J = 11.3 Hz, CH_2), 7.68 (dqu, 2 H, $J_1 = 7.6$ Hz, $J_2 = 1.9$ Hz, Ar−H), 7.83 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.8$ Hz, Ar−H), 8.01 (d, 1 H, J = 8.5 Hz, Ar−H), 8.07 (d, 1 H, J = 8.7 Hz, Ar−H), 8.15 (d, 1 H, J = 7.6 Hz, Ar−H), 8.46 (s, 1 H, Ar−H), 9.43 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 491 (MH^+, 29), 126 (100); IR (KBr): 3224, 2979, 1730, 1542, 1434, 1235, 1208, 1040, 892, 647 cm^{-1}; mp: 145–152 °C; yield: 28%.

3.4.7.8. Methyl 4-{[1-(4-morpholinylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6h**)

^{1}H NMR (DMSO-d_6): δ 0.92 (m, 2 H, CH_2), 1.51 (m, 2 H, CH_2), 1.88 (m, 1 H, CH), 2.69 (m, 2 H, CH_2), 2.91 (m, 4 H, CH_2), 3.12 (m, 6 H, CH_2), 3.55 (s, 3 H, COO−CH_3), 3.90 (d, 2 H, J = 11.3 Hz, CH_2), 7.71 (dqu, 2 H, $J_1 = 6.7$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.78 (d, 1 H, J = 8.7 Hz, Ar−H), 8.06 (d, 1 H, J = 7.9 Hz, Ar−H), 8.13 (d, 1 H, J = 8.7 Hz, Ar−H), 8.18 (d, 1 H, J = 7.7 Hz, Ar−H), 8.45 (s, 1 H, Ar−H), 9.64 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 491 (MH^+, 22), 93 (100); IR (KBr): 3373, 2981, 1718, 1690, 1528, 1412, 1274, 1168, 1099, 988, 654 cm^{-1}; mp: 80–84 °C; yield: 22%.

3.4.7.9. Methyl 3-{[1-[(cycloheptylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6i**)

^{1}H NMR (DMSO-d_6): δ 1.02 (m, 2 H, CH_2), 1.22 (m, 4 H, CH_2), 1.69 (m, 5 H, CH, CH_2), 1.83 (m, 4 H, CH_2), 2.35 (m, 5 H, CH, CH_2), 3.52 (d, 1 H, J = 11.6 Hz, CH_2), 3.74 (s, 3 H, COO−CH_3), 3.81 (m, 3 H, CH_2, NH), 4.12 (d, 1 H, J = 10.5 Hz, CH_2), 7.66 (dqu, 2 H, $J_1 = 7.7$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.80 (dd, 1 H, $J_1 = 8.5$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.97 (d, 1 H, J = 8.6 Hz, Ar−H), 8.04 (d, 1 H, J = 8.6 Hz, Ar−H), 8.11 (d, 1 H, J = 7.5 Hz, Ar−H), 8.42 (s, 1 H, Ar−H), 9.40 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 517 (MH^+, 34), 126 (100); IR (KBr): 3413, 3186, 2937, 1685, 1430, 1335, 1168, 1026, 858, 754, 552 cm^{-1}; mp: 77–82 °C; yield: 35%.

3.4.7.10. Methyl 4-{[1-(1-azepanylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6j**)

^{1}H NMR (DMSO-d_6): δ 0.94 (m, 4 H, CH_2), 1.13 (m, 2 H, CH_2) 1.27 (m, 8 H, CH_2), 1.71 (m, 2 H, CH_2), 1.89 (m, 1 H, CH), 2.70 (m, 3 H, CH_2), 2.96 (m, 1 H, CH), 3.53 (s, 3 H, COO−CH_3), 3.82 (s, 1 H, NH), 3.90 (d, 2 H, J = 10.5 Hz, CH_2), 4.07 (s, 1 H, CH_2), 7.67 (dqu, 2 H, $J_1 = 7.3$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.80 (dd, 1 H, $J_1 = 8.5$ Hz, $J_2 = 1.7$ Hz, Ar−H), 8.01 (d, 1 H, J = 7.6 Hz, Ar−H), 8.11 (d, 1 H, J = 8.5 Hz, Ar−H), 8.16 (d, 1 H, J = 7.3 Hz, Ar−H), 8.42 (s, 1 H, Ar−H), 9.44 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 517 (MH^+, 27), 93 (100); IR (KBr): 3420, 2980, 1720, 1688, 1521, 1449, 1251, 1087, 854 cm^{-1}; mp: 76–80 °C; yield: 24%.

3.4.7.11. Methyl 3-{[1-[(cyclopentylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6k**)

^{1}H NMR (DMSO-d_6): δ 1.17–1.35 (m, 6 H, CH_2), 1.69 (m, 4 H, CH_2), 1.92 (m, 3 H, CH, CH_2), 2.14 (m, 2 H, CH_2), 2.37 (m, 1 H, CH), 3.11 (m, 1 H, CH_2), 3.48 (s, 1 H, CO−NH), 3.62 (s, 3 H, COO−CH_3), 3.75 (m, 1 H, CH_2), 4.01 (d, 2 H, J = 9.1 Hz, CH_2), 7.65 (dqu, 2 H, $J_1 = 7.5$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.80 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.7$ Hz, Ar−H), 8.00 (d, 1 H, J = 7.6 Hz, Ar−H), 8.10 (d, 1 H, J = 8.6 Hz, Ar−H), 8.14 (d, 1 H, J = 7.4 Hz, Ar−H), 8.44 (s, 1 H, Ar−H), 9.45 (s, 1 H, NH) ppm; MS (FAB+): m/z (%):489 (MH^+, 25), 168 (100); IR (KBr): 3437, 1693, 1441, 1350, 1240, 1166, 864, 753 cm^{-1}; mp: 83–88 °C; yield: 28%.

3.4.7.12. Methyl 4-{[1-[(cyclopentylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6l**)

^{1}H NMR (DMSO-d_6): δ 1.03–1.31 (m, 6 H, CH_2), 1.60 (m, 4 H, CH_2), 1.81 (m, 1 H, CH), 2.71 (m, 4 H, CH_2), 3.23 (m, 1 H, CH), 3.58 (s, 3 H, COO−CH_3), 3.62 (s, 1 H, NH), 4.02 (d, 2 H, J = 11.7 Hz, CH_2), 4.16 (q, 2 H, J = 7.3 Hz, CH_2), 7.72 (dqu, 2 H, $J_1 = 6.5$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.75 (d, 1 H, J = 8.5 Hz, Ar−H), 8.01 (d, 1 H, J = 8.0 Hz, Ar−H), 8.15 (d, 1 H, J = 8.6 Hz, Ar−H), 8.21 (d, 1 H, J = 7.6 Hz, Ar−H), 8.44 (s, 1 H, Ar−H), 9.64 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 489 (MH^+, 34), 126 (100); IR (KBr): 3309, 2956, 1716, 1537, 1426, 1208, 1036, 972, 815 cm^{-1}; mp: 71–74 °C; yield: 23%.

3.4.7.13. Methyl 3-{[1-[[cyclohexyl(methyl)amino]carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6m**)

^{1}H NMR (DMSO-d_6): δ 0.98 (m, 6 H, CH_2), 1.25 (m, 4 H, CH_2), 1.63 (m, 4 H, CH_2), 1.71 (m, 1 H, CH), 1.86 (m, 2 H, CH_2), 2.88 (s, 3 H, CH_3), 3.11 (m, 1 H, CH), 3.54 (m, 1 H, CH_2), 3.70 (s, 3 H, COO−CH_3), 3.86 (m, 2 H, CH_2), 4.05 (m, 1 H, CH_2), 7.69 (dqu, 2 H, $J_1 = 7.8$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.82 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.99 (d, 1 H, J = 8.5 Hz, Ar−H), 8.05 (d, 1 H, J = 8.7 Hz, Ar−H), 8.12 (d, 1 H, J = 7.9 Hz, Ar−H), 8.44 (s, 1 H, Ar−H), 9.37 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 517 (MH^+, 37), 126 (100); IR (KBr): 3414, 3145, 2957, 1675, 1432, 1342, 1167, 1042, 858, 748, 644, 553 cm^{-1}; mp: 133–136 °C; yield: 24%.

3.4.7.14. Methyl 4-{[1-{[cyclohexyl(methyl)amino]carbonyl}-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinecarboxylate (**6n**)

^{1}H NMR (DMSO-d_6): δ 0.86–1.02 (m, 6 H, CH_2), 1.30–1.51 (m, 4 H, CH_2), 1.67 (m, 2 H, CH_2), 1.91 (m, 1 H, CH), 2.59–2.74 (m, 3 H, CH_3), 2.86 (d, 2 H, J = 6.6 Hz, CH_2), 3.15 (m, 1 H, CH), 3.38 (m, 4 H, CH_2), 3.55 (s, 3 H, COO–CH_3), 3.90 (d, 2 H, J = 13.1 Hz, CH_2), 7.68 (dqu, 2 H, J_1 = 7.1 Hz, J_2 = 1.8 Hz, Ar–H), 7.75 (dd, 1 H, J_1 = 8.7 Hz, J_2 = 1.7 Hz, Ar–H), 8.02 (d, 1 H, J = 7.8 Hz, Ar–H), 8.08 (d, 1 H, J = 8.7 Hz, Ar–H), 8.15 (d, 1 H, J = 8.6 Hz, Ar–H), 8.42 (s, 1 H, Ar–H), 9.20 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 517 (MH^+, 28), 185 (100); IR (KBr): 3485, 3222, 2929, 2855, 1699, 1449, 1234, 1166, 957, 817, 694 cm^{-1}; mp: 67–72 °C; yield: 16%.

*3.4.8. Synthesis of compounds **7a–n**; general procedure*

Corresponding compound **6** (1.02 mmol) was dissolved in dioxane (30 ml). 2 M NaOH solution (80 ml) was added and the reaction mixture refluxed for 4 h. The solvents were removed in vacuo. Dichloromethane (30 ml) and water (50 ml) were added to the residue. The organic phase was separated and the water phase further extracted with dichloromethane (2 × 30 ml). Organic phases were combined, washed with water (25 ml) and saturated brine (25 ml), then dried over Na_2SO_4. The solvent was evaporated in vacuo and a white foamy solid was formed.

3.4.8.1. N′-[(4-Methyl-1-piperidinyl)carbonyl]-N′-(3-piperidinylmethyl)-2-naphthalenesulfonohydrazide (**7a**)

^{1}H NMR (DMSO-d_6): δ 0,86 (d, 3 H, J = 6.4 Hz, CH_3), 1.10 (m, 2 H, CH_2), 1.30 (m, 3 H, CH, CH_2), 1.48–1.73 (m, 5 H, CH, CH_2), 2.28 (m, 2 H, CH_2), 2.77 (m, 4 H, CH_2), 3.49 (m, 4 H, CH_2), 3.72 (m, 3 H, NH, CH_2), 7.63 (dqu, 2 H, J_1 = 7.2 Hz, J_2 = 1.6 Hz, Ar–H), 7.78 (dd, 1 H, J_1 = 8.5 Hz, J_2 = 1.7 Hz, Ar–H), 7.88 (d, 1 H, J = 8.2 Hz, Ar–H), 8.05 (d, 1 H, J = 8.2 Hz, Ar–H), 8.12 (d, 1 H, J = 7.7 Hz, Ar–H), 8.44 (s, 1 H, Ar–H), 9.41 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 445 (MH^+, 89), 126 (100); IR (KBr): 3327, 3028, 2984, 1702, 1538, 1224, 1019, 864, 758, 614 cm^{-1}; mp: 162–168 °C; yield: 67%.

3.4.8.2. N′-[(4-Methyl-1-piperidinyl)carbonyl]-N′-(4-piperidinylmethyl)-2-naphthalenesulfonohydrazide (**7b**)

^{1}H NMR (DMSO-d_6): δ 0.46 (d, 3 H, J = 6.0 Hz, CH_3), 0.90 (m, 1 H, CH), 1.09–1.24 (m, 5 H, CH_2), 1.56–1.71 (m, 2 H, CH_2), 1.91 (m, 1 H, CH_2), 2.06 (m, 1 H, CH), 2.31 (m, 2 H, CH_2), 2.73–2.94 (m, 4 H, CH_2), 3.26 (m, 2 H, CH_2), 3.37 (m, 1 H, CH_2), 3.52 (m, 1 H, CH_2), 3.61 (s, 1 H, NH), 7.69 (dqu, 2 H, J_1 = 8.7 Hz, J_2 = 1.8 Hz, Ar–H), 7.77 (dd, 1 H, J_1 = 8.6 Hz, J_2 = 1.7 Hz, Ar–H), 8.05 (d, 1 H, J = 7.8 Hz, Ar–H), 8.10 (d, 1 H, J = 8.7 Hz, Ar–H), 8.15 (d, 1 H, J = 7.6 Hz, Ar–H), 8.42 (s, 1 H, Ar–H), 9.49 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 445 (MH^+, 77), 126 (100); IR (KBr): 3417, 2923, 1653, 1445, 1336, 1164, 1076, 970, 750, 658, 553 cm^{-1}; mp: 158–162 °C; yield: 80%.

3.4.8.3. N′-(1-Piperidinylcarbonyl)-N′-(3-piperidinylmethyl)-2-naphthalenesulfonohydrazide (**7c**)

^{1}H NMR (DMSO-d_6): δ 1.01–1.18 (m, 6 H, CH_2), 1.65 (m, 2 H, CH_2), 1.80 (m, 3 H, CH, CH_2), 2.07 (m, 2 H, CH_2), 2.75 (m, 2 H, CH_2), 2.94 (m, 4 H, CH_2), 3.16 (m, 2 H, CH_2), 3.68 (s, 1 H, NH), 7.69 (dqu, 2 H, J_1 = 7.4 Hz, J_2 = 1.8 Hz, Ar–H), 7.78 (dd, 1 H, J_1 = 8.6 Hz, J_2 = 1.7 Hz, Ar–H), 8.05 (d, 1 H, J = 7.8 Hz, Ar–H), 8.11 (d, 1 H, J = 8.7 Hz, Ar–H), 8.16 (d, 1 H, J = 7.5 Hz, Ar–H), 8.42 (s, 1 H, Ar–H), 9.54 (s, 1 H, NH) ppm; MS (FAB+): m/z (%) : 431 (MH^+, 75), 69 (100); IR (KBr): 3408, 2935, 2856, 1714, 1537, 1221, 1087, 1036, 849, 773 cm^{-1}; mp: 153–158 °C; yield: 50%.

3.4.8.4. N′-(1-Piperidinylcarbonyl)-N′-(4-piperidinylmethyl)-2-naphthalenesulfonohydrazide (**7d**)

^{1}H NMR (DMSO-d_6): δ 1.04–1.24 (m, 8H, CH_2), 1.69 (m, 1 H, CH_2), 1.83 (m, 1 H, CH_2), 2.02 (m, 1 H, CH), 2.79–2.97 (m, 8 H, CH_2), 3.25 (d, 2 H, J = 11.5 Hz, CH_2), 3.64 (s, 1 H, NH), 7.70 (dqu, 2 H, J_1 = 7.6 Hz, J_2 = 1.9 Hz, Ar–H), 7.77 (dd, 1 H, J_1 = 8.6 Hz, J_2 = 1.7 Hz, Ar–H), 8.05 (d, 1 H, J = 7.7 Hz, Ar–H), 8.11 (d, 1 H, J = 8.7 Hz, Ar–H), 8.16 (d, 1 H, J = 7.6 Hz, Ar–H), 8.43 (s, 1 H, Ar–H), 9.49 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 431 (MH^+, 100); IR (KBr): 3418, 2928, 2734, 1660, 1472, 1335, 1224, 1163, 1126, 826, 660, 551 cm^{-1}; mp: 140–144 °C; yield: 88%.

3.4.8.5. N′-(1-Azepanylcarbonyl)-N′-(3-piperidinylmethyl)-2-naphthalenesulfonohydrazide (**7e**)

^{1}H NMR (DMSO-d_6): δ 0.98 (m, 2 H, CH_2), 1.25 (m, 2 H, CH_2), 1.54 (m, 4 H, CH_2), 1.83 (m, 1 H, CH), 2.03 (m, 2 H, CH_2), 2.33 (m, 2 H, CH_2), 2.77 (t, 2 H, J = 11.7 Hz, CH_2), 2.94 (m, 4 H, CH_2), 3.17 (m, 2 H, CH_2), 3.42 (m, 2 H, CH_2), 3.78 (m, 1 H, NH), 7.67 (dqu, 2 H, J_1 = 7.8 Hz, J_2 = 1.6 Hz, Ar–H), 7.77 (dd, 1 H, J_1 = 8.6 Hz, J_2 = 1.6 Hz, Ar–H), 7.98 (d, 1 H, J = 8.3 Hz, Ar–H), 8.03 (d, 1 H, J = 8.7 Hz, Ar–H), 8.12 (d, 1 H, J = 7.8 Hz, Ar–H), 8.47 (s, 1 H, Ar–H), 9.41 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 445 (MH^+, 25), 126 (100); IR (KBr): 3362, 2929, 1664, 1438, 1158, 948, 761, 694 cm^{-1}; mp: 153–155 °C; yield: 92%.

3.4.8.6. N′-(1-Azepanylcarbonyl)-N′-(4-piperidinylmethyl)-2-naphthalenesulfonohydrazide (**7f**)

^{1}H NMR (DMSO-d_6): δ 0.68 (m, 2 H, CH_2), 0.88 (m, 1 H, CH_2), 1.01–1.29 (m, 7 H, CH_2), 1.48–1.73 (m, 2 H, CH_2), 2.02 (m, 1 H, CH), 1.89 (m, 1 H, CH_2), 2.90 (m, 5 H, CH_2), 3.05 (m, 2 H, CH_2), 3.25 (d, 2 H, J = 11.2 Hz, CH_2), 3.66 (s, 1 H, NH), 7.68 (dqu, 2 H, J_1 = 8.0 Hz, J_2 = 1.8 Hz, Ar–H), 7.79 (dd, 1 H, J_1 = 8.6 Hz, J_2 = 1.6 Hz, Ar–H), 8.03 (d, 1 H, J = 7.8 Hz, Ar–H), 8.09 (d, 1 H, J = 8.7 Hz, Ar–H), 8.14 (d, 1 H, J = 7.6 Hz, Ar–H), 8.44 (s, 1 H, Ar–H), 9.44 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 445 (MH^+, 61), 57 (100); IR (KBr): 3409, 2937, 2856, 1669, 1418, 1331, 1166, 1075, 820, 659 cm^{-1}; mp: 170–175 °C; yield: 95%.

3.4.8.7. N′-(4-Morpholinylcarbonyl)-N′-(3-piperidinylmethyl)-2-naphthalenesulfonohydrazide (**7g**)

^{1}H NMR (DMSO-d_6): δ 1.08 (m, 2 H, CH_2), 1.47 (m, 2 H, CH_2), 1.77 (m, 3 H, CH, CH_2), 2.15 (m, 4 H, CH_2), 3.17 (m, 4 H, CH_2), 3.36 (m, 4 H, CH_2), 4.09 (s, 1 H, NH), 7.65 (dqu, 2 H, J_1 = 7.7 Hz, J_2 = 1.8 Hz, Ar–H), 7.81 (dd, 1 H, J_1 = 8.5 Hz, J_2 = 1.7 Hz, Ar–H), 8.01 (d, 1 H, J = 8.5 Hz, Ar–H), 8.04 (d, 1 H, J = 8.6 Hz, Ar–H), 8.13 (d, 1 H, J = 7.6 Hz, Ar–H), 8.44 (s, 1 H, Ar–H), 9.47 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 433 (MH^+, 68), 55 (100); IR (KBr): 3342, 3124, 1734, 1638, 1421, 1229, 1057, 832, 671 cm^{-1}; mp: 123–127 °C; yield: 82%.

3.4.8.8. N′-(4-Morpholinylcarbonyl)-N′-(4-piperidinylmethyl)-2-naphthalenesulfonohydrazide (**7h**)

^{1}H NMR (DMSO-d_6): δ 0.87 (m, 1 H, CH_2), 1.13–1.40 (m, 3 H, CH_2), 1.66–1.82 (m, 2 H, CH_2), 1.99 (m, 1 H, CH), 2.83 (m, 4 H, CH_2), 2.98–3.11 (m, 6 H, CH_2), 3.24 (d, 2 H, J = 11.85 Hz, CH_2), 3.59 (s, 1 H, NH), 7.72 (dqu, 2 H, J_1 = 7.6 Hz, J_2 = 1.8 Hz, Ar–H), 7.78 (dd, 1 H, J_1 = 8.8 Hz, J_2 = 1.7 Hz, Ar–H), 8.07 (d, 1 H, J = 7.8 Hz, Ar–H), 8.14 (d, 1 H, J = 8.7 Hz, Ar–H), 8.18 (d, 1 H, J = 7.6 Hz, Ar–H), 8.45 (s, 1 H, Ar–H), 9.69 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 433 (MH^+, 30), 154 (100); IR (KBr): 3413, 2921, 2852, 1664, 1412, 1338, 1273, 1165, 1115, 1022, 872, 754, 657, 557 cm^{-1}; mp: 195–198 °C; yield: 100%.

3.4.8.9. N-Cycloheptyl-2-(2-naphthylsulfonyl)-1-(3-piperidinylmethyl)-1-hydrazinecarboxamide (**7i**)

^{1}H NMR (DMSO-d_6): δ 1.09 (m, 2 H, CH_2), 1.25 (m, 4 H, CH_2), 1.78 (m, 5 H, CH, CH_2), 1.92 (m, 4 H, CH_2), 2.30 (m, 4 H, CH_2), 2.61 (m, 1 H, CH), 2.94 (m, 4 H, CH_2), 3.69 (s, 1 H, NH), 4.37 (s, 1 H, NH), 7.69 (dqu, 2 H, J_1 = 7.8 Hz, J_2 = 1.7 Hz, Ar–H), 7.83 (dd, 1 H, J_1 = 8.6 Hz, J_2 = 1.9 Hz, Ar–H), 8.05 (m, 3 H, Ar–H), 8.47 (s, 1 H, Ar–H), 9.38 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 459 (MH^+, 100); IR (KBr): 3429, 1733, 1651, 1559, 1457, 1338, 1162, 938, 857, 670 cm^{-1}; mp: 156–158 °C; yield: 83%.

3.4.8.10. N-Cycloheptyl-2-(2-naphthylsulfonyl)-1-(4-piperidinylmethyl)-1-hydrazinecarboxamide (**7j**)

^{1}H NMR (DMSO-d_6): δ 1.02–1.20 (m, 6 H, CH_2), 1.34 (m, 6 H, CH_2), 1.52 (m, 2 H, CH_2), 1.74 (m, 2 H, CH_2), 1.81 (m, 1 H, CH), 2.54–2.67 (m, 4 H, CH_2), 3.28 (d, 2 H, J = 10.8 Hz, CH_2), 3.45 (m, 2 H, CH_2), 3.77 (s, 1 H, NH), 7.69 (dqu, 2 H, J_1 = 7.5 Hz, J_2 = 1.7 Hz, Ar–H), 7.79 (dd, 1 H, J_1 = 8.4 Hz, J_2 = 1.8 Hz, Ar–H), 8.02 (d, 1 H, J = 7.6 Hz, Ar–H), 8.12 (d, 1 H, J = 8.5 Hz, Ar–H), 8.16 (d, 1 H, J = 7.4 Hz, Ar–H), 8.43 (s, 1 H, Ar–H), 9.51 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 459 (MH^+, 100); IR (KBr): 3417, 2931, 1694, 1531, 1407, 1224, 1163, 884, 826, 642 cm^{-1}; mp: 147–154 °C; yield: 85%.

3.4.8.11. N-Cyclopentyl-2-(2-naphthylsulfonyl)-1-(3-piperidinylmethyl)-1-hydrazinecarboxamide (**7k**)

^{1}H NMR (DMSO-d_6): δ 1.13 (m, 4 H, CH_2), 1.63 (m, 6 H, CH_2), 1.88 (m, 3 H, CH, CH_2), 2.25 (m, 2 H, CH_2), 2.33 (m, 1 H, CH), 2.61–2.87 (m, 3 H, CH_2), 2.94 (m, 1 H, CH_2), 3.54 (s, 1 H, CO-NH), 3.65 (s, 1 H, NH), 7.67 (dqu, 2 H, J_1 = 7.6 Hz, J_2 = 1.8 Hz, Ar–H), 7.81 (dd, 1 H, J_1 = 8.6 Hz, J_2 = 1.8 Hz, Ar–H), 8.03 (d, 1 H, J = 7.7 Hz, Ar–H), 8.11 (d, 1 H, J = 8.6 Hz, Ar–H), 8.14 (d, 1 H, J = 7.5 Hz, Ar–H), 8.42 (s, 1 H, Ar–H), 9.50 (s, 1 H, NH) ppm; MS (FAB+): m/z (%) : 431 (MH^+, 100); IR (KBr): 3112, 2932, 1657, 1550, 1465, 1421, 1164, 976, 743, 647 cm^{-1}; mp: 182–185 °C; yield: 84%.

3.4.8.12. N-cyclopentyl-2-(2-naphthylsulfonyl)-1-(4-piperidinylmethyl)-1-hydrazinecarboxamide (**7l**)

^{1}H NMR (DMSO-d_6): δ 1.14 (m, 4 H, CH_2), 1.37 (m, 2 H, CH_2), 1.63 (m, 4 H, CH_2), 1.77 (m, 1 H, CH), 2.56–2.73 (m, 8 H, CH_2), 3.17 (m, 1 H,

CH), 3.48 (s, 1 H, NH), 3.60 (s, 1 H, NH), 7.73 (dqu, 2 H, $J_1 = 6.5$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.78 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.6$ Hz, Ar−H), 8.03 (d, 1 H, J = 8.0 Hz, Ar−H), 8.17 (d, 1 H, J = 8.7 Hz, Ar−H), 8.21 (d, 1 H, J = 7.6 Hz, Ar−H), 8.43 (s, 1 H, Ar−H), 9.53 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 431 (MH^+, 100); IR (KBr): 3402, 3104, 2927, 1648, 1529, 1408, 1175, 972, 815, 647 cm^{-1}; mp: 165–167 °C; yield: 86%.

3.4.8.13. N-Cyclohexyl-N-methyl-2-(2-naphthylsulfonyl)-1-(3-piperidinylmethyl)-1-hydrazinecarboxamide (**7m**)

^{1}H NMR (DMSO-d_6): δ 1.04 (m, 6 H, CH_2), 1.31 (m, 4 H, CH_2), 1.75 (m, 5 H, CH, CH_2), 1.99 (m, 2 H, CH_2), 2.91 (s, 3 H, CH_3), 3.24 (m, 1 H, CH), 3.12 (m, 4 H, CH_2), 4.35 (s, 1 H, NH), 7.66 (dqu, 2 H, $J_1 = 7.6$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.81 (dd, 1 H, $J_1 = 8.5$ Hz, $J_2 = 1.9$ Hz, Ar−H), 8.02 (d, 1 H, J =8.6 Hz, Ar−H), 8.07 (d, 1 H, J = 8.5 Hz, Ar−H), 8.12 (d, 1 H, J = 7.7 Hz, Ar−H), 8.42 (s, 1 H, Ar−H), 9.40 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 459 (MH^+, 100); IR (KBr): 3457, 2989, 1652, 1558, 1384, 1275, 1164, 1038, 864, 750, 655, 545 cm^{-1}; mp: 146–154 °C; yield: 80%.

3.4.8.14. N-Cyclohexyl-N-methyl-2-(2-naphthylsulfonyl)-1-(4-piperidinylmethyl)-1-hydrazinecarboxamide (**7n**)

^{1}H NMR (DMSO-d_6): δ 0.52 (m, 1 H, CH_2), 0.66 (m, 1 H, CH_2), 0.88–1.12 (m, 4 H, CH_2), 1.24–1.43 (m, 4 H, CH_2), 1.66 (m, 1 H, CH_2), 1.97 (m, 1 H, CH_2), 2.03 (m, 1 H, CH), 2.48 (m, 8 H, CH_2), 2.73–2.91 (m, 3 H, CH_3), 3.14 (m, 1 H, CH), 3.50 (s, 1 H, NH), 7.69 (dqu, 2 H, $J_1 = 7.2$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.74 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.6$ Hz, Ar−H), 8.02 (d, 1 H, J = 7.8 Hz, Ar−H), 8.08 (d, 1 H, J = 8.7 Hz, Ar−H), 8.15 (d, 1 H, J = 7.7 Hz, Ar−H), 8.42 (s, 1 H, Ar−H), 9.25 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 459 (MH^+, 34), 83 (100); IR (KBr): 3417, 3210, 2930, 2854, 1661, 1448, 1335, 1166, 818, 688 cm^{-1}; mp: 183–187 °C; yield: 80%.

*3.4.9. Synthesis of compounds **8a–n**; general procedure*

Corresponding compound **7** (0.72 mmol) was dissolved in 20 ml of absolute ethanol. 0,20 ml 0.21 g (0.72 mmol) of *tert*-butyl-[(*tert*-butoxycarbonyl)amino](methylsulfanyl) methylidenecarbamate, 0.20 g (0.72 mmol) $HgCl_2$ and 0.20 ml of triethylamine were added and the reaction mixture stirred overnight at room temperature. After the solids were filtered off and washed with absolute ethanol, the solvent was evaporated in vacuo. The residue was dissolved in ethylacetate (25 ml) and extracted with 2 × 15 ml of 10% citric acid and 15 ml of saturated $NaHCO_3$ solution. The organic phase was washed with 15 ml of demineralised water and 15 ml of saturated brine and dried over Na_2SO_4. Ethylacetate was evaporated *in vacuo* and the crude products were further purified by column chromatography (silicagel; dichloromethane : methanol 19 : 1).

3.4.9.1. Tert-butyl [(tert-butoxycarbonyl)amino](3-{[1-[(4-methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methylidenecarbamate (**8a**)

^{1}H NMR (DMSO-d_6): δ 0,87 (d, 3 H, J = 6.5 Hz, CH_3), 1.11 (m, 2 H, CH_2), 1.39 (m, 3 H, CH, CH_2), 1.44 (s, 18 H, $C(CH_3)_3$), 1.57 (m, 4 H, CH_2), 1.82 (m, 1 H, CH), 2.36 (m, 2 H, CH_2), 2.74 (m, 2 H, CH_2), 3.51 (m, 2 H, CH_2), 3.71 (d, 1 H, J = 8.7 Hz, CH_2), 3.89 (m, 2 H, CH_2), 4.12 (m, 1 H, CH_2), 7.69 (dqu, 2 H, $J_1 = 7.5$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.82 (dd, 1 H, $J_1 = 8.4$ Hz, $J_2 = 1.7$ Hz, Ar−H), 8.04 (d, 1 H, J = 7.4 Hz, Ar−H), 8.09 (d, 1 H, J = 8.1 Hz, Ar−H), 8.16 (d, 1 H, J = 7.6 Hz, Ar−H), 8.44 (s, 1 H, Ar−H), 9.44 (s, 1 H, NH), 9.56 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 687 (MH^+, 37), 126 (100); IR (KBr): 3224, 2933, 2868, 1796, 1723, 1620, 1482, 1369, 1299, 1141, 856, 751, 686, 551 cm^{-1}; mp: 133–137 °C; yield: 81%.

3.4.9.2. Tert-butyl [(tert-butoxycarbonyl)amino](4-{[1-[(4-methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methylidenecarbamate (**8b**)

^{1}H NMR (DMSO-d_6): δ 0.46 (d, 3 H, J = 5.8 Hz, CH_3), 0.86–1.06 (m, 3 H, CH_2, CH), 1.18–1.24 (m, 4 H, CH_2), 1.40 (s, 18 H, $C(CH_3)_3$), 1.49–1.69 (m, 4 H, CH_2), 1.99 (m, 1 H, CH), 2.76 (m, 2 H, CH_2), 2.93 (m, 2 H, CH_2), 3.56 (m, 2 H, CH_2), 3.93 (m, 2 H, CH_2), 7.69 (dqu, 2 H, $J_1 = 8.5$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.78 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.5$ Hz, Ar−H), 8.04 (d, 1 H, J = 7.8 Hz, Ar−H), 8.09 (d, 1 H, J = 8.7 Hz, Ar−H), 8.15 (d, 1 H, J = 7.7 Hz, Ar−H), 8.44 (s, 1 H, Ar−H), 9.47 (s, 2 H, NH) ppm; MS (FAB+): m/z (%): 687 (MH^+, 16), 57 (100); IR (KBr): 3413, 2931, 1749, 1616, 1424, 1367, 1298, 1167, 962, 749, 642 cm^{-1}; mp: 73–78 °C; yield: 74%.

3.4.9.3. Tert-butyl [(tert-butoxycarbonyl)amino](3-{[2-(2-naphthylsulfonyl)-1-(1-piperidinylcarbonyl)hydrazino]methyl}-1-piperidinyl)methylidenecarbamate (**8c**)

^{1}H NMR (DMSO-d_6): δ 1.07 (m, 2 H, CH_2), 1.37 (m, 4 H, CH_2), 1.44 (s, 18 H, $C(CH_3)_3$), 1.52 (m, 2 H, CH_2), 1.67 (m, 2 H, CH_2), 1.76–2.01 (m, 3 H, CH, CH_2), 2.88 (m, 2 H, CH_2), 3.04 (m, 2 H, CH_2), 3.42 (m, 1 H, CH_2), 3.81 (m, 2 H, CH_2), 4.22 (m, 1 H, CH_2), 7.69 (dqu, 2 H, $J_1 = 7.6$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.78 (dd, 1 H, $J_1 = 8.7$ Hz, $J_2 = 1.8$ Hz, Ar−H), 8.03 (d, 1 H, J = 7.7 Hz, Ar−H), 8.12 (d, 1 H, J = 8.7 Hz, Ar−H), 8.18 (d, 1 H, J = 7.6 Hz, Ar−H), 8.44 (s, 1 H, Ar−H), 9.47 (s, 1 H, NH), 9.66 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 673 (MH^+, 77), 112 (100); IR (KBr): 3198, 2935, 1788, 1722, 1641, 1483, 1370, 1251, 1140, 789, 780 cm^{-1}; mp: 126–129 °C; yield: 78%.

3.4.9.4. Tert-butyl [(tert-butoxycarbonyl)amino](4-{[2-(2-naphthylsulfonyl)-1-(1-piperidinylcarbonyl)hydrazino]methyl}-1-piperidinyl)methylidenecarbamate (**8d**)

^{1}H NMR (DMSO-d_6): δ 0.86–1.05 (m, 7 H, CH_2), 1.22 (m, 1 H, CH_2), 1.40 (m, 18 H, $C(CH_3)_3$), 1.56 (m, 2 H, CH_2), 1.99 (m, 1 H, CH), 2.73–3.00 (m, 8 H, CH_2), 3.91 (d, 2 H, J = 11.7 Hz, CH_2), 7.69 (dqu, 2 H, $J_1 = 7.4$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.78 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.7$ Hz, Ar−H), 8.05 (d, 1 H, J = 7.8 Hz, Ar−H), 8.11 (d, 1 H, J = 8.7 Hz, Ar−H), 8.16 (d, 1 H, J = 7.5 Hz, Ar−H), 8.44 (s, 1 H, Ar−H), 9.46 (s, 1 H, NH), 9.48 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 473 ((M-2 × Boc)H^+, 38), 57 (100); IR (KBr): 3410, 3230, 2979, 2936, 2858, 1750, 1613, 1426, 1368, 1298, 1140, 961, 749 cm^{-1}; mp: 109–113 °C; yield: 79%.

3.4.9.5. Tert-butyl(3-{[1-(1-azepanylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)[(tert-butoxycarbonyl)amino]methylidenecarbamate (**8e**)

^{1}H NMR (DMSO-d_6): δ 1.21 (m, 4 H, CH_2), 1.45 (s, 18 H, $C(CH_3)_3$), 1.63 (m, 4 H, CH_2), 1.84 (m, 1 H, CH), 1.93 (m, 2 H, CH_2), 2.17 (m, 2 H, CH_2), 2.83 (m, 2 H, CH_2), 2.92 (m, 4 H, CH_2), 3.45 (m, 1 H, CH_2), 3.75 (m, 2 H, CH_2), 4.13 (m, 1 H, CH_2), 7.68 (dqu, 2 H, $J_1 = 7.6$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.81 (dd, 1 H, $J_1 = 8.7$ Hz, $J_2 = 1.6$ Hz, Ar−H), 8.04 (d, 1 H, J = 7.7 Hz, Ar−H), 8.09 (d, 1 H, J = 8.6 Hz, Ar−H), 8.13 (d, 1 H, J = 7.8 Hz, Ar−H), 8.46 (s, 1 H, Ar−H), 9.45 (s, 1 H, NH) 10.11 (s, 1 H, NH) ppm; MS (FAB+): m/z (%) : 687 (MH^+, 45), 57 (100); IR (KBr): 3220, 2934, 1725, 1641, 1450, 1371, 1243, 1156, 866, 779, 660 cm^{-1}; mp: 124–127 °C; yield: 87%.

3.4.9.6. Tert-butyl (4-{[1-(1-azepanylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)[(tert-butoxycarbonyl)amino]methylidenecarbamate (**8f**)

^{1}H NMR (DMSO-d_6): δ 0.70 (m, 2 H, CH_2), 0.87 (dt, 2 H, $J_1 = 9.4$ Hz, $J_2 = 3.6$ Hz, CH_2), 1.01–1.24 (m, 6 H, CH_2), 1.35 (m, 18 H, $C(CH_3)_3$), 1.63 (m, 2 H, CH_2), 1.96 (m, 1 H, CH), 2.73 (m, 2 H, CH_2), 2.89 (d, 2 H, J = 6.7 Hz, CH_2), 2.90 (m, 2 H, CH_2), 3.08 (m, 2 H, CH_2), 3.92 (d, 2 H, J = 9.3 Hz, CH_2), 7.68 (dqu, 2 H, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.80 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.7$ Hz, Ar−H), 8.03 (d, 1 H, J = 7.7 Hz, Ar−H), 8.09 (d, 1 H, J = 8.7 Hz, Ar−H), 8.15 (d, 1 H, J = 7.6 Hz, Ar−H), 8.45 (s, 1 H, Ar−H), 9.40 (s, 1 H, NH), 9.47 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 487 ((M-2 × Boc)H^+, 65), 93 (100); IR (KBr): 3412, 2931, 1750, 1637, 1617, 1420, 1298, 1145, 962, 643 cm^{-1}; mp: 107–102 °C; yield: 85%.

3.4.9.7. Tert-butyl[(tert-butoxycarbonyl)amino](3-{[1-(4-morpholinylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methylidenecarbamate (**8g**)

^{1}H NMR (DMSO-d_6): δ 1.14 (m, 2 H, CH_2), 1.43 (s, 18 H, $C(CH_3)_3$), 1.57 (m, 2 H, CH_2), 1.72–1.86 (m, 3 H, CH, CH_2), 2.14 (m, 2 H, CH_2), 3.25 (m, 4 H, CH_2), 3.43 (m, 4 H, CH_2), 3.71 (m, 1 H, CH_2), 4.10 (d, 1 H, J = 10.8 Hz, CH_2), 7.67 (dqu, 2 H, $J_1 = 7.6$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.83 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.6$ Hz, Ar−H), 7.99 (d, 1 H, J = 8.3 Hz, Ar−H), 8.05 (d, 1 H, J = 8.6 Hz, Ar−H), 8.13 (d, 1 H, J = 7.5 Hz, Ar−H), 8.42 (s, 1 H, Ar−H), 9.61 (s, 1 H, NH), 9.81 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 491 ((M-2 × Boc)H^+, 100); IR (KBr): 3302, 3210, 2987, 1652, 1512, 1337, 1204, 1082, 1036, 774, 736, 642 cm^{-1}; mp: 116–125 °C; yield: 91%.

3.4.9.8. Tert-butyl [(tert-butoxycarbonyl)amino](4-{[1-(4-morpholinylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methylidenecarbamate (**8h**)

^{1}H NMR (DMSO-d_6): δ 0.91 (m, 2 H, CH_2), 1.36 (m, 18 H, $C(CH_3)_3$), 1.51 (m, 2 H, CH_2), 1.91 (m, 1 H, CH), 2.69 (m, 2 H, CH_2), 2.83 (m, 2 H, CH_2), 2.93 (d, 2 H, J = 6.0 Hz, CH_2), 3.08 (m, 6 H, CH_2), 3.88 (d, 2 H, J = 10.2 Hz, CH_2), 7.67 (dqu, 2 H, $J_1 = 7.2$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.75 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.5$ Hz, Ar−H), 8.02 (d, 1 H, J = 7.9 Hz, Ar−H), 8.09 (d, 1 H, J = 8.7 Hz, Ar−H), 8.14 (d, 1 H, J = 7.6 Hz, Ar−H), 8.41 (s, 1 H, Ar−H), 9.43 (s, 1 H, NH), 9.62 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 475 ((M-2 × Boc)H^+, 90), 57 (100); IR (KBr): 3415, 3214, 2980, 1740, 1634, 1502, 1238, 1162, 768, 699 cm^{-1}; mp: 85–90 °C; yield: 50%.

3.4.9.9. Tert-butyl [(tert-butoxycarbonyl)amino](3-{[1-[(cycloheptylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methylidenecarbamate (**8i**)

^{1}H NMR (DMSO-d_6): δ 1.16 (m, 6 H, CH_2), 1.45 (s, 18 H, $C(CH_3)_3$), 1.69 (m, 4 H, CH_2), 1.83 (m, 5 H, CH, CH_2), 2.32 (m, 4 H, CH_2), 2.47 (m, 1 H,

CH), 3.49 (m, 1 H, CH_2), 3.72 (s, 1 H, NH), 3.85 (m, 2 H, CH_2), 4.08 (m, 1 H, CH_2), 7.69 (dqu, 2 H, $J_1 = 7.8$ Hz, $J_2 = 1.9$ Hz, Ar−H), 7.82 (dd, 1 H, $J_1 = 8.5$ Hz, $J_2 = 1.9$ Hz, Ar−H), 8.02 (d, 1 H, J = 8.6 Hz, Ar−H), 8.07 (d, 1 H, J = 8.5 Hz, Ar−H), 8.13 (d, 1 H, J = 7.8 Hz, Ar−H), 8.43 (s, 1 H, Ar−H), 9.44 (s, 1 H, NH), 9.86 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 699 (MH^+, 17), 499 (100); IR (KBr): 3476, 2931, 1595, 1406, 1229, 1117, 984, 861, 746, 660, 551 cm^{-1}; mp: 114–120 °C; yield: 78%.

3.4.9.10. Tert-butyl [(tert-butoxycarbonyl)amino](4-{[1-[(cycloheptylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methylidenecarbamate (**8j**)

^{1}H NMR (DMSO-d_6): δ 0.88 (m, 4 H, CH_2), 1.07–1.31 (m, 10 H, CH_2), 1.35 (m, 18 H, $C(CH_3)_3$), 1.73 (m, 2 H, CH_2), 1.94 (m, 1 H, CH), 2.74 (m, 2H, CH_2), 3.00 (m, 1 H, CH), 3.85 (s, 1 H, NH), 3.92 (d, 2 H, J = 11.2 Hz, CH_2), 4.12 (m, 2 H, CH_2), 7.68 (dqu, 2 H, $J_1 = 7.5$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.80 (dd, 1 H, $J_1 = 8.3$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.99 (d, 1 H, J = 7.5 Hz, Ar−H), 8.12 (d, 1 H, J = 8.5 Hz, Ar−H), 8.15 (d, 1 H, J = 7.3 Hz, Ar−H), 8.43 (s, 1 H, Ar−H), 9.49 (s, 1 H, NH), 9.66 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 501 ($(M\text{-}2\times Boc)H^+$, 100); IR (KBr): 3415, 3228, 2975, 1743, 1620, 1437, 1286, 1113, 807, 732 cm^{-1}; mp: 123–125 °C; yield: 82%.

3.4.9.11. Tert-butyl [(tert-butoxycarbonyl)amino](3-{[1-[(cyclopentylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methylidenecarbamate (**8k**)

^{1}H NMR (DMSO-d_6): δ 1.24 (m, 4 H, CH_2), 1.41 (s, 18 H, $C(CH_3)_3$), 1.57–1.71 (m, 6 H, CH_2), 1.86 (m, 1 H, CH), 2.01 (m, 2 H, CH_2), 2.19 (m, 2 H, CH_2), 2.41 (m, 1 H, CH), 3.11 (m, 1 H, CH_2), 3.48 (s, 1 H, CO-NH), 3.75 (d, 1 H, J = 10.2 Hz, CH_2), 4.01 (d, 2 H, J = 10.2 Hz, CH_2), 7.69 (dqu, 2 H, $J_1 = 7.6$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.82 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.98 (d, 1 H, J = 7.6 Hz, Ar−H), 8.12 (d, 1 H, J = 8.6 Hz, Ar−H), 8.17 (d, 1 H, J = 7.4 Hz, Ar−H), 8.40 (s, 1 H, Ar−H), 9.46 (s, 1 H, NH), 9.62 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 473 ($(M\text{-}2\times Boc)H^+$, 100); IR (KBr): 3426, 2976, 1683, 1524, 1458, 1227, 1025, 879, 642 cm^{-1}; mp: 111–114 °C; yield: 73%.

3.4.9.12. Tert-butyl [(tert-butoxycarbonyl)amino](4-{[1-[(cyclopentylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methylidenecarbamate (**8l**)

^{1}H NMR (DMSO-d_6): δ 1.09 (m, 4 H, CH_2), 1.37 (m, 20 H, $C(CH_3)_3$, CH_2), 1.63 (m, 4 H, CH_2), 1.89 (m, 1 H, CH), 2.71 (m, 4 H, CH_2), 3.23 (m, 1 H, CH), 3.64 (s, 1 H, NH), 3.97 (d, 2 H, J = 12.4 Hz, CH_2), 4.18 (q, 2 H, J = 7.6 Hz, CH_2), 7.73 (dqu, 2 H, $J_1 = 6.6$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.78 (d, 1 H, J = 8.5 Hz, Ar−H), 7.98 (d, 1 H, J = 7.9 Hz, Ar−H), 8.13 (d, 1 H, J = 8.5 Hz, Ar−H), 8.22 (d, 1 H, J = 7.6 Hz, Ar−H), 8.46 (s, 1 H, Ar−H), 9.44 (s, 1 H, NH), 9.73, (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 673 (MH^+, 6), 473 (100); IR (KBr): 3418, 3134, 2967, 1730, 1529, 1440, 1231, 993, 843, 715, 648 cm^{-1}; mp: 111–113 °C; yield: 76%.

3.4.9.13. Tert-butyl [(tert-butoxycarbonyl)amino](3-{[1-{[cyclohexyl(methyl)amino]carbonyl}-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methylidenecarbamate (**8m**)

^{1}H NMR (DMSO-d_6): δ 0.96 (m, 6 H, CH_2), 1.23 (m, 4 H, CH_2), 1.44 (s, 18 H, $C(CH_3)_3$), 1.60 (m, 4 H, CH_2), 1.74 (m, 1 H, CH), 1.92 (m, 2 H, CH_2), 2.76 (s, 3 H, CH_3), 3.14 (m, 1 H, CH), 3.53 (m, 1 H, CH_2), 3.90 (m, 2 H, CH_2), 4.11 (m, 1 H, CH_2), 7.68 (dqu, 2 H, $J_1 = 7.6$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.81 (dd, 1 H, $J_1 = 8.7$ Hz, $J_2 = 1.9$ Hz, Ar−H), 8.01 (d, 1 H, J = 8.6 Hz, Ar−H), 8.06 (d, 1 H, J = 8.8 Hz, Ar−H), 8.14 (d, 1 H, J = 7.6 Hz, Ar−H), 8.45 (s, 1 H, Ar−H), 9.43 (s, 1 H, NH), 9.65 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 501 ($(M\text{-}2\times Boc)H^+$, 100); IR (KBr): 3476, 3124, 1638, 1364, 1259, 1147, 998, 853, 727, 558 cm^{-1}; mp: 102–104 °C; yield: 77%.

3.4.9.14. Tert-butyl [(tert-butoxycarbonyl)amino](4-{[1-{[cyclohexyl(methyl)amino]carbonyl}-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methylidenecarbamate (**8n**)

^{1}H NMR (DMSO-d_6): δ 0.54 (m, 1 H, CH_2), 0.66 (m, 1 H, CH_2), 0.87–1.12 (m, 6 H, CH_2), 1.29 (m, 6 H, CH_2), 1.40 (s, 18 H, $C(CH_3)_3$), 1.69 (m, 2 H, CH_2), 1.99 (m, 1 H, CH), 2.28 (m, 2 H, CH_2), 2.73–2.89 (m, 3 H, CH_3), 3.17 (m, 1 H, CH), 3.92 (d, 2 H, J = 9.8 Hz, CH_2), 7.68 (dqu, 2 H, $J_1 = 7.5$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.75 (dd, 1 H, $J_1 = 10.4$ Hz, $J_2 = 1.6$ Hz, Ar−H), 8.02 (d, 1 H, J = 7.7 Hz, Ar−H), 8.08 (d, 1 H, J = 8.7 Hz, Ar−H), 8.16 (d, 1 H, J = 7.6 Hz, Ar−H), 8.43 (s, 1 H, Ar−H), 9.23 (s, 1 H, NH), 9.48 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 701 (MH^+, 46), 185 (100); IR (KBr): 3414, 1618, 1144, 624 cm^{-1}; mp: 112–115 °C; yield: 93%.

*3.4.10. Synthesis of compounds **9a–n**; general procedure*

Corresponding compound **8** (0.69 mmol) was dissolved in dichloromethane (25 ml) and gaseous HCl was bubbled in for 30 min. The resulting white solid was filtered, rinsed with diethylether and dried in air.

3.4.10.1. Amino(3-{[1-[(4-methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9a**)

^{1}H NMR (DMSO-d_6): δ 0,83 (d, 3 H, J = 6.7 Hz, CH_3), 1.08 (m, 2 H, CH_2), 1.20 (m, 3 H, CH, CH_2), 1.54 (m, 4 H, CH_2), 1.91 (m, 1 H, CH), 2.41 (m, 2 H, CH_2), 2.79 (m, 2 H, CH_2), 3.48 (m, 2 H, CH_2), 3.69 (m, 1 H, CH_2), 3.92 (m, 2 H, CH_2), 4.08 (m, 1 H, CH_2), 7.06 and 7.23 (2 s, 4 H, $H_2N^+{=}C{-}NH_2$), 7.71 (dqu, 2 H, $J_1 = 7.5$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.78 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.8$ Hz, Ar−H), 8.04 (d, 1 H, J = 7.9 Hz, Ar−H), 8.09 (d, 1 H, J = 8.4 Hz, Ar−H), 8.14 (d, 1 H, J = 7.8 Hz, Ar−H), 8.44 (s, 1 H, Ar−H), 9.59 (s, 1 H, NH), ppm; MS (FAB+): m/z (%): 487 ((M-HCl)H^+, 100); IR (KBr): 3394, 2928, 1654, 1443, 1334, 1165, 1074, 970, 753 cm^{-1}; mp: 109–115 °C; yield: 72%.

3.4.10.2. Amino(4-{[1-[(4-methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9b**)

^{1}H NMR (DMSO-d_6): δ 0.45 (d, 3 H, J = 5.9 Hz, CH_3), 0.87 (m, 1 H, CH), 0.88–1.49 (m, 10 H, CH_2), 1.67 (m, 2 H, CH_2), 2.06 (m, 1 H, CH), 2.93 (m, 3 H, CH_2), 3.52 (m, 1 H, CH_2), 3.84 (m, 2 H, CH_2), 7.43 (s, 4 H, $H_2N^+{=}C{-}NH_2$), 7.69 (dqu, 2 H, $J_1 = 6.7$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.77 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.6$ Hz, Ar−H), 8.05 (d, 1 H, J = 7.8 Hz, Ar−H), 8.10 (d, 1 H, J = 8.7 Hz, Ar−H), 8.15 (d, 1 H, J = 7.8 Hz, Ar−H), 8.43 (s, 1 H, Ar−H), 9.52 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 487 ((M−HCl)H^+, 79), 126 (100); IR (KBr): 3367, 2926, 1654, 1618, 1445, 1337, 1271, 1164, 968, 750 cm^{-1}; mp: 102–106 °C; yield: 75%.

3.4.10.3. Amino(3-{[2-(2-naphthylsulfonyl)-1-(1-piperidinylcarbonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9c**)

^{1}H NMR (DMSO-d_6): δ 1.11 (m, 2 H, CH_2), 1.35(m, 4 H, CH_2), 1.64 (m, 4 H, CH_2), 1.84 (m, 1 H, CH), 1.97 (m, 2 H, CH_2), 2.93 (m, 4 H, CH_2), 3.40 (m, 1 H, CH_2), 3.71 (m, 2 H, CH_2), 4.03 (m, 1 H, CH_2), 7.11 and 7.27 (2s, 4 H, $H_2N^+{=}C{-}NH_2$), 7.67 (dqu, 2 H, $J_1 = 7.2$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.78 (dd, 1 H, $J_1 = 8.7$ Hz, $J_2 = 1.8$ Hz, Ar−H), 8.05 (d, 1 H, J = 7.9 Hz, Ar−H), 8.14 (d, 1 H, J = 7.9 Hz, Ar−H), 8.19 (d, 1 H, J = 7.6 Hz, Ar−H), 8.45 (s, 1 H, Ar−H), 9.47 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 473 ((M−HCl)H^+, 28), 154 (100); IR (KBr): 3364, 2941, 1652, 1442, 1338, 1164, 1019, 855, 751 cm^{-1}; mp: 103–105 °C; yield: 76%.

3.4.10.4. Amino(4-{[2-(2-naphthylsulfonyl)-1-(1-piperidinylcarbonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9d**)

^{1}H NMR (DMSO-d_6): δ 0.84–1.12 (m, 8 H, CH_2), 1.28 (m, 2 H, CH_2), 1.64 (m, 2 H, CH_2), 2.03 (m, 1 H, CH), 2.87–2.99 (m, 6 H, CH_2), 3.83 (d, 2 H, J = 12.7 Hz, CH_2), 7.43 (s, 4 H, $H_2N^+{=}C{-}NH_2$), 7.70 (dqu, 2 H, $J_1 = 8.4$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.78 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.7$ Hz, Ar−H), 8.05 (d, 1 H, J = 7.8 Hz, Ar−H), 8.11 (d, 1 H, J = 8.7 Hz, Ar−H), 8.16 (d, 1 H, J = 7.7 Hz, Ar−H), 8.43 (s, 1 H, Ar−H), 9.52 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 473 ((M−HCl)H^+, 89), 149 (100); IR (KBr): 3409, 2929, 1731, 1663, 1618, 1438, 1269, 1168, 1132, 1074, 804, 612 cm^{-1}; mp: 104–107 °C; yield: 96%.

3.4.10.5. Amino(3-{[1-(1-azepanylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9e**)

^{1}H NMR (DMSO-d_6): δ 1.13 (m, 4 H, CH_2), 1.65 (m, 4 H, CH_2), 1.92 (m, 1 H, CH), 2.14 (m, 4 H, CH_2), 2.83 (m, 2 H, CH_2), 2.98 (m, 4 H, CH_2), 3.38 (m, 1 H, CH_2), 3.74 (m, 2 H, CH_2), 4.09 (m, 1 H, CH_2), 7.23 (s, 4 H, $H_2N^+{=}C{-}NH_2$), 7.68 (dqu, 2 H, $J_1 = 7.7$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.79 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.5$ Hz, Ar−H), 8.04 (d, 1 H, J = 8.2 Hz, Ar−H), 8.07 (d, 1 H, J = 8.5 Hz, Ar−H), 8.14 (d, 1 H, J = 7.7 Hz, Ar−H), 8.44 (s, 1 H, Ar−H), 9.45 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 487 ((M−HCl)H^+, 65), 154 (100); IR (KBr): 3343, 3175, 2934, 1657, 1443, 1337, 1163, 1019, 856, 660 cm^{-1}; mp: 124–127 °C; yield: 65%.

3.4.10.6. Amino(4-{[1-(1-azepanylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9f**)

^{1}H NMR (DMSO-d_6): δ 0.66 (m, 2 H, CH_2), 0.88 (m, 1 H, CH_2), 1.07 (m, 5 H, CH_2), 1.30 (m, 3 H, CH_2), 1.64 (m, 3 H, CH_2), 2.04 (m, 1 H, CH), 2.90–3.12 (m, 6 H, CH_2), 3.84 (d, 2 H, J = 13.4 Hz, CH_2), 7.45 (s, 4 H, $H_2N^+{=}C{-}NH_2$), 7.68 (dqu, 2 H, $J_1 = 6.7$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.79 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.7$ Hz, Ar−H), 8.03 (d, 1 H, J = 7.8 Hz, Ar−H), 8.09 (d, 1 H, J = 8.7 Hz, Ar−H), 8.14 (d, 1 H, J = 7.7 Hz, Ar−H), 8.45 (s, 1 H, Ar−H), 9.47 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 487 ((M−HCl)H^+, 93), 126 (100); IR (KBr): 3417, 3209, 2933, 1647, 1617, 1420, 1340, 1270, 1165, 1075, 966, 748, 646 cm^{-1}; mp: 214–217 °C; yield: 93%.

3.4.10.7. Amino(3-{[1-(4-morpholinylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9g**)

^{1}H NMR (DMSO-d_6): δ 1.20 (m, 2 H, CH_2), 1.58–1.74 (m, 5 H, CH, CH_2), 2.09 (m, 2 H, CH_2), 3.17 (m, 4 H, CH_2), 3.48 (m, 4 H, CH_2), 3.74 (m, 1 H, CH_2), 4.12 (m, 1 H, CH_2), 7.28 (s, 4 H, $H_2N^+{=}C{-}NH_2$), 7.69

(dqu, 2 H, $J_1 = 7.8$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.82 (dd, 1 H, $J_1 = 8.5$ Hz, $J_2 = 1.7$ Hz, Ar−H), 8.02 (d, 1 H, $J = 8.4$ Hz, Ar−H), 8.07 (d, 1 H, $J = 8.6$ Hz, Ar−H), 8.13 (d, 1 H, $J = 7.6$ Hz, Ar−H), 8.44 (s, 1 H, Ar−H), 9.48 (s, 1 H, NH), ppm; MS (FAB+): m/z (%): 475 ((M−HCl)H^+, 83), 126 (100); IR (KBr): 3412, 3027, 2976, 1635, 1571, 1447, 1204, 962, 733, 591 cm^{-1}; mp: 102–105 °C; yield: 43%.

3.4.10.8. Amino(4-{[1-(4-morpholinylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9h**)

^{1}H NMR (DMSO-d_6): δ 1.05 (m, 2 H, CH_2), 1.29 (m, 2 H, CH_2), 1.60 (m, 2 H, CH_2), 2.02 (m, 1 H, CH), 2.86–3.11 (m, 10 H, CH_2), 3.83 (d, 2 H, $J = 13.2$ Hz, CH_2), 7.44 (s, 4 H, H_2N^+=C−NH_2), 7.71 (dqu, 2 H, $J_1 = 7.8$ Hz, $J_2 = 1.6$ Hz, Ar−H), 7.79 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.3$ Hz, Ar−H), 8.07 (d, 1 H, $J = 7.7$ Hz, Ar−H), 8.13 (d, 1 H, $J = 8.7$ Hz, Ar−H), 8.18 (d, 1 H, $J = 7.7$ Hz, Ar−H), 8.45 (s, 1 H, Ar−H), 9.73 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 475 ((M−HCl)H^+, 37), 149 (100); IR (KBr): 3364, 2928, 1654, 1458, 1337, 1272, 1165, 1114, 1022, 754, 558 cm^{-1}; mp: 102–106 °C; yield: 100%.

3.4.10.9. Amino(3-{[1-[(cycloheptylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9i**)

^{1}H NMR (DMSO-d_6): δ 1.13 (m, 6 H, CH_2), 1.66–1.87 (m, 9 H, CH, CH_2), 2.28 (m, 4 H, CH_2), 2.43 (m, 1 H, CH), 3.53 (m, 1 H, CH_2), 3.70 (s, 1 H, NH), 3.88 (m, 2 H, CH_2), 4.21 (m, 1 H, CH_2), 7.32 (s, 4 H, H_2N^+=C−NH_2), 7.67 (dqu, 2 H, $J_1 = 7.9$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.82 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.9$ Hz, Ar−H), 8.03 (d, 1 H, $J = 8.2$ Hz, Ar−H), 8.08 (d, 1 H, $J = 8.6$ Hz, Ar−H), 8.15 (d, 1 H, $J = 7.8$ Hz, Ar−H), 8.45 (s, 1 H, Ar−H), 9.84 (s, 1 H, NH), ppm; MS (FAB+): m/z (%): 499 ((M−HCl)H^+, 93), 126 (100); IR (KBr): 3347, 3198, 1731, 1654, 1559, 1421, 1339, 1163, 1026, 858, 751, 671 cm^{-1}; mp: 119–125 °C; yield: 42%.

3.4.10.10. Amino(4-{[1-[(cycloheptylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9j**)

^{1}H NMR (DMSO-d_6): δ 0.86 (m, 4 H, CH_2), 1.12–1.45 (m, 10 H, CH_2), 1.80 (m, 2 H, CH_2), 2.02 (m, 1 H, CH), 2.86 (m, 2 H, CH_2), 2.98 (m, 1 H, CH), 3.67 (s, 1 H, NH), 4.01 (d, 2 H, $J = 10.3$ Hz, CH_2), 4.16 (m, 2 H, CH_2), 7.38 (s, 4 H, H_2N^+=C−NH_2), 7.65 (dqu, 2 H, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.77 (dd, 1 H, $J_1 = 8.5$ Hz, $J_2 = 1.8$ Hz, Ar−H), 8.02 (d, 1 H, $J = 7.4$ Hz, Ar−H), 8.09 (d, 1 H, $J = 8.4$ Hz, Ar−H), 8.14 (d, 1 H, $J = 7.3$ Hz, Ar−H), 8.44 (s, 1 H, Ar−H), 9.51 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 501 ((M−HCl)H^+, 100); IR (KBr): 3412, 3012, 1733, 1658, 1442, 1254, 1063, 805, 732, 631 cm^{-1}; mp: 104–109 °C; yield: 63%.

3.4.10.11. Amino(3-{[1-[(cyclopentylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9k**)

^{1}H NMR (DMSO-d_6): δ 1.19 (m, 4 H, CH_2), 1.53 (m, 2 H, CH_2), 1.64 (m, 4 H, CH_2), 1.83 (m, 1 H, CH), 2.13 (m, 2 H, CH_2), 2.22 (m, 2 H, CH_2), 2.35 (m, 1 H, CH), 3.14 (m, 1 H, CH_2), 3.39 (s, 1 H, CO−NH), 3.82 (m, 1 H, CH_2), 3.95 (d, 2 H, $J = 11.4$ Hz, CH_2), 7.42 (s, 4 H, H_2N^+=C−NH_2), 7.71 (dqu, 2 H, $J_1 = 7.6$ Hz, $J_2 = 1.7$ Hz, Ar−H), 7.80 (dd, 1 H, $J_1 = 8.5$ Hz, $J_2 = 1.7$ Hz, Ar−H), 8.02 (d, 1 H, $J = 7.5$ Hz, Ar−H), 8.11 (d, 1 H, $J = 8.6$ Hz, Ar−H), 8.15 (d, 1 H, $J = 7.6$ Hz, Ar−H), 8.43 (s, 1 H, Ar−H), 9.53 (s, 1H, NH) ppm; MS (FAB+): m/z (%): 473 ((M−HCl)H^+, 52), 126 (100); IR (KBr): 3433, 3129, 2967, 1707, 1546, 1264, 1067, 938, 856, 690 cm^{-1}; mp: 106–113 °C; yield: 68%.

3.4.10.12. Amino(4-{[1-[(cyclopentylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9l**)

^{1}H NMR (DMSO-d_6): δ 1.13 (m, 4 H, CH_2), 1.41 (m, 2 H, CH_2), 1.61 (m, 4 H, CH_2), 1.93 (m, 1 H, CH), 2.68 (m, 4 H, CH_2), 3.22 (m, 1 H, CH), 3.64 (s, 1 H, NH), 3.96 (d, 2 H, $J = 12.2$ Hz, CH_2), 4.23 (q, 2 H, $J = 7.4$ Hz, CH_2), 7.40 (s, 4 H, H_2N^+=C−NH_2), 7.74 (dqu, 2 H, $J_1 = 6.5$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.79 (d, 1 H, $J = 8.6$ Hz, Ar−H), 7.99 (d, 1 H, $J = 8.1$ Hz, Ar−H), 8.11 (d, 1 H, $J = 8.5$ Hz, Ar−H), 8.24 (d, 1 H, $J = 7.6$ Hz, Ar−H), 8.43 (s, 1 H, Ar−H), 9.54 (s, 1 H, NH), ppm; MS (FAB+): m/z (%): 473 ((M−HCl)H^+, 31), 126 (100); IR (KBr): 3424, 2943, 1715, 1542, 1441, 1151, 945, 764, 613 cm^{-1}; mp: 99–102 °C; yield: 73%.

3.4.10.13. Amino(3-{[1-{[cyclohexyl(methyl)amino]carbonyl}-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9m**)

^{1}H NMR (DMSO-d_6): δ 1.13–1.36 (m, 10 H, CH_2), 1.69 (m, 5 H, CH, CH_2), 1.98 (m, 2 H, CH_2), 2.74 (s, 3 H, CH_3), 3.22 (m, 1 H, CH), 3.62 (m, 1 H, CH_2), 3.91 (m, 2 H, CH_2), 4.13 (m, 1 H, CH_2), 7.29 (s, 4 H, H_2N^+=C−NH_2), 7.66 (dqu, 2 H, $J_1 = 7.5$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.80 (dd, 1 H, $J_1 = 8.5$ Hz, $J_2 = 1.8$ Hz, Ar−H), 8.02 (d, 1 H, $J = 8.8$ Hz, Ar−H), 8.06 (d, 1 H, $J = 8.7$ Hz, Ar−H), 8.12 (d, 1 H, $J = 7.5$ Hz, Ar−H), 8.43 (s, 1 H, Ar−H), 9.62 (s, 1 H, NH), ppm; MS (FAB+): m/z (%): 501 ((M−HCl)H^+, 68), 126 (100); IR (KBr): 3328, 3015, 2998, 1682, 1597, 1463, 1287, 1068, 952, 871, 645 cm^{-1}; mp: 93–97 °C; yield: 49%.

3.4.10.14. Amino(4-{[1-{[cyclohexyl(methyl)amino]carbonyl}-2-(2-naphthylsulfonyl)hydrazino]methyl}-1-piperidinyl)methaniminium chloride (**9n**)

^{1}H NMR (DMSO-d_6): δ 0.65 (m, 1 H, CH_2), 0.84–1.12 (m, 8 H, CH_2), 1.24–1.63 (m, 8 H, CH_2), 1.75 (m, 1 H, CH_2), 2.05 (m, 1 H, CH), 2.91 (m, 3 H, CH_3), 3.13 (m, 1 H, CH), 3.83 (d, 2 H, $J = 11.4$ Hz, CH_2), 7.42 (s, 4 H, H_2N^+=C−NH_2), 7.69 (dqu, 2 H, $J_1 = 7.3$ Hz, $J_2 = 1.8$ Hz, Ar−H), 7.75 (dd, 1 H, $J_1 = 8.6$ Hz, $J_2 = 1.5$ Hz, Ar−H), 8.02 (d, 1 H, $J = 7.6$ Hz, Ar−H), 8.08 (d, 1 H, $J = 8.7$ Hz, Ar−H), 8.15 (d, 1 H, $J = 7.5$ Hz, Ar−H), 8.42 (s, 1 H, Ar−H), 9.28 (s, 1 H, NH) ppm; MS (FAB+): m/z (%): 501 ((M-HCl)H^+, 24), 83 (100); IR (KBr): 3418, 2930, 1639, 1617, 1448, 1335, 1165, 964, 819, 642 cm^{-1}; mp: 92–96 °C; yield: 87%.

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