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Novel non-covalent azaphenylalanine thrombin inhibitors with an aminomethyl or amino group at the P1 position

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Design, synthesis and biological evaluation of a series of novel non-covalent azaphenylalanine thrombin inhibitors are presented. Replacement of the basic benzamidine moiety in azaphenylalanine derivatives by benzylamine (P1 part of a molecule) and the introduction of a *N*-cyclopentyl-*N*-methylamine moiety in the P2 part of a molecule resulted in the thrombin inhibitor LK-733 with greatly increased selectivity against trypsin and an *in vitro* K_i of 31 nM.

1. Introduction

The serine protease thrombin plays a central role in the blood coagulation cascade. It activates blood platelets via the thrombin receptor and also cleaves fibrinogen which polymerises into fibrin. Platelets and polymerized fibrin are the main components of blood clots, so the inhibition of thrombin should be beneficial in treating various cardiovascular diseases. Existing treatments for thrombotic disorders involving heparin, hirudin or oral warfarin have numerous adverse effects and limitations associated with patient compliance (Hirsh and Weitz 1999; Stone and Hoffsteenge 1986; Ammar et al. 1997). The synthesis of direct, noncovalent and orally bioavailable thrombin inhibitors is therefore an important goal for many pharmaceutical laboratories (Rewinkel and Adang 1999; Menear 1998). Thrombin is a serine protease related to thrombin and contains the characteristic catalytic triad. The active site also includes three binding pockets. The selectivity pocket is a narrow cleft with Asp-189 at the bottom with a characteristic specificity for basic residues. The other two binding sites are apolar and are separated from each other by the side chain of Leu-99. Fig. 1 is a schematic presentation of the active site with inhibitor LK-733.

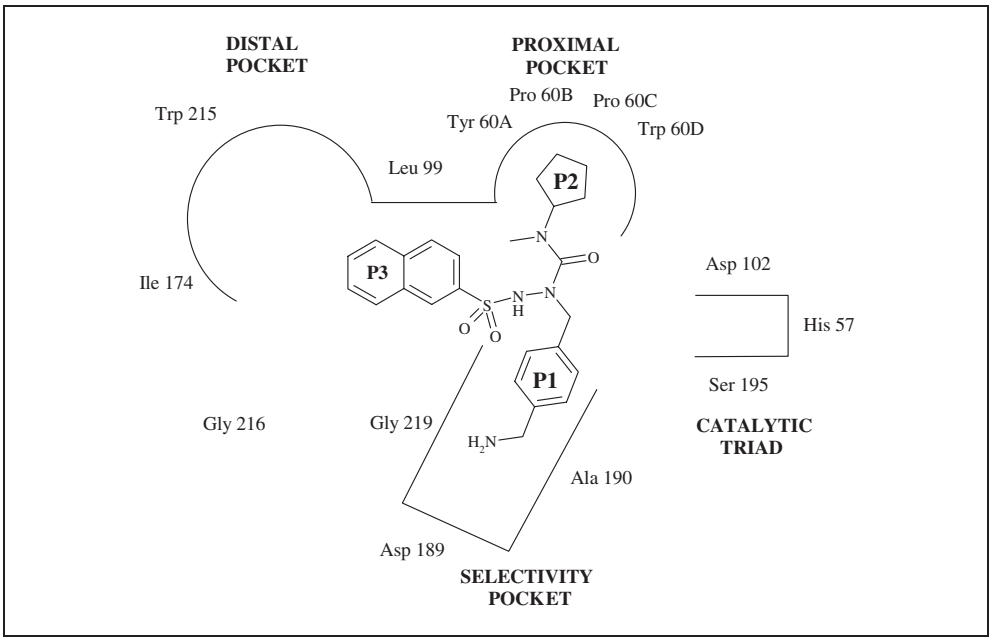
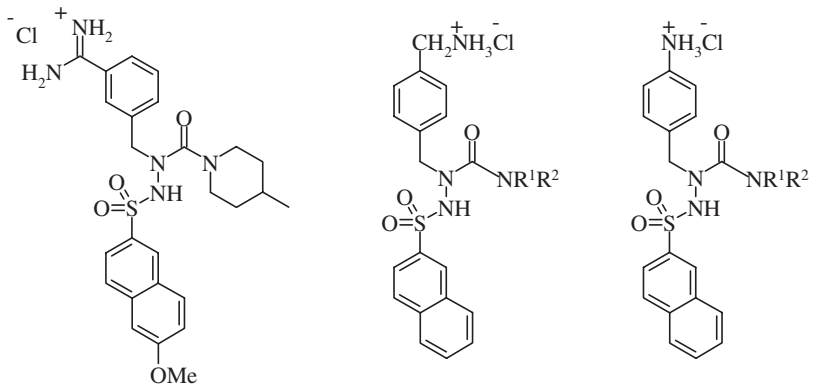


Figure 1:
Schematic presentation of the active site of thrombin with inhibitor LK-733. Different parts of inhibitor are marked with P1, P2 and P3.

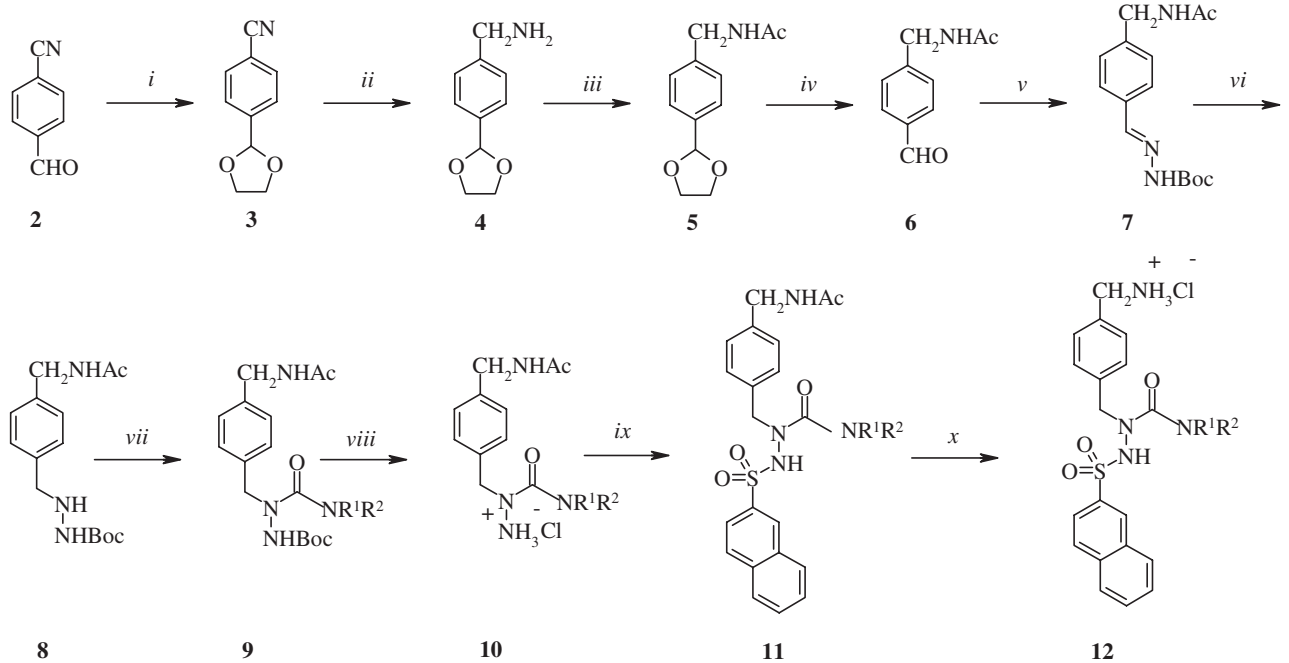


1 **12** **19**

The best studied noncovalent inhibitors of thrombin are derived from the sequence D-Phe-Pro-Arg, as in argatroban, NAPAP ([(2-naphthylsulfonyl)glycyl]-DL-*p*-amidinophenylalanylpiperidide) and melagatran (Kikumoto et al. 1980; Stürzebecher et al. 1983; Eriksson et al. 1997). Our group has prepared strongly binding thrombin inhibitors with an azaphenylalanine scaffold (The replacement of α-CH group with a nitrogen atom in the central part of a molecule), the most active being compound **1** with $K_i = 11$ nM (Zega et al. 2001a, 2001b). Although such benzamidine based inhibitors are potent, they usually tend to have poor oral bioavailability mainly due to the highly basic group which reduces membrane permeability. With this in mind we recently designed and synthesized the thrombin inhibitors **12** and **19,** in which the benzamidine group ($pK_a = 11-12$) is replaced with the less basic p-benzylamino ($pK_a = 9-10$) and aminophenyl ($pK_a = 4.5$) groups, resp. (**12, 19**).

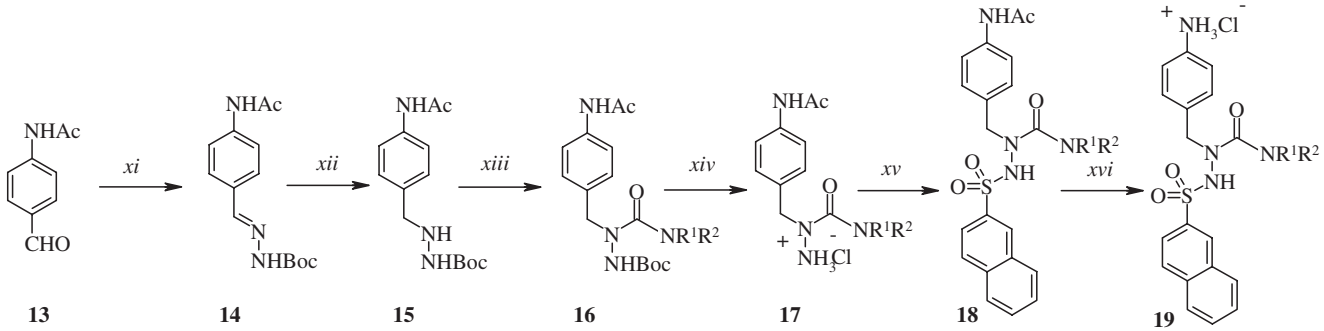
Loss of the basic amidino group, which is known to interact strongly with Asp-189 of thrombin, was expected to result in greatly diminished activity. We therefore aimed at counteracting this loss by incorporating substituents in that part of the inhibitor which binds in the P_2 pocket. Selectivity of compounds against other serine proteases can be achieved by the choice of appropriate substituents in the same part of the molecule, as demonstrated by the use of *N*-cyclopentyl-*N*-methylamine in compound LK 733. Here we describe the synthesis and *in vitro* evaluation of compounds incorporating these design principles.

Scheme 1



(i) ethylene glycol, p-TsOH, toluene, molecular sieves 4Å; (ii) $LiAlH_4$, THF; (iii) Ac_2O; (iv) 90%HCOOH; (v) NH_2NH-Boc, EtOH, reflux; (vi) H_2/Pd/C, MeOH; (vii) triphosgene, DIEA, HNR^1R^2, CH_2Cl_2; (viii) HCl, EtOAc; (ix) naphthalene-2-sulfonyl chloride, DIEA, CH_2Cl_2; (x) 4 M HCl, reflux.

Scheme 2



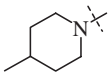
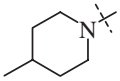
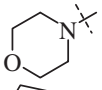
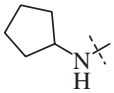
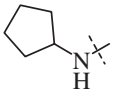
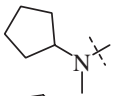
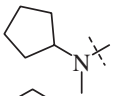
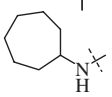
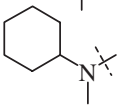
(xi) NH_2NH-Boc, EtOH, reflux; (xii) H_2/Pd/C, MeOH; (xiii) triphosgene, DIEA, HNR^1R^2, CH_2Cl_2; (xiv) HCl, EtOAc; (xv) naphthalene-2-sulfonyl chloride, DIEA, CH_2Cl_2; (xvi) 4 M HCl, reflux.

2. Investigations, results and discussion

2.1. Synthesis of the compounds

The synthesis of **12** is outlined in Scheme 1. The aldehyde moiety of 4-cyanobenzaldehyde was protected with 1,2-dihydroxyethane and *p*-toluenesulfonic acid as a catalyst to form the 1,3-dioxolane ring (**3**). The cyano group of **3** was reduced with lithium aluminium hydride and transformed into the acetaminomethyl derivative **5**. Subsequent acid hydrolysis of acetal **5** and condensation with *tert*-butyl carbazate, followed by catalytic hydrogenation, yielded the *tert*-butyl 2-{4-[(acetylamino)methyl]benzyl}-1-hydrazinecarboxylate **8**. This compound was coupled with a series of primary and secondary amines using commercially available triphosgene to give Boc protected carbazamides **9**. Deprotection of compounds **9a**–**h** with gaseous hydrogen chloride in anhydrous acetic acid and reaction with naphthalene-2-sulfonyl chloride led to compounds **11a**–**h**. Finally, the acetamide group was hydrolysed with 4 M HCl to yield the final products **12a**–**h**. The yields of some reaction steps, particularly the reactions with triphosgene and naphthalene-2-sulfonyl chloride, were relatively low. However, when using another reaction pathway, a side reaction was observed which led to the synthesis of benzaldehyde *N*-(phenylmethylidene)hydrazones (Obreza and Urleb 2002).

Table: *In vitro* activity of compounds 12a–h and 19a–f against thrombin, trypsin and factor Xa

Compd.	NR^1R^2	K_i (μM)			Compd.	NR^1R^2	K_i (μM)		
		Thrombin	Trypsin	Xa			Thrombin	Trypsin	Xa
12a		1.6	6.9	55.7	**19a**		4.5	8.6	49.9
12b		3.3	13.6	41.1	**19b**		10.7	10.8	16.7
12c		1.3	39.4	60.2	**19c**		6.4	8.1	32.3
12d		0.92	13.0	92.2	**19d**		3.3	27.1	46.6
12e		13.1	24.3	42.2	**19e**		14.6	35.6	62.0
12f		25.8	74.4	64.8	**19f**		49.2	84.7	>100
12g		0.031	10.8	0.45	**19g**		1.2	16.0	4.5
12h		21.3	29.0	37.6	**19h**		3.9	7.7	33.3

The synthesis of compounds with an aminophenyl group (Scheme 2) started from commercially available 4-acetamidobenzaldehyde, and used the same reaction steps as above, yielding compounds **19a–f**.

2.2. In vitro activity of synthesized compounds against serine proteases

The ability of the compounds to inhibit the enzymatic activity of thrombin, trypsin and factor Xa was measured by an amidolytic assay using chromogenic substrates S-2230 (for thrombin) and S-2222 (for trypsin and factor Xa). Results were expressed as inhibitory constants (K_i), calculated from the relationship between reaction velocity in the absence and presence of compound using the relevant Michaelis constant (K_m) (Brandt et al. 1987). The selectivity for thrombin over trypsin was expressed as the ratio $K_{i(trypsin)}/K_{i(thrombin)}$.

The inhibitory activity of compounds **12a–h** and **19a–f** against thrombin and the related serine proteases trypsin and factor Xa is shown in the Table. Since the introduction a of methoxy group into the naphthalene fragment in compound **1** did not markedly increase the activity of compounds of this type, we used commercially available naphthalene-2-sulfonyl chloride as a reagent for all derivatives.

Comparison of the anti-thrombin activity of compounds with aminomethyl group or aromatic amine at the P1 position on the skeleton with amidines and amidoximes shows that the activity of the newly synthesized compounds is greatly reduced due to lower basicity compared to amidines and corresponding lower interactions with Asp-198 at the bottom of the selectivity pocket in thrombin. The compounds of both series have Ki values in the micromolar range, the aminomethyl derivatives being slightly more active against thrombin because of their higher basicity and the presence of an additional methylene group which enables the amine to approach more closely to the carboxylic group of Asp 189 in the selectivity pocket of thrombin. The use of primary amines as synthons for a P2 binding part of a molecule and introduction of another heteroatom (morpholine) proved unfavourable.

Introducing *N*-cyclopentyl-*N*-methylamine as a building block of the aminomethyl derivative resulted in compound **12 g** (LK-733). The activity against thrombin is comparable to derivatives bearing the amidine group and about ten times higher than the corresponding amidoximes (Zega et al. 2001a). The same compound also exhibits higher activity against another serine protease, factor Xa, while the activity against trypsin remains the same as in other derivatives, leading to good selectivity (Ratio Ki(trypsin)/Ki(thrombin) is larger than 300).

Only slight modifications of the structure, such as removing a methyl group from the nitrogen atom in the cyclopentylamino moiety or enlarging the ring to cycloheptane, reduce the activity.

In conclusion, replacing the amidine or amidoxime groups in azaphenylalanine thrombin inhibitors by the less basic aminomethyl or aromatic amine groups leads to compounds with much lower activities. LK-733, however, exhibits high potency and selectivity for thrombin and constitutes a major step forward in the search for orally active compounds.

3. Experimental

All chemicals and solvents were supplied by Merck, Aldrich, Fluca, Acros and Carlo Erba. Chromogenic substrates S-2238 (for thrombin) and S-2222 (for trypsin and factor Xa) were purchased at Chromogenix and were used in the amidolytic assay for measuring the inhibition of enzymatic activities.

^{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. Mass spectra were measured on a VG–Analytical Autospec Q spectrometer. IR spectra were obtained on a Perkin Elmer 1600 FT–IR spectrometer. Elemental analyses were made on a Perkin Elmer 2400 CHN analyzer and the results were in an 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. Tert-butyl 2-({4-[(acetylamino)methyl]phenyl}methylidene)-1-hydrazine carboxylate (7)

7.50 g (42.4 mmol) *N*-[(4-formylphenyl)methyl]acetamide (**6**) and 8.40 g (63.6 mmol) *tert*-butylcarbazate were dissolved in 50 ml of anhydrous ethanol and refluxed for 5 h. Approximaly half the solvent was then removed in vacuo and the residue was diluted with water. The resulting white solid was filtered and dryed.

^{1}H NMR (DMSO-d_6): δ 1.47 (s, 9 H, $C(CH_3)_3$), 2.04 (s, 3 H, CO-CH_3), 4.26 (d, 2 H, J = 6.03 Hz, Ar-CH_2), 7.28 (d, 2 H, J = 8.17 Hz, Ar-H), 7.55 (d, 2 H, J = 8.20 Hz, Ar–H), 7.98 (s,1 H, CH), 8.36 (s, 1 H, NH–CO), 10.83 (s, 1 H, NH–COO) ppm; MS (FAB+): m/z (%): 292 (MH^+, 16), 236 (100); IR (KBr): ν 3318, 3196, 2977, 1717, 1656, 1556, 1364, 1277, 1179, 1058, 882, 805, 713, 592, 516 cm^{-1}; m.p.: 183–187 °C; Yield: 98%.

3.2. Tert-butyl 2-{4-[(acetylamino)methyl]benzyl}-1-hydrazine carboxylate (8)

13.1 g (45.0 mmol) of compound **7** were dissolved in 200 ml of methanol. After the addition of 1.8 g of 10% Pd/C, H_2 was bubbled in until there was no starting compound left. After the catalyst was removed, the solvent was evaporated under reduced pressure.

^{1}H NMR ($CDCl_3$): δ 1.48 (s, 9 H, $C(CH_3)_3$), 2.04 (s, 3 H, CH_3), 3.99 (s, 2 H, Ar–CH_2–NH–NH), 4.43 (d, 2 H, J = 5.65 Hz, Ar–CH_2–NH–CO), 5.82 (s, 1 H, NH–CO), 6.08 (s, 1 H, NH–NH–COO), 7.13 (d, 1 H, J = 3.02 Hz, NH–NH–COO), 7.26 (d, 2 H, J = 9.03 Hz, Ar–H), 7.33 (d, 2 H, J = 8.29 Hz, Ar–H) ppm; MS (FAB+): m/z (%): 294 (MH^+, 5), 162 (100); IR (KBr): ν 3336, 2973, 1686, 1648, 1512, 1366, 1288, 1152, 1023, 827 cm^{-1}; m.p.: 92–96 °C; Yield: 98%.

3.3. Synthesis of compounds 9a–h

Triphosgene (4.39 mmol) was dissolved in 20 ml of dichloromethane and the solution degassed with argon. 2.50 g (8.53 mmol) *tert*-butyl 2-{4-[(acetylamino)methyl]benzyl}-1-hydrazinecarboxylate (**8**) and 1.65 g (12.79 mmol) of diisopropylethylamine were dissolved in 30 ml of dichloromethane, and this solution was added dropwise to triphosgene solution at 0 °C. The mixture was stirred for 30 min at room temperature 2.00 ml of the corresponding primary or secondary amine was added and stirred for another hour at room temperature. The reaction mixture was then extracted with 4 × 25 ml of 10% citric acid solution, 30 ml of saturated sodium hydrogen carbonate solution, followed by washing with 30 ml of demineralised water and 20 ml of saturated brine. The organic phase was dried over sodium sulphate. The solvent was evaporated *in vacuo*, and the residue was dissolved in 10 ml of diethylether. A white precipitate was formed which was filtered off by suction and washed with diethylether.

3.3.1. Tert-butyl 2-{4-[(acetylamino)methyl]benzyl}-2-[(4-methyl-1-piperidinyl) carbonyl]-1-hydrazine carboxylate (9a)

^{1}H NMR ($CDCl_3$): δ 0.95 (d, 2 H, J = 6.35 Hz, CH_3), 1.10–1.25 (m, 2 H, CH_2), 1.44 (s, 9 H, $C(CH_3)_3$), 1.60–1.73 (m, 3 H, CH_2, CH), 2.03 (s, 3H, CH_3), 2.82 (t, 2 H, J = 11.75 Hz, pip-CH_2), 3.92 (d, 2 H, J = 13.19 Hz, CH_2), 4.42 (s + d, 4 H, J = 5.65 Hz, CH_2–Ar–CH_2), 5.89 (s, 1 H, NH–CO), 6.27 (s, 1 H, NH–COO), 7.27 (s, 4 H, Ar–H) ppm; MS (FAB+): m/z (%): 419 (MH^+, 9), 57 (100); IR (KBr): ν 3282, 2923, 2858, 1727, 1638, 1443, 1253, 1158, 1020, 978, 757, 611 cm^{-1}; m.p.: 124–126 °C; Yield: 59%.

3.3.2. Tert-butyl 2-{4-[(acetylamino)methyl]benzyl}-2-[(2-methyl-1-piperidinyl)carbonyl]-1-hydrazine carboxylate (9b)

^{1}H NMR ($CDCl_3$): δ 1.22 (dd, 2 H, J_1 = 2.26 Hz, J_2 = 9.42 Hz, pip-CH_2), 1.44 (s, 9 H, $C(CH_3)_3$), 1.52 (m, 2 H, CH_2), 1.60 (m, 2 H, CH_2), 1.66 (m, 3 H, CH_3), 2.02 (s, 3 H, CH_3), 3.02 (m, 1 H, CH_2), 3.69 (m, 1 H, CH_2), 4.25 (m, 1 H, CH), 4.41 (d, 4 H, J = 6.03 Hz, CH_2–Ar–CH_2NHAc), 6.01 (s, 1 H, NH–CO), 6.28 (s, 1 H, NH–COO), 7.25 (s, 4 H, Ar–H) ppm; MS (FAB+): m/z (%): 419 (MH^+, 23), 126 (100); IR (KBr): ν 3296, 2939, 1724, 1635, 1518, 1431, 1351, 1276 cm^{-1}; m.p.: 134–138 °C; Yield: 82%.

3.3.3. Tert-butyl 2-{4-[(acetylamino)methyl]benzyl}-2-(1-piperidinylcarbonyl)-1-hydrazine carboxylate (9c)

^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9 H, $C(CH_3)_3$), 1.60 (m, 6 H, CH_2), 2.03 (s, 3 H, CH_3), 3.36 (m, 4 H, CH_2), 4.42 (s + d, 4 H, J = 6,03 Hz, CH_2–Ar–CH_2), 5.89 (s, 1 H, NH–CO), 6.26 (s, 1 H, NH–COO), 7.26 (s, 4 H, Ar-H)

ppm; MS (FAB+): m/z (%): 405 (MH^+, 24), 305 (100); IR (KBr): ν 3318, 2939, 2855, 1724, 1636, 1519,1435, 1275, 1154, 1025, 875, 759, 596 cm^{-1}; m.p.: 140–143 °C; Yield: 46%.

3.3.4. Tert-butyl 2-{4-[(acetylamino)methyl]benzyl}-2-(1-azepanylcarbonyl)-1-hydrazine carboxylate (**9d**)

^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9 H, $C(CH_3)_3$), 1.58 (m, 4 H, CH_2), 1.75 (m, 4 H, CH_2), 2.04 (s, 3 H, CH_3), 3.44 (t, 4 H, J = 5.84 Hz, CH_2), 4.43 (s + d, 4 H, J = 6.03 Hz, CH_2–Ar–CH_2), 5.81 (s, 1 H, NH–CO), 6.13 (s, 1 H, NH–COO), 7.28 (m, 4 H, Ar–H) ppm; MS (FAB+): m/z (%): 419 (MH^+, 21), 319 (100); IR (KBr): ν 3274, 3217, 2934, 2857, 1725, 1631, 1434, 1283, 1160, 1023, 757, 608 cm^{-1}; m.p.: 155–160 °C; Yield: 60%.

3.3.5. Tert-butyl 2-{4-[(acetylamino)methyl]benzyl}-2-(4-morpholinylcarbonyl)-1- hydrazinecarboxylate (**9e**)

^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9 H, $C(CH_3)_3$), 2.03 (s, 3 H, CH_3), 3.44 (t, 4 H, J = 4.76 Hz, CH_2), 3.68 (t, 4 H, J = 4.71 Hz, CH_2), 4.43 (d, 2 H, J = 5.65 Hz, Ar-CH_2NHAc), 4.49 (s, 2 H, Ar–CH_2), 5.84 (s, 1 H, NH–CO), 6.27 (s, 1 H, NH–COO), 7.27 (s, 4 H, Ar–H) ppm; MS (FAB+): m/z (%): 407 (MH^+, 4), 307 (100); IR (KBr): ν 3308, 2980, 2857, 1728, 1641, 1430, 1289, 1114, 1025, 873, 746, 604 cm^{-1}; m.p.: 125–128 °C; Yield: 52%.

3.3.6. Tert-butyl 2-{4-[(acetylamino)methyl]benzyl}-2-[(cyclopentylamino)carbonyl]-1-hydrazine carboxylate (**9f**)

^{1}H NMR ($CDCl_3$): δ 1.46 (s, 9 H, $C(CH_3)_3$), 1.65 (m, 4 H, CH_2), 1.97 (m, 4 H, CH_2), 2.02 (s, 3 H, CH_3), 2.35 (s, 1 H, CH), 3.96 (m, 1 H, Ar–CH_2), 4.11 (m, 1 H, Ar–CH_2), 4.41 (m, 2 H, Ar-CH_2), 5.31 (s, 1 H, NH-CO), 6.05 (s, 1 H, CO–NH–CH), 6.12 (s, 1 H, N–NH–COO), 7.19–7.29 (m, 4 H, Ar–H) ppm; MS (FAB+): m/z (%): 405 (MH^+, 34), 305 (100); IR (KBr): ν 3347, 2964, 1722, 1652, 1538, 1368, 1252, 1160, 1021 cm^{-1}; m.p.: 127–129 °C; Yield: 85%.

3.3.7. Tert-butyl 2-{4-[(acetylamino)methyl]benzyl}-2-{[cyclopentyl(methyl)amino]carbonyl}-1-hydrazine carboxylate (**9g**)

^{1}H NMR ($CDCl_3$): δ 1.44 (s, 9 H, $C(CH_3)_3$), 1.46–1.85 (m, 8 H, CH_2), 2.03 (s, 3 H, CO–CH_3), 2.32 (m, 1 H, CH), 2.80 (s, 3 H, N–CH_3), 4.38 (m, 2 H, Ar–CH_2), 4.42 (d, 2 H, J = 5.64 Hz, Ar–CH_2), 5.93 (s, 1 H, NH–COO), 6.54 (s, 1 H, NH–CO), 7.28 (m, 4 H, Ar–H) ppm; MS (FAB+): m/z (%): 419 (MH^+, 26), 69 (100); IR (KBr): ν 3274, 2974, 1726, 1640, 1550, 1369, 1285, 1160, 1067, 794 cm^{-1}; m.p.: 124–127 °C; Yield: 46%.

3.3.8. Tert-butyl 2-{4-[(acetylamino)methyl]benzyl}-2-[(cycloheptylamino)carbonyl]-1-hydrazinecarboxylate (**9h**)

^{1}H NMR ($CDCl_3$): δ 1.48 (s, 9 H, $C(CH_3)_3$), 1.53 (m, 4 H, CH_2), 1.61 (m, 2 H, CH_2), 1.70 (s, 2 H, CH_2), 1.94 (m, 4 H, CH_2), 2.02 (s, 3 H, CH_3), 2.35 (s, 1 H, CH), 3.71 (m, 1 H, Ar–CH_2), 3.85 (m, 1 H, Ar–CH_2), 4.41 (d, 2 H, J = 5.65 Hz, Ar–CH_2), 5.53 (s, 1 H, NH–CO), 6.00 (s, 1 H, CO–NH–CH), 6.06 (s, 1 H, NH–COO), 7.23 (m, 4 H, Ar–H) ppm; MS (FAB+): m/z (%): 433 (MH^+, 14), 93 (100); IR (KBr): ν 3440, 2926, 1732, 1652, 1368, 1163, 1021, 766 cm^{-1}; m.p.: 131–133 °C; Yield: 94%.

3.4. Synthesis of compounds 10a–h

The corresponding compound **9** (4.46 mmol) was dissolved in ethyl acetate (20 ml) and gaseous HCl was bubbled in for 30 min. The resulting white or pale yellow solid was filtered, rinsed with diethylether and dried on air.

3.4.1. 2-{4-[(Acetylamino)methyl]benzyl}-2-[(4-methyl-1-piperidinyl)carbonyl] hydrazinium chloride (**10a**)

^{1}H NMR ($CDCl_3$): δ 0.97 (d, 3 H, J = 6.03 Hz, CH_3), 1.19 (m, 2 H, CH_2), 1.52–1.70 (m, 3 H, pip-CH_2, CH), 2.07 (s, 3 H, CH_3), 2.91 (t, 2 H, J = 12.43 Hz, CH_2), 3.96 (d, 2 H, J = 12.43 Hz, CH_2), 4.31 (d, 2 H, J = 4.15 Hz, Ar–CH_2NHAc), 4.61 (s, 2 H, Ar–CH_2), 7.26 (d, 2 H, J = 8.15 Hz, Ar–H), 7.32 (d, 2 H, J = 8.19 Hz, Ar–H), 7.99 (s, 1 H, NH–CO), 9.49 (s, 3 H, NH_3^+) ppm; MS (FAB+): m/z (%): 319 ((M–HCl)H^+, 100); IR (KBr): ν 3419, 3256, 2926, 2685, 1689, 1552, 1434, 1235, 972, 728 cm^{-1}; m.p.: 196–198 °C; Yield: 88%.

3.4.2. 2-{4-[(Acetylamino)methyl]benzyl}-2-[(2-methyl-1-piperidinyl)carbonyl] hydrazinium chloride (**10b**)

^{1}H NMR ($CDCl_3$): δ 1.25 (m, 2 H, CH_2), 1.74 (m, 4 H, CH_2), 1.82–1.92 (m, 3 H, CH_3), 2.09 (d, 3 H, CH_3), 2.82 (m, 1 H, CH_2), 3.10 (m, 1 H, CH_2), 3.80 (m, 1 H, CH), 4.32–4.47 (m, 3 H, Ar-CH_2), 4.61 (m, 1 H, Ar-CH_2), 7.13–7.40 (m, 4 H, Ar–H), 9.15 (s, 1 H, NH–CO) ppm; MS (70eV; EI): m/z (%): 318 ((M–HCl)$^+$, 4), 126 (100); IR (NaCl): ν 2940, 1772, 1646, 1541, 1425, 1266, 1036, 806 cm^{-1}; m.p.: 201–203 °C; Yield: 87%.

3.4.3. 2-{4-[(Acetylamino)methyl]benzyl}-2-(1-piperidinylcarbonyl)hydrazinium chloride (**10c**)

^{1}H NMR ($CDCl_3$): δ 1.60 (s, 6 H, CH_2), 2.06 (s, 3 H, CH_3), 3.41 (s, 4 H, CH_2), 4.28 (d, 2 H, J = 4.53 Hz, Ar–CH_2NHAc), 4.58 (s, 2 H, Ar–CH_2), 7.24 (d, 2 H, J = 8.21 Hz, Ar–H), 7.31 (d, 2 H, J = 8.29 Hz, Ar–H), 7.90 (s, 1 H, NH–CO), 8.86 (s, 3 H, NH_3^+) ppm; MS (FAB+): m/z (%): 305 ((M–HCl)H^+, 100); IR (KBr): ν 3254, 2942, 2046, 1691, 1552, 1434, 1251, 1144, 1018, 853 cm^{-1}; m.p.: 185–187 °C; Yield: 75%.

3.4.4. 2-{4-[(Acetylamino)methyl]benzyl}-2-(1-azepanylcarbonyl)hydrazinium chloride (**10d**)

^{1}H NMR ($CDCl_3$): δ 1.56 (m, 4 H, CH_2), 1.72 (m, 4 H, CH_2), 2.01 (s, 3 H, CH_3), 3.46 (m, 4 H, CH_2), 4.27 (s, 2 H, Ar–CH_2), 4.55 (s, 2 H, Ar–CH_2), 7.26 (m, 4 H, Ar–H), 8.29 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 319 ((M–HCl)H^+, 100); IR (KBr): ν 3400, 2933, 1686, 1560, 1422, 1230, 1204, 1021, 983, 610 cm^{-1}; m.p.: 212–214 °C; Yield: 83%.

3.4.5. 2-{4-[(Acetylamino)methyl]benzyl}-2-(4-morpholinylcarbonyl)hydrazinium chloride (**10e**)

^{1}H NMR ($CDCl_3$): δ 1.88 (s, 3 H, CO-CH_3), 3.46 (m, 4 H, CH_2), 3.61 (m, 4 H, CH_2), 4.25 (d, 2 H, J = 6.03 Hz, Ar-CH_2NHAc), 4.50 (s, 2 H, Ar-CH_2), 7.28 (s, 4 H, Ar–H), 8.43 (s, NH–CO), 9.84 (s, 3 H, NH_3^+) ppm; MS (FAB+): m/z (%): 307 ((M–HCl)H^+,100); IR (KBr): ν 3427, 1685, 1560, 1432, 1274, 1112, 1022, 892, 571 cm^{-1}; m.p.: 209–211 °C; Yield: 60%.

3.4.6. 2-{4-[(Acetylamino)methyl]benzyl}-2-[(cyclopentylamino)carbonyl]-hydrazinium chloride (**10f**)

^{1}H NMR ($CDCl_3$): δ 1.44 (m 4 H, CH_2), 1.74 (m, 4 H, CH_2), 1.87 (s, 3 H, CH_3), 2.27 (m, 1 H, CH), 4.23 (m, 2 H, Ar–CH_2), 4.78 (m, 2 H, Ar–CH_2), 7.25 (m, 4 H, Ar–H), 7.30 (s, 1 H, CO–NH–CH), 8.39 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 305 ((M–HCl)H^+, 86), 162 (100); IR (KBr): ν 3431, 1682, 1558, 1427, 1280, 1099, 1018, 885, 693, 571 cm^{-1}; m.p.: 170–174 °C; Yield: 66%.

3.4.7. 2-{4-[(Acetylamino)methyl]benzyl}-2-{[cyclopentyl(methyl)amino]-carbonyl}hydrazinium chloride (**10g**)

^{1}H NMR (DMSO-d_6): δ 1.51–1.89 (m, 8 H, CH_2), 2.02 (s, 3 H, CO–CH_3), 2.49 (m, 1 H, CH), 2.87 (s, 3 H, N–CH_3), 4.24 (m, 2 H, Ar–CH_2), 4.52 (s, 2 H, Ar–CH_2), 7.22 (m, Ar–H), 10.12 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 319 ((M–HCl)H^+, 100); IR (KBr): ν 3254, 2987, 1782, 1653, 1548, 1425, 1234, 1022, 798, 744, 602 cm^{-1}; m.p.: 165–169 °C; Yield: 77%.

3.4.8. 2-{4-[(Acetylamino)methyl]benzyl}-2-[(cycloheptylamino)carbonyl]-hydrazinium chloride (**10h**)

^{1}H NMR ($CDCl_3$): δ 1.55 (m, 2 H, CH_2), 1.60 (m, 2 H, CH_2), 1.69 (m, 2 H, CH_2), 1.78 (m, 2 H, CH_2), 1.92 (m, 4 H, CH_2), 2.03 (s, 3 H, CH_3), 2.35 (s, 1 H, CH), 4.40 (m, 2 H, Ar–CH_2), 4.76 (m, 2 H, Ar–CH_2), 7.28 (m, 4 H, Ar–H), 7.41 (m, 1 H, CO–NH–CH), 7.99 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 333 ((M–HCl)H^+, 46), 55 (100); IR (KBr): ν 3439, 2926, 1652, 1549, 1446, 022, 756 cm^{-1}; m.p.: 176–179 °C; Yield: 90%.

3.5. Synthesis of compounds 11a–h

The corresponding compound **10** (2.69 mmol) and 0.67 g (2.95 mmol) naphthalen-2-sulfonylchloride were dissolved in dichloromethane (25 ml). 1.04 g (8.06 mmol) of diisopropylethylamine was added and the solution was stirred at room temperature for 3 days. The mixture was extracted with 4 × 25 ml of 10% citric acid and 30 ml of saturated Sodium hydrogen carbonate solution. The organic phase was washed with 30 ml of demineralised water and 30 ml of saturated brine and dried over Sodium sulphate. Dichloromethane was evaporated *in vacuo* and a pale brown-yellow foamy solid was formed. Compounds **11a–h** were further purified by crystallization from ethanol and column chromatography (silicagel; dichloromethane:methanol 20 : 1).

3.5.1. N-(4-{[1-[(4-Methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)-hydrazino]methyl}benzyl)acetamide (**11a**)

^{1}H NMR ($CDCl_3$): δ 0.52 (d, 3 H, J = 6.03 Hz, CH_3), 1.28 (m, 2 H, CH_2), 1.64 (m, 3 H, CH_2, CH), 2.05 (s, 3 H, CH_3), 2.32–2.71 (m, 2 H, CH_2), 3.72 (m, 2 H, pip-CH_2), 4.32 (m, 2 H, Ar–CH_2), 4.41 (d, 2 H, J = 5.66 Hz, Ar–CH_2NHAc), 5.72 (s, 1 H, NH–CO), 7.16 (d, 2 H, J = 8.29 Hz, Ar–H), 7.22 (d, 2 H, J = 7.91 Hz, Ar–H), 7.46 (s, 1 H, NH–SO_2), 7.62 (m, 2 H, Ar–H), 7.81 (dd, 1 H, J_1 = 8.67 Hz, J_2 = 1.88 Hz, Ar–H), 7.94 (q, 3 H, J = 7.66 Hz, Ar–H), 8.45 (s, 1 H, Ar–H), ppm; MS (FAB+): m/z (%): 509 (MH^+, 26),126 (100); IR (KBr): ν 3285, 2925, 1656, 1546, 1430, 1338, 1165, 970, 750, 554 cm^{-1}; m.p.: 80–83 °C; Yield: 67%.

3.5.2. N-(4-{[1-[(2-Methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)-hydrazino]methyl}benzyl)acetamide (**11b**)

^{1}H NMR ($CDCl_3$): δ 0.85 (s 2 H, CH_2), 1.18–1.30 (m, 4 H, CH_2), 1.31–1.50 (m, 3 H, CH_3), 2.04 (s, 3 H, CH_3), 2.54 (m, 1 H, CH_2), 3.48 (m, 1 H, CH_2), 3.84 (m, 1 H, CH), 4.26 (m, 2 H, Ar–CH_2), 4.40 (d, 2 H, J = 5.65 Hz, Ar–CH_2), 5.75 (s, 1 H, NH–CO), 7.20 (m, 4 H, Ar–H), 7.41 (s, 1 H, NH–SO_2), 7.64 (m, 2 H, Ar–H), 7.80 (dd, 1 H, J_1 = 8.67 Hz, J_2 = 1.51 Hz, Ar–H), 7.93 (m, 3 H, Ar–H), 8.43 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 509 (MH^+, 100); IR (KBr): ν 3290, 2938, 1654, 1541, 1418, 1338, 1166, 1074, 818, 752, 550 cm^{-1}; m.p.: 79–83 °C; Yield: 71%.

3.5.3. N-(4-{[2-(2-Naphthylsulfonyl)-1-(1-piperidinylcarbonyl)hydrazino]-methyl}benzyl)acetamide (**11c**)

^{1}H NMR ($CDCl_3$): δ 1.12 (m, 2 H, CH_2), 1.62 (m, 4 H, CH_2), 2.05 (s, 3 H, CH_3), 3.07 (m, 2 H, CH_2), 3.17 (m, 2 H, CH_2), 4.30 (d, 2 H, J = 18.46 Hz, Ar–CH_2), 4.41 (d, 2 H, J = 6.03 Hz, Ar–CH_2), 5.73 (s, 1 H, NH–CO), 7.16 (d, 2 H, J = 8.21 Hz, Ar–H), 7.21 (d, 2 H, J = 8.20 Hz, Ar-H), 7.41 (s, 1 H, NH–SO_2), 7.65 (m, 2 H, Ar–H), 7.81 (dd, 1 H, J_1 = 8.67 Hz, J_2 = 1.88 Hz, Ar–H), 7.94 (m, 3 H, Ar–H), 8.45 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 495 (MH^+, 40), 112 (100); IR (KBr): ν 2938, 2855, 1659, 1548, 1429, 1340, 1166, 1025, 855, 751, 548 cm^{-1}; m.p.: 77–80 °C; Yield: 64%.

3.5.4. N-(4-{[1-(Azepanylcarbonyl])-2-(2-nafthylsulfo-nil)hidrazino]methyl}-benzyl)acetamide (**11d**)

^{1}H NMR ($CDCl_3$): δ 1.03 (m, 2 H, CH_2), 1.25 (m, 2 H, CH_2), 1.39 (m, 2 H, CH_2), 1.58 (m, 1 H, CH_2),1.76 (m, 1 H, CH_2), 2.03 (s, 3 H, CH_3), 3.10 (s, 2 H, CH_2), 3.24 (s, 2 H, CH_2), 4.30 (d, 2 H, J = 4.14 Hz, Ar–CH_2), 4.38 (d, 2 H, J = 5.65 Hz, Ar–CH_2), 5.84 (s, 1 H, NH–CO), 7.15 (d, 2 H, J = 8.29 Hz, Ar–H), 7.19 (d, 2 H, J = 8.29 Hz, Ar–H), 7.58 (s, 1 H, NH–SO_2), 7.63 (m, 2 H, Ar–H), 7.80 (dd, 1 H, J_1 = 8.85 Hz, J_2 = 1.70 Hz, Ar–H), 7.90 (t, 2 H, J = 8.42 Hz, Ar–H), 7.95 (d, 1 H, J = 7.68 Hz, Ar–H), 8.46 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 509 (MH^+, 23), 126 (100); IR (KBr): ν 3374, 2931, 1772, 1662, 1550, 1412, 1326, 1167, 1078, 820, 776, 678 cm^{-1}; m.p.: 84–87 °C; Yield: 65%.

3.5.5. N-(4-{[1-(4-Morpholinylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]-methyl}benzyl)acetamide (**11e**)

^{1}H NMR ($CDCl_3$): δ 2.05 (s, 3 H, CH_3), 3.14 (m, 4 H, CH_2), 3.33–3.40 (m, 2 H, CH_2), 3.58–3.81 (m, 2 H, CH_2), 4,30 (m, 2 H, Ar–CH_2), 4,41 (d, 2 H, J = 5.65 Hz, Ar–CH_2NHAc), 5.77 (s, 1 H, NH–CO), 7.19 (m, 4 H, Ar–H), 7.38 (s, NH–SO_2), 7.68 (m, 2 H, Ar–H), 7.81 (dd, 1 H, J_1 = 8.67 Hz, J_2 = 1.63 Hz, Ar–H), 7.95 (m, 3 H, Ar–H), 8.44 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 497 (MH^+, 46), 126 (100); IR (KBr): ν 3426, 2856, 1655, 1420, 1340, 1274, 1166, 1114, 1024, 752, 547 cm^{-1}; m.p.: 84–88 °C; Yield: 50%.

3.5.6. 1-{4-[(Acetylamino)methyl]benzyl}-N-cyclopentyl-2-(2-naphthylsulfo-nyl)-1-hydrazinecarboxamide (**11f**)

^{1}H NMR ($CDCl_3$): δ 1.60 (m, 4 H, CH_2), 1.73 (m, 4 H, CH_2), 2,02 (s, 3 H, CH_3), 2.35 (m, 1 H, CH), 4.39 (m, 2 H, Ar–CH_2), 4.70 (m, 2 H, Ar–CH_2), 6.13 (s, 1 H, NH–CO), 6.52 (s, 1 H, CO–NH–CH), 7.26 (m, 4 H, Ar–H), 7.48–7.59 (s, 1 H, NH–SO_2), 7.60–7.80 (m, 2 H, Ar–H), 7.81–8.01 (m, 4H, Ar–H), 8.34 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 495 (MH^+, 5), 54 (100); IR (KBr): ν 3416, 2963, 1654, 1516, 1348, 1163, 1031, 817, 675, 547 cm^{-1}; m.p.: 81–83 °C; Yield: 71%.

3.5.7. 1-{4-[(Acetylamino)methyl]benzyl}-N-cyclopentyl-N-methyl-2-(2-naphthylsulfonyl)-1-hydrazinecarboxamide (**11g**)

^{1}H NMR ($CDCl_3$): δ 1.27–1.73 (m, 8 H, CH_2), 2.06 (s, 3 H, CO–CH_3), 2.29 (m, 1 H, CH), 2.60 (s, 3 H, N–CH_3), 4.32 (m, 2 H, Ar–CH_2), 4.44 (d, 2 H, J = 6.13 Hz, Ar–CH_2), 7.15 (d, 2 H, J = 8.13 Hz, Ar–H), 7.21 (d, 2 H, J = 8.11 Hz, Ar–H), 7.42 (s, $NHSO_2$), 7.67 (m, 2 H, Ar–H), 7.79 (dd, 1 H, J_1 = 8.70 Hz, J_2 = 1.76 Hz, Ar–H), 7.90 (s, 1 H, NH–CO), 7.97 (m, 3 H, Ar–H), 8.43 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 509 (MH^+, 100); IR (KBr): ν 3448, 2962, 1772, 1651, 1558, 1395, 1262, 1166, 1025, 859, 803, 669, 549 cm^{-1}; m.p.: 91–93 °C; Yield: 60%.

3.5.8. 1-{4-[(Acetylamino)methyl]benzyl}-N-cycloheptyl-2-(2-naphthylsulfo-nyl)-1-hydrazinecarboxamide (**11h**)

^{1}H NMR ($CDCl_3$): δ 1.48–1.57 (m, 8 H, CH_2), 1.94 (m, 4 H, CH_2), 2.02 (s, 3 H, CO–CH_3), 2.32 (m, 1 H, CH), 3.40 (m, 2 H, Ar–CH_2), 4.65 (s, 2 H, Ar–CH_2), 6.12 (s, 1 H, NH–CO), 6.88 (s, 1 H, CO–NH–CH), 7.22 (m, 4 H, Ar–H), 7.51 (s, 1 H, NH–SO_2), 7.58–7.75 (m, 2 H, Ar–H), 7.78–8.06 (m, 4 H, Ar–H), 8.35 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 523 (MH^+, 71), 126 (100); IR (KBr): ν 3420, 2928, 2856, 1654, 1516, 1351, 1166, 1031, 816, 673, 546 cm^{-1}; m.p.: 83–85 °C; Yield: 76%.

3.6. Synthesis of compounds 12a–h

Compound **11** (1.33 mmol) were dissolved in 30 ml of preheated isopropyl alcohol (60 °C). 30 ml of 4M HCl were added, and the mixture was refluxed for 5 h. The solvent was evaporated *in vacuo*. The product was purified by column chromatography (silicagel; dichloromethane:methanol 9 : 1).

3.6.1. (4-{[1-[(4-Methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)-hydrazino]methyl}phenyl)methylaminium chloride (**12a**)

^{1}H NMR (DMSO-d_6): δ 0.44 (d, 3 H, J = 6.03 Hz, CH_3), 1.22 (d, 3 H, J = 10.54 Hz, CH_2, CH), 1.57 (m, 2 H, pip-CH_2), 2.27–2.74 (m, 2 H, CH_2), 3.53 (s, 2 H, CH_2), 3.97 (s, 2 H, Ar–CH_2), 4.32 (m, 2 H, Ar–CH_2), 7.22 (d, 2 H, J = 8.29 Hz, Ar–H), 7.42 (d, 2 H, J = 8,29 Hz, Ar–H), 7.69 (m, 2 H, Ar–H), 7.77 (dd, 1 H, J_1 = 8.67 Hz, J_2 = 1.88 Hz, Ar-H), 8.06 (t, 2 H, J = 8.36 Hz, Ar–H), 8.13 (d, 1 H, J = 7.44 Hz, Ar–H), 8.46 (s, 1 H, Ar–H), 8.70 (s, 1 H, NH–SO_2) ppm; MS (FAB+): m/z (%): 467 ((M–HCl)H^+, 78), 126 (100); IR (KBr): ν 2943, 1667, 1421, 1330, 1164, 1074, 907, 741, 554 cm^{-1}; m.p.: 126–130 °C; Yield: 29%.

3.6.2. (4-{[1-[(2-Methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)hydra-zino]methyl}phenyl)methylaminium chloride (**12b**)

^{1}H NMR (DMSO-d_6): δ 1.11 (m, 2 H, CH_2), 1.23 (d, 2 H, J = 6.40 Hz, CH_2), 1.44 (m, 2 H, CH_2), 1.58–1.92 (m, 3H, CH_3), 2.26 (m, 1 H, CH_2), 2.75 (m, 1 H, CH_2), 3.02 (s, 1 H, CH), 3.95 (s, 2H, Ar–CH_2), 4.18–4.39 (m, 2 H, Ar–CH_2), 7.21 (d, 2 H, J = 7.91 Hz, Ar–H), 7.43 (d, 2 H, J = 7.54 Hz, Ar–H), 7.61–7.79 (m, 2 H, Ar–H), 7.80–7.98 (m,1 H, Ar–H), 7.80–8.23 (m, 3 H, Ar–H), 8.45 (s, 1 H, Ar–H), 8.94 (s, 1 H, NH–SO_2) ppm; MS (FAB+): m/z (%): 467 ((M–HCl)H^+, 34), 126 (100); IR (KBr): ν 3444, 1647, 1559, 1456, 1163, 821, 553 cm^{-1}; m.p.: 121–123 °C; Yield: 33%.

3.6.3. (4-{[2-(2-Naphthylsulfonyl)-1-(1-piperidinylcarbonyl)hydrazino]-methyl}phenyl)methylaminum chloride (**12c**)

^{1}H NMR (DMSO-d_6): δ 1.04 (m, 2 H, CH_2), 1.68 (m, 4 H, CH_2), 2.95 (m, 4 H, CH_2), 3.94 (s, 2 H, Ar–CH_2), 4.06 (s, 2 H, Ar–CH_2), 7.19 (d, 2 H, J = 7.91 Hz, Ar–H), 7.42 (d, 2 H, J = 7.91 Hz, Ar–H), 7.68 (m, 2 H, Ar–H), 7.76 (dd, 1 H, J_1 = 8.69 Hz, J_2 = 1.67 Hz, Ar–H), 8.04 (t, 2 H, J = 8.92 Hz, Ar–H), 8.13 (d, 1 H, J = 7.69 Hz, Ar–H), 8.44 (s, 1 H, Ar–H), 8.71 (s, 1 H, NH–SO_2) ppm; MS (FAB+): m/z (%): 453 ((M–HCl)H^+, 11), 86 (100); IR (KBr): ν 3060, 2857, 1633, 1430, 1337, 1157, 1008, 855, 750, 655, 542 cm^{-1}; m.p.: 127–130 °C; Yield: 27%.

3.6.4. (4-{[1-(1-Azepanylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]methyl}phenyl)methylaminium chloride (**12d**)

^{1}H NMR (DMSO-d_6): δ 1.04 (m, 4 H, CH_2), 1.24 (m, 4 H, CH_2), 3.01 (m, 4 H, CH_2), 3.97 (s, 2 H, Ar–CH_2), 4.23 (m, 2 H, Ar–CH_2), 6.56 (s, 3 H, NH_3^+), 7.20 (d, 2 H, J = 8.29 Hz, Ar–H), 7.42 (d, 2 H, J = 8.29 Hz, Ar–H), 7.70 (m, 2 H, Ar–H), 7.77 (dd, 1 H, J_1 = 8.66 Hz, J_2 = 1.80 Hz, Ar–H), 8.07 (t, 2 H, J = 8.81 Hz, Ar–H), 8.16 (d, 1 H, J = 7.54 Hz, Ar–H), 8.46 (s, 1 H, Ar–H), 8.70 (s, 1 H, NH–SO_2) ppm; MS (FAB+): m/z (%): 467 ((M–HCl)H^+, 4), 100 (100); IR(KBr): ν 3381, 1625, 1467, 1219, 1161, 1103, 1043, 968, 834, 686, 548 cm^{-1}; m.p.: 120–123 °C; Yield: 33%.

3.6.5. (4-{[1-(4-Morpholinylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]-methyl}phenyl)methylaminium chloride (**12e**)

^{1}H NMR (DMSO-d_6): δ 2.96 (m, 2 H, CH_2), 3.11 (m, 6 H, CH_2), 3.97 (d, 2 H, J = 5.66 Hz, Ar–CH_2NHAc), 4.17–4.52 (m, 2 H, Ar–CH_2), 7.22 (d, 2 H, J = 7.53 Hz, Ar–H), 7.41 (d, 2 H, J = 7.92 Hz, Ar–H), 7.82–7.66 (m, 3 H, Ar–H, NH–SO_2), 7.99–7.84 (m, 1 H, Ar–H), 8.03–8.21 (m, 3 H, Ar–H), 8.47 (s, 1 H, Ar–H), ppm; MS (FAB+): m/z (%): 455 ((M–HCl)H^+, 17), 134 (100); IR (KBr): ν 3411, 1662, 1504, 1459, 1419, 1335, 1272, 1211, 1166, 1113, 1067, 1023, 830, 754, 688, 544 cm^{-1}; m.p.: 124–126 °C; Yield: 52%.

3.6.6. (4-{[1-[(Cyclopentylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}phenyl)methylaminium chloride (**12f**)

^{1}H NMR ($CDCl_3$): δ 1.33 (m, 4 H, CH_2), 1.55 (m, 2 H, CH_2), 1.88 (m, 2 H, CH_2), 2.21 (m, 1 H, CH), 4.01 (m, 2 H, Ar–CH_2), 4.18 (m, 2 H, Ar–CH_2), 7.27 (s, 1 H, CO–NH–CH), 7.35 (m, 2 H, Ar–H), 7.48 (m, 2 H, Ar–H), 7.53 (m, 1 H, NH–SO_2), 7.62–7.79 (m, 3 H, Ar–H), 7.84–8.01 (m, 3 H, Ar–H), 8.15 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 453 ((M–HCl)H^+, 43), 134 (100); IR (KBr): ν 3419, 2960, 1729, 1273, 1210, 1115, 10066, 913, 821, 691 cm^{-1}; m.p.: 127–131 °C; Yield: 18%.

3.6.7. (4-{[1-{[Cyclopentyl(methyl)amino]carbonyl}-2-(2-naphthylsulfonyl)-hydrazino]methyl}phenyl) methylaminium chloride (**12g**)

^{1}H NMR (DMSO-d_6): δ 1.18–1.75 (m, 8 H, CH_2), 2.34 (m, 1 H, CH), 2.57 (s, 3 H, N–CH_3), 4.22 (m, 2 H, Ar–CH_2), 4.43 (m, 2 H, Ar–CH_2), 7.18 (d,

2 H, J = 8.35 Hz, Ar–H), 7.24 (d, 2 H, J = 8.27 Hz, Ar–H), 7.37 (s, $NHSO_2$), 7.64 (m, 2 H, Ar–H), 7.82 (dd, 1 H, J_1 = 8.56 Hz, J_2 = 1.72 Hz, Ar–H), 8.04 (m, 3 H, Ar–H), 8.41 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 467 ($(M-HCl)H^+$,72), 134 (100); IR (KBr): ν 3425, 3137, 2968, 1744, 1591, 1275, 1122, 973, 815, 637 cm^{-1}; m.p.: 135–139 °C; Yield: 35%.

3.6.8. (4-{[1-[(Cycloheptylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}phenyl)methylaminium chloride (**12h**)

^{1}H NMR (DMSO-d_6): δ 1.27 (m, 2 H, CH_2), 1.34 (m, 4 H, CH_2), 1.48 (m, 2 H, CH_2), 1.63 (m, 2 H, CH_2), 1.85 (m, 2 H, CH_2), 2.30 (m, 1 H, CH), 3.98 (m, 2 H, Ar–CH_2), 4.13 (s, 2 H, Ar–CH_2), 7.13 (s, 1 H, CO–NH–CH), 7.30 (m, 2 H, Ar–H), 7,48 (m, 2 H, Ar–H), 7,54 (s, 1 H, NH–SO_2), 7.63–7.75 (m, 3 H, Ar–H), 7.84–8.00 (m, 3 H, Ar–H), 8.15 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%) 481 ($(M-HCl)H^+$, 18), 156 (100); IR (KBr): ν 3415, 2930, 1728, 1651, 1462, 1273, 1210, 1117, 1071, 812 cm^{-1}; m.p.: 128–132 °C; Yield: 17%.

3.7. Tert-butyl 2-{(E)-[4-(acetylamino)phenyl]methylidene}-1-hydrazinecarboxylate (**14**)

^{1}H NMR (DMSO-d_6): δ 1.46 (s, 9 H, $C(CH_3)_3$), 2.05 (s, 3 H, CH_3), 7.52 (d, 2 H, J = 8.70 Hz, Ar-H), 7.62 (d, 2 H, J = 8.64 Hz, Ar–H), 7.93 (s,1 H, CH), 10.05 (s, 1 H, NH–CO), 10.75 (s, 1 H, N- NH-COO) ppm; MS (FAB+): m/z (%): 278 (MH^+, 73), 134 (100); IR (KBr): ν 3333, 3288, 2982, 1703, 1662, 1524, 1365, 1250, 1162, 1055, 820 cm^{-1}; m.p.: 196–197 °C; Yield: 90%.

3.8. Tert-butyl 2-[4-(acetylamino)benzyl]-1-hydrazinecarboxylate (**15**)

^{1}H NMR ($CDCl_3$): δ 1.48 (s, 9 H, $C(CH_3)_3$), 2.03 (s, 3 H, CH_3), 3.96 (d, 2 H, J = 4.84 Hz, Ar-CH_2), 4.17 (s, 1 H, NH–NH–COO), 6.08 (s, 1 H, NH-NH-COO), 7.29 (d, 2 H, J = 8.63 Hz, Ar–H), 7.41 (s, 1 H, NH–CO), 7.33 (d, 2 H, J = 8.35 Hz, Ar–H) ppm; MS (70eV, EI): m/z (%): 279 (M^+, 14), 148 (100); IR (NaCl): ν 3316, 2983, 1687, 1612, 1512, 1368, 1291, 1149, 1046, 882, 818, 650 cm^{-1}; m.p.: 111–113 °C; Yield: 99%.

3.9. Synthesis of compounds **16**

3.9.1. Tert-butyl 2-[4-(acetylamino)benzyl]-2-[(4-methyl-1-piperidinyl)carbonyl]-1-hydrazine carboxylate (**16a**)

^{1}H NMR ($CDCl_3$): δ 0.95 (d, 2 H, J = 5.71 Hz, CH_3), 1.18 (m, 2 H, CH_2), 1.45 (s, 9 H, $C(CH_3)_3$), 1.64 (m, 2 H, CH_2), 1.74 (s, 1 H, CH), 2.17 (s, 3 H, CH_3), 2.82 (t, 2 H, J = 12.53 Hz, CH_2), 3.93 (d, 2 H, J = 13.19 Hz, CH_2), 4.43 (s, 2 H, J = 5.65 Hz, CH_2–Ar–CH_2), 6.32 (s, 1 H, NH-COO), 7.23 (d, 2 H, J = 8.30 Hz, Ar–H), 7.46 (d, 2 H, J = 8.32 Hz, Ar–H), 7.66 (s, 1 H, NH-CO) ppm; MS (FAB+): m/z (%): 405 (MH^+, 21), 148 (100); IR (KBr): ν 3243, 3125, 2956, 1733, 1672, 1633, 1544, 1456, 1372, 1256, 1162, 1022, 978, 824, 756, 606 cm^{-1}; m.p.: 152–154 °C; Yield: 89%.

3.9.2. Tert-butyl 2-[4-(acetylamino)benzyl]-2-[(2-methyl-1-piperidinyl)carbonyl]-1-hydrazine carboxylate (**16b**)

^{1}H NMR ($CDCl_3$): δ 1.22 (d, 2 H, J = 6.90 Hz, CH_2), 1.45 (s, 9 H, $C(CH_3)_3$), 1.62 (m, 2 H, CH_2), 1.68 (m, 2 H, CH_2), 1.71 (m, 3 H, CH_3), 2.18 (s, 3 H, CH_3), 3.03 (dt, 1 H, J_1 = 12.89 Hz, J_2 = 1.57 Hz, CH_2), 3.71 (d, 1 H, J = 13.30 Hz, CH_2), 4.27 (m, 1 H, pip-CH), 4.42 (s, 2 H, Ar–CH_2), 6.26 (s, 1 H, NH–COO), 7.24 (d, 2 H, J = 8.38 Hz, Ar–H), 7.46 (d, 2 H, J = 8.35 Hz, Ar–H), 7.51 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 405 (MH^+, 31), 148 (100); IR (KBr): ν 3309, 2937, 1726, 1670, 1637, 1541, 1410, 1323, 1274, 1158, 1067, 980, 769, 618 cm^{-1}; m.p.: 152–154 °C; Yield: 39%.

3.9.3. Tert-butyl 2-[4-(acetylamino)benzyl]-2-(1-piperidinylcarbonyl)-1-hydrazine carboxylate (**16c**)

^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9 H, $C(CH_3)_3$), 1.58 (m, 6 H, CH_2), 2.16 (s, 3 H, CO–CH_3), 3.37 (m, 4 H, CH_2), 4.43 (s, 2 H, Ar–CH_2), 6.35 (s, 1 H, NH–COO), 7.23 (d, 2 H, J = 8.34 Hz, Ar–H), 7.46 (d, 2 H, J = 8,34 Hz, Ar-H), 7.71 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 391 (MH^+, 12), 148 (100); IR (KBr): ν 3309, 2938, 1732, 1668, 1638, 1519, 1410, 1367, 1272, 1159, 1052, 836, 771, 661 cm^{-1}; m.p.: 153–155 °C; Yield: 78%.

3.9.4. Tert-butyl 2-[4-(acetylamino)benzyl]-2-(1-azepanylcarbonyl)-1-hydrazine carboxylate (**16d**)

^{1}H NMR ($CDCl_3$): δ 1.43 (s, 9 H, $C(CH_3)_3$), 1.57 (m, 4 H, CH_2), 1.73 (m, 4 H, CH_2), 2.13 (s, 3 H, CH_3), 3.32 (t, 4 H, J = 5.80 Hz, CH_2), 4.44 (s, 2 H, Ar–CH_2), 6.38 (s, 1 H, NH–COO), 7.22 (d, 2 H, J = 8.30 Hz, Ar–H), 7.45 (d, 2 H, J = 8.32 Hz, Ar–H), 8.10 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 405 (MH^+, 69), 148 (100); IR (KBr): ν 3249, 2931, 1718, 1668, 1622, 1546, 1438, 1322, 1166, 1014, 837, 771, 601 cm^{-1}; m.p.: 194–197 °C; Yield: 85%.

3.9.5. Tert-butyl 2-[4-(acetylamino)benzyl]-2-(4-morpholinylcarbonyl)-1-hydrazine carboxylate (**16e**)

^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9 H, $C(CH_3)_3$), 2.15 (s, 3 H, CO–CH_3), 3.43 (t, 4 H, J = 4.60 Hz, CH_2), 3.66 (t, 4 H, J = 4.62 Hz, CH_2), 4.46 (s, 2 H, Ar–CH_2), 6.45 (s, 1 H, NH–COO), 7.23 (d, 2 H, J = 8.30 Hz, Ar–H), 7.46 (d, 2 H, J = 8.29 Hz, Ar–H), 7.69 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 393 (MH^+, 19), 148 (100); IR (KBr): ν 3307, 2977, 2859, 1729, 1670, 1639, 1519, 1410, 1369, 1271, 1158, 1116, 1023, 848, 768, 623 cm^{-1}; m.p.: 152–157 °C; Yield: 66%.

3.9.6. Tert-butyl 2-[4-(acetylamino)benzyl]-2-[(cyclopentylamino)carbonyl]-1-hydrazine carboxylate (**16f**)

^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9 H, $C(CH_3)_3$), 1.62 (m, 4 H, CH_2), 1.98 (m, 4 H, CH_2), 2.18 (s, 3 H, CO–CH_3), 2.28 (s, 1 H, CH), 4.64 (s, 2 H, Ar–CH_2), 5.33 (d, 1 H, J = 8.43 Hz, CO–NH), 6.13 (s, 1 H, NH–COO), 7.20 (d, 2 H, J = 8.30 Hz, Ar–H, 7.45 (d, 2 H, J = 8.30 Hz, Ar–H), 7.61 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 391 (MH^+, 29), 148 (100); IR (KBr): ν 3439, 3312, 3201, 2959, 2870, 1733, 1668, 1516, 1411, 1367, 1274, 1156, 1049, 842, 766, 677, 602 cm^{-1}; m.p.: 151–154 °C; Yield: 65%.

3.9.7. Tert-butyl 2-[4-(acetylamino)benzyl]-2-{[cyclopentyl(methyl)amino]carbonyl}-1-hydrazinecarboxylate (**16g**)

^{1}H NMR ($CDCl_3$): δ 1.45 (s, 9 H, $C(CH_3)_3$), 1.46–1.92 (m, 8 H, CH_2), 2.18 (s, 3 H, CH_3), 2.35 (m, 1 H, CH), 2.82 (s, 3 H, N–CH_3), 4.39 (m, 2 H, Ar–CH_2), 6.28 (s, 1 H, NH–COO), 7.26 (d, 2 H, J = 8.35 Hz, Ar–H), 7.46 (d, 2 H, J = 8.29 Hz, Ar–H), 7.53 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 405 (MH^+, 18), 148 (100); IR (KBr): ν 3269, 2975, 1733, 1636, 1541, 1411, 1369, 1318, 1158, 1066, 791, 650 cm^{-1}; m.p.: 150–154 °C; Yield: 58%.

3.9.8. Tert-butyl 2-[4-(acetylamino)benzyl]-2-{[cyclohexyl(methyl)amino]carbonyl}-1-hydrazinecarboxylate (**16h**)

^{1}H NMR ($CDCl_3$): δ 1.36 (m, 2 H, CH_2), 1.45 (s, 9 H, $C(CH_3)_3$), 1.55–1.82 (m, 8 H, CH_2), 2.18 (s, 3 H, CH_3), 2.32 (s, 1 H, CH), 2.81 (s, 3 H, N–CH_3), 4.44 (s, 2 H, Ar–CH_2), 6.24 (s, 1 H, NH–COO), 7.27 (d, 2 H, J = 8.13 Hz, Ar–H), 7.46 (d, 2 H, J = 8.38 Hz, Ar–H), 7.52 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 419 (MH^+, 17), 148 (100); IR (KBr): ν 3259, 2934, 2858, 1732, 1671, 1606, 1541, 1407, 1319, 1255, 1160, 1067, 794, 651 cm^{-1}; m.p.: 151–153 °C; Yield: 85%.

3.10. Synthesis of compounds **17**

3.10.1. 2-[4-(Acetylamino)benzyl]-2-[(4-methyl-1-piperidinyl)carbonyl]hydrazinium chloride (**17a**)

^{1}H NMR (DMSO-d_6): δ 0.93 (d, 3 H, J = 6.25 Hz, CH_3), 1.17 (m, 2 H, pip-CH_2), 1.66 (m, 3 H, CH_2, CH), 2.05 (s, 3 H, CO–CH_3), 2.91 (t, 2 H, J = 12.61 Hz, CH_2), 3.95 (d, 2 H, J = 13.05 Hz, CH_2), 4.39 (s, 2 H, Ar–CH_2), 7.18 (d, 2 H, J = 8.48 Hz, Ar–H), 7.62 (d, 2 H, J = 8.45 Hz, Ar–H), 9.87 (s, 3 H, NH_3^+), 9.98 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 305 ($(M-HCl)H^+$, 100); IR (KBr): ν 3252, 2922, 1690, 1605, 1512, 1414, 1325, 1221, 1145, 995, 806, 734, 578 cm^{-1}; m.p.: 189–191 °C; Yield: 89%.

3.10.2. 2-[4-(Acetylamino)benzyl]-2-[(2-methyl-1-piperidinyl)carbonyl]hydrazinium chloride (**17b**)

^{1}H NMR (DMSO-d_6): δ 1.24 (d, 2 H, J = 6.76 Hz, CH_2), 1.59 (m, 2 H, CH_2), 1.68 (m, 2 H, CH_2), 1.86 (m, 3 H, CH_3), 2.05 (s, 3 H, CH_3), 3.09 (t, 1 H, J = 11.50 Hz, CH_2), 3.69 (d, 1 H, J = 13.19 Hz, CH_2), 4.26 (m, 1 H, CH), 4.42 (s, 2 H, Ar–CH_2), 6.62 (s, 3 H, NH_3^+), 7.25 (d, 2 H, J = 8.29 Hz, Ar–H), 7.62 (d, 2 H, J = 8.33 Hz, Ar–H), 10.23 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 305 ($(M-HCl)H^+$, 100); IR (KBr): ν 3248, 2935, 1701, 1584, 1420, 1317, 1218, 1006, 825, 598 cm^{-1}; m.p.: 191–194 °C; Yield: 72%.

3.10.3. 2-[4-(Acetylamino)benzyl]-2-(1-piperidinylcarbonyl)hydrazinium chloride (**17c**)

^{1}H NMR (DMSO-d_6): δ 1.58 (m, 6 H, CH_2), 2.05 (s, 3 H, CH_3), 3.39 (t, 4 H, J = 7.07 Hz, CH_2), 4.42 (s, 2 H, Ar–CH_2), 7.19 (d, 2 H, J = 8.48 Hz, Ar–H), 7.61 (d, 2 H, J = 8.43 Hz, Ar–H), 9.93 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 291 ($(M-HCl)H^+$, 94), 148 (100); IR (KBr): ν 3427, 2936, 1674, 1603, 1538, 1413, 1322, 1252, 1016, 851 cm^{-1}; m.p.: 183–185 °C; Yield: 91%.

3.10.4. 2-[4-(Acetylamino)benzyl]-2-(1-azepanylcarbonyl)hydrazinium chloride (**17d**)

^{1}H NMR (DMSO-d_6): δ 1.49 (m, 4 H, CH_2), 1.74 (m, 4 H, CH_2), 2.08 (s, 3 H, CH_3), 3.51 (m, 4 H, CH_2), 4.50 (s, 2 H, Ar–CH_2), 7.29 (d, 2 H,

J = 8.15 Hz, Ar–H), 7.55 (d, 2 H, J = 8.08 Hz, Ar–H), 9.85 (s, 3 H, NH_3^+) ppm; MS (FAB+): m/z (%): 305 ((M–HCl)H^+, 100); IR (KBr): ν 3428, 2933, 1688, 1604, 1513, 1413, 1323, 1206, 1020, 807, 651 cm^{-1}; m.p.: 189–191 °C; Yield: 88%.

3.10.5. 2-[4-(Acetylamino)benzyl]-2-(4-morpholinylcarbonyl)hydrazinium chloride (**17e**)

^{1}H NMR (DMSO-d_6): δ 2.07 (s, 3 H, CH_3), 3.45 (t, 4 H, J = 4.59 Hz, CH_2), 3.61 (t, 4 H, J = 4.58 Hz, CH_2), 4.45 (s, 2 H, Ar–CH_2), 7.20 (d, 2 H, J = 8.48 Hz, Ar–H), 7.60 (d, 2 H, J = 8.46 Hz, Ar–H), 9.73 (s, 3 H, NH_3^+), 9.86 (s, NH–CO) ppm; MS (FAB+): m/z (%): 293 ((M–HCl)H^+, 54), 148 (100); IR (KBr): ν 3436, 2928, 1688, 1603, 1537, 1413, 1321, 1270, 1113, 1020, 839, 653 cm^{-1}; m.p.: 190–192 °C; Yield: 80%.

3.10.6. 2-[4-(Acetylamino)benzyl]-2-[(cyclopentylamino)carbonyl]hydrazinium chloride (**17f**)

^{1}H NMR (DMSO-d_6): δ 1.43 (m 4 H, CH_2), 1.78 (m, 4 H, CH_2), 2.18 (s, 3 H, CH_3), 2.31 (m, 1 H, CH), 4.57 (m, 2 H, Ar–CH_2), 7.22 (d, 2 H, J = 8.36 Hz, Ar–H), 7.38 (s, 1 H, CO–NH), 7.47 (d, 2 H, J = 8.18 Hz, Ar-H), 9.57 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 291 ((M–HCl)H^+, 85), 148 (100); IR (KBr): ν 3324, 2955, 2869, 1626, 1536, 1414, 1371, 1319, 1266, 1019, 968, 834, 648 cm^{-1}; m.p.: 187–190 °C; Yield: 83%.

3.10.7. 2-[4-(Acetylamino)benzyl]-2-{[cyclopentyl(methyl)amino]carbonyl}-hydrazinium chloride (**17g**)

^{1}H NMR (DMSO-d_6): δ 1.54–1.91 (m, 8 H, CH_2), 2.05 (s, 3 H, CO-CH_3), 2.49 (m, 1 H, CH), 2.88 (s, 3 H, N–CH_3), 4.33 (m, 2 H, Ar–CH_2), 7.23 (d, 2 H, J = 8.49 Hz, Ar–H), 7.58 (d, 2 H, J = 8.48 Hz, Ar–H), 10.02 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 305 ((M–HCl)H^+, 100); IR (KBr): ν 3434, 2958, 1772, 1670, 1603, 1540, 1413, 1372, 1320, 1263, 1182, 1066, 1019, 913, 798, 652 cm^{-1}; m.p.: 188–190 °C; Yield: 83%.

3.10.8. 2-[4-(Acetylamino)benzyl]-2-{[cyclohexyl(methyl)amino]carbonyl}-hydrazinium chloride (**17h**)

^{1}H NMR (DMSO-d_6): δ 1.38 (m, 2 H, CH_2), 1.59–1.93 (m, 8 H, CH_2), 2.09 (s, 3 H, CH_3), 2.51 (s, 1 H, CH), 2.84 (s, 3 H, N–CH_3), 4.40 (s, 2 H, Ar–CH_2), 7.19 (d, 2 H, J = 8.21 Hz, Ar–H), 7.48 (d, 2 H, J = 8.36 Hz, Ar–H), 9.88 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 319 (MH^+, 48), 55 (100); IR (KBr): ν 3321, 2935, 1779, 1666, 1604, 1532, 1317, 1240, 1036, 984, 759 cm^{-1}; m.p.: 185–189 °C; Yield: 96%.

3.11. Synthesis of compounds 18

3.11.1. N-(4-{[1-[(4-Methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)-hydrazino]methyl}phenyl)acetamide (**18a**)

^{1}H NMR ($CDCl_3$): δ 0.53 (d, 3 H, J = 6.21 Hz, CH_3), 1.28 (m, 2 H, CH_2), 1.64 (m, 3 H, CH_2, CH), 2.16 (s, 3 H, CO–CH_3), 2.42–2.62 (m, 2 H, CH_2), 3.69 (m, 2 H, CH_2), 4.28 (m, 2 H, Ar–CH_2), 7.14 (d, 2 H, J = 8.33 Hz, Ar–H), 7.42 (s, 1 H, NH–SO_2), 7.44 (d, 2 H, J = 8.04 Hz, Ar–H), 7.51 (s, 1 H, NH–CO), 7.64 (m, 2 H, Ar-H), 7.81 (dd, 1 H, J_1 = 8.65 Hz, J_2 = 1.76 Hz, Ar–H), 7.94 (t, 2 H, J = 7.51 Hz, Ar–H), 7.99 (d, 1 H, J = 8.15 Hz, Ar–H), 8.44 (s, 1 H, Ar-H), ppm; MS (FAB+): m/z (%): 495 (MH^+, 24), 148 (100); IR (KBr): ν 3336, 3165, 2928, 1688, 1657, 1528, 1411, 1312, 1269, 1161, 1072, 970, 856, 751, 705, 550 cm^{-1}; m.p.: 194–196 °C; Yield: 40%.

3.11.2. N-(4-{[1-[(2-Methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}phenyl)acetamide (**18b**)

^{1}H NMR (DMSO-d_6): δ 1.26 (d, 2 H, J = 6.81 Hz, CH_2), 1.51–1.75 (m, 4 H, CH_2), 1.91 (m, 3 H, CH_3), 2.03 (s, 3 H, CH_3), 2.91 (t, 1 H, J = 10.86 Hz, CH_2), 3.65 (d, 1 H, J = 12.94 Hz, CH_2), 4.23 (m, 1 H, CH), 4.47 (s, 2 H, Ar–CH_2), 7.22 (d, 2 H, J = 8.61 Hz, Ar–H), 7.41 (s, 1 H, NH–SO_2), 7.52 (d, 2 H, J = 8.36 Hz, Ar–H), 7.58 (m, 2 H, Ar–H), 7.73 (dd, 1 H, J_1 = 8.45 Hz, J_2 = 1.55 Hz, Ar–H), 7.90–8.14 (m, 3 H, Ar–H), 8.43 (s, 1 H, Ar–H), 10.02 (s, 1 H, NH–CO) ppm; MS (FAB+): m/z (%): 495 ((M–HCl)H^+, 7), 106 (100); IR (KBr): ν 3418, 2962, 1670, 1603, 1540, 1515, 1412, 1317, 1165, 1030, 817, 747, 673, 545 cm^{-1}; m.p.: 191–193 °C; Yield: 16%.

3.11.3. N-(4-{[2-(2-Naphthylsulfonyl)-1-(1-piperidinylcarbonyl)hydrazino]-methyl}phenyl)acetamide (**18c**)

^{1}H NMR ($CDCl_3$): δ 1.12 (m, 2H, CH_2), 1.33 (m, 4H, CH_2), 2.16 (s, 3H, CH_3), 3.06 in 3.17 (2s, 4H, CH_2), 4.27 (d, 2H, J = 16.35 Hz, Ar–CH_2), 7.14 (d, 2H, J = 8.39 Hz, Ar–H), 7.33 (s, 1H, NH–SO_2), 7.43 (d, 2H, J = 8.33 Hz, Ar–H), 7.46 (s, 1H, NH–CO), 7.64 (m, 2H, Ar–H), 7.81 (dd, 1H, J_1 = 8.66 Hz, J_2 = 1.84 Hz, Ar–H), 7.92 (t, 2H, J = 7.59 Hz, Ar–H), 7.95 (d, 1H, J = 7.77 Hz, Ar–H), 8.43 (s, 1H, Ar–H) ppm; MS (FAB+): m/z (%): 481 (MH^+, 57), 148 (100); IR (KBr): ν 3361, 3223, 2854, 1695, 1661, 1599, 1529, 1410, 1340, 1252, 1171, 854, 751, 688 cm^{-1}; m.p.: 185–187 °C; Yield: 49%.

3.11.4. N-(4-{[1-(1-Azepanylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]-methyl}phenyl)acetamide (**18d**)

^{1}H NMR ($CDCl_3$): δ 1.05 (m, 2 H, azep-CH_2), 1.25 (m, 2 H, CH_2), 1.40 (m, 2 H, CH_2), 1.66 (m, 2 H, CH_2), 2.16 (s, 3 H, CH_3), 3.13 (s, 2 H, CH_2), 3.25 (s, 2 H, CH_2), 4.28 (d, 2 H, J = 4.38 Hz, Ar–CH_2), 7.12 (d, 2 H, J = 8.37 Hz, Ar–H), 7.40 (s, 1 H, NH–SO_2), 7.42 (d, 2 H, J = 8.41 Hz, Ar–H), 7.62 (m, 2 H, Ar–H), 7.65 (s, 1 H, NH–CO), 7.80 (dd, 1 H, J_1 = 8.68 Hz, J_2 = 1.85 Hz, Ar–H), 7.89 (t, 2 H, J = 7.22 Hz, Ar–H), 7.95 (d, 1 H, J = 7.74 Hz, Ar–H), 8.43 (d, 1 H, J = 1.43 Hz, Ar–H) ppm; MS (FAB+): m/z (%): 495 (MH^+, 44), 148 (100); IR (KBr): ν 3334, 3162, 2928, 2855, 1689, 1657, 1527, 1410, 1310, 1161, 1073, 856, 715, 548 cm^{-1}; m.p.: 180–182 °C; Yield: 59%.

3.11.5. N-(4-{[1-(4-Morpholinylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]-methyl}phenyl)acetamide (**18e**)

^{1}H NMR ($CDCl_3$): δ 2.18 (s, 3 H, CH_3), 3.06–3.37 (m, 8 H, CH_2), 4,30 (m, 2 H, Ar–CH_2), 7.14 (d, 2 H, J = 8.31 Hz, Ar–H), 7.25 (s, 1 H, NH–CO), 7.43 (s, NH–SO_2) , 7.44 (d, 2 H, J = 8.29 Hz, Ar–H), 7.67 (m, 2 H, Ar–H), 7.81 (dd, 1 H, J_1 = 8.69 Hz, J_2 = 1.68 Hz, Ar–H), 7.95 (m, 3 H, Ar–H), 8.43 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 483 (MH^+, 43), 148 (100); IR (KBr): ν 3322, 3220, 2868, 1684, 1640, 1539, 1428, 1341, 1260, 1170, 1114, 1024, 751, 682 cm^{-1}; m.p.: 199–201 °C; Yield: 26%.

3.11.6. 1-[4-(Acetylamino)benzyl]-N-cyclopentyl-2-(2-naphthylsulfonyl)-1-hydrazinecarboxamide (**18f**)

^{1}H NMR ($CDCl_3$): δ 1.27–1.76 (m, 8 H, CH_2), 2.14 (s, 3 H, CH_3), 2.21 (m, 1 H, CH), 4.28 (s, 2 H, Ar–CH_2), 4.57 (d, 1 H, J = 8.43 Hz, CO–NH), 7.08 (d, 2 H, J = 8.34 Hz, Ar–H), 7.39 (s, 1 H, NH–CO), 7.42 (d, 2 H, J = 8.17 Hz, Ar-H), 7.63 (s, NH–SO_2), 7.77 (m, 2 H, Ar–H), 7.85 (dd, 1 H, J_1 = 8.75 Hz, J_2 = 1.75 Hz, Ar–H), 7.91 (m, 3 H, Ar–H), 8.41 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 481 (MH^+, 53), 148 (100); IR (KBr): ν 3438, 2960, 1651, 1517, 1362, 1260, 1164, 1026, 866, 815, 752, 668, 546 cm^{-1}; m.p.: 184–186 °C; Yield: 60%.

3.11.7. 1-[4-(Acetylamino)benzyl]-N-cyclopentyl-N-methyl-2-(2-naphthylsulfonyl)-1-hydrazinecarboxamide (**18g**)

^{1}H NMR ($CDCl_3$): δ 1.23–1.71 (m, 8 H, CH_2), 2.15 (s, 3 H, CH_3), 2.35 (m, 1 H, CH), 2.59 (s, 3 H, N–CH_3), 4.30 (m, 2 H, Ar-CH_2), 7.12 (d, 2 H, J = 8.36 Hz, Ar–H), 7.42 (d, 2 H, J = 8.26 Hz, Ar–H), 7.45 (s, $NHSO_2$), 7.51 (s, 1 H, NH–CO), 7.64 (m, 2 H, Ar–H), 7.79 (dd, 1 H, J_1 = 8.63 Hz, J_2 = 1.79 Hz, Ar–H), 7.94 (m, 3 H, Ar–H), 8.42 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 495 (MH^+, 21), 148 (100); IR (KBr): ν 3354, 3197, 2958, 1764, 1653, 1602, 1534, 1411, 1315, 1255, 1170, 1075, 857, 821, 699, 546 cm^{-1}; m.p.: 188–191 °C; Yield: 26%.

3.11.8. 1-[4-(Acetylamino)benzyl]-N-cyclohexyl-N-methyl-2-(2-naphthylsulfonyl)-1-hydrazinecarboxamide (**18h**)

^{1}H NMR ($CDCl_3$): δ 1.10 (m, 2 H, CH_2), 1.55 (m, 8 H, CH_2), 2.17 (s, 3 H, CH_3), 2.25 (s, 1 H, CH), 2.62 (s, 3 H, N–CH_3), 4.28 (m, 2 H, Ar–CH_2), 7.14 (d, 2 H, J = 8.36 Hz, Ar–H), 7.33 (s, $NHSO_2$), 7.42 (d, 2 H, J = 8.29 Hz, Ar–H), 7.49 (s, 1 H, NH–CO), 7.63 (m, 2 H, Ar–H), 7.79 (dd, 1 H, J_1 = 8.69 Hz, J_2 = 1.81 Hz, Ar–H), 7.89 (t, 2 H, J = 7.42 Hz, Ar–H), 7.95 (d, 1 H, J = 7.54 Hz, Ar–H), 8.42 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 509 (MH^+, 25), 148 (100); IR (KBr): ν 3351, 2931, 1763, 1650, 1602, 1536, 1411, 1316, 1170, 824, 691 cm^{-1}; m.p.: 187–189 °C; Yield: 25%.

3.12. Synthesis of compounds 19

3.12.1. 4-{[1-[(4-Methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}benzenaminium chloride (**19a**)

^{1}H NMR (DMSO-d_6): δ 0.65 (d, 3 H, J = 6.03 Hz, CH_3), 1.31 (d, 3 H, J = 11.30 Hz, CH_2, CH), 1.63 (m, 2 H, CH_2), 2.71 (m, 2 H, CH_2), 3.63 (m, 2 H, CH_2), 4.28 (s, 2 H, Ar–CH_2), 7.29 (d, 2 H, J = 8.24 Hz, Ar–H), 7.51 (d, 2 H, J = 8,34 Hz, Ar–H), 7.67 (m, 2 H, Ar–H), 7.81 (d, 1 H, J = 8.69 Hz, Ar–H), 8.03 (t, 2 H, J = 8.07 Hz, Ar–H), 8.13 (d, 1 H, J = 7.29 Hz, Ar–H), 8.42 (s, 1 H, Ar–H), 8.86 (s, 1 H, NH–SO_2) ppm; MS (FAB+): m/z (%): 453 ((M–HCl)H^+, 27), 100 (100); IR (KBr): ν 3429, 2924, 2580, 1648, 1597, 1504, 1432, 1333, 1165, 1073, 823, 753, 664 cm^{-1}; m.p.: 126–128 °C; Yield: 84%.

3.12.2. 4-{[1-[(2-Methyl-1-piperidinyl)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}benzenaminium chloride (**19b**)

^{1}H NMR (DMSO-d_6): δ 1.27 (d, 2 H, J = 6.74 Hz, CH_2), 1.50–1.72 (m, 4 H, CH_2), 1.93 (m, 3 H, CH_3), 2.94 (m, 1 H, CH_2), 3.67 (d, 1 H, J = 13.12 Hz, CH_2), 4.25 (m, 1 H, CH), 4.56 (s, 2 H, Ar–CH_2), 7.27 (d, 2 H, J = 8.41 Hz, Ar–H), 7.45 (s, 1 H, NH-SO_2), 7.56 (d, 2 H, J = 8.24 Hz, Ar–H), 7.63 (m, 2 H, Ar–H), 7.80–8.16 (m, 4 H, Ar–H), 8.45 (s, 1 H,

Ar–H) ppm; MS (FAB+): m/z (%): 453 ((M–HCl)H^+,46), 100 (100); IR (KBr): ν 3451, 3126, 1653, 1384, 1166, 1132, 1031, 818, 750, 677 cm^{-1}; m.p.: 132–134 °C; Yield: 35%.

3.12.3. 4-{[2-(2-Naphthylsulfonyl)-1-(1-piperidinylcarbonyl)hydrazino]methyl}benzenaminium chloride (**19c**)

^{1}H NMR (DMSO-d_6): δ 1.05 (m, 2 H, CH_2), 1.36 (m, 2 H, CH_2), 1.66 (m, 2 H, CH_2), 2.98 (t, 2 H, J = 5.21 Hz, CH_2), 3.06 (t, 2 H, J = 5.02 Hz, CH_2), 4.22 (s, 2 H, Ar-CH_2), 7.31 (d, 2 H, J = 8.34 Hz, Ar–H), 7.46 (d, 2 H, J = 8.29 Hz, Ar-H), 7.67 (m, 2 H, Ar–H), 7.80 (d, 1 H, J = 8.57 Hz, Ar–H), 8.05 (t, 2 H, J = 8.79 Hz, Ar–H), 8.14 (d, 1 H, J = 7.70 Hz, Ar–H), 8.45 (s, 1 H, Ar–H), 8.84 (s, 1 H, NH–SO_2), 9.03 (s, 3 H, NH_3^+) ppm; MS (FAB+): m/z (%): 439 ((M–HCl)H^+, 16), 106 (100); IR (KBr): ν 3408, 2857, 2578, 1643, 1511, 1428, 1332, 1271, 1163, 1020, 822, 753, 664 cm^{-1}; m.p.: 125–129 °C; Yield: 78%.

3.12.4. 4-{[1-(1-Azepanylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]-me-thyl}benzenaminium chloride (**19d**)

^{1}H NMR (DMSO-d_6): δ 1.08 (m, 4 H, CH_2), 1.29 (m, 4 H, CH_2), 3.09 (t, 4 H, J = 5.87 CH_2), 4.24 (m, 2 H, Ar–CH_2), 7.30 (d, 2 H, J = 8.32 Hz, Ar–H), 7.46 (d, 2 H, J = 8.14 Hz, Ar–H), 7.66 (m, 2 H, Ar–H), 7.81 (dd, 1 H, J_1 = 8.70 Hz, J_2 = 1.80 Hz, Ar–H), 8.03 (t, 2 H, J = 7.53 Hz, Ar–H), 8.12 (d, 1 H, J = 7.82 Hz, Ar–H), 8.40 (s, 1 H, Ar–H), 8.70 (s, 1 H, NH–SO_2) ppm; MS (FAB+): m/z (%): 453 ((M–HCl)H^+, 42), 106 (100); IR(KBr): ν 3446, 2928, 1653, 1508, 1419, 1337, 1162, 1074 cm^{-1}; m.p.: 128–130 °C; Yield: 82%.

3.12.5. 4-{[1-(4-Morpholinylcarbonyl)-2-(2-naphthylsulfonyl)hydrazino]-methyl}benzenaminium chloride (**19e**)

^{1}H NMR (DMSO-d_6): δ 3.11 (m, 4 H, $-CH_2$), 3.44 (m, 4 H, CH_2), 4.35 (m, 2 H, Ar–CH_2), 7.29 (d, 2 H, J = 8.26 Hz, Ar-H), 7.45 (d, 2 H, J = 8.29 Hz, Ar–H), 7.65 (m, 2 H, Ar–H), 7.81 (d, 1 H, J = 8.71 Hz, Ar–H), 8.05 (t, 2 H, J = 8.24 Hz, Ar–H), 8.15 (d, 1 H, J = 8.06 Hz, Ar–H), 8.43 (s, 1 H, Ar–H), 8.97 (s, 1 H, $NHSO_2$), 9.23 (s, 3 H, NH_3^+) ppm; MS (FAB+): m/z (%): 441 ((M–HCl)H^+, 8), 106 (100); IR (KBr): ν 3448, 2854, 1653, 1507, 1419, 1336, 1270, 1164, 1114, 1021 cm^{-1}; m.p.: 134–137 °C; Yield: 39%.

3.12.6. 4-{[1-[(Cyclopentylamino)carbonyl]-2-(2-naphthylsulfonyl)hydrazino]methyl}benzenaminium chloride (**19f**)

^{1}H NMR ($CDCl_3$): δ 1.31 (m 4 H, CH_2), 1.49 (m, 4 H, CH_2), 2.31 (s, 1 H, CH), 4,56 (s, 2 H, Ar–CH_2), 5.64 (d, 1 H, J = 8.43 Hz, CO–NH), 7.09 (d, 2 H, J = 8.12 Hz, Ar–H), 7.45 (s, NH–SO_2), 7.49 (d, 2 H, J = 8.25 Hz, Ar–H), 7.76 (m, 2 H, Ar–H), 7.84 (m, 1 H, Ar–H), 8.07 (m, 3 H, Ar–H), 8.49 (s, 1 H, Ar–H) ppm; MS (FAB+): m/z (%): 439 ((M–HCl)H^+, 36), 106 (100); IR (KBr): ν 3439, 2978, 1652, 1520, 1381, 1165, 1091, 1030, 864, 817, 751, 676, 543 cm^{-1}; m.p.: 129–132 °C; Yield: 35%.

3.12.7. 4-{[1-{[Cyclopentyl(methyl)amino]carbonyl}-2-(2-naphthylsulfonyl)hydrazino]methyl}benzenaminium chloride (**19g**)

^{1}H NMR ($CDCl_3$): δ 1.25–1.69 (m, 8 H, CH_2), 2.33 (m, 1 H, CH), 2.63 (s, 3 H, CH_3), 4.31 (m, 2 H, Ar–CH_2), 7.16 (d, 2 H, J = 8.26 Hz, Ar–H), 7.42 (d, 2 H, J = 8.31 Hz, Ar–H), 7.49 (s, $NHSO_2$), 7.65 (m, 2 H, Ar–H), 7.76 (dd, 1 H, J_1 = 8.75 Hz, J_2 = 1.81 Hz, Ar–H), 7.99 (m, 3 H, Ar–H), 8.41 (s, 1 H, Ar–H), 9.35 (s, 3 H, NH_3^+) ppm; MS (FAB+): m/z (%): 453 ((M–HCl)H^+, 15), 106 (100); IR (KBr): ν 3387, 2964, 1654, 1612, 1518, 1466, 1213, 1115, 869, 749 cm^{-1}; m.p.: 125–127 °C; Yield: 36%.

3.12.8. 4-{[1-{[Cyclohexyl(methyl)amino]carbonyl}-2-(2-naphthylsulfonyl)hydrazino]methyl}benzenaminium chloride (**19h**)

^{1}H NMR (DMSO-d_6): δ 1.12 (m, 2 H, CH_2), 1.43 (m, 4 H, CH_2), 1.57 (m, 4 H, CH_2), 2.32 (s, 1 H, CH), 2.68 (s, 3 H, N-CH_3), 4.34 (m, 2 H, Ar–CH_2), 7.29 (d, 2 H, J = 8.36 Hz, Ar–H), 7.42 (d, 2 H, J = 8.29 Hz, Ar–H), 7.54 (m, 2 H, Ar–H), 7.77 (d, 1 H, J = 8.58 Hz, Ar-H), 7.95 (t, 2 H, J = 7.63 Hz, Ar–H), 8.03 (d, 1 H, J = 7.59 Hz, Ar–H), 8.40 (s, 1 H, Ar–H), 8.93 (s, $NHSO_2$), 9.97 (s, 3 H, NH_3^+) ppm; MS (FAB+): m/z (%): 467 (MH^+, 18), 106 (100); IR (KBr): ν 3418, 2927, 1636, 1512, 1327, 1163, 1024, 956, 812, 635 cm^{-1}; m.p.: 122–124 °C; Yield: 34%.

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