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Reactions of 5-oxo-1-phenylpyrrolidine-3-carbohydrazides with 1,4-naphthoquinone derivatives and the properties of the obtained products

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Abstract *N*′-(4-Oxo-1,4-dihydronaphthalen-1-ylidene)-1-phenyl-5-oxopyrrolidine-3-carbohydrazides and *N*′-(3-methyl-4-oxo-1,4-dihydronaphthalen-1-ylidene)-1-phenyl-5-oxopyrrolidine-3-carbohydrazides were synthesized by reactions of 5-oxo-1-phenylpyrrolidine-3-carbohydrazides with 1,4-naphthoquinone or 2-methyl-1,4-naphthoquinone. The alkylated analogues of the above products were obtained using ethyl iodide. The interaction of 5-oxo-1-phenylpyrrolidine-3-carbohydrazides with 2,3-dichloro-1,4-naphthoquinone was followed by formation of *N*′-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-phenyl-5-oxopyrrolidine-3-carbohydrazides. All these compounds were characterized using ^{1}H, ^{13}C NMR, IR and mass spectra. Some of the new compounds were tested for the antimicrobial and antifungal activity.

Keywords 5-Oxo-1-phenylpyrrolidine-3-carbohydrazides · 1,4-Naphthoquinones · 2,3-Dichloro-1,4-naphthoquinone · Hydrazone · NMR spectroscopy · Biological activity

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Introduction

Many quinones greatly differing in structure are provided by nature. Large numbers of substituted quinones have been synthesized recently, and their properties extensively studied. Special attention has been paid to preparing synthetic compounds which include aminoquinone moiety in their structure. Naphthoquinones and their various derivatives as a class display many types of biological activity. They are active against different strains of bacteria and fungi [1–10], show insecticidal [11, 12], molluscicidal [13], and antiproliferative [4, 14] properties, and are anticancer agents [15–20]. Furthermore, hydrazones have been demonstrated to possess many types of biological activity [21].

The present study was directed toward synthesizing novel compounds from 5-oxo-1-phenylpyrrolidine-3-carbohydrazides and 1,4-naphthoquinones and evaluating the biological properties of some of them by testing on several strains of bacteria and fungi, using diffusion and serial dilution techniques.

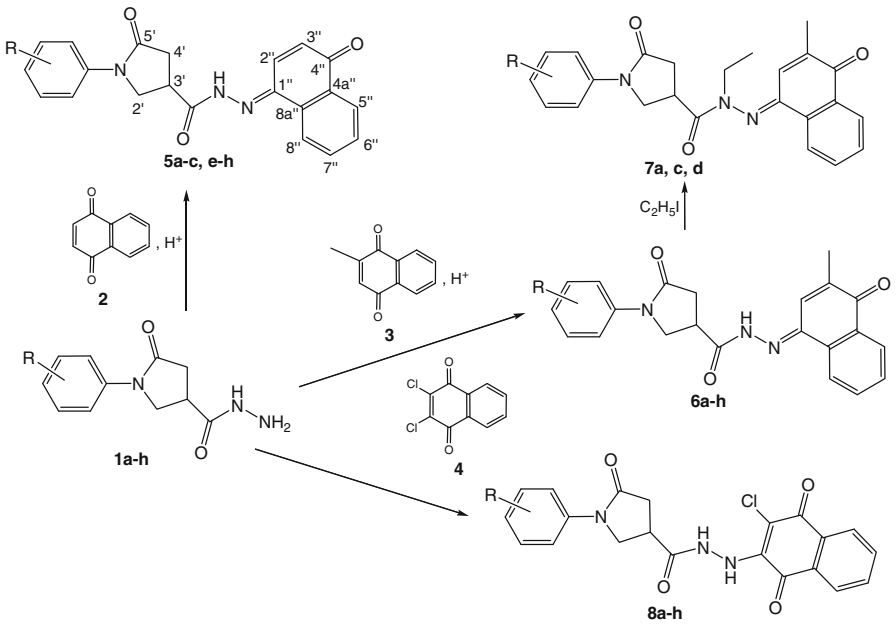
The starting compounds, 5-oxo-1-phenylpyrrolidine-3-carbohydrazides **1a–h**, were synthesized according to a standard method by refluxing the corresponding methyl esters of 5-oxopyrrolidine-3-carboxylic acids with hydrazine hydrate in 2-propanol [22].

The structure of the newly synthesized compounds was investigated using IR and ^{1}H, ^{13}C NMR spectra. The assignment of resonances in the NMR spectra was based on the chemical shift theory, using previously determined [23] and published [24] increments of substituents, signal intensity arguments, and multiplicities, and a comparison with structurally related compounds [20, 25–38]. The DEPT (^{13}C) and ^{1}H/^{13}C 2D (HETCOR) methods were used in some cases.

Results and discussion

The target *N*′-(4-oxo-1,4-dihydronaphthalen-1-ylidene)-1-phenyl-5-oxopyrrolidine-3-carbohydrazides (**5**) and *N*′-(3-methyl-4-oxo-1,4-dihydronaphthalen-1-ylidene)-1-phenyl-5-oxopyrrolidine-3-carbohydrazides (**6**) were prepared by refluxing the respective carbohydrazides **1** and 1,4-naphthoquinone (**2**) or 2-methyl-1,4-naphthoquinone (**3**) in 2-propanol in the presence of a catalytic amount of hydrochloric acid with 37–97% yields as illustrated in Scheme 1. Crystallization of hydrazones **5** and **6** occurred during the reaction. Upon completing the reaction, the crystalline products were filtered off (from a hot mixture) and washed with 2-propanol.

The structures of **5** and **6** were assigned on the basis of their ^{1}H and ^{13}C NMR spectra. NMR data showed that, during the reaction of carbohydrazides **1**, the amine functional group interacts with one of the carbonyl groups of 1,4-naphthoquinones **2**, **3**, resulting in the formation of hydrazones **5, 6**. The appearance of two doublets at 6.7 and 8.2 ppm with $J = 10.5$ Hz are characteristic of the double bond in the six-membered ring of quinone in ^{1}H NMR spectra of compounds **5 a–c, e–h**. The presence of benzene ring moiety was proven by a consistent splitting pattern of H-5″, H-6″, H-7″, and H-8″. The ^{13}C NMR spectra of **5** showed only one signal of the carbonyl group at around 184 ppm of 4-oxo-1,4-dihydronaphthalenylidene



Scheme 1 Synthetic pathway for compounds **5**–**8**. **a** R = H; **b** R = 3-CH_3; **c** R = 4-CH_3; **d** R = 2,5-$(CH_3)_2$; **e** R = 2-CH_3-5-Cl; **f** R = 3-Cl-4-CH_3; **g** R = 4-Br; **h** R = 4-Cl

moiety. Due to the restricted rotation of the amide group, a splitting of some resonances was observed. The signals of NH, H-2″, H-3″, H-8″, and H-3′ were split with the intensity ratio 0.8:0.2. The dynamic exchange processes caused by the CONH group led to the broadening of signals in NMR spectra. In this case, the resonance of C-1″ was observed only as traces at approximately 152 ppm. The structure of **6a**–**h** compounds was mainly substantiated by ^{1}H NMR spectra. The patterns of multiplets of the aromatic region were analyzed and assigned to the corresponding hydrogen atoms. A comparison of the integral intensities of multiplets confirmed the composition of compounds **6a**–**h**. The broadened singlets of 4-oxo-1,4-dihydronaphthalenylidene moiety of hydrazones **6** observed in the interval of 2.07–2.10 ppm, integrated for three protons, the doublets in the interval of 8.24–8.30 ppm, and the much more broadened singlets varying in the range 8.08–8.13 ppm, each one integrated for a single proton being attributed to the 3″-CH_3, H-8″ and H-2″ hydrogens, respectively. Only the resonance at 11.98 ppm, assigned to the NH group proton, revealed the presence of a fast exchange process of amide hydrogen of **6a–h** in DMSO-d_6 solutions. The above-mentioned broadening of resonances arises due to the interaction of CONH hydrogen with electron donating groups. The resonances of C-1″ atoms in ^{13}C NMR were greatly broadened and thus poorly observable in the noise, while the resonances of other carbonyl groups of **6a**–**h** were situated as expected.

Alkylation products of hydrazones—*N*-ethylcarbohydrazides **7a**, **c**, **d**—were obtained from the corresponding hydrazone **6**, ethyl iodide, potassium carbonate,

ethyl methyl ketone, and tetrabuthyl ammonium iodide as a phase-transfer catalyst. Reactions were carried out at a temperature of 50–55 °C and stirring the mixtures for 20 h. Purification of the product **7c** was performed by crystallization, **7a**, **d** were purified by the method of column chromatography.

A comparison of NMR spectra of **6b** and **7c** in DMSO-d_6 and $CDCl_3$ reflected changes in molecular interactions in solutions, caused by solvent properties. The spectra in $CDCl_3$ solution were characterized by a much finer resolution. The differences of chemical shifts of the corresponding atoms reveal the intramolecular interaction between the solute molecules (predominant in $CDCl_3$ solution) and the intermolecular interaction between the solute and solvent molecules (predominant in DMSO-d_6 solution). The presence of the resonances of the ethyl group and the absence of signals of the NH group confirmed the formation of compounds **7a**, **c**, **d**. The alkylation of the NH group of these compounds makes the molecules more stabile in DMSO-d_6 solution. The signal of C-1″ atom appeared at 151.20 ppm in ^{13}C NMR spectra of **7a**, **c**, **d** compounds. The different spatial location of the *N*-ethyl group with respect to adjacent atoms caused the splitting (0.8:0.2) of the signals of 2″-CH, 3″-CH_3 and protons of pyrolidinone moiety in ^{1}H NMR spectra.

Carbohydrazides **1** react with 2,3-dichloro-1,4-naphthoquinone (**4**) quite differently from 1,4-naphthoquinones **2**, **3**. In this case, *N*′-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-phenyl-5-oxopyrrolidine-3-carbohydrazides (**8a–h**) in 70–92% yields were obtained. Reactions were carried out in dimethyl sulfoxide at room temperature for 24 h. The NMR spectra of compounds **8a–h** are very complex due to their specific structure. Molecules of these compounds possess two NH groups capable of much more interactions than the other study compounds. In spite of the complication arising due to the mentioned NH groups, all fragments of the study compounds **8a–h** were indentified by NMR spectra. Two resonances of the C=O group of naphthoquinone moiety were observed in the intervals of 175.90–176.41 ppm (C-4″) and 178.95–179.11 ppm (C-1″) in ^{13}C NMR spectra. The resonances in the range 111.51–111.56 ppm (C-3″) and 144.29–145.53 ppm (C-2″) confirmed the presence of Cl and NHR substituents of naphthoquinone moiety. Several NH resonances in ^{1}H NMR spectra showed a variety of spatial structures present in DMSO-d_6 solutions.

Assessment of biological properties

Some of synthesized *N*′-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-phenyl-5-oxopyrrolidine-3-carbohydrazides (**8**) were tested for their antibacterial and antifungal activity against *Escherichia coli, Staphylococcus aureus, Mycobacterium luteum*, *Candida tenuis*, and *Aspergillus niger* strains by diffusion (Table 1) [39] and serial dilution techniques (Table 2) [determination of minimal bacteriostatic concentration (MBSC) and minimal bactericidic concentration (MBCC), minimal fungistatic concentration (MFSC) and minimal fungicidic concentration (MFCC)] [40]. Their activity was compared with that of the known antibacterial agent Vancomycin and the antifungal agent Nystatin.

Table 1 Antibacterial and fungicidal activity of some of the synthesized compounds determined by diffusion method

Compound	Concentration (%)	Inhibition diameter of microorganism growth (mm)				
		E. coli	*S. aureus*	*M. luteum*	*C. tenuis*	*A. niger*
8a	0.5	0	8.0	15.0	20.0	12.0
	0.1	0	10.0	11.0	18.0	13.0
8b	0.5	0	10.0	23.0	20.0	18.0
	0.1	0	8.0	15.0	15.0	12.0
8c	0.5	0	16.6	0	0	0
	0.1	0	0	0	0	0
8d	0.5	11.0	10.0	20.0	24.0	12.0
	0.1	6.0	9.0	13.0	20.0	9.0
8e	0.5	0	12.0	23.0	15.0	0
	0.1	0	0	15.0	10.0	0
8f	0.5	0	10.0	15.0	20.0	17.6
	0.1	0	0	12.0	13.3	12.0
Control	0.1	14.0	15.0	18.0	19.0	20.0

Diffusion technique

Antimicrobial activity of compounds has been evaluated by diffusion in agar on solid nutrient medium (nutrient agar—for bacteria; wort agar—for fungi). The disks (5 mm in diameter) were soaked in solutions of the tested compounds in DMSO (0.02 mg/mL) and then put on an exponentially growing plated culture. The microbial loading was 10^9 cells/mL. The required incubation periods were as follows: 24 h at 35 °C for bacteria and 48–72 h at 28–30 °C for fungi. The size of the zone of incubation was measured and compared with a control agent. Control disk contained Vancomycin (for bacteria) or Nystatin (for fungi) as a standard.

Serial dilution technique

Testing was performed in a flat-bottomed 96-well tissue culture plate. The test compounds were dissolved in DMSO and solutions within 500–1.9 μg mL^{-1} concentration range were prepared. The inoculum of bacteria and fungi was inoculated into a nutrient medium (nutrient meat-extract—for bacteria; wort—for fungi). The required incubation periods were as follows: 24–72 h at 37 °C for bacteria and 30 °C for fungi. The results were estimated according to the presence or absence of microorganism growth.

Data presented in Tables 1 and 2 show that there are substances with antibacterial and fungicidal action among the study compounds. The test-culture *E. coli* appeared to be sensitive only to compound **8d**. Its minimal bacteriostatic concentration was 125 μg mL^{-1}. The *S. aureus* strain was most sensitive to compound **8c** at a concentration of 0.5%, and the diameter of the inhibition zone

Table 2 Antimicrobial activity of some of the synthesized compounds determined by serial dilution method

Compound	Microorganisms									
	E. coli		*S. aureus*		*M. luteum*		*C. tenuis*		*A. niger*	
	MBSC ($\mu g\ mL^{-1}$)	MBCC ($\mu g\ mL^{-1}$)	MBSC ($\mu g\ mL^{-1}$)	MBCC ($\mu g\ mL^{-1}$)	MBSC ($\mu g\ mL^{-1}$)	MBCC ($\mu g\ mL^{-1}$)	MFSC ($\mu g\ mL^{-1}$)	MFCC ($\mu g\ mL^{-1}$)	MFSC ($\mu g\ mL^{-1}$)	MFCC ($\mu g\ mL^{-1}$)
8a	+	+	31.2	31.2	31.2	31.2	62.5	125.0	125.0	500.0
8b	+	+	62.5	250.0	15.6	31.2	31.2	31.2	31.2	31.2
8c	+	+	125.0	*	125.0	125.0	62.5	62.5	250.0	*
8d	125.0	*	62.5	62.5	31.2	31.2	62.5	62.5	250.0	250.0
8e	+	+	15.6	31.2	31.2	31.2	31.2	31.2	62.5	62.5
8f	+	+	125.0	*	3.9	31.2	7.8	15.6	31.2	125.0

+ Growth of microorganisms; * in the investigated concentrations, the indexes of biocidic effect were not determined

was 16.6 mm. **8c** completely inhibited the growth of bacteria at 125 μg mL^{-1} when the test-culture was screened by the serial dilution technique. Other compounds showed a moderate activity. *N*′-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-aryl-5-oxopyrrolidine-3-carbohydrazides **8a–f** were more efficient for inhibiting the growth of the *M. luteum* bacteria and *C. tenuis* and *A. niger* fungi. The diameters of the inhibition zones were 13.0–23.0, 13.3–24.0 and 12.0–18.0 mm, respectively. Compounds **8b, 8d,** and **8e** showed high action against *M. luteum* at 0.5% concentration. Antifungal activity against *C. tenuis* was observed for **8a**, **8b, 8d**, and **8f** at concentration of 0.5% (d = 20–24 mm). Compounds **8c** and **8e** have no antifungal activity against *A. niger* at investigative concentrations. This fungi strain is sensitive to **8a, 8b, 8d,** and **8f** at 0.1 and 0.5% concentrations.

The antimicrobial and antifungal activity of the test compounds can be correlated with their structure. *N*′-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-(3-methylphenyl)-5-oxopyrrolidine-3-carbohydrazides containing a substituent at *m*-position in the benzene ring or without it were found to show a more significant antibacterial and antifungal activity than their analogue containing a substituent in *p*-position. The exchange of the methyl group for the chloro substituent showed no clear influence on the biological activity, while the introduction of a second methyl group at the 2-position in the benzene ring had a positive effect on the antimicrobial activity.

Conclusions

The condensation of 5-oxo-1-phenylpyrrolidine-3-carbohydrazides with 1,4-naphthoquinone and 2-methyl-1,4-naphthoquinone yielded the corresponding hydrazones, while similar interactions with 2,3-dichloronaphthoquinone afforded *N*-substituted carbohydrazides with naphthoquinone moiety. Among the synthesized *N*′-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-phenyl-5-oxopyrrolidine-3-carbohydrazides, compounds with a high antimicrobial activity at low concentrations against *M. luteum* bacteria and *C. tenuis*, *A. niger* fungi in comparison with control were identified. *N*′-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-(3-methylphenyl)-5-oxopyrrolidine-3-carbohydrazide (**8b**), *N*′-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-(2,5-dimethylphenyl)-5-oxopyrrolidine-3-carbohydrazide (**8d**) and *N*′-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-(3-chloro-4-methylphenyl)-5-oxopyrrolidine-3-carbohydrazide (**8f**) are promising as biologically active compounds.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova (300 MHz, 75 MHz) spectrometer operating in the Fourier transform mode, using DMSO-d_6 and $CDCl_3$ as a solvent and TMS as an internal reference (chemical shifts in δ, ppm). IR spectra (ν, cm^{-1}) were recorded on a Perkin Elmer Spectrum BX FT–IR spectrometer using KBr tablets. Mass spectra were obtained on the Waters ZQ 2000

spectrometer using the atmospheric pressure chemical ionization (APCI) mode and operating at 20 V. Elemental analyses were performed with a CE-440 elemental analyser. Melting points were determined with an automatic APA1 melting point apparatus and are uncorrected.

General procedure for the synthesis of hydrazones **5a–c**, **e–h**

Three drops of concentrated hydrochloric acid were added to a mixture of the corresponding hydrazide **1** (10 mmol), 1,4-dihydronaphthalene-1,4-dione (**2**) (1.58 g, 10 mmol) and 2-propanol (80 mL). The reaction mixture was refluxed for 4 h and then filtered (hot). Upon completing the reaction, the reaction mixture was cooled down and the formed crystalline solid was filtered off, washed with 2-propanol and dried.

*5-Oxo-N′-(4-oxo-1,4-dihydronaphthalen-1-ylidene)-1-phenylpyrrolidine-3-carbohydrazide (**5a**)*

Yield 1.9 g (52.5%), m.p. 253–254 °C (from 2-propanol). IR, *v*: 1599, 1667, 1697 (3C=O); 3109, 3178 (NH). ^{1}H NMR (300 MHz, DMSO-d$_6$), *δ*: 2.82-2.99 (m, 2H, CH_2CO), 3.16-3.76 (m, (0.2)1H, CH), 4.02-4.26 (m, 2H, NCH_2), 4.32–4.42 (m, (0.8)1H, CH), 6.72 (d, $J = 10.5$ Hz, (0.8)1H, (3″-H)), 6.82 (d, $J = 10.5$ Hz, (0.2)1H, (3″-H)), 7.14 (t, $J = 7.4$ Hz, 1H, (4-H$_{ar}$)), 7.37 (t, $J = 7.9$ Hz, 2H, (3, 5-H$_{ar}$)), 7.63 (t, $J = 7.7$ Hz, 1H, (6″-H)), 7.68 (d, $J = 8.0$ Hz, 2H, (2, 6-H$_{ar}$)), 7.76 (d, $J = 7.6$ Hz, 1H, (7″-H)), 8.01 (d, $J = 7.8$ Hz, (5″-H)), 8.23 (d, $J = 10.5$ Hz, 1H, (2″-H)), 8.35 (d, $J = 7.9$ Hz, 1H, (8″-H)), 11.95 (s, (0.2)1H, NH), 12.29 (s, (0.8)1H, NH). Found, %: C 70.10, H 4.82. N 12.04. Calculated, %: C 70.18, H 4.77, N 11.69. $C_{21}H_{17}N_3O_3$.

*1-(3-Methylphenyl)-5-oxo-N′-(4-oxo-1,4-dihydronaphthalen-1-ylidene)pyrrolidine-3-carbohydrazide (**5b**)*

Yield 1.4 g (36.9%), m.p. 240–241 °C (from 2-propanol). IR, *v*: 1604 (N=C), 1645, 1676, 1694 (3C=O), 3112, 3173 (NH). ^{1}H NMR (300 MHz, DMSO-d$_6$), *δ*: 2.29 (s, 3H, (3-CH_3)), 2.81–2.98 (m, 2H, CH_2CO), 3.59–3.72 (m, (0.2)1H, CH), 4.00–4.23 (m, 2H, NCH_2), 4.29–4.40 (m, (0.8)1H, CH), 6.71 (d, $J = 10.5$ Hz, (0.8)1H, (3″-H)), 6.81 (d, $J = 10.5$ Hz, (0.2)1H, (3″-H)), 6.95 (d, $J = 7.1$ Hz, 1H, (6-H$_{ar}$)), 7.21–7.27 (m, 1H, (5-H$_{ar}$)), 7.47–7.51 (m, 2H, (2,4-H$_{ar}$)), 7.62 (t, $J = 7.1$ Hz, 1H, (6″-H)), 7.75 (t, $J = 7.5$ Hz, 1H, (7″-H)), 8.00 (dd, $J = 1.1$ Hz, $J = 7.8$ Hz, (5″-H)), 8.21 (d, $J = 10.5$ Hz, 1H, 2″-H), 8.33 (d, $J = 7.7$ Hz, 1H, (8″-H)), 11.93 (s, (0.2)1H, NH), 12.26 (s, (0.8)1H, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$), *δ*: 21.20 (3-CH_3), 32.12 (C-3′), 35.02 (C-4′), 50.02 (C-2′), 116.72 (C-6), 120.04 (C-2), 123.57 (C-3″), 124.80 (C-4), 125.41, 127.26 (C-5″, C-8″), 128.51 (C-5), 129.49 (C-6″, C-7″), 130.09 (C-4a″), 130.81 (C-2″), 133.03 (C-6″, C-7″), 134.49, 136.33 (C-8a″), 137.96 (C-3), 139.12 (C-1), 171.78 (C-5′), 175.61 (CONH), 184.09 (C-4″). MS *m/z* (*I*, %): 397 $[M + Na + H]^+$ (100). Found, %: C 71.08, H 5.19, N 11.36. Calculated, %: C 70.76, H 5.13, N 11.25. $C_{22}H_{19}N_3O_3$.

*1-(4-Methylphenyl)-5-oxo-N′-(4-oxo-1,4-dihydronaphthalen-1-ylidene)pyrrolidine-3-carbohydrazide (**5c**)*

Yield 1.6 g (43.4%), m.p. 226–227 °C (from 2-propanol). IR, *v*: 1599 (N=C), 1640, 1673, 1687 (3C=O), 3104, 3171 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.26 (s, 3H, (4-CH_3)), 2.79–2.96 (m, 2H, CH_2CO), 3.55–3.67 (m, (0.2)1H, CH), 3.95–4.34 (m, 2H, NCH_2 + (0.8)1H, CH), 4.29–4.40 (m, (0.8)1H, CH), 6.72 (d, J = 10.5 Hz, 1H, (3″-H)), 7.16 (d, J = 8.3 Hz, 2H, (3, 5-H_{ar})), 7.55 (d, J = 8.3 Hz, 1H, (2, 6-H_{ar})), 7.49–7.78 (m, 2H, (6″, 7″-H)), 8.00 (d, J = 7.8 Hz, 1H, (5″-H)), 8.20 (d, J = 10.5 Hz, 1H, (2″-H)), 8.32 (d, J = 8.0 Hz, 1H, (8″-H)), 11.48 (s, (0.07)1H, NH), 11.77 (s, (0.26)1H, NH), 12.18 (s, (0.67)1H, NH). Found, %: C 70.41, H 5.26, N 11.45. Calculated, %: C 70.76, H 5.13, N 11.25. $C_{22}H_{19}N_3O_3$.

*1-(2-Methyl-5-chlorophenyl)-5-oxo-N′-(4-oxo-1,4-dihydronaphthalen-1-ylidene)pyrolidine-3-carbohydrazide (**5e**)*

Yield 1.5 g (37.2%), m.p. 222–225 °C (from 2-propanol). IR, *v*: 1598 (N=C), 1649, 1680, 1696 (3C=O), 3111, 3172 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.16 (s, 3H, (2-CH_3)), 2.72–2.91 (m, 2H, CH_2CO), 3.64–4.45 (m, 1H, CH + 2H, NCH_2), 6.68–8.29 (m, 9H, (H_{ar} + 2″, 3″, 5″-8″-H)), 11.72, 11.95, 12.22 (3br. s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), *δ*: 17.07 (2-CH_3), 33.40 (C-3′), 34.41 (C-4′), 51.73 (C-2′), 123.47 (C-3″), 125.40 (C-5″, C-8″), 126.63 (C-6), 127.26 (C-5″, C-8″), 127.38 (C-4), 129.48 (C-6″, C-7″), 130.07, (C-4a″), 130.25 (C-2), 130.76 (C-2″), 132.18 (C-5), 132.93 (C-6″, C-7″), 134.47, 136.21 (C-8a″), 134.70 (C-3), 138.75 (C-1), 171.65 (C-5′), 175.62 (CONH), 184.07 (C-4″). Found, %: C 64.45, H 4.51, N 10.45. Calculated, %: C 64.79, H 4.45, N 10.30. $C_{22}H_{18}ClN_3O_3$.

*1-(3-Chloro-4-methylphenyl)-5-oxo-N′-(4-oxo-1,4-dihydronaphthalen-1-ylidene)pyrolidine-3-carbohydrazide (**5f**)*

Yield 3.2 g (78.7%), m.p. 277–278 °C (from 2-propanol). IR, *v*: 1602 (N=C), 1645, 1673, 1694 (3C=O), 3107, 3170 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.28 (s, 3H, (4-CH_3)), 2.82–2.99 (m, 2H, CH_2CO), 3.60–3.70 (m, (0.2)1H, CH), 4.04–4.22 (m, 2H, NCH_2), 4.31–4.41 (m, (0.8)1H, CH), 6.72 (d, J = 10.5 Hz, (0.8)1H, (3″-H)), 6.81 (d, J = 10.5 Hz, (0.2)1H, (3″-H)), 7.32 (d, J = 8.4 Hz, 1H, (5-H_{ar})), 7.47 (dd, J = 2.2 Hz, J = 8.4 Hz, 1H, (6-H_{ar})), 7.63 (t, J = 8.0 Hz, 1H, (6″-H)), 7.75 (t, J = 7.3 Hz, 1H, (7″-H)), 7.87 (d, J = 2.2 Hz, 1H, (2-H_{ar})), 8.01 (dd, J = 1.1 Hz, J = 7.8 Hz, (5″-H)), 8.22 (d, J = 10.5 Hz, 1H, (2″-H)), 8.34 (d, J = 8.0 Hz, 1H, (8″-H)), 11.93 (s, (0.2)1H, NH), 12.26 (s, (0.8)1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), *δ*: 18.94 (4-CH_3), 33.04 (C-3′), 34.92 (C-4′), 49.85 (C-2′), 117.82 (C-6), 119.35 (C-2), 123.59 (C-3″), 125.41, 127.28 (C-5″, C-8″), 129.50 (C-6″, C-7″), 130.09 (C-4, +C-4a″), 130.82 (C-2″), 131.09 (C-5), 133.03 (C-6″, C-7″), 133.11 (C-3), 134.49, 136.38 (C-8a″), 138.21 (C-1), 172.10 (C-5′), 175.48 (CONH), 184.09 (C-4″). Found, %: C 64.92, H 4.62, N 10.57. Calculated, %: C 64.79, H 4.45, N 10.30. $C_{22}H_{18}ClN_3O_3$.

*(4-Bromophenyl)-5-oxo-N′-(4-oxo-1,4-dihydronaphthalen-1-ylidene)pyrrolidine-3-carbohydrazide (**5g**)*

Yield 3.5 g (80.4%), m.p. 242–243 °C (from 2-propanol). IR, *v*: 1602 (N=C), 1646, 1675, 1694 (3C=O), 3107, 3170 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.83–2.97 (m, 2H, CH_2CO), 3.61–3.75 (m, (0.2)1H, CH), 3.99–4.22 (m, 2H, NCH_2), 4.28–4.39 (m, (0.8)1H, CH), 6.69 (d, $J = 10.4$ Hz, (0.8)1H, (3″-H)), 6.79 (d, $J = 10.4$ Hz, (0.2)1H, (3″-H)), 7.52 (d, $J = 8.6$ Hz, 2H, (3, 5-H_{ar})), 7.60 (t, $J = 7.5$ Hz, 1H, (6″-H)), 7.66 (d, $J = 8.6$ Hz, 2H, 2, 6-H_{ar}), 7.73 (t, $J = 7.2$ Hz, 1H, (7″-H)), 7.99 (d, $J = 7.6$ Hz, 1H, (5″-H)), 8.19 (d, $J = 10.4$ Hz, 1H, (2″-H)), 8.30 (d, $J = 7.6$ Hz, 1H, (8″-H)), 11.93 (s, (0.2)1H, NH), 12.27 (s, (0.8)1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), *δ*: 33.03 (C-3′), 34.95 (C-4′), 49.78 (C-2′), 115.94 (C-4), 121.21 (C-2, 6), 123.57 (C-3″), 125.39 (C-5″), 127.23 (C-8″), 129.47 (C-6″), 130.08 (C-4a″), 130.82 (C-2″), 131.46 (C-3, 5), 133.01 (C-7″), 134.45, 136.37 (C-8a″), 138.44 (C-1), 172.12 (C-5′), 175.44 (CONH), 184.06 (C-4″). Found, %: C 57.68, H 3.76, N 9.73. Calculated, %: C 57.55, H 3.68, N 9.59. $C_{21}H_{16}BrN_3O_3$.

*1-(4-Chlorophenyl)-5-oxo-N′-(4-oxo-1,4-dihydronaphthalen-1-ylidene)pyrrolidine-3-carbohydrazide (**5h**)*

Yield 3.2 g (82.3%), m.p. 244–245 °C (from 2-propanol). IR, *v*: 1599 (N=C), 1647, 1675, 1694 (3C=O), 3107, 3172 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.83–2.99 (m, 2H, CH_2CO), 3.58–3.71 (m, (0.2)1H, CH), 4.01–4.24 (m, 2H, NCH_2), 4.32–4.42 (m, (0.8)1H, CH), 6.72 (d, $J = 10.5$ Hz, (0.8)1H, (3″-H)), 6.82 (d, $J = 10.5$ Hz, (0.2)1H, (3″-H)), 7.42 (d, $J = 8.9$ Hz, 2H, (3, 5-H_{ar})), 7.64 (t, $J = 8.0$ Hz, 1H, (6″-H)), 7.02–7.81 (m, 1H, (7″-H) + 2H, (2, 6-H_{ar})), 8.01 (dd, $J = 1.1$ Hz, $J = 7.8$ Hz, 1H, (5″-H)), 8.23 (d, $J = 10.5$ Hz, 1H, (2″-H)), 8.35 (d, $J = 7.9$ Hz, 1H, (8″-H)), 11.94 (s, (0.2)1H, NH), 12.27 (s, (0.08)1H, NH). Found, %: C 64.08, H 4.16, N 10.62. Calculated, %: C 64.05, H 4.10, N 10.67. $C_{21}H_{16}ClN_3O_3$.

General procedure for the synthesis of hydrazones **6a**–**h**

Three drops of concentrated hydrochloric acid were added to a mixture of the corresponding hydrazide **1** (10 mmol), 2-methyl-1,4-dihydronaphthalene-1,4-dione (**3**) (0.86 g, 5 mmol) and 2-propanol (70 mL). The reaction mixture was refluxed for 19 h and filtered (hot). Upon completing the reaction, the reaction mixture was cooled down and the formed crystalline solid was isolated by filtration, washed with 2-propanol and dried.

*N′-(3-Methyl-4-oxo-1,4-dihydronaphthalen-1-ylidene)-1-phenyl-5-oxopyrrolidine-3-carbohydrazide (**6a**)*

Yield 3.39 g (88.0%), m.p. 314–315 °C (from the mixture of 2-propanol and dimethylformamide (1:1)). IR, *v*: 1645, 1675 (C=O), 3073, 3109, 3175 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.10 (s, 3H, (3″-CH_3)), 2.80–2.98 (m, 2H, CH_2CO), 4.04–4.24 (m, 2H, NCH_2), 4.33 (br. s, CH), 7.14 (t, $J = 7.4$ Hz, 1H, (4-H_{ar})), 7.37

(t, $J = 7.9$ Hz, 2H, (3, 5-H_{ar})), 7.61 (dt, $J = 1.0$ Hz, $J = 7.8$ Hz, 1H, (6″-H)), 7.68 (d, $J = 8.0$ Hz, 2H, (2, 6-H_{ar})), 7.73 (dt, $J = 1.0$ Hz, $J = 7.8$ Hz, 1H, (7″-H)), 8.02 (dd, $J = 1.0$ Hz, $J = 7.4$ Hz, (5″-H)), 8.13 (br. s, 1H, (2″-H)), 8.30 (d, $J = 7.9$ Hz, 1H, (8″-H)), 11.99 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 16.61 (3″-CH_3), 33.12 (C-3′), 35.10 (C-4′), 50.02 (C-2′); 119.44 (C-2, 6), 123.44 (C-2″), 124.07 (C-4), 124.12, 125.59 (C-5″, C-8″), 128.68 (C-3, 5), 129.44 (C-6″, C-7″), 129.97 (C-4a″), 132.71 (C-6″, C-7″), 134.53 (C-3″), 139.08 (C-8a″), 139.16 (C-1), 171.85 (C-5′), 184.21 (C-4″). MS *m/z* (*I*, %): 374 $[M + H]^+$ (100). Found, %: C 70.95, H 5.32, N 11.47. Calculated, %: C 70.76, H 5.13, N 11.25. $C_{22}H_{19}N_3O_3$.

*N′-(3-Methyl-4-oxo-1,4-dihydronaphthalen-1-ylidene)-1-(3-methylphenyl)-5-oxopyrrolidine-3-carbohydrazide (**6b**)*

Yield 3.8 g (98.0%), m.p. 262–263 °C (from the mixture of 2-propanol and dimethylformamide (1:1)). IR, *v*: 1641, 1674 (C=O), 3079, 3110, 3177 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 2.09 (s, 3H, (3″-CH_3)), 2.30 (s, 3H, (3-CH_3)), 2.79–2.96 (m, 2H, CH_2CO), 4.02–4.21 (m, 2H, NCH_2), 4.32 (br. s, CH), 6.95 (d, $J = 7.3$ Hz, 1H, (4-H_{ar})), 7.24 (t, $J = 8.2$ Hz, 1H, (5-H_{ar})), 7.49 (d, $J = 6.5$ Hz, 1H, (6-H_{ar})), 7.49 (s, 1H, (2-H_{ar})), 7.61 (dt, $J = 1.2$ Hz, $J = 7.8$ Hz, 1H, (6″-H)), 7.72 (dt, $J = 1.4$ Hz, $J = 7.7$ Hz, 1H, (7″-H)), 8.02 (dd, $J = 1.1$ Hz, $J = 7.8$ Hz, (5″-H)), 8.13 (br. s, 1H, 2″-H), 8.29 (d, $J = 7.5$ Hz, 1H, (8″-H)), 11.99 (s, 1H, NH). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.21 (d, $J = 1.2$ Hz 3H, (3″-CH_3)), 2.36 (s, 3H, (3-CH_3)), 3.02–3.17 (m, 2H, CH_2CO), 4.17–4.42 (m, 3H, NCH_2 + CH), 7.00 (d, $J = 7.0$ Hz, 1H, (4-H_{ar})), 7.26 (t, $J = 8.2$ Hz, 1H, (5-H_{ar})), 7.41 (d, $J = 8.2$ Hz, 1H, (6-H_{ar})), 7.46 (s, 1H, (2-H_{ar})), 7.59 (dt, $J = 1.3$ Hz, $J = 7.5$ Hz, 1H, (6″-H)), 7.67 (dt, $J = 1.4$ Hz, $J = 7.5$ Hz, 1H, (7″-H)), 7.72 (q, $J = 1.2$ Hz, 1H, (2″-H)), 8.17–8.23 (m, 2H, (5″, 8″-H)), 10.80 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 16.61 (3″-CH_3), 21.17 (3-CH_3), 32.58, 33.16 (C-3′), 35.10 (C-4′), 50.13 (C-2′), 116.71 (C-6), 120.04 (C-2), 123.33 (C-2″), 124.12 (C-5″, C-8″), 124.78 (C-4), 125.59 (C-5″, C-8″), 128.49 (C-5), 129.43 (C-6″, C-7″), 129.97 (C-4a″), 132.70 (C-6″, C-7″), 134.53 (C-3″), 137.95 (C-3), 139.07 (C-8a″), 139.12 (C-1), 171.71 (C-5′), 175.55 (CONH), 184.20 (C-4″). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 17.33 (3″-CH_3), 21.61 (3-CH_3), 34.05 (C-3′), 35.48 (C-4′), 50.32 (C-2′), 117.28 (C-6), 120.89 (C-2), 121.41 (C-2″), 122.96 (C-5″, C-8″), 125.91 (C-4), 126.68 (C-5″, C-8″), 128.80 (C-5), 130.02 (C-6″, C-7″), 130.66 (C-4a″), 132.78 (C-6″, C-7″), 134.15 (C-3″), 138.67, 138.90 (C-3), 139.00 (C-8a″), 142.19 (C-1), 171.53 (C-5′), 175.26 (CONH). MS *m/z* (*I*, %): 388 $[M + H]^+$ (100). Found, %: C 71.57, H 5.68, N 10.91. Calculated, %: C 71.30, H 5.46, N 10.85. $C_{23}H_{21}N_3O_3$.

*N′-(3-Methyl-4-oxo-1,4-dihydronaphthalen-1-ylidene)-1-(4-methylphenyl)-5-oxopyrrolidine-3-carbohydrazide (**6c**)*

Yield 2.6 g (67.0%), m.p. 288–289 °C (from the mixture of 2-propanol and dimethylformamide (1:1)). IR, *v*: 1643, 1675 (C=O), 3080, 3112, 3177 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 2.10 (s, 3H, (3″-CH_3)), 2.27 (s, 3H, (4-CH_3)), 2.78–2.95 (m, 2H, CH_2CO), 4.01–4.20 (m, 2H, NCH_2), 4.30 (br. s, CH), 7.17

(d, $J = 8.5$ Hz, 2H, (3, 5-H_{ar})), 7.56 (d, $J = 8.5$ Hz, 2H, (2, 6-H_{ar})), 7.61 (dt, $J = 1.2$ Hz, $J = 7.8$ Hz, 1H, (6″-H)), 7.72 (dt, $J = 1.4$ Hz, $J = 7.7$ Hz, 1H, (7″-H)), 8.02 (dd, $J = 1.1$ Hz, $J = 7.8$ Hz, (5″-H)), 8.13 (br. s, 1H, 2″-H), 8.30 (d, $J = 7.7$ Hz, 1H, (8″-H_{ar})), 11.97 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 16.59 (3″-CH_3), 20.38 (4-CH_3), 33.29 (C-3′), 35.08 (C-4′), 50.10 (C-2′), 119.45 (C-2, 6), 123.32 (C-2″), 124.11, 125.58 (C-5″, C-8″), 129.06 (C-3, 5), 129.42 (C-6″, C-7″), 129.96 (C-4a″), 132.69 (C-6″, C-7″), 133.14 (C-4), 134.53 (C-3″), 136.71 (C-1), 139.06 (C-8a″), 171.57 (C-5′), 175.39 (CONH), 184.19 (C-4″). MS *m/z* (*I*, %): 388 $[M + H]^+$ (100). Found, %: C 71.46, H 5.67, N 11.02. Calculated, %: C 71.30, H 5.46, N 10.85. $C_{23}H_{21}N_3O_3$.

*N′-(3-Methyl-4-oxo-1,4-dihydronaphthalen-1-ylidene)-1-(2,5-dimethylphenyl)-5-oxopyrrolidine-3-carbohydrazide (**6d**)*

Yield 3.0 g (75.0%), m.p. 245–246 °C (from the mixture of 2-propanol and dimethylformamide (1:1)). IR, *v*: 1650, 1703 (C=O), 3138, 3165, 3197 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 2.07 (s, 3H, (3″-CH_3)), 2.13 (s, 3H, (2-CH_3)), 2.25 (s, 3H, (5-CH_3)), 2.71–2.90 (m, 2H, CH_2CO), 3.81–4.09 (m, 2H, NCH_2), 4.32 (br. s, CH), 7.03 (d, $J = 7.7$ Hz, 1H, (4-H_{ar})), 7.05 (s, 1H, (6-H_{ar})), 7.15 (d, $J = 7.7$ Hz, 1H, (3-H_{ar})), 7.58 (t, $J = 6.5$ Hz, 1H, (6″-H)), 7.70 (t, $J = 7.8$ Hz, 1H, (7″-H)), 7.99 (dd, $J = 1.1$ Hz, $J = 7.8$ Hz, (5″-H)), 8.08 (br. s, 1H, 2″-H), 8.24 (d, $J = 7.9$ Hz, 1H, (8″-H)), 11.93 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 16.58 (3″-CH_3), 17.05 (2-CH_3), 20.31 (5-CH_3), 33.64 (C-3′), 34.28 (C-4′), 51.79 (C-2′), 123.21 (C-2″), 124.06, 125.56 (C-5″, C-8″), 127.11 (C-6), 128.17 (C-4), 129.36 (C-6″, C-7″), 129.93 (C-4a″), 130.47 (C-2), 132.19 (C-3), 132.60 (C-6″, C-7″), 134.51 (C-3″), 135.77 (C-5), 137.19 (C-1), 139.00 (C-8a″), 171.62 (C-5′), 175.61, 175.76 (CONH), 184.14 (C-4″). MS *m/z* (*I*, %): 402 $[M + H]^+$ (100). Found, %: C 71.98, H 5.99, N 10.63. Calculated, %: C 71.80, H 5.77, N 10.47. $C_{24}H_{23}N_3O_3$.

*N′-(3-Methyl-4-oxo-1,4-dihydronaphthalen-1-ylidene)-1-(2-methyl-5-chlorophenyl)-5-oxopyrrolidine-3-carbohydrazide (**6e**)*

Yield 3.4 g (82.0%), m.p. 270–271 °C (from the mixture of 2-propanol and dimethylformamide (1:1)). IR, *v*: 1645, 1679, 1695 (C=O), 3077, 3114, 3185 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 2.08 (s, 3H, (3″-CH_3)), 2.16 (s, 3H, (2-CH_3)), 2.73–2.90 (m, 2H, CH_2CO), 3.84–4.13 (m, 2H, NCH_2), 4.32 (br. s, CH), 7.27–7.33 (m, 2H, (3,4-H_{ar})), 7.39 (d, $J = 1.3$ Hz, 1H, (6-H_{ar})), 7.60 (t, $J = 6.5$ Hz, 1H, (6″-H)), 7.72 (t, $J = 7.8$ Hz, 1H, (7″-H)), 8.00 (d, $J = 7.7$ Hz, (5″-H)), 8.11 (br. s, 1H, 2″-H), 8.27 (d, $J = 7.9$ Hz, 1H, (8″-H)), 11.96 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), δ: 16.66 (3″-CH_3), 17.08 (2-CH_3), 33.53 (C-3′), 34.59 (C-4′), 51.79 (C-2′), 123.29 (C-2″), 124.14, 125.63 (C-5″, C-8″), 126.66 (C-6), 127.42 (C-4), 129.47 (C-6″, C-7″), 129.98 (C-4a″), 130.26 (C-2), 132.22 (C-5), 132.70 (C-6″, C-7″), 134.56 (C-3″), 134.73 (C-3), 138.78 (C-1), 139.07 (C-8a″), 171.70 (C-5′), 175.36 (CONH), 184.22 (C-4″). MS *m/z* (*I*, %): 422 $[M + H]^+$ (95),

424 $[M + 2 + H]^+$ (30). Found, %: C 65.70, H 4.86, N 10.05. Calculated, %: C 65.48, H 4.78, N 9.96. $C_{23}H_{20}ClN_3O_3$.

*N′-(3-Methyl-4-oxo-1,4-dihydronaphthalen-1-ylidene)-1-(3-chloro-4-methylphenyl)-5-oxopyrrolidine-3-carbohydrazide (**6f**)*

Yield 3.5 g (83.0%), m.p. 293–294 °C (from the mixture of 2-propanol and dimethylformamide (1:1)). IR, *ν*: 1642, 1678, 1691 (C=O), 3079, 3110, 3185 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.09 (s, 3H, (3″-CH_3)), 2.28 (s, 3H, (4-CH_3)), 2.73–2.97 (m, 2H, CH_2CO), 3.98–4.21 (m, 2H, NCH_2), 4.30 (br. s, CH), 7.31–7.48 (m, 2H, (5,6-H_{ar})), 7.60 (t, $J = 6.5$ Hz, 1H, (6″-H)), 7.72 (t, $J = 7.8$ Hz, 1H, (7″-H)), 7.87 (s, 1H, (2-H_{ar})), 8.02 (d, $J = 7.7$ Hz, (5″-H)), 8.12 (br. s, 1H, 2″-H), 8.30 (d, $J = 7.9$ Hz, 1H, (8″-H)), 11.98 (s, 1H, NH). MS *m/z* (*I*, %): 422 $[M + H]^+$ (85), 424 $[M + 2 + H]^+$ (40). Found, %: C 66.33, H 4.92, N 10.39. Calculated, %: C 65.48, H 4.78, N 9.96. $C_{23}H_{20}ClN_3O_3$.

*N′-(3-Methyl-4-oxo-1,4-dihydronaphthalen-1-ylidene)-1-(4-bromophenyl)-5-oxopyrrolidine-3-carbohydrazide (**6g**)*

Yield 4.5 g (99.0%), m.p. 338–339 °C (from the mixture of 2-propanol and dimethylformamide (1:1)). IR, *ν*: 1644, 1674, 1689 (C=O), 3071, 3107, 3173 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.08 (s, 3H, (3″-CH_3)), 2.72–2.98 (m, 2H, CH_2CO), 4.01–4.21 (m, 2H, NCH_2), 4.33 (br. s, CH), 7.53–7.74 (m, 6H, 2, 3, 5, 6-H_{ar} + 6″, 7″-H), 8.01 (d, $J = 7.3$ Hz, (5″-H)), 8.13 (br. s, 1H, 2″-H), 8.28 (d, $J = 7.1$ Hz, 1H, (8″-H_{ar})), 12.04 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), *δ*: 16.70 (3″-CH_3), 33.04 (C-3′), 34.98 (C-4′), 50.03 (C-2′), 115.91 (C-4), 121.21 (C-2, 6), 123.38 (C-2″), 124.14, 125.62 (C-5″, C-8″), 129.45 (C-6″, C-7″), 129.98 (C-4a″), 131.49 (C-3, 5), 132.74 (C-6″, C-7″), 134.53 (C-3″), 138.47 (C-1), 139.12 (C-8a″), 172.18 (C-5′), 175.28 (CONH), 184.22 (C-4″). MS *m/z* (*I*, %): 452 $[M]^+$ (100). Found, %: C 58.37, H 4.03, N 9.23. Calculated, %: C 58.42, H 4.01, N 9.29. $C_{22}H_{18}BrN_3O_3$.

*N′-(3-Methyl-4-oxo-1,4-dihydronaphthalen-1-ylidene)-1-(4-chlorophenyl)-5-oxopyrrolidine-3-carbohydrazide (**6h**)*

Yield 3.9 g (96.0%), m.p. 335–336 °C (cleavage). IR, *ν*: 1642, 1674, 1688 (C=O), 3073, 3109, 3173 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.09 (s, 3H, (3″-CH_3)), 2.72–2.98 (m, 2H, CH_2CO), 4.00–4.37 (m, 3H, NCH_2 + CH), 7.42 (d, $J = 8.8$ Hz, 2H (3, 5-H_{ar})), 7.61 (m, 1H, 6″-H), 7.70–7.74 (m, 3H, 7″-H + 2, 6-H_{ar}), 8.02 (d, $J = 7.6$ Hz, (5″-H)), 8.12 (br. s, 1H, 2″-H), 8.29 (d, $J = 7.7$ Hz, 1H, (8″-H)), 11.97 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), *δ*: 16.67 (3″-CH_3), 33.52 (C-3′), 35.11 (C-4′), 50.01 (C-2′), 120.89 (C-2, 6), 123.38 (C-2″), 124.14, 125.62 (C-5″, C-8″), 127.79 (C-4), 128.57 (C-3, 5), 129.47 (C-6″, C-7″), 129.98 (C-4a″), 132.74 (C-6″, C-7″), 134.53 (C-3″), 138.06 (C-1), 139.10 (C-8a″), 172.14 (C-5′), 175.71 (CONH), 184.22 (C-4″). MS *m/z* (*I*, %): 430 $[M + Na]^+$ (100). Found, %: C 64.71, H 4.41, N 10.39. Calculated, %: C 64.79, H 4.45, N 10.30. $C_{22}H_{18}ClN_3O_3$.

General procedure for the synthesis of *N*-alkylated compounds **7a**, **c**, **d**

A mixture of the corresponding compound **6** (1 mmol), ethyl iodide (20 mL), potassium carbonate (1.38 g, 10 mmol), ethyl methyl ketone (20 mL) and tetrabuthyl ammonium iodide (0.2 g, 1 mmol) was heated at 50–55 °C and stirred for 20 h, then cooled down, the inorganic salts were filtered off and the liquid fractions were separated under reduced pressure. The solid mass was collected and purified as follows: *N*-ethylcarbohydrazide **7c** was recrystallized from ethanol, compounds **7a, d** were purified by column chromatography (*Silikagel 60*). The eliuent was acetone : hexane (1:1.5).

*N-Ethyl-N′-(3-methyl-4-oxo-1,4-dihydronaphthalen-1-yl)-1-phenyl-5-oxopyrrolidine-3-carbohydrazide (**7a**)*

Yield 0.3 g (85.0%), m.p. 140–141 °C ($R_f = 0.86$). IR, *v*: 1649, 1698, 1734 (C=O). ^{1}H NMR (300 MHz, DMSO-d$_6$), *δ*: 1.18 (t, $J = 7.0$ Hz, 3H, CH_2CH_3), 2.03 (br. s, (0.2)3H, (3″-CH_3)), 2.15 (s, (0.8)3H, (3″-CH_3)), 2.71–2.92 (m, 2H, CH_2CO), 3.88–4.20 (m, 5H, NCH_2 + CH + CH_2CH_3), 7.12 (t, $J = 7.2$ Hz, 1H, (4-H_{ar})), 7.31–7.41 (m. 2H, (3, 5-H_{ar}) + 0.4H(2″-H)), 7.55 (s, 0.6H, (2″-H)), 7.63 (d, $J = 8.3$ Hz, 2H, (2, 6-H_{ar})), 7.72 (dt, $J = 1.2$ Hz, $J = 7.4$ Hz, 1H, (6″-H)), 7.79 (dt, $J = 1.2$ Hz, $J = 7.6$ Hz, 1H, (7″-H)), 8.06 (d, $J = 7.2$ Hz, (5″-H)), 8.37 (d, $J = 7.6$ Hz, 1H, (8″-H)). ^{13}C NMR (75 MHz, DMSO-d$_6$), *δ*: 12.33 (NCH_2CH_3), 16.61 (3″-CH_3), 33.89 (C-3′), 35.33 (C-4′), 45.99 (NCH_2CH_3), 50.04 (C-2′), 119.47 (C-2, 6), 124.07 (C-4), 124.21, 125.73 (C-5″, C-8″), 125.89 (C-2″), 128.69 (C-3, 5), 130.45 (C-4a″), 130.94, 133.17 (C-6″, C-7″), 133.88 (C-3″), 139.14 (C-1), 141.50 (C-8a″), 151.34 (C-1″), 171.85 (C-5′), 173.71 (CONH), 184.42 (C-4″). MS *m/z* (*I*, %): 402 $[M + H]^+$ (100). Found, %: C 71.93, H 5.83, N 10.39. Calculated, %: C 71.80, H 5.77, N 10.47. $C_{24}H_{23}N_3O_3$.

*N-Ethyl-N′-(3-methyl-4-oxo-1,4-dihydronaphthalen-1-yl)-1-(4-methylphenyl)-5-oxopyrolidine-3-carbohydrazide (**7c**)*

Yield 0.4 g (92.0%), m.p. 159–160 °C (from ethanol). IR, *v*: 1648, 1663, 1692 (C=O). ^{1}H NMR (300 MHz, DMSO-d$_6$), *δ*: 1.18 (t, $J = 6.9$ Hz, (0.2)3H, CH_2CH_3), 1.27 (t, $J = 6.9$ Hz, (0.8)3H, CH_2CH_3), 2.03 (s, (0.2)3H, (3″-CH_3)), 2.15 (s, (0.8)3H, (3″-CH_3)), 2.25 (s, 3H, (4-CH_3)), 2.73–2.96 (m, 2H, CH_2CO), 3.87–4.17 (m, 5H, NCH_2 + CH + CH_2CH_3), 7.09 (s, (0.2)H, (2″-H)), 7.15 (d, $J = 8.3$ Hz, 2H, (3, 5-H_{ar})), 7.51 (d, $J = 8.3$ Hz, 2H, (2, 6-H)), 7.55 (s, 0.8H, (2″-H), 7.71 (dt, $J = 1.4$ Hz, $J = 7.5$ Hz, 1H, (6″-H_{ar})), 7.78 (dt, $J = 1.3$ Hz, $J = 7.7$ Hz, 1H, (7″-H)), 8.06 (d, $J = 7.5$ Hz, (5″-H)), 8.36 (d, $J = 7.4$ Hz, 1H, (8″-H)). ^{1}H NMR (300 MHz, $CDCl_3$), *δ*: 1.30 (t, $J = 7.0$ Hz, 3H, CH_2CH_3), 2.23, 2.24 (2 s, 3H, (3″-CH_3)), 2.32 (s, (4-H_{ar})), 2.75–2.99 (m, 2H, CH_2CO), 2.79 (quin, $J = 8.5$ Hz, 1H, CH), 3.90–4.26 (m, 4H, NCH_2 + CH_2CH_3), 7.16 (d, $J = 8.4$ Hz, 2H, (3, 5-H_{ar})), 7.28 (q, $J = 1.4$ Hz, 1H, (2″-H)), 7.49 (d, $J = 8.4$ Hz, 2H, (2, 6-H_{ar})), 7.63–7.73 (m, 2H, (6″, 7″-H)), 8.19–8.34 (m, 2H, (5″, 8″-H)). ^{13}C NMR (75 MHz, DMSO-d$_6$), *δ*: 12.33 (NCH_2CH_3), 16.61 (3″-CH_3), 20.41 (4-CH_3), 33.89 (C-3′), 35.27 (C-4′),

45.98 (N*CH*$_2$CH$_3$), 50.09 (C-2′), 119.46 (C-2, 6), 124.19, 125.71 (C-5″, C-8″), 125.87 (C-2″), 129.07 (C-3, 5), 130.43 (C-4a″), 130.90 (C-6″, C-7″), 133.14 (C-4), 133.14 (C-6″, C-7″), 133.88 (C-3″), 136.70 (C-1), 141.46 (C-8a″), 151.18 (C-1″), 171.54 (C-5′), 173.75 (CONH), 184.40 (C-4″). MS *m/z* (*I*, %): 438 $[M + Na]^+$ (100). Found, %: C 72.38, H 6.07, N 10.02. Calculated, %: C 72.27, H 6.06, N 10.11. $C_{25}H_{25}N_3O_3$.

*N-Ethyl-N′-(3-methyl-4-oxo-1,4-dihydronaphthalen-1-yl)-1-(2,5-dimethylphenyl)-5-oxopyrrolidine-3-carbohydrazide (**7d**)*

Yield 0.4 g (84.0%), m.p. 128–129 °C ($R_f = 0.80$). IR, *v*: 1650, 1691 (C=O). ^{1}H NMR (300 MHz, DMSO-d$_6$), *δ*: 1.18 (t, $J = 6.7$ Hz, 3H, CH$_2$*CH*$_3$), 2.08 (s, 3H, (2-CH$_3$)), 2.13 (s, 3H, (3″-CH$_3$)), 2.24 (s, 3H, (4-CH$_3$)), 2.64–2.76 (m, 2H, CH$_2$CO), 3.74–4.12 (m, 5H, NCH$_2$ + CH + *CH*$_2$CH$_3$), 7.00–7.15 (m, 3H, (3, 4, 6-H$_{ar}$)), 7.54 (s, 1H, (2″-H)), 7.70–7.82 (m, 2H, (6″, 7″-H)), 8.06 (dd, $J = 1.2$ Hz, $J = 7.6$ Hz, (5″-H)), 8.34 (d, $J = 7.9$ Hz, 1H, (8″-H)). ^{13}C NMR (75 MHz, DMSO-d$_6$), *δ*: 12.27 (NCH$_2$*CH*$_3$), 16.57 (3″-CH$_3$), 17.00 (2-CH$_3$), 20.41 (4-CH$_3$), 33.73 (C-3′), 34.60, 35.06 (C-4′), 45.98 (N*CH*$_2$CH$_3$), 51.92 (C-2′), 124.11, 125.70 (C-5″, C-8″), 125.89 (C-2″), 127.16 (C-6), 128.17 (C-4), 130.46 (C-2 + C-4a″), 130.90 (C-6″, C-7″), 132.21 (C-3), 133.15 (C-6″, C-7″), 133.89 (C-3″), 135.75 (C-5), 137.18 (C-1), 141.45 (C-8a″), 151.12 (C-1″), 171.36 (C-5′), 173.98 (CONH), 184.39 (C-4″). MS *m/z* (*I*, %): 430 $[M + H]^+$ (100). Found, %: C 72.66, H 6.26, N 9.74. Calculated, %: C 72.71, H 6.34, N 9.78. $C_{26}H_{27}N_3O_3$.

General procedure for the synthesis of *N′*-(3-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-aryl-5-oxopyrrolidine-3-carbohydrazides (**8a**–**h**)

To a solution of the corresponding hydrazide **1** (5 mmol) in dimethyl sulfoxide (25 mL), 2,3-dichloro-1,4-dihydronaphthalene-1,4-dione (**4**) (1.14 g, 5 mmol) was added, and the mixture was stirred for 24 h at room temperature. Upon completing the reaction, the reaction mixture was diluted with water (25 mL) and stirred for 10–15 min. The formed precipitate was filtered off, washed with water, 2-propanol, and dried.

*N′-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-phenyl-5-oxopyrrolidine-3-carbohydrazide (**8a**)*

Yield 1.6 g (80.0%), m.p. 189–190 °C (from 1,4-dioxane). IR, *v*: 1688, 1705 (C=O), 3174, 3355 (NH). ^{1}H NMR (300 MHz, DMSO-d$_6$), *δ*: 2.65–2.97 (m, 2H, CH$_2$CO), 3.30–4.26 (m, 2H, NCH$_2$ + CH), 7.06–8.38 (m, 9H, H$_{ar}$), 9.09, 10.74, 13.67, 13.80 (4 s, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d$_6$), *δ*: 33.83 (C-3′), 35.09, 35.35 (C-4′), 49.59, 49.88, 50.16 (C-2′), 111.53 (C-3″), 119.45, 119.57 (C-2, 6), 124.12, 124.25 (C-4), 126.19, 126.43, 127.08, 127.39 (C-5″, C-8″), 128.72 (C-3, 5 + C-4a″), 130.83, 131.36 (C-6″, C-7″), 133.31 (C-8a″), 134.66, 134.99, 135.10 (C-6″, C-7″), 139.12 (C-1), 144.99 (C-2″), 171.74, 172.79 (C-5′, CONH), 175.90 (C-4″), 179.11

(C-1″). MS *m/z* (*I*, %): 410.3 $[M + H]^+$ (100). Found, %: C 61.21, H 4.17, N 10.00. Calculated, %: C 61.55, H 3.94, N 10.25. $C_{21}H_{16}ClN_3O_4$.

*N′-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-(3-methylphenyl)-5-oxopyrrolidine-3-carbohydrazide (**8b**)*

Yield 1.6 g (75.5%), m.p. 151–152 °C (from 1,4-dioxane). IR, *v*: 1698 (C=O), 3213 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.30 (s, 3H, (3-H_{ar})), 2.62–3.01 (m, 2H, CH_2CO), 3.35–4.22 (m, 2H, NCH_2 + CH), 6.94–8.39 (m, 8H, H_{ar}), 9.07, 10.65, 10.82, 13.60, 13.78 (5 s, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), *δ*: 21.16 (4-CH_3), 33.85 (C-3′), 34.97, 35.14, 35.41 (C-4′), 49.86, 50.27 (C-2′), 111.52 (C-3″), 116.64, 116.76 (C-6), 120.00, 120.14 (C-2), 124.78, 124.86 (C-4), 126.78, 126.36 (C-5″, C-8″), 127.27 (C-8″), 128.47 (C-5), 129.70 (C-4a″), 131.38 (C-6″, C-7″), 133.01, 133.07, 133.29 (C-8a″), 134.17, 134.72, 135.03, 135.51 (C-6″, C-7″), 137.93 (C-3), 138.93, 139.01 (C-1), 144.68, 145.53 (C-2″), 170.98, 171.22, 171.38, 171.55 (C-5, CONH), 176.34 (C-4″), 178.99 (C-1″). Found, %: C 62.57, H 4.69, N 9.81. Calculated, %: C 62.34, H 4.28, N 9.91. $C_{22}H_{18}ClN_3O_4$.

*N′-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-(4-methylphenyl)-5-oxopyrrolidine-3-carbohydrazide (**8c**)*

Yield 1.7 g (81.3%), m.p. 159–160 °C (from 1,4-dioxane). IR, *v*: 1671, 1698 (C=O), 3236, 3299 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.26 (s, 3H, (4-H_{ar})), 2.63–2.85 (m, 2H, CH_2CO), 3.30–4.21 (m, 2H, NCH_2 + CH), 7.15–8.38 (m, 8H, H_{ar}), 9.08, 10.71, 13.67, 13.87 (4 s, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), *δ*: 20.42 (4-CH_3), 33.35, 33.87 (C-3′), 35.16, 35.37 (C-4′), 49.99, 50.27 (C-2′), 111.53 (C-3″), 119.43, 119.88 (C-2, 6), 126.16, 126.42, 127.05 (C-5″, C-8″), 129.10, 129.22 (C-3, 5), 129.77 (C-4a″), 130.88, 131.43 (C-6″, C-7″), 133.19 (C-4), 133.33 (C-8a″), 134.63, 135.07 (C-6″, C-7″), 136.86 (C-1), 144.70 (C-2″), 171.08, 171.45 (C-5′, CONH), 175.85, 176.41 (C-4″), 179.05, 179.03 (C-1″). MS *m/z* (*I*, %): 446.3 $[M + Na]^+$ (30), 448.4 $[M + 2 + Na]^+$ (15). Found, %: C 62.59, H 4.56, N 10.03. Calculated, %: C 62.34, H 4.28, N 9.91. $C_{22}H_{18}ClN_3O_4$.

*N′-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-(2,5-dimethylphenyl)-5-oxopyrrolidine-3-carbohydrazide (**8d**)*

Yield 1.6 g (71.9%), m.p. 188–189 °C (from 1,4-dioxane). IR, *v*: 1644, 1683 (C=O), 3169 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.07 (s, 3H, (2-H_{ar})), 2.25 (s, 3H, (5-H_{ar})), 2.55–2.93 (m, 2H, CH_2CO), 3.33–3.44 (m, 1H, CH), 3.67–4.32 (m, 2H, NCH_2), 7.01–8.14 (m, 8H, H_{ar}), 9.08, 10.61, 10.81, 13.70 (4 s, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), *δ*: 17.06 (2-CH_3), 20.35 (4-CH_3), 33.99 (C-3′), 34.92 (C-4′), 52.06 (C-2′), 111.56 (C-3″), 126.16, 126.40 (C-5″, C-8″), 127.08 (C-6), 128.22 (C-4), 129.26, 129.74 (C-4a″), 130.49 (C-2), 131.40 (C-6″, C-7″), 132.24 (C-3), 133.34 (C-8a″), 134.04, 135.08 (C-6″, C-7″), 135.79 (C-5), 137.14 (C-1), 144.77 (C-2″), 171.23, 171.32 (C-5, CONH), 175.82, 176.37 (C-4″), 179.04 (C-1″). MS *m/z*

(*I*, %): 460.4 $[M + Na]^+$ (35), 462.3 $[M + 2 + Na]^+$ (17). Found, %: C 63.41, H 4.57, N 9.56. Calculated, %: C 63.09, H 4.60, N 9.60. $C_{23}H_{20}ClN_3O_4$.

*N′-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-(5-chloro-2-methylphenyl)-5-oxopyrrolidine-3-carbohydrazide (**8e**)*

Yield 1.8 g (79.2%), m.p. 182–183 °C (from 1,4-dioxane). IR, *ν*: 1678, 1691 (C=O), 3262 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.28 (s, 3H, (2-H_{ar})), 2.64–2.99 (m, 2H, CH_2CO), 3.31–4.30 (m, 2H, NCH_2 + CH), 7.31–8.38 (m, 7H, H_{ar}), 9.05, 10.64, 10.81, 13.72 (4 s, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), *δ*: 16.97 (2-CH_3), 33.83 (C-3′), 34.98 (C-4′), 51.77 (C-2′), 111.54 (C-3″), 126.13, 126.24, 126.37 (C-5″, C-8″), 126.55 (C-6), 127.36 (C-4), 129.75, 129.93 (C-4a), 130.19 (C-2), 131.39 (C-6″, C-7″), 132.15 (C-5), 133.30 (C-8a), 134.68 (C-3), 135.03 (C-6″, C-7″), 138.70 (C-1), 144.74 (C-2″), 169.57, 171.14 (CONH), 171.45 (C-5′), 176.33 (C-4″), 179.01 (C-1″). Found, %: C 58.26, H 3.91, N 9.01. Calculated, %: C 57.66, H 3.74, N 9.17. $C_{22}H_{17}Cl_2N_3O_4$.

*N′-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-(3-chloro-4-methylphenyl)-5-oxopyrrolidine-3-carbohydrazide (**8f**)*

Yield 1.6 g (70.3%), m.p. 204–205 °C (from 1,4-dioxane). IR, *ν*: 1641, 1687 (C=O), 3165 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.10, 2.14 (2 s, 3H, (4-H_{ar})), 2.56–2.92 (m, 2H, CH_2CO), 3.35–4.15 (m, 2H, NCH_2 + CH), 7.23–8.16 (m, 7H, H_{ar}), 9.07, 10.61, 10.82, 13.72 (4 s, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), *δ*: 18.87 (4-CH_3), 33.76 (C-3′), 35.36 (C-4′), 50.06 (C-2′), 111.56 (C-3″), 117.76 (C-6), 119.39 (C-2), 126.11, 126.34, 127.00 (C-5″, C-8″), 129.70 (C-4a″), 130.79 (C-5), 131.06 (C-4), 131.37 (C-6″, C-7″), 133.07 (C-3), 133.28 (C-8a″), 134.58, 135.01 (C-6″, C-7″), 138.10 (C-1), 144.69 (C-2″), 170.89, 171.85 (C-5′, CONH), 176.34 (C-4″), 178.99 (C-1″). Found, %: C 57.44, H 3.92, N 9.12. Calculated %: C 57.66, H 3.74, N 9.17. $C_{22}H_{17}Cl_2N_3O_4$.

*Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-(4-bromophenyl)-5-oxopyrrolidine-3-carbohydrazide (**8g**)*

Yield 1.8 g (74.3%), m.p. 150–151 °C (from 1,4-dioxane). IR, *ν*: 1682, 1698 (C=O), 3183 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.64–3.00 (m, 2H, CH_2CO), 3.35–4.22 (m, 2H, NCH_2 + CH), 7.25–8.37 (m, 8H, H_{ar}), 9.07, 10.68, 13.70, 13.79, 14.26 (5 s, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), *δ*: 33.73 (C-3′), 35.43 (C-4′), 49.34, 49.51, 50.04 (C-2′), 111.51 (C-3″), 115.88 (C-4), 121.14, 121.27 (C-2, 6), 126.10, 126.35, 127.00 (C-5″, C-8″), 129.69 (C-4a″), 131.14 (C-3, 5), 131.43 (C-6″, C-7″), 133.27 (C-8a″), 134.58, 135.01 (C-6″, C-7″), 138.33 (C-1), 144.64 (C-2″), 170.85, 171.88 (C-5, CONH), 176.33 (C-4″), 178.95 (C-1″). Found, %: C 51.65, H 3.05, N 7.92. Calculated, %: C 51.61, H 3.09, N 8.60. $C_{21}H_{15}BrClN_3O_4$.

*N′-(3-Chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-1-(4-chlorophenyl)-5-oxopyrrolidine-3-carbohydrazide (**8h**)*

Yield 1.7 g (77.5%), m.p. 200–201 °C (from 1,4-dioxane). IR, *v*: 1681, 1699 (C=O), 3233, 3291 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), *δ*: 2.64–2.99 (m, 2H, CH_2CO), 3.31–3.41(m, 1H, CH), 3.89–4.24 (m, 2H, NCH_2), 7.40–8.11 (m, 8H, H_{ar}), 9.08, 10.68, 10.82, 13.67 (4 s, 2H, NH). ^{13}C NMR (75 MHz, DMSO-d_6), *δ*: 33.78 (C-3′), 35.39 (C-4′), 50.14 (C-2′), 111.51 (C-3″), 120.82 (C-2, 6), 126.15, 126.39, 127.80 (C-5″, C-8″), 128.57 (C-3, 5), 129.72 (C-4a″), 131.39 (C-6″, C-7″), 133.32 (C-8a″), 135.05 (C-6″, C-7″), 137.95 (C-1), 144.65 (C-2″), 170.92, 171.93 (C-5′, CONH), 176.38 (C-4″), 179.01 (C-1″). Found, %: C 57.34, H 3.61, N 9.86. Calculated, %: C 56.77,H 3.40, N 9.46. $C_{21}H_{15}Cl_2N_3O_4$.

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