

**СИНТЕЗ НОВЫХ ПРОИЗВОДНЫХ γ -ЛАКТОННОГО КОЛЬЦА,
СОДЕРЖАЩИХ ПИРИДИНОВЫЕ И ТРИКОНДЕНСИРОВАННЫЕ СИСТЕМЫ****Р.М. Акопян, Л.А. Харатьян, С.С. Айоцян, О.С. Агтарян, Г.С. Меликян**

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Лактон-пиридиноновые кольца содержат множество биологически активных молекул природного и искусственного происхождения. Молекулы, содержащиеся в этих двух кольцах, представленные серпезином и его производными, также будут проявлять высокую биологическую активность. Также нужно принять во внимание, что как натуральные, так и синтетические мультизамещенные лактоны имеют высокую биологическую активность. Таким образом, исследования в области мультизамещенных лактонов и дальнейшие превращения имеют вполне конкретный интерес. Первоначальным этапом был синтез 2-ацетилфуранонового кольца. На следующем этапе, в результате конденсации этилцианоацетата с 2-ацетилфураноном по Кневенагелю, были получены 3-замещенные лактоны, которые по данным ^1H ЯМР спектроскопии представляют собой смесь E и Z изомеров. Затем при нагревании 3-замещенных лактонов с диметилформамид диметилацеталем ДМФА/ДМА были получены 3-замещенные лактоны, содержащие в структуре диеновый фрагмент. Стереоселективное присоединение E было обнаружено с помощью ^1H ЯМР спектра. Затем под действием соответствующего амина в результате реакций межмолекулярного замещения образуются соединения, содержащие лактонную и пиридиновую группу, изолированную σ -связью (серпезиноподобное соединение). При нагревании в щелочной среде происходит внутримолекулярная циклизация с образованием новых триконденсированных систем из-за близкого расположения циановой группы пиридинового кольца и четвертой метильной группы лактонового кольца. Таким образом, разработан оптимальный метод синтеза серпезиноподобных соединений. Данные соединения вызывают интерес тем, что в своем скелете имеют не только конденсированную систему, но и спироциклы, поэтому могут служить объектами для дальнейших исследований.

Ключевые слова: лактон, пиридон, синтез, ДМФА/ДМА, стереоселективный, нуклеофильное присоединение, нуклеофильное вычитание, активная метильная группа конденсированных систем

**SYNTHESIS OF NEW γ -LACTONE RING DERIVATIVES CONTAINING PYRIDINE
AND TRICONDENSED SYSTEMS****R.M. Hakobyan, L.A. Kharatyan, S.S. Hayotsyan, H.S. Attaryan, G.S. Melikyan**

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Lactone-pyridone rings contain many biologically active molecules of natural and artificial origin. The molecules contained in these two rings, represented by Cerpegin and its derivatives, will also exhibit high biological activity. It is also necessary to take into account that both natural and synthetic multi-substituted lactones have high biological activity. Thus, research in the field of multi-substituted lactones and further transformations are of particular interest. The synthesis of such systems began with the synthesis of a 2-acetylfuranone ring. In the next step, condensation of ethylcyanoacetate with 2-acetylfuranone by Knewenegel produced 3-substituted lactones, which according to the NMR ^1H spectroscopy are a mixture of *E* and *Z* isomers. Then, when 3-substituted lactones were heated with dimethylformamide dimethylacetal DMFA/DMA, 3-substituted lactones containing a diene fragment in the structure were obtained. Stereoselective attachment *E* was detected using the NMR ^1H spectrum. Then, under the action of the corresponding amine, the intermolecular substitution reactions produce compounds containing a lactone and pyridine group isolated by a σ -bond (serpegenous compound). Due to the proximity of the cyanide group of the pyridine ring and the fourth blight group of the lactone ring, intramolecular cyclization occurs during heating in the alkaline medium to form new tricondensed systems. Thus, an optimal method of synthesis of serpegenous compounds has been developed. These systems are of interest because in their skeleton they have not only a condensed system but also spirocycles. The connections themselves may be a promise for further exploration.

Key words: lactone, pyridone, synthesis, DMF / DMA, stereoselective, nucleophilic addition, nucleophilic substitution, active methyl group

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INTRODUCTION

Many natural and artificial biologically active compounds contain the furanone ring, γ -lactone, and its derivatives [1-8] (Fig. 1a-c). The γ -lactone ring contains lactone sesquiterpenes (SLs), which are mostly found in plants of the *Asteraceae* family [9]. These compounds have various pharmacological applications [10-13]. They show anti-cancer, cytotoxic, antibacterial, immunoregulatory, and anti-inflammatory activities.

The pyridone ring and its derivatives are also abundant in various natural and artificial molecules [16-19]. The alkaloid cordipyridone A (Fig. 1d) has anti-malarial activity [20]. It suppresses the growth of the *P. falciparum* parasite. Another natural pyridone alkaloid is fusapyridone A (Fig. 1e) which exhibits antibacterial activity [21]. (\pm)-flavopucinin (Fig. 1f) is another natural pyridone compound that exhibits antibacterial and cytotoxic activity [22]. A study in 2021 showed that cordipyridone A, fusapyridone A, (\pm)-flavopucinin, and other natural compounds containing the pyridone cycle inhibit coronavirus 2, the major prote-

ase of SARS-CoV-2, which is necessary for virus replication [23].

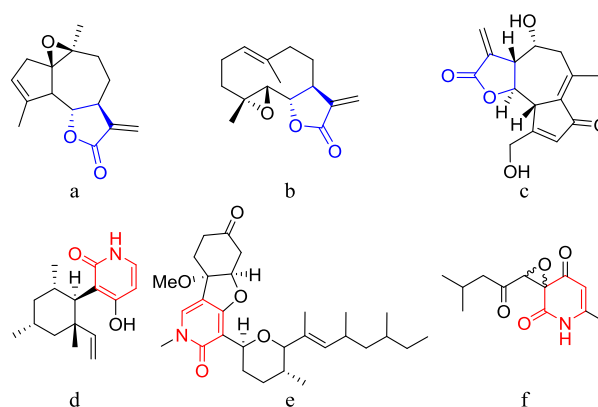


Fig. 1. Natural biological active molecules containing γ -lactone and 2-pyridone rings. a- arglabin [14], b- parthenolide [15], c- lactucine [15], d- cordipyridone A [20], e- fusapyridone A [21], f- (\pm)-flavopucinin [22].

Рис. 1. Природные биологически активные молекулы, содержащие γ -лактонное и 2-пиридоновое кольца. а- арглабин [14], б- партенолид [15], в- лактуцин [15], д- кордипиридон А [20], е- фузапиридон А [21], ф- (\pm)-флавопучин [22]

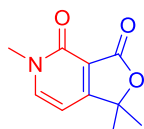


Fig. 2. Cerpegin
Рис. 2. Серпезжин

Not surprisingly, molecules containing pyridone-lactone rings will exhibit biological activity [24-27]. A classic example of this is the natural alkaloid cerpegin (Fig. 2), which was first isolated from the extract of the plant *Ceropegia Juncea* [28]. The plant has been used as a tranquilizer and anti-cancer and anti-inflammatory agent. Cerpegin and its derivatives are effective proteasome inhibitors [29-30]. Proteasome inhibitors have a regulatory effect on both cytotoxic and cell-modulatory functions [31].

Finally, the great importance has the spirofused polycyclic systems [32]. Similar molecules have antimalarial [33], anti-HIV [34], antitubercular [35], and MDM2 inhibitor [36]. That is why the synthesis of these systems is an important task.

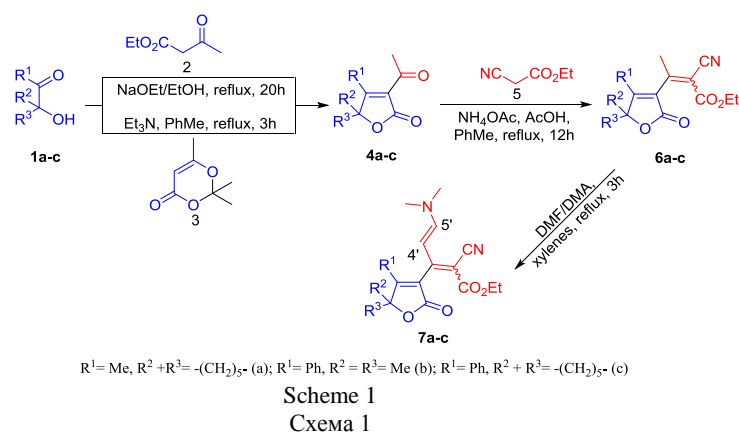
The molecules synthesized in this study are thought to inhibit the proteasome.

DESCRIPTION

The main goal of the research is to study and optimize the reactions of the synthesis of Cerpegin-like substances. The synthesis started with the sequence of (Scheme 1). 2-Acetylfuranone derivatives (**4a-c**) are the starting material for synthesis. We get them in our laboratory by two methods [37]. The first method is the aldol-crotonic condensation of **1a-c** keto alcohols and ethyl acetoacetate (**2**) in the basic medium, followed by a re-esterification reaction to form the **4a-c** compound [38]. However, in this method, the reaction takes quite a long time and the yield of the reaction is quite low. For that reason, our team gets the **4a-c** compound by the second method. In this case the condensation reaction proceeds between keto alcohols (**1a-c**) and 2,2,6-Trimethyl-4H-1,3-dioxin-4-one (**3**). With this method, compound **4a-c** is obtained with a faster and higher yield. In the next step, under the influence of ammonium acetate, the Knoevenagel condensation reaction proceeds between the **4a-c** compound and ethyl cyanoacetate (**5**) [39]. The compound **6a-c** is formed, which is a mixture of E and Z isomers.

N, N-dimethylformamide dimethyl acetal (DMF/DMA) is one-carbon block [40], which interacts with compound **6a-c** to form compound **7a-c**. Compound **6a** has two active methyl groups, one attached to the furanone ring and the other attached to the carbon chain double bond attached to the furanone ring. The second methyl group is more acidic, so with

a high yield =CH-N(Me)₂ group joins the second methyl group. Compound **7a-c** should theoretically have 4 isomers, but only two isomers in the ¹H NMR spectrum. The spin-spin interaction constant of the vicinal hydrogens in the 4' and 5' positions is 12.5, which corresponds to the spin-interaction constant in the E position hydrogens. From all this, we understand that only trans isomers arise from the connection of DMF/DMA. It is also interesting to note that the two methyl groups attached to nitrogen at compound **7a-c** are not equivalent, as these methyls differ from each other in the ¹H NMR spectrum. This phenomenon is explained by the presence of a p-π coupling between the electron pair nitrogen to double bond, which complicates the rotation of the bond and in this case the methyl groups are already different.



In the next stage, target cerpegin-like compounds have already been obtained (Scheme 2). Unlike Cerpegin, in these molecules, the pyridone-furanone rings are connected by a single bond. This stage has been implemented by our team in two ways, and those methods have been optimized. The reaction was carried out between different amines and compound **7a-c**. The reaction is initially carried out by intermolecular nucleophilic substitution, with the removal of dimethylamine and the replacement of amine. An intramolecular nucleophilic substitution then occurs, resulting in the formation of the pyridone ring. In the first method, the reaction was carried out in xylene, boiling the reaction mixture for 10 h [41]. The reaction was monitored by the release of dimethylamine. The first method has a lower yield compared to the second method. In the second method, the reaction was carried out under pressure by heating the reaction mixture in a water bath. This method produces quite high yields.

Continuing the research, our team noticed that in the basic medium **8a-i** they undergo intramolecular cyclizing, aromatic-benzene, with the formation of a ring (Scheme 3). The γ-lactone ring of **8a-n** compounds in

the 3rd position contains the active methyl group, which is easily deprotonated by the action of the base. An intramolecular nucleophilic coupling then takes place, with the negatively charged methylene anion attacking the partially positively charged carbon of the pyridone ring nitrile group.

In the ^1H NMR spectrum of **11** compounds, the C-5 amino group hydrogens chemical shift is broad in the range of 6.5-10 ppm. The reason for the wide rupture is the intracellular hydrogen bonds. Hydrogen bonds are formed between the C-5 amino group hydrogen and the C-6 position carbonyl electron pair. With

the help of ^1H NMR, it was shown that when the temperature rises, the hydrogen bonds are broken, and at 60°C they disappear completely, leaving a sharp single.

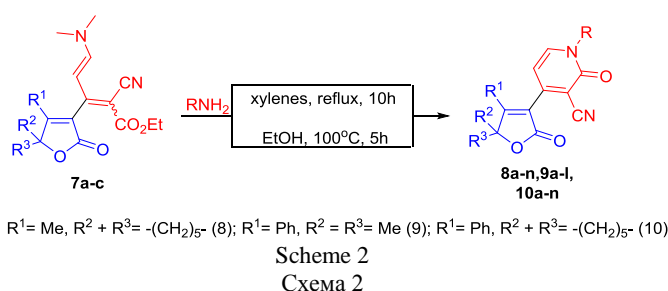


Table 1

Obtained compounds with corresponding yields
Таблица 1. Полученные соединения (8a-n, 9a-m, 10a-m) с соответствующими выходами

R =	R =	R =	R =	R =
8a (78%), 9a (82%), 10a (87%)	8b (76%), 9b (77%), 10b (85%)	8c (72%)	8d (78%)	8e (75%), 10e (69%)
R =	R =	R =	R =	R =
8f (71%), 9f (81%), 10f (81%)	8g (87%), 9g (68%), 10g (73%)	8h (90%), 10h (69%)	8i (68%), 10i (73%)	8j (81%)
R =	R =	R =	R =	R =
8k (79%)	9l (68%), 10l (62%)	8m (83%), 9m (71%), 10m (87%)	8n (72%)	

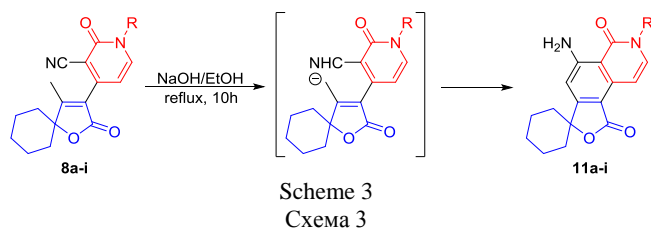


Table 2

Obtained compounds with corresponding yields
Таблица 2. Полученные соединения (11 a-i) с соответствующими выходами

R =	R =	R =
11a (69%)	11b (71%)	11c (63%)
R =	R =	R =
11d (71%)	11e (63%)	11f (68%)
R =	R =	R =
11g (79%)	11h (61%)	11i (59%)

EXPERIMENTAL

General Information

IR spectra were obtained on a Specord 75 IR spectrometer in KBr pellets. ^1H and ^{13}C NMR (300 and 75 MHz, respectively) spectra were recorded on a Varian Mercury VX 300 spectrometer in $\text{DMSO}-d_6\text{-CCl}_4$, 1:3, at 30°C (unless otherwise mentioned), using TMS as internal standard. Elemental analysis was performed on a EuroVector EA3000 instrument. Melting points were determined on a Stuart SMP10 melting point apparatus.

All starting compounds were obtained from commercial sources and were used without additional purification.

Synthesis of 3-Acetylfuran-2(5H)-one (4a-c). Method I. Dissolve 2.4 g (0.105 mol) of sodium metal in 50 ml of absolute ethanol, add 10.2 g (0.1 mol) of 3-hydroxy-3-methylbutane-2-one (**1a-c**) and 16.9 g (0.13 mol) of ethyl acetate (**2**). The resulting solution is boiled in a return refrigerator for 20 h, after which a

part of the solvent is removed, and the rest of the mass is neutralized with 1:1 diluted hydrochloric acid. The solution is extracted with diethyl ether (3×50 ml), dried over sodium sulfate, then the solvent is removed, then the residue is distilled under low pressure to obtain the corresponding **4a-c** lactone.

4-methyl-5,5-pentamethylene-3-acetylfuran-2(5H)-one (4a): It is a well-known compound, yield 87%, mp 55-56 °C, bp 120-125 °C (3 mmHg).

4-phenyl-5,5-dimethyl-3-acetylfuran-2(5H)-one (4b): It is a well-known compound, yield 90%, mp 59-60 °C, bp 130-135 °C (3 mmHg).

4-phenyl-5,5-pentamethylene-3-acetylfuran-2(5H)-one (4c): It is a well-known compound, yield 92%, mp 65-66 °C, bp 135-140 °C (3 mmHg). The physicochemical properties correspond to the literature data.

Method II. 250 ml Toluol solution of 2.55 g (25 mmol) of hydroxy ketone and 1. 1.31 g (13 mmol) of triethylamine, add 2,2,6-Trimethyl-4H-1,3-dioxin-4-one (**3**) 5.4 g (38 mmol). The reaction mixture was boiled in a reflux refrigerator for 3 h, then left to cool, neutralized with 1:1 diluted hydrochloric acid, extracted with ethyl acetate (3×100 ml). The combined organic part is dried with sodium sulfate. After removing the solvents, the residue is distilled in a deep vacuum to obtain the corresponding **4a-c** lactones.

Ethyl-2-cyano-3-(4-methyl-5,5-pentamethylene-2-oxo-2,5-dihydrofuran-3-yl)but-2-ethanone (6a): It is a well-known compound, yield 77%, mp 85-86 °C.

Ethyl-2-cyano-3-(4-phenyl-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-yl)but-2-ethanone (6b): It is a well-known compound, yield 78%, mp 88-89 °C

Ethyl-2-cyano-3-(4-phenyl-5,5-pentamethylene-2-oxo-2,5-dihydrofuran-3-yl)but-2-ethanone (6c): It is a well-known compound, yield 80%, mp 93-94 °C. The physicochemical properties correspond to the literature data.

Synthesis of Ethyl-2-cyano-3-(4,5,5-trisubstituted-2-oxo-2,5-dihydrofuran-3-yl)but-2-ethanone (General procedure) (6a-c): 5.04 g (30 mmol) of 3-Acetyl-4,5,5-trimethyl-2(5H)-one (**4**) and 3.73 g (33 mmol) of ethyl ester of cyanoacetic acid (**5**) in 20 ml of benzene solution add 1 g (13 mmol) ammonium acetate, 2 g (33 mmol) of glacial acetic acid are boiled with a Din-Stark water separator. After boiling for 12 h, leave the reaction mixture at room temperature, wash with 10 ml of concentrated brine, and extract with 3×20 ml of dichloromethane. Combine the organic parts and dry with sodium sulfate. The crystals formed after the removal of the solvents were washed with di-

ethyl ether and then recrystallized from the hexane/ethanol (4:1) system.

Synthesis of 1-Substituted-2-oxo-4-(4,5,5-trisubstituted-2-oxo-2,5-dihydrofuran-3-yl)-1,2-dihydropyridine-3-carbonitrile (8a-n, 9a-l,10a-n) (General procedure): Method I: The mixture of 1.1 mmol primary amine **1** (1 mmol) **7a-c** compounds are refluxed in 1 ml of xylene for 10 hours, after which it is left to cool. The crystals formed after freezing are filtered, washed with diethyl ether, then recrystallized from ethanol.

Method II: In a hermetically sealed tube add 1.1 mmol of the corresponding primary amine and compound **7a-c** (1 mmol) to 1 ml of ethanol **1** place in an autoclave heated to 100 °C. After staying in these conditions for 5 h, it is allowed to cool, after which the autoclave is opened, the formed crystals are filtered, and then hexane is washed with diethyl ether in a 1: 1 mixture. Then the corresponding compounds are separated.

Synthesis of 7-substituted-5-amino-3,3-pentamethylenefuro[3,4-f]isochinolidine-1,6(3H,7H)-dion (11a-i) (General procedure): 0.1 mmol 1-substituted-4-(4-methyl-,5,5-pentamethylene-2 (5H) -on-3-yl) -2-oxo-1,2-dihydropyridine-3-carbonitrile (**8a-i**) dissolve 2 ml in 1M of ethanol sodium hydroxide solution, reflux for 10 h, then filter the crystals, wash with diethyl ether, and obtain the results of intramolecular cyclizing.

Synthesis of Ethyl-2-cyano-5-(dimethylamine)-3-(4,5,5-trisubstituted-2-oxo-2,5-dihydrofuran-3-yl)penta-2,4-dienate: (General procedure) (7a-c). Compound **6a** (10 mmol) and (1.3 g, 11 mmol) DMF/DMA add to 20 ml of the xylene solution. The resulting solution is refluxed for 3 h after cooling adding 10 ml of hexane. The resulting crystals are filtered and washed with diethyl ether.

Ethyl-2-cyano-5-(dimethylamine)-3-(4-methyl-5,5-pentamethylene-2-oxo-2,5-dihydrofuran-3-yl)penta-2,4-dienate (7a): Yield 93%, mp 142 °C, green solid, IR spectrum, ν , cm^{-1} : 1100 (C-O-C), 1698 (CO), 2100 (CN), ^1H NMR spectrum, δ , ppm (*J*, Hz): 1.26t (3H, *J*=7.1, CH_3CH_2), 1.65-1.87m (10H, 5 CH_2), 1.80s (3H, 3- CH_3), 3.21s (3H, N- CH_3), 3.21s (3H, N- CH_3), 4.06q (2H, *J*=7.1, CH_2O), 5.66d (1H, *J*=12.5, CH), 7.06-6.98m (1H, CH), 1.33t (3H, *J*=7.1, CH_3CH_2), 1.65-1.87m (10H, 5 CH_2), 1.94s (3H, 3- CH_3), 3.06s (3H, N- CH_3), 3.22s (3H, N- CH_3), 4.17q (2H, *J*=7.1, CH_2O), 7.06-6.98m (2H, 2-CH). Found, %: C 67.00; H 7.33; N 7.79. $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_4$. Calculated, %: C 67.02; H 7.31; N 7.82.

Ethyl-2-cyano-5-(dimethylamine)-3-(4-phenyl-5,5-dimethyl-2-oxo-2,5-dihydrofuran-3-yl)penta-2,4-dienate (7b): Yield 94%, mp 153 °C, green solid, IR spectrum, ν , cm^{-1} : 1100 (C-O-C), 1640 (C=C), 1700 (C=O), 2100 (CN), ^1H NMR spectrum, δ , ppm (J , Hz): 1.31t (3H, $J=7.1$, CH_3CH_2), 1.48s (3H, 5- CH_3), 1.80s (3H, 5- CH_3), 2.90s (3H, N- CH_3), 3.18s (3H, N- CH_3), 4.15q (2H, $J=7.1$, CH_2O), 5.42d (1H, $J=12.5$, CH), 7.13-7.44m (6H, 5H, PH, 1CH), 1.30t (3H, $J=7.1$, CH_3CH_2), 1.59s (3H, 5- CH_3), 1.71s (3H, 5- CH_3), 2.98s (3H, N- CH_3), 3.26s (3H, N- CH_3), 4.19q (2H, $J=7.1$, CH_2O), 6.80-6.90m (1H), 7.13-7.44m (6H, 5H, PH, 1CH). Found, %: C 69.50; H 6.40; N 7.30. $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_4$. Calculated, %: C 69.46; H 6.36; N 7.36.

Ethyl-2-cyano-5-(dimethylamine)-3-(4-phenyl-5,5-pentamethylene-2-oxo-2,5-dihydrofuran-3-yl)penta-2,4-dienate (7c): Yield 91%, mp 162 °C, green solid, IR spectrum, ν , cm^{-1} : 1100(C-O-C), 1640(C=C), 1700(C=O), 2100(CN), ^1H NMR spectrum, δ , ppm (J , Hz): 1.11-1.23br (1H), 1.32t (3H, $J=7.1$, CH_3CH_2), 1.67-2.00m (9H, 5 CH_2), 2.88s (3H, N- CH_3), 3.19s (3H, N- CH_3), 4.16q (2H, $J=7.1$, CH_2O), 5.39d (1H, $J=12.5$, CH), 6.96-7.43m (5H, Ph), 7.17d (1H, $J=12.5$, CH), 1.11-1.23bz (1H), 1.30t (3H, $J=7.1$, CH_3CH_2), 1.67-2.00m (9H, 5 CH_2), 2.96s (3H, N- CH_3), 3.26s (3H, N- CH_3), 4.06-4.14m (2H, CH_2O), 6.83d (1H, $J=12.5$, CH), 6.96-6.96-7.43m (6H, 5Ph+CH). Found, %: C 71.37; H 6.74; N 6.60. $\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_4$. Calculated, %: C 71.41; H 6.71; N 6.66.

1-cyclohexyl-4-(4-methyl-2-oxo-1-oxospiro[4.5]dec-3-en-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (8a): Yield 78%, mp 186-188 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1550 (C=C-C=C), 1700 (C=O), 2200 (CN), ^1H NMR spectrum, δ , ppm (J , Hz): 1.19-1.98m (20H, 10 CH_2), 2.10s (3H, CH_3), 4.70tt (1H, $J=11.7$, 3.3, NCH), 6.31d (1H, $J=7.1$ -5-CH), 8.03d (1H, $J=7.1$, 6-CH), ^{13}C NMR spectrum, δ , ppm: 12.9, 21.4 (2C), 23.8, 24.5, 25.2 (2C), 31.17 (2C), 32.7 (2C), 54.8, 87.3, 103.2, 106.4, 114.4, 121.9, 139.3, 148.3, 158.3, 167.3, 170.7. Found, %: C 72.05; H 7.10; N 7.60. $\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_3$. Calculated, %: C 72.11; H 7.15; N 7.64.

4-(4-Methyl-2-oxo-1-oxospiro[4.5]dec-3-en-3-yl)-2-oxo-1-(2,2,6,6-tetramethylpiperidine-4-yl)-1,2-dihydropyridine-3-carbonitrile (8b): Yield 76%, mp 201-203 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1650; 1700 (C=O), 2200 (CN); 3425 (NH), ^1H NMR spectrum, δ , ppm (J , Hz): 0.7-2-br (1H, NH), 1.14s (6H, 2 CH_3), 1.29s (6H, 2 CH_3), 1.42-1.54m (2H), 1.54-1.66m (2H), 1.65-1.92m (10H, 7 CH_2), 2.09s (3H, CH_3), 5.25tt (1H, $J=12.3$, 3.0, NCH), 6.32d (1H, $J=7.1$, 5-CH), 8.00d (1H, $J=7.1$, 6-CH), ^{13}C NMR spectrum, δ , ppm: 12.8, 21.4 (2C), 23.8, 28.0 (2C), 32.7 (2C), 34.2

(2C), 42.7 (2C), 48.9, 50.9 (2C), 87.4, 103.2, 106.5, 114.3, 121.9, 139.2, 148.3, 158.5, 167.3, 170.6. Found, %: C 70.90; H 7.90; N 9.95. $\text{C}_{25}\text{H}_{33}\text{N}_3\text{O}_3$. Calculated, %: C 70.89; H 7.85; N 9.92.

4-(4-methyl-2-oxo-1-oxospiro[4.5]dec-3-en-3-yl)-2-oxo-1-((tetrahydrofuran-2-yl)methyl)-1,2-dihydropyridine-3-carbonitrile (8c): Yield 72%, mp 182-184 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1520 (C=C-C=C) 1650 (CON); 1720 (C=O), 2200 (CN), ^1H NMR spectrum, δ , ppm (J , Hz): 1.25-1.43m (1H), 1.55-1.98m (13H, 7 CH_2), 2.10s (3H, CH_3), 3.66-3.89m (3H, OCH, OCH_2), 4.15ddd (1H, $J=10.1$, 7.0, 3.0 NH^a), 4.28dd (1H, $J=13.1$, 3.1, NH^b), 6.27d (1H, $J=7.0$, 5-CH), 7.95d (1H, $J=7.0$, 6-CH), ^{13}C NMR spectrum, δ , ppm: 12.9, 21.4 (2C), 23.8, 24.9, 28.2, 32.7, 52.3, 67.0, 75.3, 87.4, 103.2, 105.7, 114.3, 122.0, 143.93, 149.40, 158.72, 167.31, 170.65. Found, %: C 68.41; H 6.63; N 7.55. $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4$. Calculated, %: C 68.46; H 6.57; N 7.60.

1-cycloheptyl-4-(4-methyl-2-oxo-1-oxospiro[4.5]dec-3-en-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (8d): Yield 78%, mp 213-215 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1500 (C=C-C=C), 1630 (CON); 1740 (C=O), 2200 (CN), ^1H NMR spectrum, δ , ppm (J , Hz): 1.25-1.44m (1H), 1.56-1.96m (21H, 11 CH_2), 2.09ss (3H, CH_3), 4.83tt (1H, $J=10.0$, 4.3, NCH), 6.30d (1H, $J=7.0$, 6-CH), 8.00d (1H, $J=7.0$, 6-CH), ^{13}C NMR spectrum, δ , ppm: 12.9, 21.3 (2C), 23.8, 24.4 (2C), 26.5 (2C), 32.6 (2C), 33.7 (2C), 57.1, 87.3, 103.2, 106.5, 114.4, 121.9, 139.7, 148.3, 158.0, 167.3, 170.6. Found, %: C 72.50; H 7.45; N 7.40. $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_3$. Calculated, %: C 72.60; H 7.42; N 7.36.

1-(3-(1H-imidazole-1-yl)propyl)-4-(4-methyl-2-oxo-1-oxospiro[4.5]dec-3-en-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (8e): Yield 75%, mp 237-239 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1500 (C=C-C=C), 1630 (CON); 1740 (C=O), 2200 (CN), ^1H NMR spectrum, δ , ppm (J , Hz): 1.34-1.52m (1H), 1.60-1.88m (9H, 5 CH_2), 2.20p (2H, $J=7.0$, CH_2 - CH_2 - CH_2), 3.96t (2H, $J=7.0$, CH_2 - CH_2 - CH_2), 4.05t (2H, $J=7.0$, CH_2 - CH_2 - CH_2), 6.44 s (1H, CH_{Ar}), 6.84(1H,), 7.06s (1H,), 7.38d (1H, $J=7.4$), 7.43d (1H, $J=7.4$, 2 CH_{Ar}), 7.53s (1H,), 6.6-9.6br (2H, NH_2), ^{13}C NMR spectrum, δ , ppm: 21.7 (2C), 24.2, 30.1, 35.6 (2C), 43.4, 45.5, 82.9, 100.7, 102.5, 109.0, 118.3, 128.3, 135.2, 136.5, 138.5, 156.5, 160.2, 162.7, 168.0. Found, %: C 67.38; H 6.20; N 14.35. $\text{C}_{22}\text{H}_{24}\text{N}_4\text{O}_3$. Calculated, %: C 67.33; H 6.16; N 14.28.

1-(2-(1H-Indo-3-yl)ethyl)-4-(4-methyl-2-oxo-1-oxospiro[4.5]dec-3-en-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (8f): Yield 71%, mp 230-232 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1500 (C=C-C=C); 1675, 1720 (C=O); 2200 (CN); 3100, ^1H

NMR spectrum, δ , ppm (J , Hz): 1.27-1.41m (1H), 1.54-1.92 (9H, 5CH₂), 2.06s (3H, CH₃), 3.17t (2H, $J=7.1$), 4.25t (2H, $J=7.1$, NCH₂), 6.10d (1H, $J=7.0$, 5-CH), 6.92-7.04m (2H, 5, 6-CH), 7.05s (1H, 2CH), 7.29-7.33brd (1H, $J=7.9$) and 7.51-7.56brd (1H, $J=7.9$, 4,7-CH), 7.62d (1H, $J=7.0$, 6-CH), 7.99s (1H, NH), ¹³C NMR spectrum, δ , ppm: 12.75, 21.39 (2C), 23.85, 24.01, 32.7 (2C), 50.56, 87.38, 103.38, 105.66, 109.39, 111.12, 114.40, 117.63, 118.10, 120.59, 122.10, 122.82, 126.71, 136.10, 143.14, 149.20, 158.67, 167.35, 170.57. Found, %: C 73.15; H 5.95; N 9.85. C₂₆H₂₅N₃O₃. Calculated, %: C 73.05; H 5.89; N 9.83.

1-(Cyclohex-1-en-1-ylmethyl)-4-(4-methyl-2-oxo-1-oxospiro[4.5]dec-3-en-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (8g): Yield 87%, mp 210-212 °C, pale-yellow solid, IR spectrum, ν , cm⁻¹: 1500 (C=C-C=C), 1630 (CON); 1730 (C=O), 2200 (CN), ¹H NMR spectrum, δ , ppm (J , Hz): 1.25-1.42m (1H), 1.49-2.06m (7H, 10CH₂), 2.08s (3H, CH₃), 2.32t (2H, $J=7.2$, CH₂), 4.04t (2H, $J=7.2$, NCH₂), 5.36brs (1H, CH=), 6.25d (1H, $J=7.0$, 5-CH), 7.94d (1H, $J=7.0$, 6-CH), ¹³C NMR spectrum, δ , ppm: 12.81, 21.36 (2C), 21.57, 22.18, 23.83, 24.60, 27.49, 32.68(2C), 36.33, 47.87, 87.33, 102.65, 103.37, 105.72, 114.28, 122.06, 123.63, 132.92, 143.06, 149.06. Found, %: C 73.05; H 6.90; N 7.45. C₂₃H₂₆N₂O₃. Calculated, %: C 72.99; H 6.92; N 7.40.

4-(4-methyl-2-oxo-1-oxospiro[4.5]dec-3-en-3-yl)-1-(3-morpholinopropyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (8h): Yield 90%, mp 235-237 °C, pale-yellow solid, IR spectrum, ν , cm⁻¹: 1500 (C=C-C=C), 1630 (CON); 1740 (C=O), 2200 (CN), ¹H NMR spectrum, δ , ppm (J , Hz): 1.25-1.44m (1H), 1.56-1.65m (2H), 1.70-1.96m (9H, 6CH₂), 2.10s (3H, CH₃), 2.33-2.40m (6H, 3NCH₂), 3.54-3.59m (4H, 2CH₂O), 4.04t (2H, $J=7.0$, NCH₂), 6.27d (1H, $J=7.0$, 5-CH), 8.05d (1H, $J=7.0$, 6-CH), ¹³C NMR spectrum, δ , ppm: 12.84, 21.37 (2C), 23.83, 24.21, 32.67(2C), 48.14, 52.81 (2C), 54.67, 65.88(2C), 87.36, 103.44, 105.85, 114.32, 122.03, 143.46, 149.16, 158.69, 167.34, 170.56. Found, %: C 67.19; H 7.05; N 10.16. C₂₃H₂₉N₃O₄. Calculated, %: C 67.13; H 7.10; N 10.21.

4-(4-methyl-2-oxo-1-oxospiro[4.5]dec-3-en-3-yl)-2-oxo-1-(3-(pyrrolidine-1-yl)propyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (8i): Yield 68%, mp 208-210 °C, pale-yellow solid, IR spectrum, ν , cm⁻¹: 1500 (C=C-C=C), 1630 (CON); 1740 (C=O), 2200 (CN), ¹H NMR spectrum, δ , ppm (J , Hz): 1.27-1.43m (1H), 1.54-1.65m (2H), 1.71-1.93m (13H, 8CH₂), 2.10s (3H, CH₃), 2.42-2.48m (6H, 3NCH₂), 4.04t (2H, $J=7.0$, NCH₂), 6.26d (1H, $J=7.0$, 5-CH), 8.00d (1H, $J=7.0$, 6-CH), ¹³C NMR spectrum, δ , ppm: 21.7 (2C), 24.2, 30.1, 35.6 (2C), 12.85, 21.37 (2C), 22.96 (2C),

23.83, 26.70, 32.68(2C), 48.10, 51.90, 53.04 (2C), 87.34, 103.46, 105.81, 114.32, 122.03, 143.35, 149.14, 158.63, 167.32, 170.56. Found, %: C 69.91; H 7.45; N 10.57. C₂₃H₂₉N₃O₃. Calculated, %: C 69.85; H 7.39; N 10.62.

1-(furan-2-ylmethyl)-4-(4-methyl-2-oxo-1-oxospiro[4.5]dec-3-en-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (8j): Yield 81%, mp 241-243 °C, pale-yellow solid, IR spectrum, ν , cm⁻¹: 1500 (C=C-C=C), 1630 (CON); 1740 (C=O), 2200 (CN), ¹H NMR spectrum, δ , ppm (J , Hz): 1.25-1.42m (1H) and, 1.55-1.64m (2H) and, 1.69-1.92m (7H, 5CH₂), 2.09s (3H, CH₃), 5.20s (2H, CH₂), 6.32d (1H, $J=7.0$, 5-CH), 6.37dd (1H, $J=3.0$, 1.8, 4-CH), 6.50d (1H, $J=3.0$, 5-CH), 7.48d (1H, $J=1.6$, 3-CH), 8.05d (1H, $J=7.0$, 6-CH), ¹³C NMR spectrum, δ , ppm: 12.9, 21.3 (2C), 23.81, 32.6 (2C), 44.4, 87.45, 103.8, 106.4, 109.9, 110.2, 114.1, 121.9, 142.4, 142.6, 147.9, 149.6, 158.2, 167.3, 170.9. Found, %: C 69.18; H 5.59; N 7.74. C₂₁H₂₀N₂O₄. Calculated, %: C 69.22; H 5.53; N 7.69.

4-(4-methyl-2-oxo-1-oxospiro[4.5]dec-3-en-3-yl)-2-oxo-1-(thiophen-2-ylmethyl)-1,2-dihydropyridine-3-carbonitrile (8k): Yield 79%, mp 218-220 °C, pale-yellow solid, IR spectrum, ν , cm⁻¹: 1550 (C=C-C=C), 1690, 1720 (C=O), 2200 (CN), ¹H NMR spectrum, δ , ppm (J , Hz): 1.24-1.42m (1H), 1.52-1.60m (2H), 1.63-1.93m (7H), 2.07s (3H, 4-CH₃), 5.36s (2H, CH₂N), 6.34d (1H, $J=7.0$, 5-CH), 6.97dd (1H, $J=5.1$, 3.5, 4-CH), 7.24dd (1H, $J=3.5$, 0.9, 5-CH), 7.37dd (1H, $J=5.1$, 0.9, 3-CH), 8.24d (1H, $J=7.0$, 6-CH), ¹³C NMR spectrum, δ , ppm: 12.8, 21.4 (2C), 23.7, 32.6 (2C), 46.5, 87.6, 103.5, 106.7, 114.2, 121.9, 126.3, 126.5, 128.0, 136.9, 142.7, 149.7, 158.4, 167.4, 171.1. Found, %: C 66.40; H 5.35; N 7.40. C₂₁H₂₀N₂O₃S. Calculated, %: C 66.30; H 5.30; N 7.36.

4-(4-methyl-2-oxo-1-oxospiro[4.5]dec-3-en-3-yl)-2-oxo-1-(pyridine-3-ylmethyl)-1,2-dihydropyridine-3-carbonitrile (8m): Yield 83%, mp 224-226 °C, pale-yellow solid, IR spectrum, ν , cm⁻¹: 1550 (C=C-C=C), 1650; 1700 (C=O), 2200 (CN), ¹H NMR spectrum, δ , ppm (J , Hz): 1.26-1.43m (1H), 1.50-1.94m (9H, 5CH₂), 2.08s (3H, CH₃), 5.22s (2H, NCH₂), 8.37d (1H, $J=7.0$, 5-CH), 7.34dd (1H, $J=7.8$, 4.8, 5-CH), 7.81dt (1H, $J=7.8$, 1.7, 4¹-CH), 8.34d (1H, $J=7.0$, 6-CH), 8.49dd (1H, $J=4.8$, 1.7, 6¹-CH), 8.65d (1H, $J=1.7$, 2¹-CH), ¹³C NMR spectrum, δ , ppm: 12.83, 21.39 (2C), 23.74, 32.56 (2C), 49.85, 87.68, 103.74, 106.83, 114.29, 121.85, 123.15, 131.17, 135.81, 143.28, 148.78, 149.44, 149.82, 158.79, 167.45, 171.27. Found, %: C 70.42; H 5.60; N 11.22. C₂₂H₂₁N₃O₃. Calculated, %: C 70.38; H 5.64; N 11.19.

1-(2-(dimethylamino)ethyl)-4-(4-methyl-2-oxo-1-oxospiro[4.5]dec-3-en-3-yl)-2-2-oxo-1,2-dihydropyridine-3-carbonitrile (8n): Yield 72%, mp 221-223 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1500 (C=C-C=C), 1630 (CON); 1740 (C=O), 2200 (CN), ^1H NMR spectrum, δ , ppm (J , Hz): 1.28-1.42m (1H), 1.56-1.64m (2H), 1.70-1.92m (7H), 2.10s (3H, 4-CH₃), 2.26s (6H, 2CH₃N), 2.59t (2H, $J=6.0$, N-CH₂), 4.06t (2H, $J=6.0$, NCH₂), 6.25d (1H, $J=6.9$, 5-CH), 7.97d (1H, $J=6.9$, 6-CH), ^{13}C NMR spectrum, δ , ppm: 12.9, 21.4 (2C), 23.8, 32.7 (2C), 44.9 (2C), 46.6, 56.8, 87.3, 103.21, 105.6, 114.3, 122.0, 143.6, 149.1, 158.6, 167.3, 170.6. Found, %: C 67.65; H 7.15; N 11.87. C₂₀H₂₅N₃O₃. Calculated, %: C 67.58; H 7.09; N 11.82.

1-cyclohexyl-4-(5,5-dimethyl-2-oxo-4-phenyl-2,5-dihydrofuran-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (9a): Yield 82%, mp 223-225 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1500 (C=C-C=C), 1630 (CON); 1740 (C=O), 2200 (CN), ^1H NMR spectrum, δ , ppm (J , Hz): 1.20-1.33 (1H, m, C₆H₁₁), 1.40-1.79 (5H, m, C₆H₁₁), 1.67 (6H, 2xCH₃), 1.82-1.95 (4H, m, C₆H₁₁), 4.62 (1H, tt, $J_1=11.6$, $J_2=3.2$, NCH), 6.34 (1H, d, $J=7.0$, =CH), 7.27-7.33 (2H, m, C₆H₅), 7.40-7.46 (3H, m, C₆H₅), 7.97 (1H, d, $J=7.0$, N=CH), ^{13}C NMR spectrum, δ , ppm: 24.5, 24.7(2C), 25.1(2C), 31.2(2C), 55.0, 86.4, 103.3, 106.5, 114.2, 123.4, 127.2(2C), 128.4(2C), 129.6, 130.0, 139.6, 148.8, 158.1, 166.9, 170.2. Found, %: C 74.28; H 6.30; N 7.26. C₂₄H₂₄N₂O₃. Calculated, %: C 74.21; H 6.23; N 7.21.

4-(5,5-dimethyl-2-oxo-4-phenyl-2,5-dihydrofuran-3-yl)-2-oxo-1-(2,2,6,6-tetramethylpiperidine-4-yl)-1,2-dihydropyridine-3-carbonitrile (9b): Yield 77%, mp 236-238 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1500 (C=C-C=C), 1630 (CON); 1730 (C=O), 2200 (CN), 3421 (NH), ^1H NMR spectrum, δ , ppm (J , Hz): 0.7-2.0 br (1H, NH), 1.12s (6H, 2CH₃), 1.25s (6H, 2CH₃), 1.43t (2H, $J=12.2$, CH₂), 1.67s (6H, 2CH₂), 1.63-1.74m (2H, CH₂), 5.17tt (1H, $J=12.4$, 3.0, N-CH), 6.36d (1H, $J=7.0$, 5-CH_{Ar}), 7.27-7.33m (2H, Ph), 7.41-7.47m (3H, Ph), 7.95d (1H, $J=7.0$, 6-CH_{Ar}), ^{13}C NMR spectrum, δ , ppm: 24.7 (2C), 28.0 (2C), 34.1 (2C), 42.6 (2C), 49.0, 51.0, 86.4, 103.2, 106.6, 114.1, 123.3, 127.1 (2C), 128.4 (2C), 129.5, 129.9, 139.6, 148.8, 158.2, 166.9, 170.1. Found, %: C 72.85; H 6.97; N 9.40. C₂₇H₃₁N₃O₃. Calculated, %: C 72.78; H 7.01; N 9.43.

1-(2-(1H-indole-3-yl)ethyl)-4-(5,5-dimethyl-2-oxo-4-phenyl-2,5-dihydrofuran-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (9f): Yield 81%, mp 239-241 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1550 (C=C-C=C), 1675 (CON); 1720 (C=O), 2200 (CN), ^1H NMR spectrum, δ , ppm (J , Hz): 1.14-1.28m

(1H), 1.71-1.90m (9H, 5CH₂), 5.14s (2H, NCH₂), 6.32d (1H, $J=6.9$, 5-CH), 7.22-7.26m (2H, Ph), 7.39ddd (1H, $J=7.8$, 4.7, 0.7, 5-CH), 7.39-7.43m (3H, Ph), 7.74ddd (1H, $J=7.8$, 2.3, 1.7, 4-CH), 8.20d (1H, $J=6.9$, 6-CH), 8.46dd (1H, $J=4.7$, 1.7, 6-CH), 8.59dd (1H, $J=2.3$, 0.7, 2-CH), ^{13}C NMR spectrum, δ , ppm: 21.4 (2C), 23.7, 32.8 (2C), 49.8, 88.1, 104.0, 106.8, 113.86, 123.0, 124.1, 127.1 (2C), 128.3 (2C), 129.3, 130.1, 130.9, 135.7, 143.0, 148.7, 149.3, 150.0, 158.3, 166.8, 170.7. Found, %: C 74.75; H 5.11; N 9.29. C₂₈H₂₃N₃O₃. Calculated, %: C 74.82; H 5.16; N 9.35.

1-(cyclohex-1-en-1-ylmethyl)-4-(5,5-dimethyl-2-oxo-4-phenyl-2,5-dihydrofuran-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (9g): Yield 68%, mp 218-220 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1550 (C=C-C=C), 1680 (CON); 1740 (C=O), 2200 (CN), ^1H NMR spectrum, δ , ppm (J , Hz): 1.43-1.64m (4H, 2CH₂), 1.67s (6H, 2CH₂), 1.82-1.98m (4H, 2CH₂), 2.25t (2H, $J=6.9$, CH₂), 3.98t (2H, $J=6.9$, N-CH₂), 5.16-5.21m (1H, CH=), 7.26-7.32m (2H, Ph), 7.38-7.44m (3H, Ph), 7.85d (1H, $J=6.9$, 6-CH), ^{13}C NMR spectrum, δ , ppm: 21.5, 22.1, 24.6, 24.7 (2C), 27.4, 36.1, 47.8, 86.3, 103.4, 106.7, 114.0, 123.5, 123.8, 127.1 (2C), 128.3 (2C), 129.5, 129.9, 132.7, 143.4, 149.5, 158.2, 166.8, 169.9. Found, %: C 74.92; H 6.10; N 6.95. C₂₅H₂₄N₂O₃. Calculated, %: C 74.98; H 6.04; N 7.00.

4-(5,5-dimethyl-2-oxo-4-phenyl-2,5-dihydrofuran-3-yl)-1-(2-hydroxyethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (9l): Yield 68%, mp 242-244 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1530 (C=C-C=C), 1675 (CON), 1730 (C=O), 2200 (CN), 3200-3400(OH), ^1H NMR spectrum, δ , ppm (J , Hz): 1.67s (6H, 2CH₂), 3.67dd (2H, $J=10.3$, 5.2, OCH₂), 3.95-4.01m (2H, N-CH₂), 4.79t (1H, $J=5.5$, OH), 6.28d (1H, $J=6.9$, 5-CH), 7.29-7.33m (2H, Ph), 7.41-7.46m (3H, Ph), 7.89d (1H, $J=6.9$, 6-CH), ^{13}C NMR spectrum, δ , ppm: 24.7 (2C), 52.2, 57.7, 86.4, 103.2, 106.7, 114.2, 123.5, 127.2 (2C), 128.5 (2C), 129.5, 129.9, 144.6, 149.7, 158.5, 166.9, 169.9. Found, %: C 68.51; H 5.14; N 7.93. C₂₀H₁₈N₂O₄. Calculated, %: C 68.56; H 5.18; N 8.00.

4-(5,5-dimethyl-2-oxo-4-phenyl-2,5-dihydrofuran-3-yl)-2-oxo-1-(pyridine-3-ylmethyl)-1,2-dihydropyridine-3-carbonitrile (9m): Yield 71%, mp 238-240 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1500 (C=C-C=C), 1630 (CON), 1690, 1740 (C=O), 2200 (CN), ^1H NMR spectrum, δ , ppm (J , Hz): 1.66s (6H, 2CH₂), 5.16s (2H, NCH₂), 6.37d (1H, $J=7.0$, 5-CH), 7.26-7.33m (3H, Ph+3CH), 7.40-7.45m (3H, Ph), 7.75dt (1H, $J=7.9$, 1.9, 4-CH_{Py}), 8.24d (1H, $J=7.0$, 6-CH), 8.47dd (1H, $J=4.8$, 1.9, 6-CH_{Py}), 8.60d (1H, $J=1.9$, 2-CH_{Py}), ^{13}C NMR spectrum, δ , ppm: 24.7 (2C),

49.8, 86.4, 103.9, 106.8, 113.8, 123.0, 123.2, 127.2 (2C), 128.5 (2C), 129.7, 129.8, 131.0, 135.7, 143.3, 148.7, 149.3, 150.1, 158.4, 166.7, 170.3. Found, %: C 72.58; H 4.79; N 10.52. C₂₄H₁₉N₃O₃. Calculated, %: C 72.53; H 4.82; N 10.57.

1-cyclohexyl-2-oxo-4-(2-oxo-4-phenyl-1-oxospiro[4.5]dec-3-en-3-yl)-1,2-dihydropyridine-3-carbonitrile (10a): Yield 87%, mp 222-224 °C, pale-yellow solid, IR spectrum, ν , cm⁻¹: 1500 (C=C-C=C), 1650 (CON); 1700 (C=O), 2200 (CN), ¹H NMR spectrum, δ , ppm (*J*, Hz): 1.13-1.33m (2H), 1.39-1.65m (4H), 1.68-1.93m (14H, 10CH₂), 4.60tt (1H, *J*=11.8, 3.3, NCH), 6.29d (1H, *J*=7.1, 5-CH), 7.20-7.28m (2H) and 7.37-7.45m (3H, Ph), 7.93d (1H, *J*=7.1, 6-CH), ¹³C NMR spectrum, δ , ppm: 21.42 (2C), 23.7, 24.5, 25.1 (2C), 31.1 (2C), 32.8 (2C), 54.9, 85.0, 103.4, 106.5, 114.2, 124.2, 127.0 (2C), 128.2 (2C), 129.1, 130.2, 139.3, 148.7, 158.0, 166.9, 170.5. Found, %: C 75.74; H 7.04; N 6.50. C₂₇H₂₈N₂O₃. Calculated, %: C 75.68; H 6.59; N 6.54.

2-oxo-4-(2-oxo-4-phenyl-1-oxospiro[4.5]dec-3-en-3-yl)-1-(2,2,6,6-tetramethylpiperidine-4-yl)-1,2-dihydropyridine-3-carbonitrile (10b): Yield 85%, mp 246-248 °C, pale-yellow solid, IR spectrum, ν , cm⁻¹: 1550 (C=C-C=C), 1630 (CON); 1700 (C=O), 2200 (CN), 3350 (NH), ¹H NMR spectrum, δ , ppm (*J*, Hz): 0.83-1.50br (1H, NH), 1.11s (6H, 2CH₃), 1.11-1.34m (1H), 1.24s (6H, 2CH₃), 1.35-1.47m (2H, CH₂), 1.70dd (2H, *J*=12.0, 3.0, CH₂), 1.72-1.90m (9H, 5CH₂), 5.15tt (1H, *J*=12.0, 3.0, NCH), 6.31d (1H, *J*=7.0, 5-CH), 7.22-7.27m (2H) and 7.39-7.45m (3H, Ph), 7.90d (1H, *J*=7.0, 6-CH), ¹³C NMR spectrum, δ , ppm: 21.5 (2C), 23.8, 28.0 (2C), 32.8 (2C), 34.1 (2C), 42.7 (2C), 49.0, 50.9 (2C), 88.1, 103.35, 106.7, 114.2, 124.2, 127.1 (2C), 128.3 (2C), 129.3, 130.2, 139.4, 148.7, 158.2, 167.0. Found, %: C 74.25; H 7.31; N 8.70. C₃₀H₃₅N₃O₃. Calculated, %: C 74.20; H 7.26; N 8.65.

1-(3-(1H-imidazole-1-yl)propyl)-2-oxo-4-(2-oxo-4-phenyl-1-oxospiro[4.5]dec-3-en-3-yl)-1,2-dihydropyridine-3-carbonitrile (10e): Yield 69%, mp 208-210 °C, pale-yellow solid, IR spectrum, ν , cm⁻¹: 1530 (HetAr), 1550 (C=C-C=C), 1650 (CON); 1730 (C=O), 2200 (CN), ¹H NMR spectrum, δ , ppm (*J*, Hz): 1.14-1.30m (1H), 1.73-1.90m (9H, 5CH₂), 2.10-2.23m (2H, CH₂), 3.88-3.97m (2H, N-CH₂), 4.03t (2H, *J*=7.1, NCH₂), 6.26d (1H, *J*=6.9, 5-CH), 6.79-6.80m (1H, *J*=1.0), 7.01-7.02t (1H, *J*=1.2), 7.22-7.27m (2H) and 7.39-7.44m (3H, Ph), 7.48-7.49m (1H, imidaz), 7.91d (1H, *J*=6.9, 6-CH), ¹³C NMR spectrum, δ , ppm: 21.5 (2C), 23.7, 29.7, 32.8 (2C), 43.3, 47.1, 88.1, 103.6, 106.6, 114.1, 118.4, 124.2, 127.1 (2C), 128.2, 128.3 (2C), 129.3, 130.1, 130.6, 143.3, 149.8, 158.4, 167.0, 170.7. Found, %: C 71.40; H 5.80; N 12.30.

C₂₇H₂₆N₄O₃. Calculated, %: C 71.35; H 5.77; N 12.33.

1-(2-(1H-indole-3-yl)ethyl)-2-oxo-4-(2-oxo-4-phenyl-1-oxospiro[4.5]dec-3-en-3-yl)-1,2-dihydropyridine-3-carbonitrile (10f): Yield 81%, mp 241-243 °C, pale-yellow solid, IR spectrum, ν , cm⁻¹: 1500 (C=C-C=C), 1630 (CON); 1740 (C=O), 2200 (CN), 3100 (NH), ¹H NMR spectrum, δ , ppm (*J*, Hz): 1.12-1.30m (1H), 1.71-1.91m (9H, 5CH₂), 3.10t (2H, *J*=7.0, CH₂), 4.17t (2H, *J*=7.0, CH₂N), 6.08d (1H, *J*=6.8, 5-CH), 6.90d (1H, *J*=2.4, 2-CH(indol)), 6.94ddd (1H, *J*=8.1, 7.0, 1.2 indol), 7.03ddd (1H, *J*=8.1, 7.0, 1.2 indol), 7.20-7.25m (2H, Ph), 7.32dt (1H, *J*=8.1, 1.2 indol), 7.41-7.46m (3H, Ph), 7.50d (1H, *J*=6.8, 6-CH), 7.49-7.53m (1H, indol), 10.62s (1H, NH), ¹³C NMR spectrum, δ , ppm: 21.5 (2H), 23.8, 24.0, 32.8(2C), 50.4, 88.00, 103.5, 105.8, 109.2, 111.1, 114.2, 117.6, 118.1, 120.6, 122.8, 124.3, 126.5, 127.1 (2C), 128.3 (2C), 129.2, 130.2, 136.1, 143.1, 149.5, 158.3, 166.9, 170.5. Found, %: C 76.10; H 5.60; N 8.63. C₃₁H₂₇N₃O₃. Calculated, %: C 76.05; H 5.56; N 8.58.

1-(cyclohex-1-en-1-ylmethyl)-2-oxo-4-(2-oxo-4-phenyl-1-oxospiro[4.5]dec-3-en-3-yl)-1,2-dihydropyridine-3-carbonitrile (10g): Yield 73%, mp 193-195 °C, pale-yellow solid, IR spectrum, ν , cm⁻¹: 1550 (C=C-C=C), 1650 (CON); 1730 (C=O), 2200 (CN), ¹H NMR spectrum, δ , ppm (*J*, Hz): 1.13-1.31m (1H), 1.43-1.62m (4H, 2CH₂), 1.74-1.97m (13H, 2CH₂+5CH₂), 2.24t (2H, *J*=6.9, CH₂C), 3.96t (2H, *J*=6.9, NCH₂), 5.17br (1H, CH=), 6.21d (1H, *J*=6.9, 5-CH), 7.20-7.26m (2H) and 7.37-7.43m (3H, Ph), 7.80d (1H, *J*=6.9, 6-CH), ¹³C NMR spectrum, δ , ppm: 21.4 (2C), 21.5, 22.1, 23.7, 24.5, 27.4, 32.8 (2C), 36.0, 47.8, 88.0, 103.3, 105.8, 114.2, 123.8, 124.3, 127.0 (2C), 128.2 (2C), 129.2, 130.1, 132.7, 143.4, 143.4, 149.5, 158.2, 166.9, 170.5. Found, %: C 76.40; H 6.47; N 6.40. C₂₈H₂₈N₂O₃. Calculated, %: C 76.34; H 6.41; N 6.36.

1-(3-morpholinepropyl)-2-oxo-4-(2-oxo-4-phenyl-1-oxospiro[4.5]dec-3-en-3-yl)-1,2-dihydropyridine-3-carbonitrile (10h): Yield 69%, mp 187-189 °C, pale-yellow solid, IR spectrum, ν , cm⁻¹: 1200-1300 (C-O-C), 1530 (C=C-C=C), 1650 (CON); 1720 (C=O), 2200 (CN), ¹H NMR spectrum, δ , ppm (*J*, Hz): 1.12-1.30m (1H), 1.73-1.90m (11H, CH₂+5CH₂), 2.24-2.33m (6H, 3NCH₂), 3.46-3.52m (4H, 2CH₂O), 3.96t (2H, *J*=7.0, N-CH₂), 6.22d (1H, *J*=6.9, 5-CH), 7.20-7.27m (2H) and 7.38-7.45m (3H, Ph), 7.94d (1H, *J*=6.9, 6-CH), ¹³C NMR spectrum, δ , ppm: 21.5 (2C), 23.7, 23.8, 32.8 (2C), 48.2, 52.6, 54.6, 65.7, 88.1, 103.3, 106.1, 114.2, 124.3, 127.0 (2C), 128.3 (2C), 129.2, 130.1, 143.9, 149.6, 158.4, 167.0, 170.6. Found, %: C 70.98; H 6.62; N 8.84. C₂₈H₃₁N₃O₄. Calculated, %: C 71.02; H 6.60; N 8.87.

2-oxo-4-(2-oxo-4-phenyl-1-oxospiro[4.5]dec-3-en-3-yl)-1-(3-(pyrrolidine-1-yl)propyl)-1,2-dihydropyridine-3-carbonitrile (10i): Yield 73%, mp 214-216 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1500 (C=C-C=C), 1630 (CON); 1740 (C=O), 2200 (CN), ^1H NMR spectrum, δ , ppm (J , Hz): 1.13-1.29m (1H), 1.67-1.73m (4H, 2CH₂), 2.46-2.51m (4H, 2N-CH₂), 2.70t (2H, $J=6.2$, NCH₂), 3.98t (2H, $J=6.2$, NCH₂), 6.22d (1H, $J=6.9$, 5CH), 7.20-7.28m (2H) and 7.36-7.45m (3H, Ph), 7.87d (1H, $J=6.9$, 6CH), ^{13}C NMR spectrum, δ , ppm: 21.5, 23.1(2C), 23.8, 32.9(2C), 48.1, 53.2(2C), 53.44(2C), 88.0, 103.4, 105.8, 114.1, 124.3, 127.1(2C), 128.2(2C), 129.2, 130.2, 143.6, 149.5, 158.2, 166.9, 170.6. Found, %: C 73.50; H 6.83; N 9.18. C₂₈H₃₁N₃O₃. Calculated, %: C 73.50; H 6.83; N 9.18.

1-(2-hydroxyethyl)-2-oxo-4-(2-oxo-4-phenyl-1-oxospiro[4.5]dec-3-en-3-yl)-1,2-dihydropyridine-3-carbonitrile (10l): Yield 62%, mp 235-237 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1530 (C=C-C=C), 1640 (CON), 1750 (C=O), 2200 (CN), 3300 (OH), ^1H NMR spectrum, δ , ppm (J , Hz): 1.13-1.30m (1H), 1.72-1.93m (9H, 5CH₂), 3.61-3.69m (2H, CH₂O), 3.92-4.00m (2H, CH₂N), 4.78t (1H, $J=5.1$, OH), 6.23d (1H, $J=6.9$, 5-CH), 7.23-7.29m (2H), 7.39-7.45m (3H, Ph), 7.85d (1H, $J=6.9$, 6-CH), ^{13}C NMR spectrum, δ , ppm: 21.5 (2C), 23.7, 32.8 (2C), 52.1, 57.8, 88.2, 103.2, 105.9, 114.4, 124.4, 127.1 (2C), 128.4 (2C), 129.3, 130.1, 144.7, 149.8, 158.6, 167.2, 170.6. Found, %: C 70.71; H 6.00; N 7.13. C₂₃H₂₂N₂O₄. Calculated, %: C 70.75; H 5.68; N 7.18.

2-oxo-4-(2-oxo-4-phenyl-1-oxospiro[4.5]dec-3-en-3-yl)-1-(pyridine-3-ylmethyl)-1,2-dihydropyridine-3-carbonitrile (10m): Yield 87%, mp 229-231 °C, pale-yellow solid, IR spectrum, ν , cm^{-1} : 1550 (C=C-C=C), 1620 (CON); 1730 (C=O), 2200 (CN), ^1H NMR spectrum, δ , ppm (J , Hz): 1.14-1.28m (1H), 1.71-1.90m (9H, 5CH₂), 5.14s (2H, NCH₂), 6.32d (1H, $J=6.9$, 5-CH), 7.22-7.26m (2H, Ph), 7.39ddd (1H, $J=7.8$, 4.7, 0.7, 5-CH), 7.39-7.43m (3H, Ph), 7.74ddd (1H, $J=7.8$, 2.3, 1.7, 4-CH), 8.20d (1H, $J=6.9$, 6-CH), 8.46dd (1H, $J=4.7$, 1.7, 6-CH), 8.59dd (1H, $J=2.3$, 0.7, 2-CH), ^{13}C NMR spectrum, δ , ppm: 21.4 (2C), 23.7, 32.8 (2C), 49.8, 88.1, 104.0, 106.8, 113.86, 123.0, 124.1, 127.1 (2C), 128.3 (2C), 129.3, 130.1, 130.9, 135.7, 143.0, 148.7, 149.3, 150.0, 158.3, 166.8, 170.7. Found, %: C 74.19; H 5.36; N 9.55. C₂₇H₂₃N₃O₃. Calculated, %: C 74.13; H 5.30; N 9.60.

5'-amino-7'-cyclohexyl-1'H-spiro[cyclohexyl-1,3'-furo[3,4-f]isochinoline]-1',6'(7'H)-dion (11a): Yield 69%, mp 181-183 °C, yellow solid, IR spectrum, ν , cm^{-1} : 1530 (C=C-C=C), 1690 (CON), 1725 (COO), 3380 (NH₂), ^1H NMR spectrum, δ , ppm (J , Hz): 1.22-

1.97m (20H, 10CH₂), 4.79tt (1H, $J=11.6$, 3.5, NCH), 6.42s (1H, CH_{Ar}), 7.41s (2H, 2CH_{Ar}), 6.71-7.54br (2H, NH₂), ^{13}C NMR spectrum, δ , ppm: 21.7 (2C), 24.2, 24.7, 25.4 (2C), 31.4 (2C), 35.6 (2C), 52.5, 82.8, 100.9, 101.2, 102.4, 109.0, 130.8, 137.9, 156.7, 160.1, 162.1, 168.0. Found, %: C 72.18; H 7.20; N 7.60. C₂₂H₂₆N₂O₃. Calculated, %: C 72.11; H 7.15; N 7.64.

5'-amino-7'-(2,2,6,6-tetramethylpiperidine-4-yl)-spiro[cyclohexyl-1,3'-furo[3,4-f]isochinoline]-1',6'(7'H)-dion (11b): Yield 71%, mp 216-218 °C, yellow solid, IR spectrum, ν , cm^{-1} : 1585 (C=C), 1645 (CON), 1725 (COO), 3315 (NH), 3415 (NH₂), ^1H NMR spectrum, δ , ppm (J , Hz): 0.83-0.97br (1H, NH), 1.14s (6H, 2CH₃), 1.30s (6H, 2CH₃), 1.35-1.53br (1H, 5CH₂), 1.39-1.49m (2H, CH₂), 1.66dd (2H, $J=12.0$, 3.1, CH₂), 1.70-1.87m (9H, 5CH₂), 5.37tt (1H, $J=12.0$, 3.1, N-CH), 6.42s (1H, CH-Ar), 7.39s (2H, 2CH-Ar), 9.48-7.52br (2H, NH₂), ^{13}C NMR spectrum, δ , ppm: 21.7 (2C), 24.2, 28.1 (2C), 34.3 (2C), 35.6 (2C), 43.0 (2C), 50.9 (2C), 82.8, 100.9, 101.2, 102.3, 108.9, 130.7, 137.8, 156.6, 160.2, 162.2, 168.0. Found, %: C 70.95; H 7.90; N 9.87. C₂₅H₃₃N₃O₃. Calculated, %: C 70.89; H 7.85; N 9.92.

5'-amino-7'-((tetrahydrofuran-2-yl)methyl)-spiro[cyclohexyl-1,3'-furo[3,4-f]isochinoline]-1',6'(7'H)-dion (11c): Yield 63%, mp 193-195 °C, yellow solid, IR spectrum, ν , cm^{-1} : 1585 (C=C), 1645 (CON), 1720 (COO), 3340(NH₂), ^1H NMR spectrum, δ , ppm (J , Hz): 1.34-1.51m (1H), 1.55-2.07m (13H, 7CH₂), 3.67dd (1H, $J=4.4$, 7.3, CHO), 3.79-3.89m (2H, CH₂O), 4.07-4.23m (2H, NCH₂), 6.42s (1H, CH), 7.35d (1H, $J=7.4$, CH_{Ar}), 7.39d (1H, $J=7.4$, CH_{Ar}), 6.5-9.9br (2H, NH₂), ^{13}C NMR spectrum, δ , ppm: 21.7 (2C), 24.2, 25.0, 28.2, 35.6 (2C), 51.0, 67.0, 76.3, 82.8, 100.4, 100.8, 102.5, 108.9, 136.2, 138.7, 156.6, 160.2, 162.7, 167.9. Found, %: C 68.46; H 6.63; N 7.64. C₂₁H₂₄N₂O₄. Calculated, %: C 68.46; H 6.57; N 7.60.

5'-amino-7'-cycloheptyl-spiro[cyclohexyl-1,3'-furo[3,4-f]isochinoline]-1',6'(7'H)-dion (11d): Yield 71%, mp 231-233 °C, yellow solid, IR spectrum, ν , cm^{-1} : 1585 (C=C), 1645 (CON), 1725 (COO), 3415 (NH₂), ^1H NMR spectrum, δ , ppm (J , Hz): 1.31-1.51m (1H), 1.52-1.95m (21H, 11CH₂), 4.85-4.99m (1H, N-CH), 6.41s (1H, CH₄), 7.37d (1H, $J=7.6$, CH_{Ar}), 7.41d (1H, $J=7.6$, CH_{Ar}), 6.8-9.8br (2H, NH₂), ^{13}C NMR spectrum, δ , ppm: 21.7 (2C), 24.2, 24.7 (2C), 26.7 (2C), 33.9 (2C), 35.6 (2C), 54.7, 82.8, 100.9, 101.4, 102.4, 109.0, 131.3, 137.9, 156.6, 160.1, 161.7, 168.0. Found, %: C 72.65; H 7.47; N 7.40. C₂₃H₂₈N₂O₃. Calculated, %: C 72.60; H 7.42; N 7.36.

7'-(3-(1H-imidazole-1-yl)propyl)-5'-amino-spiro[cyclohexyl-1,3'-furo[3,4-f]isochinoline]-1',6'(7'H)-dion (11e): Yield 63%, mp 243-245 °C, yellow solid, IR spectrum, ν , cm^{-1} : 1530 (C=C), 1680 (C=O), 1720

(C=O), 3320 (NH₂), ¹H NMR spectrum, δ, ppm (*J*, Hz): 1.34-1.52m (1H), 1.60-1.88m (9H, 5CH₂), 2.20p (2H, *J*=7.0, CH₂-CH₂-CH₂), 3.96t (2H, *J*=7.0, CH₂-CH₂-CH₂), 4.05t (2H, *J*=7.0, CH₂-CH₂-CH₂), 6.44 s (1H, CH_{Ar}), 6.84(1H,), 7.06s (1H,), 7.38d (1H, *J*=7.4), 7.43d (1H, *J*=7.4, 2CH_{Ar}), 7.53s (1H,), 6.6-9.6br (2H, NH₂), ¹³C NMR spectrum, δ, ppm: 21.7 (2C), 24.2, 30.1, 35.6 (2C), 43.4, 45.5, 82.9, 100.7, 102.5, 109.0, 118.3, 128.3, 135.2, 136.5, 138.5, 156.5, 160.2, 162.7, 168.0. Found, %: C 67.33; H 6.16; N 14.28. C₂₂H₂₄N₄O₃. Calculated, %: C 67.33; H 6.16; N 14.28.

7'-(2-(1H-indole-3-yl)ethyl)-5'-amino-spiro[cyclohexyl-1,3'-furo[3,4-f]isochinoline]-1',6'(7'H)-dion (11f): Yield 68%, mp 249-251 °C, yellow solid, IR spectrum, ν, cm⁻¹: 1530 (C=C), 1680 (CON), 1720 (CO), 3200 (NH) 3320 (NH₂), ¹H NMR spectrum, δ, ppm (*J*, Hz): 1.32-1.54m (1H), 1.62-1.89m (9H, 5CH₂), 3.13t (2H, *J*=7.3, CH₂), 4.19t (2H, *J*=7.3, NCH₂), 6.44s (1H, CH_{Ar}), 6.93-7.08m (2H, 5',6'-CH), 6.99s (1H, 2'-CH), 7.17d (1H, *J*=7.4) and 7.25d (1H, *J*=7.4, 7',4'-CH), 7.32d (1H, *J*=7.8) and 7.62d (1H, *J*=7.8, 2CH_{Ar}), 6.6-9.8br (2H, NH₂), 10.59s (1H, NH), ¹³C NMR spectrum, δ, ppm: 21.7 (2C), 24.2, 24.7, 35.6 (2C), 49.2, 82.8, 100.7, 100.8, 102.5, 109.1, 110.1, 111.11, 117.8, 118.0, 120.6, 127.5, 126.7, 135.6, 138.5, 156.5, 160.1, 162.5, 168.0. Found, %: C 73.11; H 5.94; N 9.80. C₂₆H₂₅N₃O₃. Calculated, %: C 73.05; H 5.89; N 9.83.

5'-amino-7'-(cyclohex-1-en-1-ylmethyl)-spiro[cyclohexyl-1,3'-furo[3,4-f]isochinoline]-1',6'(7'H)-dion (11g): Yield 79%, mp 225-227 °C, yellow solid, IR spectrum, ν, cm⁻¹: 1585 (C=C), 1680 (CON), 1720 (COO), 3320 (NH₂), ¹H NMR spectrum, δ, ppm (*J*, Hz): 1.34-1.49m (1H), 1.48-1.87m (13H, 5CH₂+2CH₂), 1.87-2.07m (4H, 2CH₂), 2.29t (2H, *J*=7.1, CH₂), 3.93-4.00m (2H, NCH₂), 5.37bs (1H, CH=), 6.42s (1H, CH_{Ar}), 7.30d (1H, *J*=7.4, CH_{Ar}), 7.35d (1H, *J*=7.4, CH_{Ar}), 6.56-9.72br (2H, NH₂), ¹³C NMR spectrum, δ, ppm: 21.7 (2C), 22.3, 24.2, 24.6, 27.6, 27.6, 35.6 (2C), 36.7, 46.9, 82.8, 100.6, 100.8, 102.5, 109.1, 123.1, 133.5, 135.2, 138.5, 156.5, 160.1, 162.4, 168.0. Found, %: C 73.03; H 6.98; N 7.35. C₂₃H₂₆N₂O₃. Calculated, %: C 72.99; H 6.92; N 7.40.

5'-amino-7'-(3-morpholinen propyl)-spiro[cyclohexyl-1,3'-furo[3,4-f]isochinoline]-1',6'(7'H)-dion (11h): Yield 61%, mp 238-240 °C, yellow solid, IR spectrum, ν, cm⁻¹: 1100-1200(C-O-C), 1585 (C=C), 1680 (CON), 1720 (CO), 3330 (NH₂), ¹H NMR spectrum, δ, ppm (*J*, Hz): 1.33-1.52m (1H), 1.61-1.93m (11H, 5CH₂+CH₂), 2.30-2.40m (6H, 3NCH₂), 3.56-3.62m (4H, 2OCH₂), 3.97t(2H, *J*=6.9, NCH₂), 6.42s (1H, CH_{Ar}), 7.36d (1H, *J*=7.3, CH_{Ar}), 7.42d (1H, *J*=7.3, CH_{Ar}), 6.74-9.57 br (2H, NH₂), ¹³C NMR spectrum, δ,

ppm: 21.7 (2C), 24.2, 24.7, 35.6 (2C), 46.5, 52.8 (2C), 54.6, 65.9 (2C), 82.8, 100.7, 100.8, 102.5, 109.1, 135.6, 138.5, 156.5, 160.1, 162.6, 167.9. Found, %: C 67.18; H 7.16; N 10.25. C₂₃H₂₉N₃O₄. Calculated, %: C 67.13; H 7.10; N 10.21.

5'-amino-7'-(3-(pyrrolidine-1-yl)propyl)-spiro[cyclohexyl-1,3'-furo[3,4-f]isochinoline]-1',6'(7'H)-dion (11i): Yield 59%, mp 236-238 °C, yellow solid, IR spectrum, ν, cm⁻¹: 1550 (C=C), 1670 (CON), 1720 (COO), 3315 (NH₂), ¹H NMR spectrum, δ, ppm (*J*, Hz): 1.27-1.43m (1H), 1.54-1.65m (2H), 1.71-1.93m (13H, 8CH₂), 2.10s (3H, CH₃), 2.42-2.48m (6H, 3NCH₂), 4.04t (2H, *J*=7.0, NCH₂), 6.26d (1H, *J*=7.0, 5-CH), 8.00d (1H, *J*=7.0, 6-CH), ¹³C NMR spectrum, δ, ppm: 12.85, 21.37 (2C), 22.96 (2C), 23.83, 26.70, 32.68(2C), 48.10, 51.90, 53.04 (2C), 87.34, 103.46, 105.81, 114.32, 122.03, 143.35, 149.14, 158.63, 167.32, 170.56. Found, %: C 69.90; H 7.44; N 10.65. C₂₃H₂₉N₃O₃. Calculated, %: C 69.85; H 7.39; N 10.62.

The authors declare the absence a conflict of interest warranting disclosure in this article.

Авторы заявляют об отсутствии конфликта интересов, требующего раскрытия в данной статье.

REFERENCES ЛИТЕРАТУРА

1. Seaman F.C. Sesquiterpene lactones as taxonomic characters in the asteraceae. *Bot. Rev.* 1982. V. 48. P. 121-594. DOI: 10.1007/BF02919190.
2. Sebastián O.S., Enrique L.L., Andrea B.J.B., Teodoro S.K. Angular tricyclic benzofurans and related natural products of fungal origin. Isolation, biological activity, and synthesis. *Nat. Prod. Rep.* 2013, V. 30. P. 941. DOI: 10.1039/C3NP70014C.
3. Huynh B.L., Duong T.H., Do T.M., Pinnock T.G., Pratt L.M., Yamamoto S., Watarai H., Tanahashi T., Nguyen K.P. New [gamma]-Lactone Carboxylic Acids from the Lichen Parmotrema praesorediosum (Nyl.) Hale, Parmeliaceae. *Rec. Nat. Prod.* 2016. 10 (3). P. 332.
4. Blunt J.W., Copp B.R., Keyzers R.A., Munroa M.H., Prinsep M.R. Natural product reports. *Nat. Prod. Rep.* 2016. V. 33. P. 382-431. DOI: 10.1039/c6np00124f.
5. Li Q., Wang Z., Xie Y., Hu H. Antitumor activity and mechanism of costunolide and dehydrocostus lactone: Two natural sesquiterpene lactones from the Asteraceae family. *Biomed. Pharmacother.* 2020. V. 125. P. 109955. DOI: 10.1016/j.biopha.2020.109955.
6. Gładkowski W., Skrobiszewski A., Mazur M., Siepka M., Pawlak A., Obmińska-Mrukowicz B., Bialońska A., Poradowski D., Drynda A., Urbaniak M. Synthesis and anticancer activity of novel halolactones with β-aryl substituents from simple aromatic aldehydes. *Tetrahedron.* 2013. V. 69(48). P. 10414-10423. DOI: 10.1016/j.tet.2013.09.094.
7. Khlebnikov A.I., Schepetkin I.A., Kishkentaeva A.S., Shaimerdenova Z.R., Atazhanova G.A., Adekenov S.M., Kirpotina L.N., Quinn M.T. Inhibition of T cell receptor activation by semi-synthetic sesquiterpene lactone derivatives and molecular modeling of their interaction with glutathione

- and tyrosine kinase ZAP-70. *Molecules*. 2019. V. 24(2). P. 350. DOI: 10.3390/molecules24020350.
8. Hur J., Jang J., Sim J. A review of the pharmacological activities and recent synthetic advances of γ -butyrolactones. *Int. J. Molec. Sci.* 2021. V. 22(5). P. 2769. DOI: 10.3390/ijms22052769.
 9. Heinrich M., Robles M., West J.E., Ortiz De Montellano B.R., Rodriguez E. Ethnopharmacology of Mexican asteraceae. *Ann. Rev. Pharmacol. Toxicol.* 1998. V. 38(1). P. 539-565. DOI: 10.1146/annurev.pharmtox.38.1.539.
 10. Rodriguez E., Towers G.H.N., Mitchell J.C. Biological activities of sesquiterpene lactones. *Phytochemistry*. 1976. V. 15(11). P. 1573-1580. DOI: 10.1016/S0031-9422(00)97430-2.
 11. Matejić J., Šarac Z., Randelović V. Pharmacological activity of sesquiterpene lactones. *Biotechnol. Biotechnol. Equip.* 2010. V. 24(sup1). P. 95-100. DOI: 10.1080/13102818.2010.10817819.
 12. Siutkina A.I., Chashchina S.V., Makhmudov R.R., Novikova V.V., Chernov I.N., Igidov N.M. Synthesis, analgesic and antimicrobial activity of N-hetarylamides of 2-(2-(diarylmethylene)hydrazono)-5,5-dimethyl-4-oxohexanoic acid. *ChemChemTech [Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.]*. 2022. V. 65. N 3. P. 74-82. DOI: 10.6060/ivkkt.20226503.6522.
 - Сюткина А.И., Чашчина С.В., Махмудов Р.Р., Новикова В.В., Чернов И.Н., Игидов Н.М. Синтез, анальгетическая и противомикробная активность N-гетариламидов 2-(2-(диарилметил)гидразоно)-5,5-диметил-4-оксогексановой кислоты. *Изв. вузов. Химия и хим. технология*. 2022. Т. 65. Вып. 3. С. 74–82. DOI: 10.6060/ivkkt.20226503.6522.
 13. Kataria Y.V., Klushin V.A., Kashparova V.P., Sokolova V.A., Smirnova N.V. Synthesis and properties of polyimines based on dialdehydes of the furan series and various diamines. *ChemChemTech [Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.]*. 2023. V. 66. N 6. P. 6-12. DOI: 10.6060/ivkkt.20236606.6763.
 - Катария Я.В., Клушин В.А., Кашпарова В.П., Соколова В.А., Смирнова Н.В. Синтез и свойства полииминов на основе диальдегидов фуранового ряда и различных диаминов. *Изв. вузов. Химия и хим. технология*. 2023. Т. 66. Вып. 6. С. 6–12. DOI: 10.6060/ivkkt.20236606.6763.
 14. Lone S.H., Bhat K.A., Khuroo M.A. Arglablin: From isolation to antitumor evaluation. *Chemico-Biolog. Interact.* 2015. V. 240. P. 180-198. DOI: 10.1016/j.cbi.2015.08.015.
 15. Paço A., Brás T., Santos J.O., Sampaio P., Gomes A.C., Duarte M.F. Anti-inflammatory and immunoregulatory action of sesquiterpene lactones. *Molecules*. 2022. V. 27(3). P. 1142. DOI: 10.3390/molecules27031142.
 16. Jessen H.J., Gademann K. 4-Hydroxy-2-pyridone alkaloids: structures and synthetic approaches. *Nat. Product Rep.* 2010. V. 27(8). P. 1168-1185. DOI: 10.1039/B911516C.
 17. Bao J., Zhai H., Zhu K., Yu J.H., Zhang Y., Wang Y., Jiang C.S., Zhang X., Zhang Y., Zhang H. Bioactive pyridone alkaloids from a deep-sea-derived fungus *Arthrimum* sp. UJNMF0008. *Marine Drugs*. 2018. V. 16(5). P. 174. DOI: 10.3390/md16050174.
 18. Verissimo E., Berry N., Gibbons P., Cristiano M.L.S., Rosenthal P.J., Gut J., Ward S.A., O'Neill P.M. Design and synthesis of novel 2-pyridone peptidomimetic falcipain 2/3 inhibitors. *Bioorg. Medic. Chem. Lett.* 2008. V. 18(14). P. 4210-4214. DOI: 10.1016/j.bmcl.2008.05.068.
 19. Luo T., Li Y., Xu Y., Zhang S., Wang Y., Kou X., Xiao D. Rapid synthesis of a hyperfluorescence 2-pyridone derivative as a fluorescent molecular sensor for picric acid. *Sensors Actuators B: Chemical*. 2017. V. 253. P. 231-238. DOI: 10.1016/j.snb.2017.06.080.
 20. Isaka M., Tanticharoen M., Kongsaree P., Thebtaranonth Y. Structures of cordypyridones A–D, antimalarial N-hydroxy- and N-methoxy-2-pyridones from the insect pathogenic fungus *Cordyceps nipponica*. *J. Org. Chem.* 2001. V. 66(14). P. 4803-4808. DOI: 10.1021/jo0100906.
 21. Tsuchinari M., Shimanuki K., Hiramatsu F., Murayama T., Koseki T., Shiono Y. Fusapyridones A and B, novel pyridone alkaloids from an endophytic fungus, *Fusarium* sp. YG-45. *Z. Naturforsch. B.* 2007. V. 62(9). P. 1203-1207. DOI: 10.1515/znb-2007-0916.
 22. Kusakabe Y., Mizutani S., Kamo S., Yoshimoto T., Tomoshige S., Kawasaki T., Takasawa R., Tsubaki K., Kuramochi K. Synthesis, antibacterial and cytotoxic evaluation of flavipucine and its derivatives. *Bioorg. Medic. Chem. Lett.* 2019. V. 29(11). P. 1390-1394. DOI: 10.1016/j.bmcl.2019.03.034.
 23. Forrestall K. L., Burley D. E., Cash M. K., Pottie I. R., Darvesh S. 2-Pyridone natural products as inhibitors of SARS-CoV-2 main protease. *Chem.-Biol. Interact.* 2021. V. 335. P. 109348. DOI: 10.1016/j.cbi.2020.109348.
 24. Lena G., Trapani J.A., Sutton V.R., Ciccone A., Browne K.A., Smyth M.J., Denny W.A., Spicer J.A. Dihydrofuro [3, 4-c] pyridinones as inhibitors of the cytolytic effects of the pore-forming glycoprotein perforin. *J. Med. Chem.* 2008. V. 51(23). P. 7614-7624. DOI: 10.1021/jm801063n.
 25. Hovhannisyanyan A., Pham T.H., Bouvier D., Piroyan A., Dufau L., Qin L., Cheng Y., Melikyan G., Reboud-Ravaux M., Bouvier-Durand M. New C4- and C1-derivatives of furo [3, 4-c] pyridine-3-ones and related compounds: Evidence for site-specific inhibition of the constitutive proteasome and its immunisoform. *Bioorg. Medic. Chem. Lett.* 2014. V. 24(6). P. 1571-1580. DOI: 10.1016/j.bmcl.2014.01.072.
 26. Husain A., Khan S. A., Iram F., Iqbal M. A., Asif M. Insights into the chemistry and therapeutic potential of furanones: A versatile pharmacophore. *Eur. J. Med. Chem.* 2019. V. 171. P. 66-92. DOI: 10.1016/j.ejmech.2019.03.021.
 27. Simon H., Nicolas P., Hovhannisyanyan A., Alves de Sousa R., Nassima B., Laura E., Enzo T., Stephanie A., Claude S., Julien D., Olivier D., Vincent L., Sebastien N., Melikyan G., Jean-Philippe H., Pierre-Olivier V. Cerpegin-derived furo [3, 4-c] pyridine-3, 4 (1H, 5H)-diones enhance cellular response to interferons by de novo pyrimidine biosynthesis inhibition. *Eur. J. Med. Chem.* 2020. V. 186. P. 111855. DOI: 10.1016/j.ejmech.2019.111855.
 28. Sivakumar K., Eswaramurthy S., Subramanian K., Natarajan S. Structure of Cerpegin, a new alkaloid. *Acta Crystallograph. Sect. C: Cryst. Struct. Commun.* 1990. V. 46(5). P. 839-841. DOI: 10.1107/S0108270189009595.
 29. Génin E., Reboud-Ravaux M., Vidal J. Proteasome inhibitors: recent advances and new perspectives in medicinal chemistry. *Curr. Topics Med. Chem.* 2010. V. 10(3). P. 232-256. DOI: 10.2174/156802610790725515.
 30. Hovhannisyanyan A., Pham T.H., Bouvier D., Qin L., Melikyan G., Reboud-Ravaux M., Bouvier-Durand M. C1 and N5 derivatives of Cerpegin: Synthesis of a new series based on structure-activity relationships to optimize their inhibitory effect on 20S proteasome. *Bioorg. Medic. Chem. Lett.* 2013. V. 23(9). P. 2696-2703. DOI: 10.1016/j.bmcl.2013.02.079.
 31. Meiners S., Ludwig A., Stangl V., Stangl K. Proteasome inhibitors: poisons and remedies. *Med. Res. Rev.* 2008. V. 28(2). P. 309-327. DOI: 10.1002/med.20111.
 32. Singh G.S., Desta Z.Y. Isatins as privileged molecules in design and synthesis of spiro-fused cyclic frameworks. *Chem. Rev.* 2012. V. 112(11). P. 6104-6155. DOI: 10.1021/cr300135y.
 33. Yeung B.K., Zou B., Rottmann M., Lakshminarayana S.B., Ang S.H., Leong S.Y., Tan J., Wong J., Keller-

- Maerki S., Fischli C., Goh A.** Spirotetrahydro β -carboline (spiroindolones): a new class of potent and orally efficacious compounds for the treatment of malaria. *J. Med. Chem.* 2010. V. 53(14). P. 5155-5164. DOI: 10.1021/jm100410f.
34. **Kumari G., Modi M., Gupta S.K., Singh R.K.** Rhodium (II) acetate-catalyzed stereoselective synthesis, SAR and anti-HIV activity of novel oxindoles bearing cyclopropane ring. *Eur. J. Med. Chem.* 2011. V. 46(4). P. 1181-1188. DOI: 10.1016/j.ejmech.2011.01.037.
35. **Vintonyak V.V., Warburg K., Kruse H., Grimme S., Hübel K., Rauh D., Waldmann, H.** Identification of thiazolidinones spiro-fused to indolin-2-ones as potent and selective inhibitors of the mycobacterium tuberculosis protein tyrosine phosphatase B. *Angew. Chem.* 2010. V. 122(34). P. 6038-6041. DOI: 10.1002/ange.201002138.
36. **Ding K., Lu Y., Nikolovska-Coleska Z., Wang G., Qiu S., Shangary S., Gao W., Qin D., Stuckey J., Krajewski K., Roller P.P.** Structure-based design of spiro-oxindoles as potent, specific small-molecule inhibitors of the MDM2–p53 interaction. *J. Med. Chem.* 2006. V. 49(12). P. 3432-3435. DOI: 10.1021/jm051122a.
37. **Melikyan G.S., Hovhannisyan A.A., Hayotsyan, S.S.** Synthesis of some heterocyclic compounds from enamines of 3-acetylfuran-2 (5 H)-ones. *Synth. Commun.* 2012. V. 42(15). P. 2267-2276. DOI: 10.1080/00397911.2011.555591.
38. **Peixoto P.A., Boulangé A., Leleu S., Franck X.** Versatile Synthesis of Acylfuranones by Reaction of Acylketenes with α -Hydroxy Ketones: Application to the One-Step Multicomponent Synthesis of Cadiolide B and Its Analogues. *Eur. J. Org. Chem.* 2013. V. 16. P. 3316-3327. DOI: 10.1002/ejoc.201300166.
39. **Bhuiyan M.M.H., Hossain M.I., Alam M.A., Mahmud M.M.** Microwave assisted Knoevenagel condensation: Synthesis and antimicrobial activities of some arylidene-malononitriles. *Chem. J.* 2012. V. 2(1). P. 31-37.
40. **Modi A., Ali W., Patel B.K.** N,N-Dimethylacetamide (DMA) as a Methylene Synthone for Regioselective Linkage of Imidazo [1, 2-a] pyridine. *Adv. Synth. Catal.* 2016. V. 358(13). P. 2100-2107. DOI: 10.1002/adsc.201600067.
41. **Piroyan A., Melikyan G.** Convenient synthetic route to 3-cyanopyridine-2 (1 H)-one derivatives with aromatic substituents. *Heterocycl. Commun.* 2012. V. 18(5-6). P. 233-237. DOI: 10.1515/hc-2012-0158.

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