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Synthesis of Amides of Carboxylic Acids with an Imide and Alicyclic Fragments and a Study of Their Genotoxic Activity in the Allium Test

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Abstract—A method for the high-yield synthesis of several amides of carboxylic acids containing an imide, a cyclohexene, and a norbornene cycle as well as fragments of natural amino acids has been developed. The compounds synthesized have been tested for mutagenic activity on plant objects using the Allium test. It has been shown that the presence of a nitro group endows the compound with inhibitory property and the capacity to induce chromosomal rearrangements, whereas the presence of an aliphatic carbon chain, a methyl group, and a morpholine fragment, on the contrary, confers growth-regulating properties without inducing the mutagenic effect. The study has confirmed that the resulting biologically active compounds are of interest for practical implementation in agriculture.

Keywords: amides of carboxylic acids, cyclohexene and norbornene fragments, imide cycle, biological activity, Allium test

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INTRODUCTION

A search for new compounds capable of improving the properties of seeding material, increasing the productivity, and enhancing the resistance of crops to phytopathogens, drought, and cold is currently a topical problem in the optimization of agriculture. It is known that compounds containing an amide fragment possess a high biological activity and constitute a wide spectrum of fungicidal [1, 2], insecticidal [3], and herbicidal [4] preparations [5–7]. However, at present, there are problems associated with the stable resistance of pathogens to available preparations, large amounts of wastes during their production, and, as a consequence, harmful effects on the environment. Thus, the search for, and the creation of, compounds free from these shortcomings is a timely task in the chemistry of pesticides [8, 9].

It is worth noting that the imide group is an integral structural part of some known biologically active compounds, such as fumaramidmycin [10, 11], granulatimide [12], isogranulatimide [13], and rebekkamycin [14]. These compounds exhibit a wide spectrum of biological activities: antitumor [15, 16], anti-inflammatory [17], and antimicrobial [18]. Some compounds containing an imide fragment that are known to possess biological activity and low cytotoxicity [19] have found application as growth-regulating reagents [20].

Our work is devoted to the synthesis of amides of carboxylic acids containing an imide and cycloalkenyl fragments and the study of their mutagenic activity and influence on farm crops. We synthesized several potentially bioactive compounds in which we combined the active structure of an amide with imide and cycloalkenyl fragments and selected biologically active samples from them using the Allium test. The results showed that most of the compounds have growth-regulating activity. As far as we know, this study is the first to show the growth-regulating properties of a comparatively large series of amide derivatives.

RESULTS AND DISCUSSION

Compounds (**III**)–(**VII**), (**XI**), (**XII**), (**XVII**)–(**XXV**) have been synthesized earlier [21–25]; however, the methods of their synthesis are very complicated and involve the use of either expensive reagents or elaborate procedures.

Alicyclic endic (**I**) and tetrahydrophthalic anhydrides (**II**) were used as initial compounds. These compounds were chosen because they are readily available, inexpensive, and easily obtainable from petroleum chemical products (divinyl, maleic anhydride) [26].

Abbreviations: CDI, *N*,*N*′-carbonyldiimidazole; QSAR, Quantitative Structure-Activity Relationship.

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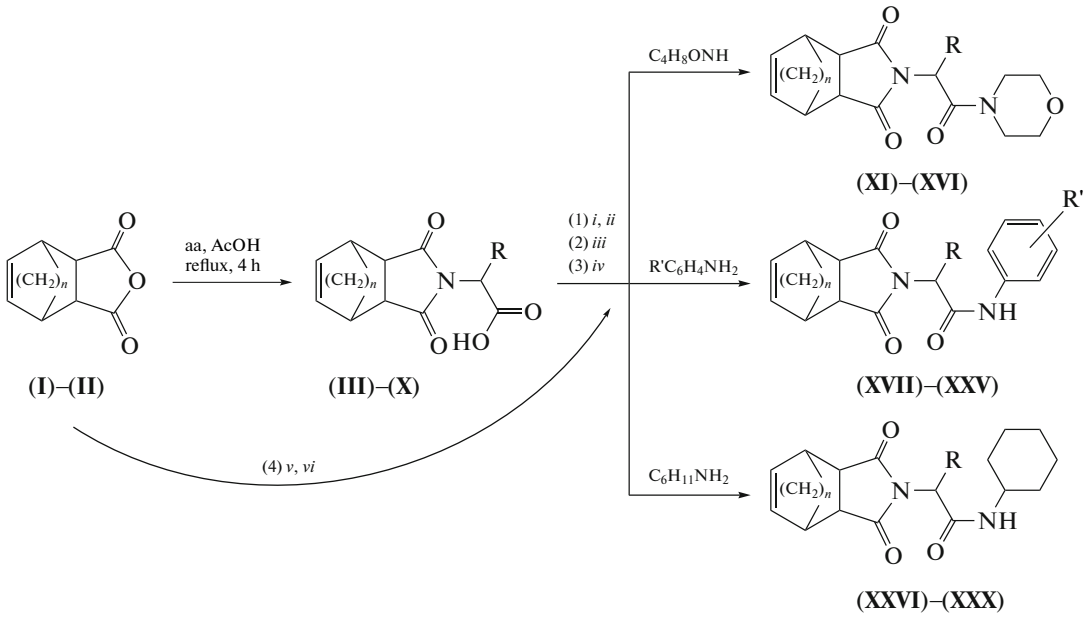

Reagents and conditions: (1) *i*: $SOCl_2$, DMF, reflux for 3 h or PCl_5, CH_2Cl_2, *ii*: amine, Et_3N, reflux for 5 h; (2) *iii*: CDI, amine, reflux for 4–7 h; (3) *iv*: EtOCOCl, amine, Et_3N, reflux for 2–4 h; (4) *v*: amino acid, DMSO, 1% K_2CO_3; reflux for 1 h; *vi*: amine, reflux for 1 h; **(I)** $n = 0$; **(II)** $n = 1$; **(III)** $n = 0$, R = H; **(IV)** $n = 1$, R = H; **(V)** $n = 0$, R = *i*Pr; **(VI)** $n = 1$, R = *i*Pr; **(VII)** $n = 0$, R = CH_2Ph; **(VIII)** $n = 1$, R = CH_2Ph; **(IX)** $n = 0$, R = *i*Bu; **(X)** $n = 1$, R = *i*Bu; **(XI)** $n = 0$, R = H; **(XII)** $n = 1$, R = H; **(XIII)** $n = 0$, R = *i*Pr; **(XIV)** $n = 1$, R = *i*Pr; **(XV)** $n = 1$, R = CH_2Ph; **(XVI)** $n = 0$, R = *i*Bu; **(XVII)** $n = 0$, R = H, R' = NO_2; **(XVIII)** $n = 1$, R = *i*Bu, R' = NO_2; **(XIX)** $n = 0$, R = *i*Bu, R' = NO_2; **(XX)** $n = 1$, R = H, R' = OH; **(XXI)** $n = 1$, R = *i*Pr, R' = OH; **(XXII)** $n = 0$, R = *i*Bu, R' = OH; **(XXIII)** $n = 1$, R = *i*Bu, R' = OH; **(XXIV)** $n = 1$, R = CH_2Ph, R' = CH_3; **(XXV)** $n = 0$, R = *i*-Bu, R' = CH_3; **(XXVI)** $n = 1$, R = H; **(XXVII)** $n = 1$, R = *i*Bu; **(XXVIII)** $n = 0$, R = H; **(XXIX)** $n = 1$, R = *i*Pr; **(XXX)** $n = 0$, R = *i*Bu

Scheme 1. Synthesis of amides of carboxylic acids containing cycloalkenyl and imide fragments.

N-Substituted imides of dicarboxylic acids **(III)**–**(X)** were obtained by refluxing anhydrides **(I)** and **(II)** with native amino acids (L-leucine, L-alanine, and glycine) in acetic acid. For the synthesis, the reagents were taken in the equimolar ratio (scheme) [27]. Then, the functionalization of *N*-substituted imides of acids **(III)**–**(X)** at the carboxyl group was carried out using the known and available methods for the synthesis of amides of carboxylic acid. At the first stage, acid chlorides of *N*-substituted alicyclic acids were obtained by method **1** (Scheme 1) using phosphorus pentachloride (PCl_5) or thionyl chloride ($SOCl_2$). Methylene chloride served as a solvent. In both cases, acid chlorides were obtained in good yields (75–95%). They were not subjected to additional purification and were immediately introduced into the acylation reaction of amines. However, the yield of the resulting amides **(XI)**–**(XXX)** was no higher than 50%, and the final reaction mixtures contained the corresponding initial *N*-substituted imides **(III)**–**(X)**. It may be suggested that the acyl derivative that forms during amidation is unstable and either dissociates yielding the initial acid or forms in minor amounts.

In the amidation reaction of compounds **(III)**–**(X)**, we also tested method **2** in which CDI serves as an activation agent. This approach appeared to be effective; the reaction proceeded in one stage for 3.5 h, and the yield of target products was 60–95%. The structures of compounds **(XI)**–**(XXX)** were confirmed by spectroscopy.

However, it should be noted that, the reaction time during the synthesis of amides **(XVII)**–**(XIX)** increased from 8 to 12 h as compared with the synthesis of compounds **(III)**–**(X)**, which is explained by a low nucleophilicity of *p*-nitroaniline. Therefore, the problem facing us was to develop a method that would make it possible to minimize the reaction time. This problem was solved by using ethyl chloroformate as an agent activating the carboxyl group in compounds **(III)**–**(X)** (method **3**) [28, 29]. With this method, target amides were obtained with high yields, and the reaction time was reduced from eight to two hours, compared with method **2**. Acetone and 1,4-dioxane were used as solvents; no substantial differences in the reaction course with the use of the two reagents were observed.

Although these methods of amidation are widely used for synthesizing carboxylic acid amides and afford high yields, it should be noted that they had some limitations in our case, namely, a high cost of reagents and particular terms and conditions of storage. It should also be taken into account that the com-

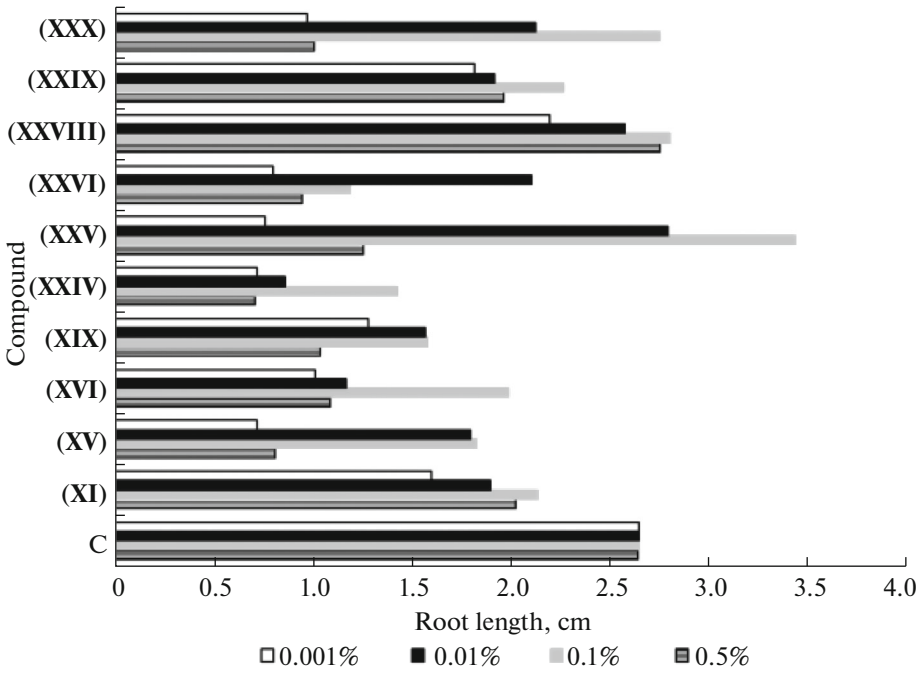

Fig. 1. Effect of the concentration of test compounds on the length of *Allium cepa* roots in the experiment on the determination of total genotoxicity. Here and below, differences between the experimental and control samples were significant at $p < 0.05$.

pounds synthesized are intended for use in agriculture where the cost price of materials is an important factor. Therefore, the next step was to develop a method of synthesis using available and inexpensive reagents.

In the literature, the methods of amidation with the use of weakly alkaline dioxane–water solvents [30, 31] or an inert solvent (e.g., toluene) in the presence of triethylamine [32, 33] are described. Based on the literature data, we developed a new method, which is presented on the scheme (method **4**). *N*-Substituted imides of alicyclic dicarboxylic acids were obtained in the in situ reaction of the corresponding amines with the products of the reaction of anhydrides (**I**) and (**II**) with natural amino acids in the equimolar ratio in the presence of a 1% solution of K_2CO_3 in DMSO. This method makes it possible to obtain target compounds with high yields over a short time without intermediate isolation and with the use of readily available reagents.

For the primary estimation of the biological activity and toxicity, a computer screening of QSAR was performed. Compounds having a low (from 0.5 to 1.0 mmol/kg) factor of bioaccumulation ((**XI**), (**XV**), (**XVI**), (**XIX**), (**XXIV**)–(**XXX**)) were chosen [34–36].

It is known that many organic compounds possessing biological activity are capable of passing through biological membranes but are poorly soluble in water. However, a necessary condition for biological testing is the use of liquid forms of preparations. Therefore, in experiments on biological objects, we used test compounds in the form of their aqueous solutions containing 1% DMSO. This compound has a high solvent capacity, compatibility with water, and low toxicity toward biological organisms [37].

A characteristic that adequately estimates the general toxicity of organic compounds is the capacity to affect seed germination [38]. The biological activity of the compounds was determined under laboratory conditions on onion *Allium cepa* plantlets. In control experiments, distilled water was used. The results of tests are shown in Fig. 1.

It can be concluded from the data on Fig. 1 that the optimal concentration of test compounds that affects germination is 0.1%. Therefore, in subsequent experiments, we used this concentration of the solutions. Compounds (**XXV**), (**XXVI**), (**XXIX**), and (**XXX**) at a concentration of 0.1 and 0.01% increase seed germination. Compounds (**XVI**), (**XIX**), and (**XXIV**) decrease germination, i.e., act as inhibitors. Compounds with these properties can be used in agriculture for weed control.

Because the compounds synthesized are potentially useful for agricultural applications, it was necessary to estimate their biological effects, such as genotoxicity, i.e., the capacity to adversely affect the genetic material of the cell. To examine the mutagenic activity, which characterizes the genotoxicity of preparations, we analyzed the frequency of induced chromosome aberrations in the meristematic tissue of *Allium cepa* plantlet roots (the Allium test). This method has been recommended by the World Health Organization for the primary estimation of mutagenicity; the results of the test correlate well with the data on mutagenicity obtained on mammalian and human

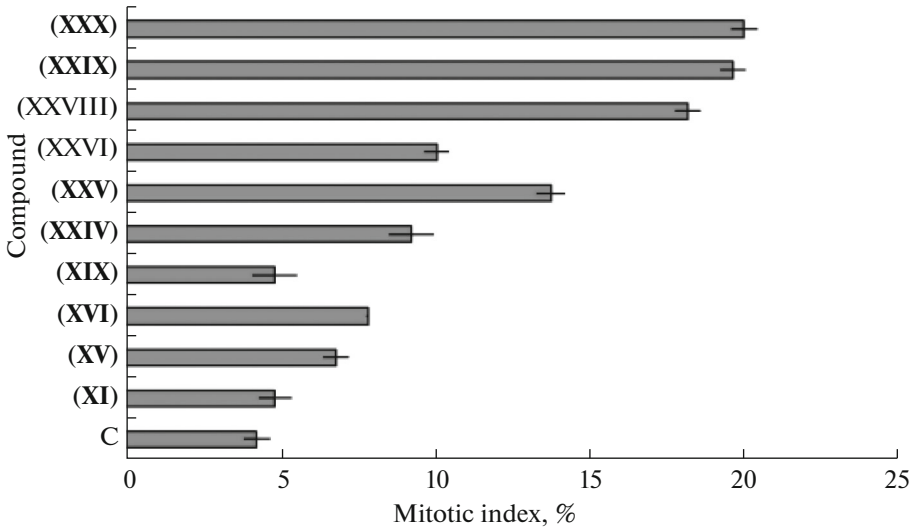

Fig. 2. Mitotic index (%) by the action of compounds at a concentration of 0.1% on onion *Allium cepa*.

cells [39]. A major characteristic that enables one to estimate the cytotoxicity of compounds is the mitotic index. It shows the ratio of the number of cells in mitosis to the total number of cells in a tissue preparation being analyzed. The mitotic index may indicate a normal course of mitosis, an inhibition of cell division, or, conversely, an enhancement of the mitotic activity of tissues [39, 40]. The data on the effect of the compounds on the proliferative activity are given in Fig. 2.

As seen from Fig. 2, all test compounds possess proliferative activity; however, the mitotic index of compounds **(XXIII)**, **(XXV)**, **(XXVI)**, and **(XXVIII)**–**(XXX)** is 1.5–4 times higher than that of the control (distilled water), indicating an increase in the mitosis rate and, as a consequence, the appearance of growth-regulating properties. The mitotic indices for compounds **(IX)** and **(XI)** are comparable with the control; these compounds had no modifying effect on mitosis.

The mutagenic activity was estimated by the anatelophase assay [41]. This method makes it possible to record chromosome aberrations such as fragments, bridges, and lagging chromosomes, which result from chromosome mutations and abnormal behavior of chromosomes on the mitotic spindle [40]. The data obtained by this assay are given in Fig. 3.

The frequency of induced chromosome aberrations of compounds **(XI)**, **(XV)**, **(XVI)**, and **(XXIV)**–**(XXX)** does not exceed the control level (C); consequently, these compounds do not exhibit mutagenic activity in this test system. At the same time, compound **(XIX)** increases the frequency of induced chromosome aberrations to $6.00 \pm 0.0049\%$, which exceeds the control level three times, with the frequency of lagging chromosomes being unchanged. Compound **(XIX)** is capable of inducing chromosome rearrangements but does not affect the formation and behavior of the mitotic spindle.

It may be concluded from the results of biotesting that the compounds synthesized possess growth-regulating properties. Evidence from three biotests indicates that compounds **(XXV)**, **(XXVI)**, **(XXIX)** and **(XXX)** are the safest toward the plant test objects and can be recommended for further studies as plant growth regulators.

Based on the study of the structure–activity relationship for the test compounds, it may be suggested that the presence of a nitro group in the structure of a compound endows it with inhibitory properties and the capacity to induce chromosome rearrangements, whereas the presence of an aliphatic carbon chain, a methyl group, and a morpholine fragment, on the contrary, imparts growth-regulating properties without inducing a mutagenic effect.

EXPERIMENTAL

The following commercially available domestic reagents of pure or chemically pure grade were used: morpholine, aromatic amines, maleic anhydride, divinyl, cyclopentadiene, triethylamine, and phosphorus pentachloride. Ethyl chloroformate and CDI were from Sigma-Aldrich. Endic anhydride **(I)** and tetrahydrophthaleic anhydride **(II)** were obtained as described in [26]. Before use, solvents were dried and distilled by standard methods [26].

Spectroscopy. ^{1}H and ^{13}C NMR spectra (δ, ppm, *J*, Hz) were recorded on a Bruker MSL-300 spectrometer (Germany) with a working frequency of 300 and 75.5 MHz, respectively. The spectra were recorded for the solutions of test compounds in DMSO-d_6 relative to residual protons of the solvent. IR spectra (ν, cm^{-1}) were measured in KBr pellets in Vaseline oil on a Spectrum RXI FT-IR device (Great Britain). High-resolution mass spectra were recorded on a MicrOTOF-Q II

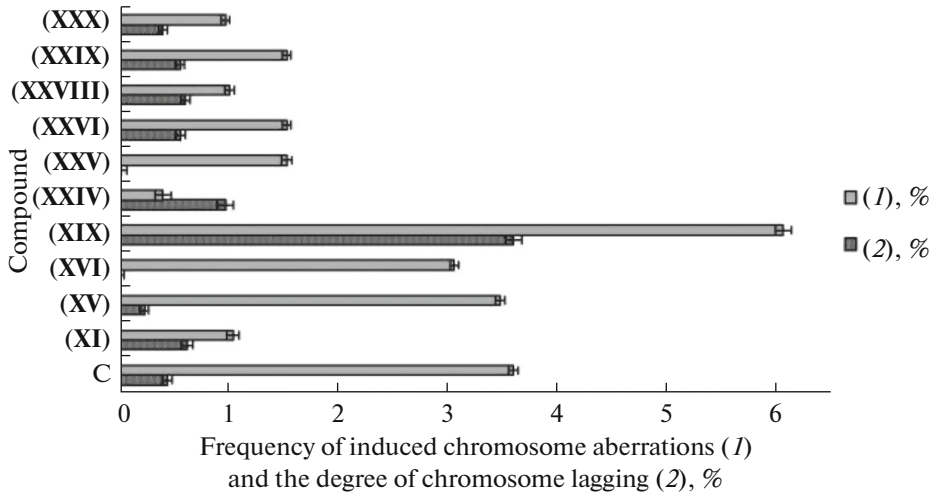

Fig. 3. Frequency of chromosome aberrations (%, *1*) and the degree of chromosome lagging (%, *2*) by the action of compounds at a concentration of 0.1% on *Allium cepa* bulbs during their sprouting.

mass spectrometer (Bruker Daltonics) using the electrospray ionization method; the temperature of the ionization source was 180°C, and the eluent was acetonitrile. TLC was performed on Sulifol 201S plates in a petroleum ether–toluene–acetone–acetic acid system 100 : 60 : 100 : 2 (v). The melting temperature of compounds was determined on an Electrothermal IA9300 Series device (Great Britain).

The general method of the synthesis of *N*-substituted imides of alicyclic dicarboxylic acids (III)–(X). Acyclic anhydride (**I**) or (**II**) (0.05 mol), an amino acid (55 mmol), and acetic acid (15 mL) were placed in a round-bottomed flask equipped with a reflux condenser and refluxed for 4 h. Then, the reaction mixture was poured into water (100 mL), and the sediment was filtered, washed with water, and dried at 40°C.

(1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2*H*-isoindol-2-yl)acetic acid (III). Yield 93%; mp 69–72°C; IR: 2724, 2671, 923 (OH); 1791, 1757, 1684 (C=O, imide); 1633 (C=C); 1178 (C–O); ^{1}H NMR: 2.37 (4 H, m, CH_2), 3.22 (2 H, m, HC–C=O), 4.04 (2 H, s, NCH_2), 5.87 (2 H, m, HC=CH), 13.07 (1 H, s, COOH); MS, *m/z*: found $[M + H]^+$ 210.076. Calculated for $C_{10}H_{11}NO_4$: 210.068.

(3,5-Dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-acetic acid (IV). Yield 83%; mp 139–143°C; IR: 2725, 2669, 920 (OH); 1791, 1758, 1680 (C=O, imide); 1643 (C=C); 1128 (C–O); ^{1}H NMR: 1.58 (2 H, m, CH_2 bridge), 2.51 (1 H, m, HC–C=O), 3.26 (1 H, m, HC–C=O), 3.44 (2 H, m, CH), 3.89 (2 H, m, NCH_2), 6.02 (2 H, m, HC=CH), 12.95 (1 H, s, COOH); MS, *m/z*: found $[M + H]^+$ 222.088. Calculated for $C_{11}H_{11}NO_4$: 222.068.

2-(1,3-Dioxo-3*a*,4-dihydro-1*H*-isoindol-2(3*H*,7*H*,7a*H*)-yl)-3-methylbutanoic acid (V). Yield 60%; mp 123–127°C; IR: 2728, 2661, 2594, 901 (OH); 1769, 1744, 1673 (C=O, imide); 1192 (C–O); ^{1}H NMR: 1.20 (3 H, m, CH_3), 1.50 (3 H, m, CH_3), 1.80 (1 H, m, HC-C=O), 2.51 (1 H, m, HC–C=O), 3.42 (2 H, m, CH_2), 3.72 (1 H, m, CHN), 4.10 (2 H, m, CH_2), 4.45 (1 H, m, CH), 6.03 (2 H, m, HC=CH), 12.61 (1 H, s, COOH); MS, *m/z*: found $[M + H]^+$ 252.125. Calculated for $C_{13}H_{17}NO_4$: 252.115.

2-(3,5-Dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-3-methylbutanoic acid (VI). Yield 73%; mp 105–108°C; IR: 2728, 2603, 901 (OH); 1769, 1706 (C=O, imide); 1682 (C=C); 1192 (C–O); ^{1}H NMR: 0.84 (6 H, m, CH_3). 1.31 (2 H, m, CH_2 bridge), 1.63 (1 H, m, HC–C=O), 1.81 (1 H, m, HC–C=O), 3.37 (1 H, m, CHN), 3.42 (2 H, m, CH), 4.41 (1 H, m, CH), 6.03 (2 H, m, CH=CH), 12.86 (1 H, s, COOH); MS, *m/z*: found $[M + H]^+$ 264.128. Calculated for $C_{14}H_{17}NO_4$: 264.115.

2-(1,3-Dioxo-3*a*,4-dihydro-1*H*-isoindol-2(3*H*,7*H*,7*aH*)-yl)-3-phenylpropanoic acid (VII). Yield 60%; mp 123–127°C; IR: 2728, 2661, 2594, 901 (OH); 1769, 1744, 1673 (C=O, imide); 1192 (C–O); ^{1}H NMR: 2.08 (2 H, m, CH_2–Ph), 2.33 (1 H, m, HC–C=O), 3.18 (1 H, m, HC–C=O), 3.43 (4 H, m, CH_2), 4.85 (1 H, m, CHN), 5.57 (2 H, m, HC=CH), 7.12 (2 H, d, *J* 7.0, Ar), 7.27 (1H, d, *J* 7.5 Ar), 7.29 (2H, t, *J* 14.2, Ar), 13.01 (1H, s, COOH); MS, *m/z*: found $[M + H]^+$ 300.124. Calculated for $C_{17}H_{17}NO_4$: 300.115.

2-(3,5-Dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-3-phenylpropanoic acid (VIII). Yield 74%; mp 136–139°C; IR: 2721, 2661, 929 (OH); 1769, 1751 (C=O, imide); 1684 (C=C); 1603, 1398 (Ar); 1169 (C–O); ^{1}H NMR: 1.42 (2 H, m, CH_2–Ph), 2.49 (2 H, m, CH_2 bridge), 3.11 (1 H, m, HC-C=O), 3.19 (1 H, m, HC-C=O), 3.33 (2 H, m, CH), 4.86 (1 H, m, CHN), 5.24 (1 H, m, HC=CH), 5.67 (1 H, m,

HC=CH), 7.12 (2 H, d, *J* 7.0, Ar), 7.20 (1 H, d, *J* 7.5, Ar), 7.26 (2 H, t, *J* 14.2, Ar), 13.02 (1 H, s, COOH); MS, *m/z*: found $[M + H]^+$ 312.123. Calculated for $C_{18}H_{17}NO_4$: 312.115.

2-(1,3-Dioxo-3*a*,4-dihydro-1*H*-isoindol-2(3*H*,7*H*,7*aH*)-yl)-3-methylpentanoic acid (IX). Yield 80%; mp 132–134°C; IR: 2591, 950 (OH); 1701 (C=O, imide); 1616 (C=C); 1263 (C–O–); ^{1}H NMR: 0.79 (6 H, m, CH_3), 1.28 (1 H, m, CH), 1.67 (2 H, m, CH_2), 1.97 (1 H, m, HC–C=O), 2.22 (1 H, m, HC–C=O), 3.17 (4 H, m, CH_2), 4.49 (1 H, m, CHN), 5.84 (2 H, m, HC=CH), 12.77 (1 H, s, COOH); MS, *m/z*: found $[M + H]^+$ 266.139. Calculated for $C_{14}H_{19}NO_4$: 266.131.

2-(3,5-Dioxo-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-4-yl)-3-methylpentanoic acid (X). Yield 93%; mp 103–105°C; IR: 2723, 2656, 2597, 904 (OH); 1746, 1706 (C=O, imide); 1677 (C=C); 1190 (C–O); ^{1}H NMR: 0.71 (3 H, m, CH_3), 0.93 (3 H, m, CH_3), 1.56 (2 H, m, CH_2 bridge), 2.23 (1 H, m, CH), 2.34 (2 H, m, CH_2), 3.37 (2 H, m, HC–C=O), 3.45 (2 H, m, CH), 4.07 (1 H, m, CHN), 6.01 (2H, m, HC=CH), 11.95 (1 H, s, COOH); MS, *m/z*: found $[M + H]^+$ 278.135. Calculated for $C_{15}H_{19}NO_4$: 278.131.

Synthesis of Amides of N-Substituted Imides of Dicarboxylic Acids (XI)–(XXX).

Method 1. Synthesis of amides of N-substituted imides of dicarboxylic acids from the corresponding acid chlorides. 1. An N-substituted imide of a dicarboxylic acid (**III**)–(**X**) (0.01 mol), thionyl chloride (0.07 mol), and a catalytic amount of DMF were placed in a flask equipped with a stirrer and a reflux condenser, and the reaction mixture was boiled for 4 h. Excess thionyl chloride was distilled under vacuum. The resulting sediment was used without additional purification in the next stages.

2. An *N*-substituted imide of a dicarboxylic acid (**III**)–(**X**) (0.01 mol) dissolved in dichloromethane (15 mL) was added to a flask, and phosphorus pentachloride (0.012 mol) was added in portions. The reaction mixture was refluxed for 4 h. Dichloromethane was distilled under vacuum. *n*-Hexane was added to the remaining reaction mixture, and the precipitate was filtered. The resulting sediment was used at the next stages without additional purification.

Triethylamine (0.013 mol) and then the acid chloride of an *N*-substituted imide of a dicarboxylic acid (1 mol) obtained earlier were added to a solution of amine (morpholine, *p*-toluidine, *p*-nitroaniline, *o*-hydroxyaniline, cyclohexylamine) (0.011 mol) in dichloromethane (15 mL). The reaction mixture was refluxed for 4 h and then poured into water (100 mL). The residue was filtered and dried at 40°C.

Method 2. Synthesis of amides of *N*-substituted imides of dicarboxylic acids (XI)–(XXX) using CDI. An *N*-substituted imide of a dicarboxylic acid (**III**)–(**X**) (0.01 mol), dioxane (10 mL), and CDI (0.11 mol) were placed in a flask equipped with a stirrer and a reflux condenser, and the reaction mixture was heated for 1.5 h to 70°C. Then, an amine (morpholine, *p*-toluidine, *p*-nitroaniline, *o*-hydroxyaniline, cyclohexylamine) was added, and the mixture was heated for an additional two hours. The reaction mass was poured into water (100 mL), and the resulting residue was filtered and dried at 40°C.

Method 3. Synthesis of amides of *N*-substituted imides of dicarboxylic acids (XI)–(XXX) using chloroethylformate. An *N*-substituted imide of a dicarboxylic acid (**III**)–(**X**) (0.01 mol), acetone (15 mL), and triethylamine (0.012 mol) were placed in a flask equipped with a stirrer and a reflux condenser. Ethylchloroformate (0.012 mol) was added gradually under intensive stirring, and the reaction mixture was refluxed for 0.5 h. Then, an amine (morpholine, *p*-toluidine, *p*-nitroaniline, *o*-hydroxyaniline, cyclohexylamine) was added, and the mixture was further boiled for 5 h. The reaction mixture was poured into water (100 mL), and the residue was filtered and dried at 40°C.

Method 4. One-top synthesis of amides of *N*-substituted imides of dicarboxylic acids (XI)–(XXX). A natural amino acid (glycine, L-valine, L-leucine, L-phenylalanine) (0.011 mol), DMSO (15 mL), K_2CO_3 (1 mmol), and then acyclic anhydride (**I**) or (**II**) (0.01 mol) were placed in a flask equipped with a stirrer and a reflux condenser. The mixture was heated for 1 h to 70°C after which an amine (morpholine, *p*-toluidine, *p*-nitroaniline, *o*-hydroxyaniline, cyclohexylamine) was added, and the mixture was refluxed for 2 h. The reaction mixture was poured into water (100 mL), and the residue was filtered and dried at 40°C.

2-(2-(Morpholin-4-yl)-2-oxoethyl-3*a*,4,7,7*a*-tetrahydro-1*H*-isoindol-1,3(2*H*)dione (XI). Yield 67%; mp 167–171°C; IR: 1762, 1690 (C=O, imide); 1667 (C=O, amide); 1625 (C=C); 1116 (–O–); ^{1}H NMR: 2.23 (2 H, m, CH_2), 2.33 (2 H, m, CH_2), 3.19 (2 H, m, CH_2), 3.39 (2 H, m, CH_2), 3.49 (1 H, m, HC=O), 3.55 (1 H, m, HC=O), 3.60 (4 H, m, CH_2), 4.25 (2 H, m, NCH_2), 5.85 (2 H, m, HC=CH); ^{13}C NMR: 23.57, 39.05, 39.56, 39.77, 40.09, 40.19, 40.40, 42.52, 45.13, 66.02, 67.02, 127.97, 164.31, 180.14; MS, *m/z*: found $[M + H]^+$ 279.128. Calculated for $C_{14}H_{18}N_2O_4$: 279.126.

2-(2-(Morpholin-4-yl)-2-oxoethyl-4-azatricyclo-[5,2,1,0]dec-8-en-3,5-dione (XII). Yield 68%; mp 93–95°C; IR: 1768, 1703 (C=O, imide), 1673 (C=O, amide); 1630 (C=C); 1114 (–O–); ^{1}H NMR: 1.55 (2 H, m, CH_2 bridge), 3.34 (2 H, m, CH_2), 3.38 (2 H, m, CH_2), 3.42 (4 H, m, CH_2), 3.46 (2 H, m, HC=O), 3.54 (2 H, m, CH), 4.10 (2 H, m, NCH_2), 6.04 (2 H, m, HC=CH); ^{13}C NMR: 25.72, 26.04, 27.03, 39.74, 40.36, 40.47, 40.68, 41.12, 52.23, 53.35, 133.13, 135.48, 164.24, 174.44, 175.68; MS, *m/z*: found $[M + H]^+$ 291.175. Calculated for $C_{15}H_{18}N_2O_4$: 291.167.

2-(2-Methyl-1-(morpholin-4-yl)-1-oxobytan-2-yl]-3*a*,4,7,7*a*-tetrahydro-1*H*-isoindol-1,3-dione (XIII). Yield 80%; mp 87–90°C; IR: 1776, 1702, 1657 (C=O, imide); 1116 (–O–); ^{1}H NMR: 0.69 (3 H, m, CH_3), 0.87 (3 H, m, CH_3), 2.21 (1 H, m, HC=O), 2.43 (1 H, m, HC=O), 2.63 (1 H, m, CH), 3.23 (4 H, m, CH_2), 3.31 (4 H, m, CH_2), 3.49 (4 H, m, CH_2), 4.39 (1 H, m, NCH), 5.88 (2 H, m, HC=CH); ^{13}C NMR: 20.51, 21.32, 25.71, 27.04, 27.13, 39.94, 41.36, 41.47, 41.68, 42.12, 52.23, 53.35, 134.13, 135.48, 167.24, 174.47, 175.70; MS, *m/z*: found $[M + H]^+$ 321.162. Calculated for $C_{17}H_{24}N_2O_4$: 321.174.

4-(3-Methyl-1-(morpholin-4-yl)-1-oxobytan-2-yl]-4-azatricyclo[5,2,1,0]dec-8-en-3,5-dione (XIV). Yield 80%; mp 83–87°C; IR: 1770, 1708, 1701, 1692 (C=O, imide); 1655 (C=O, amide); 1625 (C=C); 1113 (–O–); ^{1}H NMR: 1.09 (2 H, m, CH_2 bridge), 1.58 (3 H, m, CH_3), 2.49 (3 H, m, CH_3), 3.26 (2 H, m, HC=O), 3.42 (4 H, m, CH_2), 3.47 (2 H, m, CH), 3.56 (4 H, m, CH_2), 3.31 (1 H, m, CH),), 4.10 (1 H, m, NCH), 6.04 (2 H, m, HC=CH); ^{13}C NMR: 20.41, 20.62, 24.71, 28.04, 28.13, 39.91, 41.05, 41.47, 42.22, 46.21, 52.23, 53.37, 134.15, 135.53, 167.27, 174.49, 175.80; MS, *m/z*: found $[M + H]^+$ 333.162. Calculated for $C_{17}H_{24}N_2O_4$: 333.174.

2-(1-Benzyl-2-morpholin-2-oxo-ethyl)-4-azatricyclo[5,2,1,0]dec-8-en-3,5-dione (XV). Yield 76%; mp 172–175°C; IR: 3445, 3350, 3288, 3137, 3064 (NH); 1766, 1698 (C=O, imide); 1653 (C=O, amide); 1604 (Ar); 1115 (–O–); 741 (mono substitution Ar); ^{1}H NMR: 1.45 (2 H, m, CH_2 bridge), 3.11 (4 H, m, CH_2), 3.20 (2 H, m, HC=O), 3.31 (2 H, m, CH_2), 3.41 (2 H, m, CH_2), 3.53 (4 H, m, CH_2), 4,99 (1 H, m, NCH), 5.57 (1 H, m, HC=CH), 5.76 (1 H, m, HC=CH), 7.13 (2 H, d, Ar, *J* 6.8), 7.18 (2 H, d, Ar, *J* 7.3), 7.26 (1 H, t, Ar, *J* 16.4); ^{13}C NMR: 34.13, 52.06, 52.40, 52.43, 66.73, 127.10, 127.12, 128.66, 128.68, 129.99, 130.01, 134.68, 134.70, 135.21, 135.23, 137.74, 137.77, 166.49, 166.51, 177.13, 177.15, 177.35; MS, *m/z*: found $[M + H]^+$ 381.181. Calculated for $C_{22}H_{24}N_2O_4$: 381.174.

2-(4-Methyl-1-(morpholin-4-yl)-1-oxopentan-2-yl]-3*a*,4,7,7*a*-tetrahydro-1*H*-isoindol-1,3(2*H*)-dione (XVI). Yield 68%; mp 101–104°C; IR: 1778, 1699 (C=O, imide); 1657 (C=C); 1663 (C=O, amide); 1113, 1021 (–O–); ^{1}H NMR: 0.9 (6 H, m, CH_3). 1.32 (2 H, m, CH_2), 1.97 (1 H, m, CH), 2.19 (1 H, m, HC=O), 2.38 (1 H, m, HC=O), 2.50 (4 H, m, CH_2), 3.21 (4 H, m, CH_2), 3.57 (4 H, m, CH_2), 4.78 (1 H, m, NCH), 5.87 (2 H, m, HC=CH); ^{13}C NMR: 20.23, 21.45, 24.54, 39.01, 39.26, 39.67, 40.09, 40.19, 40.30, 40.41, 40.61, 42.12, 45.13, 66.12, 67.12, 128.97, 175.31, 180.14; MS, *m/z*: found $[M + H]^+$ 335.196. Calculated for $C_{18}H_{26}N_2O_4$: 335.189.

2-(1,3-Dioxo-3*a*,4-dihydro-1*H*-isoindol-2(3*H*,7*H*,7*aH*)-yl-*N*-(4-nitrophenyl)acetamide (XVII). Yield 78%; mp 171–174°C; IR: 3481, 3359 (NH), 1748, (C=O, imide), 1712 (C=O, I amide), 1631 (C=C), 1597 (Ar), 1549, 1325 (NO_2); ^{1}H NMR: 1.57 (1 H, m, HC=O), 2.50 (1 H, m, HC=O), 3.27 (4 H, m, CH_2), 4.12 (2 H, m, NCH_2), 6.07 (2 H, m, HC=CH), 6.75 (1 H, d, Ar, *J* 7.2), 6.86 (1 H, d, Ar, *J* 6.8), 6.92 (1 H, d, Ar, *J* 7.2), 7.77 (1 H, d, Ar, *J* 7.9), 9.81 (1 H, s, NH); ^{13}C NMR: 23.88, 39.78, 40.18, 40.41, 40.60, 40.83, 53.45, 120.37, 126.46, 127.19, 128.28, 143.83, 145.58, 168.59, 180.55, 180.78; MS, *m/z*: found $[M + H]^+$ 330.109. Calculated for $C_{16}H_{15}N_3O_5$: 330.101.

2-(3,5-Dioxo-4-azatricyclo[5.2.1.0]dec-8-en-4-yl)-4-methyl-*N*-(4-nitrophenyl)pentanamide (XVIII). Yield 70%; mp 93–95°C; IR: 3480, 3360 (NH), 1750 (C=O, imide), 1714 (C=O, I amide), 1630 (C=C), 1600 (Ar), 1549, 1325 (NO_2); ^{1}H NMR: 0.85 (6 H, m, CH_3), 1.35 (2 H, m, CH), 1.54 (2 H, m, CH_2 bridge), 1.74 (1 H, m, CH), 3.33 (2 H, m, HC=O), 3.45 (1 H, m, NCH), 4.1 (2 H, m, CH_2), 6.11 (2 H, m, HC=CH), 6.76 (1 H, d, Ar, *J* 7.8), 6.93 (2 H, d, Ar, *J* 8.8), 7.78 (1 H, d, Ar, *J* 8.6), 9.82 (1 H, s, NH); ^{13}C NMR: 20.34, 21.72, 22.88, 24.23, 26.05, 39.75, 40.18, 40.68, 41.79, 46.34, 53.35, 120.27, 125.46, 128.19, 128.28, 143.13, 145.48, 168.49, 180.44, 180.68 ; MS, *m/z*: found $[M + H]^+$ 397.172. Calculated for $C_{21}H_{23}N_3O_5$: 397.164.

2-(1,3-Dioxo-1,3,3*a*,4,7,7*a*-hexahydro-2*H*-isoindol-2-yl)-4-methyl-*N*-(4-nitrophenyl)pentanamide (XIX). Yield 76%; mp 138–143°C; IR: 3330 (NH); 1720, 1688 (C=O, imide);1615 (I amide, C=O); 1549 (II amide, C=O, NO_2), 1344 (NO_2); 1599, 1509 (Ar); 852 (1,4-disubstitution Ar); ^{1}H NMR: 0.83 (6 H, m, CH_3), 1.81 (1 H, m, CH), 2.05 (2 H, m, CH_2), 2.22 (1 H, m, HC=O), 2.42 (1 H, m, HC=O), 3.22 (4 H, m, CH_2), 4.75 (1 H, m, NCH), 5.86 (2 H, m, HC=CH), 7.82 (2 H, d, *J* 9.2), 8.22 (2 H, d, Ar, *J* 9.2), 10.32 (1 H, s, NH); ^{13}C NMR: 21.34, 23.72, 23.88, 24.04, 25.03, 39.74, 40.16, 40.37, 40.58, 40.79, 53.35, 120.27, 125.46, 128.19, 128.28, 143.13, 145.48, 168.49, 180.44, 180.68; MS, *m/z*: found $[M + H]^+$ 386.172. Calculated for $C_{20}H_{23}N_3O_5$: 386.164.

2-(3,5-Dioxo-4-azatricyclo[5,2,1,0]dec-8-en-4-yl)-*N*-(2-hydroxyphenyl)acetamide (XX). Yield 70%; mp 177–180°C; IR: 3408 (OH); 3161 (NH), 1776, 1707 (C=O, imide); 1679 (I amide, C=O); 1610 (C=C); 1596 (Ar); 1545 (II amide, C=O); 1183 (C–O), 776 (1,2-disubstitution Ar); ^{1}H NMR: 1.58 (2 H, m, CH_2 bridge), 3.27 (2 H, m, HC=O), 3.44 (2 H, m, CH_2), 4.12 (2 H, m, NCH_2), 6.07 (2 H, m, HC=CH), 6.75 (1 H, t, Ar, *J* 15.8), 6.86 (1 H, d, Ar, *J* 6.8), 6.94 (1 H, t, Ar, *J* 15.7), 7.77 (1 H, d, Ar, *J* 8.1),9.34 (1 H, s, OH), 9.81 (1 H, s, NH); ^{13}C NMR: 25.04, 25.20, 40.18, 40.37, 40.68, 46.79, 54.35, 120.27, 121.46, 124.27, 125.19, 126.28, 143.13, 145.48, 168.49, 180.54, 180.78;

MS, *m/z*: found $[M + H]^+$ 313.119. Calculated for $C_{17}H_{16}N_2O_4$: 313.111.

2-(3,5-Dioxo-4-azatricyclo[5,2,1,0]dec-8-en-4-yl)-*N*-(2-hydroxyphenyl)-3-methyl butanamide (XXI). Yield 70%; mp 82–85°C; IR: 3460 (OH); 3389, 3355 (NH); 1766, 1693 (C=O, imide); 1678 (I amide, C=O); 1599 (Ar); 1546 (II amide, C=O); ^{1}H NMR: 1.43 (2 H, m, CH_2), 2.50 (2 H, m, CH_2) 3.18 (1 H, m, HC=O), 3.20 (1 H, m, HC=O), 3.27 (1 H, m, CH), 3.42 (1 H, m, CH), 5.08 (1 H, m, NCH), 5.41 (1 H, m, HC=CH), 5.59 (1 H, m, HC=CH), 6.76 (1 H, t, Ar, *J* 15.4), 6.88 (1 H, d, Ar, *J* 7.1), 6.97 (1 H, t, Ar, *J* 15.9), 7.17 (3 H, dd, Ar, *J* 19.7), 7.29 (2 H, t, Ar, *J* 14.5), 7.74 (1 H, d, Ar, *J* 7.7), 8.92 (1 H, s, OH), 9.78 (1 H, s, NH); ^{13}C NMR: 15.05, 20.04, 21.45, 40.28, 40.57, 40.79, 46.79, 48.12, 52.39, 54.36, 120.25, 121.47, 124.28, 125.29, 126.38, 143.33, 145.58, 168.79, 180.55, 180.77; MS, *m/z*: found $[M + H]^+$ 354.133. Calculated for $C_{20}H_{22}N_2O_4$: 354.127.

2-(1,3-Dioxo-3*a*,4-dihydro-1*H*-isoindol-2(3*H*,7*H*,7*aH*)-yl)-*N*-(2-hydroxyphenyl)-4-methyl pentanamide (XXII). Yield 86%; mp 177–178°C; IR: 3390. 3295 (NH), 1769, 1693 (C=O, imide, "I amide"), 1615 (C=C), 1601 (Ar), 1537 (C=O, "II amide"), 1202 (C–O), 753 (1,2-disubstitution Ar); ^{1}H NMR: 1.4 (3 H, m, CH_3), 1.6 (3 H, m, CH_3), 1.81 (1 H, m, CH), 1.90 (1 H, m, CH), 2.19 (1 H, m, HC=O), 3.21 (1 H, m, HC=O), 3.45 (4 H, m, CH_2), 4.48 (2 H, m CH_2), 4.64 (1 H, m, NCH), 6.04 (2 H, m, HC=CH), 6.7 (1 H, t, Ar, *J* 15.3), 6.8 (1 H, d, Ar, *J* 8.6), 6.9 (1 H, t, Ar, *J* 16.3), 7.62 (1 H, d, Ar, *J* 8.2), 8.79 (1 H, s, OH), 9.65 (1 H, s, NH); ^{13}C NMR: 22.50, 23.25, 24.76, 24.98, 25.07, 25.09, 36.95, 40.05, 40.40, 40.18, 40.39, 40.60, 40.81, 53.27, 128.22, 128.29, 129.63, 133.32, 136.61, 167.34; MS, *m/z*: found $[M + H]^+$ 357.183. Calculated for $C_{20}H_{24}N_2O_4$: 357.173.

2-(3,5-Dioxo-4-azatricyclo[5,2,1,0]dec-8-en-4-yl)-*N*-(2-hydroxyphenyl)-4-methylpentanamide (XXIII). Yield 80%; mp 84–85°C; IR: 3408 (OH); 3148 (NH), 1773, 1706 (C=O, imide); 1679 (I amide, C=O); 1610 (C=C); 1596 (Ar); 1544 (II amide, C=O); 1183 (C–O), 776 (1,2-disubstitution Ar); ^{1}H NMR: 0.92 (6 H, m, CH_3), 1.43 (2 H, m, CH_2 bridge), 1.9 (2 H, m, CH_2), 2.4 (1 H, m, HC=O), 2.6 (1 H, m, HC=O), 2.92 (1 H, m, CH), 3.21 (1 H, m, CH), 3.45 (1 H, m, CH), 4.88 (1 H, m, NCH), 6.05 (2 H, m, HC=CH),6.7 (1 H, t, Ar, *J* 15.3), 6.8 (1 H, d, Ar, *J* 8.2), 6.9 (1H, t, Ar, *J* 15.3), 7.60 (1 H, d, Ar, *J* 8.3), 8.80 (1 H, s, OH), 9.75 (1 H, s, NH); MS, *m/z*: found $[M + H]^+$ 369.183. Calculated for $C_{21}H_{24}N_2O_4$: 369.181.

2-(3,5-Dioxo-4-azatricyclo[5,2,1,0]dec-8-en-4-yl)-3-phenyl-*N*-*p*-tolyl propanamide (XXIV). Yield 80%; mp 149–151°C; IR: 3296, 3274 (NH); 1766, 1686 (C=O, imide, I amide); 1648 (C=C), 1601 (Ar); 1541 (II amide, C=O), 1171 (C–O); ^{1}H NMR: 1.43 (2 H, m, CH_2 bridge), 2.54 (1 H, m, HC=O), 3.09 (4 H, m, CH_2), 3.22 (1 H, m, HC=O), 3.28 (1 H, m, CH), 3.47 (1 H, m, CH), 4.99 (1 H, m, NCH), 5.21 (2 H, m, HC=CH), 5.5 (1 H, m, HC=CH), 7.12 (2 H, d, Ar, *J* = 8.1), 7.22 (1 H, d, Ar, *J* 7.0), 7.18 (2 H, d, Ar, *J* 7.6), 7.28 (2 H, d, Ar, *J* 7.5), 7.41 (2 H, d, Ar, *J* 8.3), 9.70 (1 H, s, NH); MS, *m/z*: found $[M + H]^+$ 401.173. Calculated for $C_{25}H_{24}N_2O_3$: 401.187.

2-(1,3-Dioxo-1,3,3*a*,4,7,7*a*-hexahydro-2*H*-isoindol-2-yl)-4-methyl-*N*-*p*)-tolyl pentanamide (XXV). Yield 83%; mp 173–175°C; IR: 3259 (NH); 1772, 1701 (C=O, imide); 1664 (C=C, I amide, C=O); 1603 (Ar); 1545 (II amide, C=O), 815 (1,4-disubstitution Ar); ^{1}H NMR: 0.81 (6 H, m, CH_3). 1.29 (1 H, m, CH), 1.77 (2 H, m, CH2), 2.21 (1 H, m, HC=O), 2.21 (1 H, m, HC=O), 2.42 (4 H, m, CH_2), 3.2 (3 H, m, CH_3), 4.66 (1 H, m, NCH), 5.86 (2 H, m, HC=CH), 7.11 (2 H, d, *J* 8.4), 7.38 (2 H, d, *J* 8.4), 9.61 (1 H, s, NH); ^{13}C NMR: 21.10, 21.24, 23.76, 23.96, 24.07, 25.08, 36.85, 39.05, 39.34, 39.97, 40.18, 40.39, 40.60, 40.81, 53.27, 128.22, 128.29, 129.63, 133.32, 136.61, 167.34; MS, *m/z*: found $[M + H]^+$ 355.203. Calculated for $C_{21}H_{26}N_2O_3$: 355.194.

2-(3,5-Dioxo-4-azatricyclo[5,2,1,0]dec-8-en-4-yl)-*N*-cyclohexyl)acetamide (XXVI). Yield 60%; mp 120–121°C; IR: 3307, 3266 (NH), 1769, 1699 (C=O, imide); 1658 (I amide, C=O); 1610 (C=C); 1551 (II amide, C=O); ^{1}H NMR: 1.26–1.11 (6 H, m, CH_2), 1.35 (2 H, m, CH_2 bridge), 1.71 (1 H, m, HC=O), 1.84 (1 H, m, HC=O), 1.97 (2 H, m, CH_2), 2.26 (1 H, m, CH), 2.42 (2 H, m, CH_2), 3.27 (2 H, m, CH_2), 4.75 (2 H, m, NCH_2), 5.84 (2 H, m, HC=CH), 9.32 (1 H, s, NH); ^{13}C NMR: 24.10, 24.73, 25.76, 31.32, 32.47, 45.85, 45.95, 46.05, 46.34, 52.27, 135.22, 135.29, 167.34, 169.30, 170.34, 175.12, 175.35; MS, *m/z*: found $[M + H]^+$ 303.70. Calculated for $C_{17}H_{22}N_2O_3$: 303.163.

2-(3,5-Dioxo-4-azatricyclo[5,2,1,0]dec-8-en-4-yl)-*N*-cyclohexyl)pentanamide (XXVII). Yield 73%; mp 110–111°C; IR: 3327, 3136 (NH), 1769, 1703 (C=O, imide); 1664 (I amide, C=O); 1605 (C=C); 1538 (II amide, C=O); ^{1}H NMR: 1.11 (6 H, m, CH_3). 1.37 (2 H, m, CH_2 bridge), 1.56 (4 H, m, CH_2), 1.82–1.55 (10 H, m, CH_2), 2.03 (1 H, m, HC=O), 3.35 (1 H, m, HC=O), 3.57 (2 H, m, CH), 4.25 (1 H, m, NCH), 6.02 (2 H, m, HC=CH), 7.52 (1 H, d, NH, *J* 8.1); MS, *m/z*: found $[M + H]^+$ 359.270. Calculated for $C_{21}H_{30}N_2O_3$: 359.233.

2-(1,3-Dioxo-3*a*,4-dihydro-1*H*-isoindol-2(3*H*,7*H*,7*aH*)-yl)-*N*-cyclohexyl)acetamide (XXVIII). Yield 75%; mp 110–114°C; IR: 3287 (NH), 1779, 1708 (C=O, imide); 1658 (I amide, C=O); 1605 (C=C); 1560 (II amide, C=O); ^{1}H NMR: 1.26–1.11 (5 H, m, CH_2), 1.57 (2 H, m, CH_2), 1.71 (4 H, m, CH_2), 3.25 (2 H, m, HC=O), 3.48 (3 H, m, CH), 3.77 (2 H, m, CH), 6.04 (2 H, m, HC=CH), 7.83 (1 H, m, CH),

8.32 (1 H, s, NH); MS, *m/z*: found $[M + H]^+$ 291.180. Calculated for $C_{16}H_{22}N_2O_3$: 291.171.

2-(3,5-Dioxo-4-azatricyclo[5,2,1,0]dec-8-en-4-yl)-*N*-cyclohexyl)methyl butanamide (XXIX). Yield 80%; mp 115–119°C; IR: 3261 (NH), 1773, 1706 (C=O, imide); 1645 (I amide, C=O); 1605 (C=C); 1544 (II amide, C=O); ^{1}H NMR: 0.75 (6 H, m, CH_3), 1.35 (2 H, m, CH_2 bridge), 1.55 (2 H, m, CH_2), 1.82–1.53 (10 H, m, CH_2), 2.02 (1 H, m, HC=O), 3.37 (1 H, m, HC=O), 3.47 (2 H, m, CH),4.27 (1 H, m, NCH), 6.04 (2 H, m, HC=CH), 7.44 (1 H, d, NH, *J* 8.1); MS, *m/z*: found $[M + H]^+$ 345.220. Calculated for $C_{20}H_{28}N_2O_3$: 345.217.

2-(1,3-Dioxo-3*a*,4-dihydro-1*H*-isoindol-2(3*H*,7*H*,7*aH*)-yl)-*N*-cyclohexyl)pentanamide (XXX). Yield 80%; mp 125–129°C; IR: 3285 (NH), 1772, 1704 (C=O, imide); 1647 (I amide, C=O); 1605 (C=C); 1543 (II amide, C=O); ^{1}H NMR: 0.91 (6 H, m, CH_3), 1.60 (2 H, m, HC=O), 1.74–1.21 (12 H, m, CH_2), 3.54 (2 H, m, CH), 3.37 (4 H, m, CH_2), 3.62 (1 H, m, NCH), 6.23 (2 H, m, HC=CH), 7.52 (1 H, d, NH, *J* 7.8); MS, *m*/z: found $[M + H]^+$ 347.240. Calculated for $C_{20}H_{30}N_2O_3$: 347.231.

Study of genotoxicity using the Allium test [41]. The onion *Allium cepa* variety Stuttgarter Riesen was used as an object. For experiments, equalized material was used: bulbs had the shape typical of the variety and were equal in size.

Bulbs were placed in reservoirs containing test solutions and distilled water (as a control). The material was let germinate in the light. Then, roots were cut from each bulb and washed with water after which their sprouting and length were determined. Five experiments for each concentration of a test solution were carried out. The error in the determination of root length was 1.1–2.2%.

The material (roots) was fixed for three days by the Clarke's fixative (96% ethanol with glacial acetic acid in the ratio 3 : 1). Before staining, rootlets were washed from ethanol in water for better dyeing and placed in a dye (2% acetoorsein). A crucible with the dye and roots was heated in the flame of an alcohol burner until vapors appeared on the cover glass [41].

Staining was carried out for at least 40 min. Then, squeezed root meristem preparations were made. Rootlets were washed from the dye in 45% acetic acid. The top 2–3 mm long was cut from a rootlet, placed onto a slide into a drop of 45% acetic acid, and covered with a cover glass after which the preparation was squeezed using a match until a cell monolayer formed.

Preparations were examined under a microscope. Small meristematic cells with well stained nuclei were analyzed. Dividing cells at all stages of mitosis were taken into account; separately, normal cells at ana- and telophases and cells with chromosome aberrations and lagging chromosomes at these phases were recorded. Then, the mitotic index was calculated, i.e., the ratio of the number of cells in mitosis to the total number of cells in a sample, and statistical processing of the results was performed [41].

COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflict of interest. This article does not contain any studies involving animals or human participants performed by any of the authors.

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