Synthesis of novel pyrroloazepinones by Schmidt expansions of 6-indolones

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Abstract

New derivatives of pyrroloazepinones were synthesized. The synthesis route consisted of three stages: the formation of a dimedone-derived tricarbonyl compound, the formation of a pyrrole ring resulting from the use of the Paal-Knorr method to generate tetrahydroindole-6-ones, and the expansion of the ketone by following the Schmidt method to generate lactams. The obtained 6-indolones were used to generate new derivatives: the pyrrolo[2,3-c]azepin-6-one and the pyrrolo[2,3-d]azepin-7-one ring systems. The synthesized pyrroloazepinones were evaluated for inhibitory activity in cancer cell lines and they did not show activity and cytotoxic effects on the non-tumor cells HEK239, with $IC_{50} \geq 215 \pm 5.41$ μM.

R = -H, -Cl, -F, -OCH$_3$, -CO$_2$CH$_2$CH$_3$
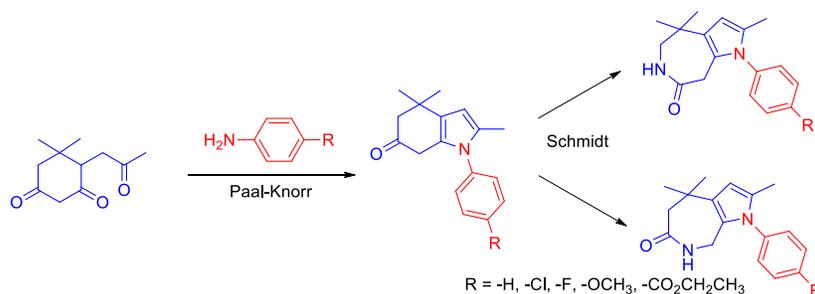
Keywords: Pyrroloazepinone, indolone, Schmidt expansion, Wacker oxidation.

Introduction

Pyrroloazepinones are biheterocyclic compounds that display an important diversity of biological properties, which have been used for the treatment of Alzheimer's,[1] arthritis and many types of cancer[2-6] (**Scheme 1**). They have been found in derivatives of natural products such as paullones[6], hymenialdisine[1], and stevensine[7]. Their mechanism of action is very versatile, involving mainly the inhibition of kinases (CDK1 or MEK1)[1,6], specifically via competitive inhibition of ATP binding.[4] However, few reported works have focused on obtaining pyrroloazepinone derivatives.
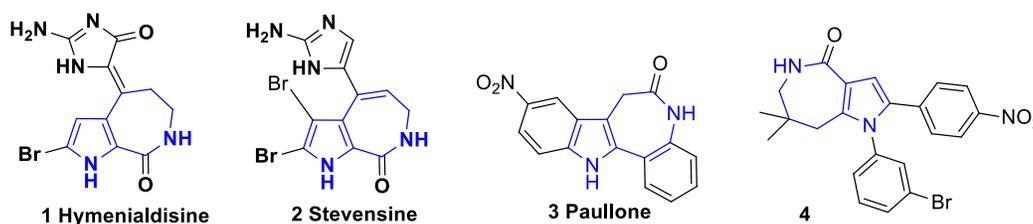

Scheme 1. Natural and synthetic products with a pyrroloazepinone structure.

The most common key step for the syntheses of pyrroloazepinone derivatives is the construction of the bicyclic ring system. For example, typical aromatic electrophilic substitution and acid hydrolysis reactions are used to obtain hymenialdisine derivatives[8,9], which have also been obtained by carrying out catalytic cyclizations of coordination compounds.[10] On the other hand, pyrroloazepinones can be obtained by carrying out ring-expanding Beckmann rearrangements[11,12] and Schmidt reactions of tetrahydroindole-4-ones.[13] Tetrahydroindolones are aromatic heterocycles formed by fusing benzene and pyrrole rings. Their syntheses are based on methodologies such as the application of the Paal-Knorr method to synthesize pyrroles; this method is carried out with 1,4-dicarbonyl compounds and aliphatic or aromatic amines in an acidic medium.[14] Also, the routes of formation of pyrrole rings have been developed using different types of metal catalysts used for the formation of indoles[15] and even tetrahydroindole-4-one.[16] To the best of our knowledge, the synthesis of a pyrroloazepinone from the expansion of a tetrahydroindole-6-one has not yet been reported.

In the current work, we set out to develop a route for the syntheses of new indole derivatives, as well as the formation in one step of novel isomers of pyrrolo[2,3-d]azepin-7-ones and pyrrolo[2,3-c]azepin-6-ones using the Schmidt expansion. These products may be considered to be hymenialdisine analogues, with therapeutic potential for various diseases.

Results and Discussion

To carry out the synthesis of 6-indole and later of the pyrroloazepinones, the commercial compound 5,5-dimethyl-1,3-cyclohexanodione (**5**, see **Scheme 2**) was first converted to the enol ether **6**[17], which was then C-alkylated at position 6 by carrying out a nucleophilic substitution of **6** with allyl bromide to obtain the alkyl ketone **7**. Subsequently, compound **7** was hydrolyzed with an aqueous-acid solution of p-toluenesulfonic and water to form the compound **8**[18].
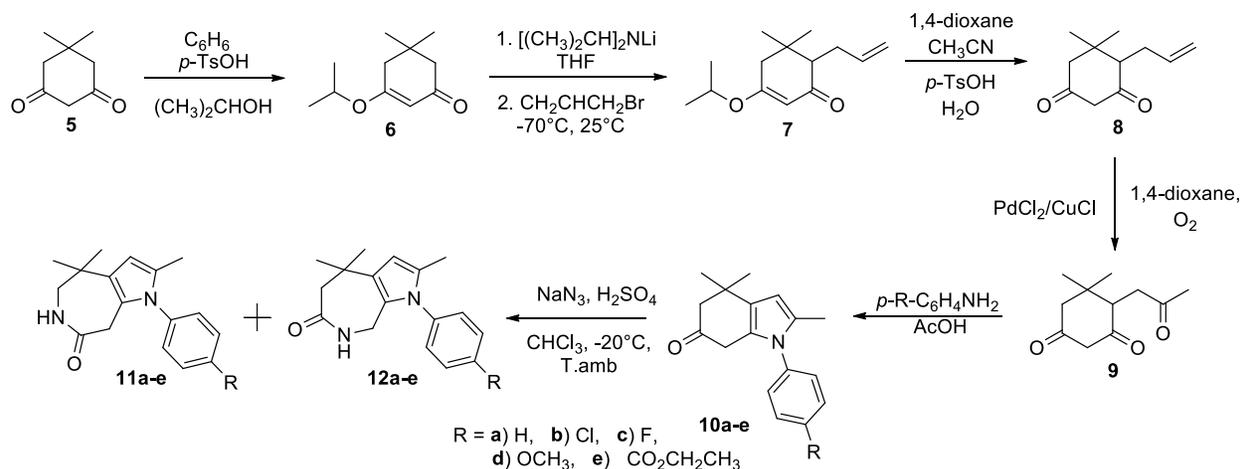
Scheme 2. Synthesis of 1-(4-R-phenyl)-2,4,4-trimethyl-4,5,6,8-tetrahydropyrrolo[2,3-d]azepin-7(1*H*)-one and 1-(4-R-phenyl)-2,4,4-trimethyl-4,5,7,8-tetrahydropyrrolo[2,3-c]azepin-6(1*H*)-one.

The preparation of the tricarbonyl compound **9** was performed by using a Wacker-type process to oxidize the terminal alkene group of **8**. Here, various tests were performed by modifying the variables of the reaction forming compound **9** to obtain the best working conditions. The results of these experiments are listed in **Table 1**, with a 37% yield of tricarbonyl **9** being the best case (from the relative percentage of the area under each gas chromatography-mass spectrum (GC-MS) curve) and achieved when using 0.5 equiv. of PdCl$_2$, 1.5 equiv. of CuCl, an O$_2$ atmosphere, and 1,4-dioxane as a solvent for 2 hours of reaction.

Table 1. Screening of the reaction conditions[a] for the formation of the tricarbonyl **9**.

Entry	Equiv. of PdCl$_2$	Atm	Reaction Time (h)	Solvent	Yield (%)[b]
1	1	O$_2$ atm	1.5	DMF	< 3
2	0.1	O$_2$ atm	18	DMF	15
3	0.1	O$_2$ atm	24	DMF	< 3
4	0.1	O$_2$	24	THF	16
5	0.1	O$_2$	24	1,4-dioxane	6
6	0.1	O$_2$	1	DMF	<5
7	0.1	O$_2$	2	DMF	14
8	0.1	O$_2$	4	DMF	13
9	0.5	O$_2$	6	DMF	18
10	0.5	O$_2$	8	DMF	12
11	0.5	O$_2$	24	DMF	<5

12	0.5	O_2	0.5	DMF	5
13	0.5	O_2	1	DMF	13
14	0.5	O_2	1.5	DMF	16
15	0.5	O_2	2	DMF	25
16	0.5	O_2	3	DMF	14,5
17	0.5	O_2	2	1,4-dioxane	37

[a]Reaction conditions: 4-allyl-5,5-dimethylcyclohexane-1,3-dione (1 equiv., 27.7 mmol), CuCl (1.5 equiv., 41.6 mmol), H_2O (20 equiv.), $PdCl_2$ and solvent.
[b]The yields corresponded to the percentage relative to 100% of the area under the curve of the GC-MS peaks of the reaction mixture.

From the crude compound **9**, the syntheses of tetrahydroindole-6-ones **(10a-e)** were performed based on the Paal-Knorr methodology. For each of these five syntheses, a different *p*-R-aniline was used, as was glacial acetic acid and infrared light as a source of energy, all in a nitrogen atmosphere. From each reaction mixture, a viscous black liquid product was obtained, and was purified using column chromatography. **Table 2** lists the appearance, melting point, and yield of each of the tetrahydroindole-6-one **(10a-e)** products.

Table 2. Appearance, melting point, and yield of each of the tetrahydroindole-6-ones.

R = **a**) H, **b**) Cl, **c**) F, **d**) OCH_3, **e**) $CO_2CH_2CH_3$
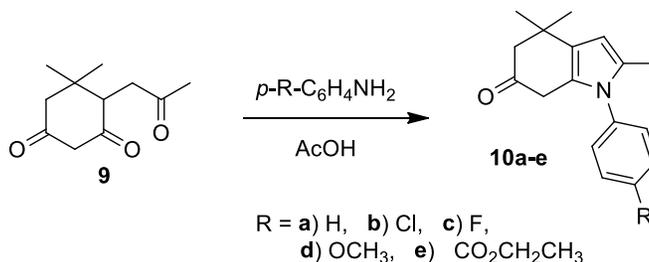
| Compound	Appearance	mp (°C)	Yield (%)[a]
10a	Yellow solid	114	15
10b	Yellow solid	111	25
10c	Yellow solid	161	25
10d	Viscous coffee liquid	-	36
10e	Orange solid	96	20

[a]Paal Knorr conditions: 5,5-dimethyl-4-(2-oxopropyl)cyclohexane-1,3-dione (1 equiv., 5.1 mmol), *p*-R-anilines (1 equiv., 5.1 mmol), 10 ml AcOH, N_2, 92-93°C, IR lamp, 2 h.

Presence of other significant size peaks on the chromatogram obtained by GC-MS showed that other compounds with a higher molecular ion signal where present along with compound **9**, this suggest that side reactions between products and/or reagents happened. Since compound **9** is a liquid, purification by and the column chromatography purification was not possible because it decomposes. These two facts indicate that compound **9** is unstable in acidic medium, the above explains the use of the reaction mixture to obtain compounds **10a-e**, as well as the low yield of compound **9** and consequently the Paal-Knorr reaction efficiency to obtain compounds **10a-e**.

As a final synthesis step, the Schmidt method was used for the formation of the new pyrroloazepinones from compounds **10a-e**. Here, *in situ*-generated hydrazoic acid induced the direct ring expansion of each tetrahydroindole-6-one. The advantage of the Schmidt method here was that two isomers of pyrroloazepinones, specifically pyrrolo [2,3-d]azepin-7-one and pyrrolo[2,3-c]azepin-6-one, were generated in a single step with yields above 61% (**Table 3**). After the reaction, the mixture of pyrroloazepinones was purified, and the purified material was characterized using IR, MS, HETCOR, DEPT and FLOCK.

The Beckmann expansion of ketones in order to obtain lactams, is the alternative method for Schmidt method, the Beckmann method was also used to obtain the pyrroloazepinones **11** and **12** in polyphosphoric acid medium, however the obtained products are from decomposition.

**Table 3.** Reactions forming pyrrolo[2,3-*d*]azepin-7-one and pyrrolo[2,3-*c*]azepin-6-one derivatives[a].

R = **a**) H,   **b**) Cl,   **c**) F,
     d) OCH$_3$,   **e**) CO$_2$CH$_2$CH$_3$
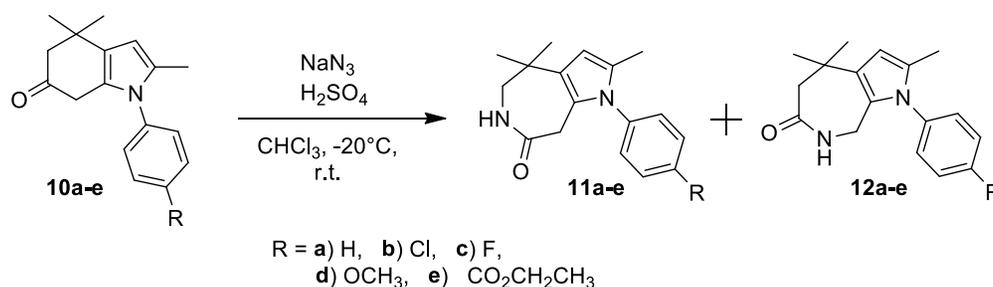
Compound	PRZ Mixture Ratio a:b	% Yield for Mixture of Isomers (11 and 12)	% Individual Yield[b]
11a	1:1.54	75	29.5
11b	1:1.54	79	31.1
11c	1:1.23	82	36.8
11d	1:1.25	61	27.1
11e	1:1.48	79	31.9
12a	1:1.54	75	45.5
12b	1:1.54	79	47.9
12c	1:1.23	82	45.2
12d	1:1.25	61	33.9
12e	1:1.48	79	47.1

[a]Reaction conditions: sodium azide (1.5 equiv., 0.9 mmol), sulfuric acid (8.4 mmol, 14 equiv.), 1-(4-R-phenyl)-2,4,4-trimethyl-4,5-dihydro-1*H*-indol-6(7*H*)-one (1 equiv., 0.6 mmol), chloroform, -20 °C then room temperature.
[b]The ratio between the amounts of the pyrroloazepinone isomers was obtained using GC-MS.

HETCOR, DEPT AND FLOCK
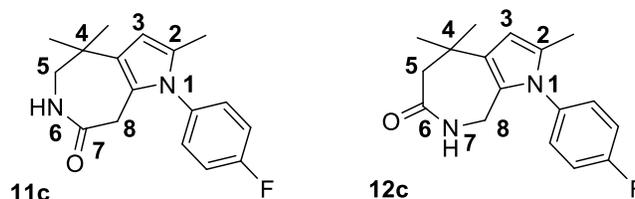
Scheme 3. Carbon assignments for the NMR signals of the pyrroloazepinones **11c** and **12c**.

Isomerism of the pyrroloazepinones compounds **11c** and **12c** was analyzed by assigning the carbon-carbon connectivity of the annular pyrroloazepinone systems from the results of mono-nuclear NMR experiments, specifically ^{1}H-NMR, ^{13}C-NMR, and DEPT experiments, and from the results of correlative 2D-NMR heteronuclear experiments, specifically HETCOR and FLOCK experiments. The DEPT experiment for **11c** showed signals at ∂ = 33.68 ppm and ∂ = 52.80 ppm, corresponding to secondary carbons. And in the HETCOR experiment, a correlation was observed between a signal at ∂ = 3.36 ppm and that at ∂ = 3.28 ppm of the ^{1}H spectrum. So these secondary carbons in turn corresponded to C-8 and C-5. The connectivity of the C-5, C-6, C-7 and C-8 atoms with other atoms was confirmed from the results of the FLOCK experiment: the signal at ∂ = 1.24 ppm from the C-4 methyl protons showed correlations with the signals at ∂ = 28.34 ppm from the methyl carbons, at ∂ = 35.26 ppm from the two sigma bonds made with C-4, and at ∂ = 52.79 ppm from C-5. In turn, the doublet ^{1}H signal at ∂ = 3.28 ppm correlated with the signal assigned to C-5 in the HETCOR experiment.

For compound **12c**, the DEPT experiment showed the signals of the secondary carbons at ∂ = 38.19 ppm and ∂ = 48.03 ppm, which were found to correlate with the signals at ∂ = 3.97 ppm and ∂ = 2.67 ppm, respectively, in the HETCOR experiment; these C signals were assigned to C-8 and C-5. Similar to the case for the **11c** isomer, the connectivity of the C-5, C-6, C-7 and C-8 atoms of **12c** was confirmed from the results of the FLOCK experiment. The signal at ∂ = 1.34 ppm of the ^{1}H spectrum correlated with the signal at ∂ = 32.58 ppm from   C-4 to two sigma bonds and with the signal at ∂ = 48.04 ppm from C-5 to three sigma bonds. The latter signal correlated, in the HETCOR experiment, with the simple signal at ∂ = 2.67 ppm in the ^{1}H spectrum, and was hence assigned to C-5. The connectivity of C-5 with a carbonyl was also indicated by the observed correlation of the signal at ∂ = 2.67 ppm of the ^{1}H spectrum with the signal at ∂ = 175.94 ppm of the ^{13}C spectrum to two bonds.

Cytotoxic activity

To assess *in vitro* the cytotoxicities of the isomeric pyrroloazepinone products, the MTT assay was used to determine their abilities to inhibit the growth of cancer cells such as cervical carcinoma (SiHa), lung adenocarcinoma (SKLU1), breast carcinoma (ZR-75-1), and colorectal adenocarcinoma (SW480) cells, and of cells of the non-tumor human embryonic kidney 293 (HEK293) cell line. Cisplatin was used as a positive control and cell growth inhibition was evaluated after 48 h of exposure with compounds **11a-e** and **12a-e** each at a concentration of 100 μM for the cancer cells and of up to 800 μM for the HEK239 cells. These compounds showed no cytotoxic effects on the non-tumor cells (HEK239), with the IC_{50} determined to be above 215 ± 5.41 μM, and they did not show cytotoxic activity on the evaluated cancer cells.

Conclusions

Five novel 6-indole derivatives were subjected to Schmidt ring expansions to produce new derivatives of pyrroloazepinones. These products included the pyrrolo[2,3-c]azepin-6-one and pyrrolo[2,3-d]azepin-7-one ring system analogs of hymenialdisine. The pyrroloazepinones obtained were indicated to not be cytotoxic.

Experimental Section

General. All reagents and solvents were purchased from Sigma-Aldrich Co. The melting points were determined in a Melt-Temp apparatus, using open and uncorrected capillary tubes. The purification of the products was carried out by performing column chromatography, using E. Merck Kieselgel 60 silica gel (230-400 mesh), grade 9385, and hexane-ethyl acetate as eluent. The progress of the reactions and purity of the products were monitored by performing thin layer chromatography (TLC), using 60 F254 silica gel plates (Merck) and ultraviolet light as a developer. The FT-IR spectra were obtained using a Thermo Nicolet NEXUS 470 FT-IR spectrometer, with thin films on a KBr disk for solids and ATR with germanium crystals for liquids. The mass spectra (MS) were obtained using a Jeol AX505HA mass spectrometer. The purity levels of compounds **11a-e** and **12a-e** were determined by using an Agilent Technologies 6890N chromatograph coupled to an Agilent Technologies 5973 Network mass spectrometer operated at 70 eV and equipped with a DB-5HT capillary column (15 m, 0.25 i.d.) with (5%-phenyl)-methylpolysiloxane (0.10-μm-thick film). Here, helium was used as the carrier gas at a flow rate of 1 ml/min. The injector and MS transfer line temperatures were set at 320 °C. Diluted samples (1:10 v/v, in acetone) 2.0 μL in volume were manually injected. After sample injection, the initial temperature in the oven (50°C) was held constant for 2 min, then increased to 320 °C (at a rate of 15°C/min). This temperature was then maintained for 5 min. After a delay of 1.8 min to permit passage of the solvent, the mass spectra were obtained by scanning from 15 to 800 *m/z*. The ^{1}H-NMR and ^{13}C-NMR spectra were obtained using a Varian-Unity 300 MHz apparatus with deuterated chloroform (CDCl$_3$) as the solvent and tetramethylsilane (TMS) as the internal reference. Chemical shifts were reported in parts per million (ppm) relative to the residual peak. Multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants in Hertz (Hz) were reported for the Individual peaks. HRMS-EST spectra were obtained with a JEOL The AccuTOF JMS-T100LC mass spectrometer. The cytotoxicity activity levels of the newly synthesized compounds were assessed by testing these compounds against cells of a human liver carcinoma cell line, against cervical carcinoma (SiHa), lung adenocarcinoma (SKLU1), mammary breast carcinoma (ZR-75-1), and colon adenocarcinoma (SW480) cells, and against cells of the non-tumor human embryonic kidney 293 (HEK293) cell line.

3-Isopropoxy-5,5-dimethylcyclohex-2-enone (6). Into a flask were placed 5 g (35.7 mmol, 1 equiv.) of 5,5-dimethyl-1,3-cyclohexanedione, 8.2 mL (107.1 mmol, 3 equiv.) of isopropyl alcohol, 6.8 g (35.7 mmol, 1 equiv.) of p-toluenesulfonic acid and 50 mL of benzene. The resulting reaction mixture was heated to reflux for 4 h, and then cooled. The benzene and excess isopropyl alcohol were distilled in vacuo. Then water was poured into the flask, the remaining contents of which were neutralized with NaHCO$_3$. Extractions were made with diethyl ether (3x30 mL), and the resulting organic phase was dried with anhydrous sodium sulfate, decanted and then concentrated. The target compound was obtained as a colorless crystal. Yield 92% (5.9 g). *Rf* = 0.59 (hexane-AcOEt, 60:40). mp: 47°C. MS (EI): *m/z* 182 (M+, 21), 140 (11), 84 (100), 69 (11). IR (KBr, cm^{-1}): 3060 (C-H$_{sp2}$), 2960 (C-H$_{sp3}$), 1647 and 1600 (C=O), 1226 (C-O).

6-Allyl-3-isopropoxy-5,5-dimethylcyclohex-2-enone (7). Into a two-neck flask sealed and drained with nitrogen were added, via cannula, a little dry and distilled tetrahydrofuran, and then 4.6 mL (32.9 mmol, 1.2 equiv.) of dry diisopropylamine. The flask was placed on a bath cooled to -70 ° C and 22 mL (35.7 mmol, 1.3 equiv.) of 1.6 M n-butyllithium in hexane was added into the flask, and its contents were stirred for 20 minutes. Subsequently, a mass of 5 g (27.5 mmol, 1 equiv.) of 3-isopropoxy-5,5-dimethylcyclohex-2-enone dissolved in tetrahydrofuran was added via cannula into the flask, followed by 2.7 mL (33 mmol, 1.2 equiv.) of allyl bromide. The resulting contents of the flask were stirred for 30 minutes at -70 °C and 90 minutes at room temperature. The reaction was stopped with a 10% NaCl solution, the product was extracted with diethyl ether, and the resulting organic phase was dried with anhydrous sodium sulfate, decanted and concentrated to dryness. The target compound was obtained as a yellow liquid. Yield 96% (5.8 g). *Rf* = 0.6 (hexane-AcOEt, 70:30). MS (EI): *m/z* (%): 222 (M+, 15), 207 (27), 165 (78), 109 (50), 82 (100). IR (KBR, cm^{-1}): 2973 (C-H$_{sp2}$), 2933 (C-H$_{sp3}$), 1648 and 1608 1608(C=O), 1220 (C-O).

4-Allyl-5,5-dimethylcyclohexane-1,3-dione (8). We combined 5 g (22.5 mmol, 1 equiv.) of 6-allyl-3-isopropoxy-5,5-dimethylcyclohex-2-enone and 4.2 g (22.5 mmol, 1 equiv.) of *p*-toluenesulfonic acid into a mixture of 10 mL of acetonitrile, 15 mL of 1,4-dioxane and 10 mL of water. This reaction mixture was refluxed for 4 h. Then water was added to the resulting mixture, which was then extracted with dichloromethane. The organic phase was dried with anhydrous sodium sulfate and concentrated to dryness. The target compound was obtained as a yellow liquid. Yield 98% (3.9 g). *Rf* = 0.67 (hexane-AcOEt, 70:30). MS (EI): *m/z* (%): 180 (M+, 41), 124 (100), 95 (9), 69 (40), 56 (11), 41 (9). IR (KBr, cm^{-1}): 3075 (C=C-H), 1645,1621 (C=C-C=O), 1233 (C-O-C).

5,5-Dimethyl-4-(2-oxopropyl)cyclohexane-1,3-dione (9). Into a round-bottomed flask were placed 2.46 g (13.9 mmol) of palladium chloride (II), 4.12 g (41.6 mmol) of copper chloride (I), 40 mL (17 equiv., 0.469 mol) of 1,4-dioxane and 10 mL (20 equiv., 0.555 mol) of water. The flask was left under an oxygen atmosphere and its contents were stirred for 1 h. Then a mass of 5 g (27.8 mmol) of 4-allyl-5,5-dimethylcyclohene-1,3-dione dissolved in 1,4-dioxane was added to the flask and the resulting reaction mixture was stirred for 2 h. The reaction was then quenched with water and filtered over diatomaceous earth and washed with water, and then the product was extracted with dichloromethane and concentrated. The final target product was obtained as a brown viscous liquid. Yield 37% (2 g). MS (EI): *m/z* (%): 196 (M+,9), 138 (27), 83 (39), 43 (100).

General procedure for the synthesis of 1-(4-R-phenyl)-2-4,4-trimethyl-4,5-dihydro-1*H*-indol-6(7*H*)-one (10a-e). Into a round-bottomed flask was placed 1 g (5.1 mmol, 1 equiv.) of 5,5-dimethyl-4-(2-oxopropyl) cyclohexane-1,3-dione, 5.1 mmol (1 equiv.) of *p*-R-aniline and 10 mL of glacial acetic acid. A coolant was also placed in the flask and drained with nitrogen. The reaction mixture was heated to reflux (92-93 °C) using an infrared lamp for 2 h. The reaction was then stopped with water; the resulting mixture was neutralized with NaHCO$_3$ and extracted with ethyl acetate. The resulting organic phase was concentrated, and a dark brown viscous liquid was obtained. Subsequently, the indole compound was purified using silica gel column chromatography with a gradient of 3-97% ethyl acetate in hexane as eluent.

2,4,4-Trimethyl-1-phenyl-4,5-dihydro-1*H*-indol-6(7*H*)-one (10a). The compound was obtained as a yellow solid. Yield 15% (0.2 g). *Rf* = 0.65 (hexane-AcOEt, 80:20). mp: 114 °C. MS (EI): *m/z* (%): 253 (M+, 58), 238 (55), 210 (100). IR (KBR, cm^{-1}): 2947s (C-H), 1708vs (C=O), 1500vs (C-N), 1234m (C-O). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm): 1.29 (s, 6H), 2.09 (d, 3H), 2.52 (s, 2H), 3.20 (s, 2H), 5.96 (d, 1H), 7.20 (dd, 2H, *Jo* = 8.2 Hz, *Jm* = 1.3 Hz), 7.43 (m, 3H). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂: 12.7 (CH$_3$), 30.5 (2CH$_3$), 33.9 (C), 38.5 (CH$_2$), 55.3 (CH$_2$), 102.8 (CH), 121.8 (CH$_{arom}$), 126.6 (C), 127.6 (2CH$_{arom}$) 127.8 (C), 129.2 (2CH$_{arom}$), 129.8 (C), 138 (CN), 208.9 (C=O).

1-(4-Chorophenyl)-2,4,4-trimethyl-4,5-dihydro-1*H*-indol-6(7*H*)-one (10b). The compound was obtained as a yellow-orange solid. Yield 25% (0.37 g). *Rf* = 0.68 (hexane-AcOEt, 80:20). mp: 111 °C. MS (EI): *m/z* (%): 287 (M+, 53), 272 (59), 244 (100). IR (KBR, cm^{-1}): 2952m (C-H), 1704s (C=O), 1495vs (C-N), 1091s (C-O). ^{1}H-NMR

(300 MHz, CDCl$_3$) ∂ (ppm): 1.28 (s, 6H), 2.08 (d, 3H), 2.52 (s, 2H), 3.18 (s, 2H), 5,96 (d, 1H), 7.15 (d, 2H, *Jo*=8.7 Hz), 7.42 (d, 2H, *Jo*=8.7 Hz). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 12.7 (CH$_3$), 30.5 (2CH$_3$), 33.9 (C), 38.4 (CH$_2$), 55.2 (CH$_2$), 103.2 (CH), 121.9 (C), 127 (C), 128.9 (2CH$_{arom}$), 129.5 (2CH$_{arom}$), 129.8 (CCl), 133.7 (C), 136.6 (CN), 208.5 (C=O).

1-(4-Fluorophenyl)-2,4,4-trimethyl-4,5-dihydro-1*H*-indol-6(7*H*)-one (10c). The compound was obtained as a brown solid. Yield 25% (0.34 g). *Rf* = 0.63 (hexane-AcOEt, 80:20). mp: 161 °C. MS (EI): *m/z* (%): 271 (M+, 52), 256 (50), 228 (100). IR (KBR, cm^{-1}): 2947m (C-H), 1708s (C=O), 1508vs (C-N), 1217s (C-O). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm): 1.28 (s, 6H), 2.07 (d, 3H), 2.52 (s, 2H), 3.17 (s, 2H), 5.95 (d, 1H), 7.16 (m, 4H). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 12.7 (CH$_3$), 30.5 (CH$_3$), 33.9 (C), 38.4 (CH$_2$), 55.3 (CH$_2$), 102.9 (CH), 116.0 (CH$_{arom}$), 116.3 (CH$_{arom}$), 122.0 (C), 126.8 (C), 129.9 (C), 129.3 (CH$_{arom}$), 129.4 (CH$_{arom}$), 160.3 (CN), 163.5 (CF), 208.6 (C=O).

1-(4-Methoxyphenyl)-2,4,4-trimethyl-4,5-dihydro-1*H*-indol-6(7*H*)-one (10d). The compound was obtained as a dark-brown viscous liquid. Yield 36% (0.52 g). *Rf* = 0.55 (hexane-AcOEt, 80:20). MS (EI) (%): *m/z* 283 (M+, 67), 268 (62), 240 (100), 207 (19). IR (KBR, cm^{-1}): 2956vs (C-H), 1713m (C=O), 1513vs (C-N), 1247vs (C-O). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm): 1.28 (s, 6H), 2.07 (d, 3H), 2.52 (s, 2H), 3.18 (s, 2H), 5.93 (d, 1H), 6.95 (d, 2H, *Jo*=9.0 Hz), 7.13 (d, 2H, *Jo*= 9.0 Hz). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 12.7 (CH$_3$), 30.6 (2CH$_3$), 33.9 (C), 38.5 (CH$_2$), 55.4 (CH$_2$), 55.5 (CH$_3$), 102.3 (CH), 114.4 (2CH$_{arom}$), 126.6 (C), 128.7 (2CH$_{arom}$), 130 (C), 130.8 (C), 145.8 (CN), 159 (C-O), 209.1 (C=O).

Ethyl 4-(2,4,4-trimethyl-6-oxo-4,5,6,7-tetrahydro-1*H*-indol-1-yl)benzoate (10e). The compound was obtained as an orange solid. Yield 20% (0.33 g). *Rf* = 0.53 (hexane-AcOEt, 80:20). mp: 96 °C. MS (EI): *m/z* (%): 325 (M+, 71), 310 (87), 282 (100), 254 (24). IR (KBR, cm^{-1}): 2952m (C-H), 1717vs (C=O), 1513m (C-N), 1273vs (C-O). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm): 1.29 (s, 6H), 1.42 (t, 3H), 2.10 (d, 3H), 2.52 (s, 2H), 3.21 (s, 2H), 4.41 (q, 2H), 5.99 (d, 1H), 7.28 (d, 2H, *Jo*= 8.7 Hz), 8.14 (d, 2H, *Jo*= 8.7 Hz). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 12.8 (CH$_3$), 14.3 (CH$_3$), 30.5 (2CH$_3$), 33.9 (C), 38.5 (CH$_2$), 55.1 (CH$_2$), 61.2 (CH$_2$), 103.8 (CH), 121.7 (C$_{arom}$), 127.3 (2CH$_{arom}$), 127.4 (C), 129.7 (C), 129.8 (C), 130.6 (2CH$_{arom}$), 142 (CN), 165.7(COO), 208.4 (C=O).

General procedure for the synthesis of 1-(4-R-phenyl)-2,4,4-trimethyl-4,5,6,8-tetrahydropyrrolo[2,3-d]azepin-7(1*H*)-one and 1-(4-R-phenyl)-2,4,4-trimethyl-4,5,7,8-tetrahydropyrrolo[2,3-c]azepin-6(1*H*)-one

In a round-bottomed flask were placed 58.5 milligrams of sodium azide (0.9 mmol, 1.5 equiv.). Then the flask was covered with a septum and placed in a bath with ice and salt. Then a volume of 0.45 mL of concentrated sulfuric acid (8.4 mmol, 14 equiv.) was poured into round-bottomed flask and 1-(4-R-phenyl)-2,4,4-trimethyl-4,5-dihydro-1*H*-indole-6(7*H*)-one (0.6 mmol, 1 equiv. dissolved in chloroform) was added. The addition was carried out dropwise, after which round-bottomed flask was removed from the bath with ice and salt and left at room temperature and stirring for 1 h. The reaction was stopped by adding cold water, drop by drop, and the resulting mixture was extracted with chloroform, the resulting organic phase was washed with a 10% NaHCO$_3$ solution, dried with anhydrous sodium sulfate, decanted and concentrated. The reaction mixture was separated using column chromatography on silica gel with a gradient of 40-60% ethyl acetate in hexane as eluent.

2,4,4-Trimethyl-1-phenyl-4,5,6,8-tetrahydropyrrolo[2,3-d]azepin-7(1*H*)-one (11a). The compound was obtained as a white powder. Yield 29.5% (46.9 mg). *Rf* = 0.63 (AcOEt, 100%). mp: 219°C. MS (EI): *m/z* (%): 268 (M+, 100), 253 (40), 225 (36), 210 (57), 198 (30). IR (KBR, cm^{-1}): 3429w (N-H), 3212m (C-H$_{sp2}$), 2956m (C-H$_{sp3}$), 1666vs (C=O), 1496s (C=C). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm): 1.25 (s, 6H), 2.00 (s, 3H), 3.28 (d, 2H), 3,4 (s, 2H), 5.88 (s, 1H), 6.5 (t, 1H), 7.18 (d, 2H, *Jo*= 8.2 Hz), 7.41 (m, 3H). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 12.98 (CH$_3$), 28.42 (2CH$_3$), 33.73 (CH$_2$), 35.29 (C), 52.86 (CH$_2$), 105.2 (CH$_{pyrr}$), 117.5 (CH$_{arom}$), 126.72 (C$_{pyrr}$), 127.85 (C$_{pyrr}$), 128.62 (2CH$_{arom}$), 129.1 (C$_{pyrr}$), 129.18 (2CH$_{arom}$), 137.92 (CN), 174.25 (C=O). GC-MS purity = 99.9%; t$_R$ = 14.5 min. HRMS (ESI+): Calcd. for [C$_{17}$H$_{20}$N$_2$O+H]$^+$: 269.15460, found: 269.15399.

2,4,4-Trimethyl-1-phenyl-4,5,7,8-tetrahydropyrrolo[2,3-c]-6(1*H*)-one (12a). The compound was obtained as a white powder. Yield 45.5% (72.2 mg). *Rf* = 0.54 (AcOEt, 100%). mp: 179°C. MS (EI): *m/z* (%): 268 (M+, 97), 253 (80), 225 (8), 210 (100). IR (KBR, cm^{-1}): 3427w (N-H), 3193w (C-H$_{sp2}$), 2962m (C-H$_{sp3}$), 1670vs (C=O), 1498m (C=C). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm): 1.35 (s, 6H), 2.00 (s, 3H), 2.67 (s, 2H), 3.98 (d, 2H), 5.89 (s, 1H), 6.83 (t, 1H), 7.18 (d, 2H, *Jo*= 8.2 Hz, *Jm*= 1.23 Hz) 7.44 (d, 3H, *Jo*= 7.5 Hz). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 12.67 (CH$_3$), 31.8 (2CH$_3$), 32.58 (C), 38.31 (CH$_2$), 48.11 (CH$_2$), 105.42 (CH$_{pyrr}$), 123.34 (CH$_{arom}$), 127.97 (C$_{pyrr}$), 128.25 (2CH$_{arom}$), 128.36 (C$_{pyrr}$), 128.53 (C$_{pyrr}$), 129.25 (2CH$_{arom}$), 137.77 (CN), 175.92 (C=O). GC-MS purity = 99.9%; t$_R$ = 15.0 min. HRMS (ESI+): Calcd. for [C$_{17}$H$_{20}$N$_2$O-H]$^+$: 267.13895, found: 267.13995.

1-(4-Cholophenyl)-2,4,4-trimethyl-4,5,6,8-tetrahydropyrrolo[2,3-d]azepin-7(1*H*)-one (11b). The compound was obtained as a yellow powder. Yield 31.1% (49.2 mg). *Rf* = 0.7 (AcOEt, 100%). mp: 212°C y 159°C. MS (EI): *m/z* (%): 302 (M+, 100), 287 (43), 259 (38), 244 (58), 232 (37). IR (KBR, cm^{-1}): 3421w (N-H), 3201w (C-H$_{sp2}$), 2960m (C-H$_{sp3}$), 1679vs (C=O), 1494s (C=C), 1089m (C-Cl). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm): 1.24 (s, 6H), 1.99 (s, 3H), 3.27 (d, 2H), 3.36 (s, 2H), 5.87 (s, 1H), 6.45 (t, 1H), 7.12 (d, 2H, *Jo* = 8.4 Hz) 7.42 (d, 2H, *Jo* = 8.7 Hz). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 12.92 (CH$_3$), 28.34 (2CH$_3$), 33.69 (CH$_2$), 35.32 (C), 52.86 (CH$_2$), 105.72 (CH$_{pyrr}$), 117.51 (C$_{pyrr}$), 127.17 (C$_{pyrr}$), 129.1 (C$_{pyrr}$), 129.44 (2CH$_{arom}$), 129.91 (2CH$_{arom}$), 133.87 (C-Cl), 136.52 (CN), 173.96 (C=O). GC-MS purity = 99.6%; t$_R$ = 15.7 min. HRMS (ESI+): Calcd. for [C$_{17}$H$_{19}$N$_2$O^{35}Cl+H]$^+$: 303.11563, found: 303.11680.

1-(4-Chlorophenyl)-2,4,4-trimethyl-4,5,7,8-tetrahydropyrrolo[2,3-c]azepin-6(1*H*)-one (12b). The compound was obtained as a yellow powder. Yield 47.9% (75.7 mg). *Rf* = 0.6 (AcOEt, 100%). mp: 159°C. MS (EI): *m/z* (%): 302 (M+, 89), 287 (81), 259 (10), 244 (100). IR (KBR, cm^{-1}): 3428w (N-H), 3207w (C-H$_{sp2}$), 2965m (C-H$_{sp3}$), 1635vs (C=O), 1496s (C=C), 1255s (C-O) 1089m (C-Cl). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm): 1.35 (s, 6H), 2.00 (s, 3H), 2.69 (s, 2H), 5.9 (d, 2H), 5.9 (s, 1H), 7.11 (d, 2H, *Jo* = 8.7 Hz), 7.44 (d, 2H, *Jo* = 8.7 Hz), 7.76 (t, 1H). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 12.67 (CH$_3$), 31.69 (2CH$_3$), 33.69 (C), 38.15 (CH$_2$), 47.65 (CH$_2$), 105.79 (CH$_{pyrr}$), 122.93 (C$_{pyrr}$), 128.47 (C$_{pyrr}$), 128.76 (C-Cl), 129.47 (2CH$_{arom}$), 129.53 (2CH$_{arom}$), 134.00 (C$_{pyrr}$), 136.12 (CN), 177.28 (C=O). GC-MS purity = 99.8%; t$_R$ = 16.1 min. HRMS (ESI+): Calcd. for [C$_{17}$H$_{19}$N$_2$O^{37}Cl]$^+$: 304.12345, found: 304.12242.

1-(4-Fluorophenyl)-2,4,4-trimethyl-4,5,6,8-tetrahydropyrrolo[2,3-d]azepin-7(1*H*)-one (11c). The compound was obtained as a white powder. Yield 36.8% (52.1 mg). *Rf* = 0.69 (AcOEt, 100%). mp: 191°C. MS (EI): *m/z* (%): 286 (M+, 100), 271 (37), 243 (36), 228 (57), 216 (30). IR (KBR, cm^{-1}): 3430w (N-H), 3199m (C-H$_{sp2}$), 2964m (C-H$_{sp3}$), 1670s (C=O), 1510vs (C=C), 1217m (C-F). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm): 1.24 (s, 6H), 1.98 (s, 3H), 3.27 (d, 2H), 3.36 (s, 2H), 5.87 (s, 1H), 6.65 (t, 1H), 7.14 (m, 4H). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 12.92 (CH$_3$), 28.34 (2CH$_3$), 33.68 (CH$_2$), 35.26 (C), 52.78 (CH$_2$), 105.35 (CH$_{pyrr}$), 115.97 (CH$_{arom}$), 116.28 (CH$_{arom}$), 117.63 (C$_{pyrr}$), 126.85 (C$_{pyrr}$), 129.18 (C$_{pyrr}$), 130.22 (CH$_{arom}$), 130.33 (CH$_{arom}$), 160.3 (CN), 163.58 (CF), 174.15 (C=O). GC-MS purity = 99.9%; t$_R$ = 14.4 min. HRMS (ESI+): Calcd. for [C$_{17}$H$_{19}$N$_2$OF+H]$^+$: 287.14518, found: 287.14644.

1-(4-Fluorophenyl)-2,4,4-trimethyl-4,5,7,8-tetrahydropyrrolo[2,3-c]azepin-6(1*H*)-one (12c). The compound was obtained as a white powder. Yield 45.2% (71.6 mg). *Rf* = 0.59 (AcOEt, 100%). mp: 203°C. MS (EI): *m/z* (%): 286 (M+, 91), 271 (72), 243 (8), 228 (100). IR (KBR, cm^{-1}): 3423w (N-H), 3203w (C-H$_{sp2}$), 2973m (C-H$_{sp3}$), 1656vs (C=O), 1515vs (C=C), 1222s (C-F). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm): 1.34 (s, 6H), 1.98 (s, 3H), 2.67 (s, 2H), 3.97 (d, 2H), 5.9 (s, 1H), 6.96 (t, 1H), 7.14 (s, 2H), 7.16 (s, 2H). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 12.61 (CH$_3$), 31.75 (2CH$_3$), 32.58 (C), 38.20 (CH$_2$), 48.04 (CH$_2$), 105.54 (CH$_{pyrr}$), 116.1 (CH$_{arom}$), 116.4 (CH$_{arom}$), 123.49 (C$_{pyrr}$), 128.64 (C$_{pyrr}$), 129.88 (CH$_{arom}$), 130 (CH$_{arom}$), 133.76 (C$_{pyrr}$), 160.34 (CN), 163.65 (CF), 175.94 (C=O). GC-MS purity = 99.9%; t$_R$ = 14.9 min. HRMS (ESI+): Calcd. for [^{13}C$_{17}$H$_{19}$N$_2$OF+H]$^+$: 288.15300, found: 288.15334.

1-(4-Methoxyphenyl)-2,4,4-trimethyl-4,5,6,8-tetrahydropyrrolo[2,3-d]azepin-7(1*H*)-one (11d). The compound was obtained as a yellow powder. Yield 27.1% (42.8 mg). *Rf* = 0.61 (AcOEt, 100%). mp: 175°C y

168°C. MS (EI): *m/z* (%): 298 (M+, 100), 283 (46), 255 (35), 240 (46), 228 (23). IR (KBR, cm^{-1}): 3417w (N-H), 3216m (C-H$_{sp2}$), 2960s (C-H$_{sp3}$), 1679vs (C=O), 1513vs (C=C), 1249vs (C-O). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm): 1.24 (s, 6H), 1.98 (s, 3H), 3.27 (d, 2H), 3.37 (s, 2H), 3.84 (s, 3H), 5.85 (s, 1H), 6.62 (t, 1H), 6.95 (d, 2H, *Jo* = 9.0 Hz), 7.10 (d, 2H, *Jo* = 9.0 Hz). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 12.90 (CH$_3$), 28.40 (2CH$_3$), 33.68 (CH$_2$), 35.22 (C), 52.84 (CH$_2$), 55.45 (CH$_3$), 104.76 (CH$_{pyrr}$), 114.32 (2CH$_{arom}$), 117.77 (C$_{pyrr}$), 126.37 (C$_{pyrr}$), 129.25 (C$_{pyrr}$), 129.60 (2CH$_{arom}$), 130.64 (CN), 158.99 (C-O), 174.34 (C=O). GC-MS purity = 99.9%; t$_R$ = 16.0 min. HRMS (ESI+): Calcd. for [^{13}C$_{18}$H$_{22}$N$_2$O$_2$+H]$^+$: 300.17299, found: 300.17340.

1-(4-Methoxyphenyl)-2,4,4-trimethyl-4,5,7,8-tetrahydropyrrolo[2,3-c]azepin-6(1*H*)-one (12d). The compound was obtained as a yellow powder. Yield 33.9% (53.3 mg). *Rf* = 0.55 (AcOEt, 100%). mp: 168°C. MS (EI): *m/z* (%): 298 (M+, 100), 283 (92), 255 (8), 240 (100). IR (KBR, cm^{-1}): 3401w (N-H), 3205w (C-H$_{sp2}$), 2962m (C-H$_{sp3}$), 1668vs (C=O), 1513vs (C=C), 1247vs (C-O). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm): 1.35 (s, 6H), 1.98 (s, 3H), 2.67 (s, 2H), 3.85 (s, 3H), 3.97 (d, 2H), 5.87 (s, 1H), 6.62 (t, 1H), 6.95 (d, 2H, *Jo* = 8.7 Hz), 7.09 (d, 2H, *Jo* = 9 Hz). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 12.61 (CH$_3$), 31.84 (2CH$_3$), 32.58 (C), 38.28 (CH$_2$), 48.14 (CH$_2$), 55.50 (CH$_3$), 105 (CH$_{pyrr}$), 114.44 (2CH$_{arom}$), 123.62 (C$_{pyrr}$), 128.19 (C$_{pyrr}$), 128.63 (C$_{pyrr}$), 129.31 (2CH$_{arom}$), 130.48 (CN), 159.15 (C-O), 175.84 (C=O). GC-MS purity = 99.9%; t$_R$ = 16.4 min. HRMS (ESI+): Calcd. for [C$_{18}$H$_{22}$N$_2$O$_2$+H]$^+$: 299.17595, found: 299.17595.

Ethyl 4-(2,4,4-trimethyl-7-oxo-5,6,7,8-tetrahydropyrrolo[2,3-d]azepin-1(4*H*)-yl)benzoate (11e). The compound was obtained as a white powder. Yield 31.9% (50 mg). *Rf* = 0.6 (AcOEt, 100%). mp: 167°C. MS (EI): *m/z* (%): 340 (M+, 100), 325 (46), 297 (45), 282 (38), 270 (32). IR (KBR, cm^{-1}): 3394w (N-H), 3211m (C-H$_{sp2}$), 2968m (C-H$_{sp3}$), 1706vs and 1675vs (2C=O), 1606s (C=C), 1278vs and 1101s (C-O). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm): 1.25 (s, 6H), 1.42 (t, 3H), 2.00 (s, 3H), 3.28 (d, 2H), 3.39 (s, 2H), 4.41 (q, 2H), 5.90 (s, 1H), 6.35 (t, 1H), 7.25 (d, 2H, *Jo* = 8.7 Hz), 8.14 (d, 2H, *Jo* = 8.4 Hz). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 13.00 (CH$_3$), 14.30 (CH$_3$), 28.31 (2CH$_3$), 33.79 (CH$_2$), 35.38 (C), 52.83 (CH$_2$), 61.21 (CH$_2$), 106.18 (CH$_{pyrr}$), 117.41 (C-COO), 127.55 (C$_{pyrr}$), 128.50 (2CH$_{arom}$), 128.99 (C$_{pyrr}$), 129.92 (C$_{pyrr}$), 130.57 (2CH$_{arom}$), 141.97 (CN), 165.78 (COO), 173.80 (C=O). GC-MS purity = 99.8%; t$_R$ = 17.3 min. HRMS (ESI+): Calcd. for [C$_{20}$H$_{24}$N$_2$O$_3$+H]$^+$: 341.18652, found: 341.18737.

Ethyl 4-(2,4,4-trimethyl-6-oxo-5,6,7,8-tetrahydropyrrolo[2,3-c]azepin-1(4*H*)-yl)benzoate (12e). The compound was obtained as a white powder. Yield 47.2% (74 mg). *Rf* = 0.51 (AcOEt, 100%). mp: 129°C. MS (EI): *m/z* (%): 340 (M+, 100), 325 (100), 297 (9), 295 (20), 282 (85). IR (KBR, cm^{-1}): 3405w (N-H), 3218w (C-H$_{sp2}$), 2958m (C-H$_{sp3}$), 1712vs and 1664vs (2C=O), 1274vs and 1103s (C-O). ^{1}H-NMR (300 MHz, CDCl$_3$) ∂ (ppm)*:* 1.35 (s, 6H), 1.42 (t, 3H), 2.02 (s, 3H), 2.68 (s, 2H), 4.00 (d, 2H), 4.42 (q, 2H), 5.92 (s, 1H), 6.75 (t, 1H), 7.24 (d, 2H, *Jo* = 9 Hz), 8.14 (d, 2H, *Jo* = 8.7 Hz). ^{13}C-NMR (CDCl$_3$, 75 MHz) ∂ (ppm): 12.76 (CH$_3$), 14.28 (CH$_3$), 31.69 (2CH$_3$), 32.63 (C), 38.28 (CH$_2$), 47.95 (CH$_2$), 61.28 (CH$_2$), 106.37 (CH$_{pyrr}$), 123.25 (C-COO), 128.05 (2CH$_{arom}$), 128.31 (C$_{pyrr}$), 129.34 (C$_{pyrr}$), 130.01 (C$_{pyrr}$), 130.62 (2CH$_{arom}$), 141.71 (CN), 165.64 (COO), 175.77 (C=O). GC-MS purity = 99.9%; t$_R$ = 17.7 min. HRMS (ESI+): Calcd. for [C$_{20}$H$_{24}$N$_2$O$_3$+H]$^+$: 341.18652, found: 341.18776.

Cell lines and culture conditions. We used the cervical carcinoma (SiHa), lung adenocarcinoma (SKLU1), breast carcinoma (ZR-75-1), and colorectal adenocarcinoma (SW480) cell lines as well as the non-tumor human embryonic kidney 293 (HEK293) cell line. It was cultured in DMEM medium supplemented at 10% with fetal bovine serum and antibiotics (100 U/ml penicillin and 100 pg/ml streptomycin). Cells from each line were kept in incubation for their proliferation at 37 °C in a humidified atmosphere of 5% CO$_2$. The viability levels of the various types of cells were determined with trypan blue.

MTT cell proliferation assay. Cells from each of the various cell lines were seeded into 96-well microplates at a density of 5000 cells / well. After 24 h of incubation, the PRZ compounds were added at concentrations of 25 to 800 µM. Cisplatin was used as a positive control. Each culture was exposed for 48 h to the compound, and subsequently the MTT assay (Sigma-Aldrich M2128) was performed according to the manufacturer's

instructions using an ELISA reader (Thermo Scientific Multiskan FC) at a wavelength of 570 nm. The viability levels of the treated cells were estimated by considering relative growth as described by Jacobo-Salcedo et al., (2011). The wells without cells were considered to be white. The viability levels of the cells were specifically estimated from the relative growth by using the formula:

$$\text{relative viability} = \frac{\text{control O.D.} - \text{sample O.D.}}{\text{control O.D.}} \times 100$$

The concentration leading to a 50% inhibition of viability (IC_{50}) was calculated using regression analysis (percent survival versus log concentration).

Acknowledgements

Supplementary Material

MS , ^{1}H and ^{13}C NMR, spectra for compounds **11a-e** and **12a-e** and HETCOR and FLOCK spectra for compounds **11c** and **12c** were appended.

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