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Chemistry of *N*-functionalized spirodihydroquinolines. Unusual access to the 3-methyl-4-(2-oxo-pyrrolidinyl-1)spiro[indane-1,1′-cyclohexanes] from 1-(3-cyanopropyl)-3,4-dihydrospiro[quinoline-2,1′-cyclohexanes]

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Abstract—The transformation of *N*-substituted 3,4-dihydrospiro[quinoline-2,1′-cyclohexanes] **2** and **3** has been examined in strong acid media, at elevated temperature. It was demonstrated that the *N*-(γ-cyanopropyl) spirodihydroquinolines **2** in the presence of concentrated sulfuric acid or PPA underwent hydrolysis affording the γ-aminoacids **3**. The spirodihydroquinoline ring rearrangement readily produces 4-(2-oxopyrrolidinyl-1)spiro[indane-1,1′-cyclohexanes] **5** in good yields. The structures of all synthesized compounds were established by means of homonuclear and inverse-detected 2D NMR experiments.

1. Introduction

The chemistry and synthesis of diverse partially reduced quinolines and benzazepines have been of considerable interest to organic chemists for many years.[1–4] We have also been engaged in systematic study of spiroannulated quinolines and benzazepines preparation from the 1-allyl-1-*N*-aryl(benzyl)aminocyclanes, by using intramolecular Friedel–Crafts alkylation.[5–7] Besides rich and very interesting chemistry of these heterocycles, our attention was focused on chemical behavior of *N*-acyl- or *N*-alkyl-substituted tetrahydroquinolines in a strong acid media. Based on previous works on the acid rearrangement of 1-acetyl-2,2,4-trimethyl-3,4-dihydroquinoline to give 4-aminoindane derivatives,[8] and on the classical intramolecular cyclization of 1-(2-chloroacetyl)-1,2,3,4-tetrahydroquinolines to afford the lilolidine derivatives,[9] we adopted these procedures to investigate chemical and biological properties of unknown *N*-substituted 3,4-dihydrospiro-[quinoline-2,1′-cyclohexanes]. Our studies on these *N*-substituted spiranes showed that they had an ambident reactivity, which could be used in the construction of more complex heterocycles and alkaloids.[10–15] For example, the intramolecular acid cyclization of *N*-(2-chloroacetyl) or *N*-acetylspirodihydroquinolines **A** gave rise to spirololidones **B** (cyclized product) and aminospiroindanes **C**–**E** (rearranged product).[11,12] We also demonstrated that *N*-methyl spirodihydroquinolines were very resistant to strong acids action and did not suffer any structural modification,[10] while *N*-carbethoxymethyl spirodihydroquinolines in the presence of PPA underwent a novel cyclization with formation of unexpected spirojulolidine ring system **F**[14,15] (Scheme 1).

Our interest in the chemistry of *N*-alkylsubstituted spirodihydroquinolines with potential electrophilic center, which could be exploited in the construction of the spirobenzazepinone and/or aminospiroindane ring systems under acidic conditions, led us to carry out the current study.

2. Results and discussion

Our approach to the both possible types of desired compounds **4**, **5** involved three classical steps: (i) cyanopropylation of the spirodihydroquinolines **1**; (ii) acid hydrolysis of the obtained nitriles **2**; (iii) cyclization of the γ-aminoacids **3** (Scheme 2). All these steps proceeded smoothly and in good yields.

As a first step, the required *N*-substituted heterocycles **2a**–**e**

Keywords: intramolecular Friedel–Crafts alkylation; aminospiroindanes; spirodihydroquinolines.

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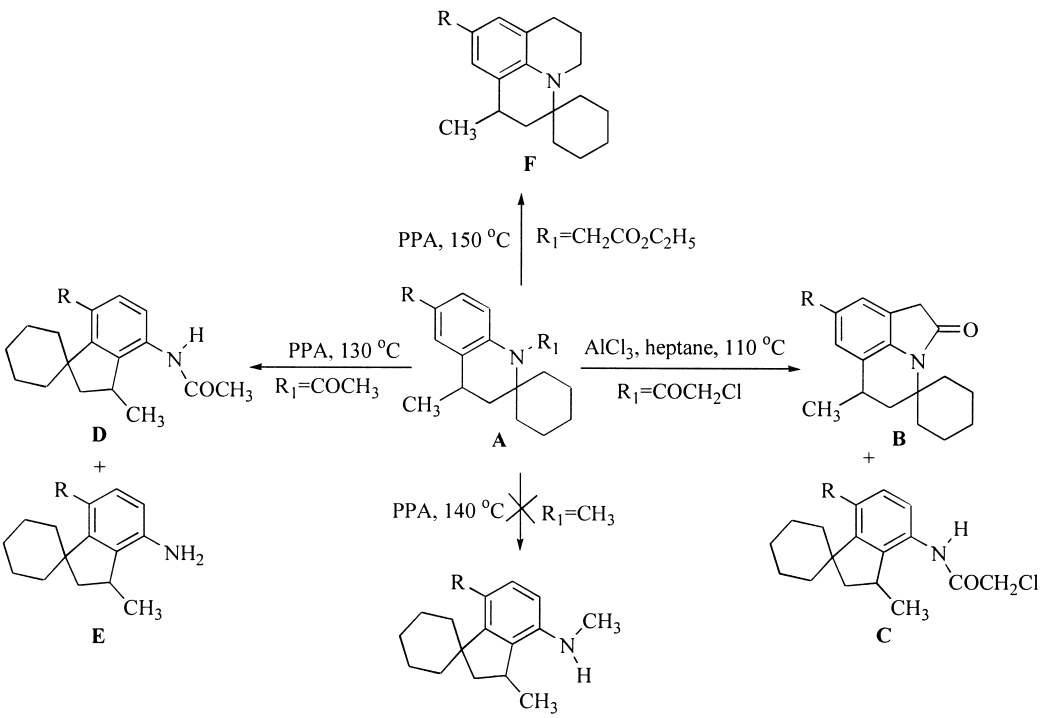


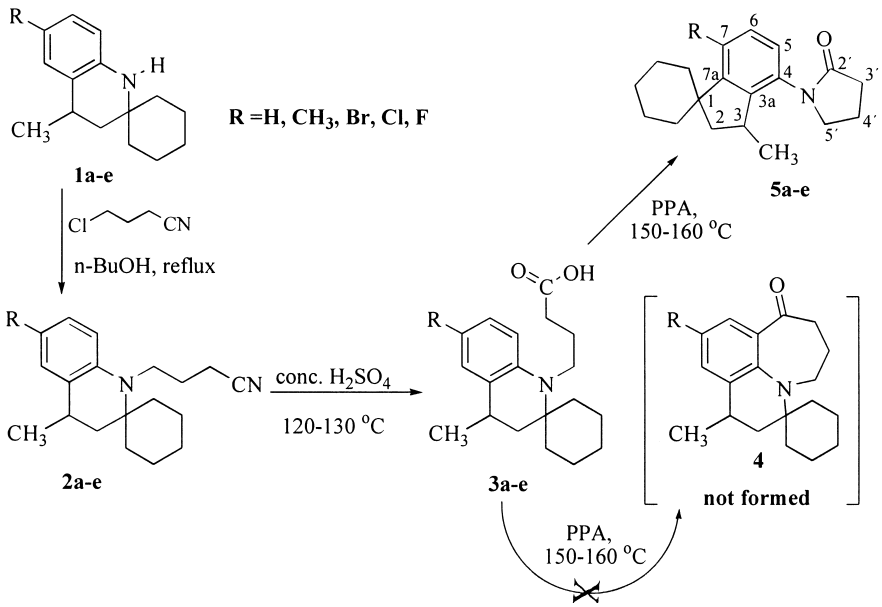
Scheme 1.

were obtained from the respective 3,4-dihydro-4-methylspiro[1*H*-quinoline-2,1′-cyclohexanes] **1a–e**[10,16,17] in a common cyanopropylation procedure with 4-chlorobutyronitrile in boiling 1-butanol (K_2CO_3/KI).[18] Column chromatography led to the isolation of colorless crystalline products in 59–95% yield.

As a second step, we attempted to cyclize nitriles **2a–e** in the presence of PPA or concentrated sulfuric acid (120–130°C, 20–25 h) to obtain the spiro[3,2,1-*jk*]benz-1-azepine ring **4**. In all cases, all the synthesized nitriles were resistant to cyclization and the only result obtained was the recovery of the γ-aminoacids **3a–e** in 91–98% yield. The γ-aminoacids **3a–e** formation was confirmed by observation of an OH and C=O strong absorption bands in the infrared spectra, which appeared at 3344–3460, 3152–3201, and 1646–1666 cm^{-1}, respectively.

The ^1H NMR spectra of **3a–e** were very similar to those of nitrile precursors, except for the signals of the carboxylic proton, which appeared as two well-resolved broad singlets with a chemical shift of 5.48–5.90 and 5.50–6.21 ppm, indicating the presence of both free and coordinated hydroxylic group.

Finally, in the third step, prolonged (20–25 h) treatment of



Scheme 2.

γ-aminoacids **3a–e** with PPA at 150–160°C did not achieve the cyclization to expected spiroannulated pyridobenz-1-azepinones **4**, but promoted their exclusively conversion into spiroindanes **5a–e**, which were isolated by column chromatography as colorless crystals in an overall yield of 58–87%.

The 4-(2-oxopyrrolidine) spiroindane structure of compounds **5a–e** was confirmed unambiguously by means of homonuclear and inverse-detected 2D NMR experiments. Thus, the ^{1}H NMR spectra displayed an AB system (except for compound **5a**) of coupling constants around 7.9–9.0 Hz. In the spectrum of compound **5a**, three signals corresponding to three adjacent 5-H, 6-H and 7-H aromatic protons, each of them resonated at 6.98 ppm (dd, J=8.5, 1.2 Hz), 7.22 ppm (t, J=8.5 Hz) and 7.08 ppm (dd, J=8.5, 1.2 Hz), respectively, were observed. The chemical shift of carbonyl signal C=O (173.1–174.1 ppm) in ^{13}C NMR spectra is more consistent with a pyrrolidone structure than that with an aryl–alkyl cyclic ketone. On the other hand, large downfield shifts of the spirocarbon signal (48.5–50.2 ppm) in comparison with those of precursors (57.6–57.8 ppm) indicate that this carbon is not connected to a nitrogen atom but is linked to sp^2 aromatic carbon. Extensive COSY, DEPT-135, HMQC and HMBC measurements allowed the assignment of all the signals and correlations, corroborating the synthesized *N*-(spiroindanyl) pyrrolidones structure. The γ-lactam structure was also supported by the infrared spectra, in which the carbonyl vibration band appeared around 1687–1698 cm^{-1}. Additionally, the mass spectra showed molecular ion peaks of higher intensity, which agreed with the molecular mass of the obtained compounds.

It should be noted, that during this acid cyclization, 6-bromosubstituted heterocycle **3c** produced a mixture of bromosubstituted spiroindane **5c** and debromated spiroindane **5a** in a ratio 2.5:1, which was determined by ^{1}H NMR.

Based on previous works,[8,19] and our studies[10,13] the formation of compounds **5a–e** could be better explained by the following mechanistic scheme (Scheme 3).

Under heating, protonated compounds **3** (species **I**) formed simultaneously pyrrolidone ring and stable tertiary carbocation **II**, the latter rapidly attacked benzene ring via concerted mechanism, to give protonated 4-(2-oxopyrrolidinyl-1)spiro[indane-1,1′-cyclohexane] molecule **III**. These results suggest that the PPA not only acts as a tetrahydroquinoline ring-opening promoting agent, but also facilitates the ring-closure step in the pyrrolidone formation.

3. Conclusion

The transformation of γ-aminoacids **3a–e** in PPA at 150–160°C can be a suitable route towards the synthesis of 3-methyl-4-(2-oxo-pyrrolidinyl-1)spiro[indane-1,1′-cyclohexanes] **5a–e**, which contains two structure moieties—indane and 2-oxo-pyrrolidine, whose pharmacological properties are well documented.[20–23]

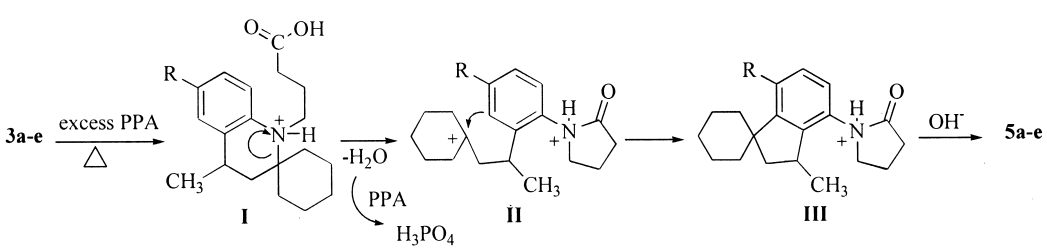
4. Experimental

4.1. General methods

Melting points were taken on a Fisher–Johns melting point apparatus and are uncorrected. IR spectra were obtained on a Nicolet Avatar 360-FTIR spectrometer as potassium bromide pellets. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-400 spectrometer (400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR), using $CDCl_3$ as the solvent. TMS was used as an internal standard. Chemical shifts (δ) and J values are reported in ppm and Hz, respectively. On DEPT-135 spectra, the signals of CH_3, CH_2, and CH carbons are shown as positive (+), negative (−), and positive (+), respectively, and quaternary carbons are not shown. A Hewlett–Packard (HP) 5890 A series II Gas Chromatograph interfaced to a HP 5972 Mass Selective Detector with a HP MS ChemStation Data system was used for MS identification. Elemental analyses were performed on a Perkin–Elmer 2400 Series II analyzer. The reaction progress was monitored using thin layer chromatography on a Silufol UV 254 TLC aluminum sheets. Column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). All reagents were purchased from Merck, Sigma and Aldrich Chemical Co. and used without further purification. Final purification of all products for elemental analyses was done by recrystallization. Started spirodihydroquinolines **1a–e** were synthesized according to our methodology.[10,16,17]

4.2. General procedure for the synthesis of *N*-(γ-cyanopropyl) spirodihydroquinolines 2a–e

A solution of 4-chlorobutyronitrile (0.15 mol) in anhydrous 1-butanol (50 mL) was added dropwise to a mixture of spirodihydroquinolines **1a–e** (0.10 mol), anhydrous sodium carbonate (0.16 mol), and potassium iodide (0.02 mol) at 115°C. The reaction mixture was stirred at reflux for 24–30 h. After cooling to room temperature, the mixture was filtered and the solid was washed with ether. The combined filtrate and washings were extracted with 2N HCl



Scheme 3.

(2×25 mL), and the resulting acid solution was washed with ether (2×80 mL), made basic with potassium carbonate, and extracted with ether (3×100 mL). The final ether extracts were dried over anhydrous sodium sulfate and filtered, and the ether was evaporated to obtain the desired compounds, which were purified by column chromatography (silica gel, heptane–ethyl acetate) to give colorless crystals after recrystallization (heptane–ethyl acetate).

4.2.1. *N*-(γ-Cyanopropyl)-3,4-dihydro-4-methylspiro-[quinoline-2,1′-cyclohexane] 2a. Yield 95%; mp 74–75°C; IR $\nu_{C\equiv N}$ 2243 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.11 (1H, t, *J*=14.5 Hz, 3-H_{ax}), 1.34 (3H, d, *J*=6.8 Hz, 4-CH_3), 1.39–1.83 (10H, m, cyclohexane protons), 1.85 (1H, dt, *J*=15.5, 6.8 Hz, N-β-H_B), 1.95 (1H, dt, *J*=15.5, 6.8 Hz, N-β-H_A), 2.28 (2H, t, *J*=6.8 Hz, N-γ-*H*), 2.65 (1H, dd, *J*=14.0, 3.5 Hz, 3-H_{eq}), 2.69 (1H, m, 4-*H*), 3.23 (1H, dt, *J*=15.0, 7.8 Hz, N-α-H_B), 3.52 (1H, ddd, *J*=10.1, 9.0, 3.6 Hz, N-α-H_A), 6.55 (1H, d, *J*=7.5 Hz, 8-*H*), 6.70 (1H, t, *J*=7.4 Hz, 6-*H*), 7.09 (1H, t, *J*=7.4 Hz, 7-*H*), 7.13 (1H, d, *J*=7.5 Hz, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 14.6 (−, N-γ-*C*), 19.9 (+, 4-*C*H_3), 22.4–37.3 (−, cyclohexane carbons), 25.0 (−, N-β-*C*), 27.1 (+, 4-*C*), 40.0 (−, 3-*C*), 43.0 (−, N-α-*C*), 57.6 (2-*C*), 112.0 (+, 8-*C*), 115.8 (+, 6-*C*), 119.7 (*C*≡N), 125.3 (+, 7-*C*), 126.9 (+, 5-*C*), 129.5 (4a-*C*), 145.1 (8a-*C*). Mass spectrum (EI): *m*/*z* (%) 282 (M^+, 25), 267 (49), 253 (3), 239 (100), 228 (8), 211 (14), 200 (6), 186 (8), 184 (6), 172 (8), 170 (9), 168 (6), 159 (24), 156 (8), 146 (8), 144 (36), 132 (12), 130 (19), 128 (7), 117 (16), 115 (10), 103 (6), 91 (10), 77 (16), 65 (5), 55 (8). Anal. calcd for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92%. Found: C, 80.53; H, 9.09; N, 9.78%.

4.2.2. *N*-(γ-Cyanopropyl)-3,4-dihydro-4,6-dimethyl-spiro[quinoline-2,1′-cyclohexane] 2b. Yield 79%; mp 72–73°C; IR $\nu_{C\equiv N}$ 2247 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.08 (1H, t, *J*=13.0 Hz, 3-H_{ax}), 1.33 (3H, d, *J*=6.4 Hz, 4-CH_3), 1.40–1.80 (10H, m, cyclohexane protons), 1.83 (1H, dt, *J*=13.6, 6.4 Hz, N-β-H_B), 1.89 (1H, dt, *J*=14.0, 6.9 Hz, N-β-H_A), 2.33 (2H, t, *J*=7.2 Hz, N-γ-*H*), 2.31 (1H, dd, *J*=14.0, 3.6 Hz, 3-H_{eq}), 2.63 (1H, m, 4-*H*), 3.20 (1H, dt, *J*=14.8, 7.6 Hz, N-α-H_B), 3.48 (1H, ddd, *J*=14.4, 8.3, 5.6 Hz, N-α-H_A), 6.47 (1H, d, *J*=8.0 Hz, 8-*H*), 6.90 (1H, d, *J*=8.4 Hz, 7-*H*), 6.95 (1H, s, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 14.6 (−, N-γ-*C*), 19.3 (+, 4-*C*H_3), 19.3–32.1 (−, cyclohexane carbons), 24.5 (−, N-β-*C*), 27.0 (+, 4-*C*), 40.8 (−, 3-*C*), 41.9 (−, N-α-*C*), 57.8 (2-*C*), 112.2 (+, 8-*C*), 119.7 (*C*≡N), 125.5 (6-*C*), 125.7 (+, 5-*C*), 127.0 (+, 7-*C*), 131.2 (4a-*C*), 142.0 (8a-*C*). Mass spectrum (EI): *m*/*z* (%) 296 (M^+, 35), 281 (54), 267 (3), 253 (100), 242 (9), 225 (14), 214 (6), 200 (8), 198 (6), 186 (7), 184 (8), 182 (4), 173 (24), 170 (8), 158 (26), 156 (7), 146 (10), 144 (16), 131 (10), 130 (10), 117 (6), 115 (9), 105 (3), 103 (3), 91 (11), 77 (7), 65 (4), 55 (6), 41 (21). Anal. calcd for $C_{20}H_{28}N_2$: C, 81.03; H, 9.52; N, 9.45%. Found: C, 80.66; H, 9.68; N, 9.23%.

4.2.3. 6-Bromo-*N*-(γ-cyanopropyl)-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexane] 2c. Yield 64%; mp 90–92°C; IR $\nu_{C\equiv N}$ 2245 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.07 (1H, t, *J*=13.1 Hz, 3-H_{ax}), 1.32 (3H, d, *J*=6.7 Hz, 4-CH_3), 1.35–1.78 (10H, m, cyclohexane protons), 1.83 (1H, dt, *J*=13.0, 7.2 Hz, N-β-H_B), 1.91 (1H, dt, *J*=14.6, 7.2 Hz, N-β-H_A), 2.34 (2H, t, *J*=7.0 Hz, N-γ-*H*), 2.32 (1H, dd, *J*=13.1, 4.1 Hz, 3-H_{eq}), 2.65 (1H, m, 4-*H*), 3.22 (1H, dt, *J*=15.2, 7.8 Hz, N-α-H_B), 3.48 (1H, ddd, *J*=15.2, 8.8, 4.9 Hz, N-α-H_A), 6.41 (1H, d, *J*=8.7 Hz, 8-*H*), 7.15 (1H, dd, *J*=8.7, 2.2 Hz, 7-*H*), 7.18 (1H, s, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 14.6 (−, N-γ-*C*), 19.2 (+, 4-*C*H_3), 22.4–36.9 (−, cyclohexane carbons), 24.2 (−, N-β-*C*), 27.1 (+, 4-*C*), 40.3 (−, 3-*C*), 41.9 (−, N-α-*C*), 58.3 (2-*C*), 109.0 (+, 8-*C*), 113.4 (6-*C*), 113.7 (+, 5-*C*), 119.4 (*C*≡N), 127.8 (+, 7-*C*), 129.3 (4a-*C*), 143.5 (8a-*C*). Mass spectrum (EI): *m*/*z* (%) 361 (M^+, ^{80}Br, 26), 346 (47), 332 (2), 318 (100), 305 (9), 290 (12), 279 (6), 265 (8), 249 (6). Anal. calcd for $C_{19}H_{25}BrN_2$: C, 63.16; H, 6.97; N, 7.75%. Found: C, 62.93; H, 6.85; N, 7.83%.

4.2.4. 6-Chloro-*N*-(γ-cyanopropyl)-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexane] 2d. This compound was obtained as maroon oil in 59% yield; IR $\nu_{C\equiv N}$ 2246 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.06 (1H, t, *J*=13.0 Hz, 3-H_{ax}), 1.31 (3H, d, *J*=6.6 Hz, 4-CH_3), 1.35–1.80 (10H, m, cyclohexane protons), 1.82 (1H, dt, *J*=15.2, 7.8 Hz, N-β-H_B), 1.90 (1H, dt, *J*=15.4, 6.6 Hz, N-β-H_A), 2.32 (1H, dd, *J*=13.2, 3.7 Hz, 3-H_{eq}), 2.34 (2H, t, *J*=7.0 Hz, N-γ-*H*), 2.64 (1H, m, 4-*H*), 3.23 (1H, m, N-α-H_B), 3.47 (1H, ddd, *J*=14.5, 9.6, 5.0 Hz, N-α-H_A), 6.44 (1H, d, *J*=8.8 Hz, 8-*H*), 7.02 (1H, d, *J*=8.6 Hz, 7-*H*), 7.10 (1H, s, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 14.7 (−, N-γ-*C*), 19.2 (+, 4-*C*H_3), 22.5–37.0 (−, cyclohexane carbons), 24.3 (−, N-β-*C*), 27.2 (+, 4-*C*), 40.4 (−, 3-*C*), 42.0 (−, N-α-*C*), 58.3 (2-*C*), 113.2 (+, 8-*C*), 119.5 (*C*≡N), 121.5 (6-*C*), 125.0 (+, 5-*C*), 126.4 (+, 7-*C*), 133.0 (4a-*C*), 143.1 (8a-*C*). Mass spectrum (EI): *m*/*z* (%) 316 (M^+, 32), 301 (52), 273 (100), 262 (8), 245 (13), 134 (8), 221 (8), 206 (8), 204 (6), 193 (25), 190 (6), 178 (21), 168 (8), 164 (12), 154 (7), 143 (10), 140 (5), 130 (12), 115 (9), 103 (5), 89 (4), 77 (8), 67 (4), 55 (9). Anal. calcd for $C_{19}H_{25}ClN_2$: C, 72.02; H, 7.95; N, 8.84%. Found: C, 72.38; H, 7.62; N, 8.58%.

4.2.5. 6-Fluoro-*N*-(γ-cyanopropyl)-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexane] 2e. Yield 67%; mp 81–82°C; IR $\nu_{C\equiv N}$ 2240 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.06 (1H, t, *J*=12.9 Hz, 3-H_{ax}), 1.31 (3H, d, *J*=6.7 Hz, 4-CH_3), 1.32–1.72 (10H, m, cyclohexane protons), 1.85 (1H, dt, *J*=13.0, 7.1 Hz, N-β-H_B), 1.89 (1H, dt, *J*=13.2, 7.1 Hz, N-β-H_A), 2.31 (1H, dd, *J*=13.2, 4.1 Hz, 3-H_{eq}), 2.33 (2H, t, *J*=7.1 Hz, N-γ-*H*), 2.64 (1H, m, 4-*H*), 3.22 (1H, dt, *J*=15.0, 7.8 Hz, N-α-H_B), 3.45 (1H, ddd, *J*=14.8, 7.9, 4.9 Hz, N-α-H_A), 6.47 (1H, dd, *J*=8.8, 4.7 Hz, 8-*H*), 6.77 (1H, td, *J*=8.5, 2.9 Hz, 7-*H*), 6.85 (1H, dd, *J*=9.5, 2.7 Hz, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 14.6 (−, N-γ-*C*), 18.9 (+, 4-*C*H_3), 22.5–37.0 (−, cyclohexane carbons), 24.3 (−, N-β-*C*), 27.4 (+, 4-*C*), 40.9 (−, 3-*C*), 41.9 (−, N-α-*C*), 58.1 (2-*C*), 111.7 (+, 5-*C*), 112.4 (+, 7-*C*), 112.9 (+, 8-*C*), 119.6 (*C*≡N), 133.7 (4a-*C*), 140.5 (8a-*C*), 155.6 (6-*C*). Mass spectrum (EI): *m*/*z* (%) 300 (M^+, 25), 285 (44), 271 (2), 257 (100), 246 (8), 229 (13), 218 (6), 207 (6), 205 (8), 204 (5), 202 (5), 191 (6), 190 (8), 188 (7), 177 (27), 174 (7), 164 (8), 162 (29), 161 (10), 150 (14), 148 (18), 146 (6), 136 (8), 135 (19), 133 (7), 124 (3), 122 (3), 115 (4), 109 (9), 107 (2), 101 (6), 95 (6), 83 (5), 67 (5), 55 (13), 41 (22). Anal. calcd for $C_{19}H_{25}FN_2$: C, 75.96; H, 8.39; N, 9.32%. Found: C, 76.20; H, 8.17; N, 9.21%.

4.3. General procedure for the synthesis of *N*-(γ-carboxypropyl)-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexanes] 3a–e

A suspension of the nitriles **2a–e** (1.0 g) in concentrated sulfuric acid (7 mL) or PPA (10 g) was stirred at 120–130°C for 20–25 h. After cooling to room temperature, the solution was treated with Na_2CO_3 to pH 5 and extracted with CH_2Cl_2 (2×50 mL). The organic layer was separated, dried ($MgSO_4$), filtered and evaporated to dryness in vacuo. The residue was purified by recrystallization (heptane–ethyl acetate) to give colorless crystals.

4.3.1. *N*-(γ-Carboxypropyl)-3,4-dihydro-4-methylspiro-[quinoline-2,1′-cyclohexane] 3a. Yield 96%; mp 130–131°C; IR ν_{O-H} 3456, 3158 cm^{-1}, $\nu_{C=O}$ 1647 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.13 (1H, t, *J*=13.3 Hz, 3-H_{ax}), 1.33 (3H, d, *J*=6.6 Hz, 4-CH_3), 1.37–1.68 (10H, m, cyclohexane protons), 1.83 (2H, m, N-β-*H*), 2.25 (2H, t, *J*=7.3 Hz, N-γ-*H*), 2.32 (1H, dd, *J*=13.2, 4.4 Hz, 3-H_{eq}), 2.71 (1H, m, 4-*H*), 3.13 (1H, dt, *J*=15.1, 6.9 Hz, N-α-H_B), 3.43 (1H, dd, *J*=15.1, 9.8 Hz, N-α-H_A), 5.48 and 5.67 (1H, br. s, O*H*), 6.59 (1H, d, *J*=8.0 Hz, 8-*H*), 6.64 (1H, t, *J*=7.3 Hz, 6-*H*), 7.07 (1H, t, *J*=7.3 Hz, 7-*H*), 7.11 (1H, d, *J*=7.4 Hz, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 19.9 (+, 4-*C*H_3), 22.4–37.3 (−, cyclohexane carbons), 25.0 (−, N-β-*C*), 26.8 (+, 4-*C*), 31.9 (−, N-γ-*C*), 40.0 (−, 3-*C*), 43.0 (−, N-α-*C*), 57.7 (2-*C*), 112.0 (+, 8-*C*), 115.8 (+, 6-*C*), 125.3 (+, 7-*C*), 126.9 (+, 5-*C*), 129.5 (4a-*C*), 145.1 (8a-*C*), 175.1 (*C*OOH). Mass spectrum (EI): *m*/*z* (%) 301 (M^+, 9), 300 (49), 285 (28), 272 (2), 257 (49), 242 (7), 229 (23), 228 (41), 214 (21), 200 (40), 186 (15), 184 (12), 172 (66), 170 (16), 159 (57), 146 (26), 144 (54), 132 (29), 130 (34), 117 (27), 115 (17), 103 (9), 91 (15), 86 (100), 79 (13), 77 (24), 67 (8), 55 (20). Anal. calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65%. Found: C, 75.49; H, 9.11; N, 4.69%.

4.3.2. *N*-(γ-Carboxypropyl)-3,4-dihydro-4,6-dimethylspiro[quinoline-2,1′-cyclohexane] 3b. Yield 92%; mp 116–118°C; IR ν_{O-H} 3344, 3194 cm^{-1}, $\nu_{C=O}$ 1666 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.08 (1H, t, *J*=13.0 Hz, 3-H_{ax}), 1.33 (3H, d, *J*=6.4 Hz, 4-CH_3), 1.36–1.82 (10H, m, cyclohexane protons), 1.82 (2H, m, N-β-*H*), 2.27 (3H, s, 6-CH_3), 2.33 (2H, t, *J*=7.2 Hz, N-γ-*H*), 2.31 (1H, dd, *J*=14.0, 3.6 Hz, 3-H_{eq}), 2.63 (1H, m, 4-*H*), 3.13 (1H, dt, *J*=15.1, 6.9 Hz, N-α-H_B), 3.48 (1H, dd, *J*=14.8, 8.3 Hz, N-α-H_A), 5.90 and 6.21 (1H, br. s, O*H*), 6.47 (1H, d, *J*=8.0 Hz, 8-*H*), 6.90 (1H, d, *J*=8.4 Hz, 7-*H*), 6.95 (1H, s, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 19.5 (+, 4-*C*H_3), 20.5 (+, 6-*C*H_3), 22.3–36.8 (−, cyclohexane carbons), 24.4 (−, N-β-*C*), 26.7 (+, 4-*C*), 32.0 (−, N-γ-*C*), 40.8 (−, 3-*C*), 41.9 (−, N-α-*C*), 57.6 (2-*C*), 112.6 (+, 8-*C*), 125.6 (+, 5-*C*), 127.0 (6-*C*), 127.5 (+, 7-*C*), 131.3 (4a-*C*), 141.5 (8a-*C*), 175.5 (*C*OOH). Mass spectrum (EI): *m*/*z* (%) 315 (M^+, 20), 314 (88), 299 (41), 281 (6), 272 (16), 271 (77), 256 (9), 253 (11), 243 (33), 242 (64), 228 (22), 214 (57), 207 (16), 200 (19), 198 (12), 187 (22), 186 (100), 184 (19), 173 (74), 160 (26), 158 (57), 146 (30), 144 (36), 131 (26), 130 (25), 120 (9), 117 (13), 115 (17), 105 (6), 91 (24), 86 (83), 77 (11), 67 (9), 55 (20), 45 (3). Anal. calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44%. Found: C, 76.03; H, 9.22; N, 4.50%.

4.3.3. 6-Bromo-*N*-(γ-carboxyropyl)-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexane] 3c. Yield 98%; mp 155–156°C; IR ν_{O-H} 3387, 3192 cm^{-1}, $\nu_{C=O}$ 1655 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.09 (1H, t, *J*=12.6 Hz, 3-H_{ax}), 1.31 (3H, d, *J*=6.6 Hz, 4-CH_3), 1.35–1.68 (10H, m, cyclohexane protons), 1.82 (2H, m, 10-*H*), 2.25 (2H, t, *J*=7.2 Hz, N-γ-*H*), 2.31 (1H, dd, *J*=13.3, 4.0 Hz, 3-H_{eq}), 2.67 (1H, m, 4-*H*), 3.01 (1H, dt, *J*=13.8, 9.6 Hz, N-α-H_B), 3.38 (1H, dd, *J*=13.9, 8.6 Hz, N-α-H_A), 5.52 and 5.75 (1H, br. s, O*H*), 6.47 (1H, d, *J*=8.4 Hz, 8-*H*), 7.13 (1H, d, *J*=8.9 Hz, 7-*H*), 7.16 (1H, s, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 19.6 (+, 4-*C*H_3), 22.3–37.0 (−, cyclohexane carbons), 24.5 (−, N-β-*C*), 26.8 (+, 4-*C*), 32.9 (−, N-γ-*C*), 39.6 (−, 3-*C*), 43.1 (−, N-α-*C*), 57.8 (2-*C*), 113.6 (6-*C*), 127.8 (+, 8-*C*), 127.9 (+, 5-*C*), 129.3 (+, 7-*C*), 131.8 (4a-*C*), 144.0 (8a-*C*), 174.9 (*C*OOH). Mass spectrum (EI): *m*/*z* (%) 380 (M^+, ^{80}Br, 30), 365 (15), 345 (1), 335 (20), 322 (6), 308 (22), 292 (12), 278 (18), 264 (8), 250 (21), 237 (28), 224 (16), 212 (12), 198 (7), 184 (8), 170 (9), 158 (8), 143 (14), 130 (32), 117 (11), 102 (6), 86 (100), 67 (6), 55 (14), 44 (42), 41 (17). Anal. calcd for $C_{19}H_{26}BrNO_2$: C, 60.00; H, 6.89; N, 3.68%. Found: C, 60.15; H, 6.63; N, 3.52%.

4.3.4. 6-Chloro-*N*-(γ-carboxypropyl)-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexane] 3d. Yield 91%; mp 140–142°C; IR ν_{O-H} 3398, 3201 cm^{-1}, $\nu_{C=O}$ 1650 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.87 (1H, t, *J*=13.0 Hz, 3-H_{ax}), 1.30 (3H, d, *J*=6.7 Hz, 4-CH_3), 1.03–1.63 (10H, m, cyclohexane protons), 1.81 (2H, m, 10-*H*), 2.24 (2H, t, *J*=7.2 Hz, N-γ-*H*), 2.30 (1H, dd, *J*=13.3, 3.9 Hz, 3-H_{eq}), 2.66 (1H, m, 4-*H*), 3.14 (1H, dt, *J*=15.0, 7.9 Hz, N-α-H_B), 3.38 (1H, dd, *J*=15.1, 8.2 Hz, N-α-H_A), 5.50 (1H, br. s, O*H*), 6.50 (1H, d, *J*=8.7 Hz, 8-*H*), 7.00 (1H, d, *J*=8.7 Hz, 7-*H*), 7.03 (1H, s, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 19.2 (+, 4-*C*H_3), 22.0–36.8 (−, cyclohexane carbons), 24.0 (−, N-β-*C*), 26.5 (+, 4-*C*), 32.6 (−, N-γ-*C*), 39.6 (−, 3-*C*), 42.9 (−, N-α-*C*), 57.6 (2-*C*), 113.2 (+, 8-*C*), 121.1 (6-*C*), 125.4 (+, 5-*C*), 126.6 (+, 7-*C*), 133.4 (4a-*C*), 144.0 (8a-*C*), 175.2 (*C*OOH). Mass spectrum (EI): *m*/*z* (%) 335 (M^+, ^{35}Cl, 9), 320 (2), 301 (1), 291 (30), 276 (5), 262 (25), 248 (13), 134 (17), 220 (8), 206 (25), 193 (34), 180 (18), 178 (20), 164 (12), 154 (8), 143 (10), 130 (16), 115 (8), 103 (7), 86 (100), 77 (8), 67 (6), 55 (14), 45 (1). Anal. calcd for $C_{19}H_{26}ClNO_2$: C, 67.95; H, 7.80; N, 4.17%. Found: C, 67.81; H, 7.93; N, 4.10%.

4.3.5. 6-Fluoro-*N*-(γ-carboxypropyl)-3,4-dihydro-4-methylspiro[quinoline-2,1′-cyclohexane] 3e. Yield 97%; mp 140–141°C; IR ν_{O-H} 3460, 3152 cm^{-1}, $\nu_{C=O}$ 1646 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.12 (1H, t, *J*=12.9 Hz, 3-H_{ax}), 1.31 (3H, d, *J*=6.7 Hz, 4-CH_3), 1.02–1.63 (10H, m, cyclohexane protons), 1.81 (2H, m, N-β-*H*), 2.25 (2H, t, *J*=7.0 Hz, N-γ-*H*), 2.29 (1H, dd, *J*=13.2, 4.2 Hz, 3-H_{eq}), 2.67 (1H, m, 4-*H*), 3.11 (1H, dt, *J*=14.9, 7.8 Hz, N-α-H_B), 3.35 (1H, dd, *J*=14.8, 7.9 Hz, N-α-H_A), 5.50 and 5.65 (1H, br. s, O*H*), 6.52 (1H, dd, *J*=8.8, 4.7 Hz, 8-*H*), 6.77 (1H, td, *J*=8.5, 2.9 Hz, 7-*H*), 6.84 (1H, dd, *J*=9.6, 2.7 Hz, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 19.5 (+, 4-*C*H_3), 22.4–36.8 (−, cyclohexane carbons), 24.5 (−, N-β-*C*), 27.1 (+, 4-*C*), 33.0 (−, N-γ-*C*), 40.2 (−, 3-*C*), 43.3 (−, N-α-*C*), 57.6 (2-*C*), 111.7 (+, 5-*C*), 112.3 (+, 7-*C*), 112.8 (+, 8-*C*), 132.0 (4a-*C*), 141.2 (8a-*C*), 155.0 (6-*C*), 175.0 (*C*OOH). Mass spectrum (EI): *m*/*z* (%) 319 (M^+, 11), 304 (3), 290 (1), 275 (50), 260 (6), 247 (20), 246 (39), 232 (20), 218 (26), 204 (12), 202 (10), 190 (63), 188 (12), 177 (50), 164 (20), 162

(49), 150 (25), 148 (28), 135 (24), 121 (13), 109 (7), 86 (100), 55 (14). Anal. calcd for $C_{19}H_{26}FNO_2$: C, 71.45; H, 8.20; N, 4.39%. Found: C, 71.31; H, 8.35; N, 4.31%.

4.4. General procedure for the synthesis of 3-methyl-4-(2-oxopyrrolidinyl-1) spiro[indane-1,1′-cyclohexanes] 5a–e

A suspension of the γ-aminoacids **3a–e** (1.0 g) in PPA (14 g) was stirred at 150–160°C for 20–25 h. After cooling to room temperature, the solution was neutralized with Na_2CO_3 (pH≈7) and extracted with CH_2Cl_2 (2×50 mL). The organic layer was separated, dried ($MgSO_4$), filtered and evaporated to dryness in vacuo. The residue was purified by column chromatography (silica gel, heptane–ethyl acetate). The new spiroindanes were given as viscous maroon oils and colorless crystals after recrystallization (heptane–ethyl acetate).

4.4.1. 3-Methyl-4-(2-oxopyrrolidinyl-1) spiro[indane-1,1′-cyclohexane] 5a. This compound was obtained as maroon oil in 87% yield; IR $\nu_{C=O}$ 1698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.17 (3H, d, *J*=7.0 Hz, 3-CH_3), 1.20–1.84 (10H, m, cyclohexane protons), 1.49 (1H, m, 2-H_B), 1.70 (1H, m, 4′-H_B), 2.26 (2H, m, 4′-H_A), 2.39 (1H, dd, *J*=13.0, 7.9 Hz, 2-H_A), 2.56 (2H, t, *J*=7.3 Hz, 3′-*H*), 3.37 (1H, ddd, *J*=8.0, 7.1, 7.0 Hz, 3-*H*), 3.58 (1H, qtt, *J*=9.4, 2.0, 1.6 Hz, 5′-H_B), 3.97 (1H, qdd, *J*=9.4, 2.4 Hz 5′-H_A), 6.98 (1H, dd, *J*=8.5, 1.2 Hz, 5-*H*), 7.08 (1H, dd, *J*=8.5, 1.2 Hz, 7-*H*), 7.22 (1H, t, *J*=8.5 Hz, 6-*H*). Mass spectrum (EI): *m/z* (%) 283 (M^+, 100), 268 (14), 255 (5), 240 (65), 226 (59), 214 (8), 212 (19), 200 (4), 198 (22), 187 (20), 184 (11), 170 (10), 156 (20), 155 (17), 142 (23), 141 (15), 128 (19), 120 (3), 115 (17), 102 (4), 91 (6), 77 (8), 69 (8), 55 (11). Anal. calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.89; N, 4.94%. Found: C, 80.23; H, 8.58; N, 4.73%.

4.4.2. 3,7-Dimethyl-4-(2-oxopyrrolidinyl-1) spiro-[indane-1,1′-cyclohexane] 5b. Yield 71%; mp 140–142°C; IR $\nu_{C=O}$ 1698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.16 (3H, d, *J*=7.0 Hz, 3-CH_3), 1.22–1.90 (10H, m, cyclohexane protons), 1.57 (1H, dd, *J*=12.9, 7.1 Hz, 2-H_B), 1.70 (1H, m, 4′-H_B), 2.19 (2H, m, 4′-H_A), 2.38 (1H, dd, *J*=13.0, 8.6 Hz, 2-H_A), 2.45 (3H, s, 7-CH_3), 2.54 (2H, t, *J*=7.6 Hz, 3′-*H*), 3.28 (1H, ddd, *J*=8.2, 7.1, 7.0 Hz, 3-*H*), 3.56 (1H, qtt, *J*=9.6, 2.0, 1.6 Hz, 5′-H_B), 3.90 (1H, qdd, *J*=9.6, 2.3 Hz, 5′-H_A), 6.84 (1H, d, *J*=7.9 Hz, 5-*H*), 6.89 (1H, d, *J*=7.9 Hz, 6-*H*); ^{13}C NMR ($CDCl_3$): δ 20.0 (+, 7-CH_3), 20.7 (+, 3-CH_3), 23.2–34.2 (−, cyclohexane carbons), 31.2 (−, 3′-*C*), 35.6 (+, 3-*C*), 36.3 (−, 4′-*C*), 44.6 (−, 2-*C*), 49.3 (1-*C*), 50.6 (−, 5′-*C*), 113.9 (7-*C*), 124.5 (+, 5-*C*), 131.2 (+, 6-*C*), 133.6 (7a-*C*), 144.3 (3a-*C*), 150.4 (4-*C*), 174.1 (2′-*C*). Mass spectrum (EI): *m/z* (%) 297 (M^+, 100), 282 (19), 268 (4), 254 (54), 240 (66), 228 (13), 226 (22), 212 (54), 201 (14), 198 (10), 197 (9), 188 (6), 184 (16), 182 (10), 180 (5), 171 (14), 170 (32), 169 (29), 157 (25), 156 (51), 142 (16), 141 (25), 128 (22), 120 (6), 115 (20), 105 (4), 91 (8), 77 (8), 69 (9), 55 (16), 53 (6), 51 (3). Anal. calcd for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71%. Found: C, 80.37; H, 8.89; N, 4.53%.

4.4.3. 7-Bromo-3-methyl-4-(2-oxopyrrolidinyl-1) spiro-[indane-1,1′-cyclohexane] 5c. This compound was obtained as maroon oil in 58% yield; IR $\nu_{C=O}$ 1698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.16 (3H, d, *J*=6.8 Hz, 3-CH_3), 1.20–1.72 (10H, m, cyclohexane protons), 1.51 (1H, m, 2-H_B), 1.49 (1H, m, 4′-H_B), 2.20 (1H, m, 4′-H_A), 2.37 (1H, dd, *J*=13.2, 9.2 Hz, 2-H_A), 2.55 (2H, t, *J*=6.8 Hz, 3′-*H*), 3.33 (1H, ddd, *J*=8.4, 7.2, 6.8 Hz, 3-*H*), 3.55 (1H, qtt, *J*=9.6, 2.3, 1.9 Hz, 5′-H_B), 3.90 (1H, qdd, *J*=9.2, 2.2 Hz, 5′-H_A), 6.74 (1H, d, *J*=8.5 Hz, 5-*H*), 7.26 (1H, d, *J*=8.5 Hz, 7-H); ^{13}C NMR ($CDCl_3$): δ 18.9–35.5 (−, cyclohexane carbons), 21.0 (+, 3-CH_3), 31.3 (−, 3′-*C*), 34.1 (−, 4′-*C*), 36.1 (+, 3-*C*), 44.5 (−, 2-*C*), 50.0 (1-*C*), 50.5 (−, 5′-*C*), 118 (7-*C*), 125.8 (+, 5-*C*), 132.5 (+, 6-*C*), 134.5 (7a-*C*), 147.5 (3a-*C*), 149.8 (4-*C*), 173.8 (2′-*C*). Mass spectrum (EI): *m/z* (%)361 (M^+, ^{80}Br, 100), 346 (31), 320 (10), 306 (14), 292 (11), 282 (19), 278 (79), 261 (29), 254 (13), 236 (47), 224 (21), 221 (22), 211 (40), 208 (25), 197 (20), 182 (40), 167 (24), 156 (37), 141 (32), 128 (34), 115 (35), 98 (75), 86 (41), 69 (22), 55 (36), 43 (24), 41 (77).

4.4.4. 7-Chloro-3-methyl-4-(2-oxopyrrolidinyl-1) spiro-[indane-1,1′-cyclohexane] 5d. Yield 79%; mp 133–134°C; IR $\nu_{C=O}$ 1698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.15 (3H, d, *J*=6.9 Hz, 3-CH_3), 1.21–1.70 (10H, m, cyclohexane protons), 1.44 (1H, m, 2-H_B), 1.44 (1H, m, 4′-H_B), 2.21 (2H, m, 4′-H_A), 2.38 (1H, dd, *J*=13.0, 9.1 Hz, 2-H_A), 2.54 (2H, t, *J*=8.6 Hz, 3′-*H*), 3.34 (1H, ddd, *J*=8.7, 6.9, 6.8 Hz, 3-*H*), 3.55 (1H, qtt, *J*=9.5, 1.9, 1.7 Hz, 5′-H_B), 3.90 (1H, qdd, *J*=9.5, 2.2 Hz, 5′-H_A), 6.92 (1H, d, *J*=8.3 Hz, 5-*H*), 7.15 (1H, d, *J*=8.3 Hz, 6-*H*); ^{13}C NMR ($CDCl_3$): δ 19.0–33.7 (−, cyclohexane carbons), 21.0 (+, 3-CH_3), 31.2 (−, 3′-*C*), 35.2 (−, 4′-*C*), 36.4 (+, 3-*C*), 44.3 (−, 2-*C*), 50.2 (1-*C*), 50.6 (−, 5′-*C*), 120.3 (7-*C*), 125.9 (+, 5-*C*), 130.1 (+, 6-*C*), 134.0 (7a-*C*), 147.0 (3a-*C*), 148.7 (4-*C*), 174.1 (2′-*C*). Mass spectrum (EI): *m/z* (%) 317 (M^+, ^{35}Cl, 100), 302 (10), 282 (6), 274 (40), 260 (57), 246 (24), 232 (32), 221 (9), 218 (8), 212 (7), 204 (10), 190 (12), 176 (43), 168 (15), 154 (19), 141 (17), 128 (22), 115 (18), 102 (4), 86 (7), 77 (7), 69 (10), 55 (19), 51 (3). Anal. calcd for $C_{19}H_{24}ClNO$: C, 71.80; H, 7.61; N, 4.41%. Found: C, 71.53; H, 7.49; N, 4.17%.

4.4.5. 7-Fluoro-3-methyl-4-(2-oxopyrrolidinyl-1) spiro-[indane-1,1′-cyclohexane] 5e. Yield 80%; mp 118–119°C; IR $\nu_{C=O}$ 1687 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.05 (3H, d, *J*=6.9 Hz, 3-CH_3), 1.15–2.10 (10H, m, cyclohexane protons), 1.50 (1H, m, 2-H_B), 1.57 (1H, m, 4′-H_B), 2.03 (2H, m, 4′-H_A), 2.27 (1H, dd, *J*=13.1, 9.1 Hz, 2-H_A), 2.42 (2H, t, *J*=8.1 Hz, 3′-*H*), 3.26 (1H, ddd, *J*=7.4, 6.9 Hz, 3-*H*), 3.44 (1H, dd, *J*=8.7, 7.8 Hz, 5′-H_B), 3.76 (1H, dd, *J*=8.1, 7.8 Hz, 5′-H_A), 6.75 (1H, dd, *J*=9.0, 8.4 Hz, 6-*H*), 6.83 (1H, dd, *J*=8.4, 4.5 Hz, 5-*H*); ^{13}C NMR ($CDCl_3$): δ 18.9–35.4 (−, cyclohexane carbons), 20.6 (+, 3-CH_3), 31.2 (−, 3′-*C*), 36.9 (−, 4′-*C*), 37.3 (+, 3-*C*), 44.1 (−, 2-*C*), 48.5 (1-*C*), 50.8 (−, 5′-*C*), 115.3 (+, 5-*C*), 126.3 (+, 6-*C*), 131.0 (7a-*C*), 139.2 (3a-*C*), 146.9 (4-*C*), 157.6 (7-*C*), 174.1 (2′-*C*). Mass spectrum (EI): *m/z* (%) 301 (M^+, 100), 286 (9), 284 (8), 272 (3), 258 (65), 244 (77), 232 (10), 230 (25), 216 (24), 205 (11), 202 (9), 190 (5), 188 (14), 175 (14), 174 (21), 173 (17), 161 (24), 160 (50), 159 (15), 147 (14), 146 (23), 133 (16), 125 (3), 115 (3), 107 (2), 98 (3), 86 (7), 77 (2), 69 (10), 55 (11), 41 (21). Anal. calcd for $C_{19}H_{24}FNO$: C, 75.72; H, 8.03; N, 4.65%. Found: C, 75.90; H, 7.90; N, 4.53%.

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