Syntheisis

2,2-dimethyl-2,3-dihydro-4H-chromen-4-one (5a)

The compound was obtained from acetone following the general procedure A as a dark brown oil (94% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.47 (s, 6H, $(CH_3)_2$), 2.73 (s, 2H, CH_2-3 chrom.), 6.91-6.97 (m, 2H, CH-6, CH-8 chrom.), 7.47 (ddd, *J*= 1.7, 7.3, 8.2 Hz, 1H,CH-7 chrom.), 7.86 ppm (dd, *J*= 1.5, 7.8 Hz; 1H, CH-5 chrom.).

Spiro[chromene-2,1'-cyclopentan]-4(3H)-one (6a)

The compound was obtained from cyclopentanone following the general procedure A as a dark brown oil (96% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.53-2.36 (m, 8H, $(CH_2)_4$ cyclopen.), 2.81 (s, 2H, CH_2-3 chrom.), 6.88-6.99 (m, 2H, CH-6, CH-8 chrom.), 7.43 (ddd, *J*= 1.5, 7.3, 8.2 Hz, 1H, CH-7 chrom.), 7.85 ppm (dd, *J*= 1.5, 7.8 Hz; 1H, CH-5 chrom.).

Spiro[chromene-2,1'-cyclohexan]-4(3H)-one (7a)

The compound was obtained from cyclohexanone following the general procedure A as a yellow oil (95% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.34-1.78 (m, 8H, CHa-2', CHa-6', CH_2-3', CH_2-4', CH_2-5' cyclohex.), 1.99-205 (m, 2H, CHb-2', CHb-6' cyclohex.), 2.69 (s, 2H, CH_2-3 chrom.), 6.91-6.99 (m, 2H, CH-6, CH-8 chrom.), 7.45 (ddd, *J*= 1.8, 7.3, 8.2 Hz, 1H, CH-7 chrom.), 7.82 ppm (dd, *J*= 1.8, 8.2 Hz, 1H, CH-5 chrom.).

Spiro[chromene-2,1'-cycloheptan]-4(3H)-one (8a)

The compound was obtained from cycloheptanone following the general procedure A as brown oil (54% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.42-1.82 (m, 10H, CHa-2', CHa-7', $(CH_2)_4$ cyclohept.), 1.99-207 (m, 2H, CHb-2', CHb-7' cyclohept.) 2.72 (s, 2H, CH_2-3 chrom.), 6.90-6.97 (m. 2H, CH-6, CH-8 chrom.), 7.44-7.52 (m, 1H, CH-7 chrom.), 7.82 ppm (dd, *J*= 1.7, 8.2 Hz, 1H, CH-5 chrom.).

2',3',5',6'-tetrahydrospiro[chromene-2,4'-thiopyran]-4(3H)-one (9a)

The compound was obtained from tetrahydro-4H-thiopyran-4-one following the general procedure A as dark oil (95% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.74-1.89 (m, 2H, CHa-3, CHa-5 thyopyr.), 2.34-2.46 (m, 4H, CHa-2, CHa-6, CHb-5, CHb-3 thyopyr.) 2.69 (s, 2H, CH_2-3 chrom.), 3.00-3.15 (m, 2H, CHb-2', CHb-6 thyopir.), 6.98-7.04 (m, 2H, CH-6, CH-8 chrom.), 7.46-7.54 (m, 1H, CH-7 chrom.), 7.86 ppm (d, *J*= 8.1 Hz, 1H, CH-5 chrom.).

2',3',5',6'-tetrahydrospiro[chromene-2,4'-pyran]-4(3H)-one (10a)

The compound was obtained from tetrahydro-4H-pyran-4-one following the general procedure A as dark oil (94% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.56-1.83 (m, 4H, CH_2-3, CH_2-5, pyran), 2.73 (s, 2H, CH_2-3 chrom.), 3.69-3.90 (m, 4H, CH_2-2, CH_2-6 pyran), 6.83-7.06 (m, 2H, CH-6, CH-8 chrom.), 7.41-7.52 (m, 1H, CH-7 chrom.), 7.84 ppm (dd, *J*= 1.8, 8.2 Hz, 1H, CH-5 chrom.).

1'-methylspiro[chromene-2,4'-piperidin]-4(3H)-one (11a)

The compound was obtained from 1-methylpiperidin-4-one following the general procedure A as dark oil (95% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.63-1.84 (m, 2H, CHa-3, CHa-5 pipd.), 1.98-2.05 (m, 2H, CHb-3, CHb-5 pipd.), 2.31 (s, 3H, CH_3), 2.34-2.44 (m, 2H, CHa-2, CHa-6 pipd.), 2.49-2.60 (m, 2H, CHb-2, CHb-6 pipd.), 2.66 (s, 2H, CH_2-3 chrom.), 6.82-6.97 (m, 2H, CH-6, CH-8 chrom.), 7.32-7.47 (ddd, *J*= 1.7, 7.2, 8.2 Hz, 1H, CH-7 chrom.), 7.80 ppm (dd, *J*= 1.8, 8.1 Hz, 1H, CH-5 chrom.).

1'-ethylspiro[chromene-2,4'-piperidin]-4(3H)-one (12a)

The compound was obtained from 1-ethylpiperidin-4-one following the general procedure A as yellow oil (92% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.04 (t, *J*= 7.1 Hz, 3H, CH_3), 1.62-1.86 (m, 2H, CHa-3, CHa-5 pipd.), 1.91-2.14 (m, 2H, CHb-3, CHb-5 pipd.), 2.33-2.50 (m, 4H, CH_2, CHa-2, CHa-6 pipd.), 2.61-2.69 (m, 4H, CH_2-3 chrom., CHb-2, CHb-6 pipd.), 6.92-6.99 (m, 2H, CH-6, CH-8 chrom.), 7.41-7.49 (ddd, *J*= 1.5, 7.6, 8.2 Hz, 1H, CH-7 chrom.), 7.82 ppm (d, *J*= 8.1 Hz, 1H, CH-5 chrom.).

1'-(methylsulfonyl)spiro[chromene-2,4'-piperidin]-4(3H)-one (13a)

The compound was obtained from 1-(methylsulfonyl)piperidin-4-one following the general procedure A as yellow oil (91% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.69-1.85 (m, 2H, CHa-3/CHa-5, CHb-3/CHb-5 pipd.), 2.11-2.17 (m, 2H, CHa-3/CHa-5, CHb-3/CHb-5 pipd.), 2.71 (s, 2H, CH_2-3 chrom.), 2.81 (s, 3H, CH_3), 2.71-2.81 (m, 2H, CHa-2, CHa-6 pipd.), 3.58 (d, *J*= 11.9 Hz, 2H, CHb-2, CHb-6 pipd.), 6.95-7.03 (m,

2H, CH-6, CH-8 chrom.), 7.44-7.52 (m, 1H, CH-7 chrom.), 7.80 ppm (d, *J*= 7.7 Hz, 1H, CH-5 chrom.).

1'-acetylspiro[chromene-2,4'-piperidin]-4(3H)-one (14a)

The compound was obtained from 1-acetylpiperidin-4-one following the general procedure A as yellow oil (94% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.47-1.64 (m, 2H, CHa-3, CHa-5 pipd.), 2.03-2.10 (m, 4H, CH_3 pipd., CHb-3/CHb-5 pipd.), 2.65 (s, 2H, CH_2-3 chrom.), 2.96-3.07 (m, 1H, CHb-3/CHb-5 pipd.), 3.38-3.51 (m, 3H, CHa-2, CHa-6, CHb-2/CHb-6 pipd.), 4.30 (d, *J*= 13.4 Hz, 1H, CHb-2/CHb-6 pipd.), 6.91,6.98 (m, 2H, CH-6, CH-8 chrom.) ,7.40-7.48 (m, 1H, CH-7 chrom.), 7.79 ppm (dd, *J*= 1.6, 8.4 Hz, 1H, CH-5 chrom.).

2-phenyl-2,3-dihydro-4H-chromen-4-one (15a)

The compound was obtained from benzaldehyde following the general procedure A as yellow white solid (37% yield).

mp: 76-77 °C, ^{1}H NMR (400MHz, $CDCl_3$): δ= 2.95 (dd, *J*= 2.9, 16.8 Hz, 1H, CHa-3 chrom.), 3.13 (dd, *J*= 13.3, 16.8 Hz, 1H, CHb-3 chrom.), 5.53 (dd, *J*= 2.9, 13.3 Hz, 1H, CH-2 chrom.), 7.10-7.15 (m, 2H, CH-6, CH-8 chrom), 7.30-7.60 (m, 6H, CH-7 chrom., 5H phen.), 7.99 ppm (dd, *J*= 1.7, 8.2 Hz, 1H, CH-5 chrom.).

3,3-dimethyl-2,3-dihydro-4H-chromen-4-one (17a)

A solution of **4a** (0.5 g, 3.37 mmol) and iodomethane (2.1 mL, 16.8 mmol) in THF (15mL) was added to a solution of potassium tert-butoxide (0.6 g, 16.8 mmoli) in anhydrous THF (5mL), cooled at -70°C (bath temperature), under nitrogen atmosphere. During this process, the temperature of the reaction mixture was kept at -70 °C to avoid exothermic reaction. White precipitate was formed, and the reaction mixture became supernatant. The resulting white slurry was allowed to warm to room temperature over a period of 15h and was filtered through a celite cake. The filtrate was concentrated *in vacuo* to give the desired compound **17a** (0.390g, 2.13 mmol, 63% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.21 (s, 6H, $(CH_3)_2$), 4.15 (s, 2H, CH_2-2 chrom.), 6.94-7.06 (m, 2H, CH-6, CH-8 chrom.), 7.47 (m, 1H, CH-7 chrom.), 7.91 ppm (dd, *J*= 1.2, 7.5 Hz, 1H, CH-5 chrom.).

5-fluoro-2,3-dihydro-4H-chromen-4-one (18a)

Step A

A solution of 3-fluorophenol (1.38 mL, 1.5 mmol) and Triton B (benzyltrimethylammonium hydroxide, 1 mL) in acrylonitrile (5 mL) was heated for 36 h to reflux. The reaction mixture was diluted with diethyl ether (300 ml) and washed with 1 N sodium hydroxide solution (3 x 200 ml). The organic phase was washed with 1 N hydrochloric acid and saturated sodium chloride solution, dried over calcium chloride, and concentrated to dryness. The title compound was obtained as a yellow oil (1.20 g, 7.26 mmol, 48% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 2.83 (t, J= 6.3 Hz, 2H, CH_2-CN), 4.18 (t, J= 6.3 Hz, 2H, O-CH_2), 6.60-6.77 (m, 3H, CH-2, CH-4, CH-6 arom.), 7.20-7.34 ppm (m, 1H, CH-5 arom.).

Step B

A suspension of 3-(3-fluorophenoxy)propanenitrile (1.20 g, 7.26 mmol) in concentrated hydrochloric acid (10 ml) was heated to reflux for 4 h. The resulting suspension was filtered. The solid was washed with water and suspended in 1 N sodium hydroxide solution. After a period of 15 minutes, the resulting solution was acidified to pH 1 by addition of concentrated hydrochloric acid. After a period of 1 hour, the formed precipitate was isolated by filtration, washed with water, and dried. The title compound was obtained as a colourless solid (0.79 g, 4.3 mmol, 59% yield).

mp: 93-94 °C, ^{1}H NMR (200MHz, $CDCl_3$): δ= 2.87 (t, J= 6.2 Hz; 2H, CH_2-COOH), 4.25 (t, J= 6.3 Hz, 2H, O-CH_2), 6.61-6.73 (m, 3H, CH-2, CH-4, CH-6 arom.), 7.18-7.29 ppm (m, 1H, CH-5 arom.).

Step C, D

A solution of 3-(3-fluorophenoxy)propanoic acid (0.79 g, 4.3 mmol) in toluene (5 ml) and thionyl chloride (1.8 mL, 25.8 mmol) was refluxed for 17 hours. The reaction mixture was concentrated to dryness. A solution of the resulting yellow oily residue in chloroform (10 ml) was cooled to -65 °C and treated with trifluoromethanesulfonic acid (0.56 mL, 6.4 mmol). The brown solution was gradually warmed to room temperature. After a period of 17 h, the reaction mixture was poured on ice water and the phases were separated. The aqueous phase was extracted with chloroform. The combined organic phases were washed with 1 N sodium hydroxide solution, water, and saturated sodium chloride solution, and dried over Na_2SO_4. Evaporation of the solvent afforded the title compound 5-fluoro-2,3-dihydro-4H-chromen-4-one (0.68 g, 4.2 mmol, 95% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 2.80 (t, J= 6.5 Hz; 2H, CH_2-3 chrom.), 4.55 (t, J= 6.4 Hz; 2H, CH_2-2 chrom.), 6.62-6.78 (m, 2H, CH-6, CH-8 chrom.), 7.92 ppm (dd, J= 6.7, 8.7 Hz, 1H, CH-7 chrom.).

2,2-dimethyl-3,4-dihydro-2H-chromen-4-ol (5b)

The compound was obtained from **5a** following the general procedure B as an oil (99% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.32 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.86 (dd, *J*= 8.7, 13.4 Hz, 1H, CHa-3 chrom.), 2.17 (dd, *J*= 6.0, 13.4 Hz, 1H, CHb-3 chrom.), 4.84 (m, 1H, CH-4 chrom.), 6.80 (d, *J*= 8.2 Hz, 1H, CH-8 chrom.), 6.93 (ddd, *J*= 0.8, 7.1, 7.7 Hz, 1H, CH-6 chrom.), 7.18 (ddd, *J*= 1.3, 7.1, 8.2 Hz, 1H, CH-7 chrom.), 7.45 ppm (dd, *J*= 8.2 Hz, 1H, CH-5 chrom.).

3,4-dihydrospiro[chromene-2,1'-cyclopentan]-4-ol (6b)

The compound was obtained from **6a** following the general procedure B as an oil (98% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.68-2.17 (m, 10H, CH_2-3 chrom., $(CH_2)_4$ cyclopen.), 4.82 (m, 1H, CH-4 chrom.), 6.77 (d, *J*= 8.2 Hz, 1H, CH-8 chrom.), 6.90 (ddd, *J*= 0.8, 7.6, 8.2 Hz, 1H, CH-6 chrom.), 7.16 (ddd, *J*= 1.2, 7.1, 8.2 Hz, 1H, CH-7 chrom.), 7.42 ppm (d, *J*= 7.6 Hz, 1H, CH-5 chrom.).

3,4-dihydrospiro[chromene-2,1'-cyclohexan]-4-ol (7b)

The compound was obtained from **7a** following the general procedure B as an oil (99% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.32-1.93 (m, 11H, CHa-3 chrom., $(CH_2)_5$ cyclohex.), 2.18 (dd, *J*= 6.2, 13.4 Hz, 1H, CHb-3 chrom.), 4.81 (m, 1H, CH-4 chrom.), 6.82-6.94 (m, 2H, CH-8, CH-6 chrom.), 7.18 (ddd, *J*= 1.2, 7.2, 8.3 Hz, 1H, CH-7 chrom.), 7.43 ppm (d, *J*= 7.5 Hz, 1H, CH-5 chrom.).

3,4-dihydrospiro[chromene-2,1'-cycloheptan]-4-ol (8b)

The compound was obtained from **8a** following the general procedure B as an oil (97% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.44-2.01 (m, 14H, $(CH_2)_6$ cyclohept., CHa-3 chrom., -OH), 2.29 (dd, *J*= 5.3, 13.1 Hz, 1H, CHb-3 chrom.), 4.81 (m, 1H, CH-4 chrom.), 6.81 (d, *J*= 8.1 Hz, 1H, CH-8 chrom.), 6.92 (m, 1H, CH-6 chrom.), 7.18 (m, 1H, CH-7 chrom.), 7.45 ppm (d, *J*= 7.5 Hz, 1H, CH-5 chrom.).

2',3,3',4,5',6'-hexahydrospiro[chromene-2,4'-thiopyran]-4-ol (9b)

The compound was obtained from **9a** following the general procedure B as dark oil (96% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.67-1.92 (m, 3H, CHa-3, CHa-5 thyopyr., CHa-3 chrom.), 2.08-2.37 (m, 3H, CHb-3, CHb-5 thyopyr., CHb-3 chrom.), 2.39-2.46 (m, 2H, CHa-2, CHa-6 thyopyr.), 2.9-3.18 (m, 2H, CHb-2, CHb-6 thyopyr.), 4.80-4.87 (m, 1H, CH-4 chrom.), 6.83-6.96 (m, 2H, CH-8, CH-6 chrom.), 7.18 (ddd, *J*= 1.5, 7.4, 8.1 Hz, 1H, CH-7 chrom.), 7.41 ppm (d, *J*= 7.6 Hz, 1H, CH-5 chrom.).

2',3,3',4,5',6'-hexahydrospiro[chromene-2,4'-pyran]-4-ol (10b)

The compound was obtained from **10a** following the general procedure B as yellow oil (98% yield). ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.70-2.04 (m, 5H, CHa-3 chrom., CH_2-3, CH_2-5 pyran), 2.15 (dd, *J*= 6.0, 12.8 Hz, 1H, CHb-3 chrom.), 3.62-3.98 (m, 4H, CH_2-2, CH_2-6 pyran), 3.72 (dd, *J*= 6.0, 7.2 Hz, 1H, CH-4 chrom.), 6.86-6.98 (m, 2H, CH-6, CH-8 chrom.), 7.17-7.24 (m, 1H, CH-7 chrom.), 7.43 ppm (d, *J*= 6.7 Hz, 1H, CH-5 chrom.).

1'-methyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-4-ol (11b)

The compound was obtained from **11a** following the general procedure B as an oil (94% yield). ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.56-1.97 (m, 5H, CH_2-3, CH_2-5 pipd., CHa-3 chrom.), 2.02-2.19 (m, 1H, CHb-3 chrom.), 2.31 (s, 3H, CH_3), 2.43-2.66 (m, 4H, CH_2-2, CH_2-6, pipd.), 2.82-3.39 (s broad, -OH), 4.76-4.83 (dd, *J*= 6.8, 8.0 Hz, 1H, CH-4 chrom.), 6.74-6.94 (m, 2H, CH-6, CH-8 chrom.), 7.11-7.20 (ddd, *J*= 1.4, 7.7, 7.4 Hz, 1H, CH-7 chrom.), 7.42 ppm (d, *J*= 7.3 Hz, 1H, CH-5 chrom.).

1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidin]-4-ol (12b)

The compound was obtained from **12a** following the general procedure B as yellow oil (88% yield). ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.09 (t, *J*= 7.1 Hz, 3H, CH_3), 1.53-2.16 (m, 6H, CH_2-3, CH_2-5 pipd., CH_2-3 chrom.), 2.27-2.50 (m, 4H, CH_2, CHa-2, CHa-6 pipd.), 2.75-2.82 (m, 2H, CHb-2, CHb-6 pipd.), 4.82 (t, *J*= 6.9 Hz, 1H, CH-4 chrom.), 6.81-6.95 (m, 2H, CH-6, CH-8 chrom.), 7.11 (t, *J*= 7.2 Hz, 1H, CH-7 chrom.), 7.43 ppm (d, *J*= 7.4 Hz, 1H, CH-5 chrom.).

1'-(methylsulfonyl)-3,4-dihydrospiro[chromene-2,4'-piperidin]-4-ol (13b)

The compound was obtained from **13a** following the general procedure B as yellow oil (80% yield). ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.67-2.28 (m, 6H, CH_2-3, CH_2-5 pipd., CH_2-3 chrom.), 2.81 (s, 3H, CH_3), 3.00-3.17 (m, 2H, CHa-2, CHa-6 pipd.), 3.58 (d, *J*= 11.5 Hz, 2H, CHb-2, CHb-6 pipd.), 4.80-4.86 (m, 1H, CH-4 chrom.), 6.82-6.99 (m, 2H, CH-6, CH-8 chrom.), 7.16-7.27 (m, 1H, CH-7 chrom.), 7.42 ppm (d, *J*= 7.4 Hz, 1H, CH-5 chrom.).

1-(4-hydroxy-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)ethanone (14b)

The compound was obtained from **14a** following the general procedure B as yellow oil (97% yield). ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.38-1.71 (m, 2H, CHa-3, CHa-5 pipd.), 1.78-2.23 (m, 4H, CH_2-3 chrom., CHb-3, CHb-5 pipd.), 2.1 (s, 3H, CH_3), 2.56 (bs, -OH), 2.96-3.14 (m, 1H, CHa-2/CHa-6 pipd.), 3.39-3.55 (m, 2H, CHb-2/CHb-6, CHa-2/CHa-6 pipd.),4.29-4.34 (m, 1H, CHb-2/CHb-6

pipd.), 4.81-4.87 (m, 1H, CH-4 chrom.), 6.81-6.96 (m, 2H, CH-6, CH-8 chrom.), 7.14-7.21 (m, 1H, CH-7 chrom.), 7.43 ppm (d, *J*= 7.3 Hz, 1H, CH-5 chrom.).

Cis 2-phenyl-3,4-dihydro-2H-chromen-4-ol (15b)

The compound was obtained from **15a** following the general procedure B as a white solid (84% yield).

mp: 138-139°C, ^{1}H NMR (400MHz, $CDCl_3$): δ= 1.60 (d, *J*= 10.0 Hz, 1H, OH), 2.08 (m, 1H, CHa-3 chrom.), 2.40-2.56 (m, 1H, CHb-3 chrom.), 5.05 (dd, *J*= 6.5, 10.5 Hz, 1H, CH-4 chrom.), 5.14 (dd, *J*= 1.5, 12 Hz, 1H, CH-2 chrom.), 6.85 (dd, *J*= 1.0, 8.2 Hz, 1H, CH-8 chrom.), 6.92 (ddd, *J*= 1.0, 8.4, 8.6 Hz, 1H, CH-6 chrom.), 7.10-7.24 (m, 1H, CH-7 chrom.), 7.35 (m, 5H phen.), 7.45 ppm (dd, *J*= 2.0, 10.0 Hz, 1H, CH-5 chrom.).

3,3-dimethyl-3,4-dihydro-2H-chromen-4-ol (17b)

The compound was obtained from **17a** following the general procedure B as yellow oil (97% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 0.92 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.08 (bs , 1H, OH), 3.71 (dd, *J*= 1.0, 10.5 Hz, 1H, CHa-2 chrom.), 3.92 (d, *J*= 10.5 Hz, 1H, CHb-2 chrom.), 4.18 (s, 1H, CH-4 chrom.), 6.80 (dd, *J*= 0.5, 8.0 Hz, 1H, CH-8 chrom.), 6.90-7.01 (m, 1H, CH-6 chrom.), 7.17-7.23 (m, 1H, CH-7 chrom.), 7.28 ppm (dd, *J*= 1.0, 7.5 Hz, 1H, CH-5 chrom.).

5-fluoro-3,4-dihydro-2H-chromen-4-ol (18b)

The compound was obtained from **18a** following the general procedure B as yellow oil (99% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.90-2.16 (m, 2H, CH_2-3 chrom.), 2.27 (bs, 1H, OH), 4.24 (dd, *J*= 3.9, 7.1 Hz, 2H, CH_2-2 chrom.), 4.72 (t, *J*= 3.9 Hz, 1H, CH-4 chrom.), 6.54 (dd, *J*= 2.5, 10.4 Hz, 1H, CH-8 chrom.), 6.64 (ddd, *J*= 2.5, 8.4, 8.5 Hz, 1H, CH-6 chrom.), 7.23 ppm (dd, *J*= 6.7, 8.4 Hz, 1H, CH-7 chrom.).

4-chloro-2,2-dimethyl-3,4-dihydro-2H-chromene (5c)

The compound was obtained from **5b** following the general procedure C as a black oil (98% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.34 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.23-2.43 (m, 2H, CH_2-3 chrom.), 5.27 (m, 1H, CH-4 chrom.), 6.81 (d, *J*= 8.2 Hz, 1H, CH-8 chrom.), 6.95 (ddd, *J*= 1.2, 7.3, 7.8 Hz, 1H, CH-6 chrom.), 7.20 (ddd, *J*= 1.2, 7.3, 8.2 Hz, 1H, CH-7 chrom.), 7.51 ppm (d, *J*= 7.8 Hz, 1H, CH-5 chrom.).

4-chloro-3,4-dihydrospiro[chromene-2,1'-cyclopentane] (6c)

The compound was obtained from **6b** following the general procedure C as a black oil (84% yield). ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.59-2.17 (m, 8H, $(CH_2)_4$ cyclopen.), 2.37-2.56 (m, 2H, CH_2-3 chrom.), 4.29-4.35 (m, 1H, CH-4 chrom.), 6.79 (d, *J*= 8.2 Hz, 1H, CH-8 chrom.), 6.94 (ddd, *J*= 1.2, 7.3, 7.8 Hz, 1H, CH-6 chrom.), 7.19 (ddd, *J*= 1.2, 7.3, 8.2 Hz, 1H, CH-7 chrom.), 7.48 ppm (d, *J*= 7.8 Hz, 1H, CH-5 chrom.).

4-chloro-3,4-dihydrospiro[chromene-2,1'-cyclohexane] (7c)

The compound was obtained from **7b** following the general procedure C as a black oil (95% yield). ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.29-2.06 (m, 10H, $(CH_2)_5$ cyclohex.), 2.27 (dd, *J*= 8.0, 14.0 Hz, 1H, CHa-3 chrom.), 2.41 (dd, *J*= 6.5, 14.0 Hz, 1H, CHb-3 chrom.), 5.27-5.41 (m, 1H, CH-4 chrom.), 6.81-7.00 (m, 2H, CH-8, CH-6 chrom.), 7.20-7.26 (m, 1H, CH-7 chrom.), 7.49 ppm (d, *J*= 7.7 Hz, 1H, CH-5 chrom.).

4-chloro-3,4-dihydrospiro[chromene-2,1'-cycloheptane] (8c)

The compound was obtained from **8b** following the general procedure C as a black oil (98% yield). ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.40-2.06 (m, 12H, $(CH_2)_6$ cyclohept.), 2.25 (dd, *J*= 9.0, 14.0 Hz 1H, CHa-3 chrom.), 2.48 (dd, *J*= 6.4, 14.0 Hz, 1H, CHb-3 chrom.), 5.24 (dd, *J*= 6.4, 9.0 Hz, 1H, CH-4 chrom.), 6.80 (dd, *J*= 0.9, 8.2 Hz, 1H, CH-8 chrom.), 6.93 (ddd, *J*= 1.2, 7.3, 7.8 Hz, 1H, CH-6 chrom.), 7.19 (ddd, *J*= 1.2, 7.3, 8.2 Hz, 1H, CH-7 chrom.), 7.50 ppm (d, *J*= 7.8 Hz; 1H, CH-5 chrom.).

4-chloro-2',3,3',4,5',6'-hexahydrospiro[chromene-2,4'-thiopyran] (9c)

The compound was obtained from **9b** following the general procedure C as a black oil (94% yield). ^{1}H NMR (200MHz, $CDCl_3$): δ= 1.85-2.15 (m, 3H, CHa-3, CHa-5 thiopyran., CHa-3 chrom.), 2.25-2.50 (m, 5H, CHa-2, CHa-6, CHb-3, CHb-5 thiopyran., CHb-3 chrom.), 2.9-3.16 (m, 2H, CHb-2, CHb-6 thiopyran.), 5.23-5.29 (m, 1H, CH-4 chrom.), 6.85-6.99 (m, 2H, CH-8, CH-6 chrom.), 7.17-7.27 (m, 1H, CH-7 chrom.), 7.47 ppm (d, *J*= 7.7 Hz, 1H, CH-5 chrom.).

4-chloro-2',3,3',4,5',6'-hexahydrospiro[chromene-2,4'-pyran] (10c)

The compound was obtained from **10b** following the general procedure C as a black oil (95% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.69-1.78 (m, 2H, CHa-3, CHa-5 pyran), 1.80-2.16 (m, 2H, CHb-3, CHb-5 pyran), 2.23-2.44 (m, 2H, CH_2-3 chrom.), 3.74-3.91 (m, 4H, CH_2-2, CH_2-6 pyran), 5.22-

5.26 (m, 1H, CH-4 chrom.), 6.79-6.97 (m, 2H, CH-6, CH-8 chrom.), 7.16-7.23 (m, 1H, CH-7 chrom.), 7.46 ppm (d, *J*= 7.4 Hz, 1H, CH-5 chrom.).

4-chloro-1'-methyl-3,4-dihydrospiro[chromene-2,4'-piperidine] (11c)

The compound was obtained from **11b** following the general procedure C as a black oil (94% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 2.35-2.68 (m, 6H, CH_2-3, CH_2-5 pipd., CH_2-3 chrom.), 2.75 (s, 3H, CH_3), 3.12-3.50 (m, 4H, CH_2-2, CH_2-6, pipd.), 5.22-5.26 (m, 1H, CH-4 chrom.), 6.79-6.97 (m, 2H, CH-6, CH-8 chrom.), 7.16-7.23 (m, 1H, CH-7 chrom.), 7.46 ppm (d, *J*= 7.4 Hz, 1H, CH-5 chrom.).

4-chloro-1'-ethyl-3,4-dihydrospiro[chromene-2,4'-piperidine] (12c)

The compound was obtained from **12b** following the general procedure C as a black oil (94% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.45 (t, *J*= 7.1 Hz, 3H, CH_3), 1.89-2.04 (m, 2H, CH_2-3 chrom.), 2.30-2.63 (m, 4H, CH_2-3, CH_2-5 pipd.), 2.99-3.18 (m, 4H, CH_2, CHb-2, CHb-6 pipd.), 3.39 (m, 2H, CHa-2, CHa-6 pipd.), 5.18-5.26 (m, 1H, CH-4 chrom.), 6.83 (d, *J*= 8.1 Hz, 1H, CH-8 chrom.), 6.95 (t, *J*= 7.4 Hz, 1H, CH-6 chrom.), 7.10-7.22 (m, 1H, CH-7 chrom.), 7.43 ppm (d, *J*= 7.7 Hz, 1H, CH-5 chrom.).

4-chloro-1'-(methylsulfonyl)-3,4-dihydrospiro[chromene-2,4'-piperidine] (13c)

The compound was obtained from **13b** following the general procedure C as a black oil (96% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.79-1.92 (m, 3H, CH_2-3 chrom., CHa-3/CHa-5 pipd.), 2.19-2.38 (m, 3H, CHa-3/CHa-5, CHb-3, CHb-5 pipd.), 2.82 (s, 3H, CH_3), 3.04-3.16 (m, 2H, CHa-2, CHa-6 pipd.), 3.61 (d, *J*= 11.6 Hz, CHb-2, 2H, CHb-6 pipd.), 5.26 (dd, *J*= 5.2, 11.7 Hz, 1H, CH-4 chrom.), 6.83-7.01 (m, 2H, CH-6, CH-8 chrom.), 7.18-7.25 (m, 1H, CH-7 chrom.), 7.47 ppm (d, *J*= 7.4 Hz, 1H, CH-5 chrom.).

1-(4-chloro-3,4-dihydro-1'H-spiro[chromene-2,4'-piperidin]-1'-yl)ethanone (14c)

The compound was obtained from **14b** following the general procedure C as a black oil (97% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.41-1.67 (m, 2H, CHa-2, CHa-6 pipd.), 1.76-2.23 (m, 2H, CHb-2, CHb-6 pipd.), 2.69 (s, 2H, CH_2-3 chrom.), 2.85-3.48 (m, 4H, CH_2-3, CH_2-5 pipd.), 6.83-6.98 (m,

2H, CH-6, CH-8 chrom.) ,7.41-7.49 (m, 1H, CH-7 chrom.), 7.69-7.83 ppm (d, *J*= 7.3 Hz, 1H, CH-5 chrom.).

Trans 4-chloro-2-phenyl-3,4-dihydro-2H-chromene (15c)

The compound was obtained from **15b** following the general procedure C as a black oil (98% yield).

^{1}H NMR (400MHz, $CDCl_3$): δ= 2.04-2.41 (m, 2H, CH_2-3 chrom.), 5.29-5.32 (m, 1H, CH-2 chrom.), 5.36-5.42 (m, 1H, CH-4 chrom.), 6.73-7.13 (m, 2H, CH-6, CH-8 chrom.), 7.19-7.72 ppm (m, 7H, CH-5, CH-7 chrom., 5H phen.).

4-chloro-3,3-dimethyl-3,4-dihydro-2H-chromene (17c)

The compound was obtained from **17b** following the general procedure C as an oil (58% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 1.11 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 3.75 (m, 1H, CHa-2 chrom.), 4.18 (m, 1H, CHb-2 chrom.), 4.82 (s, 1H, CH-4 chrom.), 6.83 (d, *J*= 8.2 Hz; 1H, CH-8 chrom.), 6.96 (t, *J*= 7.7 Hz, 1H, CH-6 chrom.), 7.21-7.26 (m, 1H, CH-7 chrom.), 7.32 ppm (d, *J*= 7.7 Hz, 1H, CH-5 chrom.).

4-chloro-5-fluoro-3,4-dihydro-2H-chromene (18c)

The compound was obtained from **18b** following the general procedure C as brown oil (97% yield).

^{1}H NMR (200MHz, $CDCl_3$): δ= 2.24-2.56 (m, 2H, CH_2-3 chrom.), 4.29-4.54 (m, 2H, CH_2-2 chrom.), 5.21 (t, *J*= 2.9 Hz, 1H, CH-4 chrom.), 6.55 (dd, *J*= 2.5, 10.2 Hz, 1H, CH-8 chrom.), 6.65 (ddd, *J*= 2.5, 8.3, 8.4 Hz, 1H, CH-6 chrom.), 7.26 ppm (dd, *J*= 6.5, 8.4 Hz, 1H, CH-7 chrom.).

8-(2,2-dimethylchroman-4-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (5)

The compound was obtained from **5c** following the general procedure D as white solid (42% yield).

mp: 224-225 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ= 1.24 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.61-1.72 (m, 1H, CHa-6/CHa-10 tasd), 1.78-1.83 (m, 2H, CHa-3 chrom., CHa-6/CHa-10 tasd), 1.86-1.93 (m, 1H, CHb-3 chrom.), 2.46-2.49 (m, 1H, CHa-7/CHa-9 tasd), 2.62 (ddd, *J*= 5.1, 10.1, 12.3 Hz, 1H, CHb-6/CHb-10 tasd), 2.78-2.93 (m, 3H, CHb-6/CHb-10 tasd, CHa-7/CHa-9 tasd, CHb-7/CHb-9 tasd), 3.32-3.39 (m, 1H, CHb-7/CHb-9 tasd), 4.02 (dd, *J*= 6.0, 11.8 Hz, 1H, CH-4 chrom.), 4.74 (dd, *J*= 4.2, 10.1 Hz, 2H, CH_2-2 tasd), 6.75 (d, *J*= 8.1 Hz, 1H, CH-8 chrom.), 6.84-6.92 (m, 2H, CH-6 chrom., CH-4 arom. tasd), 6.97 (d, *J*= 8.4 Hz, 2H, CH-2, CH-6 arom. tasd), 7.11 (ddd, *J*= 1.2, 7.7, 8.2 Hz, 1H, CH-7 chrom.), 7.28 (s, 1H, NH), 7.33 (m, 2H, CH-3, CH-5 arom. tasd), 7.70 ppm (d, *J*= 7.7 Hz, 1H, CH-5 chrom.); ^{13}C NMR (400MHz, $CDCl_3$): δ= 24.0 (CH_3), 29.1 (C-6/C-10

tasd), 29.6 (C-6/C-10 tasd), 30.4 (CH_3, C-3 chrom.), 41.3 (C-7/C-9 tasd), 48.1 (C-7/C-9 tasd), 56.8 (C-4 chrom.), 59.0 (C-2 tasd), 59.1 (C-5 tasd), 75.1 (C-2 chrom.), 114.3 (C-2, C-6 arom. tasd), 116.9 (C-8 chrom.), 118.2 (C-4 arom. tasd), 119.8 (C-6 chrom.), 122.7 (C-4a chrom.), 127.1 (C-5 chrom.), 127.8 (C-7 chrom.), 129.0 (C-3, C-5 arom. tasd), 142.9 (C-1 arom. tasd), 154.5 (C-8a chrom.), 178.3 ppm (CO tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.
mp: 148-149 °C; ^{1}H NMR (200MHz, DMSO): δ= 1.20 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.58-1.83 (m, 3H, CHa-6/CHa-10 tasd, CH_2-3 chrom.), 2.03-2.12 (m, 1H, CHa-6/CHa-10 tasd), 2.50-2.54 (m, 2H, CHa-7/CHa-9 tasd, CHb-6/CHb-10 tasd), 2.83 (m, 1H, CHb-6/CHb-10 tasd), 2.99-3.05 (m, 2H, CHa-7/CHa-9 tasd, CHb-7/CHb-9 tasd), 3.43-3.48 (m, 1H, CHb-7/CHb-9 tasd), 4.30 (m, 1H, CH-4 chrom.), 4.59 (s, 2H, CH_2-2 tasd), 6.72-6.82 (m, 2H, CH-8, CH-6 chrom.), 6.91-6.99 (m, 3H, CH-2, CH-4, CH-6 arom. tasd), 7.11-7.19 (m, 1H, CH-7 chrom.), 7.24-7.32 (m, 2H, CH-3, CH-5 arom. tasd), 7.68 (d, *J*= 7.5, 1H, CH-5 chrom.), 8.73 ppm (s, 1H, oxalic ac.).
HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{24}H_{30}N_3O_2$: 392.2333, found: 392.2336; Anal. Calcd for $C_{26}H_{31}N_3O_6$: C, 64.85; H, 6.49; N, 8.73, found C, 64.42; H, 6.99; N, 8.71.

1-phenyl-8-(spiro[chroman-2,1'-cyclopentan]-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one (6)
The compound was obtained from **6c** following the general procedure D as white solid (42% yield).
mp: 123-124 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ= 1.37-1.45 (m, 1H, CHa-2' cyclopen.), 1.59-1.94 (m, 11H, CHa-6,CHa-10 tasd, CH_2-3 chrom., CHb-2' cyclopen., $(CH_2)_3$ cyclopen.), 2.48-2.51 (m, 1H, CHa-7/CHa-9 tasd), 2.62 (ddd, *J*= 5.1, 12.3, 13.3 Hz, 1H, CHb-6/CHb-10 tasd), 2.78-2.93 (m, 3H, CHb-6/CHb-10 tasd, CHa-7/CHa-9 tasd, CHb-7/CHb-9 tasd), 3.32-3.38 (m, 1H, CHb-7/CHb-9 3 tasd), 4.04 (dd, *J*=5.4, 11.9 Hz, 1H, CH-4 chrom.), 4.73 (dd, *J*= 4.1, 10.0 Hz, 2H, CH_2-2 tasd), 6.73 (d, *J*= 8.1 Hz, 1H, CH-8 chrom.), 6.84-6.91 (m, 2H, CH-6 chrom. CH-4 arom. tasd), 6.97 (d, *J*= 8.2 Hz, 2H, CH-2, CH-6 arom. tasd), 7.09-7.15 (m, 1H, CH-7 chrom.), 7.26-7.34 (m, 3H, CH-3, CH-5 arom. tasd, NH), 7.68 ppm (d, *J*= 7.6 Hz, 1H, CH-5 chrom.); ^{13}C NMR (400MHz, $CDCl_3$): δ= 23.4 (C cyclopen.), 23.9 (C cyclopen.), 28.7 (C-3 chrom.), 29.0 (C-6/C-10 tasd), 29.6 (C-6/C-10 tasd), 35.6 (C cyclopen.), 40.1 (C cyclopen.), 41.3 (C-7/C-9 tasd), 48.1 (C-7/C-9 tasd), 57.9 (C-4 chrom.), 59.0 (C-2 tasd), 59.2 (C-5 tasd), 86.5 (C-2 chrom.), 114.3 (C-2, C-6 arom. tasd), 117.0 (C-8 chrom.), 118.1 (C-4 arom. tasd), 119.7 (C-6 chrom.), 123.5 (C-4a chrom.), 127.1 (C-5 chrom.), 127.6 (C-7 chrom.), 129.0 (C-3, C-5 arom. tasd), 142.9 (C-1 arom. tasd), 154.6 (C-8a chrom.), 178.3 ppm (CO tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.
mp: 131-132 °C; ^{1}H NMR (200MHz, DMSO): δ= 1.65-2.16 (m, 12H, CHa-6, CHa-10 tasd, CH_2-3 chrom., $(CH_2)_4$ cyclopen.), 2.62-2.71 (m, 2H, CHa-7, CHa-9 tasd), 2.89-2.93 (m, 1H, CHb-6/CHb-10 tasd), 3.25-3.34 (m, 2H, CHb-7/CHb-9 tasd, CHb-6/CHb-10 tasd), 3.66-3.72 (m, 1H, CHb-7/CHb-9 tasd), 4.60 (s, 3H, CH_2-2 tasd, CH-4 chrom.), 6.76-6.84 (m, 2H, CH-8, CH-6 chrom.), 6.96-7.01 (m, 3H, CH-2, CH-4, CH-6 arom. tasd), 7.16-7.32 (m, 3H, CH-7 chrom., CH-3, CH-5 arom. tasd), 7.70 (d, *J*= 7.4 Hz, 1H, CH-5 chrom.), 8.83 ppm (s, 1H, oxalic ac.).
HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{26}H_{32}N_3O_2$: 418.2489, found: 418.2490; Anal. Calcd for $C_{28}H_{33}N_3O_6{\cdot}(COOH)_2$: C, 60.29; H, 5.90; N, 7.03, found C, 59.84; H, 6.27; N, 7.13.

1-phenyl-8-(spiro[chroman-2,1'-cyclohexan]-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one (7)
The compound was obtained from **7c** following the general procedure D as white solid (39% yield).
mp: 214-215°C; ^{1}H NMR (400MHz, $CDCl_3$): δ= 1.33-1.38 (m, 3H, 3 CHa cyclohex.), 1.55-1.68 (m, 5H, 2 CHb, CH_2 cyclohex., CHa-6/CHa-10 tasd), 1.73-1.87 (m, 5H, CHa-3 chrom., CHa-6/CHa-10 tasd, 3 CHa cyclohex.), 1.98 (dd, *J*= 5.8, 13.0 Hz; 1H, CHb-3 chrom.), 2.48 (m, 1H, CHa-7/CHa-9 tasd), 2.64 (ddd, *J*= 5.1, 12.1, 13.3 Hz, 1H, CHb-6/CHb-10 tasd), 2.80-2.95 (m, 3H, CHb-6/CHb-10 tasd, CHa-7/CHa-9 tasd, CHb-7/CHb-9 tasd), 3.33-3.38 (m, 1H, CHb-7/CHb-9 tasd), 4.04 (dd, *J*= 5.6, 11.9 Hz, 1H, CH-4 chrom.), 4.75 (dd, *J*= 4.2, 10.5 Hz, 2H, CH_2-2 tasd), 6.82 (d, *J*= 8.0 Hz, 1H, CH-8 chrom.), 6.85-6.93 (m, 2H, CH-6 chrom., CH-4 arom tasd), 6.98 (d, *J*= 8.2 Hz, 2H, CH-2, CH-6 arom tasd), 7.13-7.19 (m, 1H, CH-7 chrom.), 7.34-7.44 (m, 2H, CH-3, CH-5 arom tasd), 7.70 (d, *J*= 7.6 Hz, 1H, CH-5 chrom.), 7.86 ppm (bs, 1H, NH); ^{13}C NMR (400MHz, $CDCl_3$): δ= 21.4 (C cyclohex.), 21.5 (C cyclohex.), 25.6 (C cyclohex.), 29.0 (C-6/C-10 tasd), 29.1 (C-3 chrom.), 29.6 (C-6/C-10 tasd), 32.1 (C cyclohex.), 38.8 (C cyclohex.), 41.3 (C-7/C-9 tasd), 48.1 (C-7/C-9 tasd), 56.05 (C-4 chrom.), 59.2 (C-2 tasd, C-5 tasd), 75.8 (C-2 chrom.), 114.2 (C-2, C-6 arom tasd), 117.0 (C-8 chrom.), 118.0 (C-4 arom tasd), 119.7 (C-6 chrom.), 123.3 (C-4a chrom.), 127.1 (C-5 chrom.), 127.7 (C-7 chrom.), 129.0 (C-3, C-5 arom tasd), 142.9 (C-1 arom tasd), 154.3 (C-8a chrom.), 178.7 ppm (C=O tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.
mp: 225-226°C; ^{1}H NMR (400MHz, DMSO): δ= 1.39-1.40 (m, 4H, CHa-6,CHa-10 tasd, CH_2-3, chrom.), 1.57-1.75 (m, 10H, $(CH_2)_5$ cyclohex..), 2.50-2.60 (m, 1H, CHb-6/CHb-10 tasd, CHa-7/CHa-9 tasd), 2.81-2.91 (m, 1H, CHb-6/CHb-10 tasd), 3.08-3.19 (m, 2H, CHa-7/CHa-9 tasd, CHb-7/CHb-9 tasd), 3.42-3.43 (m, 1H, CHb-7/CHb-9 tasd), 4.31-4.38 (m, 1H, CH-4 chrom.), 4.59 (s, 2H, CH_2-2 tasd), 6.77-6.79 (m, 2H, CH-6, CH-8 chrom.), 6.94-6.96 (m, 3H, CH-2, CH-4, CH-6

arom. tasd), 7.15-7.21 (m, 1H, CH-7 chrom.), 7.29-7.36 (m, 2H, CH-3, CH-5 arom. tasd;), 7.64 (d, *J*= 7.3 Hz, 1H, CH-5 chrom.), 8.75 ppm (s, 1H, ac. Oxalic ac.).
HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{27}H_{34}N_3O_2$: 432.2646, found: 432.2644; Anal. Calcd for $C_{29}H_{35}N_3O_6$: C 66.78, H 6.76, N 8.06, found C, 65.31, H 7.21, N 7.99.

1-phenyl-8-(spiro[chroman-2,1'-cycloheptan]-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one (8)
The compound was obtained from **8c** following the general procedure D as white solid (50% yield).
mp: 199-200 °C; ^{1}H NMR (400MHz, $CDCl_3$): *δ*= 1.37-1.85 (m, 13H, 2×CHa cyclohept., $(CH_2)_4$ cyclohept., CHa-6, CHa-10 tasd, CHa-3 chrom.), 1.90-1.99 (m, 2H, 2×CHb cyiclohept.), 2.06 (dd, *J*= 5.6, 13.0 Hz, 1H, CHb-3 chrom.), 2.47-2.51 (m, 1H, CHa-7/CHa-9 tasd), 2.63 (ddd, *J*= 5.2, 12.3, 13.2 Hz, 1H, CHb-6/CHb-10 tasd), 2.78-2.94 (m, 3H, CHb-6/CHb-10 tasd, CHa-7/CHa-9 tasd, CHb-7/CHb-9 tasd), 3.33-3.39 (m, 1H, CHb-7/CHb-9 tasd), 3.98 (dd, *J*= 5.5, 12.1 Hz, 1H, CH-4 chrom.), 4.74 (dd, *J*= 4.2, 10.8 Hz, 2H, CH_2-2 tasd), 6.77 (d, *J*= 8.1 Hz, 1H, CH-8 chrom.), 6.84-6.91 (m, 2H, CH-6 chrom., CH-4 arom. tasd), 6.97 (d, *J*= 8.3 Hz, 2H, CH-2, CH-6 arom. tasd), 7.10 (m, 1H, CH-7 chrom.), 7.33-7.37 (m, 2H, CH-3, CH-5 arom. tasd), 7.38 (s, 1H, NH), 7.68 ppm (d, *J*= 7.6 Hz, 1H, CH-5 chrom.); ^{13}C NMR (400MHz, $CDCl_3$): *δ*= 21.6 (C cyclohept.), 22.1 (C cyclohept.), 29.1 (C-6/C-10 tasd), 29.6 (2×C cyclohept.), 29.7 (C-6/C-10 tasd), 30.2 (C-3 chrom.), 32.1 (C cyclohept.), 41.3 (C-7/C-9 tasd), 42.4 (C cyclohept.), 48.1 (C-7/C-9 tasd), 56.3 (C-4 chrom.), 59.1 (C-5 tasd), 59.2 (C-2 tasd), 80.3 (C-2 chrom.), 114.2 (C-2, C-6 arom. tasd), 117.2 (C-8 chrom.), 118.1 (C-4 arom. tasd), 119.6 (C-6 chrom.), 123.4 (C-4a chrom.), 127.0 (C-5 chrom.), 127.7 (C-7 chrom.), 129.0 (C-3, C-5 arom. tasd), 142.9 (C-1 arom. tasd), 154.4 (C-8a chrom.), 178.4 ppm (CO tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.
mp: 208-209 °C; ^{1}H NMR (200MHz, DMSO): *δ*= 1.45-1.89 (m, 15H, 2×CHa-6/CHa-10 tasd, CHa-3 chrom., $(CH_2)_6$ cyclohept.), 2.21-2.24 (m, 1H, CHb-3 chrom.), 2.34-2.69 (m, 2H, CHb-6/CHb-10 tasd, CHa-7/CHa-9 tasd), 2.84-2.91 (m, 1H, CHb-6/CHb-10 tasd), 3.11-3.15 (m, 2H, CHa-7/CHa-9 tasd, CHb-7/CHb-9 tasd), 3.53-3.61 (m, 1H, CHb-7/CHb-9 tasd), 4.33-4.41 (m, 1H, CH-4 chrom.), 4.59 (s, 3H, CH_2-2 tasd), 6.79-6.83 (m, 2H, CH-8, CH-6 chrom.), 6.91-6.99 (m, 3H, CH-2, CH-4, CH-6 arom. tasd), 7.12-7.32 (m, 3H, CH-7 chrom., CH-3, CH-5 arom. tasd), 7.67 (d, *J*= 7.5 Hz, 1H, CH-5 chrom.), 8.76 ppm (s, 1H, oxalic ac.).
HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{28}H_{36}N_3O_2$: 446.2802, found: 446.2799; Anal. Calcd for $C_{30}H_{37}N_3O_6 \cdot H_2O$: C, 65.08; H, 7.10; N, 7.59, found C, 64.85; H, 7.50; N, 7.59.

1-phenyl-8-(2',3',5',6'-tetrahydrospiro[chroman-2,4'-thiopyran]-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one (9)

The compound was obtained from **9c** following the general procedure D as white solid (47% yield). mp: 222-223°C; ^{1}H NMR (400MHz, $CDCl_3$): δ= 1.62-1.72 (m, 2H, CHa-6, CHa-10 tasd), 1.78-1.89 (m, 2H, CHa-3 chrom, CHa-3/CHa-5 thiopyran.), 1.90-2.03 (m, 2H, CHb-3 chrom, CHa-3/CHa-5 thyopyran.), 2.11-2.30 (m, 2H, CHb-6/CHb-10 tasd, CHb-3/CHb-5 thiopyran.), 2.30-2.43 (m, 1H, CHb-3/CHb-5 thiopyran), 2.44-2.60 (m, 2H, CHa-2/CHa-6 thiopyran, CHa-7/CHa-9 tasd), 2.68 (ddd, *J*= 5.1, 12.1, 13.3 Hz, 1H, CHb-6/CHb-10 tasd), 2.80-3.0 (m, 4H, CHb-7/CHb-9 tasd, CHa-7/CHa-9 tasd, CHa-2/CHa-6, CHb-2/CHb-6 thiopyran.), 3.27-3.33 (m, 1H, CHb-2/CHb-6 thiopyran.), 3.37-3.42 (m, 1H, CHb-7/CHb-9 tasd), 4.11 (dd, *J*= 5.9, 11.8 Hz, 1H, CH-4 chrom.), 4.79 (dd, *J*= 4.2, 10.2 Hz, 2H, CH_2-2 tasd), 6.86-6.95 (m, 2H, CH-4 arom. tasd, CH-8 chrom.), 6.96-7.06 (m, 3H, CH-2, CH-6 arom. tasd, CH-6 chrom.), 7.20 (dd, *J*= 8.0, 7.0 Hz, 1H, CH-7 chrom.), 7.30 (bs, 1H, NH), 7.39 (dd, *J*= 7.6, 8.3 Hz, 2H, CH-3, CH-5 arom tasd), 7.75 ppm (d, *J*= 7.6 Hz, 1H, CH-5 chrom); ^{13}C NMR (400MHz, $CDCl_3$): δ= 23.8 (C-2, C-6, C-3/C-5 thiopyran,), 29.3 (C-6/C-10 tasd), 30.44 (C-3 chrom.), 33.4 (C-6/C-10 tasd), 39.9 (C-3/C-5 thiopyran), 41.5 (C-7/C-9 tasd), 48.3 (C-7/C-9 tasd), 55.7 (C-4 chrom.), 59.4 (C-2, C-5 tasd), 74.0 (C-2 chrom.), 114.5 (C-2, C-6 arom. tasd), 117.0 (C-8 chrom.), 118.4 (C-4 arom. tasd), 120.6 (C-6 chrom.), 123.3 (C-4a chrom.), 127.62 (C-7 chrom.), 128.3 (C-5 chrom.), 129.3 (C-3, C-5 arom. tasd), 143.2 (C-1 arom. tasd), 153.8 (C-8a chrom.), 178.53ppm (C=O tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.
mp: 232-234°C; ^{1}H NMR (200MHz, DMSO): δ= 1.56-1.74 (m, 3H, CHa-6/CHa-10 tasd, CHa-3 chrom., CHa-3/CHa-5 thiopyran), 1.86-2.18 (m, 4H, CHb-3 chrom., CHa-3/CHa-5 thiopyran., CHb-6/CHb-10 tasd, CHb-3/CHb-5 thiopyran), 2.42-2.82 (m, 7H, CHb-3/CHb-5, CHa-2/CHa-6 thiopyran, CHa-7, CHa-9, CHb-6/CHb-10, CHb-7/CHb-9, CHa-2/CHa-6 tasd), 3.00-3.11 (m, 2H, CHb-2, CHb-6 thiopyran), 3.37-3.47 (m, 1H, CHb-7/CHb-9 tasd), 4.28 (dd, *J*= 5.9, 11.8 Hz, 1H, CH-4 chrom.), 4.79 (s, 2H, CH_2-2 tasd), 6.74-6.93 (m, 2H, CH-4 arom tasd, CH-8 chrom.), 6.97 (bs, NH), 6.99-7.06 (m, 3H, CH-2 arom tasd, CH-6 arom tasd, CH-6 chrom.), 7.24 (m, 3H, CH-3, CH-5 arom tasd, CH-7 chrom.), 7.65 ppm (d, *J*= 7.3, 1H, CH-5 chrom.).
HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{26}H_{32}N_3O_2S$: 450.2209, found: 450.2221; Anal. Calcd for $C_{28}H_{33}N_3O_6S$: C 62.32, H 6.16, N 7.79, found C 62.44, H 6.19, N 7.65

1-phenyl-8-(2',3',5',6'-tetrahydrospiro[chroman-2,4'-pyran]-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one (10)

The compound was obtained from **10c** following the general procedure D as white solid (21% yield).

mp: 252-253°C; ^{1}H NMR (400MHz, $CDCl_3$): δ= 1.59-1.72 (m, 2H, CHa-6/CHa-10 tasd, CHa-3/CHa-5 pyran.), 1.74-2.06 (m, 5H, CHa-3/CHa-5, CHb-3/CHb-5 pyran., CH_2-3 chrom., CHa-6/CHa-10 tasd), 2.46-2.60 (m, 1H, CHa-7/CHa-9 tasd), 2.60-2.67 (m, 1H, CHb-6/CHb-10 tasd), 2.82-3.0 (m, 3H, CHa-7/CHa-9, CHb-7/CHb-9, CHb-6/CHb-10 tasd), 3.35-3.47 (m, 1H, CHb-7/CHb-9 tasd), 3.70-3.81 (m, 2H, CHa-2/CHa-6, CHb-2/CHb-6 pyran), 3.83-3.92 (m, 1H, CHa-2/CHa-6 pyran), 4.01-4.08 (m, 1H, CHb-2/CHb-6 pyran), 4.11 (dd, *J*= 5.9, 11.8 Hz, 1H, CH-4 chrom.), 4.79 (dd, *J*= 4.2, 9.9 Hz, 2H, CH_2-2 tasd), 6.89-6.94 (m, 2H, CH-4 arom tasd, CH-8 chrom.), 6.97-7.03 (m, 3H, CH-2, CH-6 arom tasd, CH-6 chrom.), 7.15-7.24 (m, 2H, CH-7 chrom., NH), 7.38 (dd, *J*= 7.4, 8.6 Hz, 2H, CH-3, CH-5 arom tasd), 7.75 ppm (d, *J*= 7.6 Hz, 1H, CH-5 chrom.): ^{13}C NMR (400MHz, $CDCl_3$): δ= 29.3 (C-6/C-10 tasd), 29.8 (C-6/C-10 tasd), 30.36 (C-3 chrom.), 32.8 (C-3/C-5 pyran), 38.6 (C-3/C-5 pyran), 41.5 (C-7/C-9 tasd), 48.3 (C-7/C-9 tasd), 55.9 (C-4 chrom.), 59.3 (C-2, C-5 tasd), 63.4 (C-2 ,C-6 pyran), 73.1 (C-2 chrom.), 114.6 (C-2, C-6 arom tasd), 117.3 (C-8 chrom.), 118.5 (C-4 arom tasd), 120.5 (C-6 chrom.), 123.4 (C-4a chrom.), 127.5 (C-5 chrom.), 128.2 (C-7 chrom.), 129.3 (C-3, C-5 arom tasd), 143.2 (C-1 arom tasd), 154.0 (C-8a chrom.), 178.3 ppm (C=O tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.

mp: 181-182°C; ^{1}H NMR (200MHz, DMSO): δ= 1.62-1.83 (m, 6H, CHa-6, CHa-10 tasd, CH_2-3, CH_2-5 pyran), 2.07-2.17 (m, 2H, CH_2-3 chrom.), 2.49 (m, 3H, CHa-7,CHa-9, CHb-6/CHb-10 tasd), 2.73-3.02 (m, 3H, CHb-7,CHb-9, CHb-6/CHb-10 tasd), 3.39-3.87 (m, 4H, CH_2-2, CH_2-6, pyran), 4.31 (m, 1H, CH-4 chrom.), 4.58 (s, 2H, CH_2-2 tasd), 6.75-6.97 (m, 5H, CH-4, CH-2, CH-6 arom tasd, CH-8 chrom., NH), 7.13-7.21 (m, 2H, CH-6, CH-7 chrom.), 7.24-7.32 (m, *J*= 7.4, 8.6 Hz, 2H, CH-3, CH-5 arom tasd), 7.65 ppm (d, *J*= 7.3 Hz, 1H, CH-5 chrom.).

HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{26}H_{32}N_3O_3$: 434.2438, found: 434.2451; Anal. Calcd for $C_{28}H_{33}N_3O_7$: C 62.09, H 6.51, N 7.76, found C 62.30, H 6.64, N 7.92

8-(1'-methylspiro[chroman-2,4'-piperidin]-4-yl)-1-phenyl-1,3,8- triazaspiro[4.5]decan-4-one (11)

The compound was obtained from **11c** following the general procedure D as white solid (20% yield).

mp: 134-135°C; ^{1}H NMR (400MHz, $CDCl_3$): δ= 1.52-1.65 (m, 2H, CHa-6, CHa-10 tasd), 1.71-1.95 (m, 6H, CH_2-3 chrom., CHb-6/CHb-10 tasd, CHa-3, CHa-5, CHb-3/CHb-5 pipd.), 2.21-2.29 (m,

1H, CHa-2/CHa-6 pipd.), 2.32 (s, 3H, CH_3), 2.39-2.49 (m, 1H, CHa-7/CHa-9 tasd), 2.50-2.74 (m, 4H, CHb-6/CHb-10 tasd, CHa-2/CHa-6, CHb-2, CHb-6 pipd.), 2.75-2.94 (m, 3H, CHb-3/CHb-5 pipd., CHa-7/CHa-9, CHb-7/CHb-9 tasd), 3.30-3.37 (m, 1H, CHb-7/CHb-9 tasd), 4.02 (dd, *J*= 7.4, 10.4 Hz, 1H, CH-4 chrom.), 4.65-4.77 (m, 2H, CH_2-2 tasd), 6.77-6.87 (m, 2H, CH-8 chrom., CH-4 arom tasd), 6.90 (dd, *J*= 7.8, 8.2 Hz, 1H, CH-6 chrom.), 6.95 (d, *J*= 8.2 Hz, 2H, CH-2, CH-6 arom tasd), 7.10 (dd, *J*= 7.0, 8.3 Hz, 1H, CH-7 chrom.), 7.31 (dd, *J*= 7.4, 8.5 Hz, 2H, CH-3, CH-5 tasd), 7.69 (d, *J*= 7.5, 1H, CH-5 chrom.), 8.00 ppm (bs, 1H, NH); ^{13}C NMR (400MHz, $CDCl_3$): δ= 29.3 (C-6/C-10 tasd), 29.84 (C-3, C-5 pipd.), 31.9 (C-6/C-10 tasd), 38.0 (C-3 chrom.), 41.6 (C-7/C-9 tasd), 46.1 (CH_3 pipd.), 48.3 (C-7/C-9 tasd), 51.0 (C-2/C-6 pipd.), 56.2 (C-4 chrom.), 58.8 (C-2/C-6 pipd.), 59.4 (C-2, C-5 tasd), 73.0 (C-2 chrom.), 114.4 (C-2, C-6 arom. tasd), 117.3 (C-8 chrom.), 118.3 (C-4 tasd), 120.4 (C-6 chrom.), 123.5 (C-4a chrom.), 127.6 (C-5 chrom.), 128.1 (C-7 chrom.), 129.3 (C-3/C-5 arom. tasd) 129.4 (C-3/C-5 arom tasd), 143.2 (C-1 arom. tasd), 154.0 (C-8a chrom.), 178.8 ppm (C=O tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.
mp: 202-203°C; ^{1}H NMR (200MHz, DMSO): δ= 1.61-1.67 (m, 2H, CHa-6, CHa-10 tasd), 1.79-2.07 (m, 6H, CH_2-3 chrom., CHb-6/CHb-10 tasd, CHa-3, CHa-5, CHb-3/CHb-5 pipd.), 2.38-2.54 (m, 3H, CH_3), 2.79-3.01 (m, 6H, CHb-6/CHb-10 tasd, CH_2-2, CH_2-6, CHb-3/CHb-5 pipd.), 3.19-3.34 (m, 4H, CH_2-7, CH_2-9 tasd), 4.17 (m, 1H, CH-4 chrom.), 4.58 (s, 2H, CH_2-2 tasd), 6.73-7.01 (m, 5H, CH-2, CH-4, CH-6 arom. tasd, CH-6, CH-8 chrom.), 7.14-7.32 (m, 3H, CH-3, CH-5 arom tasd, CH-7 chrom.), 7.66 (d, *J*= 7.3 Hz, 1H, CH-5 chrom.), 7.94 ppm (bs, NH).
HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{27}H_{36}N_4O_2$: 447.2755, found: 447.2764; Anal. Calcd for $C_{27}H_{34}N_4O_2 \cdot 2\ (COOH)_2$: C 59.42, H 6.11, N 8.94, found C 59.44, H 5.97, N 9.06.

8-(1'-ethylspiro[chroman-2,4'-piperidin]-4-yl)-1-phenyl-1,3,8- triazaspiro[4.5]decan-4-one (12)
The compound was obtained from **12c** following the general procedure D as white solid (42% yield).
mp: 135-136°C; ^{1}H NMR (400MHz, $CDCl_3$): δ= 1.17 (t, *J*= 7.2 Hz, 3H, CH_3), 1.64-1.68 (m, 2H, CHa-6, CHa-10 tasd), 1.73-2.00 (m, 6H, CH_2-3 chrom., CHb-6/CHb-10 tasd, CHa-3, CHa-5, CHb-3/CHb-5 pipd.), 2.44-2.56 (m, 4H, CH_2, CHa-7, CHa-9 tasd), 2.57-2.76 (m, 3H, CHb-6/CHb-10 tasd, CHa-2/CHa-6, CHb-2/CHb-6 pipd.), 2.78-3.01 (m, 4H, CHa-2/CHa-6, CHb-2/CHb-6, CHb-3/CHb-5 pipd., CHb-7/CHb-9 tasd), 3.32-3.45 (m, 1H, CHb-7/CHb-9 tasd), 4.09 (dd, *J*= 6.9, 10.8 Hz, 1H, CH-4 chrom), 4.72-4.84 (m, 2H, CH_2-2 tasd), 6.79-6.86 (m, 2H, CH-4 arom. tasd, CH-8 chrom.), 6.89-6.93 (m, 1H, CH-6 chrom.), 7.00-7.02 (d, *J*= 8.1 Hz, 2H, CH-2, CH-6 arom. tasd),

7.15-7.19 (ddd, *J*=1.3, 8.2, 7.0 Hz, 1H, CH-7 chrom.), 7.36 (t, *J*= 8.5 Hz, 2H, CH-3, CH-5 arom. tasd), 7.63 (bs, NH), 7.75 ppm (d, *J*= 7.5 Hz, 1H, CH-5 chrom.); ^{13}C NMR (400MHz, $CDCl_3$): δ= 12.0 (CH_3), 29.3 (C-6/C-10 tasd), 29.8 (C-3, C-5 pipd.), 31.8 (C-6/C-10 tasd), 37.97 (C-3 chrom.), 41.5 (C-7/C-9 tasd), 48.3 (C-7/C-9 tasd), 48.5 (C-2/C-6 pipd.), 48.6 (C-2/C-6 pipd.), 52.4 (CH_2), 56.2 (C-4 chrom.), 59.3 (C-2, C-5 tasd), 73.7 (C-2 chrom.), 114.5 (C-2, C-6 arom. tasd), 117.2 (C-8 chrom.), 118.3 (C-4 arom. tasd), 120.3 (C-6 chrom.), 123.0 (C-4a chrom.), 127.5 (C-5 chrom.), 128.1 (C-7 chrom.), 129.3 (C-3, C-5 arom. tasd), 143.2 (C-1 arom. tasd), 154.0 (C-8a chrom.), 178.5 ppm (C=O tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.
mp: 196-197°C; ^{1}H NMR (200MHz, DMSO): δ= 1.23 (t, *J*= 7.0 Hz, 3H, CH_3), 1.51-1.86 (m, 2H, CHa-6, CHa-10 tasd), 1.73-2.00 (m, 6H, CH_2-3 chrom., CHb-6/CHb-10 tasd, CHa-3, CHa-5, CHb-3/CHb-5 pipd.), 2.44-2.56 (m, 4H, CH_2, CHa-7, CHa-9 tasd), 2.57-2.76 (m, 3H, CHb-6/CHb-10 tasd, CHa-2/CHa-6, CHb-2/CHb-6 pipd.), 2.78-3.01 (m, 4H, CHa-2/CHa-6, CHb-2/CHb-6, CHb-3/CHb-5 pipd., CHb-7/CHb-9 tasd), 3.32-3.45 (m, 1H, CHb-7/CHb-9 tasd), 4.13 (m, 1H, CH-4 chrom.), 4.58-4.62 (m, 2H, CH_2-2 tasd), 6.79-6.86 (m, 2H, CH-4 arom. tasd, CH-8 chrom.), 6.89-6.93 (m, 1H, CH-6 chrom.), 7.00-7.02 (d, *J*= 8.2 Hz, 2H, CH-2, CH-6 arom. tasd), 7.15-7.19 (m, 1H, CH-7 chrom.), 7.36 (dd, *J*= 8.3, 8.5 Hz, 2H, CH-3, CH-5 arom. tasd), 7.63 (bs, NH), 7.75 ppm (d, *J*= 7.5 Hz, 1H, CH-5 chrom.).
HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{28}H_{37}N_4O_2$: 461.2911, found: 461.2926; Anal. Calcd for $C_{28}H_{36}N_4O_2 \cdot 2(COOH)_2 \cdot 2(H_2O)$: C 56.80, H 6.55, N 8.28, found C 56.15, H 6.12, N 8.16.

8-(1'-(methylsulfonyl)spiro[chroman-2,4'-piperidin]-4-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (13)

The compound was obtained from **13c** following the general procedure D as white solid (41% yield).
mp: 225-226°C; ^{1}H NMR (400MHz, $CDCl_3$): δ= 1.59-1.73 (m, 2H, CHa-6, CHa-10 tasd), 1.82-2.05 (m, 5H, CH_2-3 chrom., CHb-6/CHb-10 tasd, CHa-3, CHa-5 pipd.), 2.61-2.75 (m, 1H, CHb-6/CHb-10 tasd), 2.39-2.44 (m, 1H, CHa-7/CHa-9 tasd), 2.87 (s, 3H, CH_3), 2.88-3.04 (m, 5H, CHa-2/CHa-6, CHb-3,CHb-5 pipd., CHa-7/CHa-9, CHb-7/CHb-9 tasd), 3.23-3.34 (m, 1H, CHa-2/CHa-6 pipd.), 3.35-3.47 (m, 1H, CHb-7/CHb-9 tasd), 3.55-3.64 (m, 1H, CHb-2/CHb-6 pipd.), 3.69-3.77 (m, 1H, CHb-2/CHb-6 pipd.), , 4.05-4.15 (m, 1H, CH-4 chrom.), 4.78 (d, *J*= 4.5 Hz, 1H, CHa-2 tasd), 4.81 (d, *J*= 4.5 Hz, 1H, CHb-2 tasd), 6.87 (d, *J*= 8.1 Hz, 1H, CH-8 crom.), 6.92 (t, *J*= 7.4 Hz, 1H, CH-4 arom. tasd), 7.00-7.02 (m, 3H, CH-2, CH-6 tasd, CH-6 chrom.), 7.16-7.23 (m, 1H, CH-7 chrom.),

7.35-7.42 (dd, *J*= 7.3, 7.5 Hz, 2H, CH-3, CH-5 arom tasd), 7.59 (bs, NH), 7.77 ppm (d, *J*= 7.3 Hz, 1H, CH-5 chrom.); ^{13}C NMR (400MHz, $CDCl_3$): δ= 29.3 (C-6/C-10 tasd), 29.8 (C-3/C-5 pipd.), 30.0 (C-3/C-5 pipd.), 31.6 (C-6/C-10 tasd), 34.6 (CH_3), 37.6 (C-3 chrom.), 41.5 (C-7/C-9 tasd), 41.6 (C-2/C-6 pipd.), 41.7 (C-2/C-6 pipd.), 48.2 (C-7/C-9 tasd), 55.9 (C-4 arom. tasd), 59.3 (C-2, C-5 tasd), 72.8 (C-2 chrom.), 114.6 (C-2, C-6 arom. tasd), 117.1 (C-8 chrom.), 118.5 (C-4 arom. tasd), 120.9 (C-6 chrom.), 123.3 (C-4a chrom.), 127.7 (C-5 chrom.), 128.3 (C-7 chrom.), 129.3 (C-3, C-5 arom. tasd), 143.2 (C-1 arom. tasd), 153.5 (C-8a chrom.), 178.5 ppm (C=O tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.
mp: 254-256°C; ^{1}H NMR (200MHz, DMSO): δ= 1.62-1.67 (m, 2H, CHa-6, CHa-10 tasd), 1.74-1.92 (m, 5H, CH_2-3 chrom., CHb-6/CHb-10 tasd, CHa-3, CHa-5 pipd.), 2.14-2.19 (m, 1H, CHb-6/CHb-10 tasd), 2.56-2.59 (m, 1H, CHa-7/CHa-9 tasd), 2.79-2.87 (m, 5H, CHa-2/CHa-6, CHb-3,CHb-5 pipd., CHa-7/CHa-9, CHb-7/CHb-9 tasd), 2.92 (s, 3H, CH_3), 3.06-3.09 (m, 1H, CHa-2/CHa-6 pipd.), 3.17-3.23 (m, 1H, CHb-7/CHb-9 tasd), 3.33-3.36 (m, 1H, CHb-2/CHb-6 pipd.), 3.46-3.49 (m, 1H, CHb-2/CHb-6 pipd.), 4.05-4.15 (m, 1H, CH-4 chrom.), 4.37 (d, *J*= 4.5 Hz, 1H, CHa-2 tasd), 4.60 (d, *J*= 4.5 Hz, 1H, CHb-2 tasd), 6.79 (d, *J*= 8.1 Hz, 1H, CH-8 chrom.), 6.87 (t, *J*= 7.4 Hz, 1H, CH-4 arom. tasd), 6.95-7.01 (m, 3H, CH-2, CH-6 arom. tasd, CH-6 chrom.), 7.18-7.22 (m, 1H, CH-7 chrom.), 7.27-7.31 (m, 3H, CH-3, CH-5 arom. tasd, NH), 7.69 ppm (d, *J*= 7.3 Hz, 1H, CH-5 chrom.).
HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{27}H_{35}N_4O_4$: 511.2373, found: 511.2370; Anal. Calcd for $C_{29}H_{36}N_4O_8$: C 66.78, H 6.76, N 8.06, found C 65.31, H 7.21, N 7.99.

8-(1'-acetylspiro[chroman-2,4'-piperidin]-4-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (14)

The compound was obtained from **14c** following the general procedure D as white solid (34% yield).
mp: 227-228°C; ^{1}H NMR (400MHz, $CDCl_3$): δ= 1.39-1.57 (m, 1H, CHa-3/CHa-5 pipd.), 1.69-1.80 (m, 2H, CHa-3/CHa-5 pipd., CHa-6/CHa-10 tasd), 1.81-2.04 (m, 4H, CH_2-3 chrom., CHa-6/CHa-10 tasd, CHb-3/CHb-5 pipd.), 2.07-2.23 (m, 3H, CH_3), 2.43-2.57 (m, 1H, CHa-7/CHa-9 tasd), 2.60-2.75 (m, 1H, CHb-6/CHb-10 tasd), 2.81-3.02 (m, 3H, CHa-7/CHa-9, CHb-6/CHb-10 tasd, CHb-3/CHb-5 pipd.), 3.19-3.32 (m, 1H, CHa-2/CHa-6 pipd.), 3.52-3.64 (m, 2H, CHa-2/CHa-6, CHb-2/CHb-6 pipd.), 3.65-3.79 (m, 1H, CHb-7/CHb-9 tasd), 4.03-4.18 (m, 1H, CH-4 chrom.), 4.39-4.49 (m, 1H, CHb-2/CHb-6 pipd.), 4.73-4.86 (m, 2H, CH_2-2 tasd), 6.83-6.94 (m, 2H, CH-4 arom. tasd, CH-8 chrom.), 6.96-7.07 (m, 3H, CH-6 chrom., CH-2, CH-6 arom. tasd), 7.20 (dd, *J*= 7.5, 7.6 Hz,

1H, CH-7 chrom.) 7.38 (dd, *J*= 7.9, 8.0 Hz, 2H, CH-3, CH-5 arom. tasd), 7.76 ppm (d, *J*= 7.6 Hz, 1H, CH-5 chrom.); ^{13}C NMR (400MHz, $CDCl_3$): δ= 21.4 (CH_3), 29.3 (C-6/C-10 tasd), 29.8 (C-3/C-5 pipd.), 30.0 (C-3/C-5 pipd.), 31.6 (C-6/C-10 tasd), 37.7 (C-3 chrom.), 41.5 (C-7/C-9 tasd), 41.5 (C-2/C-6 pipd.), 42.1 (C-2/C-6 pipd.), 48.3 (C-7/C-9 tasd), 56.0 (C-4 chrom.), 59.3 (C-2, C-5 tasd), 73.8 (C-2 chrom.), 114.5 (C-2, C-6 arom. tasd), 117.3 (C-8 chrom.), 118.4 (C-4 arom. tasd), 120.7 (C-6 chrom.), 123.3 (C-4a chrom.), 127.7 (C-5 chrom.), 128.3 (C-7 chrom.), 129.3 (C-3, C-5 arom. tasd), 143.2 (C-1 arom. tasd), 153.7 (C-8a chrom.), 169.0 (C=O pipd.), 178.6 ppm (C=O tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.
mp: 185-187°C; ^{1}H NMR (200MHz, DMSO): δ= 1.31-1.92 (m, 7H, CHa-3, CHa-5 pipd., CHa-6, CHa-10 tasd, CH_2-3 chrom., CHb-3/CHb-5 pipd.), 1.98-2.23 (m, 3H, CH_3), 2.43-2.57 (m, 2H, CHa-7/CHa-9, CHb-6/CHb-10 tasd), 2.66-3.31 (m, 5H, CHa-7/CHa-9, CHb-7/CHb-9, CHb-6/CHb-10 tasd, CHa-2/CHa-6, CHb-3/CHb-5 pipd.), 3.37-3.73 (m, 3H, CHb-7/CHb-9 tasd, CHa-2/CHa-6, CHb-2/CHb-6 pipd), 3.90-4.45 (m, 2H, CH-4 chrom., CHb-2/CHb-6 pipd.), 4.47-4.71 (m, 2H, CH_2-2 tasd), 6.63-6.86 (m, 2H, CH-4 arom. tasd, CH-8 chrom.), 6.87-7.07 (m, 3H, CH-6 chrom., CH-2, CH-6 arom. tasd), 7.01-7.41 (m, 3H, CH-7 chrom., CH-3, CH-5 arom. tasd), 7.66 (d, *J*= 7.4 Hz, 1H, CH-5 chrom.).
HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{28}H_{35}N_4O_3$: 475.2703, found: 475.2710; Anal. Calcd for $C_{30}H_{38}N_4O_8$: C 61.84, H 6.57, N 9.62, found C 61.88, H 6.48, N 9.36.

Cis 1-phenyl-8-(2-phenylchroman-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one (15)
The compound was obtained from **15c** following the general procedure D as white solid (29% yield).
mp: 254-255°C; ^{1}H NMR (400MHz, $CDCl_3$): δ= 1.64-1.72 (m, 1H, CHa-6/CHa-10 tasd), 1.79-1.90 (m, 1H, CHa-6/CHa-10 tasd), 2.15-2.24 (m, 1H, CHa-3 chrom.), 2.27-2.38 (m, 1H, CHb-3 chrom.), 2.54-2.64 (m, 1H, CHa-7/CHa-9 tasd), 2.65-2.76 (m, 1H, CHb-6/CHb-10 tasd), 2.86-3.03 (m, 3H, CHb-6/CHb-10 tasd, CHa-7/CHa-9 tasd, CHb-7/CHb-9 tasd), 3.39-3.52 (m, 1H, CHb-7/CHb-9 tasd), 4.37 (dd, *J*= 5.4, 11.6 Hz, 1H, CH-4 chrom.), 4.73-4.84 (m, 2H, CH_2-2 tasd), 5.17 (d, *J*= 11.2 Hz, 1H, CH-2 chrom.), 6.88-6.97 (m, 2H, CH-8 chrom., CH-4 arom tasd), 6.98-7.07 (m, 3H, CH-2, CH-6 arom. tasd, CH-6 chrom.), 7.12 (s, 1H, NH), 7.21 (dd, *J*= 7.4, 7.8Hz, 1H, CH-7 chrom.), 7.33-7.44 (m, 3H, CH-3, CH-5 arom. tasd, CH-4 phen.), 7.46 (dd, *J*= 7.4, 7.6 Hz, 2H, CH-3, CH-5 phen.), 7.52 (d, *J*= 7.4 Hz, 2H, CH-2, CH-6 phen.), 7.79 ppm (d, *J*= 7.7 Hz, 1H, CH-5 chrom.); ^{13}C NMR (400MHz, $CDCl_3$): δ= 28.7 (C-3 chrom.), 28.9 (C-6/C-10 tasd), 29.6 (C-6/C-10 tasd), 41.1 (C-7/C-9 tasd), 48.0 (C-7/C-9 tasd), 58.9 (C-4 chrom.), 59.0 (C-2 tasd), 60.1 (C-5 tasd), 77.7 (C-2

chrom.), 114.2 (C-2, C-6 arom. tasd), 116.6 (C-8 chrom.), 118.1 (C-4 arom. tasd), 120.5 (C-6 chrom.), 123.7 (C-4a chrom), 125.7 (C-4 phen.), 127.1 (C-2, C-6 phen.), 127.8 (C-7 chrom.), 128.3 (C-3, C-5 phen.), 128.4 (C-5 chrom.), 129.0 (C-3, C-5 arom. tasd), 141.3 (C-1 phen.), 142.9 (C-1 arom. tasd), 155.8 (C-8a chrom.), 177.9 ppm (C=O tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.
mp: 183-184°C, ^{1}HNMR (200MHz, DMSO): δ= 1.51-1.66 (m, 1H, CHa-6/CHa-10 tasd), 1.66-1.78 (m, 1H, CHa-6/CHa-10 tasd), 1.93-2.05 (m, 1H, CHa-3 chrom.), 2.19-2.37 (m, 1H, CHb-3 chrom.), 2.49-2.52 (m, 1H, CHa-7/CHa-9 tasd), 2.71-2.87 (m, 1H, CHb-6/CHb-10 tasd), 2.89-3.03 (m, 3H, CHb-6/CHb-10, CHa-7/CHa-9, CHb-7/CHb-9 tasd), 3.38-3.59 (m, 1H, CHb-7/CHb-9 tasd), 4.52-4.66 (m, 3H, CH_2-2 tasd, CH-4 chrom.), 5.21 (d, *J*= 11.2 Hz, 1H, CH-2 chrom.), 6.79 (t, *J*= 7.2 Hz, 1H, CH-4 arom. tasd), 6.86 (d, 1H, J= 8.0 Hz, CH-8 chrom.), 6.96 (d, 2H, *J*= 8.2 Hz, CH-2, CH-6 arom. tasd), 7.02 (dd, *J*= 7.3, 7.4 Hz, 1H, CH-6 chrom.), 7.19 (dd, *J*= 7.2, 7.7 Hz, 1H, CH-7 chrom.), 7.30 (dd, *J*= 7.6, 8.3 Hz, 2H, CH-3, CH-5 arom. tasd) 7.37 (t, *J*= 7.1 Hz, 1H, CH-4 phen.), 7.43 (dd, *J*= 7.1, 7.6 Hz, 2H, CH-3, CH-5 phen.), 7.52 (d, *J*= 7.1 Hz, 2H, CH-2, CH-6 phen.), 7.69 (d, *J*= 7.5 Hz, 1H, CH-5 chrom.).
HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{28}H_{30}N_3O_2$: 440.2332, found: 440.2341; Anal. Calcd for $C_{30}H_{31}N_3O_6 \cdot (H_2O)$: C 65.80, H 6.07, N 7.67, found C 65.67, H 5.85, N 7.56.

1-phenyl-8-(spiro[chroman-2,4'-piperidin]-4-yl)-1,3,8-triazaspiro[4.5]decan-4-one (16)
To a stirred solution of NaOH 10% (3.9 mL) in methanol (5 mL), compound **14** (0.18 g, 0.38 mmol) was added portionwise; the resulting mixture was stirred and refluxed overnight. Once the reaction was completed, methanol was evaporated under vacuum. Water and EtOAc were added to the residue and HCl 1M to neutralize. The aqueous phase was extracted with EtOAc, the organic layers were combined, dried over anhydrous Na_2SO_4 and the suspension obtained was filtered. The solution was the then concentrated under vacuum to yield the desired compound (0.160 g, 0.37 mmol, 97% yield).
mp: 271-272°C; ^{1}H NMR (400MHz, $CDCl_3$): δ= 1.43-1.57 (m, 1H, CHa-6/CHa-10 tasd), 1.58-1.66 (m, 1H, CHa-6/CHa-10 tasd), 1.71-2.03 (m, 6H, CH_2-3 chrom., CHb-6/CHb-10 tasd, CHa-3, CHa-5, CHb-3/CHb-5 pipd.), 2.44-2.59 (m, 1H, CHa-7/CHa-9 tasd), 2.60-2.74 (m, 1H, CHb-6/CHb-10 tasd), 2.75-3.10 (m, 6H, CHa-7/CHa-9 tasd, CHb-3/CHb-5, CH_2-2, CH_2-6 pipd.), 3.17-3.38 (m, 1H, CHb-7/CHb-9 tasd), 3.38-3.44 (m, 1H, CHb-7/CHb-9 tasd), 4.14 (dd, *J*= 6.0, 11.4 Hz, 1H, CH-4 chrom.), 4.58-4.81 (m, 2H, CH_2-2 tasd), 6.77-6.97 (m, 3H, CH-4 arom. tasd, CH-6, CH-8 chrom.), 6.99 (d, *J*= 8.1 Hz, 2H, CH-2, CH-6 arom. tasd), 7.19 (dd, *J*= 7.2 ,7.6 Hz, 1H, CH-7 chrom.), 7.38

(dd, *J*= 7.4, 8.1 Hz, 2H, CH-3, CH-5 arom. tasd), 7.75 (d, *J*= 7.6 Hz, 1H, CH-5 chrom.); ^{13}C NMR (400MHz, $CDCl_3$): δ= 29.3 (C-6/C-10 tasd), 29.9 (C-3/C-5 pipd.), 30.0 (C-3/C-5 pipd.), 32.4 (C-6/C-10 tasd), 38.5 (C-3 chrom.), 41.4 (C-7/C-9 tasd, C-2, C-6 pipd.), 48.3 (C-7/C-9 tasd), 55.9 (C-4 chrom.), 59.4 (C-2 tasd, C-5 tasd), 73.9 (C-2 chrom.), 114.4 (C-2, C-6 arom. tasd), 117.3 (C-8 chrom.), 118.3 (C-4 arom. tasd), 120.5 (C-6 chrom.), 123.4 (C-4a chrom.), 127.6 (C-5 chrom.), 128.2 (C-7 chrom.), 129.3 (C-3, C-5 arom. tasd), 143.2 (C-1 arom. tasd), 154.0 (C-8a chrom.), 178.7 ppm (C=O tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.
mp: 210-211°C; ^{1}H NMR (200MHz, DMSO): δ= 1.42-1.574 (m, 1H, CHa-6/CHa-10 tasd), 1.54-1.63 (m, 1H, CHa-6/CHa-10 tasd), 1.64-1.76 (m, 2H, CH_2-3 chrom.), 1.78-2.00 (m, 4H, CHb-6/CHb-10 tasd, CHa-3, CHa-5, CHb-3/CHb-5 pipd.), 2.16-2.37 (m, 1H, CHa-7/CHa-9 tasd), 2.58-2.72 (m, 1H, CHb-6/CHb-10 tasd), 2.61-2.82 (m, 4H, CHb-3/CHb-5, CH_2-2, CHa-6/CHb-6 pipd.), 3.121-3.44 (m, 4H, CHa-7/CHa-9, CHb-7, CHb-9 tasd, CHa-6/CHb-6 pipd.), 4.21 (m, 1H, CH-4 chrom.), 4.58-4.81 (m, 2H, CH_2-2 tasd), 6.70 (dd, *J*= 7.4, 7.5 Hz, 1H, CH-6 chrom.), 6.78 (d, *J*= 8.2 Hz, 1H, CH-8 chrom.), 6.82-6.96 (m, 3H, CH-4, CH-2, CH-6 arom. tasd), 7.10 (dd, *J*= 7.4, 8.2 Hz, 1H, CH-7 chrom.), 7.21 (dd, *J*= 7.6, 8.3 Hz, 2H, CH-3, CH-5 arom. tasd), 7.59 ppm (d, *J*= 7.5 Hz, 1H, CH-5 chrom.).
HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{26}H_{33}N_4O_2$: 433.2598, found: 433.2616; Anal. Calcd for $C_{30}H_{36}N_4O_{10}$ ($C_{26}H_{32}N_4O_2 \cdot 2\ (COOH)_2$): C 58.82, H 5.92, N 9.15, found C 58.52, H 5.73, N 9.02.

8-(3,3-dimethylchroman-4-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (17)
The compound was obtained from **17c** following the general procedure D as white solid (36% yield).
mp: 230-232 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ= 0.94 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.57-1.61 (m, 1H, CHa-6/CHa-10 tasd), 1.66-1.70 (m, 1H, CHa-6/CHa-10 tasd), 2.34 (m, 1H, CHa-7/CHa-9 tasd), 2.62-2.69 (m, 1H, CHb-6/CHb-10 tasd), 2.75-2.83 (m, 2H, CHb-6/CHb-10 tasd, CHa-7/CHa-9 tasd), 2.92-2.96 (m, 1H, CHb-7/CHb-9 tasd), 3.29 (s, 1H, CH-4 chrom.), 3.45-3.51 (m, 1H, CHb-7/CHb-9 tasd), 3.70 (d, *J*= 10.6 Hz, 1H, CHa-2 chrom), 3.95 (d, *J*= 10.6 Hz, 1H, CHb-2 chrom.), 4.71-4.79 (m, 2H, CH_2-2 tasd), 6.78-6.92 (m, 5H, CH-6, CH-8 chrom.; CH-2, CH-4, CH-6 arom. tasd), 7.13-7.18 (m, 1H, CH-7 chrom.), 7.18 (dd, *J*= 7.5 Hz, 1H, CH-5 chrom.), 7.27 (dd, *J*= 7.6, 8.2 Hz, 2H, CH-3, CH-5 arom. tasd), 7.77 (bs, 1H, NH); ^{13}C NMR (400MHz, $CDCl_3$): δ= 21.5 (CH_3), 24.2 (CH_3), 29.7 (C-6, C-10 tasd), 34.8 (C-3 chrom.), 48.2 (C-7/C-9 tasd), 52.4 (C-7/C-9 tasd), 59.1 (C-2 tasd), 59.2 (C-5 tasd), 67.7 (C-4 chrom.), 72.1 (C-2 chrom.), 114.3 (C-2, C-6 arom. tasd),

115.9 (C-8 chrom.), 118.0 (C-4 arom. tasd), 119.6 (C-6 chrom.), 120.9 (C-4a chrom.), 128.2 (C-7 chrom.), 128.9 (C-3, C-5 arom. tasd), 131.2 (C-5 chrom.), 143.0 (C-1 arom. tasd), 155.7 (C-8a chrom.), 178.6 ppm (CO tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.
mp: 80-81 °C, ^{1}H NMR (200MHz, DMSO): δ= 0.88 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.45-1.61 (m, 2H, CHa-6, CHa-10 tasd), 2.31-2.99 (m, 5H, 2·CHa-7/CHa-9 tasd, 2·CHb-6/CHb-10 tasd, CHb-7/CHb-9 tasd), 3.48-3.54 (m, 2H, CHb-7/CHb-9 tasd, CH-4 chrom.), 3.74 (d, *J*= 10.9 Hz, 1H, CHa-2 chrom.), 3.92 (d, *J*= 10.9 Hz, 1H, CHb-2 chrom.), 4.55 (s, 2H, CH_2-2 tasd), 6.72-6.93 (m, 5H, CH-6 chrom.; CH-2, CH-4, CH-6 arom. tasd, NH), 7.13-7.27 (m, 5H, CH-5, CH-7, CH-8 chrom., CH-3, CH-5 arom. tasd), 8.58 ppm (s, 1H, oxalic ac.).
HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{24}H_{30}N_3O$: 392.2333, found: 392.2319; Anal. Calcd for $C_{26}H_{31}N_3O_6\cdot(COOH)_2$: C 58.84; H, 5.82; N, 7.35, found C, 58.79; H, 5.44; N, 7.16.

8-(5-fluorochroman-4-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (18)
The compound was obtained from **18c** following the general procedure D as white solid (52% yield).
mp: 97-98 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ= 1.64-1.69 (m, 1H, CHa-6/CHa-10 tasd), 1.78-1.85 (m, 1H, CHa-6/CHa-10 tasd), 1.96-2.02 (m, 1H, CHa-3 chrom.), 2.05-2.14 (m, 1H, CHb-3 chrom.), 2.54-2.62 (m, 2H, CHb-6/CHb-10 tasd, CHa-7/CHa-9 tasd), 2.78-2.87 (m, 3H, CHb-6/CHb-10 tasd, CHa-7/CHa-9 tasd, CHb-7/CHb-9 tasd), 3.27-3.34 (m, 1H, CHb-7/CHb-9 tasd), 3.89 (dd, *J*= 5.9, 8.4 Hz, 1H, CH-4 chrom.), 4.07-4.16 (m, 1H, CHa-2 chrom.), 4.34-4.39 (m, 1H, CHb-2 chrom.), 4.74 (dd, *J*= 4.3, 7.7 Hz, 2H, CH_2-2 tasd), 6.48 (dd, *J*= 2.5, 10.2 Hz, 1H, CH-8 chrom.), 6.61 (ddd, *J*= 2.5, 8.3, 8.4 Hz, 1H, CH-6 chrom.), 6.86 (t, *J*= 7.3 Hz, 1H, CH-4 arom. tasd), 6.93 (d, *J*= 8.3 Hz, 2H, CH-2, CH-6 arom. tasd), 7.31-7.39 (m, 2H, CH-3, CH-5 arom. tasd), 7.53-7.59 (m, 1H, CH-7 chrom.), 7.58 ppm (bs, 1H, NH); ^{13}C NMR (400MHz, $CDCl_3$): δ= 21.2 (C-3 chrom.), 29.1 (C-6/C-10 tasd), 29.5 (C-6/C-10 tasd), 42.2 (C-7/C-9 tasd), 47.8 (C-7/C-9 tasd), 58.2 (C-4 chrom.), 59.1 (C-5 tasd), 59.2 (C-2 tasd), 65.4 (C-2 chrom.), 103.5 (C-8 chrom.), 107.3 (C-6 chrom.), 114.5 (C-2, C-6 arom. tasd), 118.4 (C-4 arom. tasd), 119.5 (C-4a chrom.), 129.0 (C-3, C-5 arom. tasd), 129.4 (C-7 chrom.), 142.9 (C-1 arom. tasd), 156.4 (C-8a chrom.), 156.5 (C-5 chrom.), 178.4 ppm (CO tasd).

The free amine was then converted in the corresponding hydrogenoxalate from acetone.

mp: 141-142 °C; ^{1}H NMR (200MHz, DMSO): δ= 1.70 (m, 2H, CHa-6/CHa-10 tasd), 2.08-2.14 (m, 2H, CH_2-3 chrom.), 2.57-2.80 (m, 2H, CHb-6/CHb-10 tasd, CHa-7/CHa-9 tasd), 3.05-3.17 (m, 2H, CHa-7/CHa-9 tasd, CHb-7/CHb-9 tasd), 3.50-3.57 (m, 1H, CHb-7/CHb-9 tasd), 4.15-4.40 (m, 3H, CH-4, CH_2-2 chrom.), 4.59-4.67 (m, 2H, CH_2-2 tasd), 6.66 (dd, *J*= 2.6, 10.5 Hz, 1H, CH-8 chrom.), 6.74-6.84 (m, 2H, CH-4 arom. tasd; C-6 chrom.), 6.93 (d, *J*= 8.2 Hz, 2H, CH-2, CH-6 arom. tasd), 7.26-7.34 (m, 2H, CH-3, CH-5 arom. tasd), 7.58-7.64 (m, 1H, CH-7 chrom.), 8.77 ppm (bs, 1H, oxalic ac.).

HRMS-ESI *m/z* $[M+H]^+$ calc. for $C_{22}H_{25}FN_3O_2$: 382.1925, found: 382.1928; Anal. Calcd for $C_{24}H_{26}FN_3O_6$: C, 61.14; H, 5.54; N, 8.91, found C, 60.66; H, 5.55; N, 8.50.

Crystallography

X-ray diffraction data on a single crystal of (+)-*R*-**4**·$H_2C_2O_4$·1/2H_2O were collected at 140(2) K on an Oxford Diffraction Xcalibur3 four-circle diffractometer equipped with an Onyx CCD detector, Enhance (Cu) X-ray Source and a Cryostream 600 cryostat. $C_{24}H_{28}N_3O_{6.50}$,M_r = 462.49 g mol^{-1}, crystal size 0.34 ×0.18 ×0.13 mm, orthorhombic, space group $P2_12_12_1$,a = 13.65385(7)Å, b = 16.90593(8) Å, c = 18.91252(8)Å, V = 4365.60(4) Å^3,T = 140(2) K, Z = 8, D_{calc} =1.407 g cm^{-3},λ = 1.54184Å, μ($Cu_{K\alpha}$) = 0.856 mm^{-1}, 48692 reflections collected, R_{int} = 0.0306, θ_{max} = 72.32°, data/parameters/restraints:8473/744/34, $wR2$ = 0.0937,$R1$ = 0.0331 (on data with I> 2σ(I)), GoF = 1.132. The asymmetric unit contains two (+)-*R*-**4** molecules protonated on the piperidine nitrogen atom and showing identical absolute configuration, two hydrogenoxalate anions and one water molecule, interacting through a network of hydrogen bonds. One hydrogenoxalate is disordered over two positions with 0.82:0.18 occupancies. Absolute configuration was determined by anomalous-dispersion effects in diffraction measurements. Flack parameter was -0.01(14) for the correct and 1.00(14) for the inverted structure. CCDC 982474 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Computational methods

All the ligand structures were constructed using the software Spartan'08 (Wavefunction Inc., 18401 Von Karman Avenue, Suite 370 Irvine, CA 92612) installed on an Intel Pentium 4 computer employing the crystal structure of (+)-*R*-**4** as input file. The NOP receptor (PDB code 4EA3) was imported in MVD (Molegro Virtual Docker) and all water molecules and ligand were deleted. The receptor was prepared employing the option implemented in the software. The docking was

performed with a maximum of 5 cavity detected using a sphere with a 15 Å of radius centered on the Asp-130 (X=-34,68, Y= 50.2, Z= 7.80). A distance constrained (4 Å) between the piperidine nitrogen of the ligands and the carbonyl moiety of Asp-130 was selected. All docking calculations were carried out using the grid-based MolDock score (GRID) function with a grid resolution of 0.30 Å. The MolDock optimization search algorithm with a maximum of 100 runs was used through the calculations, with all other parameters kept as defaults and with a maximum of 10 poses returned for each run. The docking protocol was initially validated on the peptide mimetic antagonist "C-24" to verify whether the docking method can reproduce the crystal binding model. The average root-mean- square distance (rmsd) of the best ranking pose of the compound as compared to its binding pose in the respective crystal structures was found to be 0.68 Å. The value of the other poses obtained where within 2.00 Å proving that MVD is able to accurately dock this type of compounds (Figure 1).

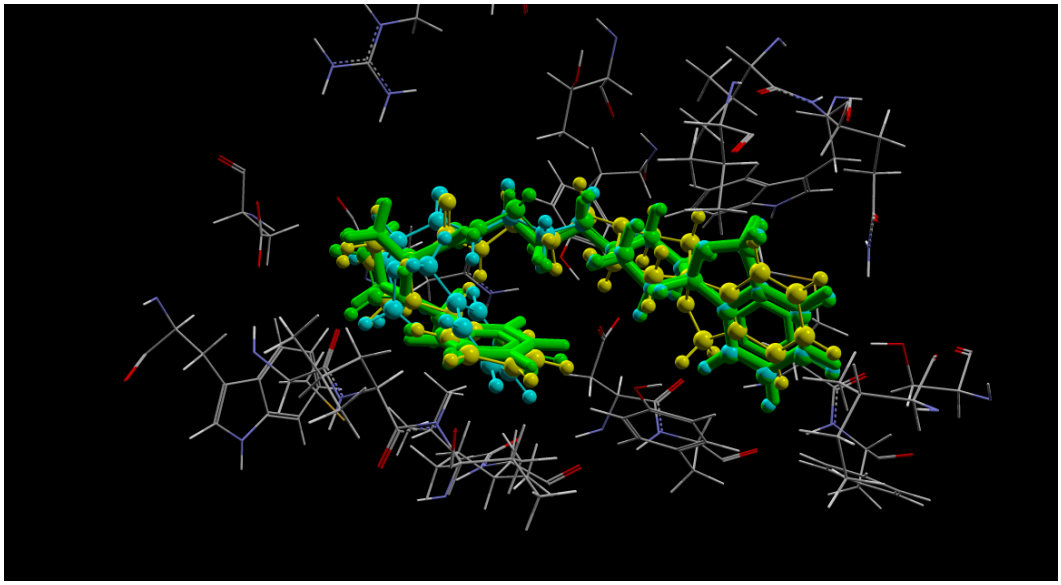

Figure 1. Best poses obtained for C-24 antagonist employing MVD software.

The protocol was then applied on selected compounds. The results were analysed manually and the best poses were retained. Minimization of the sidechains of the amino acids within 4 Å from the best pose obtained was performed in order to increase docking efficiency.