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On the Way to Selective PARP-2 Inhibitors. Design, Synthesis and Preliminary Evaluation of a Series of Isoquinolinone Derivatives

Roberto Pellicciari, Emidio Camaioni, Gabriele Costantino, Laura Formentini, Paola Sabbatini, Francesco Venturoni, Gocken Eren, Daniele Bellocchi, Alberto Chiarugi, and Flavio Moroni

Contents:

Experimental data

General procedure A: To a solution of hydroxyl-derivative (1 mmol) in MeOH (5 mL), NaOH (0.04 g, 1 mmol) was added and refluxed for 30 min. The reaction mixture was then evaporated under reduced pressure and the residue was taken-up with water (12 mL). The residue was then opportunely divided in the Carosel tubes and treated with the suitable aryl-chloride or -bromide reagent (5 mmol) and nBu_4NHSO_4 (0.02 mmol); the obtained suspension was heated overnight at 95 °C. The reaction mixture was then acidified by 3N HCl and extracted with EtOAc. The organic layers were collected, washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The mixture was submitted to flash chromatography thus obtain the desired derivatives. These compounds were obtained as pure solid after crystallization by a mixture of ethyl acetate/n-hexane (about 9:1).

General procedure B: To a solution of hydroxyl-derivative (1 mmol) in dry DMF (5 mL), K_2CO_3 (5 mmol) and the suitable halide reagent (1.2 mmol) were added and the mixture was stirred in the carosel® tubes at room temperature for 16 h. H_2O (20 mL) was then added to the reaction mixture and extracted with EtOAc. The organic layers were collected, dried over Na_2SO_4 and evaporated under reduced pressure. The mixture was submitted to flash chromatography thus obtain the desired derivatives. These compounds were obtained as pure solid after crystallization by a mixture of ethyl acetate/n-hexane (about 9:1).

5-hydroxy-3,4-dihydroisoquinolin-1(2*H*)-one (4) and 5-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (11): To a solution of 4-hydroxyindan-1-one (**10**) (5.0 g, 33.8 mmol) in trichloroacetic acid (110.0 g, 675.6 mmol) preheated at 90°C, sodium azide (4.4 g, 67.6 mmol) was added portionwise and the resulting mixture was stirred at 90°C for 4 h. The reaction mixture was then cooled, poured into cracked ice (about 250 mL) and neutralized by adding $NaHCO_3$ (56.8 g, 675.6 mmol). The acqueous phase was extracted with EtOAc (8 x 200 mL) and the organic layers were collected, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography (light petroleum/ EtOAc = 1:1) and crystallizated (from EtOAc/hexane) to obtain **4** (3.16 g, 57%) and **11** (1.38 g, 25%) as solids. Analytical data of compound **4**[1,2] and **11**[3] are in agreement with those reported in the literature.

5-hydroxyisoquinolin-1(2*H*)-one (5): 5-Isoquinoline sulfonic acid (**12**) (2 g, 9.6 mmol) was fused with sodium and potassium hydroxyde (4 g, 1:1) at 230°C for 1h. The mixture was allowed to cooled at room temperature and added of H_2O (20 mL) and the resulted mixture was acidified up to pH 4 with 6N HCl. This acqueous mixture was then extracted

with EtOAc (5 x 150 mL), the organic layers were collected, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH = 98:2) to afford **5** (0.52 g, 34%) as solid. Analytical data are in agreement with those reported in the literature.[20]

Methyl 2-methyl-3-methoxybenzoate (14): To a suspension of the 2-methyl-3-methoxybenzoic acid (**13**) (1.0 g, 6.02 mmol) in toluene (10 mL), $SOCl_2$ (0.65 mL, 9.03 mmol) and DMF (0.05 ml) were added and the resulting mixture was refluxed for 2 h. The reaction mixture was evaporated under reduced pressure and the residue was dissolved in MeOH (30 mL) at 0°C and stirred at room temperature overnight. The reaction mixture was evaporated under reduced pressure, the residue dissolved in EtOAc (40 mL), washed with saturated $NaHCO_3$ water solution (30 mL), water (30 mL), dried over Na_2SO_4 and evaporated under reduced pressure to provide **14** (0.99 g, 92%) as yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz): *d*= 2.42 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 6.98 (bd, 1H), 7.21 (dd, *J*= 5.5 and 13.6 Hz, 1H), 7.40 (dd, *J*= 1.2 and 7.8 Hz, 1H).

Methyl 2-methyl-3-bromomethylbenzoate (15): To a solution **14** (1.0 g, 5.50 mmol) and AIBN (0.009 g, 0.055 mmol) in CCl_4 (10 mL), NBS (0.98 g, 5.50 mmol) was added and the mixture was refluxed for 12 h. The reaction mixture was then cooled, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (light petroleum/ EtOAc = 8:2) to obtain **15** (0.94 g, 65%) as a colourless oil; ^{1}H NMR ($CDCl_3$, 200 MHz): *d*= 3.93 (s, 3H), 3.94 (s, 3H), 5.06 (s, 2H), 7.07 (dd, *J*= 0.9 and 8.0 Hz, 1H), 7.34 (t, *J*= 8.2 Hz, 1H), 7.53 (dd, *J*= 1.26 and 7.8 Hz, 1H).

4-Methoxyisoindolin-1-one (16): To a solution of **15** (0.31 g, 1.19 mmol) in MeOH (50 mL), NH_3 was bubbled to saturation and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was evaporated to under reduced pressure to obtain the 4-methoxy isoindolin-1-one **16** (0.18g, 95%) as white solid that was utilized without further purifications: mp: >200°C; ^{1}H NMR (DMSO-d_6, 200 MHz): *d*= 3.83 (s, 3H), 4.15 (s, 2H), 7.20 (m, 2H), 7.43 (d, *J*= 7.4 Hz, 1H), 8.60 (bs, 1H).

4-Hydroxyisoindolin-1-one (6): A suspension of **16** (0.30 g, 1.8 mmol) in BBr_3 2M in CH_2Cl_2 (5.5 mL, 11.00 mmol) was refluxed for 3 h. The rection mixture was then cooled, poured into water (50mL) and extracted with EtOAc (8 x 15 mL). The organic layers were collected, dried over Na_2SO_4 and evaporated under reduced pressure to obtain **6** (0.20 g, 73%) as a white solid. Analytical data are in agreement with those reported in the literature.[4]

2-Methyl-3-methoxybenzamide (17): To a solution of 2-methyl-3-methoxy benzoic acid (**13**) (0.71 g, 4.3 mmol) and CDI (1.20 g, 7.40 mmol) in THF (15 mL), NH_3 was bubbled up to saturation and the reaction mixture was refluxed for 2 h. The reaction mixture was then cooled, poured into water (30 mL) and extracted with EtOAc (3 x 20 mL). The collected organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by crystallization from EtOAc to afford **17** (0.6 g, 85%).as white solid. Analytical data are in agreement with those reported elsewere.[1]

2-Methyl-3-hydroxybenzamide (7): To a solution of **17** (0.40 g, 2.40 mmol) in CH_2Cl_2 (8 mL) BBr_3 2M in CH_2Cl_2 (6.0 mL, 12.0 mmol) was added and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then evaporated under reduced pressure, the residue was dissolved with water (30 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were collected, washed with saturated $NaHCO_3$ water solution (30 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by crystallization from EtOAc to provide **6** (0.28 g, 79%). Analytical data are in agreement with those reported in the literature.[1]

3-Hydroxy-*N*-methylbenzamide (8): To a suspension of 3-hydroxybenzoic acid **18** (1.00 g, 7.25 mmol) in toluene (10 mL) was added $SOCl_2$ (0.79 mL, 10.87 mmol), and the reation mixture was refluxed overnight. The mixture was then cooled and evaporated under reduced pressure. The residue was dissolved in dry THF (15 mL), cooled to 0°C and added dropwise to solution of methylamine (2M in THF) (1.9 mL, 38 mmol) and stirred at room temperature for 5 h. The reaction mixture was then evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH = 9.6:0.4) to obtain **8** (0.43 g, 38%) as white solid: mp: 130-132°C; ^{1}H NMR (DMSO-d_6, 200 MHz): d= 2.71 (s, 3H), 6.84-6.92 (m, 1H), 7.19-7.22 (m, 3H,), 8.29 (bs,1H), 9.65 (m, 1H).

3-Hydroxybenzamide (9): To a suspension of 3-hydroxybenzoic acid (**18**) (1.00 g, 7.25 mmol) in benzene (10 mL) was added $SOCl_2$ (0.79 mL, 10.87 mmol), and the reation mixture was refluxed overnight. The mixture was then cooled and evaporated under reduced pressure. The residue was dissolved in dry THF (15 mL) and NH_3 was bubbled up to saturation and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was then poured into brine (60 mL) and extracted with EtOAc (5 x 30 mL). The organic layers were collected, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH = 9.4:0.6) to provide **9** (0.39 g, 40%). Analytical data are in agreement with those reported elsewere.[5]

5-(3-Chlorobenzoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (20): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 3-chlorobenzoylchloride (1.06 g, 6.1 mmol) the title compound **20** was obtained as pure solid (0.138 g, 37 %): mp 178-179 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 2.91 (t, *J*= 6.6 Hz, 2H), 3.57 (dt, *J*= 1.7 and 6.3 Hz, 2H), 6.49 (bs, 1H), 7.34 (, d, *J*= 8.0 Hz, 1H), 7.44 (t, *J*= 7.9 Hz, 1H), 7.49 (t, *J*= 7.9 Hz, 1H), 7.65 (dd, *J*= 0.9 and 8.0 Hz, ArH), 8.05 (d, *J*= 7.6 Hz, 1H), 8.10 (d, *J*= 7.8 Hz, 1H), 8.20 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 22.45, 39.51, 125.71, 126.08, 127.59, 128.26, 130.00, 130.14, 130.50, 131.21, 133.91, 134.88, 147.16, 163.37, 165.35; anal.: calcd for $C_{16}H_{12}ClNO_3$: C 63.69%, H 4.01%, N 4.64%, found: C 63.75%, H 3.71%, N 4.84%.

5-(4-Chlorobenzoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (21): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 4-chlorobenzoylchloride (1.06 g, 6.1 mmol) the title compound **21** was obtained as pure solid (0.156 g, 42 %): mp 225-226 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 2.90 (t, *J*= 6.7 Hz, 2H), 3.56 (dt, *J*= 2.5 and 6.7 Hz, 2H), 6.91 (bs, 1H), 7.34 (dd, *J*= 1.3 and 8.1 Hz, 1H), 7.43 (t, *J*= 8.0 Hz, 1H), 7.50-7.53 (m, 2H), 8.04 (dd, *J*= 1.2 and 7.7 Hz, 1H), 8.13-8.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 22.41, 39.45, 125.74, 125.94, 127.20, 127.53, 129.06, 130.51, 131.28, 131.50, 140.50, 147.22, 163.71, 165.56; anal.: calcd for $C_{16}H_{12}ClNO_3$: C 63.69%, H 4.01%, N 4.64%, found: C 63.45%, H 3.98%, N 4.55%.

5-(2-Fluorobenzoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (22): Following the general procedure B starting from **4** (0.2 g, 1.22 mmol) and 2-fluorobenzoylchloride (0.23 g, 1.47 mmol) the title compound was obtained as pure solid (0.130 g, 37 %); mp 159-160 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 2.97 (t, *J*= 6.5 Hz, 2H), 3.58 (t, *J*= 6.3 Hz, 2H), 6.29 (bs, 1H), 7.22-7.25 (m, 1H), 7.31 (dt, *J*= 1.0 and 7.6 Hz, 1H), 7.38-7.46 (m, 2H), 7.63-7.66 (m, 1H), 8.05 (dd, *J*= 1.5 and 7.4 Hz, 1H), 8.11 (dt, *J*= 1.8 and 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 22.41, 39.58, 116.13, 116.89, 117.22 ($^{2}J_{C\text{-}F}$= 22.3 Hz), 117.35, 124.23, 125.93 ($^{3}J_{C\text{-}F}$= 13.0 Hz), 127.50, 130.30, 131.19, 132.54, 135.51 ($^{3}J_{C\text{-}F}$= 9.2 Hz), 147.15, 160.91, 165.38; anal.: calcd for $C_{16}H_{12}FNO_3$: C 67.36%, H 4.24%, N 4.91%, found: C 67.31%, H 4.26%, N 4.78%.

5-(4-Fluorobenzoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (24): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 4-fluorobenzoylchloride (0.967 g, 6.1 mmol) the title compound **24** was obtained as pure solid (0.184 g, 53 %): mp 193-194 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 2.91 (t, *J*= 6.7 Hz, 2H), 3.57 (dt, *J*= 2.7 and 6.7 Hz, 2H), 6.86 (bs, 1H), 7.19-7.24 (m, 2H), 7.35 (dd, *J*= 1.2 and 8.1 Hz, 1H), 7.43 (t, *J*= 7.9 Hz, 1H), 8.05 (dd, *J*= 1 and 7.7 Hz, 1H), 8.22-8.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 22.37,

39.46, 116.04 ($^2J_{C\text{-}F}$= 22.2 Hz), 124.98, 125.89, 127.56, 130.35, 131.31, 132.46, 132.81 ($^3J_{C\text{-}F}$= 9.4 Hz), 147.28, 164.06 ($^1J_{C\text{-}F}$= 155.6 Hz), 165.74, 167.55; anal.: calcd for $C_{16}H_{12}FNO_3$: C 67.36%, H 4.24%, N 4.91%, found: C 67.66%, H 4.05%, N 5.12%.

5-(4-Bromobenzoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (25): Following the general procedure B starting from 4 (0.15 g, 0.92 mmol) and 4-bromobenzoylchloride (0.24 g, 1.1 mmol) the title compound **25** was obtained as pure solid (0.055 g, 0.16 mmol, 18 %); mp 240-241 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 2.91 (t, *J*= 5.8 Hz, 2H), 3.56 (t, *J*= 5.1 Hz, 2H), 6.47 (bs, 1H), 7.35 (d, *J*= 7.9 Hz, 1H), 7.44 (t, *J*= 7.9 Hz, 1H), 7.69 (dt, *J*= 2.1 and 6.9 Hz, 2H), 8.04-8.09 (m, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 22.42, 39.54, 125.83, 126.04, 127.58, 127.65, 129.22, 130.39, 131.23, 131.58, 132.07, 147.23, 163.84, 165.41; anal.: calcd for $C_{16}H_{12}BrNO_3$: C 55.51%, H 3.49%, N 4.05%, found: C 55.35%, H 3.66%, N 3.76%.

5-(4-Methylbenzoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (26): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 4-methylbenzoylchloride (0.949 g, 6.1 mmol) the title compound **26** was obtained as pure solid (0.168 g, 49 %): mp 180-181 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): *d*= 2.47 (s, 3H), 2.91 (t, *J*= 6.6 Hz, 2H), 3.55 (dt, *J*= 2.5 and 6.7 Hz, 2H), 6.69 (bs, 1H), 7.26-7.43 (m, 4H), 8.01-8.13 (m, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): *d*= 21.78, 22.44, 39.57, 125.79, 126.03, 127.54, 129.44, 130.26, 131.47, 144.91, 147.53, 164.67, 165.73; anal.: calcd for $C_{17}H_{15}NO_3$: C 72.58%, H 5.37%, N 4.98%, found: C 72.36%, H 5.01%, N 5.05%.

5-(4-Ethylbenzoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (27): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 4-ethylbenzoylchloride (1.03 g, 6.1 mmol) the title compound **27** was obtained as pure solid (0.20 g, 55 %): mp 141-142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 1.30 (t, *J*= 7.6 Hz, 3H), 2.76 (q, *J*= 7.6 Hz, 2H), 2.93 (t, *J*= 6.4 Hz, 2H), 3.56 (t, *J*= 6.1 Hz, 2H), 6.35 (bs, 1H), 7.35-7.38 (m, 3H), 7.44 (t, *J*= 8.1 Hz, 1H), 8.04 (dd, *J*= 1.2 and 7.7 Hz, 1H), 8.12-8.14 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 15.14, 22.34, 28.98, 39.59, 125.81, 126.17, 127.55, 127.84, 128.20, 129.97, 130.32, 131.37, 147.51, 151.04, 164.56, 165.65; anal.: calcd for $C_{18}H_{17}NO_3$: C 73.20%, H 5.80%, N 4.74%, found: C 72.96%, H 6.10%, N 4.87%.

5-(4-Propylbenzoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (28): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 4-propylbenzoylchloride (1.114 g, 6.1 mmol) the title compound **28** was obtained as pure solid (0.23 g, 61 %): mp 147-148 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): *d*= 0.97 (t, *J*= 7.2 Hz, 3H), 1.70 (m, 2H), 2.70 (t, *J*= 7.2 Hz, 2H), 2.92 (t, *J*= 6.6 Hz, 2H), 3.56 (dt, *J*= 2.4 and 6.7 Hz, 2H), 7.17 (bs, 1H), 7.27-7.47 (m,

4H), 8.03 (dd, *J*= 1.6 and 7.3 Hz, 1H), 8.12-8.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): *d*= 13.73, 22.41, 24.23, 38.10, 39.50, 125.72, 126.02, 126.25, 127.51, 128.87, 130.28, 131.53, 147.54, 149.57, 164.68, 165.96; anal.: calcd for $C_{19}H_{19}NO_3$: C 73.77%, H 6.19%, N 4.53%, found: C 73.55%, H 5.90%, N 5.06%.

5-(4-Butylbenzoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (29): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 4-butylbenzoylchloride (1.19 g, 6.1 mmol) the title compound **29** was obtained as pure solid (0.198 g, 50 %); mp 163-164 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): *d*= 0.91-0.98 (m, 3H), 1.25-1.43 (m, 2H), 1.57-1.69 (m, 2H), 2.72 (t, *J*= 7.4 Hz, 2H), 2.91 (t, *J*= 6.7 Hz, 2H), 3.55 (dt, *J*= 2.6 and 6.5 Hz, 2H), 7.27 (bs, 1H), 7.32-7.46 (m, 4H), 8.03 (dd, *J*= 1.6 and 7.3 Hz, 1H), 8.10-8.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): *d*= 13.89, 22.28, 22.40, 33.24, 35.77, 39.49, 125.71, 126.01, 126.21, 127.50, 128.82, 130.30, 130.46, 131.54, 147.54, 149.82, 164.68, 165.02; anal.: calcd for $C_{20}H_{21}NO_3$: C 74.28%, H 6.55%, N 4.33%, found: C 73.94%, H 6.63%, N 4.21%.

5-(4-*tert*-Butylbenzoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (30): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 4-*tert*-butylbenzoylchloride (1.2 g, 6.1 mmol) the title compound **30** was obtained as pure solid (0.21 g, 53 %): mp 208-209 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): *d*= 1.38 (s, 9H), 2.91 (t, *J*= 6.6 Hz, 2H), 3.56 (dt, *J*= 2.4 and 6.7 Hz, 2H), 7.32-7.46 (m, 3H), 7.53-7.58 (m, 2H), 8.03 (dd, *J*= 1.6 and 7.4 Hz, 1H), 8.13-8.18 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): *d*= 22.41, 31.07, 35.24, 39.46, 125.73, 125.96, 127.47, 130.15, 130.56, 131.56, 147.54, 157.85, 164.60, 166.00; anal.: calcd for $C_{20}H_{21}NO_3$: C 74.28%, H 6.55%, N 4.33%, found: C 74.05%, H 6.75%, N 4.45%.

5-(1-Bisphenylcarbonyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (31): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 1-bisphenylcarbonylchloride (1.32 g, 6.1 mmol) the title compound **31** was obtained as pure solid (0.18 g, 43 %): mp 235-236 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 2.95 (t, *J*= 6.6 Hz, 2H), 3.57 (dt, *J*= 2.0 and 6.7 Hz, 2H), 6.55 (bs, 1H), 7.37-7.53 (m, 5H), 7.66-7.68 (m, 2H), 7.77 (dt, *J*= 1.8 and 8.6 Hz, 2H), 8.06 (dd, *J*= 1.3 and 7.6 Hz, 1H), 8.29 (dt, *J*= 1.8 and 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 22.45, 39.55, 125.86, 125.94, 127.24, 127.31, 127.53, 128.38, 128.96, 130.37, 130.69, 131.38, 139.61, 146.68, 147.45, 164.43, 165.51; anal.: calcd for $C_{22}H_{17}NO_3$: C 76.95%, H 4.99%, N 4.08%, found: C 76.81%, H 5.20%, N 3.85%.

5-(1-Naphtoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (32): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 1-naphtoylchloride (1.163 g, 6.1 mmol) the title compound **32** was obtained as pure solid (0.116 g, 30 %): mp 148-149 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 3.00 (t, *J*= 6.6 Hz, 2H), 3.58 (dt, *J*= 2.6 and 6.7 Hz, 2H), 6.42

(bs,1H), 7.43 (dd, *J*= 1.6 and 8.0 Hz, 1H), 7.48 (t, *J*= 8.0 Hz, 1H), 7.59-7.63 (m, 2H), 7.65-7.68 (m, 1H), 7.95 (dd, *J*= 0.7 and 8.1 Hz, 1H), 8.08 (dd, *J*= 1.6 and 7.4 Hz, 1H), 8.15 (d, *J*= 8.2 Hz, 1H), 8.54 (dd, *J*= 1.3 and 7.3 Hz, 1H), 9.05 (d, *J*= 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 22.57, 39.58, 124.43, 124.89, 125.51, 125.91, 126.06, 126.51, 127.58, 128.38, 128.72, 130.45, 131.31, 131.52, 131.70, 133.91, 134.74, 147.50, 165.02, 165.51; anal.: calcd for $C_{20}H_{15}NO_3$: C 75.70%, H 4.76%, N 4.41%, found: C 75.38%, H 4.70%, N 4.52%.

5-(4-Nitrobenzoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (33): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 4-nitrobenzoylchloride (1.13 g, 6.1 mmol) the title compound **33** was obtained as pure solid (0.121 g, 32 %): mp 239-240 °C; ^{1}H-NMR (DMSO-d_6, 400 MHz): *d*= 2.78 (t, *J*= 6.5 Hz, 2H), 3.32-3.41 (m, under H_2O, 2H), 7.44-7.53 (m, 2H), 7.84 (d, *J*= 7.5 Hz, 1H), 8.07 (bs, 1H), 8.38-8.43 (m, 4H); ^{13}C-NMR (DMSO-d_6, 100.6 MHz): *d*= 24.35, 40.89, 126.51, 127.74, 127.99, 129.84, 133.49, 133.88, 133.99, 136.37, 149.40, 153.18, 165.24, 166.09; anal.: calcd for $C_{16}H_{12}N_2O_5$: C 61.54%, H 3.87%, N 8.97%, found: C 61.86%, H 4.05%, N 8.60%.

5-(4-Cyanobenzoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (34): Following the general procedure B starting from **4** (0.15 g, 0.92 mmol) and 4-cyanobenzoylchloride (0.23 g, 1.38 mmol) the title compound **34** was obtained as pure solid (0.065 g, 24 %): mp 254-256°C; ^{1}H NMR (DMSO-d_6, 400 MHz): *d*= 2.77 (t, *J*= 6.6 Hz, 2H), 3.32 (m, under H_2O, 2H), 7.43-7.51 (m, 2H), 7.84 (d, *J*= 7.4 Hz, 1H), 8.04 (bs, 1H), 8.09 (d, *J*= 8.2 Hz, 2H), 8.3 (d, *J*= 8.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100.6 MHz): *d*= 23.79, 40.34, 118.11, 119.83, 127.10, 127.38, 129.20, 132.41. 132.95, 133.43, 134.35, 134.89, 148.85, 164.89, 165.49. $C_{17}H_{12}N_2O_3$: C 69.86%, H 4.14%, N 9.58%, found: C 69.48%, H 4.35%, N 9.35%.

5-(2-Furoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (35): Following the general procedure B starting from **4** (0.2 g, 1.22 mmol) and 2-furoylchloride (0.192 g, 1.47 mmol) the title compound 34 was obtained as pure solid (0.115 g, 0.45 mmol, 37 %): mp 184-185 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 2.94 (t, *J*= 6.6 Hz, 2H), 3.56 (dt, *J*= 2.8 and 6.7 Hz, 2H), 6.30 (bs, 1H), 6.63 (dq, *J*= 1.7 and 3.6 Hz, 1H), 7.34-7.48 (m, 3H), 7.71-7.72 (m, 1H), 8.04 (dd, *J*= 1.7 and 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 24.51, 41.61, 114.34, 121.92, 127.82, 128.12, 129.59, 132.58, 133.39, 145.41, 148.67, 149.50, 158.32, 167.32; anal.: calcd for $C_{14}H_{11}NO_4$: C 65.37%, H 4.31%, N 5.44%, found: C 65.13%, H 4.05%, N 5.22%.

5-(2-Thienoyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (36): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 2-thienoylchloride (0.89 g, 6.1 mmol)

the title compound **36** was obtained as pure solid (0.098 g, 29 %): mp 188-189 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): *d*= 2.95 (t, *J*= 6.8 Hz, 2H), 3.57 (dt, *J*= 2.4 and 6.8 Hz, 2H), 6.56 (bs, 1H), 7.22 (dd, *J*= 5.9 and 4.9, 1H), 7.36-7.48 (m, 2H), 7.71 (dd, *J*= 1.3 and 5.0 Hz, 1H), 8.01-8.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.3 MHz): *d*= 22.44, 39.58, 125.98, 127.55, 128.24, 130.41, 131.44, 131.96, 133.96, 135.09, 147.04, 159.99, 165.55; anal.: calcd for $C_{14}H_{11}SNO_3$: C 61.52%, H 4.06%, N 5.12%, found: C 61.31%, H 4.35%, N 4.88%.

5-(Cyclohexylcarbonyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (37): Following the general procedure B starting from **4** (0.2 g, 1.22 mmol) and cyclohexylcarbonylchloride (0.22 g, 1.47 mmol) the title compound **37** was obtained as pure solid (0.084 g, 25 %): mp 163-164 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 1.28-1.40 (m, 3H), 1.61 (dd, *J*= 3.1 and 12.3 Hz, 2H), 1.70-1.73 (m, 1H), 1.82-1.87 (m, 2H), 2.09 (dd, *J*= 3.0 and 12.9 Hz, 2H), 2.60 (m, 1H), 2.84 (t, *J*= 6.5 Hz, 2H), 3.55 (t, *J*= 6.2 Hz, 2H), 6.46 (bs, 1H), 7.20 (dd, *J*= 1.1 and 8.1 Hz, 1H), 7.37 (t, *J*= 7.9 Hz, 1H), 7.99 (dd, *J*= 0.9 and 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 22.25, 25.26, 25.55, 28.98, 39.53, 43.09, 125.60, 125.79, 127.37, 130.22, 131.11, 147.27, 165.52, 173.88; anal.: calcd for $C_{16}H_{19}NO_3$: C 70.31%, H 7.01%, N 5.12%, found: C 70.55%, H 6.75%, N 4.93%.

5-Benzyloxy-3,4-dihydroisoquinolin-1(2*H*)-one (38): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and benzylchloride (0.77 g, 6.10 mmol) the title compound **38** was obtained as pure solid (0.090 g, 29%), mp 168-169 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): *d*= 2.84 (t, *J* = 6.7 Hz, 2H), 3.33 (m, under H_2O, 2H), 5.14 (s, 2H), 7.21-7.33 (m, 3H), 7.38 (pt, 2H), 7.45 (pd, 3H), 7.88 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100.6 MHz): *d*= 23.19, 71.54, 116.99, 121.14, 128.86, 129.32, 129.70, 130.34, 132.32, 138.88, 156.33, 166.26; anal.: calcd for $C_{16}H_{15}NO_2$: C 75.87%, H 5.97%, N 5.53%, found: C 75.52%, H 5.86%, N 5.32%.

5-(4-Chlorobenzyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (39): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 4-chlorobenzylchloride (0.98 g, 6.10 mmol) the title compound **39** was obtained as pure solid (0.056 g, 16 %): mp 215-216 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 3.02 (t, *J*= 6.6 Hz, 2H), 3.56 (t, *J*= 6.6 Hz, 2H), 5.07 (s, 2H), 6.48 (bs, 1H), 7.06 (dd, *J*= 0.7 and 8.2 Hz, 1H), 7.26-7.37 (m, 5H), 7.72 (dd, *J*= 0.7 and 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 21.50, 39.79, 69.61, 115.15, 120.42, 127.31, 127.99, 128.54, 128.75, 129.72, 133.85, 135.07, 154.51, 166.19; anal.: calcd for $C_{16}H_{14}NO_2$: C 66.79%, H 4.90%, N 4.87%, found: C 66.82%, H 5.12%, N 4.73%.

5-(Benzenesulfonyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (40): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and benzenesulfonylchloride (1.07 g, 6.1

mmol) the title compound **40** was obtained as pure solid (0.176 g, 47 %): mp 216-217 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 2.75 (t, *J*= 6.5 Hz, 2H), 3.39 (t, *J*= 6.4 Hz, 2H), 6.57 (bs, 1H), 7.13 (dd, *J*= 1.1 and 8.2 Hz, 1H), 7.29 (t, *J*= 8.0 Hz, 1H), 7.54-7.58 (m, 2H), 7.69-7.73 (m, 1H), 7.83-7.86 (m, 2H), 8.00 (dd, *J*= 0.9 and 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 22.53, 39.40, 126.15, 126.87, 127.52, 128.37, 129.31, 130.87, 132.71, 134.50, 135.36, 146.01, 164.97; anal.: calcd for. $C_{15}H_{13}NO_4S$: C 59.39%, H 4.32%, N 4.62%, found: C 59.21%, H 4.55%, N 4.81%.

5-(4-Methylbenzenesulfonyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (41): Following the general procedure A starting from **4** (0.2 g, 1.22 mmol) and 4-methylbenzenesulfonylchloride (1.16 g, 6.10 mmol) the title compound **41** was obtained as pure solid (0.204 g, 53 %): mp 175-176 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 2.46 (s, 3H), 2.76 (t, *J*= 6.6 Hz, 2H), 3.38 (dt, *J* = 2.8 and 6.7 Hz, 2H), 6.86 (bs, 1H), 7.13 (dd, *J*= 1.2 and 8.2 Hz, 1H), 7.27-7.35 (m, 3H,), 7.69-7.72 (m, 2H), 7.98 (dd, *J*= 1.0 and 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 23.74, 24.61, 41.42, 128.15, 128.76, 129.51, 130.47, 131.97, 132.98, 134.39, 134.83, 147.83, 148.12, 167.21; anal.: calcd for $C_{16}H_{15}NO_4S$: C 60.55%, H 4.74%, N 4.41%, found: C 60.48%, H 4.45%, N 4.53%.

5-(*E*-Cinnamyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (42): Following the general procedure B starting from **4** (0.1 g, 0.61 mmol) and cinnamylbromide (0.145 g, 0.73 mmol) the title compound **42** was obtained as pure solid (0.107 g, 63 %): mp 186-187 °C; ^{1}H NMR ($CDCl_3$, 200 MHz): *d*= 3.04 (t, *J*= 6.7 Hz, 2H), 3.56 (dt, *J*= 2.2 and 6.7 Hz, 2H), 4.74 (dd, *J*= 1.2 and 5.6 Hz, 2H), 6.43 (dt, *J*= 15.9 and 5.6 Hz, 1H), 6.75 (d, *J*= 16.0 Hz, 1H), 6.88 (bs, 1H), 7.10 (d, *J*= 7.6 Hz, 1H), 7.24-7.47 (m, 6H), 7.73 (d, *J*= 7.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50.3 MHz): *d*= 21.58, 39.80, 69.11, 115.04, 120.11, 124.14, 126.55, 127.26, 128.03, 128.64, 130.07, 133.02, 136.26, 154.72, 166.51; anal.: calcd for $C_{17}H_{15}NO_2$: C 76.96%, H 5.70%, N 5.28%, found: C 76.88%, H 5.99%, N 5.32%.

5-(Phenylacetyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (43): Following the general procedure B starting from **4** (0.1 g, 0.61 mmol) and phenacetylchloride (0.112 g, 0.73 mmol) the title compound **43** was obtained as pure solid (0.034 g, 20 %): mp 150-152 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 2.65 (pt, 2H), 3.47 (pt, 2H), 3.89 (s, 2H), 6.20 (bs, 1H), 7.20 (d, *J*= 7.9 Hz, 1H), 7.31-7.40 (m, 6H), 7.97 (d, *J*= 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 22.07, 39.56, 41.29, 125.69, 125.87, 127.40, 127.51, 128.76, 129.23, 131.12, 133.08, 147.14, 169.36; anal.: calcd for $C_{17}H_{15}NO_3$: C 72.58%, H 5.37%, N 4.98%, found: C 72.48%, H 5.05%, N 4.90%.

5-[2-(2-Chlorophenyl)-2-oxo-etoxy]-3,4-dihydroisoquinolin-1(2*H*)-one (45): Following the general procedure B starting from **4** (0.15 g, 0.92 mmol) and 2-chloro-ω-bromoacetophenone (0.32 g, 1.38 mmol) the title compound **45** was obtained as pure solid (0.085 g, 0.27 mmol, 29.4 %); mp138-140 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 2.94 (t, *J*= 6.7 Hz, 2H), 3.50 (dt, *J*= 2.4 and 6.8 Hz, 2H), 5.23 (s, 2H), 6.2 (bs, 1H), 6.93 (d, *J*= 8.2 Hz, 1H), 7.29 (d, *J*=8.0 Hz, 1H), 7.34-7.38 (m, 1H), 7.45-7.47 (m, 2H), 7.54-7.56 (m, 1H), 7.72 (d, *J*= 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 22.75, 41.28, 74.52, 116.56, 122.49, 128.55, 128.77, 129.68, 131.24, 131.84, 132.98, 134.17, 137.76, 155.37, 199.25; anal.: calcd for $C_{17}H_{14}ClNO_3$: C 64.67%, H 4.47%, N 4.44%, found: C 64.55%, H 4.40%, N 4.75%.

5-[2-(4-Fluorophenyl)-2-oxo-etoxy]-3,4-dihydroisoquinolin-1(2*H*)-one (46): Following the general procedure B starting from **4** (0.15 g, 0.92 mmol) and 4-fluoro-ω-bromoacetophenone (0.30 g, 1.38 mmol) the title compound **46** was obtained as pure solid (0.164 g, 60 %): mp 182-184 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 3.08 (t, *J*= 6.5 Hz, 2H), 3.57 (t, *J*= 6.5 Hz, 2H), 5.30 (s, 2H), 6.4 (bs, 1H), 6.93 (d, *J*= 8.2 Hz, 1H), 7.17-7.30 (m, 3H), 7.73 (d, *J*= 7.7 Hz, 1H), 8.03 (dd, *J*= 5.4 and 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 23.02, 41.28, 72.50, 116.53, 117.55 ($^{2}J_{C\text{-}F}$= 21.9 Hz), 122.56, 128.77, 129.72, 131.56, 132.26 ($^{3}J_{C\text{-}F}$= 9.0 Hz), 155.54, 167.52, 166.70 ($^{1}J_{C\text{-}F}$= 256.8 Hz), 193.99; anal.: calcd for $C_{17}H_{14}FNO_3$: C 68.22%, H 4.71%, N 4.68%, found: C 67.96%, H 4.89%, N 5.04%.

5-[2-(4-Nitrophenyl)-2-oxo-etoxy]-3,4-dihydroisoquinolin-1(2*H*)-one (48): Following the general procedure B starting from **4** (0.15 g, 0.92 mmol) and 4-nitro-ω-bromoacetophenone (0.33 g, 1.38 mmol) the title compound **48** was obtained as pure solid (0.05 g, 18 %): mp 215-216 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): *d*= 2.90 (t, *J*= 6.6 Hz, 2H), 3.37 (m, under H_2O, 2H), 5.69 (s, 2H), 7.17 (d, *J*= 8.2 Hz, 1H), 7.25 (t, *J*= 7.9 Hz, 1H), 7.47 (d, *J*= 7.6 Hz, 1H), 7.90 (bs, 1H), 8.23 (d, *J*= 8.8 Hz, 2H), 8.37 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100.6 MHz): *d*= 23.22, 73.00, 117.11, 121.54, 125.74, 128.78, 129.64, 131.28, 132.39, 144.88, 152.11, 155.85, 166.22, 195.82; anal.: calcd for $C_{17}H_{14}N_2O_5$: C 62.57%, H 4.32%, N 8.59%, found: C 62.88%, H 4.05%, N 8.25%.

5-[2-Oxo-etoxy-2-(4-trifluoromethylphenyl)]-3,4-dihydroisoquinolin-1(2*H*)-one (49): Following the general procedure B starting from **4** (0.10 g, 0.61 mmol) and 4-trifluoromethyl-ω-bromoacetophenone (0.20 g, 0.73 mmol) the title compound **49** was obtained as pure solid (0.08 g, 40 %): mp 198-200 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): *d*= 2.91 (t, *J*= 6.5 Hz, 2H), 3.35 (m, under H_2O, 2H), 5.69 (s, 2H), 7.16 (d, *J*= 8.2 Hz, 1H), 7.25

(t, *J*= 7.8 Hz, 1H), 7.48 (d, *J*=7.6, 1H), 7.91-7.94 (m, 3H), 8.20 (d, *J*= 8.1 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100.6 MHz): *d*= 23.23, 72.86, 117.09, 121.49, 127.64, 128.77, 129.64, 130.64, 132.39, 134.90 ($^2J_{C\text{-}F}$=31.9 Hz), 139.44, 155.90, 166.23,195.99; anal.: calcd for $C_{18}H_{14}F_3NO_3$: C 61.89%, H 4.04%, N 4.01%, found: C 61.58%, H 3.84%, N 3.97%.

5-[2-Oxo-etoxy-2-(2-thienyl)]-3,4-dihydroisoquinolin-1(2*H*)-one (50): Following the general procedure B starting from **4** (0.15 g, 0.92 mmol) and 2-(2-bromoacetyl)tiophene (0.28 g, 1.38 mmol) the title compound **50** was obtained as pure solid (0.188 g, 49 %): mp 201-202 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): *d*= 2.90 (t, *J*= 6.6 Hz, 2H), 3.36 (m, under H_2O, 2H), 5.52 (s, 2H), 7.10 (d, *J*= 8.2 Hz,1H), 7.25 (t, *J*= 8.0 Hz, 1H), 7.30 (t, *J*=4.0 Hz, 1H), 7.47 (d, *J*= 7.6 Hz, 1H), 7.92 (bs, 1H), 8.09 (d, *J*= 4.9 Hz, 1H), 8.12 (d, *J*=3.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100.6 MHz): *d*= 23.26, 72.36, 116.95, 121.53, 128.79, 129.67, 130.77, 132.43, 135.57, 137.29, 142.27, 155.98, 166.18, 189.69; anal.: calcd for $C_{15}H_{13}NO_3S$: C 62.70%, H 4.56%, N 4.87%, found: C 62.35%, H 4.20%, N 4.53%.

5-(2-Benzoisoxazolyloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (52): Following the general procedure B starting from **4** (0.1 g, 0.61 mmol) and 2-chlorobenzoisoxazole (0.112 g, 0.73 mmol) the title compound **52** was obtained as pure solid (0.112 g, 66 %): mp 245-246 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): *d*= 2.79 (t, *J*= 6.4 Hz, 2H), 3.26-3.60 (m, under H_2O, 2H), 7.21-7.26 (m, 2H), 7.9-7.45 (m, 2H), 7.54-7.59 (m, 1H), 7.65 (dd, *J*=1.1 and 8.2 Hz, 1H), 7.82 (dd, *J*= 1.0 and 7.7 Hz 1H), 8.01 (bs, 1H); ^{13}C-NMR (DMSO-d_6, 50.6 MHz): *d*= 22.01, 110.70, 118.76, 124.14, 124.99, 125.21, 126.04, 128.23, 131.40, 131.69, 140.60, 148.59, 149.29, 161.88, 163.98; anal.: calcd for $C_{16}H_{12}N_2O_3$: C 68.56%, H 4.32%, N 9.99%, found: C 68.44%, H 4.70%, N 9.73%.

5-(Isoquinolin-1-yloxy)-3,4-dihydroisoquinolin-1(2*H*)-one (53): Following the general procedure B starting from **4** (0.1 g, 0.6 mmol) and 1-chloroisoquinoline (0.12 g, 0.74 mmol) the title compound **53** was obtained as pure solid (0.092 g, 53 %): mp 197-198 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 2.90 (t, *J*= 6.6 Hz, 2H), 3.52 (t, *J*= 6.5 Hz, 2H), 6.40 (bs, 1H), 7.34 (d, *J*= 5.6 Hz, 1H), 7.39 (dd, *J*= 1.3 and 8.0 Hz, 1H), 7.46 (t, J=7.9 Hz, 1H), 7.64-7.68 (m, 1H), 7.74-7.79 (m, 1H), 7.84 (d, *J*= 8.1 Hz, 1H), 7.93 (d, *J*= 5.8 Hz, 1H), 8.04 (dd, *J*= 1.1 and 7.5 Hz, 1H), 8.46 (d, *J*= 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz): *d*= 23.99, 41.14, 118.04, 120.68, 125.43, 126.66, 127.76, 127.85, 128.80, 129.09, 131.84, 132.53, 133.41, 139.99, 141.07, 151.58, 161.30, 167.29; anal.: calcd for $C_{18}H_{14}N_2O_2$: C 74.47%, H 4.86%, N 9.65%, found: C 74.51%, H 4.99%, N 9.42%.

4-Benzoyloxy-2,3-dihydroisoindolin-1(2*H*)-one (56): Following the general procedure B starting from **6** (0.075 g, 0.5 mmol) and benzoylchloride (0.14 g, 0.22 ml, 1.0 mmol) the

title compound **56** was obtained as pure solid (0.028 g, 22 %); mp 190-192 °C; ^{1}H NMR (DMSO-*d*6, 400 MHz): *d*= 4.34 (s, 2H), 7.55-7.65 (m, 5H), 7.75-7.77 (m, 1H), 8.17 (dd, *J*= 1.3 and 8.4 Hz, 2H), 8.68 (bs, 1H); ^{13}C NMR (DMSO-*d*6, 100.6 MHz): *d*= 44.64, 122.67, 126.82, 130.23, 130.93, 131.43, 131.86, 136.21, 136.74, 137.71, 147.69, 165.62, 171.03; anal.: calcd for $C_{15}H_{11}NO_3$: C 71.14%, H 4.38%, N 5.53%, found: C 71.52%, H 4.35%, N 5.62%.

3-Benzoyloxy-2-methylbenzamide (57): Following the general procedure B starting from **7** (0.1 g, 0.66 mmol) and 2-benzoylchloride (0.11 g, 0.79 mmol) the title compound **57** was obtained as pure solid (0.07 g, 42 %):mp 178-180 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): *d*= 2.17 (s, 3H,), 7.29-7.30 (m, 3H), 7.48 (pd, 1H), 7.62 (t, *J*= 7.6 Hz, 2H), 7.76 (pt, 1H), 7.85 (1H, pd, ArH), 8.15 (d, *J*= 7.2 Hz, 2H,); ^{13}C NMR (DMSO-d_6, 100.6 MHz): *d*= 14.57, 125.10, 126.69, 128.39, 129.44, 130.49, 130.96, 131.66, 136.06, 141.10, 151.27, 166.16, 172.08; anal.: calcd for $C_{15}H_{13}NO_3$: C 70.58%, H 5.13%, N 5.49%, found: C 70.46%, H 5.35%, N 5.55%.

3-Benzoyloxy-*N*-methylbenzamide (58): Following the general procedure B starting from **8** (0.1 g, 0.66 mmol) and benzoylchloride (0.18 g, 0.15 ml, 1.32 mmol) the title compound **58** was obtained as pure solid (0.034 g, 22 %): mp 111-113 °C; ^{1}H NMR (DMSO-d_6, 400 MHz): *d*= 2.78 (d, *J*= 4.5 Hz, 3H), 7.45 (pd, 1H), 7.55 (t, *J*= 7.9 Hz, 1H), 7.61 (t, *J*= 7.7 Hz, 2H), 7.72-7.78 (m, 3H), 8.14 (d, *J=7.5* Hz, 2H), 8.51 (pd, 1H); ^{13}C-NMR (DMSO-d_6, 100.6 MHz): *d*= 28.16, 122.49, 126.54, 130.59, 130.90, 131.49, 131.68., 136.05, 137.90, 152.39, 166.43, 167.39; anal.: calcd for $C_{15}H_{13}NO_3$: C 70.58%, H 5.13%, N 5.49%, found: C 70.22%, H 4.95%, N 5.25%.

3-Benzoyloxybenzamide (59): Following the general procedure B starting from **9** (0.1 g, 0.73 mmol) and benzoylchloride (0.12 g, 0.10 ml, 0.87 mmol) the title compound **59** was obtained as pure solid (0.03 g, 17 %): mp 134-136 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): *d*= 5.85 (bs, 1H), 6.11 (bs, 1H), 7.41 (pd, 1H), 7.53 (pt, 3H), 7.64-7.73 (m, 3H), 8.20 (d, *J=7.5* Hz, 2H); ^{13}C NMR (DMSO-d_6, 100.6 MHz): *d*= 122.87, 126.76, 126.99, 130.59, 130.90, 131.43, 131.68, 136.05, 137.69, 152.36, 166.47, 168.70; anal.: calcd for $C_{14}H_{11}NO_3$: C 69.70%, H 4.60%, N 5.81%, found: C 69.39%, H 4.22%, N 6.01%.

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Table 1S. Purity of tested compounds **3**, **19**-**59** by HPLC.

Compounds	HPLC 1 (System A) rt, (purity %)	HPLC 2 (System B) rt, (purity %)
3	6.9 (>98)	5.7 (>98)
19	8.1 (>98)	6.4 (>98)
20	10.8 (>98)	8.1 (>98)
21	11.9 (>98)	7.7 (>98)
22	6.1 (98)	6.2 (>98)
23	7.5 (>98)	6.0 (>98)
24	8.1 (>98)	5.6 (>98)
25	11.9 (>98)	8.6 (>98)
26	10.7 (98)	7.3 (>98)
27	14.7 (>98)	9.34 (98)
28	22.3 (>98)	13.2 (>98)
29	37.9 (98)	19.7 (>98)
30	26.4 (98)	14.8 (>98)
31	25.0 (>98)	18.0 (98)
32	14.5 (98)	10.1 (>98)
33	7.4 (>98)	5.3 (>98)
34	5.7 (>98)	4.3 (>98)
35	5.1 (>98)	3.9 (>98)
36	5.9 (>98)	5.8 (>98)
37	11.1 (97)	7.6 (96)
38	9.3 (96)	6.8 (96)
39	14.1 (97)	9.3 (96)
40	6.1 (>98)	4.6 (>98)
41	7.5 (>98)	5.4 (>98)
42	15.2 (>98)	10.6 (>98)
43	6.7 (>98)	4.8 (>98)
44	5.4 (>98)	4.6 (>98)
45	6.5 (>98)	5.2 (>98)
46	5.8 (>98)	4.6 (>98)
47	4.8 (>98)	3.9 (>98)
48	5.6 (>98)	4.5 (>98)
49	9.2 (>98)	5.9 (>98)
50	4.8 (>98)	3.9 (>98)
51	6.2 (>98)	3.8 (>98)
52	6.5 (>98)	5.8 (>98)
53	8.6 (>98)	6.9 (>98)
54	6.9 (>98)	6.0 (>98)
55	5.5 (>98)	4.9 (>98)
56	5.8 (97)	5.2 (>98)
59	5.5 (>98)	4.4 (>98)
58	6.4 (96)	5.0 (96)
59	5.4 (>98)	4.6 (>98)

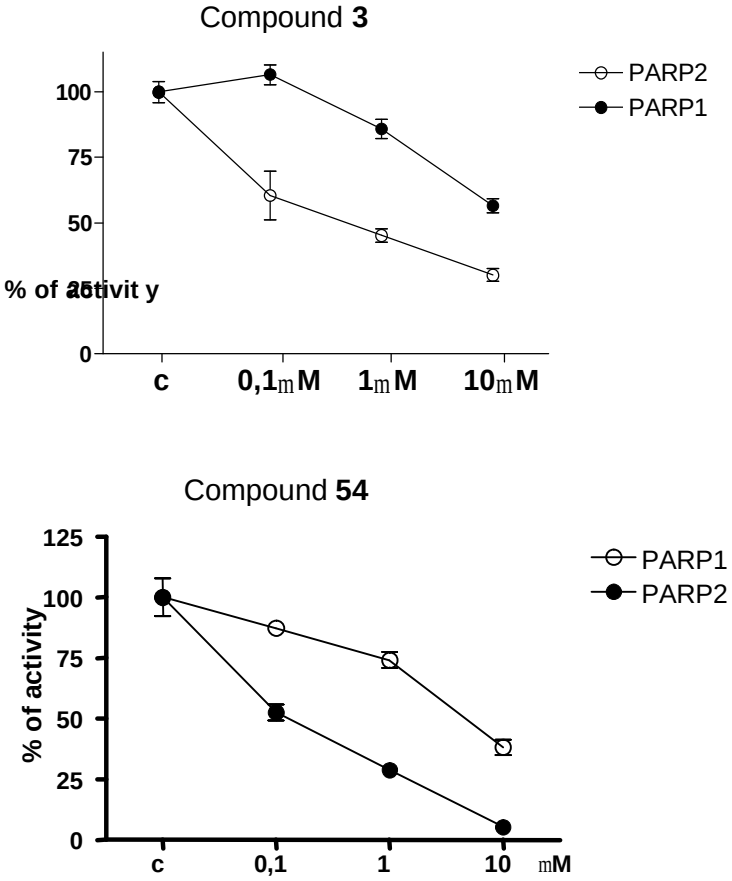

Figure 1S. Dose-effect curves of compounds **3** and **54**.

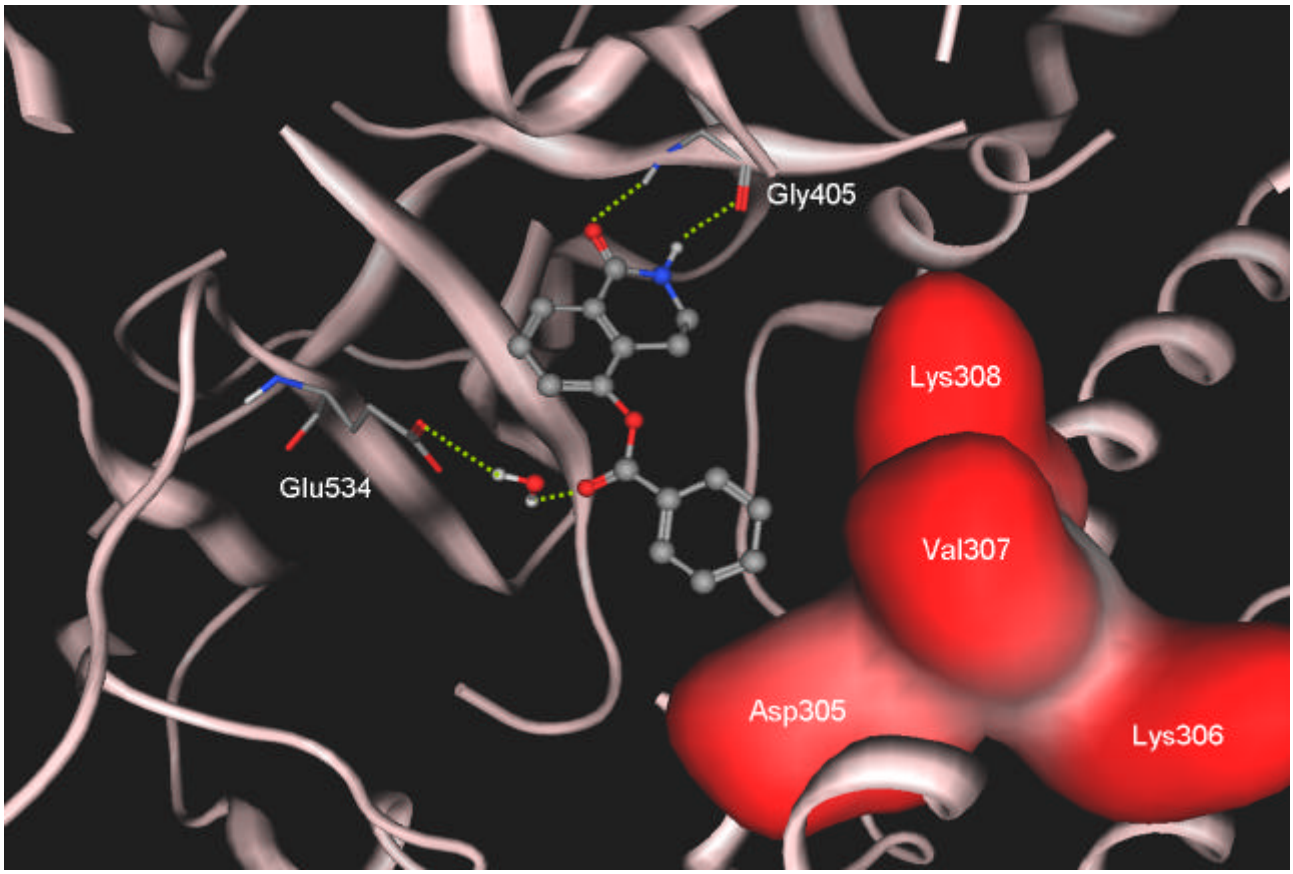

Figure 2S. Docking pose of derivative **3** on mouse-PARP2. In red, residues defining the PARP-2 selectivity region, are highlighted.