Thiazolides as Novel Antiviral Agents: I. Inhibition of Hepatitis B Virus Replication

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Supporting Information

Spectroscopic and analytical data for new compounds described in this paper using methods described in the main MS; experimental procedures and characterisation for thiazolides that are not key compounds in activity terms; microanalytical data for selected compounds; descriptors used in QSAR study; additional references.

For general methods of preparation, see main MS.

2-Hydroxy-3-methylbenzoyl-*N*-(5-nitrothiazol-2-yl)amide (4). Mp 209-211°C (dec.); ^{1}H NMR [400 MHz, $(CD_3)_2SO$] 2.45 (3 H, s, $ArCH_3$), 6.84 (1 H, t, J = 7.5 Hz, ArH), 7.37 (1 H, d, J = 6.8 Hz, ArH), 7.87 (1 H, d, J = 7.2 Hz, ArH) and 8.71 (1 H, s, 4´-H); ^{13}C NMR [125 MHz, $(CD_3)_2CO$] 15.8, 113.7, 120.0, 126.8, 128.1, 137.9, 141.8, 144.2, 160.6, 162.2 and 170.2; m/z (ES -ve ion mode) 278 (M-H, 100%); Found: m/z, 278.0249; $C_{11}H_8N_3O_4S$ requires m/z, 278.0241.

2-Hydroxy-4-methylbenzoyl- *N*-(5-nitrothiazol-2-yl)amide (5). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] 2.21 (3 H, s, $ArCH_3$), 6.72 (1 H, d, J = 7.9 Hz, ArH), 7.21 (1 H, s, ArH), 7.73 (1 H, d, J = 8Hz, ArH) and 8.55 (1 H, s, 4´-H); MS (CI) m/z 280 (MH^+); m/z (ES -ve ion mode) 278 (M-H, 100%); Found: m/z, 278.0234; $C_{11}H_8N_3O_4S$ requires m/z, 278.0241.

2-Hydroxybenzoyl-*N*-(5-bromothiazol-2-yl) amide (**6**). Mp 196-197°C; Anal. ($C_{10}H_7BrN_2O_2S$) C, H, N; ^{1}H NMR [$(CD_3)_2SO$] 7.00 (1 H, t, J = 7.9 Hz, ArH), 7.05 (1 H, d, J = 8.2 Hz, ArH), 7.49 (1 H, t, J = 8.2 Hz, ArH), 7.65 (1 H, s, 4′-H) and 7.96 (1 H, d, J = 7.9 Hz, ArH); ^{13}C NMR [$(CD_3)_2SO$] 102.1, 116.3, 117.1, 119.7, 130.3, 134.5, 138.4, 157.4, 158.2 and 164.6; MS (CI) m/z 299 and 301 (M^+ for ^{79}Br, ^{81}Br respectively); HRMS, found, m/z 298.9489, $C_{10}H_8BrN_2O_2S$ (MH^+ for ^{79}Br) requires m/z, 298.9490.

4-Fluoro-2-hydroxybenzoyl-*N*-(5-bromothiazol-2-yl)amide (9). Mp 203-204°C; ^{1}H NMR (250 MHz, $CDCl_3$) 8.01 (1H, q, *J* = 7.1, 8.6, C**H**$_{ar}$), 7.66 (1H, s, C**H**), 6.87-6.81 (2H, m, 2 x C**H**$_{ar}$); *m/z* (CI) 317 (40%, M^+); Found (CI) 316.94014, $C_{10}H_7N_2O_2SBrF$ (MH^+) requires 316.93958.

5-Chloro-2-hydroxybenzoyl-*N*-(5-bromothiazol-2-yl)amide (10). Mp 221-222°C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] 8.00 (1H, d, *J* = 2.7, C**H**$_{ar}$), 7.68 (1H, s, C**H**), 7.51 (1H, dd, *J* = 2.7, 8.8, C**H**$_{ar}$), 7.01 (1H, d, *J* = 8.8 C**H**$_{ar}$); *m/z* (CI) 333 (30%, MH^+); Found (CI) 332.90930, $C_{10}H_7N_2O_2SBrCl$ (MH^+) required 332.91003.

2-Hydroxy-3-methylbenzoyl-*N*-(5-chlorothiazol-2-yl)amide (11). Mp 196-197°C dec.; ^{1}H NMR (500 MHz, $CDCl_3$) 2.33 (3 H, s, MeAr), 6.87 (1 H, t, J = 7.5 Hz, 5-H), 7.23 (1 H, s, 4´-H), 7.41 and 7.51 (2 H, approx. ds, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) 15.8, 111.9, 121.7, 123.8, 128.2, 134.8, 136.7, 156.2, 160.4 and 168.1; m/z (ES +ve ion mode) 291 (MNa^+, 100%); Found: m/z, 290.9958; $C_{11}H_9{}^{35}ClN_2O_2SNa$ requires m/z, 290.9965.

2-Hydroxy-4-methylbenzoyl-*N*-(5-chlorothiazol-2-yl) amide (**13**). Mp 223-225°C dec.; ^{1}H NMR [500 MHz, $(CD_3)_2SO$] 2.31 (3 H, s, CH_3Ar), 6.83 (1 H, dd, J = 8 Hz and 1 Hz, 5-H), 6.93 (1 H, d, J = 1 Hz, 3-H), 7.59 (1 H, s, 4´-H) and 7.87 (1 H, d, J = 8 Hz, 6-H); ^{13}C NMR [125 MHz, $(CD_3)_2SO$] 21.2, 113.5, 117.3, 118.4, 120.9, 130.2, 135.8, 145.5, 155.8, 157.5 and 164.7; m/z (ES +ve ion mode) 291 (MNa^+, 100%) Found: m/z, 290.9964; $C_{11}H_9{}^{35}ClN_2O_2SNa$ requires m/z, 290.9965.

2-Hydroxybenzoyl-*N*-(5-fluorothiazol-2-yl) amide (**14**). A solution of 2-acetamidothizole **38** (0.284 g, 2 mmol) and SelectFluor (0.920 g, 2.6 mmol) in anhydrous MeCN (10 mL) was stirred

and heated at 80°C for 3h. After cooling, the solution was partitioned between water and EtOAc, then the organic phase was separated, washed with satd. aq. $NaHCO_3$ and 1M HCl. Evaporation followed by chromatography (EtOAc-hexane) afforded the 5-fluoro product **39** (0.097 g, 30%) which was pure enough to progress {^{1}H NMR [$(CD_3)_2SO$, 500 MHz] 2.11 (3 H, s, CH_3CO), 7.26 (1 H, d, ^3J = 2.5 Hz, 4 –H) and 12.1 (1 H, br s, NH)}. This product (0.056 g, 0.35 mmol) was heated with 4M HCl (1 mL) in MeOH (2 mL) at 55°C for 16h, then the solution was evaporated, neutralised cautiously with satd. aq. $NaHCO_3$ and extracted with EtOAc. Evaporation afforded 2-amino-5-fluorothiazole **40** (0.030 g, 73%) [^{1}H NMR ($CDCl_3$, 500 MHz) 4.90 (2 H, br s, NH_2) and 6.65 (1 H, d, ^3J = 2.5 Hz, 4-H)].

The amine was coupled using general method 1 (main MS) to afford the *O*-acetyl intermediate (0.053 g, 70%) as a solid {^{1}H NMR ($CDCl_3$, 500 MHz) 2.42 (3 H, s, CH_3CO), 6.82 (1 H, d, ^3J = 2.5 Hz, 4´-H), 7.26 (1 H, d, 3-H), 7.43, 7.61 (2 H, 2t, 4-H and 5-H), 7.96 (1 H, d, 6-H) and 10.54 (1 H, br s, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) 21.1, 117.6, 123.7, 125.1, 126.5, 130.3, 133.5, 147.5, 148.5, 157.6 and 159.9 [d, C(5´),^{13}C-^{19}F coupling, ^2J = 293 Hz], 162.6 and 168.5}. Deprotection using NH_3 (see **23** above) finally afforded the desired 5-fluoro analogue **14** (0.018 g, 60%), mp 214-215°C dec.; ^{1}H NMR [500 MHz, $(CD_3)_2CO$] 7.03 (1 H, t, ArH), 7.09 (1 H, d, 3-H), 7.24 (1 H, d, J = 2.5 Hz, 4´-H), 7.54 (1 H, t, ArH) and 8.17 (1 H, d, 6-H); ^{13}C NMR [125 MHz, $(CD_3)_2CO$] 116.2, 118.3, 118.5, 120.6, 130.6, 135.9, 148.7, 158.1 and 160.4 (5´-C; ^2J = 289 Hz), 160.1 and 166.8; m/z (ES +ve ion mode) 261 (MNa^+, 100%); Found: m/z, 261.0102; $C_{10}H_7FN_2O_2SNa$ requires m/z, 261.0104.

2-Hydroxybenzoyl-*N*-(5-isopropylthiazol-2-yl)amide (17). At -5°C, bromine (4.81 cm^3, 93.93 mmol, 1.01 eq.) was added dropwise to a mixture of 3-methylbutanal (8.0 g, 93 mmol, 1.0 eq.), dioxane (0.31 cm^3) and diethyl ether (100 cm^3), over a period of two hours. After sustaining the bromine colour in solution, it was neutralized with satd. aq. $NaHCO_3$. The organic fraction was separated and washed with water and brine solution and concentrated in *vacuo* to give the crude α-bromoaldehyde, which was used directly; 15 g (90.9 mmol, 1.0 eq.) of this crude product was added to a solution of thiourea (6.9 g, 90.9 mmol, 1.0 eq.) in THF (100 cm^3). The reaction was allowed to reflux and after 16 hours most of the starting material was disappeared. After cooling the mixture, it was neutralized with satd. aq. $NaHCO_3$ solution and the THF was removed in *vacuo*. The crude product was partitioned between EtOAc (400 cm^3) and water (100 cm^3); the

organic fraction was separated, washed with water and brine solution and dried over $MgSO_4$. Purification by flash column chromatography afforded 2-amino-5-isopropylthiazole (9.5 g, 74%),[66] R_f = 0.16 (EtOAc:Hex, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) 1.24 (6H, d, *J* = 6.8 Hz, $2CH_3$), 2.98 (1H, dhept, *J* = 1.2, 6.8 Hz, CH), 5.40 (2H, s, NH_2), and 6.70 (1H, d, *J* = 1.2 Hz, CH) ^{13}C NMR ($CDCl_3$, 100 MHz) 24.7 (x2), 28.1, 132.5, 137.0, and 167.1; MS (CI) m/z 143 (MH^+); HRMS, found, m/z 143.06468, $C_6H_{11}N_2S$ (MH^+) requires m/z, 143.06430. The acetate of **17** was prepared from this amine using general method 2 (above) on a 10 mmolar scale (2.67 g, 89%); mp 150-151°C; ^{1}H NMR [$(CD_3)_2SO$, 400 MHz] 1.29 (6H, d, *J* = 6.8 Hz, $2CH_3$), 2.23 (3H, s, CH_3) 3.15 (1H, dhept, *J* = 1.0, 6.8 Hz, CH), 7.22 (1H, d, *J* = 1.0 Hz, CH), 7.26 (1H, dd, *J* = 1.0, 8.2 Hz, ArH), 7.39 (1H, td, *J* = 1.0, 7.6 Hz, ArH), 7.60 (1H, td, *J* = 1.6, 8.2 Hz, ArH), 6.76 (1H, dd, *J* = 1.6, 8.2 Hz, ArH) and 12.40 (1H, s, CONH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$] 20.6, 24.3 (x2), 26.7, 123.2, 125.7, 127.0, 129.5, 131.6, 132.3, 139.5, 148.4, 156.3, 163.7, and 168.7; MS (CI) m/z 305 (MH^+); HRMS, found, m/z 305.09601, $C_{15}H_{17}N_2O_3S$ (MH^+) requires m/z, 305.09664. Deprotection as described for **23** but using THF rather than acetone afforded the desired product **17** (2.1 g, 98%) which was purified through crystallization; mp 194-195°C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] 1.29 (6H, d, *J* = 6.8 Hz, $2CH_3$), 3.12 (1H, dhept, *J* = 1.0, 6.8 Hz, CH), 6.92-7.00 (2H, m, ArH), 7.25 (1H, d, *J* = 1.0, Hz, CH), 7.44 (1H, td, *J* = 1.6, 8.2 Hz, ArH), 8.00 (1H, dd, *J* = 1.6, 8.2 Hz, ArH) and 12.40 (1H, s, CONH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$] 23.8, 26.9, 30.6, 117.1 (x2), 117.4, 119.1, 130.1 (x2), 133.9 (x2), 138.1 (x2), 138.1 and 158.5; MS (CI) m/z 263 (MH^+); Found: m/z 263.08485; $C_{13}H_{15}N_2O_2S$ (MH^+) requires m/z, 263.08542.

2-Hydroxybenzoyl-*N*-[5-(4-chlorophenyl)thiazol-2-yl]amide (18). The known[67] 2-amino-5-(4-chlorophenyl)thiazole was obtained by the aldehyde bromination/Hantzsch thiazole sequence described in the main MS (compound**17**). Coupling using general method 2, then aq. NH_3 deprotection as for compound **23**, afforded **18**: mp 277-279°C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] 7.98 (1H, t, *J* = 7.6 Hz, ArH), 7.12 (1H, d, *J* = 8.0 Hz, ArH), 7.45 (1H, dd, *J* = 1.5, 7.6 Hz, ArH), 7.49 (2H, d, *J* = 8.5 Hz, ArH), 7.68 (2H, d, *J* = 8.5 Hz, ArH), 7.99 (1H, dd, *J* = 1.5, 8.0 Hz, ArH) and 8.03 (1H, s, 4′-H); ^{13}C NMR [100 MHz, $(CD_3)_2SO$] 117.3, 117.6 (x2), 119.8 (x2), 127.6 (x2), 129.5 (x2), 130.6 (x2), 132.4, 134.6, and 158.3; MS (CI) m/z 331 (MH^+); Found: m/z, 331.03039; $C_{16}H_{12}ClN_2O_2S$ (MH^+) requires m/z, 331.03082.

2-Hydroxybenzoyl-*N*-(4-phenylthiazol-2-yl)amide (19). [Known compound but no spectroscopic data: *Chem. Abstr.* **1964**, *60*, 5508c, mp 233 ^{o}C; *Agric. Biol. Chem.* **1973,** *37*, 1375, mp 155 ^{o}C] Mp 245-246^{o}C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] 8.04 (1H, d, *J* = 7.8, ArH), 7.94 (2H, d, *J* = 7.7, 2 x ArH), 7.70 (1H, s, 5´-H), 7.50-7.34 (4H, m, 4 x ArH), 7.09-7.02 (2H, m, 2 x ArH); ^{13}C NMR [125 MHz, $(CD_3)_2SO$] 108.8, 116.7, 117.2, 119.8, 125.8, 127.9, 128.7, 130.3, 134.5, 149.1, 157.3 and 164.3; *m/z* (ES +ve mode) 319 (100%, MNa^+); Found 319.0501 $C_{16}H_{12}N_2O_2SNa$ requires m/z, 319.0512.

3-Chloro-2-hydroxybenzoyl-*N*-(4-phenylthiazol-2-yl)amide (21). Mp 195-196^{o}C; ^{1}H NMR [400 MHz, $(CD_3)_2SO$] 8.06 (1H, d, *J* = 7.9, ArH), 7.93 (2H, d, *J* = 8.6, 2 x ArH), 7.70 (1H, s, 5´-H), 7.65 (1H, dd, *J* = 1.4, 7.9, ArH), 7.49 (2H, t, *J* = 7.4, 2 x ArH), 7.39 (1H, t, *J* = 7.4, ArH), 6.99 (1H, t, *J* = 7.9, ArH); ^{13}C NMR [125 MHz, $CDCl_3$ plus a few drops of $(CD_3)_2SO$] 107.7, 115.9, 119.1, 122.4, 125.6, 126.5, 128.0, 128.4, 133.1, 134.6, 147.7, 156.2, 158.7 and 167.2; *m/z* (CI) 331 (20%, $[M+H]^+$); m/z (ES +ve ion mode) 353 (MNa^+, 100%); Found: m/z 353.0116; $C_{16}H_{11}ClN_2O_2SNa$ requires m/z, 353.0122.

2-Hydroxybenzoyl-N-[(4-methanesulfonyl)thiazol-2-yl]amide (24). Under N_2, sodium methanesulfinate (408 mg, 4.0 mmol) and CuI (457 mg, 2.4 mmol) were added to a solution of 2-[(5-bromothiazol-2-yl)carbamoyl]phenyl acetate (682 mg, 2.0 mmol) in *N, N*-dimethylacetamide (50 mL). The reaction mixture was stirred at 120°C overnight, then the solvent was removed *in vacuo*, the residue was dissolved in EtOAc and washed twice each with aq. NH_4Cl and satd. aq. $NaHCO_3$. The organic extract was dried, and then the solvent was evaporated *in vacuo*. The crude product was purified by flash column chromatography (EtOAc-hexane, 1:1), affording compound **24** (220 mg, 37%); mp 221-222°C; ^{1}H NMR [400MHz, $(CD_3)_2SO$)] 3.26 (3H, s, CH_3SO_2), 7.00 (1H, d, *J* = 7.5 Hz, ArH), 7.07 (1H, d, *J* = 6.5 Hz, ArH), 7.52 (1H, t, *J* = 6.5 Hz, ArH), 7.98 (1H, d, *J* = 7.5 Hz, ArH) and 8.12 (1H, s, 5′-H); ^{13}C NMR [100 MHz, $(CD_3)_2SO$)] 42.3, 117.7, 120.1, 121.0, 130.6, 135.1, 148.7 (x2), 157.8, 160.1 and 165.6; MS (CI) m/z 299 (MH^+) and 316 (MNH_4^+); Found: m/z 299.01644; $C_{11}H_{11}N_2O_4S_2$ (MH^+) requires m/z, 299.01602.

2-Hydroxybenzoyl-N-[(5-methanesulfonyl)thiazol-2-yl]amide (25). A solution of 2-amino-5-bromothiazole (6.88 g, 38.46 mmol) in absolute ethanol (50 mL) was added dropwise over 5 min to a stirred solution of sodium thiomethoxide (2.7 g, 38.5 mmol) in methanol (50 mL). After stirring at 45˚C for 1 h, further sodium thiomethoxide (170 mg) in methanol was added and reaction was continued for 30 min, then the solution was heated to 70˚C for 30 min. Solvent was evaporated and the crude product dissolved in DCM, then washed with water (2x). Drying and evaporation afforded crude 2-amino-5-(methylthio) thiazole (5.35 g , 95%), which was used directly; ^{1}H (200 MHz, $CDCl_3$) 2.35 (3H, s, CH_3), 5.46 (2H, s, NH_2), 7.06 (1H, s, CH); m/z (CI + H)$^+$ 147; Found: m/z 147.00540; $C_4H_7N_2S_2$ (MH^+) requires m/z, 147.00507. Coupling with acetylsalicyloyl chloride using general method 2 afforded crude product (10.3 g, 92%) containing a little bis-adduct, which was hydrolyzed by adding 1M HCl (2 mL) to a THF solution of the above and standing at room temperature for 72h. After standard workup, the product (0.5 g) was purified through crystallization; mp 145-147°C; ^{1}H [400MHz, $(CD_3)_2SO$] 2.23 (3H, s, CH_3), 2.47 (3H, s, CH_3), 7.28 (1H, dd, *J* = 1.0, 8.0 Hz, ArH), 7.41 (1H, td, *J* = 1.0, 7.6 Hz, ArH), 7.56 (1H, s, CH), 7.63 (1H, td, *J* = 1.7, 8.0 Hz, ArH), 7.78 (1H, dd, *J* = 1.7, 7.6 Hz, ArH) and 12.70 (1H, s, NH); ^{13}C [100MHz, $(CD_3)_2SO$] 21.1, 22.0, 123.7, 124.6, 126.2, 126.9, 130.0, 133.1, 141.6, 148.9, 160.0, 164.5 and 169.2; m/z (CI) 309 (MH^+); Found 309.03654, $C_{13}H_{13}N_2O_3S_2$ requires 309.03677. A solution of MCPBA (70-75%, 4 g, ~16.2 mmol) in DCM (30 mL) was added dropwise to a stirred solution of this intermediate (5 g, 16.22 mmol) in DCM (200 mL) over a period of 30 min and the reaction was stirred for further 30 min at room temperature. Further portions of MCPBA (4 g, then 0.8 g) in DCM were added dropwise until TLC analysis showed complete conversion of starting material of product in solution mixture. The reaction was then quenched with aq. $Na_2S_2O_3$, the organic phase was separated and washed with satd. aq. $NaHCO_3$ (2x) and with 1M HCl solution. Drying ($MgSO_4$) and concentration to a volume of 30 cm^3 led to crystallization of the *O*-acetate of **25** (5.40 g, 98% yield): mp 175°C; ^{1}H NMR [200MHz, $(CD_3)_2SO$] 2.25 (3H, s, CH_3), 3.38 (3H, s, CH_3), 7.31 (1H, dd, *J* = 1.0, 8.0 Hz, ArH), 7.44 (1H, td, *J* = 1.0, 7.6 Hz, ArH), 7.68 (1H, td, *J* = 1.6, 7.6 Hz, ArH), 7.83 (1H, dd, *J* = 1.6, 8.0 Hz, ArH), 8.17 (1H, s, CH); m/z CI (MH^+) 341 (100%), 299 (16%), 238 (32%) 221 (40%); Found: m/z 341.0255; $C_{13}H_{13}N_2O_5S_2$ (MH^+) requires m/z, 341.0266. Standard deprotection using aq. HCl (above) afforded compound **25** (8.3 g, 95%); mp 282-283°C; ^{1}H NMR [200MHz, $(CD_3)_2SO$] 3.39 (3 H, s, CH_3SO_2), 7.01 (1H, t, *J* = 7.5 Hz, ArH), 7.10 (1 H, d, *J* = 7.5 Hz, ArH), 7.52 (1 H, t,

J = 7.5 Hz, ArH), 7.96 (1 H, d, *J* = 7.5 Hz, ArH) and 8.17 (1 H, s, 4′-H); ^{13}C NMR [100 MHz, $(CD_3)_2SO$] 46.2, 117.0, 117.6, 120.1, 130.5, 130.8, 135.2, 144.2, 157.7, 163.1 and 165.6; MS (CI) m/z 299 (MH^+); Found: m/z, 299.01505; $C_{11}H_{11}N_2O_4S_2$ (MH^+) requires m/z, 299.01602.

2-Hydroxybenzoyl-*N*-(5-cyanothiazol-2-yl)amide (**26**). Mp 206-208.5°C (from EtOAc); ^{1}H NMR [400 MHz, $(CD_3)_2SO$] 7.05 (1 H, t, J = 7.4 Hz, ArH), 7.07 (1 H, d, J = 8.3 Hz, ArH), 7.50 (1 H, m, ArH), 7.93 (1 H, dd, J = 7.8 and 1.6 Hz, ArH), 8.45 (1 H, s, 4´-H) and 11.87 (1 H, br s, NH); ^{13}C NMR [125 MHz, $(CD_3)_2SO$] 98.0, 113.3, 116.5, 117.1, 119.8, 130.5, 134.9, 150.0, 157.2, 161.9 and 165.2; m/z (CI) 246 (MH^+); m/z (ES -ve ion mode) 244 (M-H, 100%); Found: m/z 244.0180; $C_{11}H_6N_3O_2S$ requires m/z, 244.0186.

2-Hydroxybenzoyl-*N*-[5-(ethoxycarbonyl)thiazol-2-yl]amide (**27**). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] 1.30 (3 H, t, J = 7.1 Hz, CH_3CH_2O), 4.29 (2 H, q, J = 7.1 Hz, CH_3CH_2O), 6.98-7.06 (2 H, m, ArH), 7.50 (1 H, t, J = 7.5 Hz, ArH), 7.96 (1 H, d, J = 7.9 Hz, ArH) and 8.22 (1 H, s, 4´-H); ^{13}C NMR [125 MHz, $(CD_3)_2SO$] 14.2, 61.0, 116.7, 117.2, 119.8, 121.4,130.5, 134.7, 144.2, 157.4, 161.3, 162.2 and 165.0; m/z (ES -ve ion mode) 315 (MNa^+, 100%); Found: m/z 315.0411; $C_{13}H_{12}N_2O_4SNa$ requires m/z, 315.0410.

2-Hydroxybenzoyl-*N*-[(5-trifluoromethyl)thiazol-2-yl]amide (28). Base-catalysed epoxidation of 1,1,1-trifluoro-3-phenylsulfonylpropene **51**[33] followed by reaction of the unpurified product **52** with thiourea afforded 2-amino-5-trifluoromethylthiazole **53** as previously described. [34] Acylation of the amine **53** (6.4 mmol) with acetylsalicyloyl chloride (8.04 mmol) under the anhydrous conditions given above afforded the *O*-acetate of **28** (0.883 g, 42%) which was deprotected using standard acidic conditions (above) to give **28** as a colourless powder (94%), mp 260-264°C (sealed tube, sublimes 253-259°C); HPLC area purity 97.7% (conditions C); ^{1}H NMR [400 MHz, $(CD_3)_2SO$] 7.01 (1 H, m), 7.06 (1 H, dd, J = 8.3 and 0.8 Hz), 7.50 (1 H, m), 7.95 (1 H, dd, J = 7.9 and 1.7 Hz), 8.20 (1 H, s, 4´-H), 11.73 (1 H, br s) and 13.24 (1 H, br s); MS (ES+ve mode) *m/z* 289.0 $(M+H)^+$ and (ES-ve mode) 287.1 $(M-H)^-$.

The salicyloyl anilides **30-37** were prepared by coupling of the appropriate aniline to acetylsaliciloyl chloride as described in the main MS. Three examples are given below to illustrate this different class; compounds **30,**[71] **31,**[71] **32,**[72] **33**[73] and **34**[73] are known, but with little or no spectroscopic data for **32** and **33**; finally, compounds **35**-**37** are new.

2-Hydroxybenzoyl-*N*-(4-chlorophenyl)amide (31).[71] ^{1}H NMR [400 MHz, $(CD_3)_2SO$] 6.98 (2 H, m, ArH), 7.43 (3 H, m, ArH), 7.76 (2 H, m, ArH), 7.94 (1 H, dd, J = 7.8 and 1.5 Hz, Ar H), 10.5 and 11.6 (2 s, br, NH and OH); ^{13}C NMR [100 MHz, $(CD_3)_2SO$] 117.6, 118.0, 119.4, 122.8, 128.2, 129.0, 129.5, 134.1, 137.6, 158.7 and 167.0; m/z 248 (100%, MH^+, ^{35}Cl); Found: m/z, 248.04850. $C_{13}H_{11}ClNO_2$ (MH^+) requires m/z, 248.04782.

2-Acetoxybenzoyl-*N*-(4-bromophenyl)amide (32).[72] ^{1}H NMR [400 MHz, $CDCl_3$] 2.32 (3 H, s, CH_3CO), 7.16 (1 H, dd, J = 8 Hz and 1 Hz, ArH), 7.35 (1 H, m, ArH), 7.44-7.54 (5 H, m, ArH), 7.82 (1 H, dd, J = 7.6 and 1.4 Hz, ArH) and 8.05 (1 H, br s, NH); ^{13}C NMR [100 MHz, $CDCl_3$] 21.4, 117.7, 121.8, 123.8, 127.0, 129.0, 130.3, 132.6, 132.7, 137.3, 148.2, 164.0 and 169.6; m/z 351, 353 (MH^+ for ^{79}Br, ^{81}Br, 100%); Found: m/z, 334.00786. $C_{15}H_{13}{}^{79}BrNO_3$ (MH^+) requires m/z, 334.00790.

2-Hydroxybenzoyl-*N*-(4-iodophenyl)amide (33).[72] [NB this compound was screened as the *O*-acetate] Mp 184-186°C (from EtOAc); ^{1}H NMR [400 MHz, $CDCl_3$] 6.96 (2 H, m, ArH), 7.49 (1 H, approx. dd, J = 7.3 and 1.6 Hz, ArH), 7.64 (2 H, d, ArH), 7.75 (2 H, m, ArH), 8.00 (1 H, dd, J = 8.3 and 1.6 Hz, 6-H) and 9.87 (1 H, br s, NH); ^{13}C NMR [125 MHz, $(CD_3)_2CO$] 88.4, 116.2, 118.8, 119.8, 124.2, 128.4, 135.4, 138.6, 139.0, 162.2 and 169.5; m/z 351 $(M-H)^-$; Found: m/z, 337.9682. $C_{13}H_9INO_2$ $[M-H]^-$ requires m/z, 337.9683.

2-Hydroxybenzoyl-*N*-[2-chloro-5-(trifluoromethyl)phenyl]amide (35). Mp 198-199°C (from EtOAc); ^{19}F NMR [376 MHz, $(CD_3)_2CO$], -63.2 (s); ^{1}H NMR [400 MHz, $(CD_3)_2CO$] 7.07 (1 H, m, ArH), 7.13 (1 H, d, J = 7.7 Hz), 7.51 (2 H, m, ArH), 7.77 (1 H, d, J = 8.4 Hz), 8.16 (1 H, dd, J = 8.0 and 1.7 Hz, ArH), 8.94 (1 H, d, J = 2.0 Hz), 10.72 (1 H, br s, OH) and 11.18 (1 H, br s, NH); m/z (ES –ve ion mode) 314 $[M-H]^-$; Found: m/z, 314.0213. $C_{14}H_9NO_2ClF_3$ (M-H) requires m/z, 314.0201.

2-Acetoxybenzoyl-N-[3,5-bis(trifluoromethyl)phenyl]amide (36). Mp = 118-125°C (sealed tube); HPLC t_R = 8.79 min (99.0%, condition C). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] 10.99 (1 H, s, NH), 8.39 (2 H, s, ArH), 7.83 (1 H, s, ArH), 7.77 (1 H, dd, *J* =7.5 and 1.2 Hz, ArH), 7.64 (1 H, ddd, *J* = 7.5, 7.5 and 1.6 Hz, ArH), 7.44 (1 H, ddd, *J* = 7.5, 7.5 and 0.8 Hz, ArH), 7.30 (1 H, dd, *J* = 7.5 and 0.8 Hz, ArH), and 2.21 (3 H, s, CH_3CO); m/z (ES+ve mode) 350.0 (MH^+), (ES-ve mode) 348.1$[M-H]^-$.

2-Hydroxybenzoyl-*N*-[(5-chloro-2-methyl-4-nitro)phenyl]amide (37). ^{1}H NMR [400 MHz, $(CD_3)_2SO$] 2.39 (3 H, s, CH_3Ar), 7.02 (1 H, m, ArH), 7.06 (1 H, m, ArH), 7.47 (1 H, m, ArH), 8.02 (1 H, d, ArH), 8.10 (1 H, s, 6´-H), 8.69 (1 H, s, 3´-H) and 10.79 (1H, br, NH); ^{13}C NMR [125 MHz, $(CD_3)_2SO$] 16.9, 117.0, 118.1, 120.0, 121.9, 124.0, 127.7(x2), 130.9, 134.2, 141.2, 142.0, 156.4 and 164.1; m/z (ES –ve ion mode) 305 $[M-H]^-$; Found: m/z, 305.0338. $C_{14}H_{10}ClN_2O_4$ $[M-H]^-$ requires m/z, 305.0335.

<u>Table 1</u>: Microanalytical data for target compounds.

Compound	Microanalysis	
	Found	Required
7	C, 42.0; H, 2.9; N, 8.9	C, 42.2; H, 2.9; N, 9.0%
6	C, 40.1; H, 2.35; N, 9.4	C, 40.2; H, 2.3; N, 9.3%
12	C, 49.1; H, 3.4; N, 10.4	C, 49.2; H, 3.4; N, 10.4%

Table 2 Descriptors correlated to descriptors in pEC_{90} RI QSAR model.

Descriptor in Model	Correlated Descriptors	Correlation

IDDE	BEHm7:	0.861281986
	GGI3:	0.783576531
	MATS6m:	0.773745656
BEHp7	Num_Atoms:	0.844749676
	Num_Bonds:	0.844749676
	nSK:	0.844749676
	nBO:	0.844749676
	SCBO:	0.826301685
	RBN:	0.750190558
	RBF:	0.750190558
	IAC:	0.789075626
	ZM1:	0.846797402
	ZM1V:	0.754286602
	ZM2:	0.854556367
	ZM2V:	0.768351292
	Qindex:	0.814547771
	SNar:	0.831981016
	GNar:	-0.773425642
	Dz:	0.797444139
	Ram:	0.814547771
	Pol:	0.858220776
	LPRS:	0.840772213
	VDA:	0.827546911
	SMTI:	0.838462906
	SMTIV:	0.793605448
	GMTI:	0.836546733
	GMTIV:	0.757028816
	Xu:	0.832991454
	SPI:	0.87755358
	W:	0.839665955
	WA:	0.790013527

RDSUM:	0.853655398
Har:	0.851333339
QW:	0.84442264
TI1:	0.835439202
TI2:	0.779138987
HyDp:	0.82975299
RHyDp:	0.852608687
w:	0.856897179
ww:	0.858399403
Rww:	0.835287364
D/D:	0.83141711
Wap:	0.850990279
WhetZ:	0.83563367
Whetm:	0.835234974
Whetv:	0.821757732
Whete:	0.843593124
Whetp:	0.818644261
X0:	0.846541976
X1:	0.842913656
X2:	0.822730781
X3:	0.854511459
X4:	0.781338655
X0A:	0.752213547
RDCHI:	0.799927194
RDSQ:	0.854570362
S1K:	0.826829687
S2K:	0.768265113
CSI:	0.769066836
ECC:	0.77580203
MDDD:	0.79205354
UNIP:	0.812838046

CENT:	0.861268169
VAR:	0.853148107
BAC:	0.853271622
Lop:	0.750467337
IDM:	0.843658654
IDDM:	0.841554032
IDET:	0.836096512
IDMT:	0.843699624
IVDM:	0.762295322
HDcpx:	0.84154367
Uindex:	0.846181699
TIC0:	0.789075626
TIC1:	0.784601437
Eig1Z:	0.815366714
Eig1m:	0.814728499
Eig1v:	0.798506006
Eig1e:	0.833619249
Eig1p:	0.794033671
VEA1:	0.816337587
VEA2:	-0.810640212
VRA1:	0.842101407
VRA2:	0.762205893
VED1:	0.845990949
VED2:	-0.828853472
VRD1:	0.846661618
VRD2:	0.839497462
VEZ1:	0.847174731
VEZ2:	-0.829727071
VRZ1:	0.843014962
VRZ2:	0.823854909
VEm1:	0.847107603

VEm2:	-0.829727071
VRm1:	0.842861628
VRm2:	0.824056559
VEv1:	0.848908496
VEv2:	-0.828575699
VRv1:	0.841943587
VRv2:	0.82595908
VEe1:	0.842472332
VEe2:	-0.829936258
VRe1:	0.849203535
VRe2:	0.83959698
VEp1:	0.84719035
VEp2:	-0.82075906
VRp1:	0.840591367
VRp2:	0.822296912
NGS:	0.845174619
MPC03:	0.858220776
MPC04:	0.840453556
MPC05:	0.826493449
MPC06:	0.765796806
MPC07:	0.867842496
MPC08:	0.811106024
MPC09:	0.85881934
MPC10:	0.839913741
piPC03:	0.858911153
piPC04:	0.845516917
piPC05:	0.794547154
piPC08:	0.803047194
piPC09:	0.862415583
piPC10:	0.832591874
TPC:	0.852622863

piID:	0.83378489
PCD:	0.831481064
CID:	0.843556972
BID:	0.845492605
D/Dr05:	0.820579222
D/Dr06:	0.839324497
MWC01:	0.844749676
MWC02:	0.846797402
MWC03:	0.853611084
MWC04:	0.847874941
MWC05:	0.861429937
MWC06:	0.856015245
MWC07:	0.836581673
TWC:	0.851209562
SRW02:	0.844749676
SRW04:	0.846440667
SRW06:	0.851366209
SRW08:	0.850264562
SRW10:	0.842396673
BEHv2:	0.82078774
BEHv7:	0.865829512
BELv8:	0.78641661
BEHe6:	0.798161194
BEHe8:	0.828430183
BELe8:	0.83914614
BELp8:	0.793370565
GGI2:	0.834510962
GGI4:	0.842790731
GGI6:	0.846641647
GGI8:	0.855578606
JGI4:	0.77679818

	ATS1e:	0.7624105
	ATS3e:	0.756641217
	BCUTc-1h:	0.846110927
	nB:	0.844749676
	SCH-6:	-0.821406876
	SCH-7:	0.840044514
	SC-5:	0.773098206
	SP-0:	0.84654258
	SP-1:	0.842941781
	SP-2:	0.822905684
	SP-3:	0.854423678
	SP-4:	0.781359307
	SP-7:	0.797694169
	SPC-4:	0.843175937
	SPC-5:	0.775923816
	SPC-6:	0.777737071
	ECCEN:	0.769066836
	Kier1:	0.844974658
	Kier2:	0.802816569
	VAdjMat:	0.838959522
	WTPT-1:	0.843579833
	WTPT-2:	-0.774461863
	WPATH:	0.839665955
	WPOL:	0.858220776
	Zagreb:	0.846797402
ATSc7	-	-

Additional References (Numbers follow on from the main MS).

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