Supporting Information

1-Benzhydryl-3-phenylurea and 1-Benzhydryl-3-phenylthiourea Derivatives: New Templates among the CB_1 Cannabinoid Receptor Inverse Agonists.

Giulio G. Muccioli[†], Johan Wouters[#], Gerhard K.E. Scriba[‡], Wolfgang Poppitz[§], Jacques H. Poupaert[†], and Didier M. Lambert[†]

Table of contents

General Procedure for the Synthesis of Benzils (X = Cl, Br): Briefly, suitably substituted benzaldehyde derivatives (0.27 mole) and sodium cyanide (0.08 mole) were refluxed in ethanol (65 mL) and water (50 mL) for 3 hours. After cooling, the resulting oil was extracted with chloroform. Following removal of the solvent under reduced pressure, the resulting benzoin was oxidized by heating with nitric acid. Upon completion of the oxidation, the solution was poured into water and the precipitate crystallized.

4,4'-Dichlorobenzil: (CAS number: 3457-46-3) Spectral data in accordance to the literature[1]. Yield after crystallization: 54%

4,4'-Dibromobenzil: (CAS number: 35578-47-3) Spectral data in accordance to the literature[1]. Yield after crystallization: 48%

General Procedure for the Synthesis of Substituted Phenylureas : The phenylurea derivatives were synthesized according to the method described by Kurzer[2]. Briefly, the aniline (0.05 mole) was dissolved in glacial acetic acid (24 mL) and water (48 mL). To this solution, was slowly added under stirring the sodium cyanate (0.1 mole) dissolved in water (45 mL). When a white precipitate appeared, the solution was stirred for 1 additional hour, then it was allowed to stand at RT for 2-3 hours. The solution was cooled to 0° before filtration. The resulting phenylurea was washed with cold water, and was used without any further purification.

General Procedure for the Synthesis of Substituted Phenylthioureas : The phenylisothiocyanate (0.05 mole) was dissolved in acetone (25mL) and an excess of concentrate ammonia was slowly added under stirring. The solution was stirred at RT until a white precipitate of phenylthiourea appeared. After two additional hours of stirring the precipitate was filtered off and subsequently washed with water. The phenylthiourea was used without any further purification.

^{1}H NMR and IR characterization of synthesized derivatives

1-Benzhydryl-3-(4-fluorophenyl)urea (4). ^{1}H NMR (DMSO-d_6) δ 5.96 (d, *J*=7.41 Hz, 1H), 7.03-7.37 (m, 15H), 8.51 (s, 1H). IR (KBr, cm^{-1}) ν 3349 (NH), 3295 (NH), 1652 (C=O), 1492 (C=C).

1-Benzhydryl-3-(4-bromophenyl)urea (6). ^{1}H NMR (DMSO-d_6) δ 5.96 (d, *J*=7.35 Hz, 1H), 7.20-7.37 (m, 15H), 8.61 (s, 1H). IR (KBr, cm^{-1}) ν 3334 (NH), 3284 (NH), 1645 (C=O), 1485 (C=C).

1-Benzhydryl-3-(2-fluorophenyl)urea (8). ^{1}H NMR (DMSO-d_6) δ 5.87 (d, *J*=7.41 Hz, 1H), 7.11-7.45 (m, 15H), 8.53 (s, 1H). IR (KBr, cm^{-1}) ν 3343 (NH), 3294 (NH), 1646 (C=O), 1487 (C=C).

1-Benzhydryl-3-(4-methoxyphenyl)urea (9). ^{1}H NMR (DMSO-d_6) δ 3.68 (s, 3H), 5.96 (d, *J*=7.35, 1H), 7.24-7.37 (m, 15H), 8.27 (s, 1H). IR (KBr, cm^{-1}) ν 3383 (NH), 3263 (NH), 1641 (C=O), 1500 (C=C), 1245 (C-O-C).

1-Benzhydryl-3-(4-hexylphenyl)urea (10). ^{1}H NMR (DMSO-d_6) δ 0.84 (m, 3H), 1.24 (m, 8H), 1.50 (m, 2H), 5.96 (d, *J*=7.35 Hz, 1H), 7.01-7.37 (m, 15H), 8.37 (s, 1H). IR (KBr, cm^{-1}) ν 3331 (NH), 3214 (NH), 1625 (C=O), 1479 (C=C).

1-[Bis(4-chlorophenyl)methyl]-3-(4-chlorophenyl)urea (14). ^{1}H NMR (DMSO-d_6) δ 5.96 (d, *J*=5.88 Hz, 1H), 7.25-7.56 (m, 13H), 8.62 (s, 1H). IR (KBr, cm^{-1}) ν 3359 (NH), 3315 (NH), 1655 (C=O), 1475 (C=C).

1-[Bis(4-bromophenyl)methyl]-3-(4-chlorophenyl)urea (16). ^{1}H NMR (DMSO-d_6) δ 5.96 (d, *J*=7.35 Hz, 1H), 7.24-7.42 (m, 13H), 8.60 (s, 1H). IR (KBr, cm^{-1}) ν 3371 (NH), 3324 (NH), 1642 (C=O), 1471 (C=C).

---

[1] Wang, X.; Zhang, Y. Samarium Diiodide Promoted Formation of 1,2-Diketones and 1-Acylamido-2-substituted Benzimidazoles from *N*-Acylbenzotriazoles. *Tetrahedron* **2003**, *59*, 4201-4207.

[2] Kurzer, F. In *Organic Synthesis*; Wiley: New-York, **1964**, Vol. IV, 49-50.

1-[Bis(4-iodophenyl)methyl]-3-(4-bromophenyl)urea (18). ^{1}H NMR (DMSO-d_6) δ 5.87 (d, *J*=7.35 Hz, 1H), 7.09-7.96 (m, 13H), 8.62 (s, 1H). IR (KBr, cm^{-1}) ν 3368 (NH), 3315 (NH), 1621 (C=O), 1454 (C=C).

1-[Bis(4-bromophenyl)methyl]-3-(4-hydroxymethylphenyl)urea (20). ^{1}H NMR (DMSO-d_6) δ 4.46 (CH_2), 5.31 (d, *J*=7.35 Hz, 1H), 6.90-7.73 (m, 13H), 8.30 (s, 1H). IR (KBr, cm^{-1}) ν 3303 (large peak, OH) 1634 (C=O), 1487 (C=C).

1-[Bis(4-bromophenyl)methyl]-3-(4-hexylphenyl)urea (21). ^{1}H NMR (DMSO-d_6) δ 0.87 (m, 3H), 1.27 (m, 8H), 1.53 (m, 2H), 5.98 (d, *J*=7.35 Hz, 1H), 7.04-7.60 (m, 13H), 8.39 (s, 1H). IR (KBr, cm^{-1}) ν 3381 (NH), 3334 (NH), 1664 (C=O), 1445 (C=C).

1-[Bis(4-chlorophenyl)methyl]-3-phenylthiourea (22). ^{1}H NMR (DMSO-d_6): δ 6.75 (d, *J*=5.88 Hz, 1H), 7.06-7.52 (m, 13H), 8.71 (d, *J*=8.82 Hz , 1H) 9.60 (s, 1H). IR (KBr, cm^{-1}) ν 3281 (NH), 3214 (NH), 1476 (C=C) , 1080 (C=S).

1-[Bis(4-bromophenyl)methyl]-3-phenylthiourea (23). ^{1}H NMR (DMSO-d_6): δ 6.72 (d, *J*=8.82 Hz, 1H), 7.08-7.58 (m, 13H), 8.70 (d, *J*=7.35 Hz , 1H) 9.60 (s, 1H). IR (KBr, cm^{-1}) ν 3280 (NH), 3217 (NH), 1479 (C=C) , 1085 (C=S).

1-[Bis(4-chloro-phenyl)methyl]-3-(4-chlorophenyl)thiourea (24). ^{1}H NMR (DMSO-d_6): δ 6.74 (s, 1H), 7.28-7.56 (m, 12H), 8.79 (s, 1H) 9.67 (s, 1H). IR (KBr, cm^{-1}) ν 3289 (NH), 3228 (NH), 1489 (C=C) , 1089 (C=S).

1-[Bis(4-bromophenyl)methyl]-3-(4-chlorophenyl)thiourea (25). ^{1}H NMR (DMSO-d_6): δ 6.70 (d, *J*=8.07 Hz, 1H), 7.23-7.58 (m, 12H), 8.77 (d, *J*=7.35 Hz , 1H) 9.66 (s, 1H). IR (KBr, cm^{-1}) ν 3288 (NH), 3223 (NH), 1487 (C=C) , 1092 (C=S).

3,5,5'-Triphenylimidazolidin-2,4-dione (26). ^{1}H NMR (DMSO-d_6): δ 7.35-7.49 (m, 15H), 9.92 (s, 1H). IR (KBr, cm^{-1}) ν 3226 (NH), 1782 (C=O), 1724 (C=O), 1477 (C=C).

3-(4-Bromophenyl)-5,5'-diphenylimidazolidine-2,4-dione (**27**). ^{1}H NMR (DMSO-d_6): δ 7.40-7.69 (m, 14H), 10.03 (s, 1H). IR (KBr, cm^{-1}) ν 3216 (NH), 1779 (C=O), 1716 (C=O), 1492 (C=C).

5,5'-Bis(4-fluorophenyl)-3-phenylimidazolidine-2,4-dione (**28**). ^{1}H NMR (DMSO-d_6): δ 7.27-7.53 (m, 13H), 9.99 (s, 1H). IR (KBr, cm^{-1}) ν 3224 (NH), 1775 (C=O), 1722 (C=O), 1505 (C=C).

5,5'-Bis(4-bromophenyl)-3-phenylimidazolidine-2,4-dione (**29**). ^{1}H NMR (DMSO-d_6): δ 7.37-7.68 (m, 13H), 9.46 (s, 1H). IR (KBr, cm^{-1}) ν 3285 (NH), 1775 (C=O), 1712 (C=O), 1499 (C=C).

5,5'-Bis(4-bromophenyl)-3-phenyl-2-thioxoimidazolidin-4-one (**30**). ^{1}H NMR (DMSO-d_6): δ 7.34-7.71 (m, 13H), 11.96 (s, 1H). IR (KBr, cm^{-1}) ν 3128 (NH), 1753 (C=O), 1490 (C=C), 1390 (C=S).

5,5'-Bis(4-bromophenyl)-3-(4-chlorophenyl)-2-thioxoimidazolidin-4-one (**31**). ^{1}H NMR (DMSO-d_6): δ 7.26-7.70 (m, 13H), 12.01 (s, 1H). IR (KBr, cm^{-1}) ν 3122 (NH), 1761 (C=O), 1490 (C=C), 1395 (C=S).

Appendix : Elemental analysis data

1-Benzhydryl-3-(4-fluorophenyl)urea (4). Anal. Calc. for $C_{20}H_{17}FN_2O$: C, 74.98; H, 5.35; F, 5.93; N, 8.74; O, 4.99 %. Found : C, 74.58; H, 5.18; N, 8.60 %.

1-Benzhydryl-3-(4-bromophenyl)urea (6). Anal. Calc. for $C_{20}H_{17}BrN_2O$: C, 63.01; H, 4.49; Br, 20.96; N, 7.35; O, 4.20 %. Found : C, 62.25; H, 4.29; N, 7.2 5%.

1-Benzhydryl-3-(4-methoxyphenyl)urea (9). Anal. Calc. for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43; O, 9.63 %. Found : C, 75.47; H, 5.84; N, 8.38 %.

1-Benzhydryl-3-(4-hexylphenyl)urea (10). Anal. Calc. for $C_{26}H_{30}N_2O$: C, 80.79; H, 7.82; N, 7.25; O, 4.14 %. Found : C, 80.52; H, 7.75; N, 7.23 %.

1-[Bis-(4-chlorophenyl)methyl]-3-(4-chlorophenyl)urea (14). Anal. Calc. for $C_{20}H_{15}Cl_3N_2O$: C, 59.21; H, 3.73; Cl, 26.22; N, 6.90; O, 3.94 %. Found : C, 59.15; H, 3.63; N, 6.61 %.

1-[Bis(4-bromophenyl)methyl]-3-(4-chlorophenyl)urea (16). Anal. Calc. for $C_{20}H_{15}Br_2ClN_2O$: C, 48.57; H, 3.06; Br, 32.31, Cl, 7.17; N, 5.66; O, 3.23 %. Found : C, 48.31; H, 2.86; N, 5.44 %.

1-[Bis(4-bromophenyl)methyl]-3-(4-hexylphenyl)urea (17). Anal. Calc. for $C_{26}H_{28}Br_2N_2O$: C, 57.37; H, 5.18; Br, 29.36; N, 5.15; O, 2.94 %. Found : C, 57.14; H, 5.25; N, 5.06%.

1-[Bis(4-iodophenyl)methyl]-3-(4-bromophenyl)urea (18). Anal. Calc. for $C_{20}H_{15}BrI_2N_2O$: C, 37.95; H, 2.39; Br, 12.62; I, 40.09; N, 4.43; O, 2.53 %. Found : C, 37.65; H, 2.01; N, 4.77 %.

1-[Bis(4-bromophenyl)methyl]-3-(4-hydroxymethylphenyl)urea (20). Anal. Calc. for $C_{21}H_{18}Br_2N_2O_2*1/2H_2O$: C, H, N. C, 50.53; H, 3.84; Br, 32.01; N, 5.61; O, 8.01 %. Found : C, 50.72; H, 3.66; N, 5.49 %.

1-[Bis(4-chlorophenyl)methyl]-3-phenythiourea (22). Anal. Calc. for $C_{20}H_{16}Cl_2N_2S*1/4H_2O$: C, 61.31; H, 4.24; Cl, 18.10; N, 7.15; O, 1.02; S, 8.18 %. Found : C, 61.52; H, 3.86; N, 6.97 %.

1-[Bis(4-bromophenyl)methyl]-3-phenylthiourea (23). Anal. Calc. for $C_{20}H_{16}Br_2N_2S$: C, 50.44; H, 3.39; Br, 33.56; N, 5.88; S, 6.73 %. Found : C, 50.38; H, 3.18; N, 5.75 %.

1-[Bis(4-chlorophenyl)methyl]-3-(4-chlorophenyl)thiourea (24). Anal. Calc. for $C_{20}H_{15}Cl_3N_2S$: C, 56.95; H, 3.58; Cl, 25.22; N, 6.64; S, 7.60 %. Found : C, 57.02; H, 3.42; N, 6.50 %.

1-[Bis(4-bromophenyl)methyl]-3-(4-chlorophenyl)thiourea (25). Anal. Calc. for $C_{20}H_{15}Br_2Cl_1N_2S$: C, 47.04; H, 2.96; Br, 31.29; Cl, 6.94; N, 5.49; S, 6.28 %. Found : C, 47.05; H, 2.80; N, 5.31 %.

3-(4-Bromophenyl)-5,5'-diphenylimidazolidine-2,4-dione (**27**). Anal. Calc. for $C_{21}H_{15}Br_2N_2O_2$: C, 61.93; H, 3.71; Br, 19.72; N, 6.88; O, 7.86 %. Found : C, 61.74; H, 3.81; N, 6.59 %.

5,5'-Bis(4-fluorophenyl)-3-phenyl-imidazolidine-2,4-dione (**28**). Anal. Calc. for $C_{21}H_{14}F_2N_2O_2$: C, 69.23; H, 3.87; F, 10.43; N, 7.69; O, 8.78 %. Found : C, 69.34; H, 3.99; N, 7.51 %.

5,5'-Bis(4-bromophenyl)-3-phenylimidazolidine-2,4-dione (**29**). Anal. Calc. for $C_{21}H_{14}Br_2N_2O_2$: C, 51.88; H, 2.90; Br, 32.87; N, 5.76; O, 6.58 %. Found : C, 51.54; H, 3.15; N, 5.52 %.

5,5'-Bis(4-bromophenyl)-3-phenyl-2-thioxoimidazolidin-4-one (**30**). Anal. Calc. for $C_{21}H_{14}Br_2N_2OS$: C, 50.22; H, 2.81; Br, 31.82; N, 5.58; O, 3.19; S, 6.38 %. Found : C, 50.22; H, 2.53; N, 5.47 %.

5,5'-Bis(4-bromophenyl)-3-(4-chlorophenyl)-2-thioxoimidazolidin-4-one (**31**). Anal. Calc. for $C_{21}H_{13}Br_2ClN_2OS$: C, 47.00; H, 2.44; Br, 29.78; Cl, 6.61; N, 5.22; O, 2.98; S, 5.97 %. Found : C, 47.03; H, 2.18; N, 5.14 %.