

2015-11-11 2-Phenyl Benzofuran Derivatives for A β and Amylin Disaggregation

Preparation of 2-phenylbenzofuran derivatives for the treatment of central nervous system disorders and other disorders

John C. Warner, Srinivasa R. Cheruku and Jeffery A. Gladding

The Warner Babcock Institute for Green Chemistry

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The present application discloses 2-phenylbenzofuran derivatives represented by formula I [R₆ = NR₃R₄, R₃, OR₃, or halo and R₅ = (CR:CR)_n(CR:CR₂)_mR₁; or R₆ = (CR:CR)_n(CR:CR₂)_mR₁ and R₅ = NR₃R₄, R₃, OR₃, or halo, and further wherein m = 0-1, n = an integer of 0-10; R₁, R₂ = independently H, cyano, CO₂R, CONHR, CON(H)OR, SO₃R, SO₂R, OSO₃R, PO₃HR, OPO₃HR, further wherein at least one of R₁ and R₂ ≠ H, and if n = m = 0 then R₁ ≠ H; R = independently H or C₁₋₆ linear or branched alkyl; R₃, R₄ = independently H or each (un)substituted linear or branched C₁₋₁₀ alkyl, Ph, C₆₋₁₀ aryl, C₅₋₁₀ heteroaryl, C₅₋₁₀ cycloalkyl, or C₅₋₁₀ heterocycloalkyl; or R₃ and R₄ attached to their N together form (un)substituted C₅₋₁₀ heterocycloalkyl]. The compounds I are useful for treating ocular diseases (macular degeneration, retinitis pigmentosa, retinopathy, glaucoma, and cataracts), neurol. disorders (neurodegenerative, neurodevelopmental or neuropsychiatric disorder), or protein aggregation-related disorders. Thus, 0.61 mL acetonitrile, 0.012 g cyanoacetic acid, and 0.018 mL piperidine were added to 0.048 g 4-[6-(diphenylamino)benzofuran-2-yl]benzaldehyde and the resulting mixture was heated to reflux for 2.5 h, cooled to room temperature, and treated with 10 mL. The aqueous fraction was acidified to pH = 2 with 1 M HCl, then extracted with dichloromethane (3x 15 mL). The combined organic fractions were dried over sodium sulfate, filtered, and the filtrate was concentrated and purified by chromatog. on silica gel to afford 0.034 g 2-cyano-3-[4-[6-(diphenylamino)benzofuran-2-yl]phenyl]acrylic acid (II). II showed EC₅₀ of 0.54 μM for disaggregation of 15 μM Zn²⁺-induced aggregation of A β 42 and EC₅₀ of 0.52 μM for disaggregation of amylin.

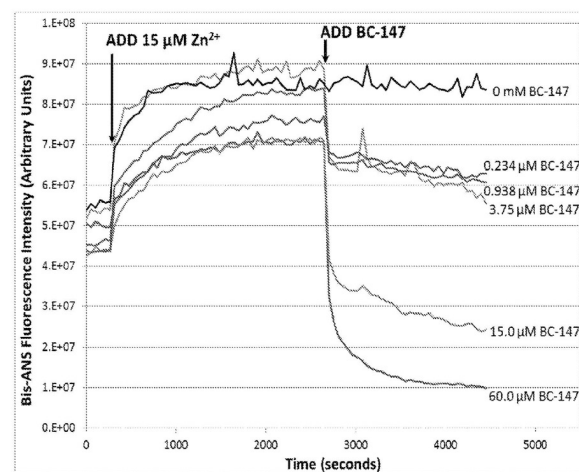
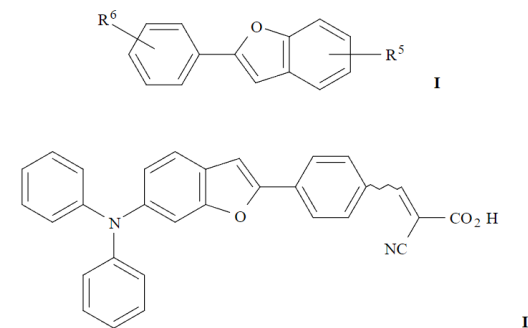


Figure 1

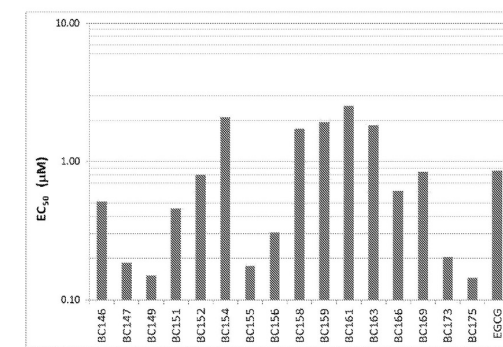
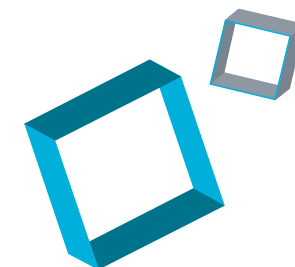
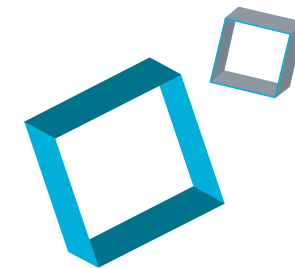


Figure 6



2017-05-09 Stilbene Compounds for A β and Amylin Disaggregation



Preparation of stilbene derivatives for use as central nervous system agents

John C. Warner

The Warner Babcock Institute for Green Chemistry

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Title compounds I [R⁵ = CH=CH₂, CH=CHCH=CH₂, CH=CHCN, etc.; R⁶ = H, halo, OH, NH₂, etc.; with provisions], and their pharmaceutically acceptable salts, are prepared and disclosed as central nervous system (CNS) agents. Thus, e.g., II was prepared by a multistep procedure (preparation given). I were evaluated in fluorescence-based assays of A₃ disaggregation, e.g., II demonstrated an EC₅₀ value of 31.041 (avg).

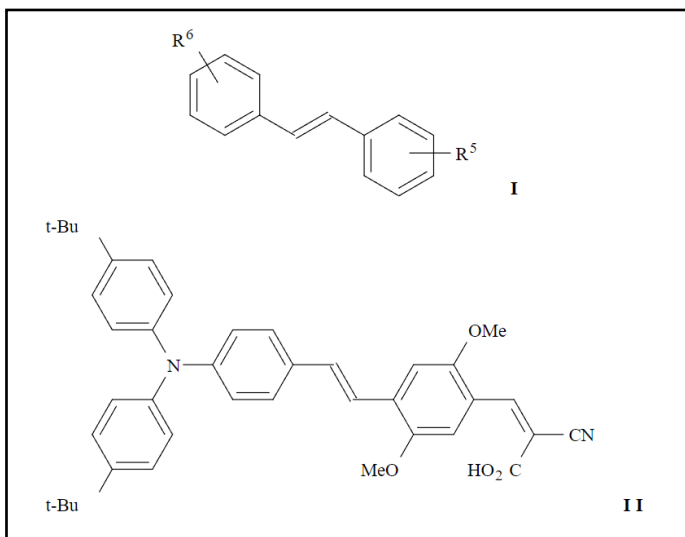


TABLE 1

EC₅₀ values of A β 1-42:Zn disaggregation by select compounds

Compound	EC ₅₀ (Avg)	StDev
PC-063	31.041	16.945
PC-064	0.747	0.090
PC-078	1.376	0.110
PC-081	0.338	0.031
PC-174	49.650	238.498
PC-190	0.649	0.072
PC-191	1.613	0.281
PC-192	2.848	0.550
CQ	2.693	0.196
DCVJ	0.533	0.188
EDTA	46.120	38.551
AC-068(PBT2)	2.215	0.271

TABLE 2

EC₅₀ values of Amylin Disaggregation by select compounds

Compound	EC ₅₀	StdDev
PC-063	1.259	0.693
PC-064	0.024	0.043
PC-066	1.191	0.309
PC-081	0.207	0.111
PC-174	3.740	6.464
CQ	4.074	3.036
EGCG	0.857	0.491