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Potent CYP19 (aromatase) 1-(benzofuran-2-yl)(phenylmethyl) pyridine, -imidazole, and -triazole inhibitors: Synthesis and biological evaluation

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Abstract

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The synthesis of a series of novel 1-[(benzofuran-2-yl)phenylmethyl]- pyridine, -imidazole, and -triazole derivatives is described. All the compounds were evaluated in vitro for inhibitory activity against aromatase (P450 $_{AROM}$, CYP19), using human placental microsomes. The 6-methoxy- and 6-hydroxy-substituted benzofuran derivatives were shown to be potent CYP19 inhibitors (IC $_{50}$ = 0.01 - 1.46 μM) with activity greater than that observed for the unsubstituted parent compounds and inhibitory activity comparable with or greater than the reference compound arimidex (IC $_{50}$ = 0.6 μM). Six of the benzofuran derivatives were subjected to in vitro cytotoxicity assays, using rat liver hepatocytes with cytotoxicity determined from alteration in cell morphology and lactate dehydrogenase enzyme retention over a period of 24 h, and selectivity (CYP17, 17β-HSD types 1 and 3, CYP24, and CYP26) determination; negligible inhibitory activity was observed, suggesting a good selectivity for CYP19. The pyridine benzofuran 4a containing the 4-fluorophenyl group was the most promising (IC $_{50}$ = 44 nM; LC $_{50}$ > 100 μM) compared with arimidex (IC $_{50}$ = 600 nM; LC $_{50}$ > 200 μM). © 2006 American Chemical Society.

Reaxys Database Information

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Indexed Keywords

EMTREE drug terms: 1 [(benzofuran 2 yl)phenylmethyl]imidazole; 1 [(benzofuran 2 yl) phenylmethyl]pyridine; 1 [(benzofuran 2 yl)phenylmethyl]triazole; anastrozole; aromatase inhibitor; imidazole derivative; lactate dehydrogenase; pyridine derivative; tamoxifen; triazole derivative; unclassified drug

EMTREE medical terms: article; breast cancer; cell strain MCF 7; cytotoxicity; drug determination; drug potency; drug screening; evaluation; human; human cell; liver cell; microsome membrane; molecular model; synthesis

MeSH: Animals; Aromatase; Aromatase Inhibitors; Benzofurans; Hepatocytes; Humans; Imidazoles; L-Lactate Dehydrogenase; Male; Microsomes; Models, Molecular; Placenta; Pyridines; Rats; Rats, Sprague-Dawley; Stereoisomerism; Structure-Activity Relationship; Triazoles

Medline is the source for the MeSH terms of this document.

Chemicals and CAS Registry Numbers: anastrozole, 120511-73-1; lactate dehydrogenase, 9001-60-9; tamoxifen, 10540-29-1;6-methoxybenzofuran-2-yl-(4-fluorophenyl)-3-pyridylmethanol; Aromatase Inhibitors; Aromatase, EC 1.14.14.1; Benzofurans; Imidazoles; L-Lactate Dehydrogenase, EC 1.1.1.27; Pyridines; Triazoles

Drug tradename: arimidex.

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