Synthesis and structure-activity relationship study of novel 3-heteroarylcoumarins based on pyridazine scaffold as selective MAO-B inhibitors

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Compounds of hybrid structure pyridazine-coumarin were discovered as potent, selective and reversible inhibitors of monoamine oxidase B (MAO-B). These compounds were synthesized in good yield following a multistep approach based on Knoevenagel reaction and using as key intermediate pyridazinone 16, which was obtained from maleic anhydride and furan. Compounds 9b and 9d are the most active compounds of these series, with IC50 values in the sub-micromolar range, and lack of cytotoxic effects. Theoretical calculation of ADME properties also suggested a good pharmacokinetic profile for both compounds. Docking simulations provided insights into enzyme inhibitor interactions and allowed us to rationalize the observed structure-activity relationships (SARs).

ADME

Coumarin

MAO-B

Molecular modeling

Neurodegenerative disorders

Pyridazine

3 (6 bromopyridazin 3 yl) 6 methoxycoumarin

3 (6 bromopyridazin 3 yl) 6 methylcoumarin

3 (6 bromopyridazin 3 yl) 7 methoxycoumarin

3 (6 bromopyridazin 3 yl) 7 methylcoumarin

3 (6 bromopyridazin 3 yl) 8 methoxycoumarin

3 (6 bromopyridazin 3 yl) 8 methylcoumarin

3 (6 chloropyridazin 3 yl) 6 methoxycoumarin

3 (6 chloropyridazin 3 yl) 6 methylcoumarin

3 (6 chloropyridazin 3 yl) 7 methoxycoumarin

3 (6 chloropyridazin 3 yl) 7 methylcoumarin

3 (6 chloropyridazin 3 yl) 8 methoxycoumarin

3 (6 chloropyridazin 3 yl) 8 methylcoumarin

3 (6 methoxypyridazin 3 yl) 6 methylcoumarin

3 (6 methoxypyridazin 3 yl) 7 methylcoumarin

3 (6 methoxypyridazin 3 yl) 8 methylcoumarin

6 methoxy 3 (6 methoxypyridazin 3 yl)coumarin

6 methoxy 3 (6 oxo 1,6 dihydropyridazin 3 yl)coumarin

7 methoxy 3 (6 methoxypyridazin 3 yl)coumarin

7 methoxy 3 (6 oxo 1,6 dihydropyridazin 3 yl)coumarin

7 methyl 3 (6 oxo 1,6 dihydropyridazin 3 yl)coumarin

8 methoxy 3 (6 methoxypyridazin 3 yl)coumarin

8 methoxy 3 (6 oxo 1,6 dihydropyridazin 3 yl)coumarin

8 methyl 3 (6 oxo 1,6 dihydropyridazin 3 yl)coumarin

coumarin derivative

ethyl 2 (6 oxo 1,6 dihydropyridazin 3 yl)acetate

furan

maleic anhydride

monoamine oxidase B inhibitor

pyridazine

unclassified drug

amine oxidase (flavin containing)

coumarin derivative

monoamine oxidase inhibitor

pyridazine

pyridazine derivative

Article

controlled study

cytotoxicity

drug potency

drug selectivity

drug synthesis

human

human cell

hybrid

IC50

Knoevenagel condensation

molecular docking

structure activity relation

theoretical model

chemical structure

chemistry

dose response

metabolism

structure activity relation

synthesis

Coumarins

Dose-Response Relationship, Drug

Humans

Molecular Docking Simulation

Molecular Structure

Monoamine Oxidase

Monoamine Oxidase Inhibitors

Pyridazines

Structure-Activity Relationship