Journal of Enzyme Inhibition and Medicinal Chemistry
Volume 32, Issue 1, 1 January 2017, Pages 1143-1151

New quinoxalinone inhibitors targeting secreted phospholipase A2 and α-glucosidase (Article)

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Abstract

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Elevated blood glucose and increased activities of secreted phospholipase A2 (sPLA2) are strongly linked to coronary heart disease. In this report, our goal was to develop small heterocyclic compound that inhibit sPLA2. The title compounds were also tested against α-glucosidase and α-amylase. This array of enzymes was selected due to their implication in blood glucose regulation and diabetic cardiovascular complications. Therefore, two distinct series of quinoxalinone derivatives were synthesised; 3-[N′-(substituted-benzylidene)-hydrazino]-1H-quinoxalin-2-ones 3a–f and 1-(substituted-phenyl)-5H-[1,2,4]triazolo[4,3-a]quinoxalin-4-ones 4a–f. Four compounds showed promising enzyme inhibitory effect, compounds 3f and 4b–d potently inhibited the catalytic activities of all of the studied proinflammatory sPLA2. Compound 3e inhibited α-glucosidase (IC_{50} = 9.99 ± 0.18 μM); which is comparable to quercetin (IC_{50} = 9.93 ± 0.66 μM), a known inhibitor of this enzyme. Unfortunately, all compounds showed weak activity against α-amylase (IC_{50} > 200 μM). Structure-based molecular modelling tools were utilised to rationalise the SAR compared to co-crystal structures with sPLA2-GX as well as α-glucosidase. This report introduces novel compounds with dual activities on biochemically unrelated enzymes mutually involved in diabetes and its complications. © 2017 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

Reaxys Database Information

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Author keywords

coronary heart disease diabetic complications phospholipase A2 Quinoxalinone α-amylase α-glucosidase

Indexed keywords

EMTREE drug terms: 1 (2,4 dihydroxyphenyl)[1,2,4]triazolo[4,3 a]quinoxalin 4(5h) one
1 (2,4 dinitrophenyl)[1,2,4]triazolo[4,3 a]quinoxalin 4(5h)one
1 (3 methoxyphenyl)[1,2,4]triazolo[4,3 a]quinoxalin 4(5h) one
1 (3,4 dichlorophenyl)[1,2,4]triazolo[4,3 a]quinoxalin 4(5h) one
1 (3,4,5 trimethoxyphenyl)[1,2,4]triazolo[4,3 a]quinoxalin 4(5h) one
1 (thiophen 2 yl)[1,2,4]triazolo[4,3 a]quinoxalin 4(5h) one
3 [2 (2,4 dihydroxybenzylidene)hydrazinyl]quinoxalin 2(1h) one
3 [2 (2,4 dinitrobenzylidene)hydrazinyl]quinoxalin 2(1h) one
3 [2 (3 methoxybenzylidene)hydrazinyl]quinoxalin 2(1h) one
3 [2 (3,4 dichlorobenzylidene)hydrazinyl]quinoxalin 2(1h) one
3 [2 (3,4,5 trimethoxybenzylidene)hydrazinyl]quinoxalin 2(1h) one
3 [2 (thiophen 2 ylmethylene)hydrazinyl]quinoxalin 2(1h) one alpha glucosidase amylase enzyme inhibitor heterocyclic compound quercetin quinoxalinone inhibitor secretory phospholipase A2 unclassified drug alpha glucosidase enzyme inhibitor quinoxaline derivative secretory phospholipase A2

EMTREE medical terms: Article cardiovascular disease catalysis crystal structure cyclization diabetes mellitus drug structure drug synthesis drug targeting enzyme inhibition glucose blood level IC50 molecular model priority journal structure activity relation substitution reaction antagonists and inhibitors chemical structure chemistry dose response human metabolism synthesis

MeSH: alpha-Glucosidases Dose-Response Relationship, Drug Enzyme Inhibitors Humans Models, Molecular Molecular Structure Phospholipases A2, Secretory Quinoxalines Structure-Activity Relationship

Chemicals and CAS Registry Numbers:

alpha glucosidase, 9001-42-7; amylase, 9000-90-2, 9000-92-4, 9001-19-8; quercetin, 117-39-5;

alpha-Glucosidases; Enzyme Inhibitors; Phospholipases A2, Secretory; Quinoxalines

Funding details

Funding number	Funding sponsor	Acronym	Funding opportunities
	King Saud University		See opportunities↗
	Female Center for Scientific and Medical Colleges, King Saud University		See opportunities↗
	Deanship of Scientific Research, King Faisal University		See opportunities↗

Funding text

This research project was supported by a grant from the “Research Center of the Center for Female Scientific and Medical Colleges”, Deanship of Scientific Research, King Saud University.

ISSN: 14756366
CODEN: JEIMA
Source Type: Journal
Original language: English
DOI: 10.1080/14756366.2017.1363743
PubMed ID: 28856929
Document Type: Article
Publisher: Taylor and Francis Ltd

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