

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/49656740>

In vitro evaluation of 5-arylidene-2-thioxo-4-thiazolidinones active as aldose reductase inhibitors. Bioorg Med Chem Lett

ARTICLE *in* BIOORGANIC & MEDICINAL CHEMISTRY LETTERS · JANUARY 2011

Impact Factor: 2.42 · DOI: 10.1016/j.bmcl.2010.11.041 · Source: PubMed

CITATIONS

21

READS

42

6 AUTHORS, INCLUDING:



Rosanna Maccari

Università degli Studi di Messina

51 PUBLICATIONS 1,228 CITATIONS

SEE PROFILE



Roberta Moschini

Università di Pisa

20 PUBLICATIONS 215 CITATIONS

SEE PROFILE



Umberto Mura

Università di Pisa

104 PUBLICATIONS 1,473 CITATIONS

SEE PROFILE



Rosaria Ottanà

Università degli Studi di Messina

73 PUBLICATIONS 1,435 CITATIONS

SEE PROFILE



Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl



In vitro evaluation of 5-arylidene-2-thioxo-4-thiazolidinones active as aldose reductase inhibitors

Rosanna Maccari^{a,*}, Antonella Del Corso^b, Marco Giglio^a, Roberta Moschini^b, Umberto Mura^b, Rosaria Ottanà^a

^a Dipartimento Farmaco-chimico, Faculty of Pharmacy, University of Messina, Polo Universitario Annunziata, 98168 Messina, Italy

^b Dipartimento di Biologia, Unità di Biochimica, University of Pisa, Via S. Zeno, 51, 56126 Pisa, Italy

ARTICLE INFO

Article history:

Received 30 September 2010

Revised 4 November 2010

Accepted 4 November 2010

Available online 12 November 2010

Keywords:

Aldose reductase

Enzyme inhibition

Diabetes complications

4-Thiazolidinones

ABSTRACT

2-Thioxo-4-thiazolidinone derivatives were evaluated as aldose reductase inhibitors (ARIs) and most of them exhibited good or excellent in vitro efficacy. Out of the tested compounds, most N-unsubstituted analogues were found to possess inhibitory effects at low micromolar doses and two of them exhibited higher potency than sorbinil, used as a reference drug. The insertion of an acetic chain on N-3 of the thiazolidinone scaffold led to analogues with submicromolar affinity for ALR2 and IC₅₀ values very similar to that of epalrestat, the only ARI currently used in therapy.

© 2010 Elsevier Ltd. All rights reserved.

Aldose reductase (EC 1.1.1.21, ALR2) is an aldo-keto reductase which catalyses the NADPH-dependent reduction of glucose to sorbitol in the first step of the polyol pathway. Sorbitol is subsequently oxidized to fructose by sorbitol dehydrogenase with concomitant reduction of NAD⁺. Under conditions of hyperglycaemia, such as in diabetes mellitus (DM), increased flux of glucose through this metabolic process occurs in tissues possessing insulin-independent glucose transport (retina, lens, kidney, peripheral nerves) and this has been shown to be critically linked to the aetiology of hyperglycaemia-induced long-term diabetes complications.^{1–3} In fact, the intracellular accumulation of sorbitol, which is not diffusible through biomembranes, leads to osmotic changes and cellular damage, particularly in lenses. Moreover, the concurrent NADPH deprivation causes alterations in cellular redox potentials and in the activity of other NADPH-dependent enzymes, such as nitric oxide synthase and glutathione reductase, thus inducing intracellular oxidative stress and producing changes in cytokine signalling. The increased production of fructose can also cause pathological changes, by promoting protein glycation and formation of advanced glycation-end products (AGEs) and thus causing alterations in protein functions. These effects result in oxidative stress, inflammation and vascular damage which trigger a sequence of tissue dysfunction

and thus are responsible for the development of atherosclerosis, retinopathy, cataracts, nephropathy, neuropathy and for increased risk of myocardial infarction and stroke.^{1–6}

On these bases, ALR2 is considered an attractive molecular target to develop drugs able to prevent the onset and progression of secondary pathologies associated with DM, even in the presence of imperfect control of glycaemia. In fact, although an opportune antihyperglycaemic treatment can delay the emergence of diabetes complications and decreases the risk of microvascular damage, the normalization of glycaemic levels is not always feasible in diabetic patients and the onset of these pathologies, especially macrovascular diseases, is almost unavoidable.⁷ In addition, it has been suggested that the hyperglycaemia-induced cascade of phenomena, such as increased production of AGEs and reactive oxygen species, activation of protein kinase C and nuclear factor κB, can affect gene expression leading to molecular changes which could be responsible for the onset of chronic complications even during the antihyperglycaemic therapy.⁸ Thus, taking into account the worldwide soaring rates of DM⁹ and the seriousness of its complications, it is urgent to find drugs which can control the development of hyperglycaemia-induced damage and the consequent pathologies.

In addition, recently it has emerged that ALR2 may also be up-regulated under normal glycaemic conditions and it can be implicated in the development of other pathological processes, such as a number of human cancers, cardiovascular and inflammatory diseases. Thus, ALR2 inhibition may represent a novel approach for the management of these pathologies, although further investiga-

Abbreviations: AGEs, advanced glycation-end products; ALR2, aldose reductase; ARIs, aldose reductase inhibitors; 2,4-TZDs, 2,4-thiazolidinediones.

* Corresponding author. Tel.: +39 90 6766406; fax: +39 90 6766402.

E-mail address: rmaccari@pharma.unime.it (R. Maccari).

tions are ongoing to elucidate the pathophysiological role of ALR2 under normoglycaemic conditions.^{10–12}

Over the last three decades, numerous ALR2 inhibitors (ARIs) have been identified, many of which belonging to either carboxylic acid (such as epalrestat; Fig. 1) or cyclic imide (especially hydantoin, such as sorbinil and fidarestat; Fig. 1) classes of compounds.^{11,13–15} However, many of the clinically tested ARIs proved to be therapeutically inadequate because of adverse pharmacokinetics, toxic side-effects or low efficacy. The search for new ARIs has been supported by the knowledge of several crystal structures of ALR2/inhibitor complexes. This contributed to the definition of the structural requirements for ALR2 inhibition, which are: (a) a polar ‘head’ containing an acidic hydrogen which can bind the polar recognition region of the ALR2 active site formed by the positively charged nicotinamide ring of the oxidized cofactor NADP⁺ and the hydrophilic amino acid residues Tyr48 and His110; (b) a hydrophobic portion, generally containing an aromatic moiety, which can establish hydrophobic interactions with the lipophilic specificity pocket of the enzyme lined with Trp20, Trp111, Phe122, Pro218, Trp219, Leu300.^{16–19}

In this context, 2,4-thiazolidinediones (2,4-TZDs) and 2-thioxo-4-thiazolidinones are considered compounds of significant interest as ARIs, since they can act as hydantoin bioisosteres that are potentially devoid of the hypersensitivity reactions imputed to the hydantoin ring, which caused the withdrawal of sorbinil from clinical trials. Following the discovery of glitazones as oral antidiabetic drugs, numerous 2,4-TZDs have been reported or patented as ARIs, many of which are also endowed with antihyperglycaemic effect.^{13,14,20} Many effective ARIs also feature among the 2-thioxo-4-thiazolidinone analogues, including epalrestat (Fig. 1) which is the only ARI currently used in therapy.^{21–24}

2,4-TZDs and 2-thioxo-4-thiazolidinones share structural features which appear to be optimal for the interaction with the target enzyme. The portion that can interact with the positively charged recognition region of the ALR2 active site consists of the imidic/thioimidic function or an acetic chain inserted on N-3 of the thiazolidinone framework, whereas a lipophilic portion can be easily inserted in position 5 of the pentatomic scaffold in an orientation which proved to be useful to fit the specificity pocket of the target enzyme.^{25–28}

We have recently reported numerous 5-arylidene-2,4-thiazolidinediones, which were shown to be efficacious in vitro ARIs at micromolar or submicromolar doses.^{26–30} Among them, acids **1** (Fig. 1) were shown to be the most active in vitro ALR2 inhibitors, with submicromolar IC₅₀ values. Although the removal of the acetic chain on

N-3 of the thiazolidinedione ring led to a generally significant decrease in potency, certain N-unsubstituted derivatives **2** (Fig. 1) were also found to possess appreciable inhibitory effects.^{26,29}

In the context of our continuing search for new efficacious ARIs, we decided to evaluate the in vitro ALR2 inhibitory activity of analogous 2-thioxo-4-thiazolidinones **3** and **4** (Fig. 2). This appeared to be a logical continuation of our studies on thiazolidinone derivatives as ARIs, in order both to identify further active analogues and to refine the structure/activity relationships of this class of inhibitors. Most derivatives **3** and **4** possess a 5-arylidene moiety comprising two aromatic rings, since this structural feature proved to favour the activity of the corresponding series of 2,4-TZDs and to be related to high inhibition levels.^{26,29} Hydroxy- and methoxybenzylidene substituted analogues have also been included for comparison.

Although most compounds **3** and **4** (with the exception of **3b**) are already known and commercially available,³¹ to the best of our knowledge their ALR2 inhibitory activity was not reported up to now. It is worth noting that, out of compounds **4a**, **4b**, **4f–j**, which were studied as antihyperglycaemic agents, **4b**, **4g–j** produced a moderate reduction of glycaemic levels in obese diabetic mice.³² In the same patent, their inhibitory activity towards cathepsin D was reported. Compounds **4a** and **4b** resulted to be good inhibitors of this enzyme and, consequently, of the formation of β -amyloid protein, which would be expected to be useful in treating Alzheimer's disease.³² 2-Thioxo-4-thiazolidinones **4a**, **4c**, **4d**, **4f**, **4g** and **4j** were also proposed as zinc-binding ligands which can reversibly bind to a HisB¹⁰ Zn²⁺ site of the insulin hexamer, resulting in improved stability of insulin preparations.³³ Analogue **4j** resulted to be a good inhibitor of human arylamine N-acetyltransferase 1, which is under study as a new diagnostic marker and drug target in breast cancer.³⁴

Rhodanine derivatives **3** and **4** were synthesised for this study by means of the Knoevenagel condensation of the suitable aldehydes with (4-oxo-2-thioxothiazolidin-3-yl)acetic acid or 2-thioxo-4-thiazolidinone, respectively, in refluxing acetic acid in the presence of sodium acetate (Scheme 1).

The results relative to the evaluation of the in vitro ALR2 inhibitory activity of 2-thioxo-4-thiazolidinones **3a–e** and **4a–j** are reported in Table 1. The assay was performed by using highly purified ALR2 from bovine lenses.³⁵ Sorbinil and epalrestat were used as reference drugs. In Table 1 the IC₅₀ values of the previously assayed corresponding 2,4-TZDs (**1**, **2**)^{26,29} were also included for comparison and clarity of discussion.

Most of the tested 2-thioxo-4-thiazolidinones **3**, **4** were found to be more effective ALR2 inhibitors than the corresponding 2,4-TZDs (Table 1), analogous to other rhodanine derivatives present

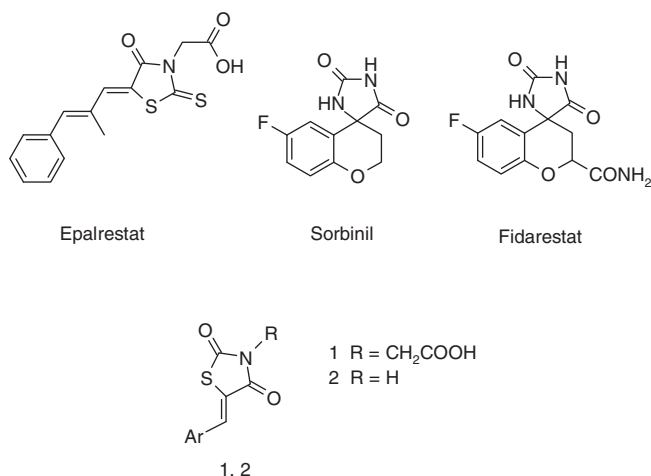


Figure 1. Structures of some ARIs.

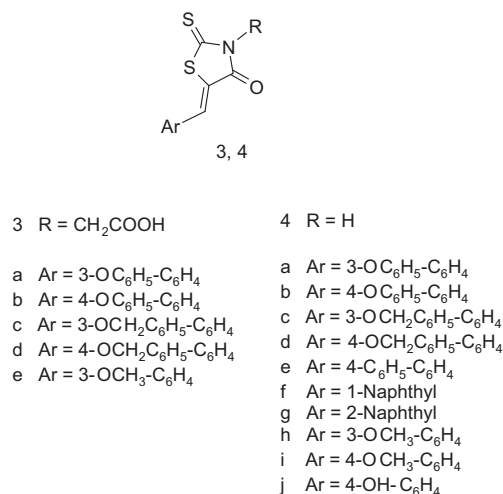
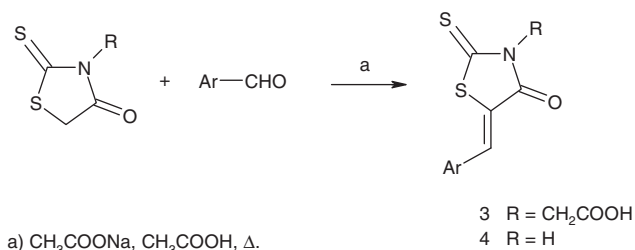


Figure 2. Structures of tested 2-thioxo-4-thiazolidinones **3** and **4**.



Scheme 1.

in the literature.²⁵ The gain in potency ranged from a moderate increase (1.5-fold for compound **3d**, about twice for compounds **4a**, **4h**, **4j**) to a marked improvement of activity (8-fold for compound **4i**, more than 30-fold for compound **4b**). A molecular rationalization of the observed gain in potency could be found in the higher size and polarizability of the sulphur atom of the thiocarbonyl group (compounds **3**, **4**) in comparison with the oxygen one of the corresponding carbonyl group (compounds **1**, **2**), which would allow novel interactions with the surrounding aminoacid residues in the ALR2 active site. Moreover, the consequently lower pK_a values³⁶ of N-unsubstituted 2-thioxo-4-thiazolidinones **4**, compared to those of corresponding 2,4-TZDs **2**, can favour the more efficient binding of these compounds to the polar recognition region of the ALR2 active site. Accordingly, acetic acid derivatives **1** and **3**, both of which are expected to be totally ionized at physiological pH values, can establish similarly effective interactions with the target enzyme, as indicated by the slight differences between the inhibitory effects of these two series of analogues (Table 1).

(5-Arylidene-4-oxo-2-thioxothiazolidin-3-yl)acetic acids **3a–e** were shown to be significantly more active (from 7-fold to more than 58-fold) than their N-unsubstituted counterparts (**4a–d** and **4h**), as already observed in the series of the previously reported 2,4-TZD analogues **1**, **2**. Furthermore, all acids **3** were significantly more effective than sorbinil and as potent as epalrestat, with the only exception of **3a** which was about twice less active (Table 1).

The IC_{50} values of acids **3** resulted to be included in a narrow range (between 0.11 and 0.41 μM), whereas the activity levels of N-unsubstituted analogues **4** varied within a wider range, from low micromolar IC_{50} values to moderate inhibitory effects produced at micromolar doses. This finding suggested that, in the presence of the acetic chain on N-3 that can establish the strongest interactions with the polar recognition region of the ALR2 active site, the influence of the 5-arylidene moiety on the inhibitory activity could become less evident. Indeed, 2-thioxo-4-thiazolidinone analogues possessing different lipophilic portions in position 5, such as compounds **3b–e** (phenoxy-, benzyloxy- and methoxybenzylidene substituted, respectively) and the reference drug epalrestat (2-methyl-3-phenylpropenylidene substituted) exhibited very similar efficacy with IC_{50} values in the range from 0.11 μM (**3b**) to 0.19 μM (**3d**) (Table 1). On the other hand, the aromatic portion resulted to be more relevant to the inhibitory effects of the N-unsubstituted analogues, both in 2-thioxo-4-thiazolidinone **4** and 2,4-TZD **2** series.^{26,29}

Out of N-unsubstituted derivatives **4**, compounds **4b** and **4c** were the most effective. They proved to be twice more active than sorbinil and **4b** also resulted to be more than 30-fold more potent than corresponding 2,4-TZD **2b** (Table 1). The 5-(3-phenoxybenzylidene) and 5-(naphthalene-1-ylmethylidene) substituted derivatives (**4a** and **4f**) showed effectiveness similar to that of sorbinil. The introduction of a methoxybenzylidene or hydroxybenzylidene moiety in position 5 (compounds **4h–j**) also afforded good inhibitors with low micromolar IC_{50} values, although they did not reach the activity of their phenoxy- and benzyloxybenzylidene substituted analogues (Table 1).

Thus, as observed for 2,4-TZDs, the presence of a phenoxy, benzyloxy or naphthyl moiety in the 5-arylidene portion generally proved to be favourable for the ALR2 inhibitory activity of 5-arylidene-2-thioxo-4-thiazolidinones. The 3-benzyloxybenzylidene and 4-phenoxybenzylidene moieties resulted to be related to the highest inhibition levels, in both series of compounds **3** and **4** (Table 1).

On the whole, the in vitro evaluation of rhodanine derivatives here reported provided several interesting results. Firstly, most of the tested compounds exhibited good or excellent ALR2 inhibitory

Table 1

In vitro bovine lens ALR2 inhibitory activity of 2-thioxo-4-thiazolidinones **3** and **4** in comparison with the corresponding 2,4-thiazolidinediones

		1, 2 X = O 3, 4 X = S			
R	Ar	Compd	$\text{IC}_{50}^{a,b}$	Compd	IC_{50}^a
CH_2COOH	3- OC_6H_5 - C_6H_4	1a ^c	0.13	3a	0.41 (0.14–1.22)
CH_2COOH	4- OC_6H_5 - C_6H_4	1b ^c	0.82	3b	0.11 (0.07–0.16)
CH_2COOH	3- $\text{OCH}_2\text{C}_6\text{H}_5$ - C_6H_4	1c ^c	—	3c	0.13 (0.09–0.18)
CH_2COOH	4- $\text{OCH}_2\text{C}_6\text{H}_5$ - C_6H_4	1d ^c	0.28	3d	0.19 (0.13–0.29)
CH_2COOH	3- OCH_3 - C_6H_4	1e ^d	0.48	3e	0.15 (0.12–0.19)
H	3- OC_6H_5 - C_6H_4	2a ^c	6.14	4a	2.94 (1.90–4.56)
H	4- OC_6H_5 - C_6H_4	2b ^c	41% (37 μM)	4b	1.10 (0.70–1.71)
H	3- $\text{OCH}_2\text{C}_6\text{H}_5$ - C_6H_4	2c ^c	—	4c	1.08 (0.73–1.60)
H	4- $\text{OCH}_2\text{C}_6\text{H}_5$ - C_6H_4	2d ^c	10% (50 μM)	4d	7% (11 μM)
H	4- C_6H_5 - C_6H_4	2e ^c	20% (50 μM)	4e	28% (13 μM)
H	1-Naphthyl	2f ^c	10.7	4f	2.27 (1.81–2.85)
H	2-Naphthyl	2g ^c	—	4g	40% (16 μM)
H	3- OCH_3 - C_6H_4	2h ^d	13.28	4h	6.24 (3.93–9.91)
H	4- OCH_3 - C_6H_4	2i ^d	40.83	4i	5.23 (3.92–6.97)
H	4-OH- C_6H_4	2j ^c	8.96	4j	4.55 (3.73–5.53)
				Sorbinil	2.0 (1.7–3.5)
				Epalrestat	0.17 (0.09–0.34)

^a IC_{50} (μM) (95% C.L.) or % inhibition at the given concentration.

^b IC_{50} values refer to an assay performed by using partially purified ALR2 from bovine lenses.^{26,29}

^c Ref. 26.

^d Ref. 29.

effectiveness and, in addition, the structure–activity relationships relevant to 5-arylidene-4-thiazolidinone ARIs were further refined. In particular, it was observed that the replacement of the carbonyl group in position 2 of the 2,4-thiazolidinedione scaffold with the bioisoster thiocarbonyl group can improve inhibitory efficacy in most of the tested compounds. Further studies will be needed to confirm the proposed hypotheses which could rationalize this gain in potency. Moreover, out of the tested 2-thioxo-4-thiazolidinones, two N-unsubstituted analogues (**4b** and **4c**) were found to be more active than sorbinil. As observed for 2,4-TZDs, the insertion of an acetic chain on N-3 significantly enhanced potency, thus leading to derivatives **3b–e** with in vitro efficacy very similar to that of the structural analogue epalrestat, the only ARI currently used in therapy.

Acknowledgements

This work was supported by University of Messina and University of Pisa. We are indebted to Dr. G. Pasqualetti and Dr. R. Di Sacco (veterinary staff of Consorzio Macelli S. Miniato, Pisa) for their valuable cooperation in bovine lens collection.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.bmcl.2010.11.041](https://doi.org/10.1016/j.bmcl.2010.11.041).

References and notes

- Kador, P. F. *Med. Res. Rev.* **1988**, *8*, 325.
- Yabe-Nishimura, C. *Pharmacol. Rev.* **1998**, *50*, 21.
- Brownlee, M. *Nature* **2001**, *414*, 813.
- Ramana, K. V.; Friedrich, B.; Srivastava, S.; Bhatnagar, A.; Srivastava, S. K. *Diabetes* **2004**, *53*, 2910.
- Srivastava, S. K.; Ramana, K. V.; Bhatnagar, A. *Endocr. Rev.* **2005**, *26*, 380.
- Gleissner, C. A.; Galkina, E.; Nadler, J. L.; Ley, K. *Drug Discovery Today Dis. Mech.* **2007**, *4*, 131.
- Turner, R. C.; Holman, R. R.; Cull, C. A.; Stratton, I. M.; Matthews, D. R.; Frighi, V.; Manley, S. E.; Neil, A.; McElroy, H.; Wright, D.; Kohner, E.; Fox, C.; Hadden, D. UK Prospective Diabetes Study (UKPDS) Group *Lancet* **1998**, *352*, 837.
- Zozulinska, D.; Wierusz-Wysocka, B. *Diabetes Res. Clin. Pract.* **2006**, *74S*, S12.
- Wild, S.; Roglic, G.; Green, A.; Sicree, R.; King, H. *Diabetes Care* **2004**, *27*, 1047.
- Tammali, R.; Ramana, K. V.; Srivastava, S. K. *Cancer Lett.* **2007**, *252*, 299.
- Alexiou, P.; Pegklidou, K.; Chatzopoulou, M.; Nicolaou, I.; Demopoulos, V. J. *Curr. Med. Chem.* **2009**, *16*, 734.
- Ramana, K. V.; Srivastava, S. K. *Int. J. Biochem. Cell Biol.* **2010**, *42*, 17.
- Costantino, L.; Rastelli, G.; Cignarella, G.; Vianello, P.; Barlocco, D. *Exp. Opin. Ther. Patents* **1997**, *7*, 843.
- Miyamoto, S. *Chem. Biol. Inform. J.* **2002**, *2*, 74.
- Suzen, S.; Buyukbingol, E. *Curr. Med. Chem.* **2003**, *10*, 1329.
- Urzhumtsev, A.; Tête-Favier, F.; Mitschler, A.; Barbanton, J.; Barth, P.; Urzhumtseva, L.; Biellmann, J. F.; Podjarny, A.; Moras, D. *Structure* **1997**, *5*, 601.
- El-Kabbani, O.; Wilson, D. K.; Petrash, J. M.; Quijcho, F. A. *Mol. Vis.* **1998**, *4*, 19.
- Howard, E. I.; Sanishvili, R.; Cachau, R. E.; Mitschler, A.; Chevrier, B.; Barth, P.; Lamour, V.; Van Zandt, M.; Sibley, E.; Bon, C.; Moras, D.; Schneider, T. R.; Joachimiak, A.; Podjarny, A. *Proteins* **2004**, *55*, 792.
- Sottriffer, C. A.; Krämer, O.; Klebe, G. *Proteins* **2004**, *56*, 52.
- Costantino, L.; Rastelli, G.; Vianello, P.; Cignarella, G.; Barlocco, D. *Med. Res. Rev.* **1999**, *19*, 3.
- Kikkawa, R.; Hatanaka, I.; Yasuda, H.; Kobayashi, N.; Shigeta, Y.; Terashima, H.; Morimura, T.; Tsuboshima, M. *Diabetologia* **1983**, *24*, 290.
- Terashima, H.; Hama, K.; Yamamoto, R.; Tsuboshima, M.; Kikkawa, R.; Hatanaka, I.; Shigeta, Y. *J. Pharmacol. Exp. Ther.* **1984**, *229*, 226.
- Ramirez, M. A.; Borja, N. L. *Pharmacotherapy* **2008**, *28*, 646.
- Hotta, N.; Kawamori, R.; Atsumi, Y.; Baba, M.; Kishikawa, H.; Nakamura, J.; Oikawa, S.; Yamada, N.; Yasuda, H.; Shigeta, Y. *Diabetes Med.* **2008**, *25*, 818.
- Fresneau, P.; Cussac, M.; Morand, J.; Szymonski, B.; Tranqui, D.; Leclerc, G. *J. Med. Chem.* **1998**, *41*, 4706.
- Maccari, R.; Ottanà, R.; Curinga, C.; Vigorita, M. G.; Rakowitz, D.; Steindl, T.; Langer, T. *Bioorg. Med. Chem.* **2005**, *13*, 2809.
- Maccari, R.; Ottanà, R.; Ciurleo, R.; Vigorita, M. G.; Rakowitz, D.; Steindl, T.; Langer, T. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3886.
- Maccari, R.; Ottanà, R.; Ciurleo, R.; Rakowitz, D.; Matuszczak, B.; Laggner, C.; Langer, T. *Bioorg. Med. Chem.* **2008**, *16*, 5840.
- Bruno, G.; Costantino, L.; Curinga, C.; Maccari, R.; Monforte, F.; Nicolò, F.; Ottanà, R.; Vigorita, M. G. *Bioorg. Med. Chem.* **2002**, *10*, 1077.
- Maccari, R.; Ciurleo, R.; Giglio, M.; Cappiello, M.; Moschini, R.; Del Corso, A.; Mura, U.; Ottanà, R. *Bioorg. Med. Chem.* **2010**, *18*, 4049.
- SciFinder, <https://scifinder.cas.org>.
- Bue-Valleskey, J. M.; Hunden, D. C.; Jones, C. D.; Panetta, J. A.; Shaw, W. N. U.S. **1996**, US 5523314.
- Kaarsholm, N. C.; Madsen, P.; Schlein, M.; Olsen, H. B.; Havelund, S.; Steensgaard, D. B.; Ludvigsen, S.; Jakobsen, P.; Petersen, A. K.; Schluckebier, G. PCT Int. Appl. WO 2004056347, 2004.
- Russell, A. J.; Westwood, I. M.; Crawford, M. H. J.; Robinson, J.; Kawamura, A.; Redfield, C.; Laurieri, N.; Lowe, E. D.; Davies, S. G.; Sim, E. *Bioorg. Med. Chem.* **2009**, *17*, 905.
- Del Corso, A.; Barsacchi, D.; Giannesi, M.; Tozzi, M. G.; Camici, M.; Houben, J. L.; Zandomeneghi, M.; Mura, U. *Arch. Biochem. Biophys.* **1990**, *283*, 512.
- Values calculated by means of the freely accessible web tool Marvin Calculator Plugins, <http://www.chemaxon.com>. Calculated log *P*, p*K*_a and molecular polarizability values of compounds **1–4** are available in the [Supplementary data](#).