Bioorganic & Medicinal Chemistry Letters 18 (2008) 3492–3494

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

5-Substituted isophthalamides as insulin receptor sensitizers

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ARTICLE INFO

Article history:
Received 17 March 2008
Revised 6 May 2008
Accepted 8 May 2008
Available online 15 May 2008

Keywords:
Diabetes
Insulin receptor
SAR
Insulin resistance

ABSTRACT

A novel series of 5-substituted isophthalamides and their structure–activity relationship as insulin receptor sensitizers is discussed.

Type 2, or non-insulin dependent, diabetes mellitus occurs in an estimated 6% of adults in the industrialized nations.[1] It is characterized by a deficiency in insulin secretion and an insensitivity of target tissues to the actions of insulin (insulin resistance).[2–4] Taken together these two defects result in the inability of the body to maintain glucose homeostasis leading to overt hyperglycemia.

The insulin receptor is a ligand-activated tyrosine protein kinase. It is tetrameric consisting of two identical extracellular α-subunits that bind the hormone and two transmembrane β-subunits possessing tyrosine kinase activity.[4–7] On ligand binding rapid autophosphorylation of several tyrosine residues on the β-subunits occurs resulting in activation of the IR tyrosine kinase toward exogenous substrates. A cascade of signaling events then ensue, one of which results in the translocation of the glucose transporter, GLUT4, to the cell surface leading to cellular uptake of glucose.[8] Several steps in this pathway including autophosphorylation of the IR tyrosine kinase in response to insulin binding have been shown to be impaired in insulin-resistant tissue and cells.[8] Therefore, small molecules that enhance IR function would be useful in the treatment of type 2 diabetes. Indeed, recently such a molecule has been disclosed by researchers at Merck. The quinone, L-783,281 (Fig. 1) is reported to be an orally active IR activator showing antidiabetic action in two mouse models of type 2 diabetes.[9,10]

Using our target-related affinity profiling (TRAP) technology,[11] TLK 16998 (**1**) was discovered (Fig. 1). This compound acts as an IR sensitizer in vitro and in vivo,[12] however, it does require the presence of insulin to exert any effect. In our primary screen, the effect of test compounds on the insulin-stimulated glucose uptake

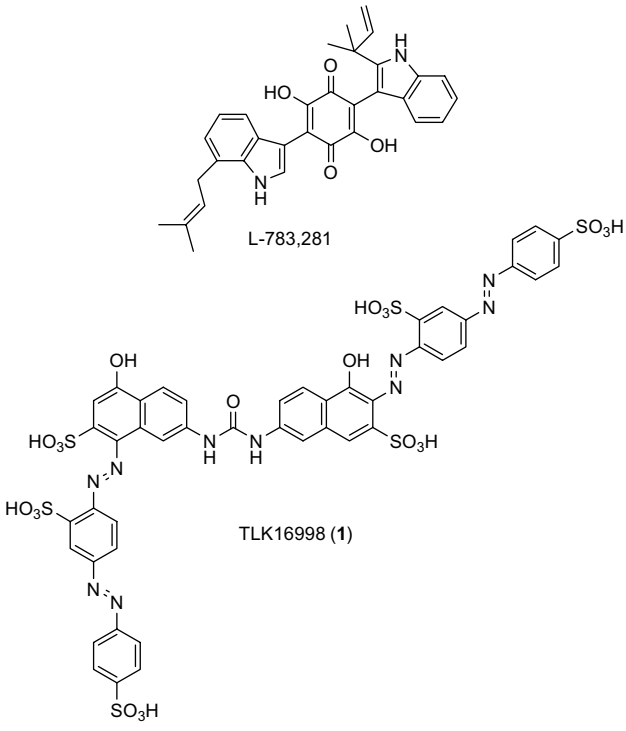

Figure 1. Structures of L-783,281 and TLK 16998.

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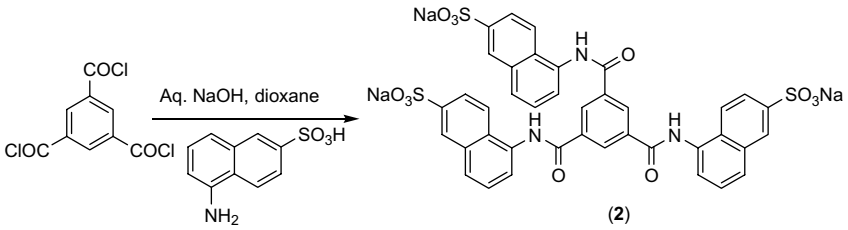
doi:10.1016/j.bmcl.2008.05.031



Scheme 1. Synthesis of trimesic acid triamide **2**.

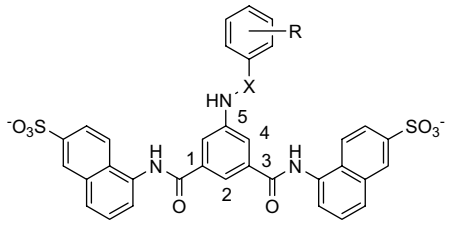
in 3T3-L1 adipocytes was evaluated and EC_{50} values were calculated with respect to the activity of 100 nM insulin. In this assay compound **1** had an EC_{50} of 90 μM.

From a medicinal chemistry point of view, compound **1** is unattractive as a lead structure: it possesses six sulfonic acid groups as well as four azo linkages and has a molecular weight greater than 1200. We envisaged a simpler, but still fairly rigid, structure which maintained some of the acidic groups of the parent compound. Therefore, a series of nine symmetrical trimesic acid amides were prepared by reaction of 1,3,5-benzenetricarbonyl trichloride with aminonaphthalene-monosulfonic acids. The 5-aminonaphthalene-2-sulfonic acid derived triamide **2** (Scheme 1) was the only compound in this series to show activity. It was very weakly active, having an EC_{50} value of 135 μM.

A more promising series arose from 5-substituted isophthalamides (Table 1). Again the 5-aminonaphthalene-2-sulfonic acid-derived diamides were superior to other aminonaphthalene-sulfonic acid isomers. Compounds in this series were prepared by the route shown in Scheme 2. Briefly, starting from 5-nitroisophthalic acid amidation was followed by reduction of the nitro group with subsequent functionalization of the aniline.

For the derivatives containing a substituted phenylcarbonylamino group at C-5, substituents *meta* to the linker were preferably to those *para* to the linker as illustrated by the chloro pairs **3** and **4** (EC_{50}s 5.7 μM and 72.8 μM, respectively). The *meta* fluoro derivative **5** also shows good activity whilst the *meta* nitro-substituted compound **7** shows diminished activity. Replacement of the amide linkage at C5 of the isophthalamide scaffold with either urea or sulfonamide linkers produced compounds that were inactive (**9** and **10**) as did addition of an extra carbon to that amide (**11**). *N*-Methylation of the isophthalamide functionality also produced a compound devoid in activity (data not shown) indicating that this functionality is necessary for activity.

Table 1
Glucose uptake data for compounds **3**–**11**



Compound	X	R	EC_{50}[a] (μM)
3	CO	3-Cl	5.7[b]
4	CO	4-Cl	72.8[c]
5	CO	3-F	19.4[d]
6	CO	4-F	78.5[e]
7	CO	3-NO_2	44.5[f]
8	CO	4-NO_2	NA
9	SO_2	4-F	NA
10	CONH	3-Cl	NA
11	$COCH_2$	3-Cl	NA

p-value is the probability associated with a Student's *t*-test (two-tailed distribution, two-sample unequal variance). NA, not active.

[a] Values are means of three experiments. Average *p*-values.

[b] 0.02.

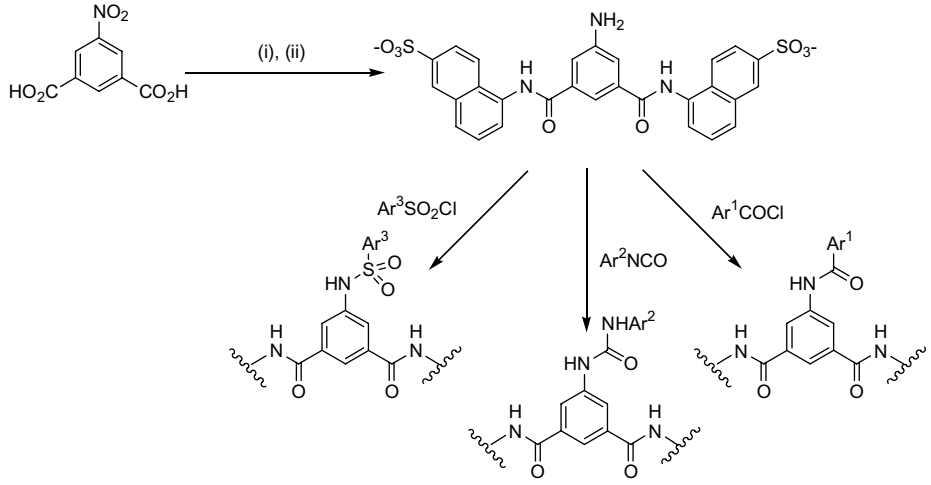
[c] 0.38.

[d] 0 0.04.

[e] 0.36.

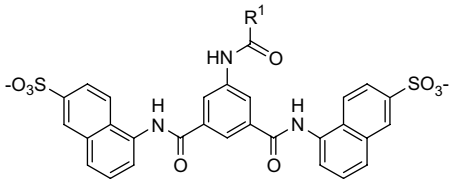
[f] 0.08

Having established the C-5 amide linker as an essential requirement (compare **3** and **6** with **9**–**11**), we next investigated the effect of various heterocyclic and extended aromatic replacements for the *meta* chloro phenyl of compound **2**



Scheme 2. Reagents: (i) a—$SOCl_2$, pyridine; b—5-aminonaphthalene-2-sulfonic acid, pyridine; (ii) $SnCl_2$, concd HCl.

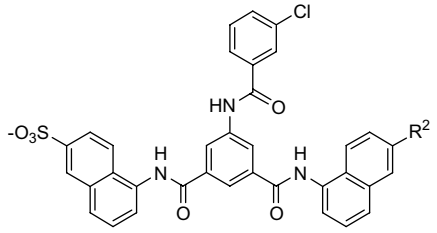
Table 2
Glucose uptake data for compounds **3**, **12**–**18**



Compound	R^1	EC_{50}[a] (μM)
3	3-Cl-phenyl	5.7[b]
12	2-Naphthayl	3.7[c]
13	1-Naphthyl	12.8[d]
14	Cyclohexyl	NA
15	2-Furyl	NA
16	4-Pyridyl	NA
17	3-Pyridyl	NA
18	2-Quinoxyl	NA

p-value is the probability associated with a Student's *t*-test (two-tailed distribution, two-sample unequal variance). NA, not active.
[a] Values are means of three experiments. Average *p*-values.
[b] 0.02.
[c] 0.01.
[d] 0.41.

Table 3
Glucose uptake data for compounds **2**, **19, and 20**



Compound	R^2	EC_{50}[a] (μM)
2	SO_3^-	5.7[b]
19	H	66.5[c]
20	OH	61.7[d]

p-value is the probability associated with a Student's *t*-test (two-tailed distribution, two-sample unequal variance). NA, not active.
[a] Values are means of three experiments. Average *p*-values.
[b] 0.02.
[c] 0.23.
[d] 0.16.

(Table 2). All the aromatic heterocycles tried gave compounds with no activity (**15**, **16**, **17**, and **18**). However, the 2-naphthyl derivative **12** showed excellent activity having an EC_{50} of 3.7 μM with the 1-naphthyl analog **13** exhibiting slightly diminished activity.

Finally, the need for two sulfonic acid groups was explored (Table 3). Two asymmetric derivatives were prepared in which the one sulfonic acid moiety was exchanged for either a proton **19** or a hydroxyl **20**. Both derivatives are ten times less active than the parent. The symmetrical derivative containing two carboxylic acids instead of two sulfonic acids was inactive. These data suggest that at least one sulfonic acid group is a necessity for activity but the presence of two such groups increases potency.

In summary, a series of isophthalamides that enhance glucose transport have been disclosed. Unlike L-783,281, the compounds reported herein are inactive in the absence of insulin. Of course, such insulin-dependent activity may offer unique advantages in the control of hyperglycemia by modulation of their effects as insulin levels change in response to physiological stimuli.

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