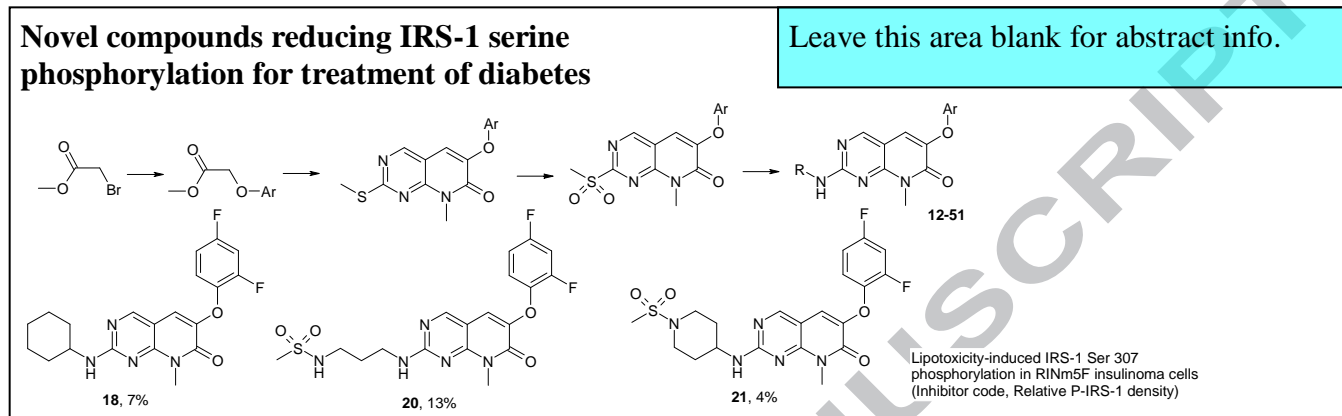


## Graphical Abstract

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## Novel compounds reducing IRS-1 serine phosphorylation for treatment of diabetes

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### ABSTRACT

Activation of various interacting stress kinases, particularly the c-Jun N-terminal kinases (JNK), and a concomitant phosphorylation of insulin receptor substrate 1 (IRS-1) at serine 307 play a central role both in insulin resistance and in  $\beta$ -cell dysfunction. IRS-1 phosphorylation is stimulated by elevated free fatty acid levels through different pathways in obesity. A series of novel pyrido[2,3-d]pyrimidin-7-one derivatives were synthesized as potential antidiabetic agents, preventing IRS-1 phosphorylation at serine 307 in a cellular model of lipotoxicity and type 2 diabetes.

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† We regret to write that our co-author Zoltán Greff passed away on 25<sup>th</sup> July 2014. We dedicate this paper to his memory.

Type 2 diabetes is a metabolic disorder based on insulin resistance and the inability of pancreatic  $\beta$ -cells to adapt by a compensatory increase in insulin secretion.

Activation of various interacting stress kinases, and a concomitant phosphorylation of insulin receptor substrate 1 (IRS-1) at serine 307 play a central role both in insulin resistance and in  $\beta$ -cell dysfunction.<sup>1</sup> Obesity-induced elevation in plasma free fatty acid (FFA) levels is deleterious to most cells, and this lipotoxicity<sup>2</sup> is known to enhance IRS-1 serine 307 phosphorylation, too.<sup>3</sup>

Multiple interaction with inflammatory signaling, oxidative and endoplasmic reticulum (ER) stress as well as accumulation of diacylglycerols and ceramide, constitute the major mechanisms of FFA-induced serine kinase activation and IRS-1 serine 307 phosphorylation.<sup>4</sup>

Insulin acts as an autocrine survival signal in pancreatic  $\beta$ -cells. Therefore, insulin resistance is pro-apoptotic in these cells, and creates a vicious circle by interfering with compensatory insulin secretion. Certain stress-activated protein kinases, such as c-Jun N-terminal kinases (JNKs) and p38 mitogen-activated protein kinase (p38 MAPK) play a prominent role in IRS-1 serine phosphorylation. Their inhibition proved to be  $\beta$ -cell protective in isolated islets of Langerhans.<sup>5</sup> Attenuation of IRS-1 Ser307 phosphorylation as well as reduced JNK phosphorylation and activity have been demonstrated to contribute to  $\beta$ -cell protection by the widely used insulin sensitizer metformin in ER stress<sup>6</sup> and in lipotoxicity.<sup>7</sup> Accordingly, JNK inhibitors have been shown to protect human  $\beta$ -cells from the deleterious effects of high glucose and leptin<sup>8</sup> and to reduce FFA-induced AP-1 activation and apoptosis in INS-1 insulinoma cells.<sup>9</sup> Moreover, they improved functional  $\beta$ -cell mass in transplanted human pancreatic islets both in vitro and in vivo in the early post-transplant period.<sup>10</sup> In addition, several JNK inhibitors have been shown to improve insulin sensitivity and glucose tolerance in db/db diabetic mice<sup>11-13</sup> and in mice fed a high-fat diet.<sup>14</sup> Consequently, JNK inhibitors are generally considered as potential antidiabetic agents.<sup>15,16</sup>

JNK as a member of MAPK family also controls cell proliferation, survival and DNA repair through phosphorylating a wide array of transcription factors (e.g. c-Jun, p53). Therefore, specific JNK inhibitors are relevant for multiple medical aspects.<sup>17</sup> However, the molecules that efficiently inhibit IRS-1 serine 307 phosphorylation are of special importance for anti-diabetic treatment. The aim of the present study was to apply cellular models of lipotoxicity-related and non-related IRS-1 Ser307 phosphorylation to select inhibitors with the potential to prevent or reduce insulin resistance and  $\beta$ -cell dysfunction.

The compounds tested in this work belong to the NCL of Vichem Chemie Research Ltd (Budapest).<sup>18</sup> We have screened Vichem's EVL library for JNK inhibition. Two compound families were identified to be druglike and suitable for optimization. The published hit compounds listed in Table 1 were used as reference compounds in our experiments. Bisphenylamino pyrimidines, the more active JNK inhibitors, have nanomolar  $IC_{50}$  values, and the general method of their synthesis is well established.<sup>19</sup> The best known representative of this compound family is pazopanib, a multitarget receptor tyrosine kinase inhibitor, which acts against renal cell carcinoma and soft tissue sarcoma via inhibition of angiogenesis.<sup>16</sup> Around 32 000 compounds can be found in SciFinder having bisphenylamino pyrimidine core structure, and 610 biological activity values were published in 1776 publications, including 353 review articles. These data show that the chemical space is well covered for this core structure.

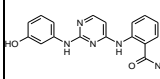
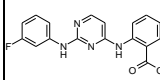
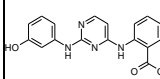
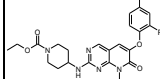
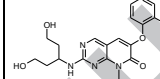
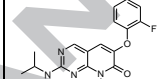
Cpd	Structure	literature JNK1 $IC_{50}$ ( $\mu$ M) [28]	in-house JNK1 $IC_{50}$ ( $\mu$ M)	IRS-1-P % of anisomycin control at 10 $\mu$ M	c-jun-P % of anisomycin control at 10 $\mu$ M
1		0.009	0.17	97	104
2		0.028	0.05	69	46
3		0.025	0.04	161	88
4			2.75	0	42
5			5.42	14	94
6			4.22	15	81

Table 1 Reference compounds synthesized and used in our experiments

The 2,6-disubstituted 7-oxo-pyrido[2,3-d]pyrimidines (WO02064594) are p38 MAPK inhibitors of nanomolar  $IC_{50}$  values with JNK1 inhibitory effect in the micromolar range. The most prominent representative of the pyrido[2,3-d]pyrimidin-7-one core family is palbociclib (Pfizer) (PD-0332991), which is known as a selective inhibitor of CDK4 and CDK6 and has been recently approved by FDA in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer.<sup>20</sup> SciFinder search on the pyrido[2,3-d]pyrimidin-7-one core revealed that 9123 such derivatives have been published in 681 publications, including 27 review articles. Based on the literature search, we have found a white spot in the chemical space and designed a novel compound group containing the pyrido[2,3-d]pyrimidin-7-one core. These novel derivatives (listed in Table 2) were synthesized according to the scheme shown in Fig 1. Based on Vichem's in-house data on JNK pathway inhibitors, 46 analogues were selected for our experiments. Instant JChem was used for structure database and biological data management.<sup>21</sup>

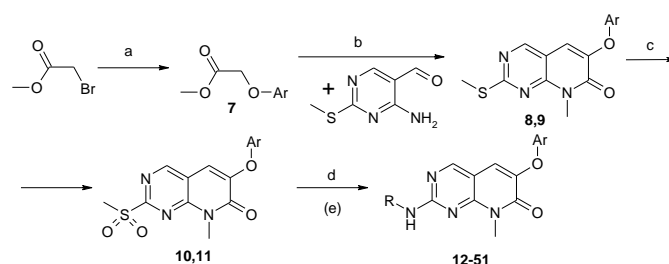


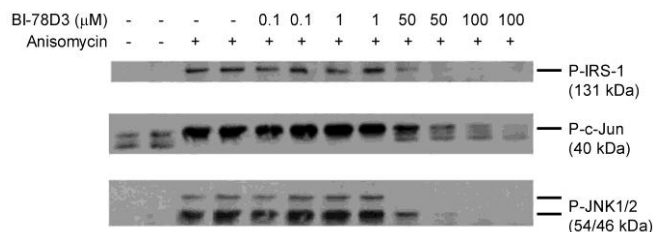
Figure 1.a: substituted phenol, N-methyl-pyrrolidone,  $K_2CO_3$ , 6 h, RT; b: N-methyl-pyrrolidone,  $K_2CO_3$ , 12 h, 120°C; c: 3-chloro-perbenzoic acid,  $CHCl_3$ ; d: R-amine; e: removing protecting group, salt formation

Cpd	Ar	R	in-house JNK1 IC <sub>50</sub> (μM)	IRS-1-P % of anisomycin control at 10μM	JNK-P % of anisomycin control at 10μM	c-jun-P % of anisomycin control
12	2,4-F <sub>2</sub> -Ph	1-Methanesulfonylpiperidin-4-yl	0.65	2.72	77.17	87.07
13	2,4-F <sub>2</sub> -Ph	Piperidin-4-yl	10.93	0.00	80.95	118.95
14	2,4-F <sub>2</sub> -Ph	Cyclopentyl	5.93	0.00	40.03	66.47
15	2,4-F <sub>2</sub> -Ph	4-(4-Hydroxypiperidin-1-yl)-phenyl	3.79	0.00	29.64	57.48
16	2,4-F <sub>2</sub> -Ph	3-Trifluoromethylbenzyl	>23	0.00	94.08	100.89
17	2,4-F <sub>2</sub> -Ph	3-(4-Methylpiperazin-1-yl)-propyl	19.10	0.00	152.84	137.28
18	2,4-F <sub>2</sub> -Ph	Cyclohexyl	16.14	0.00	37.58	32.37
19	2,4-F <sub>2</sub> -Ph	Cycloheptyl	6.73	0.00	84.01	118.90
20	2,4-F <sub>2</sub> -Ph	3-Methanesulfonamidopropyl	2.77	0.00	52.85	73.54
21	2,4-F <sub>2</sub> -Ph	1-Aminosulfonylpiperidin-4-yl	0.91	0.00	30.50	89.38
22	2,4-F <sub>2</sub> -Ph	4-(4-Methylpiperazin-1-yl)-phenyl	3.34	2.08	133.12	76.93
23	2,6-Cl <sub>2</sub> -Ph	Pyridin-2-yl-methyl	>23	2.15	35.29	114.89
24	2,4-F <sub>2</sub> -Ph	Cyclopropyl	7.17	2.61	173.60	142.31
25	2,6-Cl <sub>2</sub> -Ph	Tetrahydropyran-4-yl	2.48	8.05	55.20	68.02
26	2,6-Cl <sub>2</sub> -Ph	Cyclopentyl	19.32	8.18	108.40	114.87
27	2,6-Cl <sub>2</sub> -Ph	4-(4-Hydroxypiperidin-1-yl)-phenyl	>23	9.09	58.93	74.00
28	2,4-F <sub>2</sub> -Ph	2-Methanesulfonamidoethyl	18.94	12.21	75.80	67.53
29	2,6-Cl <sub>2</sub> -Ph	4-(4-Methylpiperazin-1-yl)-phenyl	>23	13.20	45.05	60.88
30	2,6-Cl <sub>2</sub> -Ph	2-(Pyridine-2-yl)-ethyl	>23	14.31	81.60	115.66
31	2,6-Cl <sub>2</sub> -Ph	Cyclopropyl	14.92	14.66	96.10	127.74
32	2,4-F <sub>2</sub> -Ph	2-Morpholin-4-yl-ethyl	>23	26.71	96.14	102.06
33	2,6-Cl <sub>2</sub> -Ph	4-Hydroxypiperidin-1-yl	>23	40.48	96.27	99.10
34	2,6-Cl <sub>2</sub> -Ph	4-Piperidin-1-yl-phenyl	>23	46.31	129.39	107.95
35	2,4-F <sub>2</sub> -Ph	3-Hydroxypyrrolodone-1-yl	>23	51.06	131.36	111.23
36	2,4-F <sub>2</sub> -Ph	Pyridin-2-methyl	>23	68.20	68.20	86.15
37	2,6-Cl <sub>2</sub> -Ph	2-Morpholin-4-yl-ethyl	27.07	71.26	138.96	114.48
38	2,6-Cl <sub>2</sub> -Ph	3-Hydroxypyrrolodone-1-yl	>23	74.50	74.50	82.55
39	2,4-F <sub>2</sub> -Ph	3-Hydroxymethylpiperidin-1-yl	>23	79.38	21.12	103.36
40	2,4-F <sub>2</sub> -Ph	2-Pyridin-2-yl-ethyl	6.75	81.98	81.98	96.42

41	2,4-F <sub>2</sub> -Ph	4-Piperidin-1-yl-phenyl	>23	84.01	148.70	130.80
42	2,4-F <sub>2</sub> -Ph	3-Hydroxy-piperidin-1-yl	>23	88.71	38.07	103.90
43	2,6-Cl <sub>2</sub> -Ph	3-Hydroxy-piperidin-1-yl	>23	93.59	36.24	133.35
44	2,4-F <sub>2</sub> -Ph	4-Pyrrolidin-1-yl-phenyl	>23	98.90	98.90	107.86
45	2,6-Cl <sub>2</sub> -Ph	3-Hydroxy-methyl-piperidin-1-yl	>23	99.30	99.30	102.90
46	2,4-F <sub>2</sub> -Ph	4-Hydroxy-methyl-piperidin-1-yl	>23	102.35	91.58	120.51
47	2,4-F <sub>2</sub> -Ph	2-Dimethyl-amino-ethyl	>23	104.31	104.31	110.16
48	2,6-Cl <sub>2</sub> -Ph	2-Hydroxy-methyl-piperidin-1-yl	>23	110.36	110.36	117.82
49	2,4-F <sub>2</sub> -Ph	4-Hydroxy-piperidin-1-yl	>23	123.96	121.82	131.10
50	2,6-Cl <sub>2</sub> -Ph	4-Hydroxy-methyl-piperidin-1-yl	>23	127.11	119.26	148.70
51	2,6-Cl <sub>2</sub> -Ph	4-Pyrrolidin-1-yl-phenyl	>23	165.10	135.70	103.97

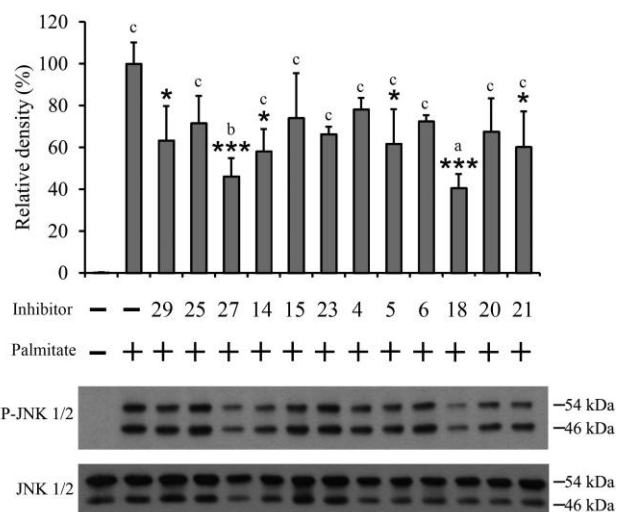
**Table 2** The synthesized novel 7-oxo-pyrido[2,3-d]pyrimidines

Effect of 46 potential inhibitors on JNK activation and JNK-related protein phosphorylation was tested on HEK293 cells treated with the direct (ER-stress-independent) JNK-activator, anisomycin. The cellular model was first validated by using BI-78D3, a known inhibitor of JNK activation. Cells were treated with BI-78D3 (various concentrations between 0.1 and 100  $\mu$ M) and anisomycin (50 ng/ml) simultaneously and incubated for 30 min. Phosphorylated JNK, phosphorylated c-Jun and Ser307-phosphorylated IRS-1 protein levels were assessed in the cell lysates by Western blot. Anisomycin-induced JNK, c-Jun and IRS-1Ser307 phosphorylations were counteracted by BI-78D3 in a concentration dependent manner (Fig 2). It diminished all these three parameters to the limit of detection at 50  $\mu$ M, and hence it was applied at this concentration as a positive control in further experiments. The tested molecules were used uniformly at 10  $\mu$ M final concentration among the same experimental conditions.



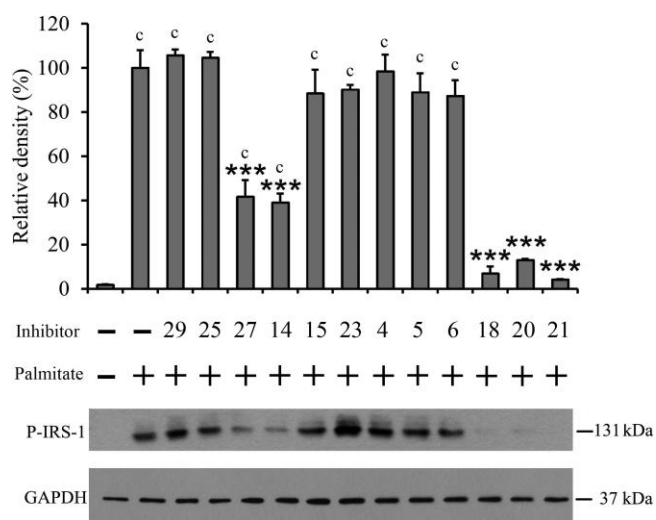
**Figure 2** Inhibition of JNK, c-Jun and IRS-1 Ser 307 phosphorylation in anisomycin treated HEK293 cells

The relative P-JNK, P-c-Jun and Ser307-P-IRS-1 densities were quantified by densitometry and compared to those of the anisomycin-only-treated samples, which were regarded as 100% of activation. As expected, there was a correlation between the phosphorylation of JNK and c-Jun proteins, and some tested molecules exerted remarkable inhibitory effect on these parameters (Table 1 and 2). The observed changes in IRS-1 Ser307 phosphorylation are less tightly correlated with the extent of JNK phosphorylation, in accordance with the multiplicity of IRS-1 Ser307 kinases. Further investigation in the present study was narrowed down to 12 selected inhibitors (highlighted in the tables) based on two inclusion criteria of reducing JNK phosphorylation below 65% and also lowering IRS-1 Ser307 phosphorylation to at least 15% (Table 1 and 2). These compounds share 2,6-disubstituted 7-oxo-pyrido[2,3-d]pyrimidine core structure.



**Figure 3** Lipotoxicity-induced JNK phosphorylation in RINm5F insulinoma cells

The 12 kinase inhibitors selected on the basis of their effectiveness in anisomycin-treated HEK293 cells were further examined in a cellular model of lipotoxicity. A JNK phosphorylation level below 61% and an IRS-1 Ser307 phosphorylation level below 15% in comparison with anisomycin-only-treated samples comprised the selection criteria. The stress response of RINm5F rat insulinoma cells, including JNK, c-Jun and IRS-1 Ser307 phosphorylations, to short term saturated fatty acid treatment, has been studied earlier in our laboratory.<sup>18</sup> In this study, the levels of P-JNK and P-IRS-1 were assessed in the cells after incubation in the presence of 500  $\mu$ M albumin-conjugated palmitate for 8 hr. JNK phosphorylation was inhibited to less than 50% of palmitate only treatment by two of the investigated kinase inhibitors, **27** and **18** (54% and 59% inhibition, respectively) (Fig 3). These two compounds also exerted a remarkable albeit different inhibitory effect on IRS-1 Ser307 phosphorylation (58% and 93%, respectively) (Fig 4).



**Figure 4** Lipotoxicity-induced IRS-1 Ser307 phosphorylation in RINm5F insulinoma cells

Interestingly, IRS-1 phosphorylation was also markedly reduced by another three inhibitors, namely **14** (61%), **20** (87%) and **21** (96%) (Fig 4), which in turn did not decrease the level of phosphorylated JNK at similar extent (Fig 3).

Our most effective inhibitors of IRS-1 phosphorylation are containing disubstituted phenoxy substituent in position 6 of the pyrido-pyrimidine core. 2,4-Difluorophenoxy derivatives showed close to 100% inhibition in case of various substituents on position 2 amino group e.g. cyclopentylamino, cyclohexylamino, methanesulfonamido-propylamino, 1-aminosulfonyl-piperidine-4-yl substituents gave excellent results. 2,6-Dichlorophenoxy substituent in position 6 still resulted <10% IRS-1 phosphorylation e.g. with tetrahydropyran-4-yl substituent in position 2, but several other substituents in position 2 caused similar effect also (Table 2). Small scale kinase selectivity of 10 compounds having IRS-1 Ser307 phosphorylation level below 15% were determined by Proteros Biostructures at 10  $\mu$ M or 1  $\mu$ M compound concentration (see supplementary material). Based on these results the following kinases were hit remarkably: Abl, c-kit, DDR1, JNK1, PDGFR $\beta$ , Ret, c-Src, VEGFR2. We determined IC<sub>50</sub> of the reported compounds at 24<sup>h</sup> on HEK293 as a measure of cytotoxicity. We found that every compound has IC<sub>50</sub> over 10  $\mu$ M and most of them have over 30  $\mu$ M (see supplementary material).

We aimed to identify and develop new compounds with the potential to reduce IRS-1 Ser307 phosphorylation. The selected 46 compounds were first tested in anisomycin-treated HEK293 cells and 12 of them were further studied in a cellular model of palmitate induced lipotoxicity. Although the signaling mechanism that leads to IRS-1 Ser307 phosphorylation in palmitate-treated insulinoma cells is more complex, the effects observed in this model are much more relevant with respect to diabetes pathology and treatment. A remarkable reduction in lipotoxicity-induced IRS-1 Ser307 phosphorylation was observed in case of 5 compounds, 4 of which also decreased JNK phosphorylation at statistically significant, yet smaller extent. It seems likely that these molecules act by inhibiting other protein kinases involved in IRS-1 phosphorylation beside JNK.

We have successfully achieved our triple aim: we have started a medicinal chemistry optimization starting from druglike JNK inhibitor structures in order to obtain novel compounds

potentially applicable for the treatment of type 2 diabetes. We have mapped the structural features taking into account novelty, druglikeness, and IRS-1 serine phosphorylation inhibitory activity. The development process yielded a narrow group of novel structures with excellent inhibitory effect on IRS-1 Ser307 phosphorylation, opening the opportunity for further drug development.

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## Supplementary Material

Supplementary data (detailed synthetic methods, analytical data, kinase selectivity and cytotoxicity data) associated with this article can be found, in the online version.

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