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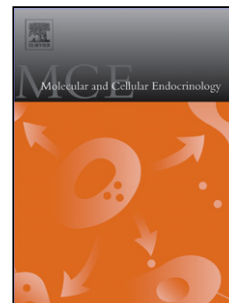
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11 β -HYDROXYSTEROID DEHYDROGENASE TYPE 1 INHIBITORS WITH OLEANAN AND URSAN SCAFFOLDS

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Abstract

The enzyme 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) converts cortisone to the active glucocorticoid cortisol, thereby acting as a cellular switch to mediate glucocorticoid action in many tissues. Several studies have indicated that 11 β -HSD1 plays a crucial role in the onset of type 2 diabetes and central obesity. As a consequence, selective inhibition of 11 β -HSD1 in humans might become a new and promising approach for lowering blood glucose concentrations and for counteracting the accumulation of visceral fat and its related metabolic abnormalities in type 2 diabetes. In this study, we present the synthesis and the biological evaluation of ursan or oleanan type triterpenoids which may act as selective 11 β -HSD1 inhibitors in liver as well as in peripheral tissues, like adipocytes and muscle cells. In order to rationalise the outcomes of the inhibition data, docking simulations of the ligands were performed on the experimentally determined structure of 11 β -HSD1. Furthermore, we discuss the structural determinants that confer enzymatic specificity. From our investigation, valuable information has been obtained to design selective 11 β -HSD1 blockers based on the oleanan and ursan scaffold.

1. Introduction

In humans, the ratio of active/inactive glucocorticoids is controlled by two enzyme isoforms: 11 β -hydroxysteroid dehydrogenase type 1 and type 2 (11 β -HSD1 and 11 β -HSD2, respectively) (Seckl, 2004). 11 β -HSD1 converts cortisone to the active glucocorticoid cortisol, thereby controlling access of glucocorticoid hormones to the glucocorticoid receptor (Seckl, 2004). Overexpression of 11 β -HSD1 has been shown to play a crucial role in the onset of type 2 diabetes, and rodent models support the hypothesis that it might also be involved in the development of central obesity (Livingstone *et al.*, 2000; Masuzaki *et al.*, 2001; Liu *et al.*, 2003). 11 β -HSD1 deficient mice show enhanced glucose tolerance, attenuated gluconeogenic responses and improved lipid and lipoprotein profiles (Kotelevtsev *et al.*, 1997; Morton *et al.*, 2001). On the other hand, transgenic over-expression of 11 β -HSD1 in mice adipose tissues causes visceral obesity, insulin resistance, diabetes, dyslipidemia and hypertension (Masuzaki *et al.*, 2001; Masuzaki *et al.*, 2003). All these data suggest that selective inhibition of human 11 β -HSD1 might become a new and promising approach for lowering blood glucose

concentrations and for counteracting the accumulation of visceral fat and its related metabolic abnormalities in type 2 diabetes (reviewed in: (Hughes *et al.*, 2008)).

Triterpenoids like carbenoxolone, dexamethasone or glycyrrhetic acid are non-selective inhibitors of 11 β -HSD since they also inhibit 11 β -HSD2, the second isoform (Stewart *et al.*, 1987; Walker *et al.*, 1995). 11 β -HSD2 acts as a dehydrogenase by converting active cortisol into inactive cortisone, thereby preventing inappropriate mineralocorticoid receptor activation by glucocorticoids in aldosterone target tissues. Non-selective inhibition of 11 β -HSD2 results in serious side-effects like sodium retention, hypokalaemia and hypertension (Sandeep *et al.*, 2004).

Pentacyclic triterpenes of the ursan and oleanan type are widespread in the plant kingdom and many of them have been described as physiological active compounds (Yoshikawa *et al.*, 1997; Shimizu *et al.*, 1997; Kim *et al.*, 1998; Murakami *et al.*, 2001) (Fig. 1). Clinical interests in ursan and oleanan type triterpenes relate to their anti-inflammatory, hypoglycemic, anti-viral and apoptosis inducing properties. As indicated above, 18 β -glycyrrhetic acid, a compound with an oleanan scaffold, is known as strong inhibitor of 11 β -hydroxysteroid dehydrogenase activity but because of its non-selective behaviour, it cannot be used in therapy. However, the structure of 18 β -glycyrrhetic acid may serve as a lead in the chemical synthesis of new and selective 11 β -HSD1 blockers.

Previously, we successfully purified 11 β -HSD1 in an active state from human and mouse liver microsomes (Maser and Bannenberg, 1994; Maser *et al.*, 2002). Furthermore, we produced recombinant human 11 β -HSD1 enzyme by overexpression of the corresponding gene in *E. coli* and *P. pastoris* (Maser and Bannenberg, 1994; Blum *et al.*, 2000; Maser *et al.*, 2002). In the present investigation, we performed studies on potential and selective 11 β -HSD1 inhibitors. We present new compounds with an oleanan or ursan scaffold which selectively inhibit 11 β -HSD1 in the nM range, whereas 11 β -HSD2 activity is affected only in μ M concentrations of the inhibitor. Furthermore, we discuss the structural determinants that confer 11 β -HSD1 specificity to these compounds and show new approaches to synthesize selective 11 β -HSD1 inhibitors with an oleanan or ursan scaffold. Selective 11 β -HSD1 inhibitors with an oleanan or ursan scaffold should have the advantage of low toxicity, the possibility of straightforward modifications of the scaffold to influence pharmacokinetic and pharmacodynamic properties, and sufficient resources in nature to get enough starting material.

2. Experimental

2.1. Preparation of biological fractions

Enzymatically active 11 β -HSD1 fractions (purified human 11 β -HSD1, human liver microsomes, as well as recombinant 11 β -HSD1 overexpressed in *E. coli* and *P. pastoris*) were prepared as previously described (Blum *et al.*, 2000; Maser *et al.*, 2002). Human placental microsomes containing 11 β -HSD2 were prepared as follows: The placenta samples were homogenized in 4 volumes of homogenization buffer (20 mM Tris/HCl, 250 mM sucrose, 1 mM EDTA, 0.1 mM PMSF, pH 7.4) using a glass-Teflon Potter-Elvehjem homogenizer. The homogenate was centrifuged at 600 x g for 10 min and at 10000 x g for 10 min to sediment nuclei, cell debris and mitochondria. The supernatant at this stage was centrifuged at 170.000 x g for 1 h to sediment the microsomes. The microsomal pellet was resuspended in the homogenization buffer finally yielding a protein concentration of about 20 mg/ml.

2.2. Synthesis of selective 11 β -HSD1 inhibitors.

To elucidate the structural determinants of oleanan and ursan type triterpenes which confer 11 β -HSD1 specific inhibition, a variety of pentacyclic triterpenes was prepared from 18 β -glycyrrhetic acid or other commercially available oleanan and ursan type triterpenes as starting material. The preparation was performed according to standard protocols of chemical synthesis and is described in detail under patent application PCT/DE 2007 / 002218.

2.3. Enzyme Assays

For analysis of 11 β -HSD1 reductase inhibition the carbonyl reduction of cortisone to cortisol was measured. The assay performed contained an NADPH-regenerating system and was incubated for 3h at 37°C. For analysis of 11 β -HSD1 dehydrogenase inhibition the oxidation of cortisol to cortisone was assayed in the presence of NADP and an incubation time of 60 min. Inhibition experiments were performed with human liver microsomes containing 11 β -HSD1, with microsomes isolated from *P. pastoris* strains expressing recombinant human 11 β -HSD1, and with purified 11 β -HSD1 from human liver. For 11 β -HSD2 inhibition experiments human placental microsomes were used. The assay conditions for 11 β -HSD2 inhibition corresponded to those for 11 β -HSD1. All experiments have been done at least five times. The inhibition experiments of 11 β -HSD1 activity, using different 11 β -HSD1 preparations, resulted in similar inhibition pattern. The glucocorticoid concentration in the assays was 2 μ M.

2.4. Docking simulations

For all docking calculations we used the crystal structure of 11 β -HSD type 1 available at the Protein Data Bank (PDB) (Berman *et al.*, 2000) in complex with carbenoxolone (PDB code 2bel). The protein structure was treated with the protein preparation wizard in Maestro (Maestro, 2007) whilst the simulations were performed using Glide (Glide, 2007), both from the Schrödinger suite of programs. The ligands dataset was manually built in Maestro. During the protein preparation all water molecules were removed, hydrogen atoms were added and the complex was energy minimised using the default settings. The enclosing docking box, whose size in each direction was 27.5 Å, was centred on the nicotinamide C4 atom. The docking runs were performed in Standard Precision (SP) mode and in order to soften the potential for non polar parts of the ligands, the van der Waals radii of ligand atoms with partial atomic charge less than 0.15 were scaled by 0.8. Only the top 5 energy ranked poses were retained and energy minimised for each studied compound: The top scoring conformer for each ligand was identified on the basis of the Emodel score whilst the subsequent comparison between different compounds was performed taking into account their corresponding Gscore values (this is a recommended procedure in Glide).

3. Results and Discussion

Some triterpenoids like carbenoxolone, dexamethasone or glycyrrhetic acid are already known to inhibit 11 β -HSD1 but their use in therapy is limited by the fact that they block the activity of 11 β -HSD2 as well, thereby provoking renal mineralocorticoid excess at higher dosage (Stewart *et al.*, 1987; Walker *et al.*, 1995; Walker and Seckl, 2003). Clinical interest in pentacyclic ursan and oleanan type triterpenes relate to their anti-inflammatory, anti-viral, apoptosis inducing and hypoglycemic properties, although the underlying mechanism in most cases is still unknown (Bühler *et al.*, 1991; Matsuda *et al.*, 1998). Corosolic acid, an ursan type triterpene isolated from the leaf of Banaba (*Lagerstroemia speciosa*), a traditional oriental medicine to treat diabetes, induces GLUT4 translocation and lowers plasma insulin levels in KK-Ay mice (Miura *et al.*, 2004). Oleanoic acid, an oleanan type triterpene found in many plants with hypoglycemic activity e.g. *M. charantia*, *G. sylvestre*, exhibits the hypoglycemic activity on oral glucose-loaded rats by decreasing the rate of gastric emptying and inhibiting the glucose transport system at the small intestinal brush border (Matsuda *et al.*, 1998).

18 β -Glycyrrhetic acid, an oleanan type triterpene and principal active ingredient of liquorice root, as well as its hemisuccinyl derivate carbenoxolone are potent inhibitors of 11 β -HSD activity (Stewart *et al.*, 1987; Hult *et al.*, 2006), but display poor selectivity towards the two isoforms. Carbenoxolone has earlier been demonstrated to improve insulin sensitivity and to decrease glucose production in healthy human volunteers, but the 11 β -HSD2 inhibitory activity of carbenoxolone was a limiting factor because it induces renal mineralocorticoid excess at higher dosis (Walker *et al.*, 1995). By using 18 β -glycyrrhetic as a lead structure, we prepared a variety of pentacyclic triterpenes from or other commercially available compounds (PCT/DE 2007 / 002218).

The results of our investigation emphasise the importance of a carbonyl group in 11-position of the pentacyclic scaffold for selective 11 β -HSD1 recognition, whereas an acidic function in 20-position is responsible for a strong, non-selective inhibition of both 11 β -HSD isoenzymes (Fig. 2). Cleavage or masking of the acidic function of 18 β -glycyrrhetic acid resulted in selective 11 β -HSD1 inhibition. Thereby, the selective inhibitory potency of the compound can be modulated by selection of the substituent in 20-position.

The comparison between oleanan and ursan triterpenes revealed that the methyl group in 19-position of ursan type is accountable for a weak selective inhibition of 11 β -HSD1. The presence of a keto-function in 11-position enhanced the overall inhibition, whereas an acidic function in 4-position affects the recognition of the 11-keto-function by 11 β -HSD1, resulting in high IC₅₀ values (Fig. 2).

In Fig. 3 the putative binding mode of the most selective compound of the series (Cpd04) is compared to carbenoxolone binding mode as found in the X-ray structure deposited at the PDB (PDB code 2bel). The inhibitor is stabilised in the binding cleft mainly by hydrophobic interactions. Moreover a hydrogen bond between the carbonyl group of the ligand and the hydroxyl group of a serine (S170) ensures further stabilisation (see Fig. 3B). Interestingly enough, experimental evidence shows that the non selective inhibitor carbenoxolone binds the enzyme in a similar fashion (see Fig. 3A). The condensed cycles of both inhibitors appear surrounded mainly by hydrophobic side chains while few polar interactions are established with the protein thanks to their carbonyl (Cpd04 and CBO) and carboxyl (CBO) functional groups. Furthermore, as shown in Fig. 4, the good correlation found between experimentally obtained pIC₅₀ values and calculated docking scores (Gscores), for the molecules in the dataset, highlights the robustness of the chosen docking method in producing reliable poses. All the compounds docked the protein in a similar way.

Selective 11β -HSD1 inhibitors that act in all tissues, particularly in adipocytes and skeletal muscles, have considerable potential as a drug directed against glucocorticoid related metabolic disorders. In particular, these inhibitors will improve insulin sensitivity and glucose uptake, reduce lipolysis, and counteract accumulation of visceral fat and its related metabolic abnormalities. Our findings highlight the possibility of obtaining potent selective 11β -HSD1 inhibitors based on the triterpene scaffold of the oleanan and ursan types. Selective 11β -HSD1 inhibitors, based on those moieties, should have the advantage of low toxicity, the possibility of operating modifications of the scaffold to influence pharmacokinetic and pharmacodynamic properties, and sufficient resources in nature to get enough starting material. Finally, the good correlation between experimental data and docking calculations is currently used to design more potent and selective 11β -HSD1 inhibitors.

Legends to the Figures

Fig. 1.

Ursan and oleanan type triterpenes.

Fig. 2.

Inhibition of 11 β -HSD1 and 11 β -HSD2 by various ursan and oleanan type triterpenoids. For 11 β -HSD1, glucocorticoid oxidation (Ox.) and reduction (Red.) was measured. For 11 β -HSD2, cortisol oxidation was assayed. Inhibition constants are given as IC₅₀ values. Experiments have been repeated at least 5 times; n.d. = not detectable. For details see Experimental section.

Fig. 3.

Carbenoxolone (CBO) at the 11 β -HSD1 active site (A), as it appears in the X-ray structure available at the PDB (pdb code 2bel), compared to Cpd04 estimated binding pose (B). Residues S170, Y183, NADPH cofactor, carbenoxolone and Cpd04 are highlighted as dark grey and yellow coloured stick models, respectively. The dashed lines are drawn between atoms likely involved in H-bond interactions.

Fig. 4.

Plot of observed pIC₅₀ values (11 β -HSD1_{Red.}) versus docking scores (Gscore values obtained from Glide). The two compounds whose inhibitory potencies were not detectable were not included in the plot.

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Fig: 1

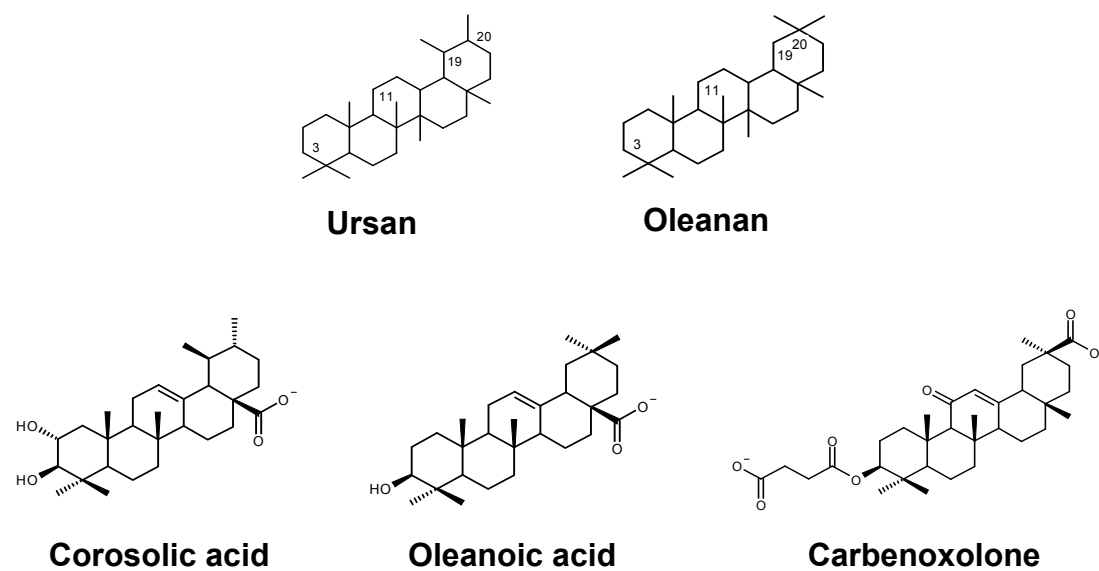


Fig. 2

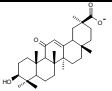
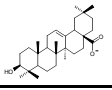
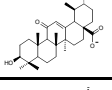
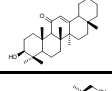
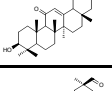
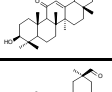
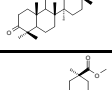
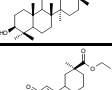
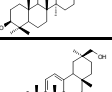
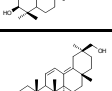
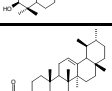
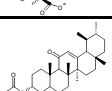
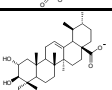
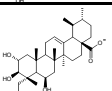
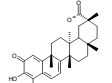

Id	Sketch	11 β -HSD1 _{Ox.} (IC ₅₀)	11 β -HSD1 _{Red.} (IC ₅₀)	11 β -HSD2
Cpd01		12 nM	12 nM	8 nM
Cpd02		> 200 μ M	n.d.	n.d.
Cpd03		1 μ M	68 μ M	n.d.
Cpd04		56 nM	244 nM	12 μ M
Cpd05		49 nM	149 nM	16 μ M
Cpd06		177 nM	122 nM	25 μ M
Cpd07		74 nM	124 nM	16 μ M
Cpd08		61 nM	119 nM	> 200 μ M
Cpd09		68 nM	141 nM	> 200 μ M
Cpd10		2 μ M	39 μ M	> 200 μ M
Cpd11		2 μ M	37 μ M	> 200 μ M
Cpd12		9 μ M	> 200 μ M	n.d.
Cpd13		11 μ M	74 μ M	n.d.
Cpd14		5 μ M	> 200 μ M	n.d.
Cpd15		3 μ M	112 μ M	n.d.
Cpd16		n.d.	n.d.	n.d.

Fig. 3

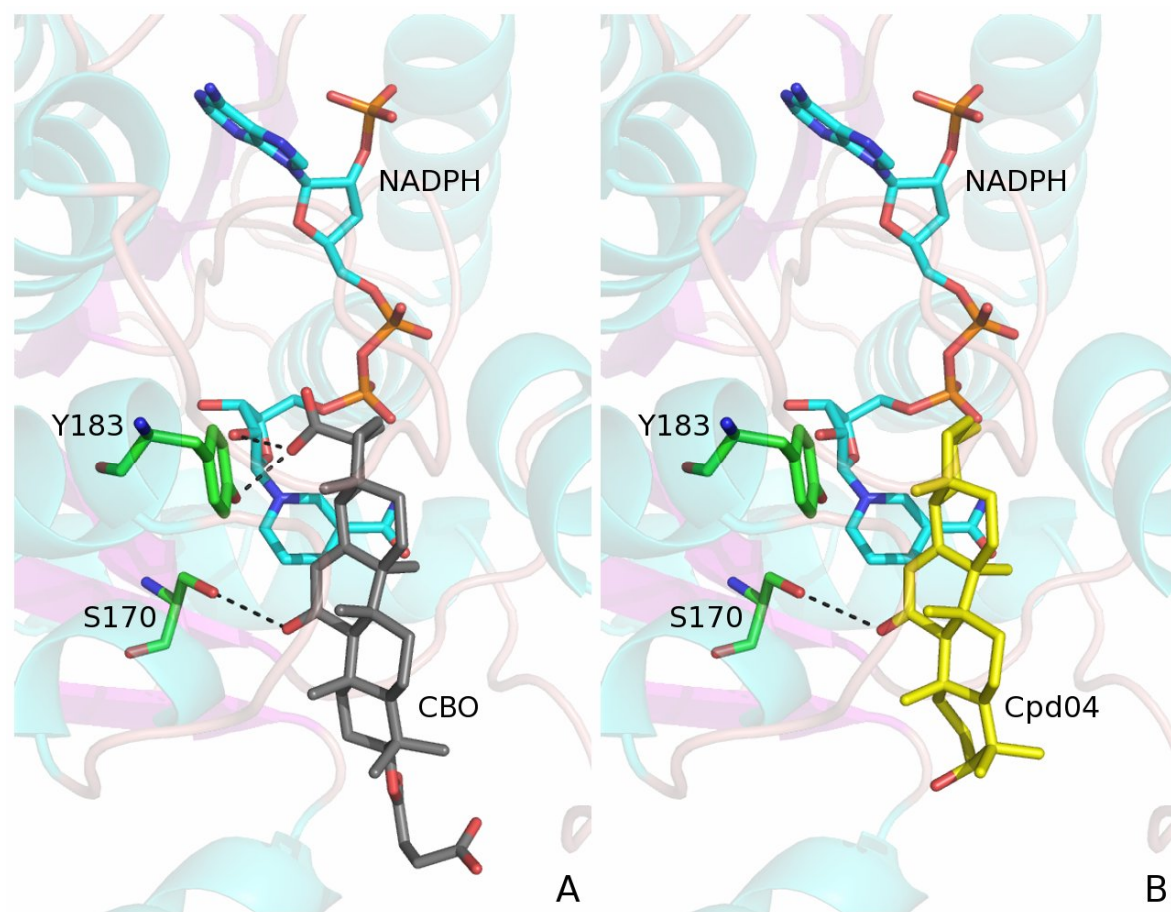
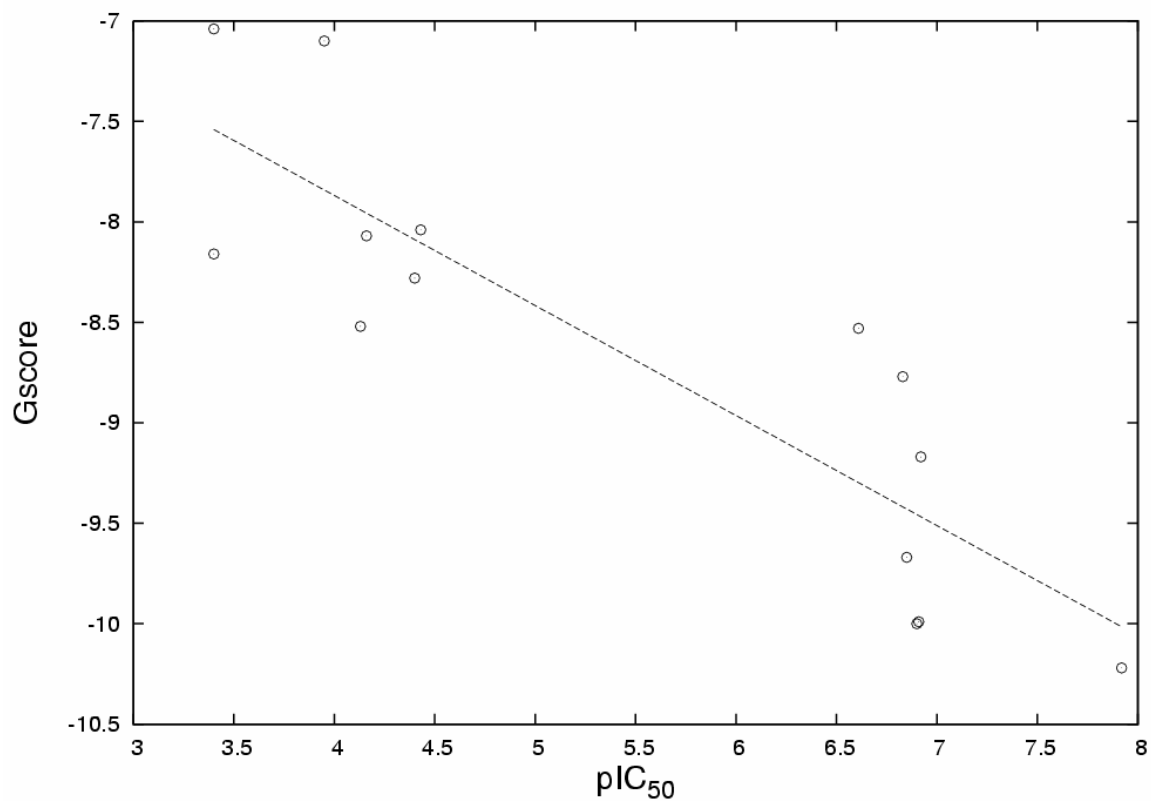


Fig. 4



Id	pIC ₅₀ Red.	Gscore
Cpd01	7.920	-10.22
Cpd08	6.924	-9.17
Cpd06	6.914	-9.99
Cpd07	6.907	-10
Cpd09	6.852	-9.67
Cpd05	6.827	-8.77
Cpd04	6.613	-8.53
Cpd11	4.432	-8.04
Cpd10	4.409	-8.28
Cpd03	4.167	-8.07
Cpd13	4.131	-8.52
Cpd15	3.951	-7.1
Cpd12	3.398	-8.16
Cpd14	3.398	-7.04