Based on this strategy and as part of our ongoing programme to develop new anti-obesity drugs[4], we have designed and synthesized a new series of non-imidazole derivatives, based on a basic pyrrolidine ring connected through an alkyl spacer of variable length to a phenoxysulfonylurea moiety. These compounds were initially evaluated for histamine $H_3$ receptor binding affinities suggesting that a propoxy chain linker between the amine and the core ring could be essential to the optimal binding affinity. The results confirmed these derivatives as a promising starting point for the design of new $H_3$-antagonists with anti-diabetic activity.

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POSTER COMMUNICATIONS – **PC.068**

# P-PIPERIDINYLALKYL-PHENOXYSULFONYLUREAS: NEW DERIVATIVES AS DUAL $H_3$ RECEPTOR ANTAGONISTS AND ANTI-DIABETIC ACTIVITY

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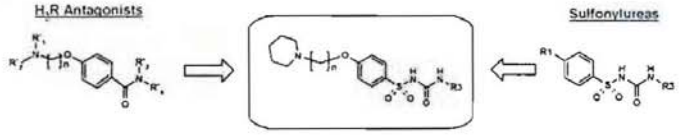
A new threat has appeared in worldwide health: the diabesity epidemic. The World Health Organization estimated in 2005 that 1.1 million people died as a result of diabetes[1]. Due to obesity is the major risk factor in type 2 diabetes, it's necessary to develop new treatments to the prevention in this epidemic.

It is known that histamine $H_3$ receptor antagonists are able to promote weight loss or prevent weight gain. Although most $H_3$ receptor antagonists had an imidazol moiety in their structure, recent studies have shown that N-containing non-aromatic heterocycles act as a potent anti-obesity agents[2]. A-331440 is a novel non-imidazol-based antagonist of the histamine H3 receptor which apparently reduces weight[3].

The American Diabetes Association has suggested that sulfonylurea system is clinically significant due to its anti-diabetic properties. Glimepiride is the first third-generation sulfonylurea approved as oral anti-diabetic drug[4].

Based on current findings, our research group proposed new compounds with dual activity as anti-obesity and anti-diabetic agents. Our aim was the design and synthesis of 22 new p-piperidinylalkylphenoxysulfonylurea derivatives in order to evaluate the biological activity against $H_3R$ and their affinity with hERG receptor.

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POSTER COMMUNICATIONS – **PC.069**

# DOCKING OF SUBSTRATES AND INHIBITORS INTO THE SUBSTRATE BINDING SITE OF TWO SEROTONIN TRANSPORTER MODELS

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The serotonin transporter (SERT) belongs to the neurotransmitter:sodium symporter (NSS) family. Located in the membranes of presynaptic neurons, the transporter removes serotonin (5-HT) from the synaptic cleft, thus reducing the number of neurotransmitters available for interaction with postsynaptic receptors. The transporter is targeted by two of the main classes of antidepressant drugs - the selective serotonin reuptake inhibitors (SSRIs) and the tricyclic antidepressants (TCAs) - and is also the target for psychostimulants such as cocaine, MDMA (ecstasy), and d-amphetamine. The three-dimensional structure of SERT has not yet been determined. However, the first three-

dimensional structure of a NSS family member, the *Aquifex* aeolicus leucine transporter, LeuT, is available both in an occluded conformation (1) as well as in an outward-facing conformation (2). Based on a comprehensive alignment of NSS family members (3), two different homology models of SERT representing two different conformational states were generated using the ICM program package and the two LeuT crystal structures as templates and the models were used for docking of a set of known substrates and several inhibitors into the putative substrate binding site. Our results indicated that the bacterial leucine transporter crystal structures are reliable templates for generating SERT homology models for subsequent docking of substrates and inhibitors. The docking indicated that D98 is a key amino acid for binding both substrate and inhibitors. Transmembrane helixes 1, 3, 6 and 8 were involved in interactions with substrates and inhibitors in both SERT models.


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# DI- AND TRI-SUBSTITUTED PURINES WITH THE PHENYL GLYCIDYL ETHER MOIETY: SYNTHESIS AND ANTICANCER ACTIVITIES


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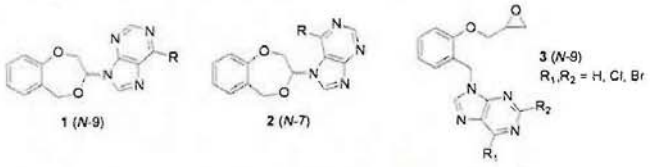
Despite major breakthroughs in many areas of modern medicine over the past 100 years, the successful treatment of cancer remains a significant challenge in the 21st century. Therefore, the development of new drugs against cancer belongs among the priorities of the development of science and fundamental research. Alkylating agents have been used for the treatment of cancer for over six decades and yet their repertoire continues to grow.

Studies on the synthesis and pharmacological evaluation of (*RS*)-6-substituted-7 or 9-(2,3-dihydro-5*H*-1,4-benzodioxepin-3-yl)-7*H*- or -9*H*-purines were published.[1] The microwave-assisted organic synthesis has provided faster access to the target compounds with the advantage of selective obtaining the *N*-9' (**1**) or *N*-7' (**2**) regioisomers simplifying their isolation[2].




Figure

Trying to increase the anticancer activity of compounds **1** their structure was modified as followed: a) The salicyl alcohol fragment (present in the 2,3-dihydro-5*H*-1,4-benzodioxepin fragment) and the purine of **1** were maintained; b) The interaction of xenobiotics with DNA and the resulting adducts have been studied extensively, in order to understand how they exhibit their cytotoxic and carcinogenic properties[3]. It is within this philosophy that our group has focused on simple epoxides on which until now only little research has been performed. As a lead moiety the phenyl glycidyl ether was chosen (Figure).

We describe herein the synthesis and biological evaluation of a series of substituted 9-(2-oxiranylmethoxybenzyl)-9*H*-purines **3**.

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# ENANTIOMERS OF 9-[1-(*p*-NITROBENZENESULFONYL)-1,2,3,5-TETRAHYDRO-4,1-BENZOXAZEPIN-3-YL]-2,6-DICHLORO-9*H*-PURINE, AS ANTICANCER AGENTS


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Knowledge of the molecular signalling pathways that stimulate tumours has led to the identification of both Epidermal Growth Factor Receptor (EGFR) and Vascular Endothelial Growth Factor (VEGF) as key components implicated in the regulation of the tumour proliferation and angiogenesis, respectively. The dual inhibition of both molecular signalling pathways such as EGFR and VEGF may solve the multidrug resistance (MDR) problem and promote synergism[1]. There are about ten scientific publications that deal with the dual EGFR and VEGF inhibition, and all of them concentrate in the period 2004-2010, which supports