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The development of the analytical methods for studying capsules containing Temozolomide active substance

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The aim of this work was to develop analytical methods used for studying Temozolomide, an anti-cancer drug from imidazotetrazine group. Temodal 5 mg, 20 mg capsules manufactured SP Labo N.V. Belgia were used as the reference products.

An RP-HPLC method was developed for the study of assay, dosage uniformity & quantity of the active substance released from the drug form, as well as the purity of the preparation.This method was compared with the spectrophotometric method.

During the purity study, it was observed that the solutions containing Temozolomide were unstable at room temperature. The Temozolomide degradation product was identified as 5(4)-aminoimidazole-4(5)-carboxyamide (AIC).
The described method succesfully separated the observed impurity from the active substance. The metod was used for the routine analysis of Temozolomide capsules.

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Tripeptides with C-terminal arginine as potential inhibitors of urokinase

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The urokinase plasminogen activator system consists of the serine protease urokinase (uPA), its cell surface-associated receptor (uPAR), plasminogen activator inhibitors (PAIs) and the proenzyme plasminogen (Plg). uPA is responsible for the Plg activation to plasmin (Plm) by the Arg561-Val562 bond hydrolysis in Plg.

Plm, the key enzyme of fibrinolysis, is a non-specific trypsin-like protease, which cleaves after numerous Lys or Arg bonds. It attacks fibronectin, fibrin/fibrinogen, clotting factors V/Va and VIII/VIIIa, latent TGF-β, IGF binding proteins and the zymogen forms of several metalloproteases. In contrast, uPA is a highly specific serine protease, which catalyses cleaving single Arg-X or Lys-X bonds in for example the hepatocyte growth factor, fibronectin, diphtheria toxin, uPAR and uPA itself. The two-chain active form of uPA is activated from a single chain precursor (prouPA) by plasmin or possibly via enzymes commonly enriched in cancer cells such as thiol cathepsins. uPA is unique in having its own high affinity cell-surface receptor uPAR. The urokinase receptor is focalized in the cell-cell connection and on the edge of invading cells. Thus, the uPA system plays a pivotal role in degradating and regenerating of the basement membrane which leads directly to tissue remodelling, invasiveness and angiogenesis. The binding of uPA to uPAR also initiates signalling cascades that does not require the uPA catalytic activity but only receptor occupancy. The expression of uPA and uPAR has been demonstrated in essentially every cancer type, such as gastric, colorectal, ovarian, breast, endometrial and prostate cancer.

We present the synthesis and the investigation of effect peptides of general formula H-D-Ser-AA-Arg-OH (AA = leucine, norleucine, izoleucine, valine, norvaline, α-metyloalanine, α-aminobutanoic acid, homoleucine, tert-leucine, neoglycine) on amidolytic activity of urokinase, thrombin, plasmin, trypsin, t-PA and kallikrein. We expected that the use of specific tripeptide sequence to urokinase would cause high urokinase selectivity [1, 2]. The peptides were synthesized on the solid phase manually using standard Fmoc-based strategy.

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17:00 Poster 82

Interaction fingerprints patterns. Binding mode analysis of mGlu2 receptor model based on docking studies

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One of the most troublesome stages of Computer Aided Drug Design (CADD) process is analyzing huge amount of data provided by docking studies. Simple scoring functions alone can provide only shallow information about ligand-receptor interactions, since they do not distinguish neither residues nor single atoms. Very often a visual inspection is the only way to determine binding mode. In this study we would like to introduce an implementation of interaction profiles(1)based on Structural Interaction Fingerprints (SIFt)(2)to analyze known ligands docking poses within mGluR2 model. The use of interaction patterns allows precise and rapid binding site description.

The mGluR family consists of eight proteins divided into three groups corresponding to sequence similarities, pharmacology and physiological role. These groups are: I (mGluR1, -5), II (mGluR2, -3) and III (mGluR4, -6, -7, -8). Group II lies in field of our interest due to its potential as therapeutic target for antidepressant and

anxiolytic drugs. Research was performed on population of 100 mGluR2 models created on Rhodopsin crystal structure template. Building that many virtual receptors provided us with semi conformational search on residues assembling incriminated receptor. Library of 179 known allosteric modulators of group II mGluR was used for docking studies and thus forging the binding mode.

Acknowledgments

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Synthesis and anticonvulsant activity of new N-[4-(arylpiperazin 1-yl)]- 1,3-dioxo-1,3-dihydro-2H- isoindole- and 1,3-dioxooctahydro-2H-isoindole-2-carboxamides

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Numerous compounds are synthesized and screened for their anticonvulsant activity each year. To make the discovery of new anticonvulsants more rational many investigators identified structural fragments essential for anticonvulsant properties. One of the structural features that play a significant role in relation to antiepileptic activity is an amide function.[1,2] In the course of developing new anticonvulsant agents as well as taking into consideration the above and vital influence of 4-arylpiperazine moieties on anticonvulsant activity of pyrrolidine-2,5-diones differently substituted at 3-positon of succinimide ring,[3,4] in the present studies we have synthesized a library of 1,3-dioxo-1,3-dihydro-2*H*-isoindole- and 1,3-dioxooctahydro-2*H*-isoindole-2-carboxamides with the 4-arylpiperazine derivatives as an amide function. The structures of compounds obtained are shown on **Figure 1**.

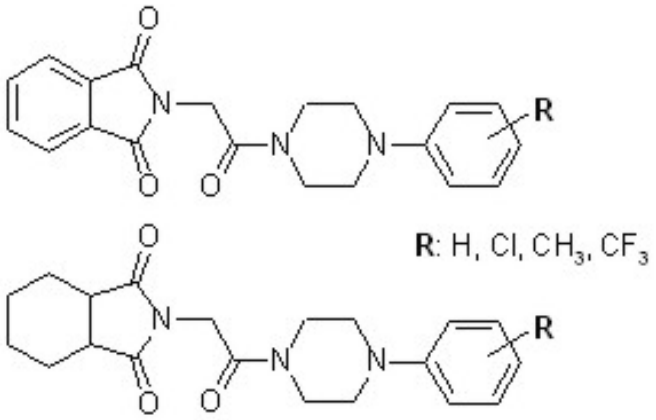

Figure 1.

The desired compounds were prepared by condensation of (1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)- or (1,3-dioxooctahydro-2*H*-isoindol-2-yl)- acetic acids with the appropriately substituted 4-arylpiperazines, in the presence of the *N,N*-carbonyldiimidazole (CDI) reagent. The compounds were evaluated for their anticonvulsant activity and neurotoxic properties within the Antiepileptic Drug Development (ADD) Program (Epilepsy Branch, Neurological Disorders Program, National Institute of the Neurological and Communicative Disorders and Stroke (NINCDS), Rockville, USA).[5]

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17:00	Poster	86

Enzyme-catalyzed synthesis of (R)-2-(1-methyl-2-pyrrolidine)ethanol - clemastine substrate

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Clemastine is an effective antihistamine drug having sedative and anticholinergic effects. The main substrate for manufacturing of clemastine is (*R*)-2-(1-mehyl-2-pyrrolidine)ethanol, which can be also an important chiral building block for the synthesis of biologically active compounds. Starting from the racemic 2-(1-methyl-2-pyrrolidine)ethanol as a substrate, an enzymatic procedure was developed for the efficient synthesis of corresponding highly enantiomerically enriched (*R*) and (*S*)-2-(1-methyl-2-pyrrolidine)ethanol. Various commercially available immobilized and not immobilized lipases were examined and several acyl donors, as a acylating agents in enzymatic kinetic resolution were applied. Some parameters of enzymaticreactions, as temperature, solvent, time andsubstrates ratiowere optimized. Spectroanalysisdata,enantiomer excess,specyficrotation andotherphysical parameters of obtained compounds were determined.