

CONSTRUCTION, SYNTHESIS AND EVOLUTION OF NEW P-SULPHONAMIDOBENZOYLAMINO 2-OXINDOLE DERIVATIVES WITH POTENTIAL CHEMOTHERAPEUTIC PROPERTIES

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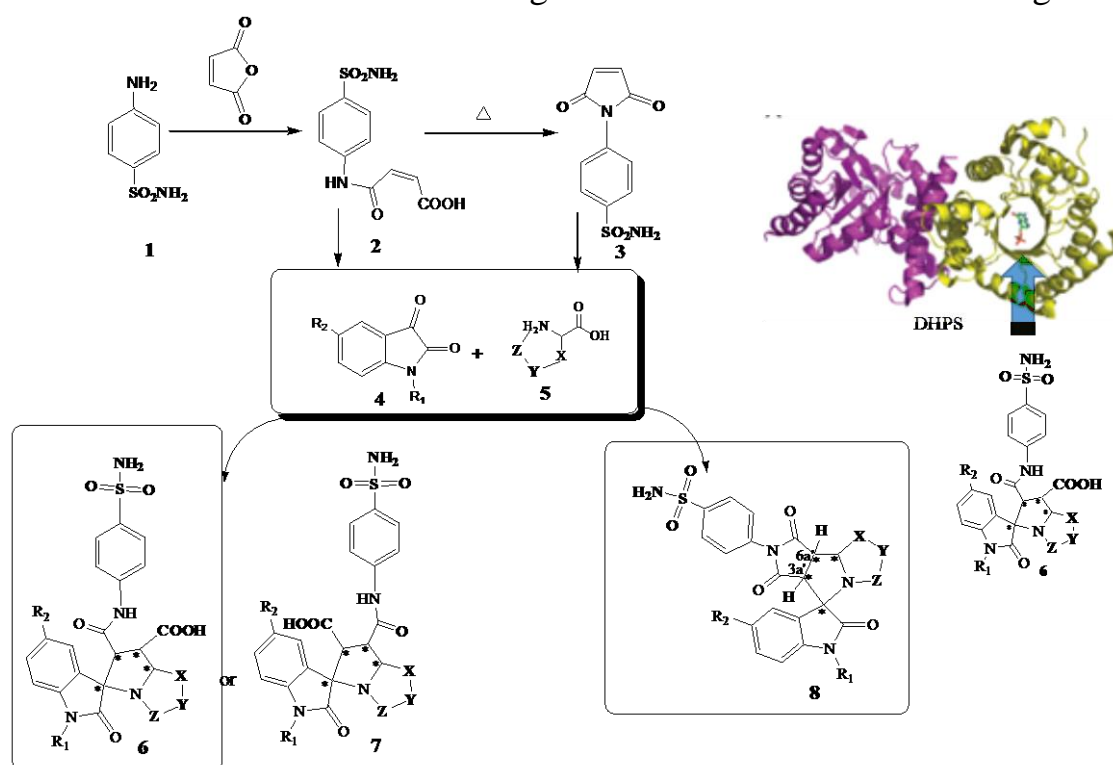
Introduction. Spiro-2-oxindoles called privileged molecules to search for and construction of new biologically active substances. They have significant chemotherapeutic potential. Thus, among them, compounds with antimicrobial and anti-tuberculosis activity have been found, some of them are capable of suppressing HIV. At the same time it would be interesting to include in their composition pharmacophore of sulfonamide. The rapid expansion of extensive resistance to the sulfonamides soon after their introduction and the growing use of the broader-spectrum penicillins in the treatment of infectious disease diminished the usefulness of sulfonamides. Sulfa drugs interrupt the essential folate pathway in bacteria and primitive eukaryotes; they target the enzyme dihydropteroate synthase (DHPS). It has been demonstrated as a primary target for the longest standing antibiotic class, the sulfonamides. Today, sulfonamides occupied a rather small place in the list of therapeutic agents that can be used for infectious disease. Therefore, the need for new antimicrobials is great in face of a growing pool of resistant pathogenic organisms.

Aim. Construction, synthesis and evolution of *p*-sulphonamidobenzoylamino spiro-2-oxindole derivatives and search potential chemotherapeutical activities.

Materials and methods. Synthesis of compounds using three-component condensation in alcoholic-aqueous medium; proof of the structure was performed by X-Ray, ^1H , ^{13}C NMR spectroscopy. ^1H NMR spectra were recorded on instruments Varian Mercury VX-200 (200 MHz) in DMSO- d_6 solution, TMS internal standard. Commercially available reagents and solvents were used without further purification. AtomicChargeCalculator (ACC) offers an efficient, user-friendly, interactive and platform independent environment for the calculation, visualization and analysis of conformationally dependent, quantum mechanics quality atomic charges in both biomacromolecules and drug-like molecules (<https://webchem.ncbr.muni.cz>). It was employed to predict the chemical reactivity and regioselectivity of reaction. The CADD Group's Chemoinformatics Tools and user Services online server (<https://cactus.nci.nih.gov>) was used to predict *in silico* toxicity, and specific antimicrobial activity according to QSAR models (Ampc Beta-Lactamase Inhibitor, inhibition of HIV-1 integrase, HIV-1 reverse transcriptase etc.). Molinspiration web

server (Molinspiration Cheminformatics, 2016) were respectively used for predicting bioactivity of the compound too.

Results and discussion. For synthesis of key synthons **2** and **3** was used streptocide **1**. The regioselective three-component condensation of azomethine ylides derived from isatins **4** and α -amino acids **5** with **2** or **3** as dipolarophiles has been realized through a one-pot 1,3-dipolar cycloaddition protocol in boiling aqueous alcohols afforded to the spirooxindoles (amides **6** and imides **8**) in moderate to excellent yields. The possible regioisomers **7** were not observed. The regiochemical outcome of the cycloaddition was unambiguously confirmed by Rotating-frame Overhauser Effect Spectroscopy experiments ^1H NMR and chemical reactivity and regioselectivity of reaction. Some classical (e.g. DHPS) and new potential targets (e.g. Ampc Beta-Lactamase Inhibitor, inhibition of HIV-1 integrase, HIV-1 reverse transcriptase) for library of compounds **6** and **8** were been evolved *in silico*. Spiro compounds **6** and **8** were tested according standard test-strains of microorganisms.



Conclusions. The 1,3-dipolar cycloaddition of azomethine ylides generated *in situ* from isatins and α -amino acids to N-(p-sulfonamido)-maleaminic acid **2** and N-(p-sulfonamido)-maleimide **3** afforded regio- and stereoselectively the spirooxindoles **6** and **8** in moderate to good yields. By using chemoinformatics complex computational analysis *in silico* we have found, that the obtained compounds are potentially non-toxic, does not have mutagenic and carcinogenic properties, and their potential as new chemotherapeutical and antiviral (HIV-1 reverse transcriptase) activity was been evaluated.