SYNTHESIS OF SPIRO-2-OXINDOLE DERIVATIVES AS POTENTIAL SODIUM CHANNEL BLOCKERS

Babchenko A. A., Redkin R. G., Schemchuk L. A., Chernykh V. P.
National University of Pharmacy, Kharkiv, Ukraine
ruslan.red.chem@gmail.com

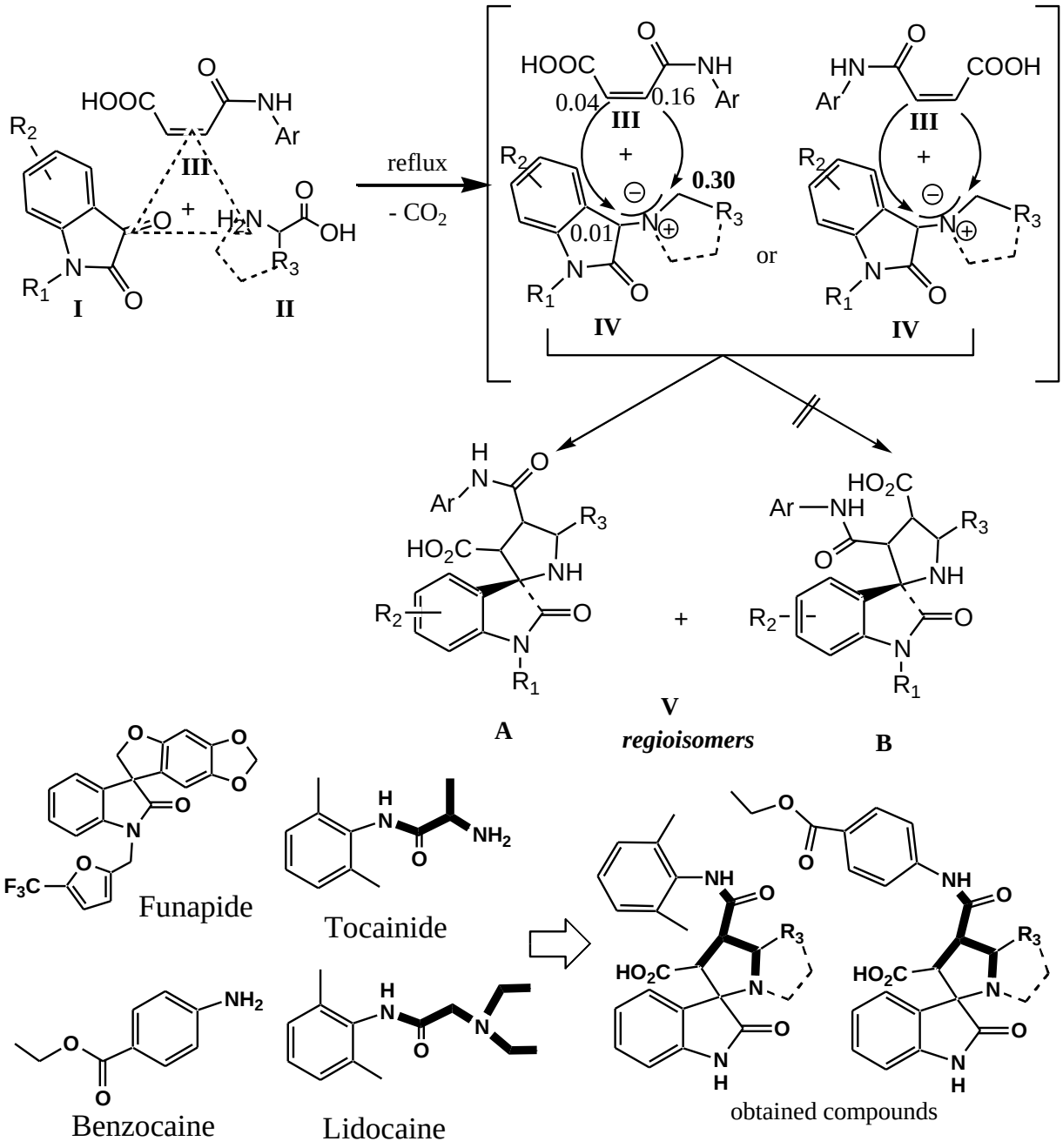
Introduction. Voltage-gated sodium channels (Na_vs) are an important family of transmembrane ion channel proteins and Na_v drug discovery is an exciting field. Sodium channel blockers are used as local anesthetics, in the treatment of cardiac arrhythmia and anticonvulsants. The study of literature dates showed that spiro-2-oxindole derivatives may be promising Na_v-inhibitors, for example, funapide is a novel analgesic. As part of an ongoing work on the research of potent and selective sodium channel blockers among small-molecule inhibitor of the sodium channels.

Aim. Synthesis of spiro-2-oxindole derivatives and search potential sodium channel blockers among them. For the design of the synthesized molecules, we used the structural design and incorporated in their molecules pharmacophores of benzocaine and tocainide, lidocaine.

Materials and methods. ^{1}H NMR spectra were recorded on instruments Varian Mercury VX-200 (200 MHz) in DMSO-d_6 solution, TMS internal standard. The COSY, NOESY, HSQC, and HMBC spectra were recorded using the standard procedure with gradient separation of the signal. Mass spectrum obtained on the instrument GC-MS Varian 1200L with ionizing voltage of 70 eV. Elemental analysis was performed on the elementary analyzer EA 3000 "Eurovektor" (CHNS-analysis). Commercially available reagents and solvents were used without further purification.

3V web server was employed to predict the channel through comprehensive analyses of the internal volumes considering difference as large as possible probe radius and the solvent radius (typically 1.5 Å for water). LAZAR online server was used to predict *in silico* toxicity. T.E.S.T software (2012, U.S. Environmental Protection Agency) and Molinspiration web server (Molinspiration Cheminformatics 2016) were respectively used for predicting LC_{50} and bioactivity of the compound. ADMET profiles were calculated using admeSAR (Laboratory of Molecular Modeling and Design. Copyright 2012, East China University of Science and Technology, Shanghai Key Laboratory for New Drug Design).

Results and discussion. The regioselective three-component condensation of azomethine ylides derived from isatins (I) and α-amino acids (II) with N-arylmaleaminic acids (III) as dipolarophiles (IV) has been realized through a one-pot 1,3-dipolar cycloaddition protocol in boiling aqueous alcohols afforded to the spirooxindoles (V) (possible regioisomers A and B both in racemic) in moderate to excellent yields.



New (V) cyclo-adducts obtained by the above method were characterized by mass-spectrometry, ^{1}H and ^{13}C NMR, and elemental analyses. The regiochemical outcome of the cycloaddition was unam-biguously confirmed by NOE experiments in ^{1}H NMR.

Conclusions. The 1,3-dipolar cycloaddition of azomethine ylides (IV) generated *in situ* from isatins and sarcosine or cyclic amino acids to N-arylmaleaminic acids afforded regio- and stereoselectively the spirooxindoles (V) in moderate to good yields. By using computational chemistry *in silico* methods we have found, that the obtained compounds are potentially non-toxic, does not have mutagenic and carcinogenic properties, and are a potential sodium channel blockers.