SYNTHESIS AND INVESTIGATION OF THE 7-AMINO-4-METHYLCOUMARIN'S MALEIC DERIVATIVE IN THE DOMINO-THREE-COMPONENT REACTION WITH ISATIN AND *L*-VALINE

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Introduction. 7-Amino-4-methylcoumarin **1** is a far-famed useful fluorescent labeling reagent for trace determination of different proteins. Also useful as a reference standard in enzyme assays. Nevertheless, at 2011 R. Tandon and coauthors were discover that it displayed the lowest *MIC* of 1 mg/L against not only *Mycobacterium tuberculosis* H37Rv strain but also the susceptible as well as the multidrug-resistant clinical isolates. Certain 7-acylamino coumarins were also found to inhibit the aforementioned strains and isolates with MICs in the range of 1.0-3.5 mg/L. They were also found to act in synergy with isoniazid/rifampicin. Electron microscopy revealed the cell-wall-attacking characteristic of these compounds, while fluorescence microscopy indicated that mycolic acid might be the target of action.

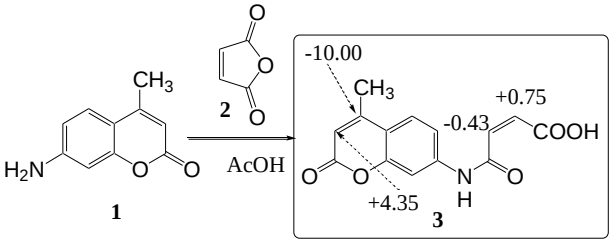
On the other hand, spiro-2-oxindoles are known for their antimicrobial potential. Therefore, we were interested to explore the possibility of 7-amino-4-methylcoumarin as dipolarofile using in the construction of new spiro-2-oxindoles.

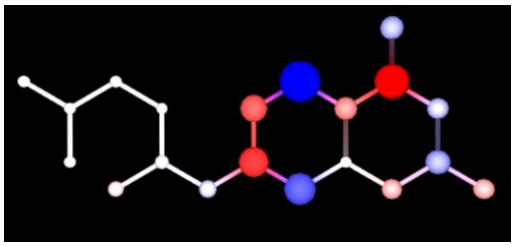
Aim. Investigation of chemical reactivity of 7-amino-4-methylcoumarin in the domino-tree-component reaction with isatin and *L*-valine.

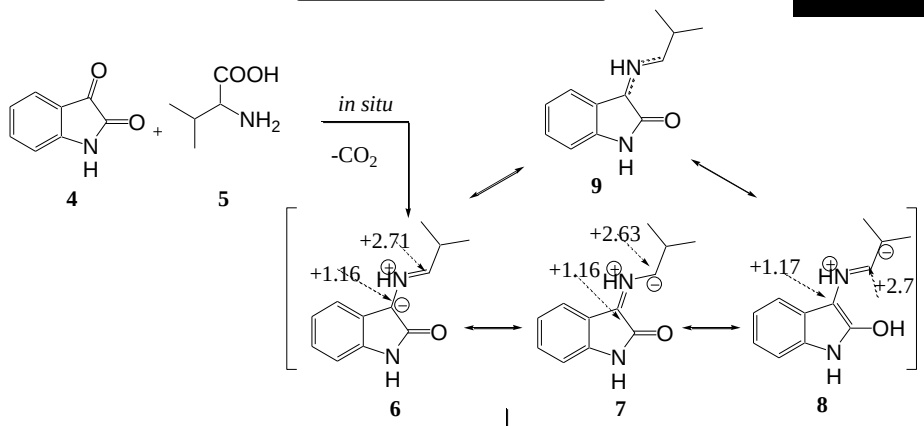
Materials and methods. Synthesis of compounds using acylation in glacial acetic acid, three-component condensation in alcoholic-aqueous medium; proofing of the structure was performed by UV-, ^{1}H NMR spectroscopy. ^{1}H NMR spectra were recorded on instruments Varian Mercury VX-200 (200 MHz) in DMSO-d_6 solution, TMS internal standard. UV-spectrums were record in EtOH on the SPEKOL-1500. AtomicChargeCalculator (ACC) offers an efficient based on the Electronegativity Equalization Method (EEM), user-friendly, interactive and platform independent environment for the calculation, visualization and analysis of quantum mechanics quality atomic charges in 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.

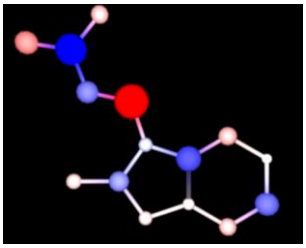
Results and discussion. The synthesis of 7-(N-maleylamino)-4-methylcoumarin **3** were carry out acylation of **1** by treatment with maleic anhydride **2**. Obtained N-(7-amino-4-methylchromen-2-one-7-yl)maleamiic acid **3** can be

considered as a bifunctional 1,3-dipolarophile. The calculation of atom charges using the ACC protocol for molecule **3** shows that the largest charge is concentrated on the π-bond of the lactone cycle and to a reduced extent on the π-bond maleic acid residue. Comparison with **1** and **3** chromophores, the difference of absorption ($\Delta\lambda_{max}$ 11 nm) between becomes less, and hence the absorption maxima would shift towards shortest wavelength for 7-acylamino chromophore, the *p*-electron is less free to move for **3**. One-pot protocol in boiling aqueous ethanol the regioselective three-component condensation of azomethine ylide (hybrid structures **6-9**) derived from isatin **4** and *L*-valine **5** *via* Shtreker reaction and then with **3** has been realized through a 1,3-dipolar cycloaddition with 92 % yield **10**. The possible regioisomer **11** were not observed. Adduct **10** absorbed at 329 nm.

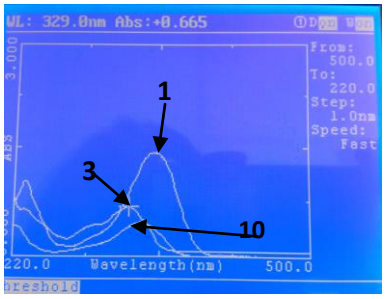


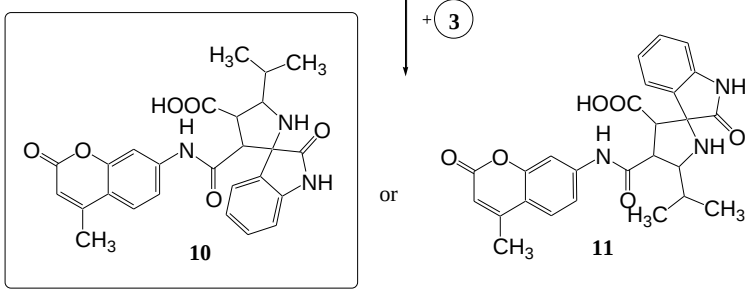






Absorption spectra of comp. **1,3,10**





Conclusions. The chemical reactivity of 7-amino-4-methylcoumarin in the domino-tree-component reaction with isatin and *L*-valine was been evaluated. The 1,3-dipolar cycloaddition of azomethine ylide generated *in situ* from isatin and *L*-valine to the spiro-adduct **10** to good yield. Despite the higher charges of the π-bond of the lactone cycle, the most reactive was the maleic acid residue at the 7 position of the 7-amino-4-methylcoumarin core. This may be due to steric limitation at the position 4 of the pyran ring, which are triggered by the 4-methyl group of lactone cycle.