CHEMOINFORMATICS APPROACH FOR MOLECULAR DESIGN OF NEW INHIBITORS OF TOLL-LIKE RECEPTORS AND NLRP3 INFLAMMASOME

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Inflammation is triggered by a repertoire of receptors detecting infections and damages. Some of these receptors directly bind microbial ligands, while others recognize endogenous molecules exposed under stress conditions, including infections. Toll-like receptors (TLRs) and Nod-like receptors (NLRs) are two major forms of innate immune sensors, which provide immediate responses against pathogenic invasion or tissue injury. Activation of these sensors induces the recruitment of innate immune cells such as macrophages and neutrophils, initiates tissue repair processes, and results in adaptive immune activation. Abnormalities in any of these innate sensor-mediated processes may cause excessive inflammation due to either hyper responsive innate immune signaling or sustained compensatory adaptive immune activation.

The inflammasome is a multiprotein oligomer responsible for the activation of inflammatory responses. The inflammasome promotes the maturation and secretion of pro-inflammatory cytokines interleukin 1β (IL-1β) and interleukin 18 (IL-18). The secretion of these cytokines results in pyroptosis, a form of programmed pro-inflammatory cell death distinct from apoptosis. In the case of dysregulation of the inflammasome, an assortment of major diseases may arise. The most studied at the moment is NLRP3 inflammasome. NLRP3 oligomerization is activated by a large number of stimuli, which has implicated studies into its activation pathway. Its activity has been shown to be induced and/or increased by low intracellular potassium concentrations, viruses e.g. influenza A, HCV and bacteria e.g. Neisseria gonorrhoeae, bacterial toxins e.g. nigericin and maitotoxin, liposomes, urban particulate matter, and most notably, crystallized endogenous molecules. Cholesterol crystals and monosodium urate (MSU) crystals increase NLRP3-induced IL-1β-production and this process is thought to be abrogated in atherosclerosis and gout, where these crystals form respectively in the cell. It has also been proven that inorganic particles like titanium dioxide, silicon dioxide and asbestos trigger the inflammasome-response. Pore-forming toxins and ATP-activated pannexin-1 may also trigger K+ efflux and grant access of toxins into the cell to directly activate NLRP3. Evidence indicates that NLRP3 inflammasome activation is involved in sleep regulation. Therefore, ıınhibition of toll-like receptor signaling and NLRP3 inflammasome can be considered as promising therapy for inflammatory diseases.

In order to research new scaffolds that could be inhibitors of the Toll-like receptors and NLRP3 inflammasome, we planned to carry out chemoinformatics analysis of the existing inhibitors of these receptors. At present, only a few compounds are known, with significantly proven activity and they are presented in Figure 1. As data sources, we analyzed the most comprehensive reviews of recent years [1-3], the largest chemical databases – *PubChem* and *ChemBL*, as well as commercial catalogs of the most famous suppliers of chemical and biological reagents – *MedChemExpress, InvivoGen and Sigma-Aldrich*. Chemoinformatics investigation was conducted using of the ChemAxon software platform under free academic license. For structure database management, search and analysis data the Instant JChem has been used (Instant JChem 17.3.27.0, 2017, ChemAxon, http://www.chemaxon.com). Data analysis and visualization was carried out by constructing a combination of all possible scatter plots and radar charts.

In the beginning for all 12 inhibitors such descriptors were calculated as – LogP, TPSA, Weiner index, Weiner polarity, H bond acceptors, H bond donors, number of chain bonds, number of rotatable bonds, fraction of Sp3 carbon atoms (fsp3).

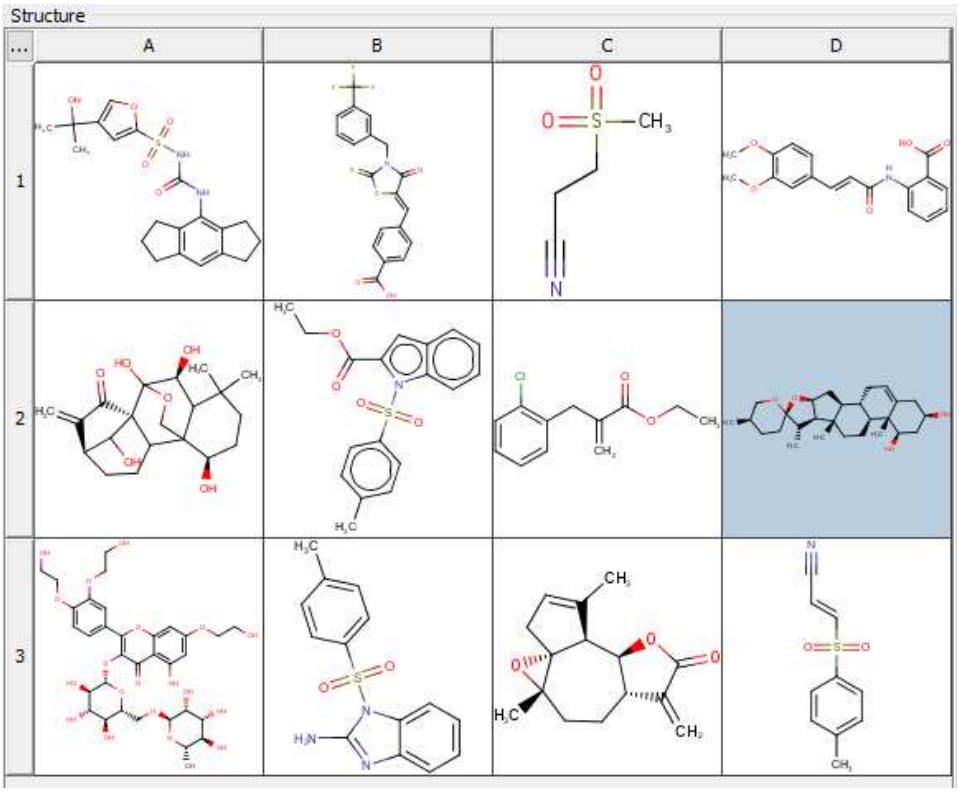


Fig. 1. Structures of compounds that are inhibitors of TLR and NLRP3 inflammasome

As the analysis showed, all compounds have a small molecular weight except for two boundary structures, and this range is 200-600 Da. Moreover, 7 compounds, and this is 58% of the total number of inhibitors, have a molecular weight in the range of 200-400 Da (Fig.2)

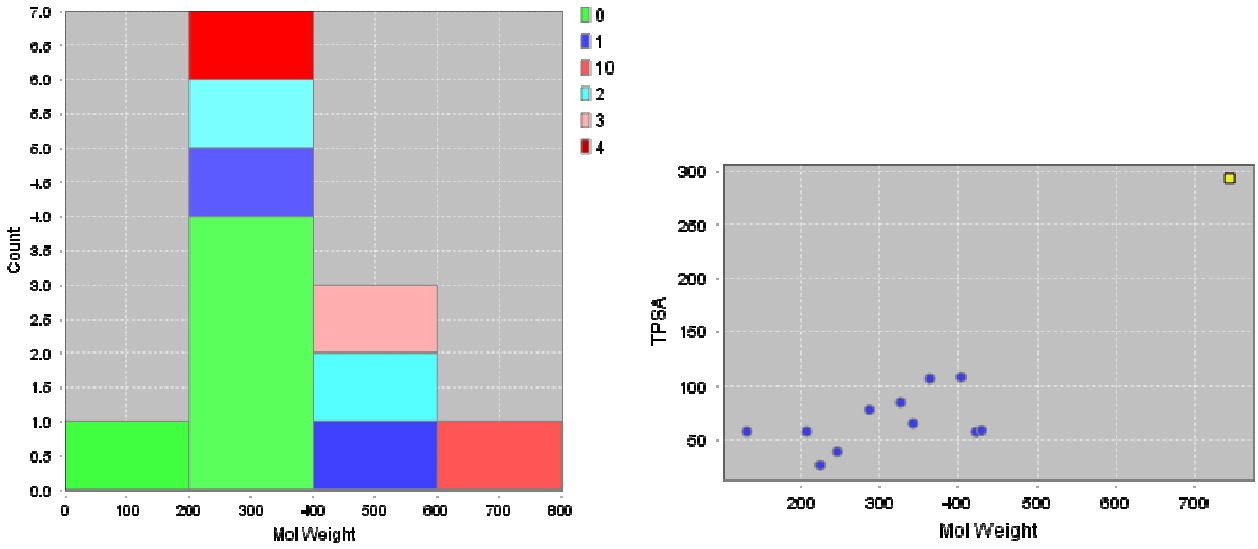
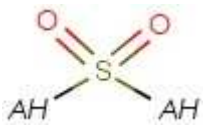


Fig. 2. Graphical representation of the distribution of compounds depending on their molecular weight and TPSA.

Molecular polar surface area (PSA) is a descriptor showing the correlation with passive molecular transport through membranes, which allows prediction of human intestinal absorption, Caco-2 monolayers permeability, and blood-brain barrier penetration. Molecules with a polar surface area of greater than 140 angstroms squared tend to be poor at permeating cell membranes. For molecules to penetrate the blood–brain barrier (and thus act on receptors in the central nervous system), a PSA less than 90 angstroms squared is usually needed. In the array that has been studied, 11 compounds have TPSA less than 140, and 9 compounds less than 100 angstroms, which suggests good cell permeability in all organs of the body Da (Fig.2).

It should be noted another structural specialty of currently known inhibitors of the Toll-like receptors and NLRP3 inflammasome, which is the presence of sulfo group in the molecules.



The query carried out according to the molecular pattern, which is given above, showed that 5 out of 12 compounds bear the sulfo group in their structures.

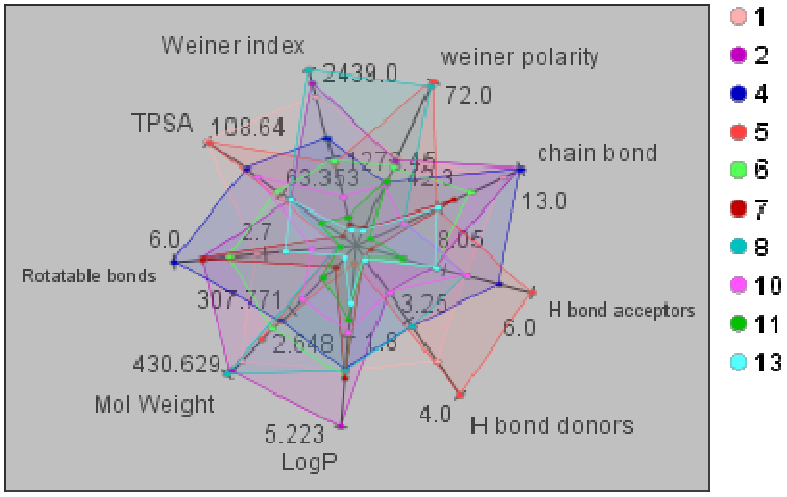


Fig. 3. Aggregated radar chat of the molecular descriptors of the inhibitors TLR and NLRP3 inflammasome.

The result of chemoinformatics investigation was summarized in the radar chart (Fig. 3). The use of this chart allows us to understand the direction in which the molecular design and synthesis of new potential inhibitors of the Toll-like receptors and NLRP3 inflammasome should be carried out.

1. Gao, W.; Xiong, Y.; Li, Q.; Yang, H. Inhibition of Toll-Like Receptor Signaling as a Promising Therapy for Inflammatory Diseases: A Journey from Molecular to Nano Therapeutics. Frontiers in physiology 2017, 8, DOI: 10.3389/fphys.2017.00508.
2. Mangan, M. S. J.; Olhava, E. J.; Roush, W. R.; Seidel, H. M.; Glick, G. D.; Latz, E. Targeting the NLRP3 inflammasome in inflammatory diseases. Nature reviews. Drug discovery 2018, 17, 588–606.
3. Yang, Y.; Wang, H.; Kouadir, M.; Song, H.; Shi, F. Recent advances in the mechanisms of NLRP3 inflammasome activation and its inhibitors. Cell Death & Disease 2019, 10, 128.