hes. This variety of sources can produce inconsistency in the data, defined as diverging activity results for the same compound against the same target. Because such inconsistency can reduce the accuracy of predictive models built from these data, we are addressing the two questions (i) how best to use data from publicly and commercially accessible databases to create accurate and predictive QSAR models; (ii) how the data from different sources (including databases as well as the scientific publications) might be mixed and matched.

Earlier we have investigated the suitability of commercially and publicly available databases to QSAR modeling of antiviral activity (HIV-1 reverse transcriptase (RT) inhibition). We presented several methods for the creation of modeling (i.e., training and test) sets from two, either commercially or freely available, databases: Thomson Reuters Integrity and ChEMBL. We found that the performances of QSAR models obtained using these different modeling set compilation methods differ significantly from each other. The best results were obtained using training sets compiled for compounds tested using only one method and material (i.e., a spec ific type of biological assay performed using specific biological material). Compound sets aggregated by target only typically yielded poorly predictive models. We discussed the possibility of «mix-and-matching» assay data across aggregating databases such as ChEMBL and Integrity and their current severe limitations for this purpose. One of them is the general lack of complete and semantic/computer-parsable descriptions of assay methodology carried by the databases of these two investigated biologically active compounds that would allow one to determine mix-and-matchability of result sets at the assay level.

Currently we develop an approach to estimate the similarity of the experimental protocols using the descriptions extracted from the scientific publications based on the text-mining. We believe, such an approach allows to create homogenous data sets for the creation of the accurate and predictive (Q)SAR models of RT inhibition, which can be further used for the design of the new HIV-1 antiretroviral chemicals and drugs.

Novel nonnucleoside inhibitors of HIV-1 reverse transcriptase inhibitors based on substituted pyrimidines

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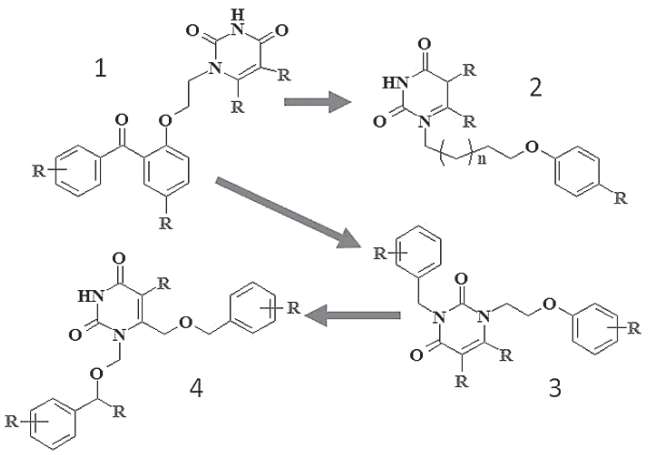
To this moment, the fact that more than 30 anti-HIV drugs were approved by FDA leads to the personification of HAART for each patient. However drug resistance is still a huge problem due to HIV high variability. Some combinations of drug-resistant mutations can make a whole class of anti-HIV drugs completely ineffective and this stimulates a search for new antiretroviral compounds. NNRTIs are a prime example of a struggle between scientific society versus drug resistance. Discovery of the second generation of NNRTIs (ETV, RPV) made possible to efficiently inhibit viral replication in case of patients with a full resistance to NVP, DLV and EFV that are usually used in the first line of HAART drug combinations.

This study was focused on a development of highly effective NNRTIs based on substituted pyrimidines. Rational drug design allows to find some new classes of compounds with high antiretroviral activity and genetic barrier to drug resistance. New highly active compounds with a benzophenone moiety (1) were obtained using the molecular hybridization paradigm. Rational drug design based on a structure-activity relationship improved IC_{50} against a wild type reverse transcriptase (WT RT) of HIV to submicromolar values (the best was 86 nM) and a study of the inhibitory activity of compounds highly active against WT RT on a panel of drug-resistant mutants of RT led to identification of lead compounds with high genetic barrier against drug resistance. Along with the development of these compounds during this study some more classes of pyrimidine-based NNRTIs were found. Compounds with IC_{50}<1μM were identified within classes of N1 (**2**), N1-N3 (**3**) and N1-C6 (**4**) substituted pyrimidines.



The search of informative biomarkers for early immunological diagnosis of tuberculosis in patients with HIV Infection.

HIV is a major cause of dilated cardiomyopathy

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Human immunodeficiency virus (HIV) disease is recognized as an important cause of dilated cardiomyopathy also

known as eccentric ventricular hypertrophy, which leads to impaired contraction of the ventricles due to volume overload and the result to heart failure. An inflammation of the myocardium caused by infection and/or autoimmune reactions plays a crucial role in dilated cardiomyopathy and heart failure. The annual incidence of HIV associated dilated cardiomyopathy was 15,9/1000 before the introduction of highly active antiretroviral therapy (HAART). However, in 2014, a study found that 17,6% of HIV patients have dilated cardiomyopathy (176/1000) meaning the incidence has greatly increased. HIV-1 virions appear to infect myocardial cells in a patchy distribution with no direct association between the presence of the virus and myocyte dysfunction. Immune cells infiltrating myocardium in dilated cardiomyopathy seem to play a significant pathogenetic role by activating multifunctional cytokines such as tumor necrosis factor-α and the inducible form of nitric oxide synthase that contribute to progressive and late myocardial tissue damage. The mode of entry of HIV into myocytes remains unclear since they are CD4 receptor negative.

Tumour necrosis factor-α (TNF-α) induces cardiomyocyte dysfunction and pathological changes. TNF-α is produced by infected macrophages and by lymphocytes infiltrating myocardium in dilated cardiomyopathy. The intensity of the stains for TNF-α and inducible nitric oxide synthase (iNOS) of the myocardium was greater in patients with HIV associated cardiomyopathy (as opposed to idiopathic cardiomyopathy), myocardial viral infection and was inversely correlated with CD4 count with antiretroviral therapy having no effect.

TNF-α has been recognized as important physiopathogenetic factor in the initiation and continuation of inflammatory cardiomyopathies. Experimental and human studies have demonstrated that TNF-α plays a crucial role in viral-induced myocarditis. Myocardial expression of TNF-α was correlated with different clinical and pathologic findings. Among TNF-α-positive cases, the greater TNF-α mRNAs, the more impaired was cardiac function. Some findings suggest that the expression of TNF-α may play an important role in the pathogenesis of viral myocarditis and cardiomyopathy of any etiology and may influence the severity of cardiac dysfunction. Whether myocyte damage in the early phase of the disease is primarily linked to the viral presence or to immunomediated damage is still under discussion; however, it is now accepted that the progression of the disease is mainly sustained by immunomechanisms. Previous clinical works have demonstrated that there is an association between depressed myocardial function and elevated TNF-α mRNA and protein levels either in plasma or in the myocardium of patients with myocarditis and dilated cardiomyopathy.TNF-α elicits its biological effects by binding to two distinct cell surface receptors with approximate molecular masses of 55 kDa (TNFRI) and 75 kDa (TNFRII), both expressed in human cardiac myocytes. Cytokine expression was then correlated with the main clinic hemodynamic and pathologic parameters. The direct effect of TNF in human cardiomyocytes has not been investigated yet. In our study we investigated pathological changes induced by inflammatory cytokine TNF-α in human cardiomyocytes.

Human fetal cardiomyocytes were stimulated with inflammatory agent TNF-α for up to 24 h and time-dependent changes in the expression of established markers of pathological hypertrophy were assessed by quantitative PCR. mRNA levels of ANF, marker of hypertrophy were increased following treatment with the inflammatory cytokine TNF-α. Induction of hypertrophic marker genes was gradual (peaking at 24 h). Elevated ANF expression levels are associated with pathological hypertrophic cardiomyocyte changes.

Our results demonstrate that TNF-α directly induces cardiomyocyte pathological changes

TNF-α produced by cardiomyocytes themselves as a response to TNF-α produced by lymphocytes might have an autocrine effect, thus contributing to the progression of cardiomyocyte damage. The role of intramyocardial TNF-α in the disease provides not only new insights to the pathogenesis of dilated cardiomyopathy but also suggests new targets for therapeutic intervention.

The search of informative biomarkers for early immunological diagnosis of tuberculosis in patients with HIV Infection

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Introduction. According to estimates of the World Health Organization, 13% of the 9 million people become ill with tuberculosis (TB) in 2013 were to have been infected with HIV. Since the human immunodeficiency virus affects the immune system, weakening it, to people with HIV causative agent of tuberculosis (*Mycobacterium tuberculosis*) is transmitted seven times more, often occurs more malignant, it has a tendency to generalize and much more goes into the active form. Therefore, early diagnosis of tuberculosis infection in these patients is critical in controlling the spread of the disease.

Own data. Previously we, like many other authors, have shown that QuantiFERON®-TB Gold In-Tube, is effective in the diagnosis of tuberculosis in patients without HIV. We also showed that the chemokine IP-10 (IFNγ — indu-