# TARIMAD - TO01000078 - Articles – published in 2021

1. **Structure-activity relationships of dually-acting acetylcholinesterase inhibitors derived from tacrine on N-methyl-D-Aspartate receptors**

https://doi.org/10.1016/j.ejmech.2021.113434

ABSTRACT: Tacrine is a classic drug whose efficacy against neurodegenerative diseases is still shrouded in mystery. It seems that besides its inhibitory effect on cholinesterases, the clinical benefit is co-determined by NMDAR-antagonizing activity. Our previous data showed that the direct inhibitory effect of tacrine, as well as its 7-methoxy derivative (7-MEOTA), is ensured via a "foot-in-the-door" open-channel blockage, and that interestingly both tacrine and 7-MEOTA are slightly more potent at the GluN1/GluN2A receptors when compared with the GluN1/GluN2B receptors. Here, we report that in a series of 30 novel tacrine derivatives, designed for assessment of structure-activity relationship, blocking efficacy differs among different compounds and receptors using electrophysiology with HEK293 cells expressing the defined types of NMDARs. Selected compounds (4 and 5) potently inhibited both GluN1/GluN2A and GluN1/GluN2B receptors; other compounds (7 and 23) more effectively inhibited the GluN1/GluN2B receptors; or the GluN1/GluN2A receptors (21 and 28). QSAR study revealed statistically significant model for the data obtained for inhibition of GluN1/Glu2B at _60 mV expressed as IC50 values, and for relative inhibition of GluN1/Glu2A at ţ40 mV caused by a concentration of 100 mM. The models can be utilized for a ligand-based virtual screening to detect potential candidates for inhibition of GluN1/Glu2A and/or GluN1/Glu2B subtypes. Using in vivo experiments in rats we observed that unlike MK-801, the tested novel compounds did not induce hyperlocomotion in open field, and also did not impair prepulse inhibition of startle response, suggesting minimal induction of psychotomimetic side effects. We conclude that tacrine derivatives are promising compounds since they are centrally available subtype-specific inhibitors of the NMDARs without detrimental behavioral side-effects.

2. **Dimethyl fumarate does not mitigate cognitive decline and β-amyloidosis in female APPPS1 mice**

https://doi.org/10.1016/j.brainres.2021.147579

A B S T R A C T Introduction: Alzheimer's disease (AD) is the leading cause of dementia and a major global health issue. Currently, only limited treatment options are available to patients. One possibility to expand the treatment repertoire is repurposing of existing drugs such as dimethyl fumarate (DMF). DMF is approved for treatment of multiple sclerosis and previous animal studies have suggested that DMF may also have a beneficial effect for the treatment of AD. Methods: We used an APPPS1 transgenic model of senile β-amyloidosis and treated female mice orally with DMF in two treatment paradigms (pre and post onset). We quantified learning and memory parameters, β-amyloidosis, and neuroinflammation to determine the potential of DMF as AD therapeutics. Results: Treatment with DMF had no influence on water maze performance, β-amyloid accumulation, plaque formation, microglia activation, and recruitment of immune cells to the brain. Compared to vehicle-treated animals, oral DMF treatment could not halt or retard disease progression in the mice. Discussion: Our results do not favour the use of DMF as treatment for AD. While our results stand in contrast to previous findings in other models, they emphasize the importance of animal model selection and suggest further studies to elucidate the mechanisms leading to conflicting results.

3. **Scaffold fragmentation and substructure hopping reveal potential, robustness, and limits of computer-aided pattern analysis (C@PA)**

https://doi.org/10.1016/j.csbj.2021.05.018

ABSTRACT Computer-aided pattern analysis (C@PA) was recently presented as a powerful tool to predict multitarget ABC transporter inhibitors. The backbone of this computational methodology was the statistical analysis of frequently occurring molecular features amongst a fixed set of reported small-molecules that had been evaluated toward ABCB1, ABCC1, and ABCG2. As a result, negative and positive patterns were elucidated, and secondary positive substructures could be suggested that complemented the multitarget fingerprints. Elevating C@PA to a non-statistical and exploratory level, the concluded secondary positive patterns were extended with potential positive substructures to improve C@PA's prediction capabilities and to explore its robustness. A small-set compound library of known ABCC1 inhibitors with a known hit rate for triple ABCB1, ABCC1, and ABCG2 inhibition was taken to virtually screen for the extended positive patterns. In total, 846 potential broad-spectrum ABCB1, ABCC1, and ABCG2 inhibitors resulted, from which 10 have been purchased and biologically evaluated. Our approach revealed 4 novel multitarget ABCB1, ABCC1, and ABCG2 inhibitors with a biological hit rate of 40%, but with a slightly lower inhibitory power than derived from the original C@PA. This is the very first report about discovering novel broadspectrum inhibitors against the most prominent ABC transporters by improving C@PA.

## 4. C@PA: Computer-Aided Pattern Analysis to Predict Multitarget ABC Transporter Inhibitors

https://dx.doi.org/10.1021/acs.jmedchem.0c02199

ABSTRACT: Based on literature reports of the last two decades, a computer-aided pattern analysis (C@PA) was implemented for the discovery of novel multitarget ABCB1 (P-gp), ABCC1 (MRP1), and ABCG2 (BCRP) inhibitors. C@PA included basic scaffold identification, substructure search and statistical distribution, as well as novel scaffold extraction to screen a large virtual compound library. Over 45,000 putative and novel broad-spectrum ABC transporter inhibitors were identified, from which 23 were purchased for biological evaluation. Our investigations revealed five novel lead molecules as triple ABCB1, ABCC1, and ABCG2 inhibitors. C@PA is the very first successful computational approach for the discovery of promiscuous ABC transporter inhibitors.

## 5. Machine Learning-Supported Analyses Improve Quantitative Histological Assessments of Amyloid-Beta Deposits and Activated Microglia

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ABSTRACT: Background: Detailed pathology analysis and morphological quantification is tedious and prone to errors. Automatic image analysis can help to increase objectivity and reduce time. Here, we present the evaluation of the DeePathology STUDIOTM for automatic analysis of histological whole-slide images using machine learning/artificial intelligence.
Objective: To evaluate and validate the use of DeePathology STUDIO for the analysis of histological slides at high resolution.
Methods: We compared the DeePathology STUDIO and our current standard method using macros in AxioVision for the analysis of amyloid-_ (A_) plaques and microglia in APP-transgenic mice at different ages. We analyzed density variables and total time invested with each approach. In addition, we correlated A_ concentration in brain tissue measured by ELISA with the results of A_ staining analysis.
Results: DeePathology STUDIO showed a significant decrease of the time for establishing newanalyses and the total analysis time by up to 90%. On the other hand, both approaches showed similar quantitative results in plaque and activated microglia density in the different experimental groups. DeePathology STUDIO showed higher sensitivity and accuracy for small-sized plaques. In addition, DeePathology STUDIO allowed the classification of plaques in diffuse- and dense-packed, which was not possible with our traditional analysis.
Conclusion: DeePathology STUDIO substantially reduced the effort needed for a new analysis showing comparable quantitative results to the traditional approach. In addition, it allowed including different objects (categories) or cell types in a single analysis, which is not possible with conventional methods.

6. Role of ABCA7 in Human Health and in Alzheimer's Disease

https://doi.org/10.3390/ijms22094603

ABSTRACT: Several studies, including genome wide association studies (GWAS), have strongly suggested a central role for the ATP-binding cassette transporter subfamily A member 7 (ABCA7) in Alzheimer's disease (AD). This ABC transporter is now considered as an important genetic determinant for late onset Alzheimer disease (LOAD) by regulating several molecular processes such as cholesterol metabolism and amyloid processing and clearance. In this review we shed light on these new functions and their cross-talk, explaining its implication in brain functioning, and therefore in AD onset and development.

7. Development of deep learning models for microglia analyses in brain tissue using DeePathology™ STUDIO

https://doi.org/10.1016/j.jneumeth.2021.109371

ABSTRACT: Background: Interest in artificial intelligence-driven analysis of medical images has seen a steep increase in recent years. Thus, our paper aims to promote and facilitate the use of this state-of-the-art technology to fellow researchers and clinicians.
New method: We present custom deep learning models generated in DeePathology™ STUDIO without the need for background knowledge in deep learning and computer science underlined by practical suggestions.
Results: We describe the general workflow in this commercially available software and present three real-world examples how to detect microglia on IBA1-stained mouse brain sections including their differences, validation results and analysis of a sample slide.
Comparison with existing methods: Deep-learning assisted analysis of histological images is faster than classical analysis methods, and offers a wide variety of detection possibilities that are not available using methods based on staining intensity.
Conclusions: Reduced researcher bias, increased speed and extended possibilities make deep-learning assisted analysis of histological images superior to traditional analysis methods for histological images.