NINTH INDO-US WORKSHOP ON MATHEMATICAL CHEMISTRY

with Application to Drug Discovery, Computational Toxicology, Cheminformatics and Bioinformatics

JAN 06-10, 2025

BOOK OF ABSTRACTS

Workshop Series Founder Chairman: Dr Subhash C. Basak, USA
Ninth Workshop Organizer: Dr Ramanathan Natarajan, India

Host Institute

SARANATHAN COLLEGE OF ENGINEERING, TIRUCHIRAPPALLI, TAMIL NADU, INDIA

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Neuroprotective AMPA receptor modulators: from computer-aided drug design to synthesis and preclinical studies

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The glutamate receptors are of crucial importance in CNS functioning. Among the substances acting on the glutamatergic system, the most promising are allosteric modulators of AMPA and KA receptors.[1] The positive allosteric modulators (PAMs) of AMPA receptors as compared to direct agonists are more safe and able to perform the fine tuning of the glutamatergic system since they do not cause any effects in the absence of the natural ligand in the synapse. PAMs of AMPA receptor reveal such neurophysiological effects as significant increase of nerve growth factors expression as well as induction of long-term potentiation of synaptic excitation, considered as a substrate for learning and memory. This makes them privileged compounds for the development of nootropic and neuroprotective agents. The negative modulators of AMPA receptors can be employed as antiepileptic drugs.

The *de novo* design of AMPA receptor modulators using previously refined receptor models was supplemented in our work with molecular dynamics simulation of the modulator-agonist-receptor complexes for various possible receptor binding sites. The Molecular Field Topology Analysis (MFTA) QSAR technique was quite beneficial in the modeling of ligand potency within the series of closely related compounds. The 3D QSAR and pharmacophore models of the AMPA receptor PAMs as well as predicted ADMET parameters served as useful additional filters. That allowed us to find a series of new positive and negative highly potent allosteric modulators based on several new scaffolds. They include novel tricyclic derivatives of bispidine, substituted bis(pyrimidines) and bis-amides with various linkers/spacers. Convenient synthetic approaches were elaborated and scaled-up for the designed compounds. Electrophysiological patch clamp *in vitro* experiments have demonstrated the pronounced influence of the studied compounds in sub-nanomolar concentrations on the kainate-induced currents recorded for Purkinje neurons from rat cerebellum. The *in vivo* studies based on behavioral models have shown cognition-enhancing properties for the designed positive modulators. The combinations of these properties with low toxicity allowed several compounds to successfully pass preclinical studies.

This study was supported by the Russian Science Foundation, grant No. 22-15-00041.

Keywords: AMPA receptor; positive allosteric modulators; molecular dynamics; QSAR; neuroprotective agents.

References

1. E.A. Golubeva, M.I. Lavrov, E.V. Radchenko, V.A. Palyulin, *Biomolecules* **2023**, *13*, 56.

6 Technical Sessions

There were 15 technical sessions conducted in hybrid mode (online and offline combined) featuring 20 oral presentations and 12 poster presentations and 31 invited lectures in various domains by subject experts from 15 countries. The presentation topics and the extensive Global coverage made the workshop a historic event.

6.1 DAY-1: January 6, 2025

The technical sessions started after the inauguration, social mixing and group photograph session. The first presentation of the Ninth Workshop was presented by Dr Valdimir Palyulin from Moscow, Russia. The next lecture was by Dr S. C. Basak the founder chairman of the workshop series. The speakers and the titles of their presentations are given below:

DAY-1: JAN 6, 2025	
TECHNICAL SESSION-1 GENERAL	
11.00-11.45 **Invited Lecture-1**	"*Neuroprotective AMPA receptor modulators: from computer-aided drug design to synthesis and preclinical studies*" by **Dr Valdimir A Palyulin**, **Russia.**
11.45-12.30 **Invited Lecture-2**	"*Adventures in the evolving landscape of mathematical descriptors of molecules and biomolecules: A tortuous journey of fifty years*" by **Dr Subhash C. Basak**, **USA.**
TECHNICAL SESSION-2: VECTOR CONTROL	
13.30-14.10 **Invited Lecture-3**	"*Pharmacophore recognition of bioactive molecules may aid in more efficient AI -driven database searches for discovery of potent compounds*" by **Dr Apurba K. Bhattacharjee**, **USA.**
14.15-14.45 **Invited Lecture-4**	"Bioinformatics, computer modeling and mosquitos: Insect sodium channels functioning from a theoretical perspective" by **Dr Wieslaw Nowak, Poland.**
14.45-15.00 **Oral Presentation -1**	"*Essential oils from a tropical medicinal plant, Ruta chalepensis as a potential raw material in the manufacture of vector control formulations*" by **Dharani Jayagopal.**
15.00-15.15 **Oral Presentation -2**	"*Bioactive compounds from Ocimum tenuiflorum as vector agent against Aedes albopictus*" by **Joel Jaison**
TECHNICAL SESSION-3 GENERAL	
15.45-16.15 **Invited Lecture-5**	"*Simulating optical properties of organic and biomaterials*" by **Dr Nađa Došlić**, **Croatia.**
16.15-16.45 **Invited Lecture-6**	"*Topological indices: Physicochemical significance in QSARs*" by **Dr A.K. Saxena, India**
16.45-17.30 **Invited Lecture-7**	"*Higher-dimensional structures for a better understanding of the chemical space and its evolution*" by **Dr Guillermo Restrepo, Germany.**