ChemMedChem

Chemistry Europe
European Chemical Societies Publishing
ChemMedChem

REVIEW

Kainate Receptor Allosteric Modulators: State of the Art and Future Directions

Thomas Colson | Bernard Pirotte | Pierre Francotte

Laboratory of Medicinal Chemistry, CIRM, Department of Pharmacy, University of Liège, Liège, Belgium

Correspondence: Thomas Colson (t.colson@uliege.be) | Pierre Francotte (Pierre.Francotte@uliege.be)

Received: 18 February 2026 | **Revised:** 24 April 2026 | **Accepted:** 28 April 2026

Keywords: allosteric modulation | kainate receptors | positive and negative modulators | structure-guided drug design | subunit selectivity

ABSTRACT

Kainate receptors (KARs) are under-explored ionotropic glutamate receptors with growing interest as therapeutic targets in disorders involving dysregulated glutamatergic signaling. Allosteric modulation of KARs represents an attractive drug discovery strategy, enabling fine control of receptor activity without competing with glutamate at the orthosteric site. This review summarizes current knowledge on positive (KARPAMs) and negative (KARNAMs) allosteric modulators of KARs, integrating recent structural and pharmacological insights. We describe the limited set of known modulators, including BPAM344, BPAM521, endogenous tuning ions, lectins, galectins, perampanel, and selected AMPA-derived compounds, with emphasis on their binding sites, mechanisms of action, and selectivity profiles. Finally, we highlight the critical lack of truly subunit-selective KAR modulators and discuss how recent structural advances can enable rational design of next-generation chemical probes and drug candidates targeting KARs.

1 | Introduction

Glutamate is the most abundant neurotransmitter in the central nervous system (CNS). It exerts its effects through both ionotropic (iGluRs) and metabotropic (mGluRs) receptors. Ionotropic glutamate receptors are tetrameric structures that form ion channels permeable to sodium and potassium and, to a lesser extent, to calcium. Based on their selective agonists, iGluRs were classified into three main subtypes: NMDA receptors, which respond to *N-methyl-D-aspartic acid*; AMPA receptors (AMPARs), activated by *2-amino-3-(5-methyl-3-hydroxy-1,2-oxazol-4-yl)propanoic acid*; and kainate receptors (KARs), sensitive to kainic acid (*2-carboxy-3-carboxymethyl-4-isopropenylpyrrolidine*) (Figure 1). A fourth, less well-characterized group, the delta receptors (GluD), also belongs to the iGluR family [1–3].

Ionotropic glutamate receptors (iGluRs) are tetrameric assemblies of structural subunits, which are modular proteins composed of several distinct domains: an extracellular amino-terminal domain (ATD), an extracellular ligand-binding domain (LBD), a transmembrane domain (TMD), and an intracellular carboxyl-terminal domain (CTD) [4] (Figure 2). These structural domains are assembled to form various subunits that define each receptor subtype. NMDA receptors are typically composed of GluN1 and GluN2 (A-D) subunits, with GluN3 (A-B) also contributing to certain receptor assemblies. AMPA receptors are built from combinations of GluA1 to GluA4 subunits, while kainate receptors consist of the assembly of GluK1 to GluK5 subunits [2, 4–7].

The physiology of KARs remains less comprehensively understood than that of AMPARs. Nevertheless, their structural

Abbreviations: ADHD, Attention deficit hyperactivity disorder; AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR(s), AMPA receptor(s); ATD, Amino-terminal domain; CNS, Central nervous system; CTD, Carboxyl-terminal domain; Galectins, β-galactoside-binding lectins; GluA1-4, AMPA receptor subunits 1-4; GluD, Delta glutamate receptors; GluK1-5, Kainate receptor subunits 1-5; GluN1-3, NMDA receptor subunits 1-3; GluR(s), Metabotropic glutamate receptor(s); GluR(s), Ionotropic glutamate receptor(s); HTS, High-throughput screeningi; KAR(s), Kainate receptor(s); KARPAMs, Kainic acid receptors positive allosteric modulators; LBD, Ligand-binding domainm; PMP, Perampanel; NAM(s), Negative allosteric modulator(s); NMDA, N-methyl-D-aspartate; NMDAR(s), NMDA receptor(s); TMD, Transmembrane domain.

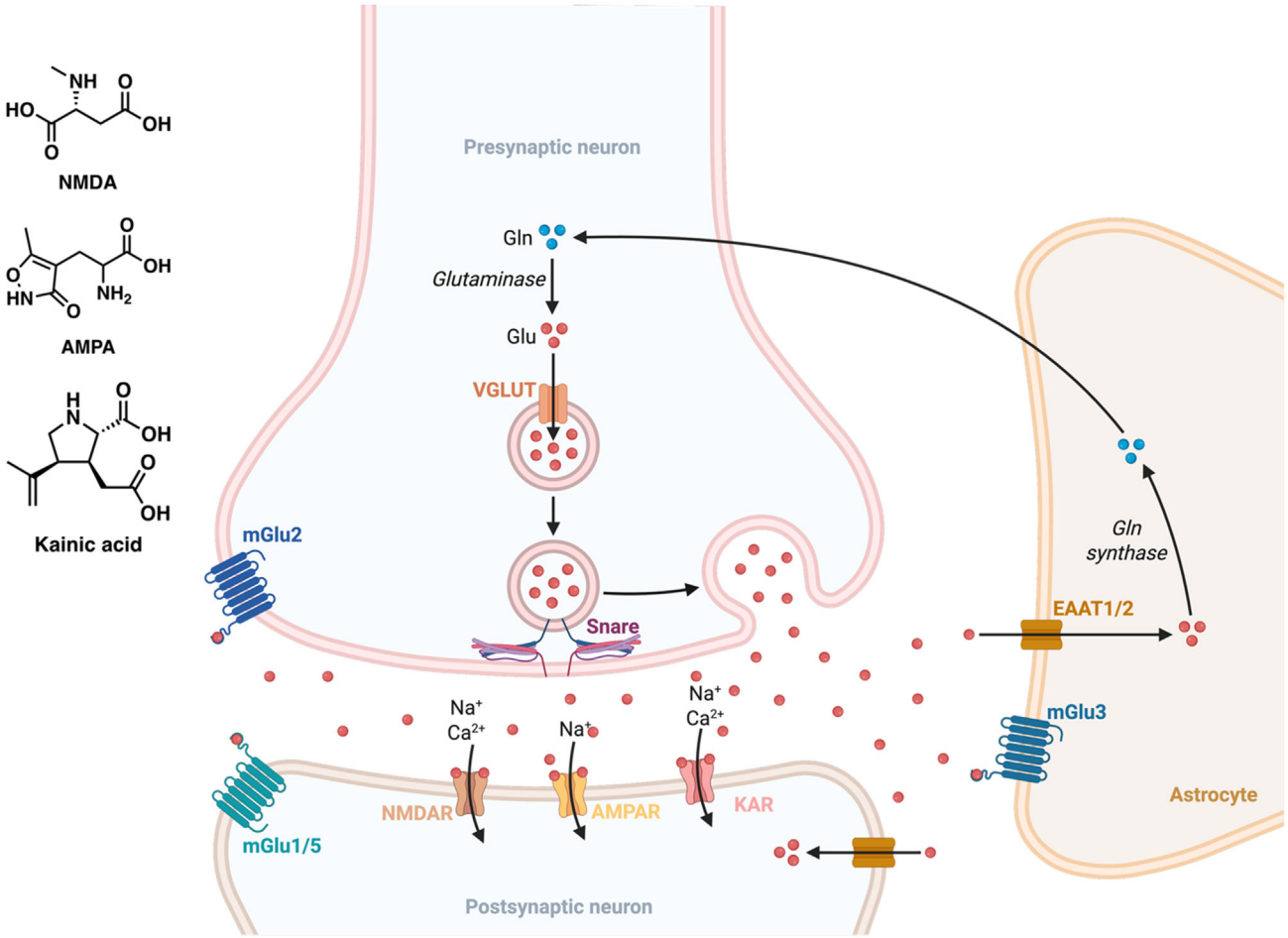


FIGURE 1 | Schematic representation of the glutamatergic synapse, illustrating glutamate cycling and the main ionotropic and metabotropic glutamate receptors, including kainate receptors (KARs).

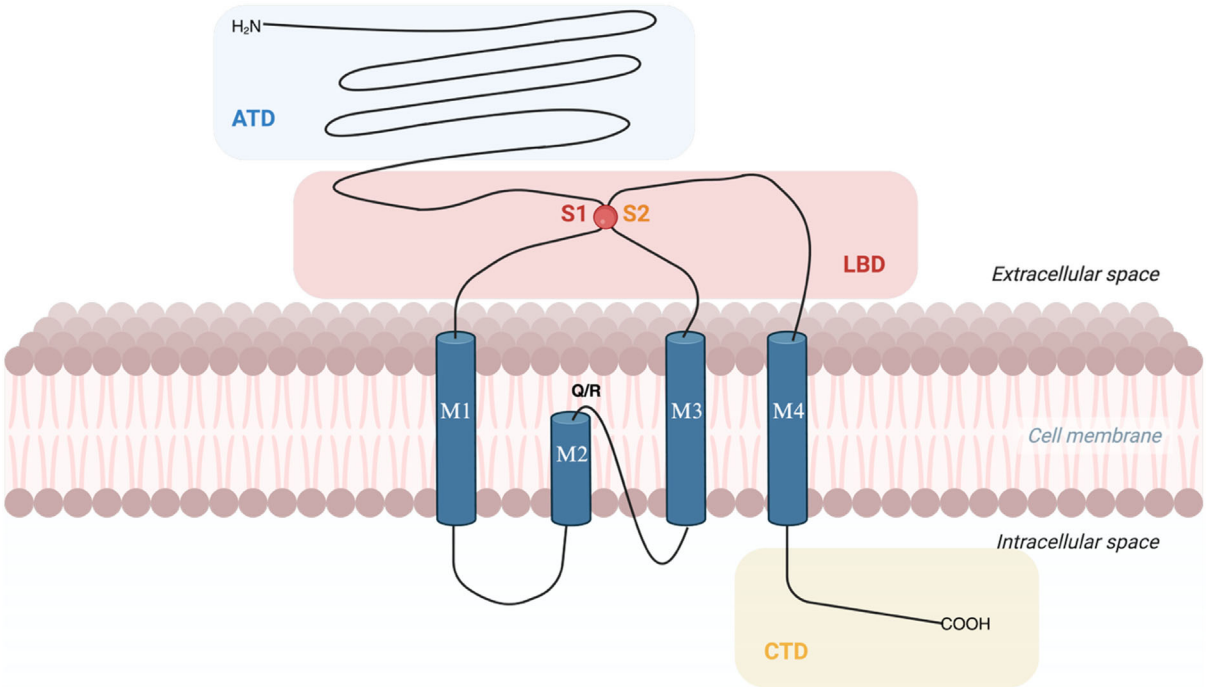


FIGURE 2 | Schematic representation of the structural organization of an ionotropic glutamate receptor subunit, highlighting the extracellular amino-terminal domain (ATD), the ligand-binding domain (LBD) formed by S1 and S2 segments, the four transmembrane regions (M1–M4) including the M2 pore loop (Q/R site), and the intracellular carboxy-terminal domain (CTD).

organization follows the general blueprint of ionotropic glutamate receptors: KARs assemble as tetrameric complexes built from distinct subunits. These receptors can incorporate any of the five identified KAR subunits, GluK1 to GluK5 [8, 9], which combine to form homomeric or heteromeric assemblies contributing to the functional and pharmacological diversity observed within this receptor family [10, 11]. The GluK1, GluK2, and GluK3 subunits can assemble into both homotetrameric and heterotetrameric receptors, providing considerable structural versatility [11, 12] (Figure 3). In contrast, the GluK4 and GluK5 subunits are obligate heteromeric partners and must associate with GluK1−3 subunits to form functional tetramers, thereby creating additional diversity to the receptor repertoire without forming channels on their own [3, 13, 14].

AMPARs are thought to mediate the rapid depolarization necessary to relieve the magnesium block of nearby NMDARs, thereby permitting efficient synaptic information transfer [15]. KARs display similar fast-acting properties, enabling ion flux almost immediately upon glutamate binding. However, unlike certain AMPAR subtypes, KARs are generally less permeable to calcium ions, which distinguishes their contribution to excitatory signaling and downstream cellular responses [16]. While AMPARs are predominantly located on the postsynaptic membrane, accumulating evidence indicates that KARs occupy a broader range of synaptic sites. They can be found not only postsynaptically but also presynaptically, where they modulate neurotransmitter release and contribute to bidirectional regulation of synaptic function [17–20]. Postsynaptic KARs function in a manner similar to AMPARs, contributing to the depolarization required to overcome the magnesium block of NMDARs, thereby facilitating downstream NMDA receptor activation [16].

On a broader functional scale, KARs participate in a significant portion of fast excitatory neurotransmission throughout the brain. In addition to mediating rapid synaptic signaling, they also contribute to various forms of synaptic plasticity processes that are essential for learning, memory formation, and the dynamic modulation of neural circuits [5, 17]. In addition, iGluRs play crucial roles in neural development, circuit maturation, and the maintenance of neuronal health. Dysregulation of their activity is strongly linked to numerous neurological and neuropsychiatric disorders, including epilepsy, ischemic stroke, ADHD, and a range of neurodegenerative diseases such as Alzheimer's and Parkinson's disease [21], Huntington's disease, and amyotrophic lateral sclerosis [5, 16, 22]. Dysregulation of extracellular glutamate levels has also been implicated in several psychiatric conditions, including schizophrenia, obsessive–compulsive disorder, major depressive disorder, and bipolar disorder, where altered glutamatergic signaling may contribute to both symptoms and disease progression [23]. Because of their broad involvement in both physiological and pathological processes, iGluRs, and of course KARs, have become important targets in drug discovery, attracting substantial interest for the development of therapeutics aimed at modulating glutamatergic signaling [5, 22]. Several studies on KARs have also demonstrated that receptor subunit composition can influence disease susceptibility. In particular, heterotetrameric assemblies combining GluK1−3 with GluK4 or GluK5 have been associated with various neurological and neuropsychiatric disorders, including epilepsy, autism, schizophrenia, and depression [24–27].

2 | Exploring Kainate Receptor Modulation

2.1 | What's Targeted?

As described earlier, KARs are ionotropic glutamate receptors assembled from GluK1−5 subunits, with GluK1−3 capable of forming functional homomeric receptors, while GluK4 and GluK5 serve as modulatory subunits within heteromeric

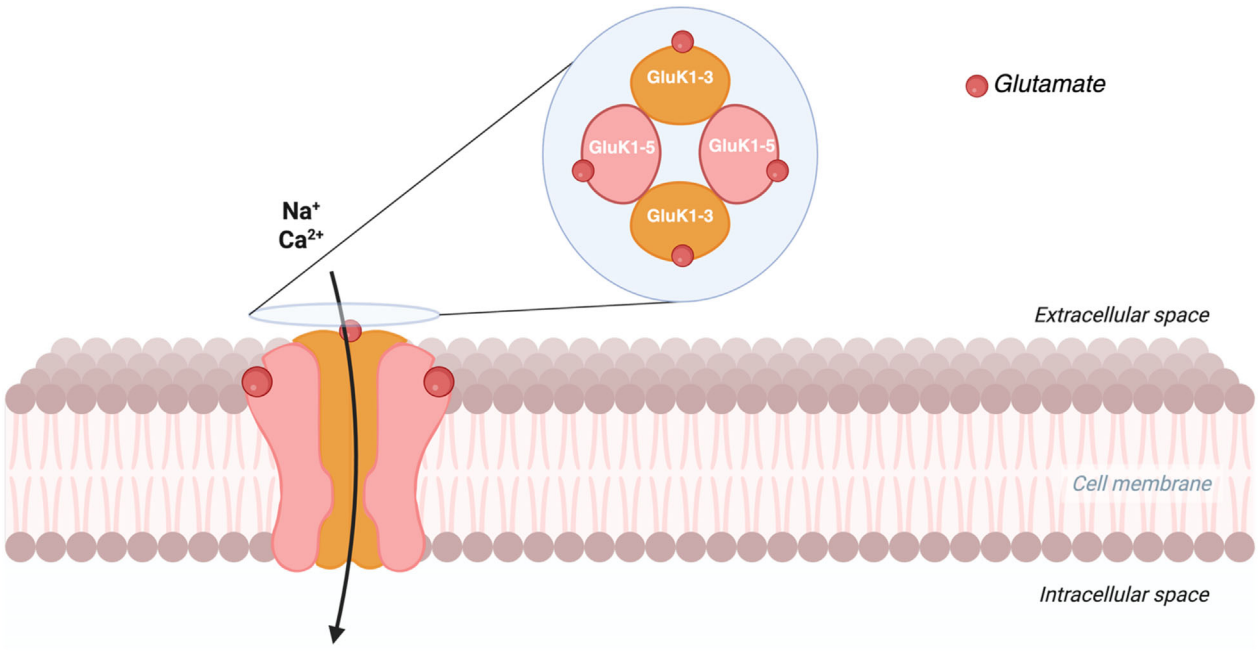


FIGURE 3 | Schematic representation of a heterotetrameric or homomeric kainate receptor (KAR) arrangement.

assemblies [3, 13, 14]. Allosteric modulators act by binding outside the orthosteric glutamate site, most commonly at the ligand-binding domain (LBD) dimer interface, within the channel "collar" surrounding the ion pore, or at extracellular regions involved in ion-dependent or auxiliary-subunit interactions [22, 23].

2.2 | Why Is It Interesting to Modulate KARS?

Most currently known KAR allosteric modulators were identified either as AMPAR tool compounds later found to modulate KARs, or as biochemical probes that primarily alter desensitization, rather than through systematic, KAR-selective medicinal chemistry programs. Consequently, the available pharmacological toolbox remains limited and is largely biased toward GluK2 [28, 29].

2.3 | Why Is It Interesting to Modulate KARS?

Known allosteric modulators of kainate receptors (KARs) currently include a limited set of small molecules such as previously described AMPARPAMs belonging to benzo- and thienothiadiazines BPAM307 **(1)**, BPAM344 **(2)**, BPAM521 **(3)**, BPAM538 **(4)**, perampanel **(5)**, 2,3-benzodiazepines (**6**) and (**7**), quinazolinone (**8**) (Scheme 1), and several AMPA-derived NAMs as well as various lectins, galectins, and endogenous ions like Zn^{2+} and Na^{+}, which fine-tune channel gating in a subunit- and context-dependent manner. All of these are reassembled in Table 1 just below:

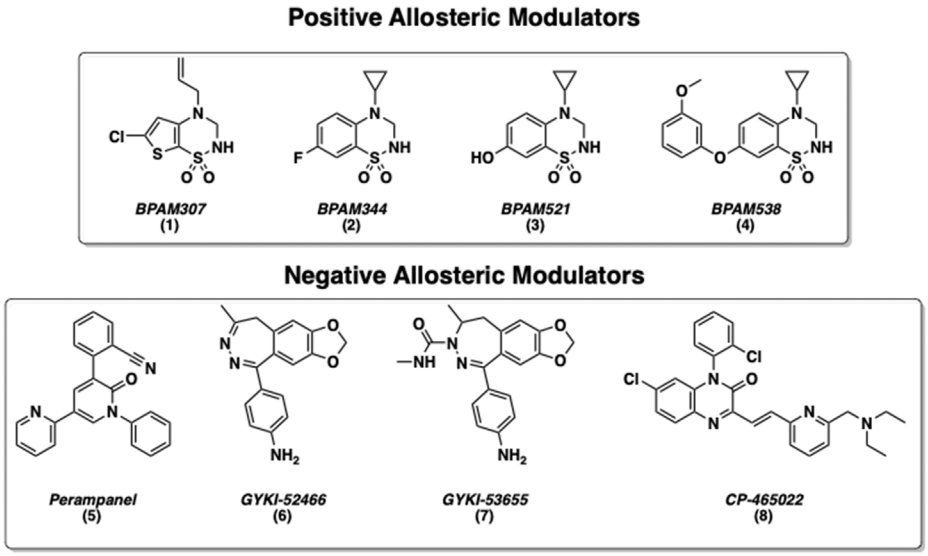
2.4 | Interest of KARPAMS

Positive allosteric modulators of kainate receptors (KARPAMs) potentiate glutamatergic transmission by stabilizing glutamate-bound KARs in active, non-desensitized conformations, thereby prolonging and enhancing excitatory currents without activating the receptors in the absence of the endogenous ligand [28, 49]. Unlike direct agonists, PAMs offer a more physiologically relevant and selective modulation of receptor activity, as their effect is limited upon the presence of the endogenous ligand, L-glutamate, in the synaptic cleft. This ligand-dependence reduces the risk of overstimulation and confers a potentially improved safety profile compared with direct agonists such as this observed previously for the AMPARPAMs [28, 50, 51]. In contrast, orthosteric agonists at KARs can cause excessive depolarization and excitotoxic neuronal damage when overdosed, since they drive receptor activation independently of endogenous glutamate dynamics [52].

Compounds such as the KARPAM BPAM344, which markedly slows GluK2 desensitization and increases steady-state currents, illustrate how KARPAMs can amplify KAR function in a controlled, activity-dependent manner [6]. Conceptually, KARPAMs therefore constitute attractive pharmacological tools for targeting KAR-dependent circuits in brain disorders, with the potential to restore or fine-tune excitatory neurotransmission while minimizing excitotoxic side effects associated with nonselective glutamate receptor activation.

To date, BPAM344 remains the most efficacious small-molecule positive allosteric modulator of kainate receptors described. This drug is widely used as a pharmacological tool compound in leading iGluR laboratories where BPAM344 is routinely employed to stabilize GluK2 for high-resolution structural and functional studies [28, 49, 53].

Some attempts were made in medicinal chemistry to develop new potent KARPAMs. Recently, it was showed that replacing the 4-cyclopropyl moiety of BPAM344 with an allyl chain and the fluorobenzene ring with a chlorothiophene ring providing BPAM307 (see Scheme 1) demonstrates that the nature and the orientation of the C4 lipophilic substituent critically influence receptor subtype preference, with the allyl group conferring enhanced potentiation at kainate receptors relative to AMPA receptors. However, the maximal activity of BPAM307 did not surpass that of BPAM344, and its overall selectivity profile was not improved compared with BPAM344 [30].



SCHEME 1 | Chemical structures of positive (PAMs) and negative (NAMs) allosteric modulators of kainate receptors.

TABLE 1 | Overview of pharmacologicalmodulatorsof kainate receptors, summarizing their chemical or biological class, binding site, subunit selectivity, and principal mechanisms of action on receptor gating and desensitization.

Modulator	Type	Chemical/biological class	Binding site	Selectivity	Mechanism
***BPAM307* (1)**	**PAM**	3,4-Dihydro-2*H*-thieno[3,2-e]−1,2,4-thiadiazine 1,1-dioxide derivative	Two molecules at the LBD dimer interface [30]	It potentiates GluK1−3 but originally designed for AMPA receptors but seems to have a good potential on KARs [30]	Stabilizes the active non-desensitized state and enhances glutamate-evoked responses [30]
***BPAM344* (2)**	**PAM**	1,2,4-Benzothiadiazine 1,1-dioxide derivative	Two molecules at the LBD dimer interface [13]	Potentiates GluK1−3 but originally designed for AMPA receptors, higher potency at AMPARs than KARs [29]	Stabilizes closed clamshell, reduces desensitization [28]
***BPAM521* (3)**	**PAM**	1,2,4-Benzothiadiazine 1,1-dioxide derivative	Two molecules at the LBD dimer interface [13]	KARPAM with limited detailed subunit profiling; used as tool compound [6, 13]	Stabilizes the non-desensitized state and reduces desensitization [6]
***BPAM538* (4)**	**PAM**	1,2,4-Benzothiadiazine 1,1-dioxide derivative	1 molecule at the LBD dimer interface [31]	It's a PAM originally designed for AMPA receptors; it potentiates GluK1 but displays much higher potency at AMPARs ($EC_{50} \approx 2$ nM) [32] than at GluK1 kainate receptors ($EC_{50} \approx 58$ μM) [31]	It reduces GluK1 desensitization by stabilizing the active dimer interface of the receptor [31]
CONCANAVALIN A	**PAM**	Plant lectin [33]	It binds at N-glycans in the highly glycosylated extracellular regions of GluK1-GluK5 subunits [34]	Nonselective lectin, broadly used to probe desensitization of KARs and AMPARs[29] [28]	Promotes stabilization of the open-channel state of the kainate receptor, thereby limiting desensitization [28, 34]
GALECTIN-1	**PAM**	Human galectin [35]	Fixation at the same spot as Concanavalin A on the glycosylated extracellular regions between ATD and LBD of GluK2 subunit [36]	Not kainate subunit-selective and also active on AMPA receptors [36]	It stabilizes non-desensitized receptor conformations, thereby slowing desensitization in a subunit- and glycan-dependent manner [36].
CONGERIN-1	**PAM**	Fish (eel) galectin [37]	Fixation at the same spot as Concanavalin A on the glycosylated extracellular regions between ATD and LBD of GluK2 subunit [36]	Allosteric modulator that strongly potentiates GluK2 containing KARs but also AMPA GluA4 [36]	Similar mechanism as Galectin-1 [36]
Zn^{2+}	**PAM/ tuner**	Divalent cation	Binds an extracellular Zn^{2+} site at the LBD dimer interface [29, 38]	Selective of the GluK3 subunit but also active on AMPARs (potentiation at low concentration and inhibition at higher) and NMDARs (inhibition) [39]	Potentiates glutamate-evoked currents and attenuates desensitization by targeting Asp790 [29] (equivalent to Asp759 at the LBD dimer interface) [38]

(Continues)

TABLE 1 | (Continued)

Modulator	Type	Chemical/biological class	Binding site	Selectivity	Mechanism
Na^+	**PAM/ tuner**	Monovalent cation	Fixed in a cavity around the D1 interface near Lys533 and neighboring residues [29]	There is a selectivity for the kainate subtype receptor in which the Na^+ binding site is kept in the GluK1−3 subunits [40].	Na^+ sites stabilize the active LBD dimer, increasing the fraction of receptors that are activatable by glutamate and slowing desensitization. It's important for physiological tuning rather than classic drug-like PAM action [40–42]
Cl^-	**PAM/ tuner**	Monovalent anion	The Cl^- site sits at the center of the D1–D1 interface, where the anion interacts with Lys533 from both subunits [29]	N/A	Chloride ion binds to a dedicated anion site at the kainate receptor LBD dimer interface, where its occupancy stabilizes the active dimer, thereby slowing desensitization and increasing the fraction of receptors available for glutamate-gated opening [40]
***PERAMPANEL* (5)**	**NAM**	Phenyl-pyridyl	PMP binds in an extracellular allosteric pocket formed by the pre-M1 linker and the M1, M3, and M4 helices at the LBD-TMD interface, within the "extracellular collar" region surrounding the pore of kainate receptors [28, 43]	It is a clinically used antiepileptic drug that acts as non-competitive inhibitor at AMPARs [44, 45] and as NAM at KARs [43]	Stabilizes the closed channel conformation and decreases the maximal glutamate-evoked current [43]
***GYKI-52 466* (6)**	**NAM**	2,3-Benzodiazepine derivative	Limited structural data for KARs	Not selective and lower potency at KARs than AMPARs [46]	Noncompetitive allosteric inhibitor that stabilizes the closed (non-conducting) channel conformation and reduces the maximal glutamate-evoked current [46]
***GYKI-53 655* (7)**	**NAM**	2,3-Benzodiazepine derivative	Limited structural data for KARs	Tool compound with modest KAR activity (only observed at high doses) and poor selectivity [47, 48]	Not yet investigated
***CP-465 022* (8)**	**NAM**	Quinazolinone derivative	Limited structural data for KARs	Primarily characterized at AMPARs, with secondary effects at KARs [48].	Not yet investigated

One of the most potent AMPARPAM reported, BPAM538, was also evaluated at GluK1. This compound, which combines a 4-cyclopropyl substituent with a 7-methoxyphenoxy group, is predicted to adopt a binding pose that occupies the volume normally accessible to a second PAM molecule at the LBD dimer interface, thereby favoring a single-ligand binding mode. This "built-in dimer" architecture is expected to increase the local shape complementarity and interaction density within the allosteric pocket, thereby maintaining some degree of positive allosteric efficacy at kainate receptors. Nonetheless, although BPAM538 displays measurable activity at GluK1, its potency remains clearly inferior to that observed at AMPA receptors [31].

2.5 | Interest of KARNAMS

Negative allosteric modulators of kainate receptors (KARNAMs) represent a complementary strategy to KARPAMs by selectively dampening glutamatergic transmission through allosteric inhibition of KAR function in an agonist-dependent way. By binding to topographically distinct allosteric sites, KARNAMs destabilize or prevent active glutamate-bound conformations and/or favor desensitized or nonconducting states, thereby decreasing the amplitude or probability of KAR-mediated currents without directly competing with L-glutamate at the orthosteric site [28].

3 | Discussion

Despite the growing number of identified positive and negative allosteric modulators of kainate receptors (KARs), none of the currently available small molecules exhibits genuine receptor selectivity (KAR vs. AMPAR selectivity). Moreover, no ligand has yet been demonstrated to selectively and effectively target a single KAR subunit. Most compounds reported to date show significant overlap in their activity profiles across KAR subtypes, or display cross-reactivity with other ionotropic glutamate receptor families, thereby limiting their utility as precise pharmacological tools. Consequently, our current understanding of subunit-specific KAR signaling, physiology, and pharmacology remains constrained by the lack of highly selective modulators. Expanding the chemical and pharmacological space of KARPAMs and NAMs, with the explicit goal of achieving subunit discrimination, therefore represents a critical frontier for both basic research and the development of therapeutic agents targeting excitatory neurotransmission.

Future efforts should therefore focus on integrating structure-guided drug design with high-throughput screening (HTS) of chemically diverse libraries. Leveraging the growing body of structural data will enable the rational design and optimization of ligands targeting specific binding sites and conformational states of KARs. In parallel, large-scale screening campaigns combined with advanced and physiologically relevant functional assays will facilitate the identification of truly receptor- and subunit-selective modulators. Such complementary approaches will be essential to disentangle the distinct physiological and pathological roles of GluK1-GluK5-containing receptors and to accelerate the development of selective pharmacological tools and therapeutic candidates.

Acknowledgments

This work was supported in part by the Leon Fredericq Foundation and the Fonds de la Recherche Scientifique – FNRS (Belgium). T. Colson and C. Lesenfants are Research Fellows of the F.R.S.-FNRS. The authors also thank their collaborators and colleagues for valuable scientific discussions that contributed to this review. Figures were created using BioRender Francotte, P. (2026) (https://biorender.com) and ChemDraw (PerkinElmer).

Funding

This study was supported by the Fonds De La Recherche Scientifique - FNRS and the Fonds Léon Fredericq.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. P. Francotte, P. de Tullio, P. Fraikin, S. Counerotte, E. Goffin, and B. Pirotte, "In Search of Novel AMPA Potentiators," *Recent Patents on CNS Drug Discovery* 1, no. 3 (2006): 239–246, https://doi.org/10.2174/157488906778773661.

2. B. Pirotte, P. Francotte, E. Goffin, and P. A. M. P. A. de Tullio, "AMPA Receptor Positive Allosteric Modulators: A Patent Review," *Expert Opinion on Therapeutic Patents* 23, no. 5 (2013): 615–628, https://doi.org/10.1517/13543776.2013.770840.

3. K. B. Hansen, L. P. Wollmuth, D. Bowie, et al., "Structure, Function, and Pharmacology of Glutamate Receptor Ion Channels," *Pharmacological Reviews* 73, no. 4 (2021): 1469–1658, https://doi.org/10.1124/pharmrev.120.000131.

4. A. I. Sobolevsky, M. P. Rosconi, and E. Gouaux, "X-Ray Structure, Symmetry and Mechanism of an AMPA-Subtype Glutamate Receptor," *Nature* 462, no. 7274 (2009): 745–756, https://doi.org/10.1038/nature08624.

5. S. F. Traynelis, L. P. Wollmuth, C. J. McBain, et al., "Glutamate Receptor Ion Channels: Structure, Regulation, and Function," *Pharmacological Reviews* 62, no. 3 (2010): 405–496, https://doi.org/10.1124/pr.109.002451.

6. A. P. Larsen, S. Fièvre, K. Frydenvang, et al., "Identification and Structure-Function Study of Positive Allosteric Modulators of Kainate Receptors," *Molecular Pharmacology* 91, no. 6 (2017): 576–585, https://doi.org/10.1124/mol.116.107599.

7. C. Lesenfants, T. Colson, E. Goffin, et al., "Exploration around 4-Cyclopropyl-Substituted 1,2,4-Benzothiadiazine 1,1-Dioxides: Impact of the Dihalo-Substitution of the Benzene Ring on α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) Receptor Potentiation," *Journal of Medicinal Chemistry* 68, no. 17 (2025): 18641–18659, https://doi.org/10.1021/acs.jmedchem.5c01662.

8. J. Lerma and J. M. Kainate Marques, "Receptors in Health and Disease," *Neuron* 80, no. 2 (2013): 292–311, https://doi.org/10.1016/j.neuron.2013.09.045.

9. P. Pinheiro and C. Mulle, "Kainate Receptors," *Cell and Tissue Research* 326, no. 2 (2006): 457–482, https://doi.org/10.1007/s00441-006-0265-6.

10. J. L. Fisher and D. D. Mott, "Distinct Functional Roles of Subunits Within the Heteromeric Kainate Receptor," *The Journal of Neuroscience* 31, no. 47 (2011): 17113–17122, https://doi.org/10.1523/JNEUROSCI.3685-11.2011.

11. P. Selvakumar, J. Lee, N. Khanra, et al., "Structural and Compositional Diversity in the Kainate Receptor Family," *Cell Reports* 37, no. 4 (2021): 109891, https://doi.org/10.1016/j.celrep.2021.109891.

12. H. Zhao, S. Lomash, S. Chittori, C. Glasser, M. L. Mayer, and P. Schuck, "Preferential Assembly of Heteromeric Kainate and AMPA Receptor Amino Terminal Domains," *ELife* 6 (2017): e32056, https://doi.org/10.7554/eLife.32056.

13. K. Frydenvang, D. S. Pickering, and J. S. Kastrup, "Structural Basis for Positive Allosteric Modulation of AMPA and Kainate Receptors," *The Journal of Physiology* 600, no. 2 (2022): 181–200, https://doi.org/10.1113/JP280873.

14. O. Kristensen, L. B. Kristensen, S. Møllerud, K. Frydenvang, D. S. Pickering, and J. S. Kastrup, "The *Structure* of a High-Affinity Kainate Receptor: GluK4 Ligand-Binding Domain Crystallized with Kainate," *Structure* 24, no. 9 (2016): 1582–1589, https://doi.org/10.1016/j.str.2016.06.019.

15. T. Colson, C. Lesenfants, E. Goffin, et al., "Exploration of the Isosteric Concept Applied to 1,2,4-Benzothiadiazine 1,1-Dioxides in the Discovery of Novel AMPA Receptor Positive Allosteric Modulators," *ACS Omega* 10, no. 29 (2025): 32496–32506, https://doi.org/10.1021/acsomega.5c05172.

16. A. Lau and M. Tymianski, "Glutamate Receptors, Neurotoxicity and Neurodegeneration," *Pflügers Archiv European Journal of Physiology*460, no. 2 (2010): 525–542, https://doi.org/10.1007/s00424-010-0809-1.

17. D. R. Madden, "The Structure and Function of Glutamate Receptor Ion Channels," *Nature Reviews. Neuroscience* 3, no. 2 (2002): 91–101, https://doi.org/10.1038/nrn725.

18. R. Chittajallu, M. Vignes, K. K. Dev, J. M. Barnes, G. L. Collingridge, and J. M. Henley, "Regulation of Glutamate Release by Presynaptic Kainate Receptors in the Hippocampus," *Nature* 379, no. 6560 (1996): 78–81, https://doi.org/10.1038/379078a0.

19. P. E. Castillo, R. C. Malenka, and R. A. Nicoll, "Kainate Receptors Mediate a Slow Postsynaptic Current in Hippocampal CA3 Neurons," *Nature* 388, no. 6638 (1997): 182–186, https://doi.org/10.1038/40645.

20. M. Vignes and G. L. Collingridge, "The Synaptic Activation of Kainate Receptors," *Nature* 388, no. 6638 (1997): 179–182, https://doi.org/10.1038/40639.

21. D. Gautam, U. P. Naik, M. U. Naik, S. K. Yadav, R. N. Chaurasia, and D. Dash, "Glutamate Receptor Dysregulation and Platelet Glutamate Dynamics in Alzheimer's and Parkinson's Diseases: Insights into Current Medications," *Biomolecules* 13, no. 11 (2023): 1609, https://doi.org/10.3390/biom13111609.

22. H. Fu, Z. Chen, L. Josephson, Z. Li, and S. H. Liang, "Positron Emission Tomography (PET) Ligand Development for Ionotropic Glutamate Receptors: Challenges and Opportunities for Radiotracer Targeting *N* -Methyl- d -Aspartate (NMDA), α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) And Kainate Receptors: Miniperspective," *Journal of Medicinal Chemistry* 62, no. 2 (2019): 403–419, https://doi.org/10.1021/acs.jmedchem.8b00714.

23. C. A. Zarate and H. K. Manji, "The Role of AMPA Receptor Modulation in the Treatment of Neuropsychiatric Diseases," *Experimental Neurology* 211, no. 1 (2008): 7–10, https://doi.org/10.1016/j.expneurol.2008.01.011.

24. A. Das, G. C. Wallace, C. Holmes, et al., "Tissue of Patients with Refractory Temporal Lobe Epilepsy Is Associated with Astrocyte Activation, Inflammation, and Altered Expression of Channels and Receptors," *Neuroscience* 220 (2012): 237–246, https://doi.org/10.1016/j.neuroscience.2012.06.002.

25. M. I. Aller, V. Pecoraro, A. V. Paternain, S. Canals, and J. Lerma, "Increased Dosage of High-Affinity Kainate Receptor Gene, *Grik4*, Alters Synaptic Transmission and Reproduces Autism Spectrum Disorders Features," *The Journal of Neuroscience* 35, no. 40 (2015): 13619–13628, https://doi.org/10.1523/JNEUROSCI.2217-15.2015.

26. T. A. Greenwood, L. C. Lazzeroni, M. E. Calkins, et al., "Genetic Assessment of Additional Endophenotypes from the Consortium on the Genetics of Schizophrenia Family Study," *Schizophrenia Research* 170, no. 1 (2016): 30–40, https://doi.org/10.1016/j.schres.2015.11.008.

27. J. S. Catches, J. Xu, and A. Contractor, "Genetic Ablation of the GluK4 Kainate Receptor Subunit Causes Anxiolytic and Antidepressant-Like Behavior in Mice," *Behavioural Brain Research* 228, no. 2 (2012): 406–414, https://doi.org/10.1016/j.bbr.2011.12.026.

28. S. P. Gangwar, L. Y. Yen, M. V. Yelshanskaya, and A. I. Sobolevsky, "Positive and Negative Allosteric Modulation of GluK2 Kainate Receptors by BPAM344 and Antiepileptic Perampanel," *Cell Reports* 42, no. 2 (2023): 112124, https://doi.org/10.1016/j.celrep.2023.112124.

29. Y. Bay, R. Venskutonytė, S. M. Frantsen, et al., "Small-Molecule Positive Allosteric Modulation of Homomeric Kainate Receptors GluK1 -3: Development of Screening Assays and Insight into GluK3 Structure," *The Febs Journal* 291, no. 7 (2024): 1506–1529, https://doi.org/10.1111/febs.17046.

30. P. Francotte, Y. Bay, E. Goffin, et al., "Exploring Thienothiadiazine Dioxides as Isosteric Analogues of Benzo- and Pyridothiadiazine Dioxides in the Search of New AMPA and Kainate Receptor Positive Allosteric Modulators," *European Journal of Medicinal Chemistry* 264 (2024): 116036, https://doi.org/10.1016/j.ejmech.2023.116036.

31. Y. Bay, F. J. M. Cabello, C. C. Koens, et al., "Structure of the GluK1 Ligand-Binding Domain with Kainate and the Full-Spanning Positive Allosteric Modulator BPAM538," *Journal of Structural Biology* 216, no. 3 (2024): 108113, https://doi.org/10.1016/j.jsb.2024.108113.

32. E. Goffin, T. Drapier, A. P. Larsen, et al., "7-Phenoxy-Substituted 3,4-Dihydro-2 *H* -1,2,4-Benzothiadiazine 1,1-Dioxides as Positive Allosteric Modulators of α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid (AMPA) Receptors with Nanomolar Potency," *Journal of Medicinal Chemistry* 61, no. 1 (2018): 251–264, https://doi.org/10.1021/acs.jmedchem.7b01323.

33. Z. Wang, J. Wang, A. R. Kahkoska, J. B. Buse, and Z. Gu, "Developing Insulin Delivery Devices with Glucose Responsiveness," *Trends in Pharmacological Sciences* 42, no. 1 (2021): 31–44, https://doi.org/10.1016/j.tips.2020.11.002.

34. C. U. Gonzalez, E. Carrillo, V. Berka, and V. Jayaraman, "Structural Arrangement Produced by Concanavalin A Binding to Homomeric GluK2 Receptors," *Membranes* 11, no. 8 (2021): 613, https://doi.org/10.3390/membranes11080613.

35. I. Camby, M. Le Mercier, F. Lefranc, and R. Kiss, "Galectin-1: A Small Protein with Major Functions," *Glycobiology* 16, no. 11 (2006): 137R–157R, https://doi.org/10.1093/glycob/cwl025.

36. B. A. Copits, C. G. Vernon, R. Sakai, and G. T. Swanson, "Modulation of Ionotropic Glutamate Receptor Function by Vertebrate Galectins," *The Journal of Physiology* 592, no. 10 (2014): 2079–2096, https://doi.org/10.1113/jphysiol.2013.269597.

37. T. Shirai, C. Mitsuyama, Y. Niwa, et al., "High-Resolution Structure of the Conger Eel Galectin, Congerin I, in Lactose-Liganded and Ligand-Free Forms: Emergence of a New Structure Class by Accelerated Evolution," *Structure* 7 (1999): 1223–1233, https://doi.org/10.1016/S0969-2126(00)80056-8.

38. J. Veran, J. Kumar, P. S. Pinheiro, et al., "Zinc Potentiates GluK3 Glutamate Receptor Function by Stabilizing the Ligand Binding Domain Dimer Interface," *Neuron* 76, no. 3 (2012): 565–578, https://doi.org/10.1016/j.neuron.2012.08.027.

39. F.-A. Rassendren, P. Lory, J.-P. Pin, and J. Nargeot, "Zinc Has Opposite Effects on NMDA and Non-NMDA Receptors Expressed in Xenopus Oocytes," *Neuron* 4, 1990). 733–740, https://doi.org/10.1016/0896-6273(90)90199-P.

40. A. J. R. Plested, R. Vijayan, P. C. Biggin, and M. L. Mayer, "Molecular Basis of Kainate Receptor Modulation by Sodium," *Neuron* 58, no. 5 (2008): 720–735, https://doi.org/10.1016/j.neuron.2008.04.001.

41. S. P. Gangwar, M. V. Yelshanskaya, L. Y. Yen, T. P. Newton, and A. I. Sobolevsky, "Structure and Gating of Kainate Receptors," *Frontiers in Pharmacology* 16 (2025): 1662316, https://doi.org/10.3389/fphar.2025.1662316.

42. A. Y. C. Wong, A.-M. L. Fay, and D. Bowie, "External Ions Are Coactivators of Kainate Receptors," *The Journal of Neuroscience* 26, no. 21 (2006): 5750–5755, https://doi.org/10.1523/JNEUROSCI.0301-06.2006.

43. S. Taniguchi, J. R. Stolz, and G. T. Swanson, "The Antiseizure Drug Perampanel Is a Subunit-Selective Negative Allosteric Modulator of Kainate Receptors," *The Journal of Neuroscience* 42, no. 28 (2022): 5499–5509, https://doi.org/10.1523/JNEUROSCI.2397-21.2022.

44. S. Hibi, K. Ueno, S. Nagato, et al., "Discovery of 2-(2-Oxo-1-Phenyl-5-Pyridin-2-Yl-1,2-Dihydropyridin-3-Yl)Benzonitrile (Perampanel): A Novel, Noncompetitive α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropanoic Acid (AMPA) Receptor Antagonist," *Journal of Medicinal Chemistry* 55, no. 23 (2012): 10584–10600, https://doi.org/10.1021/jm301268u.

45. C.-Y. Chen, L. Matt, J. W. Hell, and M. A. Rogawski, "Perampanel Inhibition of AMPA Receptor Currents in Cultured Hippocampal Neurons," *PLoS ONE* 9, no. 9 (2014): e108021, https://doi.org/10.1371/journal.pone.0108021.

46. S. D. Donevan and M. A. Rogawski, "GYKI 52466, a 2,3-Benzodiazepine, Is a Highly Selective, Noncompetitive Antagonist of AMPA/Kainate Receptor Responses," *Neuron* 10, 1993): 51–59, https://doi.org/10.1016/0896-6273(93)90241-I.

47. C. Krintel, J. Dorosz, A. H. Larsen, et al., "Binding of a Negative Allosteric Modulator and Competitive Antagonist Can Occur Simultaneously at the Ionotropic Glutamate Receptor GluA2," *The Febs Journal* 288, no. 3 (2021): 995–1007, https://doi.org/10.1111/febs.15455.

48. D. Perrais, P. S. Pinheiro, D. E. Jane, and C. Mulle, "Antagonism of Recombinant and Native GluK3-Containing Kainate Receptors," *Neuropharmacology* 56, no. 1 (2009): 131–140, https://doi.org/10.1016/j.neuropharm.2008.08.002.

49. S. P. Gangwar, M. V. Yelshanskaya, K. D. Nadezhdin, et al., "Kainate Receptor Channel Opening and Gating Mechanism," *Nature* 630, no. 8017 (2024): 762–768, https://doi.org/10.1038/s41586-024-07475-0.

50. B. Pirotte, P. Francotte, E. Goffin, et al., "Ring-Fused Thiadiazines as Core Structures for the Development of Potent AMPA Receptor Potentiators," *Current Medicinal Chemistry* 17, no. 30 (2010): 3575–3582, https://doi.org/10.2174/092986710792927859.

51. S. E. Ward and M. Harries, "Recent Advances in the Discovery of Selective AMPA Receptor Positive Allosteric Modulators," *Current Medicinal Chemistry* 17, no. 30 (2010): 3503–3513, https://doi.org/10.2174/092986710792927840.

52. J. Lerma, A. V. Paternain, A. Rodríguez-Moreno, and J. C. López-García, "Molecular Physiology of Kainate Receptors," *Physiological Reviews* 81, no. 3 (2001): 971–998, https://doi.org/10.1152/physrev.2001.81.3.971.

53. S. P. Gangwar, M. V. Yelshanskaya, L. Y. Yen, T. P. Newton, and A. I. Sobolevsky, "Activation of Kainate Receptor GluK2–Neto2 Complex," *Nature Structural & Molecular Biology* 32, no. 11 (2025): 2176–2184, https://doi.org/10.1038/s41594-025-01656-9.

Biographies

Thomas Colson is a Ph.D. candidate in Medicinal Chemistry at the University of Liège. His research focuses on the design and synthesis of positive allosteric modulators of kainate receptors (KARPAMs), bridging medicinal chemistry and neuropharmacology with an emphasis on chemical reference compounds. He has presented his work at international conferences and received competitive awards, including recognition from the FNRS and the Leon Fredericq Foundation (Hope Prize 2024). He is also involved in scientific coordination and research valorization initiatives.

Pierre Francotte is Head of the Laboratory of Medicinal Chemistry at the University of Liège, where he teaches organic and medicinal chemistry in the pharmacy curriculum. His research focuses on the design, synthesis and structural optimization of bioactive small molecules targeting the central nervous system, and on interdisciplinary projects at the interface of organic synthesis, pharmacology, with a particular interest in natural products. He is also actively involved in mentoring young scientists and in academic and scientific evaluation at the national and international levels.