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List of Publications

Publication from thesis: Research Article:

1. **Uniyal A**, Akhilesh, Rahore AS, Keshri PS, Singh SP, Singh S, **Tiwari V*** Inhibition of Pan-Aurora Kinase Attenuates Evoked and Ongoing Pain in Nerve Injured Rats via Regulating KIF17-NR2B Mediated Signaling. ***International Immunopharmacology*** **2022**. **(Impact factor 4.93)**

2. **Uniyal A,** Gadepalli A, Modi A, **Tiwari V***. Modulation of KIF-17/NR2B Crosstalk by Tozasertib Attenuates Inflammatory Pain in Rats. ***Inflammopharmacology*** **2022**. **(Impact factor 4.47)**.

3. **Uniyal A**, Shantanu PA, Vaidya S, Belinskaia DA, Shestakova NN, Kumar R, Singh S, **Tiwari V***. Tozasertib Attenuates Neuropathic Pain by Interfering with Aurora Kinase and KIF11 Mediated Nociception. ***ACS Chemical Neuroscience.*** **2021** May 24. **(Impact factor 4.418)**

Publication from thesis: Review Article:

1. **Uniyal A**, Thakur, V, Rani, M, Tiwari, V, Akhilesh, Gadepalli, A, Ummadisetty, O, Modi, A**, Tiwari, V***. Neurobiology of Kinesin Nanomotors mediated Trafficking of NMDA-Loaded Cargo in Chronic Pain. ***ACS Chemical Neuroscience.*** **2021 (Impact factor 4.21)**.

Other publications:

1. A, **Uniyal A,** Gadepalli A, Tiwari V, Allani M, Chouhan D, Ummadisetty O, Verma N, **Tiwari V***. Unlocking the potential of TRPV1 based siRNA therapeutics for the treatment of chemotherapy-induced neuropathic pain. ***Life Sciences.*** **2022** Jan 1; 288:120187. **(Impact factor 5.03)**

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3. Gadepalli A, Akhilesh, **Uniyal A**, Modi A, Chouhan D, Ummadisetty O, Khanna S, Solanki S, Allani M, **Tiwari V***. Multifarious Targets and Recent Developments in the Therapeutics for the Management of Bone Cancer Pain. ACS chemical neuroscience. 2021 Nov 1;12(22):4195-208. ***ACS Chemical Neuroscience***. **2021 (Impact factor 4.21)**
4. **Uniyal A**, Kotiyal A, Gadepalli A, Ummadisetty O, **Tiwari V***. Epigallocatechin-3-gallate Improves Chronic Alcohol Induced Cognitive Dysfunction in Rats by Interfering with the Neuro-inflammatory, Cell Death and Oxido-nitrosative Stress Pathways**.** ***Metabolic Brain Disease*****. 2021 (Impact Factor: 3.584)**
5. Thakur V, **Uniyal A**, **Tiwari V***. A Comprehensive Review on Pharmacology of Efflux Pumps and their Inhibitors in Antibiotic Resistance. ***European journal of pharmacology***. **2021** May 5:174151. (**Impact Factor: 4.432)**
6. Akhilesh, Baidya A TK, **Uniyal A**, Das B, Kumar R, **Tiwari V***. Structure-based Virtual Screening and Molecular Dynamics Simulation for the Identification of Sphingosine Kinase-2 Inhibitors as Potential Analgesics. ***Journal of Biomolecular Structure and Dynamics*** **2021 (Impact Factor: 3.3)**
7. **Uniyal A**, Rani M, Tiwari V, **Tiwari V***. Immune-Microbiome Interplay and its Implications in Neurodegenerative Disorders. ***Metabolic Brain Disease*** **2021 (Impact Factor: 3.584)**
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16. **Uniyal A**, Singh R, Akhtar A, Bansal Y, Kuhad A, Sah SP. Co-treatment of piracetam with risperidone rescued extinction deficits in experimental paradigms of post-traumatic stress disorder by restoring the physiological alterations in cortex and hippocampus. ***Pharmacology Biochemistry and Behavior***. **2019** Aug 22:172763. **(Impact Factor: 3.533)**
17. Ahuja S, **Uniyal A**, Akhtar A, Sah SP. Alpha lipoic acid and metformin alleviates experimentally induced insulin resistance and cognitive deficit by modulation of TLR2 signaling. ***Pharmacological Reports***. **2019** Feb 23. **(Impact factor 3.024)**

National/International Conference Presentations/Participation:

1. Participated in 8th International Symposium on Current Trends in Drug Discovery Research organized by CSIR-Central Drug Research Institute, Lucknow, India and presented research findings entitled *"Investigating Kinesin Mediated Regulation of Nociceptors as A Novel Therapeutic Target for Chronic Pain"*. March 12-14, 2022
2. Participated in "Nepal IBRO Associate School on Neurophysiology of Pain: Mechanism to Medicine organized by Nepalgunj Medical College Chisapani, Banke Nepal, and presented research findings entitled *"Tozasertib Attenuates Neuropathic Pain by Interfering with Aurora Kinase and KIF11 Mediated Nociception".* 31 Aug-5 Sep 2021
3. Participated in "5th IBRO/APRC Chandigarh Neuroscience School" organized by Panjab University, Chandigarh, August 23-27, 2021
4. IBRO-APRC School on "Understanding Neuroscience and the Spectrum of Neurogenetic Disorders", organized by Kathmandu University School of Medical Science, Kathmandu Nepal, August 20, 2021 - August 25, 2021
5. Participated in SPARC sponsored Indo-US Workshop on Pain Mechanisms & Therapeutics, May 06, 2021 to May 10, 2021, organized by the Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, India
6. Participated in A short-term course on Pre-Clinical Models in Drug Discovery & Development organized by the Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, India. March 30, 2021 – April 3, 2021
7. Participated in Brain Awareness week organized by Gujrat Forensic Science University (IBS) and Centre for Cognitive and brain Sciences (IIT Gandhinagar), funded by IBRO and Dana foundation 22-28 May 2020
8. Participated in "IBRO-APRC Associate School on Neurological and Neuromuscular Disorders: An Insight into its Approach and Neurodiagnostic Techniques" March 10 - March 14, 2019, held at B. P. K. I. H. S, Nepal

RECOGNITION: Awards, Achievements and Honors:

1. Awarded travel grant by International Association for Study of Pain (IASP) for attending World Congress on Pain 2021 at Amsterdam
2. Awarded travel grant by international Brain Research Organization-Asia Pacific regional Committee (IBRO-APRC) to attend IBRO school held at B. P. K. I. H. S, Nepal in March, 2019
3. Awarded 3 years Senior Research Fellowship award by Indian Council of Medical Research (ICMR) in March 2019 for the project entitled "Development of Green Nanotherapeutics for the Treatment and Relapse of Drug and Alcohol Addiction"

Dr. Vinod Tiwari, is an Assistant Professor at the Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, India. Dr. Tiwari is currently PI of the Neuroscience and Pain Research Lab at IIT (BHU), Varanasi and Ph.D. supervisor of Mr. Ankit Uniyal. Dr. Tiwari has done his Ph.D. in neuropharmacology, and he was able to identify key signaling pathways involved in alcoholic neuropathy and associated cognitive deficits, diabetic neuropathy, and musculoskeletal pain. His Ph.D. research work was published in peer-reviewed international journals such as the International Journal of Neuropsychopharmacology; Journal of Neurochemistry; Pharmacology, Biochemistry & Behavior; PAIN & The Journal of Pain, and is being highly cited. With his postdoc mentors Prof. Srinivasa N. Raja and Prof. Yun Guan at Johns Hopkins University, U.S.A he investigated different spinal and supraspinal mechanisms involved in peripheral opioid-induced amelioration of spontaneous ongoing pain (affective component of pain) after spinal and sciatic nerve injury by using conditioned place preference. Apart from this he also studied the role of MOR and DOR heterodimerization in peripheral opioid-induced tolerance and hyperalgesia which is currently a big clinical problem. He has published his postdoctoral findings in Nature Neuroscience, Proceedings of National Academy of Science (PNAS), U.S.A, PAIN, Anesthesiology and The Journal of Clinical investigation. Before joining IIT (BHU), Varanasi Dr. Tiwari worked as Assistant Professor in National Institute of Pharmaceutical Education and Research, Ahmedabad. Dr. Tiwari's research work in pain field is being rapidly cited worldwide and at present he has more than 3297 citation, h-index 33 and i10-index 54. Recently, his research interest is focused on the kinesin-mediated regulation of nociceptors and dissecting out the different neuronal circuitries involved in pain relief and drug addiction so that better analgesic drugs devoid of drug addiction can be developed.

Mr. Ankit Uniyal, is a Ph.D. scholar at the Department of Pharmaceutical Engineering & Technology, Indian Institute of Technology (Banaras Hindu University), Varanasi, India. Ankit has joined Dr. Tiwari's lab in October 2018 and he studied the role of kinesin nanomotors in the regulation of chronic pain during his Ph.D. His research findings were published in high-impact peer-reviewed international journals such as International Immunopharmacology, Inflammopharmacology, Life Sciences, European Journal of Pharmacology, ACS Chemical Neuroscience, etc. Ankit was awarded Senior Research Fellowship by the Indian Council of Medical Research, Govt. of in India in 2019. Apart from this, he has received various travel grants and awards from the International Brain Research Organization (IBRO) and the International Association for the Study of Pain (IASP). His goals after completing Ph.D. are to get trained in a highly competitive environment to shape his research skills, and to pursue a career in neuroscience aspiring to unfold the novel paradigms associated with chronic pain and to develop novel analgesics devoid of side effects.

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Research Article

Tozasertib Attenuates Neuropathic Pain by Interfering with Aurora Kinase and KIF11 Mediated Nociception

Ankit Uniyal,[#] P. A. Shantanu,[#] Shivani Vaidya, Daria A. Belinskaia, Natalia N. Shestakova, Rajnish Kumar, Sanjay Singh, and Vinod Tiwari*

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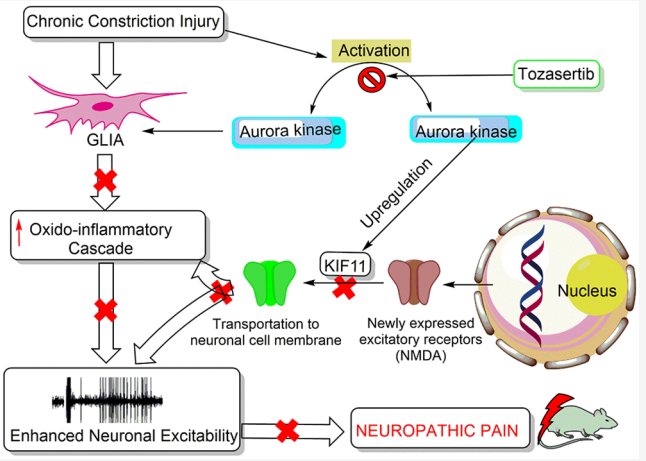
ABSTRACT: Kinesins are the motor proteins that transport excitatory receptors to the synaptic membrane by forming a complex with receptor cargo leading to central sensitization causing neuropathic pain. Many regulatory proteins govern the transit of receptors by activating kinesin, and Aurora kinases are one of them. In this study, we have performed in silico molecular dynamics simulation to delineate the dynamic interaction of Aurora kinase A with its pharmacological inhibitor, tozasertib. The results from the molecular dynamics study shows that tozasertib-Aurora kinase A complex is stabilized through hydrogen bonding, polar interactions, and water bridges. Findings from the *in vitro* studies suggest that tozasertib treatment significantly attenuates lipopolysaccharide (LPS)-induced increase in oxidonitrosative stress and kif11 overexpression in C6 glial cell lines. Further, we investigated the regulation of kif11 and its modulation by tozasertib in an animal model of neuropathic pain. Two weeks post-CCI surgery we observed a significant increase in pain hypersensitivity and kif11 overexpression in DRG and spinal cord of nerve-injured rats. Tozasertib treatment significantly attenuates enhanced pain hypersensitivity along with the restoration of kif11 expression in DRG and spinal cord and oxidonitrosative stress in the sciatic nerve of injured rats. Our findings demonstrate the potential role of tozasertib for the management of neuropathic pain.



KEYWORDS: *Aurora kinase, Kif11, chronic constriction injury, neuropathic pain, molecular dynamics simulation, tozasertib*

1. INTRODUCTION

Chronic pain is accompanied by many neurological diseases such as brain or spinal cord injury, tumors, neurodevelopmental disorders, neurodegeneration, neuroinflammation, etc. Neuropathic pain occurs when there is actual or potential damage to the somatosensory system. Due to this damage, various inflammatory mediators and toxins are released which causes nonspecific stimulation of nociceptors resulting in increased synaptic plasticity leading to both peripheral and central sensitization.[1] Recent epidemiological studies suggest that about a quarter of the world's population suffers from the pain of which 7−8% of cases are neuropathic in origin. Even for more than a century of research on nociception and analgesia, 35% of neuropathic pain patients do not respond to standard treatment and show serious side effects.[2] The clinically available drugs fail to provide adequate pain relief as neuropathic pain progresses to a chronic state due to its dose-limiting side effects and the inability of current pharmacotherapy to counteract the pain progression as they fail to act on cellular and molecular mechanisms driving neuropathic pain which remains elusive.[3] Thus, identifying the potential targets and development of efficacious drugs with minimal side effects is of utmost clinical importance.[4]

Various receptors are involved in the development and maintenance of neuropathic including TRPV-1, Nav1.6, NMDA, and LPA1, etc.[5] The pathogenesis of chronic neuropathic pain has been proven to include hyperactivation of glutamatergic transmission.[6,7] Prolonged activation of nociceptors or damage to the afferent nerve leads to the central sensitization of the nociceptive system. The putative electrophysiological mechanism of this sensitization (wind-up phenomenon) depends on the activation of *N*-methyl-D-aspartate receptors (NMDAR).[7] Blocking glutamate receptors has been shown to alleviate both acute and chronic pain in animal models. It has been proven that NMDA receptors play

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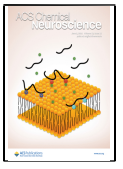

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Inhibition of pan-Aurora kinase attenuates evoked and ongoing pain in nerve injured rats via regulating KIF17-NR2B mediated signaling

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ARTICLE INFO

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Spontaneous ongoing pain
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ABSTRACT

Kinesins (KIF's) are the motor proteins which are recently reported to be involved in the trafficking of nociceptors leading to chronic pain. Aurora kinases are known to be involved in the regulation of KIF proteins which are associated with the activation of N-methyl-D-aspartate (NMDA) receptors. Here, we investigated the effect of tozasertib, a pan-Aurora kinase inhibitor, on nerve injury-induced evoked and chronic ongoing pain in rats and the involvement of kinesin family member 17 (KIF17) and NMDA receptor subtype 2B (NR2B) crosstalk in the same. Rats with chronic constriction injury showed a significantly decreased pain threshold in a battery of pain behavioural assays. We found that tozasertib [10, 20, and 40 mg/kg intraperitoneally (*i.p.*)] treatment showed a significant and dose-dependent inhibition of both evoked and chronic ongoing pain in rats with nerve injury. Tozasertib (40 mg/kg *i.p.*) and gabapentin (30 mg/kg *i.p.*) treatment significantly inhibits spontaneous ongoing pain in nerve injured rats but did not produce any place preference behaviour in healthy naïve rats pointing towards their non-addictive analgesic potential. Moreover, tozasertib (10, 20, and 40 mg/kg *i.p.*) and gabapentin (30 mg/kg i.p.) treatment did not altered the normal pain threshold in healthy naïve rats and didn't produce central nervous system associated side effects as well. Western blotting and reverse transcription polymerase chain reaction studies suggested enhanced expressions of NR2B and KIF-17 along with increased nuclear factor kappa β (NFkβ), tumour necrosis factor-α (TNF-α), interleukin 1β (IL-1β), and interleukin 6 (IL-6) levels in dorsal root ganglion (DRG) and spinal cord of nerve injured rats which was significantly attenuated on treatment with different does of Tozasertib. Findings from the current study suggests that inhibition of pan-Aurora kinase decreased KIF-17 mediated NR2B activation which further leads to significant inhibition of evoked and chronic ongoing pain in nerve-injured rats.

1. Introduction

Chronic pain is a devastating disorder affecting more than 20% of the population worldwide [1,2]. A subtype of this is chronic neuropathic pain which occurs due to the damage to the somatosensory nervous system including peripheral nerve fibers such as Aδ, Aβ, and C fibres. The prevalence of neuropathic pain ranges from 6 to 10 % globally [3] and the patients suffering from the same exhibits significant hyperalgesia, shooting sensations, numbness, allodynia, and spontaneous ongoing pain. Unfortunately, the currently available analgesics provide only mild symptomatic relief and that too at the cost of several side effects including but not limited to sedation, motor incoordination, drug addiction and development of tolerance [4]. The pathophysiology of neuropathic pain has both nociceptive and inflammatory components and requires an effective strategy to mitigate the same. N-methyl-aspartate-receptors (NMDAR's) are known to be involved in the development and maintenance of neuropathic pain both in preclinical and clinical studies [5,6]. A subset of this receptor unit, NMDA receptor subtype 2B (NR2B) is essential for the localization of NMDARs into the synaptic membrane [7] and plays an important role in learning and memory and chronic pain. Central sensitization which is a primary feature of neuropathic pain pathophysiology develops due to the over-

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Inflammopharmacology

ORIGINAL ARTICLE

Modulation of KIF17/NR2B crosstalk by tozasertib attenuates inflammatory pain in rats

Ankit Uniyal[1] · Anagha Gadepalli[1] · Ajay Modi[1] · Vinod Tiwari[1]

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Abstract

Chronic pain is among the most burdensome and devastating disorders affecting millions of people worldwide. Recent studies suggest the role of kinesin nanomotors in development and maintenance of chronic pain. KIF17 is a member of kinesin superfamily that binds to NR2B cargo system via mLin10 scaffolding protein and makes the NMDARs functional at cell surface. NMDA receptor activation is known to induce the central sensitization and excitotoxicity which can be recognized by the glial cells followed by the release of cytokine storm at spinal and supraspinal level leading to chronic pain. In this study, we have investigated the role of aurora kinase in the regulation of KIF17 and NR2B trafficking in the animal model of chronic inflammatory pain. Tozasertib (10, 20, and 40 mg/kg *i.p.*), a pan aurora kinase inhibitor, significantly attenuates acute inflammatory pain and suppresses enhanced pain hypersensitivity to heat, cold, and mechanical stimuli in CFA-injected rats. Molecular investigations suggest enhanced expression of KIF17/mLin10/NR2B in L4–L5 dorsal root ganglion (DRG) and spinal cord of CFA-injected rats which was significantly attenuated on treatment with tozasertib. Moreover, tozasertib treatment significantly attenuated CFA-induced oxido-nitrosative stress and macrophage activation in DRG and microglia activation in spinal cord of rats. Findings from the current study suggest that tozasertib mediates anti-nociceptive activity by inhibiting aurora kinase-mediated KIF17/mLin10/NR2B signaling.

Keywords Aurora kinase · Kinesin · Neuroinflammation · Microglia · Pain

Introduction

Chronic pain is one of the most prevalent clinical disorders which occurs due to persistent activation of neural pain pathways. Every person experiences pain at some point in their life span but the number of patients seeking medical care due to chronic pain is about 30% across the globe (Cohen et al. 2021). Chronic pain may consist of both neuropathic and inflammatory components, involving complex mechanisms such as excitatory synaptic transmission, microglial and macrophage activation, altered action potential in nociceptive fibers, and central as well as peripheral sensitization (Powell et al. 2021; Xie et al. 2021). Release of various inflammatory mediators from the tissue injury site or activated immune system occurs in chronic pain condition that simulates the nociceptors and manipulate the central projections involved in pain processing. The complex pathophysiological mechanisms and lack of potential druggable targets are the key factors that put a substantial barrier to analgesic drug development (Yu et al. 2013). Moreover, currently available analgesics fail to treat chronic pain adequately and produce several side effects that lead to treatment withdrawal and poor quality of life (Fitzgerald 2017; Uniyal et al. 2020). Opioids are one of the most commonly prescribed medicines for the treatment of chronic pain but they carry potential side effects including drug addiction, respiratory depression, hypotension, sleep apnea and constipation (Uniyal et al. 2020; Powell et al. 2021). Non-steroidal anti-inflammatory drugs are the first line of therapy for the treatment of chronic inflammatory pain but their contraindications and adverse effects along with drug-drug interaction are the key limiting factors putting them on the back-foot (Marcum and Hanlon 2010; Cohen et al. 2021).

Inside the cell, small molecules such as glucose and gases get diffused to their destination easily but the large

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ACS Chemical Neuroscience

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Kinesin Nanomotors Mediated Trafficking of NMDA-Loaded Cargo as A Novel Target in Chronic Pain

Ankit Uniyal, Vaibhav Thakur, Mousmi Rani, Vineeta Tiwari, Akhilesh, Anagha Gadepalli, Obulapathi Ummadisetty, Ajay Modi, and Vinod Tiwari*

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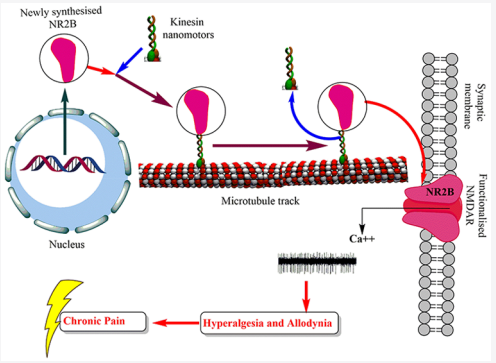
ABSTRACT: Chronic pain is among the most prevalent burdensome disorders worldwide. The *N*-methyl-D-aspartate (NMDA) receptor system plays a critical role in central sensitization, a primary feature of chronic pain. Despite the proven efficacy of exogenous ligands to this receptor system in preclinical studies, evidence for the clinical efficacy of NMDA antagonists for the treatment of chronic pain is weak. Researchers are studying alternate approaches, rather than direct inhibition of the NMDA receptors in pain processing neurons. This indirect approach utilizes the modulation of molecular switches that regulates the synthesis, maturation, and transport of receptors from cellular organelles to the synaptic membrane. Kinesins are nanomotors that anterogradely transport the cargo using microtubule tracks across the neurons. Various members of the kinesin family, including KIF17, KIF11, KIF5b, and KIF21a, regulate the intracellular transport of NMDA receptors. Pharmacological targeting of these ATP-driven nanomotors could be a useful tool for manipulating the NMDAR functioning. It could provide the potential for the development of a novel strategy for the management of chronic pain.



KEYWORDS: *Kinesin nanomotors, NR2B, KIF17, mLin-10, Cargo binding, Chronic pain*

1. INTRODUCTION

Acute pain resulting from tissue injury acts as an alarm for the body and serves a protective function. However, acute pain can transit to a chronic state due to the pathophysiological changes at multiple sites along the peripheral and central nervous systems. Chronic pain can be debilitating and is usually associated with significant distress and suffering. Everyone experiences pain at some point during their whole life span. In terms of pain, seeking medical care possesses a worldwide prevalence range from 1% to 76% that varies demographically,[1] whereas the proportion of chronic pain in developing countries was estimated to be 18%.[2] On average, the prevalence in developing countries is more than that of developed countries. Generally, in the elderly population, the prevalence of chronic pain is reported to be 25−85%.[3] The economic burden of chronic pain accounts for more than that of cardiovascular diseases and cancer. The available treatment options for chronic pain are limited and are ineffective in a significant proportion of patients. In addition, most approved therapies are associated with considerable adverse effects that result from their off-target effects at CNS sites. Thus, there is an urgent need to develop new efficacious molecular entities with a higher therapeutic safety index.

Research from the past few decades that focused on the neurobiology of chronic pain has substantially increased the understanding of the disease. Various ionotropic channel receptors are widely implicated in the pathophysiology of various disorders and hold the glory of therapeutical implications. The recent decade in pain research has witnessed a shift from the discovery of direct exogenous ligands to alternate strategies, such as modulating receptor synthesis, maturation, and transport processes.[4−6]

The role of the *N*-methyl-D-aspartate (NMDA) receptors system in chronic pain is well supported with preclinical evidence.[7−10] However, the direct blockade of NMDA receptors failed in clinical trials for chronic pain.[11] This suggests that targeting NMDA receptors after their insertion into the synaptic membrane may not be an optimal approach. Meanwhile, the potential of this receptor system cannot be ignored due to the high rate of success in basic research studies.[9,12−14] Thus, developing an indirect approach to target this receptor system could provide a new series of therapeutics for the management of chronic pain. We have previously

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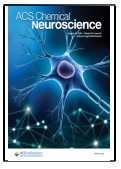

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