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A mimetic of the mSin3-binding helix of NRSF/REST ameliorates abnormal pain behavior in chronic pain models

Hiroshi Ueda [a], Jun-ichi Kurita [b], Hiroyuki Neyama [a], Yuuka Hirao [b], Hiroyuki Kouji [c,d], Tadashi Mishina [c], Masaji Kasai [c], Hirofumi Nakano [c,e], Atsushi Yoshimori [f], Yoshifumi Nishimura [b,*]

[a] Department of Pharmacology and Therapeutic Innovation, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki 852-8521, Japan
[b] Graduate School of Medical Life Science, Yokohama City University, 1-7-29 Suehiro-cho, Tsurumi-ku, Yokohama 230-0045, Japan
[c] PRISM BioLab Co., Ltd., 4259-3, Nagatsuda-cho, Midori-ku, Yokohama 226-8510, Japan
[d] Oita University, Faculty of Medicine, 1-1, Idaigaoka, Hasama-machi, Yufu-city, Oita 879-5593, Japan
[e] Kitasato University, Kitasato Life Science Institute, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan
[f] Institute of Theoretical Medicine, Inc., 4259-3, Nagatsuda-cho, Midori-ku, Yokohama 226-8510, Japan

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ABSTRACT

The neuron-restrictive silencing factor NRSF/REST binds to neuron-restrictive silencing elements in neuronal genes and recruits corepressors such as mSin3 to inhibit epigenetically neuronal gene expression. Because dysregulation of NRSF/REST is related to neuropathic pain, here, we have designed compounds to target neuropathic pain based on the mSin3-binding helix structure of NRSF/REST and examined their ability to bind to mSin3 by NMR. One compound, mS-11, binds strongly to mSin3 with a binding mode similar to that of NRSF/REST. In a mouse model of neuropathic pain, mS-11 was found to ameliorate abnormal pain behavior and to reverse lost peripheral morphine analgesia. Furthermore, even in the less well epigenetically defined case of fibromyalgia, mS-11 ameliorated symptoms in a mouse model, suggesting that fibromyalgia is related to the dysfunction of NRSF/REST. Taken together, these findings show that the chemically optimized mimetic mS-11 can inhibit mSin3-NRSF/REST binding and successfully reverse lost peripheral and central morphine analgesia in mouse models of pain.

Epigenetics is a challenging but promising topic for better understanding of genetic memory, and much literature has been published on the epigenetic regulation of chronic pain,[1] which involves an aspect of pain memory. The design of chemicals to affect the genetic/epigenetic regulation of key molecules involved in pain processing is therefore expected to provide a new medicinal solution for intractable chronic pain.[2,3]

Nerve injury-induced neuropathic pain is characterized by negative signs such as unique hyposensitivity to C-fiber pain fiber stimulation and loss of peripheral morphine analgesia, as well as conventional positive signs including hyperalgesia and allodynia.[4] Recent studies have revealed that the negative factors are attributed to epigenetic silencing of the C-fiber $Na_v1.8$ channel and μ-opi-

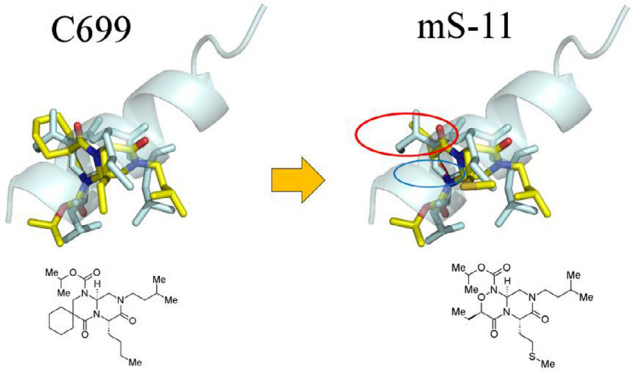

Fig. 1. Structural comparison of the NRSF/REST helix with C699 and mS-11. The spirocyclohexyl group in C699 was changed into an ethyl group in mS-11 to improve structural similarity to the natural isoleucine; in addition, a pyrimidine ring in C699 was changed into an oxadiazine ring to improve solubility.

Abbreviations: MOPr, μ-opioid receptor; NRSF, neuron-restrictive silencer factor; REST, repressor element 1 silencing transcription factor; HDAC, histone deacetylase; nrse, neural restrictive silencer element; re1, repressor element 1; PAH, paired amphipathic helix; STD, saturation transfer difference; HSQC, heteronuclear single quantum coherence; CSP, chemical shift perturbation; ICS, intermittent cold stress; IPS, intermittent psychological stress; PWL, paw withdrawal latency; pSNL, partial sciatic nerve ligation.

* Corresponding author.
E-mail address: nisimura@yokohama-cu.ac.jp (Y. Nishimura).

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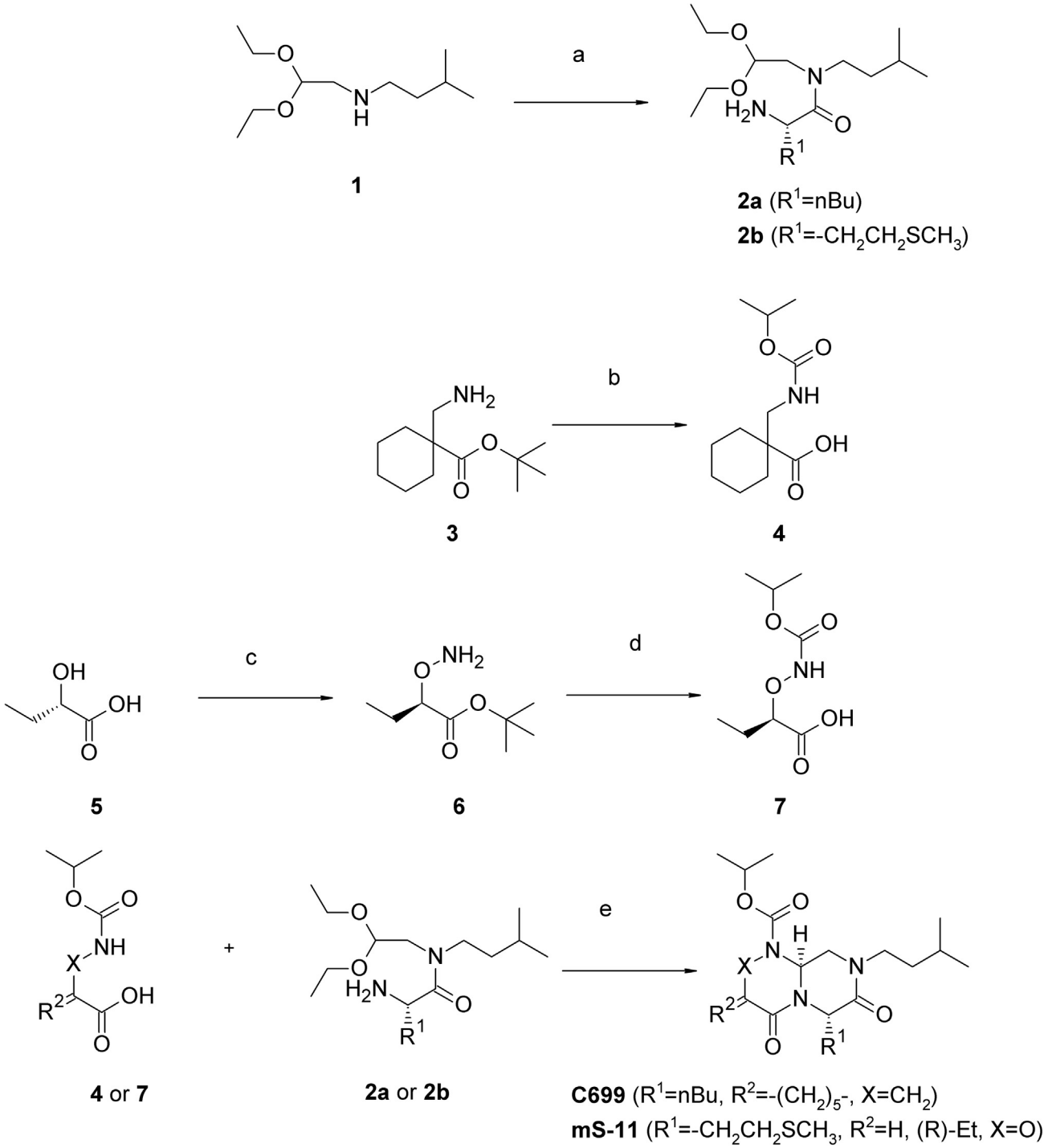
oid receptor (MOPr) through mechanisms involving a repressor, neuron-restrictive silencing factor (NRSF; also known as repressor element 1 silencing transcription factor, REST),[5] together with histone deacetylase (HDAC).[6,7]

NRSF/REST was originally identified as an essential transcriptional repressor that inhibits the expression of neuronal genes in both non-neuronal cells and neuronal progenitor cells. It binds to a 21-base-pair DNA element, termed neuron-restrictive silencer element (nrse) or repressor element 1 (re1), of which approximately 1900 copies are found in the human genome.[8] The N-terminal repressor domain of NRSF/REST recruits a corepressor, mSin3,[4] which consists of four paired amphipathic helix (PAH) domains, termed PAH1-PAH4. The structure of the PAH1 domain of mSin3B, an isoform of mSin3, in complex with the N-terminal repressor domain of NRSF/REST was previously determined by NMR: the minimal repressor domain of NRSF/REST is an intrinsically disordered domain containing 44–54 N-terminal amino acid residues that form an α helix after binding to the mSin3B PAH1 domain



Scheme 1. Synthesis of C699 and mS-11. The following reagents and conditions were used in each step. (a) (i) Cbz-norLeu-OH or Fmoc-Met-OH, HATU, DIEA, CH_2Cl_2 (DCM); (ii) H_2, Pd-C, MeOH or piperidine, DCM. (b) (i) i-PrOCOCl, Et_3N, DCM; (ii) HCOOH. (c) (i) AcCl (ii) *t*-BuOH, DMAP, DCC, DCM; (iii) K_2CO_3, MeOH, H_2O; (iv) *N*-hydroxyphthalimide, Ph_3P, DEAD, THF; (v) hydrazine haydrate, MeOH. (d) (i) i-PrOCOCl, pyridine, CH_3CN; (ii) HCOOH. (e) (i) HATU, DIEA, DCM or DMT-MM, NMM, MeOH; (ii) HCOOH.