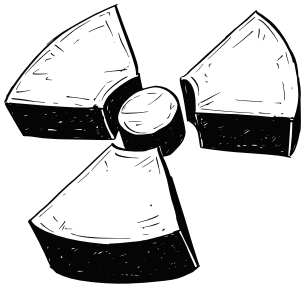
ARALEZ BIO

THE NONCANONICAL CHRONICLE

Q2 2024 | Vol. 1

Q2 2024: Contents



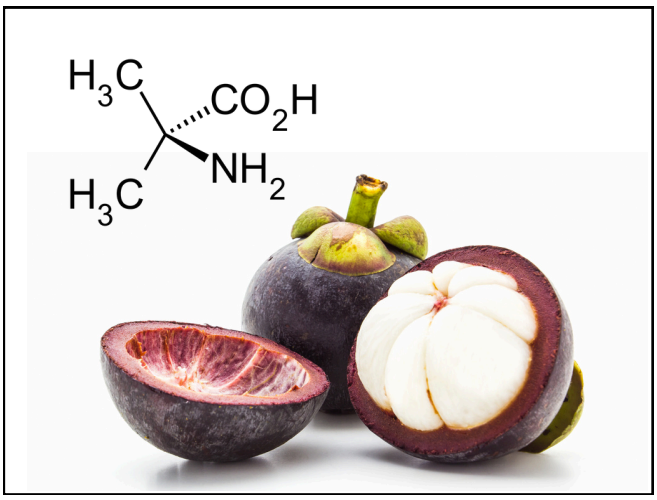
So Hot Right Now: Radiopharmaceutical Acquisitions

1. AstraZeneca acquires Fusion (June 2024)
2. Novartis to acquire Mariana (May 2024)
3. BMS acquires RayzeBio (Feb 2024)
4. Lilly acquires POINT Biopharma (Dec 2023)

ncAA Fun Fact

In addition to being the defining amino acid of peptaibiotics, a stabilizing residue in popular GLP-1 analogs, and a helix-inducing amino acid, α-aminoisobutyric acid (Aib) is highly abundant in the late stages of the mangosteen's ripening process.

doi.org/10.1016/j.jbiosc.2017.08.013



ncAAs IN THE NEWS

Industry Update

Clinical Readouts

June 2024

Sapience Therapeutics reported their Phase 2 readout for ST101, a protease-stable peptide antagonist of the transcription factor, C/EBP-beta, for advanced solid tumors. The clinical study demonstrated uptake across the BBB, increased macrophage and T-Cell infiltration into brain tumor tissue, and a shift from M2 (immune-suppressive) to M1 (immune-active) macrophages. Monotherapy achieved durable partial responses and stable disease. The peptide was well tolerated and safe in combination with radiotherapy and temozolomide.

Entera Bio presents Phase I PK and PD data in healthy adult males after oral administration of their PTH(1-34) peptide tablet to treat hypoparathyroidism. The company reports "significant systemic exposure" of the unmodified peptide that is formulated for oral dosing using their N-Tab™ technology.

Start-Up Deal Recap

- **Insamo**
$12 million in seed capital
- **Unnatural Products**
$220M Merck deal for macrocyclic peptides following a Series A raise of $32M
- **Amide Technologies**
$7.5 million Series A Extension
- **Pearl Bio**
$1 billion in biobucks from Merck
- **Vilya Inc.**
$50 million in Series A
- **Peptyde Bio**
Acquired by Invaio

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Interesting Reads

FORMATION OF EXTRATERRESTRIAL PEPTIDES AND THEIR DERIVATIVES

S. A. Krasnokutski, C. Jäger, Th. Henning, C. Geffroy, Q. B. Remaury, P. Poinot
Sci. Adv. 10 (6) (2024)

Serge A. Krasnokutski and co-authors describe peptide bond formation via the polymerization of aminoketenes (NH2CH=C=O) in the presence of water to form short chains of Gly. The work supports the possibility of peptide synthesis on star dust and has implications for delivery of peptides to prebiotic Earth via comets and meteors.

DIVERSIFICATION OF PHAGE-DISPLAYED PEPTIDE LIBRARIES WITH NONCANONICAL AMINO ACID MUTAGENESIS AND CHEMICAL MODIFICATION

J. Trae Hampton and Wenshe Ray Liu
Chemical Reviews. 124 (9), 6051-6077 (2024)

In this review, the authors walk through the progression of genetic code expansion in phage to enable the incorporation of noncanonical amino acids and review post-translational chemical modifications to increase peptide diversity and introduce conformational constraint. An interesting element of the publication is the extent of functional group chemical space that can be incorporated into phage using mutant/engineered tRNA synthetases, though the scaffolds are primarily Lys, Phe, and Tyr that have been adorned with groups ranging from trifluoromethyl to boronic acid.

BLAST FROM THE PAST:

ALPHA-AMINOISOBUTYRIC ACID, BETA-HYDROXYLEUCINE, AND GAMMA-METHYLPROLINE FROM THE HYDROLYSIS OF A NATURAL PRODUCT

G. W. Kenner and R. C. Sheppard
*Nature 181, 48 (**1958**).*

In this 1-page publication from Nature in 1958, Kenner and Sheppard reveal structural analysis of the antibiotic, I.C.I. No. 13959, using elementary analysis, IR spectroscopy, optical rotation, and paper chromatography. This peptide, isolated from yeast, had *in vivo* activity against *Trypanosoma congoles*. Three noncanonical residues were identified, namely alpha-aminoisobutyric acid (Aib), beta-hydroxyleucine, and gamma-methylproline. The authors note that Aib "has not previously been obtained from natural sources; its closest relatives are alpha-methylserine, also a component of an antibiotic, and 1-aminocyclopropane carboxylic acid, which has recently been found among the free amino acids of pears and cowberries."

HIGHLIGHTS

ncAA Highlight

This quarter, we highlight halogenated amino acids. Halogenated amino acids don't just occur in the chemist's flask; they are also found in nature and can influence a variety of biochemical pathways as well as be incorporated into defense peptides. From a medicinal chemistry perspective, halogenation is a tool to alter lipophilicity, membrane permeation, pharmacokinetics, and pharmacodynamics (1).

An interesting example of SAR by fermentation is the switch from 5-chlorotryptophan to 5-bromotryptophan in NAI-107, a lantibiotic produced by the bacterium, Actinoallomurus (2). Bromination was achieved by incubation with KBr. The brominated product, NAI-108, has a different antimicrobial activity profile compared to NAI-107 (3).

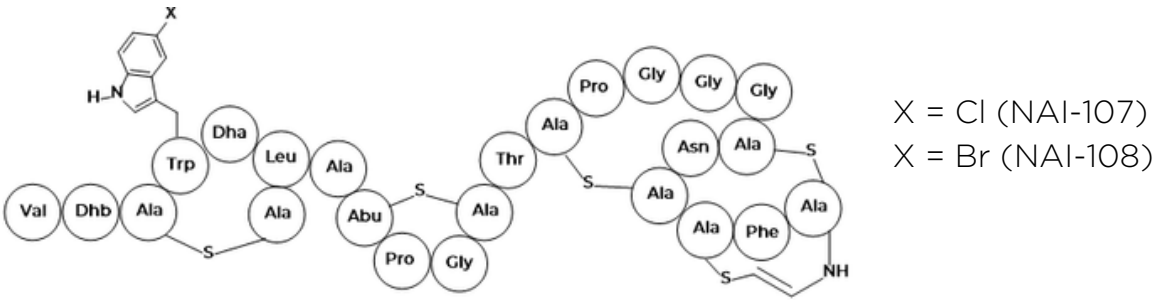

Figure 1. Structure of NAI-107/108.

As one navigates the structures of approved therapeutic peptides, chlorophenylalanine stands out as one of the more common halogenated amino acids and is prevalent in gonadotropin-releasing hormone antagonists (4). Chlorophenylalanine, in one form or another, is found in peptides like abarelix, ganirelix, degarelix, and cetrorelix (Figure 2).

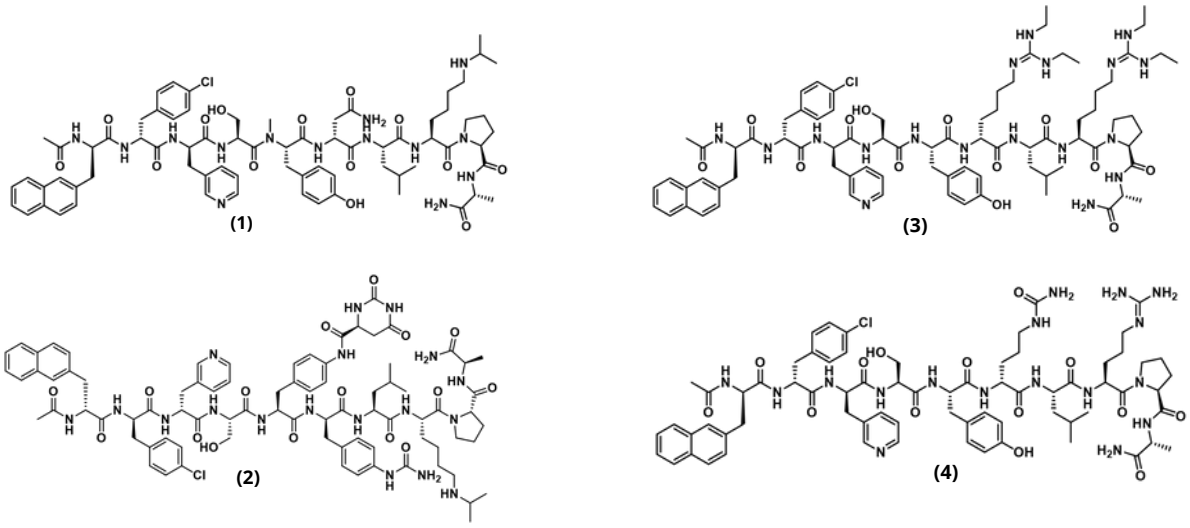

Figure 2. Structures of abarelix (1), degarelix (2), ganirelix (3), and cetrorelix (4).

HIGHLIGHTS

Of the halogens, chlorine and fluorine are consistently present in FDA approved therapeutics (5). The incorporation of fluorine can have profound effects on electronics and alter folding, PK, affinity, and other peptide properties (6). The orally active peptides, MK-0616 from Merck (7) and Luna18 from Chugai (8), both contain fluorinated amino acids among a plethora of other noncanonical amino acids (ncAAs).

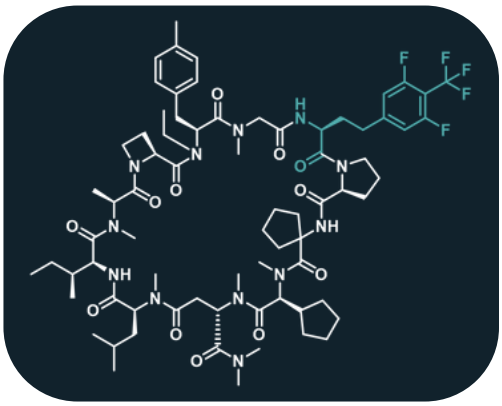

Figure 3. Structure of Luna18.

Small molecule medicinal chemists have long harnessed the power of diverse halogen interactions to optimize molecular attributes (9). As we expand our repertoire of ncAAs, the peptide medicinal chemist will increasingly gain access to that diversity enabling even finer tuning of molecular interactions in peptide-based therapeutics.

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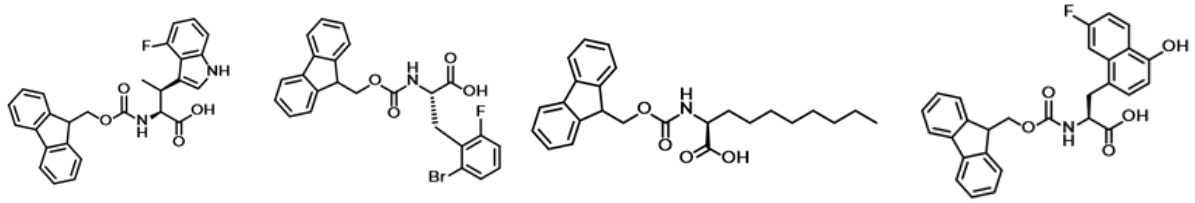

Explore diverse ncAAs at www.aralezbio.com

UPCOMING EVENTS

We Are Presenting!

Wendy Hartsock
Director of Strategic Partnerships

Jimmy Mann
Account Executive

We Are Attending!

boulderpeptide.org

zED Events

Virtual and in-person educational & networking events for scientists.

Did you miss zED Event #4? Check out the next issue (Q3) of the Noncanonical Chronical for a recap.

Event from Thursday, June 20th, 2024
Peptide transformation: fostering diversity in amino acid chemistry and peptide libraries.

Residue-selective peptide cyclization strategies enabled by in situ generated N4-linked triazoline-3,5-diones

Dr. Andrew G. Roberts, Asst. Prof.,
University of Utah
Department of Chemistry

Light-directed chemical synthesis of massively parallel peptide libraries and its application towards oral peptide therapeutics

Dr. Lauren Goodrich-Berto, PhD,
Vice President, Therapeutic Discovery,
Nimble Therapeutics

NONCANONICAL INSIGHTS

Scratching the Surface of Non-canonical Peptide Space

By Christopher Ing

"Peptide design is like finding a needle in a haystack!" If you work with peptides, you've likely thought this, even if you haven't shouted it aloud as I frequently do. The space of all possible peptides is vast, and the strategies available to optimize molecules within this space are scarce; they inevitably require a blend of skill, luck, and "Tony Stark"-level resources. Peptide design is a challenge nearly as old as solid-phase peptide synthesis itself (1), but the rapid pace of technological development invites us to step back and evaluate the modern design process and explore potential paths for improvement.

In drug discovery, optimizing within the peptide chemical space is driven by the desire to meet a defined target-candidate profile through iterative rounds of design-make-test-analyze (DMTA) cycles. Exploring this space can be daunting. For instance, the chemical space of a linear peptide of 8 amino acids, composed of any of the 20 natural amino acids, comprises approximately 25 billion possibilities (2.56 x 10^10). The size of non-canonical amino acid space for a single position may be estimated by noting that 110.9 million stereoisomers can be enumerated with only 11 heavy atoms (2). In practice, with only 100 non-canonical amino acids, the size of non-canonical space far exceeds the screening capacity of the highest throughput methods for typical peptide lengths. Nevertheless, these screening methods are the best we have and can be used to search peptide space in complementary ways, broadly categorized into two approaches: exploration and exploitation.

We define the exploration of chemical space as a "hypothesis-free" search, distributing chemical diversity broadly across a peptide of fixed length. This can be accomplished through display screening or systematic residue scanning, which provides a foundation for discovering structure-activity relationships, which in turn reveal the importance of side chain and backbone chemistry on biological activity. Techniques like residue scanning with alanine, as well as proline, enantiomeric amino acids, N-alkyl, lactam, hydrocarbon staple, and aza-amino acids, have long been employed to delve deeper into specific pockets of chemical space without making any system-specific assumptions (3). Conversely, the exploitation of chemical space is a "hypothesis-driven" search targeting chemical diversity in specific regions based on emerging structure-activity relationships or structural models (4). This method might involve testing hundreds of non-canonical amino acids at a single position or making extensive modifications to the peptide scaffold, such as truncation or cyclization. But given the vast chemical space of peptides, are these approaches sufficient?

Even in successful peptide design programs, discussions on chemical space exploration are infrequent. The quality and effectiveness of these searches can be quantified by the breadth of property space explored, the number of calendar days to advance a program, and the overall design success rate.

NONCANONICAL INSIGHTS

DMTA cycle efficiency has previously been reported in small molecule development (5), but it's the peptide search trajectories which underscore recurrent areas for methodological enhancement. For instance, peptide discovery projects could benefit from unique design hypotheses (through the increased availability of "rare" non-canonical amino acids), broader property space exploration (via enhanced property prediction models), increased hit diversity (through multi-point mutations or scaffold hopping), and improved design success rates (through higher accuracy structural models). An abundance of structural data, advances in computational methods, and accessible computing power hold promise for making drug discovery more efficient and notably more "hypothesis-driven" (6), but peptide-specific solutions remain essential. While compelling examples of peptide ligand design using these methods exist (7), we must remember that we've still only scratched the surface of peptide chemical space.

Our team has presented research related to this topic at the "Chemical Computing Group UGM & Conference 2024", entitled "Efficiently traversing non-canonical sequence space for interpretable peptide drug design".

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About the Author

ProteinQure

Chris Ing is the Co-founder and Chief Scientific Officer of ProteinQure, a biotechnology company focused on the development of next-generation peptide-based therapeutics. He received a PhD in Biochemistry at the University of Toronto focusing on structural biology and biophysics of ion channels, enzymes, and membrane receptors. He currently leads computational biology methods development and applications to internal drug discovery at ProteinQure, based in Toronto, Canada.

NONCANONICAL INSIGHTS

Noncanonicals: New Technology for Molecular Camouflage

By Charles Johannes

Molecular chameleons are programmable multifunctional modalities that help to address the long-standing challenge of delivering Bro5 macromolecules inside cells and developing a balance of permeability and solubility for oral therapeutics. Here is an excellent review entitled "Molecular chameleons in drug discovery" (1) by researchers from Uppsala University. A primary design challenge is the synchronization of sufficient rigidity to optimize target binding and obviate unwanted off-target effects with enough flexibility to manage NH bonds to enable passage through the membrane. A grand challenge still remains to prospectively predict permeable and pharmacologically relevant macrocyclic peptides.

A recent publication from researchers at Merck, ASTAR, and Karolinska (2) describes some design rules for helical peptides and provides a nice example of the optimization for selectivity. Here, the authors develop a hyper-stabilized alpha-helical peptide antagonist of MDM2/X that has distinct *in cellulo* pharmacological advantages over clinical small molecules and Aileron's clinical candidate ALRN-6924 (3). However, the hyper-stabilized alpha helix in this case, despite the amide backbone NH bonds being managed, is not passively permeable.

Another macrocyclic peptide structure referred to as a "doughnut shape" can also provide opportunities to access chameleonic-like properties. Researchers from UnNatural Products (UNP) recently published a DNA-encoded library approach to discovery leads against MDM2 (4). One advantage of this approach is the ability to incorporate all non-canonical amino acids to discover new chameleon space. While the peptide UNP-6457 showed impressive binding, it was not permeable in a PAMA assay. There are valuable learnings from the structural analysis of the binding and I look forward to seeing how UNP leverages their platform to convert this to a permeable chameleon-like scaffold.

A longer-term advantage is that this new data can be used to develop improved machine learning tools to prospectively help with design space. There is significant interest in capturing this value and building sufficient data to train our models. A consortium to harness world expertise and interest in peptide therapeutics is the Peptide Drug Hunting Consortium (5). In the literature, a recent deep learning method called Multi_CycGT (6) uses an already publicly available database (7). To help our computational toolbox, matched molecular pairs for permeability that do not lose their propensity to bind to the desired target without off-target different target binding with different conformations will be required.

NONCANONICAL INSIGHTS

Underpinning all of the approaches above is the use of non-canonical amino acids as a key strategy to develop new modalities and technologies for innovative targeted medicines(8). Aralez Bio (9) has the technology to supply research quantities of non-canonicals and develop a sustainable, scalable supply of these building blocks for future medicines.

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About the Author

EPOC Scientific

Charles Johannes, Ph.D., is currently Chief Scientist at EPOC Scientific LLC and former VP of Exploratory Chemistry at Fog Pharma. Charles has deep expertise in peptides, small molecules, and chemistry platforms in biotech and pharma and has applied over 25 years of experience in the development of new modalities with an interest in targeted protein degradation, molecular glues, and ML/AI.

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Fun Fact:
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Clinical Readouts:
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2. Entera Bio: https://investors.enterabio.com/news-releases/news-release-details/entera-bio-present-phase-1-data-first-class-pth1-34-peptide

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Amide Technologies: https://www.amidetech.com/
Pearl Bio: https://www.pearlbio.com/
Vilya Inc: https://vilyatx.com/
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