ARALEZ BIO

CHRONICLE

THE NONCANONICAL

Q1 2024 | Vol. 1

Q1 2024: Contents

"Aralez Bio has unlocked the potential at Nimble to comprehensively tune peptides at tryptophan positions in ways that were not previously feasible... We look forward to seeing what additional non-canonical amino acids Aralez Bio can unlock in the future!" - Lauren Goodrich-Berto, PhD

ncAA Fun Fact

>50%

of approved peptide drugs contain at least one noncanonical amino acid.

ncAAs IN THE NEWS

Industry Update

“FDA's early review finds no evidence linking Novo, Lilly weight-loss drugs to suicidal thoughts.”

Source: Fierce News

Interesting reads:

In this review (1), Marcos and colleagues examined the differences between canonical and noncanonical amino acids (ncAAs), described classes of ncAAs, and discussed the impact of ncAAs on peptidomimetic structure and stability.

1. Castro, T.G.; Melle-Franco, M.; Sousa, C.E.A.; Cavaco-Paulo, A.; Marcos, J.C. Non-Canonical Amino Acids as Building Blocks for Peptidomimetics: Structure, Function, and Applications. Biomolecules, 2023, 13, 981. https://doi.org/10.3390/ biom13060981

Scientists at Roche report a new class of tethered macrocyclic peptide antibiotics, exemplified by their lead candidate, zosurabalpin (2). Unlike previously known antibiotics, these peptides target the lipopolysaccharide transporter of Gram-negative bacteria, enabling efficacy against pathogens resistant to existing therapies.

2. Zampaloni, C., Mattei, P., Bleicher, K. et al. A novel antibiotic class targeting the lipopolysaccharide transporter. Nature 625, 566–571, (2024). https://doi.org/10.1038/s41586-023-06873-0

HIGHLIGHTS

Customer Highlight

Rapid access to diverse chemical space is critical for identifying peptide hits and transforming them into clinical candidates. One of the most successful strategies in peptide discovery is the incorporation of noncanonical amino acids. However, access to noncanonical amino acids has been extremely costly, even with significantly restricted chemical space. This is especially true for building blocks in the d-configuration.

Aralez Bio has unlocked a vast toolbox of noncanonical amino acids, enhancing Nimble's platform and allowing us to tune peptides in ways that were not previously feasible. Our scientists are excited to access new amino acid space for the discovery and optimization of peptide ligands. The icing on the cake is that the enzymatic process is significantly greener than "traditional" amino acid synthesis.

We look forward to seeing what additional noncanonical amino acids Aralez Bio can unlock in the future.

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

Nimble Therapeutics harnesses light-directed chemical synthesis to construct massively parallel peptide libraries that exploit vast amino acid chemical space for the discovery of novel peptide therapeutics.

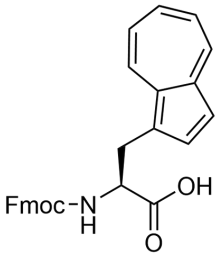
https://nimbletherapeutics.com/

nimble therapeutics

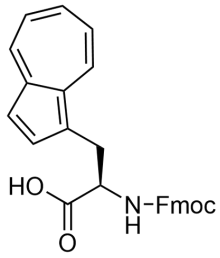
HIGHLIGHTS

ncAA Highlight

This quarter's highlight is β-(1-azulenyl)-alanine. The synthesis of this fluorescent noncanonical was published by Klem et al. in 1989 (1) and subsequently by the Moroder group in 2000 (2). The Arnold lab reported the enzymatic synthesis in 2020 using TrpB (3). Korendovych and team used β-(1-azulenyl)-alanine to study protein-protein interactions by exploiting the weak environmental dependence on fluorescence (4), and the Walport group incorporated this fluorophore into macrocycles to study permeability with minimal impact on the physicochemical properties of the peptide (5). This blue residue has also been incorporated into tryptophan-rich antimicrobial peptides (6).



Fmoc-β-(1-azulenyl)-L-alanine [AE]



Fmoc-β-(1-azulenyl)-D-alanine [AE]

1. LeRoy H. Klem , Bruce S. Hudson & Jennifer J. Lu (1989) Preparation of azulene derivatives: an amino acid, dicarboxylates, an isothiocyanate, and related compounds, Organic Preparations and Procedures International, 21:5, 633-641, DOI: 10.1080/00304948909356428
2. Loidl, G.; Musiol, H.J.; Budisa, N.; Huber, R.; Poirot, S.; Fourmy, D.; Moroder, L. Synthesis of beta-(1-azulenyl)-L-alanine as a potential blue-colored fluorescent tryptophan analog and its use in peptide synthesis. J. Pept. Sci. 2000, 6, 139–144, DOI: 10.1002/(SICI)1099-1387(200003)6:3<139::AID-PSC240>3.0.CO;2-6
3. Watkins, E. J., Almhjell, P. J., and Arnold, F. H. (2020). Direct enzymatic synthesis of a deep-blue fluorescent noncanonical amino acid from azulene and serine. ChemBioChem 21, 80–83, DOI: 10.1002/cbic.201900497
4. Moroz, Y.S.; Binder, W.; Nygren, P.; Caputo, G.A.; Korendovych, I.V. Painting proteins blue: Beta-(1-azulenyl)-L-alanine as a probe for studying protein-protein interactions. Chem. Commun. 2013, 49, 490–492, DOI: https://doi.org/10.1039/C2CC37550H
5. Wu, Y.; Bertran, M.T.; Rowley, J.; Calder, E.D.D.; Joshi, D.; Walport, L.J. Fluorescent Amino Acid Initiated de novo Cyclic Peptides for the Label-Free Assessment of Cell Permeability. ChemMedChem 2021, 16, 3185–3188, DOI:10.1002/cmdc.202100315
6. D'Souza, A.R.; Necelis, M.R.; Kulesha, A.; Caputo, G.A.; Makhlynets, O.V. Beneficial Impacts of Incorporating the Non-Natural Amino Acid Azulenyl-Alanine into the Trp-Rich Antimicrobial Peptide buCATHL4B. Biomolecules 2021, 11, 421, DOI: 10.3390/biom11030421

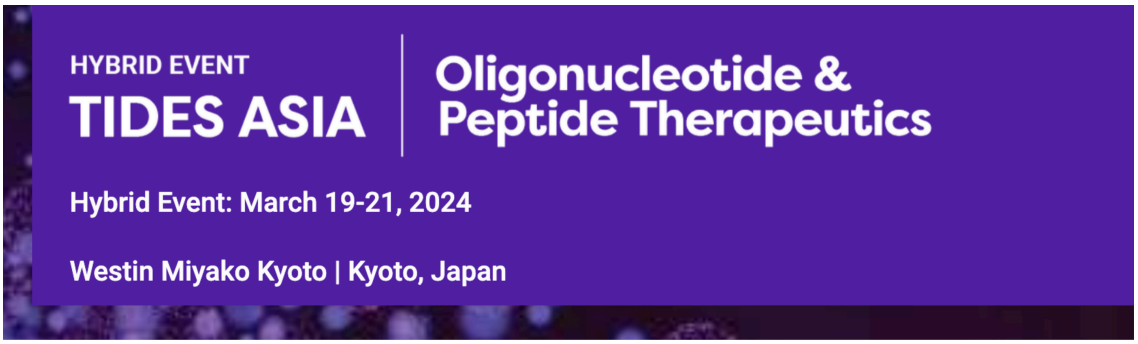
UPCOMING EVENTS

We Are Attending!

Wendy Hartsock, PhD,
Director of Strategic Partnerships

Paul Yu-Yang, PhD,
Director of Technical Operations

TIDES ASIA, Osaka, JA



Drug Discovery Chemistry, San Diego, CA

East Coast TIDEtalks, Boston, MA

zED Events

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

zED Event #3: Virtual talks

Wednesday, March 27th, 2024

10:00-11:00 PDT | 13:00-14:00 EDT | 17:00-18:00 UTC

Moderated by Dr. Michael Kopach, Assoc. VP, Eli Lilly

Register through Zoom

Minimal Protection Strategies in SPPS

John Phipps,
Sr. Director BD, CPC Scientific

CPC scientific
Tides Partner. Concept to Commercial.

Advancing the Boundaries of CEPS

Dr. Leendert van den Bos
CEO, EnzyTag

EnzyTag
Traceless Ligation

NONCANONICAL INSIGHTS

Importance & Opportunity for Noncanonical amino acids

By Charles Johannes

Our curiosity to understand natural biological processes has inspired numerous scientific innovations, such as the development of display technologies and directed evolution, which were awarded the Nobel Prize in 2018. Of interest to this commentary is the elegant simplicity of how nature generates complexity from simple building blocks that encode genetic information, synthesize proteins, and then orchestrate cellular processes.

The notion of incorporating innovative building blocks and harnessing cellular processes that generate novel properties and functions is a huge opportunity for medicine. Recent progress to expand the genetic code and harness biology to synthesize novel proteins via directed evolution and contemporary approaches have been highlighted in a recent review by Wang et al. (1) and in a classic overview from the Tirrell group (2).

Another lesson from nature is the implementation of post-translational modifications to control the function of proteins and regulate cellular processes. Therefore, incorporating chemical handles for programmed post-translational modifications can provide exponential diversity to modulate function through specific divergent chemistry to conjugate imaging agents, radiotherapeutics, or other tailor-made ligands for targeting.

While this can be achieved in a limited manner with biological processes and evolved enzymes, chemists have the ability to fully synthesize proteins, mini-proteins, or complex macrocyclic peptides with secondary structural motifs such as α-helices and β-turns.

For example, fast-flow and automated synthesis technologies (3) attempt to rival the ribosome and make completely noncanonical proteins, such as all-D proteins, that can be leveraged in mirror image phage display. Recently, this has been commercialized by Amide Technologies (4).

Fast flow has also been achieved for the synthesis of phosphoramidite morpholino oligomers (PMOs), as described by Pentelute and colleagues (5). These chemical processes can incorporate AI and ML to enable deep learning, and more innovations are on the way.

NONCANONICAL INSIGHTS

Incorporation of specifically designed building blocks to prospectively identify novel diagnostic tools, therapeutics, materials, and research tools all require compatible technologies in biology, chemistry, and engineering. At the heart of these limitless opportunities lies the ability to synthesize and have key noncanonical amino acid building blocks at the ready and scale. A recent review by Hickey et al. (6) highlights the prospects and challenges.

Aralez Bio harnesses directed evolution to develop enzymes that can sustainably synthesize noncanonical amino acids. This empowers us to decrease development costs as well as provide key noncanonical linchpin amino acids for SAR and diversity-driven explorations.

References:
1. https://pubs.acs.org/doi/abs/10.1021/acs.chemrev.1c00260
2. https://www.sciencedirect.com/science/article/abs/pii/S0958166903001629
3. https://www.science.org/doi/10.1126/science.abb2491
4. https://www.amidetech.com/
5. https://pubs.acs.org/doi/10.1021/acscentsci.0c00979
6. https://pubs.acs.org/doi/10.1021/acsmedchemlett.3c00037?ref=pdf

EPOC Scientific

About the Author

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.