Insulin Analogues Derived from Venom Insulins are Potential Treatments for Type 1 Diabetes

Chemical synthesis and evaluation of insulins derived from a venom insulin of the cone snail *Conus geographus*

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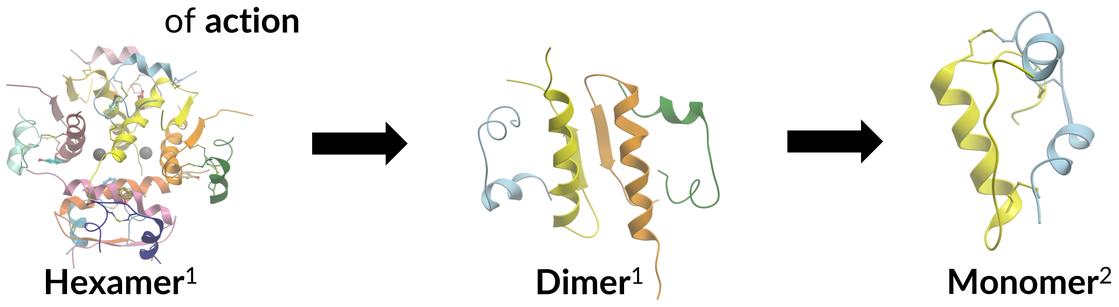
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Introduction

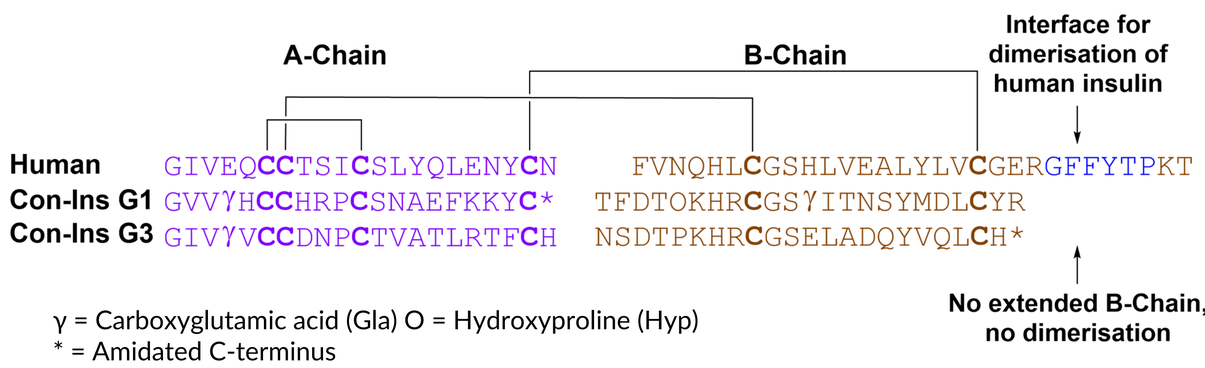
- **Human insulin**, and **analogues** thereof:
  - **Essential** for **managing type 1 diabetes** (**T1D**)
- **Major limitation** of insulin therapy:
  - **Delayed onset** and **prolonged action leading** to **increased risk** of **hyper-** and **hypoglycemia**, respectively, because:
    - **All insulin formulations** (human and analogues) are **hexameric**
    - **Hexamer** to **dimer** to **monomer** dissociation at the injection site is **slow**
    - **Monomer formation** is required for **activation** of **the human insulin receptor (hIR)**

  → Overall kinetics result in **slow onset** and **offset** (clearance) of **action**



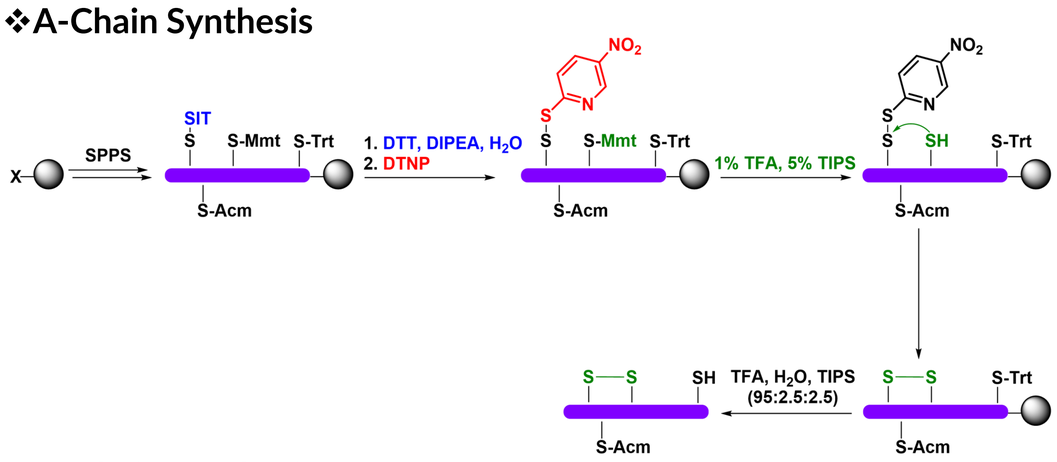
- **Novel insulins**, **Con-Ins G1** and **G3**,[3,4] found in the **venom** of ***Conus geographus*** (**pictured**), a fish-hunting cone snail:
  - **Rapidly lower blood glucose** in fish prey
  - **Monomeric**
  - **Potent agonists** of the **hIR**
  - **Scaffolds** for the **development** of **ultra-fast acting insulins**



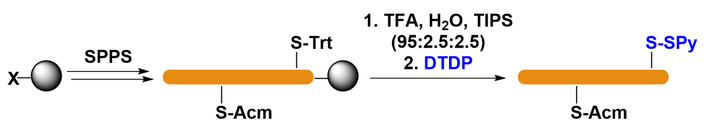


Insulin Synthesis

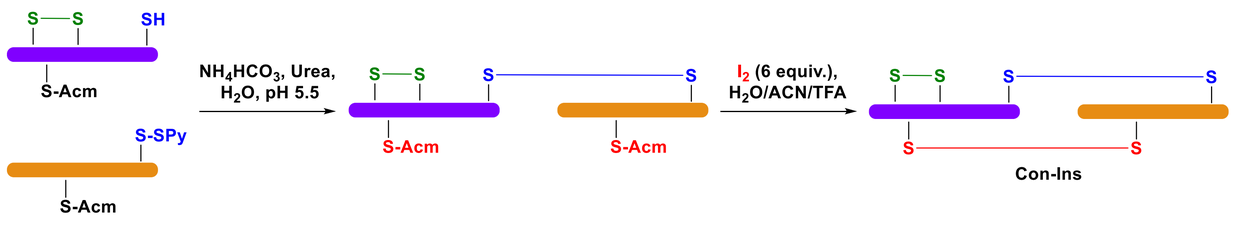
❖A-Chain Synthesis

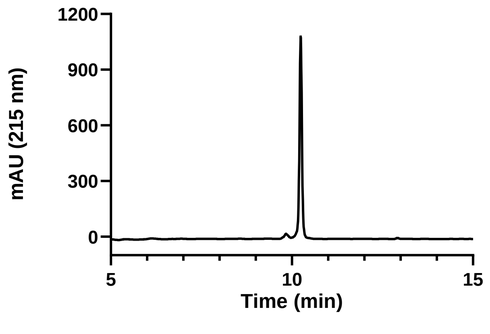


❖B-Chain Synthesis

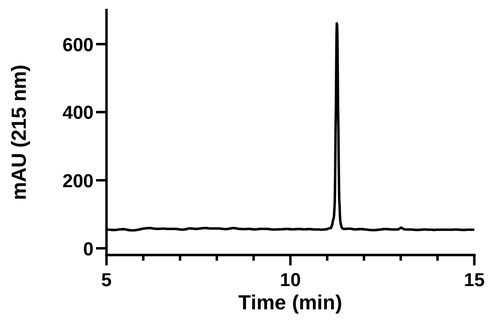


❖A-B Conjugation and Oxidation (One Pot Reaction)





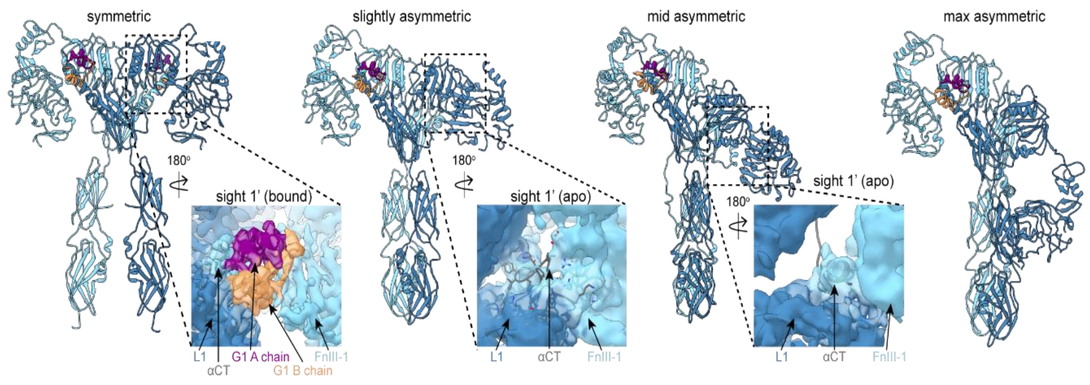
Con-Ins G1
Purity: 96.0%
Overall yield: 0.5%
83-fold yield improvement
compared to literature synthesis[3]



Con-Ins G3
Purity: 97.3%
Overall yield: 4.7%
684-fold yield improvement
compared to literature synthesis[4]

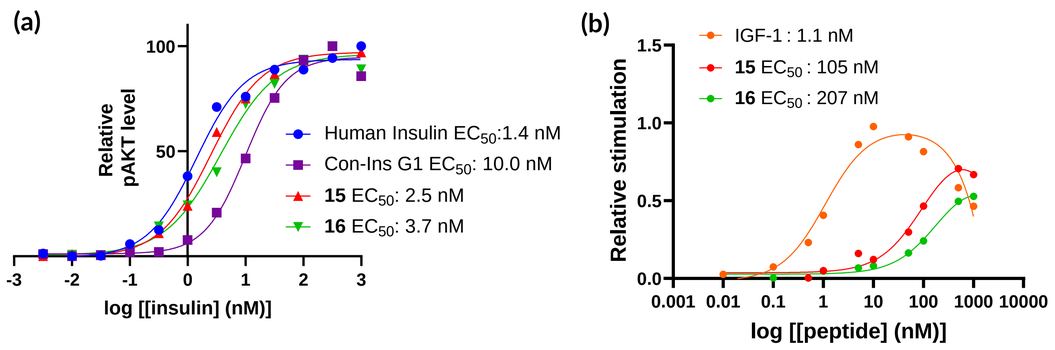
Structural Studies

- A **cryo-EM** structure of **Con-Ins G1** bound to the **hIR** was obtained
- The **hIR** has **two binding sites**: **site-1** and **site-2** as a dimer of αβ-protomers $(\alpha\beta)_2$, thereby having **four total binding sites**
  - **Con-Ins G1** binds to **only site-1**, even under **saturating conditions**. From the **ensemble** of the **ligand-receptor complex conformations**, Con-Ins G1 binds in both a **symmetric** and **asymmetric fashion** (**multiple hybrid states**) to **site-1**
  - **Human insulin**, however, binds to all **four binding sites** in **symmetric fashion** under **saturating conditions**



Biochemical Evaluation of 15 & 16

- The **cryo-EM** data provides **valuable** insight into **critical binding interactions** between **Con-Ins G1** and the **hIR**
  - **Seventeen** Con-Ins G1 **analogues** were **designed and synthesized**
  - The potencies of analogues were assessed in an **IR pAKT assay**
  - Two analogues, **15** and **16**, were identified with **potencies approaching human insulin**
  - **15** and **16 do not** strongly activate the **IGF-1R**, a **receptor** associated with **mitogenicity**
  - **15** and **16** retain the **monomeric** character of Con-Ins G1



(a) Activity of human Insulin, Con-Ins G1, **15** and **16** in a pAKT signaling assay at IR-B, **(b)** Activity of human Insulin, Con-Ins G1, **15** and **16** in a pAKT signaling assay at IGF-1R, **(c)** SV-AUC data for human Insulin, **15** and **16**

Future Directions

- **Additional biochemical and in vivo evaluation of 15 and 16:**
  - **Activation** of **Akt** versus **ERK** (biased signaling)
  - **Aggregation propensities** (monomeric insulins have a higher propensity to aggregate)
  - **Insulin tolerance test** (blood glucose lowering capacity) in a T1D model of:
    - **Mice**
    - **Minipig** (better model for subcutaneous injection)

References

1. PDB: 1AIO, **2.** PDB: 3I40, **3.** Safavi-Hemami, H., et al., Specialized insulin is used for chemical warfare by fish-hunting cone snails. *PNAS* **2015**, *112* (6), 1743-8. **4.** Ahorukomeye, P., et al., Fish-hunting cone snail venoms are a rich source of minimized ligands of the vertebrate insulin receptor. *eLife* **2019**, *8*, e41574.