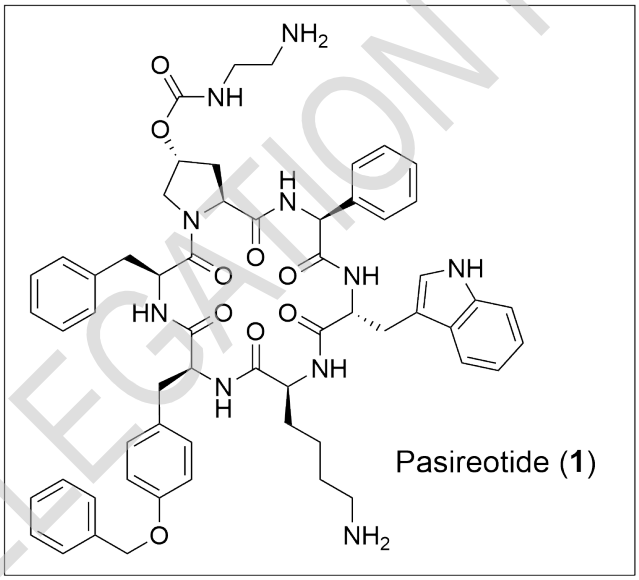
Switzerland - The Country of Pharmaceuticals

6% of total								
Question	10.1	10.2	10.3	10.4	10.5	10.6	10.7	**Total**
Points	2	11	6	6	6	6	2	**39**
Score								

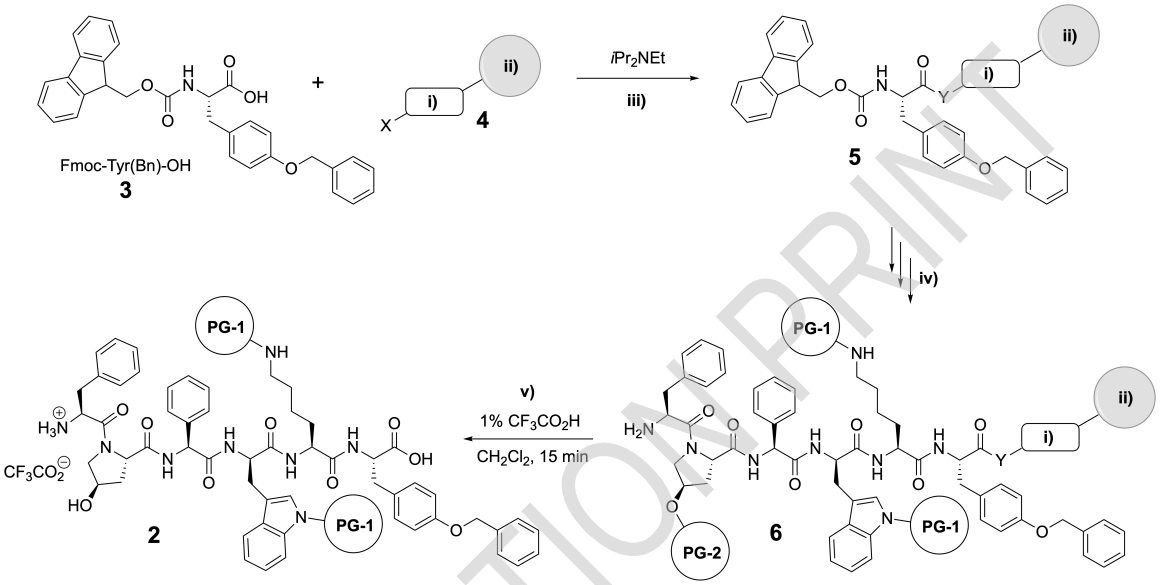
Pasireotide (**1**) is a peptide-based drug developed by the Swiss pharmaceutical company Novartis to treat the Cushing's disease.



Pasireotide (**1**)

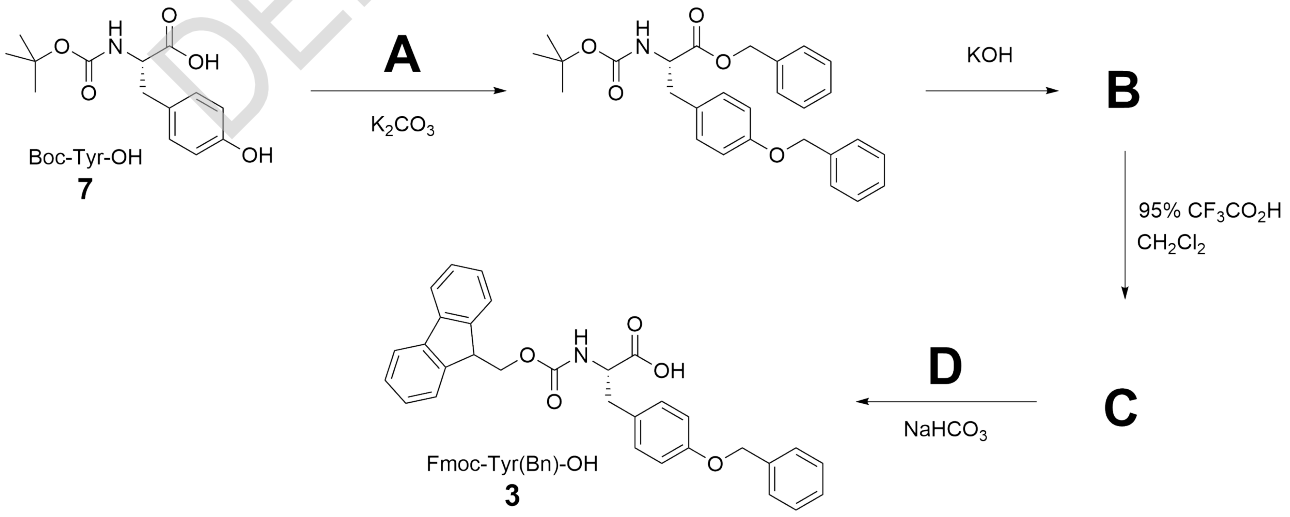
10.1 **Determine** the number of stereogenic centers (n) in Pasireotide (**1**). **Calculate** the total number of all possible stereoisomers (t) of Pasireotide (**1**). 2pt

Pasireotide (**1**) is a cyclic peptide. An advanced intermediate in its synthesis (linear peptide **2**) can be prepared by solid-phase peptide synthesis (SPPS) using the Fmoc/^{t}Bu strategy as shown in **Scheme 1**.



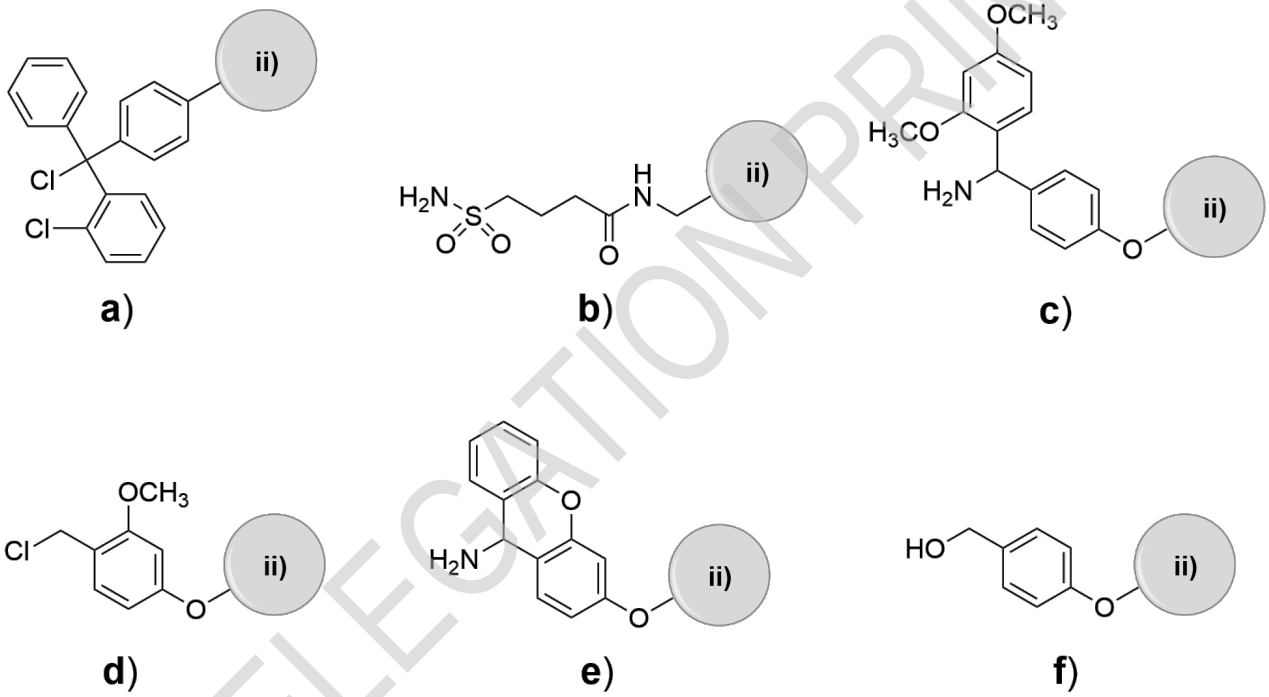
Scheme 1. SPPS of peptide **2**. i) Linker; ii) Resin; iii) Resin loading; iv) SPPS: repetition of 1. Fmoc deprotection 2. amino acid coupling + final Fmoc deprotection; v) Peptide cleavage from resin and deprotection of **PG-2**.

The synthesis starts with the preparation of Fmoc-Tyr(Bn)-OH (**3**) from Boc-Tyr-OH (**7**).



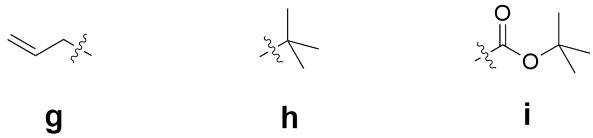
10.2	**Draw** reagents **A** and **D** and intermediates **B** and **C** in the synthesis of Fmoc-Tyr(Bn)-OH (**3**) as shown above.	11pt

The SPPS of intermediate **2** begins with attaching the Fmoc-Tyr(Bn)-OH (**3**) to a suitable resin-bound linker.



Scheme 2. Suggested structures of linkers **4**. ii) Resin; a) 2-Chlorotrityl-chloride linker; b) Safety-catch linker; c) Rink amide linker; d) SASRIN-chloride linker; e) Sieber amide linker; f) Wang linker.

10.3	**Choose** the linker(s) **4** that are appropriate for SPPS of peptide **2** according to **Scheme 1**. Incorrect answers will result in deductions of points but the total score may not be negative.	6pt



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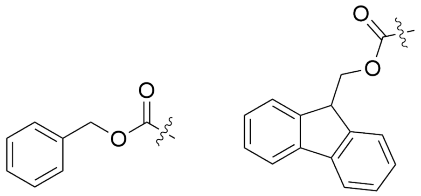

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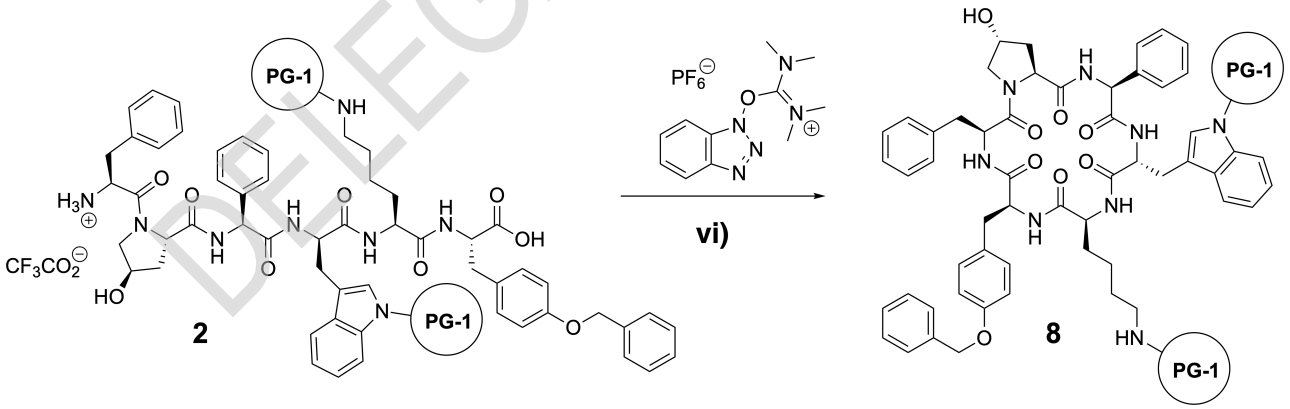
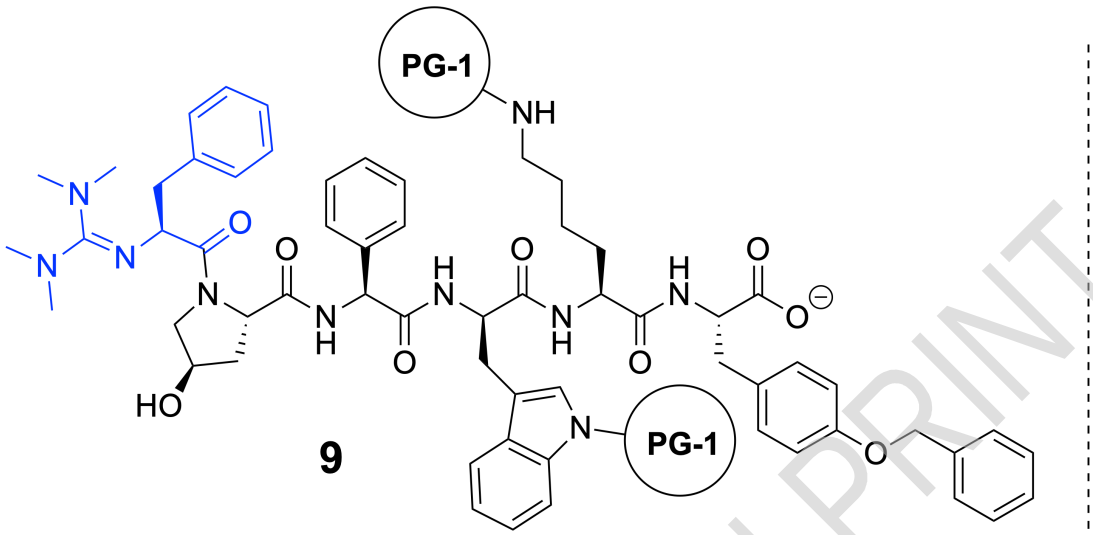
10.4 **Choose** the most suitable side-chain protecting groups **PG-1** and **PG-2** for SPPS of **2** according to **Scheme 1** that can be orthogonally cleaved in the presence of all other functional groups present in Pasireotide (**1**). Only one answer is correct for each of the protecting groups. 6pt

Next, linear peptide **2** undergoes an intramolecular coupling reaction to form cyclic peptide **8** according to the following scheme:



Scheme 3. vi) Base.

10.5 **Choose** the correct statement(s) on the answer sheet about the cyclization of peptide **2** to **8** shown above. Relevant structures are shown in **Scheme 4** below. Incorrect answers will result in deductions of points but the total score may not be negative. 6pt



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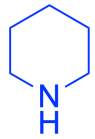

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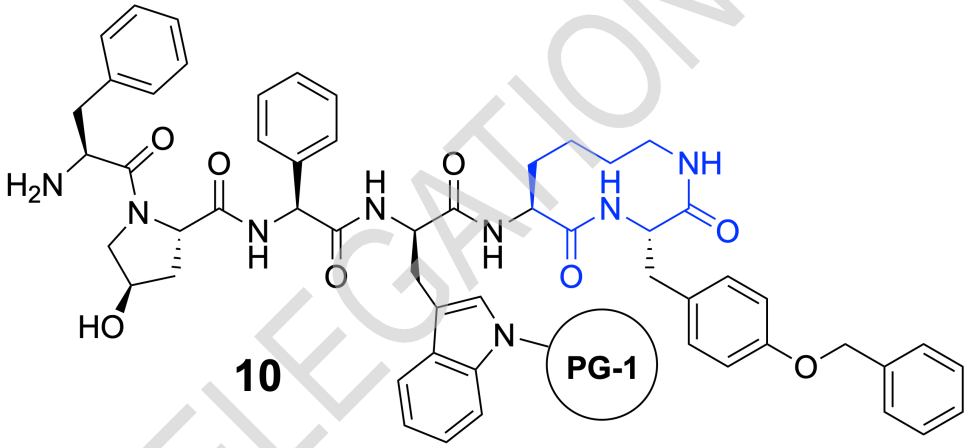

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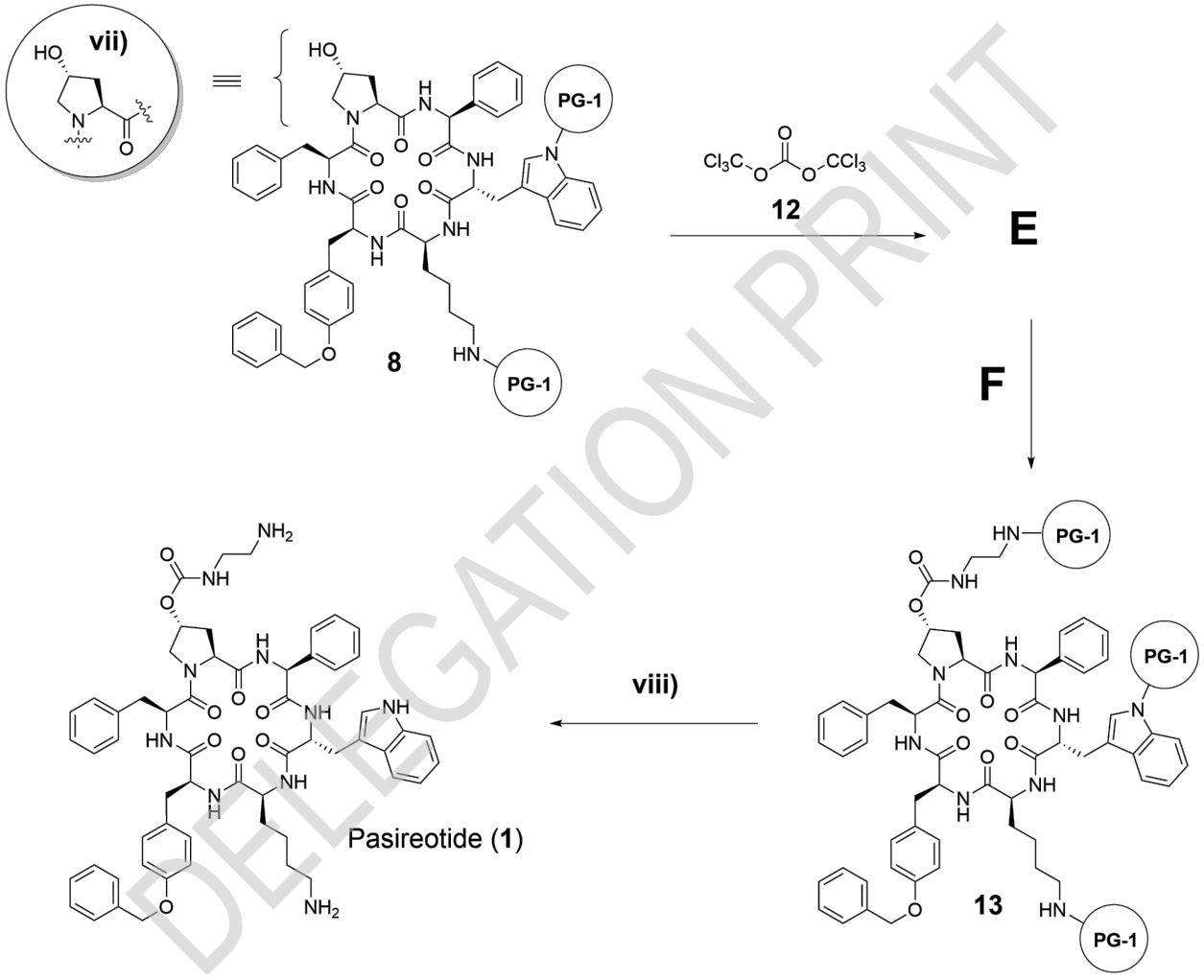
Scheme 4. Relevant structures for question **10.5**.

The last steps of the synthesis involve functionalization of the OH-group of the 4-hydroxyproline residue in **8**, followed by cleavage of all protecting groups to give Pasireotide (**1**).



Scheme 5. vii) can be used as simplification of **8**; viii) Cleavage of protecting groups.

10.6	**Draw** the structures of intermediate **E** (including stereochemistry) and reagent **F**. Abbreviate intermediate **8** as **(vii)** and the protecting group as **PG-1** in structures **E** and **F** as depicted in **Scheme 5**.	6pt

10.7	**Determine** the lowest possible molar equivalents of compound **12** that are necessary to enable full conversion of **8** to **13**.	2pt