Indoles are ubiquitous throughout the natural world. Examples of which include:
- The amino acid tryptophan (Trp, W).
- Plant hormones, eg auxin (growth hormone).
- Many natural products, eg psilocybin (hallucinogen found in magic mushrooms).
- A constituent of coal tar.

Indoles are also very important in the pharmaceutical industry and can be found in many drugs: eg pindolol (β-blocker used to treat arrhythmia).

1. Due to their importance, there are many reported syntheses of indoles. Please provide a mechanism for the following named reactions:

a) Bartoli indole synthesis:

b) Bischler-Möhlau indole synthesis:
c) Fisher indole synthesis:

\[
\begin{align*}
\text{Ph-NH}_2 & \quad \text{R}^1 \text{R}^2 \quad \text{H}^+ \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[
\text{Ph-NH}_2 + \text{R}^1 \text{R}^2 \rightarrow \text{Ph-N} = \text{N} - \text{R}^1 \text{R}^2
\]

d) Gassman indole synthesis:

\[
\begin{align*}
\text{Ph-NHCl} & \quad \text{S} \quad \text{Et}_3\text{N} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[
\text{Ph-NHCl} + \text{S} \rightarrow \text{Ph-N} = \text{N} - \text{R}
\]

e) Hegedus indole synthesis:

\[
\begin{align*}
\text{MeO}_2\text{C-Ph-NH}_2 & \quad \text{PdCl}_2(\text{MeCN})_2 \quad \text{THF, Et}_3\text{N} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[
\text{MeO}_2\text{C-Ph-N} = \text{N} \rightarrow \text{MeO}_2\text{C-Ph-N} = \text{N}
\]

f) Larock indole synthesis:

\[
\begin{align*}
\text{Ph-NH}_2 & \quad \text{HO-} \equiv \equiv \cdot \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[
\text{Ph-NH}_2 \rightarrow \text{Ph-N} = \text{N} - \text{OH}
\]

g) Madelung indole synthesis:

\[
\begin{align*}
\text{Ph-N} = \text{N} & \quad \text{R} \quad \text{n-BuLi, rt} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[
\text{Ph-N} = \text{N} \rightarrow \text{Ph-N} = \text{N} - \text{R}
\]

h) Mori-Ban indole synthesis:

\[
\begin{align*}
\text{Ph-N} & \quad \text{Br} \quad \text{CO}_2\text{Me} \\
\text{Ph} & \quad \text{Ph} \\
\end{align*}
\]

\[
\text{Ph-N} \rightarrow \text{Ph-N} - \text{CO}_2\text{Me}
\]

i) Nenitzescu indole synthesis (Remember this one from Fede's problems?):

\[
\begin{align*}
\text{Ph-N} & \quad \text{R}^1 \text{O} \\
\text{Ph-N} & \quad \text{R}^2 \text{H} \quad \text{R}^3 \text{CO}_2 \\
\end{align*}
\]

\[
\text{Ph-N} \rightarrow \text{Ph-N} - \text{O} - \text{H} \quad \text{R}^1 \text{R}^2 \text{R}^3
\]
Part 2:

Bristol-Myers Squibb recently published their work towards the development of corticotrophin-releasing factor-1 (CFT) receptor antagonists for the potential treatment of stress related disorders such as anxiety and depression.

They synthesised and tested a library of compounds with the general structure:

1. Please perform a retrosynthetic analysis for the following fragments:

   ![Fragment A](image1.png)  ![Fragment B](image2.png)

   **Fragment A**  **Fragment B**

2. What is the name of the core heterocycle within fragment B?

Staying in the field of neuroscience, another research group recently published their efforts towards the development of nicotinic acetylcholine receptor (nAChR) binders. This receptor has several sub-types which are implicated in numerous CNS disorders (cognitive dysfunction, neurodegenerative conditions, substance abuse and pain). The core structure of their library is shown below:

3. Please provide a synthesis of the following bicyclic fragment used to generate the library:

![Bicyclic Fragment](image3.png)
In a separate project, Bristol-Myers Squibb were interested in identifying CCR2 antagonists for the potential treatment of inflammation. They required a scalable, enantioselective synthesis of the following core intermediate:

![Core Intermediate Image]

4. Can you propose how this compound was synthesised, starting from cheap, readily available starting materials?

*Hints: There is a Curtius rearrangement near the beginning of the route; while the key transformation (shown below) is a 3-step-1-pot transformation:*

![Key Transformation Image]