M1 Development of Drug and Health Products

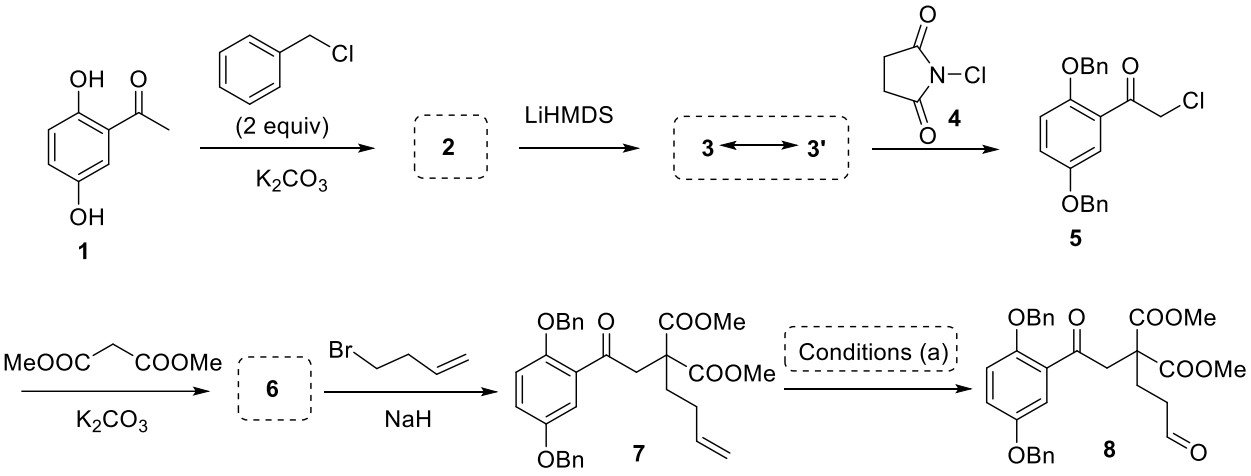
TU07 : The Medicinal Chemist's Toolbox

1st Session 2023-2024

Approaches of the Synthesis of Natural and Synthetic Drugs (around 1h30)

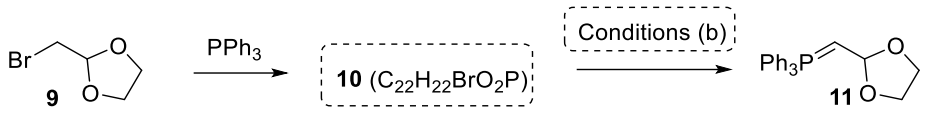
Exercise 1 (15 points)

This exercise concerns the total synthesis of (±)-applanatumol B, a meroterpenoid isolated from *Ganoderma applanatum*. The beginning of the synthesis is described below.



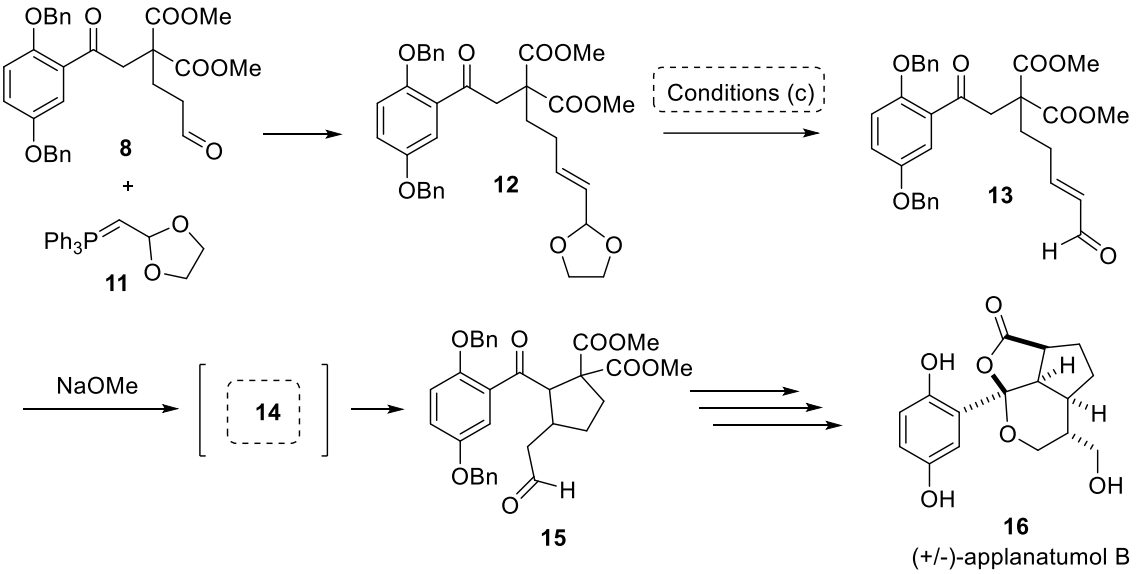
1. Give the structure of compound **2**
2. Give the structures of **3** and **3'**, which are mesomeric forms.
3. What is the nature of the chlorine atom linked to the nitrogen atom of **4**?
4. Give the structure of compound **6**.
5. What type of mechanism is involved in the reaction allowing access to compound **7** starting from reagent **6**?
6. Propose conditions **(a)** allowing access to compound **8** starting from reagent **7**. What type of reaction is it?

Next, the synthesis requires the preparation of the fragment **11**.



7. Give the structure of compound **10**.
8. Propose conditions **(b)** allowing access to compound **11** starting from reagent **10**. Is this new product nucleophilic or electrophilic?

Having scaffolds **8** and **11** in hands, they are next combined as described below:

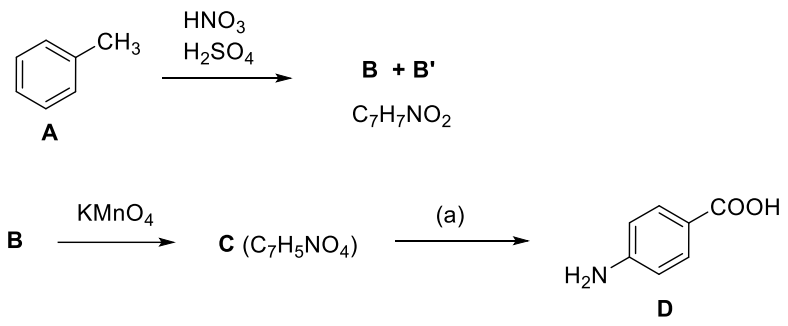


9. Reaction between compound **8** and **11** leads to compound **12**. What is the name of this reaction?
10. Propose conditions **(c)** allowing deprotection of reagent **12**
11. Give the structure of intermediate **14**. What is the role of NaOMe?
12. What is the name of the reaction leading to cyclization into **15**? Propose a mechanism explaining this transformation.

Exercise 2 (15 points)

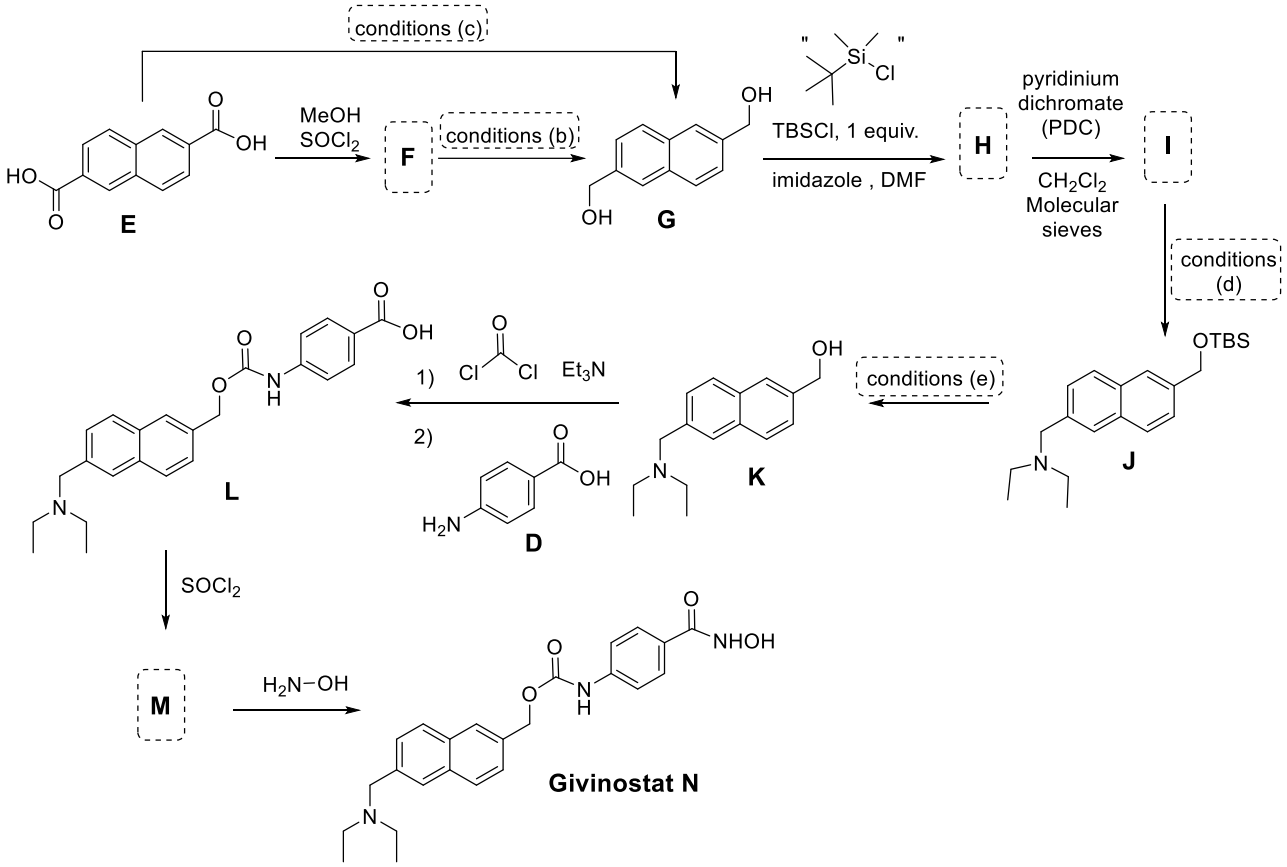
Givinostat (**N**) is a histone deacetylase inhibitor used to treat Duchenne muscular dystrophy. It was approved by the FDA in 2024. Givinostat can be synthesized from 4-amino benzoic acid (**D**) and naphthalene-2,6-dicarboxylic acid (**E**) following the steps below.

1st part: Synthesis of 4-amino-benzoic acid (D).



1. Give the structures of compounds **B** and **B'**, **B** being the major compound.
2. What is the relationship between **B** and **B'**?
3. Justify the substitution position for the transformation **A** -> **B** + **B'**.
4. Give the structure of compound **C**.
5. Give the conditions **(a)** to access compound **D**.

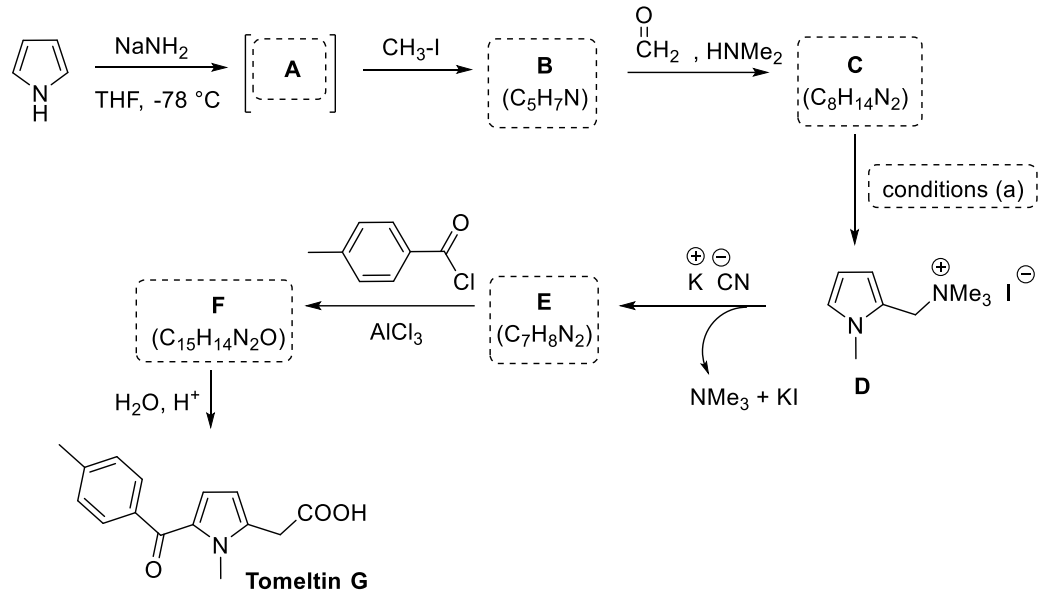
2nd part: Synthesis of Givinostat (N) from E



6. Give the structure of compound **F.**
7. Propose conditions **(b)** to transform compound **F** into **G**.
8. Give an alternative reagent to make **G** in one step from compound **E**.
9. Give the structures of compounds **H** and **I**.
10. Pyridinium dichromate is not a suitable reagent for an industrial-scale synthesis. Give one of the reasons.
11. Give an alternative reagent **(c)** that will fit better with an industrial scale-up.
12. Give conditions **(d)** to transform compound **I** into **J.**
13. Give conditions **(e)** to transform compound **J** into **K.**
14. Give the structure of compound **M**.

Exercise 2 (10 points)

Tomeltin **G** is a non-steroidal anti-inflammatory agent used to treat acute flares of various painful conditions and for long-term management of arthritis. Tomeltin is synthesized from pyrrole according to the following steps:



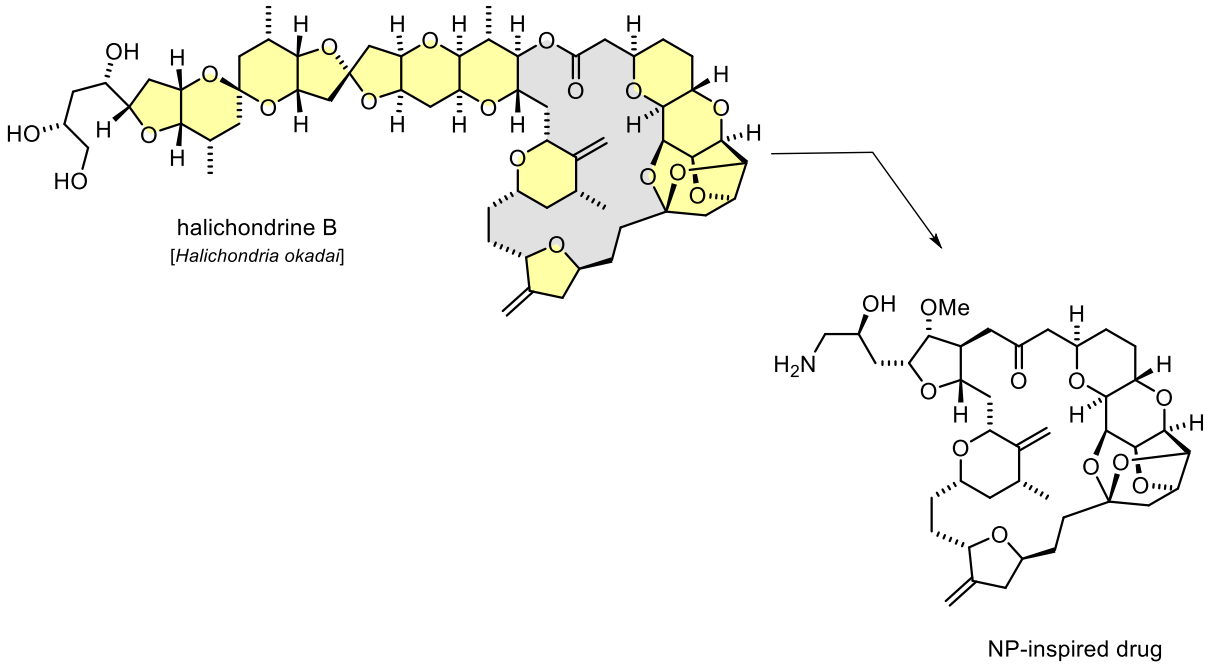
1. Give the structures of compounds **A**, **B** and **C**.
2. What is the name of the reaction allowing access to compound **C** starting from reagent **B**?
3. Give the conditions **(a)** to access compound **D**.
4. Give the structures of compounds **E** and **F**.
5. For the **E** to **F** transformation, give the name of the reaction, the type of mechanism involved and explain the regioselectivity observed.

Main Strategies of Drug Discovery (around 30 minutes)

Question 1: 10 points

1. What are the main sources of natural products ?

2. Halichondrine B is a natural product (NP) that served as an inspiration to design a drug.



A. What could you say about its (halichondrine B) natural origin?

B. What is the name of the drug inspired by this natural product?

C. Could you show the main structural modifications in the figure below (on the NP-inspired drug)? Explain the consequences of those modifications.

D. Which therapeutic strategy has been involved in the renewing interest in natural product drug discovery?

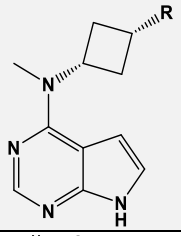
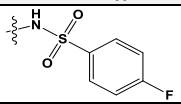
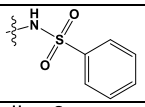
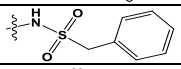
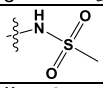
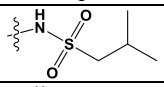
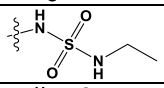
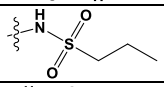
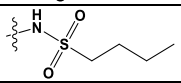
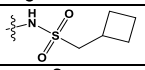
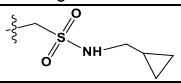
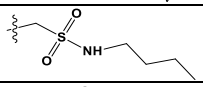
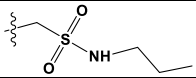
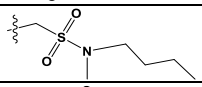
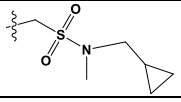
Question 2: 10 points

Context:

Treatment with abrocitinib has been associated with a dose-dependent reduction in serum biomarkers of inflammation [interleukin-31 (IL-31 and 22)] in atopic dermatitis. This is a recently discovered selective inhibitor of the Janus kinase (JAK) enzyme by Pfizer and was approved in 2022 by the FDA under the name CIBINQO®.

The **JAK1** enzyme possesses the broadest cytokine signaling profile among the JAK family members. Compounds that have activity against **JAK2** carry the potential for **anemia and thrombocytopenia**. Based on human genetic data, **loss of JAK3** function through mutation leads to **severe combined immunodeficiency**. The results of the inhibition of **JAK1** and **JAK2** kinases, as well as the stability with respect to human liver microsome (**HLM**) of molecules **1** to **14**, are summarized in **Table 1**.

Table 1. [a] *In vitro* biological and physical properties of sulfonamide-pyrrolopyrimidine analogues.

Cmpd N°	**Structure** 	**JAK1** IC_{50} (µM)	**JAK2** IC_{50} (µM)	**JAK2/JAK1** ratio	**HLM @ 1 µM Clint** (µL/min/mg)[a]	**LogD**[b] pH 7.4
1		0,003	0,240	80	39	2,8
2		0,1	0,2	2	58	2,8
3		0,092	1,99	22	24	2,6
4		0,09	1,29	14	<8	1,2
5		0,014	0,542	38	18	2,4
6		0,141	1,39	10	<8	1,6
7		0,02	0,90	45	<8	1,9
8		0,012	0,788	65	17	2,4
9		0,01	0,538	54	31	2,4
10		0,011	0,199	18	18	2,2
11		0,03	0,708	24	47	2,6
12		0,019	0,326	17	15	2,1
13		0,02	0,888	44	117	3,0
14		0,005	0,199	40	81	2,7

[a] *In vitro* stability in human liver microsomes. [b] Log D measured between octanol/water phosphate buffered to pH 7.4.

1. Among these molecules, which one appears to have the structure of the "**hit**" molecule? After briefly recalling the definition of so-called "**hit**" molecules, **justify your answer**.

2. Based on the analysis of **metabolic stability**, identify the **3 most stable molecules** and the **3 least stable molecules**. Is there a link between metabolic stability and the logD? Justify your answer.

3. After briefly recalling the definition of so-called "**lead**" molecules, which molecule would you select as the **lead compound** for **preclinical development**? **Justify your answer**.

4. Why did the authors of this work determine **the selectivity** of the molecules against the **JAK2** kinase? Justify your answer.

5. The **pyrrole nucleus** is present in all the molecules studied (Table 1); **propose two bioisosteric heterocycles** for this nucleus in the context of structural optimization. After briefly defining the concept of bioisosterism, specify the benefits of bioisosteric replacement.