Contrôle Continu CHIMIE HETEROCYCLIQUE

M2, Université Aix-Marseille, 2021-2022

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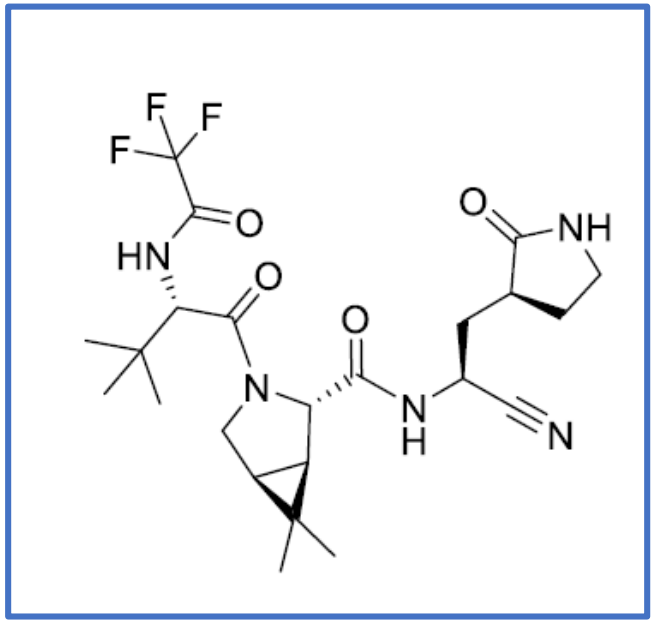
FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Authorizes First Oral Antiviral for Treatment of COVID-19

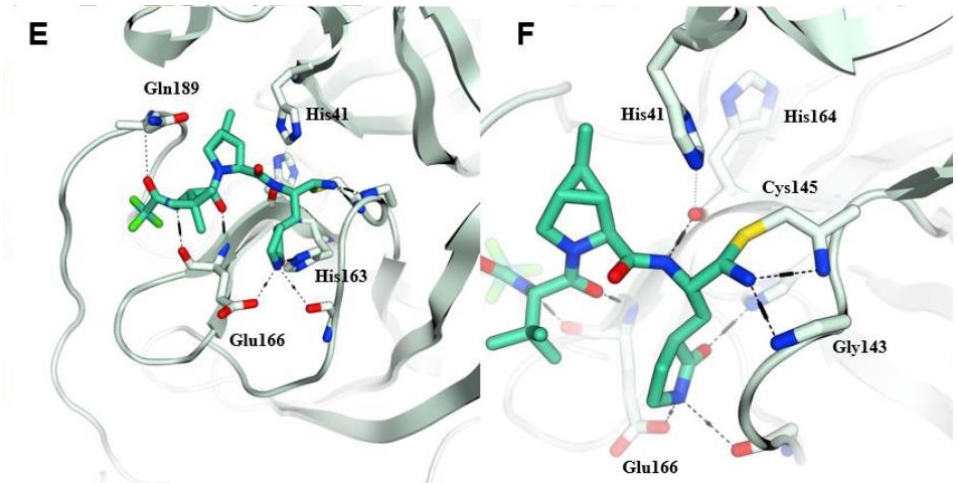
For Immediate Release: December 22, 2021

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for Pfizer's Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) for the treatment of mild-to-moderate coronavirus disease (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kilograms or about 88 pounds) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Paxlovid is available by prescription only and should be initiated as soon as possible after diagnosis of COVID-19 and within five days of symptom onset.

"Today's authorization introduces the first treatment for COVID-19 that is in the form of a pill that is taken orally — a major step forward in the fight against this global pandemic," said Patrizia Cavazzoni, M.D., director of the FDA's Center for Drug Evaluation and Research. "This authorization provides a new tool to combat COVID-19 at a crucial time in the pandemic as new variants emerge and promises to make antiviral treatment more accessible to patients who are at high risk for progression to severe COVID-19."

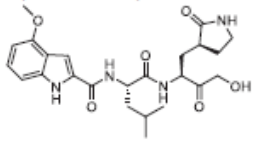
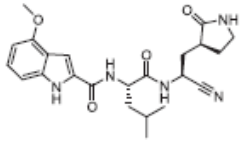
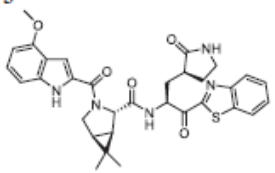
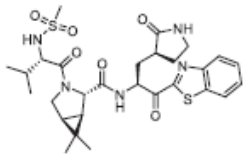
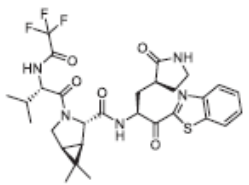
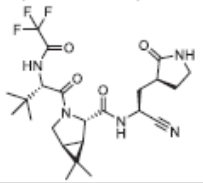


PAXLOVID® (PF-07321332)



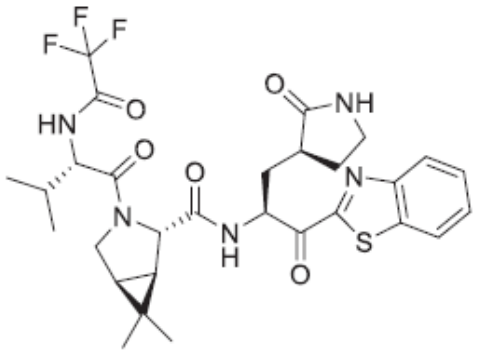
(E) SARS-CoV-2 Mpro–bound crystal structure of clinical candidate PF-07321332
(F) A reversible covalent Cys145 adduct is formed with the nitrile substituent

Réf. : Owen *et al.*, *Science* **374**, 1586–1593 (2021)

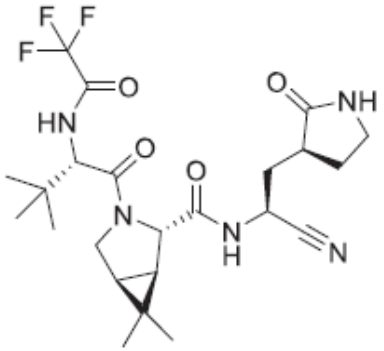
Number/Structure	SARS-CoV2 M^{pro} K_i (nM)*	VeroE6-enACE2 CPE EC_{50} (nM)†	MDCK-LE P_{app} (x 10^{-6} cm/sec)‡	HLM CL_{int} (µl/min/mg)§	Rat CL_p (mL/min/kg)¶	Oral F (%)¶#	F_a x F_g (%)¶††
1 (PF-00835231) 	0.271 (0.155 – 0.471, n=6)	231 (158 – 338, n=8)	< 0.207 ± 0.048 (n=6)	7.47 ± 0.88	27.0 ± 3.1	1.4 ± 0.8	3.3
2 	27.7 (18.4 – 41.7, n=5)	1364 (860 – 2164, n=15)	0.945 ± 0.281 (n=6)	34.4 ± 0.7	39.3 (37.0, 41.5)	7.6 (7.4, 7.8)	38
3 	230 (181 – 292, n=4)	5593 (3457 – 9051, n=8)	10.3 ± 2.4 (n=6)	337 ± 9	N.D.	N.D.	N.D.
4 	7.93 (3.62 – 17.4, n=5)	909 (557 – 1482, n=14)	1.56 ± 0.38 (n=6)	127 ± 3	42.9 (38.2, 47.6)	10 (7.5, 13)	84
5 	12.1 (8.05 – 18.1, n=7)	85.3 (76.5– 95.2, n=36)	13.1 ± 2.0 (n=8)	30.3 ± 0.6	31.0 (30.6, 31.4)	33 (33, 34)	100
6 (PF-07321332) 	3.11 (1.47 – 6.59, n=6)	74.5 (66.5 – 83.4, n=20)	1.71 ± 0.28 (n=4)	24.5 ± 0.2	27.2 (22.5, 31.9)	50 (30, 71), 34 ±19**	95, 65**

SAR (Structure-Activity Relationship) towards the discovery of PF-07321332

5

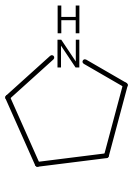


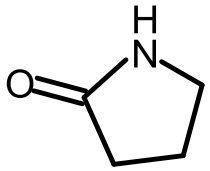
6 (PF-07321332)

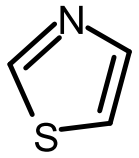


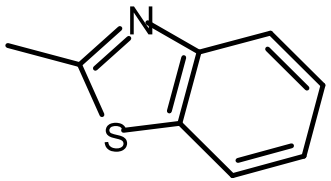
Faced with a choice between compounds **5** and **6**, the nitrile **6** was selected as the clinical candidate (referred to as PF-07321332) based on ease of synthetic scale-up, enhanced solubility that allowed for a simple formulation vehicle in support of pre-clinical toxicology, and reduced propensity for epimerization at the P1 stereocenter.

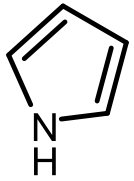
Nommez les hétérocycles suivants (**3 points**) :

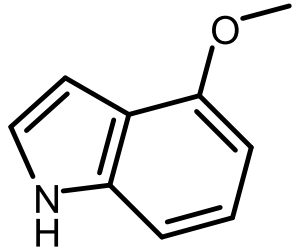




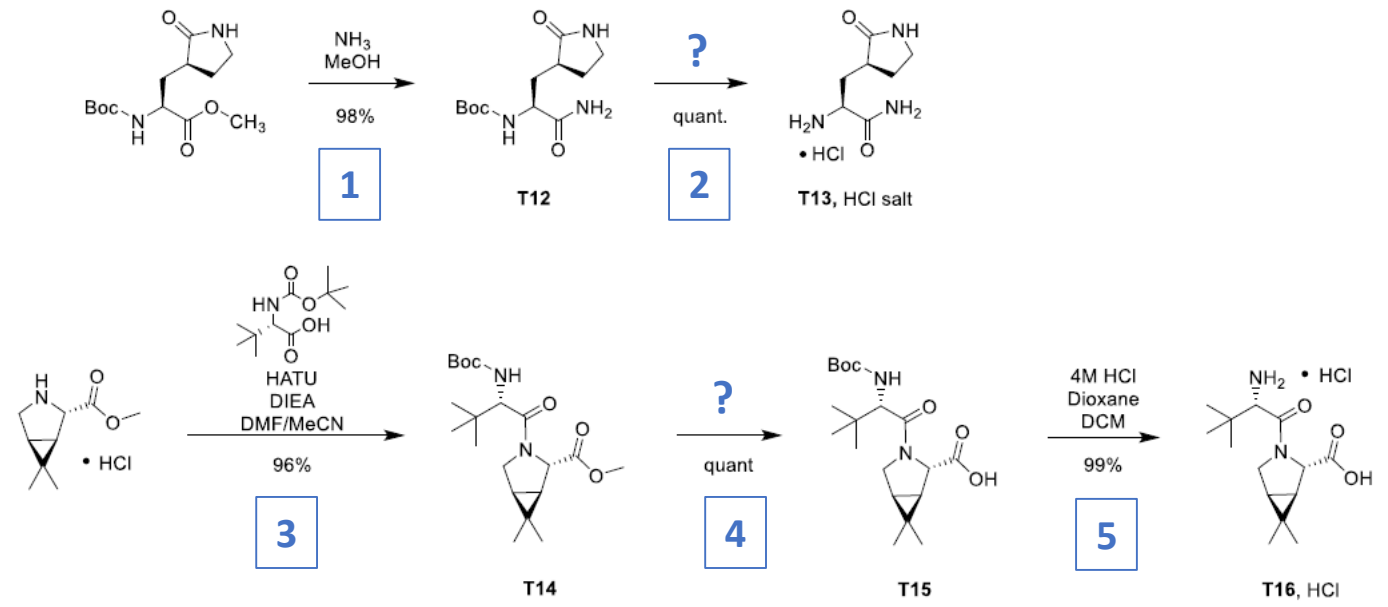








Synthesis of PF-07321332 (Compound **6**): Anhydrous, MTBE solvate form



1 Indiquez le type de transformation observée (**0.5 point**) : .....

2 Indiquez le type de transformation observée (**0.5 point**) : .....

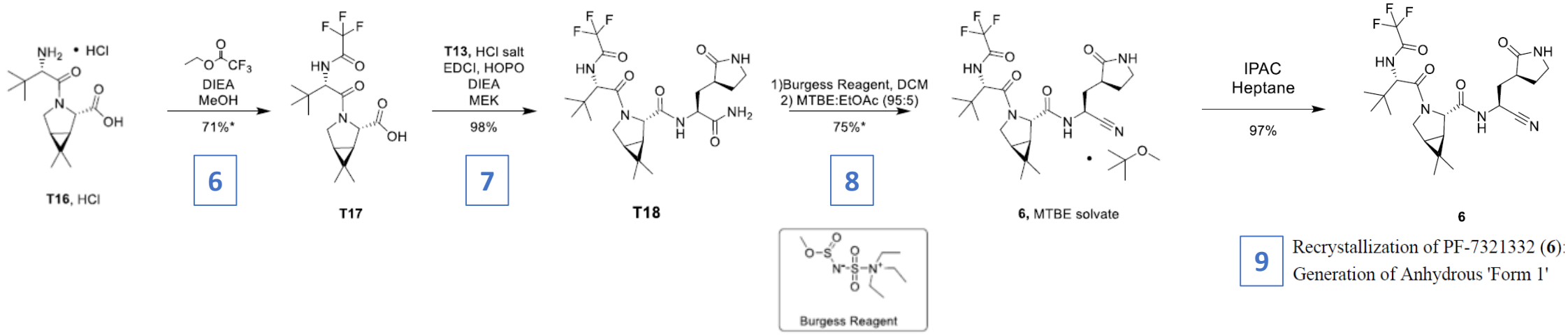
Proposez des réactifs permettant de faire la transformation voulue (**0.5 point**) : .....

3 Indiquez le type de transformation observée (**0.5 point**) : .....

4 Indiquez le type de transformation observée (**0.5 point**) : .....

Proposez des réactifs permettant de faire la transformation voulue (**0.5 point**) : .....

Synthesis of PF-07321332 (Compound **6**): Anhydrous, MTBE solvate form

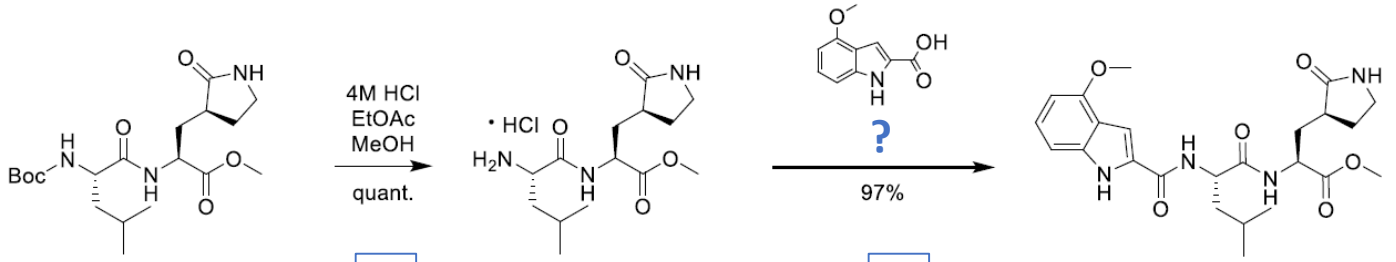


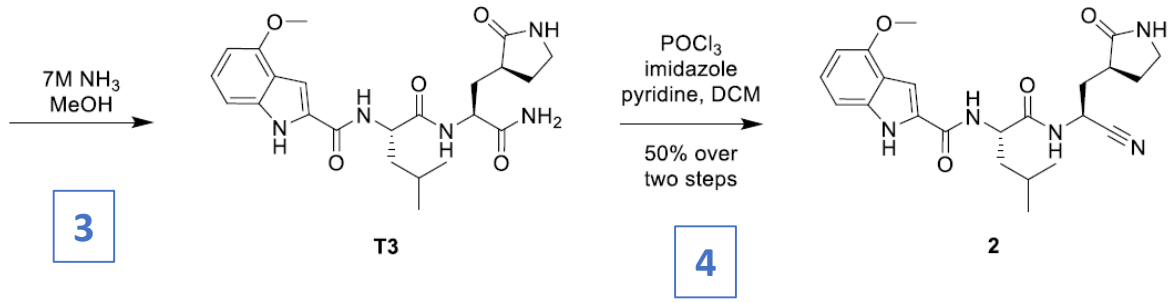
6 Indiquez le type de transformation observée (**0.5 point**) : .....

8 Indiquez le type de transformation observée dans la 1ère étape (**0.5 point**) : .....

Cette réaction peut aussi se faire en présence de $POCl_3$ + base (voir dernière étape de la synthèse du composé 2.
Proposez un mécanisme expliquant la transformation observée (**2.5 points**) :

Synthesis of Compound **2**

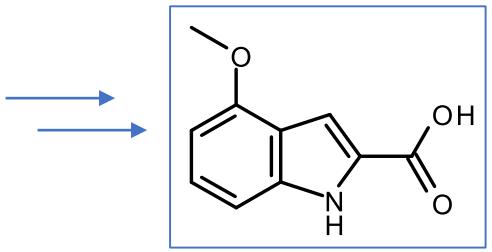




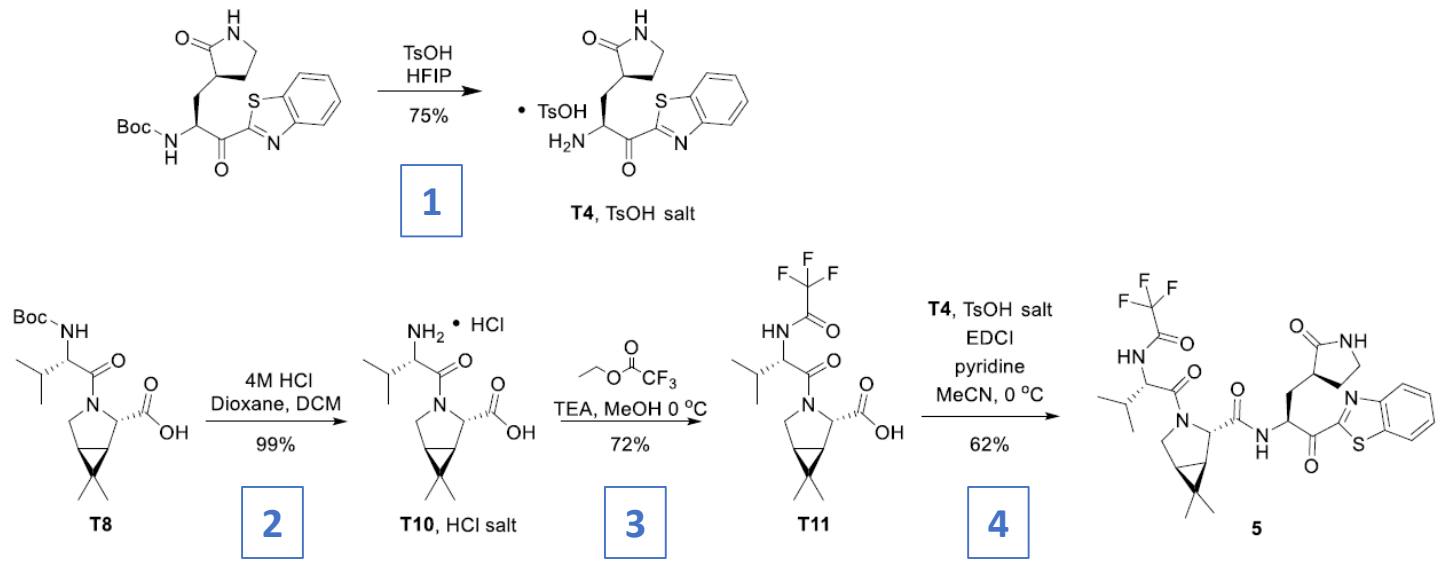
2 Indiquez le type de transformation observée (**0.5 point**) : .....

Proposez des réactifs permettant de faire la transformation voulue (**0.5 point**) : .....

Proposez une méthode de synthèse du noyau hétérocyclique suivant en détaillant le mécanisme (**3 points**) :

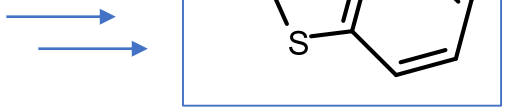


Synthesis of compound **5**



1 Indiquez le type de réaction (**0.5 point**) : .....

Proposez une méthode de synthèse du noyau hétérocyclique suivant en détaillant le mécanisme (**3 points**) :



Le **MOLNUPIRAVIR®**, aussi appelé MK-4482 ou Lagevrio, est un antiviral expérimental à large spectre, initialement destiné à soigner la grippe et l'hépatite C. Il a montré *in vitro* et chez l'animal une certaine efficacité contre divers coronavirus dont le virus SARS-CoV-2 responsable de la pandémie de Covid-19. Merck demande une autorisation d'utilisation d'urgence à la FDA pour un traitement précoce des sujets à risque. Avant même que les résultats des essais cliniques soient publiés, il est autorisé au Royaume-Uni en novembre 2021 pour les personnes à risque atteintes de Covid-19 dans des formes légères à modérées, au tout début de la maladie. Le 19 novembre 2021, l'Agence européenne des médicaments autorise son utilisation pour les mêmes indications, en prévention des formes graves. En France, la Haute Autorité de Santé estime le 10 décembre 2021 que l'efficacité estimée de 30% contre les formes graves est insuffisante comparée à celle de 80% du Ronapreve et donne un avis défavorable au Lagevrio.

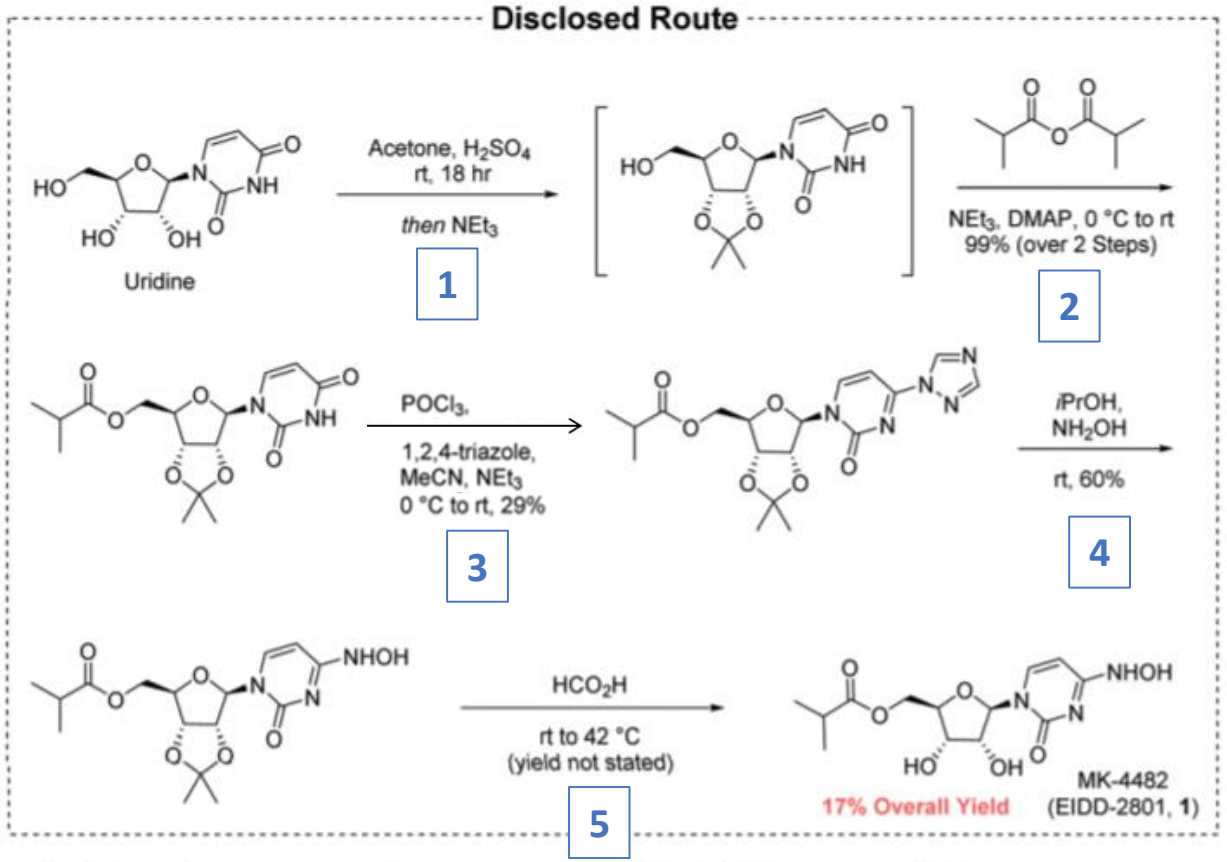
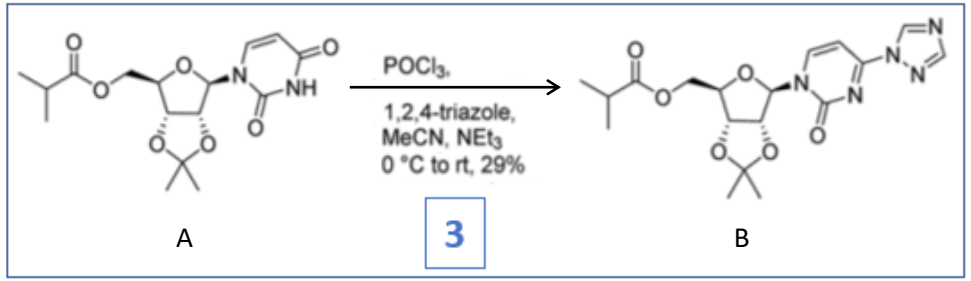


Fig. 1 The first generation route to MK-4482 from uridine.



3 Nommez les 3 hétérocycles principaux présents dans la molécule B (**1.5 points**) :

Détaillez le mécanisme permettant la transformation de A vers B (**1.5 points**) :