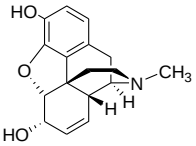
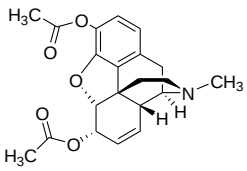
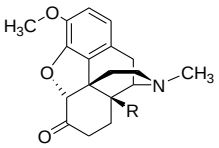
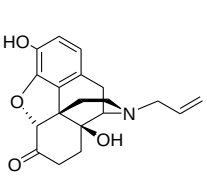
Exercícios Analgésicos Opioides)

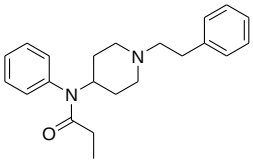
O cantor americano Prince morreu em sua cidade natal em Minnesota, EUA, em 21/04/2016. Esse episódio ganhou grande destaque na mídia mundial. A morte de Prince também reacendeu os debates sobre óbitos devido a prescrições e uso ilícito de opioides nos EUA, pois inicialmente suspeitou-se que o famoso cantor morreu devido à overdose de um agente opioide, **Oxicodona** ou **Hidrocodona**. Houve uma tentativa prévia de intervenção emergencial com administração do fármaco **Narcan (Naloxona)**, o que forçou um pouso de seu avião na cidade de Moline, em Illinois. Para acirrar os debates, um *drug dealer* (Doctor D) revelou ao Daily Mail que por mais de 20 anos vendeu ao cantor Prince os medicamentos **Fentanila** e **Dilaudid** (**Hidromorfona**), pois o cantor tinha fobia de médicos e estava dependente de opioides devido a um problema de dores crônicas no quadril (ver quadro abaixo com notícias da época). De fato, comprovou-se posteriormente que Prince morreu em decorrência de uma overdose de **Fentanila**. Atualmente, nos EUA há mais pessoas morrendo de overdose por opioides em comparação às mortes por acidentes de trânsito, tanto que a mídia americana tem discutido profundamente o assunto.

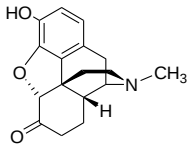

(**1**) morfina


(**2**) heroína


(**3**) R = OH oxicodona
(**4**) R = H hidrocodona


(**5**) naloxona


(**6**) fentanila


(**7**) hidromorfona

Todas as estruturas apresentadas correspondem a agentes opioides. Observe o modelo de interação morfina-receptor ao lado (questão 4) e explique

1) Porque o avião do cantor Prince fez pouso de emergência na cidade de Moline para que ele tomasse injeção de Narcan?

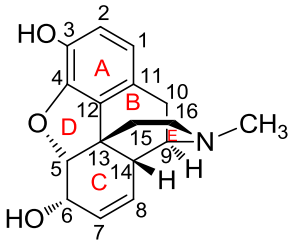
2) Por que a heroína não é usada como fármaco? Explique como a diferença estrutural interfere na potência.

"Suspected links between Prince's death and prescription narcotics come amid an opioid abuse epidemic in Minnesota that worsened last year, according to a Star Tribune review of new state death certificate data.
State records show 336 deaths last year linked to excessive or abusive use of prescription opioids, such as **oxycodone**, or illicit opioids, such as **heroin**. That is six times higher than the opioid-related deaths in 2000, and an increase from 313 deaths in 2014. Two-thirds of the deaths involved legal painkillers or the addiction treatment **methadone**, which can help wean drug abusers off opioids but is addictive itself. Ongoing autopsy and toxicology testing will determine whether Prince's April 21 death was related to opioids, but law enforcement sources have told the Star Tribune that they found opioids at Prince's Paisley Park complex and that they are investigating how he received them. Sources also said Prince overdosed on an opioid medication six days earlier, forcing his plane to divert to Moline, Ill., where he received an emergency dose of **Narcan**."
(fonte: http://www.startribune.com/prince-s-death-a-reminder-of-state-opioid-problem/377649911/)

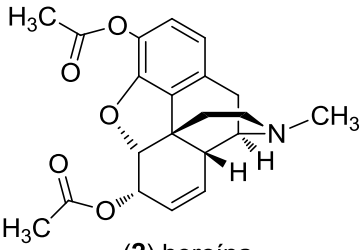
"They say an emergency landing in Moline, Illinois was to administer a "save shot" of **Narcan** to save his life....
Opiod abuse is a problem often overshadowed by the scourge of heroin. But they are really two sides of the same coin." (fonte: http://fox2now.com/2016/04/22/princes-death-shines-a-spotlight-on-the-spike-in-prescription-drug-addiction/)

"Quoting sources familiar with the investigation into Prince's death, the Minneapolis Star Tribune reported that emergency providers at the airport administered **Narcan**, a drug that quickly reverses the potentially deadly side effects of an opioid overdose; opioids such as **oxycodone** and **hydrocodone** are some of the most powerful prescription painkillers. Though EMS took Prince to a local hospital, he "left within a few hours" on his jet, home to Minneapolis." (fonte: http://edition.cnn.com/2016/04/28/opinions/massachusetts-opioid-treatment-prince-vox/)

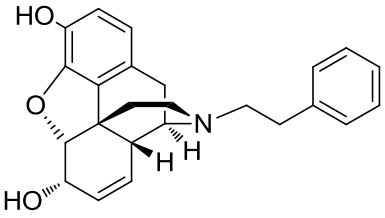
"EXCLUSIVE: Prince's former drug dealer tells how the legend spent $40,000 at a time on six-month supplies of **Dilaudid** pills and **Fentanyl** patches - highly addictive opioid pain killers - for 25 years" (fonte: http://www.dailymail.co.uk/news/article-3555292/Prince-s-former-drug-dealer-reveals-extent-addiction.html#ixzz47RAJ6XVW)



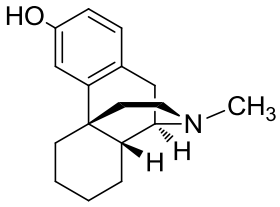
(**1**) morfina



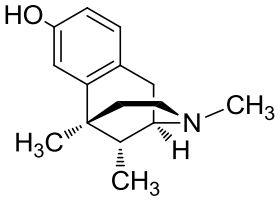
(**2**) heroína
2X mais potente que morfina



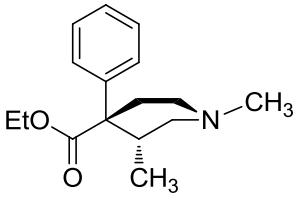
(**3**) feniletilmorfina
14X mais potente que morfina



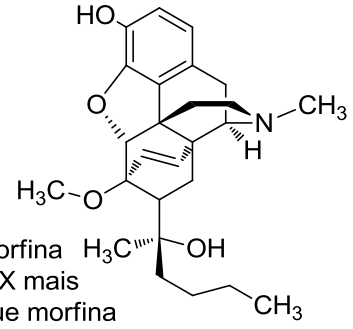
(**4**) levorfanol
5X mais potente que morfina



(**5**) metazocina
equipotente a morfina



(**6**) meperidina
5X menos potente que morfina



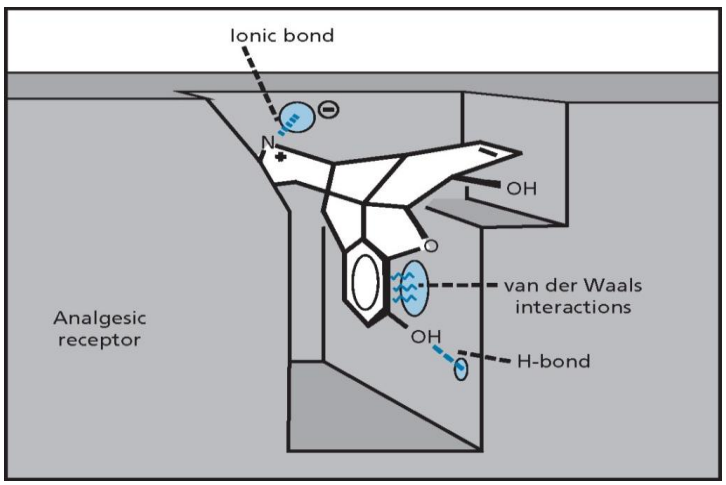
(**7**) etorfina
10.000X mais potente que morfina

3) Indique qual a estratégia de modificação molecular predominante para a obtenção dos analgésicos opioides da figura acima (**2-7**) a partir da morfina (**1**):

1→ 2:_____
1→ 3:_____
1→ 4:_____
1→ 5:_____
1→ 6:_____
1→ 7:_____

Estratégias de modificação molecular:
(A) variação dos substituintes
(B) simplificação molecular
(C) extensão molecular
(D) introdução de rigidez

4) Observe abaixo o modelo de interação da morfina no receptor opioide e assinale nas estruturas **1-7** os grupos farmacofóricos. Indique os anéis (**A-E**) fundamentais para atividade analgésica.



5) Como você explicaria as maiores atividades observadas para as estruturas **3** e **7**?
6) A diferença estrutural entre **hidrocodona** e **hidromorfona** pode impactar na atividade farmacológica?