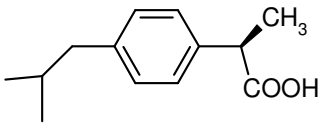
Exercise to the lecture „Modern Methods in Drug Discovery“ WS13/14

5th Assignment to be handed in until 06.01.2014

your name:

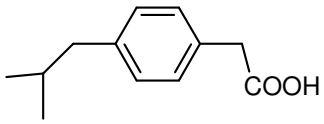
1. The analgesic and anti-inflammatory Ibuprofen faced a series of „me-too“ drugs shortly after its commerical launch, since the corresponding patent claimed the structure of ibuprofen (see compound **A**), only.

A



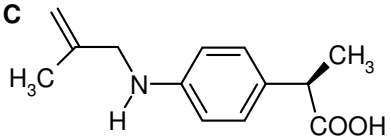
Ibuprofen 1966 Upjohn

B



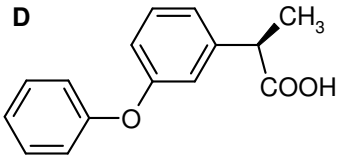
Ibufenac 1968 Boots Pure Drug

C



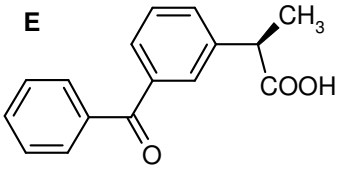
Alminoprofen 1971 Bouchera

D



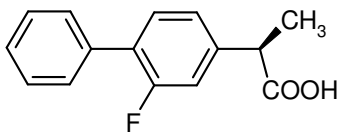
Fenoprofen 1971 Lilly

E



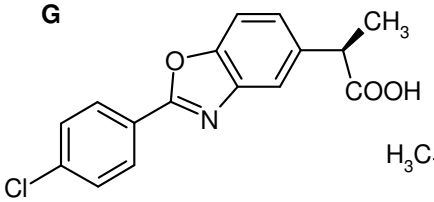
Ketoprofen 1972 AHP

F



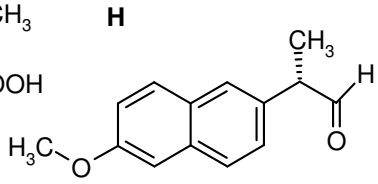
Flurbiprofen 1973 Upjohn

G



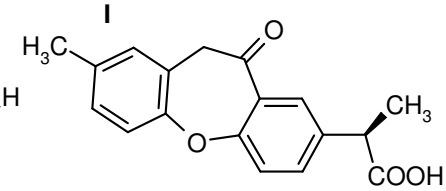
Benoxaprofen 1973 Lilly

H



Naproxen 1975 Syntec

I



Bermoprofen 1970 Dainippon

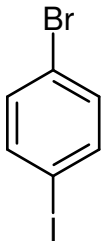
a) Which one of the following SMARTS strings (1, 2, or 3) would have been appropriate to claim Ibuprofen, Fenoprofen, Ketoprofen, as well as Flurbiprofen? (5 points)
Hint: The stereochemistry does not have to be considered.
b) Write down the matching compound(s) for each SMARTS string (5 points for each correctly assigned).

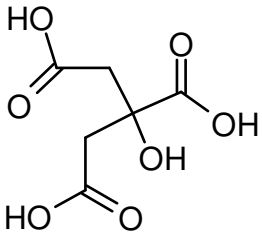
1: C(C)(C(=O)O)c1ccc([H,CC(C)(C),#6])c([H,F])c1

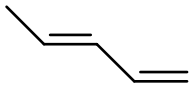
2: C(C)(C(=O)O)c1ccc([H,CC(C)(C),c2ccccc2])c([H,F,[C(=O),O]c3ccccc3])c1

3: C(C)(C(=O)O)c1ccc([H,CC(C)(C),c2ccccc2])c([H,F,[C,O]c3ccccc3])c1

2. Sort the following substances in order of increasing logP without computing or looking up the actual logP. (10 points)







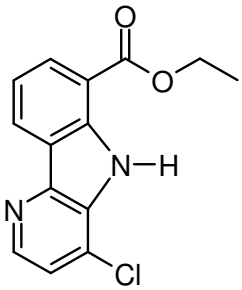
3. Suggest one SMARTS each that matches

a) hydrogen-bond acceptors (N, O) but not including hydrogen-bond donors (N-H, NH_2, O-H) at the same time (4 points)

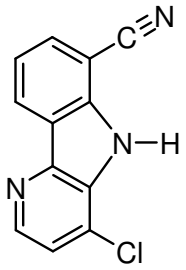
b) carbon with three subsituents, one of those being hydrogen (4 points)

c) sulfur with four substituents in a six-membered ring (4 points)

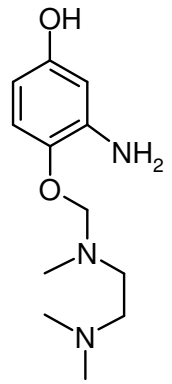
4. Chemical alterations shall be carried for the shown compounds. Draw a new structure that includes the suitable modifications. (28 points)



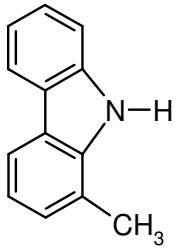
a) should become more hydrophilic by adding one group



b) should be come lipophilic by replacing one group



c) suggest a modification that reduces the number of freely rotatable bonds



d) suggest a modification that will lead to increased metabolic stability of the lower benzene ring