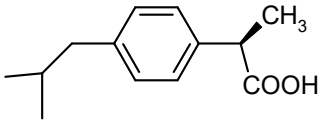
Exercise to the lecture „Modern Methods in Drug Discovery“ WS24/25

5th Assignment

your name:

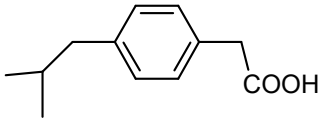
1. The analgesic and anti-inflammatory Ibuprofen faced a series of „me-too“ drugs shortly after its commerical launch, since the corresponding patent claimed the structure of ibuprofen (see compound **A**), only.

A



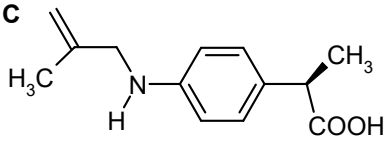
Ibuprofen 1966 Upjohn

B



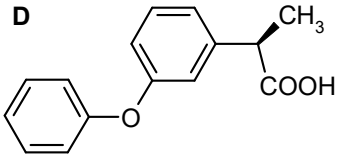
Ibufenac 1968 Boots Pure Drug

C



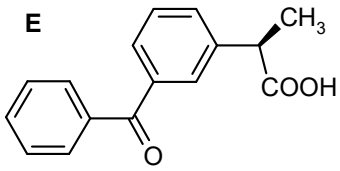
Alminoprofen 1971 Bouchera

D



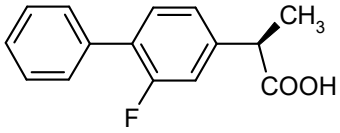
Fenoprofen 1971 Lilly

E



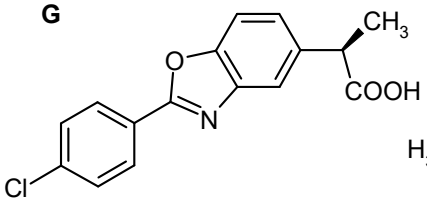
Ketoprofen 1972 AHP

F



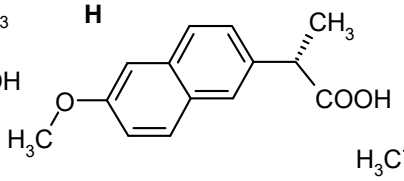
Flurbiprofen 1973 Upjohn

G



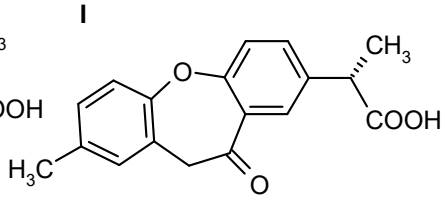
Benoxaprofen 1973 Lilly

H



Naproxen 1975 Syntec

I



Bermoprofen 1970 Dainippon

Report the matching compounds(s) (alphabetic character is sufficient) for the given SMARTS 1 to 4. Not all compounds may me matched (5 points for each correct assignment, deduction if more than one is falsely assigned)

1: OC(=O)C(C)c1ccc([C,N])cc1

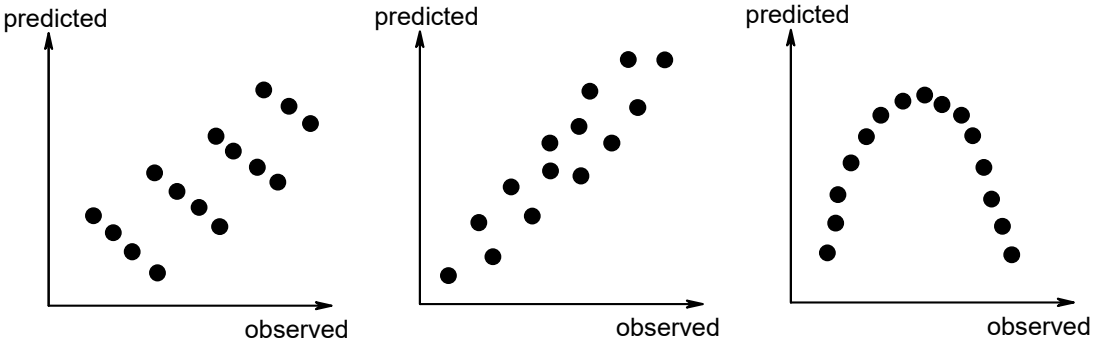
2: OC(=O)C(C)c1cccc([C,O,F])c1

3: OC(=O)C(C)c1cccc([#6])c1

4: OC(=O)C(C)c1cccc([C,O,#7])c1

Which compound is not matched by any of the SMARTS strings? (4 points)

2. Mark the correct value of the linear correlation for each of the plots, respectively (9 points)



$r^2 = 0.00$	$r = -0.98$	$r^2 = 0.00$
$r^2 = 0.60$	$r = 0.00$	$r^2 = 0.50$
$r^2 = 0.90$	$r = 0.90$	$r^2 = 0.60$
$r^2 = 0.95$	$r = 0.98$	$r^2 = 0.85$

3. Which of the QSAR equations (A or B, respectively C or D) is „better“ ? (According to which criteria ?) (10 points)

n: number of molecules; r^2: squared correlation coefficient;
q^2: cross-validated r^2; *s*: standard error

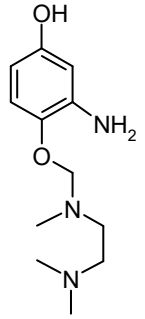
A) $\log 1/K_i = 0.26(\pm0.14)\text{ClogP} - 1.36(\pm0.43)\text{NHB} + 9.66(\pm0.39)\text{HL}$
where $n = 21$, $r^2 = 0.853$, $q^2 = 0.746$, $s = 0.326$

B) $\log 1/K_i = 0.34(\pm0.13)\text{ClogP} - 0.96(\pm0.27)\text{MR} + 0.85(\pm0.19)\text{B5Y}$
where $n = 21$, $r^2 = 0.853$, $q^2 = 0.807$, $s = 0.302$

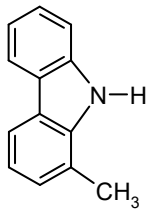
C) $\log 1/C = 0.26(\pm0.18)\text{ClogP} - 1.36(\pm0.43)\text{MR} + 9.66(\pm0.39)\text{B5Y}$
where $n = 16$, $r^2 = 0.821$, $q^2 = 0.794$, $s = 0.354$

D) $\log 1/C = 0.23(\pm0.15)\text{ClogP} - 1.20(\pm0.56)\text{MR} + 10.74(\pm0.67)\text{B5Y} - 0.62(\pm0.12)\text{NN4} + 0.14(\pm0.05)\text{GEOM6}$
where $n = 16$, $r^2 = 0.892$, $q^2 = 0.632$, $s = 0.325$

4. Chemical alterations shall be carried for the shown compounds. Draw a new structure that includes the suitable modifications. (12 points)



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



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