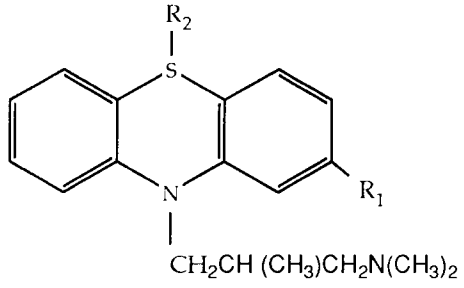
QSAR OF TRIMEPRAZINE CONGENERS - CORRELATION OF LOG D TO HPLC CAPACITY FACTOR

T. Appelqvist, M. Dennis* and G. Taylor. Welsh School of Pharmacy, UWCC, PO BOX 13, Cardiff. *Rhône-Poulenc Ltd, Dagenham, Essex.

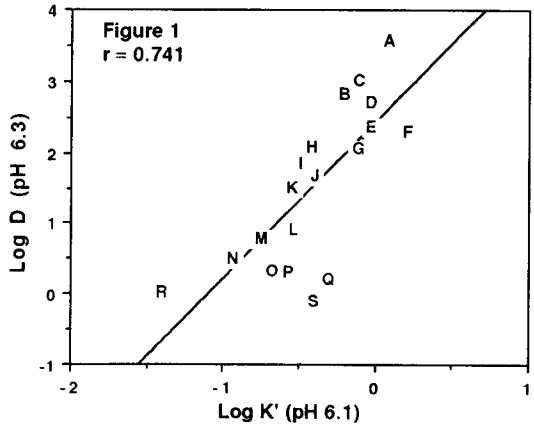
This work compares the apparent Log P (Log D) for a series of trimeprazine congeners (all weak bases), obtained by the shake-flask method at pH 6.3, 7.0 and 7.4, with their capacity factors (Log K'), obtained by reverse phase HPLC (RP-HPLC), at eluent pH of 6.1.
The drugs used are as follows;

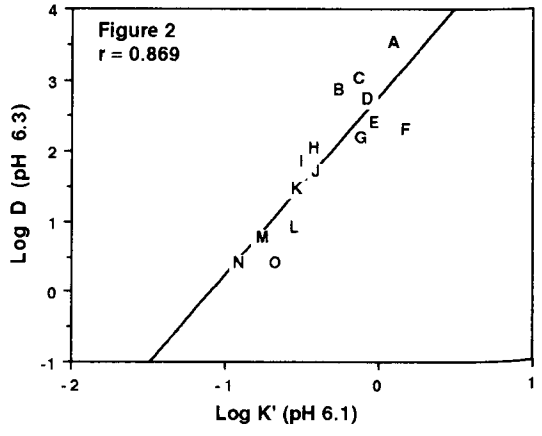


a, R1 = C_6H_5COO
b, R1 = CH_3
c, R1 = Cl
d, R1 = CF_3
e, R1 = CH_3S
f, R1 = $CH_3(CH_2)_4CO$
g, R1 = CH_3CH_2
h, R1 = NO_2
i, R1 = H (trimeprazine)
j, R1 = NC
k, R1 = OH
l, R1 = CH_3O R2 = O_2
m, R1 = $(CH_3)_2NSO_2$
n, R1 = NC R2 = O_2
o, R1 = COOH
p, R1 = H R2 = O
q, R1 = CH_3S R2 = O
r, R1 = NC R2 = O
s, R1 = CH_3O R2 = O

(Compounds a - k, m and o, where R2 is not specified, are sulphides).

1ml of octanol, previously saturated with Sorensen's phosphate buffer, was shaken gently with 40ml of Sorensen's phosphate buffer, 67mM, previously saturated with octanol, at 37°C under darkness for 8 hours. The phenothiazines were previously dissolved in the buffer at concentrations of 10^{-5} to 10^{-4} M to avoid micellar aggregation (1).
The concentration of phenothiazine in the buffer phase before (Co) and after (Ce) shaking with the octanol to equilibrium, was analysed by injecting 100µl aliquots of buffer onto a S5C6 Spherisorb column, (4.9 i.d. x 25cm), with UV detection at 254nm. The eluent consisted of 69% methanol with 31% Sorensen's phosphate buffer, 67mM, with 25mM TEMED as amine modifier. The flow rate was 1ml per minute.
The apparent partition coefficient was obtained via the method of Caccia et al (2). The capacity factor (Log K'), was obtained using $K' = (tr - t_0) / t_0$; where t_0 = retention time of unretained solute and tr = retention time of the phenothiazine.





The best correlation for Log D versus Log K' is obtained at pH 6.3, (Fig. 1) which is closest to the eluent pH. If we exclude the sulphoxides, which are very polar, the correlation improves, (Fig. 2). Excluding the sulphones decreases the correlation, which suggests that the sulphones, due to mutual cancellation of polarity by the two oxygen groups, behave like phenothiazines without substituents at the R2 position, whereas the sulphoxides do not. Measurement of the pK_as of the phenothiazines reveals that the sulphones have similar values to the unsubstituted R2 phenothiazines (range 8.80 to 9.92), whilst the sulphoxides have values ranging from 5.70 to 6.60.

(1) Ahmed, A. (1986) Ph.D. Thesis, University of Wales
(2) Caccia, S. et al (1985) J. Pharm. Pharmacol. 37: 567-570