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Short communication

First relationships between detoxication properties of some 1,2-dithiole-3-thiones and their log *P*

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Abstract

First quantitative structure-activity relationships (QSAR) between electrophile detoxication properties of 1,2-dithiole-3-thiones and their log *P* values were checked. A very significant linear property was found with some disubstituted derivatives. In all cases, it was found that the less lipophilic dithiolethiones were the most active.

Keywords: 1,2-Dithiole-3-thiones; Electrophile detoxication; Water/*n*-octanol log *P*; Quantitative structure-activity relationships

1,2-Dithiole-3-thiones (see below) are potent inducers of enzymes involved in the maintenance of reduced glutathione pools as well as phase-2 enzymes important to electrophile detoxication (Egner et al., 1994). Moreover, these compounds exhibit lower mammalian toxicity. As a result, this family is endowed with very promising cancer chemoprotective properties. Besides, one dithiolethione (Oltipraz 35972 R.P.) is currently undergoing phase-I clinical trials as a chemoprotective agent in humans (Dimitrov et al., 1992).

There is, as yet, no salient feature concerning the influence of substituents R1 and R2 on the inducing power of phase-2 enzymes and no quantitative structure-activity relationships (QSAR) have been established. We have been engaged for a long time in the chemistry of these compounds (Burgot and Vialle, 1969; Abazid et al., 1994) and, because of the great importance of lipophilic factors (Hansch and Leo, 1973), we determined very recently the water/*n*-octanol log *P* of basic dithiolethiones, and we inferred from these results some simple rules to calculate the log *P* values of unknown dithiolethiones, their synthesis proving eventually to be tedious and the pharmacological activities uninteresting. Such studies, however, may provide considerable help in the discovery of new derivatives with more chemoprotective activities. We present here the first QSAR concerning

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induction of phase-2 enzymes by dithiolethiones. Two biological parameters were used in these studies: the specific activity of quinone reductase (QR) and the production of growth hormone (GH) in particular cells, both induced by some concentrations of dithiolethiones (C_D) (Table 1). The corresponding numerical values were introduced in the quantitative relationships as log $1/C$ ones. They were those found by Egner et al. (1994). Log P was the independent parameter.

A first look at diagrams log $(1/C_{DQR})$/log P and log $(1/C_{DQH})$/log P indicated immediately that no clear relationship exists between these parameters. A further insight into the influence of log P was obtained by testing linear relationships with a limited number of dithiolethiones chosen among those mentioned in Table 1. The following groups of compounds were tested: dithiolethiones substituted only in 4; those substituted only in 5; 4,5-disubstituted dithiolethiones; 5-unsubstituted dithiolethiones with an electro-withdrawing group in 4; 4-unsubstituted ones with an electro-donating group in 5. In each group the dithiolethione parent was incorporated for the sake of comparison. (Other combinations were not possible owing to the rather limited number of biological activities at our disposal).

The only very significant correlation was that obtained with disubstituted dithiolethiones (15, 17, 18, 16 and 1).

$$\log(1/C_{D_{GH}}) = -0.291\log P - 0.087 (r^2 = 0.876) (1)$$

$$\log(1/C_{D_{QR}}) = -0.529\log P + 0.586 (r^2 = 0.776) (2)$$

The significance of the regression fell dramatically ($r^2 = 7.29 \times 10^{-2}$ and $r^2 = 0.23$, respectively) by adjunction of the two remaining disubstituted dithiolethiones (14 and 19) to the regression. However, their biological values seemed to us somewhat suspicious when we compared them to that found for dithiolethione 16, the chemical structure of which is very similar to that of the first two dithiolethiones (Fig. 1 and Fig. 2).

The negative slopes of the linear relationships (1) and (2) indicate that the less lipophilic dithiolethiones are, the more active they are. This

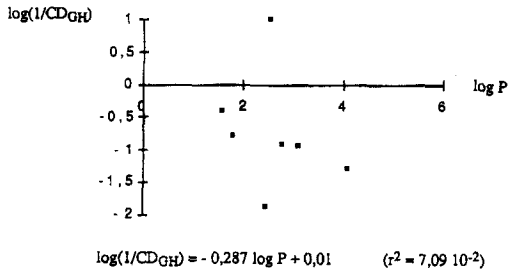


Fig. 1. log $(1/C_{DGH}/F$ (log P).

result was confirmed by all the other groups of tested correlations, even though they were poorly significant.

Today, the existence of an optimal log P value is open to question. It will be difficult to give an answer because very weakly lipophilic dithiolethiones are difficult to synthetize. Currently, this synthesis remains a challenge.

In our opinion, this weak significance is probably the result of the interference of one, perhaps two, parameters together with log P. It is also likely that the biological results obtained with functionalized dithiolethiones (5, 6, 11, 12) must be read with caution because of possible metabolism.

Further studies involving other physico-chemical parameters of 1,2-dithiole-3-thiones are currently being performed.

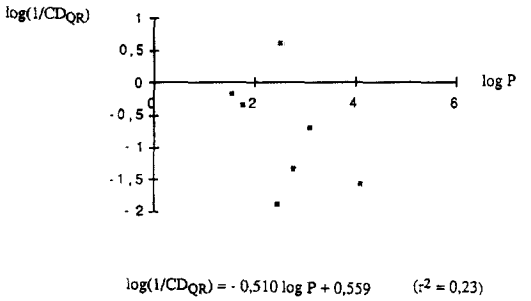


Fig. 2. log $(1/C_{DQR})/F$ (log P).

Table 1: Biological parameters and log *P* used in different tested quantitative structure activity relationships

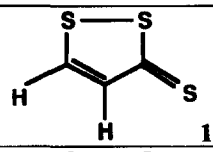
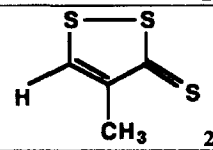
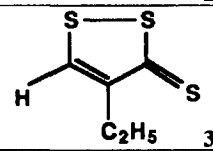
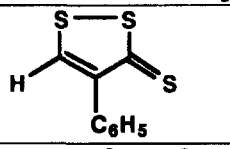
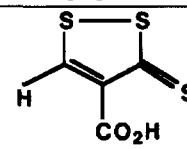
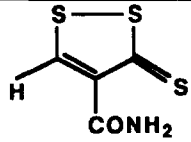
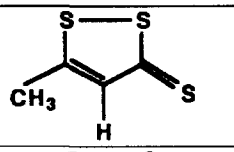
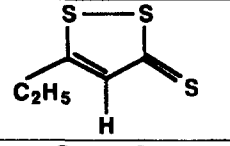
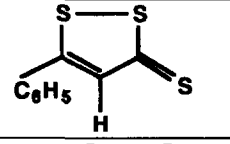
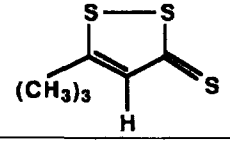
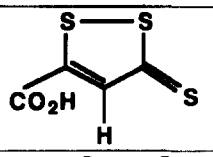
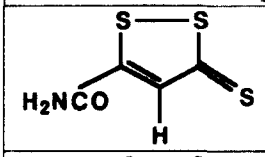
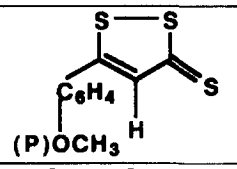
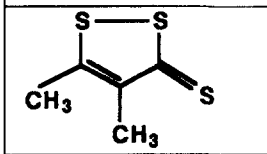
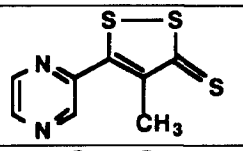
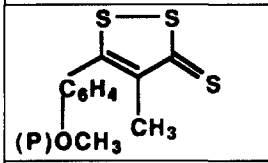
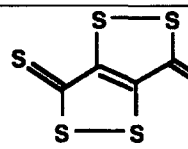
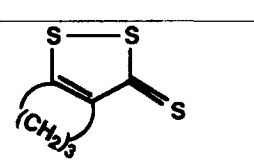
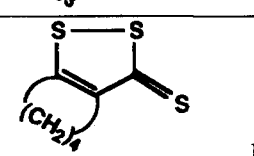
structures of 1,2-dithiole-3-thiones	CD_{QR}*** (μM)	log(1/CD_{QR})	CD_{GH}** (μM)	log(1/CD_{GH})	log P
 1	1,5	-0,176	2,6	-0,415	1,58
 2	12	-1,079	13	-1,114	2,18
 3	8	-0,903	31	-1,491	2,67
 4	2	-0,301	18	-1,255	3,20
 5	24	-1,380	30	-1,477	1,33****
 6	46	-1,662	38	-1,579	0,30
 7	17	-1,230	13	-1,114	1,85
 8	8	-0,903	26	-1,415	2,31
 9	20	-1,301	21	-1,322	3,67
 10	5	-0,699	30	-1,477	3,25****

Table 1 (continued)

structures of 1,2-dithiole-3-thiones	CD_{QR}*** (μM)	log(1/CD_{QR})	CD_{GH}**	log(1/CD_{GH})	log P
 11	>80	>-1,903	>80	>-1,903	1,05****
 12	20	-1,301	4,5	-0,653	0,01****
 13	18	-1,255	10	-1	3,82
 14	80	-1,903	75	-1,875	2,45
 15	22	-1,342	8	-0,903	2,79
 17	38	-1,580	20	-1,301	4,10
 18	2,2	-0,342	6	-0,778	1,80****
 19	0,25	0,602	0,10	1	2,53
 16	5	-0,698	8,5	-0,929	3,10

*Published values (Egner et al, 1994).
**CD_{QR}(μM) concentration required to double quinone reductase specific activity in Hepa 1c1c7 cells.
***CD_{GH}(μM) concentration required to double growing hormone production in Hepa 1c1c7 cells transfected with p41-284GH.
****calculated log *P* (see-text)

Acknowledgements

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