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Experimental and Theoretical Study on Lipophilicity of Novel 1.2-Dithiole-3-thiones Synthetic

Z. RAHMANI[1,*], M. SAIDI[1], M. YOUSFI[2] and M. DAKMOUCHE[1]

[1]Laboratoire de Valorisation et Promotion des Ressources Sahariennes, Université Kasdi Merbah de Ouargla, (30000) Ouargla, Algeria
[2]Laboratoire des Sciences Fondamentales, Université Amar Telidji, (16000) Laghouat, Algeria

*Corresponding author: E-mail: zhor_rahmani@hotmail.com; zhorrahmani@gmail.com

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The aim of this work is to determine the partition coefficients log P_{wo} of eleven compounds, dithiolethiones, dithiolone, nitrone, 1.2-dithiole-3-imine and bromines compounds which is carried out by two experimental methods: UV-VIS and HPLC. According to the procedure of the traditional method shake-flask and we confirm the results by using a theoretical method for calculating the values of log P_{wo}. Another aim is to obtain the value of the unknown fragmental constant of imine(C=N) and the value found of imine $f_{C=N}$ underlined in the calculatation of log P_{wo} (N-*p*-nitrophenyl 5-phenyl-1.2-dithiole-3-imine); then to compare the calculated log P_{wo} value with the experimental. The results show that: (i) the dithiolones are more hydrophilic than the dithiolethiones; (ii) the values of log P_{wo} of derivatives bromines, imine and nitrone are lately given in experiments. Our analysis demonstrates good agreement between the experimentally observed and calculated log P_{wo} values.

Key Words: Dithiolethiones, Partition coefficient, Hydrophobe.

INTRODUCTION

Although many sulfur containing heterocycles have been known from the early times of organic chemistry, it has not been until recently that some of these compounds have found their most important applications. On the other hand, the study of many bioactive compounds, as oltipraz (35972 R.P.) (R_4 = CH_3; R_5 = 2-pyrazinyl) and other natural and synthetic 1.2-dithiole-3-thione[1], has drawn attention to the role of polysulfur heterocycles in the field of pharmaceutical chemistry and especially for the prevention of carcinogenesis[2].

Dithiolethiones Fig. 1 (X = S) compounds found in cruciferous vegetables increase the rate of detoxification chemical carcinogens. A high-life of cruciferous vegetables (including cabbage, broccoli and cauliflower) is associated with protection from the development of colorectal cancer.

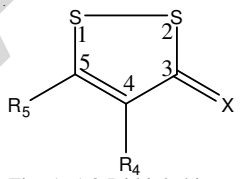

Fig. 1. 1,2-Dithiolethione

These plants all contain substantial concentrations of dithiolethiones, indoles and isothiocynates, each of which has been proposed to account for chemoprotection[3].

Reduction of oxidative stress is considered to be an attractive approach to provide neuroprotection in neurodegenerative diseases[4]. Increased formation of reactive oxygen species (ROS) and consequent oxidative stress is thought to be involved in the loss of neurons occurring in chronic (neuro) degenerative diseases and ischemic brain injury. So, astroglial cells protect neurons against oxidative damage. The antioxidant glutathione plays a pivotal role in the neuroprotective action of astroglial cells which are impaired following loss of glutathione. Anethole dithiolethione **4a**, a sulfur-containing compound which is used in humans as a secretagogue, increases glutathione levels in cultured astroglial cells under "physiological" conditions and is thought thereby to protect against oxidative damage[5].

However, 1.2-dithiole-3-thione derivatives have poor water solubility (generally < 10^{-4} mol L^{-1}) and no data concerning their lipophilicity existed in the literature before the studies of Bona *et al.*[6], one parameters of lipophilicity is water/n-octanol partition coefficient (P_{wo}), which is the quantitative parameter for an insight into the interaction between drug and biofilm, is one of the most important parameters employed for estimating a chemical's environmental fate and toxicity. P_{wo}, defined as the ratio of a chemical concentration in the *n*-octanol phase to its concentration in the aqueous phase at equilibrium. The logarithm of this coefficient, log P_{wo}, has been shown to be one key parameters in quantitative structure - activity/property relationship (QSAR/QSPR) studies[7].

In addition, log P_{wo} is essential for understanding the transport mechanisms and distribution of compounds in the environment, for example, the process involving the deposition a pollutant into bodies of water[9]. Although log P_{wo} can be measured reliably for a given compound, the experimental process might be time-consuming and expensive. This problem becomes critical when many of candidate molecules, which sometimes are just virtual, require screening during a drug design and discovery procedure. Thus, there is a clear need for calculation procedures that can give reliable estimations of log P_{wo} based merely on the chemical structure of a given compound.

During the past three decades, many methods of calculating log P have been reported in the literature[10]. At present, the most widely accepted method is classified as the 'additive method', where a molecule is dissected into basic fragments (functional groups or atoms) and its log P value is obtained by summing the contributions of each fragment. 'Correction factors' are also introduced to rectify the calculated log P value when some special substructures occur in the molecule.

This method originated with Rekker and coworkers[11,12]. Current popular fragment-additive methods include CLOGP[13,14], KLOGP[15], KOWWIN[16], CHEMICALC-2[17] *etc*. Atom-additive methods include MOLCAD[18], ALOGP[19] and SMILOGP[20]. There are also methods that try to incorporate molecular properties into the calculation, such as HINT[21] and ASCLOGP[22].

We have been engaged for a long time in the chemistry of the dithiolethiones compounds[23] and, because of the great importance of lipophilic factors[24], we determined very recently the water/*n*-octanol log P_{wo} of basic dithiolethiones.

We confirm these results in this paper. The methodology described here is using a fragmental lipophilic constant of Rekker (revised version)[25]. On other aim of our work was to correlate the experimentally determined and calculate log P_{wo} values for dithiolethiones using rapid method for the calculation (based on atom/fragment contributions). Finally, we obtained the unknown fragmental constant of imine (C=N) and the value found of imine $f_{C=N}$ underlined in the calculation of log P_{wo} (5-phenyl-1.2-dithiole-3-(N-*p*-nitrophenyl imine)).

The dithiolethiones empolyed in this study, their abbreviated are shown in following:

1a: X = S, $R_4 = CH_3$, $R_5 = CH_3$
2a: X = S, $R_4 = C_6H_5$, $R_5 = H$
3a: X = S, $R_4 = p\text{-}CH_3C_6H_4$, $R_5 = H$
4a: X = S, $R_4 = H$, $R_5 = p\text{-}CH_3OC_6H_4$
5a: X = S, $R_4 = CH_3$, $R_5 = C_6H_5(N\rightarrow O)=CH$
1b: X = O, $R_4 = C_6H_5$, $R_5 = H$
2b: X = O, $R_4 = p\text{-}CH_3C_6H_4$, $R_5 = H$
3b: X = O, $R_4 = C_6H_5$, $R_5 = Br$
4b: X = O, $R_4 = p\text{-}CH_3C_6H_4$, $R_5 = Br$
1c: $X = NO_2(p)C_6H_4=N$, $R_4 = H$, $R_5 = C_6H_5$

EXPERIMENTAL

The dithiolethiones derivatives used in these studies were synthesized as previously described[26,27]. All other chemicals were obtained from Aldrich.

To analysis the following instruments were used: UV-VIS spectrophotometer with 1 cm quartz cells.

HPLC: calibration curves were constructed by linear regression of the peak-area ration versus concentration. The RP-HPLC column was stainless steel tubing (i.d. 4.5 mm in diameter and 15 cm long) filled with 5 µm ODS2 stationary and the flow rate of the mobile phase was 1 mL min^{-1}. UV detection was achieved at an adequately wavelength. The mobile phase used for analysis was methanol-water mixtures (80-20/70-30 v/v) as the hydrophobicity of compounds.

Experimental determination of log P_{wo} values: Before each determination, the purity of the compounds was checked by determination of its melting point and also by TLC using two pairs of eluents. Let us recall only that log P_{wo} was calculated as the decimal logarithm of the ratio of the solute concentration in *n*-octanol and in water after partition equilibrium. An octanolic solution (saturated in water) of a solute 10 mL was introduced into a 250 mL separatory funnel with 50 mL of water (previously saturated in *n*-octanol). It was stirred in a mechanical shaker for 0.5 h. The solutions were then left to stand for 24 h until the two phases were seperated. At equilibrium, the aqueous solution separated then its concentration is determined by UV-VIS and HPLC may be also used to quantify the concentration of the solute. The values of the partition coefficient of compounds were listed in Table-2.

Spectrophotometric UV-VIS log P_{wo} determinations: For UV-VIS studies, one analytical working wavelength corresponding the maxima of molar absorptivities were selected for each compound. In both cases, the sample concentration was determined by comparison to a calibration curve constructed with four to five known concentrations in water saturated with *n*-octanol are usually estabilished. A straight line was according to the equation C = aH + b where C was the concentration of the solute (mol L^{-1}) and H was the absorbance at the wavelength of absorbance maximum. For dithiolethiones max was situated in the range 400-460 nm and for dithiolones between 300 and 370 nm.

Calculation method: Partition coefficients are additive-constitutive, free energy related properties. log P_{wo} represents the over-all hydrophobicity of a molecules, which includes the sum of the hydrophobic contributions of the "parent" molecule and its substituent[28]. Hansh and leo took a constructionist approach and developed a fragmental system that included correction factors for bonds and proximity effects[29]. For us, we apply these rules to the studied compounds adopting values of the following fragmentales constants which are listed in Table-1:

Fragmentation methods: This approach breaks a molecule into fragments and assumes that the total log P of a molecule is the sum total of all contributions of each fragment. However, the molecular environment affects the contributions by each fragment. Hence, correction factors are included in the calculation as shown by the following equation:

$$\log P = \sum_{i=1}^{n} a_i f_i + \sum_{i=1}^{m} b_j F_j$$

where, log P = log of the partition coefficient, a = the number of fragments, f = fragmental constant, b_j = frequency of F_j, F_j (CM) = correction factor for the jth fragment.

TABLE-1
VALUES OF FRAGMENTS

Substituant x	f_x
$f_{C_6H_5}$	1.902[25]
$f_{Br\ aliphatic}$	0.258[25]
$f_{Br\ aromatic}$	1.134[25]
$f_{CH_3\text{-}O}$	0.274[25]
f_H	0.204[25]
f_{CH_3}	0.219[25]
f_C	0.724[25]
log P $_{pyridin}$	0.110[25]
$f_{S\ aromatic}$	0.099[25]
$f_{NO_2\ aromatic}$	-0.039[25]
$f_{NO\ aromatic}$	-1.000[36]
$f_{C=H\ aromatic}$	0.315[25]
log P_{exp}(parent dithiolethione)	1.580[24]
log P_{exp} (parent dithiolone)	0.820[24]

1a: X = S, $R_1 = CH_3$, $R_2 = CH_3$ (4.5-dimethyl-1.2-dithiole-3-thione) log $P_{\mathbf{1a}}$ = log $P_{(exp\ of\ parent\ DTT)}$ − [f_H + C_M (H linked to a strongly attractive group (5-[1.2-dithiole-3-thione,one]-yl)[26]] - f_H + 2f_{CH_3}, log $P_{\mathbf{1a}}$ = 2.401.

2a: X = S, $R_1 = C_6H_5$, R_2 = H (4-phenyl-1.2-dithiole-3-thione), log $P_{\mathbf{2a}}$ = log $P_{(exp\ of\ parent\ DTT)}$ - f_H + $f_{C_6H_5}$, log $P_{\mathbf{2a}}$ = 3.278.

3a: X = S, R_1 = *p*-$CH_3C_6H_4$, R_2 = H (4-*p*-tolyl-1.2-dithiole-3-thione), log $P_{\mathbf{3a}}$ = log $P_{(exp\ of\ parent\ DTT)}$ - f_H + [$f_{C_6H_5}$ + f_{CH_3} - f_H], log $P_{\mathbf{3a}}$ = 3.798.

4a: X = S, R_1 = H, R_2 = *p*-$CH_3OC_6H_4$ (5-*p*-methoxyphenyl-1.2-dithiole-3-thione), log $P_{\mathbf{4a}}$ = log $P_{(exp\ of\ parent\ DTT)}$ - [f_H + C_M (H linked to a strongly attractive group (5-[1.2-dithiole-3-thione,one]-yl)[26]] + [$f_{C_6H_5}$ - f_H + $f_{CH_3\text{-}O}$] + C_M(conjugation), log $P_{\mathbf{4a}}$ = 3.348.

5a: X = S, $R_4 = CH_3$, $R_5 = C_6H_5(N\rightarrow O)$=CH (4-methyl-5-[oxo (phenyl) imino] methyl-1.2-dithiole-3-thione, log $P_{\mathbf{5a}}$ = log $P_{(exp\ of\ parent\ DTT)}$ - [f_H + C_M (H linked to a strongly attractive group (5-[1.2-dithiole-3-thione,one]-yl)[26]] + [$f_{C_6H_5}$ + f_{NO} + $f_{C=H}$] - f_H + f_{CH_3}, log $P_{\mathbf{5a}}$ = 2.894.

1b: X = O, $R_1 = C_6H_5$, R_2 = H (4-phenyl-1.2-dithiole-3-one), log $P_{\mathbf{1b}}$ = log $P_{(exp\ of\ parent\ DTO)}$ - f_H + $f_{C_6H_5}$, log $P_{\mathbf{1b}}$ = 2.518.

2b: X = O, R_1 = *p*-$CH_3C_6H_4$, R_2 = H (4-*p*-tolyl-1.2-dithiole-3-one), log $P_{\mathbf{2b}}$ = log $P_{(exp\ of\ parent\ DTO)}$ - f_H + f_{CH_3} - f_H + $f_{C_6H_5}$ + C_M, log $P_{\mathbf{2b}}$ = 3.038.

3b: X = O, $R_1 = C_6H_5$, R_2 = Br (5-bromo 4-phenyl-1.2-dithiole-3-one), log $P_{\mathbf{3b}}$ = log $P_{(exp\ of\ parent\ DTO)}$ - [f_H + C_M (H linked to a strongly attractive group (5-[1.2-dithiole-3-thione,one]-yl)[26]] + $f_{Br\ aromatic/aliphatic}$ - f_H + $f_{C_6H_5}$ + C_M(conjugation), log P_{3b} (Br aromatic) = 3.448, log $P_{\mathbf{3b}}$ (Br aliphatic) = 2.572.

4b: X=O, R_1 = *p*-$CH_3C_6H_4$, R_2 = Br (5-bromo 4-*p*-tolyl-1.2-dithiole-3-one), log $P_{\mathbf{4b}}$ = log $P_{(exp\ of\ parent\ DTO)}$ - [f_H + C_M (H linked to a strongly attractive group (5-[1.2-dithiole-3-thione,one]-yl)[26]] + $f_{Br\ aromatic/aromatic}$) + f_{CH_3}- f_H + $f_{C_6H_5}$ + C_M (conjugation), log $P_{\mathbf{4b}}$ (Br aromatic) = 3.968, log $P_{\mathbf{4b}}$ (Br aliphatic) = 3.092.

Fragmental lipophilic constant of imine fragment: Finally, we were interested in finding the value of $f_{C=N}$, because dithiolethiones are aromatic compounds[30].

We check the $f_{C=N}$ in pyridin which is an aromatic compound. We applied the relation:

$$\log P_{pyridin} = f_{C=N} + 5f_H + 4f_C + 1C_M = 0.65^{29}$$

We found $f_{C=N}$ = - 1.029

This value [$f_{C=N}$ = -1.029] was entered in eqn. 1 for calculating log $P_{(cal)}$ 5-phenyl-1.2-dithiole-3-(N-*p*-nitrophenyl imine).

If we use the aliphatic fragment it is necessary to add $1C_M$ as a correction[25].

$$\log P_{(5\text{-phenyl-1,2-dithiole-3-(N-p-nitrophenyl imine))}} = 2f_S + f_H + 2f_C + 1C_M \text{ cross conjugation} + f_{C_6H_5} + f_{C=N} + f_{C_6H_5} - f_H + f_{NO_2} \quad (1)$$

$$\log P_{(5\text{-phenyl-1.2-dithiole-3-(N-}p\text{-nitrophenyl imine))}} = 3.373$$

But the value of log $P_{(5\text{-phenyl-1.2-dithiole-3 - (N-}p\text{-nitrophenyl imine))}}$ obtained by HPLC is log P_{exp} = 3.31.

The differences (Δ log P) between log P_{exp} and calculated data for 5-phenyl-1,2-dithiole-3- (N-*p*-nitrophenyl imine) exceed ± 0.063 is qualified as acceptable.

From experimental log $P_{exp\ (5\text{-phenyl-1.2-dithiole-3-(N-p-nitrophenyl imine))}}$ and fragmental constants of Rekker we were calaculated the new value of $f_{C=N}$ according to these equation:

$f_{C=N}$ = log $P_{exp\ (5\text{-phenyl-1.2-dithiole-3-(N-p-nitrophenyl imine))}}$ - 2f_S - f_H - 2f_C -1C_M cross conjugation - $f_{C_6H_5}$ - $f_{C_6H_5}$ - f_{NO_5} + f_H, $f_{C=N}$ = -1.092.

This results is in agreement with the value $f_{C=N}$ = -1.064 given by Liudmil Antonov *et al.*[30] according to the equation:

$$f_{C=N} = f_{CH=N} - f_H$$
$$f_{C=N} = -0.86 - 0.204$$
$$f_{C=N} = -1.064$$

RESULTS AND DISCUSSION

Experimental and calculated log P_{wo} data obtained in this study for derivatives **1a**-**1c** are listed in the Table-2.

TABLE-2
EXPERIMENTALLY DETERMINED AND CALCULATED log P_{wo}

Compound	log P_{exp}	log P_{cal}
1a	2.440, 2.450*	2.401
2a	3.230, 3.200*	3.278
3a	3.490, 3.700*	3.798
4a	3.820, 3.820*	3.348
5a	0.760	2.894
1b	2.560, 2.600*	2.518
2b	2.680, 3.290*	3.038
3b	2.700, 2.800*	$2.572_{(al)}$/$3.448_{(ar)}$
4b	3.437, 3.420*	$3.092_{(al)}$/$3.968_{(ar)}$
1c	3.310, 3.300*	3.373

*HPLC. All other values are obtained by UV-VIS.

Modeling and prediction: For the validation of correlation between the values log P_{exp} and log P_{cal}, we use partial least squares (PLS) model. The statistical parameters used to assess the quality of the model is the prediction error sum of squares (PRESS) of validation and finally the standard correlation coefficients R^2 [31].

$$PRESS = \sum_{i=1}^{n} (y_i - \hat{y}_i)^2$$

$$R^2 = 1 - \left(\frac{PRESS}{\sum_{i=1}^{n} ((y_i - \bar{y})^2)} \right)$$

In these equations, n is the number of compounds used for cross-validation, $\hat{y}_i$ and y_i represent the calculated and

the experimental value of the partition coefficient, respectively. $PRESS_{cal}$ is the prediction error sum of squares for all samples included in the model. One reasonable choice for the optimum number of factors would be that number which yielded the minimum PRESS value.

The Fisher test determine the significance of PRESS values whose F-ratio probability drops below 0.05 was selected as the optimum. Data were processed by an Eviews statistical package (Version 4 for Window). The results of all models built from PLS analysis are summarized in Table-3.

TABLE-3
CALCULATIONS OF STATISTICAL

Type of log P_{wo}	PRESS	Pro (Fisher-statistic)	Correlation coefficients R^2
log P^*- log $P_{cal(Br\ aliphatic)}$	0.31	0.0007	0.82
log P- log $P_{cal(Br\ aromatic)}$	0.53	0.0019	0.77
log P- log $P_{cal(Br\ aliphatic)}$	0.84	0.0210	0.55
log P^* - log $P_{cal(Br\ aromatic)}$	0.77	0.0194	0.56

log P* and log P (respectively were obtained by HPLC and UV-VIS).

Experimental log P_{wo} data obtained in this study for derivatives **1a**-**1c** are listed in the Table-2 together with calculated data. For most of compounds, experimental values were obtained by both HPLC and spectrophotometry UV-VIS; their close coincidence unequivocally proves the validity of the experimental results.

As mentioned in the Introduction section, many approaches have already been developed for log P calculation. Some of them offer results comparable to experimental measurement. As far as the cost is concerned, they are even superior. However, routine application of log P calculation procedures demand a continuous check of their validity by comparing with experimental data.

The great majority of these calculations are quite close to the experimental data. The models are acceptable according to the probability of fisher at a significance 95 % ($P < 5$ %) and the correlation between log P* obtained by HPLC and log P_{cal} (Br aliphatic) perform significantly better than the other models.

It must be noticed that when the fragmental f_{Br} aromatic value was used, the discrepancy between the experimental and calculated log P_{wo} was still higher than with the fragmental f_{Br} is aliphatic one. Also we inspected on the basis of (PRESS) values demonstrates that the correlation [log P-log $P_{cal\ (Br\ aromatic)}$] is superior to [log P-log $P_{cal\ (Br\ aliphatic)}$]. However, we found that the (PRESS) of correlation between the experimental partition coefficient obtained by UV-VIS and calculated log P is superior when we use the aliphatic value of bromine.

This finding reflects the importance of choice the type for the fragment (aromatic or aliphatic), since 1.2-dithiole-3-thione are considered as aromatic compounds[32], but Bortel *et al*., reported that these molecules contain a disulfide group forming, with three additional carbon atoms, an heterocyclic moiety displaying a weak aromatic character, with one carbonyl oxygen atom or one thio-carbonyl sulfura tom linked to one of the carbons of the dithiolic ring[33].

Another possible explanation is that the value of f_{Br} aromatic, might be overestimated. Indeed, a large difference between the value of f_{Br} aromatic given in the Ref.[25] and f_{Br} aromatic = 0.86 given in Ref.[29]. Also, the differences between experiment and calculation (Δ log P) exceeding ± 2.134 are observed for compound **5a**. Our results are insufficient because we have not the value of partition coefficient for **5a** obtained by HPLC.

In 4-aryldithiolethiones (ones): The comparison between the 4-aryl-1.2-dithiole-3-thiones and 4-aryl-1.2-dithiole-3-ones shows that the first are more lipophilic than the 4-aryl-1.2-dithiole-3-ones; the explanation of this result as we propose to its effect electronic attraction of the dithiolethiones and dithiolones. The 5-dithiolethiones-yl group is very strongly withdrawing group (as a nitro group) and the 5-dithiolones-yl group is slightly less attractive[26]. Another character is affected to the lipophilie is could be explained by considering the difference in hydrogen-bond capabilities of the water. The application of the bond hydrogen theory is more affirmative to the dithiolones that the dithiolethiones, it is demonstrated to compound next one like Fig. 2 (3-oxo-1.2-dithiole-4-carboxylic acid)[34].

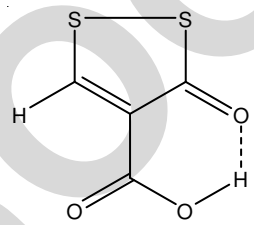

Fig. 2. 3-Oxo-1.2-dithiole-4-carboxylic acid

These characteristics indicate that the dithiolethiones and dithiolones nuclei and their respective substituents mutually disturb their physicochemical behaviour including partitioning.

On the other hand, in 4-aryldithiolethiones, the aryl fragment is not conjugated with the dithiole nucleus as shown by molecular modeling[8] (dihedral angle) 111º between aryl and dithiole nuclei) and the aryl fragments have a normal behaviour[6].

In 5-aryldithiolethiones (4a, 5a): The hydrophilicity of the **5a** can be explained through the function of nitroso which has a $f_{NO} = -1$[16].

log P (**4a**) = 3.82 is very higher than the value of log P (**5a**), we attributed this difference to the presence of a nitrogen or oxygen atom generally lowers the hydrophobicity[36].

For 5-bromo 4-aryl-1.2-dithiole-3-one: We note an elevation of log P_{wo} according to the very high steric hindrance. The effect of bromine in position 5 according to our semi-empiric calculations, these calculations are achieved with the help of the software MOPAC. The optimization of the geometry of the compounds have been produced with the PM3 method which PM3 calculations provide a simple, efficient and rapid methodology study of the structure of many molecules belonging to the same series[24]. Calculations give a the (dihedral angle) torsion angle Φ: Br-C_5-C_4-C_3 = 180º at stable conformation (low-energy)[36]. Therefore this result makes the growth of lipophilicity by the effect of conjugation[24].

Finally, we found $f_{C=N} = -1.092$, in good agreement with the value $f_{C=N} = -1.064$[31]. However, it is necessary to make additional research in order to study an exact value of this fragment.

Conclusion

Our analysis show experimental difficulties in the determination of log P_{wo} of dithiolethiones and their derivatives one of these difficulties arise from the fact that they are highly hydrophobobic.

The chemistry of dithiolethiones and dithiolones is, indeed, characterized by two main physico-chimical properties which may be born in mind: (i) they are aromatic compounds. (ii) the 3-thioxo-1.2-dithiole-5-yl group is a very strong electron-withdrawing. These two properties are important for lipophilicity of dithiolethione derivatives. We use the PLS method which has been shown to be an useful and power full tool to allow the prediction of the properties not available yet in the literature for **3b** and 4b.

However, it is necessary to make additional research in order to study other physic-chemical properties and biological activities for quite different sets of molecules. Work on this field is presently being made in our laboratory.

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