International Journal of Chemistry; Vol. 15, No. 1; 2023
ISSN 1916-9698 E-ISSN 1916-9701
Published by Canadian Center of Science and Education

Characterisation of the Molecular Lipophilicity of a Series of Seven Benzymidazolyl-Chalcone Molecules with Anthelmintic Activities

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Received: January 25, 2023 Accepted: February 27, 2023 Online Published: February 27, 2023

doi:10.5539/ijc.v15n1p1 URL: https://doi.org/10.5539/ijc.v15n1p1

Abstract

The aim of this work is to develop and improve anthelmintics that can contribute effectively to the control of certain new and resistant races of nematodes in the treatment of parasitic diseases in humans. This situation is of increasing concern to the agricultural, medical and health communities. The research carried out is particularly interested in the determination of the lipophilicity of a series of substituted molecules of the benzymidazolyl-chalcone family, molecules with proven activity against worms. This work has enabled us to predict and better understand their biological activities (antihistamines, antifungals, antiallergics, antibacterials and antivirals). It has also allowed us to identify the best anthelmintics that offer a broad spectrum of action, a high degree of efficacy, a good safety margin and a high degree of flexibility of use in order to limit resistance problems. The REKKER, KLOPMAN and IROFF methods and the MOLINSPIRATION software were used to determine the lipophilicity of these molecules. The values obtained for the partition coefficients revealed that these molecules are naturally lipophilic. These results allow us to appreciate the important role of molecular lipophilicity calculation methods in determining the mode of action of bioactive molecules.

Keywords: Benzymidazolyl-chalcone, partition coefficient, molecular lipophilicity

1. Introduction

Benzimidazolyl chalcones are organic compounds with two main structures: benzimidazole and chalcone. These two structures are well known in the pharmaceutical and medical community for their many interesting biological activities. Anthelmintics have been developed from these two bases to combat these parasites. However, for more than two decades, the constant appearance of new, resistant races of nematodes has increasingly threatened agricultural, medical and health communities. This threat is at least as alarming as the number of people infected throughout the world. These nematodes constitute a major cause of child mortality in developing countries. Moreover, transmission is human-to-human. The nematodes produce eggs in the intestines of the infected patient, who in turn releases them via the stool. The eggs may then contaminate water and food (fruit, vegetables, etc.), and thus contaminate the person who consumes them. This threat is exacerbated by the lack of effective anthelmintic drugs against these parasites due to the emergence and proliferation of resistant strains (Geerts & Gryseels, 2000; Waller, 2003). In this context of ineffectiveness of most anthelmintics, the health, nutritional and economic security of rural populations is hypothetical. To resolve this health problem, several solutions can be envisaged. Among these, the development of new and more efficient methods of improving anthelmintics is an excellent way forward. The human body is subject to numerous exogenous and endogenous pollutants which contribute to its destruction. It is constantly working to eliminate these pollutants. To free itself from all these pollutants, the organism must undergo a process of detoxification, which includes transforming lipophilic substances into hydrophiles. Lipophilicity is an important molecular parameter. It is closely related to the notion of sharing a molecule between an aqueous phase and a lipid phase. It is now known that the ability of a molecule to interact between two phases partly

conditions its biological properties such as transport, passage through membranes, bioavailability (distribution and accumulation), affinity for a receptor, binding by a protein, pharmacological activity, toxicity and accumulation in aquatic organisms. This work, which is part of the nematode control programme, focuses on a series of seven molecules selected from the benzymidazolyl-chalcone family. It aims to determine the lipophilicity of these molecules using the REKKER, KLOPMAN and IROFF methods as well as the MOLINSPIRATION software in order to predict and better understand their biological activities. Such a study makes it possible to propose a mechanism for eliminating the chimeric resistance of anthelmintics.

2. Materials and Methods

2.1 Materials

Several hundred compounds derived from benzimidazoles have been synthesised from which a few have been selected for their effective broad spectrum anthelmintic activity. Thus, the core of benzimidazolyl-chalcones is presented in Figure 1.

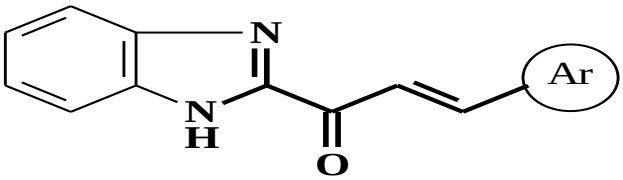
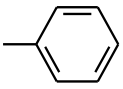
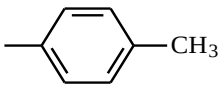
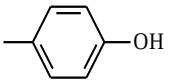
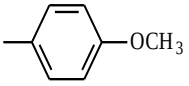
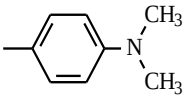
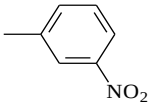
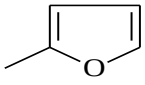


Figure 1. Substituted benzimidazolyl-chalcone compound

For this reason, for many years, several research teams have been interested in the synthesis of molecules based on chalcone rings and their numerous derivatives (Fatih, Adnan, & Vesile, 2006). In this work, we are interested in seven molecules, derivatives of benzimidazolyl-chalcones obtained by variation of the aryl substituent (Ar) as indicated in Table 1 and coded HM.

Table 1. Presentation of the molecular series studied (Benzimidazolyl- Chalcone, Serie HM)

CODE	Ar
HM_1	
HM_2	
HM_3	
HM_4	
HM_5	
HM_6	
HM_7	

These different molecules were synthesised by OUATTARA et al (Ouattara, et al., 2011). Benzimidazolyl-chalcone derivatives are of considerable pharmacological interest because of their therapeutic properties in many diseases. Several studies have shown that benzimidazolyl derivatives possess antihistaminic (Souness, Aldous, & Sargent, 2004), antifungal (Sanja, Podunavac, & Dragoljub, 2011), antiallergic (Ayhan-Kilcigil, Kus, Can-Eke, & Iscan, 2004), antibacterial (Carta, Loriga, Zanetti, & Sechi; Andriole, 2000; Emami, Shafiee, & Foroumadi, 2005) and antiviral (Mertens, Muller-Beckmann, Kampe, Holck, & W. Von der Saal, 1987) properties. These therapeutic properties are related to the conformation of the molecules and the interactions they can establish with each other. Knowledge of the molecular conformation and interactions requires the determination of physicochemical descriptors through theoretical chemistry. In order to combat substances that are more or less intoxicating to our organism, studies carried out in recent years have made it possible to determine an important parameter (the logarithm of the partition coefficient P). Knowledge of this parameter makes it possible to effectively assess the molecular properties of various organic substances. The logarithm of the partition coefficient P of a compound between water and octanol. Hansch and Fujita (Fujita, Iwana, & Hansch, 1964) in 1964, based on the work of Richet (Richet, 1893), Meyer (Meyer, 1899) and Overton (Overton, 1901) , proposed to use the logarithm of the partition coefficient log(P), (as a replacement for the olive oil-water system (Kubinyi, 2002)) to understand the interactions of this molecule with biological membranes. The value of log(P) is obtained by expression (1) below:

$$\boldsymbol{logP = log\left(\frac{C_{octanol}}{C_{H_2O}}\right)} \quad (1)$$

The higher this coefficient (p>1, log(P)>0), the more the substance is considered lipophilic and the lower this coefficient (p<1, log(P) <0), the substance is considered hydrophilic. Various statistical studies have highlighted the optimal values of logP, and this has resulted in a log(P) scale presented in Figure 2 (Lipinski, 1997).

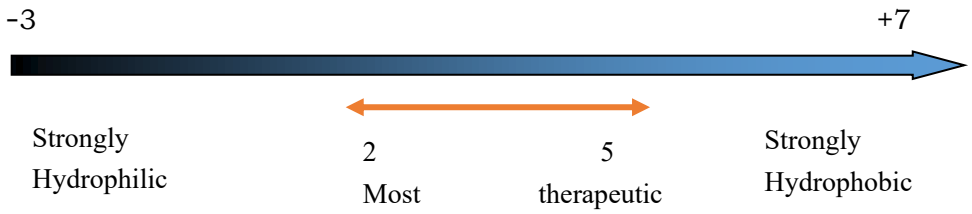


Figure 2. Log (P) scale

2.2 Methods

Most of the methods for determining the partition coefficient P suffer from the same problem, namely that their range of application is relatively narrow. On the other hand, due to the intrinsic nature of certain molecules, their logP is inaccessible to experiment. With the development of computing resources, especially computers, the determination of logP in the field of computer-aided design has become possible. To this end, there are several methods for determining logP, which differ from each other in the type of approximation used. The main methods for determining the partition coefficient are the following:

2.2.1 HANSCH Method

HANSCH (Sanja, Podunavac, & Dragoljub, 2011) considers that the substitution of a hydrogen of a group R which can be the benzene ring by a substituent X ($X = O$, NH_2, CH_2 ⋯), is equivalent to the insertion of a constituent of type $X - H$ to this radical, i.e. a OH for $X = O$, a NH for $X = NH_2$, a $CH3$ for $X = CH_2$ ⋯, etc. He assigned to each substituent its own lipophilicity called the HANSCH parameter noted $\boldsymbol{\pi X}$, thus knowing the partition coefficient of the molecule RH, one can easily deduce the logP of the RX molecule using formula (2) below:

$$\mathbf{logP_{RX} = logP_{RH} + \pi X + \pi_{corr}} \quad (2)$$

P_{RX}: Partition coefficient of the molecule RX ;

P_{RH}: Partition coefficient of the RH molecule

π_X: Lipophilic parameter of substituent X;

π_{Corr} : Corrective term taking into account the effect caused by branching, double bonds, ring closure, intramolecular bonds and molecular folding. The HANSCH parameter π for benzene substituents is defined by expression (3) below:

$$\boldsymbol{\pi(X) = logP_{C_6H_5-X} - logP_{C_6H_6}} \quad (3)$$

2.2.2 ABRAHAM's Equation

The Abraham equation (Andriole, 2000) allows the logP to be expressed from a set of parameters characteristic of the solute, namely molecular volume (favouring lipophilicity), acidity and basicity by hydrogen bonding (favouring hydrophilicity) and polarity or polarisability (also favouring hydrophilicity). The form of this equation is given by expression (4):

$$\mathbf{logP} = \mathbf{v}.\mathbf{V} + \mathbf{s}.\mathbf{S} + \mathbf{a}.\mathbf{A} + \mathbf{b}.\mathbf{B} + \mathbf{e}.\mathbf{E} + \mathbf{c} \quad (4)$$

The capital letters indicate the properties of the solute:

- V: molecular volume (ml/mol/100) ;
- S: polarity/polarisability;
- A: acidity by hydrogen bonding;
- B: basicity by hydrogen bonding;
- E: molar refractive excess (ml/mol/10) (depends on V and S).
- Lower case letters denote the properties of the solvent relative to water:
- v: Intensity of intermolecular bonds (v varies in the opposite direction) ;
- s: Polarity/polarizability ;
- a: Basicity by hydrogen bonding ;
- b: Acidity by hydrogen bonding;
- e: Combined influence of v and s

2.2.3 REKKER's Method

The REKKER method is used not only for its simplicity of application, but also for its efficiency in determining the lipophilicity of various molecules. According to REKKER, a molecule can be divided (theoretically) into elementary fragments each with a partial hydrophobicity constant f_n and the number of identical fragments in the molecule noted an. The logarithm of the partition coefficient P is obtained by adding the product of the constants an and f_n of all the fragments in the molecule (Rekker, Ter Laak, & Mannhold, 1993). It also takes into account some intermolecular effects (proximity of polar groups, hydrogen atom linked to a negative site, conjugation...). These lead to adding, for each of them, an additional contribution to the sum of the fn. This contribution is the product of a constant known as the "magic constant" noted C_M (**C_M = 0.219**), by a variable factor k_j called "key number". Thus, the expression of logP is translated by equation 5 below:

$$\mathbf{logP} = \sum_{\mathbf{n}} \mathbf{a_n} \,.\, \mathbf{f_n} + \mathbf{C_M} \sum_{\mathbf{j}} \mathbf{k_j} \quad (5)$$

The value of k_j is fixed by rules of thumb. On the other hand, the values of f_n have been tabulated for different organic solvent-water systems but are largely more numerous for the octanol-water system. This organic solvent has many analogies between its physico-chemical properties and those of biological membranes. **Table 2** gives the values of the hydrophobic constants for the main fragments. The constant is noted f_{al} when the fragment is bound to an aliphatic chain and f_{ar} when it is bound to an aromatic ring.

Table 2. Values of the fragment constants of lipophilicity according to REKKER

Fragment	$f_{aliphatic}$	$f_{aromatic}$
H	0.204	
C	0.110	
CH	0.315	
CH_2	0.519	
CH_3	0.724	
C_6H_5	-	1.902
N	-2.074	-0.979
O	-1.545	-0.450
F	-0.213	0.444
Cl	0.057	0.933
Br	0.258	1.134
NO_2	-0.915	-0.039
OH	-1.448	-0.353
CO	-1.633	-0.976
OCH_3	-0.821	0.274
Linked aromatic cycles	$+1C_m$	For each pair of common vertices, as well as for each link between two cycles
Conjugate bonds	$+1C_m$	By double or triple bond pair

Although the REKKER method is effective in the rapid and simple determination of molecular lipophilicity, it also has a number of shortcomings, including the incorrect description of the lipophilicity of complex molecules and the attribution of the same contribution to identical fragments belonging to different molecules. These shortcomings indicate the limitations of its application and the exploration of other new methods of calculation. Table 3 gives the corrective terms according to the chemical structure of the molecule and the related remarks.

Table 3. Corrective terms of the REKKER formula

CHEMICAL COMPOSITION	CORRECTION:$k\ C_M$	REMARKS
Non-conjugated aliphatic hydrocarbons		
Alkanes	$+2C_M$	Except methane and cyclopropane: $+1C_M$
Alkenes	0	No correction
Alkynes	$-1C_M$	By triple bond
Aromatic cycles		
Aromatic cycles	$+1C_M$	If we calculate from (C) and (H)
Aromatic cycles	0	If we use the constants $faromatic$
Bonded aromatic rings	$+1C_M$	For each pair of common vertices, as well as for each link joining two cycles
Basic fragment linked to two	$+1C_M$	
Conjugated hydrocarbons		
Conjugated bonds	$+1C_M$	By double or triple bond pair or triple bond
Compounds of types $X-(CH_2)-Y$		
Compounds of types $X-(CH_2)-Y$	$+4C_M$ $+2C_M$ 0	For $n=1$ For $n=2$ For $n>2$

2.2.4 KLOPMAN–IROFF Method

The KLOPMAN - IROFF quantum method (Klopman & Wang, 1991) (based on a log partition coefficient estimation approach) is based on quantum chemical calculations. For 61 simple organic compounds, the atomic charge densities were determined using the MINDO/3 method and a HÜCKEL method (Schrödinger, 1926) . The mathematical model thus developed is given by expression (6).

$$\mathbf{logP = 0,344 + 0,2078\ n_H + 0,093\ n_C - 2,119\ n_N - 1,937\ n_O - 1389\ q_C^2 - 17,28\ q_N^2 + 0,7316\ q_O^2 + 2,844\ n_A + 0,910\ n_T + 1,709\ n_M} \quad (6)$$

n_H, n_C, n_N, n_O : Respective number of atoms of hydrogen, carbon, nitrogen and oxygen;

$q_C^2\ q_N^2\ q_O^2$: Sum of the squared charges of the respective carbon, nitrogen and oxygen atoms or groups.

$n_A, n_T\ et\ n_M$: Indicator variables that indicate the presence of acid/ester, nitrile and amide groups respectively.

This method has some limitations due to its applicability only to compounds containing hydrogen, carbon, oxygen and nitrogen atoms and also due to the fact that the calculated charge distribution is not sufficient to characterise the solubility of a compound. These shortcomings indicate the limits of its application and the exploration of other new calculation methods.

2.2.5 Methods Using Free Software

The development of computer tools has contributed greatly to the availability of numerous means and automated methods of data processing. Thus, it is becoming possible with computer technology to find free software such as MOLINSPIRATION, ACD/ChemSketch and EPIWED adapted to the calculation of the partition coefficient (Fujita, Iwana, & Hansch, 1964; Richet, 1893; Meyer, 1899; Overton, 1901; Kubinyi, 2002; Lipinski, 1997; Rekker, Ter Laak, & Mannhold, 1993; Klopman & Wang, 1991; Schrödinger, 1926; Gunawardana, et al., 1999). These methods will be used to evaluate the molecular lipophilicity of mycolactones A/B and C. Indeed, KOWWIN/logP, Mi/logP and ACD/logP are substructure methods. KOWWIN/logP is a method that takes into account steric interactions between atoms, H-bonding and polar substructure effects. While the Mi/logP approach is based on functional groups taking into account intramolecular H-bonds and charge interactions. The ACD/logP approach is based on the contributions of individual atoms and structural fragments and on the intramolecular interactions between the different fragments. During the ACD/logP calculation, when fragment and interaction contributions are missing from the internal database, a special secondary algorithm is used to calculate them. In any case, the calculated values are provided with an uncertainty more or less equal to 0.6, a value indicated by the free ACD/ChemSketch software (Petrauskas, Maximowitsch, & Matulis, 2015). Beyond this uncertainty, it can be concluded that the compounds explored are new to the ACD/logP database.

3. Results and Discussion

The different 2D and optimised structures at the B3LYP/6- 31+G** level of the seven selected molecules in the benzimidazolyl-chalcone family are presented in Table 4.

Table 4. 2D and optimised structures at B3LYP/6- 31+G** level

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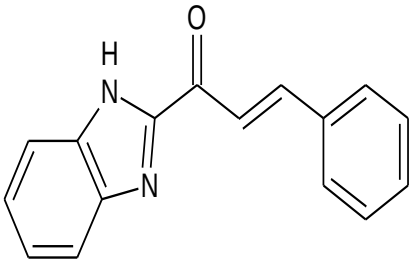
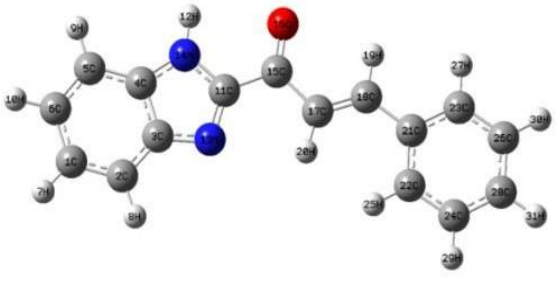
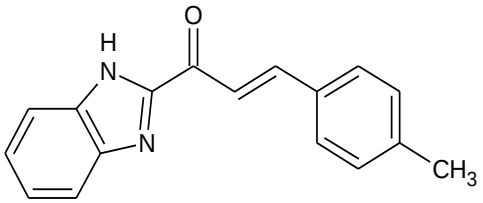
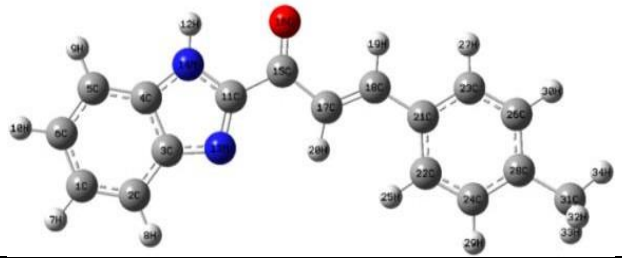
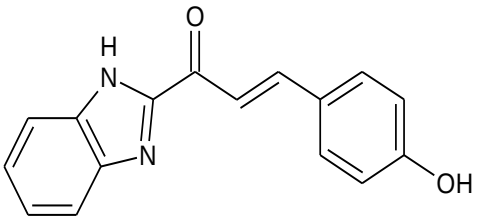
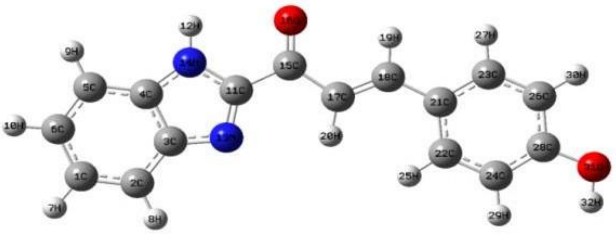
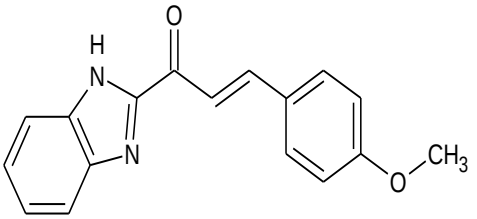
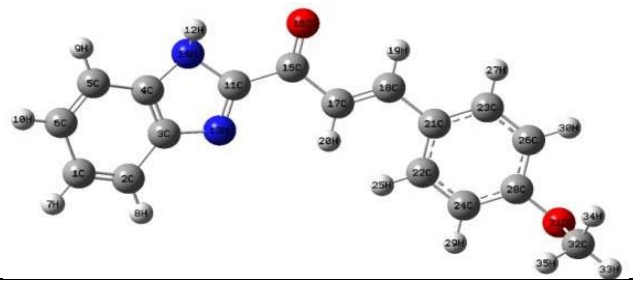
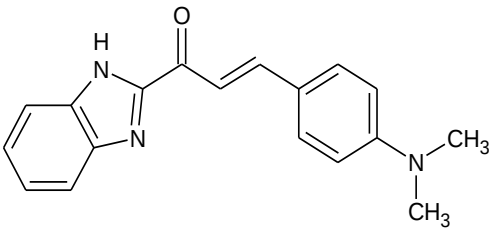
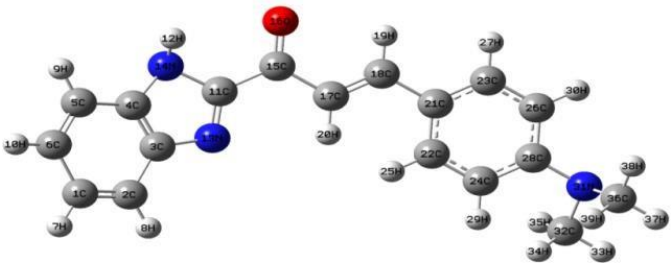
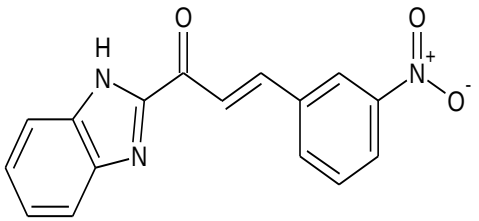
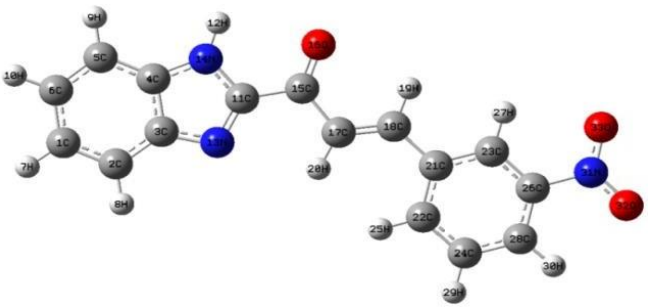
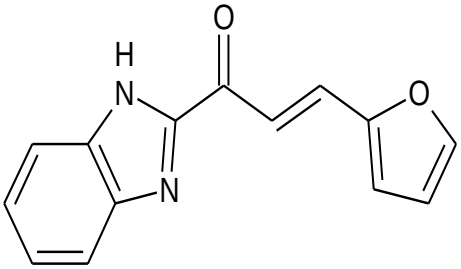
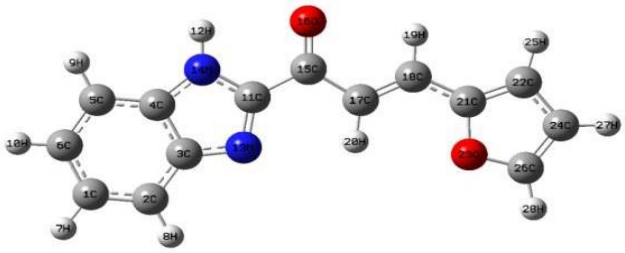
HM_1		

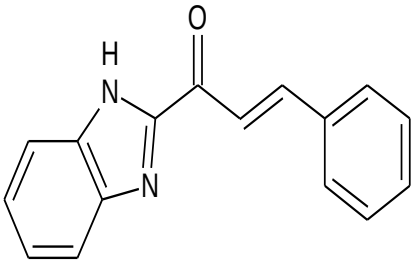
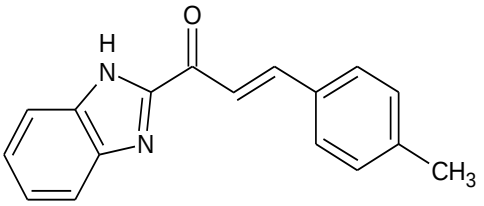
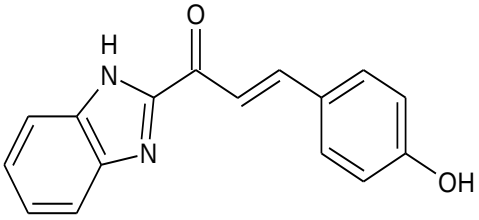
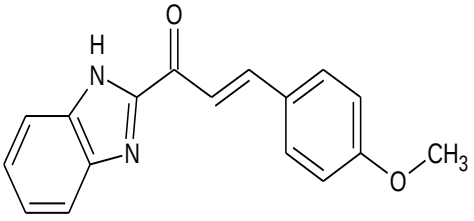
HM_2		
HM_3		
HM_4		
HM_5		
HM_6		

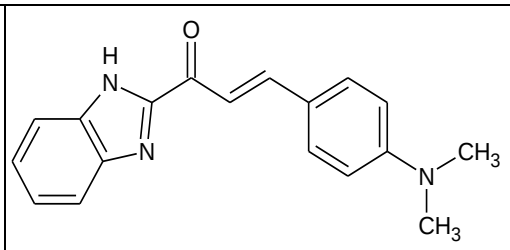
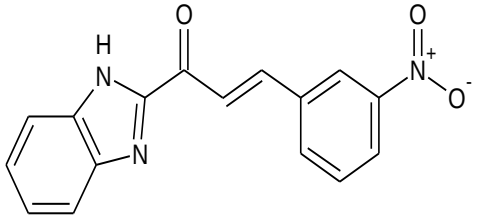
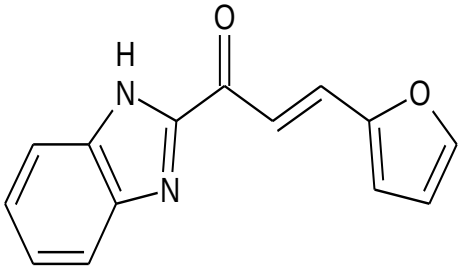
HM_7		

3.1 Calculation of Lipophilicity by the REKKER Method

Taking into account tables 2 and 3, the following calculations are obtained:

Table 5. Lipophilicity values by REKKER method

CODE	2D Structure	LogP values
HM_1		$\boldsymbol{logP}$ **(HM_1)** = $3f_{ar}\,(C_6H_5) + 2f_{ar}\,(N) + f_{ar}\,(CO) + 2f\,(CH) - 2f\,(C) + C_M\,(somet\ commun)$ $logP\,(HM\_1) = 3 \times 1.902 + 2 \times (-0.979) + (-0.976) + 2 \times 0.315 - 2 \times 0.110 + 0.219$ $\boldsymbol{logP(HM\_1) = 3.401}$
HM_2		**logP(HM_2)** = $logP(HM\_1) + f(CH_3)$ = 3.401 + 0.724 $\boldsymbol{logP(HM\_2) = 4.125}$
HM_3		**logP(HM_3)** = $logP(HM\_1) + f_{ar}(OH)$ = 3.401 − 0.353 $\boldsymbol{logP(HM\_3) = 3.048}$
HM_4		**logP(HM_4)** = $logP(HM\_1) + f_{ar}(OCH_3)$ = 3.401 + 0.274 $\boldsymbol{logP(HM\_4) = 3.675}$

HM_5		$\mathbf{logP(}\boldsymbol{HM\_5}\mathbf{)} = logP(HM\_1) + f_{ar}(N) + 2f(CH_3) =$ $3.401 - 0.979 + 2 \times 0.724$ $\boldsymbol{logP}(\boldsymbol{HM\_5}) = \mathbf{3.870}$
HM_6		$\mathbf{logP(}\boldsymbol{HM\_6}\mathbf{)} = logP(HM\_1) + f_{ar}(NO_2)$ $= 3.401 - 0.039$ $\boldsymbol{logP}(\boldsymbol{HM\_6}) = \mathbf{3.362}$
HM_7		$\mathbf{logP(}\boldsymbol{HM\_7}\mathbf{)} = 3f_{ar}(C_6H_5) - 3f(C) + 2f_{ar}(N) +$ $f_{ar}(CO) + 2f(CH) + f_{ar}(O) + C_M$ $\log P(HM\_7) = 3 \times 1.902 - 3 \times 0.110 + 2 \times (-0.979) -$ $0.976 + 2 \times 0.315 - 0.450 + 0.219$ $\boldsymbol{logP}(\boldsymbol{HM\_7}) = \mathbf{2.841}$

3.1.1 Discussion

All the lipophilicity values of the series of molecules are positive, so we can say that these seven molecules are all lipophilic:

$log(HM\_2) > logP(HM\_1)$: This increase in lipophilicity is due to the substitution of a hydrogen by a hydrophobic fragment CH_3 ;

$(HM\_3) < l(HM\_1)$: We have a decrease in lipophilicity due to the substitution of a hydrogen by a hydrophilic fragment OH ;

For the molecule HM_4, we have a slight increase in lipophilicity compared to HM_1, this is due to the substitution of the H of the OH fragment by $CH3$. Admittedly, the OCH_3 moiety is hydrophilic but its hydrophilicity is mitigated by CH_3.

For HM_5, the hydrophilicity of the nitrogen is attenuated by two CH_3 moieties, accounting for the increased lipophilicity of this molecule.

For HM_6, there is a decrease in lipophilicity due to the hydrophilic NO_2 fragment which is an electron-withdrawer.

There is a considerable decrease in the lipophilicity of HM_7 due to the presence of the fragment (2-Methylfuran). The presence of the oxygen atom (electronegative) in this ring favours hydrophilicity. According to REKKER's method, we obtain the following classification in increasing order of lipophilicity:

$$\mathbf{HM\_7 < HM\_3 < HM\_6 < HM\_1 < HM\_4 < HM\_5 < HM\_2}$$

3.2 Calculation of Lipophilicity by the Method of KLOPMAN and IROFF

The optimised 3D chemical structures at the B3LYP/6-31+G** level are shown in **Figure 3**. The optimisation is necessary since it is intended to record the value of the dipole moment of each of the molecules. After the optimisation of the molecules at the B3LYP/6-31+G** level, a single point calculation was then carried out at the MINDO/3 and HF/6-31+G** levels to obtain the dipole moment values. MINDO/3//B3LYP/6-31+G**.

Table 6. Lipophilicity and dipole moment values of the series of molecules at the MINDO/3//B3LYP/6-31+G** calculation level.

MINDO/3 level.									
Molecule	$\mu(D)$	n_H	n_C	n_N	n_O	q_C^2	q_N^2	q_O^2	$logP$
HM_1	**1.3476**	12	16	2	1	0.3735	0.0382	0.2933	**-2.8141**
HM_2	**1.5016**	14	17	2	1	0.3800	0.0383	0.2940	**-2.3153**
HM_3	**1.8622**	12	16	2	2	0.5950	0.0388	0.4934	**-4.9220**
HM_4	**2.1607**	14	17	2	2	0.7354	0.0388	0.4688	**-4.6272**
HM_5	**2.2647**	17	18	3	1	0.4982	0.0614	0.2852	**-4.2872**
HM_6	**5.0850**	11	16	3	3	0.4111	1.2074	0.9478	**-28.7909**
HM_7	**1.5989**	10	14	2	2	0.4812	0.0373	0.3990	**-5.4096**

Table 7. Lipophilicity and dipole moment values of the series of molecules at the HF/6- 31+G**//B3LYP/6-31+G** calculation level

Level HF/6-31+G**									
Molecule	$\mu(D)$	n_H	n_C	n_N	n_O	q_C^2	q_N^2	q_O^2	$logP$
HM_1	**0.9380**	12	16	2	1	1.3107	0.3813	0.3503	**-10.0022**
HM_2	**1.7197**	14	17	2	1	1.7959	0.3833	0.3525	**-10.2009**
HM_3	**1.789**	12	16	2	2	2.1912	0.3826	0.6748	**-12.9481**
HM_4	**2.4448**	14	17	2	2	2.0595	0.3823	0.5552	**-12.3381**
HM_5	**2.5856**	17	18	3	1	2.7684	0.4256	0.3314	**-13.7013**
HM_6	**5.5855**	11	16	3	3	3.3646	0.3861	0.3874	**-19.1125**
HM_7	**1.6665**	10	14	2	2	2.7713	0.3864	0.4903	**-14.5557**

3.2.1 Discussion

For all seven (7) molecules, the logP values are all negative for both calculation levels. This means that all these molecules are hydrophilic. The hydrophilic character is much more accentuated at the HF/6-31+G** level than at the MINDO/3 level, except for the HM_6 molecule. The HM_6 molecule is very hydrophilic (logP is -28.79 or -19.11), this character is due to the presence of the electron-withdrawing group NO_2. The HM_2 molecule is the least hydrophilic (-2.315) for MINDO/3 but not in the case of HF/6-31+G**. In contrast to the MINDO/3 level, the values of the HF/6-31+G** level are very high in absolute value. The 6-31+G** basis is an ab initio method that takes into account the diffuse functions of anions/heteroatoms characterised by non-bonding orbitals occupying a larger region of space. This level of calculation predicts more hydrophilic molecules than the semi-empirical MINDO/3 method. The ranking in order of increasing lipophilicity according to the MINDO/3 method is as follows:

HM_6 < *HM*_7 < *HM*_3 < *HM*_4 < *HM*_5 < *HM*_1 < *HM*_2

Using the HF/6-31+G** method, the following ranking is obtained:

HM_6 < *HM*_7 < *HM*_5 < *HM*_3 < *HM*_4 < *HM*_2 < *HM*_1

3.3 Calculation of Lipophilicity by the Free Software MOLINSPIRATION

Using the MOLINSPIRATION software, the molecular lipophilicity values for the HM series are given in Table 8.

Table 8. Lipophilicity values by MOLINSPIRATION

Molecule	HM_1	HM_2	M_3	HM_4	HM_5	HM_6	HM_7
$logP$	**3.408**	**3.857**	**929**	**3.465**	**3.511**	**3.367**	**2.486**

3.3.1 Discussion

The lipophilicity values of the seven molecules are all positive. Thus, according to MOLINSPIRATION, we have lipophilic molecules. The arguments put forward in the case of REKKER are valid here because the lipophilicity of the molecules follow the same evolution, in increasing order.

$$\mathbf{HM\_7 < HM\_3 < HM\_6 < HM\_1 < HM\_4 < HM\_5 < HM\_2}$$

3.4 Comparison of the Values of the $logP$ of the Three Methods

The analysis of the logP values obtained by the three approaches is shown in Table 9.

Table 9. Comparison of the lipophilicity of the three methods

	REKKER	**MOLINSPIRATION**	**KLOPMAN - IROFF**	
			MINDO/3	**HF/6-31+G****
Molecules	$logP$	$logP$	$logP$	$logP$
HM_1	3.401	3.408	-2.814	-10.002
HM_2	4.125	3.857	-2.315	-10.201
HM_3	3.048	2.929	-4.922	-12.948
HM_4	3.675	3.465	-4.627	-12.338
HM_5	3.870	3.511	-4.287	-13.701
HM_6	3.362	3.367	-28.791	-19.112
HM_7	2.841	2.486	-5.4096	-14.556

3.4.1 Discussion

The results obtained by the semi-empirical or ab initio quantum methods indicate hydrophilic molecules. However, the logP values obtained by either method are not in agreement, although all are negative. On the other hand, the results from the empirical methods of REKKER and the MOLINSPIRATION software agree, unlike those of KLOPMAN-IROFF. It should be borne in mind that the KLOPMAN-IROFF method was established on the basis of a sample of only 61 simple organic compounds. Moreover, the atomic charges on which this method is based are not sufficient to characterise the solubility of a compound. Indeed, the atomic charges in a molecule are not observable quantities and imply a "sharing" of electrons between the atoms which always presents a more or less arbitrary character. Their absolute values are likely to vary considerably depending on the basis used.

We are therefore inclined to favour the results obtained using REKKER's methods and the MOLINSPIRATION software. However, it should not be forgotten that the ideal would be to obtain experimental values for these molecules. This would allow us to confirm or deny the lipophilic nature of these molecules.

4. Conclusion

This work has enabled us to recall the notions of the partitioning phenomenon and the partition coefficient, which enable the molecular lipophilicity to be calculated. Generally speaking, there are several methods for calculating molecular lipophilicity. Of these, experimental methods are the most accurate. As for the theoretical methods, they make it possible to predict the lipophilicity of molecules. The REKKER fragment method discussed in this study is in perfect agreement with the QSAR method of the MOLINSPIRATION software. These two methods showed us that the seven molecules are lipophilic. On the other hand, the KLOPMAN-IROFF quantum method is difficult to implement because of certain parameters such as the indicator variables linked to certain chemical functions, and notably the atomic charge, an arbitrary parameter, on which this method is based. Thus the quantum method of KLOPMAN. IROFF results in a rather hydrophilic nature of the seven molecules. To decide on the lipophilic nature of these molecules, it would be judicious to determine the experimental values of lipophilicity of the series of HM molecules in order to confront them with the theoretical values obtained. The difficulties in calculating molecular lipophilicity arise from the fact that most methods do not have a wide range of application. This purely theoretical work allowed us to familiarise ourselves with the computer tool used in quantum chemistry through the use of the GAUSSIAN 03 software for the determination of the MULLIKEN charges and the dipole moment of the seven molecules.

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