HYDROBET – a novel method for calculation of hydrophobic/hydrophilic balance of New Asymmetric Porphyrins as Potential Photosensitizers in Photodynamic Therapy. The usefulness of the new APORBET index in the QSPR studies

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Abstract: - Experimental values of molecular hydrophobicity R_{M0} have been correlated with the values calculated by using a novel method of calculation, named HYDROBET, resulting satisfactory values for correlation coefficient ($R^2 = 0.865$). A new molecular descriptor named APORBET was formulated and used in QSPR studies for modelling of some parameters such as: retention time (R_T), chromatographic parameter R_f and the maximum of lenghtwave ($\lambda_{max.}$) regarding new asymmetric porphyrins involved in this study, lending confidence in increased predictive power of the above mentioned QSPR models.

Key-Words: - porphyrins, photosentisizers, molecular hydrophobicity R_{M0}, HYDROBET, APORBET, QSPR

1 Introduction

Tetrapyrrolic macrocicles such as porphyrins, chlorines and bacteriochlorins play a vital role to life and implicit in chemical, biological and physical research. Porphyrins are synthetically interesting and a ubiquitous class of medically useful compounds as DNA binding agents [1-3] in photodynamic therapy (PDT), boron neutron capture therapy (BNCT), radiation therapy (RT) and in magnetic resonance imaging (MRI) [4-6].

PDT is a non-invasive treatment method that is based on combined action of a photosensitizer, light and molecular oxygen to attack pathological tissues.

An ideal so-called second generation photosensitizer has to be a pure compound, absorb light strongly at wavelengths above 650 nm (longer wavelengths of activation allow for deeper tissue penetration), have no systemic toxicity, be characterized by a high fluorescence quantum yield, long triplet life time, localize with high selectivity in the damaged tissue that shall be destroyed and induce a high amount of tumor necrosis.

To overcome the mischief of the current family of photosensitizers on the market [7], it is critical to rapidly expand our present knowledge with an interdisciplinary research approach based at the interface of chemical, computational, physical, biological, and medical sciences.

The quality of a photosensitizer depends on chemical and physical parameters such as lipophilicity, type and number of electrical charges, charge-to-mass ratio, type and number of ring and core substituents.

It was reported that substitution in phenyl groups with hydroxyl [8] confers some degree of hydrophilicity and may cause a bathochromic shift-moving Q Band to red and this was a start to find an innovative formulation for new photosensitizers based on hydroxyphenyl systems.

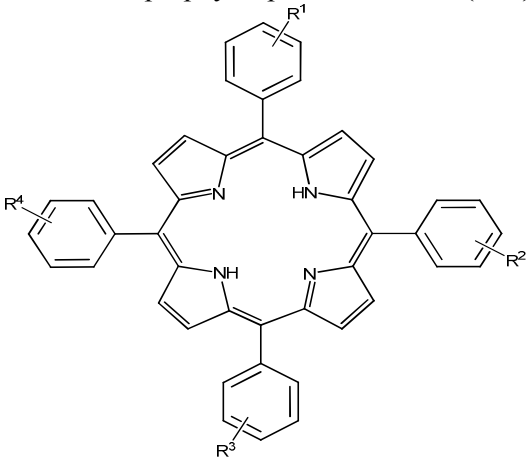
On the other hand, tailoring porphyrins by modifying the *meso*-aryl groups typically further increases the size and molecular weight, which is undesirable for medical applications wherein molecules passively cross the blood–brain barrier

and a molecular weight of less than 800 u is considered limitative [9-10].

As a consequence of previous published research involving synthesis of novel second-generation porphyrin photosentisizers [11] and of some hybrid porphyrin-silica advanced optoelectronic materials [12] and taking into consideration our experience in computational chemistry [13] we try to pave the way for possible further intense theoretical and applicative studies in this way.

Biological applications of chemical compounds are dependent by the way in which the compounds are interacting with biomembranes, these interactions being governed by hydrophobic/hydrophilic balance of these compounds.

This paper is focused on promoting a new method of calculation (HYDROBET) of hydrophobic parameter R_{M0} (hydrophobic /hydrophilic balance) for six porphyrin photosentisizers [11] **(1a-f)** but also the formulation of novel APORBET index used for modelling of some physical-chemical characteristics of the six above mentioned porphyrin photosentisizers **(1a-f).**



where:

$R^1 = R^2 = R^3 = 3$, 4-diMeO; $R^4 = 3$-OH; (**1a**)
$R^1 = R^2 = R^3 = R^4 = 3$, 4-diMeO; (**1b**)
$R^1 = R^2 = 3$, 4-diMeO; $R^3 = R^4 = 3$-OH; *cis*-(**1c**)
$R^1 = R^2 = 3$, 4-diMeO; $R^3 = R^4 = 3$-OH; *trans*-(**1d**)
$R^1 = R^2 = R^3 = 3$-OH; $R^4 = 3$, 4-diMeO; (**1e**)
$R^1 = R^2 = R^3 = R^4 = 3$-OH; (**1f**)

Fig. 1. Structures of porphyrin photosentisizers **1a-f**

2 Results and discussions

Starting from experimental TLC data (R_f) molecular hydrophobicity R_{M0} was calculated (Table 1) by applying the following equations:

$$R_M = \log(1/R_f - 1) \quad (1)$$

$$R_M = R_{M0} + bK \quad (2)$$

where R_{M0} is the extrapolated R_M for zero concentration in the water – organic solvent mixture, and *b* is the change in the R_M value caused by increasing the concentration (*K*) of the organic component in the mobile phase. The hydrophobicity of compounds **1a-f** decreases in the order **1c=1d>1a>1b>1e>1f** (hydrophilicity increasing obviously in the reverse order) (Table 1).

The present paper is promoting a novel method of calculation (HYDROBET) for hydrophobic parameter R_{M0} (hydrophobic/hydrophilic balance), based on equation (3), in case of some new asymmetrical porphyrins, and we consider that the method has potential of application for determining the value of hydrophobic parameter R_{M0} both in cases of other classes of porphyrinoid derivatives.

$$R_{MO_{(calcd.)}} = \log P + \left(\frac{R}{HSA}\right)^{HIN} \cdot P + \frac{\log(VM - RM)}{D} \quad (3)$$

where R_{M0} is the calculated molecular hydrophobicity, *logP* is the hydrophobicity calculated via Hansch fragment constants [14], *R* is radius of gyration [17], *HSA* is hydrophilic surface area, *HIN* is hydrophilic intensity number, *P* is Hansen polarity [18], *VM* is molar volume, *RM* is molar refractivity and *D* is number of donor hydrogen bonds.

Molar volume (VM) and molar refractivity (RM) were calculated by using ChemSketch 11.0 Freeware [19], logP by using EPI Suite v. 3.20 [14] and the other parameters were calculated by using DRAGON software [20].

In Table 2 and Figure 2 we present the calculated logP values, the experimental and calculated values of the molecular hydrophobicity R_{M0} according to Eq. (3).

2.1 The new molecular descriptor APORBET used in QSPR (Quantitative Structure-Property Relationship) modelling of some physical-chemical properties in case of new asymmetric porphyrins involved in this study

For improvement of predictive quality of QSPR models implying retention time (R_T), R_f values or maximum wavelenght (λ_{max}) concerning new asymmetric porphyrins a new molecular descriptor named APORBET was introduced, comprising an energetic component (E), one hydrophobic/hydrophilic (R), an electronic component (H) and a topological one (T). APORBET is presented in equation 4:

$$APORBET = TE + R_{M0(calcd.)} + HE + J/NB \quad (4)$$

where: E = TE represents the total energy (energetic component), R = $R_{M0\ (calcd.)}$ represents molecular hydrofobicity calculated by means of equation 3 (Table 2) (hydrophobic/hydrophilic component),

Comp.	Exp.									Calcd. logP[14]
	R_M in aqueous THF, conc.(v/v)				Statistical parameters					
	90%	85%	80%	70%	R_{M0}	*b*	*R*	*F*	*SD*	
1a	-0.720	-0.688	-0.907	-0.788	-2.674	0.022	0.951	19.22	0.075	6.303
1b	-0.698	-0.688	-0.907	-1.123	-2.740	0.023	0.963	25.95	0.067	6.015
1c+1d	-0.720	-0.788	-1.004	-1.123	-2.629	0.021	0.966	27.93	0.059	6.328
1e	-0.865	-0.954	-1.278	-1.278	-2.887	0.022	0.891	6.428	0.128	5.982
1f	-0.788	-0.937	-1.004	-1.362	-3.314	0.028	0.988	88.21	0.044	5.868

Table 1. Experimental hydrophobicity (RM0, b)[a] and calculated (log P) [14] for compounds **1a-f**

[a]RM0 = molecular hydrophobicity (eq. 2); *b* = change in RM value caused by increasing the concentration (K) of the organic component in the mobile phase (eq. 1); *R* = correlation coefficient for parameters RM0 and *b* in eq. 2 [15,16]

Compds.	logP	R	HSA	HIN	P	VM	RM	D	$R_{M0(calc.)}$	$R_{M0(exp.)}$
1a	6.303	8.622	10.87	9.931	8.074	655.1	229.7	3	7.988	-2.674
1b	6.015	8.959	9.987	15.77	3.313	694.6	240.7	2	7.941	-2.740
1c	6.328	8.301	11.75	6.088	11.08	615.5	218.7	4	8.313	-2.629
1d	6.328	8.262	11.75	6.100	11.08	615.9	218.7	4	8.270	-2.629
1e	5.982	8.036	12.64	6.247	13.60	576.1	207.7	5	7.298	-2.887
1f	5.868	7.623	13.53	5.458	15.93	536.5	196.7	6	6.985	-3.314

Table 2. Structural parameters, calculated logP values, experimental and calculated R_{M0} values, Eq. (3), for porphyrin photosentisizers **1a-f**

H = HE represents the sum of Hammett [21, 22] and quasi-Hammett electronic constants [23], T = J/NB is the ratio between the Balaban (J) [24] topologic index and the number of bonds (NB) (topological component). The values of total energy, of topologic index J and the number of bonds for the novel asymmetric structures of porphyrins involved in the present study have been calculated by using DRAGON programme.[20] The values of APORBET index and the values of the other parameters involved in formulation of this index for porphyrinic compounds **1a-f** are presented in Table 3.

APORBET index (as presented in Table 3) represents a modality for discrimination of *cis/trans* (**1c/1d**) isomers when it is used in QSPR modeling.

2.2 Results of QSPR by using APORBET index as one of the descriptors

2.2.1 Modelling of retention times (R_T, min) for porphyrin photosentisizers 1a-f

The optimal multilinear regression with two descriptors is:

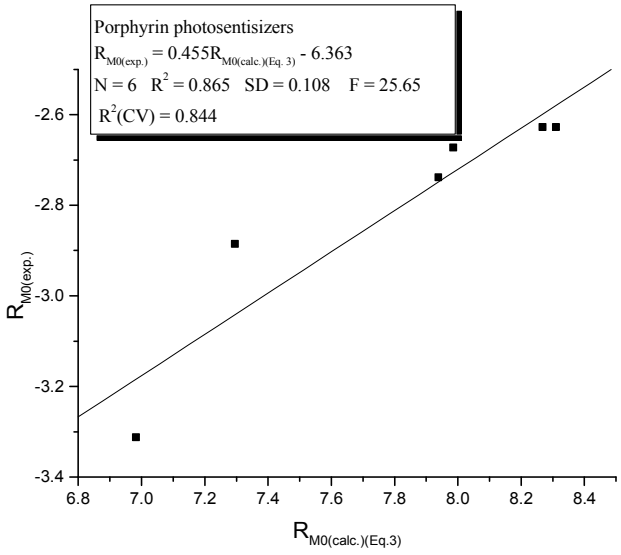


Fig. 2. Experimental versus estimated, Eq. (3), molecular hydrophobicity (R_{M0}) values for porphyrin photosentisizers **1a-f**

Compd.	TE (Kcal/mol)	$R_{M0\ (calc.)}$ (eq.3, Table 2)	ΣHE	J	NB	APORBET (eq. 4)
1a	149.2	7.988	-0.33	1.3357	111	156.8
1b	156.8	7.941	-0.60	1.3423	118	164.1
1c	141.5	8.313	-0.06	1.3321	104	149.7
1d	214.2	8.270	-0.06	1.3321	104	222.4
1e	133.8	7.298	0.21	1.3388	97	141.3
1f	126.4	6.985	0.48	1.3412	90	133.8

Table 3. Values of structural parameters and APORBET index for porphyrin photosentisizers **1a-f**

$$R_T=3.501\cdot10^{-3}(\pm6.893\cdot10^{-4})\text{APORBET}-2.272\cdot10^{-2}(\pm3.350\cdot10^{-3})\text{MW}+22.04 \quad (5)$$

N = 6 R^2 = 0.941 SD = 0.447 F = 24.11 R^2(CV) = 0.895

where: MW is molecular weight calculate by means of CODESSA programme [25].

In Table 4 we present the values of the indices involved in construction of QSPR model (Eq. 5) besides the experimental [11] and estimated values (Eq. 5) of the retention times for compounds **1a-f**.

2.2.2 Modelling of R_f parameter for porphyrin photosentisizers 1a-f

The model with the most predictive power in case of chromatographic parameter R_f for porphyrin photosentisizers **1a-f** is presented in equation 6:

$$R_f=-7.098\cdot10^{-4}(\pm6.002\cdot10^{-4})\ \text{APORBET}+5.358\cdot10^{-3}(\pm6.646\cdot10^{-4})\text{IC}(0)-0.277 \quad (6)$$

N = 6 R^2 = 0.957 SD = 0.038 F = 33.48 R^2(CV) = 0.908

where: IC(0) is information content (order 0) calculated by using CODESSA programme [25].

In Table 5 we present both the values of the indices involved in construction of QSPR model (Eq. 6) and the experimental [11] and estimated values (Eq. 6) of the chromatographic parameter R_f for compounds **1a-f**.

Compd.	APORBET (Table 3)	MW	R_T (calc., min.) (Eq. 5)	R_T (exp.) (min.) [11]	Resid.
1a	156.8	810.9	4.165	3.973	0.192
1b	164.1	854.9	3.191	3.560	-0.369
1c	149.7	766.8	5.142	4.573	0.569
1d	222.4	766.8	5.396	5.373	0.023
1e	141.3	722.7	6.114	6.427	-0.313
1f	133.8	678.7	7.088	7.230	-0.142

Table 4. Values of the indices involved in construction of QSPR model (Eq. 5) and experimental and estimated retention times (R_T) values for porphyrin photosentisizers **1a-f**

Compd.	APORBET (Table 3)	IC(0)	R_f (calc.) (Eq. 6)	R_f(exp.)[11]	Resid.
1a	156.8	182.8	0.59	0.60	-0.01
1b	164.1	199.6	0.67	0.66	0.01
1c	149.7	165.0	0.50	0.54	-0.04
1d	222.4	165.0	0.44	0.45	-0.01
1e	141.3	145.5	0.40	0.35	0.05
1f	133.8	121.8	0.28	0.29	-0.01

Table 5. Values of the indices involved in construction of QSPR model (Eq. 6) besides experimental and estimated chromatographic parameter (R_f) values for porphyrin photosentisizers **1a-f**

3 Conclusion

It can be concluded that the molecular hydrophobicity R_{M0} for the novel asymmetric porphyrins **1a-f** could be modeling by using the original mathematical relation (HYDROBET) (eq. 3).

By comparing the experimental values of molecular hydrophobicity R_{M0} with the values calculated by using equation 3 (Table 2) it was obtained a good agreement for correlation coefficient ***R*** (Figure 2). This demonstrates that the new method is offering an efficient way in prediction of hydrophobic/hydrophilic balance also for other classes of porphyrins and porphyrin analogues.

The promoting of the new molecular descriptor APORBET (Table 3) in QSPR models in case of retention times (R_T) (Eq. 5, Table 4), chromatographic parameters R_f (Eq. 6, Table 5) respectively for porphyrin photosentisizers **1a-f** increase the predictive value of the models. The complex structure of APORBET index allow *cis/trans* (**1c/1d**) isomers discrimination.

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