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Correlation between structure, retention, property, and activity of biologically relevant 1,7-bis(aminoalkyl)diazachrysene derivatives

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ABSTRACT

The physicochemical properties, retention parameters (R_M^0), partition coefficients ($\log P_{OW}$), and pK_a values for a series of thirteen 1,7-bis(aminoalkyl) diazachrysene (1,7-DAAC) derivatives were determined in order to reveal the characteristics responsible for their biological behavior. The investigated compounds inhibit three unrelated pathogens (the Botulinum neurotoxin serotype A light chain (BoNT/A LC), *Plasmodium falciparum* malaria, and Ebola filovirus) *via* three different mechanisms of action. To determine the most influential factors governing the retention and activities of the investigated diazachrysenes, R_M^0, $\log P_{OW}$, and biological activity values were correlated with 2D and 3D molecular descriptors, using a partial least squares regression. The resulting quantitative structure–retention (property) relationships indicate the importance of descriptors related to the hydrophobicity of the molecules (*e.g.*, predicted partition coefficients and hydrophobic surface area). Quantitative structure–activity relationship models for describing biological activity against the BoNT/A LC and malarial strains also include overall compound polarity, electron density distribution, and proton donor/acceptor potential. Furthermore, models for Ebola filovirus inhibition are presented qualitatively to provide insights into parameters that may contribute to the compounds' antiviral activities. Overall, the models form the basis for selecting structural features that significantly affect the compound's absorption, distribution, metabolism, excretion, and toxicity profiles.

1. Introduction

Physicochemical screens are increasingly being used during the early stages of drug discovery to provide a more comprehensive understanding of the key properties that affect the biological disposition (*i.e.*, ADME—absorption, distribution, metabolism, and excretion) of promising leads [1,2]. The most commonly measured physicochemical properties are permeability and solubility (due to their importance in the gastrointestinal absorption of orally administered drugs), and lipophilicity, pK_a, integrity, and stability (as these properties generally affect the pharmaceutical potential of a compound).

Lipophilicity is a fundamental property of compounds that serves as a benchmark for predicting solubility, permeability, and protein binding [2], as it is indicative of a compound's preference for van der Waals interactions with other molecules *versus* hydrogen bonds or polar interactions with water and protein receptors. The lipophilicity is usually expressed as a logarithm of partitioning between 1-octanol and water ($\log P_{OW}$) [3]. The Organization for Economic Co-operation and Development (OECD) Guidelines for the Testing of Chemicals [4], Test 117, describes a method for determination of $\log P_{OW}$ using reversed-phase high performance liquid chromatography (RPHPLC). In several publications the HPLC method is substituted with thin-layer chromatography (TLC) [5], keeping the same principles as in Test 117, with RP-18 stationary phase and the composition of the mobile phase that provide optimal selectivity. The advantages of RPTLC method are: (1) only a small amount of sample is needed for estimation, (2) low sensitivity to impurities, (3) rapid determination, (4) good accuracy and reproducibility, and (5) greater applicability to compounds with higher lipophilicity [6]. Thus, the RPTLC enables determination of a retention parameter, R_M^0 [7], which reflect the partition of the compound between non-polar stationary phase and polar aqueous mobile phase, thereby enabling the estimation of the lipophilicity of the tested compounds.

A second compounds' descriptor—the ionization coefficient (represented by the acidity constant pK_a), is also pivotal for estimating the physicochemical behavior of compounds and their

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distribution over a pH gradient. Determination of pK_a values rely on the measurement of any physical property that varies with protonation [8]. Over the past few decades, it has been found that potentiometric and spectrophotometric determination, although among the oldest of methods, are the most useful in this capacity, as simple equipment and solutions are used [9].

Quantitative structure–retention relationship (QSRR) and quantitative structure activity (property) relationship (QSA(P)R) models correlate solute molecular structures, to their chromatographic behavior, *i.e.* their pharmaco-biochemical activities. For such studies, mathematical models are developed to facilitate the prediction of activities, or properties, of compounds that have not yet been synthesized or examined in *in vitro* and/or *in vivo* experiments. These models can aid in rationalizing hypotheses for the mechanism of compound–receptor binding [10,11].

Recently, a series of 1,7-diazachrysene (1,7-DAAC)-based derivatives were synthesized and determined to be potent inhibitors of three unrelated pathogens: the BoNT/A LC, a Zn(II) metalloprotease (which causes the paralysis associated with botulism), *Plasmodium falciparum* (which causes malaria), and Ebola filovirus (EBOV) (which causes hemorrhagic fever) [12,13]. With respect to mode of action, three different mechanisms are employed, thus demonstrating the unique antipathogenic potential of this chemotype. Hence, based on the significant and diverse biological activities of the indicated compounds, they form an ideal test set for further determination of the fundamental chemical characteristics responsible for their behavior in the biological environment.

The goals of this study were: (i) to experimentally determine the physicochemical properties, retention parameter (R_M^0), and partition coefficient ($\log P_{OW}$) as measures of lipophilicity, as well as pK_a values, for the series of indicated 1,7-DAAC derivatives (*vide supra*), and (ii) to determine the compound's 2D and 3D molecular descriptors, and in conjunction with their physicochemical parameters and empirical biological data [12], use multivariate statistical analysis (principal component analysis and partial least square regression) to determine crucial factors governing retention and activity to propose structural features that contribute to the ADME-Tox profiles for the compounds.

2. Experimental

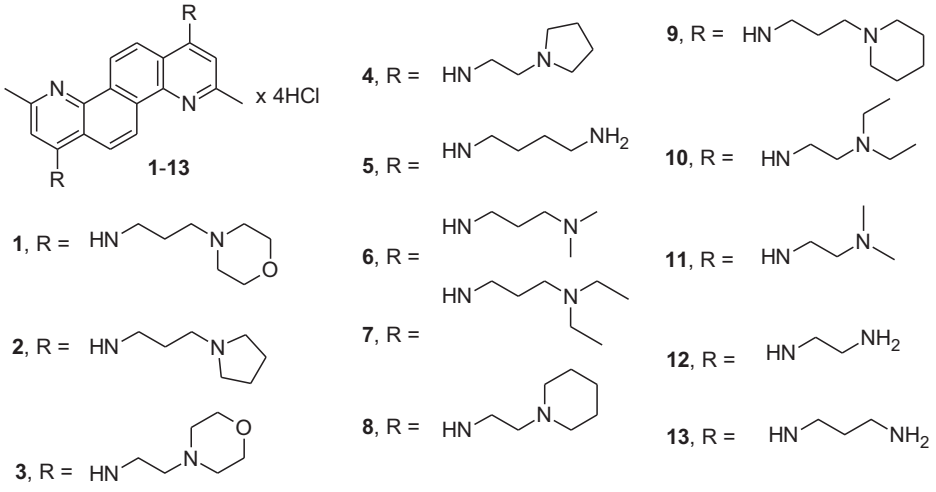
2.1. Reagents

The synthesis and characterization of the studied 1,7-DAAC derivatives (Table 1) has been reported [12].

All standard compounds were purchased from Aldrich (Milwaukee, WI, USA), Fluka (Buchs, Switzerland), or Merck (Darmstadt, Germany), while their experimentally determined $\log P_{OW}$ values were obtained from the literature [14]. Standards were chosen based on their structural similarity to the investigated 1,7-DAAC derivatives. The optimal range of $\log P_{OW}$ values was considered broad enough to provide reliable regression performance ($1-4\log P_{OW}$ units). The following nine compounds with known $\log P_{OW}$ values (provided in parentheses) were selected as standards (mainly naphthalene and quinoline

Table 1
Experimentally determined parameters of lipophilicity and biological activity for investigated compounds **1**–**13**.

Comp.	R_M^0 [b]	$\log P_{OW}$	Biological activity[a]			
			BoNT/A LC (%)	D6 IC_{50} (nM)	W2 IC_{50} (nM)	C235 IC_{50} (nM)
1	2.29	4.24	55.6	5.23	2.00	8.05
2	3.41	5.39	73.5	14.84	7.75	34.29
3	2.18	3.88	39.0	5.93	6.13	9.84
4	3.02	5.13	60.3	16.76	8.11	25.9
5	2.29	4.00	72.3	1029.42	345.68	1027.45
6	3.15	5.66	68.9	103.47	352.71	54.82
7	3.75	5.80	64.7	30.01	8.65	66.5
8	3.06	4.74	63.4	8.79	5.50	10.55
9	3.49	5.39	66.1	9.26	6.98	24.84
10	2.91	5.13	55.4	6.01	3.48	3.32
11	2.56	4.49	57.0	15.61	9.19	15.27
12	1.76	3.51	62.7	270.29	871.25	1021.04
13	2.09	4.12	70.0	708.29	1701.59	2030.86



[a] Taken from Ref. [12].
[b] R_M^0 = retention parameter.