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Convenient way to experimentally determine the lipophilicity (logP) of new synthetic biologically active compounds using high-performance liquid chromatography in the series of 2,2-disubstituted 4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolanes

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Abstract

Using high-performance liquid chromatography with a reversed phase, the lipophilicity indices ($logP_{OW}$) of synthetic biologically active compounds in the series of 2,2-disubstituted 4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolanes have been experimentally determined by high-performance liquid chromatography with a reversed phase. It has been determined using standards – the known azol fungicides. The method is fast, productive, simple and accurate.

Keywords: lipophilicity, logP, HPLC, fungicides, 1,2,4-triazoles, dioxolanes.

INTRODUCTION

Lipophilicity is a physico-chemical property that characterizes the ability of a chemical compound to dissolve in fats (lipids) and non-polar solvents. Lipophilicity plays an important role in the development of drugs and pesticides, since this parameter affects the pharmacokinetic and pharmacodynamic behavior of a biologically active substance [1, 2]. According to IUPAC, lipophilicity reflects the affinity of a molecule or a fragment thereof with a lipophilic medium [3].

Log P is a component of the Lipinski's rule. This empirical rule allows to estimate the bioavailability of a chemical compound and its ability to be a drug on the basis of the structural and physicochemical characteristics of a molecule [4].

QSAR played an important role in the design of the commercial agrochemicals: herbicides, insecticide and fungicides. The initial postulates are that there are three major factors needed to rationalize variations in a set of congeners producing a standard response in a test system: electronic, hydrophobic, and steric. Hammett Taft electronic parameters and logP or hydrophobic parameters could account for two of these three major factors, then it might be possible to discern steric effects. It is surprising that this simple set of principles has been used to elucidate literally thousands of QSAR for almost every imaginable type of chemicobiological interaction [5].

The translocation of agrochemicals in plants has been shown to be connected to their hydrophobicity in term of the $logP_{OW}$ value (P: 1-octanol / water partition coefficient) in certain respects, «the systemic activity» of agrochemicals in relation to their systemicity in plants has been well understood. Taking into account the lipophilicity index of new synthesized compounds is also important when searching for synthetic fungicides and plant growth regulators. [6]. Since 1990, a further 11 new triazoles have reached the agricultural market stage. The value of $logP_{ow}$ for the majority of systemic fungicides is 3.2-3.85, only for the two remaining more lipophilic compounds, it reaches values of 4.21 and 4.94 [7].

QSAR have been performed to a series of known and new antifungal azoles (tetraconazole) in their control of two diseases, caused by *Erysiphe graminis* and *Puccinia graminis*. The dependence of fungicidal activity on logP has been revealed. [8].

In particular, we have previously shown [9-14] that 2,2-disubstituted 4-(azol-1-ylmethyl)-1,3-dioxolanes exhibit a high fungicidal activity with the values of $logP_{OW}$ equal to 3.0-4.0 [10].

The experimental determination of lipophilicity using a classical method, consisting in determining the concentration of the substances distributed between the two phases: 1-octanol and water [15, 16] - cannot always be applied because of the possible insolubility of the test compounds in both octanol and water.

MATERIALS AND METHODS

To determine lipophilicity experimentally, we used a known correlation between the chromatographic retention time of a substance and its lipophilicity that is implemented in practice using high-performance liquid chromatography with a reversed phase or reversed phase TLC plates [17-59]. The method we have chosen has a number of advantages as compared to the classical method for determining lipophilicity: it is characterized by high accuracy and productivity, and requires the use of small

amounts of the test substances, time, and allows to use substances with a purity of less than 90% or a mixture of substances with a basic substance content of up to 50%.

To determine lipophilicity values using the HPLC method, a calibration «Retention time-logP» curve was constructed for the reference substances with the known $logP_{OW}$ values previously experimentally determined using a classical method (**Tab. 1, Fig.2 A**). To reduce the differences between the reference substances and the test substances related to the specific interactions of the fragments of molecules of substances with the stationary phase, we used azol fungicides with the known logP values: flutriafol (**1**), triadimenol (**2**), cyproconazole (**3**), triadimefon (**4**), tebuconazole (**5**) and diniconazole (**6**) as the reference substances [61]. These widely used azole fungicides were chosen because their structures comprise 1,2,4-triazole, aromatic and aliphatic fragments as well as the structures of 2,2-disubstituted 4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolanes **7-10.**

A homologous series of the previously synthesized 2-(4-chlorophenyl)-2-alkyl-4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolanes **7, 8, 9, 10** with a high fungicidal activity [9, 10]: (**Fig. 1**) was chosen as the objects for determining $logP_{OW}$.

When carrying out the studies using reversed-phase HPLC, the samples were analyzed using a «Waters» liquid chromatograph with a Nova-PakC18 column (7.0x390 mm) and a photodiode matrix. The detection wavelength is 254 nm. Aqueous acetonitrile 80% was used as the mobile phase. The flow rate was 1 ml/min at a pressure of 13.3 MPa.

The test substance (3 mg) and 2 ml of eluent were added into a standard tube of 15 ml, the tube was shaken for 1 minute and filtered in a vacuum of a water jet pump. The samples were injected in 3µl with a «Hamilton» micro-syringe. The repetition of the experiment was threefold. The eluent was chosen in such a way that the retention time of the most hydrophilic compound was longer than the «dead volume» yield time, and did not exceed that of the most lipophilic compound by 10 minutes.

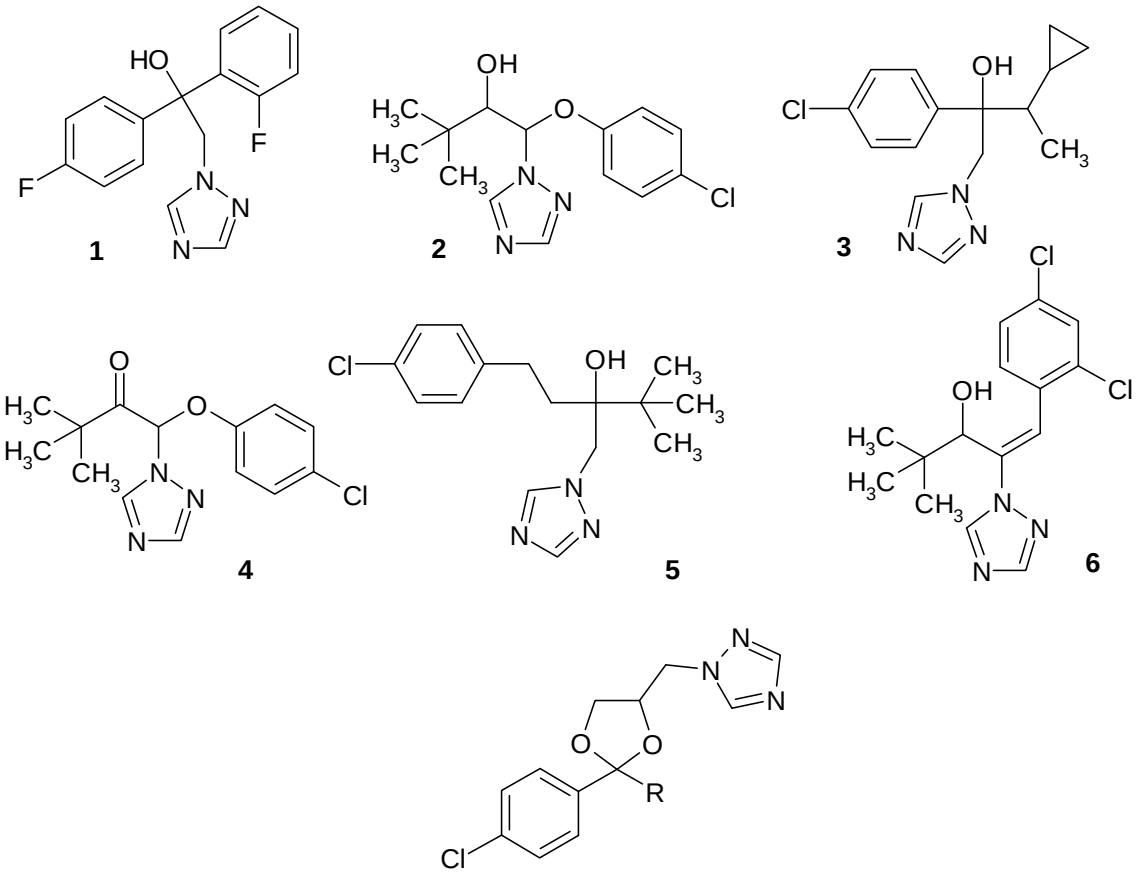

Fig. 1

Table 1. Chromatographic retention time of reference substances

№	Reference substances	Retention time, min	Known (reference) $logP_{OW}$ [61]
1	flutriafol	2.27	2.29
2	triadimenol	2.75	3.08
3	cyproconazole	2.90	2.91
4	triadimefon	2.96	3.11
5	tebuconazole	3.23	3.70
6	diniconazole	3.69	4.30

Table 2. Chromatographic retention time of the test compounds and the calculated $logP_{OW}$ value

№	R	Retention time, min	Determined $logP_{OW}$	Calculated (ACD Labs[62]) $logP_{OW}$
1	CH_3	2.13	2.20	2.10
2	C_2H_5	3.14	2.91	2.63
3	n-C_3H_7	3.76	3.34	3.17
4	n-C_4H_9	4.45	3.82	3.70

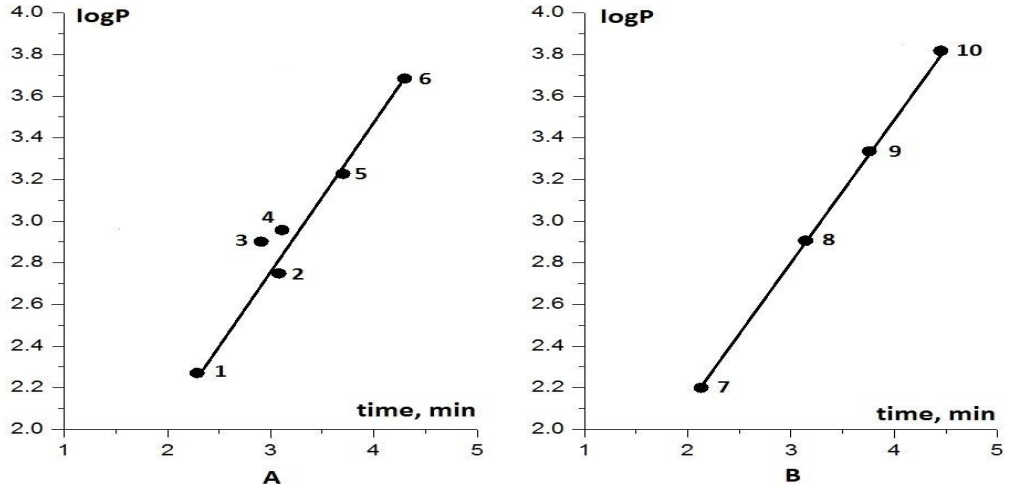

Fig. 2. Calibration curve (**A**) and the experimental values of lipophilicity (**B**) obtained therefrom

RESULTS AND DISCUSSION

After determining the retention time of each of the drugs studied, their lipophilicity (logP) was determined using the calibration curve (**Tab. 2, Fig. 2B**).

The deviation from linear dependence for triadimefon **4** is probably caused by its structural distinction. The latter is a ketone in contrast to the other substances which are a number of alcohols. A deviating lipophilicity value of the cyproconazole **3** is likely due to the presence of strained cyclopropyl fragment in its structure.

CONCLUSION.

The method of high performance liquid chromatography with a reversed phase is convenient for measuring the lipophilicity index of synthetic biologically active substances of the series of 2,2-disubstituted 4-(1,2,4-triazol-1-ylmethyl)-1,3-dioxolanes. The obtained lipophilicity indices are comparable with the theoretically calculated values of the lipophilicity index using commercial computer programs [62].

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