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Preparation and Hydrophobic Properties of 5 Arylalkylidenerhodanines

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Abstract: Some 5-arylalkylidene-2-thioxo-1,3-thiazolidine-4-one derivatives were prepared as potential antimicrobial compounds. General synthetic approach of all newly synthesized compounds is presented. All the discussed rhodanine derivatives were analyzed using the reversed phase high performance liquid chromatography (RP-HPLC) method for the lipophilicity measurement. The procedure was performed under isocratic conditions with methanol as an organic modifier in the mobile phase using end-capped non-polar C_{18} stationary RP column. In the present study the correlation between RP-HPLC retention parameter log *K* (the logarithm of capacity factor *K*) and log *P* values calculated in various ways is discussed as well as the relationships between the lipophilicity and chemical structure of the studied compounds.

Keywords: 5-Arylalkylidenerhodanines; Lipophilicity measurement; Structure-lipophilicity relationships.

Introduction

Rhodanine scaffold is present in many classes of biologically active compounds. A number of them showed antimicrobial and antifungal activities [1, 2]. Some rhodanine derivatives showed also anti-inflammatory activity [3]. Benzylidene rhodanines have gained strong attention recently due to their activity as perspective antineoplastic agents [4].

In view of a wide spectrum of biological properties a pilot series of new substituted rhodanine derivatives were prepared especially as potential antifungal agents.

Prediction of absorption, *e.g.* the transport of a molecule through cellular membranes, is one of major prerequisites for pharmacological screening and drug development. The drugs most frequently cross the biological barriers by the passive transport, which strongly depends on the lipophilicity. Therefore hydrophobicity is one of the most important physical properties of biologically active compounds. This thermodynamic parameter describes the partitioning of a compound between an aqueous and an organic phase and is characterized by the partition (log *P*) coefficient. Classical methods for the determination of these constants are time consuming and not always sufficiently reliable. Therefore, reversed phase high performance liquid chromatography (RP-HPLC) methods have become popular and widely used for lipophilicity measurement. A general procedure is the measurement of the directly accessible retention time under isocratic conditions with varying amounts of an organic modifier in the mobile phase using end-capped non-polar C_{18} stationary RP columns and calculating the capacity factor *K*. Log *K*, calculated from the capacity factor *K*, is used as the lipophilicity index converted to log *P* scale [5].

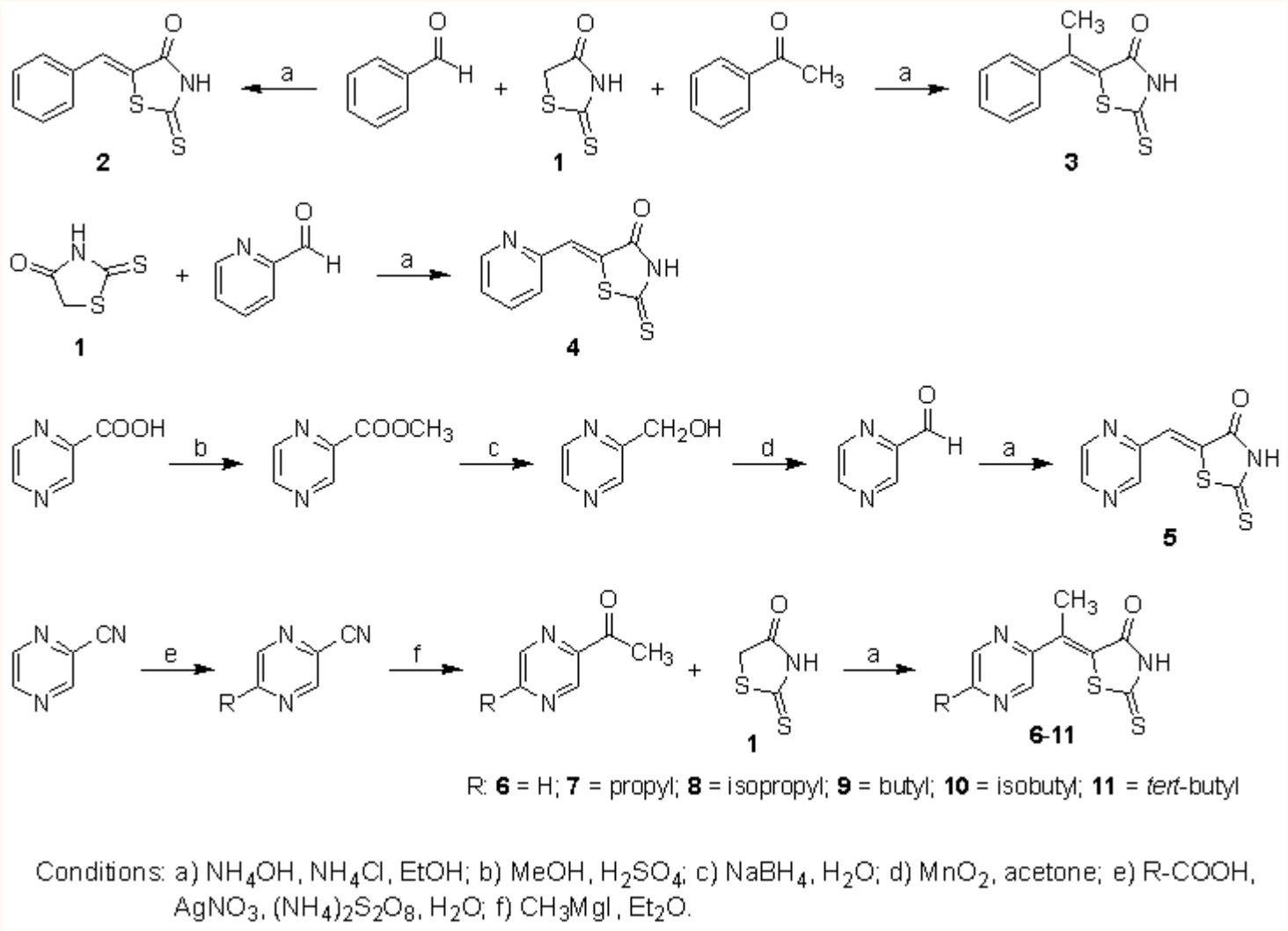
This contribution is a follow-up work to the previous papers [6—15] aimed at the synthesis, physicochemical properties and biological testing of newly prepared potential drugs based on nitrogen containing heterocycles.

Results and Discussion

Benzaldehyde, pur. (VEB Laborchemie), pyridine-2-carboxaldehyde, 99% (Aldrich), acetophenone, pur. (Reachim) and rhodanine, puriss. p.a. (Fluka), were used for the synthesis. Pyrazine-2-carbaldehyde was prepared using a procedure reported previously [6, 16]. Acetylpyrazines were synthesized according to refs. [7—10]. Condensation of the starting compounds to 5-arylmethylidenerhodanines and 5-(1-arylethylidene)rhodanines was performed in ethanol using NH_4OH / NH_4Cl as a catalyst.

A mixture of an aldehyde or a ketone (0.015 mol), rhodanine (0.015 mol) and ethanol (15 ml) was heated under reflux condenser until all solid components dissolved. Concentrated ammonia solution (1.1 ml) and solution of ammonium chloride (1.0 g) in 2 ml of hot (80 °C) distilled water were then added, and the reaction mixture was refluxed for 2 h (aldehydes) or 5 h (ketones). After cooling, the separated solid was filtered through a sintered filter, washed with distilled water (50 ml) and then with 50% ethanol (50 ml). For analysis, the product was crystallized from absolute ethanol and dried 24 hours in the desiccator at 1.33 kPa. The purity of samples was checked by RP-HPLC and elemental analysis. Their structures were confirmed by melting points and spectral data (UV, IR, ^{1}H NMR and ^{13}C NMR).

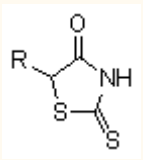
Scheme 1. Synthesis and structures of the target 5-substituted rhodanine derivatives **1**—**11**.

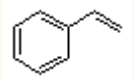


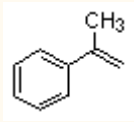
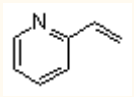
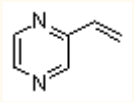
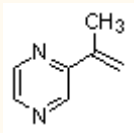
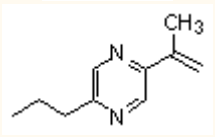
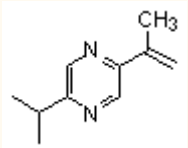
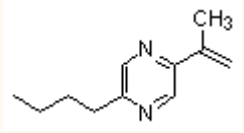
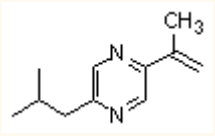
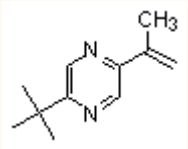
Hydrophobicities (log *P* / Clog *P* data) of the studied compounds **1**—**11** were calculated using two commercially available programs and measured by means of RP-HPLC determination of capacity factors *K* with a subsequent calculation of log *K*. The procedure was performed under isocratic conditions with methanol as an organic modifier in the mobile phase. The results are shown in Table 1 and illustrated in Figure 1. In the figure they are arranged in the ascending manner according to the experimental log *K* values.

Substituted 5-aryl- and 5-(1-heteroarylethylidene)rhodanines reported here are much more hydrophobic than the starting material pyrazinecarbonitriles and acetylpyrazines described previously [8].

Table 1. Calculated lipophilicities (log *P* / Clog *P*) and determined log *K* of the studied compounds **1**—**11**.

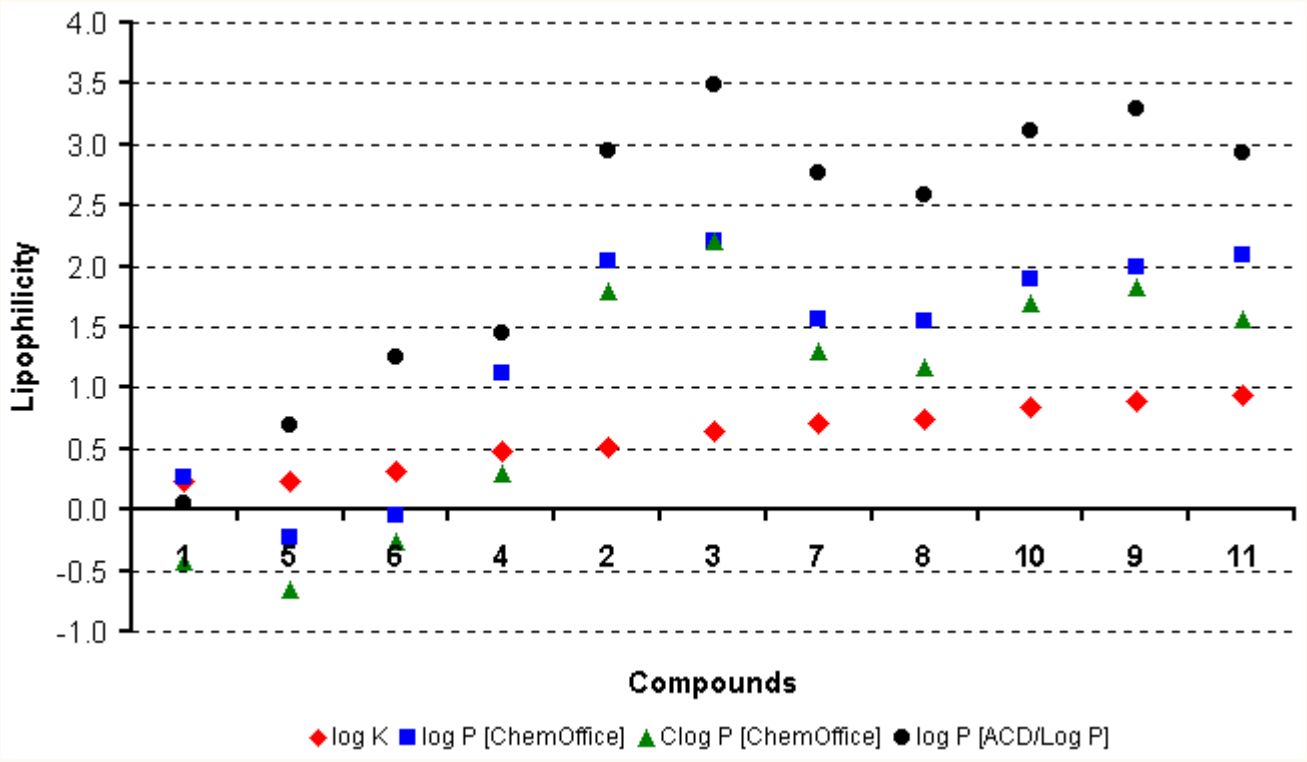


Compound	R	log *K*	log *P* / Clog *P* ChemOffice	log *P* ACD/Log P
1	H	0.2272	0.26 / -0.431	0.06 ± 0.76
2		0.5122	2.04 / 1.802	2.94 ± 0.76
3		0.6484	2.21 / 2.201	3.49 ± 0.77

				
4		0.4864	1.12 / 0.305	1.45 ± 0.76
5		0.2359	-0.22 / -0.652	0.69 ± 0.77
6		0.3187	-0.04 / -0.253	1.25 ± 0.79
7		0.7134	1.57 / 1.304	2.77 ± 0.79
8		0.7365	1.55 / 1.174	2.59 ± 0.79
9		0.8872	1.99 / 1.833	3.30 ± 0.79
10		0.8390	1.90 / 1.703	3.12 ± 0.79
11		0.9424	2.09 / 1.573	2.93 ± 0.79

The results obtained with most compounds show that the experimentally determined lipophilicities (log *K* values) are lower than those indicated by the calculated log *P* / Clog *P*, see Figure 1. The results show that the experimentally determined log *K* values correlate relatively well with log *P* values calculated by means of the ACD/Log P program, whereas log *P* / Clog *P* data calculated using the ChemOffice software did not show good agreement.

Figure 1. Comparison of the log *P* / Clog *P* data calculated using the two programs with the experimentally found log *K* values. The discussed compounds are ordered according to the log *K* values increase.



As expected, unsubstituted rhodanide (**1**) showed the lowest lipophilicity. 5-[1-(5-*tert*-Butylpyrazin-2-yl)ethylidene]rhodanine **11** possessed the highest hydrophobicity. As expected, the dependence between log *K* and the length of the non-branched alkyl substituents in pyrazine ring **6**, **7**, **9** (H, C_3H_7, C_4H_9) as well as the dependence between log *K* and the length of the connection linker in compounds **2**, **3** or **5**, **6** (H, CH_3) is approximately linear.

5-[1-(5-Isopropylpyrazin-2-yl)ethylidene]rhodanine **8** is slightly more lipophilic than the corresponding propyl derivative **7**, contrary to all the computed data. 5-[1-(5-Isobutylpyrazin-2-yl)ethylidene]rhodanine **10** is slightly less lipophilic than its congeners **9** (R = butyl) and **11** (R = *tert*-butyl). This is in good agreement with the results of our previous studies [8, 9], but contrary to the calculated log *P* data.

Unsubstituted 5-(pyrazin-2-ylmethylidene)rhodanine (**5**) and 5-[1-(pyrazin-2-yl)ethylidene]rhodanine (**6**) show significantly low hydrophobicity), see Figure 1. As expected, both pyrazine derivatives **5** and **6** possess lower lipophilicity than 5-(pyridin-2-ylmethylidene)rhodanine (**4**), which shows hydrophobicity similar to that of 5-benzylidenerhodanine (**2**).

The discussed molecules are highly functionalized structures, especially due to the rhodanine part of the molecule. Great differences between the experimental and calculated lipophilicity values could be observed for some compounds. This fact may be caused by intramolecular interaction, as reported in the references [8—11 and 14, 15].

Experimetal

Lipophilicity HPLC determination (capacity factor K / calculated log K)

The HPLC separation module Waters Alliance 2695 XE and Waters Photodiode Array Detector 2996 (Waters

Corp., Milford, MA, U.S.A.) were used. The chromatographic column Symmetry® C_{18} 5 µm, 4.6 × 250 mm, Part No. WAT054275, (Waters Corp., Milford, MA, U.S.A.) was used. The HPLC separation process was monitored by Millennium32® Chromatography Manager Software, Waters 2004 (Waters Corp., Milford, MA, U.S.A.). The mixture of MeOH p.a. (70.0%) and H_2O-HPLC — Mili-Q Grade (30.0%) was used as a mobile phase. The total flow of the column was 0.9 mL/min, injection 30 µL, column temperature 30 °C and sample temperature 10 °C. The detection wavelength 210 nm was chosen. The KI methanolic solution was used for the dead time (T_D) determination. Retention times (T_R) were measured in minutes.

The capacity factors *K* were calculated using the Millennium32® Chromatography Manager Software according to the formula $K = (T_R - T_D) / T_D$, where T_R is the retention time of the solute, whereas T_D denotes the dead time obtained via an unretained analyte. Log *K*, calculated from the capacity factor *K*, is used as the lipophilicity index converted to log *P* scale. The log *K* values of the individual compounds are shown in Table 1.

Lipophilicity calculations

Log *P*, *i.e.* the logarithm of the partition coefficient for *n*-octanol / water, was calculated using the programs CS ChemOffice Ultra ver. 7.0 (CambridgeSoft, Cambridge, MA, U.S.A.) and ACD/Log P ver. 1.0 (Advanced Chemistry Development Inc., Toronto, Canada). Clog *P* values (the logarithm of *n*-octanol / water partition coefficient based on established chemical interactions) were generated by means of CS ChemOffice Ultra ver. 7.0 (CambridgeSoft, Cambridge, MA, U.S.A.) software. The results are shown in Table 1.

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