12th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-12) 1-30 November 2008
http://www.usc.es/congresos/ecsoc/12/ECSOC12.htm & http://www.mdpi.org/ecsoc-12

[C0006]

Rhodanineacetic Acid Derivatives as Potential Drugs: Preparation and Hydrophobic Properties of 5-Arylalkylidene-3-carboxymethylrhodanines

Veronika Opletalova[1], Josef Jampilek[2,3*], Jan Dolezel[1], Petra Hirsova[1], Jiri Dohnal[1,3]

[1] Department of Pharmaceutical Chemistry and Drug Control, Charles University in Prague, Faculty of Pharmacy in Hradec Kralove, 500 05 Hradec Kralove, Czech Republic

[2] Zentiva a.s., U kabelovny 130, 102 37 Prague 10, Czech Republic; e-mail: josef.jampilek@zentiva.cz, tel.: +420-2-67243695, fax: +420-2-72701331

[3] Department of Chemical Drugs, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Palackeho 1/3, 61242 Brno, Czech Republic

* Author to whom correspondence should be addressed.

Abstract: Some (5-arylalkylidene-4-oxo-2-thioxothiazolidin-3-yl)acetic acids were prepared as potential antimicrobial compounds. General synthetic approach of all synthesized compounds is presented. All the discussed rhodanine-3-acetic acid 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. RP-HPLC retention parameter log *k* (the logarithm of capacity factor *k*) is compared with log *P* values calculated *in silico*. The relationships between the lipophilicity and chemical structure of the studied compounds are discussed as well.

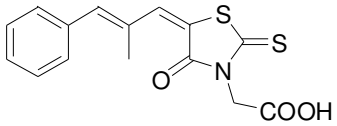
Keywords: 5-Arylalkylidenerhodanine-3-acetic acid derivatives; Lipophilicity measurement; Structure-lipophilicity relationships.

INTRODUCTION

In 1997, a study based on database search showed that the prevalence of rhodanine-containing compounds of pharmaceutical interest is very small despite the fact that the compounds exhibit a wide variety of bioactivity [1]. One of the reasons may be poor solubility of rhodanine derivatives in water. However, in rhodanineacetic acids this problem can be overcome by preparing suitable salts.

Rhodanine-3-acetic acid was prepared by Korner [2] in 1908, and condensation products of the acid with various aldehydes were reported in the same year [3]. Since that time, many

5-arylalkylidene-3-carboxymethylrhodanines have been prepared and studied as potential antimycobacterial [4,5], antifungal [6-12], pesticidal [13-15], antihypertensive [16], and antineoplastic [17,18] agents. Rhodanine carboxylic acid derivatives have also be patented for the treatment and prevention of metabolic bone disorders. It was found that they stimulate parathyroid hormone receptor-mediated cAMP formation and could be useful for the local and systemic treatment of rheumatoid arthritis, osteoarthritis and degenerative arthrosis [19]. The only rhodanineacetic acid derivative that has been used clinically is an aldose reductase inhibitor **epalrestat**. It is marketed in Japan and used to slow eye damage associated with diabetes and to prevent diabetic peripheral neuropathy [1,20,21].



epalrestat

Aldose reductase is not the only enzyme inhibited by rhodaninecarboxylic acids. It was found that many other enzymes are inhibited by the derivatives of this structural class, and the enzyme inhibition may be, at least in part, the mechanism responsible for various biological effects of rhodanine derivatives [22-36].

Prediction of 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 [37].

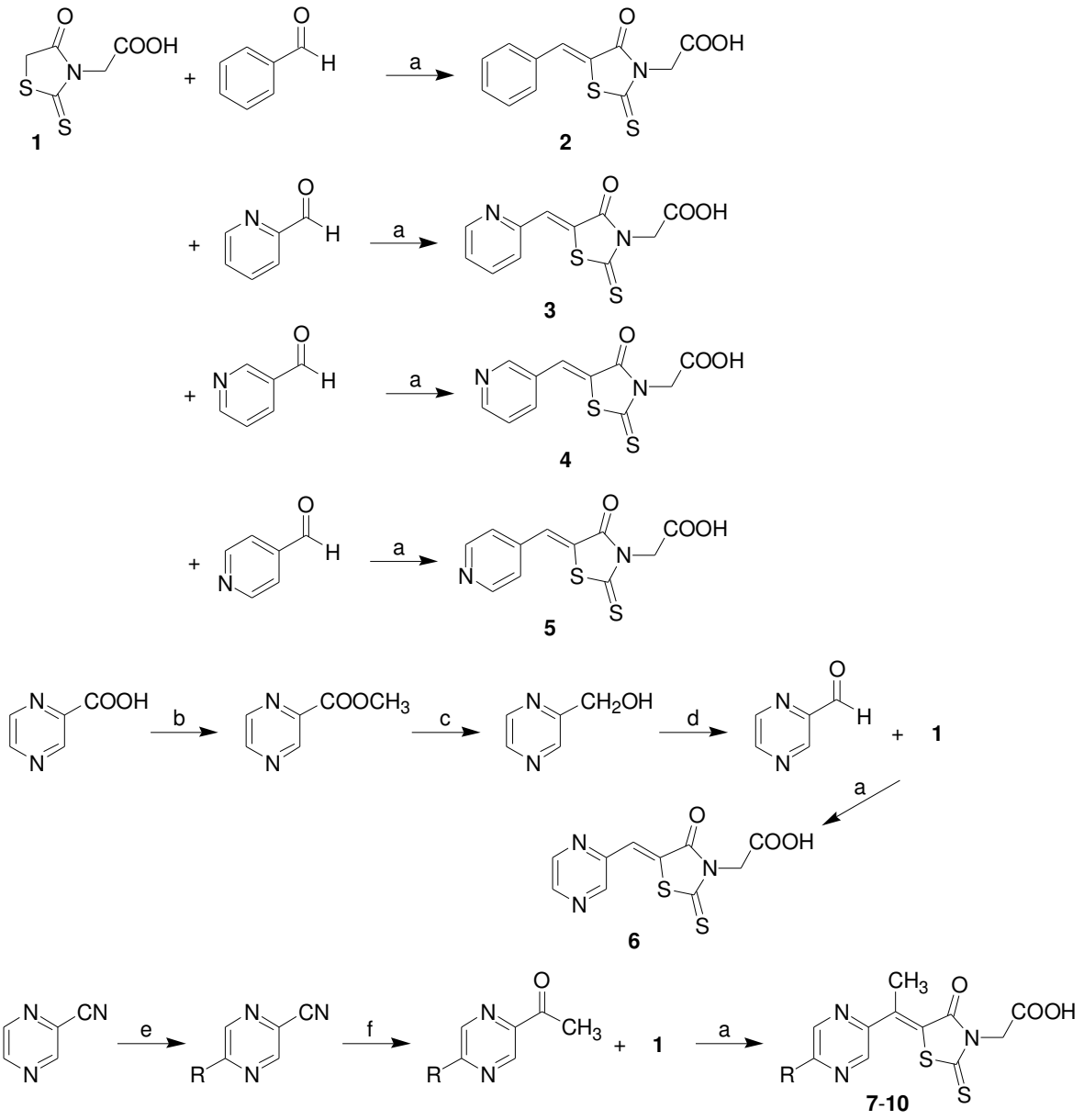
This contribution is a follow-up work to the previous papers [38-51] aimed at the synthesis, physicochemical properties and biological testing of newly prepared potential drugs based on nitrogen containing heterocycles.

RESULTS AND DISCUSSION

The preparation of the studied compounds is indicated in Scheme 1. 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).

Arylmethylidenerhodanines can form two isomers. According to references [24,52-54] syntheses of these compounds result in *Z*-izomer. Configuration on the exocyclic double bond can be determined on the basis of NMR spectra. ^{1}H-NMR signals of the methine-group hydrogens for *Z*-isomers are more downfield compared to *E*-isomers. Based on the NMR results the compounds presented here were obtained as single isomers, most probably *Z*-ones. However, definite determination of the configuration on the double bond would require additional experiments.

Scheme 1. Synthesis and structures of the target 5-substituted rhodanine-3-acetic acid derivatives **1**-**10**.



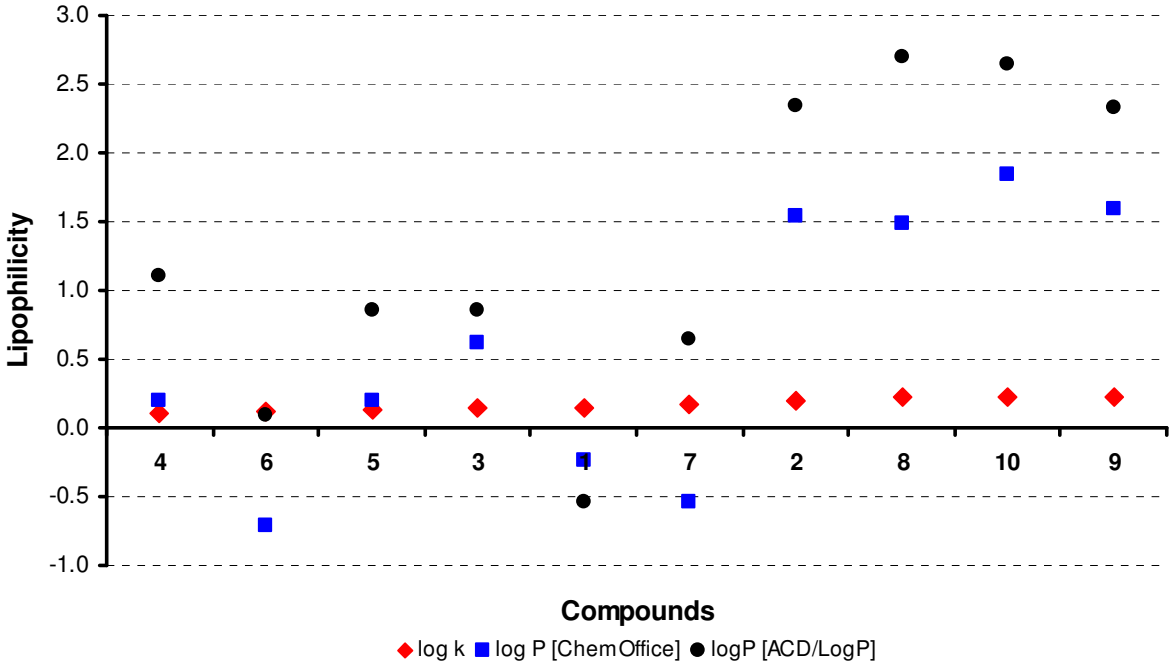
Conditions: a) CH_3COOH, CH_3COONa, $(CH_3CO)_2O$; b) MeOH, H_2SO_4; c) $NaBH_4$, H_2O; d) MnO_2, acetone; e) R-COOH, $AgNO_3$, $(NH_4)_2S_2O_8$, H_2O; f) CH_3MgI, Et_2O.

Hydrophobicities (log *P*) of the studied compounds **1**-**10** 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 results are illustrated in Figure 1.

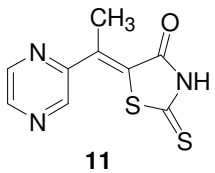
As expected, methylation of the connection linker increases lipophilicity, *i.e.* compound **6** (log k = 0.1165) is less hydrophobic than its alkylated congener **7** (log k = 0.1734). Among the arylmethylidene derivatives 2-(5-benzylidene-4-oxo-2-thioxothiazolidin-3-yl)acetic acid **2** is more lipophilic than its 5-heteroarymethylidene congeners **3**-**6**. Surprisingly, in RP-HPLC measurements 2-[4-oxo-5-(pyridin-3-ylmethylidene)-2-thioxothiazolidin-3-yl]acetic acid **4**

showed much lower lipophilicity than expected on the basis of calculated log *P* data. 2-{5-[(5-*tert*-butylpyrazin-2-yl)methylidene]-4-oxo-2-thioxothiazolidin-3-yl}acetic acid **9** is the most lipophilic compound, which is in a good agreement with the results of our previous studies [40,42,47,49].

Figure 1. Comparison of the log *P* data calculated using the two programs with the experimentally found log *k* values. The compounds are arranged in the ascending manner according to the experimental log *k* values.



The results of our previous studies [40,47] showed that the condensation of acetylpyrazine (log *k* = 0.1697) with *N*-nonsubstituded rhodanine results in an approximately twofold increase in lipophilicity (log *k* for **11** = 0.3187) [47]. Surprisingly, the lipophilicity of the corresponding 3-(2-hydroxyethyl)-5-(1-pyrazin-2-ylethylidene)-2-thioxothiazolidin-4-one **12** was slightly higher (log *k* = 0.3964) than that of **11** in spite of the presence of hydroxyl group in the side chain [48]. On the contrary, rhodanineacetic acids **1**-**10** reported in the present paper have lower lipophilicity than the corresponding arylalkylidenerhodanines of general formula **13** (Table 1).



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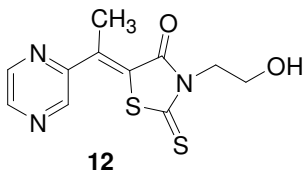

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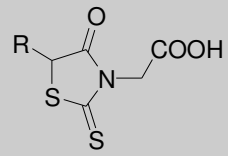
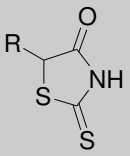
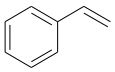
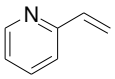
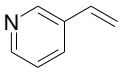
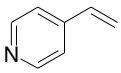
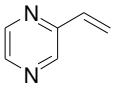
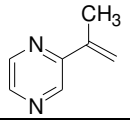
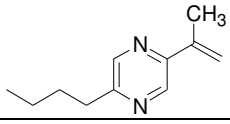
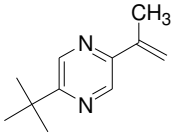
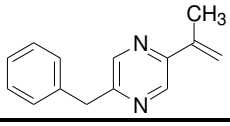
Table 1. Comparison of the lipophilicities of 5-arylalkylidenerhodanine-3-acids **1**-**10** with those of 5-arylalkylidenerhodanines **13**-**22**.

								
log *P* ACD/LogP	**log *P*** ChemOffice	**log *k***	**Comp.**	**R**	**Comp.**	**log *k***	**log *P*** ChemOffice	**log *P*** ACD/LogP
-0.54 ± 0.81	-0.24	0.1420	**1**	H	**13**	0.2272	0.26	0.06 ± 0.76
2.34 ± 0.81	1.54	0.2013	**2**		**14**	0.5122	2.04	2.94 ± 0.76
0.85 ± 0.82	0.62	0.1399	**3**		**15**	0.4864	1.12	1.45 ± 0.76
1.10 ± 0.82	0.20	0.1116	**4**		**16**	n.d.	0.70	1.70 ± 0.77
0.85 ± 0.82	0.20	0.1342	**5**		**17**	n.d.	0.70	1.45 ± 0.76
0.09 ± 0.82	-0.71	0.1165	**6**		**18**	0.2359	-0.22	0.69 ± 0.77
0.65 ± 0.84	-0.54	0.1734	**7**		**19**	0.3187	-0.04	1.25 ± 0.79
2.70 ± 0.84	1.49	0.2270	**8**		**20**	0.8872	1.99	3.30 ± 0.79
2.33 ± 0.84	1.59	0.2301	**9**		**21**	0.9424	2.09	2.93 ± 0.79
2.64 ± 0.84	1.84	0.2276	**10**		**22**	n.d.	2.34	3.23 ± 0.79

EXPERIMENTAL

Synthesis of the studied compounds **1**-**10**

Benzaldehyde, pur. (VEB Laborchemie), pyridine-2-carboxaldehyde, 99% (Aldrich) and rhodanine-3-acetic acid, 99% (Fluka), were used for the synthesis. Pyrazine-2-carbaldehyde was prepared using a procedure reported previously [38,55]. Acetylpyrazines were synthesized according to refs. [39,49]. Condensation of the starting compounds to 5-arylmethylidene- and 5-(1-arylethylidene)rhodanine-3-acetic acid derivatives was performed in glacial acetic acid using $CH_3COONa/(CH_3CO)_2O$ as a catalyst.

A mixture of an aldehyde or a ketone (0.009 mol), rhodanine-3-acetic acid (0.009 mol) was dissolved in glacial acetic acid and equivalent amount of acetanhydride and sodium acetate

were added. Then the reaction mixture was refluxed for 3 h. After cooling, the separated solid was filtered through a sintered filter, washed with distilled water (50 mL) and then with 50% ethanol (50 mL). The product was crystallized from glacial acetic acid.

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. 9.0 (CambridgeSoft, Cambridge, MA, U.S.A.) and ACD/LogP ver. 1.0 (Advanced Chemistry Development Inc., Toronto, Canada). The results are shown in Table 1.

Acknowledgements. This study was supported by the Ministry of Education of the Czech Republic MSM 0021620822.

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