Nucleophilic substitution reactions, molecular aggregation, structure and lipophilicity of 6-chloro-3-chloromethyl-1,2,4-triazolo[4,3-*b*]pyridazine

Anna Katrusiak*[a] and Andrzej Katrusiak[b]

[a]*Department of Organic Chemistry, Poznań University of Medical Sciences, Grunwaldzka 6, 60-780 Poznań, Poland;*

[b]*Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland*

E-mail: akatrus@ump.edu.pl

DOI: http://dx.doi.org/10.3998/ark.5550190.0011.929

Abstract

The synthesis of 6-chloro-3-chloromethyl-1,2,4-triazolo[4,3-*b*]pyridazine and its vicarious nucleophilic substitution products are described and characterized by spectroscopic methods and X-ray diffraction. The lipophilicities of the title compound, its acetate**,** and the derived 3-methyl tetrazolopyridazine have been measured and correlated with the chlorine substitution. The title compound co-crystallizes with acetic acid in the structure of the same symmetry and very similar layered arrangement as the crystals of its acetoxymethyl analog, despite the considerably different substituents and intermolecular contacts. The details of the intermolecular interactions are discussed.

Keywords: 1,2,4-Triazolo[4,3-*b*]pyridazine, vicarious nucleophilic substitution, lipophilicity, crystal structure

Introduction

Azolopyridazines are known for their pharmaceutical activities. Pre-clinical tests on animals have shown anxiolytic activity without the sedative side effects caused by benzodiazepines.[1] A selective affinity to GABAA receptors was reported for 6-pyridazine-2-ylmethoxy-1,2,4-triazolo[4,3-b]pyridazines substituted at C-3 with methyl-, ethyl-, methoxymethyl- or thiomethyl- groups. According to those reports, all the derivatives investigated are antagonistic for the GABAA receptors, and therefore they may also exhibit sedative and anticonvulsant activity.[2-4] In rats, azolopyridazines lowered blood pressure with no effects on the heart rate.[5]

However, no systematic studies on the bio-accessibility of azolopyridazines have been reported so far.

The bio-accessibility and hence pharmaceutical activity of compounds depend strongly on their lipophilicity. This in turn can be markedly affected by even subtle chemical changes, such as the introduction of a chlorine atom. An example of such a change in lipophilicity is the modification of the neuroleptic promazine by chlorination, leading to chlorpromazine, known as Fenactil – the increase of its lipophilicity markedly increased its bio-accessibility and allowed its therapeutic dose to be reduced.

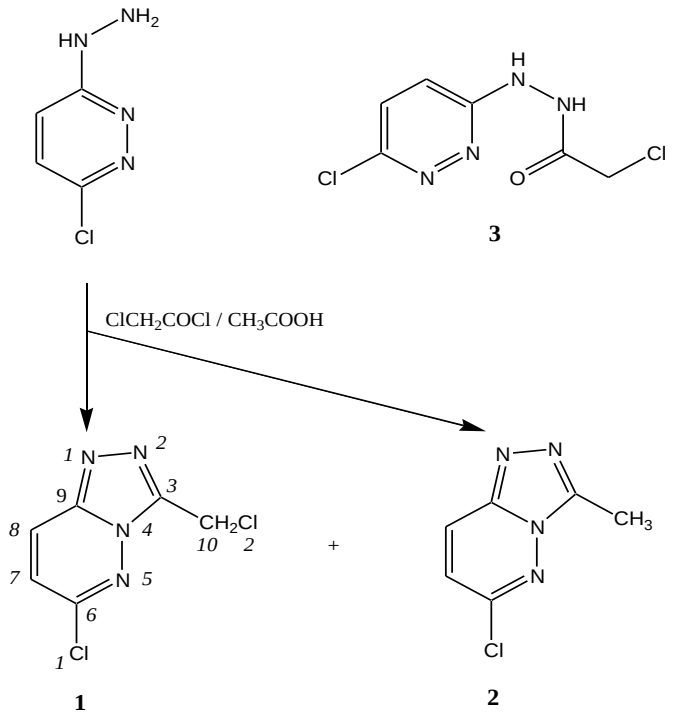
In this study the synthesis of 6-chloro-3-chloromethyl-1,2,4-triazolo[4,3-*b*]pyridazine **1**, its reactivity in the vicarious nucleophilic substitution (*VNS*), a specific type of nucleophilic substitution, and lipophilicity measurements have been described. *VNS* is a well-known method of synthesizing heterocyclic systems[6] and introducing carbon[7] and amine[8] substituents into nitro arenes or heterocycles. The *VNS* reaction mechanism has been investigated by computing the charge distribution in **1.**

Results and Discussion

3-Chloro-6-hydrazinopyridazine when treated with chloroacetyl chloride yielded two products: 6-chloro-3-chloromethyl-1,2,4-triazolo[4,3-*b*]pyridazine **1**, and 6-chloro-3-methyl-1,2,4-triazolo[4,3-b]pyridazine, **2**. Compounds **1** and **2** were previously described in the literature.[9,10] Compound **1** was obtained by Čuček and Verček from 2-chloro-*N*'-(6-chloropyridazin-3-yl)acetohydrazide **3**, synthesized earlier by Shinozaki *et al*.[11] We have modified their synthesis by heating hydrazinopyridazine simultaneously with chloroacetic acid chloride and acetic acid. In this way, the reaction procedure has been simplified by eliminating the need to isolate the intermediate acetohydrazide, **3** (Scheme 1).

The structure of compound **1** was confirmed by the ^{1}H-NMR spectrum. The signals of the hydrogen atoms at C-7 and C-8 appear at δ 7.25 and 8.16, as a pair of doublets with J = 9.9 Hz; the methylene protons give a singlet at δ 5.13. The molecular structure of **1** was also determined by X-ray diffraction, and it forms preferably a complex with acetic acid, shown in Figure **1a**.

Owing to the presence of four nitrogen atoms in the molecule, compound **1** is highly electrophilic. The charge-distribution computation with the MNDO method[12] shows that there is a negative net charge magnitude of -0.092*e* at C-7, and a positive charge of 0.021*e* at C-8 (Table 1). Therefore, the C-8 site is activated toward *VNS* attacks by such standard nucleophilic agents as chloromethyl-, *α*-chloroethyl-, *α*-chloropropyl phenyl sulfone, and chloromethyl-, and *α*-chloroethyl *p*-tolyl sulfone, which are the carbanion precursors.



Scheme 1. Synthesis of 6-chloro-3-chloromethyl-1,2,4-triazolo[4,3-*b*]pyridazine, **1**.

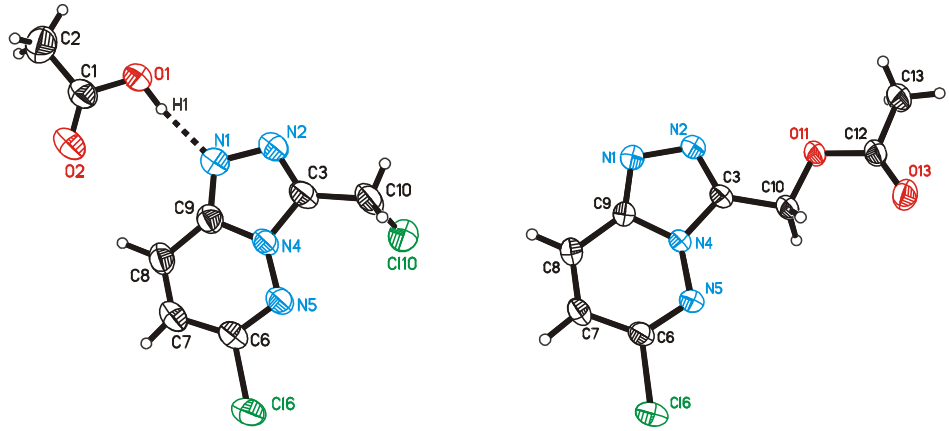
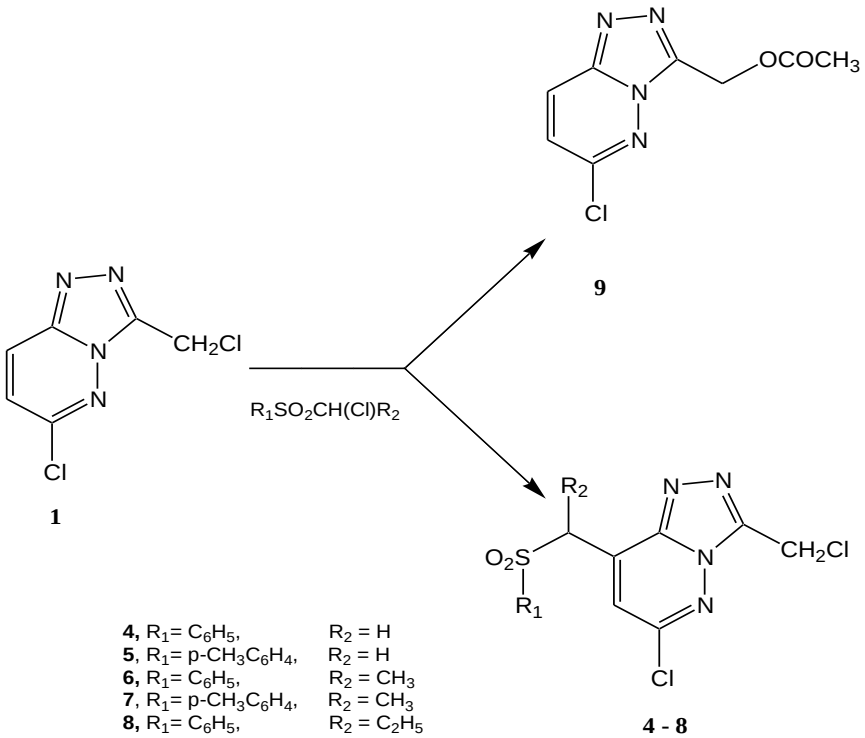


Figure 1. (a) 6-Chloro-3-chloromethyl-1,2,4-triazolo[4.3-*b*]pyridazine **1** – acetic-acid, 1:1 complex; and (b) 6-chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-ylmethyl acetate, **9**, viewed perpendicular to their rings. The hydrogen bond is indicated by the dashed line and the thermal ellipsoids drawn at the 50% probability level.

The *VNS* reactions were carried out using KOH in dry DMF as base-solvent system at 0-5 °C, yielding compounds **4-8** (Scheme 2), characterized by elementary analysis, ^{1}H- NMR and MS. Compounds **4** and **5** showed four methylene protons at δ 5.19 and 5.25 or δ 4.84 and

5.05, respectively. The methyl protons of **6** and **7** gave ^{1}H- quartets at about δ 3.7 (J = 6.0 Hz) and 3.0 (J = 7.1 Hz), respectively. The ethyl protons in compound **8** give a triplet at δ 1.27 (J = 8.1 Hz) and a multiplet at about δ 3.0, while the methine proton appears as a triplet at δ 4.85 (J = 8.1 Hz).

In all cases the typical *VNS* products were obtained together with 6-chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-ylmethyl acetate, **9**, which is a substitution product with a chlorine atom bonded to the C-3 methyl group (Scheme 2). In compound **1** there are two chlorine atoms susceptible to the attack of nucleophilic agents: that at C-6 of the pyridazine ring, and that bonded to the methylene group attached to triazole carbon atom C-3. It can be noted that despite different reaction mechanisms of S_NAr, for the nucleophilic substitution of chlorine Cl-1 at C-6, and S_N2, for the nucleophilic substitution of the aliphatic chlorine, the product formation can be correlated with the charge distribution in the azolopyridazine molecule. According to the charge distribution in **1,** computed with the MNDO method (Table 1),[12] the chlorine Cl-1 at pyridazine carbon C-6 is more susceptible to nucleophilic substitution, whereas the heat of formation magnitudes (HoF) of the two possible products indicate, that this one substituted at methylene group at C-3 is energetically more stable (223 kcal/mol and 206 kcal/mol, respectively). The structure of compound **9** was confirmed by ^{1}H- NMR and X-ray diffraction (Figure 1). The mixture of *VNS* products and compound **9** was separated by column chromatography.



Scheme 2. The *VNS* reaction of compound **1**.

Table 1. Net atomic charges in the molecule of compound **1** (labeled as in Scheme 1)

Atom	Charge	Atom	Charge	Atom	Charge	Atom	Charge
N-1	-0.104	N-4	-0.274	C-7	-0.092	C-10	-0.153
N-2	-0.191	N-5	-0.054	C-8	0.021	Cl-1	-0.008
C-3	-0.051	C-6	0.055	C-9	0.089	Cl-2	-0.138

The charge distribution in molecule **1** is reflected in its intermolecular interactions in the complex with acetic acid. The structures of **1**:CH_3COOH and **9** resemble each other: they both crystallize in monoclinic space group $P2_1/c$, have similar shapes of the unit cells, and the molecules are arranged into sheets and the 1,2,4-triazolo[4.3-*b*]pyridazine moieties are similarly oriented, as shown in Figure 2. However, the molecular sheets are parallel to crystallographic planes (100) in **1**:CH_3COOH, and to crystallographic plane (102) in **9** (Figure 3). These isostructural features are surprising, because the strongest interactions binding the molecules within the sheets are different: OH···N hydrogen bonds in **1**:CH_3COOH, and O···Cl halogen bridges and weak CH···N bonds in **9**. It can be observed from Figure 2 and Table 2, that the only repeating type of short contacts present in the molecular-sheet aggregates in **1**:CH_3COOH and in **9** are weak CH···N hydrogen bonds, whereas the remaining interactions are of different types.

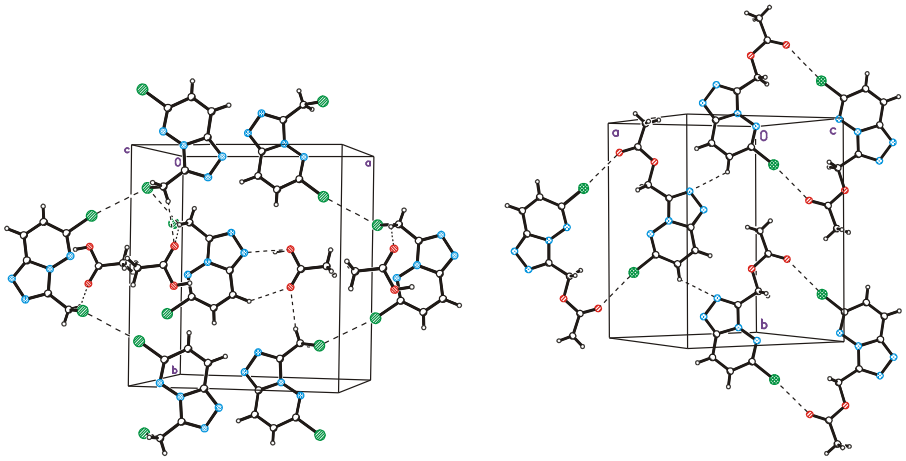


Figure 2. Sheets of hydrogen-bonded molecules in the crystal structures of (a) 6-chloro-3-chloromethyl-1,2,4-triazolo[4.3-*b*]pyridazine acetic-acid complex, **1**:CH_3COOH; and (b) 6-chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-ylmethyl acetate, **9**. The hydrogen bonds are indicated by the dashed lines.

Thus C-l6···Cl-10 contacts in **1**:CH_3COOH are replaced by Cl-6···O-13 contacts in **9**, and the O-1-H-1···N-1 hydrogen bond by C-13H···N-1, respectively. The weak C-8H···O-2 bond in **1**:CH_3COOH has its corresponding intermolecular C-8H···O-13' bond in **9**. The corresponding contacts in **1**:CH_3COOH and **9** are compared in Table 2. This "substitution" of interactions, and

the similar shape of the 1,2,4-triazolo[4.3-b]pyridazine moiety, explain the iso-structural association in crystals **1**:CH_3COOH and **9**. The phenomenon of chlorphobic aggregation, postulated by Grinieva and Zorki,[13] is consistent with the large number of Cl···Cl contacts in **1**:CH_3COOH – owing to the presence of stronger interactions between other atoms, the chlorine atoms form weak chlorine bridges between themselves (Table 2).

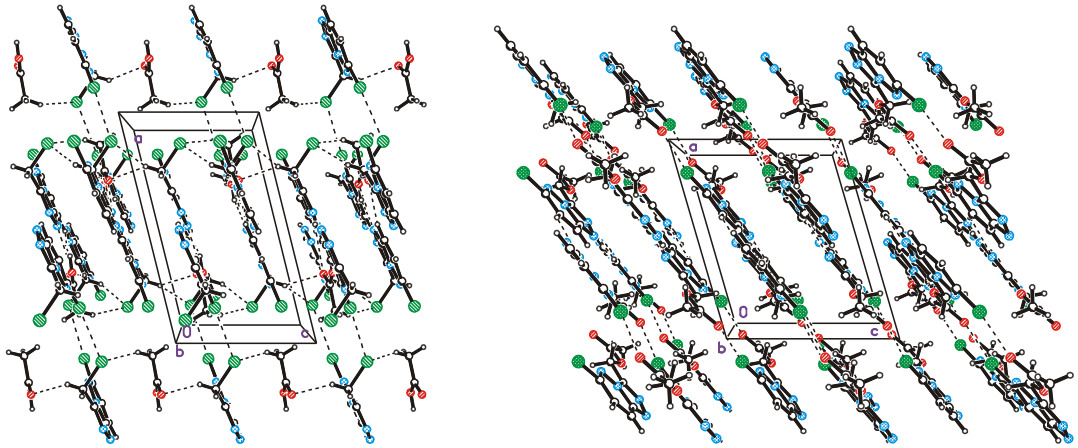


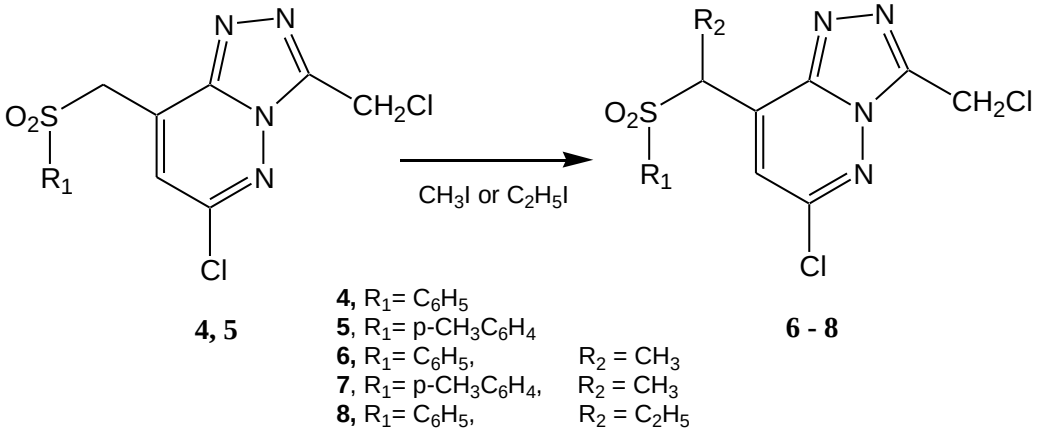
Figure 3. The crystal packing of (a) 6-chloro-3-chloromethyl-1,2,4-triazolo[4.3-b]pyridazine acetic-acid complex **1**:CH_3COOH; and (b) 6-chloro-1,2,4-triazolo[4,3-b]pyridazin-3-ylmethyl acetate, **9**. The hydrogen bonds are indicated by the dashed lines.

We have also obtained compounds **6-8** in another way, by adapting the literature method for other *VNS* products,[14] by the alkylation of *VNS* products **4** and **5** with methyl iodide or ethyl bromide in DMSO and potassium *tert*-butoxide (Scheme 3).

The lipophilicity measurements (Table 3) reveal a considerable difference between compounds **1**, **2** and **9.**[15] The larger magnitudes of parameter R_M of compounds correspond to their higher lipophilicity. Thus, the dichloro- derivative has the highest R_M value, and is more lipophilic than the monochloro- compounds **2** and **9.** This correlation of lipophilicity and the chlorine substitution in the molecular structure is also consistent with nephrotoxicity of amino- and chlorophenols.[16]

Table 2. Dimensions of shortest intermolecular contacts in the crystal structures of **1**:CH_3COOH and **9**. Values without standard derivatives involve H-atoms located from molecular geometry

Contact/Compound:	**1**:CH_3COOH		**9**
O(1)H(1)···N(1)	164(2)°	C(13)H(132)···N(1^{j})	157(3)°
H(1)···N(1)	1.79(2) Å	H(132)···N(1^{j})	2.89(3) Å
O(1)···N(1)	2.688(2) Å	C(13)···N(1^{j})	3.781(3) Å
Symmetry code	–		[j)]1–x, y–0.5, 0.5–z
C(8)H(8)···O(2^{i})	136(2)°	C(8)H(8)···O(11^{j})	168.1°
H(8)···O(2^{i})	2.58(2) Å	H(8)···O(11^{j})	2.71 Å
C(8)···O(2^{i})	3.383(2) Å	C(8)···O(11^{j})	3.651(3)Å
Symmetry code	[i)] 1–x, –y, 2–z		[j)]1–x, y–0.5, 0.5–z
C(7)H(7)···N(2^{ii})	125(2)°	C(7)H(7)···N(2^{jj})	124(3)°
H(7)···N(2^{ii})	3.06(2) Å	H(7)···N(2^{jj})	2.57(3) Å
C(7)···N(2^{ii})	3.632(2) Å	C(7)···N(2^{jj})	3.193(3) Å
Symmetry code	[ii)] 1–x, 0.5+y, 1.5–z		[jj)] 1–x, y+0.5, 0.5–z
Cl(6)···Cl(10^{iii})	3.527(1) Å	Cl(6)···O(13^{jjj})	3.048(3) Å
Symmetry code	[iii)] 2–x, 0.5+y, 1.5–z		[j)] 1–x, y–0.5, 0.5–z
Cl(6)···Cl($6^{iv/v}$)	3.782(1) Å		
Symmetry codes	[iv)] x, 0.5–y, z–0.5		
	[v)] x, 0.5–y, z+0.5		
Cl(6)···Cl(10^{vi})	3.877(1) Å		
Symmetry code	[vi)] 2-x, –y, 2–z		



4, 5

4, R_1= C_6H_5
5, R_1= p-$CH_3C_6H_4$
6, R_1= C_6H_5, R_2 = CH_3
7, R_1= p-$CH_3C_6H_4$, R_2 = CH_3
8, R_1= C_6H_5, R_2 = C_2H_5

6 - 8

Scheme 3. Alkylation of *VNS* products **4** and **5.**

Table 3. Lipophilicity of azolopyridazines. The R_M values have been calculated from the experimental R_f values, according to the formula $R_M = \log[1/R_f - 1]$

Compound	1	2	9
$\mathbf{R_f}$	0.61	0.69	0.69
$\mathbf{R_M}$	-0.19	-0.35	-0.35

Conclusions

6-Chloro-3-chloromethyl-1,2,4-triazolo[4,3-*b*]pyridazine **1** has been synthesized and its reactivity in *VNS* has been investigated. The observed reaction path is consistent with the MNDO calculations and the charge distribution, indicating that the hydrogen atom at C-8 in **1** is susceptible to the attack of nucleophilic reagents, such as carbanions. The magnitudes of lipophilicity measured for **1** and its two derivatives **2** and **9** correlate with the number of Cl substituents in the molecules: the dichlorinated compound **1** has higher lipophilicity than the mono-chlorinated compounds **2** and **9**. This considerably improves bio-accessibility of this potential pharmaceutical agent.

Experimental Section

General. Melting points were determined on a Boetius apparatus and are uncorrected. ^{1}H- NMR (300 MHz) and ^{13}C- NMR (75 MHz) spectra were recorded in $CDCl_3$ or DMSO with TMS as internal standard; chemical shifts are given in δ (ppm) and *J*-values in Hz. Mass spectra were obtained on an AMD 604 Inectra GmbH instrument. The products were separated by column chromatography using an acetone/hexane mixture (3:2) as mobile phase, with silica gel (0.040-0.063 mm, 23 -400 mesh ASTM, Merck). 3-Chloro-6-hydrazinopyridazine was obtained from 3,6-dichloropyridazine using hydrazine hydrate.[17] Chloromethyl phenyl sulfone, and chloromethyl *p*-tolyl sulfone were prepared by known methods.[18,19] *α*-Chloroethyl-, *α*-chloropropyl phenyl sulfone, and *α*-chloroethyl *p*-tolyl sulfone were synthesized by alkylation of chloromethyl phenyl- or *p*-tolyl sulfone in a catalytic two-phase system.[19] The lipophilicity measurement was made according to the literature.[15] Separation was carried out on precoated RP-TLC plates of RP-18F 254s (Merck, Darmstadt, Germany). The polar mobile phase was a methanol/water mixture (8:2). Each compound was dissolved in methanol (1 mg/mL) and the solution (5 μL) was applied onto the plate with the aid of a Hamilton syringe. After development, the plates were dried and the spots were localized with 254 nm UV.

6-Chloro-3-chloromethyl-1,2,4-triazolo[4,3-*b*]pyridazine (1), and 6-chloro-3-methyl-1,2,4-triazolo[4,3-*b*]pyridazine (2). 3-Chloro-6-hydrazinopyridazine (1.44 g, 10 mmol) was refluxed with 2.26 g (20 mmol) of chloroacetyl chloride in acetic acid for 4 h. Then the whole was poured

into water and extracted with dichloromethane. The extracts were washed with water, dried (anhydrous $MgSO_4$) and evaporated. The residue was separated by column chromatography. Two triazolopyridazine derivatives were isolated.

6-Chloro-3-chloromethyl-1,2,4-triazolo[4,3-*b*]pyridazine (1). Yield 68%; m.p. 132 °C (lit.[10] 132-134 °C); ^{1}H- NMR ($CDCl_3$) δ 5.13 (s, 2H), 7.25 (d, *J* = 9.9 Hz, 1H), 8.16 (d, *J* = 9.9 Hz, 1H); ^{13}C- NMR δ 55.02, 123.58, 127.22, 143.89, 144.91, 150.06, 168.99. MS (*m/z*, M^+): 203 (6.58%). Anal. Calcd for $C_6H_4Cl_2N_4$: C, 35.49; H, 1.99; N, 27.60. Found C, 35.33; H, 2.03; N, 27.52%.

6-Chloro-3-methyl-1,2,4-triazolo[4,3-*b*]pyridazine (2). Yield 19%. is the by-product. Its identity was assigned by comparison with literature data.[9]

General procedure for VNS reaction

To a stirred suspension of powdered KOH (100 mmol) in dry DMF a solution of the compound **1** (10 mmol) and a carbanion precursor (10 mmol) in DMF was added dropwise at 0-5 °C. The reaction mixture was stirred for 30 min. and then poured into diluted acetic acid and extracted with dichloromethane. The extracts were dried with $MgSO_4$ and evaporated. Crude products were purified by column chromatography.

6-Chloro-3-chloromethyl-8-phenylsulfonylmethyl-1,2,4-triazolo[4,3-*b*]pyridazine (4). Yield 65%; m.p. 188-189 °C; ^{1}H- NMR (DMSO) δ 5.19 (s, 2H), 5.25 (s, 2H), 7.35 (s, 1H), 7.71 (m, 5H); ^{13}C- NMR δ 40.33, 55.08, 124.31, 128.33, 129.43, 129.62, 134.60, 137.74, 143.32, 146.39, 148.91. MS (*m/z*, M^+): 357 (8.62%). Anal. Calcd for $C_{13}H_{10}Cl_2N_4O_2S$: C, 43.71; H, 2.82; N, 15.68. Found: C, 43.56; H, 2.67; N, 15.62%.

6-Chloro-3-chloromethyl-8-*p*-methylphenylsulfonylmethyl-1,2,4-triazolo[4,3-*b*]pyridazine (5). Yield 58%; m.p. 239-240 °C. ^{1}H- NMR ($CDCl_3$) δ 2.41 (s, 3H), 4.84 (s, 2H), 5.05 (s, 2H), 7.45 (s, 1H), 7.65 (m, 4H); ^{13}C- NMR δ 22.32, 41.13, 55.76, 123.65, 128.98, 129.75, 129.81, 135.34, 137.83, 143.69, 146.47, 148.99; MS (*m/z*, M^+): 371 (7.23%). Anal. Calcd for $C_{14}H_{12}Cl_2N_4O_2S$: C, 45.29; H, 3.26; N, 15.09. Found: C, 45.12; H, 3.13; N, 15.01%.

6-Chloro-3-chloromethyl-8-[1-(phenylsulfonyl)ethyl]-1,2,4-triazolo[4,3-*b*]pyridazine (6). Yield 62%; m.p.158-159 °C. ^{1}H- NMR (DMSO) δ: 0.99 (d, *J* = 6.0 Hz, 3H), 3.73 (q, *J* = 6.0 Hz, 1H), 5.18 (s, 2H), 7.31 (s, 1H), 7.72 (m, 5H); ^{13}C- NMR δ: 10.67, 41.33, 55.87, 123.61, 128.75, 129.64, 129.69, 135.21, 137.86, 143.56, 146.39, 148.78; MS(*m/z*, M^+): 371 (7.68%). Anal. Calcd for $C_{14}H_{12}Cl_2N_4O_2S$: C, 45.29; H, 3.26; N, 15.09. Found: C, 45.22; H, 3.18; N, 14.98%.

6-Chloro-3-chloromethyl-8-[1-(*p*-methylphenylsulfonyl)ethyl]-1,2,4-triazolo[4,3-*b*]-pyridazine (7). Yield 52%; m.p.202-203 °C. ^{1}H- NMR ($CDCl_3$) δ 1.83 (d, *J* = 7.1, 3H), 2.40 (s, 3H), 3.02 (q, *J* = 7.1, 1H), 5.04 (s, 2H), 7.45 (s, 1H), 7.59 (m, 4H); ^{13}C- NMR δ: 14.01, 21.22, 21.42, 40.69, 55.12, 124.46, 128.76, 129.45, 129.64, 134.73, 137.89, 144.08, 146.57, 149.97. MS (*m/z*, M^+): 385 (10.23%). Anal. Calcd for $C_{15}H_{14}Cl_2N_4O_2S$: C, 46.76; H, 3.66; N, 14.54. Found: C, 46.27; H, 3.58; N, 14.32%.

6-Chloro-3-chloromethyl-8-[1-(phenylsulfonyl)propyl]-1,2,4-triazolo[4,3-*b*]pyridazine (8). Yield 58%; m.p.165-168 °C. ^{1}H- NMR ($CDCl_3$) δ 1.27 (t, *J* = 8.1 Hz, 3H), 3.07 (m, 2H), 4.85 (t,

J = 8.1 Hz, 1H), 5.04 (s, 2H), 7.45 (s, 1H), 7.69 (m, 5H); ^{13}C- NMR δ 11.89, 22.45, 41.54, 55.23, 125.67, 128.96, 130.23, 130.36, 134.54, 138.12, 145.78, 147.92, 150.03. MS (*m/z*, M^+): 385 (12.63%). Anal. Calcd for $C_{15}H_{14}Cl_2N_4O_2S$: C, 46.76; H, 3.66; N, 14.54. Found: C, 46.34; H, 3.54; N, 14.39%.

In all these reactions apart from products **4**-**8**, also compound **9** was separated by column chromatography.

6-Chloro-1,2,4-triazolo[4,3-*b*]pyridazin-3-ylmethyl acetate (9). Yield 39%; m.p. 160-161 °C. ^{1}H- NMR (DMSO) δ: 2.09 (s, 3H), 5.56 (s, 2H), 7.58, 7.61 (d, *J* = 9.6 Hz, 1H), 8.52, 8.55 (d, *J* = 9.6 Hz, 1H); ^{13}H- NMR δ: 20.39, 54.08, 123.47, 127.11, 143.36, 144.90, 149.57, 169.82. MS (*m/z*, M^+): 226 (10.45%). Anal. Calcd for $C_8H_7ClN_4O_2$: C, 42.40; H, 3.11; N, 24.72. Found: C, 42.25; H, 3.03; N, 24.38%.

General procedure of alkylation VNS products (according to reference 14)

A mixture of compound **4** or **5** (15 mmol) and potassium tert-butoxide (16 mmol) was stirred for 1 min in DMSO. Methyl iodide (16 mmol) or ethyl bromide (16 mmol) was added and the solution was stirred for another 10 min. The mixture was poured into water and extracted with dichloromethane. The extracts were dried with $MgSO_4$ and evaporated. The products were purified by column chromatography or recrystallization from ethanol.

6-Chloro-3-chloromethyl-8-[1-(phenylsulfonyl)ethyl]-1,2,4-triazolo[4,3-b]pyridazine (6). Yield 38%.

6-Chloro-3-chloromethyl-8-[1-(*p*-methylphenylsulfonyl)ethyl]-1,2,4-triazolo[4,3-*b*]pyridazine (7). Yield 48%.

6-Chloro-3-chloromethyl-8-[1-(phenylsulfonyl)propyl]-1,2,4-triazolo[4,3-*b*]pyridazine (8). Yield 44%.

X-Ray diffraction

The single crystals of compounds **1** and **9** for X-ray diffraction measurements were grown from dichloromethane solution by evaporation. The diffraction data were recorded using a 4-circle KUMA KM4-CCD diffractometer. The structures were solved by direct methods with program ShelXS-97 and refined with ShelXL-97 (Sheldrick, 2009).[20] The crystal data of **1** and **9** are listed in Table 2. The crystal structures have been also deposited with the Cambridge Crystallographic Database Centre as supplementary publications No. CCDC 771942 and CCDC 771943; copies can be obtained free of charge on request from www.ccdc.cam.ac.uk.

References

1. Atack, J. R.; Wafford, K. A.; Tye, S. J.; Cook, S. M.; Sohal, B.; Pike, A.; Sur, C.; Melillo, D.; Bristow, L.; Bromidge, F.; Ragan, I.; Kerby, J.; Street, L.; Carling, R.; Castro, J. L.; Whiting, P.; Dawson, G. R.; McKernan, R. M. *J. Pharmacol. Exp. Ther.* **2006**, *316*, 410.
2. Street, L. J.; Sternfeld, F.; Jelley, R. A.; Reeve, A. J.; Carling, R. W.; Moore, K. W.; McKernan, R. M.; Sohal, B.; Cook, S.; Pike, A.; Dawson, G. R.; Bromidge, F. A.; Wafford, K. A.; Seabrook, G. R.; Thompson, S. A.; Marshall, G.; Pillai, G. V.; Castro, J. L.; Atack, J. R.; MacLeod, A. M. *J. Med. Chem.* **2004**, *47*, 3642.
3. Lebsack, A. D.; Gunzner, J.; Wang, B.; Pracitto, R.; Schaffhauser, H. *Bioorg. & Med. Chem. Lett.* **2004**, *14*, 2463.
4. Russell, M. G.; Carling, R. W.; Atack, J. R.; Bromidge, F. A.; Cook, S. M.; Hunt, P.; Isted, C.; Lucas, M.; McKernan, R. M.; Moore, K. W. *J. Med. Chem.* **2005**, *48*, 1367.
5. Katrusiak, A.; Melzer, E.; Bałoniak, S.; Bobkiewicz, T.; Polcyn, P. *Acta Pol. Pharm. - Drug Res.* **2001**, *58*, 217.
6. Mąkosza, M. *Pure Appl. Chem.* **1997**, *69*, 559.
7. Goliński, J.; Mąkosza, M. *Tetrahedron Lett.* **1978**, *19*, 3495.
8. For example: (a) Rykowski, A.; Mąkosza, M. *Liebigs Ann. Chem.* **1988**, 627. (b) Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282.
9. Bałoniak, S.; Katrusiak, A. *Pol. J. Chem.* **1994**, *68*, 683.
10. Čuček, K.; Verček, B. *Arkivoc* **2001**, (*v*), 79.
11. Shinozaki, K.; Kimura, T.; Kawada, T.; Okazaki, T.; Sugai, S.; Akaboshi, S.; Ikegami, S.; Kajiwara, Y.; Kanbara, Y. *Jpn. Kokai Tokkyo Koho JP* 61 151 177 (*Chem. Abstr.*; **1987**, 106,33084r).
12. MOPAC is a semi-empirical quantum-mechanical method: Quantum Chemistry Program Exchange, No. 455, Indiana University, USA; Stewart, J. J. P. *J. Comput. Chem.* **1983**, *10*, 209 221.
13. (a) Grinieva, O. V.; Zorkii, P. M. *J. Struct. Chem.* **2002**, *43*, 995. (b) Podsiadło, M.; Katrusiak, A. *J. Phys. Chem. B* **2008,** *112*, 5355.
14. Mąkosza, M.; Chylińska, B.; Mudryk, B. *Liebigs Ann. Chem.* **1984**, 8.
15. (a) Biagi, G. L.; Barbaro, A. M.; Gamba, M. F.; Guerra, M. C. *J. Chromatogr.* **1969**, *41*, 371. (b) Granero, G. E.; Bertorello, M. M.; Briñón, M. C. *J. Liq. Chromatogr. Rel. Technol.* **1999**, *22*, 229.
16. Valentovic, M; Ball, J. G.; Hong S. K.; Rogers, B. A.; Meadows, M. K.; Harmon, R. C.; Rankin, G. O, *Toxicol. in Vitro* **1996**, *10*, 713.
17. Pollak, A.; Tišler, M. *Tetrahedron* 1966, *22*, 2073.
18. Mąkosza, M.; Goliński, J.; Baran, J. *J. Org. Chem.* **1984**, *49*, 1488.
19. Mąkosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* **1987**, 711.
20. Sheldrick, G.M.; SHELXS 97 and SHELXL 97; University of Göttingen, Germany, 1997.