

Full Paper

## Synthesis of a New Scaffold: the 7H,8H-Pyrimido[1,6-b]pyridazin-6,8-dione Nucleus

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**Abstract:** This paper describes a modified method of preparation of a number of  $\alpha$ -aryl- $\alpha$ -(pyridazin-3-yl)-acetonitriles via the C-arylation reaction of the corresponding carbanions of phenylacetonitriles using 3-chloropyridazine derivatives. KOH and DMSO were used in the deprotonation process, which made the reaction very simple and safe to perform. Nitriles were obtained in the hydrolysis reaction to the corresponding  $\alpha$ -aryl- $\alpha$ -(pyridazin-3-yl)-acetamide derivatives, which were next subjected to cyclization to afford the final products. A number of new derivatives of 7H,8H-pyrimido[1,6-b]pyridazin-6,8-dione were synthesized in the cyclocondensation reaction of respective  $\alpha$ -aryl- $\alpha$ -(pyridazin-3-yl)-acetamides with diethyl carbonate in the presence of EtONa. The structure and composition of the new compounds were confirmed by IR, <sup>1</sup>H- and <sup>13</sup>C- NMR analyses and by elemental C, H and N analysis.

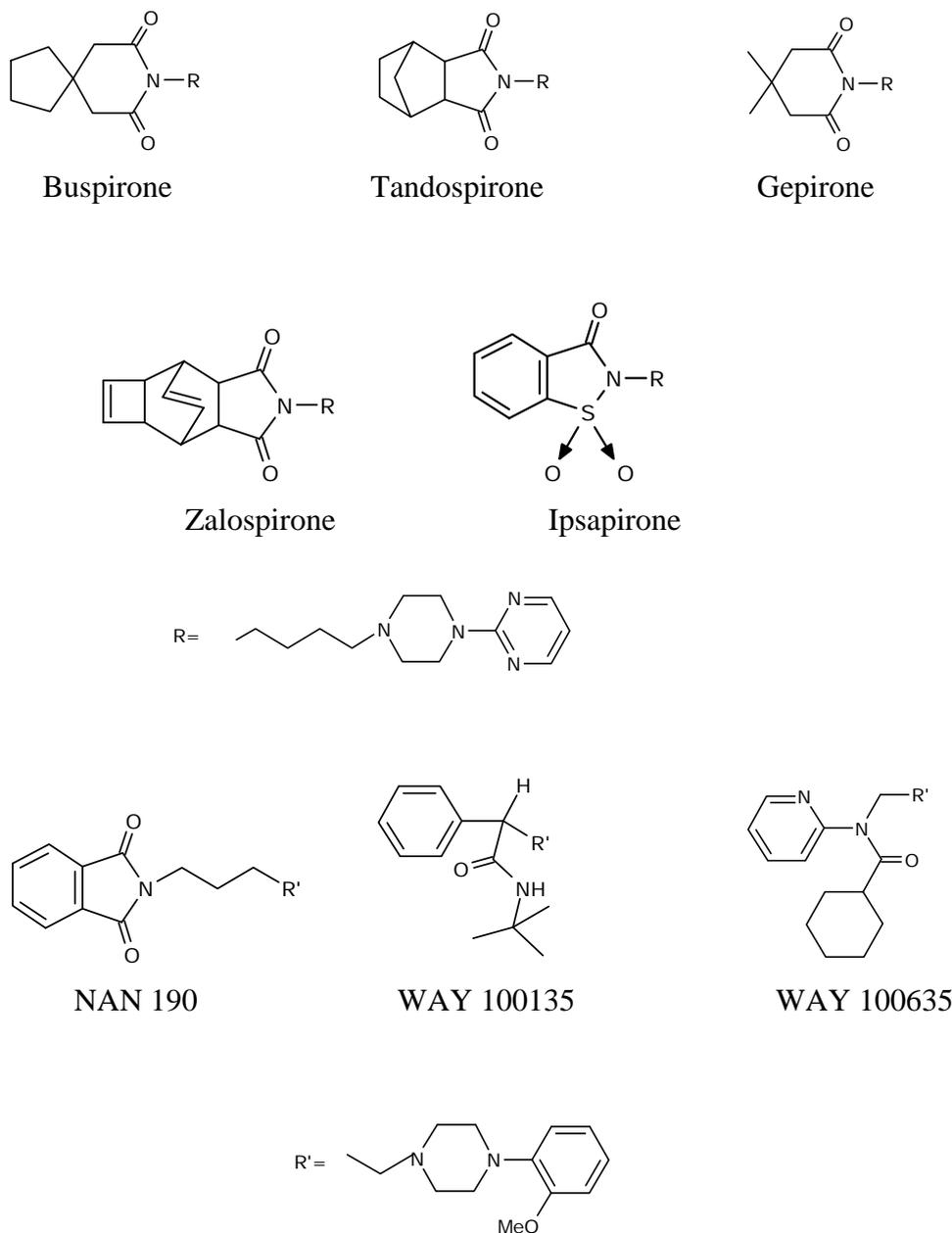
**Keywords:**  $\alpha$ -Aryl- $\alpha$ -(pyridazin-3-yl)-acetonitrile, C-arylation,  $\alpha$ -aryl- $\alpha$ -(pyridazin-3-yl)-acetamides, 7H,8H-pyrimido[1,6-b]pyridazin-6,8-diones

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## Introduction

The imide moiety, which is present in various heterocyclic systems, may have a significant effect on the biological activity of their derivatives. This functionality is a significant structural element of an important group of compounds belonging to the so-called long-chain arylpiperazines (LCAPs), ligands of 5-HT<sub>1A</sub> receptors of high affinity (see Figure 1) [1-5].

**Figure 1.** LCAPs with an amide and imide moiety.



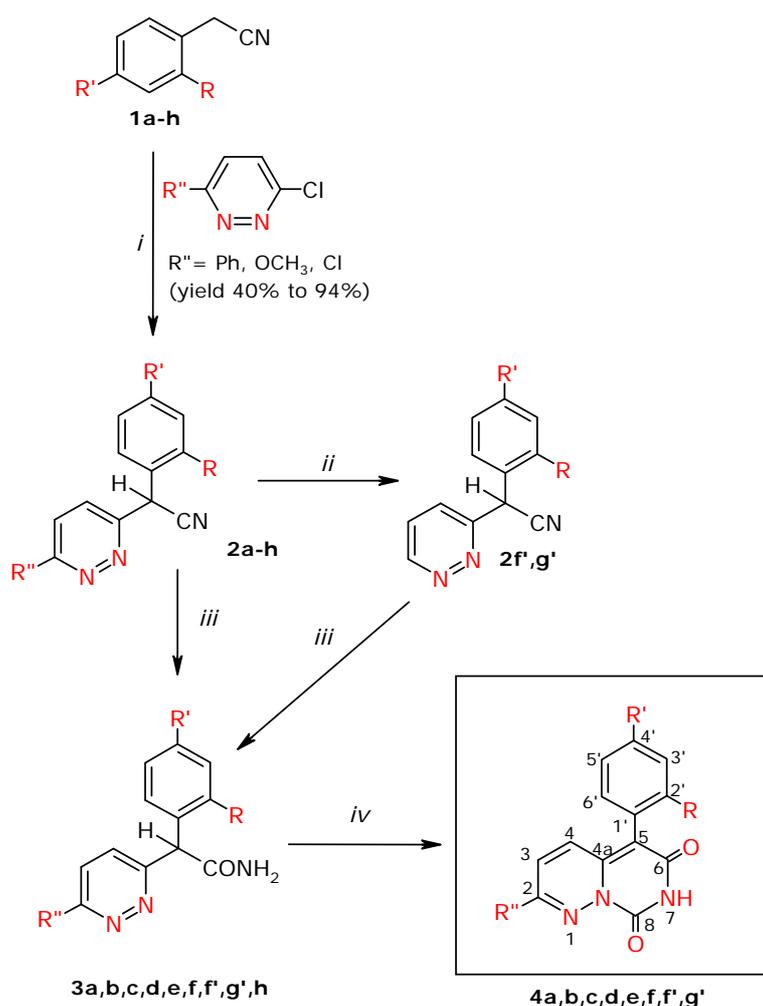
First Buspirone and then Tandospirone were introduced for medicinal purposes; both of them are prominent representatives of the LCAPs group. These drugs, as 5-HT<sub>1A</sub> receptor agonists, revolutionized the treatment of anxiety disorder by the mechanism of serotonergic neurotransmission [2,4,5-10]. As shown by the investigations to date, the imide group in Buspirone is an element of the

nonpharmacophore part and plays an important role in stabilization of the ligand – 5-HT<sub>1A</sub> receptor complex. Moreover, it also affects the lipophilicity of the ligand, which in turn has a significant effect on selectivity of the ligand to 5-HT<sub>1A</sub> receptor, with respect to other receptors such as 5-HT<sub>2A</sub> or  $\alpha_1$  [2,7,9]. Our earlier investigations also dealt with the preparation of new heterocyclic systems, such as for instance the derivatives of pyrido[1,2-*c*]pyrimidine and pyrrole[1,2-*a*]pyrazine, which have the afore-mentioned grouping [11-13]. We have now focused our studies on a little known pyrimido[1,6-*b*]pyridazine system, the derivatives of which had already been described by Bemis *et al.* Our investigations were concerned with Kinase p38 inhibitors which possess antitumor activity [14]. The aim of our investigations was to synthesize the new 7*H*,8*H*-pyrimido[1,6-*b*]pyridazin-6,8-dione derivatives **4a-f**, **4f'** and **4g'**, which contain the imide moiety in their structure. These derivatives should be important substrates for further synthesis of the potential ligands of 5-HT<sub>1A</sub> receptors of higher selectivity in the LCAPs group.

## Results and Discussion

The compounds described in this paper were obtained according to Scheme 1.

**Scheme 1.** Synthesis of the title compounds and substituents.



*Reagents and conditions:* (i) KOH, DMSO,  $\Delta$ ; (ii) CH<sub>3</sub>OH, Pd/C, HCOONH<sub>4</sub>, N<sub>2</sub>,  $\Delta$ ; (iii) H<sub>2</sub>SO<sub>4</sub> or H<sub>2</sub>SO<sub>4</sub>/CH<sub>3</sub>COOH (1:3 v/v),  $\Delta$ ; (iv) C<sub>2</sub>H<sub>5</sub>ONa, CO(OC<sub>2</sub>H<sub>5</sub>)<sub>2</sub>,  $\Delta$ ;

Scheme 1. Cont.

Compounds	R	R'	R''
<b>2a</b>	H	H	Ph
<b>2b</b>	H	F	Ph
<b>2c</b>	H	CH <sub>3</sub>	Ph
<b>2d</b>	H	OCH <sub>3</sub>	Ph
<b>2e</b>	OCH <sub>3</sub>	H	Ph
<b>2f</b>	H	H	Cl
<b>2g</b>	H	F	Cl
<b>2h</b>	H	H	OCH <sub>3</sub>
<b>2f'</b>	H	H	H
<b>2g'</b>	H	F	H
<b>3a</b>	H	H	Ph
<b>3b</b>	H	F	Ph
<b>3c</b>	H	CH <sub>3</sub>	Ph
<b>3d</b>	H	OCH <sub>3</sub>	Ph
<b>3e</b>	OCH <sub>3</sub>	H	Ph
<b>3f</b>	H	H	Cl
<b>3f'</b>	H	H	H
<b>3g'</b>	H	F	H
<b>3h</b>	H	H	OCH <sub>3</sub>
<b>4a</b>	H	H	Ph
<b>4b</b>	H	F	Ph
<b>4c</b>	H	CH <sub>3</sub>	Ph
<b>4d</b>	H	OCH <sub>3</sub>	Ph
<b>4e</b>	OCH <sub>3</sub>	H	Ph
<b>4f</b>	H	H	OC <sub>2</sub> H <sub>5</sub>
<b>4f'</b>	H	H	H
<b>4g'</b>	H	F	H

The starting  $\alpha$ -aryl- $\alpha$ -(pyridazin-3-yl)-acetonitriles **2a-h**, which were necessary for the synthesis, were obtained in a C-arylation reaction of stabilized carbanions of appropriate arylacetonitriles using 3-chloropyridazine derivatives. A modified method of deprotonation of the above-mentioned arylacetonitriles was applied, using KOH in DMSO. This method was elaborated by us earlier and was used for the synthesis of a number of derivatives of  $\alpha$ -aryl- $\alpha$ -(2-pyridyl)-acetonitriles in a C-arylation reaction using 2-bromopyridine [11,12]. The aim of the present studies was first of all to simplify the process of C-arylation to obtain a method which gives reproducible yields and is safe to perform.

The deprotonation processes used to obtain stabilized carbanions in C-arylation, were previously carried out using NaH, NaNH<sub>2</sub> in anhydrous solvents such as THF or benzene [14-17]. Yamada *et al.* described the preparation of  $\alpha$ -phenyl- $\alpha$ -(6-phenyl-pyridazin-3-yl)-acetonitrile **2a** in the C-arylation reaction of phenylacetonitrile using 3-chloro-6-phenylpyridazine in the presence of NaNH<sub>2</sub> in benzene [15]. The derivative **2f'** was obtained by Yamada *et al.* in a C-arylation of phenylacetonitrile using 3-chloropyridazine in the presence of NaNH<sub>2</sub> in benzene [15]. The same derivative was obtained by C-arylation of the above-mentioned phenylacetonitrile using 3-methoxypyridazine in the presence of

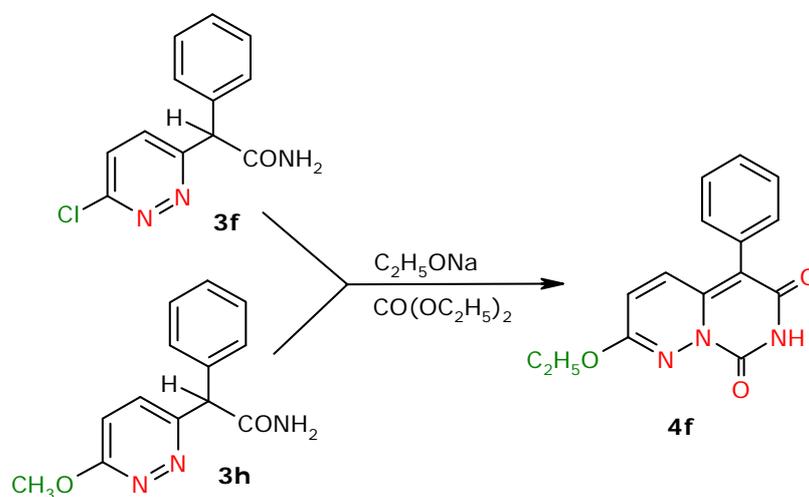
NaH in THF [17]. Abboto *et al.* described synthesis of **2f'** in a C-arylation reaction of phenylacetonitrile using 3,6-dichloropyridazine in presents of NaH in THF [16].

The modified method used in the present work allowed us to obtain a number of new nitriles **2b-e**, **2g**, **2h**, **2g'** in good yields. During the next stage of our studies the nitriles **2g** and **2f**, possessing chlorine in position 6 of the pyridazine moiety, were subjected to dehalogenation using ammonium formate and Pd/C in MeOH, instead of the hydrogenolysis process which had been used by Abboto *et al.* during preparation of the derivative **2f'** [16].

A number of new derivatives of  $\alpha$ -aryl- $\alpha$ -(pyridazin-3-yl)-acetamide **3a-f**, **3h**, **3f'** and **3g'**, were obtained by hydrolyzing the above-obtained nitriles **2a-f**, **2h**, **2g'**, **2f'** in acidic medium. The hydrolysis process was performed under different conditions. The nitriles **2a-f**, **2h**, **2f'** and **2g'** were hydrolyzed with sulphuric acid at the temperature of 50 °C. Hydrolysis of the nitriles **2c** and **2d** was performed in the sulphuric acid – acetic acid mixture at the temperature of 100 °C for 1 h for compound **3c**, whereas the derivative **3d** was obtained at 50 °C and the process was continued for 10 h.

The final compounds, the derivatives of 7H,8H-pyrimido[1,6-b]pyridazin-6,8-dione **4a-f**, **4f'** and **4g'** were obtained in good yields in an intermolecular cyclocondensation reaction of the respective amides **3a-f**, **3h**, **3f'** and **3g'** with diethyl carbonate in the presence of EtONa. During the cyclization process of the derivatives **3f** and **3h** the formation of one cyclization product **4f** was observed as a result of simultaneous chlorine substitution in position 2 of the cyclic compound on the -OEt group in amide **3f**, whereas in the case of amide **3h** the -OMe group was exchanged into -OEt (see Scheme 2).

Scheme 2.



The structures and composition of the new intermediate and final compounds were confirmed by analysis of their IR,  $^1H$ - and  $^{13}C$ -NMR spectra, and also by elemental C, H and N analyses. The NMR spectra are mutually correlated and were in agreement with the literature data for similar systems, as well as with the theoretical spectra calculated according to ACD/NMR Predictor v. 8.09 program. In the amide proton spectra (compounds of series **3**) we observed two NH proton signals from the  $NH_2$  group, which could indicate that there is nonequivalence of magnetic surroundings of these protons due to inhibited rotation about the C-N bond.

## Conclusions

Applying a modified method (KOH, DMSO) for the deprotonation of phenylacetonitrile derivatives, we obtained a number of  $\alpha$ -aryl- $\alpha$ -(pyridazin-3-yl)acetonitriles **2b-e**, **2g**, **2h**, **2g'** that were not described previously in a C-arylation reaction of the carbanions obtained. Next, the nitriles were hydrolyzed in an acidic medium and thus we obtained another group of new compounds, the  $\alpha$ -aryl- $\alpha$ -(pyridazin-3-yl)-acetamide derivatives **3a-f**, **3h**, **3f'** and **3g'**. The title compounds, the 7*H*,8*H*-pyrimido[1,6-*b*]pyridazin-6,8-dione derivatives **4a-f**, **4f'**, **4g'** were obtained in the cyclocondensation reaction of amides **3a-f**, **3h**, **3f'**, **3g'** with diethyl carbonate in the presence of EtONa. All the intermediate and title compounds described in this paper were obtained in good yields.

## Experimental

### General

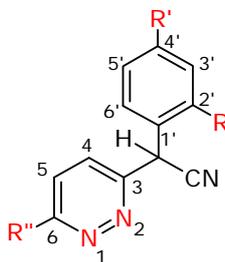
Melting points of the substances were determined on a Mel-Temp® 3.0 (Barnsted/Thermolyne, USA) apparatus and are uncorrected. Elemental analysis was performed on a Perkin-Elmer CHN model 2400 analyzer. The IR spectra (KBr tablets) were performed on a Shimadzu FT IR-8300 apparatus. <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded on the following spectrometers: a Bruker Avance DMX WB of basic frequency for the protons: 400.133 MHz, for nuclei <sup>13</sup>C: 100.623 MHz and a Varian type Unity Plus of basic frequency for the protons: 500.605 MHz, for nuclei <sup>13</sup>C: 125.877 MHz at room temperature. CDCl<sub>3</sub> was used as solvent and tetramethylsilane as internal standard. The chemical shifts of resonance signals are given in ppm, and the coupling constants are in Hz. Thin-layer chromatography (TLC) was performed on Merck DC-Platten Kieselgel 60 F<sub>254</sub> plates, developed in the dioxane, toluene, ethanol systems, 25% NH<sub>4</sub>OH (6.0:3.2:0.5:0.2, v/v) or chloroform, methanol, diethyl ether, 25% NH<sub>4</sub>OH (6.0:2.0:1.8:0.2, v/v) and visualized on a UV lamp. Analytical samples of the compounds were obtained by purification on the chromatographic column using the flash technique and Merck Kieselgel 60 (230-400 mesh) filling. They were eluted with methylene chloride/methanol mixtures (99:1; 97:3; 95:5, v/v). The starting phenylacetonitrile derivatives, 3,6-dichloropyridazine and 3-chloro-6-methoxypyridazine were commercial products purchased from Aldrich and used without further purification. The other starting reagent 3-chloro-6-phenylpyridazine was prepared by the reported procedure [18,19].

### General procedure for the preparation of $\alpha$ -aryl- $\alpha$ -(3-pyridazin-3-yl)acetonitriles **2a-h**

To DMSO (32.5 mL) was added KOH (16.5 g, 0.29 mol) and the mixture was stirred for 0.5 h at room temperature. Next an appropriate phenylacetonitrile derivative (0.11 mol) in DMSO (10 mL) was added dropwise and stirring was continued for another 0.5 h at room temperature. Next the appropriate 3-chloropyridazine derivative (0.07 mol) was added portionwise to the mixture, which was stirred at a temperature of 50 °C for 12 h. Next the post-reaction mixture was poured into ice water (1000 mL). The separated precipitates were filtered off. The obtained crude products **2c**, **2d**, **2e**, **2f**, **2f'** were purified by flash chromatography using CH<sub>2</sub>Cl<sub>2</sub>/MeOH (97:3 v/v), and then CH<sub>2</sub>Cl<sub>2</sub>/MeOH (99:1 v/v) as eluents, and then compounds **2c** crystallized from absolute EtOH, **2d** and **2f'** from EtOH.

Compounds **2a**, **2h**, **2g'** were macerated with the ethyl acetate – hexane (1:1 v/v) mixture, and were then crystallized from EtOH. Compound **2b** was crystallized from EtOH, **2g** with ethyl acetate.

**Figure 2.** Numbering system for compounds **2a-h**.



*α*-Phenyl-*α*-(6-phenylpyridazin-3-yl)-acetonitrile (**2a**). Yield 65%; white crystals; m.p. 206.0-207.0°C; {lit. [15], 201-203°C}; IR (cm<sup>-1</sup>): 2246 (CN); <sup>1</sup>H-NMR (500 MHz) δ: 5.73 (s, 1H, CH), 7.36 (tt, <sup>3</sup>J=7.0, <sup>4</sup>J=1.0, 1H, C4'H), 7.41 (td, <sup>3</sup>J=7.5, <sup>4</sup>J=1.5, 2H, C3'H, C5'H), 7.49- 7.56 (m, 5H, C2''H-C6''H), 7.63 (d, <sup>3</sup>J=9.0, 1H, C4H), 7.88 (d, 1H, C5H), 8.07 (dd, <sup>3</sup>J=7.5, <sup>4</sup>J=2.0, 2H, C2'H, C6'H); <sup>13</sup>C-NMR (125 MHz) δ: 43.6 (CH), 118.1 (CN), 125.1 (C5), 125.8 (C4), 127.2 (C3'', C5''), 127.6 (C2', C6'), 128.9 (C4'), 129.2 (C3', C5'), 129.5 (C2'', C6''), 130.6 (C4''), 133.5 (C1'), 135.4 (C1''), 157.0 (C3), 159.1 (C6); Anal. calcd. for C<sub>18</sub>H<sub>13</sub>N<sub>3</sub>: C, 79.68; H, 4.83, N, 15.49; found: C, 79.62; H, 4.83; N, 15.44.

*α*-(4-Fluorophenyl)-*α*-(6-phenylpyridazin-3-yl)-acetonitrile (**2b**). Yield 40%; white crystals; m.p. 200.8-201.2 °C; IR (cm<sup>-1</sup>): 2248 (CN); <sup>1</sup>H-NMR (500 MHz) δ: 5.70 (s, 1H, CH), 7.10 (m, 2H, C3'H, C5'H), 7.49-7.56 (m, 5H, C2''H-C6''H), 7.64 (d, <sup>3</sup>J=9.0, 1H, C4H), 7.90 (d, 1H, C5H), 8.08 (m, 2H, C2'H, C6'H); <sup>13</sup>C-NMR (125 MHz) δ: 42.9 (CH), 116.6 (d\*, <sup>2</sup>J=22, C3', C5'), 117.9 (CN), 125.2 (C4), 125.6 (C5), 127.2 (C2'', C6''), 129.2 (C3'', C5''), 129.4 (d\*, <sup>4</sup>J=3.6, C1'), 129.4 (d\*, <sup>3</sup>J=8.7, C2', C6'), 130.6 (C4''), 135.3 (C1''), 156.7 (C3), 159.1 (C6), 162.9 (d\*, <sup>1</sup>J=249.1, C4'); Anal. calcd. for C<sub>18</sub>H<sub>12</sub>N<sub>3</sub>F: C, 74.73; H, 4.18, N, 14.52; found: C, 74.64; H, 4.08; N, 14.56.

*α*-(4-Tolyl)-*α*-(6-phenylpyridazin-3-yl)-acetonitrile (**2c**). Yield 71%; white crystals; m.p. 143.9-144.6 °C; IR (cm<sup>-1</sup>): 2250 (CN); <sup>1</sup>H-NMR (400 MHz) δ: 2.34 (s, 3H, CH<sub>3</sub>), 5.67 (s, 1H, CH), 7.20 (d, 2H, C3'H, C5'H), 7.40 (d, <sup>3</sup>J=7.6, 2H, C2'H, C6'H), 7.51 (m, 3H, C3''H, C4''H, C5''H), 7.60 (d, 1H, C4H), 7.86 (d, <sup>3</sup>J=8.8, 1H, C5H), 8.06 (m, 2H, C2''H, C6''H); <sup>13</sup>C-NMR (100 MHz) δ: 21.3 (CH<sub>3</sub>), 43.4 (CH), 118.5 (CN), 125.3 (C5), 125.9 (C4), 127.3 (C2', C6'), 127.6 (C3'', C5''), 129.3 (C2'', C6''), 130.3 (C3', C5'), 130.7 (C4''), 131.8 (C1'), 135.6 (C4'), 139.0 (C1''), 157.3 (C6), 159.1 (C3); Anal. calcd. for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>: C, 79.98; H, 5.30, N, 14.72; found: C, 79.20; H, 5.26; N, 15.54.

*α*-(4-Methoxyphenyl)-*α*-(6-phenylpyridazin-3-yl)-acetonitrile (**2d**). Yield 94%; white crystals; m.p. 206.8-209.4 °C; IR (cm<sup>-1</sup>): 2250 (CN); <sup>1</sup>H-NMR (400 MHz) δ: 3.80 (s, 3H, OCH<sub>3</sub>), 5.66 (s, 1H, CH), 6.92 (d, 2H, C3'H, C5'H), 7.44 (d, <sup>3</sup>J=8.4, 2H, C2'H, C6'H), 7.52 (m, 3H, C3''H, C4''H, C5''H), 7.61 (d, 1H, C4H), 7.88 (d, <sup>3</sup>J=8.8, 1H, C5H), 8.08 (m, 2H, C2''H, C6''H); <sup>13</sup>C-NMR (100 MHz) δ: 42.1 (CH), 55.6 (OCH<sub>3</sub>), 114.4 (C3', C5'), 116.2 (C4), 117.9 (CN), 124.8 (C1'), 127.9 (C5), 127.9 (C2', C6'), 128.4 (C6), 129.1 (C2'', C6''), 129.6 (C3'', C5''), 131.7 (C4''), 133.7 (C1''), 157.3 (C3), 159.2 (C4'); Anal. calcd. for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>O: C, 75.73; H, 5.02, N, 13.94; found: C, 75.77; H, 5.42; N, 13.95.

*α*-(2-Methoxyphenyl)-*α*-(6-phenylpyridazin-3-yl)-acetonitrile (**2e**). Yield 85%; white crystals; m.p. 151.0-152.0 °C; IR (cm<sup>-1</sup>): 2245 (CN); <sup>1</sup>H-NMR (400 MHz) δ: 3.84 (s, 3H, OCH<sub>3</sub>), 5.93 (s, 1H, CH), 6.92 (d, <sup>3</sup>J=8.4, 1H, C3'H), 7.04 (t, <sup>3</sup>J=7.2, 1H, C5'H), 7.36 (t, <sup>3</sup>J=7.6, 1H, C4'H), 7.51 (ps, 3H, C3''H, C4''H, C5''H), 7.57 (pt, 2H, C4H, C6'H), 7.85 (d, <sup>3</sup>J=8.8, 1H, C5H), 8.08 (pd, 2H, C2''H, C6''H); <sup>13</sup>C-NMR (100 MHz) δ: 38.4 (CH), 55.9 (OCH<sub>3</sub>), 111.5 (C3'), 118.4 (CN), 121.6 (C5'), 122.3 (C1'), 124.7 (C5), 126.2 (C4), 127.3 (C2'', C6''), 129.3 (C3'', C5''), 129.8 (C6'), 130.6 (C4''), 130.7 (C4'), 135.8 (C1''), 156.4 (C3), 156.8 (C6), 158.8 (C2'); Anal. calcd. for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>O: C, 75.73; H, 5.02, N, 13.94; found: C, 75.47; H, 5.10; N, 13.71.

*α*-Phenyl-*α*-(6-chloropyridazin-3-yl)-acetonitrile (**2f**). Yield 69%; white crystals; m.p. 131.1-131.3 °C; {lit. [16], 125-126°C}; IR (cm<sup>-1</sup>): 2239 (CN); <sup>1</sup>H-NMR (500 MHz) δ: 5.67 (s, 1H, CH), 7.38 (m, 1H, C4'H), 7.41 (m, 2H, C3'H, C5'H), 7.47 (m, 2H, C2'H, C6'H), 7.55 (m, 2H, C4H, C5H); <sup>13</sup>C-NMR (125 MHz) δ: 43.1 (CH), 117.6 (CN), 127.5 (C2', C6'), 127.7 (C5), 129.1 (C4'), 129.6 (C4), 129.7 (C3', C5'), 132.8 (C1'), 157.0 (C3), 157.9 (C6); Anal. calcd. for C<sub>12</sub>H<sub>8</sub>N<sub>3</sub>Cl: C, 62.75; H, 3.51, N, 18.30; found: C, 62.85; H, 3.43; N, 18.46.

*α*-(4-Fluorophenyl)-*α*-(6-chloropyridazin-3-yl)-acetonitrile (**2g**). Yield 75%; white crystals; m.p. 133.0-133.5 °C; IR (cm<sup>-1</sup>): 2251 (CN); <sup>1</sup>H-NMR (500 MHz) δ: 5.65 (s, 1H, CH), 7.08-7.11 (m, 2H, C2'H, C6'H), 7.44-7.47 (m, 2H, C3'H, C5'H), 7.55-7.66 (m, 2H, C4H, C5H); <sup>13</sup>C-NMR (125 MHz) δ: 42.4 (CH), 116.8 (C3', C5'), 117.5 (CN), 127.7 (C5), 129.4 (C2', C6'), 129.5 (C1'), 129.7 (C4), 157.6 (C3), 157.7 (C6), 163.9 (C4'); Anal. calcd. for C<sub>12</sub>H<sub>7</sub>N<sub>3</sub>FCl: C, 58.20; H, 2.85; N, 16.97; found: C, 58.07; H, 2.86; N, 16.77.

*α*-Phenyl-*α*-(6-methoxypyridazin-3-yl)-acetonitrile (**2h**). Yield 53%; white crystals; m.p. 153.0-156.0 °C; IR (cm<sup>-1</sup>): 2245 (CN); <sup>1</sup>H-NMR (500 MHz) δ: 4.14 (s, 3H, OCH<sub>3</sub>), 5.59 (s, 1H, CH), 6.99 (d, 1H, C5H), 7.37 (dd, 3H, C3'H, C4'H, C5'H), 7.42 (d, <sup>3</sup>J=9.0, 1H, C4H), 7.47 (d, 2H, <sup>3</sup>J=8.0, C2'H, C6'H); <sup>13</sup>C-NMR (125 MHz) δ: 43.1 (CH), 55.1 (OCH<sub>3</sub>), 118.1 (CN), 118.9 (C5), 127.5 (C2', C6'), 128.2 (C4), 128.8 (C4'), 129.5 (C3', C5'), 133.6 (C1'), 153.8 (C3), 164.8 (C6); Anal. calcd. for C<sub>13</sub>H<sub>11</sub>N<sub>3</sub>O: C, 69.32; H, 4.92, N, 18.65; found: C, 69.01; H, 5.31; N, 18.52.

#### Synthesis of *α*-phenyl-*α*-(pyridazin-3-yl)-acetonitrile (**2f'**) and *α*-(4-fluorophenyl)-*α*-(pyridazin-3-yl)-acetonitrile (**2g'**)

The appropriate nitrile **2f** or **2g** (0.06 mol) was placed in MeOH (300 mL), along with ammonium formate (18.9 g, 0.3 mol) and Pd/C (10%, 3.4g). The combined mixture was brought to boiling while stirring, the reaction was performed under nitrogen. For compound **2f'** the reaction time was 2 h, for compound **2g'** it was 1.5 h (TLC). After cooling the whole was filtered off from the catalyst and the filtrate was evaporated to dryness. The obtained precipitate was dissolved in CHCl<sub>3</sub> – H<sub>2</sub>O mixture (1:1 v/v, 100 mL) and then extracted with CHCl<sub>3</sub> (3 x 100 mL). The combined chloroform extracts were dried with anhydrous MgSO<sub>4</sub>. After filtering off the drying agent the filtrate was evaporated to dryness. The obtained precipitate **2f'** was purified on the chromatographic column by flash technique, using CH<sub>2</sub>Cl<sub>2</sub>/MeOH eluents (97:3 v/v), and then it was crystallized from ethanol. Compound **2g'** was purified by maceration with the hexane : ethyl acetate mixture (1:1 v/v).

*α*-Phenyl-*α*-(pyridazin-3-yl)-acetonitrile (**2f'**). Yield 57%; white crystals; m.p. 139.8-141.7 °C; {lit. [15,16], 136-137 °C; lit. [17], 138-140 °C}; IR (cm<sup>-1</sup>): 2245 (CN); <sup>1</sup>H-NMR (500 MHz) δ: 5.69 (s, 1H, CH), 7.37 (m, 1H, C4'H), 7.41 (m, 2H, C3'H, C5'H), 7.50 (m, 2H, C2'H, C6'H), 7.52 (m, 1H, C5H), 7.59 (m, 1H, C4H), 9.19 (m, 1H, C6H); <sup>13</sup>C-NMR (125 MHz) δ: 44.2 (CH), 118.3 (CN), 125.7 (C4, C5), 127.9 (C2', C6'), 129.3 (C4'), 129.9 (C3', C5'), 133.7 (C1'), 151.4 (C6), 159.1 (C3); Anal. calcd. for C<sub>12</sub>H<sub>9</sub>N<sub>3</sub>: C, 73.83; H, 4.65, N, 21.52; found: C, 73.62; H, 4.87; N, 21.46.

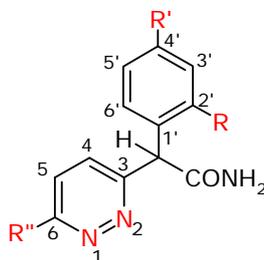
*α*-(4-Fluorophenyl)-*α*-(pyridazin-3-yl)-acetonitrile (**2g'**). Yield 58%; white crystals; m.p. 127.0-128.0 °C; IR (cm<sup>-1</sup>): 2248 (CN); <sup>1</sup>H-NMR (500 MHz) δ: 5.66 (s, 1H, CH), 7.07-7.11 (m, 2H, C2'H, C6'H), 7.46-7.61 (m, 4H, C4H, C5H, C3'H, C5'H), 9.18-9.20 (dd, 1H, C6H); <sup>13</sup>C-NMR (125 MHz) δ: 43.2 (CH), 116.7 (C3', C5'), 117.8 (CN), 127.7 (C5), 129.2 (C2', C6'), 129.4 (C1'), 129.5 (C4), 151.2 (C6), 158.6 (C3), 163.9 (C4'); Anal. calcd. for C<sub>12</sub>H<sub>8</sub>N<sub>3</sub>F: C, 67.60; H, 3.78; N, 19.71; found: C, 66.41; H, 3.75; N, 19.45.

### General procedure for the preparation of *α*-aryl- *α*-(pyridazin-3-yl)-acetamides **3a-f**, **3h**, **3f'**, **3g'**

To concentrated sulphuric acid (50 mL) was added the appropriate nitrile **2a**, **b**, **c**, **f**, **h**, **f'**, **g'** (0.03 mol). The mixture was stirred for 12 h at the temperature of 50 °C. Compounds **2e** and **2d** were hydrolyzed in the mixture of concentrated sulphuric acid (10 mL) and glacial acetic acid (30 mL) for 1 h at the temperature of 100 °C (**2e**) and for 10 h at the temperature of 50 °C (**2d**).

Then the post-reaction mixture was cooled and made alkaline at a temperature of 5 °C with concentrated NH<sub>4</sub>OH to pH~8. The separated reaction product was extracted with chloroform (3 x 150 mL). The combined chloroform extracts were dried with anhydrous MgSO<sub>4</sub>. After filtering the drying agent the solvent was distilled off and the crude product was macerated with acetonitrile **3c**, **3d**; hexane **3e** and **3f**, and the ethyl acetate- hexane mixture (1:1 v/v). After maceration for compounds **3d** and **3e** flash column chromatography was applied, using the following mixtures for elution: for **3d** CHCl<sub>3</sub>-MeOH mixture (99:1 v/v), whereas for **3e** CH<sub>2</sub>Cl<sub>2</sub>:CHOH (98:2 v/v). Next the compounds were purified by crystallization from EtOH **3a**, **3b**, **3c**, **3d**, **3f**, **3h**, **3f'**, **3g'**.

**Figure 3.** Numbering system for compounds **3a-f**, **3h**, **3f'**, **3g'**.



*α*-Phenyl-*α*-(6-phenylpyridazin-3-yl)-acetamide (**3a**). Yield 74%; white crystals; m.p. 177.7-179.8 °C; IR (cm<sup>-1</sup>): 1655 (CO-NH<sub>2</sub>); <sup>1</sup>H-NMR (500 MHz) δ: 5.36 (s, 1H, CH), 5.77 (bs, 1H, NH(2)), 7.17 (bs, 1H, NH (1)), 7.29 (tt, <sup>3</sup>J=7.5, <sup>4</sup>J=1.0, 1H, C4'H), 7.36 (td, <sup>3</sup>J=7.5, <sup>4</sup>J=1.5, 2H, C3'H, C5'H), 7.47 – 7.55 (m, 5H, C2'H-C6'H), 7.62 (d, <sup>3</sup>J=8.5, 1H, C4H), 7.83 (d, 1H, C5H), 8.05 (dd, <sup>3</sup>J=7.5, <sup>4</sup>J=1.5, 2H, C2'H, C6'H); <sup>13</sup>C-NMR (125 MHz) δ: 58.8 (CH), 124.7 (C5), 127.1 (C2',C6'), 127.9 (C4), 128.2 (C4'), 128.5 (C3'', C5''), 129.0 (C3', C5'), 129.1 (C2'', C6''), 130.2 (C4''), 135.9 (C1'), 137.4 (C1''),

158.4 (C3), 159.8 (C6), 172.2 (CO); Anal. calcd. for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O: C, 74.72; H, 5.23, N, 14.52; found: C, 74.74; H, 5.24; N, 14.48.

*α*-(4-Fluorophenyl)-*α*-(6-phenylpyridazin-3-yl)-acetamide (**3b**). Yield 63%; beige crystals; m.p. 199.5-200.7 °C; IR (cm<sup>-1</sup>): 1686 (CO-NH<sub>2</sub>); <sup>1</sup>H-NMR (500 MHz) δ: 5.31(s, 1H, CH), 6.82 (bs, 1H, NH (2)), 7.05 (m, 2H, C3'H, C5'H), 7.23 (bs, 1H, NH(1)), 7.46-7.56 (m, 5H, C2''H-C6''H), 7.60 (d, <sup>3</sup>J=9.0 Hz, 1H, C4H), 7.85 (d, 1H, C5H), 8.05 (m, 2H, C2'H, C6'H); <sup>13</sup>C-NMR (125 MHz) δ: 57.9 (CH), 116.0 (d\*, <sup>2</sup>J=22.0, C3', C5'), 124.9 (C4), 127.1 (C2'', C6''), 128.1 (C5), 129.1 (C3'', C5''), 130.2 (d\*, <sup>3</sup>J=8.2, C2', C6'), 130.3 (C4''), 133.2 (d\*, <sup>4</sup>J=3.3, C1'), 135.8 (C1''), 158.5 (C3), 159.6 (C6), 162.4 (d\*, <sup>1</sup>J=249.5, C4'), 171.9 (CO); Anal. calcd. for C<sub>18</sub>H<sub>14</sub>N<sub>3</sub>OF: C, 70.35; H, 4.59, N, 13.67; found: C, 70.30; H, 4.58; N, 13.77.

*α*-(4-Tolylo)-*α*-(6-phenylpyridazin-3-yl)-acetamide (**3c**). Yield 46 %; white crystals; m.p. 208.5-209.4 °C; IR (cm<sup>-1</sup>): 1683 (CO-NH<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz) δ: 2.33 (s, 3H, CH<sub>3</sub>), 5.33 (s, 1H, CH), 5.64 (bs, 1H, NH(2)), 7.12 (bs, 1H, NH(1)), 7.18 (d, 2H, C3'H, C5'H), 7.40 (d, <sup>3</sup>J=8.0, 2H, C2'H, C6'H), 7.53 (m, 3H, C3''H, C4''H, C5''H), 7.63 (d, <sup>3</sup>J=9.2, 1H, C4H), 7.85 (d, 1H, C5H), 8.06 (dd, <sup>3</sup>J=7.6, <sup>4</sup>J=2.4, 2H, C2''H, C6''H); <sup>13</sup>C-NMR (100 MHz) δ: 21.3 (CH<sub>3</sub>), 58.4 (CH), 125.3 (C5), 127.3 (C2', C6'), 128.6 (C3'', C5''), 128.8 (C4), 129.4 (C3', C5'), 130.1 (C2'', C6''), 130.6 (C4''), 134.5 (C1'), 136.0 (C1''), 138.2 (C4'), 158.6 (C3), 160.0 (C6), 172.4 (CO); Anal. calcd. for C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>O: C, 75.22; H, 5.65, N, 13.85; found: C, 74.32; H, 5.51; N, 14.16.

*α*-(4-Methoxyphenyl)-*α*-(6-phenylpyridazin-3-yl)-acetamide (**3d**). Yield 70%; white crystals; m.p. 168.2-170.7 °C; IR (cm<sup>-1</sup>): 1662 (CO-NH<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz) δ: 3.67 (s, 3H, OCH<sub>3</sub>), 5.32 (s, 1H, CH), 6.17 (s, 2H, NH<sub>2</sub>), 6.77 (m, 2H, C3'H, C5'H), 7.19 (m, 2H, C2'H, C6'H), 7.40 (m, 3H, C3''H, C4''H, C5''H), 7.57 (m, 1H, C4H), 7.71 (m, 1H, C5H), 7.93 (m, 2H, C2''H, C6''H); <sup>13</sup>C-NMR (100 MHz) δ: 55.4 (OCH<sub>3</sub>), 57.7 (CH), 114.6 (C3', C5'), 124.9 (C4), 127.2 (C2'', C6''), 128.2 (C5), 128.5 (C1''), 129.2 (C2', C6'), 129.8 (C3'', C5''), 130.6 (C4''), 136.1 (C1'), 158.4 (C6), 159.3 (C3), 160.4 (C4'), 173.2 (CO); Anal. calcd. for C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>: C, 71.46; H, 5.37, N, 13.16; found: C, 71.33; H, 5.57; N, 13.01.

*α*-(2-Methoxyphenyl)-*α*-(6-phenylpyridazin-3-yl)-acetamide (**3e**). Yield 16%; white crystals; m.p. 183.0-184.0 °C; IR (cm<sup>-1</sup>): 1686 (CO-NH<sub>2</sub>); <sup>1</sup>H-NMR (400 MHz) δ: 3.82 (s, 3H, OCH<sub>3</sub>), 5.78 (bs, 1H, NH(1)), 5.88 (s, 1H, CH), 6.91 (d, <sup>3</sup>J=8.4, 1H, C3'H), 6.97 (bs, 1H, NH(2)), 6.99 (t, <sup>3</sup>J=7.6, 1H, C5'H), 7.31 (t, <sup>3</sup>J=7.6, 1H, C4'H), 7.52 (m, 4H, C6'H, C3''H, C4''H, C5''H), 7.72 (d, 1H, C4H), 7.89 (d, <sup>3</sup>J=8.8, 1H, C5H), 8.06 (dd, <sup>3</sup>J=6.4, <sup>4</sup>J=2.4, 2H, C2''H, C6''H); <sup>13</sup>C-NMR (100 MHz) δ: 51.9 (CH), 55.8 (OCH<sub>3</sub>), 111.3 (C3'), 121.4 (C5'), 125.4 (C5), 125.7 (C1'), 127.3 (C2'', C6''), 129.3 (C4, C3'', C5''), 129.6 (C4'), 129.7 (C6'), 130.6 (C4''), 135.7 (C1''), 157.1 (C3), 158.3 (C6), 160.0 (C2'), 172.4 (CO); Anal. calcd. for C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>: C, 71.46; H, 5.37, N, 13.16; found: C, 71.46; H, 5.45; N, 13.08.

*α*-Phenyl-*α*-(6-chloropyridazin-3-yl)-acetamide (**3f**). Yield 29 %; white crystals; m.p. 140.0-141.0 °C; IR (cm<sup>-1</sup>): 1685 (CO-NH<sub>2</sub>); <sup>1</sup>H-NMR (500 MHz) δ: 5.45 (s, 1H, CH), 6.21 (bs, 1H, NH(2)), 6.83 (bs, 1H, NH(1)), 7.23-7.45 (m, 5H, <sup>3</sup>J=8.8, 5H, C2'H, C3'H, C4'H, C5'H, C6'H), 7.44 (d, 1H, <sup>3</sup>J=8.8, C5H), 7.64 (d, 1H, C4H); <sup>13</sup>C-NMR (125 MHz) δ: 57.8 (CH), 128.1 (C5), 128.3 (C2', C6'), 128.7

(C4'), 129.2 (C3', C5'), 130.2 (C4), 136.8 (C1'), 156.1 (C3), 160.9 (C6), 175.0 (CO); Anal. calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>3</sub>OCl: C, 58.19; H, 4.07, N, 16.97; found: C, 58.01; H, 4.02; N, 16.88.

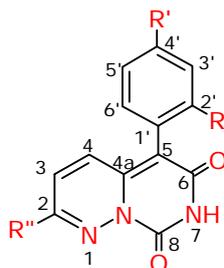
*α*-Phenyl-*α*-(pyridazin-3-yl)-acetamide (**3f'**). Yield 47%; white crystals; m.p. 177.0-178.0 °C; IR (cm<sup>-1</sup>): 1679 (CO-NH<sub>2</sub>); <sup>1</sup>H-NMR (500 MHz) δ: 5.61 (bs, 1H, NH(2)), 5.29 (s, 1H, CH), 6.96 (bs, 1H, NH(1)), 7.28-7.38 (m, <sup>3</sup>J<sub>0</sub>=7.0, <sup>4</sup>J<sub>m</sub>=1.5, 3H, C3'H, C4'H, C5'H), 7.43-7.48 (m, 3H, C5H, C2'H, C6'H), 7.56 (dd, <sup>3</sup>J<sub>0</sub>=8.5, <sup>4</sup>J<sub>m</sub>=1.5, 1H, C4H), 9.11 (dd, <sup>3</sup>J<sub>0</sub>=5.0, <sup>4</sup>J<sub>m</sub>=2.0, 1H, C6H); <sup>13</sup>C-NMR (125 MHz) δ: 59.1 (CH), 127.1 (C5), 127.8 (C4), 128.0 (C4'), 128.4 (C2', C6'), 129.2 (C3', C5'), 137.2 (C1'), 150.4 (C6), 161.4 (C3), 171.9 (CO); Anal. calcd. for C<sub>12</sub>H<sub>11</sub>N<sub>3</sub>O: C, 67.59; H, 5.20, N, 19.71; found: C, 67.52; H, 4.91; N, 19.78.

*α*-(4-Fluorophenyl)-*α*-(pyridazin-3-yl)-acetamide (**3g'**). Yield 66%; white crystals; m.p. 157.5-158.5 °C; IR (cm<sup>-1</sup>): 1690 (CO-NH<sub>2</sub>); <sup>1</sup>H-NMR (500 MHz) δ: 5.37 (s, 1H, CH), 5.94 (bs, 1H, NH(2)), 7.03 (t, <sup>3</sup>J=8.4, 2H, C3'H, C5'H), 7.24 (bs, 1H, NH(1)), 7.40-7.52 (m, 3H, C5H, C2'H, C6'H), 7.62 (d, <sup>3</sup>J=8.4, 1H, C4H), 9.12 (d, 1H, C6H); <sup>13</sup>C-NMR (125 MHz) δ: 57.9 (CH), 116.0 (d\*, <sup>2</sup>J=21.6, C3', C5'), 127.4 (C4), 127.8 (C5), 130.2 (d\*, <sup>3</sup>J=8.2, C2', C6'), 132.9 (C1'), 150.5 (C6), 161.4 (C3), 162.4 (d\*, <sup>1</sup>J=246.4, C4'), 171.9 (CO); Anal. calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>3</sub>FO: C, 62.33; H, 4.36; N, 18.17; found: C, 61.99; H, 4.31; N, 17.94.

*α*-Phenyl-*α*-(6-methoxypyridazin-3-yl)-acetamide (**3h**). Yield 69%; white crystals; m.p. 165-168 °C; IR (cm<sup>-1</sup>): 1688 (CO-NH<sub>2</sub>); <sup>1</sup>H-NMR (500 MHz) δ: 4.10 (s, 3H, OCH<sub>3</sub>), 5.28 (s, 1H, CH), 6.10 (s, 1H, NH(2)), 6.94 (d, 1H, C5H), 7.15 (bs, 1H, NH(1)), 7.27 (m, 1H, C4'H), 7.32 (m, 2H, C3'H, C5'H), 7.42 (m, 2H, C2'H, C6'H), 7.46 (d, <sup>3</sup>J=9.0, 1H, C4H); <sup>13</sup>C-NMR (125 MHz) δ: 54.8 (OCH<sub>3</sub>, J=1.0), 58.2 (CH), 118.2 (C5), 127.8 (C4), 128.4 (C2',C6'), 129.1 (C3', C5'), 130.6 (C4'), 137.6 (C1'), 156.7 (C3), 164.5 (C6), 172.6 (CO); Anal. calcd. for C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: C, 64.19; H, 5.39, N, 17.27; found: C, 64.59; H, 5.37; N, 17.36.

#### General procedure for the preparation of 7H,8H-pyrimido[1,6-b]pyridazin-6,8-dione derivatives **4a-f**, **4f'**, **4g'**

To absolute ethanol (30 mL) was added sodium (0.18 mol) and the mixture was stirred until they had reacted. Next diethyl carbonate (0.17 mol) was added and the respective amide **3a-f**, **3h**, **3f'**, **3g'** (0.1 mol) was added portionwise. The reaction was performed in boiling for 12 h. After cooling the post-reaction mixture was poured into distilled water (100 mL) and acidified with acetic acid to pH~3. The yellow precipitate separated and was filtered off. Compounds **4a**, **4b**, **4e** were purified on a chromatographic column by the flash technique, using the CH<sub>2</sub>Cl<sub>2</sub>-MeOH (97:3 v/v) and CH<sub>2</sub>Cl<sub>2</sub>-MeOH (99:1 v/v) mixtures as eluents. Compound **4c** was macerated with acetonitrile, **4d** was crystallized from MeOH and **4f'** was crystallized from EtOH, and next was flash chromatographed using the CH<sub>2</sub>Cl<sub>2</sub>-MeOH (98:2 v/v) mixture as eluent. Compound **4g'** was crystallized from EtOH. Compound **4f** was purified by flash chromatography with CHCl<sub>3</sub>-MeOH (97:3 v/v) and next was crystallized from MeOH.

**Figure 4.** Numbering system for compounds **4a-f**, **4f'**, **4g'**.

**2,5-Diphenyl-7H,8H-pyrimido[1,6-b]pyridazin-6,8-dione (4a).** Yield 94%; yellow crystals; m.p. 302-303 °C; IR (cm<sup>-1</sup>): 1660 (CO), 1725 (CO); <sup>1</sup>H-NMR (500 MHz) δ: 7.17(d, <sup>3</sup>J=10.0, 1H, C3H), 7.34 (dd, <sup>3</sup>J=8.0, <sup>4</sup>J=1.5, 2H, C2'H, C6'H), 7.40 (d, 1H, C4H), 7.42 (tt, <sup>3</sup>J=7.0, <sup>4</sup>J=1.0, 1H, C4''H), 7.46-7.54 (m, 5H, C3'H, C4'H, C5'H, C3''H, C5''H), 7.92 (dd, <sup>3</sup>J=6.4, <sup>4</sup>J=1.6, 2H, C2''H, C6''H) 8.51 (bs, 1H, NH); <sup>13</sup>C-NMR (125 MHz) δ: 107.5 (C5), 122.8 (C4), 126.7 (C3'', C5''), 128.7 (C4'), 129.0 (C2'', C6''), 129.2 (C3', C5'), 130.6 (C1'), 131.01 (C2', C6'), 131.03 (C4''), 131.1 (C3), 133.5 (C1''), 141.3 (C2), 147.5 (C8), 150.0 (C4a), 160.2 (C6); Anal. calcd. for C<sub>19</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>: C, 72.37; H, 4.15, N, 13.33; found: C, 71.61; H, 4.15; N, 13.20.

**2-Phenyl-5-(4-fluorophenyl)-7H,8H-pyrimido[1,6-b]pyridazin-6,8-dione (4b).** Yield 91%; yellow crystals; m.p. 292.8-293.2 °C; IR (cm<sup>-1</sup>): 1654 (CO), 1709 (CO); <sup>1</sup>H-NMR (400 MHz) δ: 7.23-7.30 (m, 3H, C3H, C3'H, C5'H), 7.30-7.40 (m, 2H, C2'H, C6'H), 7.50-7.64 (m, 4H, C4H, C3''H, C4''H, C5''H), 7.92-8.20 (m, 2H, C2''H, C6''H), 12.03 (s, 1H, NH); <sup>13</sup>C-NMR (100 MHz) δ: 107.1 (C5), 117.4 (d\*, <sup>2</sup>J=21.4, C3', C5'), 125.0 (C4), 128.4 (C3'', C5''), 130.1 (d\*, <sup>4</sup>J=3.0, C1'), 131.1 (C2'', C6''), 132.7 (C4''), 132.8 (C3), 135.3 (d\*, <sup>3</sup>J=8.0, C2', C6'), 135.6 (C1''), 143.0 (C2), 149.7 (C8), 150.6 (C4a), 162.8 (C6), 163.7 (d\*, <sup>1</sup>J=244.8, C4'); Anal. calcd. for C<sub>19</sub>H<sub>12</sub>N<sub>3</sub>O<sub>2</sub>F: C, 68.46; H, 3.63, N, 12.61; found: C, 68.84; H, 4.01; N, 13.00.

**2-Phenyl-5-(4-tolyl)-7H,8H-pyrimido[1,6-b]pyridazin-6,8-dione (4c).** Yield 92%; yellow crystals; m.p. 321.0-321.4 °C; IR (cm<sup>-1</sup>): 1659 (CO), 1728 (CO); <sup>1</sup>H-NMR (400 MHz) δ: 2.35 (s, 3H, CH<sub>3</sub>), 7.19 (d, <sup>3</sup>J=7.6, 2H, C3'H, C5'H), 7.26(m, 3H, C3H, C2'H, C6'H), 7.55 (m, 4H, C4H, C3''H, C4''H, C5''H), 7.97 (m, 2H, C2''H, C6''H), 11.97 (s, 1H, NH); <sup>13</sup>C-NMR (100 MHz) δ: 22.9 (CH<sub>3</sub>), 108.1 (C5), 124.8 (C4), 128.4 (C3'', C5''), 130.8 (C1'), 131.1 (C2', C6', C2'', C6''), 132.8 (C4''), 132.9 (C3), 133.0 (C3', C5'), 135.6 (C1''), 139.1 (C4'), 142.8 (C2), 149.7 (C8), 150.5 (C4a), 162.8 (C6); Anal. calcd. for C<sub>20</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>: C, 72.94; H, 4.59; N, 12.76; found: C, 72.56; H, 4.45; N, 13.06.

**2-Phenyl-5-(4-methoxyphenyl)-7H,8H-pyrimido[1,6-b]pyridazin-6,8-dione (4d).** Yield 98%; yellow crystals; m.p. 306.6-308.4 °C; IR (cm<sup>-1</sup>): 1654 (CO), 1717 (CO); <sup>1</sup>H-NMR (400 MHz) δ: 3.86 (s, 3H, OCH<sub>3</sub>), 7.02 (d, <sup>3</sup>J=10.0, 2H, C3'H, C5'H), 7.17 (d, <sup>3</sup>J=10.0, 1H, C3H), 7.27 (d, 2H, C2'H, C6'H), 7.42 (d, 1H, C4H), 7.52 (m, 3H, C3''H, C4''H, C5''H), 7.92 (m, 2H, C2''H, C6''H), 8.60 (bs, 1H, NH); <sup>13</sup>C-NMR (100 MHz) δ: 55.6 (OCH<sub>3</sub>), 107.4 (C5), 114.7 (C3', C5'), 122.8 (C4), 125.0 (C1'), 126.9 (C3'', C5''), 129.4 (C2'', C6''), 131.3 (C4''), 131.4 (C3), 132.4 (C2', C6'), 133.7 (C1''), 141.3 (C2), 148.4 (C8), 150.2 (C4a), 155.5 (C4'), 159.9 (C6); Anal. calcd. for C<sub>20</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>: C, 69.56; H, 4.38, N, 12.17; found: C, 69.46; H, 4.68; N, 11.78.

2-Phenyl-5-(2-methoxyphenyl)-7H,8H-pyrimido[1,6-b]pyridazin-6,8-dione (**4e**). Yield 60%; yellow crystals; m.p. 275.0-277.0 °C; IR (cm<sup>-1</sup>): 1643 (CO), 1747 (CO); <sup>1</sup>H-NMR (400 MHz) δ: 3.79 (s, 3H, OCH<sub>3</sub>), 7.02 (d, <sup>3</sup>J=8.4, 1H, C3'H), 7.07 (t, <sup>3</sup>J=7.6, 1H, C5'H), 7.11 (d, <sup>3</sup>J=10.0, 1H, C3H), 7.16 (d, 1H, C4H), 7.25 (d, 1H, C6'H), 7.42 (td, <sup>3</sup>J=8.0, 1H, C4'H), 7.50 (m, 3H, C3''H, C4''H, C5''H), 7.92 (m, 2H, C2''H, C6''H), 8.52 (bs, 1H, NH); <sup>13</sup>C-NMR (100 MHz) δ: 55.2 (OCH<sub>3</sub>), 103.3 (C5), 111.1 (C3'), 118.7 (C1'), 120.6 (C5'), 121.9 (C4), 126.3 (C2'', C6''), 128.7 (C3'', C5''), 130.0 (C4'), 130.5 (C4''), 131.2 (C3), 132.4 (C6'), 133.2 (C1''), 141.1 (C2), 147.3 (C8), 149.3 (C4a), 157.3 (C2'), 159.7 (C6); Anal. calcd. for C<sub>20</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>: C, 69.56; H, 4.38, N, 12.17; found: C, 69.36; H, 4.57; N, 11.26.

2-Ethoxy-5-phenyl-7H,8H-pyrimido[1,6-b]pyridazin-6,8-dione (**4f**). Yield 31% (from **3f**), 72% (from **3h**); yellow crystals; m.p. 272.0-274.0 °C; IR (cm<sup>-1</sup>): 1636 (CO), 1738 (CO); <sup>1</sup>H-NMR (500 MHz) δ: 1.42 (t, 3H, <sup>3</sup>J=7.0, C2H<sub>et</sub>), 4.40 (k, 2H, C1H<sub>et</sub>), 6.48 (d, <sup>3</sup>J=9.5, 1H, C3H), 7.25 (d, 1H, C4H), 7.28-7.33 (m, 2H, C3'H, C5'H), 7.37-7.42 (m, 1H, C4'H), 7.42-7.48 (m, 2H, C2'H, C6'H), 8.82 (bs, NH); <sup>13</sup>C-NMR (125 MHz) δ: 14.0 (C2<sub>et</sub>), 64.1 (C1<sub>et</sub>), 108.5 (C5), 121.0 (C3), 128.6 (C4'), 128.9 (C2', C6'), 130.9 (C1'), 131.1 (C3', C5'), 132.6 (C4), 141.0 (C4a), 147.3 (C8), 156.5 (C6), 160.4 (C2); Anal. calcd. for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>3</sub>: C, 63.60; H, 4.62, N, 14.83; found: C, 63.26; H, 4.60; N, 14.74.

5-Phenyl-7H,8H-pyrimido[1,6-b]pyridazin-6,8-dione (**4f'**). Yield 27 %; yellow crystals; m.p. 265.5-266.3 °C; IR (cm<sup>-1</sup>): 1651 (CO), 1751 (CO); <sup>1</sup>H-NMR (500 MHz) δ: 6.85 (dd, <sup>3</sup>J<sub>1</sub>=12.0, <sup>3</sup>J<sub>2</sub>=4.5, 1H, C3H), 7.27 (dd, <sup>3</sup>J=12.0, <sup>4</sup>J=2.0, 1H, C4H), 7.32 (dd, <sup>3</sup>J=10.5, <sup>4</sup>J=2.0, 2H, C2'H, C6'H), 7.40 (tt, <sup>3</sup>J=8.0, <sup>4</sup>J=2.5, 1H, C4'H), 7.47 (t, <sup>3</sup>J=8.0, 2H, C3'H, C5'H), 8.06 (m, 1H, C2H), 9.5 (bs, 1H, NH); <sup>13</sup>C-NMR (125 MHz) δ: 105.0 (C5), 125.2 (C4), 129.6 (C4'), 130.0 (C3', C5'), 131.7 (C3), 132.3 (C1'), 132.5 (C2', C6'), 144.5 (C2), 147.0 (C8), 150.3 (C4a), 163.5 (C6); Anal. calcd. for C<sub>13</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>: C, 65.27; H, 3.79, N, 17.56; found: C, 65.58; H, 3.82 N, 17.14.

5-(4-Fluorophenyl)-7H,8H-pyrimido[1,6-b]pyridazin-6,8-dione (**4g'**). Yield 69%; yellow crystals; m.p. 278.0-278.5 °C; IR (cm<sup>-1</sup>): 1625 (CO), 1756 (CO); <sup>1</sup>H-NMR (500 MHz) δ: 6.67-6.69 (dd, 1H, C4H), 7.13-7.18 (m, 2H, C2'H, C6'H), 7.25-7.30 (m, 3H, C3H, C3'H, C5'H), 7.98 (d, 1H, C2H), 8.65 (s, 1H, NH); <sup>13</sup>C-NMR (125 MHz) δ: 106.8 (C5), 116.4 (C3', C5'), 123.3 (C1'), 126.2 (C4), 130.5 (C2', C6'), 132.8 (C3), 142.3 (C8), 142.4 (C2), 147.4 (C4a), 161.9 (C6), 163.8 (C4'); Anal. calcd. for C<sub>13</sub>H<sub>8</sub>N<sub>3</sub>O<sub>2</sub>F: C, 60.70; H, 3.13; N, 16.34; found: C, 60.83; H, 3.37; N, 16.56.

## References

1. Olivier, B.; Soudijn, W.; van Wijngaarden, J. The 5-HT<sub>1A</sub> receptor and its ligands: structure and function. *Prog. Drug Res.* **1999**, *52*, 103-165.
2. López-Rodríguez, M.L.; Ayala, D.; Benhamú, B.; Morcillo, M.J.; Viso, A. Arylpiperazine Derivatives Acting at 5-HT<sub>1A</sub> Receptors. *Curr. Med. Chem.* **2002**, *9*, 443-469.
3. Barnes, N.M.; Sharp, T. A review of central 5-HT receptors and their function. *Neuropharmacology* **1999**, *38*, 1083-1115.
4. Hoyer, D.; Hannon, J.P.; Martin, G.R. Molecular, pharmacological and functional diversity of 5-HT receptors. *Pharmacol. Biochem. Behav.* **2002**, *71*, 533-554.

5. Jones, B.J.; Blackburn, T.P. The medical benefit of 5-HT research. *Pharmacol. Biochem. Behav.* **2002**, *71*, 555-568.
6. Ishizumi, K.; Kojima, A.; Antoku, F. Synthesis and anxiolytic activity of N-substituted cyclic imides (1*R*\*, 2*S*\*, 3*R*\*, 4*S*\*)-N-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-2,3-bicyclo[2.2.1]-heptanedicarboximide (Tandospirone) and related compounds. *Chem. Pharm. Bull (Tokio)* **1991**, *39*, 2288-2300.
7. Abou-Gharbia, M.A.; Childres, W.A. Jr.; Fletcher, H.; McGaughey, G.; Patel, U.; Webb, M.B.; Yardley, J.; Andree, T.; Boast, C.; Kucharik, R.J.Jr.; Marquis, K.; Morris, H.; Scerni, R.; Moyer, J.A. Synthesis and SAR of adatsensin: novel adamantyl aryl- and heteroaryl piperazines with dual serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> activity as potential anxiolytic and antidepressant agents. *J. Med. Chem.* **1999**, *42*, 5077-5094.
8. Den Boer, J.A.; Bosker, F.J.; Slaap, B.R. Serotonergic drugs in the treatment of depressive and anxiety disorders. *Hum. Psychopharmacol.* **2000**, *15*, 315-356.
9. Lopez-Rodriguez, M.L.; Morcillo, M.J.; Rovat, T.K.; Fernández, E.; Vicente, B.; Sanz, A.M.; Hernández, M.; Orensanz, L. Synthesis and structure-activity relationships of a new model of arylpiperazines. 4. 1-[ω-(4-Arylpiperazin-1-yl)alkyl]3-(diphenylmethylene)-2,5-pyrrolidinediones and -3-(9H-fluoren-9-ylidene)-2,5-pyrrolidinediones: study of the steric requirements of the terminal amide fragment on 5-HT<sub>1A</sub> affinity/selectivity. *J. Med. Chem.* **1999**, *42*, 36-49.
10. Caliendo, G.; Fiorino, F.; Grieco, P.; Perissutti, E.; Santagarda, V.; Albrizio, S.; Spadola, L.; Bruni, G.; Romeo, M.R. Synthesis and binding affinities for 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors of a series of 1- and 2-(4-arylpiperazinylalkyl)-4-(benzoyl)-1,2,3-triazole derivatives. *Eur. J. Med. Chem.* **1999**, *34*, 719-727.
11. Herold, F.; Wolska, I.; Helbin, E.; Król, M.; Kleps, J. Synthesis and Structure of Novel 4-Aryl-hexahydro-1*H*,3*H*-pyrido[1,2-*c*]pyrimidine Derivatives. *J. Heterocycl. Chem.* **1999**, *36*, 389-396.
12. Herold, F.; Kleps, J.; Anulewicz-Ostrowska, R.; Szczęśna, B. Synthesis and Molecular Structure of Novel 4-Aryloctahydropyrido[1,2-*c*]pyrimidine Derivatives. *J. Heterocycl. Chem.* **2002**, *39*, 773-782.
13. Herold, F.; Dawidowski, M.; Wolska, I.; Chodkowski, A.; Kleps, J.; Turło, J.; Zimniak, A. The synthesis of new diastereomers of (4*S*,8*aS*)- and (4*R*,8*aS*)-4-phenyl-perhydropyrrole[1,2-*a*]pyrazine-1,3-dione. *Tetrahedron: Asymmetr.* **2007**, *18*, 2091-2098.
14. Bemis, G.W.; Salituro, F.G.; Duffy, J.P.; Cochran, J.E.; Harrington, E.M.; Murcko, M.A.; Wilson, K.P.; Galullo, V.P. Preparation of annelated pyrimidinones and analogs as p38 kinase inhibitors. *WO 98/27098*, **1998**; [*Chem. Abstr.* **1998**, *129*, 81749].
15. Yamada, T.; Nobuhara, Y.; Shimamura, H.; Yoshihara, K.; Yamaguchi, A.; Ohki, M. Studies on New Antiulcer Agents. I. Synthesis and Antisecretory Activity of Pyridazine Derivatives. *Chem. Pharm. Bull.* **1981**, *29*, 3433-3439.
16. Abbotto, A.; Alanzo, V.; Bradamante, S.; Pagani, G.A. Preparation of Heteroaryl † Phenylmethanes and a <sup>13</sup>C and <sup>15</sup>N NMR Spectroscopic Study of their Conjugate Carbanions. Rotational Isomerism and Charge Maps of the Anions and Ranking of the Charge Demands of the Heterocycles. *J. Chem. Soc. Perkin Trans 2* **1991**, 481-488.
17. Yamanaka, H.; Ohba, S. Reaction of Methoxy-N-Heteroaromatics with Phenylacetonitrile under Basic Conditions. *Heterocycles* **1990**, *31*, 895-909.

18. Gabriel, S.; Colman, J. Synthese des Pyridazins und seiner Derivate. *Chem. Ber.* **1899**, *32*, 395-409.
19. Libermann, D; Rouaix, A. Sur les hydrazino-dérivés de quelques series hétérocycliques. *Bull. Soc. Chim. Fr.* **1959**, 1793-1798.

*Sample Availability:* Samples of the compounds are available from authors.

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