

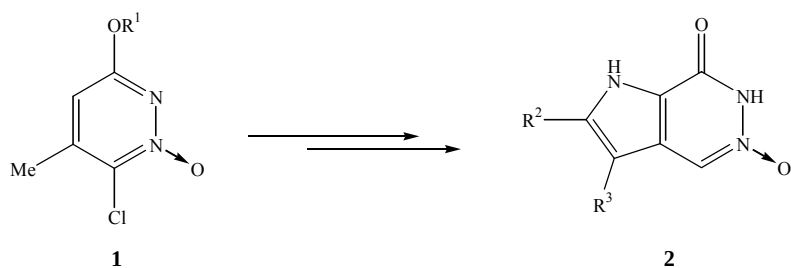
5-ALKYNYL-4-CHLORO- AND 4-ALKYNYL-5-CHLORO-2-METHYLPYRIDAZIN-3(2*H*)-ONES: CONVENIENT PRECURSORS FOR THE PREPARATION OF 2-SUBSTITUTED PYRROLO[2,3-*d*]PYRIDAZINONES

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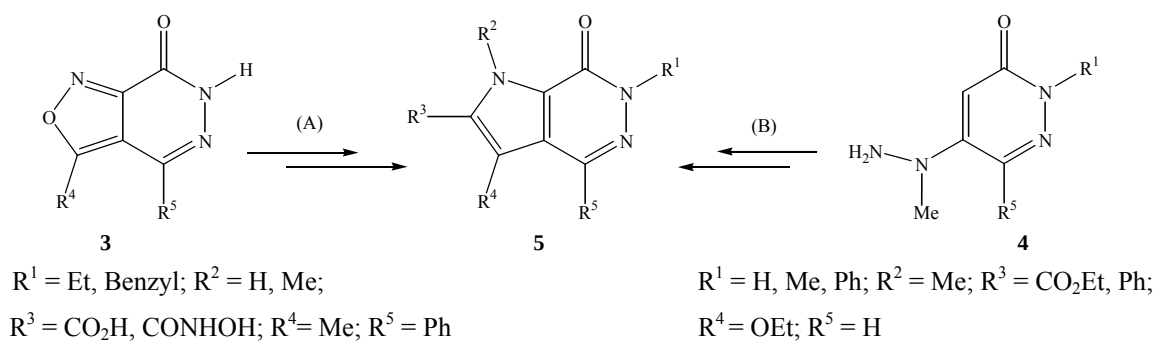
Abstract- A new synthetic route towards the synthesis of 1,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyridazin-7-ones (**10a-f**) and their regioisomers 1,5-dihydro-4*H*-pyrrolo[2,3-*d*]pyridazin-4-ones (**9a,b**) is described, based on the reaction of 5-alkynyl-4-chloro- (**7a,b**) and 4-alkynyl-5-chloropyridazinones (**8**) with different amines (ammonia, methylamine and propylamine) followed by a treatment with a NaOEt solution.

Pyrrolo[2,3-*d*]pyridazinone derivatives have attracted considerable interest in the last decade, owing to the diverse biological activities exhibited by these bicyclic heterocyclic compounds.^{1,2} They have been reported as possessing antiviral activity against human cytomegalovirus (HCMV) and herpes simplex virus type 1 (HSV-1).¹ They have also been described as potent phosphodiesterase IV inhibitors.^{2a,b} Moreover, it was also found that pyrrolo[2,3-*d*]pyridazinone derivatives exhibit important antitumour activities.^{1,2c,2d} These 5,6-diazaindole analogues were first synthesized by Fischer *et al.* in 1928, starting from a 2,3-dicarbonylated pyrrole.³ Since then, many reports have been published dealing with the synthesis of pyrrolo[2,3-*d*]pyridazines and their pyrrolo[2,3-*d*]pyridazinone derivatives following the same strategy.⁴ There are only a few reports concerning the synthesis of this class of compounds, starting from an appropriately substituted pyridazine core. Independently, Castle⁵, Dal Piaz² and Furukawa⁶ have built up 1,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyridazin-7-ones (**2** and **5**) using 6-chloro-3-alkoxy-5-methylpyridazine 1-oxides (**1**) (Scheme 1), isoxazolo[3,4-*d*]pyridazin-7(6*H*)-ones (**3**) (Scheme 2, path A) and 5-hydrazinopyridazinones (**4**) (Scheme 2, path B) respectively as starting materials.



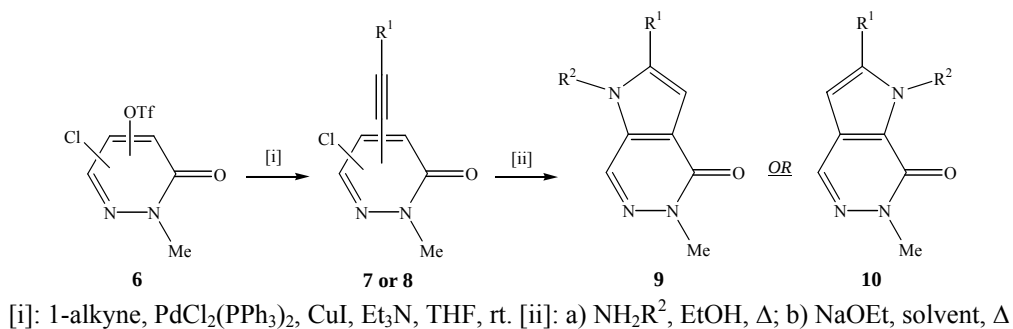
$R^1 = \text{Me, Et}; R^2 = \text{H, CO}_2\text{H, CO}_2\text{Et, NO}_2; R^3 = \text{H, CHO, COCO}_2\text{Et, NO}_2, \text{NH}_2, \text{Br}$

Scheme 1



Scheme 2

Due to the various biological activities exhibited by many pyrrolo[2,3-*d*]pyridazinone derivatives, new procedures to synthesize these compounds are of great interest. This, prompted us to examine a new synthesis of 2-substituted 1,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyridazin-7-ones (**10a-f**) and their 1,5-dihydro-4*H*-pyrrolo[2,3-*d*]pyridazin-4-one regioisomers (**9a-b**) via a reaction of 5-alkynyl-4-chloro- (**7a,b**) and 4-alkynyl-5-chloropyridazinones (**8**) with different amines (Scheme 3). The synthesis of these alkynyl-chloropyridazin-3(2*H*)-one (**7a,b** and **8**) substrates has been reported earlier by our research group (Scheme 3).^{7a}



Scheme 3

Recently, we described a new approach towards the synthesis of furo- and thieno[2,3-*d*]pyridazinones via a reaction of *o*-alkynyl-chloropyridazin-3(2*H*)-ones with KOH and Na₂S respectively.^{7b} Following a similar strategy, initial attempts to achieve the formation of a pyrrolo ring were all in vain. In fact, when reacting 4-chloro-2-methyl-5-phenylethynylpyridazin-3(2*H*)-one (**7a**) with sodium amide (NaNH₂) in DMF, a small amount of the nucleophilic substitution product (assigned by MS, ¹H-NMR and ¹³C-NMR spectra) along with unidentified products were obtained. A trial to switch the solvent from DMF to dioxane resulted only in a quantitative recovery of the starting material. Next, we tried to transform compound (**7a**) in **10a** via a reaction with a methanolic ammonia solution in a pressure tube at 100 °C. However, spectroscopic analyses (MS, ¹H-NMR and ¹³C-NMR spectra) of the reaction mixture revealed the formation of two types of products, resulting from a nucleophilic substitution of the chlorine atom and from an addition on the triple bond but no **10a** was obtained.⁸ Since we were not able to get the cyclized product in a one pot procedure, we assumed that this is due to the weak nucleophilicity of the nitrogen atom in the formed intermediate products: 4-amino-2-methyl-5-phenylethynylpyridazin-3(2*H*)-one and 5-(2-amino-2-phenylethenyl)-4-chloro-2-methylpyridazin-3(2*H*)-one. It is well documented in the literature that stronger bases (KO-*t*-Bu, NaOEt, NaH, etc.) promote effectively the cyclization of *o*-alkynylarylamines.⁹ Therefore we adjusted our protocol and treated the previously obtained mixture with NaOEt in EtOH/DMF (or MeCN) at 90 °C. Fortunately, the desired 6-methyl-2-phenyl-1,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyridazin-7-one (**10a**) was successfully obtained in 58 % overall yield (Table1).

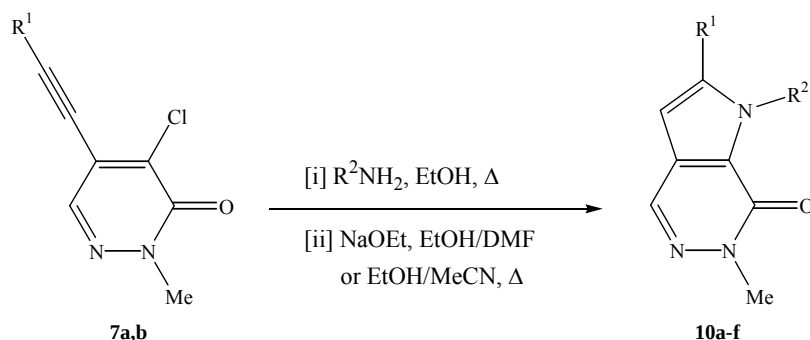
The success we encountered in preparing the compound (**10a**) encouraged us to extend our investigations to the preparation of *N*-substituted 1,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyridazin-7-ones (**10b-f**) and their 1,5-dihydro-4*H*-pyrrolo[2,3-*d*]pyridazin-4-one regioisomers (**9a,b**). Therefore, compounds (**7a,b**) and (**8**) were first subjected to a reaction with propylamine in EtOH at 90 °C. Yet again, a mixture of products due to a nucleophilic substitution of the chlorine atom and to an addition on the triple bond were obtained.⁸ Subsequent treatment of the reaction mixtures with NaOEt solution, yielded the desired 2-substituted 6-methyl-1-propyl-1,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyridazin-7-ones (**10c,d**) and 2-substituted 5-methyl-1-propyl-1,5-dihydro-4*H*-pyrrolo[2,3-*d*]pyridazin-4-one (**9a**) in good to moderate yields (Tables 1 and 2).

On the basis of these results and those obtained earlier,^{7b} as well as on the basis of literature data,¹⁰ two mechanisms to obtain the ring closed products starting from *o*-alkynyl-chloropyridazin-3(2*H*)-ones have to be considered (Figure 1): a nucleophilic substitution reaction, followed by an intramolecular addition on the triple bond (Path A), and the reverse, a nucleophilic addition on the triple bond, followed by an intramolecular nucleophilic substitution (Path B).

Further, as an extension of our approach towards the use of other amines, compounds (**7a-c**) (Table 3) and

(**8**) (Scheme 4) were allowed to react with methylamine (40 % in water) in ethanol at 90°C. Surprisingly, these reactions now led only to the formation of the nucleophilic substitution products (**11a-c** and **13**) and no addition of methylamine on the triple bond was observed.

Table 1: Preparation of 2-substituted 6-methyl-1,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyridazin-7-ones.



Product	Amine	R^1	R^2	Reaction time (h)		Overall yield (%)
				[i]	[ii]	
10a^{a,d}	ammonia	C ₆ H ₅	H	7	22	58
10b^{a,d}	ammonia	<i>t</i> -Bu	H	24	35	6
10c^{b,d}	propylamine	C ₆ H ₅	Pr	6	19	55
10d^{b,d}	propylamine	<i>t</i> -Bu	Pr	24	35	69
10e^{c,d}	methylamine	C ₆ H ₅	Me	0.5	30	55
10f^{c,d}	methylamine	<i>t</i> -Bu	Me	11	5	95

^a Reaction conditions: **7a,b** (0.68 mmol); 7N methanolic ammonia (17 mL) at 100 °C in a pressure tube.

^b Reaction conditions: **7a,b** (0.72 mmol); EtOH (1.50 mL); propylamine (0.15 mL, 1.8 mmol) at reflux.

^c Reaction conditions: **7a,b** (1 mmol); EtOH (19.7 mL); methylamine (40 % in water, 6.1 mL) at 90 °C.

^d Reaction conditions: NaOEt solution (11.6 equivalents Na in EtOH) in MeCN for **10a,b** and in DMF for **10c,e,f** at 90 °C.

In the case of **10d** the reaction temperature was 110 °C.

Interestingly, the by-products (**12a-c**) resulting from the addition of water on the triple bond have been found (Table 3).¹¹ For the regioisomer (**8**), the by-product resulting from the attack of water on the triple bond was negligible (Scheme 4). To the best of our knowledge such pyridazinone derivatives have never been reported previously in the literature.

Table 2: Preparation of 2-substituted 5-methyl-1,5-dihydro-4*H*-pyrrolo[2,3-*d*]pyridazin-4-ones.

Product	Amine	R ¹	R ²	Reaction time (h)		Overall yield (%)
				[i]	[ii]	
9a^{a,c}	propylamine	C ₆ H ₅	Pr	3	3	74
9b^{b,c}	methylamine	C ₆ H ₅	Me	1	1.5	98

^a Reaction conditions: **8** (0.72 mmol); EtOH (1.50 mL); propylamine (0.15 mL, 1.8 mmol) at reflux.

^b Reaction conditions: **8** (1 mmol); EtOH (19.7 mL); methylamine (40 % in water, 6.1 mL) at 90 °C.

^c Reaction conditions: NaOEt solution (5 equivalents Na in EtOH) at 90 °C (oil bath temperature).

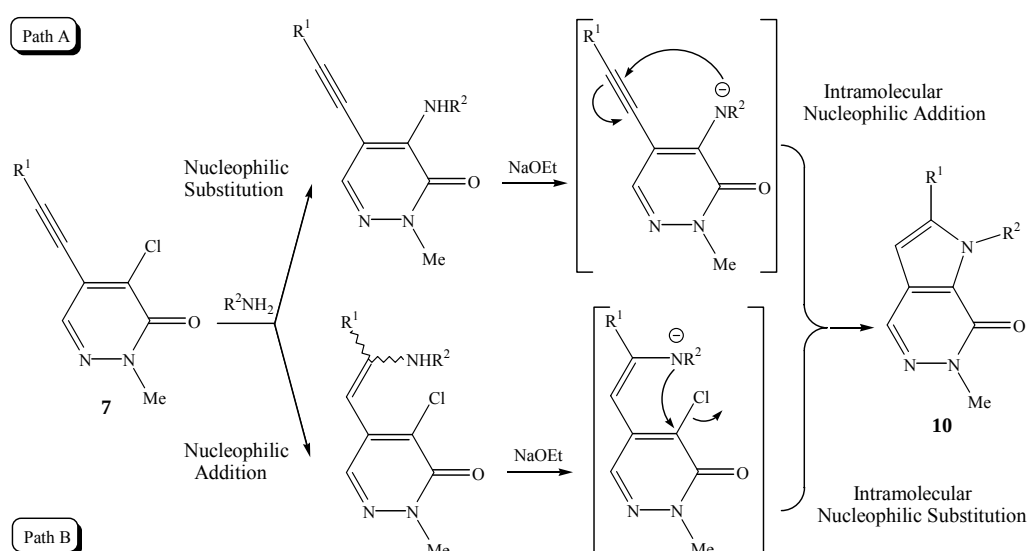
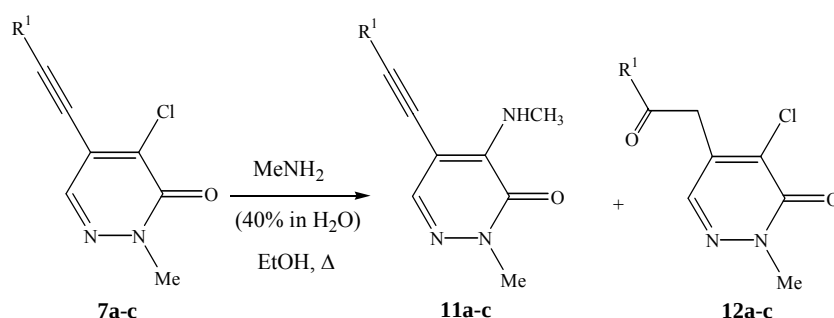


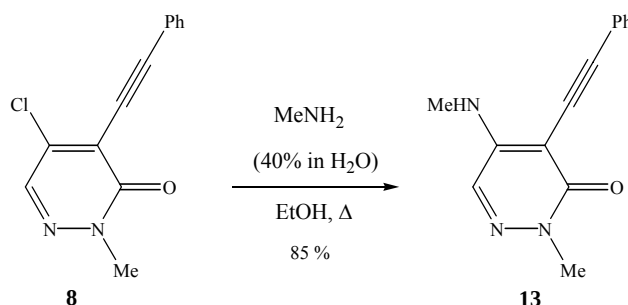
Figure 1: Proposed mechanistic pathways to obtain pyrrolo[2,3-*d*]pyridazinones from *o*-alkynylchloropyridazin-3(2*H*)-ones.

Table 3: Reaction of **7a-c** with methylamine.



Products	R^1	Reaction time (h)	Isolated yield of 11 (%)	Isolated yield of 12 (%)
11a ; 12a	C_6H_5	0.5	70	10
11b ; 12b	<i>t</i> -Bu	11	40	34
11c ; 12c	Pr	0.5	23	63

^a Reaction conditions: **7a-c** (1 mmol); EtOH (19.7 mL); methylamine (40% in water) (6.1 mL) at 90 °C .



Scheme 4

After purification of compounds (**11a,b**) from their by-products, these compounds were subsequently treated with a NaOEt solution in a similar way as described for the propylamine derived compounds, achieving a smooth formation of 2-substituted 1,6-dimethyl-1,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyridazin-7-ones (**10e,f**) and 2-phenyl-1,5-dimethyl-1,5-dihydro-4*H*-pyrrolo[2,3-*d*]pyridazin-4-one (**9b**) respectively in good to moderate yields (Tables 1 and 2). Since we were able to generate the pyrrolo ring starting from pure **11a,b** and **13**, these results prove that ring closure *via* intramolecular addition on the triple bond (Figure 1, Path A) can certainly occur from *o*-alkynyl-aminopyridazin-3(2*H*)-ones in the higher mentioned cases where we had inseparable mixtures of *o*-alkynyl-aminopyridazin-3(2*H*)-ones and (2-aminoalkenyl)chloropyridazin-3(2*H*)-ones.

In conclusion, a versatile and new approach to 1,2-substituted pyrrolo[2,3-*d*]pyridazinones has been

described, involving 5-alkynyl-4-chloro- and 4-alkynyl-5-chloro-2-methylpyridazin-3(2*H*)-ones as effective precursors to construct the pyrrolo ring. To the best of our knowledge these are the first examples of fused pyrrolopyridazinone derivatives synthesised from *o*-alkynyl-chloropyridazinones.

EXPERIMENTAL

¹H-NMR and ¹³C-NMR spectra were recorded on a Varian Unity 400 spectrometer in CDCl₃ with TMS as the internal standard. Chemical shifts are given in ppm and *J* values in Hz. HRMS and product ion spectra were recorded on a quadrupole-time of flight mass spectrometer (QToF 2, Micromass, Manchester, UK) equipped with a standard electrospray ionisation (ESI) interface. Samples were dissolved in MeOH containing 0.1 % formic acid and diluted to a concentration of approximately 10⁻⁵ mol/L. 1 μL injections were directed to the mass spectrometer at a flow rate of 5 μL/min MeOH (0.1% formic acid), using the CapLC HPLC system (Waters, Millford). For the determination of the high-resolution *m/z*-values of the molecular ion [M+H]⁺, a solution of polyethylene glycol 300 in MeOH/H₂O with 1 mmol ammonium acetate, was added just before the mass spectrometer (at a rate of 1 μL/min) to the mobile phase. The calculated mass of PEG [M+H]⁺ and [M+NH₄]⁺ ions was used as a lock mass for the measurement of the accurate mass values of the samples. Product ion spectra were recorded selecting the protonated molecule [M+H]⁺ in the quadrupole. This precursor ion is fragmented in the collision cell using Ar as collision gas and a collision energy of 20, 25 and 30 eV. IR spectra were obtained as potassium bromide pellets with a Bruker Vector 22 spectrometer. Melting points were recorded using a Büchi B-545 apparatus and are uncorrected. All reagents were purchased from commercial sources and were used as such (DMF 99.9 % (Acros), EtOH denat. with up 5% ether v/v (Acros), ammonia in methanol *ca.* 7*N* (Acros), propylamine 99+ % (Acros) and methylamine 40 wt. % solution in water (Aldrich)). Flash column chromatography was performed on Kiesel gel 60 (Merck), 0.040-0.063 mm.

General procedure for the preparation of 2-substituted 6-methyl-1,6-dihydro-7*H*-pyrrolo[2,3-*d*]pyridazin-7-ones (10a,b):

Step 1: 5-Alkynyl-4-chloro-2-methylpyridazin-3(2*H*)-ones (**7a,b**) (0.68 mmol) were weighed in a pressure tube. Then, a 7*N* methanolic ammonia solution (17 mL) was added. The tube was sealed and heated at 100 °C in an oil bath until total consumption of the starting material (TLC analysis and/or ESI-MS). The tube was cooled down to rt and the yellowish solution was poured into a round bottomed flask followed by evaporation of the solvent in *vacuo*.

Step 2: To the yellowish residue obtained, a NaOEt solution (181 mg of Na, 7.87 mmol; in 14 mL of EtOH) was added along with 14 mL of MeCN. The reaction mixture was heated at 90 °C until total consumption of the starting material (TLC analysis and/or ESI-MS). After removing the solvent, 50 mL

of H₂O was added to the residue. This mixture was extracted with CH₂Cl₂ (3x70 mL). After drying over MgSO₄, the solvent was removed in *vacuo* and the residue was purified by flash column chromatography.

6-Methyl-2-phenyl-1,6-dihydro-7H-pyrrolo[2,3-d]pyridazin-7-one (10a):

Chromatography eluent: CH₂Cl₂/MeOH 98:2; Yield: 58 %; white solid; mp 312 °C (CH₂Cl₂); $\nu_{\max}$ (KBr): 3159, 3066, 2944, 1644, 1565, 1510, 1469, 1455, 1396, 1046, 899, 806, 776, 688, 654, 500, 445 cm⁻¹; δ_{H} (DMSO): 12.94 (br s, 1H, NH), 8.22 (s, 1H, H-4), 7.97 (br d, 2H, Ph-2,6), 7.46 (br t, 2H, Ph-3,5), 7.37 (br t, 1H, Ph-4), 6.97 (s, 1H, H-3), 3.75 (s, 3H, NCH₃); δ_{C} (DMSO): 153.78, 140.65, 133.09, 130.66, 128.78, 128.25, 127.70, 125.79, 124.90, 100.25, 38.26; MS (ESI) *m/z* 226, 115 (100%); HRMS (ESI) for C₁₃H₁₂N₃O [M+H]⁺: calcd 226.0980, found 226.0975; Anal. Calcd for C₁₃H₁₁N₃O: C 69.32, H 4.92, N 18.66. Found: C 69.39, H 5.10, N 18.76.

2-tert-Butyl-6-methyl-1,6-dihydro-7H-pyrrolo[2,3-d]pyridazin-7-one (10b):

Chromatography eluent: Et₂O/Hexane 3:1; Yield: 6 %; yellowish solid; mp 203 °C (Et₂O/Hexane); $\nu_{\max}$ (KBr): 3178, 2957, 2925, 2854, 1652, 1571, 1319, 1278, 806, 665, 479 cm⁻¹; δ_{H} (CDCl₃): 11.65 (br s, 1H, NH), 8.10 (d, *J* = 0.6, 1H, H-4), 6.22 (d, *J* = 2.2, 1H, H-3), 3.92 (s, 3H, NCH₃), 1.46 (s, 9H, *t*-Bu); δ_{C} (CDCl₃): 154.78, 153.07, 133.92, 127.25, 124.95, 97.96, 39.03, 32.42, 30.08, 29.71; MS (ESI) *m/z* 206 (100 %); HRMS (ESI) for C₁₁H₁₆N₃O [M+H]⁺: calcd 206.1293, found 206.1296; Anal. Calcd for C₁₁H₁₅N₃O: C 64.37, H 7.37, N 20.47. Found: C 64.39, H 7.29, N 20.53.

General procedure for the preparation of 2-substituted 6-methyl-1-propyl-1,6-dihydro-7H-pyrrolo[2,3-d]pyridazin-7-ones (10c,d):

Step 1: To a solution of 5-alkynyl-4-chloro-2-methylpyridazin-3(2*H*)-one (**7a,b**) (0.72 mmol) in EtOH (1.50 mL) 0.15 mL (1.8 mmol) of propylamine was added. The reaction mixture was refluxed until total consumption of the starting material (TLC analysis and/or ESI-MS).

Step 2: After cooling down to rt the reaction mixture, a NaOEt solution (192 mg of Na, 8.35 mmol; in 18 mL of EtOH) was added along with 21 mL of DMF. The reaction mixture was heated at 90 °C (**10c**) or 110°C (**10d**) until total consumption of the starting material (TLC analysis and/or ESI-MS). After removing the solvent, 50 mL of H₂O was added to the residue. This mixture was extracted with CH₂Cl₂ (3x70 mL). After drying over MgSO₄, the solvent was removed in *vacuo* and the residue was purified by flash column chromatography.

6-Methyl-2-phenyl-1-propyl-1,6-dihydro-7H-pyrrolo[2,3-d]pyridazin-7-one (10c):

Chromatography eluent: Et₂O/Hexane 4:1; Yield: 55%; brownish solid; mp 72.7 °C (Et₂O/Hexane); $\nu_{\max}$

(KBr): 2943, 2880, 1650, 1513, 1461, 1325, 1111, 1011, 952, 888, 800, 777, 703, 651, 506 cm^{-1} ; δ_{H} (CDCl_3): 8.08 (s, 1H, H-4), 7.51-7.41 (m, 5H, Ph), 6.39 (s, 1H, H-3), 4.50 (br t, $J = 7.5$, 2H, NCH_2), 1.71 (h, $J = 7.5$, 2H, CH_2), 0.76 (t, $J = 7.5$, 3H, CH_3); δ_{C} (CDCl_3): 155.19, 143.96, 133.28, 131.58, 129.58, 128.87, 128.69, 126.58, 124.55, 102.65, 47.64, 38.87, 25.49, 10.81; MS (ESI) m/z 268 (100 %), 226; HRMS (ESI) for $\text{C}_{16}\text{H}_{18}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: calcd 268.1436, found 268.1443; Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}$: C 71.89, H 6.41, N 15.72. Found: C 71.79, H 6.39, N 15.75.

2-*tert*-Butyl-6-methyl-1-propyl-1,6-dihydro-7H-pyrrolo[2,3-*d*]pyridazin-7-one (10d):

For the preparation of this compound, the reaction temperature of step 2 was 110 $^{\circ}\text{C}$; Chromatography eluent: Et_2O /Hexane 3:1; yield: 69 %; dark yellow oil; ν_{max} (liquid film): 3503, 2971, 2877, 1651, 1544, 1498, 1319, 1239, 1118, 964, 831, 668 cm^{-1} ; δ_{H} (CDCl_3): 7.98 (s, 1H, H-4), 6.19 (s, 1H, H-3), 4.52 (br m, 2H, NCH_2), 3.82 (s, 3H, NCH_3), 1.88 (h, $J = 7.5$, 2H, CH_2), 1.45 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.04 (t, $J = 7.5$, 3H, CH_3); δ_{C} (CDCl_3): 154.90, 151.41, 133.20, 126.98, 124.09, 99.37, 49.38, 38.91, 32.78, 30.50, 28.08, 26.41; MS (ESI) m/z 248 (100 %), 206, 150; HRMS (ESI) for $\text{C}_{14}\text{H}_{22}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: calcd 248.1763, found 248.1753; Anal. Calcd for $\text{C}_{14}\text{H}_{21}\text{N}_3\text{O}$: C 67.98, H 8.56, N 16.99. Found: C 68.05, H 8.58, N 16.95.

Preparation of 5-methyl-2-phenyl-1-propyl-1,5-dihydro-4H-pyrrolo[2,3-*d*]pyridazin-4-one (9a):

Step 1: Similarly as for the synthesis of the isomeric pyrrolopyridazinones **10a,b** (step 1) **8** (176 mg, 0.72 mmol) was treated with propylamine.

Step 2: After cooling down the reaction mixture to rt, a NaOEt solution (96 mg of Na, 4.20 mmol; in 9 mL of EtOH) was added. The reaction mixture was refluxed (oil bath 90 $^{\circ}\text{C}$) until total consumption of the starting material (TLC analysis and/or ESI-MS). After removing the solvent, 50 mL of H_2O was added to the residue. This mixture was extracted with Et_2O (3x70 mL). After drying over MgSO_4 , the solvent was removed in *vacuo*. No further purification was performed. Yield: 74 %; brown-yellow solid; mp 96 $^{\circ}\text{C}$ (Et_2O /Hexane); ν_{max} (KBr): 3106, 2925, 2870, 1648, 1544, 1475, 1435, 1298, 1021, 957, 760, 697, 502 cm^{-1} ; δ_{H} (CDCl_3): 8.07 (d, $J = 0.8$, 1H, H-7), 7.50-7.40 (m, 5H, Ph), 6.83 (d, $J = 0.8$, 1H, H-3), 4.12 (br t, $J = 7.4$, 2H, NCH_2), 3.87 (s, 3H, NCH_3), 1.68 (h, $J = 7.4$, 2H, CH_2), 0.76 (t, $J = 7.4$, 3H, CH_3); δ_{C} (CDCl_3): 158.74, 141.87, 132.92, 131.10, 129.08, 128.58, 128.56, 125.20, 120.19, 104.68, 46.20, 38.82, 24.04, 10.75; MS (ESI) m/z 268; HRMS (ESI) for $\text{C}_{16}\text{H}_{18}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: calcd 268.1450, found 268.1441; Anal. Calcd for $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}$: C 71.89, H 6.41, N 15.72. Found: C 71.91, H 6.44, N 15.77.

General procedure for the preparation of 2-substituted 1,6-dimethyl-1,6-dihydro-7H-pyrrolo[2,3-*d*]pyridazin-7-ones (10e,f):

Step 1: To a solution of 5-alkynyl-4-chloro-2-methylpyridazin-3(2H)-one (**7a,b**) (1 mmol) in EtOH (19.7

mL) methylamine (40 wt % solution in water, 6.1 mL) was added. The reaction mixture was heated at 90°C until total consumption of the starting material (TLC analysis and/or ESI-MS). The mixture was then poured into water (60 mL) and extracted with CH₂Cl₂ (3x70 mL). After drying over MgSO₄, the solvent was removed in *vacuo*. The residue obtained was purified by flash column chromatography.

Step 2: To a solution of the purified compounds (**11a,b**) (0.7 mmol) in DMF (20 mL), a NaOEt solution (187 mg of Na, 8.13 mmol; in 20 mL of EtOH) was added. The reaction mixture was heated at 90 °C until total consumption of the starting material (TLC analysis and/or ESI-MS). After removing the solvent, 70 mL of H₂O was added to the residue. This mixture was extracted with CH₂Cl₂ (3x90 mL). After drying over MgSO₄, the solvent was removed in *vacuo* and the residue was purified by flash column chromatography.

1,6-Dimethyl-2-phenyl-1,6-dihydro-7H-pyrolo[2,3-*d*]pyridazin-7-one (10e):

Chromatography eluent: EtOAc/Hexane 4:6; Yield: 55 %; brown solid; mp 143 °C (EtOH); $\nu_{\max}$ (KBr): 3133, 2944, 1644, 1515, 1461, 1440, 1318, 1230, 1151, 1112, 1007, 948, 908, 816, 770, 751, 703, 660, 502 cm⁻¹; δ_{H} (CDCl₃): 8.00 (s, 1H, H-4), 7.42-7.38 (m, 5H, H-Ph), 6.35 (s, 1H, H-3), 4.08 (s, 3H, 1-NCH₃), 3.79 (s, 3H, 6-NCH₃); δ_{C} (CDCl₃): 155.56, 144.11, 133.41, 131.01, 129.44, 128.90, 128.74, 127.06, 124.27, 102.23, 38.78, 33.97; MS (ESI) *m/z* 240; HRMS (ESI) for C₁₄H₁₄N₃O [M+H]⁺: calcd 240.1137, found 240.1128; Anal. Calcd for C₁₄H₁₃N₃O: C 70.28, H 5.48, N 17.57, Found: C 70.32, H 5.44, N 17.60.

2-*tert*-Butyl-1,6-dimethyl-1,6-dihydro-7H-pyrolo[2,3-*d*]pyridazin-7-one (10f):

Chromatography eluent: EtOAc/Hexane 4:6; Yield: 95 %; yellowish solid; mp. 59 °C (CH₃Cl/Hexane); $\nu_{\max}$ (KBr): 3109, 2958, 2927, 2870, 1652, 1544, 1503, 1464, 1330, 1246, 1117, 873, 822, 658 cm⁻¹; δ_{H} (CDCl₃): 7.97 (s, 1H, H-4), 6.21 (s, 1H, H-3), 4.37 (s, 3H, 1-NCH₃), 3.82 (s, 3H, 6-NCH₃), 1.45 (s, 9H, *t*-Bu); δ_{C} (CDCl₃): 155.51, 152.02, 133.35, 127.24, 123.56, 99.37, 38.87, 35.14, 32.58, 29.72); MS (ESI) *m/z* 220; HRMS (ESI) for C₁₂H₁₈N₃O [M+H]⁺: calcd 220.1450, found 220.1440; Anal. Calcd for C₁₂H₁₇N₃O: C 65.73, H 7.81, N 19.16. Found: C 65.84, H 7.78, N 19.13.

2-Methyl-4-methylamino-5-phenylethynylpyridazin-3(2H)-one (11a):

Chromatography eluent: CH₂Cl₂/EtOAc 9:1; Yield: 70 %; yellowish solid; mp 165 °C (EtOH); $\nu_{\max}$ (KBr): 3297, 2925, 2854, 2359, 2206, 1637, 1607, 1579, 1496, 1418, 1121, 1041, 826, 748, 683, 623, 516 cm⁻¹; δ_{H} (CDCl₃): 7.58 (s, 1H, H-6), 7.48-7.44 (m, 2H, H_{Ph}-2,6), 7.38-7.34 (m, 3H, H_{Ph}-3,4,5), 6.3 (br s, 1H, NH), 3.75 (s, 3H, NCH₃), 3.49 (d, *J* = 5.7, 3H, NHCH₃); δ_{C} (CDCl₃): 156.10, 143.79, 141.02, 130.93, 128.56, 128.53, 123.04, 94.77, 94.09, 84.49, 77.24, 39.85, 31.02; MS (ESI) *m/z* 240; HRMS (ESI) for C₁₄H₁₄N₃O [M+H]⁺: calcd 240.1137, found 240.1142; Anal. Calcd for C₁₄H₁₃N₃O: C 70.28, H 5.48, N

17.56. Found: C 70.24, H 5.52, N 17.55.

5-(3,3-Dimethylbut-1-yn-1-yl)-2-methyl-4-methylaminopyridazin-3(2H)-one (11b):

Chromatography eluent: EtOAc/Hexane 4:6; Yield: 40 %; brownish solid; mp 99 °C (Et₂O/Hexane); $\nu_{\max}$ (KBr): 3289, 2964, 2359, 1630, 1599, 1552, 1415, 1361, 1240, 920, 881, 793, 630 cm⁻¹; δ_{H} (CDCl₃): 7.41 (s, 1H, H-6), 6.15 (br s, 1H, NH), 3.70 (s, 3H, NCH₃), 3.38 (d, J = 5.8, 3H, NHCH₃), 1.29 (s, 9H, C(CH₃)₃); δ_{C} (CDCl₃): 156.31, 143.60, 141.62, 103.87, 95.05, 74.09, 39.76, 30.91, 30.52, 28.34; MS (ESI) m/z 220, 190 (100 %), 133; HRMS (ESI) for C₁₂H₁₈N₃O [M+H]⁺: calcd 220.1405, found 220.1401; Anal. Calcd for C₁₂H₁₇N₃O: C 65.73, H 7.81, N 19.16. Found: C 65.69, H 7.78, N 19.14.

2-Methyl-4-methylamino-5-(pent-1-yn-1-yl)pyridazin-3(2H)-one (11c):

Chromatography eluent: Ether; Yield: 23 %; yellowish oil; $\nu_{\max}$ (liquid film): 3297, 2960, 2929, 2286, 1636, 1418, 1384, 1038, 873, 624, 556 cm⁻¹; δ_{H} (CDCl₃): 7.57 (s, 1H, H-6), 6.12 (br s, 1H, NH), 3.80 (s, 3H, NCH₃), 2.36 (t, J = 7.4, 2H, CH₂), 1.61 (h, J = 7.4, 2H, CH₂), 1.01 (t, J = 7.4, 3H, CH₃); δ_{C} (CDCl₃): 156.45, 143.76, 141.89, 137.51, 96.39, 95.26, 75.59, 39.98, 31.05, 22.10, 21.93; MS (ESI) m/z 206, 176 (100 %), 133; HRMS (ESI) for C₁₁H₁₆N₃O [M+H]⁺: calcd 205.1197, found 205.1201; Anal. Calcd for C₁₁H₁₅N₃O: C 64.37, H 7.37, N 20.47. Found: C 64.40, H 7.35, N 20.55.

4-Chloro-2-methyl-5-(2-oxo-2-phenylethyl)pyridazin-3(2H)-one (12a):

Chromatography eluent: CH₂Cl₂/EtOEt 9:1; Yield: 10 %; brown oil; $\nu_{\max}$ (liquid film): 3441, 2925, 2854, 1729, 1639, 1595, 1450, 1376, 1256, 1214, 871, 751, 686 cm⁻¹; δ_{H} (CDCl₃): 8.00-8.07 (m, 2H, H_{Ph}-2,6), 7.5-7.7 (m, 4H, H-6 and H_{Ph}-3,4,5), 4.38 (s, 2H, CH₂), 3.85 (s, 3H, NCH₃); δ_{C} (CDCl₃): 193.54, 157.54, 137.28, 136.61, 136.09, 134.30, 129.19, 128.52, 41.16, 40.54, 29.88; MS (ESI) m/z 263 (³⁵Cl), 265 (³⁷Cl), 105 (100%); HRMS (ESI) for C₁₃H₁₂N₂O₂Cl [M+H]⁺: calcd 263.0587, found 263.0579; Anal. Calcd for C₁₃H₁₁N₂O₂Cl: C 59.44, H 4.22, N 10.66. Found: C 59.40, H 4.21, N 10.57.

4-Chloro-5-(3,3-dimethyl-2-oxobutyl)-2-methylpyridazin-3(2H)-one (12b):

Chromatography eluent: EtOAc/Hexane 4:6; Yield: 34 %; brown oil; $\nu_{\max}$ (liquid film): 2964, 2928, 2973, 1713, 1667, 1606, 1464, 1369, 1286, 1064, 872, 765, 752 cm⁻¹; δ_{H} (CDCl₃): 7.56 (s, 1H, H-6), 3.89 (s, 2H, COCH₂), 3.82 (s, 3H, NCH₃), 1.26 (s, 9H, C(CH₃)₃); δ_{C} (CDCl₃): 208.98, 157.33, 137.31, 136.87, 128.88, 65.57, 38.62, 30.65, 29.71, 26.38; MS (ESI) m/z 243 (³⁵Cl), 245 (³⁷Cl); HRMS (ESI) for C₁₁H₁₆N₂O₂Cl [M+H]⁺: calcd 243.0900, found 243.0897; Anal. Calcd for C₁₁H₁₅N₂O₂Cl: C 54.44, H 6.23, N 11.54. Found: C 54.36, H 6.21, N 11.57.

4-Chloro-2-methyl-5-(2-oxopentyl)pyridazin-3(2H)-one (12c):

Chromatography eluent: EtOAc/Hexane 4:6; Yield: 63 %; yellowish solid; mp 90 °C (EtOH); $\nu_{\max}$ (KBr): 2964, 2879, 1707, 1644, 1611, 1411, 1318, 1123, 873, 784, 726, 610, 558 cm^{-1} ; δ_{H} (CDCl_3): 7.61 (s, 1H, H-6), 3.82 (s, 3H, NCH_3), 3.81 (s, 2H, COCH_2), 2.56 (t, $J = 7.4$, 2H, CH_2), 1.66 (h, $J = 7.4$, 2H, CH_2), 0.95 (t, $J = 7.4$, 3H, CH_3); δ_{C} (CDCl_3): 203.71, 157.29, 137.09, 136.19, 133.90, 45.17, 44.15, 40.91, 17.22, 13.58; MS (ESI) m/z 229 (^{35}Cl ; 100%), 231 (^{37}Cl), 159 (^{35}Cl), 161 (^{37}Cl); HRMS (ESI) for $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_2\text{Cl}$ $[\text{M}+\text{H}]^+$: calcd 229.0744, found. 229.0741; Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{N}_2\text{O}_2\text{Cl}$: C 52.52, H 5.73, N 12.25, found: C 52.55, H 5.71, N 12.27.

Preparation of 1,5-dimethyl-2-phenyl-1,5-dihydro-4H-pyrido[2,3-d]pyridazin-4-one (9b):

Step 1: Similarly as for the synthesis of the isomeric pyrrolopyridazinones **10a,b** (step 1) **8** (166 mg, 0.68 mmol) was treated with methylamine.

Step 2: To the compound obtained after purification (**13**; 115 mg, 0.48 mmol) a NaOEt solution (55 mg of Na, 2.39 mmol; in 5 mL of EtOH) was added. The reaction mixture was refluxed (oil bath at 90 °C) until total consumption of the starting material (TLC analysis and/or ESI-MS). After removing the solvent, 50 mL of H_2O was added to the residue. This mixture was extracted with CH_2Cl_2 (3x60 mL). After drying over MgSO_4 , the solvent was removed in *vacuo* and the residue was purified by flash column chromatography using $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ 1:1 as the eluent; Yield 98 %; white-yellow solid; mp 200 °C (Et_2O /Hexane); $\nu_{\max}$ (KBr): 3058, 2983, 1644, 1546, 1475, 1436, 1305, 1019, 956, 905, 773, 753, 703, 558, 503 cm^{-1} ; δ_{H} (CDCl_3): 8.04 (d, $J = 0.6$, 1H, H-7), 7.51-7.41 (m, 5H, Ph), 6.86 (d, $J = 0.6$, 1H, H-3), 3.86 (s, 3H, 5- NCH_3), 3.78 (s, 3H, 1H, 1- NCH_3); δ_{C} (CDCl_3): 158.96, 142.36, 133.82, 130.89, 129.35, 128.85, 128.84, 125.13, 120.39, 104.62, 39.14, 32.07; MS (ESI) m/z 240; HRMS (ESI) for $\text{C}_{14}\text{H}_{14}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: calcd 240.1137, found 240.1130; Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}$: C 70.28, H 5.48, N 17.56. Found: C 70.26, H 5.51, N 17.60.

2-Methyl-5-methylamino-4-phenylethynylpyridazin-3(2H)-one (13):

Chromatography eluent: Et_2O /Hexane 4:1; Yield: 85 %; yellow solid; mp 186 °C (decomp; EtOH); $\nu_{\max}$ (KBr): 3266, 3099, 2198, 1606, 1572, 1543, 1391, 1360, 758, 695, 611, 538, 524 cm^{-1} ; δ_{H} (CDCl_3): 7.58 (s, 1H, H-6), 7.58-7.52 (m, 2H, $\text{H}_{\text{Ph-2,6}}$), 7.36-7.32 (m, 3H, $\text{H}_{\text{Ph-3,4,5}}$), 5.06 (br s, 1H, NH), 3.75 (s, 3H, NCH_3), 3.08 (d, $J = 5.34$, 3H, NHCH_3); δ_{C} (CDCl_3): 160.15, 149.36, 131.96, 128.60, 128.31, 125.07, 122.95, 102.50, 96.00, 80.68, 39.78, 29.97; MS (ESI) m/z 240; HRMS (ESI) for $\text{C}_{14}\text{H}_{14}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: calcd 240.1137, found 240.1136; Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}$: C 70.28, H 5.48, N 17.56. Found: C 70.32, H 5.53, N 17.57.

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