Synthesis of 2,4-Disubstituted 6-Phenyl-7*H*-pyrrolo[3,2-*d*]-pyrimidin-7-one 5-Oxides

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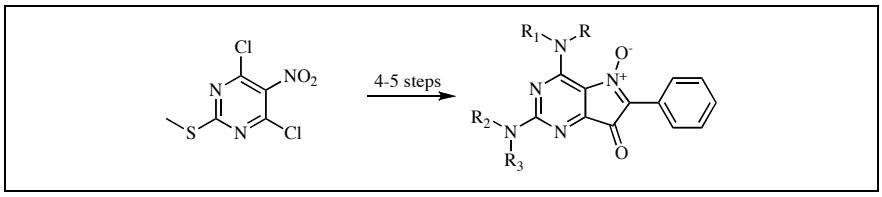

A relatively short and efficient method for the utilization of 4,6-dichloro-2-methylthio-5-nitropyrimidine (**1**) in the synthesis of the polysubstituted pyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides (**6a-g**) is reported. Some new 4-substituted 6-chloro-2-methylthio-5-nitropyrimidines (**2a-e**) were prepared by reaction of 4,6-dichloro-2-methylthio-5-nitropyrimidine (**1**) with amines. 4-Substituted 2-methylthio-5-nitro-6-phenylethynylpyrimidines (**3a-e**), obtained from 4-substituted 6-chloro-2-methylthio-5-nitropyrimidines (**2a-e**) *via* palladium-catalyzed Sonagashira coupling reaction with 1-phenylacetylene, underwent smooth cyclization reaction in boiling 2-propanol in the presence of catalytic amount of pyridine to give 4-substituted 2-methylthio-6-phenyl-7*H*-pyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides (**4a-e**). The methylthio group of the latter compounds can be easily and selectively oxidized by *m*-chloroperbenzoic acid and replaced with different amines.

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INTRODUCTION

Pyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides, being aza-analogues of isatogens, attract our attention as potential free radical traps in biological milieu [1-3]. Moreover, the pyrrolo[3,2-*d*]pyrimidine heterosystem is an important class of compounds, possessing notable biological activities, in particular purine nucleoside phosphorylase [4,5] and thymidylate synthase [6,7] inhibitory, neuropeptide Y5 receptor [8] and A_1,A_2-adenoside receptor [9] antagonistic properties. Recently we have reported that 4-amino-6-arylethynyl-5-nitropyrimidines in dry pyridine undergo smooth intramolecular cyclization to give pyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides [10–12]. As a continuation of our study aimed at the synthesis of the pyrimidine moiety containing heterocycles [13-15] with a potential biological activity, we report herein a novel method for the utilization of 4,6-dichloro-2-methylthio-5-nitropyrimidine (**1**) in the synthesis of the polysubstituted pyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides (**6a-g**).

RESULTS AND DISCUSSION

Our optimized procedure is exemplified in the synthesis of 2,4-disubstituted 6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides according to the conditions set forth in Schemes 1 and 2. Reaction of easily available 4,6-dichloro-2-methylthio-5-nitropyrimidine (**1**) [16] with different amines in methanol – diethylether mixture at 0 °C temperature provided the mono-substituted compounds **2a-e**. Palladium-catalyzed Sonagashira coupling reaction of **2a-e** with 1-phenylacetylene gave the corresponding 4-substituted 5-nitro-6-phenylethynylpyrimidines (**3a-e**) in good yields. The latter compounds could be converted to the 2-methylthio-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides (**4a-e**) during refluxing in dry pyridine (using the method which we described earlier [10]). This way was simple and rapid, but purification of the obtained products was complicated in some cases. To avoid that difficulty and to increase the yields of the compounds **4a-e**, we decided to develop a new method for the cyclization of 5-nitro-6-phenylethynylpyrimidines into pyrrolo[3,2-*d*]-pyrimidin-7-one 5-oxides. For this purpose the cyclization reaction of **3a** was studied under different conditions. Various initiators: nitrosobenzene in different solvents, pyridine, concentrated sulphuric acid, tetrabutyl-ammonium fluoride (TBAF) and UV light (the latter five

Table 1

Formation of 4-amino-2-methylthio-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide (**4a**) from 4-amino-2-methylthio-5-nitro-6-phenylethynyl-pyrimidine (**3a**) under different conditions.

Entry	Initiator	Solvent	Time, hours	Yield, %
1	-	Pyridine [a]	0.5	75
2	PhNO	CH_2Cl_2 [a]	18 - 20	50
3	PhNO	CH_3OH [a]	4	40
4	PhNO	C_2H_5OH [a]	2	80
5	PhNO	2-C_3H_7OH [a]	0.5	91
6	PhNO	1-C_4H_9OH [a]	0.5	75
7	PhNO	$C_6H_5CH_3$ [a]	0.7	70
8	PhNO	*o*-xylene [a]	2	52
9	Pyridine	2-C_3H_7OH [a]	0.5	95
10	UV	$CHCl_3$ [b]	48	0
11	TBAF	THF [b]	24	0
12	-	H_2SO_4(concd.) [c]	4	0

[a] Reactions were performed at reflux temperature; [b] Reaction was performed at room temperature; [c] Reaction was performed at 0 °C.

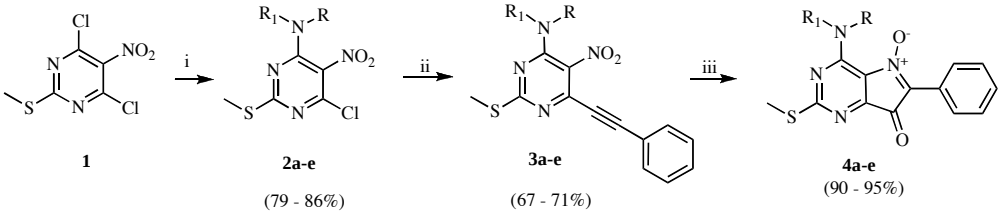
methods were employed for cyclization of *o*-(alkynyl)-nitrobenzenes into isatogens [17,18]) were used (Table 1).

The data obtained indicated that only pyridine and nitrosobezene initiated the transformations of **3a** into 4-amino-2-methylthio-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide (**4a**). UV light, TBAF and cold concentrated sulphuric acid (entries 10 - 12) had no success. In these cases after the work-up of the reaction mixtures the initial compound **3a** was recovered. Cyclization of **3a** occured using a catalytic amount of freshly-prepared nitroso-benzene in different solvents at reflux. It was found that the fastest cyclization and the highest yield of **4a** were achieved in boiling 2-propanol (entry 5). Moreover, it was established that cyclization of **3a** also proceeded using a catalytic amount of pyridine in boiling 2-propanol (entry 9). The latter method of cyclization of 5-nitro-6-phenylethynylpyrimidines into pyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides seemed to be the shortest and the most efficient.

So, the 4-substituted 2-methylthio-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides (**4a-e**) were prepared *via* pyridine initiated cyclization of 4-substituted 5-nitro-6-phenylethynylpyrimidines (**3a-e**). Reactions were performed in boiling 2-propanol during 30 minutes (Scheme 1).

The next step of synthetic approach to polysubstituted pyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides was modification of the 2-position of the pyrrolo[3,2-*d*]pyrimidine system. Substitution of methylthio moiety at the 2nd position of pyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides by nitrogen nucleophiles was exceedingly difficult. No reaction took place when compound **4a** was treated with secondary amine piperidine in dimethylsulfoxide at an elevated temperature for 24 hours. To avoid such difficulties the synthetic route was redesigned to employ another method, which is based on oxidation of the methylthio moiety followed by nucleophilic substitution reaction. Performing an oxidation of compound **4a** by a slight excess of *m*-chloroperbenzoic acid (*m*CPBA) in dichloromethane at room temperature for 1 hour led to formation of 2-methylsulfinyl derivative **5**. Nucleophilic substitution of the 2-methylsulfinyl group by various amines underwent easily and rapidly, so it could be achieved at room temperature in dimethylsulfoxide solution within 3 hours. On the other hand, the synthetic route could be realized in a one-pot method. Thus, reaction of 2-methylthiopyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides (**4a,c,d**) with *m*CPBA in dichloromethane at room temperature, followed after 1 hour by treatment of the reaction

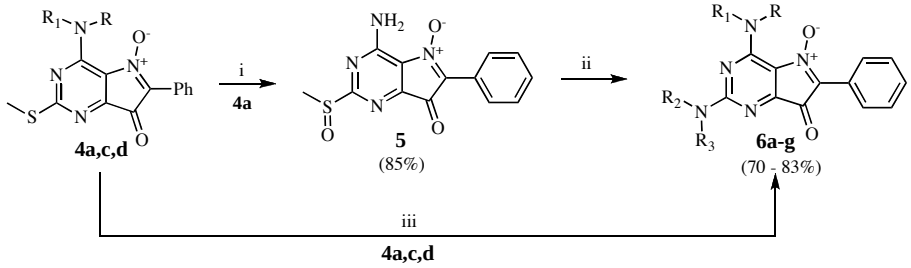
Scheme 1



2-4	NRR_1
a	NH_2
b	$NHCH_2CH_2N(CH_2)_4O$
c	$NHCH_2C_6H_5$
d	$N(CH_2)_4$
e	$N(CH_3)C_6H_5$

Reagents and conditions: i) amine (2 equivalents), methanol, 0ºC; ii) 1-phenylacetylene (1.2 equivalents), $PdCl_2(PPh_3)_2$ (2 mol %), CuI (1 mol %), Et_3N, Ar, 40ºC, 2 hours; iii) pyridine (1 drop), 2-propanol, reflux, 30 minutes.

Scheme 2



Reagents and conditions: i) *m*-CPBA (1.5 equivalents), CH_2Cl_2, r.t., 1 h; ii) amine (2 equivalents), dimethylsulfoxide, r.t., 3 hours; iii) *m*-CPBA (1.5 equivalents), CH_2Cl_2, r.t., 1 hour, then amine (3 equivalents), r.t., 3 hours.

Table 2

Synthesized 2,4-disubstituted pyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides (**6a-g**) prepared according to the presented methods.

Entry	Compound	NRR[1]	NR[2]R[3]	Yield, %
1	**6a**	NH_2	$NHCH_2CH_2CH_3$	71 [a], 80 [b]
2	**6b**	NH_2	$NHCH_2CH_2N(CH_2)_4O$	72 [a], 75 [b]
3	**6c**	NH_2	$NHCH_2C_6H_5$	74 [a], 78 [b]
4	**6d**	NH_2	$N(CH_2)_5$	75 [a], 79 [b]
5	**6e**	NH_2	$N(CH_2)_4O$	70 [a], 83 [b]
6	**6f**	$NHCH_2C_6H_5$	$NHCH_2C_6H_5$	71 [b]
7	**6g**	$N(CH_2)_4$	$N(CH_2)_4O$	78 [b]

[a] Synthesis was performed by nucleophilic substitution reaction of compound **5** with amines;
[b] Synthesis was performed by one-pot reaction based on oxidation/substitution steps.

mixture with 3 equivalents of different amines for 3 hours provided the corresponding 2,4-disubstituted pyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides (**6a-g**) in good yields (Scheme 2). Table 2 shows representative compounds which were prepared using the method described above.

In conclusion, we have developed a relatively short and efficient synthetic method of preparing 2,4-disubstituted 6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides through palladium-catalyzed coupling reaction of 4-substituted 6-chloro-5-nitropyrimidines with 1-phenylacetylene, subsequent cyclization of the obtained 4-substituted 2-methylthio-5-nitro-6-phenylethynyl-pyrimidines and one-pot oxidation/substitution of methylthio group at the 2nd position of the pyrrolo[3,2-*d*]pyrimidine heterosystem.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were run in Nujol mulls or in KBr discs on a Perkin-Elmer FT spectrophotometer Spectrum BX II. ^{1}H and ^{13}C NMR spectra were recorded with a Varian Unity INOVA spectrometer (300 MHz) using tetramethylsilane as internal standard. Mass spectra were performed using direct insertion probe on a Kratos MS-30 spectrometer (30 eV). Elemental analysis (C, H, N) results were found to be in good agreement (±0.4%) with the calculated values. All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 F_{254} aluminium plates (Merck). Visualization was accomplished by UV light.

Compound **2a** was prepared according to the method published in the literature [19].

General Procedure for the Synthesis of 4-substituted 6-chloro-2-methylthio-5-nitropyrimidines (2b-e). To a cooled to 5 °C solution of 4,6-dichloro-2-methylthio-5-nitro-pyrimidine (**1**) (5 g, 20.8 mmoles) in methanol (15 mL) and diethylether (10 mL) mixture a solution of the corresponding amine (41.6 mmoles) in methanol (10 mL) was added dropwise. The reaction mixture was stirred at 5 °C for 30 minutes. The precipitate was collected by filtration and recrystallized to give compounds **2b-e**.

6-Chloro-2-methylthio-4-[*N*-(2-morpholin-4-ylethyl)-amino]-5-nitropyrimidine (2b). This compound was obtained as yellow solid, mp 150 – 151 °C (from 2-propanol); yield: 79%; ir (KBr): 3265 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ = 2.54 (t, *J* = 3 Hz, NCH_2), 2.57 (s, 3H, SCH_3), 2.67 (t, *J* = 6 Hz, 4H, $N(CH_2)_2$), 3.69 (q, *J* = 3 Hz, 2H, $NHCH_2$), 3.77 (t, *J* = 6 Hz, 4H, $O(CH_2)_2$), 8.57 (br s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ = 14.9, 38.5, 53.4, 55.9, 67.2, 123.7, 155.1, 155.8, 176.5. *Anal.* Calcd for $C_{11}H_{16}ClN_5O_3S$: C, 39.58; H, 4.83; N, 20.98. Found: C, 39.41; H, 4.99; N, 20.67.

4-*N*-Benzylamino-6-chloro-2-methylthio-5-nitropyrimidine (2c). This compound was obtained as yellow solid, mp 92 – 93 °C (from 2-propanol); yield: 82%; ir (KBr): 3371 (NH) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ = 2.49 (s, 3H, SCH_3), 4.71 (d, *J* = 6 Hz, 2H, $NHCH_2$), 7.28 – 7.38 (m, 5H, ArH), 9.20 (t, *J* = 6 Hz, 1H, NH); ^{13}C nmr (dimethylsulfoxide-d_6): δ = 13.1, 44.9, 112.8, 127.0, 127.1, 128.4, 138.7, 146.1, 155.3, 165.1. *Anal.* Calcd for $C_{12}H_{11}ClN_4O_2S$: C, 46.38; H, 3.57; N, 18.03. Found: C, 46.49; H, 3.58; N, 17.86.

6-Chloro-2-methylthio-4-pyrrolidino-5-nitropyrimidine (2d). This compound was obtained as yellow solid, mp 141 – 143 °C (from 2-propanol); yield: 86%; ^{1}H nmr (deutériochloroform): δ = 1.98 – 2.03 (m, 4H, $(CH_2)_2$), 2.53 (s, 3H, SCH_3), 3.50 – 3.55 (m, 4H, $N(CH_2)_2$); ^{13}C NMR (deutériochloroform): δ = 14.7, 25.4, 48.7, 126.7, 151.5, 151.7, 171.6. *Anal.* Calcd for $C_9H_{11}ClN_4O_2S$: C, 39.35; H, 4.04; N, 20.39. Found: C, 39.61; H, 4.02; N, 20.49.

4-(*N*-Methyl)anilino-6-chloro-2-methylthio-5-nitropyrimidine (2e). This compound was obtained as yellow solid, mp 87 – 89 °C (from 2-propanol); yield: 75%; ^{1}H nmr (dimethylsulfoxide-d_6): δ = 2.60 (s, 3H, SCH_3), 3.56 (s, 3H, NCH_3), 7.35 – 7.40 (m, 5H, ArH); ^{13}C nmr (dimethylsulfoxide-d_6): δ = 14.8, 42.2, 125.3, 126.5, 128.7, 130.5, 143.0, 151.9, 153.9, 171.9. *Anal.* Calcd for $C_{12}H_{11}ClN_4O_2S$: C, 46.38; H, 3.57; N, 18.03. Found: C, 46.47; H, 3.55; N, 17.84.

General Procedure for the Synthesis of 4-substituted 2-methylthio-5-nitro-6-phenylethynylpyrimidines (3a-e). A mixture of the corresponding compound **2a-e** (1.15 mmoles), $PdCl_2(PPh_3)_2$ (0.016 g, 0.023 mmole), CuI (0.0022 g, 0.0115 mmole) and dry triethylamine (10 mL) was stirred under argon atmosphere for 3 minutes. Then the 1-phenylacetylene (0.14 g, 1.38 mmoles) was added, the mixture was flushed with argon and heated under stirring at 40 °C for 2 hours. After cooling to r.t. the precipitate was collected by filtration and recrystallized to give compounds **3a-e**. Data for compound **3a** have been published in the previous paper [12].

2-Methylthio-4-[*N*-(2-morpholin-4-ylethyl)-amino]-5-nitro-6-phenylethynylpyrimidine (3b). This compound was obtained as yellow solid, mp 219 – 222 °C (from 2-propanol); yield: 67%; ir (KBr): 3225 (NH), 2205 (C≡C) cm^{-1}; ^{1}H nmr (dimethyl–sulfoxide-d_6): δ = 2.47 (br s, 2H, NCH_2), 2.55 (s, 3H, SCH_3), 2.59 (t, *J* = 6 Hz, 4H, $N(CH_2)_2$), 3.65 (br s, 2H, $NHCH_2$), 3.67 (t, *J* = 6 Hz, 4H, $O(CH_2)_2$), 7.50 – 7.54 (m, 3H, ArH), 7.64 – 7.67 (m, 2H, ArH), 8.97 (br s, 1H, NH); ^{13}C nmr (dimethylsulfoxide-d_6): δ =

14.8, 38.6, 53.7, 56.4, 66.9, 87.0, 98.3, 121.0, 126.7, 129.8, 131.6, 133.1, 145.7, 154.4, 174.6. *Anal.* Calcd for $C_{19}H_{21}N_5O_3S$: C, 57.12; H, 5.30; N, 17.53. Found: C, 56.92; H, 5.28; N, 17.45.

4-Benzylamino-2-methylthio-5-nitro-6-phenylethynylpyrimidine (3c). This compound was obtained as yellow solid, mp 154 – 156 °C (from methanol); yield: 71%; ir (KBr): 3377 (NH), 2209 (C≡C) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ = 2.56 (s, 3H, SCH_3), 4.46 (d, *J* = 3 Hz, 2H, NHCH_2), 7.28 – 7.40 (m, 10H, ArH), 9.28 (t, *J* = 3 Hz, 1H, NH); ^{13}C NMR (dimethylsulfoxide-d_6): δ = 14.3, 43.8, 87.1, 98.8, 120.9, 123.4, 126.1, 126.4, 127.7, 128.7, 129.0, 139.0, 141.8, 158.3, 160.1, 175.1. *Anal.* Calcd for $C_{20}H_{16}N_4O_2S$: C, 63.81; H, 4.28; N, 14.88. Found: C, 64.00; H, 4.30; N, 15.00.

2-Methylthio-5-nitro-6-phenylethynyl-4-pyrrolidinopyrimidine (3d). This compound was obtained as yellow solid, mp 180 – 182 °C (from 2-propanol); yield: 70%; ir (KBr): 2217 (C≡C) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ = 1.91 (br s, 2H, $(CH_2)_2$), 2.52 (s, 3H, SCH_3), 3.42 (br s, 4H, $N(CH_2)_2$), 7.50 – 7.61 (m, 5H, ArH); ^{13}C nmr (dimethylsulfoxide-d_6): δ = 14.6, 26.2, 49.3, 83.6, 97.6, 120.5, 129.8, 130.8, 131.6, 132.9, 143.1, 151.2, 171.9. *Anal.* Calcd for $C_{17}H_{16}N_4O_2S$: C, 59.98; H, 4.74; N, 16.46. Found: C, 60.07; H, 4.69; N, 16.69.

4-(*N*-Methyl)anilino-2-methylthio-5-nitro-6-phenylethynylpyrimidine (3e). This compound was obtained as yellow solid, mp 138 – 140 °C (from methanol); yield: 67%; ir (KBr): 2215 (C≡C) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ = 2.59 (s, 3H, SCH_3), 3.56 (s, 3H, NCH_3), 7.31 – 7.36 (m, 5H, ArH), 7.47 – 7.55 (m, 5H, ArH); ^{13}C nmr (dimethylsulfoxide-d_6): δ = 14.0, 40.8, 82.9, 97.3, 119.6, 124.9, 127.5, 129.1, 129.5, 130.9, 131.5, 132.1, 143.0, 143.1, 152.7, 171.8. *Anal.* Calcd for $C_{20}H_{16}N_4O_2S$: C, 63.81; H, 4.28; N, 14.88. Found: C, 63.99; H, 4.25; N, 14.79.

Synthesis of 4-amino-2-methylthio-6-phenyl-pyrrolo[3,2-*d*]-pyrimidin-7-one 5-oxide (4a).

Method A. A solution of 4-amino-2-methylthio-5-nitro-6-phenylethynylpyrimidine (**3a**) (0.29 g, 1 mmole) in dry pyridine (3 mL) was refluxed for 30 minutes. The solution was concentrated under the reduced pressure. The solid residue was washed with water, dried and recrystallized to give compound **4a**.

Method B. To a solution of 4-amino-2-methylthio-5-nitro-6-phenylethynylpyrimidine (**3a**) (0.29 g, 1 mmole) in 2-propanol (3 mL) 1 drop of pyridine was added and the reaction mixture was heated to reflux for 30 minutes. After cooling to room temperature, the precipitate was collected by filtration and recrystallized to give compound **4a.**

Method C. To a solution of 4-amino-2-methylthio-5-nitro-6-phenylethynylpyrimidine (**3a**) (0.29 g, 1 mmole) in 2-propanol (3 mL) catalytic amount of freshly prepared nitrosobenzene was added and the reaction mixture was heated to reflux for 30 minutes. After cooling to room temperature, the precipitate was collected by filtration and recrystallized to give compound **4a**.

Yield: 75% (method A), Yield: 95% (method B), Yield: 91% (method C).

Data for compound **4a** have been published in the previous paper [12].

General Procedure for the Synthesis of 4-substituted 2-methylthio-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides (4b-e). To a solution of the corresponding 5-nitro-6-phenylethynylpyrimidine (**3b-e**) (1 mmole) in 2-propanol (3 mL) 1 drop of pyridine was added and the reaction mixture was heated to reflux for 30 minutes. After cooling to room temperature, the precipitate was collected by filtration and recrystallized to give compounds **4b-e**.

2-Methylthio-4-[*N*-(2-morpholin-4-ylethyl)amino]-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide (4b). This compound was obtained as dark violet solid, mp 183 – 185 °C (from 2-propanol); yield: 90%; ir (KBr): 3369 (NH), 1720 (C=O) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ = 2.51 (br s, 2H, NCH_2), 2.54 (s, 3H, SCH_3), 2.63 (t, *J* = 3 Hz, 4H, $N(CH_2)_2$), 3.43 (br s, 2H, NHCH_2), 3.64 (t, *J* = 3 Hz, 4H, $O(CH_2)_2$), 7.48 – 7.56 (m, 3H, ArH), 7.98 (t, *J* = 1 Hz, 1H, NH), 8.33 – 8.35 (m, 2H, ArH); ^{13}C nmr (dimethylsulfoxide-d_6): δ = 14.9, 37.4, 53.7, 57.0, 66.8, 120.6, 126.3, 127.5, 128.2, 129.2, 130.7, 149.6, 150.2, 174.9, 186.8. *Anal.* Calcd for $C_{19}H_{21}N_5O_3S$: C, 57.12; H, 5.30; N, 17.53. Found: C, 56.96; H, 5.44; N, 17.59.

4-Benzylamino-2-methylthio-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide (4c). This compound was obtained as dark violet solid, mp 170 - 172 °C (from 2-propanol); yield: 91%; ir (KBr): 3368 (NH), 1716 (C=O) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ = 2.45 (s, 3H, SCH_3), 4.73 (d, *J* = 6.3 Hz, 2H, NHCH_2), 7.23 – 7.41 (m, 5H, ArH), 7.50 – 7.56 (m, 3H, ArH), 8.34 – 8.37 (m, 2H, ArH), 8.60 (t, *J* = 6.3 Hz, 1H, NH); ^{13}C nmr (dimethylsulfoxide-d_6): δ = 14.2, 43.4, 119.9, 125.6, 126.9, 127.4, 127.5, 128.3, 128.5, 129.9, 135.6, 138.9, 149.2, 149.3, 173.9, 180.0. *Anal.* Calcd for $C_{20}H_{16}N_4O_2S$: C, 63.81; H, 4.28; N, 14.88. Found: C, 63.77; H, 4.45; N, 14.99.

2-Methylthio-6-phenyl-4-pyrrolidinopyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide (4d). This compound was obtained as dark violet solid, mp 207 – 209 °C (from 2-propanol); yield: 95%; ir (KBr): 1702 (C=O) cm^{-1}; ^{1}H nmr (deuterio-chloroform): δ = 2.02 (br s, 2H, $(CH_2)_2$), 2.59 (s, 3H, SCH_3), 3.49 (br s, 4H, $N(CH_2)_2$), 7.44 – 7.49 (m, 3H, ArH), 8.43 – 8.46 (m, 2H, ArH); ^{13}C nmr (deuteriochloroform): δ = 15.1, 26.6, 52.7, 121.3, 125.9, 127.7, 128.8, 130.3, 131.7, 148.2, 151.1, 174.2, 186.9. *Anal.* Calcd for $C_{17}H_{16}N_4O_2S$: C, 59.98; H, 4.74; N, 16.46. Found: C, 60.12; H, 4.76; N, 16.41.

4-(*N*-Methylanilino)-2-methylthio-6-phenylpyrrolo[3,2-*d*]-pyrimidin-7-one 5-oxide (4e). This compound was obtained as dark violet solid, mp 218 – 220 °C (from 2-propanol); yield: 94%; ir (KBr): 1697 (C=O) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ = 2.58 (s, 3H, SCH_3), 3.62 (s, 3H, NCH_3), 7.33 – 7.45 (m, 8H, ArH), 8.04 – 8.06 (m, 2H, ArH); ^{13}C nmr (dimethylsulfoxide-d_6): δ = 15.0, 41.3, 123.5, 124.2, 126.3, 127.4, 129.1, 129.8, 130.0, 130.5, 140.6, 147.8, 150.0, 153.4, 173.8, 186.3. *Anal.* Calcd for $C_{20}H_{16}N_4O_2S$: C, 63.81; H, 4.28; N, 14.88. Found: C, 63.77; H, 4.45; N, 14.97.

Synthesis of 4-amino-2-methylsulfinyl-6-phenylpyrrolo-[3,2-*d*]pyrimidin-7-one 5-oxide (5). To a solution of the 4-amino-2-methylthio-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide **4a** (0.5 g, 1.6 mmoles) in dichloromethane (25 mL) *m*-chloroperbenzoic acid was added (0.41 g, 2.4 mmoles) in portions. The resulting solution was stirred for 1 hour at room temperature. The precipitate was collected by filtration, washed with saturated aqueous sodium bicarbonate solution and dried to give compound **5**, which can be used in the next steps without purification. This compound was obtained as dark blue solid, mp 265 – 267 °C; yield: 0.41 g, 85%; ir (KBr): 3432, 3229 (NH_2), 1719 (C=O) cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ = 2.90 (s, 3H, $SOCH_3$), 7.52 – 7.57 (m, 3H, ArH), 7.91 (br s, 1H, NH), 8.37 – 8.40 (m, 2H, ArH), 8.83 (br s, 1H, NH); ^{13}C nmr (dimethylsulfoxide-d_6): δ = 34.3, 122.6, 125.4, 127.0, 127.5,

128.6, 130.4, 149.9, 152.1, 179.6, 185.4; ms: m/z 302 (M^+), 287 (M^+ - CH_3). *Anal.* Calcd for $C_{13}H_{10}N_4O_3S$: C, 51.65; H, 3.33; N, 18.53. Found: C, 52.00; H, 3.43; N, 18.72.

General Procedure for the Synthesis of 2,4-disubstituted 6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides (6a-g).

Method A. To a solution of the 4-amino-2-methylsulfinyl-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide (**5**) (0.4 g, 1.3 mmoles) in dimethylsulfoxide (10 mL) the corresponding amine (4 mmoles) was added. The resulting green solution was stirred for 3 hours at room temperature, then added to 1.0 *M* hydrochloric acid (75 mL) and extracted with dichloromethane (2 × 30 mL). The organic phases were combined and washed with brine (3 × 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give compounds **6a-e**.

Method B. To a solution of the corresponding 2-methylthio-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxides (**4a,c,d**) (1.6 mmoles) in dichloromethane (25 mL) *m*-chloro-perbenzoic acid was added (0.41 g, 2.4 mmoles) in portions. The resulting solution was stirred for 1 hour at room temperature then the corresponding amine (4.8 mmoles) was added. The reaction mixture was stirred for 3 hours at room temperature, then washed with 1.0 *M* hydrochloric acid (75 mL), brine (3 × 30 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give compounds **6a-g**.

4-Amino-6-phenyl-2-propylaminopyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide (6a). This compound was obtained as dark blue solid, mp 173 – 175 °C (from 2-propanol); yield: 71% (method A), 80% (method B); ir (KBr): 3450, 3391, 3329 (NH, NH_2), 1712 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ = 0.91 (t, *J* = 7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.54 – 1.5 (m, 2H, $CH_2CH_2CH_3$), 3.30 (q, *J* = 7.2 Hz, 2H, $NHCH_2CH_2CH_3$), 6.98 (br s, 1H, NH), 7.41 – 7.50 (m, 3H, ArH), 7.65 (br s, 1H, NH), 8.02 (br s, NH), 8.28 – 8.31 (m, 2H, ArH); ^{13}C nmr (dimethylsulfoxide-d_6): δ = 11.4, 21.9, 43.2, 112.6, 125.8, 126.2, 128.3, 128.9, 135.5, 151.5, 153.2, 163.4, 184.2. *Anal.* Calcd for $C_{15}H_{15}N_5O_2$: C, 60.60; H, 5.09; N, 23.56. Found: C, 60.54; H, 4.99; N, 23.55.

4-Amino-2-[*N*-(2-morpholin-4-ylethyl)amino]-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide (6b). This compound was obtained as dark blue solid, mp 250 – 252 °C (from 2-propanol); yield: 72% (method A), 75% (method B); ir (KBr): 3390, 3345, 3333, (NH, NH_2), 1709 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ = 2.53 – 2.54 (m, 4H, $N(CH_2)_2$), 2.63 (t, *J* = 4.8 Hz, 2H, NCH_2), 3.54 – 3.56 (m, 2H, $NHCH_2$), 3.75 – 3.77 (m, 4H, $O(CH_2)_2$), 5.45 (br s, 1H, NH), 6.36 (br s, 1H, NH), 6.75 (br s, 1H, NH), 7.46 – 7.52 (m, 3H, ArH), 8.44 – 8.47 (m, 2H, ArH); ^{13}C nmr (deuteriochloroform): δ = 35.0, 50.9, 55.2, 66.0, 119.8, 125.7, 126.3, 128.5, 129.0, 134.0, 152.2, 155.2, 170.4, 182.6. *Anal.* Calcd for $C_{18}H_{20}N_5O_3$: C, 58.69; H, 5.47; N, 22.81. Found: C, 58.58; H, 5.76; N, 22.86.

4-Amino-2-benzylamino-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide (6c). This compound was obtained as dark blue solid, mp 240 - 242 °C (from 2-propanol); Yield: 74% (method A), 78% (method B); ir (KBr): 3435, 3393, 3334 (NH, NH_2), 1709 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ = 4.56 (d, *J* = 6 Hz, 2H, $NHCH_2$), 7.00 (br s, 1H, NH), 7.24 – 7.35 (m, 8H, ArH), 7.45 (br s, 1H, NH), 8.28 – 8.31 (m, 2H, ArH), 8.49 (t, *J* = 6 Hz, $NHCH_2$); ^{13}C nmr (dimethylsulfoxide-d_6): δ = 43.3, 118.6, 125.8, 126.0, 126.2, 126.8, 127.3, 128.3, 128.9, 130.0, 134.7, 151.0, 153.6, 164.6, 185.1. *Anal.* Calcd for $C_{19}H_{15}N_5O_2$: C, 66.08; H, 4.38; N, 20.28. Found: C, 66.28; H, 4.22; N, 20.55.

4-Amino-2-piperidino-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide (6d). This compound was obtained as dark blue solid, mp 200 – 201.5 °C (from octane); yield: 75% (method A), 79% (method B); ir (KBr): 3469, 3328 (NH), 1715 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ = 1.54 – 1.66 (m, 6H, $(CH_2)_3$), 3.82 (br s, 4H, $N(CH_2)_2$), 7.01 (br s, 1H, NH), 7.42 – 7.53 (m, 3H, ArH), 7.65 (br s, 1H, NH), 8.28 – 8.31 (m, 2H, ArH); ^{13}C nmr (dimethylsulfoxide-d_6): δ = 24.2, 25.5, 44.9, 113.3, 126.3, 128.0, 128.2, 128.4, 138.9, 151.4, 152.6, 161.7, 186.9. *Anal.* Calcd for $C_{17}H_{17}N_5O_2$: C, 63.15; H, 5.30; N, 21.66. Found: C, 63.55; H, 5.55; N, 21.45.

4-Amino-2-morfolino-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide (6e). This compound was obtained as dark blue solid, mp 159 – 160 °C (from 2-propanol); yield: 70% (method A), 83% (method B); ir (KBr): 3459, 3333 (NH_2), 1709 (C=O) cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ = 3.66 (t, *J* = 3 Hz, 4H, $N(CH_2)_2$), 3.78 (t, *J* = 3 Hz, 4H, $O(CH_2)_2$), 7.03 (br s, 1H, NH), 7.42 – 7.52 (m, 3H, ArH), 7.67 (br s, 1H, NH), 8.28 – 8.30 (m, 2H, ArH); ^{13}C nmr (dimethylsulfoxide-d_6): δ = 45.1, 66.7, 114.8, 126.8, 126.9, 127.0, 129.1, 129.9, 152.1, 152.9, 162.7, 187.4. *Anal.* Calcd for $C_{16}H_{15}N_5O_3$: C, 59.07; H, 4.65; N, 21.53. Found: C, 59.44; H, 4.93; N, 21.55.

2,4-Dibenzylamino-6-phenylpyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide (6f). This compound was obtained as dark blue solid, mp 238 - 240 °C (from 2-propanol); yield: 71% (method B); ir (KBr): 3379 (NH), 3368 (NH), 1715 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ = 4.68 (d, *J* = 6 Hz, 2H, $NHCH_2$), 4.72 (d, *J* = 6 Hz, 2H, $NHCH_2$), 6.47 (br s, 1H, NH), 7.20 (br s, 1H, NH), 7.30 – 7.48 (m, 8H, ArH), 8.42 – 8.45 (m, 2H, ArH); ^{13}C nmr (dimethylsulfoxide-d_6): δ = 42.7, 43.4, 120.7, 125.0, 126.2, 126.6, 127.0, 127.4, 128.0 (2C), 128.3, 128.5 (2C), 129.9, 138.5, 140.3, 158.4, 163.3, 170.1, 184.1. *Anal.* Calcd for $C_{26}H_{21}N_5O_2$: C, 71.71; H, 4.86; N, 16.08. Found: C, 71.92; H, 5.02; N, 15.91.

2-Morfolino-6-phenyl-4-pyrrolidinopyrrolo[3,2-*d*]pyrimidin-7-one 5-oxide (6g). This compound was obtained as dark blue solid, mp 221 – 223 °C (from 2-propanol); yield: 78% (method B); ir (KBr): 1707 (C=O) cm^{-1}; ^1H nmr (deutériochloroform): δ = 1.99 (br s, 4H, $(CH_2)_2$), 3.77 – 3.94 (m, 12H, $N(CH_2)_2$, $N(CH_2)_4O$), 7.40 – 7.48 (m, 3H, ArH), 8.39 – 8.42 (m, 2H, ArH); ^{13}C nmr (deuteriochloroform): δ = 26.0, 44.9, 53.5, 66.8, 116.4, 126.2, 127.4, 128.4, 129.4, 149.2, 153.7, 161.1, 165.4, 187.0. *Anal.* Calcd for $C_{20}H_{21}N_5O_3$: C, 63.31; H, 5.58; N, 18.46. Found: C, 63.67; H, 5.60; N, 18.55.

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