

## Heterocyclic *o*-Aminonitriles: Preparation of Pyrazolo[3,4-*d*]-pyrimidines with Modification of the Substituents at the 1-Position

Eljazi I. Al-Afaleq\* and Samar A. Abubshait

Chemistry Department, Faculty of Science-Girls College 838, Dammam 31113, Saudi Arabia. Tel. (+966)-3-8647651, Fax (+966)-3-8951780.

\*Author to whom correspondence should be addressed; e-mail: [eljazii@yahoo.com](mailto:eljazii@yahoo.com)

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**Abstract:** Novel 1-[6-(*p*-tolyl) pyridazin-3-yl]pyrazole-*o*-aminonitriles (**3a-c**) were formed using 3-hydrazino-6-(*p*-tolyl)pyridazine (**2**) and ketene *S,S*-acetals (**1a**), *S,N*-acetals (**1b**) or tetracyanoethylene (**1c**). The pyrazole-*o*-aminonitriles (**3a-c**) were in turn used as precursors for the preparation of previously unreported 1-[6-(*p*-tolyl)-pyridazin-3-yl]pyrazolo[3,4-*d*]pyrimidines (**8, 9, 13-20**) and 7-[6-(*p*-tolyl) pyridazin-3-yl]2-arylpyrazolo[3,4-*d*]1,2,4-triazolo[5,1-*f*]pyrimidines (**10-12**) which are expected to possess considerable chemical and pharmacological activities.

**Keywords:** *o*-Aminonitriles; ketene acetals; pyrazolopyrimidines.

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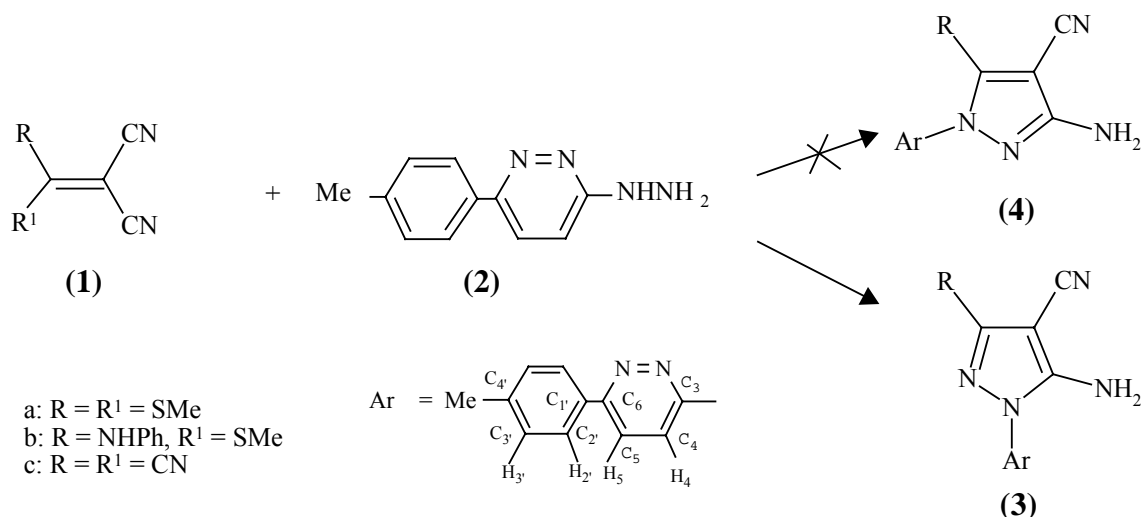
### Introduction

Pyrazolo[3,4-*d*]pyrimidines are of considerable chemical and pharmacological importance as purine analogs [1-3]. Various compounds with related structures also possess anti-tumor and anti-leukemia activities [4,5]. On the other hand, substituted pyridazines are often used in medicine thanks to their pronounced bactericidal and fungicidal effects [6]. As a continuation of our work on azoloazines [7], we aimed to incorporate the pyridazine moiety into the 1-position of the

pyrazolo[3,4-*d*]pyrimidine ring system to thus obtain a new heterocyclic system which is expected to possess notable chemical and pharmacological activities.

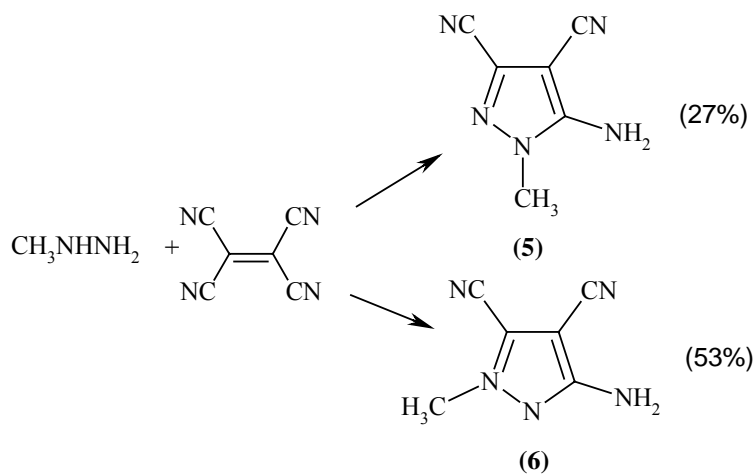
## Results and Discussion

The key pyrazole-*o*-aminonitrile precursors (**3a-c**) were prepared by the reaction of 3-hydrazino-6-(*p*-tolyl)pyridazine (**2**) [8] with ketene *S,S*- and *S,N*-acetals (**1a,b**) which were prepared using Phase Transfer Catalysis (PTC) [9], or tetracyanoethylene (**1c**).



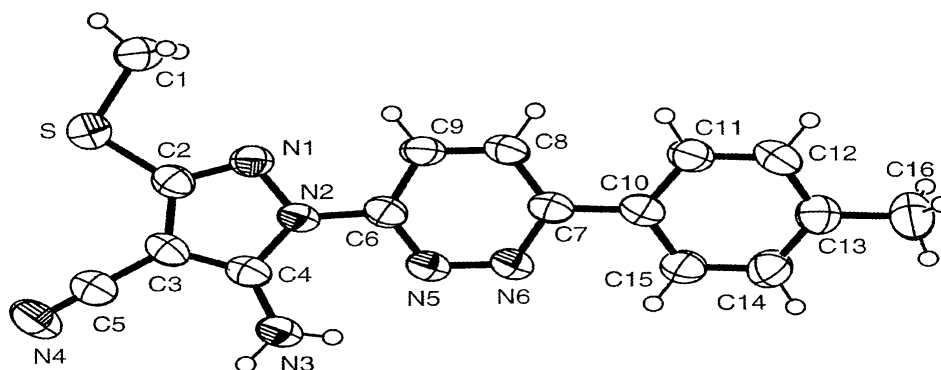
**Scheme 1**

The reaction sequence shown in Scheme 1 yielded only one product (**3**) instead of a mixture of the two possible isomeric pyrazole-*o*-aminonitriles **3** and **4**. This fact was confirmed by the several strategies. First, by using the technique of Hecht et al. [10], who found it was possible to differentiate between the isomeric pyrazoles **5** and **6** based on their different reactivity; thus, treatment of **6** with acetic anhydride in pyridine at room temperature afforded the corresponding *N*-acetyl derivative, but pyrazole **5** did not form the corresponding derivative under the same conditions, although it did form at 50-60°C (Scheme 2).



**Scheme 2**

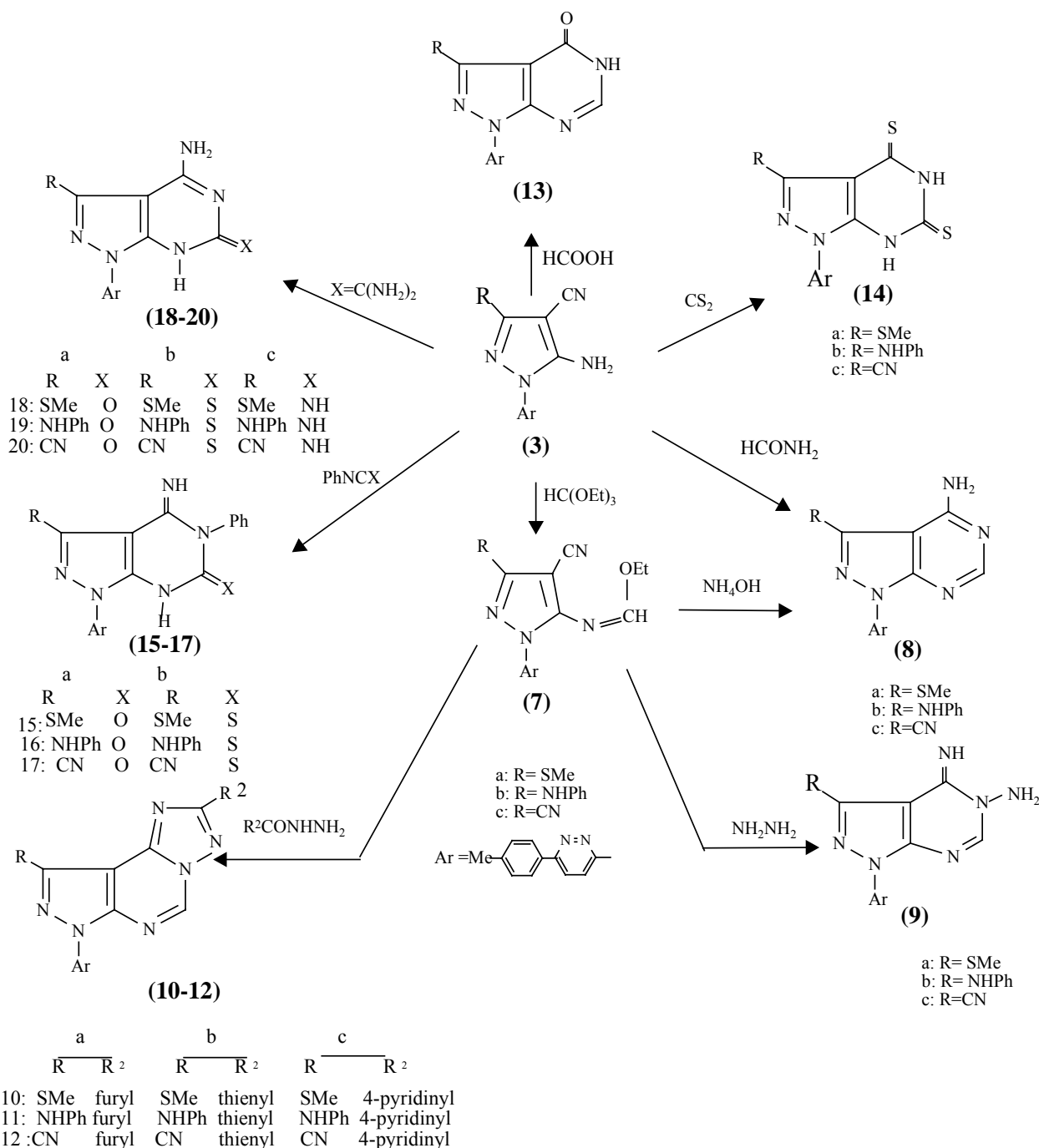
By analogy with the results of Hecht et al, when our product was treated with acetic anhydride, it formed the corresponding acetyl derivative only at higher temperatures and not at room temperature, due to the electronic and steric factors of the substituents (Ar and CN). Secondly, only one spot was obtained in TLC. Third, the structure of the product was identified as that of **3** on the basis of the X-ray crystal structure analysis, which confirmed the substituted nitrogen of the pyrazole ring is adjacent to the amino group (Figure 1). Finally, the structural assignment of **3** was also based on spectral evidence (IR,  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$  and Mass spectrometry, while COSY- 2D experiments indicated the (C-H) and (H-H) correlations).



**Fig. 1** Single-crystal X-ray analysis. **ORTEP** view of **3a** showing the atom numbering scheme,

The above mentioned pyrazoles were used as intermediates for the synthesis of new pyrazolo[3,4-*d*]pyrimidines because they contain the  $\beta$ -enaminonitrile moiety which is well known to be highly reactive. Thus, condensation of **3a-c** with triethylorthoformate in refluxing acetic anhydride afforded the intermediate ethoxymethyleneamino derivatives (**7a-c**) (Scheme 3), which were isolated and used without purification in the next step. Treatment of **7a-c** with cold aqueous alcoholic ammonia yielded 4-aminopyrazolo[3,4-*d*]pyrimidines (**8a-c**). The IR spectrum of **8a,b** displayed no absorption for the cyano group. We also attempted a direct synthesis of compounds **8a-c** by treating pyrazoles **3a-c** with formamide. When cooled compounds **7a-c** were stirred with hydrazine hydrate in ethanol and then warmed to room temperature for 6h, they yielded 5-amino-4-iminopyrazolo[3,4-*d*]pyrimidines (**9a-c**) in good yield. The proposed structures for the products **9a-c** were supported by their elemental analysis and spectral data (see Experimental).

The imidates **7a-c** gave 2-arylpyrazolo[3,4-*d*]-1,2,4-triazolo[5,1-*f*] pyrimidine systems (**10-12**) when reacted with 2-furancarboxylic acid hydrazide, 2-thiophenecarboxylic acid hydrazide and 4-pyridinecarboxylic acid hydrazide, respectively. The structures of the reaction products were assigned based on correct elemental analysis and spectral data (for example, the IR spectrum shows the absence of nitrile and amino bands, while the  $^1\text{H-NMR}$  spectrum shows the signals of hydrogen atoms respectively characteristic of the aryl moiety in 2-position).



Scheme 3

The pyrazole derivatives **3a-c** undergo cyclization to afford several other new pyrazolo [3,4-*d*] pyrimidines (**13-20**) when reacted with formic acid, carbon disulfide, phenylisocyanate, phenylisothiocyanate, urea, thiourea and guanidine respectively. The structures of the synthesized compounds were established by elemental analysis and spectral data. (see Experimental).

## Conclusions

We have presented various methods for synthesis of novel pyrazolo[3,4-d]pyrimidines with a pyridazine moiety at the 1-position.

## Acknowledgments

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## Experimental

### General

Melting points were determined on a Reichert hot stage microscope and are uncorrected. IR spectra were measured with a Nicolet Magna 520 instrument, using potassium bromide and results are given in  $\text{cm}^{-1}$ .  $^1\text{H}$ -,  $^{13}\text{C}$  NMR and 2D H-H, C-H, Cosy NMR spectra were recorded in  $\text{DMSO-d}_6$  on either a JEOL JNM-GX270, ( $^1\text{H}$ -NMR at 270 MHz), ( $^{13}\text{C}$ -NMR at 52.89MHz) or a Varian Gemini ( $^1\text{H}$ -NMR at 200 MHz), ( $^{13}\text{C}$ -NMR at 90.56 MHz ) spectrometer. The chemical shifts are reported in part per million (ppm) downfield from internal tetramethylsilane. Electron impact MS spectra were obtained on a JEOL JMS-HX 100 at 70 eV. Elemental microanalysis were done on a CARLO Erba analyzer model 110. The progress of all reactions was monitored by TLC on 2.0 cm x 6.0 cm aluminium sheets precoated with silica gel 60 containing a fluorescent indicator (Alugram SIL G/UV254 fur die DC Macherey-Nagel/ Germany), to a thickness of 0.25 mm. The developed chromatograms were viewed under ultraviolet light. Column chromatography was performed on [Merck] silica gel (70-230 mesh) (elution with 1:1 cyclohexane-ethyl acetate). The X-ray structure was determined using a NONIUS Kappa Diffractomer. Suitable crystals were grown by slow crystallization from ethanol.

*General Procedure for the Preparation of 5-Amino-3-substituted-1-[6-(p-tolyl) pyridazin-3-yl]-pyrazole-4-carbonitriles (3a-c).*

To a cold solution of hydrazine **2** (2.0g , 10 mmol) in methanol (100 mL) was added **1** (10 mmol). The reaction mixtures were then stirred at room temperature for 3-6h, left overnight, then the solvent was evaporated and the residue recrystallized from a suitable solvent.

*5-Amino-3-methylthio-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazole-4-carbonitrile (3a).*

Yield: 89 %; colorless needle-like crystals; mp 259-260 °C (from EtOH); IR:  $\nu$  max  $\text{cm}^{-1}$  3379, 3279 ( $\text{NH}_2$ ); 2210 (CN);  $^1\text{H-NMR}$ :  $\delta$ : 2.41 (s, 3H,  $\text{CH}_3\text{-S}$ ), 2.60 (s, 3H,  $p\text{-CH}_3\text{-tolyl}$ ), 7.02 (bs, 2H,  $\text{NH}_2$ ,  $\text{D}_2\text{O}$  exchangeable), 7.31 (d, 2H, H3, H5 – tolyl,  $J = 8.0$  Hz), 7.90 (d, 2H, H2, H6- tolyl,  $J = 8.0$  Hz), 8.13 (d, 1H, H5-pyridazine,  $J = 9.1$  Hz), 8.36 (d, 1H, H4-pyridazine,  $J = 9.1$  Hz);  $^{13}\text{C-NMR}$ :  $\delta$  15 ( $\underline{\text{C}}\text{H}_3\text{-S}$ ), 20 ( $p\text{-}\underline{\text{C}}\text{H}_3\text{-tolyl}$ ), 79 ( $\underline{\text{C}}\text{N}$ ), 134 ( $\underline{\text{C}}\text{-CN}$ ), 140 ( $\underline{\text{C}}\text{-SCH}_3$ ), 113, 127, 129, 153 ( $\text{C}_4, \text{C}_3, \text{C}_2$  and  $\text{C}_1$  of tolyl); 118, 126, 154, 156 (pyridazine  $\text{C}_5, \text{C}_4, \text{C}_6$  and  $\text{C}_3$ ); 157 ( $\underline{\text{C}}\text{-NH}_2$ ); MS  $m/z$  (%):  $\text{M}^+$  322 (100), 275 (77), 250 (69), 115 (54), 78 (7.7); Anal. Calc. for  $\text{C}_{16}\text{H}_{14}\text{N}_6\text{S}$  (322.39): C 59.61, H 4.38, N 26.07, S 9.94; Found: C 59.25, H 4.26, N 26.10, S 9.95.

*Single-Crystal X-ray Structure Analysis of 3a: Crystallographic Data and Refinement.*

Crystal Orthorhombic, space group  $\text{P}2_12_12_1$ ,  $a = 4.97330(10)\text{\AA}$ ,  $b = 11.1882(3)\text{\AA}$ ,  $c = 28.0997(8)\text{\AA}$ .

CELL 4.97330 11.18820 28.09970 90.0000 90.0000 90.0000.

ZERR 4 0.00010 0.00029 0.00080 0.000 0.000 0.000.

LATT –1.

SYMM 0.5-X, -Y, 0.5+Z. SYMM 0.5+X, 0.5-Y, -Z. SYMM –X, 0.5+Y, 0.5-Z.

Volume 1563.53(7)  $\text{\AA}^3$ .

Z, calculated density 4, 1.370  $\text{/m}^3$ .

Absorption coefficient 0.215  $\text{mm}^{-1}$ .

F(000) 672.

Theta range for data collection 1.96 to 27.49 deg.

Limiting indices  $-6 \leq h \leq 6$ ,  $-14 \leq k \leq 14$ ,  $-35 \leq l \leq 35$ .

Reflections collected/unique 3468/3468 [ $R(\text{int}) = 0.0000$ ].

Refinement method full-matrix least-squares on  $F^2$ .

Goodness-of-fit on  $F^2$  0.978.

Final R indices [ $I > 2\sigma(I)$ ]  $R_1 = 0.0498$ ,  $wR_2 = 0.1134$ .

R indices (all data)  $R_1 = 0.1182$ ,  $wR_2 = 0.1374$ .

*5-Amino-3-N-phenylamino-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazole-4-carbonitrile (3b).*

Yield: 70 %; white solid, mp 297 °C (from EtOH); IR:  $\nu$  max  $\text{cm}^{-1}$  3461-3311 ( $\text{NH}_2/\text{NH}$ ); 2213 (CN);  $^1\text{H-NMR}$   $\delta$ : 2.45 (s, 3H,  $p\text{-CH}_3\text{-tolyl}$ ), 6.82 (bs, 2H,  $\text{NH}_2$ ,  $\text{D}_2\text{O}$  exchangeable), 7.18 (t, 1H, H4-Ph,  $J = 7.4$  Hz), 7.34 (t, 2H, H3, H5-Ph,  $J = 7.6$  Hz), 8.21 (d, 2H, H2, H6-Ph,  $J = 7.9$  Hz), 7.61 (d, 2H, H3, H5- tolyl,  $J = 8.0$  Hz), 8.04 (d, 2H, H2, H6-tolyl,  $J = 8.0$  Hz), 8.26 (d, 1H, H5-pyridazine,  $J = 9.1$  Hz), 8.42 (d, 1H, H4-pyridazine,  $J = 9.1$  Hz), 9.22 (bs, 1H, NH,  $\text{D}_2\text{O}$  exchangeable); MS:  $m/z$  (%);  $\text{M}^+$  367 (75), 270 (100), 115 (42), 78 (8.1); Anal. Calc. for  $\text{C}_{21}\text{H}_{17}\text{N}_7$  (367.41): C 68.65, H 4.66, N 26.69; Found: C 68.49, H 4.68, N 26.70.

*5-Amino-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazole-3,4-dicarbonitrile (3c).*

Yield: 86 %; pale brown solid; mp 289-292°C (from n-BuOH); IR:  $\nu$  max  $\text{cm}^{-1}$  3369, 3282 ( $\text{NH}_2$ ); 2239, 3231(2CN);  $^1\text{H-NMR}$   $\delta$ : 2.43 (s, 3H, *p*- $\text{CH}_3$ -tolyl), 7.42 (d, 2H, H3, H5-tolyl,  $J = 8.0$  Hz), 8.04 (d, 2H, H2, H6-tolyl,  $J = 8.0$  Hz), 8.17 (d, 2H, H5-pyridazine,  $J = 9.1$  Hz), 8.51 (d, 2H, H4-pyridazine,  $J = 9.1$  Hz), 8.61 (bs, 2H,  $\text{NH}_2$ ,  $\text{D}_2\text{O}$  exchangeable); MS:  $m/z$  (%);  $\text{M}^+$  301(88), 275 (100), 78 (52), 65 (65); Anal. Calc. for  $\text{C}_{16}\text{H}_{11}\text{N}_7$  (301.31): C 63.78, H 3.68, N 32.54; Found: C 64.02, H 3.68, N 32.39.

*General Procedure for Preparation of 5-Methoxymethyleneamino-3-substituted-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazole-4-carbonitrilse (7a-c).*

A mixture of pyrazole-*o*-aminonitriles **3a-c** (10 mmol), triethylorthoformate (3mL) and acetic anhydride (3 mL) was refluxed for 6h. The solvent was removed under reduced pressure and the resulting solid was recrystallized from ethanol.

*5-Methoxymethyleneamino-3-methylthio-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazole-4-carbonitrile (7a).*

Yield: 75 %; white solid, mp 132 °C ; IR  $\nu$  max  $\text{cm}^{-1}$ : 3380 (NH), 2920, 2827 (CH), 2218 (CN).

*5-Methoxymethyleneamino-3-N-phenylamino-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazole-4-yl-carbonitrile (7b).*

Yield: 61 %; white solid, mp 230 °C; IR:  $\nu$  max  $\text{cm}^{-1}$ : 3326 (NH), 2917, 2849 (CH), 2225 (CN)

*5-Methoxymethyleneamino-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazole-3,4-yl-dicarbonitrile (7c).*

Yield: 66% yield; white solid, mp 209-210 °C; IR  $\nu$  max  $\text{cm}^{-1}$ : 3416 (NH), 2933, 2860 (CH), 2229, 2225 (2CN).

*General procedure for the Preparation of 3-Substituted-1-[6-(p-tolyl)pyridazin-3-yl]- pyrazolo[3,4-d]pyrimidine-4-amines (8a-c).*

Methanimidates **7a-c** (3 mmol) were added to methanol (20 mL) saturated with ammonia at 0°C for 1h, warmed to room temperature and the reaction mixture stirred for 6h. The solid which precipitated was collected and recrystallized from an appropriate solvent.

*3-Methylthio-1-[6-(p-tolyl)pyridazin-3-yl]pyrazolo[3,4-d]pyrimidine-4-amine (8a).*

Yield: 81 %; pale yellow solid, mp 275 °C (from n-BuOH); IR  $\nu$  max  $\text{cm}^{-1}$ : 3410, 3362 ( $\text{NH}_2$ );  $^1\text{H-NMR}$   $\delta$ : 2.46 (s, 3H, S- $\text{CH}_3$ ), 2.60 (s, 3H, *p*- $\text{CH}_3$ -tolyl), 7.43 (d, 2H, H3,H5-tolyl,  $J = 8.0$  Hz), 7.71

(bs, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 8.00 (d, 2H, H<sub>2</sub>,H<sub>6</sub>-tolyl,  $J = 8.0$  Hz), 8.20 (d, 2H, H<sub>5</sub>-pyridazine,  $J = 9.1$  Hz), 8.42 (d, 2H, H<sub>4</sub>-pyridazine,  $J = 9.1$  Hz); <sup>13</sup>C-NMR  $\delta$ : 18 (S—CH<sub>3</sub>-tolyl), 20 (*p*-CH<sub>3</sub>-tolyl), 112, 118, 124, 128, 131, 133, 138, 151, 155, 156, 158, 159, 160 (aromatic); MS:  $m/z$  (%); M<sup>+</sup> 349(100), 334(27), 274(94), 244 (49). Anal. Calc. for C<sub>17</sub> H<sub>15</sub>N<sub>7</sub>S (349.41); C 58.44, H 4.33, N 28.06, S 9.18; Found : C 58.29, H 4.34, N 27.98, S 9.20.

*3-N-Phenylamino-1-[6-(p-tolyl)pyridazin-3-yl]pyrazolo[3,4-d]pyrimidine-4-amine (8b).*

Yield 34 %; light brown solid, mp 285-287 °C (from dioxane); IR  $\nu$  max cm<sup>-1</sup>: 3370-3180 (NH<sub>2</sub>/NH); <sup>1</sup>H-NMR  $\delta$ : 2.52 (*s*, 3H, *p*-CH<sub>3</sub>-tolyl), 7.04 (*t*, 1H, H<sub>4</sub>-Ph,  $J = 7.4$  Hz), 7.30 (*t*, 2H, H<sub>3</sub>,H<sub>5</sub>- Ph,  $J = 7.6$  Hz), 7.41 (*d*, 2H, H<sub>3</sub>,H<sub>5</sub>- tolyl,  $J = 8.0$  Hz), 7.85 (*bs*, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 7.90 (*d*, 2H, H<sub>2</sub>-Ph, H<sub>6</sub>-Ph,  $J = 7.9$  Hz), 8.16 (*d*, 2H, H<sub>4</sub>. H<sub>6</sub>-tolyl,  $J = 8.0$  Hz), 8.20 (*d*, 1H, H<sub>5</sub>-pyridazine,  $J = 9.1$  Hz), 8.33 (*bs*, 1H, NH, D<sub>2</sub>O exchangeable), 8.40 (*d*, 1H, H<sub>4</sub>-pyridazine,  $J = 9.1$ Hz), 8.64 (*s*, 1H, pyrimidine); <sup>13</sup>C-NMR  $\delta$ : 20 (*p*-CH<sub>3</sub>-tolyl), 114, 121, 122, 123, 124, 128, 130, 131, 133, 135, 138, 151, 155, 156, 158, 159, 160 (aromatic); MS:  $m/z$  (%); M<sup>+</sup> 394(86), 378(52), 288(100), 244 (73), 77(15); Anal. Calc. for C<sub>22</sub> H<sub>18</sub>N<sub>8</sub> (394.44); C 66.99, H 4.60, N 28.41; Found : C 67.05, H 4.60, N 28.39.

*4-Amino-1-[6-(p-tolyl)pyridazin-3-yl]pyrazolo[3,4-d]pyrimidine-3-carbonitrile (8c).*

Yield: 65 %; yellow crystals, mp >320 °C (from EtOH); IR  $\nu$  max cm<sup>-1</sup>: 3397, 3276 (NH<sub>2</sub>), 2240 (CN); <sup>1</sup>H-NMR  $\delta$ : 2.45 (*s*, 3H, *p*-CH<sub>3</sub>-tolyl), 7.40 (*d*, 2H, H<sub>3</sub>, H<sub>5</sub>- tolyl,  $J = 8.0$  Hz), 7.93 (*bs*, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 8.00 (*d*, 2H, , H<sub>2</sub>, H<sub>6</sub>-tolyl,  $J = 8.0$  Hz), 8.12 (*d*, 1H, H<sub>5</sub>-pyridazine,  $J = 9.1$  Hz), 8.51 (*d*, 1H, H<sub>4</sub>-pyridazine,  $J = 9.1$ Hz); MS  $m/z$  (%): M<sup>+</sup> 328(95), 312(100), 302(44); Anal. Calc. for C<sub>17</sub> H<sub>12</sub>N<sub>8</sub> (328.34); C 62.19, H 3.68, N 34.13; Found: C 62.16, H 3.71, N 34.18.

*General Procedure for the Preparation of 4-imino-3-substituted-1-[6-(p-tolyl)pyridazin-3-yl]-4,5-dihydropyrazolo[3,4-d]- pyrimidine-5-amines (9a-c).*

To a well stirred cold solution of methanimidate **7a-c** (20 mmol) in ethanol (10 mL), 99 % hydrazine hydrate (3 mL) was added over 2h, then the mixture was stirred at room temperature for 6h and left overnight. The solid that precipitated was filtered off and purified by passage through a column of silica gel with cyclohexane -ethyl acetate (1:1) as eluent.

*4-Imino-3-methylthio-1-[6-(p-tolyl)pyridazin-3-yl]-4,5-dihydropyrazolo[3,4-d] pyrimidine-5-amine (9a).*

Yield: 96 %; white solid, mp 238 °C; IR  $\nu$  max cm<sup>-1</sup>: 3352-3204 (NH<sub>2</sub>/NH); <sup>1</sup>H-NMR  $\delta$ : 2.37 (*s*, 3H, S-CH<sub>3</sub>), 2.66 (*s*, 3H, *p*-CH<sub>3</sub>-tolyl), 6.35 (*bs*, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 7.41 (*d*, 2H, H<sub>3</sub>, H<sub>5</sub>-tolyl,  $J = 8.0$  Hz), 8.06 (*d*, 2H, H<sub>3</sub>, H<sub>5</sub>- tolyl,  $J = 8.0$  Hz), 8.22 (*d*, 1H, H<sub>5</sub>-pyridazine,  $J = 9.1$  Hz), 8.30 (*bs*, 1H, NH, D<sub>2</sub>O exchangeable), 8.41 (*d*, 1H, , H<sub>4</sub>-pyridazine,  $J = 9.1$ Hz) , 8.54 (*s*, 1H,



pyrimidine); MS: m/z (%); M<sup>+</sup> 364(95), 348(100), 317(33), 301 (58); Anal. Calc. for C<sub>17</sub> H<sub>16</sub>N<sub>8</sub>S (364.43): C 56.03, H 4.43, N 30.75, S 8.80; Found: C 55.96, H 4.46, N 30.70, S 8.74.

*4-Imino-3-N-phenylamino-1-[6-(p-tolyl)pyridazin-3-yl]-4,5-dihydropyrazolo[3,4-d]- pyrimidine-5-amine (9b).*

Yield: 70 %; yellow solid, mp 279-281 °C; IRv max cm<sup>-1</sup>: 3458-3120, (NH<sub>2</sub>/2NH); <sup>1</sup>H-NMR δ: 2.51 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 6.91 (t, 1H, H4-Ph, *J* = 7.4 Hz), 7.23 (t, 2H, H3, H5-Ph, *J* = 7.6 Hz), 7.36 (d, 2H, H3, H5-tolyl, *J* = 8.0 Hz), 7.42 (bs, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 7.64 (d, 2H, H2, H6-Ph, *J* = 7.9 Hz), 8.00 (d, 1H, H2, H6-tolyl, *J* = 8.0 Hz), 8.10 (d, 1H, , H5-pyridazine, *J* = 9.1 Hz), 8.41 (d, 1H, H4-pyridazine, *J* = 9.1Hz), 8.55 (s, 1H, pyrimidine), 9.03 (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS: m/z (%); M<sup>+</sup> 409 (100), 394 (51), 288 (84). Anal. Calc. for C<sub>22</sub> H<sub>19</sub>N<sub>9</sub> (409.45): C 64.54, H 4.68, N 30.79; Found: C 64.18, H 4.67, N 31.01.

*5-amino-4-imino-1-[6-(p-tolyl)pyridazin-3-yl]-4,5-dihydropyrazolo[3,4-d]pyrimidine-3-carbonitrile (9c).*

Yield: 89 %; beige solid, mp 271-273 °C; IR v max cm<sup>-1</sup> 3420-3230 (NH<sub>2</sub>, 2NH); 2236 (CN); <sup>1</sup>H-NMR δ 2.42 (3H, *s*, *p*-CH<sub>3</sub>-tolyl), 7.33 (d, 2H, H3, H5-tolyl, *J* = 8.0 Hz), 7.65 (2H, bs, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 8.00 (d, 2H, H2, H6-tolyl, *J* = 8.0 Hz), 8.21 (d, 1H, H5-pyridazine, *J* = 9.1 Hz), 8.42 (d, 1H, H4-pyridazine, *J* = 9.1Hz), 8.77 (1H, bs, NH, D<sub>2</sub>O exchangeable); MS m/z (%): M<sup>+</sup> 343 (100), 237 (66), 211 (87). Anal. Calc. for C<sub>17</sub>H<sub>13</sub>N<sub>9</sub> (343.35): C 59.47; H 3.82 ; N 36.71; Found: C 59.47, H 3.84, N 36.70.

*General procedure for the Preparation of 2-Aryl-9-substituted-7-[6-(p-tolyl) pyridazin-3-yl]-pyrazolo[3,4-d]-1,2,4-triazolo[5,1-f] pyrimidines (10-12).*

Methanimidates **7a-c** (20 mmol) were dissolved in dioxane (20 mL), and 2-furancarboxylic acid hydrazide, 2-thiophenecarboxylic acid hydrazide or 4-pyridinecarboxylic acid hydrazide (22 mmol) was added. The mixture was refluxed for 6-14 h, cooled, the solvent removed under reduced pressure and the resulting precipitate was purified by recrystallization or column chromatography.

*2-(2-Furyl)-9-methylthio-7-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]-1,2,4-triazolo[5,1-f]-pyrimidine (10a).*

Yield: 78 %; pale yellow solid, mp 215-216 °C (from DMF/H<sub>2</sub>O); IR v max cm<sup>-1</sup>: 3096, 2919, 1628; <sup>1</sup>H-NMR δ: 2.54 (s, 3H, S-CH<sub>3</sub>), 2.66 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 6.81 (m, 1H, furyl), 7.42 (m, 2H + 1H, H-tolyl+ 1H-furyl), 7.65 (d, 2H, H3, H5- tolyl, *J* = 8.0 Hz), 7.87 (m, 1H, furyl), 8.01 (d, 1H, H5-pyridazine, *J* = 9.1 Hz), 8.32 (d, 1H, , H4-pyridazine, *J* = 9.1 Hz), 8.65 (s, 1H, pyrimidine); MS m/z (%): M<sup>+</sup> 440 (95), 393 (100), 326 (39); Anal. Calc. for C<sub>22</sub> H<sub>16</sub>N<sub>8</sub>SO (440.48): C 59.99, H 3.66, N 25.44, S 7.28; Found : C 59.85, H 3.61, N 25.40, S 7.29.

2-(2-Thienyl)-9-methylthio-7-[6-(*p*-tolyl)pyridazin-3-yl]-pyrazolo[3,4-*d*]-1,2,4-triazolo[5,1-*f*]pyrimidine (**10b**).

Yield: 47 %; beige solid, mp 247-249 °C (from DMF/ H<sub>2</sub>O); IR v max cm<sup>-1</sup>: 3101, 2918, 1625; <sup>1</sup>H-NMR δ: 2.53 (*s*, 3H, S-CH<sub>3</sub>), 2.64 (*s*, 3H, *p*-CH<sub>3</sub>-tolyl), 7.21 (*m*, 1H, thienyl), 7.55 (*m*, 2H + 1H, H-tolyl+1H-thienyl), 7.76 (*d*, 2H, H<sub>3</sub>, H<sub>5</sub>-tolyl, *J* = 8.0 Hz), 7.87 (*m*, 1H, thienyl), 8.21 (*d*, 1H, H<sub>5</sub>-pyridazine, *J* = 9.1 Hz), 8.43 (*d*, 1H, H<sub>4</sub>-pyridazine, *J* = 9.1 Hz), 8.71 (*s*, 1H, pyrimidine); MS m/z (%): M<sup>+</sup> 456 (95), 409 (100), 326 (57); Anal. Calc. for C<sub>22</sub> H<sub>16</sub>N<sub>8</sub>S<sub>2</sub> (456.55): C 57.88, H 3.53, N 24.54, S 14.04; Found : C 57.87, H 3.56, N 24.51, S 13.99.

2-(4-pyridyl)-9-methylthio-7-[6-(*p*-tolyl)pyridazin-3-yl]-pyrazolo[3,4-*d*]-1,2,4-triazolo[5,1-*f*]pyrimidine (**10c**).

Yield: 71 %; white solid, mp 240-243 °C [column chromatography, (5:1) cyclohexane/ethyl acetate]; IR v max cm<sup>-1</sup>: 3084, 2926, 1627; <sup>1</sup>H-NMR δ: 2.42 (*s*, 3H, S-CH<sub>3</sub>), 2.60 (*s*, 3H, *p*-CH<sub>3</sub>-tolyl), 7.43 (*d*, 2H, H<sub>3</sub>, H<sub>5</sub>-tolyl, *J* = 8.0 Hz), 7.81 (*d*, 2H, pyridyl, *J* = 8.0 Hz), 8.10 (*d*, 2H, H<sub>2</sub>, H<sub>6</sub>-tolyl, *J* = 8.0 Hz), 8.46 (*d*, 1H, H<sub>5</sub>-pyridazine, *J* = 9.1 Hz), 8.55 (*d*, 1H, H<sub>4</sub>-pyridazine, *J* = 9.1 Hz), 8.67 (*s*, 1H, pyrimidine), 8.71 (*d*, 2H, pyridyl *J* = 8.0 Hz); MS m/z (%): M<sup>+</sup> 451 (68), 404 (100), 326 (51); Anal. Calc. for C<sub>23</sub> H<sub>17</sub>N<sub>9</sub>S (451.51): C 61.18, H 3.79, N 27.92, S 7.10; Found : C 61.16, H 3.77, N 27.94, S 6.99.

2-(2-Furyl)-9-*N*-phenylamino-7-[6-(*p*-tolyl)pyridazin-3-yl]-pyrazolo[3,4-*d*]-1,2,4-triazolo-[5,1-*f*]pyrimidine (**11a**).

Yield: 64 %; white solid, mp 285 °C [column chromatography, (5:1) cyclohexane/ethyl acetate]; IR v max cm<sup>-1</sup>: 3415, 3086, 2921, 1616; <sup>1</sup>H-NMR δ: 2.50 (*s*, 3H, *p*-CH<sub>3</sub>-tolyl), 6.82 (*m*, 1H, furyl), 6.90 (*t*, 1H, H<sub>4</sub>-Ph, *J* = 7.4 Hz), 7.27 (*m*, 2H + 2H+ 1H, H-tolyl + H-phenyl + H-furyl), 7.65 (*d*, 2H, H<sub>2</sub>, H<sub>6</sub>-tolyl, *J* = 8.0 Hz), 8.00 (*m*, 1H+ 2H, H-furyl, H-phenyl), 8.19 (*d*, 1H, H<sub>5</sub>-pyridazine, *J* = 9.1 Hz), 8.34 (*d*, 1H, H<sub>4</sub>-pyridazine, *J* = 9.1 Hz), 8.52 (*s*, 1H, pyrimidine); MS m/z (%): M<sup>+</sup> 485 (93), 393 (100), 326 (69); Anal. Calc. for C<sub>27</sub> H<sub>19</sub>N<sub>9</sub>O (485.50): C 66.80, H 3.94, N 25.96; Found : C 66.80, H 3.97, N 25.98.

2-(2-Thienyl)-9-*N*-phenylamino-7-[6-(*p*-tolyl)pyridazin-3-yl]-pyrazolo[3,4-*d*]-1,2,4-triazolo- [5,1-*f*]pyrimidine (**11b**).

Yield: 83 %; pale brown solid, mp >320 °C (from dioxane); IR v max cm<sup>-1</sup>: 3413, 3110, 2921, 1607; <sup>1</sup>H-NMR δ: 2.52 (*s*, 3H, *p*-CH<sub>3</sub>-tolyl), 6.91 (*t*, 1H, H<sub>4</sub>-Ph, *J* = 7.4 Hz), 7.15 (*m*, 1H, thienyl), 7.40 (*m*, 2H, H-tolyl+ H-phenyl+ 1H-thienyl), 7.69 (*d*, 2H, H<sub>2</sub>, H<sub>6</sub>-tolyl, *J* = 8.4 Hz), 7.82 (*m*, 1H, thienyl), 8.02 (*m*, 2H-phenyl, 1H-pyridazine), 8.36 (*d*, 1H, H<sub>4</sub>-pyridazine), 8.50 (*s*, 1H, pyrimidine); MS m/z (%): M<sup>+</sup> 501 (94), 418 (100), 326 (90); Anal. Calc. for C<sub>27</sub> H<sub>19</sub>N<sub>9</sub>S (501.57): C 64.66, H 3.82, N 25.13, S 6.39; Found : C 64.66, H 3.80, N 25.09, S 6.36.

2-(4-Pyridyl)-9-N-phenylamino-7-[6-(*p*-tolyl)pyridazin-3-yl]-pyrazolo[3,4-*d*]-1,2,4-triazolo-[5,1-*f*]pyrimidine (**11c**).

Yield: 61 %; yellow flakes, mp >320 °C (from dioxane); IR  $\nu$  max  $\text{cm}^{-1}$ : 3375, 3095, 2921, 1599;  $^1\text{H-NMR}$   $\delta$ : 2.53 (d, 3H, *p*-CH<sub>3</sub>-tolyl), 7.08 (t, 1H, H4-Ph, *J* = 7.4 Hz), 7.30 (m, 2H+2H, H-toly+H-phenyl), 7.50 (d, 2H, pyridyl, *J* = 8.0 Hz), 7.82 (d, 2H, H2, H6-tolyl, *J* = 8.0 Hz), 8.06 (d, 2H, H2, H6- Ph, *J* = 7.9 Hz), 8.25 (d, 1H, H5-pyridazine, *J* = 9.1 Hz), 8.39 (d, 1H, H4-pyridazine, *J* = 9.1 Hz), 8.47 (s, 1H, pyrimidine), 8.70 (d, 2H, pyridyl *J* = 8.0Hz); MS *m/z* (%): M<sup>+</sup> 496 (100), 404 (70), 418 (61); Anal. Calc. for C<sub>28</sub> H<sub>20</sub>N<sub>10</sub> (496.53); C 67.73, H 4.00, N 28.21; Found : C 67.79, H 4.06, N 28.26.

2-(2-Furyl)-7-[6-(*p*-tolyl)pyridazin-3-yl]-pyrazolo[3,4-*d*]-1,2,4-triazolo[5,1-*f*]pyrimidine-9-carbonitrile (**12a**).

Yield: 46 %; beige solid, mp 230 °C (from dioxane); IR  $\nu$  max  $\text{cm}^{-1}$ : 3089, 2918, 2229, 1633.  $^1\text{H-NMR}$   $\delta$ : 2.35 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 7.07 (m, 1H, furyl), 7.31 (m, 2H-tolyl+1H-furyl), 8.09 (d, 2H, H2, H6-tolyl, *J* = 8.0 Hz), 8.15 (m, 1H, furyl), 8.28 (d, 1H, H5-pyridazine, *J* = 9.1 Hz), 8.45 (d, 1H, H4-pyridazine, *J* = 9.1 Hz), 8.70 (s, 1H, pyrimidine); MS *m/z* (%): M<sup>+</sup> 419 (100), 393 (60), 352 (45); Anal. Calc. for C<sub>22</sub> H<sub>13</sub>N<sub>9</sub>O (419.41); C 63.00, H 3.12, N 30.06; Found : C 62.99, H 3.15, N 30.02.

2-(2-Thienyl)-7-[6-(*p*-tolyl)pyridazin-3-yl]-pyrazolo[3,4-*d*]-1,2,4-triazolo[5,1-*f*]pyrimidine-9-carbonitrile (**12b**).

Yield: 40 %; beige solid, mp 262 °C (from dioxane); IR  $\nu$  max  $\text{cm}^{-1}$ : 3104, 2917, 2224, 1630;  $^1\text{H-NMR}$   $\delta$ : 2.35 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 7.38 (m, 1H, thienyl), 7.44 (d, 2H, H3, H5-tolyl, *J* = 8.0 Hz), 7.80 (m, 1H, H-thienyl), 7.92 (m, 1H, thienyl), 8.05 (d, 2H, H2, H6-tolyl, *J* = 8.0 Hz), 8.15 (d, 1H, H5-pyridazine, *J* = 9.1 Hz), 8.45 (d, 2H, H4-pyridazine, *J* = 9.1 Hz), 8.70 (s, 1H, pyrimidine); MS *m/z* (%): M<sup>+</sup> 435 (91), 409 (100), 352 (70); Anal. Calc. for C<sub>22</sub> H<sub>13</sub>N<sub>9</sub>S (435.47): C 60.68, H 3.01, N 28.95, S 7.36; Found : C 60.59, H 3.08, N 28.91, S 7.33.

2-(4-Pyridyl)-7-[6-(*p*-tolyl)pyridazin-3-yl]-pyrazolo[3,4-*d*]-1,2,4-triazolo[5,1-*f*]pyrimidine-9-carbonitrile (**12c**).

Yield: 70 %; pale brown crystals, mp 320 °C (from EtOH); IR  $\nu$  max  $\text{cm}^{-1}$ : 3090, 2933, 2228, 1635;  $^1\text{H-NMR}$   $\delta$ : 2.44 (d, 3H, *p*-CH<sub>3</sub>-tolyl), 7.31 (d, 2H, H3, H5-tolyl, *J* = 8.0 Hz), 7.72 (d, 2H, pyridyl, *J* = 8.0 Hz), 8.06 (d, 2H, H2, H6-tolyl, *J* = 8.4 Hz), 8.13(d, 1H, H5-pyridazine, *J* = 9.1 Hz), 8.52 (d, 1H, H4-pyridazine, *J* = 9.1 Hz), 8.62 (s, 1H, pyrimidine), 8.75 (d, 2H, pyridyl *J* = 8.0 Hz); MS *m/z* (%): M<sup>+</sup> 430 (100), 404 (78), 352 (60); Anal. Calc. for C<sub>23</sub> H<sub>14</sub>N<sub>10</sub> (430.43): C 64.18, H 3.28, N 32.54; Found : C 64.22, H 3.20, N 32.55.

*General Procedure for the Preparation of 3-Substituted-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine-4(5H)-ones (13a-c).*

Compound **3a-c** (5 mmol) was added to formic acid (5 mL, 85%) and the mixture was refluxed for 6h. The solid that precipitated was collected and recrystallized.

*3-Methylthio-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine-4(5H)-one (13a).*

Yield: 62 %; colorless needle-like crystals, mp 244 °C (from EtOH); IR v max cm<sup>-1</sup>: 3381 (NH), 1658 (CO); <sup>1</sup>H-NMR δ: 2.44 (s, 3H, S-CH<sub>3</sub>), 2.60 (s, 3H, p-CH<sub>3</sub>-tolyl), 7.42 (d, 2H, H3, H5-tolyl, J = 8.0 Hz), 8.00 (d, 2H, H2, H6-tolyl, J = 8.0 Hz), 8.14 (d, 1H, H5-pyridazine, J = 9.1 Hz), 8.35 (d, 1H, H4-pyridazine, J = 9.1 Hz), 8.53 (s, 1H, pyrimidine), 11.16 (s, 1H, NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C-NMR δ: 14 (S-CH<sub>3</sub>), 20 (p-CH<sub>3</sub>-tolyl), 114–158 (aromatic), 131 (C-S-CH<sub>3</sub>), 163 (CO, pyrimidine); MS m/z (%): M<sup>+</sup> 350 (72), 323 (100), 275 (96), 129 (84); Anal. Calc. for C<sub>17</sub>H<sub>14</sub>N<sub>6</sub>OS (350.39): C 58.27, H 4.03, N 23.98, S 9.15; Found: C 57.95, H 4.14, N 24.02, S 9.20.

*3-N-Phenylamino-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine-4(5H)-one (13b).*

Yield: 34 %; colorless needle-like crystals, mp >320 °C (from EtOH); IR v max cm<sup>-1</sup>: 3337, 3265 (2NH), 1660 (CO); <sup>1</sup>H-NMR δ: 2.60 (s, 3H, p-CH<sub>3</sub>-tolyl), 6.88 (t, 1H, H4-Ph, J = 7.4 Hz), 7.22 (d, 2H, H3, H5-tolyl, J = 8.0 Hz), 7.51 (t, 2H, H3, H5-Ph, J = 7.6 Hz) 8.01 (m, 2H+ 2H, H-tolyl + H-phenyl), 8.24 (d, 1H, H5-pyridazine, J = 9.1 Hz), 8.33 (s, 1H, NH, D<sub>2</sub>O exchangeable) 8.48 (d, 1H, H4-pyridazine, J = 9.1 Hz), 8.60 (s, 1H, pyrimidine), 11.09 (s, 1H, NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C-NMR (DMSO) δ: 15 (p-CH<sub>3</sub>-tolyl), 117-158 (aromatic), 131 (C-S-CH<sub>3</sub>), 169 (CO pyrimidine); MS m/z (%): M<sup>+</sup> 395 (100), 323 (85), 292 (75); Anal. Calc. for C<sub>22</sub>H<sub>17</sub>N<sub>7</sub>O (395.42): C 66.83, H 4.33, N 24.80; Found: C 66.81, H 4.34, N 24.78.

*4(5H)-Oxo-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine-3-carbonitrile (13c).*

Yield: 55 %; colorless needle-like crystals, mp >320 °C (from dioxane); IR v max cm<sup>-1</sup>: 3367 (NH), 1645 (CO); <sup>1</sup>H-NMR δ: 2.63 (s, 3H, p-CH<sub>3</sub>-tolyl), 7.38 (d, 2H, H3, H5-tolyl, J = 8.0 Hz), 8.16 (d, 2H, H2, H6-tolyl, J = 8.0 Hz), 8.22 (d, 1H, H5-pyridazine, J = 9.1 Hz), 8.40 (d, 1H, H4-pyridazine, J = 8.0 Hz), 8.65 (s, 1H, pyrimidine), 12.50 (s, 1H, NH, D<sub>2</sub>O exchangeable); <sup>13</sup>C-NMR (DMSO) δ: 13 (p-CH<sub>3</sub>-tolyl), 84 (CN), (115–157 aromatic), (168, CO), pyrimidine]; MS m/z (%): M<sup>+</sup> 329(90), 303(100), 271(81); Anal. Calc. for C<sub>17</sub>H<sub>11</sub>N<sub>7</sub>O (329.39): C 62.00, H 3.37, N 29.77; Found: C 62.01, H 3.40, N 29.74.

*General procedure for the Preparation of 3-Substituted-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dithiones (14a-c).*

To a solution of **3a-c** (10 mmol) in DMF (20 mL), carbon disulfide (10 mL, 15 mmol) and 10 mL sodium methoxide (prepared from 0.59g of sodium metal and 30 mL methanol) were added. The mixture was refluxed for 15h, and then poured into ice cold water. A solution of sodium hydroxide (10 mL, 1M) was added to it and left overnight. The solution was filtered and acidified with dilute acetic acid to give a yellow precipitate. It was collected, washed with dilute acetic acid, dried and recrystallized from ethanol.

*3-Methylthio-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dithione (14a).*

Yield: 50 %; yellow needle crystals, mp 269°C; IR  $\nu$  max  $\text{cm}^{-1}$ : 3344, 3320 (2NH);  $^1\text{H-NMR}$   $\delta$ : 2.45 (s, 3H, S-CH<sub>3</sub>), 2.62 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 7.50 (d, 2H, H3, H5-tolyl,  $J = 8.0$  Hz), 8.14 (d, 2H, H2, H6-tolyl,  $J = 8.0$  Hz), 8.21 (d, 1H, H5-pyridazine,  $J = 9.1$  Hz), 8.52 (d, 1H, H4-pyridazine,  $J = 9.1$  Hz), 8.70 (s, 1H, NH, D<sub>2</sub>O exchangeable), 8.90 (s, 1H, NH, D<sub>2</sub>O exchangeable); MS  $m/z$  (%): M<sup>+</sup> 398 (72), 372 (100), 325 (96); Anal. Calc. for C<sub>17</sub>H<sub>14</sub>N<sub>6</sub>S<sub>3</sub> (398.52): C 51.24, H 3.54, N 21.09, S 24.13; Found: 50.97, H 3.29, N 21.10, S 24.12.

*3-N-Phenylamino-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine-4,6(5H,7H)-dithione (14b).*

Yield: 35 %; yellow solid, mp 260 °C; IR  $\nu$  max  $\text{cm}^{-1}$ : 3376 - 3265 (3NH);  $^1\text{H-NMR}$   $\delta$ : 2.52 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 6.90 (t, 1H, H4-Ph,  $J = 7.4$  Hz), 7.16 (d, 2H, H3, H5-tolyl,  $J = 8.0$  Hz), 7.52 (t, 2H, H3, H5-Ph,  $J = 7.6$  Hz) 8.00 (m, 2H+ 2H, tolyl + H-phenyl), 8.14 (d, 1H, H5-pyridazine,  $J = 9.1$  Hz), 8.36 (s, 1H, NH, D<sub>2</sub>O exchangeable) 8.50 (d, 1H, H4-pyridazine,  $J = 9.1$  Hz), 9.04 (s, 1H, NH, D<sub>2</sub>O exchangeable), 9.77 (s, 1H, NH, D<sub>2</sub>O exchangeable); MS  $m/z$  (%): M<sup>+</sup> 443(100), 340(95), 308(81); Anal. Calc. for C<sub>22</sub> H<sub>17</sub>N<sub>7</sub>S<sub>2</sub> (443.54); C 59.58, H 3.86, N 22.11, S 14.46; Found: C 59.57, H 3.90, N 21.97, S 14.46.

*1-[6-(p-tolyl)pyridazin-3-yl]-4,6-Dithioxo-4,5,6,7-tetrahydropyrazolo[3,4-d]pyrimidine-3-carbonitrile (14c).*

Yield: 32 %; yellow solid, mp 239 °C; IR  $\nu$  max  $\text{cm}^{-1}$ : 3340- 3300 (2NH), 2220 (CN);  $^1\text{H-NMR}$   $\delta$ : 2.62 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 7.10 (d, 2H, H3, H5-tolyl,  $J = 8.0$  Hz), 7.81 (d, 2H, H2, H6-tolyl,  $J = 8.0$  Hz), 8.06 (d, 1H, H5-pyridazine,  $J = 9.1$  Hz), 8.42 (d, 1H, H4-pyridazine,  $J = 9.1$  Hz), 9.27 (s, 1H, NH, D<sub>2</sub>O exchangeable), 10.00 (s, 1H, NH, D<sub>2</sub>O exchangeable); MS  $m/z$  (%): M<sup>+</sup> 377 (100), 351 (98), 325 (75); Anal. Calc. for C<sub>17</sub> H<sub>11</sub>N<sub>7</sub>S<sub>2</sub> (377.44); C 54.10, H 2.94, N 25.98, S 16.99; Found: C 53.88, H 3.03, N 26.07, S 17.07.

*General Procedure for the Preparation of 4-Imino-5-phenyl-3-substituted-1-[6-(p-tolyl)pyridazin-3-yl]-4,5-dihydropyrazolo[3,4-d]-pyrimidine-6(7H)-thiones/ones (15-17).*

A mixture of **3a-c** (10 mmol) and phenylisocyanate or phenylisothiocyanate (10 mmol) in pyridine (20 mL) was refluxed for 5h. The reaction mixture was cooled and poured onto ice/water and neutralized with diluted HCl. The solid product so formed was collected by filtration and recrystallized from ethanol.

*4-Imino-5-phenyl-3-methylthio-1-[6-(p-tolyl)pyridazin-3-yl]-4,5-dihydropyrazolo[3,4-d]-pyrimidine-6(7H)-one (15a).*

Yield: 90 %; white solid, mp 229 °C; IR  $\nu$  max  $\text{cm}^{-1}$ : 3395, 3326 (2NH), 1649 (CO);  $^1\text{H-NMR}$   $\delta$ : 2.44 (s, 3H, S-CH<sub>3</sub>), 2.56 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 6.65 (t, 1H, phenyl,  $J = 6.6$  Hz), 7.00 (d, 2H, H3, H5-tolyl,  $J = 8.0$  Hz), 7.50 (m, 2H+ 2H, H-phenyl + H-tolyl), 7.81 (m, 2H + 2H, H-tolyl +H-phenyl), 8.06 (d, 1H, H5- pyridazine,  $J = 9.1\text{Hz}$ ), 8.32 (d, 1H, H4-pyridazine,  $J = 9.1\text{Hz}$ ), 8.80 (bs, 1H, NH, D<sub>2</sub>O exchangeable), 9.05 (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS  $m/z$  (%): M<sup>+</sup> 441 (90), 426 (100), 365 (42); Anal. Calc. for C<sub>23</sub>H<sub>19</sub>N<sub>7</sub>OS (441.50): C 62.57, H 4.34, N 22.21, S 7.26; Found: C 62.55, H 4.33, N 22.20, S 7.17.

*4-Imino-5-phenyl-3-methylthio-1-[6-(p-tolyl)pyridazin-3-yl]-4,5-dihydropyrazolo-[3,4-d]-pyrimidine-6(7H)-thione (15b).*

Yield: 79 %; beige solid, mp 275-276 °C; IR  $\nu$  max  $\text{cm}^{-1}$ : 3389-3279 (2NH);  $^1\text{H-NMR}$   $\delta$ : 2.36 (s, 3H, S-CH<sub>3</sub>), 2.60 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 6.77 (t,1H,phenyl.  $J = 6.6$  Hz), 7.00 (m, 2H, phenyl + tolyl), 7.44 (m, 2H+ 2H, phenyl + tolyl), 8.22 (d, 2H, H5-pyridazine,  $J = 9.1\text{Hz}$ ), 8.42 (bs, 1H, NH, D<sub>2</sub>O exchangeable), 8.53 (d, 1H, H4-pyridazine,  $J = 9.1\text{Hz}$ ), 9.33 (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS  $m/z$  (%): M<sup>+</sup> 457 (100), 365 (76), 318 (39); Anal. Calc. for C<sub>23</sub>H<sub>19</sub>N<sub>7</sub>S<sub>2</sub> (457.57): C 60.37, H 4.19, N 21.43, S 14.01; Found: C 60.35, H 4.10, N 21.26, S 13.98.

*4-Imino-5-phenyl-3-N-phenylamino-1-[6-(p-tolyl)pyridazin-3-yl]-4,5-dihydropyrazolo[3,4-d]pyrimidine-6(7H)-one (16a).*

Yield: 44 %; white solid, mp 255 °C; IR  $\nu$  max  $\text{cm}^{-1}$ : 3380-3210(3NH), 1648 (CO);  $^1\text{H-NMR}$   $\delta$ : 2.51 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 6.90-8.41 (m, 16H, aromatic), 8.55 (bs, 1H, NH, D<sub>2</sub>O exchangeable), 9.09 (bs, 1H, NH, D<sub>2</sub>O exchangeable), 11.08 (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS  $m/z$  (%): M<sup>+</sup> 486 (100), 394 (82), 317 (54); Anal. Calc. for C<sub>28</sub> H<sub>22</sub>N<sub>8</sub>O (486.53): C 69.12, H 4.56, N 23.03; Found: C 69.12, H 4.57, N 23.02.

*4-Imino-5-phenyl-3-N-phenylamino-1-[6-(p-tolyl)pyridazin-3-yl]-4,5-dihydropyrazolo[3,4-d]pyrimidine-6(7H)-thione (16b).*

Yield: 46 %; beige solid, mp 306 °C; IR  $\nu$  max  $\text{cm}^{-1}$ : 3460-3298 (3NH);  $^1\text{H-NMR}$   $\delta$ : 2.45 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 7.00-8.35 (m, 16H, aromatic), 8.60 (bs, 1H, NH, D<sub>2</sub>O exchangeable), 9.18 (bs, 1H, NH, D<sub>2</sub>O exchangeable), 11.13 (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS  $m/z$  (%): M<sup>+</sup> 502 (98), 410 (100),

333 (56); Anal. Calc. for C<sub>28</sub>H<sub>22</sub>N<sub>8</sub>S (502.60): C 66.91, H 4.41, N 22.29, S 6.38; Found: C 66.75, H 4.40, N 22.25, S 6.35.

*4-Imino-5-phenyl-1-[6-(p-tolyl)pyridazin-3-yl]-4,5-dihydro-6(7H)-oxo-pyrazolo[3,4-d]-pyrimidine-3-carbonitrile (17a).*

Yield: 43 %; beige solid, mp >320 °C; IR v max cm<sup>-1</sup>: 3368-3307 (2NH), 2247 (CN); <sup>1</sup>H-NMR δ: 2.42 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 6.80 (t, 1H, phenyl, *J* = 6.6 Hz), 7.33-7.50 (m, 6H, phenyl + tolyl), 7.80 (d, 2H, H2, H6-tolyl, *J* = 8.0 Hz), 8.06 (d, 1H, H5-pyridazine, *J* = 9.1 Hz), 8.38 (d, 1H, H4-pyridazine, *J* = 9.1 Hz), 8.80 (bs, 1H, NH, D<sub>2</sub>O exchangeable), 11.07 (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS m/z (%): M<sup>+</sup> 420 (100), 394 (68), 333 (66); Anal. Calc. for C<sub>23</sub>H<sub>16</sub>N<sub>8</sub>O (420.43): C 65.71, H 3.84, N 26.65; Found: C 65.71, H 3.97, N 26.61.

*4-Imino-5-phenyl-3-carbonitrile-1-[6-(p-tolyl)pyridazin-3-yl]-4,5-dihydropyrazolo-[3,4-d]-pyrimidine-6(7H)-thione (17b).*

Yield: 42 %; yellow solid, mp >320 °C; IR v max cm<sup>-1</sup>: 3343-3222 (2NH), 2247(CN); <sup>1</sup>H-NMR δ: 2.44 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 7.10 (t, 1H, phenyl, *J* = 6.6 Hz), 7.23-7.40 (m, 6H, phenyl + tolyl), 7.85 (d, 2H, H2, H6-tolyl, *J* = 8.0 Hz), 8.03 (d, 1H, pyridazine, *J* = 9.1 Hz), 8.36 (d, 1H, pyridazine, *J* = 9.1 Hz), 8.60 (bs, 1H, NH, D<sub>2</sub>O exchangeable), 11.13 (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS m/z (%): M<sup>+</sup> 436 (92), 369 (100), 353 (34); Anal. Calc. for C<sub>23</sub>H<sub>16</sub>N<sub>8</sub>S (436.49): C 63.29, H 3.69, N 25.67, S 7.34; Found: C 63.16, H 3.66, N 25.68, S 7.33.

*General Procedure for the Preparation of 4-Amino-3-substituted-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine-6-ones/thiones/amines (18-20).*

Compound **3a-c** (5 mmol) and urea (10 mmol) or thiourea (10 mmol) or guanidine carbonate (5 mmol) were mixed in a mortar, The mixture was then heated at 180 °C in an oil bath for 20 minutes, heating was continued 2h, at the melting point of the pyrazole derivatives using reduced pressure. The molten product was boiled 10 minutes with water, cooled and filtered. The product was finally recrystallized from a suitable solvent.

*4-Amino-3-methylthio-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine-6(7H)-one (18a).*

Yield: 54 %; white solid, mp 275 °C (from dioxane); IR v max cm<sup>-1</sup>: 3466-3206 (NH<sub>2</sub>/NH), 1685 (CO); <sup>1</sup>H-NMR δ: 2.42 (s, 3H, S-CH<sub>3</sub>), 2.50 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 7.35 (d, 2H, H3, H5-tolyl, *J* = 8.0 Hz), 7.70 (d, 2H, H2, H6-tolyl, *J* = 8.0 Hz), 8.12 (bs, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 8.38 (d, 1H, H5-pyridazine, *J* = 9.1 Hz), 8.55 (d, 1H, H4-pyridazine, *J* = 9.1 Hz), 11.02, (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS m/z (%): M<sup>+</sup> 365 (100), 316 (87), 318 (56); Anal. Calc. for C<sub>17</sub>H<sub>15</sub>N<sub>7</sub>OS (365.41): C 55.88, H 4.14, N 26.83, S 8.77; Found: C 55.87, H 4.08, N 26.90, S 8.75.

*4-Amino-3-methylthio-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine-6(7H)-thione (18b).*

Yield: 63 %; yellow solid, mp >320 °C (from DMF/H<sub>2</sub>O); IR v max cm<sup>-1</sup>: 3402-3180, (NH<sub>2</sub>/NH); <sup>1</sup>H-NMR δ: 2.54 (s, 3H, S-CH<sub>3</sub>), 2.62 (s, 3H, p-CH<sub>3</sub>-tolyl), 7.22 (d, 2H, H3, H5-tolyl, J = 8.0 Hz), 7.64 (d, 2H, H2, H6-tolyl, J = 8.0 Hz), 7.81 (bs, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 8.08 (d, 2H, H5-pyridazine), 8.54 (d, 1H, H4-pyridazine, J = 9.1 Hz), 9.06 (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS m/z (%): M<sup>+</sup> 381 (93), 365 (100), 334 (39); Anal. Calc. for C<sub>17</sub> H<sub>15</sub>N<sub>7</sub>S<sub>2</sub> (381.47): C 53.53, H 3.96, N 25.70, S 16.81; Found: C 53.53, H 4.02, N 25.70, S 16.79.

*4,6-Diamino-3-methylthio-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine (18c).*

Yield: 46 % yield; brown solid, mp 266 °C (from DMF/H<sub>2</sub>O); IR v max cm<sup>-1</sup>: 3410-3254 (2NH<sub>2</sub>); <sup>1</sup>H NMR δ: 2.53 (s, 3H, S-CH<sub>3</sub>), 2.60 (s, 3H, p-CH<sub>3</sub>-tolyl), 7.04 (d, 2H, H3, H5-tolyl, J = 8.0 Hz), 7.44 (d, 2H, H2, H6-tolyl, J = 8.0 Hz), 7.70 (bs, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 8.22 (d, 2H, H5-pyridazine, J = 9.1 Hz), 8.41 (bs, 1H, NH, D<sub>2</sub>O exchangeable), 8.66 (d, 1H, H4-pyridazine, J = 9.1 Hz). MS: m/z (%); M<sup>+</sup> 364(100), 348(56), 301(48); Anal. Calc. for C<sub>17</sub> H<sub>16</sub>N<sub>8</sub>S (364.43): C 56.03, H 4.43, N 30.75, S 8.80; Found: C 56.00, H 4.41, N 30.72, S 8.79.

*4-Amino-3-N-phenylamino-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine-6(7H)-one (19a).*

Yield: 43 %; white solid, mp 270 °C (from DMF/H<sub>2</sub>O); IR v max cm<sup>-1</sup>: 3411-3160 (NH<sub>2</sub>/2NH), 1675 (CO); <sup>1</sup>H-NMR δ: 2.53 (s, 3H, p-CH<sub>3</sub>-tolyl), 6.74(t, 1H, H4-phenyl, J = 7.4 Hz), 7.22 (m, 4H, H3, H5-phenyl+H3, H5-tolyl), 7.77 (t, 2H, H2, H6-phenyl, J = 7.9 Hz), 8.00(d, 2H, H2, H6-tolyl, J = 8.0 Hz), 8.15 (bs, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 8.33 (d, 1H, H5-pyridazine, J = 9.1 Hz), 8.54 (d, 2H, H4-pyridazine, J = 9.1 Hz), 12.36 (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS m/z (%): M<sup>+</sup> 410 (95), 394 (100), 318 (74); Anal. Calc. for C<sub>22</sub>H<sub>18</sub>N<sub>8</sub>O (410.43): C 64.38, H 4.42, N 27.30; Found: C 64.36, H 4.46, N 27.30.

*4-Amino-3-N-phenylamino-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine-6(7H)-thione (19b).*

Yield: 44 % yield; yellow solid, mp 276 °C (from EtOH); IR v max cm<sup>-1</sup>: 3411-3160 (NH<sub>2</sub>/2NH); <sup>1</sup>H-NMR δ: 2.54 (s, 3H, p-CH<sub>3</sub>-tolyl), 6.90(t, 1H, H4-phenyl, J = 7.4 Hz), 7.20 (m, 4H, H3, H5-phenyl+ H3, H5-tolyl), 7.66 (m, 4H, H2, H6-phenyl +H2, H6-tolyl), 8.09 (bs, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 8.26 (d, 1H, H5-pyridazine, J = 9.1 Hz), 8.40 (d, 1H, H4-pyridazine, J = 9.1 Hz), 11.45 (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS m/z (%): M<sup>+</sup> 426 (95), 334 (100), 318 (64); Anal. Calc. for C<sub>22</sub> H<sub>18</sub>N<sub>8</sub>S (426.50); C 61.96, H 4.25, N 26.27, S 7.52; Found: C 62.01, H 4.33, N 26.25, S 7.50.



*4,6-Diamino-3-N-phenylamino-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]-pyrimidine (19c).*

Yield: 52 %; yellow solid, mp >320 °C (from dioxane); IR  $\nu$  max  $\text{cm}^{-1}$ : 3397 -3110 (2NH<sub>2</sub>/NH); <sup>1</sup>H-NMR  $\delta$ : 2.61 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 6.80 (t, 1H, H4-phenyl, *J* = 7.4 Hz), 7.22 (m, 4H, H3, H5-phenyl + H3, H5-tolyl), 7.45 (bs, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable) 7.60 (m, 4H, H2, H6-phenyl + H2, H6-tolyl), 7.90 (bs, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 8.26 (d, 2H, H5-pyridazine, *J* = 9.1Hz), 8.50 (bs, 1H, NH, D<sub>2</sub>O exchangeable), 8.63 (d, 1H, H4''-pyridazine, *J* = 9.1Hz); MS *m/z* (%): M<sup>+</sup> 409 (100), 317 (80), 301 (91); Anal. Calc. for C<sub>22</sub>H<sub>19</sub>N<sub>9</sub> (409.45); C 64.54, H 4.68, N 30.79; Found: C 64.54, H 4.70, N 30.91.

*4-Amino-3-carbonitrile-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]pyrimidine-6(7H)-one (20a).*

Yield: 35 % yield; beige solid, mp >320 °C (from EtOH); IR  $\nu$  max  $\text{cm}^{-1}$ : 3421-3368 (NH<sub>2</sub>/NH), 2221 (CN), 1669 (CO); <sup>1</sup>H-NMR  $\delta$ : 2.50 (s, 3H, S-CH<sub>3</sub>), 2.63 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 7.24 (d, 2H, H3, H5-tolyl, *J* = 8.0 Hz), 7.56 (d, 2H, H2, H6-tolyl, *J* = 8.0 Hz), 8.03 (bs, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 8.28 (d, 1H, H5-pyridazine, *J* = 9.1Hz), 8.40 (d, 1H, H4-pyridazine, *J* = 9.1Hz), 12.00 (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS *m/z* (%): M<sup>+</sup> 344 (95), 328 (100), 318 (62); Anal. Calc. for C<sub>17</sub>H<sub>12</sub>N<sub>8</sub>O (344.33): C 59.30, H 3.51, N 32.51; Found: C 59.29, H 3.46, N 32.50.

*4-Amino-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d]-6(7H)-thioxopyrimidine-3-carbonitrile (20b).*

Yield: 38 %; yellow solid, mp 280 °C (from EtOH); IR  $\nu$  max  $\text{cm}^{-1}$ : 3399-3260 (NH<sub>2</sub>/NH), 2234 (CN); <sup>1</sup>H-NMR  $\delta$ : 2.45 (s, 3H, S-CH<sub>3</sub>), 2.61 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 7.06 (d, 2H, H3, H5-tolyl, *J* = 8.0 Hz), 7.47 (d, 2H, H2, H6-tolyl, *J* = 8.0 Hz), 7.55 (bs, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 8.20 (d, 2H, H5-pyridazine, *J* = 9.1 Hz), 8.43 (d, 1H, H4-pyridazine, *J* = 9.1 Hz), 9.06 (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS *m/z* (%): M<sup>+</sup> 360 (92), 344 (100), 318 (39); Anal. Calc. for C<sub>17</sub>H<sub>12</sub>N<sub>8</sub>S (360.40): C 56.66, H 3.36, N 31.09, S 8.90; Found: C 56.90, H 3.42, N 30.99, S 8.79.

*4,6-Diamino-3-carbonitrile-1-[6-(p-tolyl)pyridazin-3-yl]-pyrazolo[3,4-d] pyrimidine (20c).*

Yield: 42 %; beige solid, mp >320 °C (from DMF/H<sub>2</sub>O); IR  $\nu$  max  $\text{cm}^{-1}$ : 3411-3270 (2 x NH<sub>2</sub>), 2218 (CN); <sup>1</sup>H-NMR  $\delta$ : 2.44 (s, 3H, S-CH<sub>3</sub>), 2.61 (s, 3H, *p*-CH<sub>3</sub>-tolyl), 7.38 (d, 2H, H3, H5-tolyl, *J* = 8.0 Hz), 7.53 (d, 2H, H2, H6-tolyl, *J* = 8.0 Hz), 8.05 (bs, 2H, NH<sub>2</sub>, D<sub>2</sub>O exchangeable), 8.22 (d, 1H, H5-pyridazine, *J* = 9.1Hz), 8.53 (d, 1H, H4-pyridazine, *J* = 9.1Hz), 8.64 (bs, 1H, NH, D<sub>2</sub>O exchangeable); MS *m/z* (%): M<sup>+</sup> 343 (87), 311 (100), 285 (55); Anal. Calc. for C<sub>17</sub> H<sub>13</sub> N<sub>9</sub> (343.35): C 59.47, H 3.82, N 36.71; Found: C 59.49, H 3.80, N 36.71.

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*Sample availability:* Not available