Transformations of 3-aminopyridazines. Synthesis of 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazine and 1-(substituted pyridazin-3-yl)-1*H*-1,2,3-triazole derivatives

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Dedicated to Professor Albert Padwa, Emory University, Atlanta, GA, USA, on the occasion of his 65th birthday

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Abstract
Methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)propenoate **(1)** was treated with various 3-aminopyridazine derivatives **(2a–g)** to give the corresponding substituted 3-benzyloxycarbonyl-4-oxo-4*H*-pyrimido[1,2-*b*]pyridazines **(3a–g)**. Deprotection of the amino group gave the free amine hydrobromides **4d,e,g**. Diazotisation of the amines **4a,e** furnished substituted 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazine-3-diazonium tetrafluoro-borates **(5a,e)**. Heating of the diazonium salts **5a,e** in primary alkanols at 50–80° resulted in 'ring switching' transformation into 1-(substituted pyridazin-3-yl)-1*H*-1,2,3-triazoles **(8–16)**, while heating of **5a,e** in 2-propanol afforded the 3-unsubstituted 4*H*-pyrimido[1,2-*b*]pyridazin-4-ones **17a,e**.

Keywords: 3-(Dimethylamino)propenoates, aminopyridazines, 4*H*-pyrimido[1,2-*b*]pyridazin-4-ones, 1,2,3-triazoles, diazonium salts

Introduction

The pyridazines,[1] 1,2,3-triazoles,[2] and 4*H*-azino[1,2-*x*]pyrimidin-4-ones[3] are important and significant classes of heterocyclic compounds. In contrast to other nitrogen heterocycles such as pyrroles, imidazoles, pyridines, and pyrazines, the pyridazines and 1,2,3-triazoles have seldom been found in nature as constituents of natural products. A number of their derivatives have, however, found diverse uses in synthetic, analytical, medicinal, pharmaceutical, agrochemical, and photographic chemistry, and in other applications as corrosion inhibitors, photostabilizers, dyestuffs and fluorescent whiteners, and asymmetric dihydroxylation catalysts (Figure 1).[1,2]

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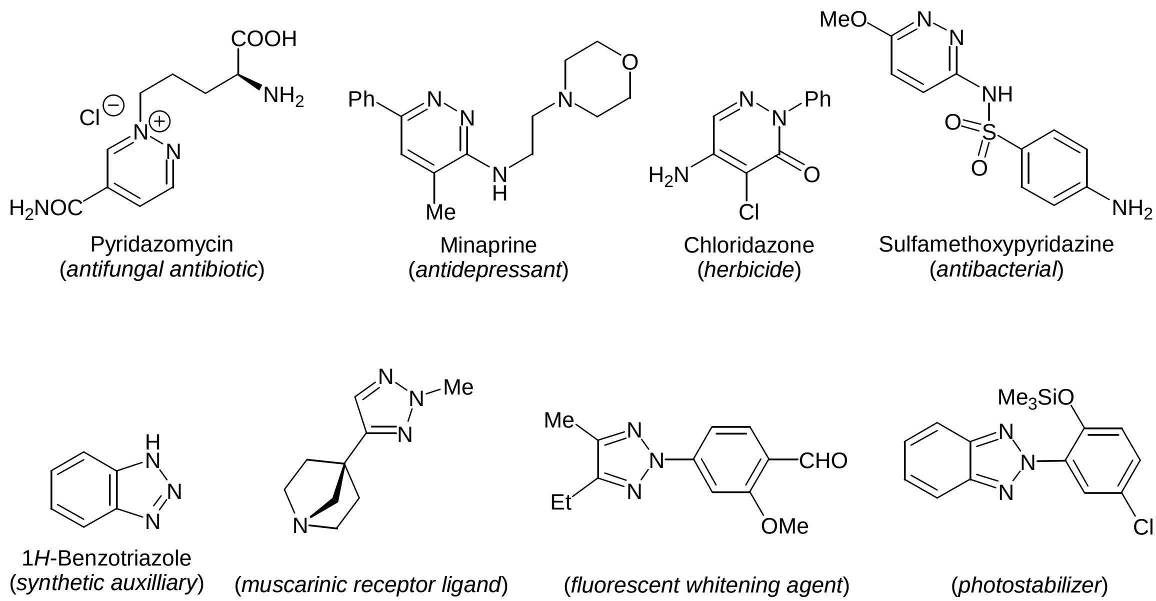


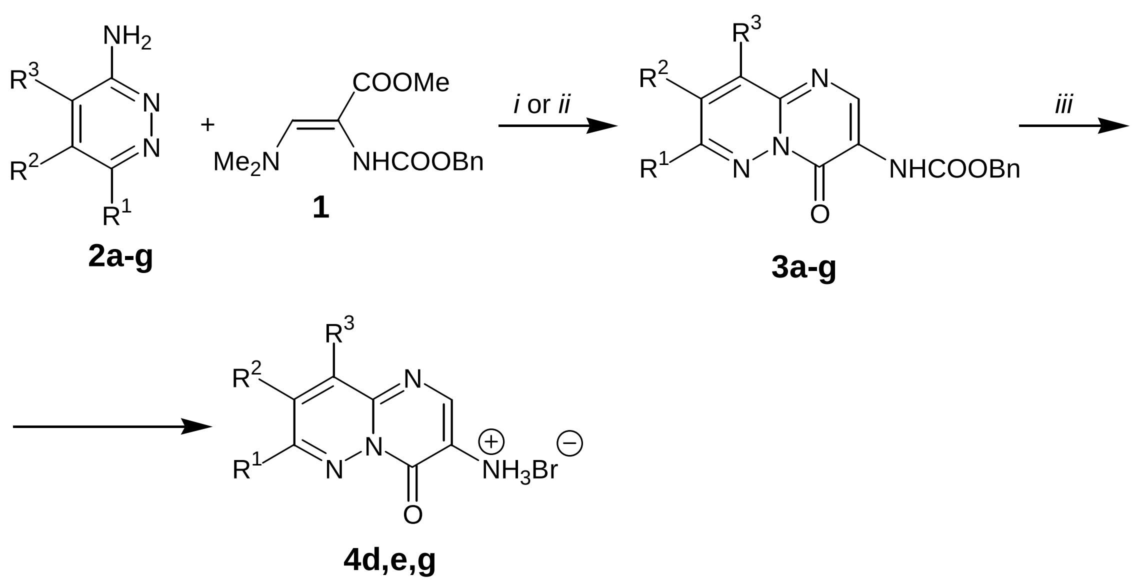
Figure 1

On the other hand, alkyl 2-substituted 3-(dimethylamino)propenoates have proved to be easily available and efficient reagents for the preparation of various heterocyclic systems.[4] For example, acid-catalyzed reactions of alkyl 2-acylamino-3-(dimethylamino)propenoates with various *o*-aminoazines and *o*-aminoazoles leads to the corresponding alkyl *N*-acyl-2,3-dehydro-3-heteroarylalaninates and azino- and azolo- fused 3-acylamino-4*H*-pyrimidin-4-ones. Deprotection of the 3-acylamino group gives free amines, usually in good yields. Similarly, 3-amino-4*H*-quinolizin-4-ones have been prepared from alkyl 2-acylamino-3-(dimethylamino)propenoates and 2-pyridinylacetic acid derivatives.[4–6] Nitrosation of such heteroarylamines gives the corresponding heteroaryldiazonium salts, which are suitable precursors for further transformations.[7,8] In this manner, methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)propenoate (**1**) has been transformed in three steps into 1-substituted 4-oxo-4*H*-quinolizine- and 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-diazonium tetrafluoroborates. Heating of 4-oxo-4*H*-quinolizine-3-diazonium salts in primary alkanols resulted in aza Wolff rearrangements to give the corresponding alkyl indolizine-3-carboxylates,[7] while 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-diazonium tetrafluoroborates underwent, under the same reaction conditions, a 'ring switching' transformation to afford the corresponding alkyl 1-(4-substituted pyridin-2-yl)-1*H*-1,2,3-triazole-4-carboxylates.[8]

Owing to the extensive use of pyridazine- and 1,2,3-triazole- derivatives in various applications, it seemed reasonable to focus our studies in this field also on synthesis and transformations of 3-amino-4*H*-pyrimido[1,2-*b*]pyridazin-4-ones. In this paper, we report the preparation of 3-benzyloxycarbonylamino-4-oxo-4*H*-pyrimido[1,2-*b*]pyridazine derivatives **3a–g**, 3-amino-4-oxo-4*H*-pyrimido[1,2-*b*]pyridazines hydrobromides **4d,e,g**, 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazine-3-diazonium tetrafluoroborates **5a,e**, and 'ring switching' transformations of diazonium salts **5a,e** into alkyl 1-(substituted pyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylates **8–16**.

Results and Discussion

The starting compound, methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)-propenoate (**1**), was prepared from *N*-(benzyloxycarbonyl)glycine according to the procedure described previously.[5] Treatment of the propenoate **1** with 3-aminopyridazines (**2a–g**) in refluxing acetic acid in the presence of 1 equivalent of sodium acetate furnished the corresponding 3-benzyloxycarbonylamino-4-oxo-4*H*-pyrimido[1,2-*b*]pyridazines (**3a–g**) in 19–93% yields. 3-Benzyloxycarbonylamino-4-oxo-4*H*-pyrimido[1,2-*b*]-pyridazine (**3a**) and 3-benzyloxycarbonylamino-7-chloro-4-oxo-4*H*-pyrimido[1,2-*b*]pyridazine (**3d**) have been prepared previously in 93 and 50% yield, respectively, by treatment of **1** with the corresponding pyridazinylamines **2a** and **2d** in refluxing acetic acid.[6] It has to be pointed out that, in most cases, the presence of 1 equivalent of sodium acetate was necessary in order to obtain the desired products **3a–g** in satisfactory yields. An example is the reaction of **1** with 3-amino-6-phenylpyridazine (**2e**) in refluxing acetic acid which gave 3-benzyloxycarbonylamino-7-phenyl-4*H*-pyrimido[1,2-*b*]pyridazin-4-one (**3e**) in only 10% yield, while in the presence of sodium acetate **3e** was obtained in 93% yield. Treatment of compounds **3d,e,g** with 33% HBr in acetic acid afforded the 3-amino-4*H*-pyrimido[1,2-*b*]pyridazin-4-ones **4d,e,g** in 92–99% yields (Scheme 1).

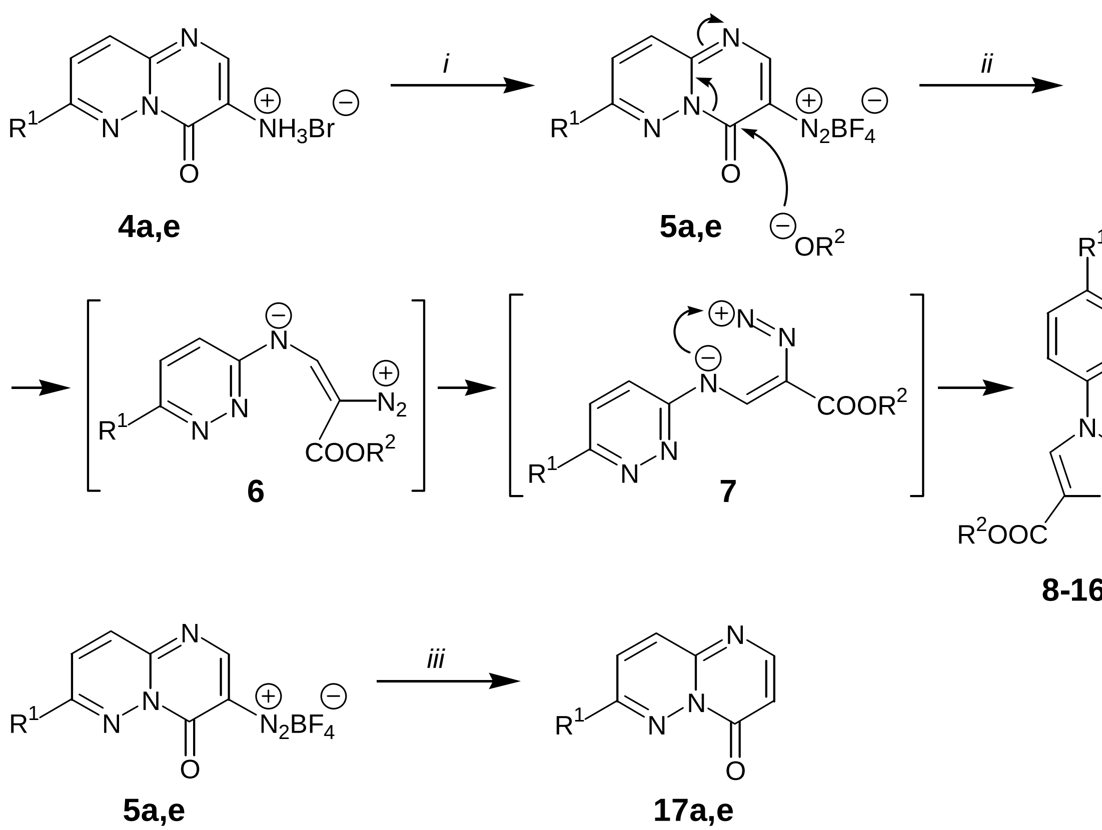


Compound	R^1	R^2	R^3	Yield [%]	
				3	4
2a, 3a	H	H	H	79	
2b, 3b	OH	H	H	19	
2c, 3c	Cl	H	Me	72	
2d, 3d, 4d	Cl	H	H	59	99
2e, 3e, 4e	Ph	H	H	93	98
2f, 3f	Ph	Ph	CN	39	
2g, 3g, 4g	Me	H	H	69	92

Scheme 1. (*i*) AcOH, AcONa, reflux; (*ii*) AcOH, Ac_2O, reflux; (*iii*) 33% HBr in AcOH, r.t.

The primary heteroarylamines **4a,e** were then treated with sodium nitrite in hydrochloric acid at 0–5°C followed by addition of 50% aqueous HBF_4 to afford the 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborates **5a,e** in 70 and 83% yield, respectively. Heating of the diazonium salts **5a,e** in primary alkanols at 50–80°C furnished the corresponding alkyl 1-(substituted pyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylates **8–16** in 23–66% yield. Since the transformation of diazonium salts **5** into triazole-4-carboxylates **8–16** is analogous to the previously reported transformations in the 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine series,[8] it could be explained by a 'ring switching' mechanism *via* opening of the pyrimidone ring by nucleophilic attack of an alkanol to give the intermediate **9**, followed by isomerisation into **10** and ring closure into the alkyl 1-(substituted pyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylates **8–16**. On the other hand, heating of diazonium salts **5a,e** in 2-propanol furnished the de-diazonized compounds, the 3-unsubstituted 4*H*-pyrimido[1,2-*b*]pyridazin-4-ones **17a,e** in 80 and 75% yield, respectively. Similar selective reduction of heteroaryldiazonium salts has been observed previously in the 4*H*-quinolizin-4-one series (Scheme 2).[7]

The structures of compounds **3–5** and **8–17** were determined by spectroscopic methods (NMR, IR, MS) and by analyses for C, H, and N. Spectroscopic data for compounds **3–5** and **8–17** were in agreement with the literature data, reported previously for closely related compounds.[1–9] The 1,2,3-triazoles **8–16** did not give satisfactory elemental analyses, but their identities were confirmed by MS, HRMS, and ^{13}C NMR.



Reaction	R^1	R^2	Yield [%]
5a + MeOH → **8**	H	Me	64
5a + EtOH → **9**	H	Et	30
5a + *n*-PrOH →**10**	H	*n*-Pr	33
5a + *n*-BuOH →**11**	H	*n*-Bu	33
5d + MeOH →**12**	Ph	Me	66
5d + EtOH →**13**	Ph	Et	23
5d + *n*-PrOH →**14**	Ph	*n*-Pr	31
5d + *n*-BuOH →**15**	Ph	*n*-Bu	34
5d + *n*-PeOH →**16**	Ph	*n*-pentyl	34

Scheme 2. (*i*) $NaNO_2$, HCl, H_2O, 0–5°C, then 50% HBF_4 in H_2O. (*ii*) R^2OH (R = Me, Et, *n*-Pr, *n*-Bu, *n*-pentyl, 60–80°C. (*iii*) 2-propanol, reflux.

The formation of the 1*H*-1,2,3-triazole system in compounds **8**–**16** is supported by significant chemical shifts of 5-H in the 1,2,3-triazole residue. Thus, the signal for 5-H appears at 9.30–9.9.32 ppm for the compounds **8**–**11** and at 9.32–9.34 ppm for the compounds **12**–**16**. These chemical shifts are in good agreement with the previously reported values in the 1-(substituted pyridin-2-yl)-1*H*-1,2,3-triazole series, where the signal for 5-H appears between 9.04–9.10 ppm.[8]

The downfield shift of 5-H in the 1-(substituted pyridazin-3-yl)-1*H*-1,2,3-triazoles **8**–**16** with respect to that in the 1-(substituted pyridin-2-yl)-1*H*-1,2,3-triazoles could be explained by the influence of an additional ring nitrogen in the azine moiety.

In conclusion, the condensation of the aminopyridazines **2** with **1** in refluxing acetic acid gives 3-benzyloxycarbonylamino-4-oxo-4*H*-pyrimido[1,2-*b*]pyridazine derivatives **3**, generally in good yields. Deprotection of the amino group in compounds **3** gives 3-amino-4*H*-pyrimido[1,2-*b*]pyridazin-4-ones **4**, which can be transformed into stable 3-diazonium tetrafluoroborates **5**. These react with primary alkanols at elevated temperature to give alkyl 1-(substituted pyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylates **8**–**16** in moderate yields. Heating under reflux of the diazonium salts **5** in 2-propanol results in a dediazonation reaction to afford 3-unsubstituted 4*H*-pyrimido[1,2-*b*]pyridazin-4-ones **17**. Ring-switching synthesis of 1-(α-azinyl)-1*H*-1,2.3-triazoles from 4-oxo-4*H*-azino[1,2-*x*]pyrimidine-3-diazonium salts represents the easiest way for the preparation of 1-(α-azinyl)-1*H*-1,2,3-triazoles, since an alternative route *via* 1,3-dipolar cycloadditions of α-azidoazines to alkynes is not favorable, owing to the well-known azido–tetrazolo isomerism as the major competitive reaction.[9] Thus, three different types of pyridazine containing heterocyclic compounds can be conveniently prepared in this manner: a) 3-[(pyridazin-3-yl)amino]-2,3-dehydroalanine-, b) 3-amino-4*H*-pyrimido[1,2-*b*]pyridazin-4-one-, and c) 1-(pyridazin-3-yl)-1*H*-1,2,3-triazole derivatives. The potential importance of these types of heterocyclic compounds, as well as methods for their preparation, relies on the fact that, despite rare occurrence of pyridazines and 1,2,3-triazoles in nature, compounds containing these two systems have already been widely used in medicinal, pharmaceutical, and industrial applications.

Experimental Section

General Procedures. Melting points were taken with a Kofler micro hot stage. The ^{1}H NMR (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were obtained with a Bruker Avance DPX 300 spectrometer with DMSO-d_6 and $CDCl_3$ as solvents and Me_4Si as internal standard. IR spectra were recorded with a Perkin-Elmer Spectrum BX FTIR spectrophotometer (KBr discs). The mass spectra were recorded with an Autospeck Q (VG-Analytical) spectrometer in the Laboratory for Mass Spectroscopy (Josef Stefan Institute, Ljubljana). The microanalyses for C, H, and N were obtained with a Perkin-Elmer CHN Analyzer 2400. TLC: Merck, Alufolien Kieselgel 60 F 254, 0.2 mm. Column chromatography was performed on silica gel (0.04–0.063 mm). In the case of the 1,2,3-triazoles **8**–**16**, the elemental analysis found values for nitrogen were as much as 2% lower than the calculated values. Such low elemental analysis values found for nitrogen are not uncommon in compounds which lose nitrogen easily upon heating (*e.g*., azides, diazo compounds, 1,2,3-triazoles). Instead of elemental analyses, HRMS and ^{13}C NMR data are given for compounds **8**–**16**.

Materials. All starting materials were commercially available (in most cases from Fluka) and purified following the standard techniques. The following compounds were prepared according to the procedures described in the literature: methyl (*Z*)-2-[(benzyloxycarbonyl)amino]-3-(dimethylamino)propenoate (**1**),[5] 3-aminopyridazine (**2a**) and 3-amino-6-chloropyridazine (**2d**),[10] 3-amino-6-hydroxypyridazine (**2b**),[11] 3-amino-6-chloro-4-methylpyridazine (**2c**),[12] 3-amino-6-phenylpyridazine (**2e**) and 3-amino-6-methylpyridazine (**2g**),[13] 3-amino-4-cyano-5,6-diphenylpyridazine (**2f**),[14] and 3-amino-4*H*-pyrimido[1,2-*b*]pyridazin-4-one (**4a**).[6]

General procedures for the preparation of substituted pyrimido[1,2-*b*]pyridazine-4-ones, 3a–g

Procedure A. A mixture of methyl (*Z*)-2-[(benzyloxycarbonyl)amino]-3-(dimethyl-amino)propenoate (**1**) (0.287 g, 1 mmol), substituted 3-aminopyridazine **2** (1 mmol), and acetic acid (100%, 2.5 mL) was heated at reflux for 1 h. Sodium acetate (0.082 g, 1 mmol) was then added and the mixture was heated at reflux for an additional 4–12 h. Volatile components were evaporated *in vacuo* and the solid residue was triturated with an appropriate solvent. The precipitate was collected by filtration and recrystallized from an appropriate solvent to give **3**.

Procedure B. A mixture of methyl (*Z*)-2-[(benzyloxycarbonyl)amino]-3-(dimethyl-amino)propenoate (**1**) (287 mg, 1 mmol), 3-aminopyridazine **2** (1 mmol), acetic acid (100%, 1.5 mL), and acetic anhydride (1.5 mL) was heated at reflux for 10 h. Volatile components were evaporated *in vacuo*, the solid residue was triturated with ethanol, and the precipitate was collected by filtration to give **3**.

The following compounds were prepared in this manner

3-[(Benzyloxycarbonyl)amino]-4*H*-pyrimido[1,2-*b*]pyridazin-4-one (3a). Prepared from **1** and 3-aminopyridazine (**2a**); Procedure A, reflux for 12 h; yellow crystals. Yield: 59% (0.195 g), lit.[6] yield: 93% (0.276); mp 183–184ºC (from ethanol/toluene), lit.[6] mp 182–184°C (from ethanol–toluene).

3-[(Benzyloxycarbonyl)amino]-7-hydroxy-4*H*-pyrimido[1,2-*b*]-pyridazin-4-one (3b). Prepared from **1** and 3-amino-6-hydroxypyridazine (**2b**); Procedure A, reflux for 12 h; Procedure B, reflux for 10 h; brown crystals. Yield: 8% (0.026 g, Procedure A), 19% (0.059 g, Procedure B), mp 255–257 ºC (from ethanol). IR (cm^{-1}): 3390, 3050, 1680, 1210, 1180. ^{1}H NMR (DMSO-d_6): δ 5.18 (2H, s, CH_2), 7.21 (1H, d, *J* 9.4 Hz, 8-H), 7.32–7.46 (5H, m, Ph), 7.39 (1H, s, 2-H), 7.85 (1H, d, *J* 9.4 Hz, 8-H), 8.68 (1H, s, NH), 8.99 (1H, s, OH). *Anal.* Calcd for $C_{15}H_{12}N_4O_4$ (312.28): C, 57.69; H, 3.87; N, 17.94. Found: C, 57.46; H, 3.79; N, 18.34.

3-[(Benzyloxycarbonyl)amino]-7-chloro-9-methyl-4*H*-pyrimido[1,2-*b*]pyridazin-4-one (3c). Prepared from **1** and 3-amino-6-chloro-4-methylpyridazine (**2c**); Procedure A, reflux for 8 h; yellow crystals. Yield: 72% (0.248 g), mp 210–212ºC (from ethanol/toluene). IR (cm^{-1}): 3230, 1680, 1550, 1480, 1220. ^{1}H NMR (DMSO-d_6): δ 2.51 (d, 3H, *J* 1.1 Hz, 9-Me), 5.19 (2H, s, CH_2), 7.33–7.46 (5H, m, Ph), 8.00 (1H, s, *J* 1.4 Hz, 8-H), 8.72 (1H, s, 2-H), 9.16 (1H, s, NH). *Anal.* Calcd for $C_{16}H_{13}N_4ClO_3$ (344.75): C, 55.74; H, 3.80; N, 16.25. Found: C, 55.86; H, 3.65; N, 16.12.

3-[(Benzyloxycarbonyl)amino]-7-chloro-4*H*-pyrimido[1,2-*b*]pyridazin-4-one (3d). This compound was prepared from **1** and 3-amino-6-chloropyridazine (**2d**); Procedure A, reflux for 12 h; yellow crystals. Yield: 59% (0.195 g), lit.[6] yield: 50%; mp 183–184º (from ethanol/toluene), lit.[6] mp 182–184ºC (from methanol/toluene).

3-[(Benzyloxycarbonyl)amino]-7-phenyl-4*H*-pyrimido[1,2-*b*]pyridazin-4-one (3e). Prepared from **1** and 3-amino-6-phenylpyridazine (**2e**); Procedure A, reflux for 4 h; orange crystals. Yield: 93% (0.346 g), mp 237–239ºC (from ethanol/toluene). IR (cm^{-1}): 3220, 3060, 1670 1540, 1480, 1220. ^1H NMR (DMSO-d_6): δ 5.27 (2H, s, CH_2), 7.34–7.44 (5H, m, Ph), 7.53–7.56 (3H, m, 3H-Ph), 7.76 (1H, d, *J* 9.8 Hz, 8-H), 7.77 (1H, s, NH), 7.91 (1H, d, *J* 9.4 Hz, 9-H), 8.06–8.10 (2H, m, 2H-Ph), 9.20 (1H, s, 2-H). *Anal.* Calcd for $C_{21}H_{16}N_4O_3$ (372.38): C, 67.73; H, 4.33; N, 15.05. Found: C, 67.94; H, 4.13; N, 14.83.

3-[(Benzyloxycarbonyl)amino]-9-cyano-7,8-diphenyl-4*H*-pyrimido[1,2-*b*]-pyridazin-4-one (3f). Prepared from **1** and 3-amino-4-cyano-5,6-diphenylpyridazine (**2f**); Procedure A, reflux for 12 h; red crystals. Yield: 39% (0.185 g), mp 212–214ºC (from ethanol). IR (cm^{-1}): 3370, 3290, 2240, 1690, 1530, 1470, 1200. ^1H NMR (DMSO-d_6): δ 5.22 (2H, s, CH_2), 7.24–7.50 (15H, m, 3Ph), 8.88 (1H, s, 2-H), 9.37 (1H, s, NH). *Anal.* Calcd for $C_{28}H_{19}N_5O_3$ (473.48): C, 71.03; H, 4.04; N, 14.79. Found: C, 70.85; H, 4.01; N, 14.59. HRMS Calcd for $C_{28}H_{19}N_5O_3$: 473.148790. Found: 473.149500.

3-[(Benzyloxycarbonyl)amino]-7-methyl-4*H*-pyrimido[1,2-*b*]-pyridazin-4-one (3g). Prepared from **1** and 3-amino-6-methylpyridazine (**2g**); Procedure A, reflux for 8 h; yellow crystals. Yield: 69% (0.214 g), mp 135–137ºC (from ethanol). IR (cm^{-1}): 3240, 1670, 1530, 1490, 1240. ^1H NMR (DMSO-d_6): δ 2.58 (3H, s, 7-Me), 5.07 (2H, s, CH_2), 7.35–7.46 (6H, m, Ph and NH), 7.54 (1H, d, *J* 9.0 Hz, 8-H), 7.90 (1H, d, *J* 9.4 Hz, 9-H), 8.75 (1H, s, 2-H). *Anal.* Calc. for $C_{16}H_{14}N_4O_3$ (310.31): C, 61.93; H, 4.55; N, 18.06. Found: C, 62.26; H, 4.47; N, 17.83. HRMS Calcd for $C_{16}H_{14}N_4O_3$: 310.106591. Found: 310.107450.

Removal of the benzyloxycarbonyl protecting group. General procedure for the preparation of substituted 3-amino-4*H*-pyrimido[1,2-*b*]pyridazin-4-one hydro-bromides, 4d,e,g

A mixture of the substituted 3-[(benzyloxycarbonyl)amino]-4*H*-pyrimido[1,2-*b*]-pyridazin-4-one **3d,e,g** (1 mmol) and hydrogen bromide in acetic acid (33%, 4 mL) was heated at 40–60ºC for 2 h. The precipitate was collected by filtration and washed with ethanol to give **4d,e,g**.

The following compounds were prepared in this manner

3-Amino-7-chloro-4*H*-pyrimido[1,2-*b*]pyridazin-4-one hydrobromide (4d). From 3-[(benzyloxycarbonyl)amino]-7-chloro-4*H*-pyrimido[1,2-*b*]pyridazine-4-one (**6d**); yellow precipitate. Yield: 99% (0.275 g), mp 235–245ºC. IR (cm^{-1}): 3340, 3230, 3140, 1710, 1640. ^1H NMR (DMSO-d_6): δ 5.83 (2H, br s, NH_2), 7.36 (1H, d, *J* 9.4 Hz, 8-H), 7.84 (1H, s, 2-H), 7.86 (1H, d, *J* 9.4 Hz, 9-H). *Anal.* Calc. for $C_7H_6BrN_4ClO$ (277.51): C, 30.30; H, 2.18; N, 20.19. Found: C, 30.30; H, 2.16; N, 18.18. HRMS Calcd for $C_7H_5N_4ClO$: 196.015189. Found: 196.015800.

3-Amino-7-phenyl-4*H*-pyrimido[1,2-*b*]pyridazin-4-one hydrobromide (4e). Prepared from 3-[(benzyloxycarbonyl)amino]-7-phenyl-4*H*-pyrimido[1,2-*b*]pyridazine-4-one (**6e**); orange precipitate. Yield: 98% (0.313 g), mp 276–277ºC. IR (cm^{-1}): 3420, 3290, 1710, 1650, 1600. ^1H NMR (DMSO-d_6): δ 5.65 (2H, br s, NH_2), 7.59–7.64 (3H, m, 3H-Ph), 7.91 (1H, s, 2-H), 7.96 (1H, d, *J* 9.4 Hz, 8-H), 8.04 (1H, d, *J* 9.4 Hz, 9-H), 8.14–8.19 (2H, m, 2H-Ph). *Anal.* Calc. for $C_{13}H_{11}BrN_4O$ (319.16): C, 48.92; H, 3.47; N, 17.55. Found: C, 49.17; H, 3.42; N, 17.52.

3-Amino-7-methyl-4*H*-pyrimido[1,2-*b*]pyridazin-4-one hydrobromide (4g). From 3-[(benzyloxycarbonyl)amino]-7-methyl-4*H*-pyrimido[1,2-*b*]pyridazine-4-one (**6g**); orange precipitate. Yield: 92% (0.237 g), mp 272–274ºC. IR (cm^{-1}): 3430, 3320 (NH_2), 1700, 1660, 1610 (CO). ^1H NMR (DMSO-d_6): δ 2.55 (3H, s, Me), 3.98 (2H, br s, NH_2), 7.33 (1H, d, *J* 9.4 Hz, 8-H), 7.79 (1H, d, *J* 9.4 Hz, 9-H), 7.91 (1H, s, 2-H). *Anal.* Calcd for $C_8H_9BrN_4O$ (257.09): C, 37.37; H, 3.53; N, 21.79. Found: C, 36.70; H, 3.38; N, 21.86. HRMS Calcd for $C_8H_8N_4O$: 176.069811. Found: 176.069900.

General procedure for the preparation of substituted 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazine-3-diazonium tetrafluoroborates 5a,e

The amine **4a,e** (10 mmol) was dissolved in the mixture of water (10 mL) and conc. hydrochloric acid (37%, 10 mL) and the solution cooled in an ice-bath for about 20 minutes. The temperature was maintained at 0−5°C and a solution of sodium nitrite (0.760 g, 11 mmol) in water (4 mL) was added portionwise to the vigorously stirred solution. After approx. 5 minutes, the completion of the reaction was checked using moist potassium iodide–starch paper as an external indicator. The solution was then stirred at 0−5°C for another 15 minutes. A cold solution of fluoroboric acid (50% aqueous solution; 6 mL) was then added. The precipitate was collected by suction filtration and carefully washed with small portions of cold water, methanol, and diethyl ether to give **5a,e**.[15]

The following compounds were prepared in this manner

4-Oxo-4*H*-pyrimido[1,2-*b*]pyridazine-3-diazonium tetrafluoroborate (5a). Prepared from 3-amino-4*H*-pyrimido[1,2-*b*]pyridazin-4-one hydrobromide (**7a**). Yield: 1.827 g (70%), yellow crystals; mp 203−204°C. IR (cm^{-1}): 3191, 2143 (N_2^+), 1718, 1134, 1023 (BF_4^-). MS (FAB): *m*/*z* 174 (M^+–BF_4^-). ^1H NMR (300 MHz, DMSO-d_6): δ 8.55 (1H, dd, *J* 4.2, 9.0 Hz, 8-H), 8.69 (1H, dd, *J* 1.5, 9.0 Hz, 9-H), 9.46 (1H, dd, *J* 1.5, 4.2 Hz, 7-H), 9.63 (1H, s, 2-H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 93.8, 137.1, 138.6, 151.0, 153.2, 157.0, 163.2. *Anal.* Calcd for $C_7H_4N_5OBF_4$ (260.94): C 32.22, H 1.55, N 26.84. Found: C 31.93, H 1.59, N 26.56.

4-Oxo-7-phenyl-4*H*-pyrimido[1,2-*b*]pyridazine-3-diazonium tetrafluoroborate (5e). From 3-amino-7-phenyl-4*H*-pyrimido[1,2-*b*]pyridazin-4-one hydrobromide (**7e**). Yield: 2.797 g (83%), yellow crystals; mp 231−233°C. IR (cm^{-1}): 3420, 2226 (N_2^+), 1760, 1489, 1067 (BF_4^-). MS (FAB): *m*/*z* 250 (M^+–BF_4). ^1H NMR (300 MHz, DMSO-d_6): δ 7.69−7.73 (3H, m, 3H-Ph), 8.29−8.33 (2H, m, 2H-Ph), 8.79 (1H, d, *J* 9.4 Hz, 8-H), 9.17 (1H, d, *J* 9.4 Hz, 9-H), 9.64 (1H, s, 2-H). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ 93.9, 128.9, 130.6, 132.9, 133.5, 136.6, 137.5, 153.1, 156.0, 157.2, 162.7. *Anal.* Calcd for $C_{13}H_8N_5OBF_4$ (337.04).0.5H_2O: C 45.12, H 2.62, N 20.24. Found: C 44.89, H 2.51, N 19.84.

General procedure for the preparation of alkyl 1-(substituted pyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylates (8–16)

A mixture of 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5a**) (0.100 g, 0.383 mmol) or 7-phenyl-4-oxo-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5e**) (0.100 g, 0.297 mmol) and the anhydrous primary alcohol (20 mL) was heated at 50–80°C for 18–48 hours. The volatile components were evaporated *in vacuo* and the solid residue was purified by column chromatography (CC). Fractions containing the product were combined and volatile components evaporated *in vacuo* to give the 1,2,3-triazole derivatives **8**–**16**.

The following compounds were prepared in this manner

Methyl 1-(pyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (8). Prepared from 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5a**) (0.10g) and methanol (20 mL), heating at 60°C for 18 h; CC, ethyl acetate. Yield: 0.053 g (64%), white crystals, mp 182°C. IR (cm^{-1}): 3142, 1729, 1249, 1038, 816. MS (FAB): *m/z* 206 (MH^+). ^1H NMR (300 MHz, $CDCl_3$): δ 4.03 (3H, s, OMe), 7.80 (1H, dd, *J* 4.9, 9.1 Hz, 5'-H), 8.49 (1H, dd, *J* 1.5, 9.1 Hz, 4'-H), 9.31 (1H, dd, *J* 1.5, 4.9 Hz, 6'-H), 9.32 (1H, s, 5-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 52.9, 119.1, 125.3, 129.9, 141.3, 152.8, 152.8, 160.9. ^{13}C DEPT-90 (75.5 MHz, $CDCl_3$): 119.1, 125.3, 129.9, 152.8. HRMS Calcd for $C_8H_8N_5O_2$ (MH^+): 206.067800. Found: 206.068100.

Ethyl 1-(pyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (9). From 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5a**) (0.10g) and ethanol (20 mL), heating at 60°C for 18 hours; CC, ethyl acetate. Yield: 0.027 g (30%), white crystals, mp 91–92°C. IR (cm^{-1}): 3085, 1727, 1467, 1248, 1039. MS (FAB): *m/z* 220 (MH^+). ^1H NMR (300 MHz, $CDCl_3$): δ 1.46 (3H, t, *J* 7.2 Hz, CH_2CH_3), 4.50 (2H, q, *J* 7.2 Hz, CH_2CH_3), 7.79 (1H, dd, *J* 4.9, 9.0 Hz, 5'-H), 8.49 (1H, dd, *J* 1.5, 9.0 Hz, 4'-H), 9.31 (1H, dd, *J* 1.5, 4.9 Hz, 6'-H), 9.31 (1H, s, 5-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.7, 62.1, 119.1, 125.2, 129.8, 141.6, 152.7, 152.8, 160.5. HRMS Calcd for $C_9H_{10}N_5O_2$ (MH^+): 220.083450. Found: 220.082950.

***n*-Propyl 1-(Pyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (10).** Prepared from 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5a**) (0.10g) and 1-propanol (20 mL), heating at 60°C for 32 hours; CC, ethyl acetate. Yield: 0.030 g (33%), white crystals, mp 83–85°C. IR (cm^{-1}): 3088, 1736, 1469, 1267, 1036, 822. MS (FAB): *m/z* 234 (MH^+). ^1H NMR (300 MHz, $CDCl_3$): δ 1.05 (3H, t, *J* 7.2 Hz, $CH_2CH_2CH_3$), 1.79–1.91 (2H, m, $CH_2CH_2CH_3$), 4.39 (2H, t, *J* 6.8 Hz, $CH_2CH_2CH_3$), 7.79 (1H, dd, *J* 4.9, 8.9 Hz, 5'-H), 8.49 (1H, dd, *J* 1.5, 8.9 Hz, 4'-H), 9.31 (1H, dd, *J* 1.5, 4.9 Hz, 6'-H), 9.31 (1H, s, 5-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 10.8, 22.4, 67.6, 119.1, 125.2, 129.9, 141.5, 152.7, 152.8, 160.6. HRMS Calcd for $C_{10}H_{12}N_5O_2$ (MH^+): 234.099100. Found: 234.098500.

***n*-Butyl 1-(pyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (11).** Prepared from 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5a**) (0.10g) and 1-butanol (20 mL), heating at 60°C for 40 hours; CC, ethyl acetate. Yield: 0.035 g (33%), white crystals, mp 71–

73°C. IR (cm^{-1}): 3150, 2962, 1736, 1466, 1238, 1035. MS (FAB): *m/z* 248 (MH^+). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (3H, t, *J* 7.2 Hz, $CH_2CH_2CH_2CH_3$), 1.46–1.56 (2H, m, $CH_2CH_2CH_2CH_3$), 1.61 (0.7 H, br s, H_2O), 1.76–1.85 (2H, m, $CH_2CH_2CH_2CH_3$), 4.44 (2H, t, *J* 6.4 Hz, $CH_2CH_2CH_2CH_3$), 7.80 (1H, dd, *J* 4.9, 8.7 Hz, 5'-H), 8.49 (1H, dd, *J* 1.5, 8.7 Hz, 4'-H), 9.30 (1H, s, 5-H), 9.31 (1H, dd, *J* 1.5, 4.9 Hz, 6'-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1, 19.5, 31.0, 65.9, 119.1, 125.1, 129.9, 141.5, 152.7, 152.8, 160.6. HRMS Calcd for $C_{11}H_{14}N_5O_2$ (MH^+): 248.114750. Found: 248.115450.

Methyl 1-(6-phenylpyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (12). Prepared from 4-oxo-7-phenyl-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5e**) (0.10g) and methanol (20 mL), heating at 55°C for 20 hours; CC, ethyl acetate. Yield: 0.055 g (66%), white crystals, mp 214–216°C. IR (cm^{-1}): 3136, 3073, 1740, 1435, 1242, 1030. MS (FAB): *m/z* 282 (MH^+). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (0.55H, br s, H_2O), 4.04 (3H, s, OMe), 7.57–7.59 (3H, m, 3H-Ph), 8.12–8.15 (2H, m, 2H-Ph), 8.16 (1H, d, *J* 9.4 Hz, 4'-H), 8.52 (1H, d, *J* 9.4 Hz, 5'-H), 9.34 (1H, s, 5-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 52.9, 119.6, 125.1, 127.3, 127.6, 129.7, 131.3, 135.2, 141.2, 151.6, 160.9, 161.0. HRMS Calcd for $C_{14}H_{11}N_5O_2$ (M^+): 281.091275. Found: 281.092120.

Ethyl 1-(6-phenylpyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (13). Prepared from 4-oxo-7-phenyl-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5e**) (0.10g) and anhydrous ethanol (20 mL), heating at 55°C for 26 hours; CC, ethyl acetate–hexane, 1:1. Yield: 0.020 g (23%), white crystals, mp 164–166°C. IR (cm^{-1}): 3154, 3075, 1740, 1236, 1180, 1029. MS (FAB): *m/z* 296 (MH^+). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.46 (3H, t, *J* 7.2 Hz, CH_2CH_3), 4.50 (2H, q, *J* 7.2 Hz, CH_2CH_3), 7.57–7.61 (3H, m, 3H-Ph), 8.12–8.15 (2H, m, 2H-Ph), 8.15 (1H, d, *J* 9.0 Hz, 4-H), 8.52 (1H, d, *J* 9.0 Hz, 5-H), 9.33 (1H, s, 5'-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.7, 62.1, 119.5, 125.1, 127.3, 127.6, 129.7, 131.3, 135.3, 141.6, 151.6, 160.6, 161.0. HRMS Calcd for $C_{15}H_{13}N_5O_2$ (M^+): 295.106925. Found: 295.107800.

***n*-Propyl 1-(6-phenylpyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (14).** Prepared from 4-oxo-7-phenyl-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5e**) (0.10g) and 1-propanol (20 mL), heating at 65°C for 20 hours; CC, ethyl acetate–hexane, 1:1. Yield: 0.028 g (31%), white crystals, mp 127–129°C. IR (cm^{-1}): 3156, 3074, 1741, 1466, 1235, 1027. MS (FAB): *m/z* 310 (MH^+). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.06 (3H, t, *J* 7.5 Hz, $CH_2CH_2CH_3$), 1.80–1.92 (2H, m, $CH_2CH_2CH_3$), 4.40 (2H, t, *J* 6.8 Hz, $CH_2CH_2CH_3$), 7.57–7.59 (3H, m, 3H-Ph), 8.12–8.15 (2H, m, 2H-Ph), 8.16 (1H, d, *J* 9.0 Hz, 4'-H), 8.52 (1H, d, *J* 9.0 Hz, 5'-H), 9.33 (1H, s, 5-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 10.8, 22.4, 67.6, 119.5, 125.0, 127.3, 127.6, 129.7, 131.3, 135.2, 141.5, 151.6, 160.7, 160.9. HRMS Calcd for $C_{16}H_{16}N_5O_2$ (MH^+): 310.129500. Found: 310.130400.

***n*-Butyl 1-(6-phenylpyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (15).** Prepared from 4-oxo-7-phenyl-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5e**) (0.10g) and 1-butanol (20 mL), heating at 65°C for 30 hours; CC, ethyl acetate–hexane, 1:2. Yield: 0.032 g (34%), white crystals, mp 128–130°C. IR (cm^{-1}): 3156, 3076, 2964, 1741, 1233, 1178, 1028. MS (FAB): *m/z* 324 (MH^+). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.00 (3H, t, *J* 7.6 Hz, $CH_2CH_2CH_2CH_3$), 1.47–1.55 (2H, m, $CH_2CH_2CH_2CH_3$), 1.77–1.84 (2H, m, $CH_2CH_2CH_2CH_3$), 4.44 (2H, t, *J* 6.8 Hz, $CH_2CH_2CH_2CH_3$), 7.57–7.59 (3H, m, 3H-Ph), 8.12–8.15 (2H, m, 2H-Ph), 8.15 (1H, d, *J* 9.4 Hz, 4'-H), 8.52 (1H, d, *J* 9.4 Hz, 5'-H), 9.32 (1H, s, 5-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.1, 19.6, 31.1, 65.9, 119.5, 125.0, 127.3, 127.6, 129.7, 131.3, 135.3, 141.5, 151.6, 160.7, 160.9. HRMS Calcd for $C_{17}H_{18}N_5O_2$ (MH^+): 324.146050. Found: 324.145050.

***n*-Pentyl 1-(6-phenylpyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (16).** Prepared from 4-oxo-7-phenyl-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5e**) (0.10g) and 1-pentanol (20 mL), heating at 65°C for 30 hours; CC, ethyl acetate–hexane, 1:2. Yield: 0.030 g (30%), white crystals, mp 127–129°C. IR (cm^{-1}): 3139, 1718, 1547, 1285, 1263. MS (FAB): *m*/*z* 338 (MH^+). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (3H, t, *J* 6.8 Hz, $CH_2CH_2CH_2CH_2CH_3$), 1.37–1.48 (4H, m, $CH_2CH_2CH_2CH_2CH_3$), 1.78–1.88 (2H, m, $CH_2CH_2CH_2CH_2CH_3$), 4.43 (2H, t, *J* 6.8 Hz, $CH_2CH_2CH_2CH_2CH_3$), 7.57–7.59 (3H, m, 3H-Ph), 8.12–8.15 (2H, m, 2H-Ph), 8.16 (1H, d, *J* 9.1 Hz, 4'-H), 8.52 (1H, d, *J* 9.1 Hz, 5'-H), 9.32 (1H, s, 5-H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 14.3, 22.7, 28.4, 28.7, 66.2, 119.5, 125.0, 127.3, 127.6, 129.7, 131.3, 135.2, 141.5, 151.6, 160.6, 160.9. HRMS Calcd for $C_{18}H_{20}N_5O_2$ (MH^+): 338.161700. Found: 338.162300.

Dediazonation of 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoro-borates 5a,e. General procedure for the preparation of 3-unsubstituted 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazin-4-ones 17a,e

A mixture of 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5a**) (0.100 g, 0.383 mmol) or 7-phenyl-4-oxo-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5e**) (0.100 g, 0.297 mmol) and 2-propanol (20 mL) was refluxed for 25–30 hours. The volatile components were evaporated *in vacuo* and the solid residue purified by column chromatography (ethyl acetate). Fractions containing the product were combined and volatile components were evaporated *in vacuo* to give 3-unsubstituted 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazine derivatives **17a,e**.

The following compounds were prepared in this manner

4*H*-Pyrimido[1,2-*b*]pyridazin-4-one (17a). Prepared from 4-oxo-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5a**) (0.10 g) and 2-propanol (20 mL), reflux for 30 hours; yield, 0.045 g (80 %), pale-yellow crystals, mp 153–156°C, lit.[16] mp 155–157°C. IR (cm^{-1}): 1704, 1486, 1250, 1118, 821. MS (EI): *m*/*z* 147 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.69 (1H, d, *J* 6.4 Hz, H_2), 7.48 (1H, dd, *J* 4.2, 9.0 Hz, H_8), 7.89 (1H, dd, *J* 1.7, 9.0 Hz, H_9), 8.25 (1H, d, *J* 6.4 Hz, H_2), 8.67 (1H, dd, *J* 1.7, 4.2 Hz, H_7). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 111.2, 127.4, 135.5, 145.6, 150.2, 153.9, 158.4. HRMS calc. for $C_7H_5N_3O$ (M^+): 147.043262; found: 147.043950.

7-Phenyl-4*H*-pyrimido[1,2-*b*]pyridazin-4-one (17e). Prepared from 4-oxo-7-phenyl-4*H*-pyrimido[1,2-*b*]pyridazin-3-diazonium tetrafluoroborate (**5e**) (0.100 g) and 2-propanol (20 mL), reflux for 25 hours; yield, 0.050 g (75 %), pale-yellow crystals, mp 160–163°C. IR (cm^{-1}): 1715, 1479, 778. MS (EI): *m*/*z* 223 (M^+), (FAB): 224 (MH^+). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (1H, d, *J* 6.2 Hz, H_2), 7.53–7.56 (3H, m, 3×Ph), 7.93 (2H, br s, H_8, H_9), 8.07–8.10 (2H, m, 2×Ph), 8.23 (1H, d, *J* 6.2 Hz, H_2). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 11.3, 126.5, 128.0, 129.7, 131.8, 134.2, 135.5, 139.0, 149.6, 153.4, 158.4. HRMS calc. for $C_{13}H_9N_3O$ (M^+): 223.074562; found: 223.075250.

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