Transformations of 3-aminopyridazines. Synthesis of 4-oxo-4H-pyrimido[1,2-b]pyridazine and 1-(substituted pyridazin-3-yl)-1H-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-4H-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-4H-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)-1H-1,2,3-triazoles (8–16), while heating of 5a,e in 2-propanol afforded the 3-unsubstituted 4H-pyrimido[1,2-b]pyridazin-4-ones 17a,e.

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

Introduction

The pyridazines,1 1,2,3-triazoles,2 and 4H-azino[1,2-x]pyrimidin-4-ones3 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
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. 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-4H-pyrimidin-4-ones. Deprotection of the 3-acylamino group gives free amines, usually in good yields. Similarly, 3-amino-4H-quinolizin-4-ones have been prepared from alkyl 2-acylamino-3-(dimethylamino)propenoates and 2-pyridinylacetic acid derivatives. Nitrosation of such heteroarylamines gives the corresponding heteroaryldiazonium salts, which are suitable precursors for further transformations. In this manner, methyl (Z)-2-benzyloxycarbonylaminom-3-(dimethylamino)propenoate (1) has been transformed in three steps into 1-substituted 4-oxo-4H-quinolizine- and 4-oxo-4H-pyrido[1,2-a]pyrimidine-3-diazonium tetrafluoroborates. Heating of 4-oxo-4H-quinolizine-3-diazonium salts in primary alkanols resulted in aza Wolff rearrangements to give the corresponding alkyl indolizine-3-carboxylates, while 4-oxo-4H-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)-1H-1,2,3-triazole-4-carboxylates.

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-4H-pyrimido[1,2-b]pyridazin-4-ones. In this paper, we report the preparation of 3-benzyloxycarbonylaminom-4-oxo-4H-pyrimido[1,2-b]pyrimidine-3-diazonium tetrafluoroborates 3a–g, 3-amino-4-oxo-4H-pyrimido[1,2-b]pyridazines hydrobromides 4d,e,g, 4-oxo-4H-pyrimido[1,2-b]pyridazine-3-diazonium tetrafluoroborates 5a,e, and ‘ring switching’ transformations of...
Results and Discussion

The starting compound, methyl (Z)-2-benzyloxy carbonylamino-3-(dimethylamino)-propenoate (1), was prepared from N-(benzyloxy carbonyl)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-benzyloxy carbonylamino-4-oxo-4\(H\)-pyrimido[1,2-\(b\)]pyridazines (3a–g) in 19–93\% yields. 3-Benzyloxy carbonylamino-4-oxo-4\(H\)-pyrimido[1,2-\(b\)]pyridazine (3a) and 3-benzyloxy carbonylamino-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-benzyloxy carbonylamino-7-phenyl-4\(H\)-pyrimido[1,2-\(b\)]pyrazidin-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-\(b\)]pyrazidin-4-ones 4d,e,g in 92–99\% yields (Scheme 1).
<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Yield [%]</th>
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<tr>
<td>3 4</td>
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<tr>
<td>2a, 3a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>79</td>
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<td>H</td>
<td>Me</td>
<td>72</td>
</tr>
<tr>
<td>2d, 3d, 4d</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>59 99</td>
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<td>93 98</td>
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<td>Ph</td>
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<tr>
<td>2g, 3g, 4g</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>69 92</td>
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</table>

Scheme 1. (i) AcOH, AcONa, reflux; (ii) AcOH, Ac₂O, 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 HBF₄ to afford the 4-oxo-4H-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)-1H-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-4H-pyrido[1,2-a]pyrimidine series, 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)-1H-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 4H-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 4H-quinolinizin-4-one series (Scheme 2).

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. The 1,2,3-triazoles 8–16 did not give satisfactory elemental analyses, but their identities were confirmed by MS, HRMS, and ¹³C NMR.
\[
\text{4a,e} \quad \xrightarrow{i} \quad \text{5a,e} \quad \xrightarrow{ii} \quad \text{6} \quad \xrightarrow{\text{iii}} \quad \text{7} \quad \xrightarrow{\text{8-16}}
\]

<table>
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<tr>
<th>Reaction</th>
<th>R¹</th>
<th>R²</th>
<th>Yield [%]</th>
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<td>5a + MeOH → 8</td>
<td>H</td>
<td>Me</td>
<td>64</td>
</tr>
<tr>
<td>5a + EtOH → 9</td>
<td>H</td>
<td>Et</td>
<td>30</td>
</tr>
<tr>
<td>5a + n-PrOH → 10</td>
<td>H</td>
<td>n-Pr</td>
<td>33</td>
</tr>
<tr>
<td>5a + n-BuOH → 11</td>
<td>H</td>
<td>n-Bu</td>
<td>33</td>
</tr>
<tr>
<td>5d + MeOH → 12</td>
<td>Ph</td>
<td>Me</td>
<td>66</td>
</tr>
<tr>
<td>5d + EtOH → 13</td>
<td>Ph</td>
<td>Et</td>
<td>23</td>
</tr>
<tr>
<td>5d + n-PrOH → 14</td>
<td>Ph</td>
<td>n-Pr</td>
<td>31</td>
</tr>
<tr>
<td>5d + n-BuOH → 15</td>
<td>Ph</td>
<td>n-Bu</td>
<td>34</td>
</tr>
<tr>
<td>5d + n-PeOH → 16</td>
<td>Ph</td>
<td>n-pentyl</td>
<td>34</td>
</tr>
</tbody>
</table>

Scheme 2. (i) NaNO₂, HCl, H₂O, 0–5°C, then 50% HBF₄ in H₂O. (ii) R²OH (R = Me, Et, n-Pr, n-Bu, n-pentyl, 60–80°C. (iii) 2-propanol, reflux.

The formation of the 1H-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)-1H-1,2,3-triazole series, where the signal for 5-H appears between 9.04–9.10 ppm.
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 $3$-benzoxycarbonylamino-4-oxo-$4H$-pyrimido[1,2-$b$]pyridazine derivatives $3$, generally in good yields. Deprotection of the amino group in compounds $3$ gives $3$-amino-$4H$-pyrimido[1,2-$b$]pyrazidin-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 de diazonation reaction to afford $3$-unsubstituted $4H$-pyrimido[1,2-$b$]pyridazine-4-ones $17$. Ring-switching synthesis of $1$-(\(\alpha\)-azinyl)$-1$-$H$-1,2,3-triazoles from $4$-exo-$4H$-azino[1,2-$x$]pyrimidine-$3$-diazonium salts represents the easiest way for the preparation of $1$-(\(\alpha\)-azinyl)$-1$-$H$-1,2,3-triazoles, since an alternative route via $1,3$-dipolar cycloadditions of $\alpha$-azidoazines to alkynes is not favorable, owing to the well-known azido–tetrazolo isomerism as the major competitive reaction. 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-$4H$-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$_4$Si as internal standard. IR spectra were recorded with a Perkin-Elmer Spectrum BX FTIR spectrophotometer (KBr discs). The mass spectra were recorded with an Autospec 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-4H-pyrimido[1,2-b]pyridazin-4-one (4a). 6

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

Procedure A. A mixture of methyl (Z)-2-[((benzyloxycarbonyl)amino)-3-(dimethylamino)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-(dimethylamino)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]-4H-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 182–184ºC (from ethanol–toluene).

3-[(Benzyloxycarbonyl)amino]-7-hydroxy-4H-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. 1H NMR (DMSO-d6): δ 5.18 (2H, s, CH2), 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 C15H12N4O4 (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-4H-pyrimido[1,2-b]pyridazin-4-one (3c). Prepared from 1 and 3-amino-6-chloro-4-methylpyridazine (2e); Procedure A, reflux for 8 h; yellow crystals. Yield: 72% (0.248 g), mp 210–212ºC (from ethanol/toluene). IR (cm−1): 3230, 3180, 1550, 1480, 1220. 1H NMR (DMSO-d6): δ 2.51 (d, 3H, J 1.1 Hz, 9-Me), 5.19 (2H, s, CH2), 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 C16H13N4ClO3 (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-4H-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.5 yield: 50%; mp 183–184°C (from ethanol/toluene), lit.6 mp 182–184°C (from methanol/toluene).

3-[(Benzyloxycarbonyl)amino]-7-phenyl-4H-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 237–239°C (from ethanol/toluene). IR (cm –1): 3220, 3060, 1670, 1540, 1480, 1220. 1H NMR (DMSO-d6): δ 5.27 (2H, s, CH2), 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 C21H16N4O3 (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-4H-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 212–214°C (from ethanol). IR (cm –1): 3370, 3290, 2240, 1690, 1530, 1470, 1200. 1H NMR (DMSO-d6): δ 5.22 (2H, s, CH2), 7.24–7.50 (15H, m, 3Ph), 8.88 (1H, s, 2-H), 9.37 (1H, s, NH). Anal. Calcd for C28H19N5O3 (473.48): C, 71.03; H, 4.04; N, 14.79. Found: C, 70.85; H, 4.01; N, 14.59. HRMS Calcd for C28H19N5O3: 473.148790. Found: 473.149500.

3-[(Benzyloxycarbonyl)amino]-7-methyl-4H-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 135–137°C (from ethanol). IR (cm –1): 3240, 1670, 1530, 1470, 1240. 1H NMR (DMSO-d6): δ 2.58 (3H, s, 7-Me), 5.07 (2H, s, CH2), 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). Anal. Calcd for C16H14N4O3 (310.31): C, 61.93; H, 4.55; N, 18.06. Found: C, 62.26; H, 4.47; N, 17.83. HRMS Calcd for C16H14N4O3: 310.106591. Found: 310.107450.

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

A mixture of the substituted 3-[(benzyloxycarbonyl)amino]-4H-pyrimido[1,2-b]pyridazin-4-one 3d,e,g (1 mmol) and hydrogen bromide in acetic acid (33%, 4 mL) was heated at 40–60°C 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-4H-pyrimido[1,2-b]pyridazin-4-one hydrobromide (4d). From 3-[(benzyloxycarbonyl)amino]-7-chloro-4H-pyrimido[1,2-b]pyridazin-4-one (6d); yellow precipitate. Yield: 99% (0.275 g), mp 235–245°C. IR (cm–1): 3340, 3230, 3140, 1710, 1640. 1H NMR (DMSO-d6): δ 5.83 (2H, br s, NH2), 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. Calcd for C7H5BrN4ClO (277.51): C, 30.30; H, 2.18; N, 20.19. Found: C, 30.30; H, 2.16; N, 18.18. HRMS Calcd for C7H5BrN4ClO: 196.015189. Found: 196.015800.
3-Amino-7-phenyl-4\textsubscript{H}-pyrimido[1,2-b]pyridazin-4-one hydrobromide (4e). Prepared from 3-[(benzyloxy carbonyl)amino]-7-phenyl-4\textsubscript{H}-pyrimido[1,2-b]pyridazine-4-one (6e); orange precipitate. Yield: 98% (0.313 g), mp 276–277ºC. IR (cm\textsuperscript{-1}): 3420, 3290, 1710, 1650, 1600. \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}): \(\delta\) 5.65 (2H, br s, NH\textsubscript{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). \textit{Anal.} Calcd for C\textsubscript{13}H\textsubscript{11}BrN\textsubscript{4}O (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\textsubscript{H}-pyrimido[1,2-b]pyridazin-4-one hydrobromide (4g). From 3-[(benzyloxy carbonyl)amino]-7-methyl-4\textsubscript{H}-pyrimido[1,2-b]pyridazine-4-one (6g); orange precipitate. Yield: 92% (0.237 g), mp 272–274ºC. IR (cm\textsuperscript{-1}): 3430, 3320 (NH\textsubscript{2}), 1700, 1660, 1610 (CO). \textsuperscript{1}H NMR (DMSO-d\textsubscript{6}): \(\delta\) 2.55 (3H, s, Me), 3.98 (2H, br s, NH\textsubscript{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). \textit{Anal.} Calcd for C\textsubscript{8}H\textsubscript{9}BrN\textsubscript{4}O (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\textsubscript{8}H\textsubscript{8}N\textsubscript{4}O: 176.069811. Found: 176.069900.

**General procedure for the preparation of substituted 4-oxo-4\textsubscript{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.\textsuperscript{15}

**The following compounds were prepared in this manner**

4-Oxo-4\textsubscript{H}-pyrimido[1,2-b]pyridazine-3-diazonium tetrafluoroborate (5a). Prepared from 3-amino-4\textsubscript{H}-pyrimido[1,2-b]pyridazin-4-one hydrobromide (7a). Yield: 1.827 g (70%), yellow crystals; mp 203–204°C. IR (cm\textsuperscript{-1}): 3191, 2143 (N\textsubscript{2}+), 1718, 1134, 1023 (BF\textsubscript{4}–). MS (FAB): \textit{m/z} 174 (M\textsuperscript{+}−BF\textsubscript{4} ). \textsuperscript{1}H NMR (300 MHz, DMSO-d\textsubscript{6}): \(\delta\) 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). \textsuperscript{13}C NMR (75.5 MHz, DMSO-d\textsubscript{6}): \(\delta\) 93.8, 137.1, 138.6, 151.0, 153.2, 157.0, 163.2. \textit{Anal.} Calcd for C\textsubscript{7}H\textsubscript{4}N\textsubscript{5}OBF\textsubscript{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\textsubscript{H}-pyrimido[1,2-b]pyridazine-3-diazonium tetrafluoroborate (5e). From 3-amino-7-phenyl-4\textsubscript{H}-pyrimido[1,2-b]pyridazin-4-one hydrobromide (7e). Yield: 2.797 g (83%), yellow crystals; mp 231–233°C. IR (cm\textsuperscript{-1}): 3420, 2226 (N\textsubscript{2}+), 1760, 1489, 1067 (BF\textsubscript{4}–). MS (FAB): \textit{m/z} 250 (M\textsuperscript{+}−BF\textsubscript{4} ). \textsuperscript{1}H NMR (300 MHz, DMSO-d\textsubscript{6}): \(\delta\) 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). \textsuperscript{13}C NMR (75.5 MHz, DMSO-d\textsubscript{6}): \(\delta\) 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_{8}N_{5}OBF_{4} (337.04).0.5H_{2}O: 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)-1H-1,2,3-triazole-4-carboxylates (8–16)**

A mixture of 4-oxo-4H-pyrimido[1,2-b]pyridazin-3-diazonium tetrafluoroborate (5a) (0.100 g, 0.383 mmol) or 7-phenyl-4-oxo-4H-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)-1H-1,2,3-triazole-4-carboxylate (8).** Prepared from 4-oxo-4H-pyrimido[1,2-b]pyridazin-3-diazonium tetrafluoroborate (5a) (0.10 g) 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, CDCl₃): 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), 9.31 (1H, s, 5-H). ¹³C NMR (75.5 MHz, CDCl₃): δ 52.9, 119.1, 125.3, 129.9, 141.3, 152.8, 152.8, 160.9. HRMS Calcd for C₈H₈N₅O₂ (MH⁺): 206.067800. Found: 206.068100.

**Ethyl 1-(pyridazin-3-yl)-1H-1,2,3-triazole-4-carboxylate (9).** From 4-oxo-4H-pyrimido[1,2-b]pyridazin-3-diazonium tetrafluoroborate (5a) (0.10 g) 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, 1469, 1248, 1039. MS (FAB): m/z 220 (MH⁺). ¹H NMR (300 MHz, CDCl₃): δ 1.46 (3H, t, J 7.2 Hz, CH₂CH₃), 4.50 (2H, q, J 7.2 Hz, CH₂CH₃), 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). ¹³C NMR (75.5 MHz, CDCl₃): δ 14.7, 62.1, 119.1, 125.3, 129.9, 141.3, 152.8, 152.8, 160.5. HRMS Calcd for C₉H₁₀N₅O₂ (MH⁺): 220.083450. Found: 220.082950.

**n-Propyl 1-(pyridazin-3-yl)-1H-1,2,3-triazole-4-carboxylate (10).** Prepared from 4-oxo-4H-pyrimido[1,2-b]pyridazin-3-diazonium tetrafluoroborate (5a) (0.10 g) 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, CDCl₃): δ 1.05 (3H, t, J 7.2 Hz, CH₂CH₂CH₃), 1.79–1.91 (2H, m, CH₂CH₂CH₃), 4.39 (2H, t, J 6.8 Hz, CH₂CH₂CH₃), 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). ¹³C NMR (75.5 MHz, CDCl₃): δ 10.8, 22.4, 67.6, 119.1, 125.2, 129.9, 141.5, 152.7, 152.8, 160.5. HRMS Calcd for C₁₀H₁₂N₅O₂ (MH⁺): 220.083450. Found: 220.082950.

**n-Butyl 1-(pyridazin-3-yl)-1H-1,2,3-triazole-4-carboxylate (11).** Prepared from 4-oxo-4H-pyrimido[1,2-b]pyridazin-3-diazonium tetrafluoroborate (5a) (0.10 g) 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⁺). ¹H NMR (300 MHz, CDCl₃): δ 0.99 (3H, t, J 7.2 Hz, CH₂CH₂CH₂CH₃), 1.46–1.56 (2H, m, CH₂CH₂CH₂CH₃), 1.61 (0.7 H, br s, H₂O), 1.76–1.85 (2H, m, CH₂CH₂CH₂CH₃), 4.44 (2H, t, J 6.4 Hz, CH₂CH₂CH₂CH₃), 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). ¹³C NMR (75.5 MHz, CDCl₃): 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 C₁₁H₁₄N₅O₂ (MH⁺): 248.114750. Found: 248.115450.

Methyl 1-(6-phenylpyrazin-3-yl)-1H-1,2,3-triazole-4-carboxylate (12). Prepared from 4-oxo-7-phenyl-4H-pyrimido[1,2-b]pyrazin-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⁺). ¹H NMR (300 MHz, CDCl₃): δ 1.60 (0.55H, br s, H₂O), 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). ¹³C NMR (75.5 MHz, CDCl₃): 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 C₁₄H₁₁N₅O₂ (M⁺): 281.091275. Found: 281.092120.

Ethyl 1-(6-phenylpyrazin-3-yl)-1H-1,2,3-triazole-4-carboxylate (13). Prepared from 4-oxo-7-phenyl-4H-pyrimido[1,2-b]pyrazin-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⁺). ¹H NMR (300 MHz, CDCl₃): δ 1.46 (3H, t, J 7.2 Hz, CH₂CH₃), 4.50 (2H, q, J 7.2 Hz, CH₂CH₃), 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). ¹³C NMR (75.5 MHz, CDCl₃): δ 14.7, 62.1, 119.5, 125.1, 127.3, 127.6, 129.7, 131.3, 135.2, 141.2, 151.6, 160.9, 161.0. HRMS Calcd for C₁₅H₁₃N₅O₂ (M⁺): 295.106925. Found: 295.107800.

n-Propyl 1-(6-phenylpyrazin-3-yl)-1H-1,2,3-triazole-4-carboxylate (14). Prepared from 4-oxo-7-phenyl-4H-pyrimido[1,2-b]pyrazin-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⁺). ¹H NMR (300 MHz, CDCl₃): δ 1.00 (3H, t, J 7.6 Hz, CH₂CH₂CH₂CH₃), 1.80–1.92 (2H, m, CH₂CH₂CH₂CH₃), 4.40 (2H, t, J 6.8 Hz, CH₂CH₂CH₂CH₃), 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). ¹³C NMR (75.5 MHz, CDCl₃): 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 C₁₆H₁₆N₅O₂ (M⁺): 310.129500. Found: 310.130400.

n-Butyl 1-(6-phenylpyrazin-3-yl)-1H-1,2,3-triazole-4-carboxylate (15). Prepared from 4-oxo-7-phenyl-4H-pyrimido[1,2-b]pyrazin-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⁺). ¹H NMR (300 MHz, CDCl₃): δ 1.00 (3H, t, J 7.6 Hz, CH₂CH₂CH₂CH₃),
1.47–1.55 (2H, m, CH₃CH₂CH₂CH₃), 1.77–1.84 (2H, m, CH₂CH₂CH₂CH₃), 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). 13C NMR (75.5 MHz, CDCl₃): 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.


n-Pentyl 1-(6-phenylpyridazin-3-yl)-1H-1,2,3-triazole-4-carboxylate (16). Prepared from 4-oxo-7-phenyl-4H-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⁺). 1H NMR (300 MHz, CDCl₃): δ 0.94 (3H, t, J 6.8 Hz, CH₂CH₂CH₂CH₂CH₃), 1.37–1.48 (4H, m, CH₂CH₂CH₂CH₃), 1.78–1.88 (2H, m, CH₂CH₂CH₂CH₂CH₃), 4.43 (2H, t, J 6.8 Hz, CH₂CH₂CH₂CH₂CH₃), 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). 13C NMR (75.5 MHz, CDCl₃): 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 C₁₈H₂₀N₅O₂ (MH⁺): 338.161700. Found: 338.162300.

n-Pentyl 1-(6-phenylpyridazin-3-yl)-1H-1,2,3-triazole-4-carboxylate (16). Prepared from 4-oxo-7-phenyl-4H-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⁺). 1H NMR (300 MHz, CDCl₃): δ 0.94 (3H, t, J 6.8 Hz, CH₂CH₂CH₂CH₂CH₃), 1.37–1.48 (4H, m, CH₂CH₂CH₂CH₂CH₃), 1.78–1.88 (2H, m, CH₂CH₂CH₂CH₂CH₃), 4.43 (2H, t, J 6.8 Hz, CH₂CH₂CH₂CH₂CH₃), 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). 13C NMR (75.5 MHz, CDCl₃): 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 C₁₇H₁₈N₅O₂ (MH⁺): 324.146050. Found: 324.145050.

Dediazonation of 4-oxo-4H-pyrimido[1,2-b]pyridazin-3-diazonium tetrafluoroborates 5a,e. General procedure for the preparation of 3-unsubstituted 4-oxo-4H-pyrimido[1,2-b]pyridazin-4-ones 17a,e
A mixture of 4-oxo-4H-pyrimido[1,2-b]pyridazin-3-diazonium tetrafluoroborate (5a) (0.100 g, 0.383 mmol) or 7-phenyl-4-oxo-4H-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-4H-pyrimido[1,2-b]pyridazine derivatives 17a,e.

The following compounds were prepared in this manner

4H-Pyrimido[1,2-b]pyridazin-4-one (17a). Prepared from 4-oxo-4H-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⁺). ¹H NMR (300 MHz, CDCl₃): δ 6.69 (1H, d, J 6.4 Hz, H₂), 7.48 (1H, dd, J 4.2, 9.0 Hz, H₈), 7.89 (1H, dd, J 1.7, 9.0 Hz, H₉), 8.25 (1H, d, J 6.4 Hz, H₂), 8.67 (1H, dd, J 1.7, 4.2 Hz, H₇). ¹³C NMR (75.5 MHz, CDCl₃): δ 111.2, 127.4, 135.5, 145.6, 150.2, 153.9, 158.4. HRMS calc. for C₇H₅N₃O (M⁺): 147.043262; found: 147.043950.

7-Phenyl-4H-pyrimido[1,2-b]pyridazin-4-one (17e). Prepared from 4-oxo-7-phenyl-4H-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⁺). ¹H NMR (300 MHz, CDCl₃): δ 6.70 (1H, d, J 6.2 Hz, H₂), 7.53–7.56 (3H, m, 3×Ph), 7.93 (2H, br s, H₈, H₉), 8.07–8.10 (2H, m, 2×Ph), 8.23 (1H, d, J 6.2 Hz, H₂). ¹³C NMR (75.5 MHz, CDCl₃): 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_{9}N_{3}O (M^+): 223.074562; found: 223.075250.

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References and Notes


15. Special care is necessary in order to dry the solid as free as possible from liquid after each washing.