Synthesis and Antimycobacterial Activity of Alkyl 1-Heteroaryl-1*H*-1,2,3-triazole-4-carboxylates.

Boštjan Japelj, Simon Rečnik, Petra Čebašek, Branko Stanovnik*, and Jurij Svete*

Faculty of Chemistry and Chemical Technology, University of Ljubljana,
Aškerčeva 5, 1000 Ljubljana, Slovenia
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A series of alkyl 1-heteroaryl-1*H*-1,2,3-triazole-4-carboxylates **6a–u** were synthesised in four steps from methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (**1**) and heterocyclic amines **2a–s**. Triazoles **6a–o** were tested against antimycobacterial activity. For the most active compound, *n*-pentyl 1-(6-phenylpyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (**6n**), minimum inhibitory concentration 3.13 μg/ml was determined.

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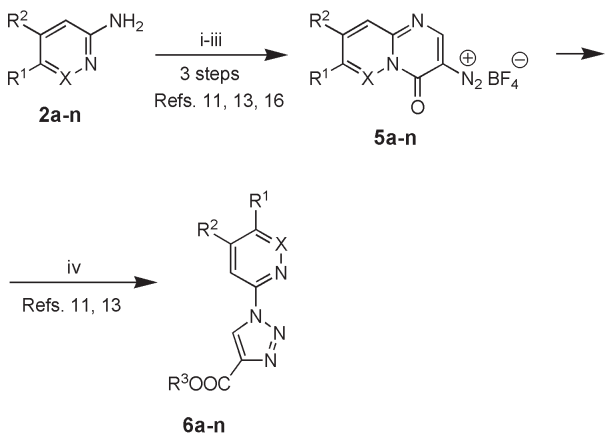
Tuberculosis (TB), a chronic and fatal bacterial infection, can be caused by *Mycobacterium tuberculosis* and, to a lesser degree, by *Mycobacterium bovis* and *Mycobacterium africanum*. Cases of TB dropped rapidly in the 1940s and 1950s when the first effective antibiotic therapies for TB were introduced. For this reason, many people think TB is a disease of the past. However, in 1985 the decline of TB ended and the number of active TB cases began to rise again. Each year, 8 million people worldwide develop active TB and 3 million die. A growing problem also is HIV-infected patients, which are particularly vulnerable to turn infection with *M. tuberculosis* into active TB [1].

In the last two decades, a series of 2-substituted alkyl 3-(dimethylamino)prop-2-enoates and related enaminones were prepared and used as versatile reagents for the preparation of various heterocyclic systems, functionalised heterocyclic compounds, and natural product analogues [2–7]. Just recently, the enaminone methodology has been employed in combinatorial synthesis [8–10]. The use of 2-acylamino and 2-vinylamino substituted alkyl 3-(dimethylamino)propenoates also offers an easy access to various 3-amino-4*H*-quinolizin-4-ones and 3-amino substituted fused pyrimidones, which can be transformed into the corresponding diazonium tetrafluoroborates as versatile intermediates for further transformations [11–15]. In this connection, we have previously reported a three-step synthesis of stable diazonium tetrafluoroborates **5a–n** starting from methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (**1**) and heterocyclic amines **2a–o**. Upon heating with primary alcohols at 60°, diazonium salts **5a–n** underwent 'ring switching' transformation to furnish alkyl 1-azinyl-1*H*-1,2,3-triazole-4-carboxylates **6a–n** [11,13] (Scheme 1).

In this paper, we report the synthesis of novel methyl 1-azolyl-1*H*-1,2,3-triazole-4-carboxylates **6o–u** and the results of antimicrobial evaluation of the previously prepared alkyl 1-azinyl-1*H*-1,2,3-triazole-4-carboxylates **6a–o** against *Mycobacterium tuberculosis*.

Heterocyclic amines **4o–s** were prepared, according to the general literature procedures [13,16], in 81–90% yields over two steps from aminoazoles **2o–s** *via* treatment with the propenoate **1** in refluxing acetic acid followed by deprotection of the amino group in azolopyrimidones **3o–s** with 33% HBr in acetic acid at 50°. Nitrosation of 6-amino-5*H*-thiazolo[3,2–*a*]pyrimidin-5-one (**4o**) and 6-aminoimidazo[1,2–*a*]pyrimidin-5(1*H*)-one (**4p**) with aqueous sodium nitrite in the presence of fluoroboric acid afforded stable diazonium tetrafluoroborates **5o** and **5p** in 80% and 75% yield, respectively. On the other hand, nitrosation of 6-aminopyrazolo[1,5–*a*]-pyrimidin-7(1*H*)-one (**4q**) and 6-amino-2-methylpyrazolo[1,5–*a*]pyrimidin-7(1*H*)-one (**4r**) with aqueous sodium nitrite furnished the 3-brominated diazo compounds **5t** and **5u**. Bromination at position 3 could be explained by oxidation of HBr with nitrous acid to give *in situ* formed bromine, which then undergoes electrophilic substitution at position 3. In order to avoid bromination, amines **4q** and **4r** were diazotised with

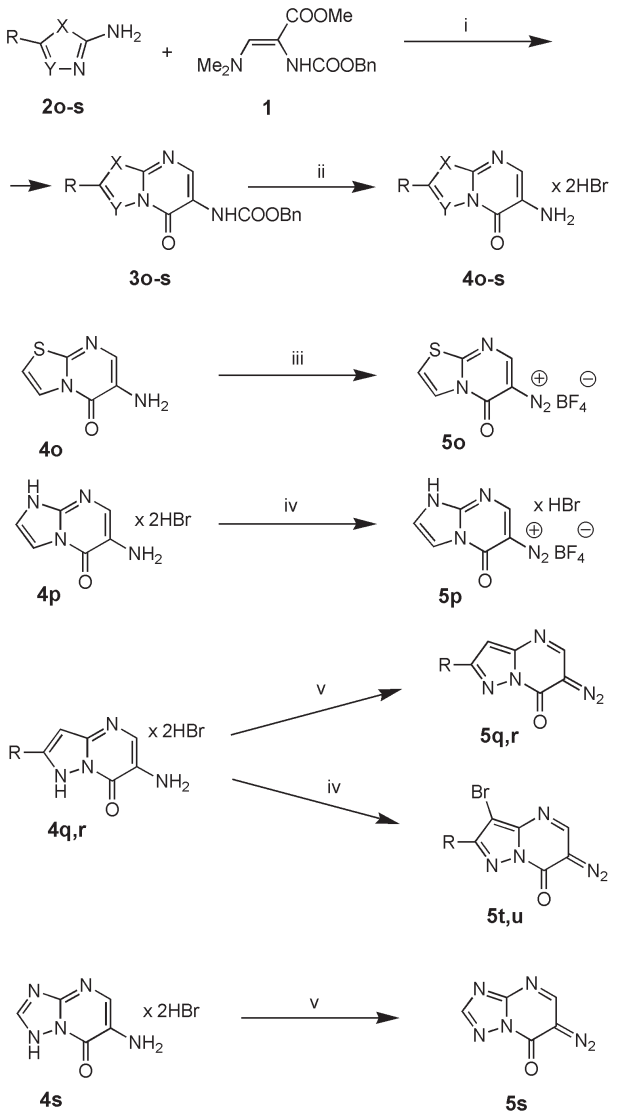
Scheme 1



X = CH, N
R^1 = H, Ph; R^2 = H, Me; R^3 = Me, Et, *n*-Pr, *n*-Bu, *n*-Pe

Reaction conditions: (i) Methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethyl-amino)prop-2-enoate (**1**), AcOH, AcONa, reflux; (ii) HBr–AcOH, 50°; (iii) $NaNO_2$ (aq.), HCl, H_2O, 0°, then 50% HBF_4 (aq.); (iv) R^3OH, 60°.

Scheme 2



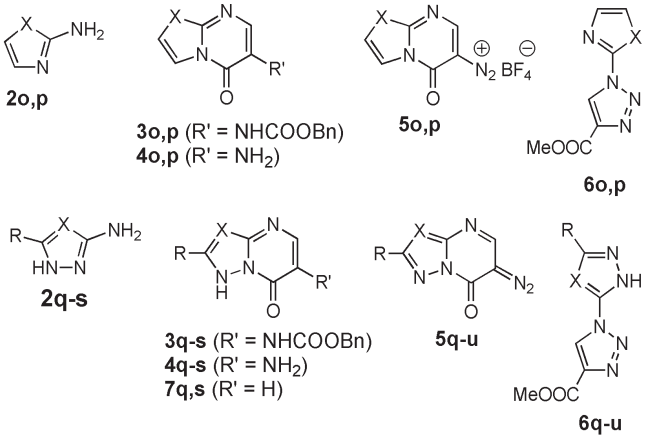
Reaction conditions: (i) AcOH, AcONa, reflux; (ii) HBr–AcOH, 50°; (iii) $NaNO_2$, HCl, H_2O, 0°, then 50% HBF_4 (aq.) (Procedure A); (iv) $NaNO_2$, 50% HBF_4 (aq.), AcOH or AcOEt, 0° (Procedure B); (v) *tert*-butyl nitrite, BF_3xEt_2O, *i*-PrOH, –15→0° (Procedure C).

tert-butyl nitrite and BF_3–Et_2O in 2-propanol to give the 3-unsubstituted diazo heterocycles **5q** and **5r**. In the same manner, 6-diazo[1,2,4]triazolo[1,5–*a*]pyrimidin-7(6*H*)-one (**5s**) was prepared (Scheme 2, Table 1).

Heating of diazonium tetrafluoroborates **5o,p** in methanol resulted in 'ring switching' transformation into 1-thiazol-2-yl (**6o**) and 1-imidazol-2-yl (**6p**) substituted methyl 1*H*-1,2,3-triazole-4-carboxylates, which were isolated in moderate yields. However, heating of 6-diazopyrazolo[1,5–*a*]pyrimidin-7(6*H*)-one (**5q**) and 6-diazo-[1,2,4]triazolo[1,5–*a*]pyrimidin-7(6*H*)-one (**5s**) in methanol resulted in reduction (dediazonation) to give

Table 1

Compounds **2–7**



Compound	R	X	Yield (%) 3	4	5	6	7
2o–6o	-	S	96	89[a]	80	40	
2p–6p	-	NH	95	95	75	48	
2q–7q	H	CH	99	90	87	33	51
2r–6r	Me	CH	90	90	57	15	
2s–7s	H	N	85	97	93	26	48
5t, 6t	H	C–Br			80	16	
5u, 6u	Me	C–Br			75	9	

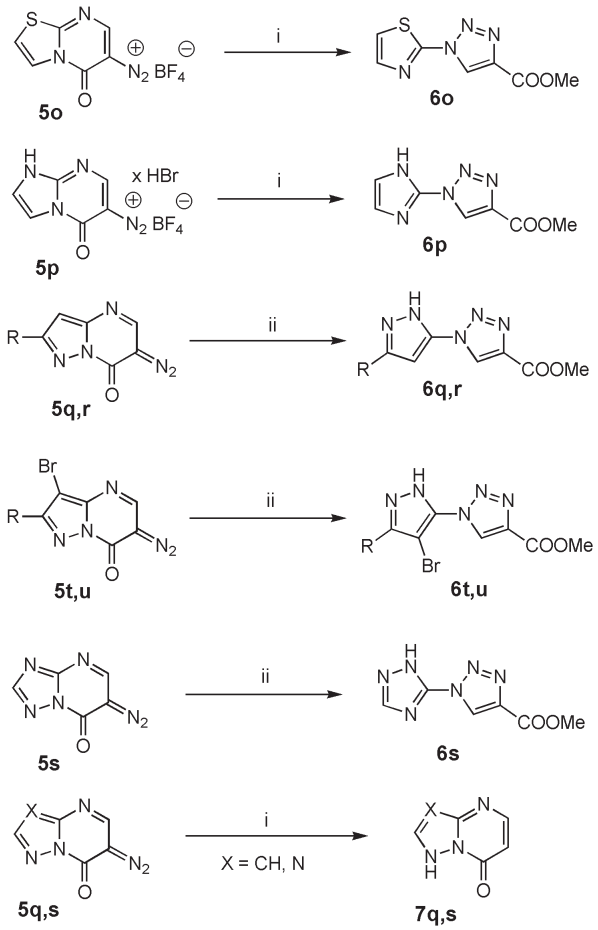
[a] Isolated as free amine.

pyrazolo[1,5–*a*]pyrimidin-7(1*H*)-one (**7q**) and [1,2,4]-triazolo[1,5–*a*]pyrimidin-7(1*H*)-one (**7s**), respectively. When heating of diazo compounds **5q–u** in methanol was carried out in the presence of 3 equivalents of 37% hydrochloric acid, the desired 'ring switching' transformation took place to give methyl 1-azolyl-1*H*-1,2,3-triazole-4-carboxylates **6q–u** in 9–48% yields (Scheme 3, Table 1).

Structures of all novel compounds were determined by spectroscopic (nmr, ir, ms, hrms) methods and by analyses for C, H, and N. Compounds **5q,r,t** and **6q–u** were not prepared in analytically pure form. Their identities were confirmed by ms and hrms. Identities of known compounds **7q** [17], and **7s** [18] were confirmed by melting points and spectral data.

1-Pyridinyl (**6a–g**), 1-pyridazinyl (**6h–n**), and thiazolyl (**6o**) substituted alkyl 1*H*-1,2,3-triazole-4-carboxylates were tested for antimicrobial activity. Primary screening was conducted at 6.25 μg/ml against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using a broth micro dilution assay, the Microplate Alamar Blue Assay [19]. Compounds exhibiting fluorescence were tested in the BACTEC 460 radiometric system [19]. Compounds **6c,e,k,n**, which exhibited more than 90% inhibition in the primary screening, were re-tested at lower concentrations against *M. tuberculosis* $H_{37}Rv$ to

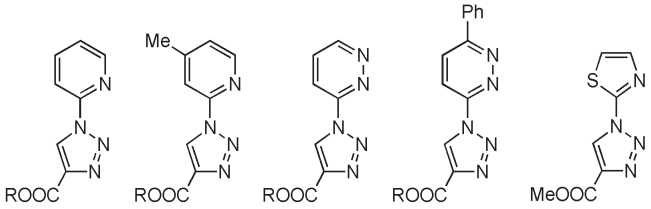
Scheme 3



Reaction conditions: (i) MeOH, reflux (Procedure A); (ii) MeOH, 37% aq. HCl (3 equiv.), reflux (Procedure B).

Table 2

In vitro antimicrobial activity of compounds **6a–o** against *Mycobacterium tuberculosis* $H_{37}Rv$.



6a-c **6d-g** **6h-j** **6k-n** **6o**

Compound [b]	R	% Inhibition[a]	MIC (µg/ml)
6a	methyl	25	[c]
6b	ethyl	74	[c]
6c	*n*-pentyl	99	>6.25
6d	methyl	0	[c]
6e	ethyl	98	>6.25
6f	*n*-propyl	70	[c]
6g	*n*-butyl	89	[c]
6h	methyl	2	[c]
6i	*n*-propyl	13	[c]
6j	*n*-butyl	20	[c]
6k	methyl	99	>6.25
6l	ethyl	4	[c]
6m	*n*-propyl	41	[c]
6n	*n*-pentyl	99	3.13
6o	-	1	[c]

[a] % Inhibition values are relative to the primary test at 6.25 µg/ml against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294) in BACTEC 12B medium using a broth micro dilution assay, the Microplate Alamar Blue Assay [19]; [b] The minimum inhibitory activity (MIC) is defined as the lowest concentration effecting a reduction in fluorescence of 90% relative to controls. The MIC values are relative to the secondary test at concentrations < 6.25 µg/ml against *Mycobacterium tuberculosis* $H_{37}Rv$ (ATCC 27294);[c] Not determined.

determine the actual minimum inhibitory concentration (MIC) in the MABA. Upon re-testing, the MIC value 3.13 µg/ml was established for *n*-pentyl 1-(6-phenylpyridazin-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (**6n**), while the MIC values for compounds **6c,e,k** were found to be >6.25 µg/ml (Table 2).

In conclusion, various 1-heteroaryl substituted alkyl 1*H*-1,2,3-triazole-4-carboxylates **6** are available in four steps starting from heterocyclic amines **2** and methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-en-oate (**1**). The yields in the last step are only moderate, however, the methodology is general and the key-intermediates **5** are available in good yields over the first three steps. The results of the primary antimicrobial evaluation of compounds **6a–o** indicate, that 1-heteroaryl-1*H*-1,2,3-triazole-4-carboxylic acid scaffold might be used in development of antimicrobial compounds. Consequently, we are now developing combinatorial approaches towards 1-heteroaryl-1*H*-1,2,3-triazole-4-carboxylic acid esters and other derivatives, which would enable preparation of libraries of 1-heteroaryl-1*H*-1,2,3-triazole-4-carboxylic acid derivatives for further biological evaluations.

Experimental

Melting points were determined on a Kofler micro hot stage. The nmr spectra were obtained on a Bruker Avance DPX 300 at 300 MHz for ^1H and 75.5 MHz for ^{13}C nucleus, using dimethyl sulfoxide-d_6 and deuteriochloroform with tetramethylsilane as the internal standard, as solvents. Mass spectra were recorded on an AutoSpecQ spectrometer, ir spectra on a Perkin-Elmer Spectrum BX FTIR spectrophotometer. Microanalyses were performed on a Perkin-Elmer CHN Analyser 2400. Column chromatography was performed on silica gel (Fluka, silica gel 60, 0.04–0.06 mm).

Heterocyclic amines **2o–s** are commercially available (Fluka AG). Methyl (*Z*)-2-benzyloxycarbonylamino-3-(dimethylamino)prop-2-enoate (**1**) was prepared according to the literature procedure [20].

General Procedure for the Synthesis of Azolo Fused Pyrimidones **3o–s**.

A mixture of enaminone **1** (1.390 g, 5 mmol), heterocyclic amine **2o–s** (5 mmol), and acetic acid (100%, 15 ml) was heated under reflux for 1–4 h. Volatile components were evaporated *in vacuo*, the residue was triturated with ethanol–water (1:3), and the precipitate was collected by filtration to give fused pyrimidones **3o–s**.

The following compounds were prepared in this manner:

6-Benzyloxycarbonylamino-5*H*-thiazolo[3,2–*a*]pyrimidin-5-one (**3o**).

Prepared from **1** and 2-aminothiazole (**2o**); reflux for 4 h. Yield: 1.45 g (96%) of a pale yellow solid, mp 182–184°, lit [16] mp 183–184°. Spectral data for compound **3o** were in agreement with those, reported in the literature [16].

6-Benzyloxycarbonylaminoimidazo[1,2–*a*]pyrimidin-5(1*H*)-one (**3p**).

Prepared from **1** and 2-aminoimidazole sulfate (**2p**); reflux for 4 h. Yield: 1.35 g (95%) of a pale yellow solid, mp 199–202°; ir (potassium bromide): 3498, 3033, 2819, 1657 (C=O), 1541, 1255, 1085, 747 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 5.10 (2H, s, CH_2), 7.31–7.46 (5H, m, Ph), 7.55 (1H, d, *J* = 2.6 Hz, 3–H), 7.64 (1H, d, *J* = 2.6, 2–H), 8.03 (1H, s, 7–H), 8.53 (1H, br s, N*H*), 12.80 (1H, br s, N*H*).

Anal. Calcd. for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.25; N, 19.71. Found: C, 59.39; H, 4.20; N, 19.46.

6-Benzyloxycarbonylaminopyrazolo[1,5–*a*]pyrimidin-7(1*H*)-one (**3q**).

Prepared from **1** and 3-aminopyrazole (**2q**); reflux for 2 h. Yield: 1.42 g (99%) of a pale yellow solid, mp >250° (decomp.); ir (potassium bromide): 3412, 3138, 1726 (C=O), 1661 (C=O), 1530, 1204, 756 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 5.12 (2H, s, CH_2), 6.18 (1H, d, *J* = 2.3 Hz, 3–H), 7.30–7.45 (5H, m, Ph), 7.90 (1H, d, *J* = 2.3 Hz, 2–H), 8.12 (1H, s, 5–H), 8.68 (1H, br s, N*H*), 12.80 (1H, br s, N*H*).

Anal. Calcd. for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.25; N, 19.71. Found: C, 59.29; H, 4.17; N, 19.44.

6-Benzyloxycarbonylamino-2-methylpyrazolo[1,5–*a*]pyrimidin-7(1*H*)-one (**3r**).

Prepared from **1** and 3-amino-5-methylpyrazole (**2r**); reflux for 1 h. Yield: 1.34 g (90%) of a yellow solid, mp 293–295°; ir (potassium bromide): 3328, 3118, 1662 (C=O), 1545, 1232, 749 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 2.29 (3H, s, Me), 5.11 (2H, s, CH_2), 5.99 (1H, s, 3–H), 7.28–7.45 (5H, m, Ph), 8.03 (1H, s, 5–H), 8.62 (1H, br s, N*H*), 12.21 (1H, br s, N*H*).

Anal. Calcd. for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78. Found: C, 60.64; H, 4.84; N, 18.88.

6-Benzyloxycarbonylamino[1,2,4]triazolo[1,5–*a*]pyrimidin-7(1*H*)-one (**3s**).

Prepared from **1** and 3-amino-1*H*-1,2,4-triazole (**2s**); reflux for 4 h. Yield: 1.22 g (85%) of a white solid, mp 222–224°, lit [16] mp 215–217°. Spectral data for compound 3s were in agreement with those, reported in the literature [16].

General Procedure for the Synthesis of Heterocyclic Amines **4o–s**.

A mixture of the protected amine **3o–s** (2 mmol) and a solution of HBr in acetic acid (33%, 5 ml) was stirred at 50–60° for 2 h. The reaction mixture was cooled to room temperature, the precipitate was collected by filtration, and washed with ethyl acetate to give aminopyrimidones **4o–s**.

The following compounds were prepared in this manner:

6-Amino-5*H*-thiazolo[3,2–*a*]pyrimidin-5-one (**4o**).

Prepared from **3o**. Yield: 0.442 g (89%) of a pale yellow solid, mp 167–170°, lit [16] mp 165–168°. Spectral data for compound **4o** were in agreement with those, reported in the literature [16].

6-Aminoimidazo[1,2–*a*]pyrimidin-5(1*H*)-one Dihydrobromide (**4p**).

Prepared from **3p**. Yield: 0.57 g (95%) of a light brown solid, mp 281–283°; ir (potassium bromide): 3150, 2681, 2488, 1718 (C=O), 1634, 1494, 1292, 750 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 7.72 (1H, d, *J* = 2.3 Hz, 2–H), 7.79 (1H, s, *J* = 2.6 Hz, 3–H), 8.19 (1H, s, 7–H), 9.75 (2H, br s, NH_2); NH proton exchanged.

Anal. Calcd. for $C_6H_8Br_2N_4O$: C, 23.10; H, 2.58; N, 17.96. Found: C, 23.45; H, 2.57; N, 17.69.

6-Aminopyrazolo[1,5–*a*]pyrimidin-7(1*H*)-one Dihydrobromide (**4q**).

Prepared from **3q**. Yield: 0.56 g (90%) of a pale yellow solid, mp >300° (decomp.); ir (potassium bromide): 3432, 3115, 2559, 1709 (C=O), 1596, 1445, 1154, 826, 738 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 6.35 (1H, d, *J* = 1.9 Hz, 3–H), 8.02 (1H, d, *J* = 1.9 Hz, 2–H), 8.24 (1H, s, 5–H), 9.82 (2H, br s, NH_2), 12.84 (1H, br s, NH).

Anal. Calcd. for $C_6H_8Br_2N_4O$: C, 23.10; H, 2.58; N, 17.96. Found: C, 23.43; H, 2.61; N, 17.62.

6-Amino-2-methylpyrazolo[1,5–*a*]pyrimidin-7(1*H*)-one Dihydrobromide (**4r**).

Prepared from **3r**. Yield: 0.59 g (90%) of a yellow solid, mp >300° (decomp.); ir (potassium bromide): 3130, 2707, 2512, 1668 (C=O), 1482, 1326, 814, 746 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 2.33 (3H, s, Me), 6.17 (1H, s, 3–H), 8.11 (1H, s, 5–H), 9.73 (2H, br s, NH_2), 12.62 (1H, br s, NH).

Anal. Calcd. for $C_7H_{10}Br_2N_4O$: C, 25.79; H, 3.09; N, 17.19. Found: C, 25.81; H, 2.94; N, 17.05.

6-Amino[1,2,4]triazolo[1,5–*a*]pyrimidin-7(1*H*)-one Dihydrobromide (**4s**).

Prepared **3s**. Yield: 0.61 g (97%) of a white solid, mp 240° (decomp.); ir (potassium bromide): 3544, 3126, 2850, 1738 (C=O), 1682 (C=O), 1643 (C=O), 1311, 1250, 751 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 8.25 (1H, s, 2–H), 8.52 (1H, s, 5–H), NH protons exchanged.

Anal. Calcd. for $C_5H_7Br_2N_5O$: C, 19.19; H, 2.25; N, 22.38. Found: C, 19.51; H, 2.41; N, 22.45.

General Procedures for the Preparation of Diazonium Salts **5o,p** and Diazo Compounds **5q–u**.

Procedure A. Synthesis of Compound **5o**.

A solution of sodium nitrite (0.760 g, 11 mmol) in water (4 ml) was added slowly to a stirred solution of the amine **4o** (1.672 g, 10 mmol) in 6 *N* hydrochloric acid (24 ml) at 0° and the reaction

mixture was stirred at 0° was for 15 min. Then aqueous fluoroboric acid (50%, 6 ml) was added and the precipitate was collected by filtration and washed thoroughly with cold (0°) water, methanol, and diethyl ether to give **5o**.

Procedure B. Synthesis of Compounds **5p,t,u**.

A mixture of amine dihydrobromide **4p,q,r** (2 mmol), aqueous fluoroboric acid (50%, 0.51 g), and acetic acid (10 ml) or ethyl acetate (10 ml) was stirred at room temperature for 30 min. Then aqueous sodium nitrite (20%, 0.7 g) was added slowly and the reaction mixture was stirred at room temperature for 1 h. The precipitate was collected by filtration and washed thoroughly with ethyl acetate and diethyl ether to give compounds **5p,t,u**.

Procedure C. Synthesis of Diazo Compounds **5q–s**.

A suspension of amine **4q–s** (1 mmol) in 2-propanol (7 ml) was added, while stirring, to cooled (–15°) boron trifluoride ethyl etherate (0.28g, 1 mmol) and the mixture was stirred at –15° for 15 min. Then a solution of *tert*-butyl nitrite (0.1 g) in 2-propanol (3 ml) was slowly added and the mixture was stirred at –15° for 30 min and at 0–5° for 1 h. The precipitate was collected by filtration and washed thoroughly with cold (0°) methanol, chloroform, and ether to give diazo compounds **5q–s**.

The following compounds were prepared in this manner:

5-Oxo-5*H*-thiazolo[3,2–*a*]pyrimidine-6-diazonium Tetrafluoroborate (**5o**).

Prepared from **4o**, Procedure A. Yield: 2.155 g (80%) of a light brown solid, mp 195–197°; ir (potassium bromide): 3128, 2194, 1726, 1510, 1035, 724 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 8.18 (1H, d, *J* = 4.9 Hz, 2–H), 8.67 (1H, d, J = 4.9 Hz, 3–H), 9.41 (1H, s, 7–H). ^{13}C nmr (DMSO-d_6): δ 90.8. 122.4, 125.5, 153.0, 160.9, 172.3. Ms (*m*/*z*) 179 (M^+–BF_4^-).

Anal. Calcd. for $C_6H_3BF_4N_4OS$: C, 27.09; H, 1.14; N, 21.06. Found: C, 27.09; H, 1.10; N, 20.84.

5-Oxo-1,5-dihydroimidazo[1,2–*a*]pyrimidine-6-diazonium Tetrafluoroborate Hydrobromide (**5p**).

Prepared from **4p** (0.620 g, 2 mmol) in acetic acid, Procedure B. Yield: 0.48 g (75%) of a light brown solid, mp 238–240°; ir (potassium bromide): 3416, 3154, 2675, 2205, 2181, 1725, 1542, 1064, 749 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 7.66 (1H, d, *J* = 1.9 Hz, 2–H), 7.98 (1H, d, *J* = 1.9 Hz, 3–H), 9.01 (1H, s, 7–H), NH proton exchanged. Ms (*m*/*z*) 162 (M^+–BF_4^-–HBr).

Anal. Calcd. for $C_6H_5BBrF_4N_5O$: C, 21.85; H, 1.53; N, 21.23. Found: C, 22.14; H, 1.29; N, 21.15.

6-Diazopyrazolo[1,5–*a*]pyrimidin-7(6*H*)-one (**5q**).

Prepared from **4q** (0.310 g, 1 mmol), Procedure C. Yield: 0.14 g (87%) of a yellow solid, mp 208° (decomp.); ir (potassium bromide): 3418, 3102, 3040, 2216, 2139, 1703, 1570, 1113, 909, 738 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 6.66 (1H, d, *J* = 1.5 Hz, 3–H), 8.06 (1H, d, *J* = 1.8 Hz, 2–H), 8.71 (1H, s, 5–H). Ms (*m*/*z*) 161 (M^+), 162 (MH^+).

6-Diazo-2-methylpyrazolo[1,5–*a*]pyrimidin-7(6*H*)-one (**5r**).

Prepared from **4r** (0.310 g, 1 mmol), Procedure C. Yield: 0.10 g (57%) of a yellow solid, mp >300° (decomp.); ir (potassium bromide): 3448, 2208, 2168, 1687, 1678, 1580, 1240, 814 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 2.31 (3H, s, Me), 6.49 (1H, s, 3–H), 8.66 (1H, s, 5–H). Ms (*m*/*z*) 175 (M^+), 176 (MH^+).

6-Diazo[1,2,4]triazolo[1,5–*a*]pyrimidin-7(6*H*)-one (**5s**).

Prepared from **4s** (0.310 g, 1 mmol), Procedure C. Yield: 0.15 g (93%) of a white solid, mp 237–239°; ir (potassium bromide): 3404, 3133, 3019, 2204, 2184, 1709, 1546, 765 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 8.43 (1H, s, 7–H), 9.10 (1H, s, 2–H). MS (*m*/*z*) 162 (M^+), 163 (MH^+).

Anal. Calcd. for $C_5H_2N_6O$: C, 37. 05; H, 1.24; N, 51.84. Found: C, 36.70; H, 1.28; N, 52.17.

3-Bromo-6-diazopyrazolo[1,5–*a*]pyrimidin-7(6*H*)-one (**5t**).

Prepared from **4q** (0.620 g, 2 mmol) in ethyl acetate, Procedure B. Yield: 0.38 g (80%) of a yellow solid, mp 224–227°; ir (potassium bromide): 3413, 3064, 3015, 2226, 2155, 1697, 1576, 1529, 949, 734 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 8.24 (1H, s, 2–H), 8.80 (1H, s, 5–H). ^{13}C nmr (dimethyl sulfoxide-d_6): δ 78.4, 91.1, 146.5, 147.7, 150.9, 154.6. Ms (*m*/*z*) 239, 241 (M^+), 240, 242 (MH^+).

3-Bromo-6-diazo-2-methylpyrazolo[1,5–*a*]pyrimidin-7(6*H*)-one (**5u**).

Prepared from **4r** (0.330 g, 1 mmol) in ethyl acetate, Procedure B. Yield: 0.19 g (75%) of a yellow solid, mp 199–201°; ir (potassium bromide): 3474, 3026, 2211, 2141, 1689, 1578, 1317, 1040, 734 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 2.32 (3H, s, Me), 8.66 (1H, s, 5–H). Ms (*m*/*z*) 253, 255 (M^+), 254, 256 (MH^+).

Anal. Calcd. for $C_7H_4BrN_5O$: C, 33.09; H, 1.59; N, 27.57. Found: C, 32.85; H, 1.53; N, 27.24.

General Procedures for the Preparation of Alkyl 1-Heteroaryl-1*H*-1,2,3-triazole-4-carboxylates **6o–u** and Azolo[1,5–*a*]pyrimidin-7(1*H*)-ones **7q,s**.

Procedure A. Synthesis of Compounds **6o,p** and **7q,s**.

A mixture of compound **5** (0.100 g) and methanol (15 ml) or ethanol (15 ml) was stirred at 60–70° for 20–40 h. Volatile components were evaporated *in vacuo* and the residue was purified by column chromatography. Fractions containing the product were combined and evaporated *in vacuo* to give compounds **6o,p** and **7q,s**.

Procedure B. Synthesis of Compounds **6q–u**.

A mixture of compound **5** (0.100 g), methanol (15 ml), and hydrochloric acid (37%, 0.2 ml) was stirred at 60–70° for 35–45 h. Volatile components were evaporated *in vacuo* and the residue was purified by column chromatography. Fractions containing the product were combined and evaporated *in vacuo* to give compounds **6q–u**.

The following compounds were prepared in this manner:

Methyl 1-(Thiazol-2-yl)-1*H*-1,2,3-triazole-4-carboxylate (**6o**).

Prepared from **5o** (0.100 g, 0.376 mmol), Procedure A, reflux for 40 h, column chromatograpy (EtOAc–hexanes, 2:1). Yield: 0.31 g (40%) of a white solid, mp 161–163°; ir (potassium bromide): 3114, 1730 (C=O), 1543, 1273, 1260, 1031 cm^{-1}. ^1H nmr (deuteriochloroform): δ 4.01 (3H, s, OMe), 7.35 (1H, d, *J* = 3.4 Hz, 5'–H), 7.73 (1H, d, *J* = 3.4 Hz, 4'–H), 8.92 (1H, s, 5–H). ^{13}C nmr (deuteriochloroform): δ 52.9, 119.3, 125.2, 140.9, 141.2, 156.7, 160.8. Ei-ms (*m*/*z*) 210 (M^+), fab-ms (*m*/*z*) 211 (MH^+).

Anal. Calcd. for $C_7H_6N_4O_2S$: C, 39.99; H, 2.88; N, 26.65. Found: C, 40.37; H, 2.92; N, 26.35.

Methyl 1-(Imidazol-2-yl)-1*H*-1,2,3-triazole-4-carboxylate (**6p**).

Prepared from **5p** (0.100 g, 0.3 mmol), Procedure A, reflux for 40 h, column chromatography (ethyl acetate). Yield: 0.028 g (48%) of a pale yellow solid, mp 180–183°; ir (potassium bromide): 3415, 3146, 2959, 1742 (C=O), 1586, 1268, 1035, 776, 768 cm^{-1}. ^1H nmr (deuteriochloroform): δ 4.00 (3H, s, OMe), 7.12 (2H, br s, 4'–H, 5'–H), 8.86 (1H, s, 5–H), 10.21 (1H, br s, NH). Ms (*m*/*z*): 193 (M^+), 194 (MH^+). Hrms Calcd. for $C_7H_7N_5O_2$: *m*/*z* = 193.059979 (M^+). Found: *m*/*z* = 193.060550 (M^+).

Methyl 1-(1*H*-Pyrazol-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (**6q**).

Prepared from **5q** (0.100 g, 0.62 mmol), Procedure B, reflux for 45 h, column chromatography (ethyl acetate). Yield: 0.040 g (33%) of a pale yellow solid, mp 229–232°; ir (potassium bromide): 3437, 3161, 2989, 2927, 1728 (C=O), 1262, 1209, 1045, 775 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 3.88 (3H, s, OMe), 6.78 (1H, deg t, *J* = 2.3 Hz, 4'–H), 7.99 (1H, deg t, *J* = 2.3 Hz, 5'–H), 9.17 (1H, s, 5–H), 13.36 (1H, br s, NH). Ms (*m*/*z*): 193 (M^+), 194 (MH^+). Hrms Calcd. for $C_7H_7N_5O_2$: *m*/*z* = 193.059979 (M^+). Found: *m*/*z* = 193.060650 (M^+).

Methyl 1-(5-Methyl-1*H*-pyrazol-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (**6r**).

Prepared from **5r** (0.100 g, 0.57 mmol), Procedure B, reflux for 45 h, column chromatography (ethyl acetate). Yield: 0.016 g (15%) of a pale yellow solid, mp 257–260°; ir (potassium bromide): 3214, 3150, 2948, 1724 (C=O), 1337, 1233, 1041 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 2.32 (3H, s, 5'–Me), 3.88 (3H, s, OMe), 6.53 (1H, s, 4'–H), 9.10 (1H, s, 5–H), 13.03 (1H, br s, NH). Ms (*m*/*z*): 207 (M^+), 208 (MH^+). Hrms Calcd. for $C_8H_9N_5O_2$: *m*/*z* = 207.075625 (M^+). Found: *m*/*z* = 207.076250 (M^+).

Methyl 1-(1*H*-1,2,4-triazol-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (**6s**).

Prepared from **5s** (0.100 g, 0.61 mmol), Procedure B, reflux for 35 h, column chromatography (ethyl acetate). Yield: 0.030 g (26%) of a pale yellow solid, mp 234–236°; ir (potassium bromide): 3273, 3125, 1718 (C=O), 1564, 1330, 1036 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 3.89 (3H, s, OMe), 8.84 (1H, s, 5'–H), 9.25 (1H, s, 5–H), 14.75 (1H, br s, NH). ^{13}C nmr (deuteriochloroform): δ 53.0, 129.0, 139.9, 146.5, 155.2, 161.1. Ms (*m*/*z*): 194 (M^+), 195 (MH^+). Hrms Calcd. for $C_6H_6N_6O_2$: *m*/*z* = 194.055224 (M^+). Found: *m*/*z* = 194.056010 (M^+).

Methyl 1-(4-Bromo-1*H*-pyrazol-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (**6t**).

Prepared from **5t** (0.100 g, 0.41 mmol), Procedure B, reflux for 45 h, column chromatography (ethyl acetate). Yield: 0.018 g (16%) of a pale yellow solid, mp 175–178°; ir (potassium bromide): 3455, 3230, 3144, 2990, 2934, 1734 (C=O), 1634, 1210, 776 cm^{-1}. ^1H nmr (deuteriochloroform): δ 4.03 (3H, s, OMe), 7.98 (1H, s, 5'–H), 8.86 (1H, s, 5–H), 12.10 (1H, br s, NH). Ms (*m*/*z*): 271, 273 (M^+), 272, 274 (MH^+). Hrms Calcd. for $C_7H_6BrN_5O_2$: *m*/*z* = 270.970486 (M^+). Found: *m*/*z* = 270.971240 (M^+).

Methyl 1-(4-Bromo-5-methyl-1*H*-pyrazol-3-yl)-1*H*-1,2,3-triazole-4-carboxylate (**6u**).

Prepared from **5u** (0.100 g, 0.39 mmol), Procedure B, reflux for 45 h, column chromatography (ethyl acetate). Yield: 0.011 g (9%) of a pale yellow solid, mp 195–198°; ir (potassium bromide): 3347, 3222, 3123, 1695 (C=O), 1337, 1239, 1036, 955, 781 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 2.32 (3H, s, 5'–Me), 3.89 (3H, s, OMe), 9.18 (1H, s, 5–H), 13.70 (1H, br s, NH). Ms (*m*/*z*): 285, 287 (M^+), 286, 288 (MH^+). Hrms Calcd. for $C_8H_8BrN_5O_2$: *m*/*z* = 284.986136 (M^+). Found: *m*/*z* = 284.987200 (M^+).

Pyrazolo[1,5–*a*]pyrimidin-7(1*H*)-one (**7q**).

Prepared from **5q** (0.100 g, 0.62 mmol) and methanol, Procedure A, reflux for 30 h, column chromatography (chloroform–hexanes, 15:1). Yield: 0.043 g (51%) of a pale yellow solid, mp 335–339°, lit [17] mp 338–340°; ir (potassium bromide): 3414, 3140, 2923, 1678 (C=O), 1624, 1582, 1360, 796 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 5.68 (1H, d, *J* = 7.4 Hz, 6–H), 6.18 (1H, d, *J* = 2.0 Hz, 3–H), 7.86 (1H, d, *J* = 7.4 Hz, 5–H), 7.87 (1H, d, *J* = 2.0 Hz, 2–H), 12.38 (1H, br s, NH).

[1,2,4]Triazolo[1,5–*a*]pyrimidin-7(1*H*)-one (**7s**).

Prepared from **5s** (0.100 g, 0.61 mmol) and methanol, Procedure A, reflux for 20 h, column chromatography (chloroform–hexanes, 15:1). Yield: 0.040 g (48%) of a pale yellow solid, mp 300°, lit [18] mp 295–299°; ir (potassium bromide): 3446, 3097, 1704 (C=O), 1595, 1475, 1314, 1169, 814, 749 cm^{-1}. ^1H nmr (dimethyl sulfoxide-d_6): δ 5.94 (1H, d, *J* = 7.5 Hz, 6–H), 7.99 (1H, d, *J* = 7.5 Hz, 5–H), 8.23 (1H, s, 2–H), 13.29 (1H, br s, NH). Ms (*m*/*z*): 136 (M^+).

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