Solvent-free Synthesis of 5-methyl-7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylic esters Catalyzed by Sulfamic Acid

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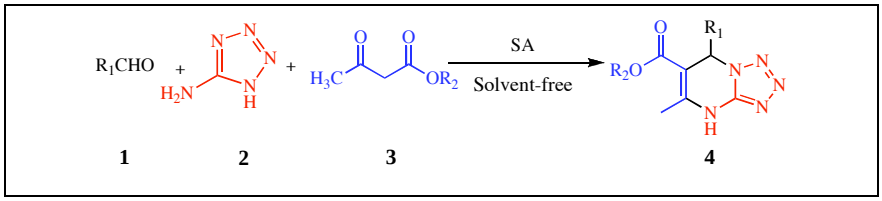

The solvent-free synthesis of 5-methyl-7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylic esters was performed and effectively catalyzed by sulfamic acid. Compared with conventional methods, this protocol features mild reaction conditions and high yields. Furthermore, it is solvent-free and thus eco-friendly.

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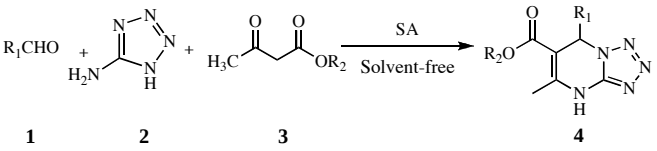
INTRODUCTION

In past decades, much attention has been devoted towards dihydropyrimidine (DHPM) derivatives due to their array of pharmacological and therapeutic properties [1,2]. They have emerged as potential calcium channel blockers [3], inhibitors of mitotic kinesin, Eg5 for treating cancer [4,5], TRPA1 modulators for treating pain [6], *etc*. Several marine alkaloids containing the dihydropyrimidine core unit were found to show interesting biological activities such as antiviral, antibacterial and anti-inflammatory activity [7,8]. Hence the preparation of this heterocyclic core unit has gained much importance.

Compounds containing the dihydrotetrazolo[1,5-*a*]-pyrimidine (DHPM) scaffold include purine derivatives which have been reported to have various biological activities, such as antimicrobial activity [9], farnesyl transferase inhibitory [10], fungicidal activity [5], antihypertensive [11], KATP channel opening [12], central nervous system stimulating [13], *etc*. In general, three main methods for synthesizing these compounds have been developed so far. The first one utilizes an azide intermediate [14-17]. The second method starts with 2-aminotetrazole and uses a three-component reaction [18-23], and the third involves the reaction of 5-aminotetrazole with β-oxo carbonyl compounds or α,β-unsaturated carbonyl compounds [24-26]. However, most of the synthetic protocols reported so far have many drawbacks, including high temperatures, prolonged reaction time, drastic reaction conditions, low yields and the use of hazardous and often expensive acid catalysts. Therefore, the development of simple, convenient and environmentally benign approaches for the synthesis of these compounds is still desirable. Recently, sulfamic acid (NH_2SO_3H, SA), a commercially available and inexpensive reagent, has been reported to catalyze the Biginelli reaction efficiently [27,28]. In continuing our work related to the DHPM scaffold and optimization of the Biginelli reaction [29,30], we report herein the solvent-free synthesis of 5-methyl-7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylic esters catalyzed by sulfamic acid (Scheme 1, Table 4).

Scheme 1



RESULTS AND DISCUSSION

The effect of solvent on the reaction was initially examined by reacting ethyl 3-oxobutanoate (1 mmol), 1*H*-tetrazol-5-amine hydrate (1 mmol) and phenyl aldehyde (1 mmol) catalyzed by SA. It was found that if the synthesis was performed in the organic solvent it gave the expected product, **4w**, in moderate to high yield (55-85%) (Table 1).

Table 1

Solvent effect on the synthesis of **4w**.

Entry	Solvent	Temp (°C)	Time (h)	Yield (%)
1	CH_3CN	reflux	9	60
2	$CHCl_3$	reflux	9	55
3	EtOH	reflux	9	85
4	HOAc	85	9	65
5	H_2O	85	9	55
6	solvent-free	85	7	85

To screen for the optimal catalyst for the sovent-free synthesis, the previous reaction was performed using H_2SO_4, $FeCl_3·6H_2O$, $MgSO_4$, $SnCl_2·2H_2O$, $NiCl_2$, $CrCl_3$, Na_2SO_4, and SA as catalysts (10 mol%) (Table 2). As shown in Table 2, SA was the best catalyst for this reaction from the viewpoint of yield.

Table 2

Catalyst optimization for the synthesis of **4w** under solvent-free media.

Entry	Catalyst	Temp (°C)	Time (h)	Yield(%)
1	H_2SO_4	85	7	54
2	$FeCl_3·6H_2O$	85	9	46
3	$MgSO_4$	85	8	65
4	$SnCl_2·2H_2O$	85	10	55
5	$NiCl_2$	85	9	52
6	$CrCl_3$	85	9	55
7	Na_2SO_4	85	10	45
8	SA	85	7	85

Table 3

The effect of catalyst loading on reaction under solvent-free media.

Entry	Catalyst (%)	Temp (°C)	Time (h)	Yield(%)
1	0	85	8	52
2	5	85	8	75
3	10	85	8	85
4	15	85	8	72
5	20	85	8	65

To find the best catalyst loading, the previous reaction was run in 1 mmol scale of substrate using different amounts of catalyst (Table 3). Table 3 shows that 10% mol amount of sulfamic acid was optimal under the experimental conditions used.

Moreover, the optimal temperature for the reaction was found to be 85°C.

Based on the optimized reaction conditions, a series of 5-methyl-7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylic esters were synthesized. The results, summarized in Table 4, show that the reaction catalyzed by sulfamic acid under solvent-free conditions gave the corresponding products in moderate to good yields. As shown in Table 4, this methodology can be applied to aromatic aldehydes either with electron-withdrawing groups (such as a nitro group, halogen) or electron-donating groups (such as a methoxy group) with moderate to excellent yields under the same conditions. Therefore, we conclud that the electronic nature of substituents of the aromatic aldehyde had no significant effect on the reaction. However, when the aliphatic aldehyde was applied to this reaction, no expected product was obtained. In addition, yields were unaffected when methyl 3-oxobutanoate or ethyl 3-oxobutanoate was used.

All of the compounds were characterized by elemental analysis, FTIR and ^{1}H NMR. . To further elucidate the structure of products, a single crystal of compound **4c** was prepared and its structure was determined by X-ray diffraction (Figure 1).

Table 4

SA catalyzed the synthesis of compound **4**.

Compound No.	R_1	R_2	Time(h)	Yield (%)	Mp(℃)
4a	3,4-$(CH_3O)_2C_6H_3$	CH_3	8	78	218-220
4b	4-$NO_2C_6H_4$	CH_3	9	82	230-232
4c	4-BrC_6H_4	CH_3	7	79	220-222
4d	2,4-$Cl_2C_6H_3$	CH_3	8	84	253-255
4e	3-FC_6H_4	CH_3	8	87	178-180
4f	3,4-$(OCH_2O)C_6H_3$	CH_3	9	80	213-215
4g	3,4,5-$(CH_3O)_3C_6H_2$	CH_3	9	77	200-202
4h	2-FC_6H_4	CH_3	8	83	223-224
4i	3-ClC_6H_4	CH_3	8	82	184-186
4j	2-ClC_6H_4	CH_3	7	81	230-232
4k	4-FC_6H_4	CH_3	7	84	197-198
4l	3-$NO_2C_6H_4$	CH_3	8	87	226-228
4m	3-$(CHO)C_6H_4$	CH_3	9	80	>300
4n	3-NO_2-4-HOC_6H_3	CH_3	9	79	247-249
4o	C_6H_5	CH_3	8	82	189-191
4p	4-BrC_6H_4	C_2H_5	7	89	237-238
4q	2,4-$Cl_2C_6H_4$	C_2H_5	8	87	257-259
4r	3,4-$(OCH_2O)C_6H_3$	C_2H_5	8	85	196-198
4s	3,4,5-$(CH_3O)_3C_6H_2$	C_2H_5	9	88	199-201
4t	3,4-$(CH_3O)_2C_6H_3$	C_2H_5	9	86	210-212
4u	3-ClC_6H_4	C_2H_5	7	81	184-186
4v	3-$NO_2C_6H_4$	C_2H_5	8	83	206-208
4w	C_6H_5	C_2H_5	7	85	204-205(Ref[21]:205-206)

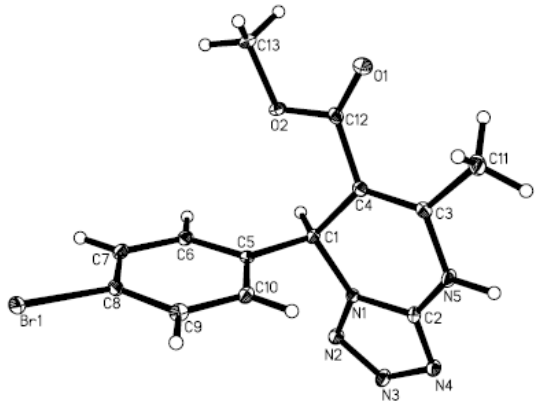


Figure 1. The crystal structure of **4c**.

In summary, we have developed an efficient, economical, safe and environmentally benign procedure for synthesizing derivatives of dihydrotetrazolo[1,5-*a*]-pyrimidine. The results show that SA is an efficient catalyst that could, in principle, be used as a catalyst in organic reactions requiring acid catalysis.

EXPERIMENTAL

Common reagents and materials were purchased from commercial sources and purified by recrystallization or distillation. NMR spectra were recorded on a Bruker DPX 400, Data for ^{1}H are reported as follows: chemical shift (ppm), integration, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), coupling constant (Hz) and number. Infrared (IR) spectra were recorded on a TENSOR 27 spectrophotometer in KBr pellet and are reported in terms of frequency of absorption (cm^{-1}). Elemental analyses were performed on a Perkin-Elmer 240 II elementary analyzer. Melting points were determined in open capillaries and are uncorrected. The single crystal diffraction data were gathered on a Rigaku Saturn diffractometer.

General Procedure for the synthesis of 5-methyl-7-aryl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylic esters (4a-4w). Acetoacetate ester **1** (1 mmol), 1*H*-tetrazol-5-amine hydrate **2** (0.103 g, 1 mmol) and aryl aldehyde **3** (1 mmol) were triturated together in an agate mortar for 5 minutes. Then the mixture was kept at 85 °C for a certain time (monitored by TLC). The resulting mixture was cooled to room temperature, washed with water and recrystallized from ethanol (95%) to give pure product **4**. A similar procedure was used in preparing the following compounds.

Methyl 7-(3,4-dimethoxyphenyl)-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate (4a). ir (potassium bromide): 3185, 3060, 2958, 1692, 1661, 1594, 1519, 1439, 1383, 1333, 1313, 1261, 1229, 1138, 1104, 1020, 992, 954, 876, 804, 783, 747, 684 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.46 (s, 3H, 5-methyl-H), 3.54 (s, 3H, $COOCH_3$), 3.72 (s, 3H, CH_3O), 3.74 (s, 3H, CH_3O), 6.20 (s, 1H, CH), 6.73 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H, ArH), 6.89 (d, J = 8.4 Hz, 1H, ArH), 6.93 (d, J=1.6Hz, 1H, ArH), 11.26 (s, 1H, NH). *Anal.* Calcd. for $C_{15}H_{17}N_5O_4$: C, 54.38; H, 5.17; N, 21.14. Found: C, 54.26; H, 5.05; N, 21.28.

Methyl 5-methyl-7-(4-nitrophenyl)-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxylate (4b). ir (potassium bromide): 3177, 3080, 2957, 1692, 1651, 1580, 1520, 1438, 1354, 1315, 1290, 1238, 1193, 1106, 993, 952, 830, 750, 735, 701, 666 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.48 (s, 3H, 5-methyl-H), 3.52 (s, 3H, $COOCH_3$), 6.86 (s, 1H, CH), 7.63 (d, J = 8.0 Hz, 2H, ArH), 8.20 (d, J = 8.0 Hz, 2H, ArH), 11.48 (s, 1H, NH). *Anal.* Calcd. for $C_{13}H_{12}N_6O_4$: C, 49.37; H, 3.82; N, 26.57. Found: C, 49.46; H, 3.77; N, 26.45.

Methyl 7-(4-bromophenyl)-5-methyl-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxylate (4c). ir (potassium bromide): 3245, 3059, 2949, 1710, 1648, 1574, 1488, 1432, 1413, 1385, 1302, 1278, 1227, 1190, 1153, 1103, 1072, 1012, 839, 813, 772, 725, 686 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.46 (s, 3H, 5-methyl-H), 3.52 (s, 3H, $COOCH_3$), 6.69 (s, 1H, CH), 7.28 (d, J = 8.0 Hz, 2H, ArH), 7.55 (d, J = 8.0 Hz, 2H, ArH), 11.38 (s, 1H, NH). *Anal.* Calcd. for $C_{13}H_{12}BrN_5O_2$: C, 44.59; H, 3.45; N, 20.00. Found: C, 44.65; H, 3.35; N, 20.16.

Methyl 7-(2,4-dichlorophenyl)-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate (4d). ir (potassium bromide): 3181, 3057, 2953, 1717, 1691, 1649, 1582, 1473, 1436, 1387, 1342, 1315, 1286, 1230, 1190, 1149, 1104, 1049, 953, 851, 818, 780, 731, 690 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.46 (s, 3H, 5-methyl-H), 3.50 (s, 3H, $COOCH_3$), 7.03 (s, 1H, CH), 7.43 (s, 2H, ArH), 7.67 (s, 1H, ArH), 11.46 (s, 1H, NH). *Anal.* Calcd. for $C_{13}H_{11}Cl_2N_5O_2$: C, 45.90; H, 3.26; N, 20.59. Found: C, 45.75; H, 3.37; N, 20.44.

Methyl 7-(3-fluorophenyl)-5-methyl-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxylate (4e). ir (potassium bromide): 3176, 3057, 2955, 1689, 1651, 1579, 1489, 1437, 1390, 1342, 1315, 1285, 1258, 1238, 1189, 1153, 1136, 1103, 993, 952, 934, 811, 775, 701, 704 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.47 (s, 3H, 5-methyl-H), 3.53 (s, 3H, $COOCH_3$), 6.49 (s, 1H, NH), 6.71 (s, 1H, CH), 7.15~7.22 (m, 3H, ArH), 7.38~7.43 (m, 1H, ArH). *Anal.* Calcd. for $C_{13}H_{12}FN_5O_2$: C, 53.98; H, 4.18; N, 24.21. Found: C, 53.86; H, 4.26; N, 24.32.

Methyl 7-(benzo[d][1,3]dioxol-5-yl)-5-methyl-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate (4f). ir (potassium bromide): 3238, 3177, 3085, 2949, 1711, 1686, 1653, 1584, 1493, 1434, 1379, 1333, 1315, 1251, 1189, 1146, 1101, 1038, 963, 924, 795, 734, 692 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.46 (s, 3H, 5-methyl-H), 3.54 (s, 3H, $COOCH_3$), 6.01 (s, 2H, OCH_2O), 6.60 (s, 1H, CH), 6.79 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H, ArH), 6.86 (d, J = 8.0 Hz, 1H, ArH), 6.87 (d, J = 1.6Hz, 1H, ArH), 11.28 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_{13}N_5O_4$: C, 53.33; H, 4.16; N, 22.21. Found: C, 53.46; H, 4.28; N, 22.35.

Methyl 5-methyl-7-(3,4,5-trimethoxyphenyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate (4g). ir (potassium bromide): 3241, 3179, 3096, 2839, 1715, 1684, 1651, 1583, 1507, 1463, 1385, 1337, 1280, 1234, 1189, 1129, 1009, 956, 816, 774, 734, 719, 699 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.47 (s, 3H, 5-methyl-H), 3.57 (s, 3H, $COOCH_3$), 3.64 (s, 3H, CH_3O), 3.73 (s, 6H, 2×CH_3O), 6.56 (s, 2H, ArH), 6.63 (s, 1H, CH), 11.28 (s, 1H, NH). *Anal.* Calcd. for $C_{16}H_{19}N_5O_5$: C, 53.18; H, 5.30; N, 19.38. Found: C, 53.26; H, 5.18; N, 19.47.

Methyl 7-(2-fluorophenyl)-5-methyl-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxylate (4h). ir (potassium bromide): 3180, 3050, 2957, 1696, 1654, 1580, 1493, 1435, 1388, 1336, 1316, 1284, 1244, 1228, 1180, 1152, 1106, 1075, 992, 961, 854, 788, 755, 733, 678 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 2.45 (s, 3H, 5-methyl-H), 3.52 (s, 3H, $COOCH_3$), 6.89 (s, 1H, CH), 7.18~7.23 (m, 2H, ArH), 7.36~7.42 (m, 2H, ArH), 11.42 (s, 1H, NH).

Anal. Calcd. for $C_{13}H_{12}FN_5O_2$: C, 53.98; H, 4.18; N, 24.21. Found: C, 53.86; H, 4.22; N, 24.36.

Methyl 7-(3-chlorophenyl)-5-methyl-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxylate (4i). ir (potassium bromide): 3272, 3187, 3058, 2956, 1672, 1579, 1476, 1433, 1388, 1339, 1302, 1285, 1235, 1193, 1146, 1100, 1078, 1000, 980, 955, 876, 791, 771, 736, 706, 687 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.47 (s, 3H, 5-methyl-H), 3.53 (s, 3H, $COOCH_3$), 6.71 (s, 1H, CH), 7.28~7.31 (m, 1H, ArH), 7.38~7.42 (m, 3H, ArH), 11.39 (s, 1H, NH). *Anal.* Calcd. for $C_{13}H_{12}ClN_5O_2$: C, 51.07; H, 3.96; N, 22.91. Found: C, 51.15; H, 4.07; N, 22.86.

Methyl 7-(2-chlorophenyl)-5-methyl-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxylate (4j). ir (potassium bromide): 3180, 3055, 2952, 1682, 1654, 1588, 1474, 1438, 1381, 1337, 1314, 1282, 1236, 1189, 1147, 1106, 1078, 1042, 991, 840, 754, 732, 703, 689 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.46 (s, 3H, 5-methyl-H), 3.49 (s, 3H, $COOCH_3$), 7.02 (s, 1H, CH), 7.33~7.40 (m, 3H, ArH), 7.46~7.49 (m, 1H, ArH), 11.41 (s, 1H, NH). *Anal*. Calcd. for $C_{13}H_{12}ClN_5O_2$: C, 51.07; H, 3.96; N, 22.91. Found: C, 50.96; H, 4.02; N, 22.78.

Methyl 7-(4-fluorophenyl)-5-methyl-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxylate (4k). ir (potassium bromide): 3177, 3079, 2952, 1172, 1689, 1649, 1605, 1576, 1510, 1435, 1387, 1335, 1313, 1284, 1228, 1190, 1158, 1104, 1079, 993, 962, 856, 819, 792, 767, 734, 696 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.46 (s, 3H, 5-methyl-H), 3.52 (s, 3H, $COOCH_3$), 6.70 (s, 1H, CH), 7.15 (t, J = 8.4 Hz, 2H, ArH), 7.36 (dd, J_1= 8.4Hz, J_2 = 5.4Hz, 2H, ArH), 11.38 (s, 1H, NH). *Anal*. Calcd. for $C_{13}H_{12}FN_5O_2$: C, 53.98; H, 4.18; N, 24.21. Found: C, 53.87; H, 4.24; N, 24.36.

Methyl 5-methyl-7-(3-nitrophenyl)-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxylate (4l). ir (potassium bromide): 3224, 3178, 3066, 2952, 1720, 1684, 1652, 1576, 1576, 1535, 1437, 1349, 1311, 1286, 1230, 1194, 1147, 1101, 1079, 737, 713 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.49 (s, 3H, 5-methyl-H), 3.52 (s, 3H, $COOCH_3$), 6.92 (s, 1H, CH), 7.67 (d, J = 6.8Hz, 1H, ArH), 7.80 (d, J = 6.8Hz, 1H, ArH), 8.20 (s, 2H, ArH), 11.48 (s, 1H, NH). *Anal.* Calcd. for $C_{13}H_{12}N_6O_4$: C, 49.37; H, 3.82; N, 26.57. Found: C, 49.28; H, 3.72; N, 26.66.

Dimethyl 7,7'-(1,3-phenylene)bis(5-methyl-4,7-dihydro-tetrazolo[1,5-*a*]pyrimidine-6-carboxylate) (4m). ir (potassium bromide): 3251, 3182, 3102, 2955, 1712, 1655, 1578, 1433, 1381, 1311, 1287, 1230, 1190, 1144, 1101, 1077, 990, 811, 787, 763, 736, 715, 694 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.45 (s, 6H, 2×5-methyl-H), 3.44 (s, 6H, 2×$COOCH_3$), 6.68 (s, 2H, 2×CH), 7.16 (d, J = 7.6Hz, 2H, ArH), 7.24 (s, 1H, ArH), 7.30 (t, J = 7.6Hz, 1H, ArH), 11.35 (s, 2H, 2×NH). *Anal.* Calcd. for $C_{20}H_{20}N_{10}O_4$: C, 51.72; H, 4.34; N, 30.16. Found: C, 51.66; H, 4.42; N, 30.28.

Methyl 7-(4-hydroxy-3-nitrophenyl)-5-methyl-4,7-dihydro-tetrazolo[1,5-*a*]pyrimidine-6-carboxylate (4n). ir (potassium bromide): 3249, 3052, 2956, 1695, 1630, 1580, 1541, 1489, 1436, 1386, 1338, 1314, 1240, 1181, 1106, 1079, 827, 764 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.46 (s, 3H, 5-methyl-H), 3.54 (s, 3H, $COOCH_3$), 6.72 (s, 1H, CH), 7.10 (d, J = 8.4 Hz, 1H, ArH), 7.47 (d, J = 8.4Hz, 1H, ArH), 7.56 (s, 1H, ArH), 11.18 (s, 1H, OH), 11.36 (s, 1H, NH). *Anal.* Calcd. for $C_{13}H_{12}N_6O_5$: C, 46.99; H, 3.64; N, 25.29. Found: C, 46.88; H, 3.54; N, 25.36.

Methyl 4,7-dihydro-5-methyl-7-phenyltetrazolo[1,5-*a*]-pyrimidine-6-carboxylate (4o). ir (potassium bromide): 3152, 3102, 2923, 1642, 1623, 1509, 1442, 1290, 1223, 1184, 1102, 987, 949, 823, 745, 729, 695, 639 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.42 (s, 3H, 5-methyl-H), 3.55 (s, 3H, $COOCH_3$), 6.84 (s, 1H, CH), 7.06 (s, 1H, CH), 7.83 (d, J = 8.0 Hz, 2H, ArH), 8.15 (d, J = 8.0 Hz, 2H, ArH), 11.48(s, 1H, NH). *Anal.* Calcd. for $C_{13}H_{13}N_5O_2$: C, 57.56; H, 4.83; N, 25.82. Found: C, 57.55; H, 4.83; N, 25.85.

Ethyl 7-(4-bromophenyl)-5-methyl-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxylate (4p). ir (potassium bromide): 3251, 3182, 3101, 3058, 2979, 1702, 1655, 1568, 1487, 1407, 1387, 1309, 1282, 1225, 1147, 1103, 1071, 1011, 839, 801, 770, 738, 699 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.00 (t, J = 6.8 Hz, 3H, OCH_2CH_3), 2.46 (s, 3H, 5-methyl-H), 3.94 (q, J = 6.8 Hz, 2H, OCH_2CH_3), 6.66 (s, 1H, CH), 7.28 (d, J = 7.6Hz, 2H, ArH), 7.54 (d, J = 7.6Hz, 2H, ArH), 11.35 (s, 1H, NH). *Anal.* Calcd. for $C_{14}H_{14}BrN_5O_2$: C, 46.17; H, 3.87; N, 19.23. Found: C, 46.28; H, 3.76; N, 19.32.

Ethyl 7-(2,4-dichlorophenyl)-5-methyl-4,7-dihydrotetra-zolo[1,5-*a*]pyrimidine-6-carboxylate (4q). ir (potassium bromide): 3233, 3169, 3060, 2954, 1706, 1655, 1574, 1472, 1388, 1365, 1301, 1284, 1227, 1142, 1100, 1077, 1048, 852, 804, 728, 691cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.98 (t, J = 6.8 Hz, 3H, OCH_2CH_3), 2.47 (s, 3H, 5-methyl-H), 3.92 (q, J = 6.8 Hz, 2H, OCH_2CH_3), 7.03 (s, 1H, CH), 7.44~7.47 (m, 2H, ArH), 7.67 (s, 1H, ArH), 11.42 (s, 1H, NH). *Anal*. Calcd. for $C_{14}H_{13}Cl_2N_5O_2$: C, 47.47; H, 3.70; N, 19.77. Found: C, 47.36; H, 3.66; N, 19.64.

Ethyl 7-(benzo[*d*][1,3]dioxol-5-yl)-5-methyl-4,7-dihydro-tetrazolo[1,5-*a*]pyrimidine-6-carboxylate (4r). ir (potassium bromide) 3233, 3169, 3060, 2954, 1706, 1655, 1574, 1472, 1388, 1365, 1301, 1284, 1227, 1142, 1100, 1077, 1048, 852, 804, 728, 691 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.18 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.45 (s, 3H, 5-methyl-H), 3.96 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 6.00 (s, 2H, OCH_2O), 6.59 (s, 1H, CH), 6.82~6.86 (m, 3H, ArH), 11.26 (s, 1H, NH). *Anal*. Calcd. for $C_{15}H_{15}N_5O_4$: C, 54.71; H, 4.59; N, 21.27. Found: C, 54.68; H, 4.64; N, 21.16.

Ethyl 5-methyl-7-(3,4,5-trimethoxyphenyl)-4,7-dihydro-tetrazolo[1,5-*a*]pyrimidine-6-carboxylate (4s). ir (potassium bromide): 3238, 3176, 2936, 1682, 1650, 1579, 1507, 1464, 1423, 1390, 1365, 1322, 1281, 1237, 1128, 1004, 825, 773, 734, 697 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.04 (t, J = 7.2 Hz, 3H, OCH_2CH_3), 2.47 (s, 3H, 5-methyl-H), 3.78 (s, 3H, OCH_3), 3.85 (s, 6H, 2×OCH_3), 3.97 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 6.58 (s, 2H, ArH), 6.61 (s, 1H, CH), 11.24 (s, 1H, NH). *Anal*. Calcd. for $C_{17}H_{21}N_5O_5$: C, 54.39; H, 5.64; N, 18.66. Found: C, 54.28; H, 5.46; N, 18.72.

Ethyl 7-(3,4-dimethoxyphenyl)-5-methyl-4,7-dihydrotetra-zolo[1,5-*a*]pyrimidine-6-carboxylate (4t). ir (potassium bromide): 3230, 3166, 3055, 2962, 1693, 1655, 1573, 1521, 1467, 1453, 1426, 1384, 1365, 1310, 1288, 1260, 1163, 1122, 1098, 1074, 1023, 982, 821, 806, 783, 757, 710 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.05 (t, J = 6.8 Hz, 3H, OCH_2CH_3), 2.45 (s, 3H, 5-methyl-H), 3.74 (s, 6H, 2×OCH_3), 3.97 (q, J = 6.8 Hz, 2H, OCH_2CH_3), 6.60 (s, 1H, CH), 6.75~6.77 (m, 1H, ArH), 6.89~6.95 (m, 2H, ArH), 11.22 (s, 1H, NH). *Anal*. Calcd. for $C_{16}H_{19}N_5O_4$: C, 55.64; H, 5.55; N, 20.28. Found: C, 55.56; H, 5.48; N, 20.36.

Ethyl 7-(3-chlorophenyl)-5-methyl-4,7-dihydrotetrazolo-[1,5-*a*]pyrimidine-6-carboxylate (4u). ir (potassium bromide): 3230, 3166, 3058, 2942, 1699, 1656, 1575, 1473, 1435, 1387, 1365, 1337, 1302, 1284, 1262, 1231, 1198, 1148, 1126, 1100, 1020, 981, 896, 836, 793, 770, 733, 719, 693 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.00 (t, J = 6.8 Hz, 3H, OCH_2CH_3), 2.47 (s, 3H, 5-methyl-H), 3.93 (q, J = 6.8 Hz, 2H, OCH_2CH_3), 6.70 (s, 1H,

CH), 7.26 (t, J = 4.4Hz, 1H, ArH), 7.39 (d, J = 4.4Hz, 2H, ArH), 7.44 (s, 1H, ArH), 11.36 (s, 1H, NH). *Anal*. Calcd. for $C_{14}H_{14}ClN_5O_2$: C, 52.59; H, 4.41; N, 21.90. Found: C, 52.59; H, 4.35; N, 21.88.

Ethyl 5-methyl-7-(3-nitrophenyl)-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carboxylate (4v). ir (potassium bromide): 3182, 3090, 2924, 1720, 1654, 1578, 1534, 1475, 1443, 1348, 1309, 1277, 1261, 1225, 1141, 1119, 1099, 1075, 1020, 989, 808, 774, 737, 716, 675 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.00 (t, J = 6.8 Hz, 3H, OCH_2CH_3), 2.47 (s, 3H, 5-methyl-H), 3.95 (q, J = 6.8 Hz, 2H, OCH_2CH_3), 6.90 (s, 1H, CH), 7.66 (s, 1H, ArH), 7.78 (s, 1H, ArH), 8.22 (s, 2H, ArH), 11.45 (s, 1H, NH). *Anal*. Calcd. for $C_{14}H_{14}N_6O_4$: C, 50.91; H, 4.27; N, 25.44. Found: C, 50.88; H, 4.38; N, 25.56.

Ethyl 4,7-dihydro-5-methyl-7-phenyltetrazolo[1,5-*a*]-pyrimidine-6-carboxylate (4w). ir (potassium bromide): 3180, 3094, 2943, 1712, 1592, 1525, 1429, 1342, 1259, 1234, 1221, 1128, 1119, 1105, 1082, 1022, 988, 812, 780, 746, 716, 652 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.00 (t, J = 6.8 Hz, 3H, OCH_2CH_3), 2.45 (s, 3H, 5-methyl-H), 3.91 (q, J= 6.8Hz, 2H, OCH_2CH_3), 6.95 (s, 1H, CH), 7.26 (s, 1H, ArH), 7.60 (s, 1H, ArH), 7.88 (s, 1H, ArH), 8.25 (s, 2H, ArH), 11.44 (s, 1H, NH). *Anal*. Calcd. for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.30; N, 24.55. Found: C, 58.92; H, 5.34; N, 24.58.

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[31] The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was was performed using a Rigaku Saturn diffractometer. Crystal data for **4c**: $C_{13}H_{12}BrN_5O_2$, crystal dimension 0.16 x 0.14 x 0.10 mm, Monoclinic, space group $P2_1/c$, a = 17.907(2), b = 10.1825(12), c = 7.5055(3) Å, β = 92.166 (6)° , V = 1367.6(3) Å^3, Mr = 350.19, Z = 4, Dc = 1.701 g/cm^3, λ = 0.71070 Å, μ (Mokα) = 3.018mm^{-1}, $F(000)$ = 704, S = 0.992, R_1= 0.0350, wR_2 = 0.0832