Synthesis of Pyrazolo[5,1-*d*][1,2,3,5]tetrazine-4(3*H*)-ones

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A solid-phase synthesis of 5-aminopyrazole has been developed and applied to the preparation of pyrazolo[5,1-*d*]-[1,2,3,5]tetrazine-4(3*H*)-ones. In this strategy, a one-pot reaction from 5-aminopyrazoles to the pyrazolo[5,1-*d*]-[1,2,3,5]tetrazine-4(3*H*)-ones which provided the compounds in good yields was demonstrated. Using this synthetic strategy, we prepared a representative set of 16 pyrazolo[5,1-*d*][1,2,3,5]tetrazine-4(3*H*)-ones.

Introduction

Azolotetrazinones constitute an interesting class of pharmacologically active compounds which have been extensively studied during the past two decades. In particular, large numbers of papers on imidazo-, pyrazolo-, and pyrrolotetrazinones have been published because these compounds show remarkable antitumor and herbicidal properties.[1] Although a number of solution-phase methodologies have been developed to satisfy the need for new chemical entities, there is still a need for new general procedures for the preparation of large libraries without massive synthetic effort. We envisage that solid-phase synthesis (SPS) which allows convenient handling and distribution of the synthetic intermediates would offer an attractive alternative pathway. To our knowledge, such a process has not been previously demonstrated. Thus, we herein describe a convenient preparation of pyrazolo[5,1-*d*][1,2,3,5]tetrazine-4(3*H*)-ones **1** via a SPS of 5-aminopyrazole **2**. Compared to the earlier reported solution-phase synthesis which commonly involved the isolation and subsequent treatment of the diazopyrazole with an isocyanate at room temperature (RT) for a prolonged period of time,[1d,g,2] our strategy provided a one-pot reaction from the crude **2** to compound **1**. 5-Aminopyrazoles have been prepared previously on solid-phase format using β-keto nitrile, β-ketoamide, or aldehyde nitrile and hydrazine,[3a−d] or dithiocarbazate and substituted 3-ethoxyacrylonitriles.[3e] However, these solid-phase strategies have several drawbacks such as long reaction times or lack of the potential for variation on one of the positions on the pyrazole ring. We herein also describe an alternative solid-phase synthetic approach to 5-aminopyrazole.

Results and Discussion

Solution-phase Synthesis. Prior to the SPS, preliminary solution-phase studies were carried out to survey the requisite reaction conditions and establish the modifications for the SPS (Scheme 1). To begin our investigation, benzyl hydrazinocarboxylate **5** was prepared by treating benzyl alcohol **3** with methyl hydrazinocarboxylate and K_2CO_3 in *N*,*N*-dimethylformamide (DMF).[4] However, in our hands, this reaction gave **5** in only 39% yield. Attempts to improve the reaction by replacing K_2CO_3 with DBU or DiEA instead resulted in no formation of **5**. In addition, attempts to synthesize compound **5** from benzyl chloroformate (prepared from compound **3** and trichloromethyl carbonochloridate[5]) and hydrazine hydrate[6] gave compound **5** in 57% yield. In our efforts to obtain **5** in good yields, we treated compound **3** with 1,1′-carbonyldiimidazole (CDI) at RT.[7] To our delight, this provided 1-(benzyloxycarvonyl)imidazole **4** in quantitative yield. Subsequent treatment of compound **4** with hydrazine hydrate in tetrahydrofuran (THF) at RT gave compound **5** in 95% yield.

Compound **5** was then reacted it with (1-ethoxyethylidene)-malononitrile in ethanol under reflux.[8] This gave a dirty reaction as observed from thin-layer chromatography (TLC). Changing the solvent to *t*-butanol or acetonitrile did not provide a cleaner reaction. Hence, we proceeded to vary the temperature and found that the reaction proceeded very cleanly in ethanol at RT to provide benzyl 5-amino-4-cyano-3-methyl-1*H*-pyrazole-1-carboxylate **6** in 82% yield. Attempts for obtain compound **1** by diazotizing **6** with 4 M HCl and sodium nitrite in water at 0 °C followed by reaction with an amine[2a] resulted instead in the formation of **2**. Further investigation confirmed that the diazotization of **6** did not proceed readily, and the carbobenzyloxy group on N1 of compound **6** was readily removed during the reaction with an amine (we have carried out the reaction with methylamine, isopropylamine, butylamine, and benzylamine) to provide **2**. Since isopropylamine has bp 33 °C and could be easily removed at the end of the reaction, isopropylamine in methanol was used for the carbobenzyloxy group cleavage reaction to produce 5-amino-3-methyl-1*H*-pyrazole-4-carbonitrile **2a** in 90% yield. Subsequent diazotization of **2a** with 4 M HCl and sodium nitrite in water at 0−5 °C followed by the addition of CH_2Cl_2 and aqueous sodium carbonate to adjust the pH of the reaction mixture to 7−8 gave **7a** which was not isolated. Instead, the two-layer (CH_2Cl_2−H_2O) reaction mixture containing **7a** was treated overnight with phenylisocyanate which provided 7-methyl-4-oxo-3-phenyl-3,4-dihydropyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carbonitrile **1a** in 72% yield.

SPS. With the solution-phase pathway established, we proceeded to demonstrate the versatility of this methodology for SPS (Scheme 2). Wang resin **8** in THF was reacted with CDI at RT. The formation of resin **9** was amenable to KBr

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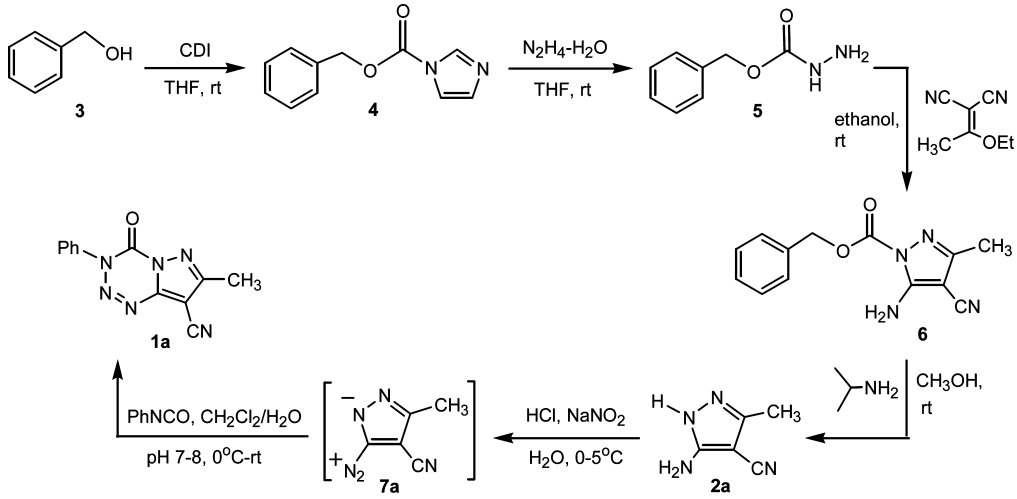
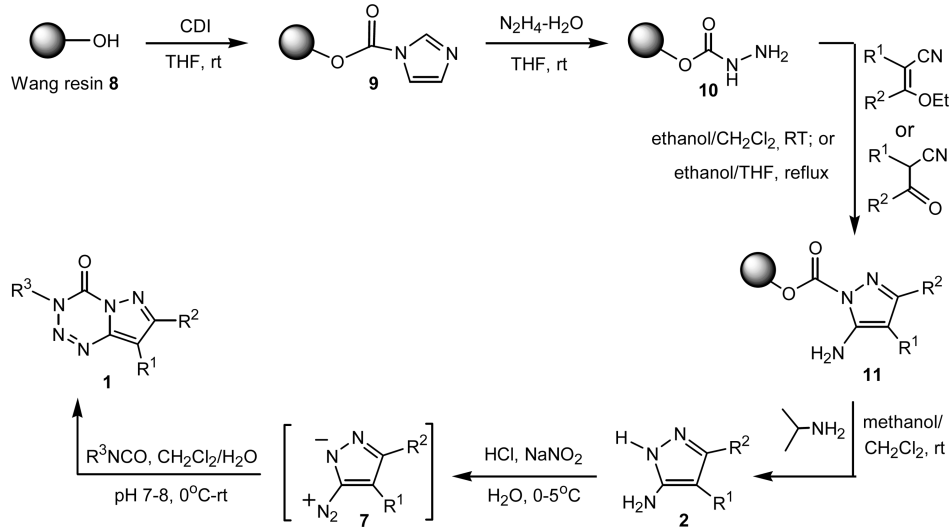
Scheme 1. Solution-Phase Synthesis



Scheme 2. SPS of Pyrazolo[5,1-*d*][1,2,3,5]tetrazine-4(3*H*)-ones



FTIR monitoring (i.e., disappearance of the OH stretch at 3566 cm^{-1} and the appearance of a strong C═O stretch at 1760 cm^{-1}) Hauske et al. had earlier reported the synthesis of resin **9** from Wang resin **8** and a 5−10 fold excess of CDI.[9] However, we found that 3-equivalence of CDI was sufficient for the reaction to proceed to completion. Hydrazide resin has been previously synthesized from phenyl carbonate resin and hydrazine.[10] In our synthesis, resin **9** was then treated with hydrazine hydrate in THF at RT to give hydrazide resin **10** which according to FTIR analysis shows NH stretching at 3415 and 3340 cm^{-1}. Since polystyrene/1% divinylbenzene has poor swelling ability in ethanol and methanol, further treatment of resin **10** with 2-(1-ethoxyethylidene)malononitrile was carried out in a ethanol-CH_2Cl_2 (v/v 1:1) mixture at RT for 5 h to provide resin **11** (R^1 = CN, R^2 = CH_3) whose formation was analyzed by the FTIR for the CN stretch at 2217 cm^{-1}.

Resin **11** was easily cleaved with isopropylamine to give crude compound **2a** in an overall yield of 73% and with 94% purity as analyzed by HPLC. Since **2a** was obtained in high purity, no purification was carried out, and the compound was directly diazotized with 4 M HCl and sodium nitrite in water at 0−5 °C to provide an intermediate diazonium which was then cycloadded with an isocyanate in a one-pot reaction to give compound **1a** in 49% overall yield, which is comparable to the overall yield (50%) obtained via solution-phase synthesis. To illustrate the versatility of this methodology, various malononitrile analogues or β-ketonitriles (Table 1) were used to prepare resin **11**. For malononitrile analogues and β-ketonitriles which are less reactive than 2-(1-ethoxyethylidene)malononitrile, the reaction had to be carried out under reflux condition as the reaction at RT provided low yields of **2**. Although the purities of compound **2** obtained from the reaction of resin **4** with β-ketonitriles were lower than the analogues of **2** obtained from the reaction of resin **4** with malononitrile analogues, this, however, did not prevent the formation of compound **1**. Using this methodology, we have synthesized a representative set of 16 pyrazolo[5,1-*d*]-[1,2,3,5]tetrazine-4(3*H*)-ones **1** (Figure 1) in 21−50% overall yield, indicating an average yield of at least 75% for each step of the reaction.

In summary, we have developed a SPS of 5-aminopyrazole **2**.

Experimental Section

General Procedures. Wang resin was purchased from Tianjin Nankai Hecheng Science and Technology Co (100−200 mesh, 1.35 mmol/g, 1% divinylbenzene cross-

Table 1. Malononitrile Analogues and β-Ketone Nitriles Used and Their Reaction Times

malononitrile/β-ketone nitriles	resin **11**	solvent	reaction condition
2-(1-ethoxyethylidene)malononitrile	$R^1 = CN$, $R^2 = CH_3$	EtOH/CH_2Cl_2 = 1:1	RT, 5 h
(ethoxy(phenyl)methylene)malononitrile	$R^1 = CN$, $R^2 = C_6H_5$	EtOH/CH_2Cl_2 = 1:1	RT, 4 h
2-(ethoxymethylene)malononitrile	$R^1 = CN$, $R^2 = H$	EtOH/CH_2Cl_2 = 1:1	RT, 6 h
ethyl 2-cyano-3-ethoxybut-2-enoate	$R^1 = CO_2Et$, $R^2 = CH_3$	EtOH/THF = 1:1	reflux, 8 h
ethyl 2-cyano-3-ethoxyacrylate	$R^1 = CO_2Et$, $R^2 = H$	EtOH/THF = 1:1	reflux, 8 h
2-phenylacetoacetonitrile	$R^1 = C_6H_5$, $R^2 = CH_3$	EtOH/THF = 1:1	reflux, 12 h
3-oxo-2,3-diphenylpropanenitrile	$R^1 = C_6H_5$, $R^2 = C_6H_5$	EtOH/THF = 1:1	reflux, 12 h
benzoylacetonitrile	$R^1 = H$, $R^2 = C_6H_5$	EtOH/THF = 1:1	reflux, 12 h

linking). All other chemical reagents were obtained from either Aldrich, Merck, Lancaster, or Fluka and used without further purification. Solid-phase, RT reactions were agitated on a flask shaker SF1 (Stuart Scientific). Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and visualized with UV light or stained with ninhydrin. Flash column chromatograph was performed with silica (Merck, 70−230 mesh).

^{1}H NMR and ^{13}CNMR spectra were measured at 298 K on a Bruker DPX 300 or DPX 500 Fourier Transform spectrometer. Chemical shifts were reported in δ (ppm), relative to the residual undeuterated solvent which was used an internal reference. The signals observed were described as follows: s (singlet), d (doublet), t (triplet), m (multiplet). The number of protons (*n*) for a given resonance was indicated as *n*H. All Infrared (IR) spectra were recorded on a Bio-Rad FTS 165 spectrometer. Mass spectra were performed on Finnigan MAT 95/XL-T spectrometer under electron impact (EI), electrospray ionization (ESI) or fast atom bombardment (FAB) techniques.

Synthesis of 1-(Benzyloxycarbonyl)imidazole 4. CDI (0.649 g, 4.0 mmol) was added to a solution of benzyl alcohol **3** (0.216 g, 2 mmol) in anhydrous THF (10 mL). The reaction mixture was stirred at RT for 30 min and then quenched with water (10 mL) and extracted with EtOAc (50 mL × 3). The combined organic layer was dried with $MgSO_4$, filtered, concentrated, and purified by column chromatography (EtOAc/hexane = 1:2) to give **4** (0.400 g, 99%) as a white oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (s, 1H, *H*C═N), 7.31−6.91 (m, 7H, Ar*H*), 5.26 (s, 2H, ArCH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.2, 136.8, 136.7, 130.3, 128.8, 128.5, 128.3, 116.8, 69.5. HRMS (EI, $C_{10}H_{11}N_2O_2$) calcd: 202.0742, found: 202.0745.

Synthesis of Benzyl Hydrazinocarboxylate 5. Hydrazine hydrate (0.100 g, 2 mmol) was added dropwise to a solution of **4** (0.202 g, 1 mmol) in THF (8 mL). The reaction mixture was stirred at RT for 30 min. The mixture was concentrated and purified by column chromatography (EtOAc/hexane = 1:1) to obtain **5** (0.158 g, 95% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40−7.37 (m, 5H, Ar*H*), 4.62 (s, 2H, ArCH_2), 3.24 (bs, 2H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.5, 135.9, 128.2, 128.0, 127.8, 66.8. HRMS (EI, $C_8H_{10}N_2O_2$) calcd: 166.0742, found: 166.0736.

Synthesis of Benzyl 5-Amino-4-cyano-3-methyl-1*H*-pyrazole-1-carboxylate 6. A mixture of compound **5** (0.166 g, 1 mmol), 2-(1-ethoxyethylidene)malononitrile (0.137 g, 1 mmol) and ethanol (10 mL) was stirred at RT for 3 h. Compound **6** precipitated from the solution, and the precipitate was filtered by suction and washed with cold ethanol. The remaining compound **6** which was in the filtrate was purified by column chromatography (EtOAc/hexane = 1:3). Yield 82%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.73 (bs, 2H,

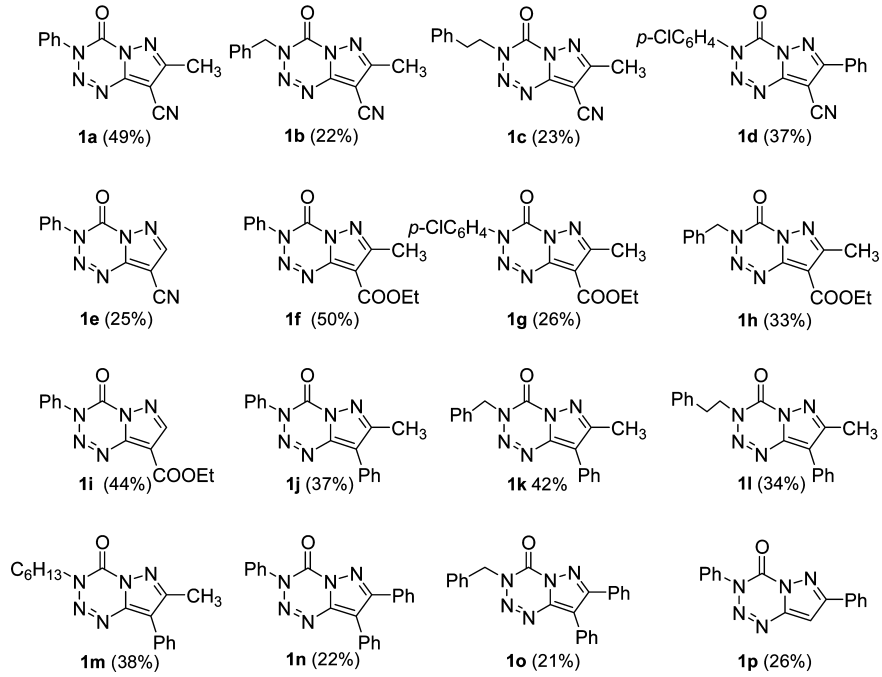


Figure 1. Library of synthesized pyrazolo[5,1-*d*][1,2,3,5]tetrazine-4(3*H*)-ones **1a**−**p**. Overall yields are based on the theoretically corrected loadings.

N*H*$_2$), 7.48−7.38 (m, 5H, Ar*H*), 5.39(s, 2H, ArC*H*$_2$), 2.11 (s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ 155.2, 152.5, 150.2, 134.7, 128.6, 128.5(×2), 113.8, 72.9, 68.9, 12.5. HRMS (ESI, $C_{13}H_{12}N_4O_2$ -H) calcd: 255.0882, found: 255.0866.

Synthesis of 5-Amino-3-methyl-1*H*-pyrazole-4-carbonitrile 2a. A mixture of compound **6** (0.256 g, 1 mmol), isopropylamine (0.177 g, 3 mmol) and methanol (10 mL) was stirred at RT for 2 h. The mixture was concentrated and purified by column chromatography (methanol/CH_2Cl_2 = 1:20) to give **2a** (0.110 g, 90% yield) as a white solid. ^{1}H NMR (300 MHz, Acetone-d$_6$): δ 11.30 (bs, 1H, N*H*), 5.42 (bs, 2H, N*H*$_2$), 2.22 (s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, Acetone-d$_6$): δ 156.6, 149.2, 115.8, 69.0, 12.2. HRMS (EI, $C_5H_6N_4$) calcd: 122.0592, found: 122.0591.

Synthesis of 7-Methyl-4-oxo-3-phenyl-3,4-dihydropyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carbonitrile 1a. To a solution of compound **2a** (0.122 g, 1 mmol) and 4 M HCl (1 mL, 4 mmol) in H_2O (5 mL) at 0−5 °C, was slowly added $NaNO_2$ (0.070 g, 1 mmol) in H_2O (2 mL). After 45 min, TLC monitoring (EtOAc/hexane = 2:1) indicated that the reaction was completed. CH_2Cl_2 (15 mL) was added, and the two-layer mixture that formed was neutralized with saturated aqueous Na_2CO_3 until pH 7−8. Thereafter, phenylisocyanate (0.120 g, 1 mmol) was added, and the mixture was stirred at 0−5 °C for 2 h and then at RT for 7 h. The reaction mixture was then extracted with CH_2Cl_2, and the combined organic layer was concentrated and purified by column chromatography (EtOAc/hexane = 1:4) to obtain **1a** (0.182 g, 72% yield) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 7.66−7.63(m, 5H, Ar*H*), 2.62(s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, DMSO-d$_6$): δ 157.4, 148.1, 139.3, 137.0, 130.0, 129.2, 126.6, 110.8, 88.1, 13.0. HRMS (EI, $C_{12}H_8N_6O$) calcd: 252.0760, found: 252.0757.

Procedure for the Preparation of Resin 9. Wang Resin **8** (10.0 g, 1.35 mmol/g) was placed in a 250 mL round-bottom flask and swollen in anhydrous THF (60 mL) for 30 min. CDI (6.56 g, 40.5 mmol) was added, and the reaction mixture was shaken at RT for 1.5 h. Thereafter, the resin was filtered, washed with DMF (40 mL × 3), H_2O (40 mL × 3), EtOH (40 mL × 3), CH_2Cl_2 (40 mL × 3), and Et_2O (40 mL × 3), and dried overnight in a vacuum oven (0.5 mbar) at 40 °C. 11.2 g of resin **9** was obtained. Elemental analysis: 3.30% N (resin **9** loading is 1.18 mmol/g).

Procedure for the Preparation of Resin 10. Resin **9** (11.0 g, 1.177 mmol/g) was placed in a 250 mL round-bottom flask and swollen in THF (60 mL) for 30 min. Hydrazine hydrate (1.18 g, 23.6 mmol) was added dropwise to the mixture, and the reaction mixture was shaken at RT for 1.5 h. Thereafter, the resin was filtered, washed with DMF (40 mL × 3), H_2O (40 mL × 3), EtOH (40 mL × 3), CH_2Cl_2 (40 mL × 3), and Et_2O (40 mL × 3) and dried overnight in a vacuum oven (0.5 mbar) at 40 °C. A 10.8 g portion of resin **10** was obtained. Elemental analysis: 3.36% N (resin **10** loading is 1.20 mmol/g).

General Procedure for the Preparation of Resin 11. A mixture of resin **10** (1.1 g 1.20 mmol/g), the respective malononitrile analogues or β-ketone nitriles (2.7 mol) and anhydrous solvent mixture (20 mL) were placed in a 100 mL round-bottomed flask and reacted for 4−12 h (Table 1). The resin was then filtered, washed with DMF (20 mL × 3), H_2O (20 mL × 3), EtOH (20 mL × 3), CH_2Cl_2 (20 mL × 3), and Et_2O (20 mL × 3), and dried overnight in a vacuum oven (0.5 mbar) at 40 °C. For resin **11a**: 1.16 g was obtained; elemental analysis: 4.94% N (resin **11a** loading is 0.88 mmol/g).

General Procedure for the Preparation of 1a−p. A mixture of resin **11** (1.0 mmol), isopropylamine (10 equiv), methanol (10 mL), and CH_2Cl_2 (10 mL) was placed in a 100 mL round-bottom flask and shaken at RT for 3 h. The resin was then filtered, washed with methanol (20 mL × 3), acetone (20 mL × 3), CH_2Cl_2 (20 mL × 3), and Et_2O (20 mL × 3). The combined filtrate and washings was concentrated by rotary evaporation and dried in a vacuum oven (0.5 mbar) at 40 °C for 2 h to obtain the crude compound **2**. To a solution of crude compound **2** and 4 M HCl (1 mL, 4 mmol) in H_2O (5 mL) at 0−5 °C was slowly added $NaNO_2$ (0.070 g, 1 mmol) in H_2O (2 mL). After 45 min, TLC monitoring (EtOAc/hexane = 2:1) indicated that the reaction was completed. CH_2Cl_2 (15 mL) was added, and then the two-layer mixture was neutralized with saturated aqueous Na_2CO_3 until pH 7−8. Therafter, the respective isocyanate (1.0 mmol) was added, and the mixture was stirred at 0−5 °C for 2 h and then at RT for 7 h. The reaction mixture was then extracted with CH_2Cl_2, and the combined organic layer was concentrated and purified by column chromatography (EtOAc/hexane) to obtain compound **1**.

3-Benzyl-7-methyl-4-oxo-3,4-dihydropyrazolo[5,1-*d*]-[1,2,3,5]tetrazine-8-carbonitrile 1b. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39−7.33 (m, 5H, Ar*H*), 4.56−4.55 (d, 2H, ArC*H*$_2$, J = 6.3 Hz), 2.80 (s, 3H, C*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.6, 148.7, 142.5, 136.5, 128.9, 128.1, 127.8, 110.7, 97.2, 44.6, 13.8. HRMS (FAB, $C_{13}H_{10}N_6O$ + H) calcd: 267.0994, found: 267.0990.

7-Methyl-4-oxo-3-phenethyl-3,4-dihydropyrazolo[5,1-*d*]-[1,2,3,5]tetrazine-8-carbonitrile 1c. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35−7.21 (m, 5H, Ar*H*), 3.65−3.61 (q, 2H, ArCH$_2$C*H*$_2$, J = 6.7 Hz), 2.94−2.91 (t, 2H, ArC*H*$_2$CH$_2$, J = 7.3 Hz), 2.77 (s, 3H, C*H*$_3$). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.5, 148.7, 142.4, 137.8, 128.8, 128.7, 126.7, 110.8, 97.1, 41.9, 35.6, 13.7. HRMS (FAB, $C_{14}H_{12}N_6O$ + H) calcd: 281.1151, found: 281.1147.

3-(4-Chlorophenyl)-4-oxo-7-phenyl-3,4-dihydropyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carbonitrile 1d. ^{1}H NMR (500 MHz, Acetone-d$_6$): δ 8.19−7.24 (m, 9H, Ar*H*). ^{13}C NMR (125 MHz, Acetone-d$_6$): δ 158.5, 151.2, 141.0, 137.9, 137.1, 133.0, 131.1, 131.0, 130.6, 129.8, 128.9, 112.6, 88.4. HRMS (FAB, C17H9ClN6O +H) calcd: 349.0605, found: 349.0609.

4-Oxo-3-phenyl-3,4-dihydropyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carbonitrile 1e. ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 8.67 (s, 1H, N=C*H*), 7.48−6.94 (m, 5H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 146.0, 132.7, 129.9, 128.8, 128.6, 128.2, 125.5, 89.8. HRMS (EI, $C_{11}H_6N_6O$) calcd: 238.0603, found: 238.0610.

Ethyl 7-Methyl-4-oxo-3-phenyl-3,4-dihydropyrazolo-[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate 1f. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63−7.49 (m, 5H, Ar*H*), 4.46−4.42 (q,

2H, -OCH_2CH$_3$, J = 7.2 Hz), 2.69 (s, 3H, CH_3), 1.43−1.40 (t, 3H, -OCH$_2$CH_3, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 158.8, 144.5, 139.3, 136.7, 129.7, 129.2, 125.7, 108.5, 61.4, 14.5, 14.2. HRMS (ESI, $C_{14}H_{13}N_5O_3$+Na) calcd: 322.0916, found: 322.0945.

Ethyl 3-(4-Chlorophenyl)-7-methyl-4-oxo-3,4-dihydropyrazolo[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate 1g. ^{1}H NMR (500 MHz, Acetone-d_6): δ 7.80−7.67 (m, 4H, Ar*H*), 4.44−4.40 (q, 2H, -OCH_2CH$_3$, J = 7.2 Hz), 2.62 (s, 3H, CH_3), 1.42−1.39 (t, 3H, -OCH$_2$CH_3, J = 6.9 Hz). ^{13}C NMR (125 MHz, Acetone-d_6): δ 162.5, 159.0, 146.7, 141.2, 138.0, 136.5, 130.8, 127.7, 109.2, 62.3, 15.3, 15.2. HRMS (ESI, $C_{14}H_{12}ClN_5O_3$+Na) calcd: 356.0526, found: 356.0516.

Ethyl 3-Benzyl-7-methyl-4-oxo-3,4-dihydropyrazolo-[5,1-*d*][1,2,3,5]tetrazine-8-carboxylate 1h. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52−7.32 (m, 5H, Ar*H*), 5.61 (s, 2H, ArCH_2), 4.47−4.43 (q, 2H, -OCH_2CH$_3$, J = 7.2 Hz), 2.69 (s, 3H, C*H*3), 1.44−1.41 (t, 3H, -OCH$_2$CH_3, J = 7.3 Hz).^{13}C NMR (125 MHz, $CDCl_3$): δ 161.3, 158.7, 145.1, 139.6, 134.1, 129.1, 129.0 (×2), 108.2, 61.4, 54.0, 14.6, 14.3. HRMS (ESI, $C_{15}H_{15}N_5O_3$+Na) calcd: 336.1073, found: 336.1072.

Ethyl 4-Oxo-3-phenyl-3,4-dihydropyrazolo[5,1-*d*]-[1,2,3,5]tetrazine-8-carboxylate 1i.[2a] ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42−8.41 (d, 1H, N=C*H*, J = 3.3 Hz), 7.56−7.42 (m, 5H, Ar*H*), 4.41−4.34 (q, 2H, -OCH_2CH$_3$, J = 7.1 Hz), 1.37−1.32 (t, 3H, -OCH$_2$CH_3, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.1, 147.6, 143.6, 139.5, 136.7, 129.8, 129.3, 125.7, 110.9, 61.7, 14.2. HRMS (ESI, $C_{13}H_{11}N_5O_3$+Na) calcd: 308.0760, found: 308.0743.

8-Methyl-3,7-diphenylpyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)-one 1j.[2a] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73−7.43 (m, 10H, Ar*H*), 2.66 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 141.7, 140.2, 137.1, 129.3, 129.2 (×2), 128.8 (×2), 128.5, 118.8, 115.0, 14.1. HRMS (ESI, $C_{17}H_{13}N_5O$+Na) calcd: 326.1018, found: 326.1003.

3-Benzyl-8-methyl-7-phenylpyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)-one 1k. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67−7.31 (m, 10H, Ar*H*), 5.56 (s, 2H, ArCH_2), 2.61 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 142.2, 140.4, 134.7, 129.1, 129.0, 128.9, 128.7, 128.5, 128.3, 118.1, 53.2, 14.0. HRMS (ESI, $C_{18}H_{15}N_5O$+Na) calcd: 340.1174, found: 340.1177.

8-Methyl-3-phenethyl-7-phenylpyrazolo[5,1-*d*][1,2,3,5]-tetrazin-4(3*H*)-one 1l. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.58−7.13 (m, 10H, Ar*H*), 4.59−4.56 (t, 2H, ArCH$_2$CH_2, J = 7.6 Hz), 3.16−3.13 (t, 2H, ArCH_2CH$_2$, J = 7.9 Hz), 2.53 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.8, 142.2, 140.4, 136.8, 129.1, 129.0, 128.8 (×2), 128.3, 126.9, 118.0, 50.9, 35.0, 14.1. HRMS (ESI, $C_{19}H_{17}N_5O$+Na) calcd: 354.1331, found: 354.1311.

3-Hexyl-8-methyl-7-phenylpyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)-one 1m. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.67−7.37 (m, 5H, Ar*H*), 4.43−4.40 (t, 3H, NCH_2, J = 7.3 Hz), 2.61 (s, 3H, CH_3), 1.94−1.88 (m, 2H, NCH$_2$CH_2), 1.41−1.28 (m, 6H, CH$_3$(CH_2)$_3$), 0.88−0.85 (t, 3H, CH_3(CH$_2$)$_3$, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.6, 142.3, 140.4, 129.1, 129.0, 128.7, 128.2, 117.8, 50.0, 31.1, 28.8, 26.0, 22.3, 14.0, 13.8. HRMS (ESI, $C_{17}H_{21}N_5O$+Na) calcd: 334.1644, found: 334.1649.

3,7,8-Triphenylpyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)-one 1n. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70−7.36 (m, 15H, Ar*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.5, 142.7, 140.4, 137.2, 130.6, 130.0, 129.7, 129.4, 129.3, 129.1, 128.8, 128.7, 128.6, 126.0, 118.3. HRMS (ESI, $C_{22}H_{15}N_5O$+Na) calcd: 388.1174, found: 388.1175.

3-Benzyl-7,8-diphenylpyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)-one 1o. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65−7.32 (m, 15H, Ar*H*), 5.62 (s, 2H, ArCH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1, 143.3, 140.5, 134.7, 130.7, 129.9, 129.6, 129.1, 128.8, 128.7, 128.5 (×2), 128.2, 127.7, 117.6, 53.4. HRMS (ESI, $C_{23}H_{17}N_5O$+Na) calcd: 402.1331, found: 402.1340.

3,7-Diphenylpyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)-one 1p.[2a] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07−7.49 (m, 10H, Ar*H*), 7.40 (s, 1H, CC*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.4, 146.3, 140.4, 137.1, 130.4 (×2), 129.6, 129.0, 127.0, 126.0, 102.0. HRMS (ESI, $C_{16}H_{11}N_5O$+Na) calcd: 312.0861, found: 312.0821.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra of compounds **1a**−**1p**, **4**−**6**, IR spectra of resin **9**−**11**, HPLC,^{1}H NMR, and MS data of unpurified compound **2**, crude yields of compounds **2a**, **2d**, **2e**, **2f**, **2i**, **2j**, **2n**, and **2p**, and the crystallographic file in CIF format of **1l**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Hickman, J. A.; Stevens, M. F. G.; Gibson, N. W.; Langdon, S. P.; Fizames, C.; Lavelle, F.; Atassi., G.; Lunt, E.; Tilson, R. M. *Cancer Res.* **1985**, *45*, 3008–3013. (b) Harding, M. J.; Northcott, D.; Smyth, J.; Stuart, N. S.; Green, J. A.; Newlands, E. *Br. J. Cancer* **1988**, *57*, 113–114. (c) Newlands, E. S.; Stevens, M. F. G.; Wedge, S. R.; Wheelhouse, R. T.; Brock, C. *Cancer Treat. Rev.* **1997**, *23*, 35–61. (d) Cheng, C. C.; Elslager, E. F.; Werbel, L. M.; Leopold, W. R., III. *J. Med. Chem.* **1986**, *29*, 1544–1547. (e) Zhu, Y.-Q.; Wu, C.; Li, H.-B.; Zou, X.-M.; Si, X.-K.; Hu, F.-Z.; Yang, H.-Z. *J. Agric. Food Chem.* **2007**, *55*, 1364–1369. (f) Paull, K. D.; Shoemaker, R. H.; Hodes, L.; Monks, A.; Scudiero, D. A.; Rubinstein, L.; Plowman, J.; Boyd, M. R. *J. Natl. Cancer Inst.* **1989**, *81*, 1088–1092. (g) Lunt, E.; Newton, C. G.; Smith, C.; Stevens, G. P.; Stevens, M. F. G.; Straw, C. G.; Walsh, R. J. A.; Warren, P. J.; Fizames, C.; Lavelle, F.; Langdon, S. P.; Vickers, L. M. *J. Med. Chem.* **1987**, *30*, 357–366. (h) Stevens, M. F. G.; Hickman, J. A.; Stone, R.; Gibson, N. W.; Baig, G. U.; Lunt, E.; Newton, C. G. *J. Med. Chem.* **1984**, *27*, 196–201.

(2) (a) Ege, G.; Gilbert, K.; Maurer, K. *Chem. Ber.* **1987**, *120*, 1375–1395. (b) Ege, G.; Gilbert, K. *Tetrahedron Lett.* **1979**, *20*, 4253–4256.

(3) (a) Watson, S. P.; Wilson, R. D.; Judd, D. B.; Richards, S. A. *Tetrahedron Lett.* **1997**, *38*, 9065–9068. (b) Wilson, R. D.; Watson, S. P.; Richards, S. A. *Tetrahedron Lett.* **1998**, *39*, 2827–2830. (c) Blass, B. E.; Srivastava, A.; Coburn, K. R.; Faulkner, A. L.; Janusz, J. J.; Ridgeway, J. M.; Seibel, W. L. *Tetrahedron Lett.* **2004**, *45*, 1275–1277. (d) Dodd, D. S.; Martinez, R. L.; Kamau, M.; Ruan, Z.; Kirk, K. V.; Cooper, C. B.; Hermsmeier, M. A.; Traeger, S. C.; Poss, M. A.

J. Comb. Chem. **2005**, *7*, 584–588. (e) Hwang, J. Y.; Choi, H.-S.; Lee, D.-H.; Yoo, S.-e.; Gong, Y.-D. *J. Comb. Chem.* **2005**, *7*, 136–141.

(4) Landscheidt, H.; Ritzer, E.; Klauserner, A. Eur. Pat. Appl. EP 770598 A2, 1997.

(5) Münch, U.; Pfleiderer, W. *Hel. Chim. Acta* **2001**, *84*, 1504–1517.

(6) Sofuku, S.; Mizumura, M.; Hagitani, A. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 177–181.

(7) Werner, T.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 4302–4304.

(8) (a) Reidlinger, C.; Dworczak, R.; Junek, H.; Graubaum, H. *Monatsh. Chem.* **1998**, *129*, 1313–1318. (b) Markwalder, J. A.; Arnone, M. R.; Benfield, P. A.; Boisclair, M.; Burton, C. R.; Chang, C.-H.; Cox, S. S.; Czerniak, P. M.; Dean, C. L.; Doleniak, D.; Grafstrom, R.; Harrison, B. A.; Kaltenbach, R. F., III; Nugiel, D. A.; Rossi, K. A.; Sherk, S. R.; Sisk, L. M.; Stouten, P.; Trainor, G. L.; Worland, P.; Seitz, S. P. *J. Med. Chem.* **2004**, *47*, 5894–5911.

(9) Hauske, J. R.; Dorff, P. *Tetrahedron Lett.* **1995**, *36*, 1589–1592.

(10) (a) Lee, M.-r.; Shin, I. *Angew. Chem, Int. Ed.* **2005**, *44*, 2881–2884. (b) Wang, S.-S. *J. Am. Chem. Soc.* **1973**, *95*, 1328–1333.

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