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Diversity-Oriented Synthesis of Functionalized Pyrrolo[3,2-*d*]pyrimidines with Variation of the Pyrimidine Ring Nitrogen Substituents

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Nine 2,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,2-*d*]pyrimidine-6-carboxylic acid benzyl esters **12** were synthesized in four steps from 4-oxo-*N*-(PhF)proline benzyl ester **7** by a general method in which elements of molecular diversity were readily added onto the pyrimidine nitrogens. Conversion of 4-oxoproline **7** into the corresponding aminopyrrole **8** using benzyl-, allyl-, and isopropylamine followed by treatment with phenyl, allyl, and ethyl isocyanate gave nine different ureas **9**. 4-Ureido-1*H*-pyrrole-2-carboxylic acid benzyl esters **9** were then converted into the respective pyrrolo-[3,2-*d*]pyrimidines **12** using trichloroacetyl chloride in acetonitrile followed by treatment with Cs_2CO_3. Crystallization from toluene gave the desired deazapurines in 37−55% overall yield from proline **7**.

Introduction

Pyrrolo[3,2-*d*]pyrimidines form a class of deazapurine analogues with interesting biological activity. For example, phenyl-substituted deazaxanthines **1** (R^1, R^3 = alkyl, R^6 = Ph, Figure 1) exhibit antagonistic activity, but moderate selectivity for the A_1- and A_2-adenosine receptors, in accordance with their structural resemblance to natural A_1/A_2 receptor antagonists such as the xanthines caffeine and theophylline.[1,2] Deazapurine-based *C*-nucleosides, such as immucilin-H (**2**), as well as the pyridinylmethyl deazapurine peldesine (**3**) are potent purine nucleoside phosphorylase (PNP) inhibitors that exhibit potential for the treatment of T-cell dependent diseases, such as T-cell leukemia.[3] *C*-Nucleosides containing pyrazolo[3,2-*d*]pyrimidine and pyrazolo[4,3-*d*]-pyrimidine moieties have also shown antibiotic and antiviral activity.[4] 6-Piperidyl-8-phenyl-9-deazapurine (**4**) was identified from a high throughput screen as a potent neuropeptide Y5 receptor antagonist and lead compound for the development of novel anti-obesity drugs.[5] In search of potential antihypertensive drugs, several pyrimido[5,4-*b*]indole-2,4-diones **5** have shown antagonist activity at the α_1-adrenoreceptors, some exhibiting selectivity for the α_{1D}-subtype.[6] In addition, pyrrolopyrimidinone **6** inhibited phosphodiesterase with subnanomolar activity.[7]

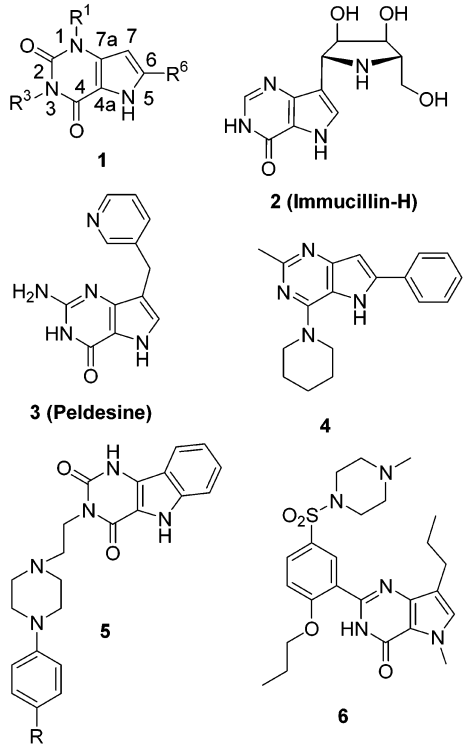

FIGURE 1. Representative examples of biologically active pyrrolo[3,2-*d*]pyrimidines.

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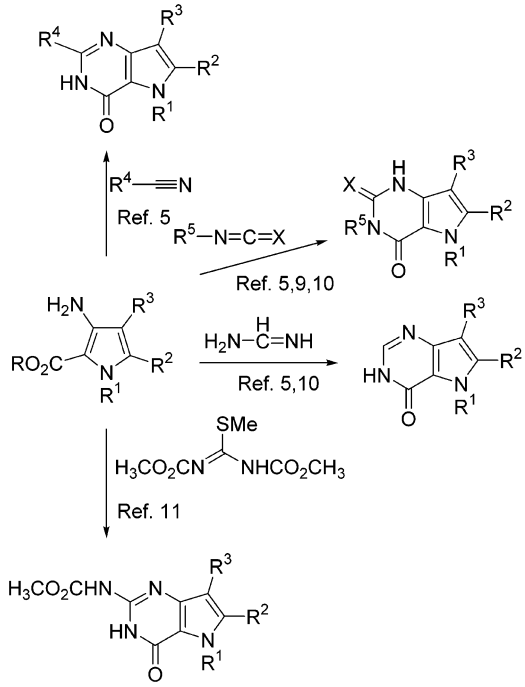
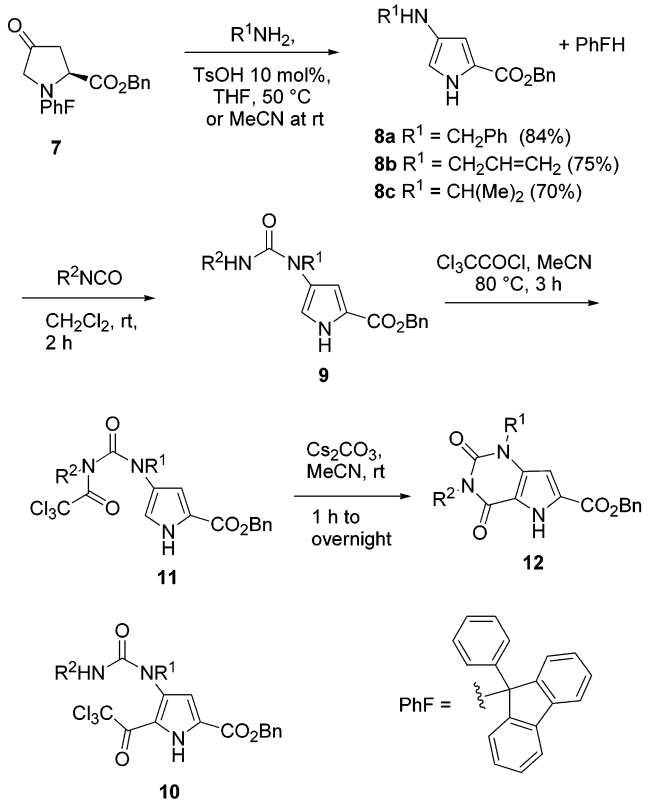


FIGURE 2. Preparations of pyrrolo[3,2-*d*]pyrimidines from 3-aminopyrrole-2-carboxylates.

Among the reported syntheses of pyrrolo[3,2-*d*]pyrimidines, most start from pyrimidines possessing reactive functional groups at positions 4 and 5.[8] Although it may be more advantageous to build the pyrrolo[3,2-*d*]pyrimidine from an appropriately substituted pyrrole in order to generate greater diversity at the pyrimidine core, few syntheses of deazapurines have used this strategy.[5,6,9−12] These strategies have all relied on the synthesis of an appropriately substituted 3-aminopyrrole-2-carboxylate intermediate which has been subsequently reacted with nitrile,[5] isothiocyanate,[5,9,10] isocyanate,[5,9] imidate,[5,10] and isothiourea[11] reagents to form the pyrimidine (Figure 2). Because of difficulties in synthesizing suitably N-alkylated 3-aminopyrrole-2-carboxylates, these approaches generally fail to provide pyrrolo[3,2-*d*]pyrimidines with N^1-substituents.

Recently, we demonstrated that 4-aminopyrroles can be effectively obtained by reacting 4-oxo-*N*-(PhF)prolinate **7** with primary and secondary amines and catalytic acid in a polar solvent (PhF = 9-(9-phenylfluorenyl), Scheme 1).[13] This method has provided various 4-aminopyrrole-2-carboxylates possessing diverse substituents at the 4-position. In light of the growing interest in deazapurines as biologically active leads for drug development, we have begun to explore the elaboration of 4-aminopyrrole-2-carboxylates **8** into deazapurines by a general approach for introducing diversity at various positions around the heterocycle. This study has now led to an effective means for preparing pyrrolo[3,2-*d*]pyrimidines possessing various substituents at the pyrimidine nitrogens.

SCHEME 1. Synthesis of Pyrrolo[3,2-*d*]pyrimidines



Results and Discussion

Previously, we reported that treatment of a 50 °C solution of 4-oxo-*N*-(PhF)prolinate **7** and 10 mol % of TsOH with benzylamine in THF and allylamine in acetonitrile, respectively, generated the corresponding 4-benzyl- and 4-allylaminopyrrole-2-carboxylates **8a** and **8b** in 84% and 75% respective yields.[13] Isopropylamine was found to react similarly with **7** in THF at 50 °C to give 4-isopropylaminopyrrole-2-carboxylic acid benzyl ester **8c** in 70% yield after chromatographic purification (Scheme 1). 4-Aminopyrroles **8** were then found to react selectively on the exocyclic amine with isocyanates in dichloromethane at room temperature to furnish a series of 4-ureidopyrroles **9** in 88−99% yields (Table 1).

Trichloroacetyl chloride had been previously used to acetylate the 2-position of pyrrole in order to generate reactive ketone analogues[14] that have been converted into different amides[15] and esters[16] via haloform reactions involving nucleophilic attack at the ketone carbonyl and

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TABLE 1. Isolated Yields of Ureidopyrroles and Pyrrolo[3,2-*d*]pyrimidines

			yield (%)	
entry	R^1	R^2	**9**	**12**
a	$CH_2C_6H_5$	CH_2CH_3	88	75[a]
b	$CH_2C_6H_5$	$CH_2CH{=}CH_2$	92	70[a]
c	$CH_2C_6H_5$	C_6H_5	94	59[a]
d	$CH(CH_3)_2$	CH_2CH_3	93	67[a]
e	$CH(CH_3)_2$	$CH_2CH{=}CH_2$	94	66[a]
f	$CH(CH_3)_2$	C_6H_5	99	53[b]
g	$CH_2CH{=}CH_2$	CH_2CH_3	88	79[c]
h	$CH_2CH{=}CH_2$	$CH_2CH{=}CH_2$	91	76[c]
i	$CH_2CH{=}CH_2$	C_6H_5	92	69[c]

[a] Procedure A. [b] Procedure B. [c] Procedure B without crystallization.

expulsion of chloroform anion as leaving group. However, to the best of our knowledge, no corresponding intramolecular cyclization of a ureidopyrrole to deazapurine has been reported. The analogous acylation of 4-ureidopyrrole-2-carboxylates **9** was thus considered as a means for preparing a similarly reactive intermediate **10** (Scheme 1), which could be converted to the desired pyrimidine by an intramolecular haloform reaction. Intramolecular cyclizations with trichloroacetyl chloride have previously been used to make cyclic carbamates, cyclic ureas, hydroxypyrrazoles, and isoxazolones.[17] Acylation of 4-ureidopyrrole **9** was effectively performed using 1000 mol % of trichloroacetyl chloride in acetonitrile at reflux for 3 h. Acylation at the pyrrole 5-position was not observed; instead, the proton NMR spectra of the product from treatment of **9** with trichloroacetyl chloride indicated a disappearance of the urea proton, which was either a triplet between 4.36 and 4.79 ppm or a singlet between 6.38 and 6.64 ppm for the *N*-alkyl- and *N*-arylureidopyrroles **9**, respectively. Additional proof that ketone **10** was not produced, and *N*-acylurea **11** was formed instead,[18] came from heterocorrelation NMR experiments. In the HMQC NMR spectra of ureas **11a**−**e**, a correlation was seen respectively between the signals of the pyrrole hydrogens (6.43−6.84 ppm) and their adjacent carbons (112.6−121.5 ppm). Although, intermolecular acylation had taken place at the urea nitrogen instead of at the pyrrole 5-position, ring closure with displacement of chloroform anion could still be effected by intramolecular pyrrole acylation.

The cyclization of **11** to the corresponding pyrrolo[3,2-*d*]pyrimidines was initially performed using 1000 mol % of cesium carbonate in acetonitrile at room temperature. The corresponding pyrimidines **12a**−**e** were isolated in 59−75% overall yields (Table 1) after this two-step procedure (A) and recrystallization. Excess of trichloroacetyl chloride was destroyed in procedure A by a brief washing of the reaction mixture with saturated aqueous $NaHCO_3$. Treatments of acylurea **11a** with ammonium hydroxide, as well as with saturated aqueous $NaHCO_3$ overnight, caused deacetylation and urea **9a** was recovered. A more expedient procedure (B) was later developed in which acylurea **11** was not isolated; instead, it was treated directly with Cs_2CO_3. Product from this two-step one-pot process could not be usually crystallized and a chromatography on silica gel was necessary for isolating pure deazapurine **12f**−**i**. Cyclization of 3-phenylureas **11c**,**f**,**i** proceeded significantly faster than their 3-alkyl counterparts. Reactions of the former were usually complete after 1 h; on the other hand, those of the latter form required stirring overnight.

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Conclusions

In summary, we have developed a novel method for synthesizing pyrimidine-functionalized deazapurines. 2,4-Dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,2-*d*]pyrimidine-6-carboxylic acid benzyl esters **12** were prepared in four steps in 37−55% isolated overall yields from 4-oxo-*N*-(PhF)proline benzyl ester **7**. In light of the potential to further modify the pyrrole core of deazapurine **12** by transformations of the carboxylate as well as nitrogen alkylation, our route should serve as a general method for preparing libraries of structurally diverse pyrrolo[3,2-*d*]pyrimidines that may exhibit interesting biological activity.

Experimental Section

4-Isopropylamino-1*H*-pyrrole-2-carboxylic Acid Benzyl Ester (8c). A stirred solution of benzyl *N*-PhF-4-oxoprolinate (**7**, 1.50 g, 3.26 mmol) in 30 mL of THF was treated with isopropylamine (1.11 mL, 13.04 mmol) followed by TsOH (62 mg, 0.33 mmol), heated to 50 °C, stirred for 8 h, and treated with 100 mL of a solution of saturated aqueous NH_4Cl followed by 100 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (50 mL × 2). The organic layers were combined, washed with brine, dried ($MgSO_4$), and concentrated to a residue that was purified by column chromatography on silica gel using 30% ethyl acetate in hexanes as eluant. Evaporation of the collected fractions yielded pyrrole **8c** (593 mg, 2.28 mmol, 70%) as a green oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (s, 1H), 7.32−7.43 (m, 5H), 6.52 (s, 1H), 6.43 (s, 1H), 5.29 (s, 2H), 3.29 (m, 1H), 3.06 (s, 1H), 1.16 (d, J = 6.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 136.7, 136.2, 129.0, 128.6, 128.5, 120.9, 110.6, 106.3, 66.3, 48.5, 23.5. HRMS: calcd for $C_{15}H_{18}N_2O_2$ 258.1368, found 258.1368.

Typical Procedure for Urea Synthesis: 4-(1-Benzyl-3-ethylureido)-1*H*-pyrrole-2-carboxylic Acid Benzyl Ester (9a). A stirred solution of pyrrole **8** (**8a**, 317 mg, 1.04 mmol, prepared as described in ref 13) in 20 mL of dry CH_2Cl_2, was treated with ethyl isocyanate (90 μL, 1.10 mmol) and stirred for 2 h at room temperature. Solvent was removed under reduced pressure. The residue was purified on a short column of silica gel using 20% ethyl acetate in hexanes as eluant. Evaporation of the collected fractions yielded urea **9a** (345 mg, 0.915 mmol, 88%) as a white powder. Mp: 165.3−166.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.28−7.41 (m, 5H), 7.21−7.26 (m, 5H), 6.70 (d, J = 1.8 Hz, 1H), 6.59 (d, J = 1.8 Hz, 1H), 5.27 (s, 2H), 4.75 (s, 2H), 4.64 (t, J = 5.5 Hz, 1H), 3.22 (q, J = 7.1 Hz, 2H), 1.06 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 158.1, 139.3, 136.2, 129.0, 128.9, 128.7, 128.6, 128.5, 127.5, 127.3, 122.3, 121.4, 114.0, 66.7, 53.5, 36.1, 15.9. HRMS: calcd for [M + H$^+$] $C_{22}H_{24}N_3O_3$ 378.1818, found 378.1800.

Synthesis of 1*H*-Pyrrolo[3,2-*d*]pyrimidines 12. Procedure A. A solution of 100 mg of urea **9** (100 mol %) in 10 mL

of dry acetonitrile was treated with 1000 mol % of distilled trichloroacetyl chloride, stirred with heating at reflux for 3 h, cooled to room temperature, and quenched with 25 mL of a saturated aqueous solution of $NaHCO_3$. Extraction of the aqueous phase with ethyl acetate (3 × 20 mL) followed by washing of the combined organic layers with brine, drying on anhydrous $MgSO_4$, and removal of the solvent yielded the crude acetylated compound **11**. Peak listings for the proton NMR data of **11a**−**e** have been reported in the Supporting Information. This residue was dissolved in 10 mL of dry acetonitrile, treated with 1000 mol % of Cs_2CO_3, and stirred for 1 h in the case of 3-phenylureas or overnight in the case of 3-alkylureas. The reaction was quenched with 25 mL of a saturated aqueous solution of NH_4Cl, and the aqueous phase was extracted with 3 × 20 mL of ethyl acetate. Washing of the combined organic layers with brine followed by drying on anhydrous $MgSO_4$ and removal of the solvent yielded the crude deazapurine, which was crystallized from toluene; an additional crop may be obtained on addition of hexanes. **Procedure B.** A solution of 100 mg of urea **9** (100 mol %) in 10 mL of dry acetonitrile was treated with 1000 mol % of distilled trichloroacetyl chloride, stirred at reflux for 3 h, cooled to room temperature, treated with 1000 mol % of Cs_2CO_3, stirred for 12 h, and quenched with 25 mL of a saturated solution of NH_4Cl. The aqueous phase was separated and extracted with 3 × 20 mL of ethyl acetate. Washing of the combined organic layers with brine, drying on anhydrous $MgSO_4$, and removal of the solvent yielded the crude deazapurine, which was purified by flash column chromatography on silica gel using a gradient of 20−50% EtOAc in hexanes. Evaporation of the collected fractions gave a residue that was crystallized from toluene with added hexanes.

1-Benzyl-3-ethyl-2,4-dioxo-2,3,4,5-tetrahydro-1*H*-pyrrolo[3,2-*d*]pyrimidine-6-carboxylic Acid Benzyl Ester (12a). Procedure A. Yield: 75% as a crystalline white solid. Mp: 190.8−191.8 °C. IR (KBr, cm^{-1}): 3214.3 (NH), 1725.3, 1696.2, 1648.2 (C═O). ^1H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 7.42−7.31 (m, 10H), 6.58 (d, J = 2 Hz, 1H), 5.34 (s, 2H), 5.14 (s, 2H), 4.15 (q, J = 7 Hz, 2H), 1.29 (t, J = 7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 155.3, 151.1, 135.6, 135.0, 133.8, 128.8, 128.7, 128.6, 127.9, 127.8, 127.3, 113.8, 99.9, 67.3, 48.9, 37.0, 13.3. HRMS: calcd for $C_{23}H_{21}N_3O_4$ 403.1532, found 403.1513. Anal. Calcd for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.42. Found: C, 68.07; H, 5.45; N, 10.19.

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Supporting Information Available: General experimental information, characterization data for **9b**−**i**, **11a**−**e**, and **12b**−**i**, ^1H and ^{13}C spectra for compound **8c**, **9a**−**i**, **11a**−**e**, and **12a**−**i**, and HMQC NMR spectra of ureas **11a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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