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A facile synthesis of novel 2-amino-6-arylmethyl-7-carboxamido-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-ones

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ABSTRACT

A facile synthesis of novel 2-amino-6-arylmethyl-7-carboxamido-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-ones is described. The synthesis was developed on solid phase and was applied to provide a series of analogs in good yield. The key reactions are acylation of a cysteine derivative with 2,4-dichloropyrimidine-5-carbonyl chloride followed by cyclization to generate a 6-arylmethyl-7-carboxamido-2-chloro-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-one, which is further derivatized with an amine to give the desired 2-amino-6-arylmethyl-7-carboxamido-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-one.

Molecules incorporating a dihydrobenzothiazepinone motif (Fig. 1, X, Y = CH) exhibit a wide and diverse range of biological activity. Dihydrobenzothiazepinones have been reported that are antipsychotics,[1] antidepressants,[2] suppressors of proliferation of the HIV virus,[3] and cysteine protease inhibitors.[4] They have also been reported to prevent cardiac arrhythmia, heart failure, and atrial fibrillation by targeting RyR receptors.[5] Syntheses of dihydrobenzothiozepinones have been extensively reported. The common methods involve reacting 2-mercaptobenzoic acids with 2-amino alcohol esters,[6] ethylenimine,[6] nitroethene,[7] β-haloamines,[8] or via a Schmidt rearrangement of 1-thio-4-chromanones.[9] Pyrimido-[1,4]-thiazepinones (Fig. 1, X, Y = N) are closely related and isosteric to dihydrobenzothiazepinones, and thus will likely also possess interesting biological activity. It is therefore somewhat surprising that no work has been reported on synthetic strategies directed toward this class of molecules. Only one report by Safonova and co-workers detailing the synthesis of the isomeric pyrimido-[1,5]-thiazepinones can be found in the literature.[10] The synthesis described below provides a facile method to generate novel 2-amino-6-arylmethyl-7-carboxamido-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-ones.

In a typical multi-step solution-phase synthesis, reaction work up and intermediate purification are often labor intensive and time consuming. Solid-phase chemistry can simplify the process, allowing the removal of excess reagents and solution impurities by washing the solid-phase resin with solvents.[11] As such, solid-phase chemistry when applicable can greatly facilitate a synthetic strategy. The synthesis of novel 2-amino-6-arylmethyl-7-carboxamido-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-ones described here was developed on solid phase.

Solid-phase synthesis was initiated by acylating aminomethyl-terminated TentaGel® resin **1** with *N*-α-*N*-ε-bis-Fmoc-lysine followed by Fmoc deprotection to generate **2** (Scheme 1). This increases the loading capacity of the resin by doubling the number of amino groups for further derivatization. The double-loaded resin **2** was subsequently acylated with the photo-labile linker precursor 4-carboxy-2-nitrobenzyl bromide to give **3**. This linker allows cleavage of intermediates and product from solid phase by irradiation with light at 330 nm, and is compatible with the chemistry utilized in this synthetic strategy.[12] Reaction of benzyl bromide **3** with a primary amine provided the resin-bound secondary amine **4**. A large excess of amine was utilized in order to minimize undesired cross-linking between unreacted benzyl bromide and the secondary amine formed during this reaction. A range of primary amines (R^1NH_2) were successfully utilized in this reaction sequence (Table 1).

The secondary amine **4** was subsequently acylated with *N*-Fmoc-*S*-Trt-cysteine, followed by Fmoc deprotection to give **5** (Scheme 2). Both enantiomers of *N*-Fmoc-*S*-Trt-cysteine were successfully utilized. The resin-bound primary amine **5** was further

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† In 2008, Pharmacopeia, Inc. was acquired by Ligand Pharmaceuticals, Inc.

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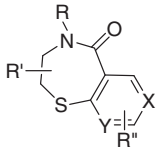
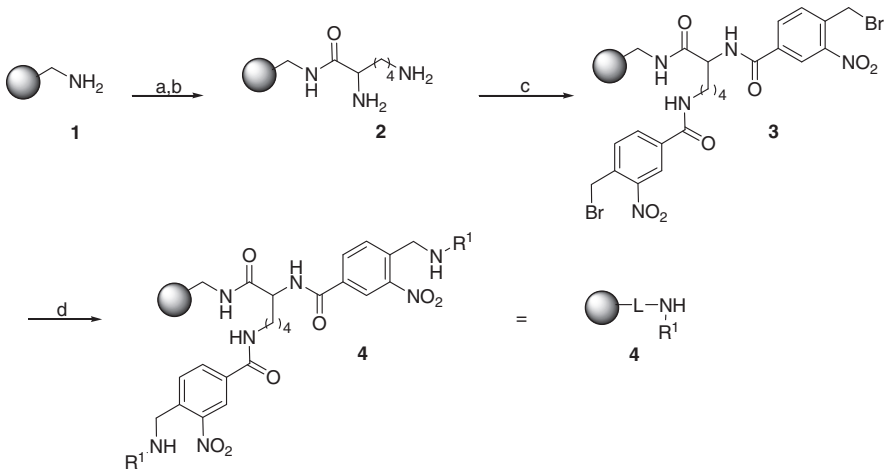
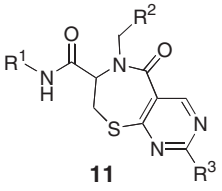


Figure 1. Dihydrobenzo-[1,4]-thiazepinone (X, Y = CH) and dihydropyrimido-[1,4]-thiazepinone (X, Y = N) motifs.

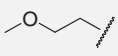
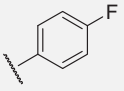
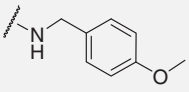
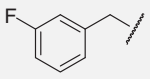
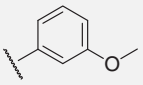
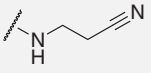
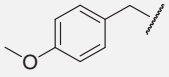
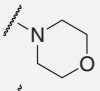
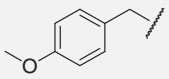
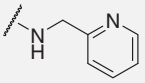
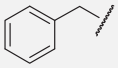
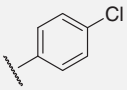
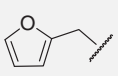
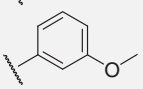
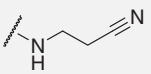
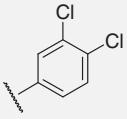
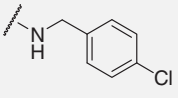


Scheme 1. Reagents and conditions: (a) *N*-α-*N*-ε-bis-Fmoc-Lys, HOBt monohydrate, DIC, CH_2Cl_2, DMF, 25 °C, 16 h; (b) piperidine, DMF, 25 °C, 1 h; (c) 4-carboxy-2-nitrobenzyl bromide, HOBt monohydrate, DIC, CH_2Cl_2, DMF, 25 °C, 16 h; (d) R^1-NH_2, THF, 25 °C, 16 h.

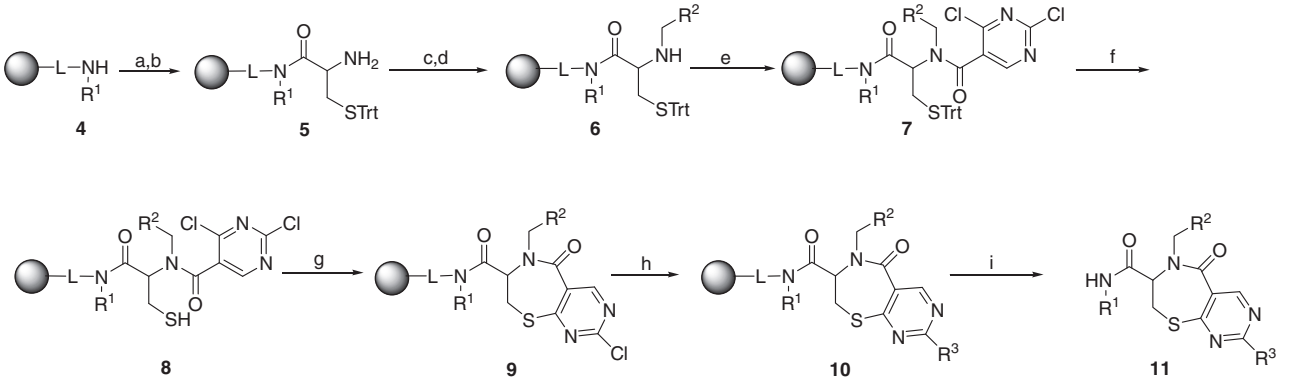
Table 1
2-Amino-6-arylmethyl-7-carboxamido-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-ones



11

Compound	R^1	Configuration	R^2	R^3	pmol per bead[a]	Yield[b] (%)	Purity[c] (%)
11a		*R*			637	49	87
11b		*S*			525	40	93
11c		*R*			538	41	91
11d		*R*			347	27	79
11e		*R*			226	17	84
11f		*S*			285	22	62
11g		*R*			497	38	78

[a] Based on comparison with an analytical reference.
[b] Based on average loading per bead.
[c] Based on HPLC analysis at 215 nm.



Scheme 2. Reagents and conditions: (a) *N*-Fmoc-*S*-Trt-cysteine, HOBt monohydrate, DIC, CH_2Cl_2, DMF, 25 °C, 16 h; (b) piperidine, DMF, 25 °C, 1 h; (c) R^2CHO, THF, 25 °C, 16 h; (d) $NaCNBH_3$, MeOH, AcOH, 25 °C, 16 h; (e) 2,4-dichloropyrimidine-5-carbonyl chloride, DIEA, CH_2Cl_2, 25 °C, 3 h; (f) TFA, Et_3SiH, CH_2Cl_2, 25 °C, 0.5 h; (g) DIEA, CH_2Cl_2, 25 °C, 3 h; (h) amine R^3H, THF, 25 °C, 16 h; (i) isopropanol/H_2O/TFA (80:20:3), *hv* (330 nm), 50 °C, 1 h.

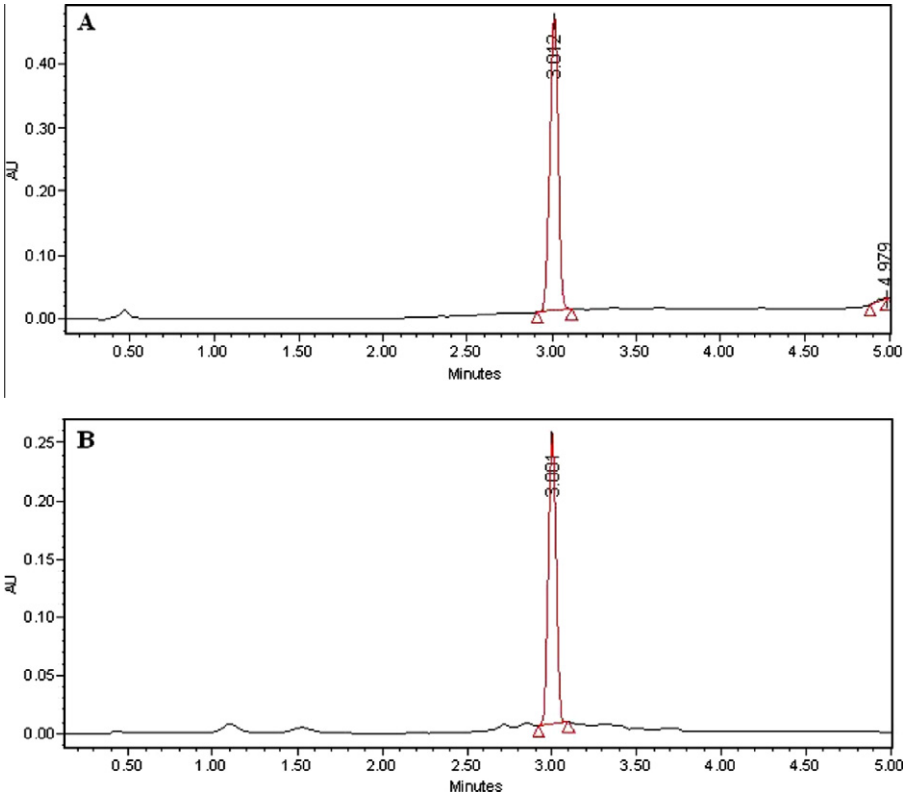


Figure 2. (A) HPLC profile of the standard of **11a** at 215 nm. (B) HPLC profile of the crude bead eluent of **11a** at 215 nm.

derivatized through reductive alkylation with an aldehyde to give **6**. To ensure mono-alkylation of the primary amine, a two-step reductive alkylation was performed. This involved imine formation, removal of excess aldehyde, and subsequent imine reduction with sodium cyanoborohydride. A number of aromatic aldehydes (R^2CHO) that incorporate both electron-rich and electron-deficient substituents were used (Table 1).

The resin-bound secondary amine **6** was subsequently acylated with 2,4-dichloropyrimidine-5-carbonyl chloride[13] to give **7**. No by-product resulting from N-arylation with the chloropyrimidine was observed. Acid-catalyzed removal of the trityl group gave thiol **8**. The key cyclization reaction to give 6-arylmethyl-7-carboxamido-2-chloro-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-one **9** was then achieved by treatment of **8** with *N*,*N*-diisopropylethylamine at room temperature. This cyclization of the thiol group with the 2,4-dichloropyrimidine moiety proceeded smoothly and in good yield. Subsequent reaction of **9** with an amine gave the resin-bound 2-amino-6-arylmethyl-7-carboxamido-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-one **10**. A range of primary and secondary amines incorporating the R^3 substitution were successfully used in this reaction (Table 1). Cleavage of **10** from solid phase via photolysis gave the desired 2-amino-6-arylmethyl-7-carboxamido-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-one **11**.

To determine the yields and purities of **11a–g** following the photolysis, the combined eluent from 20 beads of each compound was quantitatively analyzed versus an analytically pure sample of the corresponding 2-amino-6-arylmethyl-7-carboxamido-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-one.[14] Released compound

yields ranged from 17% to 49% over 10 steps (Table 1). The purity levels of crude 2-amino-6-arylmethyl-7-carboxamido-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-one **11a–g** were high, which is exemplified by the HPLC chromatogram for crude **11a** in Figure 2.

In conclusion, a facile solid-phase synthesis of novel 2-amino-6-arylmethyl-7-carboxamido-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-ones **11** has been developed. The synthesis performed well with a wide range of R^1, R^2, and R^3 components. This synthetic strategy can be readily applied to the construction of both parallel and combinatorial 2-amino-6-arylmethyl-7-carboxamido-7,8-dihydropyrimido[5,4-*f*][1,4]thiazepin-5-one libraries, which should allow the rapid and useful exploitation of this chemotype.

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13. To a stirred solution of 10 g (64 mmol, 1.0 equiv) of 2,4-dihydroxypyrimidine-5-carboxylic acid in 50 mL of phosphorus oxychloride was added 34 mL (190 mmol, 3.0 equiv) of diisopropylethylamine over approximately 2 h. The reaction mixture was heated at reflux for 16 h, allowed to cool to ambient temperature, and the volatiles removed by distillation. The remaining residue was extracted twice with diethyl ether (2×200 mL). The volatiles were removed in vacuo and the residue was purified by Kugelrohr distillation to obtain 8.7 g (41 mmol, 64%) of 2,4-dichloropyrimidine-5-carbonyl chloride as a yellow oil.
14. Analytical standards of **11a**–**g** were synthesized on solid phase via the described synthetic route and subsequently purified by semi-preparative HPLC. Analytical HPLC analysis was conducted using a PDA-linked Waters Millenium 2690 and Phenomenex Luna 3 μm 50×3 mm C8 column.