An Expedient Synthesis of an Isofervenulin Analogue

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An efficient approach has been developed for the synthesis of an isofervenulin analogue **1** employing a one-pot condensation-substitution reaction of a chlorocarboethoxytriazine (electrophile) with a urea (nucleophile). The resulting cyclization reaction resulted in the synthesis of a pyrimido-heterocycle in good yield in either acidic or basic media. The former was assisted by utilizing trimethylsilyl chloride.

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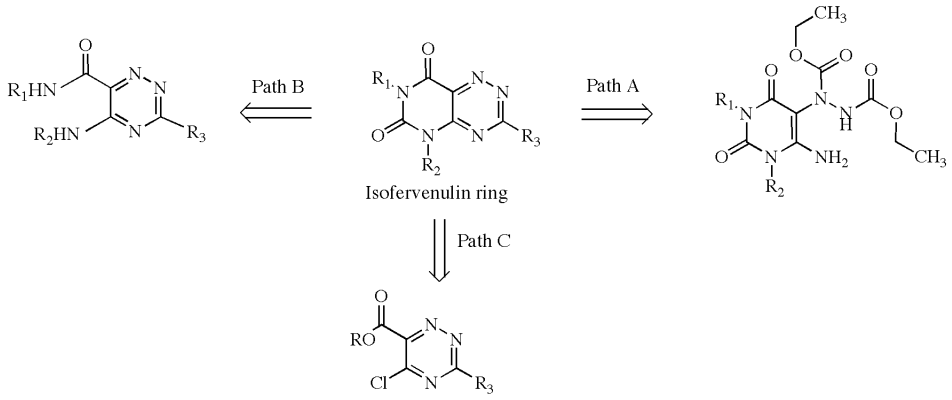
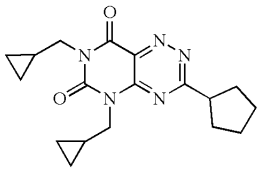
Naturally occurring pyrimidotriazines commonly referred to as fervenulins have received considerable attention in the past few decades due to their interesting biological activity [1-2]. To evaluate this family's full therapeutic potential, studies were extended to its synthetic isomers, *i.e*. isofervenulin and its analogues, which also showed interesting bioproperties [3]. Several synthetic approaches have been reported for the preparation of the isofervenulin ring system (Scheme 1). The first approach (Path A) employed an intramolecular cyclization reaction of a pyrimido derivative leading to the formation of the fused triazine ring [4-5]. The second one (Path B) utilized an intermolecular reaction of a triazine and a carbonyl donor [6-7]. The last one (Path C) involved a bimolecular condensation of a triazine with a guanidine or with a urea derivative[8-10]. These approaches either utilized a toxic reagent such as $Pd(OAc)_4$ or resulted in low yields (30-50%), so there was a need to develop a better preparative method for this class of compounds. Herein, we report an efficient methodology for assembling the pyrimidotriazine system by a one-pot condensation-substitution reaction of a chlorocarboethoxytriazine (electrophile) with a urea (nucleophile). This approach was employed successfully for the preparation of an isofervenulin analogue **1** (Figure 1), a potential anti-anxiety agent that is currently under clinical evaluation at Novartis.

The urea and triazine precursors used in our studies were synthesized according to literature (Scheme 2) [11]. Thus *N,N'*-bis(cyclopropyl)methyurea (**4**) was prepared from cyclopropylmethylamine (**2**) using carbonyldiimidazole as a coupling reagent in 70% yield. For the chlorocarboethoxytriazine (**10**) synthesis, we prepared iminyl alcohol

Scheme 1



Synthetic strategies to the isofervenulin ring system



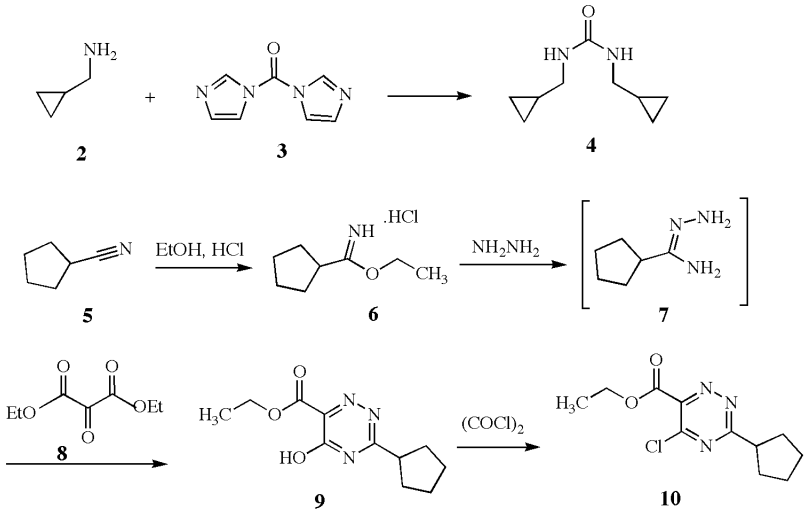
1

Figure 1. An isofervenulin analogue

6 in 90% yield from nitrile **5** and ethanol in the presence of hydrochloric acid. Treatment of **6** with hydrazine gave hydrazide **7**, which was condensed *in situ* with ketone **8** to furnish hydroxytriazine **9** in 40% yield over two steps. Chlorocarboethoxytriazine (**10**) was prepared in near quantitative yield from **9** and oxalyl chloride.

Initially, we investigated the effectiveness of the path B strategy for the synthesis of **1** (Scheme 3). Electrophilic

Scheme 2

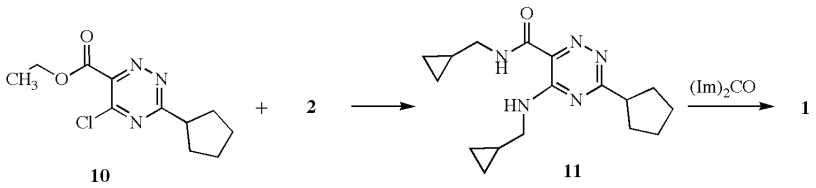


Synthetic scheme leading to precursors **4** and **10**

substitution of chlorocarboethoxytriazine **10** with **2** furnished **11** in 26% yield after chromatography. Condensation of **11** with 1,1'-carbonyldiimidazole generated only trace amounts (<5%) of the desired **1**. This poor result prompted us to investigate a modified path C strategy by employing a one-pot condensation-substitution reaction of **10** with urea **4** for the construction of the pyrimido-heterocycle. We searched for conditions or reagents which might enable activation of urea 4 for the proposed one-pot approach and ultimately lead to an efficient cyclization.

product **1** was obtained, which contained no detectable amounts of *N*,*O*-heterocyclic regioisomers **14** or **15** (Figure 2). Excellent *N*-selectivity is consistent with the Vorbrüggen reaction, where *N*-nucleosides were obtained in high yields from silylated heterocyclic bases and sugars in the presence of Lewis acids [12-13]. Another strategy to activate urea **4**, by transforming it into a dianion, was also effective. At first, deprotonation of urea **4** with NaH, followed by the reaction with triazine **10** resulted in low conversion to **1** at 0 °C as indicated by HPLC analysis. Attempts to accelerate the reaction by raising the reaction

Scheme 3



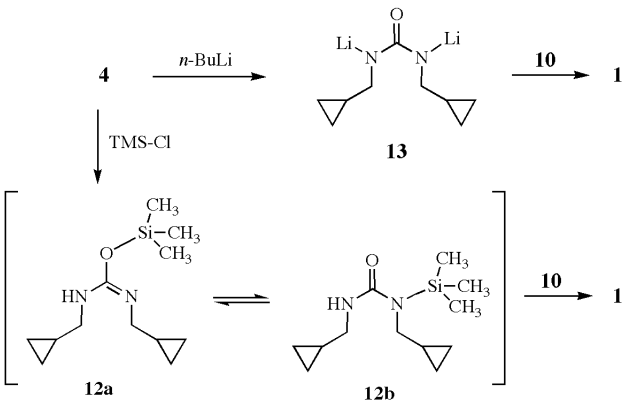
Synthesis of an isofervenulin analogue **1** from triazine **11**

Attempts to cyclize triazine **10** with urea **4** at 145-150 °C in the absence of any solvent under neutral conditions resulted in only 19% yield of the desired **1**. We found that this reaction can be promoted by trimethylsilyl chloride (TMS-Cl) at much lower temperatures. Treatment of urea **4** with TMS-Cl (0–25 °C) presumably led to silylurea **12** (Scheme 4), which reacted with **10** in THF under acidic conditions at reflux (65–67 °C) to afford **1** in 62% yield after chromatographic purification. It is noteworthy to mention that under these conditions, only the *N*,*N*'-derived

temperature to 60 °C resulted in the degradation of **1**. This illustrated the instability of **1** under basic conditions at elevated temperatures. This hurdle was overcome when *n*-BuLi was used as the base (Scheme 4). Thus, formation of dianion **13** from **4** with two equivalents of *n*-BuLi at –10 °C, followed by the addition of **10** to the reaction mixture afforded **1** as a yellow solid in 76% isolated yield (HPLC purity >90%) without chromatography. It was observed that the reaction of **13** with **10** was very rapid and led to **1** within a few minutes according to HPLC. High purity

(>99%) of **1** can easily be obtained in 90% recovery from the crude product by a simple recrystallization using aqueous ethanol as the solvent (68% yield from **10**).

Scheme 4



Synthesis of an isofervenulin analogue **1** from triazine **10** and urea **4**

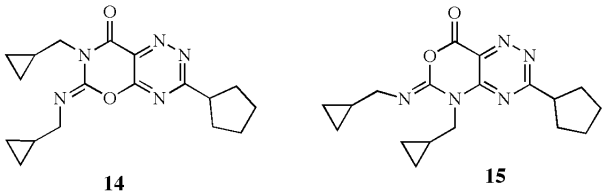


Figure 2. Potential *N,O*-regioisomers

In summary, a high yielding methodology for the synthesis of an isofervenulin analogue **1** using a triazine and a urea under either acidic or basic conditions was developed. The ease and efficiency of this one-pot approach makes it attractive for the preparation of other isofervenulin analogues.

EXPERIMENTAL

All reagents and solvents were purchased from commercial suppliers and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker ARX300 spectrometer at 300 and 75 MHz respectively. DCI/MS analyses were performed on a ThermoFinnigan Trace MS. DCI used a robotic probe (Scientific Instrument Services) with reagent grade ammonia gas. All the elemental analyses were performed by Robertson Microlit Labs (Madison, NJ). HPLC analyses were performed on a Waters HPLC system with a 996 PDA detector and Waters Symmetry Shield^{TM} RP_8 column (5 μm, 3.9 x 150 mm).

5-Chloro-3-cyclopentyl-[1,2,4]triazine-6-carboxylic Acid Ethyl Ester (**10**).

A solution of oxalyl chloride (2.13 g, 16 mmol) in dichloromethane (2 mL) was added to a solution of 3-cyclopentyl-5-hydroxy-[1,2,4]triazine-6-carboxylic acid ethyl ester **9** (2.37 g, 10 mmol) in dichloromethane (35 mL) at 20–22 °C under an argon atmosphere. The resulting clear solution was stirred for 45 min at 22 °C to give a yellow suspension. The suspension was heated to reflux and held for an additional 2 h. The resulting orange solution was evaporated to dryness under vacuum at 20 °C to give chlorocarboethoxytriazine **10** (2.55 g, 100%) as an orange oil. This residual orange oil was used without further purification. A sample of the oil (0.1 g) was dissolved in dichloromethane (1 mL), cooled to 0 °C, and quenched with excess anhydrous diethylamine. The resulting diethylamino-derivative was analyzed by ms: m/z 293 (M^+ + 1), which confirmed its identity and quality (no **9** was detected).

1-(3-Cyclopenyl-[1,2,4]triazine-6-carbonyl)-1,3-bis-cyclopropylmethyl-3-methyl-urea (**1**).

(i) Via Dianion.

A solution of *N,N'*-bis(cyclopropyl)methylurea **4** (1.83 g, 11 mmol) in THF (35 mL) under argon atmosphere was cooled to –10 ºC. A solution of 2.5 *M n*-butyllithium in hexane (8.8 mL, 22 mmol) was added at –10 ºC to give a white suspension. The suspension was warmed to 23 ºC and stirred for an additional 3 h to give dianion **13** as a white suspension, which was cooled to –20 ºC. A solution of chlorocarboethoxytriazine **10** (2.55 g, 10 mmol) in THF (35 mL) was added drop by drop over 1 h at –20 to –18 ºC. The mixture was warmed to –5 ºC, stirred for 15 min, and quenched at –5 to 0 ºC by the addition of a solution of acetic acid (5 g, 0.08 mol) in THF (5 mL) to give a yellow solution. The solution was warmed to 23 ºC and held for 30 min. The reaction mixture was evaporated to dryness at 23–26 ºC under vacuum. The residue was stirred with a mixture of ethyl acetate (200 mL) and water (100 mL). The layers were separated, and the organic phase was washed with brine (100 mL). The organic phase was evaporated at 20–26 ºC under vacuum to obtain an orange oily residue (4.8 g). The residue was dissolved in dichloromethane (10 mL) and filtered through a silica gel plug (50 g). The silica plug was rinsed with hexane/ethyl acetate (3:1 v/v, 4 x 200 mL). The third portion, containing the product, was evaporated under vacuum at 20–26 ºC to give **2** (2.6 g, 76%, HPLC >90% pure) as a yellow solid. Crude **1** was dissolved in ethanol (25 mL) at 65-70 ºC to give a yellow solution. The solution was cooled to 30 ºC over 5 min. To the solution was added water (25 mL) over 30 min. The resulting pale yellow suspension was cooled to 20 ºC and stirred for an additional 20 min. The yellow solid was collected by filtration, and the cake was washed with water (20 mL). The cake was dried at 50 ºC/0.5 mmHg for 20 h to give pure **1** (2.34 g, 68% from **10**) as a pale yellow solid, mp 115-117 ºC; HPLC purity 99.7% (Symmetry Shield RP8, 15 cm, CH_3CN/H_2O 50/50, flow rate 1 mL/min; 20 °C); ^{1}H nmr (300 MHz, $CDCl_3$): δ 4.25-4.15 (d, J = 7.1 Hz, 2H), 4.10-4.00 (d, J = 7.1 Hz, 2H), 3.80-3.60 (m, 1H), 2.35-2.15 (m, 2H), 2.00-1.70 (m, 6H), 1.45-1.25 (m, 2H), 0.40-0.60 (m, 8H); ^{13}C nmr (75 MHz, $CDCl_3$): δ 175.59, 158.41, 150.16, 149.89, 134.79, 46.92, 46.81, 46.53, 33.23, 26.20, 9.74, 9.54, 3.96, 3.83.

Anal. Calcd for $C_{18}H_{23}N_5O_2$: C, 63.32; H, 6.79; N, 20.52. Found: C, 63.36; H, 6.61; N, 20.67.

(ii) Activated with Trimethylsilyl Chloride.

A suspension of **4** (1.39 g, 8.26 mmol) in THF (15 mL) was cooled to 0 °C. Trimethylsilyl chloride (1.05 mL, 8.24 mmol)

was added. The resulting mixture was warmed to 25 °C, stirred for an additional 30 min, and cooled to 0 °C. A solution of **10** (1.91 g, 7.46 mmol) in THF (5 mL) was added. The mixture was heated to reflux (65–67 °C) for 2 h and concentrated under vacuum. The crude product was subjected to chromatography purification (ethyl acetate/hexane, 1:3) to give **1** (1.58 g, 62%) as a yellow solid.

(iii) Via Thermal Condensation.

A two-necked flask was charged with **10** (2.0 g, 7.82 mmol) and **4** (3.28 g, 19.5 mmol) and heated to 147 °C for 1 h. The crude mixture was dissolved in dichloromethane (2 mL) and subjected to chromatography purification (ethyl acetate/hexane, 1:3) to give **1** (0.5 g, 19%) as a yellow solid.

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