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Letter

Sustainable and Scalable Two-Step Synthesis of Thenfadil and Some Analogs in Deep Eutectic Solvents: From Laboratory to Industry

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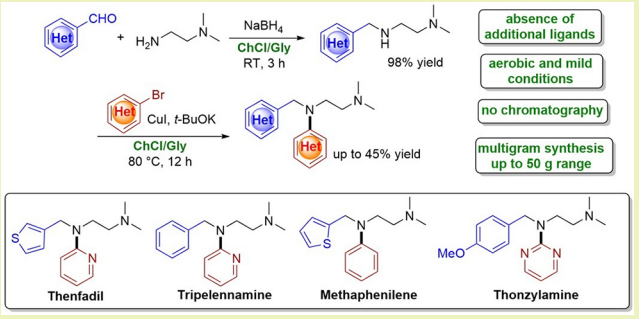
ABSTRACT: A sustainable two-step protocol was developed for the synthesis of the antihistamine drug Thenfadil by combining a reductive amination process with a Cu-catalyzed Ullmann-type C−N coupling reaction run in environmentally responsible deep eutectic solvents (DESs), constructed from biobased compounds. Under optimized conditions, both reactions proceed smoothly under aerobic conditions and in the absence of any additional ligand, with the desired active pharmaceutical ingredient isolated in an overall reaction yield of 39% with an effective suppression of the side products arising from competitive Cu-catalyzed C−O coupling reactions. A novel and simplified workup procedure has also been set up, which avoids the need for chromatographic purification, while allowing the recovery and the recycling of the unreacted intermediate secondary amine. The potential application and the robustness of the proposed methodology has been demonstrated (a) in scale-up studies up to 50 g of substrate in 0.5 kg of DES, taking place with no decrease in the reaction yield, and (b) in the synthesis of three other ethylenediamine derivatives (Thenfadil's analogs) like tripelennamine, methaphenilene, and thonzylamine in 39%−44% overall yield. Typical metrics applied at First and Second Pass, according to the CHEM21 Metrics Toolkit, have been calculated as well for the whole synthetic procedure of Thenfadil and results compared with those of the classical procedure.



KEYWORDS: *Deep eutectic solvents, Ullmann-type cross-coupling reactions, Amine synthesis, Green chemistry*

INTRODUCTION

According to the European Academy of Allergy and Clinical Immunology (EAACI), more than 150 million Europeans today suffer from chronic allergic diseases, and by 2025, more than half of all Europeans will be affected by at least one type of allergy.[1] Therefore, there is a high demand for antihistamine drugs on the market in coming years. Thenfadil belongs to the first generation of antihistamine drugs and is known to show antihistaminic and antiallergic properties for the relief of systemic allergies as urticaria, hay fever, rhinitis, and asthma.[2−4] It is also available in combination either with the nasal decongestant neo-synepherine[5] or with isoetharine, a potent bronchodilator.[6] The peculiarity of this ethylenediamine derivative, discovered by Campaigne and LeSuer in 1949,[7] is an unusually high activity and low toxicity in contrast with methapyrilene, which is one of the most popular drugs used by patients with allergies.[8] Thenfadil (**3a**) is still produced on request at 325 €/50 mg[9] by means of a procedure patented in 1951 by Campaigne and LeSuer based on the reaction of a 2-(dimethylaminoethylamino)-substituted pyridine **1** with 3-bromomethylthiophene (**2**) in dry toluene at reflux in the presence of $NaNH_2$ as a base (Scheme 1a).[10] In 1954, another synthetic procedure was developed by Campaigne and Bourgeois for the preparation of **3a**[11] through refluxing **1** with 5-bromothiophene-3-carbonyl chloride (**4**) (in turn obtained by treating 3-thenoic acid with a solution of Br_2 in glacial acid followed by an excess of thionyl chloride) in pyridine for 8 h. After acidic workup and distillation, the resulting adduct **5** (a pale orange oil) was reduced with $LiAlH_4$ in dry Et_2O, followed by crystallization with a mixture of *i*-PrOH, hydrochloric acid, and ice methanol, thereby leading to **3a** as a white solid in 8% overall yield (Scheme 1b).

To address the climate crisis, there is a pressing need for the development of next-generation technologies able to replace extensively used conventional and hazardous volatile organic compounds (VOCs) with safer and more environmentally responsible solvents.[12−16] In this vein, the goal of several leading pharmaceutical companies today is to reshape classical routes based on the massive use of VOCs and harsh reaction

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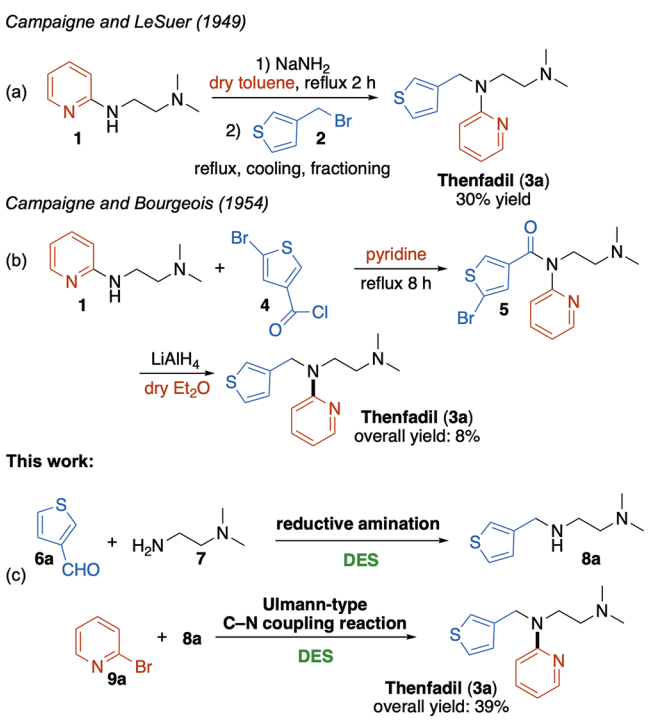
Scheme 1. Synthesis of Thenfadil (3a) by (a) Functionalization of a Preformed 2-(Dimethylaminoethylamino)-Substituted Pyridine 1 with 2-Bromomethylthiophene (2) through Refluxing in Dry toluene, (b) Functionalization of 1 with 5-Bromothiophene-3-carbonyl Chloride (4) through Refluxing in Pyridine, Followed by Reduction with $LiAlH_4$ in Dry Et_2O, (c) Combining a Reductive Amination Reaction between Thiophene 3-Carbaldehyde (6a) and *N,N*-dimethylethylenediamine (7) with a Cu-Catalyzed Ullmann-Type C−N Coupling Reaction between Adduct 8a and 2-Bromopyridine (9a), Both Run in DES under Aerobic Conditions



conditions with alternative milder processes based on waste minimization and eco-efficiency. Owing to their high thermal stability, nonflammability, and practically no vapor pressure, deep eutectic solvents (DESs) are particularly attractive to achieve this goal because of a low ecological footprint. They are binary or ternary mixtures usually made up of at least one hydrogen bond donor and one hydrogen bond acceptor showing an eutectic point temperature far below that of an ideal liquid mixture.[17−21] Especially, those mixtures formed by natural compounds (e.g., natural polyols, amino alcohols, natural carboxylic acids, urea derivatives) are highly sought after because they are biodegradable, inexpensive, and have low toxicity, and thus, they are progressively replacing VOCs in several fields of science.[22] Nevertheless, the employment of DESs in the synthesis of active pharmaceutical ingredients (APIs) is still in its infancy.[21,23−30]

Building on our research on the use on nonconventional, environmentally friendly solvents like DESs[31−37] and water[25,38−41] in synthetic organic chemistry, herein, we wish to report the first sustainable procedure for the preparation of Thenfadil (**3a**) by combining a reductive amination process between thiophene 3-carbaldehyde (**6a**) and *N,N*-dimethylethylenediamine (**7**) with a Cu-catalyzed Ullmann-type C−N coupling reaction between the resulting adduct **8a** and 2-bromopyridine (**9a**) (Scheme 1c). The following features of the proposed protocol are in order: (i) Both reaction steps have been fully optimized in DESs with an overall reaction yield of 39%, working under aerobic conditions. (ii) Impurities have been isolated and characterized, and a novel workup/purification procedure has been set up to increase the purity of the product and to favor the recycling of the unreacted intermediate secondary amine. (iii) The whole procedure has been scaled up to 50 g of substrate in 0.5 kg of DES, thereby bridging the gap between fundamental chemistry and industrial applications. (iv) The reproducibility and the robustness of the methodology has been demonstrated in the synthesis of three analogs of Thenfadil (**3a**), that is tripelennamine (**3b**), methaphenilene (**3c**), and thonzylamine (**3d**).

EXPERIMENTAL SECTION

Preparation of DESs. Deep eutectic solvents [choline chloride (ChCl)/glycerol (Gly) (1:2 mol mol^{-1}); ChCl/urea (1:2 mol mol^{-1})] were prepared by heating under stirring at 60−80 °C for 10−30 min the corresponding individual components until a clear solution was obtained. Cyclopentyl methyl ether (CPME) was used as the solvent in the workup procedures.

Experimental Procedures: Synthesis of Thenfadil. Typical Procedure. *First Step. Reductive Amination of **6a** in ChCl/Gly: Synthesis of N^1,N^1-Dimethyl-N^2-(thiophen-3-ylmethyl)ethane-1,2-diamine (**8a**).* To a stirred solution of **6a** (0.5 mmol) in ChCl/Gly (1:2 mol mol^{-1}, 1 g), at room temperature and under air, first, *N,N*-dimethylethylenediamine **7** (1 equiv, 0.5 mmol, 44 mg) was added, followed by the addition of $NaBH_4$ (1.1 equiv, 0.55 mmol, 20.7 mg) after 1 h stirring. The progress of the reaction was monitored by GC. After completion of the reaction (reaction time, 2 h), water (1 mL) was added, and the corresponding mixture was extracted with CPME (2 mL × 1 mL). Evaporation of the solvent under reduced pressure afforded amine **8a** in 98% isolated yield (81 mg).

*Second Step. Ullmann Coupling Reaction in ChCl/Gly between 2-Bromopyridine (**9a**) and Diamine **8a**: Synthesis of Thenfadil (**3a**).* In a vial with a Teflon screw tap, diamine **8a** (0.5 mmol), 2-bromopyridine (**9a**) (1 equiv, 0.5 mmol), CuI (10 mol %, 0.05 mmol, 9.5 mg), and a base (*t*-BuOK, 3 equiv, 1.5 mmol, 168 mg) were suspended in ChCl/Gly (1:2 mol mol^{-1}, 1 g), under air and vigorous stirring at 80 °C. After 12 h, the mixture was cooled to room temperature, and 1 mL of 10% NaOH aq solution was added. The corresponding mixture was vigorously stirred for 10 min and subsequently centrifugated for 30 min. A brown oil was separated from the water phase in the bottom of the tube. The separation of the oil from the water phase afforded the target product **3a** in 40% isolated yield as a free base.

*Recovery of Diamine **8a**.* The water phase was extracted with CPME (2 mL × 1 mL), and the organic phase was dried over anhydrous Na_2SO_4, thereby providing the starting diamine **8a**. Then, an HCl solution (7N) in *i*-PrOH was added to the crude, and the diamine hydrochloride **8a** was precipitated as a white solid (^{1}H NMR purity, 97%) and thus purified by impurities which remained in the organic phase. After solubilizing the diamine hydrochloride **8a** in water, treatment with NaOH 30%, followed by extraction of the water phase with EtOAc, afforded **8a** as a yellow oil.

Scaling Up the Synthesis of Thenfadil (3a) in DES. The reductive amination reaction proceeded uneventfully at room temperature in air also on a 1 g (9 mmol) scale of **6a**, using 10 g of ChCl/Gly (1:2 mol mol^{-1}) in a 50 mL round-bottomed flask, thereby affording **8a** in 98% yield (1.62 g), according to the procedure detailed for a 0.5 mmol scale reaction (*vide supra*). By scaling up further the reaction either on a 10 g (90 mmol) or a 50 g (450 mmol) scale of **6a**, in a round-bottomed flask of 500 mL or 1 L filled with 100 or 500 g ChCl/Gly, respectively, diamine **8a** could again be isolated in 98% yield (10 g scale, 16.2 g; 50 g scale, 81.0 g). As for the second step, by performing the synthesis of **3a** (*vide supra*) on a 1.62 (10 g of

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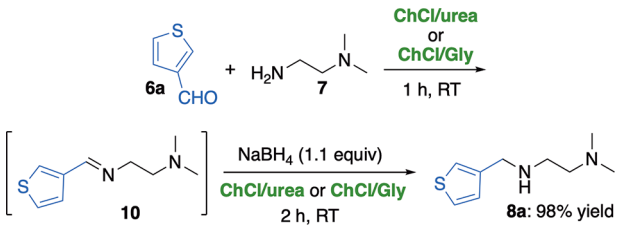
ChCl/Gly, 16.2 g (100 g of ChCl/Gly) or 81.0 g (500 g of ChCl/Gly) scale of **8a**, Thenfadil was finally isolated in 0.919, 9.2, or 45.9 g, respectively. The round-bottomed flasks used were only equipped with a reflux condenser, while monitoring the temperature and the stirring throughout the reaction. No other special equipment was required, and there was no increase either in the formation of main byproducts **11** and **12**.

Synthesis of Thenfadil Analogues. To a stirred solution of aldehyde **6b** or **6c** or **6d** (9 mmol) in ChCl/Gly (1:2 mol mol^{-1}, 10 g), at room temperature and under air, *N*,*N*-dimethylethylenediamine **7** (1 equiv, 9 mmol, 793 mg) was first added, followed by the addition of $NaBH_4$ (1.1 equiv, 9.9 mmol, 373 mg) after 1 h stirring. The progress of the reaction was monitored by GC. After completion of the reaction (reaction time: 2 h), water (10 mL) was added, and the corresponding mixture was extracted with CPME (2 × 5 mL). Evaporation of the solvent under reduced pressure afforded amine **8b** or **8c** or **8d** in 98% yield each. The isolated diamine was finally suspended in ChCl/Gly (1:2 mol mol^{-1}, 10 g), previously dried under reduced pressure, and CuI (10 mol %, 0.9 mmol, 171 mg), *t*-BuOK (3 equiv, 27 mmol, 4.536 g) and the corresponding aryl halide **9a** or **9b** or **9c** (1 equiv, 9 mmol) were added. After 12 h reaction time, the desired targets **3b**–**d** were isolated in 40–45% yield. Isolation and purification of **3b**–**d** was achieved according to the procedure reported for Thenfadil (**3a**) (*vide supra*).

RESULTS AND DISCUSSION

Our study commenced by focusing on the reductive amination process between **6a** and diamine **7** in DES. Inspired by a recent paper by Heydari et al. on the reductive amination of aldehydes/ketones in the presence of DES choline chloride (ChCl)/urea (1:2 mol mol^{-1}) as a catalyst and $NaBH_4$ as a reducing agent in MeOH,[42] we worked on setting up a straightforward one-pot, two-step procedure in DES only. To this end, a suspension of **6a** (0.5 mmol) and **7** (1 equiv) in ChCl/urea (1:2 mol mol^{-1}, 1 g) was vigorously stirred at room temperature (RT, 25 °C), and the imine formation (**10**) was monitored by GC analysis. After 1 h, the resulting mixture was treated with $NaBH_4$ in the absence of additional solvents and then stirred for additional 2 h. After this time, a complete conversion of **10** into **8a** took place. After extraction with cyclopentyl methyl ether (CPME),[43] the desired diamine **8a** was isolated in 98% yield, with a purity of 98% (^{1}H NMR analysis). Of note, the effectiveness of this transformation was still maintained when switching to ChCl/glycerol (Gly) (1:2 mol mol^{-1}, 1 g) as the DES (Scheme 2).

Scheme 2. Synthesis of Secondary Amine 8a via a Reductive Amination Reaction between Aldehyde 6a and Diamine 7, through Imine Intermediate 10, in DES at RT



The presence of impurities in a synthetic process, originating mainly from the raw materials, solvents, intermediates, and byproducts, decreases the yield of the desired product significantly. In the case of an API, impurities may also affect its industrial synthesis in terms of quality, efficiency, and safety.[44] This is why identification and characterization of impurities are of pivotal importance for the development of a good manufacturing procedure, even if this is often challenging.[45] Under the best conditions previously found for the synthesis of aromatic amines in DESs (CuI 10 mol %, *t*-BuOK 3 equiv, 100 °C, 12 h in ChCl/Gly),[46] the reaction between 2-bromopyridine (**9a**) (0.5 mmol) and diamine **8a** (1 equiv) provided Thenfadil **3a** in 10% yield only, along with two main side products, 2,2′-oxydipyridine (**11**) (46% yield) and 3-(pyridin-2-yloxy)propane-1,2-diol (**12**) (32% yield) (^{1}H NMR analysis), the latter being most probably the result of a competitive Ullmann-type C–O coupling reaction (Table 1, entry 1).[47] It was also found that the yield of **3a** could be increased up to 30% by decreasing the temperature to 60 °C, but the formation of **11** still competed strongly (40% yield) (Table 1, entry 2). Switching ChCl/Gly for ChCl/urea, the yield of ether **11** increased up to 50% at 100 °C (Table 1, entry 3). By suspending **9a** in a mixture of ChCl/Gly, CuI, and *t*-BuOK at 100 °C, without diamine **8a**, a full conversion of **9a** into **11** (70% yield) and **12** (30% yield) took place (Table 1, entry 4), whereas **11** was formed in greater than 98% yield as the sole product in ChCl/urea (Table 1, entry 5). Conversely, by leaving diamine **8a** in ChCl/Gly, in the presence of CuI and *t*-BuOK at 100 °C, only the starting material was recovered after 12 h (Table 1, entry 6). There was similarly no reaction in the absence of any copper salt (Table 1, entry 7). Overall, these results are consistent with the fact that diamine **8a** is not responsible for the formation of the observed side products **11** and **12**. According to the literature, access to symmetrical and unsymmetrical diaryl ethers (including ether **11**) can be achieved by Cu-catalyzed double arylation of a simple oxygen source, namely, H_2O or hydroxide salts.[48] This reaction takes place at high temperature (130 °C) and requires a long reaction time (up to 30 h). Fortunately, when the copper-catalyzed C–N coupling reaction between **8a** and **9a** was run at 60 °C in a previously anhydrified ChCl/Gly eutectic mixture, the formations of **11** and **12** were suppressed dramatically (<5% yield by ^{1}H NMR analysis), whereas adduct **3a** was isolated in 30% yield (35% conversion) (Table 1, entry 8). The yield of **3a** could be increased up to 40% with increasing temperature to 80 °C, the remaining being starting material only (conversion, 45%) (Table 1, entry 9). It is worth noting that the latter yield value (40%) is the result of an optimized workup and purification protocol, which avoids chromatography, while privileging extraction, centrifugation, and crystallization processes (see Experimental Section and Supporting Information).

Switching from laboratory to production scale, a scale-up reaction of **3a** in ChCl/Gly was then undertaken, in collaboration with Laboratori Alchemia.[49] As for the first step en route to **8a**, the reaction was successfully carried out on a 1, 10, or 50 g scale by reacting aldehyde **6a** (9, 90, or 450 mmol) with diamine **7** (1 equiv), at RT for 3 h, in 10, 100, or 500 g of DES, respectively, using a round-bottomed flask (volume: 50 mL, 500 mL, or 1 L) in the presence of $NaBH_4$ (1.1 equiv). In all cases, diamine **8a** was isolated in 98% yield (1 g scale, 1.62 g; 10 g scale, 16.2 g; 50 g scale, 81.0 g) after a simple extraction with CPME and subsequent removal of the volatiles under reduced pressure (purity, 98% by ^{1}H NMR analysis). By performing the Cu-catalyzed C–N coupling reaction (second step) of 1.62, 16.2, or 81.0 g of **8a** with **9a** (1 equiv) in 10, 100, or 500 g of ChCl/Gly, Thenfadil could finally be isolated in 0.919, 9.2, or 45.9 g, respectively, after 12 h stirring at 80 °C in a round-bottomed flask equipped with a reflux condenser, followed by treatment of the crude with

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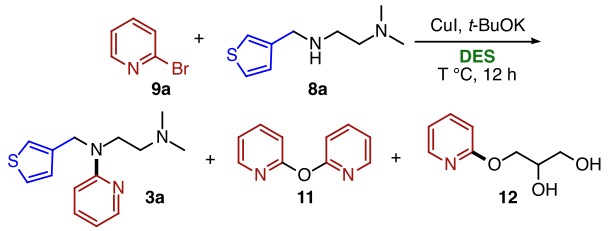
Table 1. Ullmann-Type C−N Bond Formation between 2-Bromopyridine (9a) and Diamine 8a in DES to Give Adducts 3a, 11, and 12: Optimization of Reaction Conditions[a]

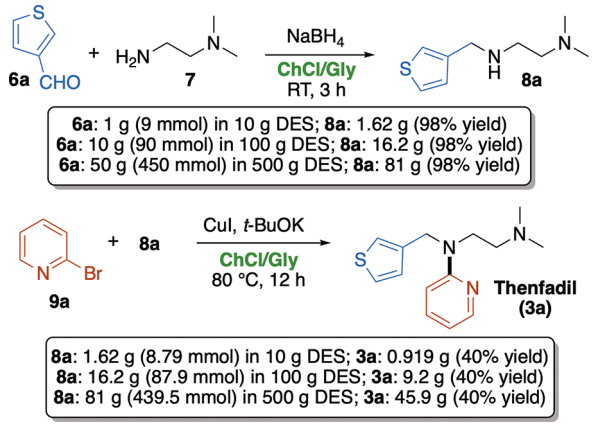


Entry	DES	T (°C)	Conversion (%)	**3a**/**11**/**12** ratio[b]	**3a** yield (%)[c]
1	ChCl/Gly	100	88	10:46:32	–
2	ChCl/Gly	60	75	30:40:<5	30
3	ChCl/urea	100	50	0:50:0	–
4	ChCl/Gly[d]	100	>98	0:70:30[e]	–
5	ChCl/urea[d]	100	>98	0:>98:0	–
6	ChCl/Gly[f]	100	NR[g]	–	–
7	ChCl/Gly[h]	100	NR[g]	–	–
8	ChCl/Gly[i]	60	35	30:<5:<5	30
9	ChCl/Gly[i]	80	45	40:<5:<5	40

[a]DES: choline chloride (ChCl)/glycerol (Gly) (1:2 mol mol^{-1}); ChCl/urea (1:2 mol mol^{-1}). Reaction conditions: diamine **8a** (0.5 mmol), 2-bromopyridine (**9a**) (0.5 mmol), CuI (10 mol %), and *t*-BuOK (3 equiv) were suspended in 1.0 g DES for 12 h. [b]Calculated by ^{1}H NMR analysis of the crude reaction mixture using an internal standard technique (NMR internal standard: CH_2Br_2). [c]Yields reported are for products isolated (see Experimental Section). [d]With no added diamine **8a**. [e]Compounds **11** and **12** were isolated in 68% and 30% yields, respectively, by column chromatography. [f]With no added 2-bromopyridine (**9a**). [g]NR = no reaction. [h]With no added CuI. [i]ChCl/Gly has previously been anhydrified under reduced pressure.

s3 267 water and centrifugation (Scheme 3). The recovery of diamine
268 **8a** was based on the extraction with EtOAc of the aqueous

Scheme 3. Scale-Up Synthesis of Thenfadil (3a), via Secondary Amine 8a, Run on Scales of 1, 10, and 50 g of 6a in 10, 100, and 500 g of DES, Respectively



269 phase and crystallization as an hydrochloride salt white solid
270 from an HCl−isopropanol solution (purity, 97% by GC), while
271 eliminating impurities (see details in the Experimental Section
272 and in the Supporting Information).

273 To better quantify the green credentials of the synthetic
274 process developed, we have made use of the First Pass
275 CHEM21 Metrics Toolkit developed by Clark et al.[50] for the
276 synthesis of Thenfadil in DESs, calculating atom economy
277 (AE), reaction mass efficiency (RME), optimum efficiency
278 (OE), effective mass yield (EM), mass intensity (MI), and
279 process mass intensity (PMI) metrics, with a breakdown of the
280 latter for "chemicals" (reactants, reagents, and catalyst) (PMI
281 rxn), chemical and reaction solvents (PMI solv), and workup
282 and reaction solvents (PMI WU) and compared these values
283 (whenever possible) with the corresponding ones related to
284 the last available synthetic procedure for Thenfadil published
285 in 1954 by Campaigne and Bourgeois (Scheme 1b, Table 2; for t2
286 details, see Supporting Information).[11] In addition, some
287 metrics typical of the Second Pass CHEM21 Metrics Toolkit
288 such as space time yield (STY), renewables intensity (RI), and
289 renewables percentage (RP) have been calculated as well.

290 The overall low impact of the two-step DES-based synthetic
291 procedure herein described is made clear especially when
292 comparing the PMI rxn (7.3 g g^{-1}) and PMI solv (21.8 g g^{-1})
293 values of this process with those of the classical approach
294 reported by Campaigne and Bourgeois (PMI rxn, 22.2 g g^{-1};

Table 2. Quantitative Metrics of Classical (Scheme 1b) and DES-Based (Scheme 1c) Approaches for Synthesis of Thenfadil (3a)

Route	Yield **3a**	AE (%)	RME (%)	OE (%)	EM (%)	PMI (g g^{-1})	PMI rxn[a] (g g^{-1})	PMI solv[b] (g g^{-1})	PMI WU[c] (g g^{-1})	STY (kg m^{-3} h^{-1})	RI[d]	RP (%)	E-factor
Scheme 1b[e]	8	61	4.5	7.4	0.6	–[f]	22.2	156.0	–[f]	–[f]	–[f]	–[f]	155[g]
Scheme 1c	39.2	51.4	14.1	27.4	6.7	35.0	7.3	21.8	27.7	1.7	27.7	79	31.8

[a]Process mass intensity: reaction. [b]Process mass intensity: chemicals and reaction solvents. [c]Process mass intensity: workup and reaction solvents. [d]Renewable sources: DESs, CPME, water. [e]Calculated metric data do not take into account the synthesis of starting materials **1** and **4** (Scheme 1b). [f]Metric data could not be calculated. [g]This value does not take into account the amount of solvent used for workup.

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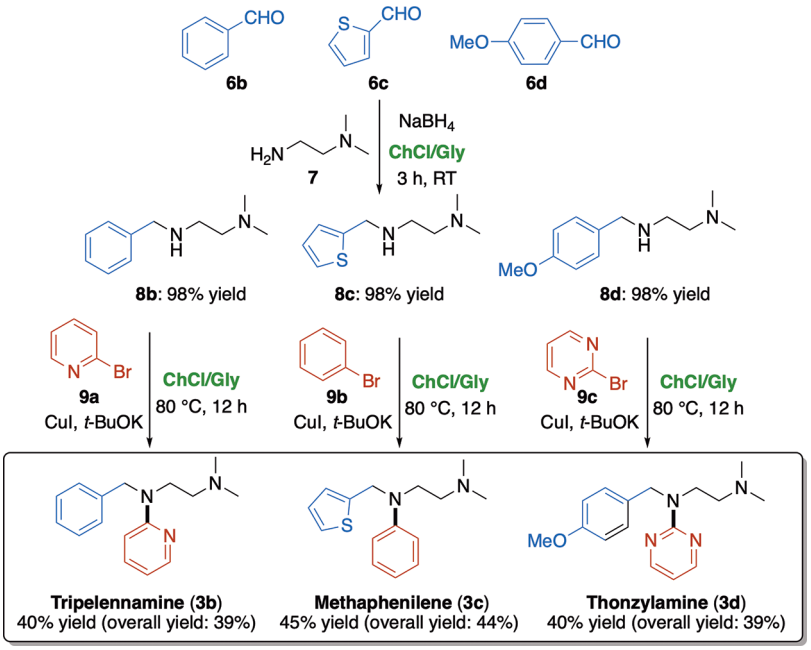
Table 3. Production Costs of Reagents for Synthesis of 51.6 mg of Thenfadil (3a) Using 1 g ChCl/Gly[a]

DES	6a	7	$NaBH_4$	CPME	DES	9a	CuI	*t*-BuOK	3a
1 g[b]	56 mg	44 mg	18.9 mg	3 mL	1g	79 mg	9.5 mg	168 mg	**51.6 mg**
0.030 €	0.051 €	0.015 €	0.004 €	0.15 €	0.030 €	0.049 €	0.002 €	0.034 €	0.365 €

[a]DES: ChCl/Gly (1:2 mol mol^{-1}). ChCl: 29 €/500 g (TCI). Gly: 12.20 €/1 L (d 1.26 g/mL) (Alfaesar). **6a**: 91.67 €/100 g (Fluorochem). **7**: 139 €/500 mL (TCI, d 0.8 g/mL). $NaBH_4$: 118 €/500 g (TCI). CPME: 30.5 €/500 g 0.86 g/mL (Fluorochem). **9a**: 310 €/500 g (TCI). CuI: 122 €/500 g (TCI). *t*-BuOK: 102€ /500g (TCI). [b]0.57 g of Gly, 0.43 g of ChCl.

Scheme 4. Synthesis of Tripelennamine (3b), Methaphenilene (3c), and Thonzylamine (3d) via Reductive Amination of Aldehydes 6b–d with Diamine 7 Followed by a Cu-Catalyzed C–N Coupling Reaction of Resulting Adducts 8b–d with (Hetero)aryl Bromides 9a–c



PMI solv, 156.0 g g^{-1}), with the former values being less than about 70% and 90%, respectively, and with an E-factor increasing from 31.8 (Scheme 1c) to 155 (Scheme 1b) (Table 2).

It is also worth highlighting that the sustainable synthetic pathway set up for the preparation of Thenfadil (**3a**) allowed us to cut current production costs from 325 €/50 mg[9] up to 0.365 €/51.6 mg (Table 3).

The reproducibility and the robustness of the above methodology was then assessed by the sustainable synthesis of Thenfadil's analogs such as tripelennamine (**3b**), methaphenylene (**3c**), and thonzylamine (**3d**) (Scheme 3). According to our protocol, by reacting aldehydes **6b–d** (9 mmol each) with diamine **7** (1 equiv) in ChCl/Gly (1:2 mol mol^{-1}, 10 g), at RT under air, followed by the addition of $NaBH_4$ (1.1 equiv) after 1 h, the desired secondary amines **8b–d** were isolated each in 98% yield, with the overall reaction time being 3 h. Each isolated amine was finally suspended in ChCl/Gly (1:2 mol mol^{-1}, 10 g), previously dried under reduced pressure, in the presence of CuI (10 mol %), *t*-BuOK (3 equiv), and the corresponding (hetero)aryl bromide (**9a**, **9b**, or **9c**) (1 equiv). After 12 h reaction time, the desired targets **3b–d** were isolated in 40%–45% yield (overall yields for the two steps: 39%–44%), after addition of water and centrifugation, with no need of column chromatography (see Experimental Section) (Scheme 4).

CONCLUSION

In summary, we have reported a sustainable synthesis of the antihistamine drug Thenfadil by combining a reductive amination process with a Cu-catalyzed Ullmann-type C–N cross-coupling reaction, both being fully optimized in environmentally friendly eutectic mixtures like ChCl/Gly and ChCl/urea from readily available and inexpensive starting materials. These reactions proceeded smoothly in DESs under aerobic conditions, with the desired target being isolated in an overall yield of 39%, by simply treating the crude with water followed by centrifugation, with no need of column chromatography (E-factor, 31.8; PMI, 35.0). The two main byproducts, deriving from competitive Cu-catalyzed arylation of oxygen sources (namely, water and alcohols as active components of eutectic mixtures) have been isolated and characterized. Their formation was effectively suppressed by working with anhydrous DESs, with the unreacted, intermediate secondary amine recovered by crystallization as a hydrochloric salt and then recycled. Of note, this route could easily be (a) scaled up to 50 g of substrate, working in an open round-bottomed flask filled with 500 g of DES, thereby delivering up to 45.9 g of Thenfadil with no decrease in the final yield (40%), and (b) successfully extended to the synthesis of other ethylenediamine derivatives like tripelennamine, methaphenilene, and thonzylamine in overall 39%–44% yield. Considering the exponential growth in the number of publications on DES chemistry over the years, scaling up DES-based processes is especially crucial

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for industries investing in green technologies. This is in order to develop a truly sustainable industrial production of pharmaceutically relevant drugs based on biobased solvents, thereby avoiding the use of toxic and harmful VOCs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.2c00417.

Details on materials and methods used for the reported synthetic procedures; details on the recovery procedure of diamine **8a**; details on scaling up the synthesis of Thenfadil (**3a**) in DES; E-factor calculation for the synthesis of Thenfadil (**3a**); typical metrics applied at Zero, First, and Second Pass according to the CHEM21 Metrics Toolkit; spectroscopic data of compounds **8a**−**d**, **3a**−**d**, **11**, and **12**; and ^{1}H and ^{13}C NMR spectra of compounds **8a**−**d**, **3a**−**d**, **11**, and **12** (PDF)

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Author Contributions

J.G.-Á., F.M.P, and V.C. conceived the study. A.F.Q. and F.V.R. undertook all the synthetic experimental works. A.F.Q., F.M.P., and P.V. analyzed and collected experimental data. J.G.-Á., F.M.P, P.V., and V.C. supervised the synthetic chemistry works. V.C. directed the project. F.M.P. and P.V. carried out the characterization chemistry works. A.F.Q. and V.C. analyzed and drafted the manuscript, while all the authors contributed to the discussion, to the writing, and the review. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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