

Natural Deep Eutectic Solvents as sustainable solvent for Suzuki-Miyaura cross-coupling reactions applied to imidazo-fused heterocycles.

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Abstract

Herein, we proposed the first Suzuki-Miyaura cross-coupling in sustainable Natural Deep Eutectic Solvent (NaDES) applied to biologically relevant imidazo-fused scaffold like imidazo[1,2-*a*]pyridine and imidazo[1,2-*b*]pyridazine. The Choline chloride/glycerol (1:2, mol:mol) NaDES allowed the functionalization of diverse positions on the heterocycles with various boronic acids, by using 2.5mol% of readily available Pd(OAc)₂. Noteworthy, the catalytic system proceeds without any ligands or additives, under air atmosphere.

Introduction

Imidazo-fused heterocycles, *e.g.* imidazo[1,2-*a*]pyridine or imidazo[1,2-*b*]pyridazine, have been widely exploited in various pharmacological areas¹, due to their diverse biological activities. Imidazo[1,2-*a*]pyridine core can be found in marketed drugs like hypnotic Zolpidem or gastroprotective Zolimidine, when imidazo[1,2-*b*]pyridazine is part of anti-cancer Ponatinib (Figure 1).

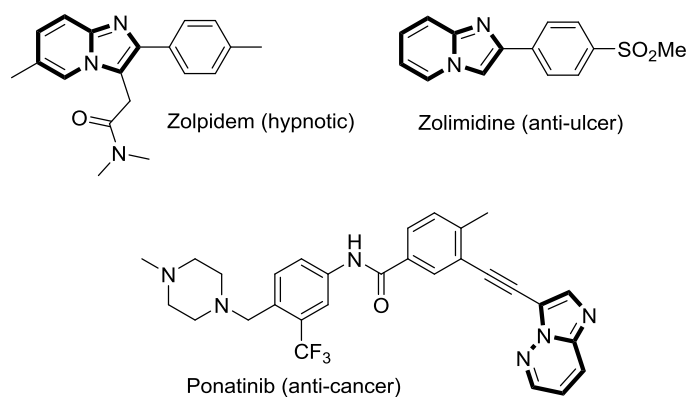


Figure 1. Structure of imidazo-fused heterocycles-containing marketed drugs Zolpidem, Zolimidine and Ponatinib

As a result, there is a continued effort to design new methods for synthesis² or functionalization³ of such scaffold. In our laboratory we have contributed to the development of palladium-catalyzed functionalization of both imidazo[1,2-*a*]pyridine and imidazo[1,2-*b*]pyridazine at diverse positions.⁴ In all cases the reactions take place in toxic organic solvent, such as DME or 1,4-dioxane. The search for alternatives of such solvents is today a major concern for chemists, with the aim of developing safer reaction media for humans and the environment. In recent decades, Deep Eutectic Solvents (DES) has emerged as highly promising sustainable media for extraction of natural products⁵, as well as for organic chemistry⁶. DES are mostly composed of a mixture of cheap, readily available and safe compounds, such as choline chloride, betaine, glycerol or sugar which are able to form a liquid phase at room temperature

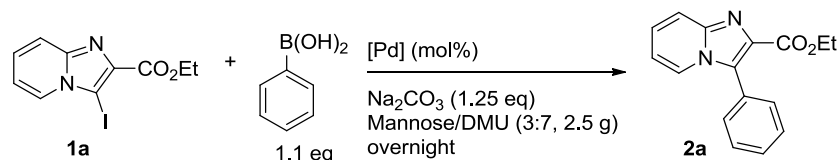
through hydrogen-bond-promoted self-association. DES has already found applications in the field of metal-catalyzed organic reactions⁷, and especially palladium-catalyzed cross-coupling, *e.g.* Suzuki-Miyaura⁸, Heck⁹, Stille¹⁰, Tsuji-Trost¹¹, Sonogashira⁹, or direct arylation *via* C-H activation.¹² To date, all these achievements were done on “model” substrate, like diphenyl synthesis for Suzuki-Miyaura.⁸ To the best of our knowledge nothing was made on more challenging heterocyclic substrates. We proposed here the first Suzuki-Miyaura cross-coupling in DES applied to biologically relevant imidazo-fused scaffold.

Results and discussion

Based on our continued interest in imidazo-fused heterocycles, we decided to test the feasibility of palladium catalyzed cross-coupling reactions in deep eutectic solvent, starting by the Suzuki-Miyaura reaction.

Optimization studies were performed on ethyl 3-iodoimidazo[1,2-*a*]pyridine-2-carboxylate **1a**, a common starting material in our laboratory, in order to determine the best catalyst (Table 1). Inspired by the work of Imperato *et al.*,^{8a} we decided to try the first attempt with phenylboronic acid in a low melting mixture (mixture of two solids forming a liquid only by heating, unlike DES which remain cold liquid) of Mannose/Dimethylurea (DMU) (3:7, wt:wt) in the presence of 20 mol % of palladium source and 1.25 equivalent of Na₂CO₃, overnight. From the five catalysts evaluated (entries 1-5), three were almost equally efficient: Pd(OAc)₂, PdCl₂, and Pd₂(dba)₃. We decided to continue the optimization process with Pd(OAc)₂. Applying microwave irradiation to the reaction mixture at 90°C, 80°C or 70°C (entries 6-8), negatively impacted the yield. Then, the reaction was repeated decreasing the catalyst loading, showing a good yield until 2.5 mol % of palladium source (entry 11). With 1 mol % the yield dropped to 76% (entry 12). Finally, we investigated the effect of time reaction. With 20 mol % of Pd(OAc)₂, full conversion by TLC can be obtained in one hour, but with a lower yield of 66% (entry 13 to be compared with 78% after overnight heating: entry 1). Using 10 mol % of catalyst, three hours are needed to insure full conversion, with unfortunately a moderate isolated yield: 57%. The conditions were then stated as Pd(OAc)₂ 2.5mol %, 90°C with conventional oil-bath heating overnight. It is interesting to note that all these reactions did not require any addition of ligands or additives, and proceed under air atmosphere.

Table 1. Optimization of the catalyst.



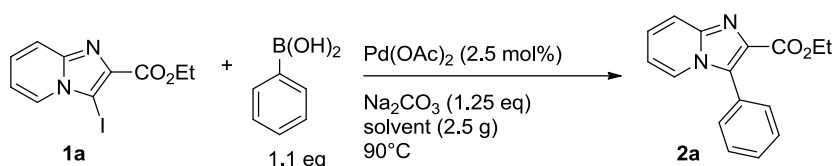
Entry	[Pd] (mol %)	Temp. (°C)	Yield ^a (%)
1	Pd(OAc) ₂ (20)	90	78
2	PdCl ₂ (20)	90	60
3	PdCl ₂ (dppf).CH ₂ Cl ₂ (20)	90	15
4	Pd ₂ (dba) ₃ (20)	90	61
5	PdCl ₂ (PPh ₃) ₂ (20)	90	30
6	Pd(OAc) ₂ (20)	90 ^c	31

7	Pd(OAc) ₂ (20)	80 ^c	30 ^b
8	Pd(OAc) ₂ (20)	70 ^c	30 ^b
9	Pd(OAc) ₂ (10)	90	86
10	Pd(OAc) ₂ (5)	90	84
11	Pd(OAc) ₂ (2.5)	90	93
12	Pd(OAc) ₂ (1)	90	76
13	Pd(OAc) ₂ (20)	90 ^d	66
14	Pd(OAc) ₂ (10)	90 ^e	57

^a Isolated yields after column chromatography. ^b Estimated yields on crude ¹H NMR. ^c Reaction performed under microwave irradiation for 30 minutes. ^d Classical heating for 1h. ^e Classical heating for 3h.

With the best palladium source and loading established, a study to find the best solvent system was initiated (Table 2). Different low melting solvents previously described by Imperato *et al.* in 2006¹⁰ and Ilgen *et al.* in 2009⁹, were first screened (entries 1-3). As previously stated in table 1, the Mannose/DMU melt (3:7, wt:wt) allowed the reaction to be completed cleanly in 93% isolated yield (entry 1). Systems containing NH₄Cl resulted in a total loss of reactivity, the starting material being fully recovered (entries 2-3). Then, we tested various deep eutectic solvents (DES) available in the laboratory for the extraction of natural products. If the reaction has proceeded in these DES, only lower yields were obtained, with 42% for glycerol/glucose (3:1, mol:mol, entry 4), 16% for Choline chloride/glucose (2:3, mol:mol, entry 5) and 32% for Choline chloride/glucose/H₂O (2:1:3, mol:mol:mol, entry 6). Choline chloride/urea (1:2, mol:mol) did not result in any conversion, the starting material being fully recovered. Finally, we moved to choline chloride/glycerol (1:2, mol:mol) used by Marsey *et al.* in 2017^{8b} and Massolo *et al.* in 2016¹³, and desired product **2a** was obtained in a good yield of 74%. Using this DES, the time reaction can be decreased to 2h (entry 8) and 1h (entry 9), with equivalent yields. This DES belongs to the class of NaDES (Natural Deep Eutectic Solvent), being composed of primary metabolites¹⁴, and is fully user-friendly, easy to prepare in bulk and can be store for months on the bench.

Table 2. Optimization of the low melting solvent/DES.

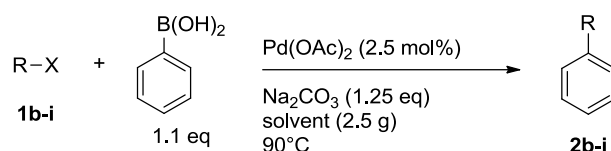


Entry	Solvent	Time	Yield (%)
1	Mannose/DMU (3:7, wt:wt)	overnight	93 ^a
2	D-sorbitol/DMU/NH ₄ Cl (7:2:1, wt:wt)	overnight	0
3	Glucose/Urea/NH ₄ Cl (6:3:1, wt:wt)	overnight	0
4	Glycerol/glucose (3:1, mol:mol)	overnight	42 ^a
5	Choline chloride/glucose (2:3, mol:mol)	overnight	16 ^a
6	Choline chloride/glucose/H ₂ O (2:1:3, mol:mol:mol)	overnight	32 ^a
7	Choline chloride/urea (1:2, mol:mol)	overnight	0
8	Choline chloride/glycerol (1:2, mol:mol)	overnight	74 ^b
9	Choline chloride/glycerol (1:2, mol:mol)	2h	71 ^a
10	Choline chloride/glycerol (1:2, mol:mol)	1h	73 ^a

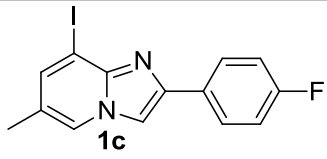
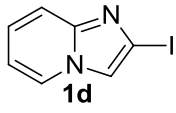
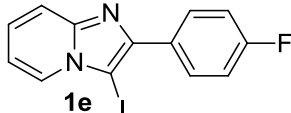
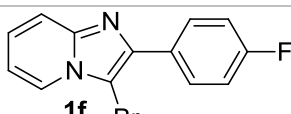
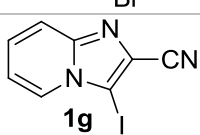
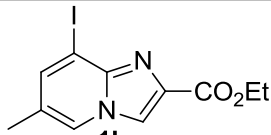
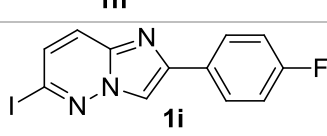
^a Isolated yields. ^b Determined by HPLC.

We then decided to explore the scope of the reaction toward different halogenated heterocycles (Table 3). For the first example **1b** (entry 1) we tested the four best different DES from Table 2: Mannose/DMU (3:7, wt:wt), Glycerol/glucose (3:1, mol:mol), Choline chloride/glucose (2:3, mol:mol), Choline chloride/glucose/H₂O (2:1:3, mol:mol:mol) and Choline chloride/glycerol (1:2, mol:mol). Unlike what we observed for **1a**, Glycerol/glucose (3:1, mol:mol) did not work with **1b**, as only starting material was recovered. Choline chloride/glucose (2:3, mol:mol) and Choline chloride/glucose/H₂O (2:1:3, mol:mol:mol) gave only low yields of 30% and 36%, respectively. Mannose/DMU (3:7, wt:wt) and Choline chloride/glycerol (1:2, mol:mol) were the two best solvents for **1b**, with yields of 66 and 89%, respectively. A yield of 88% can be obtained in the latter in one hour instead of overnight. We therefore choose to keep both mannose/DMU (3:7, wt:wt) and choline chloride/glycerol (1:2, mol:mol). In the imidazo[1,2-*a*]pyridine series, 2-,3-,6- or 8-iodinated compounds can be functionalized with PhB(OH)₂ (entries 1-4 and 6-7). In all cases NaDES choline chloride/glycerol (1:2, mol:mol) proved to be superior to mannose/DMU (3:7, wt:wt), with significantly higher yields. The reaction time required to end with full conversion highly depends on the position of the iodide. In the 6-position (entry 1, compound **1b**), two hours are enough to provide 88% of product **2b**, while the 8-iodinated isomer **1c** required 24h to yield 69% of product **2c** (entry 2). 2-iodinated **1d** was converted in product **2d** with overnight heating in a yield of 60% (entry 3), when an hour provided only 41% of **2d** (entry 3). For the most commonly used 3-iodinated imidazo[1,2-*a*]pyridines **1a**, **1e** and **1g**, the reactivity strongly depends on substituent at 2-position. As indicated previously, with an ester (compound **1a**, Table 2, entry 9), one hour at 90°C provided full conversion with a yield of 73%. With 4-fluoro-phenyl (entry 4), the yield dropped to 45% after overnight heating. Then, with 2-cyano compound **1g** (entry 6), one hour resulted with full conversion and a yield of 88%. This effect of substituent at 2-position was also observed for 8-iodinated **1h** (entry 7), for which 6h of heating is enough to furnish full conversion and a yield of 59% (to be compared with entry 2). We thus tried to evaluate the influence of halogen with 3-brominated compound **1f** (entry 5). It was found that the bromide exhibited a radically different reactivity since virtually no product was isolated after heating overnight. Thus we tested the reaction on 6-iodinated imidazo[1,2-*b*]pyridazine **1i**, and we were delightful to obtain a yield of 89% after one hour at 90°C (entry 8).

Table 3. Scope of the Suzuki-Miyaura reaction using various halogenated starting materials.



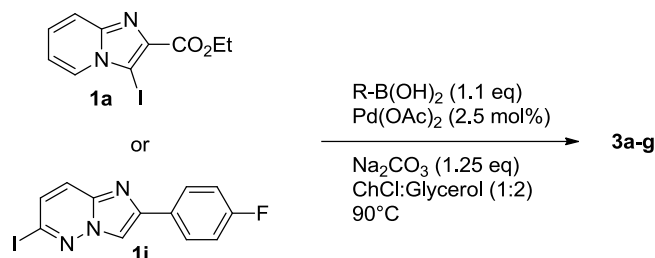
Entry	R-X	Solvent	Time	Yield (%)
1	 1b	Mannose/DMU (3:7) Glycerol/glucose (3:1) Choline chloride/glucose (2:3) Choline chloride/glucose/H ₂ O (2:1:3) Choline chloride/glycerol (1:2)	overnight overnight overnight overnight overnight 2h	66 ^a 0 30 ^b 36 ^b 89 ^a /100 ^b 88 ^a

2		Mannose/DMU (3:7) Choline chloride/glycerol (1:2)	overnight 1h 24h	14 ^a 17 ^a 69 ^a
3		Mannose/DMU (3:7) Choline chloride/glycerol (1:2)	overnight overnight 1h	14 ^a 60 ^b 41 ^a
4		Mannose/DMU (3:7) Choline chloride/glycerol (1:2)	overnight overnight	0 45 ^a
5		Mannose/DMU (3:7) Choline chloride/glycerol (1:2)	overnight overnight	2 ^a traces
6		Mannose/DMU (3:7) Choline chloride/glycerol (1:2)	overnight overnight 1h	74 ^a 82 ^b 88 ^a
7		Choline chloride/glycerol (1:2)	6h	59 ^a
8		Choline chloride/glycerol (1:2)	1h	89 ^a

^a Isolated yields. ^b Determined by HPLC.

Finally, we wanted to extend our conditions to different boronic acids (Table 4). Imidazo[1,2-*a*]pyridine **1a** and imidazo[1,2-*b*]pyridazine **1i** were selected as substrates. Starting from **1a**, electron-rich (entry 1) and electron-poor (entry 2) aryls were successfully used, providing product **3a** and **3b** with good yields of 78% (2h) and 88% (1h), respectively. Heteroaromatic 2-thienyl (entry 3) and alkyl (entry 4) can also be used, but with moderate yields of 34% (1h) and 29% (2h), respectively. Using imidazo[1,2-*b*]pyridazine **1i**, all aromatics (entries 1-3) proceeded with high yields in no more than two hours, but surprisingly CH₃B(OH)₂ (entry 4) did not allowed the formation of methylated product.

Table 4. Scope of the Suzuki-Miyaura reaction using various boronic acids.



Entry	R	Time	Yield (%) ^a from 1a (Cpd)	Yield (%) ^a from 1i (Cpd)
1	4-CH ₃ O-Ph	2h	78 (3a)	90 (3e)
2	4-F-Ph	1h	88 (3b)	92 (3f)

3	Thien-2-yl	1h	34 (3c)	82 (3g)
4	methyl	2h	29 (3d)	0

^a isolated yields

Conclusion

We described here for the first time Suzuki-Miyaura cross-coupling in sustainable Natural Deep Eutectic Solvent (NaDES) applied to imidazo-fused heterocycles of biological interest. Choline chloride/glycerol (1:2, mol:mol) was found to be the more general and efficient media for coupling in both imidazo[1,2-*a*]pyridine and imidazo[1,2-*b*]pyridazine series, in diverse positions and with a variety of boronic acids. The reaction proceeded with 2.5mol % of Pd(OAc)₂, without any ligands or additives, under air atmosphere. This represents a promising alternative to organic solvents routinely used for such coupling (*e.g.* DME or 1,4-dioxane). In view of the importance of imidazo-fused heterocycles in medicinal chemistry, development of more eco-friendly methods of pharmacomodulation is urgently needed. Extension to other palladium-catalyzed cross coupling (*e.g.* Sonogashira or Stille) is currently under investigation, as well as a protocol for the recycling of NaDES.

Experimental part

General considerations

All reagents were used directly as obtained commercially. Thin-layer chromatography (TLC) were performed using Merk[®] silica gel 60F₂₅₄ plates. Column chromatography were performed using Merck Geduran[®] Si 60 (40-63µm) silica. Melting points were determined on a capillary apparatus (Stuart, Staffordshire, United Kingdom) and are uncorrected. NMR experiments were performed at 300 MHz (¹H) and 75 MHz (¹³C) on a Bruker-Avance 300 MHz spectrometer. Assignment of carbons noted C* may be interchanged. Mass spectra were determined on a Hewlett Packard 5988A spectrometer or on a Shimadzu QP 2010 spectrometer by direct inlet at 70 eV. Compounds **2a**^{4e}, **2c**¹⁵, **2d**¹⁶, **2e**^{4e}, **2h**¹⁵, **2i**^{4f}, **3a**¹⁷, **3c**^{4e}, **3d**^{4e}, **3e**^{4f}, **3f**^{4f} and **3g**^{4f} are described in the literature, and were obtained with spectral data in accordance to it.

Low-melting and deep eutectic solvents preparation

All the low-melting and deep eutectic solvents were prepared prior to use by heating the components together at 90°C under vigorous stirring (magnetic stir bar) until a homogeneous solution was obtained (*ca.* 30min-1h). The reactions were performed in large round-bottom tubes (9.5cm high, 2.8cm diameter) closed with a rubber septum, with 5g of solvent for 1mmol of starting material. Only the choline chloride/glycerol (1:2, mol:mol) were prepared on larger amount (80mL) and stored at room temperature.

General procedure for Suzuki-Miyaura coupling in low-melting solvents and DES

In large round-bottom tube, boronic acid (1.1 eq), compounds **1a-i** (1 eq, 1mmol), Na₂CO₃ (1.25 eq), and Pd(OAc)₂ (2.5mol %) were successively added to low-melting solvent or DES (5g) at 90°C (see section above). The tube was closed with a rubber septum and the reaction mixture was stirred at 90°C until full conversion by TLC (*ca.* 1h-48h). The reaction mixture was cooled down and 50mL of water were added, followed by 10mL of brine. The reaction mixture was then extracted with four time 35mL of EtOAc. The combined organic phases were dried over MgSO₄, evaporated and purified by column chromatography on silica gel.

2-(4-Fluorophenyl)-8-methyl-6-phenylimidazo[1,2-*a*]pyridine (**2b**)

White solid, 133mg, **m.p.**: 158-162°C, yield: 89%. **¹H NMR** (300MHz, CDCl₃) δ: 8.16 (s, 1H, H-5), 7.99-7.93 (m, 2H, 4-F-Ph-2,6), 7.83 (s, 1H, H-3), 7.58-7.55 (m, 2H, Ph-2,6), 7.50-7.45 (m, 2H, Ph-3,5), 7.42-7.36 (m, 1H, Ph-4), 7.24 (s, 1H, H-7), 7.17-7.09 (m, 2H, 4-F-Ph-3,5), 2.71 (s, 3H, CH₃). **¹³C NMR** (75MHz, CDCl₃) δ: 163.3 (d, ¹J_{CF} = 317.1Hz, 4-F-Ph-4), 145.7 (C-8a*), 145.0 (C-2*), 137.7 (Ph-1), 130.4 (d, ⁴J_{CF} = 3.0Hz, 4-F-Ph-1), 129.2 (Ph-3,5), 128.0 (Ph-4*), 127.9 (4-F-Ph-2,6*), 127.4 (C-6), 127.0 (Ph-2,6), 124.5 (C-7), 120.8 (C-5), 115.7 (d, ²J_{CF} = 21.6Hz, 4-F-Ph-3,5), 108.8 (C-3), 17.4 (CH₃). **HRMS** (ESI): *m/z* calc. for C₂₀H₁₅FN₂ [M+H]⁺: 303.12920, found: 303.12699.

3-Phenylimidazo[1,2-a]pyridine-2-carbonitrile (2g)

Pale yellow solid, 96mg, **m.p.**: 159-163°C, yield: 88%. **¹H NMR** (300MHz, CDCl₃) δ: 8.24 (dt, ³J = 7.2Hz, ⁴J = 0.9Hz, 1H, H-5), 7.68 (dt, ³J = 9.3Hz, ⁴J = 0.9Hz, 1H, H-8), 7.65-7.51 (m, 5H, Ph), 7.36 (ddd, ³J = 9.2Hz, 6.7Hz, ⁴J = 1.2Hz, 1H, H-7), 6.94 (dt, ³J = 6.9Hz, ⁴J = 1.1Hz, 1H, H-6). **¹³C NMR** (75MHz, CDCl₃) δ: 145.5 (C-9a), 132.6 (C-3), 130.3 (Ph-4), 129.8 (Ph-3,5), 129.0 (Ph-2,6), 127.2 (C-7), 125.9 (Ph-1), 124.0 (C-5), 119.0 (C-8), 116.5 (C-2*), 115.3 (CN*), 114.7 (C-6). **HRMS** (ESI): *m/z* calc. for C₁₄H₉N₃ [M+H]⁺: 220.08536, found: 220.08536.

Ethyl 3-(4-fluorophenyl)imidazo[1,2-a]pyridine-2-carboxylate (3b)

Pale yellow solid, 125mg, **m.p.**: 151-155°C, yield: 88%. **¹H NMR** (300MHz, CDCl₃) δ: 7.90 (d, ³J = 7.0Hz, 1H, H-5), 7.74 (d, ³J = 9.2Hz, 1H, H-8), 7.53-7.47 (m, 2H, 4-F-Ph-2,6), 7.32-7.22 (m, 3H, H-7 & 4-F-Ph-3,5), 6.84 (dt, ³J = 6.9Hz, ⁴J = 1.0Hz, 1H, H-6), 4.35 (d, ³J = 7.1Hz, 2H, CH₂CH₃), 1.31 (t, ³J = 7.1Hz, 3H, CH₂CH₃). **¹³C NMR** (75MHz, CDCl₃) δ: 163.5 (CO), 163.4 (d, ¹J_{CF} = 248.3Hz, 4-F-Ph-4), 144.5 (C-8a), 136.4 (4-F-Ph-1), 133.2 (C-2), 132.8 (d, ³J_{CF} = 8.4Hz, 4-F-Ph-2,6), 128.4 (C-3), 126.5 (C-7), 124.0 (C-5), 119.2 (C-8), 116.2 (²J_{CF} = 21.9Hz, 4-F-Ph-3,5), 114.0 (C-6), 61.2 (CH₂CH₃), 14.4 (CH₂CH₃). **HRMS** (ESI): *m/z* calc. for C₁₆H₁₄FN₂O₂ [M+H]⁺: 285.10338, found: 285.10131.

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