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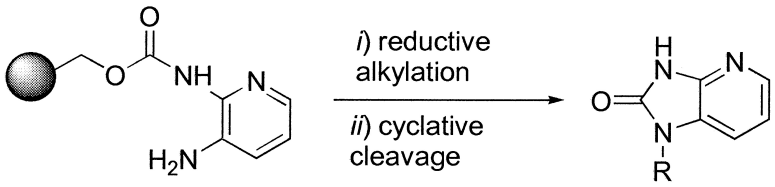

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Solid-Phase Synthesis of Imidazo[4,5-*b*]pyridin-2-ones and Related Urea Derivatives by Cyclative Cleavage of a Carbamate Linkage

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A solid-phase synthesis of substituted cyclic urea derivatives as potential heterocyclic library scaffolds is described. 2-Amino-3-nitropyridine is attached to Wang resin via a carbamate linkage. Reduction of the nitro group was achieved with $SnCl_2 \cdot 2H_2O$. Reductive alkylation with a range of substituted benzaldehydes followed by cyclative cleavage afforded a small library of 3-substituted imidazo[4,5-*b*]pyridine-2-ones in 33−45% yield and 59−88% purity. Subsequently, this methodology was applied to the synthesis of 3-substituted imidazo[4,5-*f*]quinolin-2-ones.

Introduction

1,3-Dihydro-2*H*-benzimidazol-2-ones (**1**) and related cyclic urea derivatives are useful heterocyclic building blocks and are prominent structural elements of compounds demonstrating a wide variety of pharmacological and biochemical properties. Examples of pharmacological activity exhibited by benzimidazol-2-ones **1** include antagonism of neurotransmitter receptors, inhibition of aldose reductase, antiulcer and antisecretory properties, and modulation of ion channels.[1−4] Furthermore, the closely related imidazo[4,5-*b*]pyridin-2-ones (**2**) and imidazo[4,5-*b*]quinolin-2-ones (**3**) have been described as potent inhibitors of blood platelet cAMP phosphodiesterase (PDE) (Figure 1).[5−9]

A polymer-assisted solution-phase synthesis of a benzimidazol-2-one library has been reported by our research group.[10] To extend our structure−activity relationship study, we required a versatile synthetic route to rapidly generate and purify imidazo[4,5-*b*]pyridin-2-one derivatives. However, reported solution-phase procedures involve either laborious protecting group manipulations on the urea nitrogens[11] or the thermal rearrangement of condensed dihydrodiazepinones.[1,12−14]

Reported solid-phase strategies aimed toward the synthesis of benzimidazol-2-ones are "nontraceless". They are usually based on the attachment of the heterocycle to the polymer via an ester linkage, thus resulting in a carboxylic acid residue on the final product upon cleavage.[15−17]

Herein, we report a versatile route to substituted imidazo[4,5-*b*]pyridin-2-ones and other cyclic urea derivatives involving a cyclative cleavage of a carbamate linkage as the key reaction step.

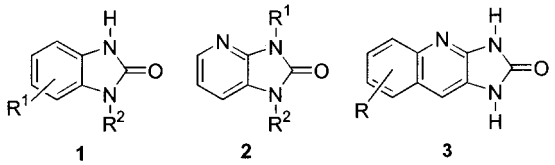
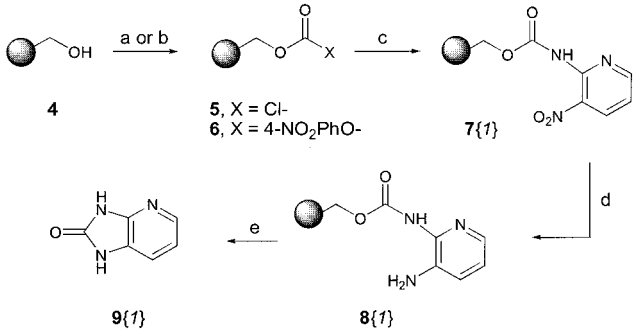


Figure 1. Biologically active cyclic urea derivatives.

Scheme 1. Solid-Phase Synthesis of 1,3-Dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one **9**{*1*}[a]



[a] Reagents and conditions: (a) phosgene (5 equiv, 1 M solution in toluene), THF, room temp, 8 h; (b) 4-nitrophenyl chloroformate (4 equiv), NMM, DCM, room temp, 16 h; (c) 2-amino-3-nitropyridine (4 equiv), BSA (5 equiv), DMAP (4 equiv), DMF, room temp, 16 h; (d) $SnCl_2 \cdot 2H_2O$ (10 equiv, 1 M in DMF), 30 °C, 16 h; (e) MP-CO_3 (3 equiv), DMF (containing 1.5% AcOH), 60 °C, 16 h.

Results and Discussion

Two types of activated carbonate resin were prepared from Wang polymer **4** (Scheme 1). Treatment of **4** with an excess of phosgene in anhydrous THF afforded the chloroformate derivative **5**.[18] Analysis of the chlorine contents was used to determine the resin loading (1.54 mmol/g) and indicated quantitative conversion. The Wang polymer was also readily transferred into its 4-nitrophenyl carbonate derivative **6** by reaction with 4-nitrophenyl chloroformate in the presence of *N*-methylmorpholine.[19−21] A loading of 1.1 mmol/g was determined by elemental analysis of the nitrogen content of

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the polymer. Hydrolysis of the carbonate linker and calculation of the nitrophenolate concentration in the cleavage solution by UV photometry gave slightly higher values (1.2 mmol/g).

Displacement of the activating groups did not occur on exposure to a solution containing 2-amino-3-nitropyridine and a base, such as diisopropylethylamine (DIEA), but was achieved under the conditions reported by Dressman et al.[19] Thus, preliminary treatment of 2-amino-3-nitropyridine with *N,O*-bis(trimethyl)silylacetamide (BSA) led to in situ silylation of the amino group, resulting in its activation and solubilization. Subsequent reaction with the activated carbonate resins in the presence of *N,N*-(dimethylamino)pyridine (DMAP) afforded polymer-bound heterocycle **7**{*1*}.

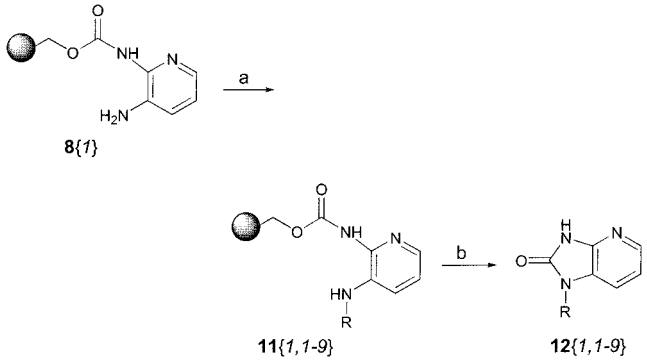
Carbamate formation was monitored by IR spectroscopy and was indicated by a shift in the carbonyl stretch absorption from 1774 cm^{-1} in the chloroformate Wang resin **5** (1757 cm^{-1} in the 4-nitrophenyl carbonate Wang polymer **6**) to 1732 cm^{-1}. To ensure that complete conversion of the carbonate linker to the resin-bound carbamate **7**{*1*} had occurred, the substrate was cleaved from the polymer and subjected to standard analytical conditions (NMR, LC−MS) and the reaction conditions were optimized accordingly. Nevertheless, a decrease in substrate loading to 0.64 mmol/g (as determined by nitrogen analysis) was not avoidable, which was attributed to the instability of the activating group.

Several reports of solid-phase reduction of nitroarenes have been published, including the use of chromium chloride,[19,22,23] lithium aluminum hydride,[24] and stannous chloride.[25−28] The last was regarded as the most suitable reagent, bearing in mind that the others might also cause reduction of the carbonate linkage. The reaction conditions were optimized to ensure complete reduction while maintaining high resin loadings by preventing premature cyclization. The reaction of the polymer-bound substrate **7**{*1*} with $SnCl_2 \cdot 2H_2O$ was investigated in two solvents, DMF and NMP, at various temperatures. The reductions at ambient temperature proceeded rather slowly, whereas at 60 °C substantial cyclative cleavage occurred resulting in lower loadings and yields. Treatment of **7**{*1*} with tin(II) chloride solution (1 M in DMF, 10 equiv) at 30 °C was found to be a good compromise of reaction time and resultant loading.

Cyclative cleavage was then induced under basic conditions; the addition of acetic acid, as recommended by Smith et al.,[29] enhanced the reaction rate. Polymer **8**{*1*} was treated with inorganic as well as organic bases, such as Et_3N, DIEA, NaH, and NaOH, at 60 °C for 24 h. However, the majority of the isolated material consisted of the base and its hydrochloride salts (from trapped $SnCl_2$ residues) with only traces of the desired product **9**{*1*}. Extractive workup proved to be inefficient because of the low solubility of the product in organic solvents. To avoid the contamination of the product by a soluble reagent, the use of polymer-supported bases (such as PS-DIEA, PS-NMM and MP-carbonate) was investigated.

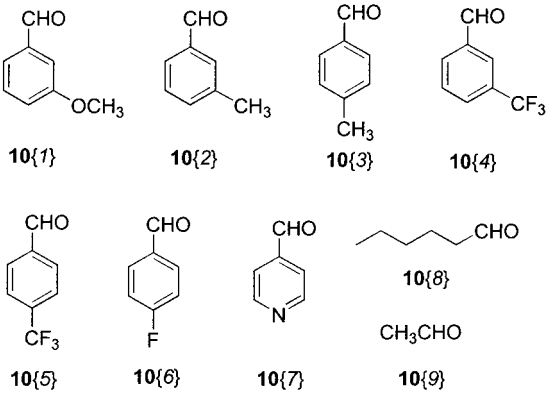
Unfortunately, PS-DIEA was found to be unstable under the reaction conditions and diisopropylamine was released into the cleavage mixture. The best result was obtained with MP-carbonate, a macroporous polystyrene anion-exchange resin that also facilitated the removal of unwanted salts, to afford the desired imidazopyrimidin-2-one **9**{*1*} in excellent purity.

Scheme 2. Reductive Alkylation and Cyclative Cleavage of Resin-Bound Intermediate **8**{*1*}[a]



[a] Reagents and conditions: (a) aldehyde **10**{*1*−*9*}, $NaBH(OAc)_3$, $NaSO_4$ (10 equiv each), DCE (containing 1% AcOH), 30 °C, 4 h; (b) MP-CO_3 (3 equiv), DMF (containing 1.5% AcOH), 60 °C, 16 h.

Table 1. Aldehydes **10**{*1*−*9*}



Although this cyclative cleavage is of a "traceless" nature, the term "hidden linker" has recently been suggested for such systems[30] in which the functionality used to attach the compound to the solid support is incorporated into the compound class being synthesized by cyclative cleavage such that the linker is somewhat hidden though definitely not traceless.

The polymer-bound intermediate **8**{*1*} represented a valuable intermediate for further elaboration. Thus, the free amino group was subjected to reductive alkylation with a range of aldehydes (Scheme 2). The conditions employed have been reported recently by Ley et al.;[31] however, the use of sonication was circumvented by a change of solvent and moderate heating to facilitate automated synthesis. Reductive alkylation with substituted benzaldehydes **10**{*1*−*7*} (Table 1) followed by cyclative cleavage proceeded in moderate yields but afforded the desired products **12**{*1,1*−*7*} in good purities (Table 2). Unfortunately, reductive alkylation with aliphatic aldehydes **10**{*8*−*9*} proved to be unsuccessful with only traces of product formation detectable by LC−MS. All members of the 1-substituted 1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-ones library were analyzed by standard analytical techniques and exhibited good homogeneity (see ^1H NMR spectra in Figure 2).

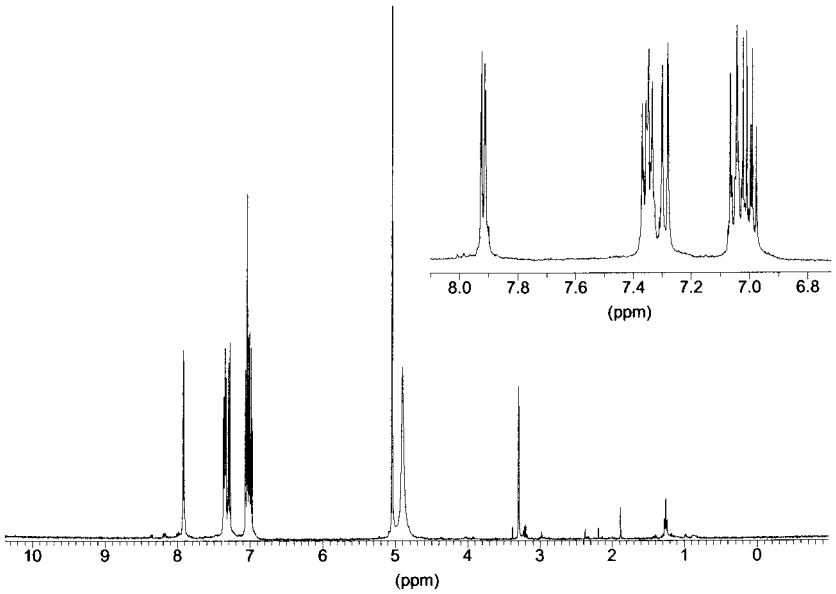


Figure 2. ^{1}H NMR spectra of 1-(4-fluorobenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-ones (**12**{*1,6*} in MeOH-d_4).

Table 2. Yields and Purities of 1-Substituted 1,3-Dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-ones **12**{*1,1−9*}

product	R−	crude yield [%]	purity[a] [%]
12{*1,1*}	3-methoxybenzyl	39	82
12{*1,2*}	3-methylbenzyl	37	88
12{*1,3*}	4-methylbenzyl	39	85
12{*1,4*}	3-trifluoromethylbenzyl	36	69
12{*1,5*}	4-trifluoromethylbenzyl	40	81
12{*1,6*}	4-fluorobenzyl	54	81
12{*1,7*}	4-pyridinylmethyl	57	59
12{*1,8*}	hexyl	0	0
12{*1,9*}	ethyl	22	26

[a] HPLC peak area at 210 nm.

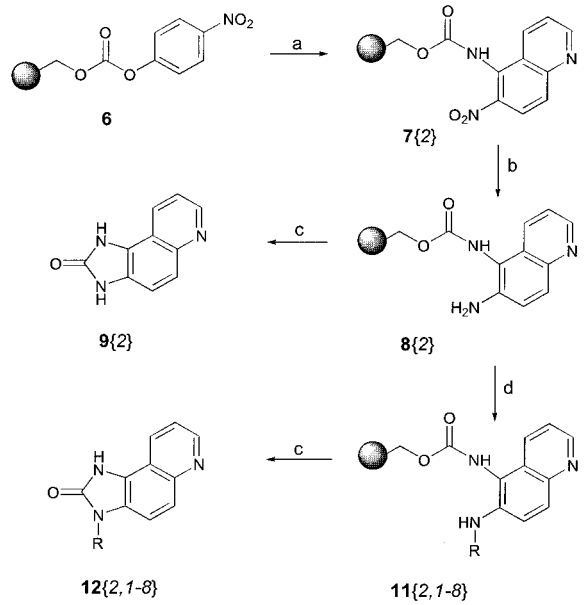
Table 3. Yields and Purities of 1-Substituted 1,3-Dihydro-2*H*-imidazo[4,5-*f*]quinolin-2-ones **12**{*2,1−8*}

product	R−	crude yield [%]	purity[a] [%]
12{*2,1*}	3-methoxybenzyl	17	52
12{*2,2*}	3-methylbenzyl	26	80
12{*2,3*}	4-methylbenzyl	21	93
12{*2,4*}	3-trifluoromethylbenzyl	24[b]	85[b]
12{*2,5*}	4-trifluoromethylbenzyl	13	83
12{*2,6*}	4-fluorobenzyl	16[b]	78[b]
12{*2,7*}	4-pyridinylmethyl	27	53
12{*2,8*}	hexyl	32	31

[a] HPLC peak area at 210 nm. [b] Purity and yield after isolation by column chromatography.

To increase the diversity of the library, the developed methodology was applied to the synthesis of other closely related urea derivatives. 5-Amino-6-nitroquinoline was chosen as a suitable aromatic core for attachment to the 4-nitrophenyl carbonate linker **6**. Reduction of the nitro group with 1 M stannous chloride in DMF afforded the resin-bound amino derivative (with a loading to the resin of 0.95 mmol/g as determined by elemental analysis). This indicated that losses through premature release were minimal. Cyclization and release gave **9**{*2*} in low yields (10%). Reductive alkylation with a range of aldehydes **10**{*1−8*}, followed by cyclative cleavage, afforded 1-substituted 1,3-dihydro-2*H*-imidazo[4,5-*f*]quinolin-2-ones **12**{*1−8*} in moderate yields and purities (Scheme 3, Table 3).

Scheme 3. Solid-Phase Synthesis of 1-Substituted 1,3-Dihydro-2*H*-imidazo[4,5-*f*]quinolin-2-ones (**12**{*2,1−8*})[a]



[a] Reagents and conditions: (a) 5-amino-6-nitroquinoline (4 equiv), BSA (5 equiv), DMAP (4 equiv), DMF, room temp, 16 h; (b) $SnCl_2 \cdot 2H_2O$ (10 equiv, 1 M in DMF), 30 °C, 16 h; (c) MP-CO_3 (3 equiv), DMF (containing 1.5% AcOH), 60 °C, 16 h; (d) aldehyde **10**{*1−8*}, $NaBH(OAc)_3$, Na_2SO_4 (10 equiv each), DCE (containing 1% AcOH), 40 °C, 4 h.

Two library members, **12**{*2,4*} and **12**{*2,6*}, afforded sufficient quantities (>50 mg) of crude products to allow further purification by flash column chromatography. Reductive alkylation with 4-pyridinecarboxaldehyde **10**{*7*} and hexanal **10**{*8*} gave crude products of low purity and unsatisfactory product homogeneity. Although the yields of **12**{*1−2,1−9*}are moderate to low, indicating incomplete cyclative cleavage or premature release during the reductive alkylation, these results exhibited potential for further optimization. Increased purities and yields might be achieved

by an extension of the reaction times for the reductive alkylation and especially the cyclization cleavage.

Conclusions

Although further optimization may be required to satisfy some purity criteria for library production, the general applicability of the synthetic methodology had been established. Moreover, the polymer-bound intermediates **8**{*1*−*2*} and other possible analogues represent useful building blocks for combinatorial library synthesis. The degree of diversity is established not only by the attached substrate and the substitution on the aniline nitrogen but also by the cleavage strategy. Acidic cleavage, reduction, base-catalyzed transesterification, as well as cyclization and release can in principle afford a wide array of pharmacologically interesting compounds.

Experimental Section

4-Benzyloxybenzylalcohol polystyrene (Wang) resin (**4**) was purchased from Polymer Laboratories. ^{1}H, ^{13}C, and ^{19}F NMR were recorded in deuterated solutions (Aldrich, Fluorochem) on Varian 300, Bruker AMX 400, and AVANCE 400 instruments. ^{1}H and ^{13}C spectra were referenced using TMS or residual solvents peaks as internal standards. Hexafluorobenzene was the external standard for ^{19}F NMR spectroscopy. Accurate mass spectra were obtained on a VG Analytical 7070E double-focusing magnetic mass spectrometer. Infrared spectra were recorded on a Perkin-Elmer FT-IR Paragon 1000 spectrometer. Resin loadings and corresponding reaction yields were calculated on the basis of the elemental distribution as determined by elemental analysis performed on a Carlo Erba elemental analyzer model 1106. Chlorine contents of polymers were obtained by oxygen combustion followed by titrimetry. Liquid chromatography−mass spectrometry (LC−MS) and HPLC analysis were carried out at Celltech, Cambridge. Compounds were analyzed by LC−MS on Thermoquest LC-Q-DUO, followed by LC analysis on HP1100 HPLC system with diode array detection. Both systems employed a Phenomenex Luna2 C18 (100 mm × 4.6 mm, 5 μm) column with a flow rate of 2 mL/min. The mass spectrometry range was set to 65−900 mass units, and UV detection was obtained at 210 nm. A solvent gradient was employed starting with 95% acetonitrile (containing 0.1% formic acid) and 5% water (containing 0.08% formic acid) to 5% acetonitrile and 95% water after 6.5 min, where it was kept for 1.5 min. The starting conditions were reestablished after a total run time of 10 min. Reversed-phase HPLC was performed using a Phenomenex Luna2 C18 (150 mm × 4.6 mm, 5 μm) column with a flow rate of 2 mL/min with UV detection at 210 nm. A solvent gradient was employed starting with 95% acetonitrile and 5% water (phosphate buffer, pH 2.2) to 10% acetonitrile and 90% water after 8 min, at which point it was kept constant for 3.5 min. The starting conditions were reestablished after a total run time of 14 min. Peak areas (%) were used as criteria for the purity of library members.

3-Nitropyridine 2-Carbamate Wang Resin (7{*1*}). 2-Amino-3-nitropyridine (1.34 g, 9.63 mmol, 4 equiv) was dissolved (with gentle heating) in anhydrous DMF (8 mL) and activated by treatment with *N*,*O*-bis(trimethylsilyl)-acetamide (2.98 mL, 12.06 mmol, 5 equiv) under nitrogen for 1 h at 50 °C. The solution was added to a suspension of 4-nitrophenyl carbonate Wang polymer **6** (1.12 mmol/g; 2.16 g, 2.42 mmol) in anhydrous DMF (25 mL). Finally, *N*,*N*-(dimethylamino)pyridine (1.18 g, 9.66 mmol, 4 equiv) was added and the reaction mixture was stirred at room temperature under nitrogen for 24 h. The polymer was separated by filtration and was washed sequentially with DMF, DCM, DMF, MeOH, DCM. The bright-yellow polymer was dried in vacuo to give **7**{*1*} (1.96 g, loading 0.77 mmol/g, 69%). N theoretical 4.70%, found 3.23; ν_{max} (KBr)/cm^{-1} 3023 (ArH), 2911 (CH), 1806, 1734 (C═O), 1596 (CH), 1534, 1491 (NO_2). TFA cleavage (50% in DCM) of **7**{*1*} afforded 2-amino-3-nitropyridine quantitatively.

3-Aminopyridine 2-Carbamate Wang Resin (8{*1*}). Polymer **7**{*1*} (500 mg, 0.71 mmol/g, 0.36 mmol) was suspended in a 1 M $SnCl_2 \cdot 2H_2O$ solution in DMF (4 mL) and stirred at 30 °C for 20 h. The resin was separated by filtration, washed sequentially with DMF, water, DMF, water, DMF, and DCM, and dried in vacuo to afford **8**{*1*} as a light-yellow polymer (450 mg, 0.63 mmol/g, 88%). N theoretical 3.01%, found 2.65; ν_{max} (KBr)/cm^{-1} 3410 (NH), 2922 (CH), 1718 (C═O), 1653 (C−N), 1560, 1507 (CH). TFA cleavage (50% in DCM) of **9**{*1*} afforded 2,3-diaminopyridine quantitatively.

General Procedure for the Cyclative Cleavage (Method A). Polymer **8**{*1*−*2*} (approximately 500 mg) and MP-carbonate (2.87 mmol/g; 400 mg, 1.15 mmol) were suspended in DMF (5 mL, containing 1.5% AcOH) and stirred at 60 °C for 20 h. The polymers were separated by filtration and washed with DMF. The filtrate was concentrated, and traces of AcOH and DMF were removed by azeotropic distillation with EtOH and *n*-hexane. The residue was dried in vacuo at 60 °C.

1,3-Dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (9{*1*}). Polymer **8**{*1*} (0.61 mmol/g; 0.5 g, 0.31 mmol) was subjected to cyclative cleavage (method A) to give the unsubstituted heterocycle **9**{*1*} as a tan solid (24 mg, 57%). R_f (DCM/MeOH, 9:1) 0.40. HRMS: found [M$^+$], 135.0433. $C_6H_5N_3O$ requires 135.0433. ν_{max} (KBr)/cm^{-1} 3448 (NH), 2983 (CH), 1685 (C═O), 1444 (CH); δ_H (400 MHz, CD_3OD) 7.03 (dd, 1 H, *J* 8.0, *J* 5.2), 7.33 (dd, 1 H, *J* 8.0, *J* 1.4), 7.92 (dd, 1 H, *J* 5.2, *J* 1.4); δ_C (100 MHz, CD_3OD) 117.22, 118.80, 125.70, 141.49, 146.00, 157.34; *m*/*z* (EI) 135 (100%, M$^+$), 107 (24, M$^+$ − CO); LCMS t_R = 1.77 min (*m*/*z* 136 [M + H$^+$]); HPLC t_R = 2.18 min (99%).

1,3-Dihydro-2*H*-imidazo[4,5-*f*]quinolin-2-one (9{*2*}). Polymer **8**{*2*} (0.95 mmol/g; 0.40 g, 0.38 mmol) was subjected to cyclative cleavage (method A) to give the unsubstituted heterocycle **9**{*2*} as a brown solid (7 mg, 10%). R_f (DCM/MeOH, 9:1) 0.29. HRMS: found [M$^+$], 185.0585. $C_{10}H_7N_3O$ requires 185.0589. ν_{max} (KBr)/cm^{-1} 3443 (NH), 2276, 1689 (C═O), 1629 (C−N), 1474, 1379 (CH); δ_H (400 MHz, CD_3OD) 7.58 (dd, 1 H, *J* 8.6, *J* 4.3), 7.65 (d, 1 H, *J* 9.1), 7.82 (dd, 1 H, *J* 9.0, *J* 0.4), 8.54 (ddd, 1 H, *J* 8.6, *J* 1.6, *J* 0.4), 8.79 (dd, 1 H, *J* 4.6, *J* 1.6); δ_C (100 MHz, CD_3OD) 115.77, 116.80, 122.50, 123.15, 127.28, 131.39, 145.07,

149.22, 167.99; *m*/*z* (EI) 185 (100%, M^+), 157 (56, $M^+ - CO$); LCMS $t_R = 2.27$ min (*m*/*z* 186 [$M + H^+$], 61%).

General Procedure for the Reductive Alkylation and Cyclative Cleavage (Method B). Polymer **8** (approximately 500 mg) and Na_2SO_4 (10 equiv) were suspended in anhydrous DCE (4 mL, containing 1% AcOH). The aldehyde **10**{*1*−*9*} (10 equiv) was added dropwise, followed by $NaBH(OAc)_3$ (10 equiv). The reaction mixture was stirred at 40 °C for 4 h under nitrogen. The polymer was separated by filtration, washed sequentially with DCM, DMF, water, DMF, and DCM, and dried in vacuo. The resin and MP-carbonate (2.87 mmol/g; 0.4 g, 1.15 mmol) were suspended in DMF (5 mL, containing 1.5% AcOH) and stirred at 60 °C for 20 h. The polymers were filtered and washed with DMF. The filtrate was concentrated, and traces of AcOH and DMF were removed by azeotropic distillation with EtOH and *n*-hexane. The residue was dried in vacuo at 60 °C.

3-(3-Methoxybenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (12{*1,1*}). Polymer **8**{*1*} (0.61 mmol/g; 400 mg, 0.25 mmol) was treated with 3-anisaldehyde **10**{*1*} according to method B to afford **12**{*1,1*} (25 mg, 39%) as an off-white solid. R_f (DCM/MeOH, 9:1) 0.61. HRMS: found [M^+], 255.1011. $C_{14}H_{13}N_3O_2$ requires 255.1008. ν_{max} (KBr)/cm^{-1} 3054 (NH), 1716 (C═O), 1603 (C−N), 1456 (CH); δ_H (400 MHz, CD_3OD) 3.74 (s, 3 H), 5.04 (s, 2 H), 6.82 (dd, 1 H, *J* 8.0, *J* 1.9), 6.84−6.88 (m, 2 H), 6.99 (dd, 1 H, *J* 7.8, *J* 5.4), 7.23 (dd as t, 1 H, *J* 8.0, *J* 7.6), 7.27 (dd, 1 H, *J* 7.6, *J* 1.4), 7.93 (dd, 1 H, *J* 5.2, *J* 1.4); δ_C (100 MHz, CD_3OD) 45.26, 55.93, 114.51, 114.55, 116.73, 118.61, 120.88, 126.20, 131.26, 139.21, 141.48, 141.80, 156.41, 161.86; *m*/*z* (EI) 255 (32%, M^+), 121 (100, $C_8H_9O^+$); LCMS $t_R = 3.77$ min (*m*/*z* 256 [$M + H^+$]); HPLC $t_R = 4.96$ min (82%).

3-(3-Methylbenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (12{*1,2*}). Polymer **8**{*1*} (0.65 mmol/g; 500 mg, 0.33 mmol) was treated with 3-tolualdehyde **10**{*2*} according to method B to afford **12**{*1,2*} (29 mg, 37%) as an off-white solid. R_f (DCM/MeOH, 9:1) 0.71. HRMS: found [M^+], 239.1057. $C_{14}H_{13}N_3O$ requires 239.1059. ν_{max} (KBr)/cm^{-1} 3432 (NH), 2913 (CH), 1709 (C═O), 1604 (C−N), 1478, 1392 (CH); δ_H (400 MHz, CD_3OD) 2.26 (s, 3 H), 5.00 (s, 2 H), 6.96 (dd, 1 H, *J* 7.6, *J* 5.3), 7.06 (m, 2 H), 7.12 (s, 1 H), 7.17 (dd, 1 H, *J* 7.6), 7.23 (dd, 1 H, *J* 7.6, *J* 1.2), 7.91 (dd, 1 H, *J* 5.3, *J* 1.2); δ_C (100 MHz, CD_3OD) 21.68, 45.27, 116.72, 118.60, 125.87, 126.19, 129.38, 129.89, 130.07, 137.58, 140.10, 141.46, 144.89, 156.38; *m*/*z* (EI) 239 (31%, M^+), 105 (100, $C_8H_9^+$), 77 (13, $C_5H_3N^+$); LCMS $t_R = 4.05$ min (*m*/*z* 240 [$M + H^+$]); HPLC $t_R = 4.05$ min (88%).

3-(4-Methylbenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (12{*1,3*}). Polymer **8**{*1*} (0.61 mmol/g; 500 mg, 0.31 mmol) was treated with 4-tolualdehyde **10**{*3*} according to method B to afford **12**{*1,3*} (29 mg, 39%) as an off-white solid. R_f (DCM/MeOH, 9:1) 0.56. HRMS: found [M^+], 239.1057. $C_{14}H_{13}N_3O$ requires 239.1059. ν_{max} (KBr)/cm^{-1} 3420 (NH), 2923 (CH), 1706 (C═O), 1620 (C−N), 1561, 1458 (CH); δ_H (400 MHz, CD_3OD) 2.28 (s, 3 H), 5.02 (s, 2 H), 6.99 (dd, 1 H, *J* 8.1, *J* 5.1), 7.13 (d, 2 H, *J* 8.4), 7.20 (d, 2 H, *J* 8.4), 7.26 (dd, 1 H, *J* 8.1, *J* 1.5), 7.92 (dd, 1 H, *J* 5.4, *J* 1.5); δ_C (100 MHz, CD_3OD) 21.39, 45.07, 116.76, 118.78, 126.19, 128.47, 130.76, 134.64, 139.13, 141.73, 144.93, 156.39; *m*/*z* (EI) 239 (19%, M^+), 105 (100, $C_8H_9^+$), 77 (14, $C_5H_3N^+$); LCMS $t_R = 4.10$ min (*m*/*z* 240 [$M + H^+$]); HPLC $t_R = 5.37$ min (85%).

3-(3-Trifluoromethylbenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (12{*1,4*}). Polymer **8**{*1*} (0.65 mmol/g; 500 mg, 0.33 mmol) was treated with 3-(trifluoromethyl)-benzaldehyde **10**{*4*} according to method B to afford **12**{*1,4*} (35 mg, 36%) as a tan solid. R_f (DCM/MeOH, 9:1) 0.61. HRMS: found [M^+], 293.0779. $C_{14}H_{10}F_3N_3O$ requires 293.0776. ν_{max} (KBr)/cm^{-1} 3427 (NH), 3068 (CH), 1721 (C═O), 1626 (C−N), 1483, 1329 (CH); δ_H (400 MHz, CD_3OD) 5.16 (s, 2 H), 6.98−7.01 (m, 1 H), 7.30 (d, 1 H, *J* 7.8), 7.49−7.56 (m, 3 H), 7.65 (s, 1 H), 7.93 (d, 1 H, *J* 5.3); δ_C (100 MHz, CD_3OD) 45.20, 116.78, 119.02, 126.13 (q, J_{CF} 270), 125.94 (q, $^3J_{CF}$ 4), 126.38 (q, $^3J_{CF}$ 4), 126.49, 131.48, 132.89 (q, $^2J_{CF}$ 32), 132.92, 141.88, 142.31, 145.69, 156.97; δ_F (376.5 MHz, CD_3OD) −66.13; *m*/*z* (EI) 293 (36%, M^+), 274 (3, $M^+ - F$), 159 (100, $C_8H_6F_3^+$); LCMS $t_R = 4.41$ min (*m*/*z* 294 [$M + H^+$]); HPLC $t_R = 4.41$ min (69%).

3-(4-Trifluoromethylbenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (12{*1,5*}). Polymer **8**{*1*} (0.65 mmol/g; 500 mg, 0.33 mmol) was treated with 4-(trifluoromethyl)-benzaldehyde **10**{*5*} according to method B to afford **12**{*1,5*} (39 mg, 40%) as a tan solid. R_f (DCM/MeOH, 9:1) 0.67. HRMS: found [M^+], 293.0776. $C_{14}H_{10}F_3N_3O$ requires 293.0776. ν_{max} (KBr)/cm^{-1} 3424 (NH), 2939 (CH), 1729 (C═O), 1622 (C−N), 1482, 1325 (CH); δ_H (400 MHz, CD_3OD) 5.18 (s, 2 H), 7.02 (dd, 1 H, *J* 5.6, *J* 7.7), 7.30 (d, 1 H, *J* 7.5), 7.51 (d, 2 H, *J* 8.0), 7.65 (d, 2 H, *J* 8.0), 7.96 (d, 1 H, *J* 5.4); δ_C (100 MHz, CD_3OD) 44.78, 116.54, 118.72, 124.49, 127.10 (q, $^3J_{FC}$ 4), 127.58 (q, J_{FC} 224), 129.33, 131.38 (q, $^2J_{FC}$ 32), 142.03, 142.31, 145.04, 156.35; δ_F (376.5 MHz, CD_3OD) −66.32; *m*/*z* (EI) 293 (35%, M^+), 274 (3, $M^+ - F$), 159 (100, $C_8H_6F_3^+$); LCMS $t_R = 4.45$ min (*m*/*z* 294 [$M + H^+$]); HPLC $t_R = 4.47$ min (81%).

3-(4-Fluorobenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (12{*1,6*}). Polymer **8**{*1*} (0.61 mmol/g; 400 mg, 0.24 mmol) was treated with 4-fluorobenzaldehyde **10**{*6*} according to method B to afford **12**{*1,6*} (32 mg, 54%). R_f (DCM/MeOH, 9:1) 0.59. HRMS: found [M^+], 243.0810. $C_{13}H_{10}FN_3O$ requires 243.0808. ν_{max} (KBr)/cm^{-1} 3421 (NH), 3006 (CH), 1708 (C═O), 1619 (C−N), 1510, 1454 (CH); δ_H (400 MHz, CD_3OD) 5.05 (s, 2 H), 6.98−7.01 (m, 1 H), 7.05 (dd as t, 2 H, *J* 8.9, J_{HF} 8.9), 7.29 (dd, 1 H, *J* 7.8, *J* 1.1), 7.36 (dd, 2 H, *J* 8.9, J_{HF} 5.0), 7.92 (dd, 1 H, *J* 5.3, *J* 1.4); δ_C (100 MHz, CD_3OD) 44.57, 116.60, 116.77 (d, $^2J_{CF}$ 22), 118.63, 126.08, 130.92 (d, $^3J_{CF}$ 8), 133.82, 141.85, 145.01, 156.35, 164.08 (d, J_{CF} 243); δ_F (346.5 MHz, CD_3OD) −117.00; *m*/*z* (EI) 243 (37%, M^+), 109 (100, $C_7H_6F^+$); LCMS $t_R = 3.80$ min (*m*/*z* 244 [$M + H^+$]); HPLC $t_R = 3.84$ min (92%).

3-(4-Pyridinylmethyl)-1,3-dihydro-2*H*-imidazo[4,5-*b*]-pyridin-2-one (12{*1,7*}). Polymer **8**{*1*} (0.61 mmol/g; 400 mg, 0.31 mmol) was treated with 4-pyridylcarboxaldehyde **10**{*7*} according to method B to afford **12**{*1,7*} (31 mg, 57%) as a tan solid. R_f (DCM/MeOH, 9:1) 0.47. HRMS: found [M^+], 226.0858. $C_{12}H_{10}N_4O$ requires 226.0855. ν_{max} (KBr)/cm^{-1} 3422 (NH), 1718 (C═O), 1622 (C═N), 1604 (C−N), 1483, 1396 (CH); δ_H (400 MHz, CD_3OD) 5.17 (s,

2 H), 7.04 (dd, 1 H, *J* 7.8, *J* 5.0), 7.31 (dd, 1 H, *J* 7.8, *J* 1.7), 7.35 (dd, 2 H, *J* 4.4, *J* 1.7), 7.98 (dd, 1 H, *J* 5.3, *J* 1.7), 8.50 (dd, 2 H, *J* 4.4, *J* 1.7); δ_C (100 MHz, CD_3OD) 44.13, 116.44, 118.77, 124.05, 126.05, 142.17, 145.08, 148.32, 150.86, 156.29; *m*/*z* (EI) 226 (100%, M^+), 92 (51, $C_6H_6N^+$); LCMS t_R = 0.72 min (*m*/*z* 227 [M + H^+]); HPLC t_R = 0.77 min (59%).

3-(3-Methoxybenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*f*]quinolin-2-one (12{*2,1*}). Polymer **8**{*2*} (0.95 mmol/g; 500 mg, 0.48 mmol) was treated with 3-anisaldehyde **10**{*1*} according to method B to afford **12**{*2,1*} (25 mg, 17%) as a tan solid. R_f (DCM/MeOH, 9:1) 0.57. HRMS: found [M^+], 305.1169. $C_{18}H_{15}N_3O_2$ requires 305.1164. ν_{max} (KBr)/cm^{-1} 3426 (NH), 3004, 2964 (CH), 1686 (C═O), 1582 (C−N), 1486, 1392 (CH); δ_H (400 MHz, CD_3OD) 3.74 (s, 3 H), 5.18 (s, 2 H), 6.83 (d, 1 H, *J* 7.6), 6.90−6.92 (m, 2 H), 7.24 (dd as t, 1 H, *J* 8.1, *J* 7.6), 7.54 (dd, 1 H, *J* 8.1, *J* 4.3), 7.58 (d, 1 H, *J* 8.6), 7.74 (d, 1 H, *J* 8.6), 8.51 (d, 1 H, *J* 8.7), 8.75 (d, 1 H, *J* 4.3); δ_C (100 MHz, CD_3OD) 45.60, 55.94, 114.38, 114.53, 114.96, 116.70, 120.78, 122.59, 123.10, 127.83, 130.74, 131.27, 131.37, 139.70, 145.21, 149.51, 157.29, 161.91; *m*/*z* (EI) 305 (27%, M^+), 184 (4, $M^+ - C_8H_9O$), 121 (100, $C_8H_6O^+$); LCMS t_R = 2.84 min (*m*/*z* 306 [M + H^+]); HPLC t_R = 2.66 min (52%).

3-(3-Methylbenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*f*]quinolin-2-one (12{*2,2*}). Polymer **8**{*2*} (0.95 mmol/g; 370 mg, 0.35 mmol) was treated with 3-tolualdehyde **10**{*2*} according to method B to afford **12**{*2,2*} (27 mg, 26%) as a tan solid. R_f (DCM/MeOH, 9:1) 0.67. HRMS: found [M^+], 289.1209. $C_{18}H_{15}N_3O$ requires 289.1215. ν_{max} (KBr)/cm^{-1} 3423 (NH), 3021, 2768 (CH), 1690 (C═O), 1580 (C−N), 1482, 1346 (CH); δ_H (400 MHz, $CDCl_3$/CD_3OD) 2.32 (s, 3 H), 5.17 (s, 2 H), 7.10 (d, 1 H, *J* 7.4), 7.13−7.16 (m, 2 H), 7.23 (dd as t, 1 H, *J* 7.4), 7.43 (d, 1 H, *J* 8.9), 7.48 (dd, 1 H, *J* 8.6, *J* 4.2), 7.77 (d, 1 H, *J* 9.0), 8.46 (d, 1 H, *J* 8.7), 8.76 (dd, 1 H, *J* 4.2, *J* 1.7); δ_C (75.5 MHz, $CDCl_3$/CD_3OD) 21.67, 45.13, 113.73, 115.71, 116.96, 121.49, 122.27, 122.51, 124.75, 126.53, 128.34, 129.12, 129.20, 130.26, 136.35, 139.13, 144.15, 148.38; *m*/*z* (EI) 289 (42%, M^+), 184 (4, $M^+ - C_8H_9$), 105 (100, $C_8H_9^+$); LCMS t_R = 3.07 min (*m*/*z* 290 [M + H^+]); HPLC t_R = 2.86 min (80%).

3-(4-Methylbenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*f*]quinolin-2-one (12{*2,3*}). Polymer **8**{*2*} (0.95 mmol/g; 500 mg, 0.48 mmol) was treated with 4-tolualdehyde **10**{*3*} according to method B to afford **12**{*2,3*} (29 mg, 21%) as a tan solid. R_f (DCM/MeOH, 9:1) 0.49. HRMS: found [M^+], 289.1216. $C_{18}H_{15}N_3O$ requires 289.1215. ν_{max} (KBr)/cm^{-1} 3428 (NH), 3178 (CH), 1688 (C═O), 1582 (C−N), 1478, 1394 (CH); δ_H (400 MHz, CD_3OD) 2.27 (s, 3 H), 5.15 (s, 2 H), 7.13 (d, 2 H, *J* 8.1), 7.24 (d, 2 H, *J* 8.1), 7.51 (dd, 1 H, *J* 8.1, *J* 4.3), 7.53 (d, 1 H, *J* 9.2), 7.70 (d, 1 H, *J* 9.2), 8.47 (d, 1 H, *J* 8.1), 8.72 (dd, 1 H, *J* 4.3, *J* 1.1); δ_C (100 MHz, CD_3OD) 21.38, 45.43, 114, 116.64, 122.54, 123.01, 127.79, 128.71, 130.31, 130.76, 131.33, 135.12, 139.04, 145.13, 149.45, 157.25; *m*/*z* (EI) 289 (16%, M^+), 105 (100, $C_8H_9^+$); LCMS t_R = 3.13 min (*m*/*z* 290 [M + H^+]); HPLC t_R = 2.87 min (93%).

3-(3-Trifluoromethylbenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*f*]quinolin-2-one (12{*2,4*}). Polymer **8**{*2*} (0.95 mmol/g; 500 mg, 0.48 mmol) was treated with 3-(trifluoromethyl)-benzaldehyde **10**{*4*} according to method B to afford the crude product. TLC showed the presence of two compounds. The desired product **12**{*2,4*} (40 mg, 24%) was separated from the unsubstituted heterocycle **9**{*2*} (10 mg) by column chromatography (SiO_2; DCM/MeOH, 9:1); R_f (DCM/MeOH, 9:1) 0.52. HRMS: found [M^+], 343.0934. $C_{18}H_{12}F_3N_3O$ requires 343.0932. ν_{max} (KBr)/cm^{-1} 3361 (NH), 3021, 2832 (CH), 1693 (C═O), 1582 (C−N), 1483, 1327 (CH); δ_H (400 MHz, $CDCl_3$) 5.29 (s, 2 H), 7.36 (d, 1 H, *J* 8.9), 7.44−7.48 (m, 2 H), 7.53−7.58 (m, 2 H), 7.70 (s, 1 H), 7.87 (d, 1 H, *J* 8.9), 8.45 (d, 1 H, *J* 8.4), 8.88 (d, 1 H, *J* 3.2), 12.35 (s, 1 H, NH); δ_C (100 MHz, $CDCl_3$) 43.41, 111.34, 114.17, 120.25, 122.61 (q, J_{CF} 226), 122.50, 123.16, 123.96, 128.04, 128.55, 129.52, 130.40 (q, $^2J_{CF}$ 32), 136.05, 143.57, 147.83, 155.50; δ_F (376.5 MHz, $CDCl_3$) −64.61; *m*/*z* (EI) 343 (71%, M^+), 184 (100, $M^+ - C_8H_6F_3$), 159 (56, $C_8H_6F_3^+$); LCMS t_R = 3.48 min (*m*/*z* 344 [M + H^+]); HPLC t_R = 3.20 min (85%).

3-(4-Trifluoromethylbenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*f*]quinolin-2-one (12{*2,5*}). Polymer **8**{*2*} (0.95 mmol/g; 500 mg, 0.48 mmol) was treated with 4-(trifluoromethyl)-benzaldehyde **10**{*5*} according to method B to afford **12**{*2,5*} (22 mg, 13%) as a tan solid. R_f (DCM/MeOH, 9:1) 0.66. ν_{max} (KBr)/cm^{-1} 3426 (NH), 2923 (CH), 1681 (C═O), 1480, 1329 (CH). HRMS: found [M^+], 343.0934. $C_{18}H_{12}F_3N_3O$ requires 343.0932. δ_H (400 MHz, CD_3OD) 5.32 (s, 2 H), 7.53−7.59 (m, 3 H), 7.60 (d, 1 H, *J* 3.8), 7.65 (d, 2 H, *J* 8.2), 7.77 (dd, 1 H, *J* 8.8, *J* 1.1), 8.52 (dd, 1 H, *J* 7.7, *J* 1.7), 8.76 (dd, 1 H, *J* 3.8, *J* 1.7); δ_C (100 MHz, CD_3OD) 45.15, 114.68, 116.76, 122.69, 123.29, 127.08 (q, J_{CF} 4), 127.32 (q, J_{CF} 31), 128.58, 129.24, 128.71 (q, J_{CF} 240), 131.41, 142.76, 145.28, 149.65, 157.23; δ_F (376.5 MHz, CD_3OD) − 66.10; *m*/*z* (EI) 343 (43%, M^+), 184 (100, $M^+ - C_8H_6F_3$), 159 (50, $C_8H_6F_3^+$); LCMS t_R = 3.54 min (*m*/*z* 344 [M + H^+]); HPLC t_R = 3.27 min (83%).

3-(4-Fluorobenzyl)-1,3-dihydro-2*H*-imidazo[4,5-*f*]quinolin-2-one (12{*2,6*}). Polymer **8**{*2*} (0.95 mmol/g; 500 mg, 0.48 mmol) was treated with 4-fluorobenzaldehyde **10**{*6*} according to method B to afford a tan residue. TLC showed the presence of two compounds. The desired product **12**{*2,6*} (22 mg, 16%) was separated from the unsubstituted heterocycle **9**{*2*} (<2 mg) by column chromatography (SiO_2; DCM/MeOH, 9:1). R_f (DCM:MeOH, 9:1) 0.61. HRMS: found [M^+], 293.0961. $C_{17}H_{12}FN_3O$ requires 293.0964. ν_{max} (KBr)/cm^{-1} 3419 (NH), 2924 (CH), 1690 (C═O), 1599 (C−N), 1509, 1390 (CH); δ_H (400 MHz, $CDCl_3$) 5.30 (s, 2 H), 7.04 (dd, as t, 2 H, *J* 8.3, J_{HF} 8.4), 7.37−7.40 (m, 3 H), 7.45 (dd, 1 H, *J* 8.5, *J* 3.8), 7.85 (d, 1 H, *J* 8.9), 8.41 (d, 1 H, *J* 8.3), 8.87 (d, 1 H, *J* 3.6), 12.13 (s, 1 H, NH); δ_C (100 MHz, $CDCl_3$) 44.17, 112.60, 115.15, 115.92 (d, $^2J_{CF}$ 19), 121.17, 121.92, 123.33, 125.44, 129.05, 129.13, 131.79, 144.53, 148.74, 156.29, 162.40 (d, J_{CF} 245); δ_F (346.5 MHz, $CDCl_3$) −117.18; *m*/*z* (EI) 293 (31%, M^+), 184 (8, $M^+ - C_7H_6F$), 109 (100, $C_7H_6F^+$); LCMS t_R = 2.90 min (*m*/*z* 294 [M + H^+]); HPLC t_R = 2.70 min (78%).

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