Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2018, **9**, 5608

Direct heterobenzylic fluorination, difluorination and trifluoromethylthiolation with dibenzenesulfonamide derivatives†

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Received 15th March 2018
Accepted 25th May 2018

DOI: 10.1039/c8sc01221k

rsc.li/chemical-science

Functionalization of heterocyclic scaffolds with mono- or difluoroalkyl groups provides unique opportunities to modulate drug pK_a, influence potency and membrane permeability, and attenuate metabolism. While advances in the addition of fluoroalkyl radicals to heterocycles have been made, direct C(sp^3)–H heterobenzylic fluorination is comparatively unexplored. Here we demonstrate both mono- and difluorination of a range of alkyl heterocycles using a convenient process that relies on transient sulfonylation by the electrophilic fluorinating agent *N*-fluorobenzenesulfonimide. We also report heterobenzylic trifluoromethylthiolation and ^{18}F-fluorination, providing a suite of reactions for late-stage C(sp^3)–H functionalization of drug leads and radiotracer discovery.

Introduction

In recent years considerable effort has been directed towards the development of new methods to selectively fluorinate C(sp^2)–H or C(sp^3)–H bonds in structurally complex molecules.[1] These efforts have been stimulated by the profound effect that fluorination can have on biological activity[2] and strategic advantages manifest by late-stage C–H functionalization in medicinal and agrochemistry.[3] For example, fluorination can significantly impact potency, selectivity, lipophilicity and membrane permeability of drug leads,[2b] and modulate the pK_a of proximal heterocycles (*e.g.*, **1**,[4] **2** [5] and **3**,[6] Fig. 1). The characteristically strong C–F bond is also routinely exploited in medicinal chemistry as a replacement for C–H bonds and, in particular, a means to block oxidative metabolism (*e.g.*, **3**).[2] Furthermore, fluorinated alkyl groups can serve as bioisosteres for more polar or less stable functionalities, and the replacement of a hydroxyl group with a fluorine atom is a common tactic.[2] Likewise, the CF_2H group (H-bond donor) is a lipophilic bioisostere for alcohols or thiols and the CF_2R group can serve as a carbonyl or alkoxy group mimic.[2c] Considering that roughly 60% of FDA approved drugs include a nitrogen-containing heterocycle,[7] the development of synthetic strategies that

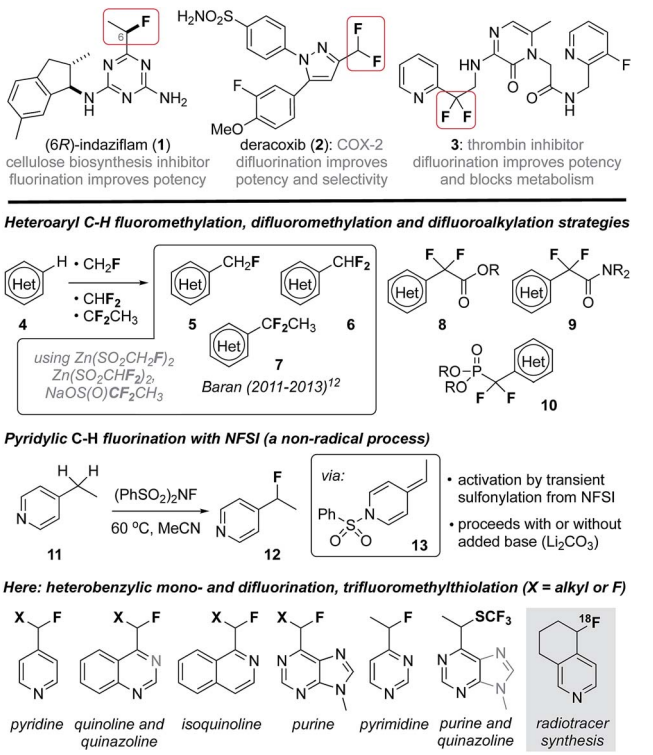

Fig. 1 Heterobenzylic fluorides in drug discovery and strategies for their synthesis.

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† Electronic supplementary information (ESI) available: Experimental procedures, purification and characterization data for all new compounds. See DOI: 10.1039/c8sc01221k

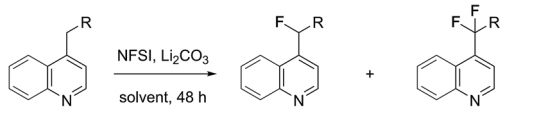
provide access to heterobenzylic fluorides is of particular interest and much success has been realized in trifluoromethylation of heterocycles.[8] However, introduction of heterobenzylic monofluoroalkyl or difluoroalkyl groups remains largely reliant on cross coupling reactions[9] or deoxyfluorination of heterobenzylic alcohols[10] and carbonyls,[11] processes that require prior functionalization. As a notable exception, Baran has reported innate C(sp^2)–H functionalization of heterocycles as a means to add each of the CHF_2,[12a] CH_2F[12b] and CF_2CH_3 [12c] groups (*e.g.*, **5–7**) by employing the corresponding zinc sulfinate salts in Minisci-like radical addition processes. Likewise, the introduction of difluoroacetates **8**,[13] difluoroacetamides **9** [14] and difluorophosphonates **10** [15] has been accomplished *via* transition metal catalysis or radical processes.[16] Unfortunately, despite considerable advances in C(sp^3)–H benzylic mono- and difluorination,[17] heterobenzylic C(sp^3)–H fluorination[10,18] or difluorination are largely unexplored owing to fundamental incompatibilities between common fluorine transfer reagents[19] (*e.g.*, *N*-fluorobenzenesulfonimide (NFSI)) and nucleophilic heterocycles.[20] Towards this goal, Van Humbeck has very recently described the fluorination of several alkylheterocycles induced by single electron transfer to Selectfluor.[18e] Previously, we reported the serendipitous finding that 2- and 4-alkylpyridines (*e.g.*, **11**) undergo pyridylic fluorination by reaction with the electrophilic fluorination agent NFSI, a process that involves the transient formation of a sulfonylpyridinium intermediate.[21] Here, we demonstrate that activation by transient sulfonylation is general for a range of alkylheterocycles and can be extended to heterobenzylic difluorination and trifluoromethylthiolation. Collectively, these convenient processes provide a platform for late-stage functionalization of drug leads and enable direct ^{18}F-fluorination of alkylheterocycles for the purpose of radiotracer synthesis for positron emission tomography (PET) imaging.

Results and discussion

Mono- and difluorination of 4-ethylpyridine and 4-alkylquinolines

While examining the scope of the pyridylic fluorination reaction depicted in Fig. 1 (**11** → **12**),[21] we found that at elevated temperatures (>65 °C) small amounts of the corresponding difluoroalkyl derivatives were formed and could be identified by a characteristic resonances at $\delta \sim -95$ ppm in ^{19}F NMR spectra recorded on crude reaction mixtures. These observations prompted us to investigate the pyridylic difluorination reaction as a complimentary process. As summarized in Table 1, heating a solution of 4-ethylpyridine in MeCN with an excess of NFSI afforded exclusively the monofluorinated adduct **15** at 60 °C (entry 1). Increasing the reaction temperature above 80 °C (in a microwave) provided a complex mixture of products that included the corresponding acetamide derived from displacement of fluoride by solvent (MeCN).[17d] However, when the reaction was repeated at 75 °C with a further increase in equivalents of NFSI, a ~1 : 1 mixture of the mono- and difluorinated ethylpyridines **15** and **16** were produced in good yield (74%, entry 2) and were readily separable by flash column chromatography. Notably, for difluorination, sequential activation by sulfonylation consumes 2 equivalents of NFSI and a further 2 equivalents are required for fluorination. The additional excess of NFSI is required to offset its slow decomposition over the course of the reaction (48 h). Several alternative solvents were evaluated and a modest increase in yield was realized in EtOAc (entry 3). The fluorination of 4-ethylquinoline (**17**) was also examined and we were pleased to find that heterobenzylic fluorination of this alkylquinoline provided the monofluoroethyl product **18** in good yield (entry 4). However, despite considerable effort, this substrate proved reluctant to undergo difluorination. Under more forcing conditions (*e.g.*, >90 °C, microwave) decomposition occurred,

Table 1 Mono- and difluorination of ethylpyridine (**14**) and alkyl quinolines **17** and **20**



14: pyridine (R = CH_3) **15**: pyridine (R = CH_3) **16**: pyridine (R = CH_3)
17: quinoline (R = CH_3) **18**: quinoline (R = CH_3) **19**: quinoline (R = CH_3)
20: quinoline (R = H) **21**: quinoline (R = H) **22**: quinoline (R = H)

Entry	Hetero aromatic	Solvent (conc. (M))	NFSI (equiv.)	Temp (°C)	Product[a] (ratio)	% Yield[b]
1	**14**	MeCN (0.1)[c]	3	60	**15** : **16** (>20 : 1)	87
2	**14**	MeCN (0.5)[d]	10	75	**15** : **16** (1 : 1)	74
3	**14**	EtOAc (0.5)[d]	10	75	**15** : **16** (2 : 3)	82
4	**17**	MeCN (0.1)[c]	3	65	**18** : **19** (>20 : 1)	71
5	**17**	EtOAc (0.5)[d]	10	75	**18** : **19** (10 : 1)	81
6	**20**	MeCN (0.1)[c]	3	65	**21** : **22** (1 : 3)	30
7	**20**	MeCN (0.3)[d]	4	75	**21** : **22** (1 : 8)	61
8	**20**	MeCN (0.5)[d]	5	75	**21** : **22** (1 : 10)	74

[a] Ratio of mono- and difluorinated products determined by analysis of crude ^{1}H and ^{19}F NMR spectra. [b] Combined isolated yield of mono- and difluorinated products. [c] 1.1 equiv. of Li_2CO_3. [d] 5 equiv. of Li_2CO_3.

and after 36 h at 75 °C with a large excess of NFSI only ~7% of the difluoroethyl quinoline **19** was produced (entry 5). Considering the importance of both the mono- and difluoromethyl groups as bioisosteres,[2c] we also investigated the fluorination of 4-methyl quinoline (**20**) and were surprised to find that difluorination predominated even at low conversion, suggesting that here the second fluorination event is a more facile process (entry 6). Increasing the equivalents of NFSI and reaction temperature (entry 7) as well as concentration (entry 8) ultimately provided the difluoromethyl quinoline **22** in excellent yield while further increases in reaction temperature, time or equivalents of NFSI failed to promote trifluorination on this or any other substrate. In both the mono- and difluorination of alkylquinolines **17** and **20**, phenylsulfonyl fluoride was observed as a by-product, suggesting that these reactions rely on activation of quinoline through transient sulfonylation by NFSI.[21] It is notable that this approach to heterobenzylic fluorination is complimentary to the Minisci-like radical reactions described by Baran, which favour trifluoromethylation at C7 or difluoromethylation at C2 of quinolines.[12]

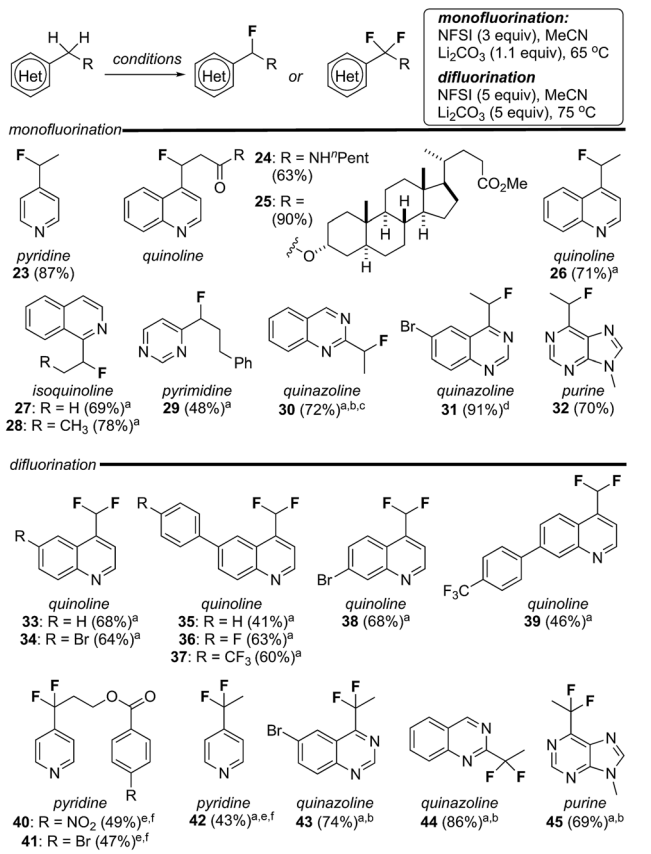


Fig. 2 Mono- and difluorination of pyridines, quinolines, isoquinolines, quinazolines, pyrimidines and purines. [a]Yield determined by analysis of NMR spectroscopic data using an internal standard; [b]reaction at 125 °C in a microwave reactor; [c]accompanied by 25% of the difluorinated quinazoline **44**; [d]reaction at 25 °C; [e]accompanied by ~40% of a monofluorinated product; [f]10 equiv. of NFSI in EtOAc.

Scope of heterobenzylic mono- and difluorination

Encouraged by the susceptibility of 4-alkylquinolines **17** and **20** to undergo mono- or difluorination, we explored the scope of these reactions with a broader range of heterocycles including pyridines, isoquinolines, pyrimidines, quinazolines and purines. As summarized in Fig. 2, by simply modifying the equivalents of reagent and temperature, in several cases mono- or difluorination could be effected selectively. For example, both mono- and difluoroalkyl pyridines, quinazolines and purines could be produced in good yield following this straightforward procedure (*e.g.*, **23**/**42**, **30**/**44**, **31**/**43** and **32**/**45**). As noted above, alkylquinolines were reluctant to difluorinate but were monofluorinated in excellent yield providing **24** and **25**. Conversely, a series of methylquinolines were transformed directly into the corresponding difluoromethylquinolines **33–39** in good yield. In addition to the obvious compatibility with azaheterocycles, substituted aromatics (*e.g.*, **36–41**), esters (*e.g.*, **25**) and amides (*e.g.*, **24**) were well tolerated. It is notable that both 2,4-dimethylquinoline and 2,4,6-trimethylpyridine failed to undergo fluorination (<5% yield) using our standard reaction conditions. Here, we postulate that steric hindrance from the adjacent alkyl group(s) impedes sulfonylation of the heterocycle by NFSI and thus prevents fluorination. In several cases, complete separation of mono- and difluorinated products by flash column chromatography proved challenging. Thus, while purified product could be isolated this way, yields for these reactions were determined by analysis of NMR spectroscopic data using an internal standard.[21]

Sulfonyl transfer promotes heterobenzylic trifluoromethylthiolation

Considering that sulfonyl transfer from NFSI is a key feature of this process (*e.g.*, **48**, Fig. 3),[21] we examined a small

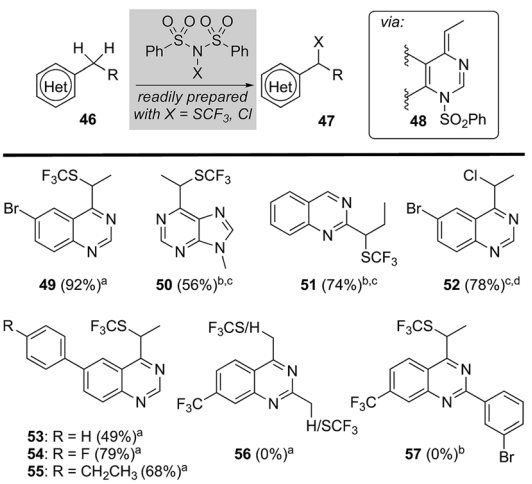
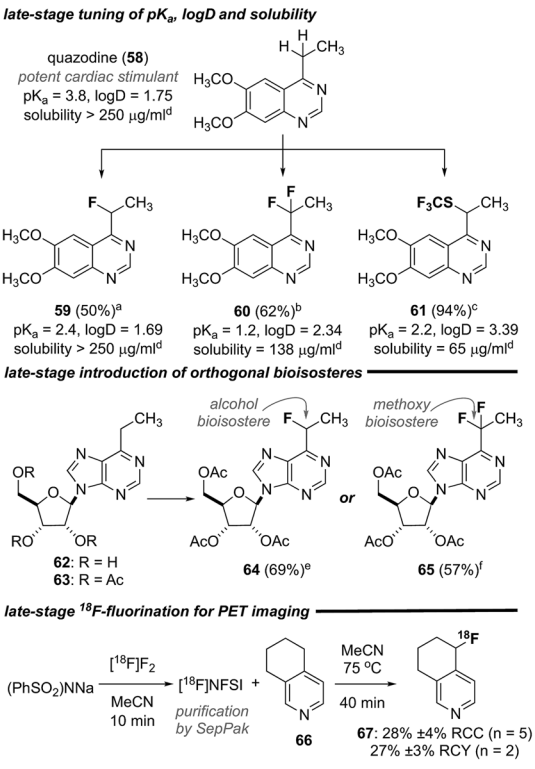


Fig. 3 Trifluoromethylthiolation and chlorination of purine and quinazolines. [a]Conditions: N(SCF3)SI (2.4 equiv.), Li_2CO_3 (1.1 equiv.), MeCN, 75 °C, 48 h; [b]N(SCF3)SI (2.4 equiv.), Li_2CO_3 (1.1 equiv.), MeCN, 125 °C (microwave), 50 min; [c]yield determined by analysis of NMR spectroscopic data using an internal standard; [d]N(Cl)SI (1.2 equiv.), Li_2CO_3 (1.1 equiv.), MeCN, 75 °C, 48 h.

collection of dibenzenesulfonamide derivatives[22] to explore their potential in the direct heterobenzylic functionalization of alkylquinazolines and purines. As depicted in Fig. 3, we found that both trifluoromethylthiolation (*e.g.*, **49–51** and **53–55**) and chlorination (*e.g.*, **52**) were facile processes. For example, 2- and 4-alkylquinazolines and 6-ethylpurine underwent heterobenzylic trifluoromethylthiolation using *N*-trifluoromethylthiodibenzenesulfonimide ($N(SCF_3)SI$).[22] Surprisingly, we observed no competing heteroaryl trifluoromethylthiolation[22] of quinazolines and purines, and attempts to effect the equivalent transformation using trifluoromethylthiophthalimide, an electrophilic trifluoromethylthiolation reagent,[23] delivered none of the expected trifluoromethylthiolated products. This later result provides support for a mechanism involving activation by transient sulfonylation with dibenzenesulfonamide derivatives. Again, 2,4-disubstituted quinazolines failed to provide any trifluoromethylthiolated product (*e.g.*, **56** or **57**) presumably due to steric hindrance impeding sulfonylation of the heterocycle by $N(SCF_3)SI$. Notably, this heterobenzylic trifluoromethylthiolation[24] reaction offers a unique opportunity to significantly alter lipophilicity (Hansch hydrophobicity parameter $\pi = 1.44$)[23] and pK_a of a drug lead.



Scheme 1 Late-stage mono- and difluorination, trifluoromethylthiolation and ^{18}F-fluorination of heterocycles. [a]NFSI (1.2 equiv.), Li_2CO_3 (1.1 equiv.), MeCN, rt, 96 h; [b]NFSI (3.0 equiv.), Li_2CO_3 (1.1 equiv.), MeCN, 125 °C (microwave), 50 min; [c]$N(SCF_3)SI$ (2.4 equiv.), Li_2CO_3 (1.1 equiv.), MeCN, 75 °C, 48 h; [d]solubility measured by lyophilisation solubility assay (LYSA) at pH 6.5 in 0.05 M phosphate buffer; [e]NFSI (3.0 equiv.), Li_2CO_3 (1.1 equiv.), MeCN, 75 °C, 48 h; [f]NFSI (5.0 equiv.), Li_2CO_3 (5.0 equiv.), MeCN, 75 °C, 48 h.

Heterobenzylic functionalization and ^{18}F-fluorination of drug leads

In an effort to further demonstrate the utility of this suite of transformations, we explored the monofluorination, difluorination and trifluoromethylthiolation of quazodine (**58**),[25] a cardiac stimulant. As depicted in Scheme 1, each of these transformations proceeded smoothly and provided access to the unique quazodine derivatives **59–61** in good to excellent yield. To gauge the impact of heterobenzylic functionalization on relevant physiochemical properties, the pK_a, distribution coefficient (log *D*) at pH 7.4 and aqueous solubility of each compound was measured. As summarized in Scheme 1, these transformations significantly affected each property and provide a straightforward means to modulate lipophilicity and basicity. Likewise, the peracetate **63** of the cytotoxic purine nucleoside analogue **62** [26] could be mono- or difluorinated, affording the analogues **64** or **65**, respectively, in good yield. Finally, we explored the direct ^{18}F-fluorination of the annulated pyridine **66** to demonstrate the additional utility of this transformation for rapidly generating radiotracers for positron emission tomography (PET) imaging. We have previously exploited [^{18}F]NFSI[27] in the direct radiofluorination of branched aliphatic amino acids[28] and were pleased to find that simply heating a solution of the annulated pyridine **66** and [^{18}F]NFSI in MeCN at 75 °C for 40 min provided the ^{18}F-labelled derivative **67** in good radiochemical conversion (RCC) and yield (RCY). This streamlined heterobenzylic ^{18}F-fluorination does not rely on prior functionalization or sensitive reagents and thus offers certain advantages for the rapid generation of radiotracers for PET imaging.

Conclusions

In summary, we demonstrate that transient sulfonylation of a range of nitrogen-containing heterocycles enables direct heterobenzylic mono or difluorination using the bench stable electrophilic fluorinating agent NFSI or radiofluorination with [^{18}F]NFSI. Taking advantage of this heterocycle activation process, both trifluoromethylthiolation and chlorination could also be achieved using the corresponding dibenzenesulfonamide derivatives. This collection of late-stage transformations should enable the rapid tuning of pK_a and lipophilicity of heterocycle-containing drug leads and provides a complimentary means to incorporate pharmaceutically relevant bioisosteres (*e.g.*, $-CHF_2$, $-CF_2R$ and $-CH(SCF_3)R$) as well as a method to rapidly generate ^{18}F-labelled imaging agents for PET imaging.

Experimental

General procedure for heterobenzylic monofluorination

To a solution of substrate in CH_3CN (0.1–0.25 M substrate) was added *N*-fluorobenzenesulfonimide (NFSI) (3.0 equiv.) and Li_2CO_3 (1.1 equiv.). The resulting reaction mixture was then heated to 65 °C and maintained at this temperature for 18–24 h. The reaction mixture was cooled, diluted with CH_2Cl_2 and

washed with saturated $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), concentrated and the crude reaction product was purified by column chromatography on silica gel.

General procedure for heterobenzylic difluorination

To a solution of substrate in CH_3CN (0.25–0.50 M substrate) was added *N*-fluorobenzenesulfonimide (NFSI) (5.0 equiv.) and Li_2CO_3 (5.0 equiv.). The resulting reaction mixture was then either heated to 75 °C and maintained at this temperature for 48 h or heated to 125 °C and maintained at this temperature for 1 h in a microwave reactor. The reaction mixture was then cooled, diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), concentrated and the crude reaction product was purified by column chromatography on silica gel.

General procedure for heterobenzylic trifluoromethylthiolation

To a solution of substrate in CH_3CN (0.25–0.50 M substrate) was added *N*-trifluoromethylthiobenzenesulfonimide (2.4 equiv.) and Li_2CO_3 (1.1 equiv.). The resulting reaction mixture was then either heated to 75 °C and maintained at this temperature for 48 h or heated to 125 °C and maintained at this temperature for 1 h in a microwave reactor. The reaction mixture was cooled, diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$), concentrated and the crude reaction product was purified by column chromatography on silica gel.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by an NSERC Discovery Grants to R. B., a MSFHR Career Investigator Award to R. B., a Hoffmann-La Roche Fellowship (RPF) for M. B. N. an NSERC PGS and a SFU MYF for M. M. We would like to thank Pascal Hasenfratz, Laura Martin, Simona Capomolla, Maria Giraldo, Silvio Binkert and Christelle Jablonski for the preparation of starting materials, Catherine Karrer for LYSA, Aynur Ekiciler for log *D* and Bjoern Wagner for pK_a measurements.

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