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Discovery of *C*-imidazole azaheptapyridine FPT inhibitors

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ABSTRACT

The discovery of C-linked imidazole azaheptapyridine bridgehead FPT inhibitors is described. This novel class of compounds are sub nM FPT enzyme inhibitors with potent cellular inhibitory activities. This series also has reduced hERG activity versus previous N-linked imidazole series. X-ray of compound **10a** bound to FTase revealed strong interaction between bridgehead imidazole 3N with catalytic zinc atom.

Farnesyl protein transferase inhibitors (FTI) are designed to inhibit post-translational modification of Ras oncogene.[1] Ras mutations are observed in 30% of all human tumors and in a very high percentage (ca. 90%) of pancreatic tumors. There are three forms of Ras: H-Ras, K-Ras and N-Ras that require prenylation to associate with the inner plasma membrane for activation. Farnesyl is the preferred lipid, although N and K forms of Ras can be activated through alternative geranylgeranylation upon inhibition of farnesylation. Several FTIs including Sch 66336 (**SARASAR**) (**1**) are being evaluated in clinical settings and some evidence of antitumor activities were reported.[2] Several studies indicate that the anti cancer effect of FTIs may stem from inhibition of farnesylation of proteins other than Ras.[3]

In previous studies, a series of bridgehead *N*-imidazole substituted azaheptapyridines were found to be potent FPT inhibitors.[4] These compounds, exemplified by **2** (Fig. 1), demonstrated sub nM potency in both enzyme and cellular assays. Compound **2** had excellent DMPK profiles and was shown to have superior efficacy in tumor xenograft models. In subsequent pre-clinical toxicology studies, heart rate reduction was observed in Guinea pigs at high dosage possibly due to hERG channel inhibition. In light of these findings, alternative compounds with different structures that addressed these deficiencies were targeted.

The imidazole group can be found in a number of other leading FPT inhibitors such as Janssen R115777 (**3**) and BMS-214662 (**4**) (Fig. 1).[5] As shown in X-ray structural analysis of these inhibitors bound to FPT enzyme, a ternary complex was formed with FPP and imidazole moiety bound to catalytic Zn in the enzyme active site.[6] The interaction with the zinc likely contributes greatly to the potency of these compounds.[7]

In the case of **2**, imidazole was N-linked while C-linked imidazole was found in **3** and **4**. Therefore *C*-imidazole linked azaheptapyridine analogs of **2** were prepared and evaluated (Scheme 1).

The synthesis started with carbonylation of compound **5** followed by CDI/$NaBH_4$ reduction to give alcohol **6**.[8] NBS bromination

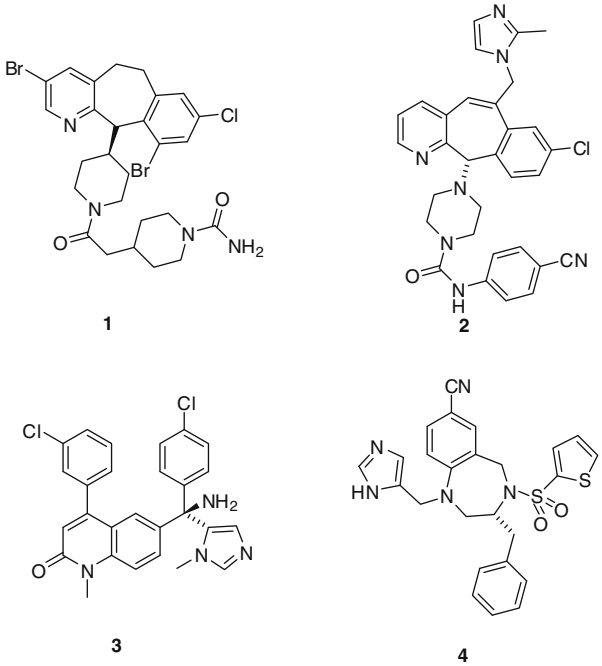

Figure 1. Representative FPT inhibitors.

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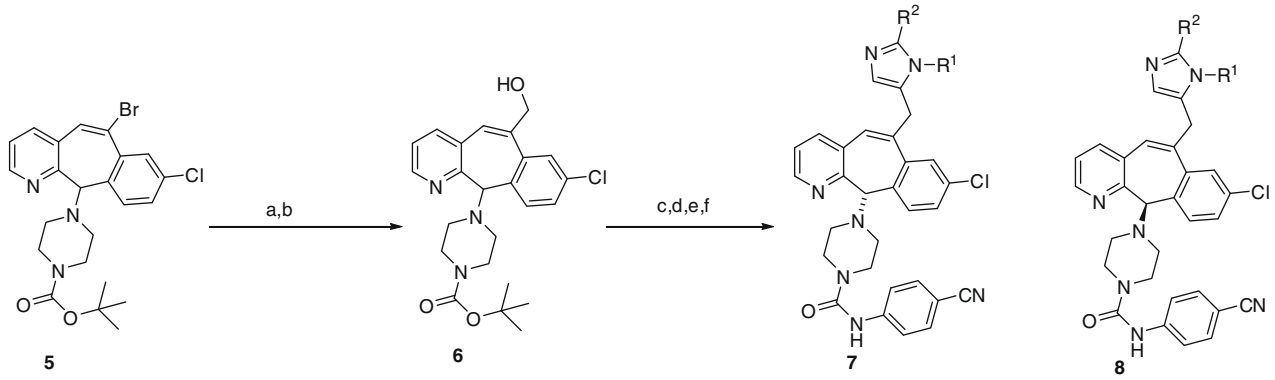


Scheme 1. Reagents: (a) CO, $PdCl_2$, PPh_3, DBU,CH_3OH/CH_3Ph; (b) (1) LiOH, MeOH; (2) CDI,THF, $NaBH_4$; (c) NBS, CH_3CN; (d) 5-I imidazole, EtMgBr, CuCN, LiCl, THF; (e) Chiracel column separation; (f) CH_2Cl_2, TFA; then 4-CN PhNCO, TEA, CH_2Cl_2.

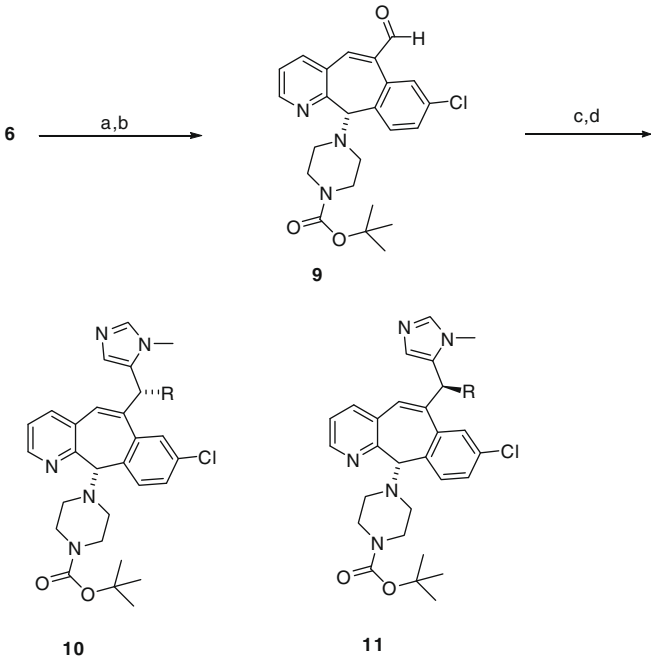
of **6** accompanied by 5-imidazole cuprate coupling installed *C*-imidazole on the bridgehead. After Chiracel HPLC separation, *N*-Boc was removed with TFA and converted to *p*-CN phenyl urea derivatives **7** and **8**. The FPT enzyme and soft agar activities on this series of compounds are listed (Table 1).

To our delight, 1*N*-methyl *C*5-imidazole compound **7a** had comparable enzymatic and cellular activities with *N*-imidazole compound **2**. There was 30-fold loss of FPT activity in C11 isomer **8a**. By the analogy to the previous series, the active isomer was assigned as **7** with S-configuration at C11.[9] 1N–H *C*5-imidazole compound **7b** and **7c** (mixture) were also very potent in enzymatic assay although **7b** was modest in soft agar cellular assay. 1*N*-methyl *C*5-imidazole was chosen for further studies due to its better human Cyp inhibition profiles (Scheme 2).

With successful installation of *C*-imidazole to the benzocycloheptapyridine core, we decided to add polar functional groups to the linker that was not previously accessible in *N*-imidazole series. Polar groups generally reduce hERG activity.[10] The targets were prepared through 5-imidazole Grignard addition to C11(S) enantiomeric aldehyde **9**. The resulting diastereomers were separated either through careful silica gel column or chiral HPLC. The hydroxyl group was further converted to O-acetate and OMe groups to explore the space at the methylene linker.

As shown in Table 2, diastereomers **10a** and **11a** showed over 20-fold difference in enzyme activities. Methylation of the OH was tolerated with lower inhibitory activity with a less profound difference between the two diastereoisomers. Therefore it was reasonable to assume hydrogen bonding from the free OH in **10a** and **11a** played a role in their activity difference. The OAc group had the similar potency to the OMe group in the enzyme assays. It was interesting to note that the OAc group had better cellular activity than enzyme data indicated. This may have been due to in cell hydrolytic conversion of the acetyl group to the more active OH compound **10a**.

The structure of **10a** bound to FPT is shown in Figure 2.[11] Compound **10a** interacts with the active site zinc through the imidazole



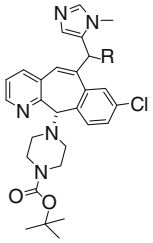
Scheme 2. Reagents and conditions: (a) MnO_2, CH_2Cl_2; (b) Chiracel AD column separation (isomer 1); (c) R = OH 2-I N1-methyl imidazole, EtMgBr, $ClCH_2CH_2Cl$; (d) R = OMe, MeI, NaH, for R = OAc, acetic anhydride, Et_3N.

Table 1
FTase, soft agar activities of *C*-imidazole benzocycloheptapyridine derivatives

Compd	R^1	R^2	FTase IC_{50}[a] (nM)	Soft agar IC_{50}[b] (nM)
7a	CH_3	H	0.29	0.5
8a	CH_3	H	9.6	NA
7b	H	H	0.31	4
7c+8c	H	CH_3	0.52	NA

[a] In vitro enzyme assay by measuring the transfer of [H3]farnesyl from [H3]farnesyl pyrophosphate to trichloroacetic acid-precipitable HaRas-CVLS.
[b] Colony forming assay by evaluating the ability to inhibit anchorage-independent growth of NIH-H tumor cell lines in soft agar.

Table 2
FPT, soft agar activities of *C*-imidazole benzocycloheptapyridine derivatives



Compd	R	FTase IC_{50} (nM)	Soft agar IC_{50} (nM)
10a	OH	0.38	0.5
11a	OH	12	NA
10b	OMe	4.8	10
11b	OMe	2.1	4
10c	OAc	5.5	1

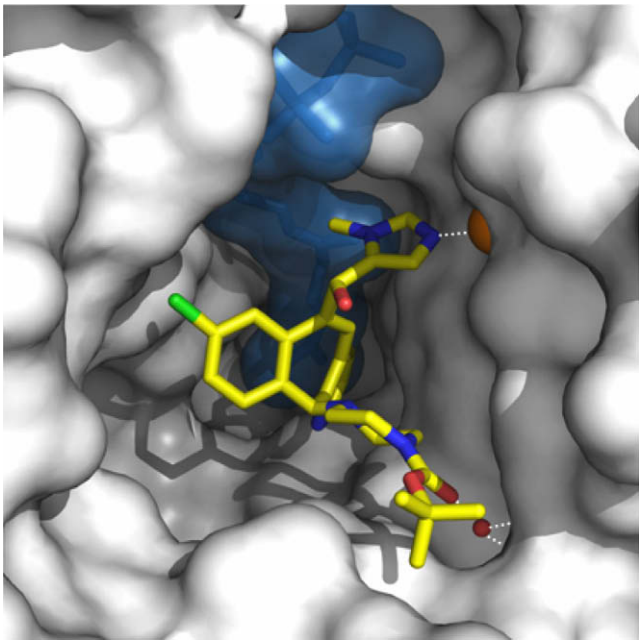
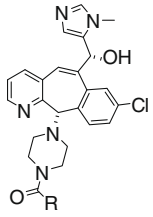
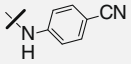
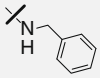


Figure 2. Structure of **10a** (yellow sticks) bound to FPT. The zinc (Orange sphere), FPP (blue surface) and several specific interactions (white lines) are illustrated.

Table 3
FPT, soft agar activities of *C*-imidazole benzocycloheptapyridine derivatives



Compd	R	FTase IC_{50} (nM)	Soft agar IC_{50} (nM)
10a		0.38	0.5
12		0.5	0.5
13		0.13	2.7
14		0.47	18
15		0.4	0.5
16		0.75	0.5
17		1.0	1.0
18		0.3	1.0
19		0.76	0.5

N3 nitrogen. The imidazole 1*N*-methyl is packed against FPP. The R configuration places the hydroxyl group towards solvent in a position to make an intra-molecular hydrogen bond to the piperazine nitrogen. The binding of the tricyclic core is similar to previous compounds lacking the zinc binding motif.[12] Carbonyl of the Boc group also contributes to the binding with interaction with surface H_2O molecule.

Further modifications on the piperazine moiety of **10a** were carried out with representative analogs shown in the Table 3. Urea and carbamate are suitable substitutions at piperazine 1-N as indicated in the X-ray structure with the carbonyl group contributing to binding. Various sized alkyl and aromatic groups were generally tolerated. Most compounds are sub nanomolar FPT inhibitors with low single digit nM inhibitors in soft agar assays.

The hERG activity of compound **12** was assessed and found to be 37% inhibition at 1 μM. It provided a large therapeutic window considering its sub nM FPT cellular potency. This compound had low rat PK (10 mpk, 0–6 h, AUC = 0.1 μM). However rat PK on carbamate analogs were generally good with AUC = 2.57 μM h (10 mpk, 0–6 h) for compound **10a** (17% hERG inhibition at 300 nM).

In conclusion, we discovered a novel series of potent FPT inhibitors featuring C-linked imidazole as the active site Zn binder. We also demonstrated that the methylene linker carbon was amendable to substitutions. DMPK properties could be modulated with these groups with notable reduction in hERG inhibition. Optimization efforts on this series will be reported in future papers.

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