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Pyridone-Containing Farnesyltransferase Inhibitors: Synthesis and Biological Evaluation

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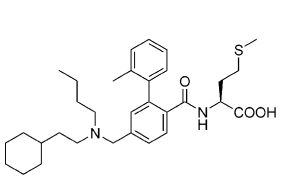
Abstract—Farnesyltransferase inhibitors (FTIs) have been developed as potential anti-cancer agents due to their efficacy in blocking malignant growth in a variety of murine models of human tumors. To that end, we have developed a series of pyridone farnesyltransferase inhibitors with potent in vitro and cellular activity. The synthesis, SAR and biological properties of these compounds will be discussed.

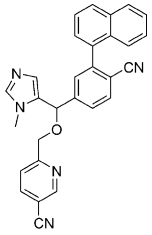
Ras oncogenes are present in a variety of human tumors. The dependence of Ras proteins on post-translational farnesylation for cell membrane anchoring led to the investigation of farnesyltransferase inhibitors (FTIs) as potential anti-cancer agents.[1] These agents possess the ability to block or reverse malignant growth while leaving non-cancerous cells virtually unaffected. The mechanism through which they work is still under debate, as it has been shown that inhibition of Ras isoprenylation is not necessary for their antineoplastic effects.[2]

In addition to farnesyltransferase, there are two other protein-isoprenyltransferases, geranylgeranyltransferase type I (GGT-I) and geranylgeranyltransferase type II (GGT-II). FT and GGT-I act similarly transferring C-15 and C-20 units, respectively; however, GGT-II acts through a different mechanism. The majority of isoprenylated proteins are geranylgeranylated by GGT-I, but all mutant Ras proteins in human cancers are modified exclusively by FT.[2] Evidence that simultaneous inhibition of both FT and GGT-I can lead to toxicity prompted us to seek a selective inhibitor of FT over GGT-I.[3]

Early work on farnesyltransferase inhibitors in our laboratories yielded ABT-839 (Fig. 1) which demonstrated good in vitro activity ($IC_{50} = 1.1$ nM), selectivity (FT/GGT-I = 75,000) and cellular potency ($EC_{50} = 16$ nM). Unfortunately, the compound suffered from poor oral bioavailability. Extensive SAR studies in our group led to the discovery that a cyano group can replace the methionine moiety of ABT-839. The tertiary amine moiety was also replaced by a methylimidazole-secondary alcohol moiety. Significant improvements were seen with these changes. An exemplary compound, A-315493 (Fig. 1), is a potent FTI with an IC_{50} of 0.73 nM and an EC_{50} of 5.9 nM. It also has a much-improved pharmacokinetic profile with approximately 50% oral bioavailability in both dog and monkey. It possesses only



ABT-839



A-315493

Figure 1. ABT-839 and A-315493.

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modest selectivity, however, at 26-fold for FT inhibition over GGT-I inhibition.[4]

Continued efforts toward the discovery of a potent and selective FTI produced several structurally different series of compounds including the pyridone series shown in Figure 2.

The effects of substituent changes with respect to in vitro activity (IC_{50}),[5] cellular potency or Ras processing (EC_{50}),[5] and pharmacokinetic properties (specifically oral bioavailability)[6] of the pyridone series were studied and the results are now presented.[7]

A representative synthesis of the pyridones is shown in Scheme 1. Intermediate **3** was prepared by treatment of **2** with *t*-BuLi followed by addition of the appropriate 4-cyanobenzaldehyde. Intermediate **8** was prepared by initial bromination of 3-cyano-6-methyl-2-(1*H*)-pyridinone (**4**) with NBS, followed by *N*-methylation with K_2CO_3 and MeI. Subsequent Suzuki reaction with various phenylboronic acids, followed by benzylic bromination with NBS/AIBN and hydrolysis in the presence of Celite® completed the synthesis of intermediate **8**.

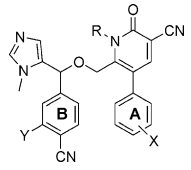
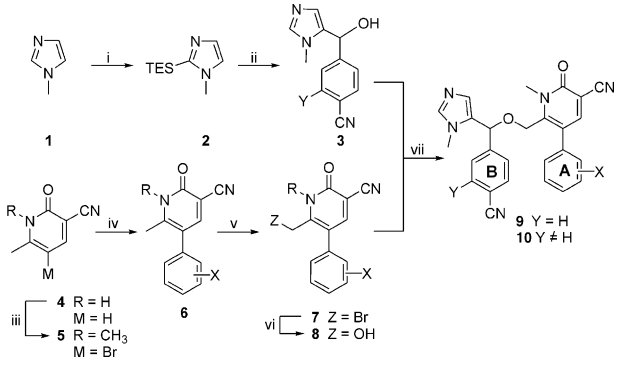


Figure 2. Structure of the pyridone series of FTIs.

Coupling of intermediates **3** and **8** under Dean–Stark conditions with *p*-TsOH in toluene provided compounds **9** and **10**.

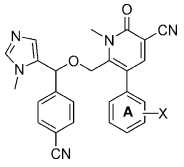
The preparation of certain phenylboronic acids used to synthesize the compounds of Table 1 is shown in Scheme 2. Each was produced through anion formation with butyllithium, followed by addition of $B(Oi\text{-}Pr)_3$ and acidic workup.

Table 1 illustrates the effects of various substituents on ring A. All of the substituents provided compounds that



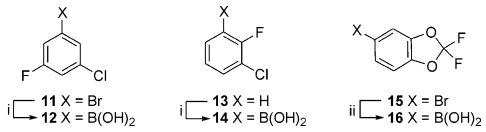
Scheme 1. (i) (a) *n*-BuLi, THF, −78 °C; (b) TESCl, −78 °C to rt, 82%; (ii) (a) *t*-BuLi, THF, −78 °C; (b) 4-cyanobenzaldehyde, −78 °C, 79%; (iii) (a) NBS, DCE, reflux, 92%; (b) K_2CO_3, DMF, rt; MeI, 0 °C, 76%; (iv) substituted phenylboronic acid, $Pd(PPh_3)_4$, 2 M Na_2CO_3, LiCl, toluene/EtOH, reflux, 84% for X = 3-Cl; (v) NBS, AIBN, CCl_4, reflux; (vi) Celite®, 1,4-dioxane/H_2O, reflux, 88% over two steps for X = 3-Cl; (vii) *p*-TsOH, toluene, reflux, 43% for X = 3-Cl.

Table 1. IC_{50}, EC_{50} and oral bioavailability (F) for compounds **9a–u**



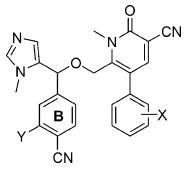
Compd	X	FT IC_{50} (nM)	GGT-I IC_{50} (nM)	FT EC_{50} (nM)	F	
					Dog (%)	Mky (%)
9a	3-Cl	0.44	2700	0.5	32	14
9b	3,5-diCl	0.46	1700	6.8	52	46
9c	3,4-diCl	0.49	2300	86	76	na
9d	2,5-diCl	1.6	2900	1.2	54	3
9e	2,3-diCl	6.1	2500	na	38	na
9f	3-F	2.1	>10,000	11	61	42
9g	3,5-diF	0.84	12,000	7.3	90	25
9h	3,4-diF	1.5	5500	10	83	na
9i	2,4-diF	5.5	4300	>100	na	na
9j	2,5-diF	2.7	15,000	110	>99	46
9k	2,3-diF	6.3	3400	na	na	na
9l	3-Cl,5-F	0.7	1800	17	40	na
9m	3-Cl,4-F	1.1	1900	15	91	28
9n	2-F,3-Cl	1.8	1500	24	59	na
9o	3-Br	0.51	3400	2.1	61	3
9p	3-OCH_3	0.41	3200	4.7	44	0
9q	3-OCH_2CH_3	0.67	1500	0.81	47	3
9r	3-OCF_3	0.42	1045	3.9	93	36
9s	4-OCF_3	0.73	1400	3.9	52	34
9t	3,4-OCH_2O–	0.42	3300	2.1	28	na
9u	3,4-OCF_2O–	0.69	6200	19	63	34

Dog, beagle; Mky, cynomolgus monkey.



Scheme 2. (i) (a) *n*-BuLi, THF, −78 °C; (b) $B(O\textit{i}\text{-}Pr)_3$, −78 °C to rt; (c) HCl; (ii) (a) *t*-BuLi, THF, −78 °C; (b) $B(O\textit{i}\text{-}Pr)_3$, −78 °C to rt; (c) HCl.

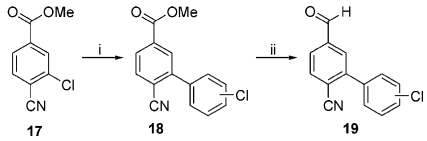
Table 2. IC_{50} and EC_{50} for compounds **9a**, **9b**, **9s**, **10a–m**



Compd	Structure (Y; X)	FT IC_{50} (nM)	GGT-I IC_{50} (nM)	FT EC_{50} (nM)
9a	H; 3-Cl	0.44	2700	0.5
10a	Cl; 3-Cl	0.97	890	24
10b	Br; 3-Cl	1.3	610	39
10c	I; 3-Cl	0.75	>1000	88
10d	3′-ClPh; 3-Cl	1.0	94	21
9b	H; 3,5-diCl	0.46	1700	6.8
10e	Cl; 3,5-diCl	0.77	190	16
10f	Br; 3,5-diCl	0.42	290	>100
10g	I; 3,5-diCl	0.81	7500	>100
10h	3′-ClPh; 3,5-diCl	2.0	120	na
9s	H; 4-OCF_3	0.73	1400	3.9
10i	Cl; 4-OCF_3	0.36	150	15
10j	Br; 4-OCF_3	0.89	220	10
10k	2′-ClPh; 4-OCF_3	3.9	110	>100
10l	3′-ClPh; 4-OCF_3	1.3	30	>100
10m	4′-ClPh; 4-OCF_3	6.5	160	>100

are potent against FT with more than half of them possessing FT IC_{50} values less than 1 nM. In addition, all substituents provided selectivities greater than 400-fold for inhibition of FT over GGT-I. The 3-Cl (**9a**) and 3-OEt (**9q**) substitutions provided compounds with the best cellular potency having EC_{50} values of 0.5 and 0.81 nM, respectively. The 3,5-diCl (**9b**) and 3,5-diF (**9g**) compounds possess similar EC_{50} values of 6.8 and 7.3 nM, respectively, unlike the 2,5- and 3,4-dihalogenated compounds (**9d**, **9j**, **9c** and **9h**) which have significantly different EC_{50} values. Of the 2,5-dihalogenated compounds, the dichloro compound is more potent by nearly 92-fold, while the reverse is seen for the 3,4-dihalogenated compounds in which the difluoro compound is more potent. Reasons for the differences seen in the EC_{50} values of the dichloro and difluoro compounds remain unclear. Although substituent changes caused wide pharmacokinetic variability in both species, oral bioavailability was consistently better in dog than monkey. Several compounds show balanced properties throughout FT IC_{50} and EC_{50}, selectivity and oral bioavailability (**9a**, **9b**, **9g**, **9r** and **9s**).

We also investigated the effects of an added substituent on the cyanophenyl ring (B). Synthesis of the chlorophenyl substituted 4-cyanobenzaldehydes (**19**) used in the preparation of compounds **10d**, **10h** and **10k–m** (Table 2) is shown in Scheme 3. Known ester (**17**)[4] was

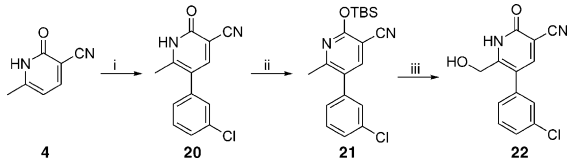


Scheme 3. (i) Chlorophenylboronic acid, $Pd(OAc)_2$, CsF, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, 1,4-dioxane, 91% for 3-Cl; (ii) (a) $NaBH_4$, $CaCl_2$, EtOH/THF, 0 °C to rt, 95% for 3-Cl; (b) Dess–Martin periodinane, CH_2Cl_2, quant for 3-Cl.

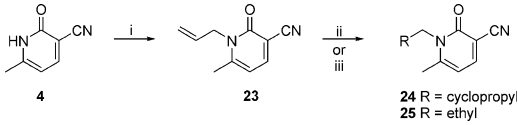
reduced by in situ formation of $Ca(BH_4)_2$, followed by Suzuki reaction with the appropriate chlorophenyl boronic acid and oxidation with Dess–Martin periodinane.

Table 2 illustrates the effects of changes to the cyanophenyl ring (B). The changes were tested using some of the better substituents from Table 1 for ring A. All substituents provided potent FTIs. Larger differences were seen in the GGT-I assay and Ras processing (EC_{50}). Selectivity for FT inhibition over GGT-I inhibition was generally reduced by the addition of a substituent to the cyanophenyl ring. The most marked decreases were seen with the large chlorophenyl group (**10d**, **10h**, **10k–m**) where selectivity was as low as 23-fold. The substituent changes also resulted in diminished potency in the cellular assay.

We further examined replacement of the pyridone *N*-methyl group with other substituents. Scheme 4 illustrates the synthesis of compound **22**, the key intermediate for the synthesis of **26**, the N–H counterpart to compound **9a**. Compound **4** (Scheme 1) was brominated with NBS. This was followed by Suzuki reaction with 3-chlorophenylboronic acid and *O*-silylation with TBSCl. Sequential benzylic bromination with NBS/AIBN, followed by hydrolysis and concomitant deprotection in the presence of Celite® provided intermediate **22**. Intermediates **3** and **22** were then coupled as described in Scheme 1 to provide **26**.

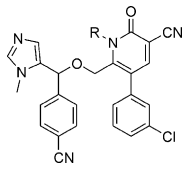


Scheme 4. (i) (a) NBS, DCE, reflux, 92%; (b) 3-chlorophenylboronic acid, $Pd(PPh_3)_4$, 2M Na_2CO_3, LiCl, toluene/EtOH, reflux, 73%; (ii) TBSCl, imidazole, DMF, 58%; (iii) (a) NBS, AIBN, CCl_4, reflux; (b) Celite®, 1,4-dioxane/H_2O, reflux, 33%.



Scheme 5. (i) allylbromide, NaH (60%), LiBr, DME/DMF, 0 °C to rt to 65 °C, 57%; (ii) 10% Pd/C, EtOAc, H_2 (1 atm.) rt, 70%; (iii) CH_2N_2/ether, THF, $Pd(OAc)_2$, 0 °C, 55%.

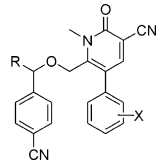
Table 3. IC_{50}, EC_{50} and oral bioavailability (F) for compounds **9a**, **26**–**29**



Compd	R	FT IC_{50} (nM)	GGT-I IC_{50} (nM)	FT EC_{50} (nM)	F	
					Dog (%)	Mky (%)
9a	CH_3	0.44	2700	0.5	32	14
26	H	0.85	820	>100	na	na
27	CH_3CH_2	0.73	3300	2.9	na	na
28	$CH_3CH_2CH_2$	0.036	3000	12	60	na
29		0.5	2000	4.8	na	na

Dog, beagle; Mky, cynomolgus monkey.

Table 4. IC_{50} and EC_{50} for compounds **9a** and **32**–**35**

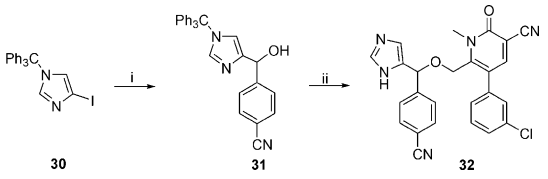


Compd	Structure R; X	FT IC_{50} (nM)	GGT-I IC_{50} (nM)	FT EC_{50} (nM)
9a	 ; 3-Cl	0.44	2700	0.5
32	 ; 3-Cl	71	na	na
33	 ; 3-Cl	5.3	>900	68–75% Inh. @ 100 nM
34	 ; 3,5-diCl	1.9	>10,000	>100
35	 ; 4-OCF_3	9.9	>10,000	na

Inh., inhibition.

Compound **27** was prepared as shown in Scheme 1 with nitrogen alkylation being effected with ethyl iodide in place of iodomethane. Compounds **28** and **29** were prepared as shown in Schemes 1 and 5. Compound **4** was alkylated according to the procedure described by Curran.[8] The resulting compound (**23**) was either hydrogenated to form intermediate **24** or cyclopropanated to form intermediate **25**. The remainder of the synthesis follows Scheme 1.

It can be seen in Table 3 that FT inhibition, selectivity and cellular potency were maintained, except in the case of R = H (**26**). Compound **26** was potent against FT and selective, but it showed weak cellular potency (EC_{50} >100 nM). Although it appears that a nitrogen substituent is required for cellular potency, groups of various sizes can be tolerated.



Scheme 6. (i) (a) EtMgBr, CH_2Cl_2, rt; (b) 4-cyanobenzaldehyde, CH_2Cl_2, −20 °C to rt, quant; (ii) (a) **7**, Ag_2O, CH_2Cl_2, 28%; (b) 80% aq AcOH, 11%.

Finally, we examined the effects of changing the *N*-methylimidazole ring. Compound **32** was prepared as shown in Scheme 6. 4-Iodo-1-trityl-1*H*-imidazole (**30**) was treated with EtMgBr in CH_2Cl_2, followed by 4-cyanobenzaldehyde according to the procedure of

Turner et al.[9] This intermediate (**31**) was then coupled with intermediate **7** (Scheme 1) using Ag_2O. Removal of the trityl group with aqueous acetic acid provided compound **32**. Compounds **33**–**35** (Table 4) were prepared as shown in Scheme 1 with replacement of thiazole or 1,2-dimethylimidazole for *N*-methylimidazole.

As seen in Table 4, compound **32** exemplifies the importance of the nitrogen methyl group. A 140-fold loss of potency was seen compared to compound **9a**. Addition of a second methyl group to the imidazole ring (**33**) also showed a loss of potency, but to a lesser extent. Replacement of *N*-methylimidazole with thiazole provided varying losses of potency as seen in examples **34** and **35**. Although selectivity was maintained in these examples, a critical loss was suffered in the Ras processing of example **34** which has an EC_{50} greater than 100 nM. Overall, these changes were not well tolerated and among these limited examples, the *N*-methylimidazole ring remains the best choice.

We have demonstrated that, with few exceptions, a variety of substituent changes were well tolerated in the in vitro assay. Although selectivity and cellular potency varied widely with the substituent changes, we have shown the pyridone series of FTIs to be potent and selective with good PK profiles.

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