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Design, synthesis, and activity of achiral analogs of 2-quinolones and indoles as non-thiol farnesyltransferase inhibitors

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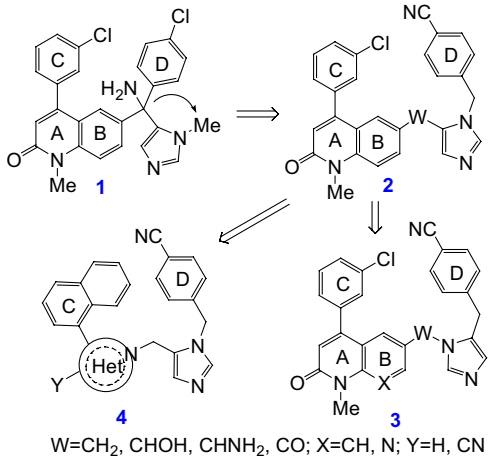
Abstract—Beginning with the structure of tipifarnib (**1**), a series of inhibitors of FTase have been synthesized by transposition of the D-ring to the imidazole and subsequent modification of the 2-quinolone motif. The compounds in the new series may be achiral and have structural features that allow for analogs that are difficult or impossible to make in the tertiary carbon-based tipifarnib series. The most potent compound (**4d**) is 4 times more active in vitro against FTase than tipifarnib.

Farnesyltransferase (FTase) inhibitors have generated much attention recently as anticancer agents because of their potential for reduced intrinsic toxicity as compared with the conventional cytotoxic agents.[1] Among the several inhibitors currently in Phase III clinical trials, tipifarnib (R115777, **1**) is perhaps the most potent and selective non-thiol FTase inhibitor.[2,3] Recently, we reported a novel series of FTase inhibitors that contain 4-quinolone and pyridone cores resulting from structural modifications of tipifarnib.[4] In this paper, we report our continued efforts to utilize tipifarnib as a template in designing novel classes of FTase inhibitors.

The rationale for this series is based on analysis of the X-ray structure of tipifarnib in complex with FTase,[4,5] in which the D-ring is close to the methyl group on the imidazole. Transposition of the D-ring to the methyl group on the imidazole should not significantly affect its binding to one of the hydrophobic pockets of FTase, while leading to a novel series which may not have a chiral center as seen in tipifarnib. This modification will lead to two different series of compounds depending on whether the D-ring is attached through a methylene group to either N-1 (**2**) or C-5 (**3**). Both series conserve the relative position of N-3 which is essential for coordinating with zinc (Fig. 1). Further structural refinement replaces the 2-quinolone of **2** with other heterocycles to yield compounds with an aromatic C-ring properly positioned to occupy the same hydrophobic pocket as in tipifarnib as represented by compound **4**.

The synthesis of the 6-iodoquinolone (**9**) and subsequent conversion to **3** is illustrated in Scheme 1. Thus



W=CH_2, CHOH, $CHNH_2$, CO; X=CH, N; Y=H, CN

Figure 1. Modifications of tipifarnib (**1**) lead to novel inhibitors of FTase **2**, **3**, and **4**.

Keywords: Tipifarnib; Zarnestra; R115777; Farnesyltransferase inhibitors; Anticancer.
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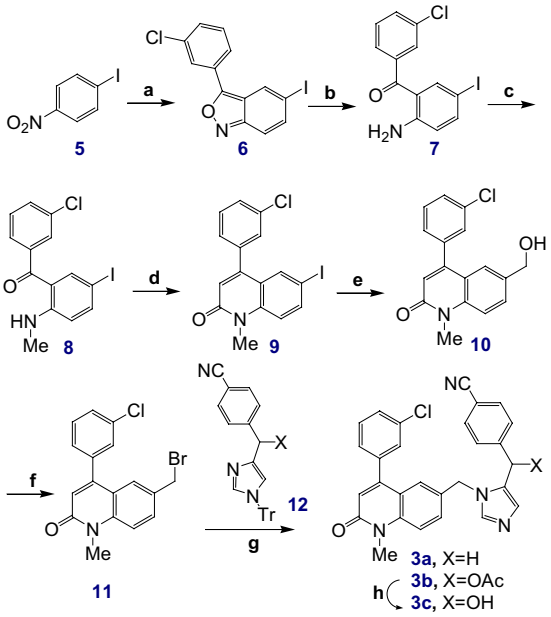
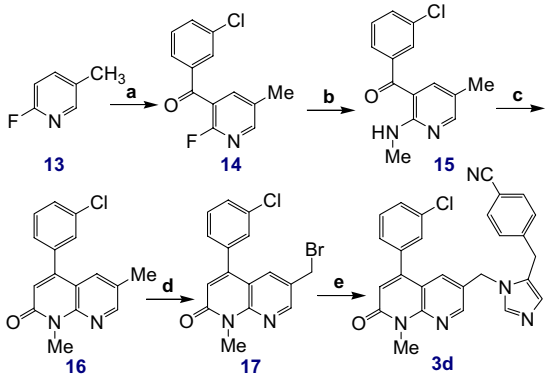


Scheme 1. Reagents and conditions: (a) 3-chlorobenzonitrile, NaOH, MeOH, 0 °C to rt, 2 days, 93%; (b) Fe, AcOH, rt, 2 h, 49%; (c) Me_2SO_4, *n*-Bu_4NBr, THF, 60 °C, 3.5 h, 86%; (d) (i) Ac_2O, toluene, reflux, 21 h; (ii) NaOH, EtOH/H_2O, reflux, 1.5 h 96%; (e) (i) *iso*-PrMgBr, THF, −25 °C, 50 min, then *N*-formylmorpholine, rt, overnight, 80%; (ii) $NaBH_4$, MeOH, −78 °C to rt, overnight, 87%; (f) PBr_3, LiBr, DMF 0 °C to rt, 2 h, 96%; (g) (i) AcOEt, 55 °C, 4 days; (ii) MeOH, reflux, 2 h, 42–46%; (h) LiOH, THF/H_2O, rt, overnight, 100%.

4-iodonitrobenzene (**5**) was reacted with 3-chlorophenylacetonitrile in the presence of NaOH in methanol[6] to produce benzisoxazole **6** (93% yield), which was reduced with iron powder in acetic acid to give aminobenzophenone **7** in 49% yield.[7] Methylation of **7** with dimethyl sulfate utilizing conditions of Mouzin et al.[8] provided *N*-methylamine **8** in 86% yield. Compound **8** underwent acetylation and base-catalyzed cyclization to furnish the quinolone (**9**) in 96% yield. Formation of alcohol **10** was accomplished by an iodine–magnesium exchange reaction of **9** with magnesium isopropylmagnesium bromide.[9] The reaction of the resulting anion with *N*-formylmorpholine and subsequent reduction of the aldehyde with sodium borohydride gave **10** in 70% yield. Reaction of **10** with PBr_3 produced bromide **11** (96%). The desired compounds **3a** and **b** were prepared in 42–46% yield by regioselectively alkylating tritylimidazole **12**[10] with bromide **11** using the reaction conditions developed by Anthony et al.[11]

Preparation of the bioisosteric 2-naphthyridone analog **3d** is shown in Scheme 2. 2-Fluoropyridine **13** was *ortho*-lithiated and reacted with 3-chlorobenzaldehyde. The alcohol was then oxidized with MnO_2 to form ketone **14** in 66% yield. Conversion of the fluoroketone (**14**) to naphthyridone **16** was achieved through nucleophilic displacement of the fluorine by methylamine (93% yield). Condensation of the resulting aminoketone (**15**) with *tert*-butyl acetate in the presence of LDA followed by thermal cyclization gave **16** in 84% yield. NBS bromination of methyl-naphthyridone **16** produced a mixture of dibromo and monobromo compounds, but



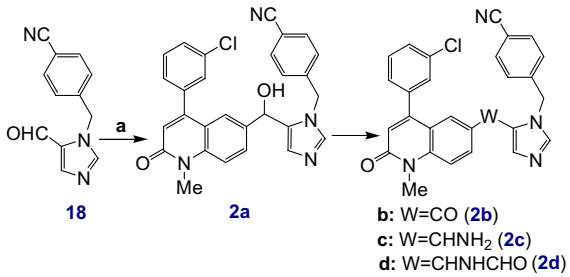
Scheme 2. Reagents and conditions: (a) (i) LDA, THF, −78 °C, 2 h, then 3-chlorobenzaldehyde, rt, overnight, 66%; (ii) MnO_2, dioxane, reflux, 1 h, 94%; (b) $MeNH_2$, EtOH, rt, 5 h, 93%; (c) (i) $AcOBu^t$, LDA, THF, −78 °C to rt, overnight; (ii) toluene, reflux, 1 h, 84%; (d) NBS, AIBN, CCl_4, reflux, 5 h, 44%; (e) **12**, AcOEt, 55 °C, 5 days, then MeOH, reflux, 2 h, 55%.

provided the desired monobromide (**17**) in a respectable yield (44%). Alkylation of **12** with bromide **17** using the same conditions used for **3a** furnished the desired naphthyridone **3d** in 55% yield.

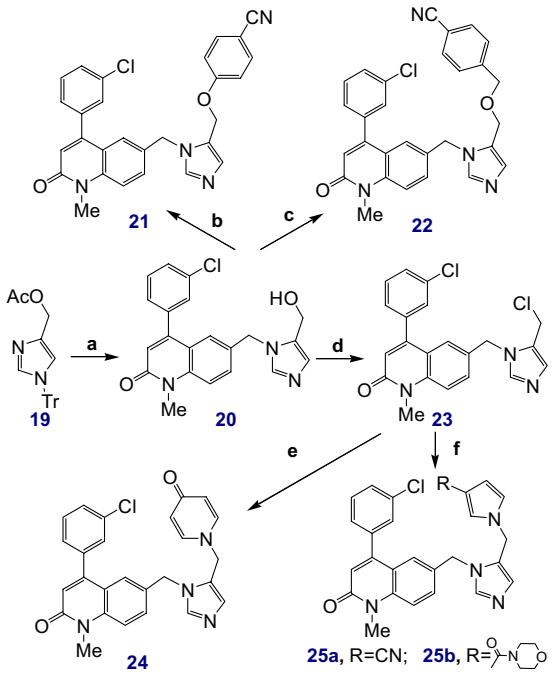
The bioisosteres of **3** (**2b** and **c**) were prepared as described in Scheme 3. Addition of the Grignard reagent of **9** to aldehyde **18**[4] provided alcohol **2a**[12] (38% yield). Our attempt to eliminate the chiral center by deoxygenating alcohol **2a** utilizing the Barton–McCombie protocol[10] was unsuccessful. Thus **2a** was converted to ketone **b**, amine **c**, and formamide **2d** as indicated in Scheme 3.

Syntheses of analogs with variable D-rings and linker lengths connecting the D-rings were executed as outlined in Scheme 4. Alkylation of **19**[13] with bromide **11** as described above followed by hydrolysis provided alcohol **20**, which was converted to **21**, **22**, and **25a**,**b** as described in Scheme 4. Compounds **26** and **27** (Table 1) were prepared from bromide **11** using similar methods described in the literature.[4,18]

Compounds with modified AB- and C-rings of **2** were prepared as depicted in Schemes 5 and 6. Thus aldehyde **28** underwent the Wadsworth–Emmons reaction to afford acrylonitrile **29** (100% yield), which was converted



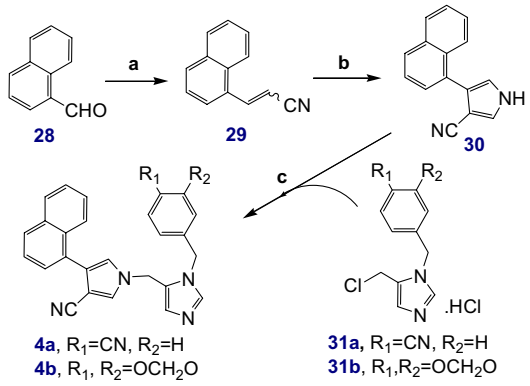
Scheme 3. Reagents and conditions: (a) **9**, *iso*-PrMgBr, THF, −25 °C, 30 min, then **18**, rt, overnight, 38%; (b) MnO_2, dioxane, reflux, 1 h, 80%; (c) (i) $SOCl_2$, CH_2Cl_2, rt, 2 h; (ii) NH_4OH, THF/H_2O, rt, 1 h, 32%; (d) $HCONH_2$, AcOH, reflux, 5 h, 100%.



Scheme 4. Reagents and conditions: (a) (i) **11**, AcOEt, 60 °C, overnight; (ii) MeOH, reflux, 1 h; (iii) LiOH, THF/H_2O, rt, 14 h, 57%; (b) 4-fluorobenzonitrile, NaH, DME, rt, overnight, 80%; (c) 4-cyanobenzyl bromide, NaH, DME, rt, 3 h, 40%; (d) $SOCl_2$, rt, 1 h, 100%; (e) 4-hydroxypyridine, NaH, DME, rt, 14 h, 79%; (f) the pyrroles,[14] NaH, THF, rt, overnight, 36–37%.

to pyrrole **30** in 75% yield by treatment with tosylmethyl isocyanide (TosMIC) utilizing the reaction conditions developed by Pavri and Trudell.[15] Displacement of chloride **31**[16] with pyrrole **30** furnished the desired compounds **4a** and **b** in 75–88% yield.

Formylation of phenol **32** by the Duff reaction afforded **33** (8% yield). Phenol **33** was converted to the triflate (87% yield), which then underwent the Suzuki coupling with 1-naphthylboronic acid to form aldehyde **34** in 46% yield. Transformation of aldehyde **34** to nitrile **35** was achieved in 93% through dehydration of the oxime intermediate. Reaction of **35** with DMF dimethyl acetal and subsequent reduction of the nitro group produced indole

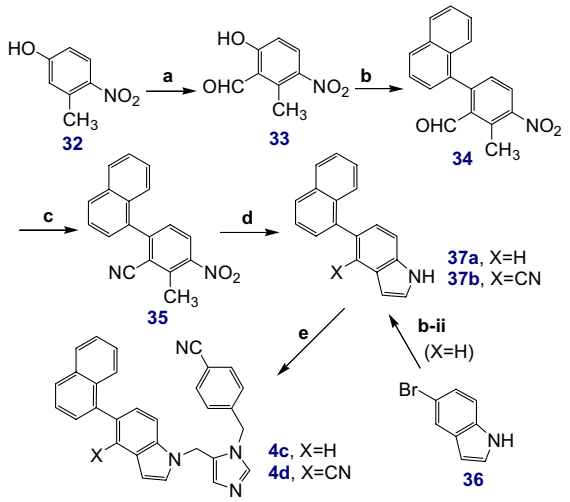


Scheme 5. Reagents and conditions: (a) $CNCH_2PO(OEt)_2$, DBU, CH_3CN, rt, overnight, 100%; (b) TosMIC, *t*-KOBu, THF, reflux, 2 h, 75%; (c) NaH, THF, rt, 5 h, 75–88%.

37b in 59% yield. Descyano compound **37a** was prepared in 37% yield by Suzuki coupling of 5-bromoindole (**36**) with 1-naphthylboronic acid. *N*-Alkylation of indoles **37** with chloride **31a** yielded the **4c** and **d** in 20–22% yield.

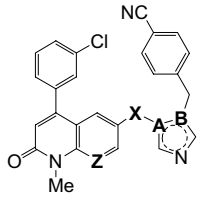
The compounds were evaluated for their activities against bovine Ftase[17] and cellular Ras processing in H-ras transformed cells.[17] Selectivity against geranylgeranyl transferase (GGTase I), a closely related enzyme that is responsible for prenylating the majority of the prenylated proteins, was also tested.[18] Because FTIs have been shown to be sufficient for achieving growth inhibition in tumors and that this effect is not enhanced with co-application of GGTase inhibitors, selective FTIs are sought to avoid potential undesirable toxicity.[19] These results are summarized in Tables 1–3.

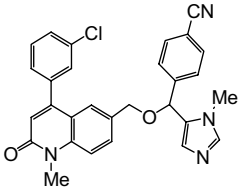
Compounds **2a–d** that have the D-ring attached to the N-1 of imidazole are potent FTase inhibitors, with IC_{50} values ranging from 2.1 nM to 29 nM (Table 1). Note that the chloro group in D ring has been replaced by a cyano group in the new series because the cyano group has been shown to dramatically boost the activity, particularly in the Ras processing assay.[4b,11,13,18] In the X-ray structure[4a] and the model (Fig. 2), the D-ring cyano group fits into a small pocket and accepts H-bonds from the main chain NH of both Tyr361 and Phe360 of the β-subunit. The most potent analogs are the amine (**2c**) and corresponding formamide **d**. Alcohol **2a** is only slightly less active as compared with amine **2c**. Oxidation of the alcohol (**2a**) to the ketone (**2b**) resulted in a 6-fold drop in activity. Bioisostere **3a**, in which the D-ring is attached to C-5, versus N-1 in **2**, displays an IC_{50} of 7.2 nM, which is 2- and 11-fold higher respectively compared to **2b** and tipifarnib (racemic, same below). The activity is markedly impaired when the linker



Scheme 6. Reagents and conditions: (a) hexamethylenetetramine, TFA, reflux, 60 h, 8%; (b) (i) Tf_2O, Et_3N, CH_2Cl_2, rt, overnight, 87%; (ii) 1-naphthylboronic acid, $Pd(PPh_3)_4$, $NaHCO_3$, EtOH/toluene, reflux, 3 h, 37–46%; (c) (i) NH_2OH, NaOAc, EtOH, reflux, overnight; (ii) Ac_2O, reflux, 4 h, 93%; (d) (i) DMF–DMA, DMF, 100 °C, 3 h; (ii) Fe, AcOH/EtOH, reflux, 0.5 h, 59%; (e) **31a**, NaH, DMF, rt, overnight, 20–22%.

Table 1. Activity of 2-quinolone farnesyltransferase inhibitors



Compd	X	Z	A	B	IC_{50} (nM)		EC_{50} (nM) Ras[c] processing
					FT[a]	GGT[b]	
2a		CH	C	N	4.7	17,000	32%[d]
2b		CH	C	N	29	<10,000	30%[d]
2c		CH	C	N	3.8	22,000	42%[d]
2d		CH	C	N	2.1	>10,000	28%[d]
3a		CH	N	C	7.2	>10,000	57%[d]
3d		N	N	C	10	4000	39%[d]
26		CH	C	N	89	nt[e]	nt[e]
27					80	nt[e]	nt[e]
1	Tipifarnib[f]				0.65	1100	1.6
	Lonafarnib[f,20]				8.3	>10,000	100

[a] Bovine farnesyltransferase.
[b] Bovine geranylgeranyltransferase.
[c] In H-ras NIH-3T3 cells.
[d] Inhibition at 100 nM.
[e] Not tested.
[f] Data from racemic mixtures.

between the AB-ring and the imidazole is extended to three atoms (**26**–**27**).

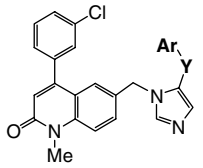
All compounds in Table 1 demonstrate excellent selectivity against GGTase I[18] with IC_{50} values equal to or greater than 4 μM. However, none of the compounds showed good cellular activity in the Ras processing assay, with the best one being **3a**, which induced 57% inhibition of the Ras processing at 100 nM. Addition of a nitrogen atom to the B-ring (**3d**) has little effect on either enzymatic or cellular activities.

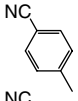
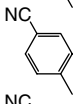
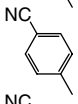
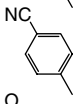
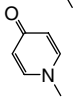
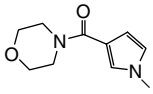
In an effort to take advantage of the easily available alcohol **20**, several compounds with various D-rings and linkers connecting the D-ring were synthesized. Pyridone **24** and amide **25b** were prepared with the hope that the cyano group in **3a** is replaceable by a carbonyl group. Unfortunately, replacing the cyanophenyl group in **3a** with 4-pyridone (**24**), 3-cyanopyrrole (**25a**), or 3-morpholinylcarbonyl-pyrrole (**25b**) all resulted in significant loss in activity, with IC_{50} values ranging from 560 nM to over 1000 nM (Table 2). The optimal linker between the cyanophenyl group and the imidazole is the methyl group. Activity of the compounds with other linkers, including substituted methyl (**3b** and **c**), two-atom linker (**21**) and three-atom linker (**22**), are markedly impaired.

With the optimal D-ring seemingly being the cyanophenyl group, we focused our attention on modification of the 2-quinolone part of compound **2**. There are two important structural features of this part of the molecule in its interaction with FTase. First, it must have an aromatic D-ring which increases the binding affinity through interaction with a hydrophobic pocket. Second, the 'heterocycle' containing either a carbonyl group as in **1** or a cyano group provides a significant potency enhancement by binding to the main chain loop consisting of residues Asp359, Phe360, and Tyr361 through a combination of electrostatic and van der Waals interactions, although the exact role is not clear.[4]

Our goal was to design moieties that can be alkylated by the easily available chloride **33**. Pyrrole **32**[21] seemed to be the ideal candidate for this purpose. Compound **4a** turned out to be a very potent inhibitor of FTase with an IC_{50} of 0.58 nM (Table 3). It also potently inhibits

Table 2. Activity of 2-quinolone farnesyltransferase inhibitors



Compd	Ar	Y	IC_{50} (nM)		EC_{50} (nM) Ras[c] processing
			FT[a]	GGT[b]	
3a			4.7	17,000	57%[d]
3b			>1000	>1000	nt[e]
3c			44	>10,000	nt[e]
21			>1000	nt[e]	nt[e]
22			>1000	nt[e]	nt[e]
24			>1000	nt[e]	nt[e]
25a			560	nt[e]	nt[e]
25b			>1000	nt[e]	nt[e]

[a] Bovine farnesyltransferase.
[b] Bovine geranylgeranyltransferase.
[c] In H-ras NIH-3T3 cells.
[d] Inhibition at 100 nM.
[e] Not tested.

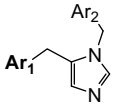
cellular Ras processing displaying an EC_{50} of 34 nM. Despite being more active than the 2-quinolone analogs against GGTase, the selectivity is still 240-fold. Substituting **31b** for **31a** resulted in compound **4b** that shows a 10-fold drop in potency, further confirming the cyanophenyl group as the optimal D-ring in this series.

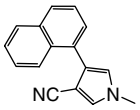
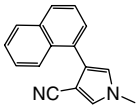
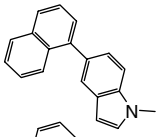
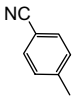
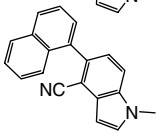
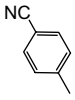
Further modification led to the discovery of the most potent compounds in this series. Indole analog **4c** shows subnanomolar activity against FTase. More importantly, **4c** demonstrates dramatically improved cellular potency with an EC_{50} of 5.7 nM. The activity of the corresponding cyano-containing analog (**4d**) improves 6-fold as compared with **4c**. It displays an IC_{50} of 0.15 nM, which is about 4-fold more active than tipifarnib. **4d** is nearly equipotent to tipifarnib as measured in Ras processing assay, with an EC_{50} of 2.1–1.6 nM for tipifarnib.

Stereoviews of overlays of models of **3a** and **4d**, which were modeled based on the crystal structure of a close chemical analog[18] and the X-ray crystal structure of tipifarnib (**1**)[4] are shown in Figure 2. The models of **3a** and **4d** superimpose very well with tipifarnib in which the methyl imidazole is interacting closely with the active site Zn^{2+} and the imidazole nitrogen. The A-ring extends out over the loop of residues Asp359-Phe360 forming good van der Waals contact with the loop. The C-ring is stacked against Trp106 and Trp102 and the D-ring stacks along the hydroxy farnesyl pyrophosphate (HFP). The C- and D-rings also stack together forming a strong π–π interaction.

In summary, beginning with the structure of tipifarnib, a series of inhibitors of FTase have been synthesized by transposition of the D-ring to the imidazole and subsequent modification of the 2-quinolone motif. The new 2-quinolone-containing compounds demonstrate single-digit nanomolar activity against FTase and are highly selective against GGTase with IC_{50} values of over 10 μM in most cases. Although inferior to tipifarnib with respect to cellular activity, the easier and more convergent synthesis allows for preparation of a large

Table 3. Activity of pyrole and indole farnesyltransferase inhibitors



Compd	Ar_1	Ar_2	IC_{50} (nM)		EC_{50} (nM) Ras[c] processing
			FT[a]	GGT[b]	
4a			0.58	140	34
4b			6.1	520	68%[d]
4c			0.93	270	5.7
4d			0.15	110	2.1

[a] Bovine farnesyltransferase.
[b] Bovine geranylgeranyltransferase.
[c] In H-ras NIH-3T3 cells.
[d] Inhibition at 1000 nM.

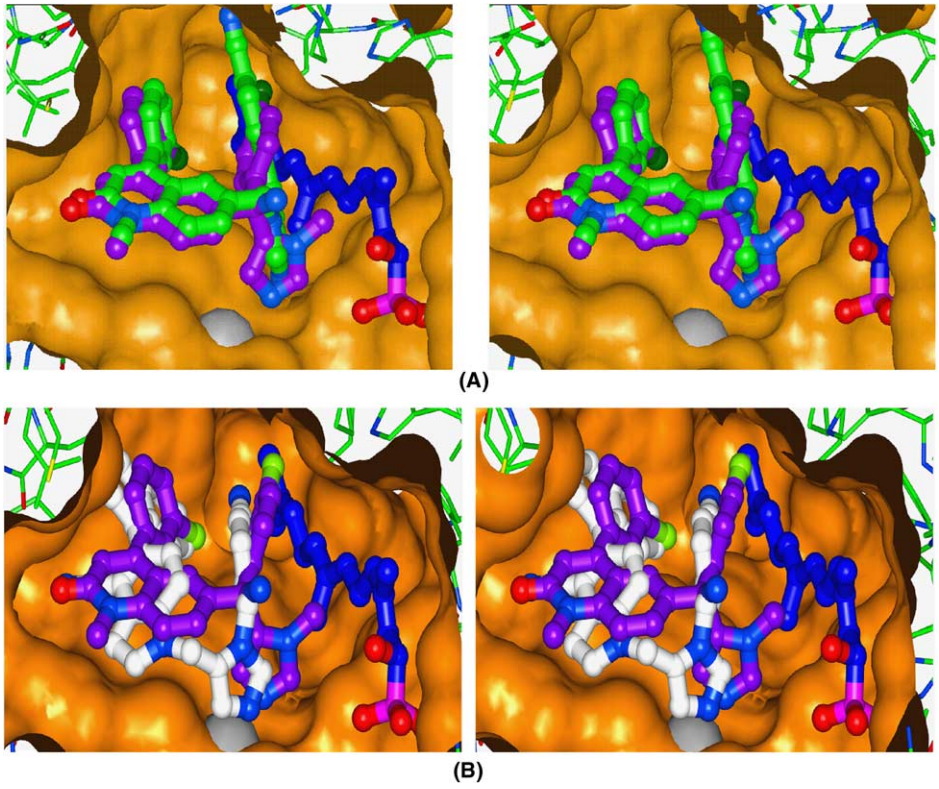


Figure 2. Stereoviews of overlays of models of (A) compound **3a** (in green) and (B) compound **4d** (in white) over the X-ray crystal structure of tipifarnib (**1**)[4] (in purple) in complex with FTase in the active site. Zn^{+2} is shown in grey and hydroxy farnesylpyrophosphate in blue.

number of achiral analogs including 4-quinolones and their bioisosteres,[4] pyrrole, indole, and other heterocycles, many of which would be difficult or impossible to make in the original tertiary carbon-based tipifarnib series. One such example is the indole analog **4d** as discussed in this paper, which shows superior in vitro

enzymatic activity to tipifarnib. These encouraging results warrant further efforts to optimize the properties of the molecules in this series.

References and notes

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