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Second Generation Analogues of the Cancer Drug Clinical Candidate Tipifarnib for Anti-Chagas Disease Drug Discovery

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We previously reported that the cancer drug clinical candidate tipifarnib kills the causative agent of Chagas disease, *Trypanosoma cruzi*, by blocking ergosterol biosynthesis at the level of inhibition of lanosterol 14α-demethylase. Tipifarnib is an inhibitor of human protein farnesyltransferase. We synthesized tipifarnib analogues that no longer bind to protein farnesyltransferase and display increased potency for killing parasites. This was achieved in a structure-guided fashion by changing the substituents attached to the phenyl group at the 4-position of the quinoline ring of tipifarnib and by replacing the amino group by OMe. Several compounds that kill *Trypanosoma cruzi* at subnanomolar concentrations and are devoid of protein farnesyltransferase inhibition were discovered. The compounds are shown to be advantageous over other lanosterol 14α-demethylase inhibitors in that they show only modest potency for inhibition of human cytochrome P450 (3A4). Since tipifarnib displays high oral bioavailability and acceptable pharmacokinetic properties, the newly discovered tipifarnib analogues are ideal leads for the development of drugs to treat Chagas disease.

Introduction

Chagas disease is caused by infection with the protozoan parasite, *Trypanosoma cruzi* (*T. cruzi*[a]). When not spread by poor hygiene, infection is the result of exposure to the blood or the feces of triatomine bugs, which live in the mud in substandard housing in an area ranging from the southern part of South America to the southern part of the United States. Once infected, individuals usually become a life-long host to the parasite because no existing therapy is completely effective in the chronic stage of the disease. Eight to eleven million people in Latin America are infected with *T cruzi*, and 30% of those can be expected to develop complications ranging from mild to terminal.[1] There is no effective treatment for Chagas disease at this time. The two drugs that have been used are the nitrofuran, nifurtimox, and the nitroimidazole, benznidazole. The toxicity of these drugs is linked to their mode of action, and treatment is unavoidably accompanied by multiple undesirable side effects. Of the more than 1200 new drugs discovered in the period from 1975 to 1997 only 4 were the result of a directed research and development effort by the pharmaceutical industry to treat a human tropical disease, and 1 of those 4 (nifurtimox) is no longer in widespread use.[2]

One of the guiding philosophies in our collaborative research effort for antiparasite drug discovery is the concept that we can "piggyback" on the large research efforts underway in the pharmaceutical industry.[3] There is extensive medicinal chemistry and pharmacology data on inhibitors of protein farnesyltransferase since they were developed as anticancer agents.[4] Our thinking at the time was that we might find a human protein farnesyltransferase inhibitor that also had high affinity for the *T. cruzi* orthologue. Thus, we previously investigated known protein farnesyltransferase inhibitors against a number of parasites including *T. cruzi*, and one compound that was highly potent at killing *T. cruzi* amastigotes (the clinically relevant parasite life cycle stage that grows in mammalian host cells) in an in vitro assay[5] is tipifarnib (compound **1**, Figure 1).[6] This compound is a candidate anticancer drug being developed by Johnson and Johnson Pharmaceuticals.[7] Our subsequent studies showed, surprisingly, that compound **1** kills *T. cruzi* not by blocking protein farnesylation but by disrupting sterol biosynthesis by inhibition of lanosterol 14α-demethylase (Tc-L14DM).[6] *T. cruzi* amastigotes use ergosterol as a critical component of their membranes and cannot use host cell derived cholesterol. Since **1** shows a high degree of oral bioavailability, has ideal pharmacokinetic properties, and is well tolerated in humans,[7] we considered **1** as an outstanding lead for the development of anti-Chagas disease drugs.

Our goal shifted to designing analogues of **1** that no longer bind to human protein farnesyltransferase and remain as highly potent inhibitors of Tc-L14DM and as cytotoxic agents for *T. cruzi* amastigotes. To this end we used the X-ray structure of **1** bound to mammalian protein farnesyltransferase[8] and a homology model of Tc-L14DM with **1** docked into

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[a] Abbreviations: Tc-14DM, lanosterol 14α-demethylase from *T. cruzi*; *T. cruzi*, *Trypanosoma cruzi*; IC_{50}, concentration of inhibitor resulting in 50% enzyme inhibition; EC_{50}, concentration of inhibitor resulting in 50% parasite growth inhibition; ESI-MS, electrospray ionization mass spectrometry.

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the active site[6] to develop novel tipifarnib analogues with the desired properties. Our model is shown in Figure 2 with bound **1** shown as a double-radii van der Waals surface. In this depiction, if the active site residues are in van der Waals contact with **1**, the stick representations of these residues approximately sit on the doubled van der Waals surface of the inhibitor. It can be seen from Figure 1 that **1** fills the active site of Tc-L4DM well with the imidazole nitrogen of **1** coordinated to the heme iron. Our modeling led to compound **2** (Figure 1),[9] which is essentially devoid of mammalian protein farnesyltransferase inhibition ($IC_{50} > 5000$ nM versus ~1 nM for **1**) and is about 10-fold more potent at killing *T. cruzi* amastigotes than **1** ($EC_{50} = 0.6$ nM versus 4 nM for **1**). Modeling suggests that the extra methyl group on the 3-chlorophenyl ring of **2** clashes with the wall of the active site of protein farnesyltransferase but is tolerated in the active site of Tc-L14M. Also, the amino group of **1** is involved in a hydrogen-bonding network in the active site of protein farnesyltransferase but not in the active site of Tc-L14M. Although **2** is one of the most potent anti-*T. cruzi* compounds reported to date, subsequent studies showed that there is hindered rotation about the bond connecting the 3-chlorophenyl group and the quinolone ring presumably because of a clash between the ortho methyl group and the vinylic proton of the

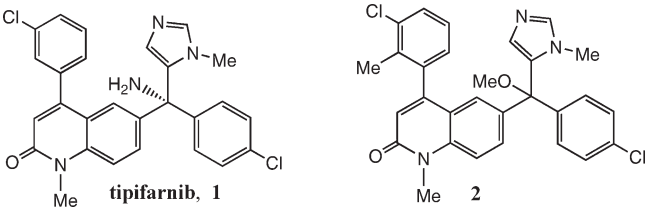


Figure 1

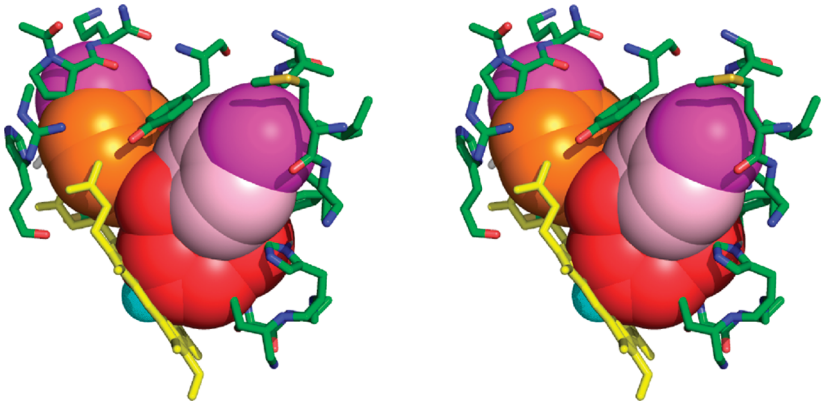
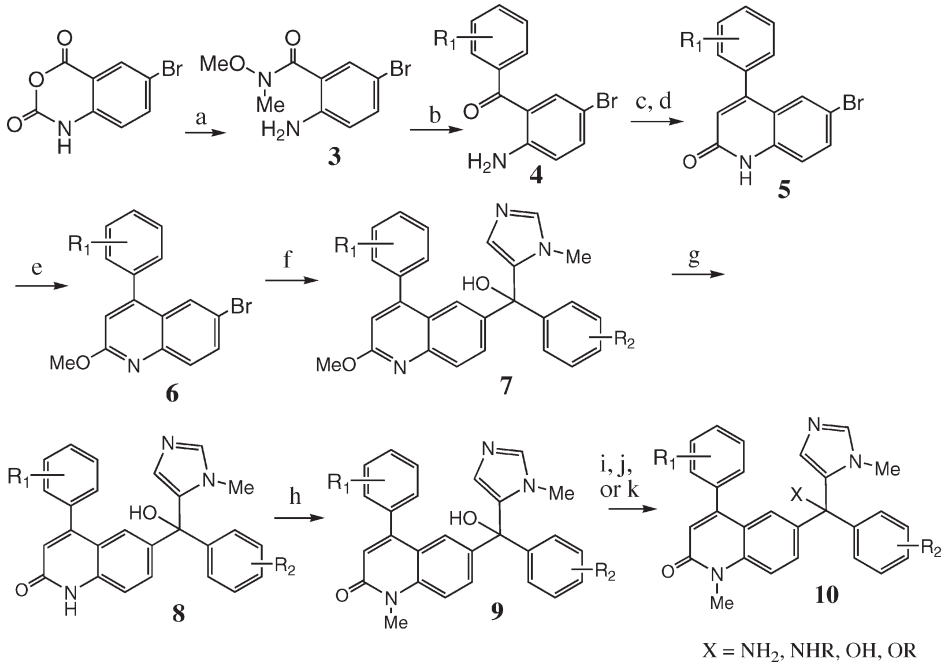


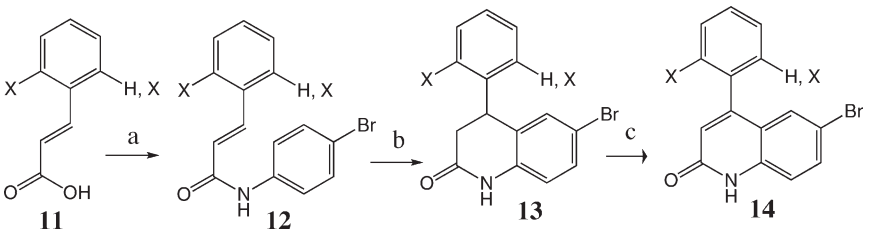
Figure 2. Stereodiagram of tipifarnib (compound **1**) docked into the active site of Tc-L14DM. The 3-chlorophenyl group is shown in orange with its Cl in magenta. The 4-chlorophenyl group is shown in light pink with its Cl in magenta, and the rest of the inhibitor is shown in red. The heme is in yellow with the heme iron in cyan. The active site protein residues are shown as sticks. The inhibitor is displayed as its doubled-radii van der Waals surface.

Scheme 1. Synthesis of Tipifarnib Analogues from 5-Bromoisatoic Anhydride[a]



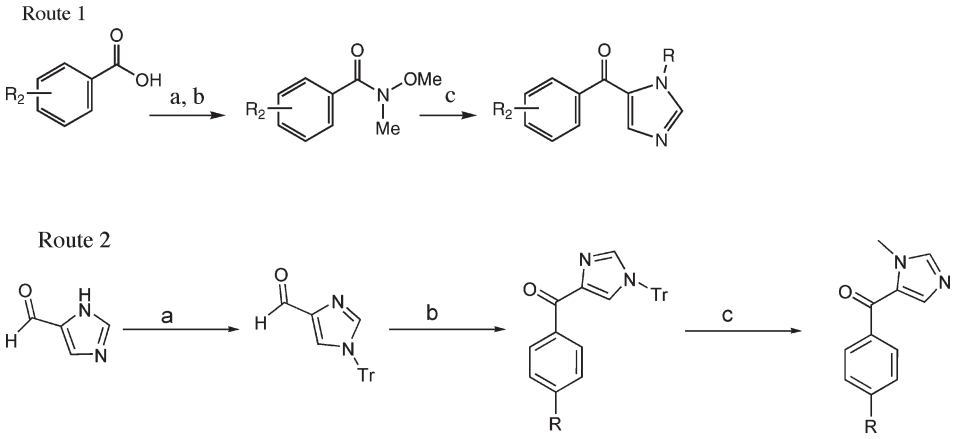
[a] (a) CH_3ONHCH_3 HCl, pyridine, CH_2Cl_2; (b) R_1PhBr (2 equiv), *n*-BuLi (2 equiv), THF; (c) Ac_2O, toluene, reflux; (d) *t*-BuOK, 1,2-dimethoxyethane; (e) (i) BF_4OMe_3, CH_2Cl_2; (ii) NaOH; (f) (i) *n*-BuLi, THF, −78 °C; (ii) *N*(Me)imidazole-CO-PhenylR_2; (g) 6 N HCl, THF, reflux; (h) CH_3I, NaOH, BTEAC, THF; (i) $SOCl_2$, neat, 12 h; (j) NH_3 (or CH_3NH_2), THF, room temp; (k) tosic acid, 1equiv + cat., MeOH, reflux.

Scheme 2. Synthesis of Tipifarnib Analogues with R_1 = Ortho Halogens[a]



[a] (a) $SOCl_2$, (neat), reflux, 6 h, then 4-bromoaniline, DIEA (1.5 equiv), CH_2Cl_2, 0 °C; (b) H_2SO_4 (conc), 105 °C; (c) DDQ, dioxane, reflux.

Scheme 3. Synthesis of Substituted 5-Benzoyl-N_1-alkylimidazoles[a]



[a] Route 1: (a) $SOCl_2$, neat; (b) CH_3ONHCH_3, pyridine, CH_2Cl_2; (c) *N*-alkylimidazole, (i) *n*-BuLi, THF −78°C; (ii) Et_3SiCl, −78 °C; (iii) *n*-BuLi, THF, −78 °C. Route 2: (a) TrCl, Et_3N, CH_3CN; (b) (i) Mg, I_2, ether, RC_6H_4Br, room temp to reflux; (ii) MnO_2, dioxane, reflux; (c) MeOTf, CH_2Cl_2.

quinolone ring. Thus, **2** is a mixture of rotamers with the ortho methyl group either above or below the plane of the quinolone ring. This is evident by the ^{1}H NMR spectrum of **2**, which shows a doubling of resonance peaks (see Supporting Information). Furthermore, the doubling does not collapse even when the temperature is raised to 65 °C (not shown), indicating that the rotamers are very stable at physiological temperature. Compound **2** also contains a chiral center, so it is a mixture of 4 stable isomers, and this greatly diminishes its potential as a drug candidate. This is because the different isomers can be expected to have different affinities for Tc-L14DM, and it is possible that only 1 of the 4 isomers would be biologically active. Also, the pharmacokinetic and toxicity profiles of all 4 compounds would have to be separately investigated to go forward with drug candidate selection. We thus went on to design new analogues that either lack a 2-substitutent on the 3-chlorophenyl ring or have a C_2-symmetric ring in order to avoid rotamer formation. In this study we reported the result of these two approaches. We also carried out additional structure−activity studies of these tipifarnib analogues.

Chemistry

Scheme 1 shows the route used to synthesize some of the compounds reported in this study. Commercially available 5-bromoisatoic anhydride is converted to Weinreb amide **3**, which reacts with a variety of phenyllithiums (formed in situ from the phenyl halide using 2 equiv of *n*-BuLi, 1 equiv needed to deprotonate the NH) to give ketone **4**. The order of addition of reagents is important to avoid lithium−bromide exchange between *n*-BuLi and the aryl−Br bond present in **3**. Acetylation of the amino group followed by intramolecular ring closure using base gives quinolone **5**. Conversion of **5** to the set of compounds **10** (Scheme 1) was carried out as described in our earlier study.[9]

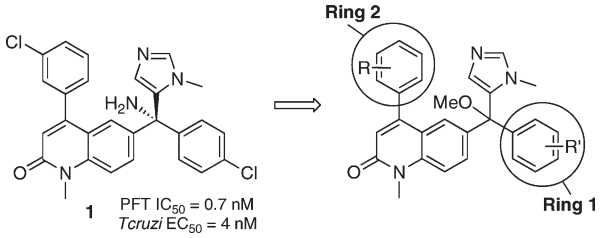
We were also interested in analogues in which R_1 is a 2-halide or a 2,6-dihalide. The use of 2-chlorophenyllithium is problematic because of benzyne formation. We formed 2,6-difluorophenyllithium but found that it reacted slugglishly with Weinreb amide **3** and also formed benzyne in the process. Thus, we developed Scheme 2 for the preparation of the additional analogues. Commercially available halogenated cinnamic acid **11** was converted to the acid chloride and then reacted with 4-bromoaniline to give amide **12**. Intramolecular Friedel−Crafts alkylation proceeded smoothly with concentrated H_2SO_4 to give lactam **13**. Conversion to the quinolone was accomplished by oxidation of **13** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to give **14**. The latter was converted to the desired tipifarnib analogues by using steps from Scheme 1.

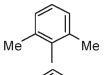
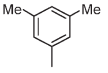
Scheme 3 shows two routes to make the methanones needed for step f in Scheme 1.

Results and Discussion

We synthesized a variety of analogues of **1** and tested them for their ability to kill *T. cruzi* amastigotes growing in mammalian host cells (3T3 cells). As noted above, adding a Me group at the 2-position of the 3-chlorophenyl ring of **1** and replacing the NH_2 with OMe led to **2**, which is devoid of protein farnesyltransferase inhibition and is ~10-fold more potent at killing parasites compared to **1**. In an attempt to make analogues that do not exist as a pair of stable rotamers (see above), we synthesized analogues of **2** that have changes to the 3-chloro-2-methylphenyl ring. Values of EC_{50} for killing

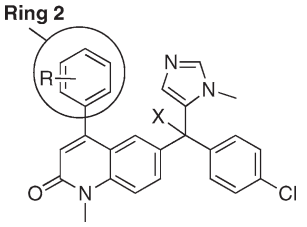
Table 1. Tipifarnib Analogues with Ring 1 and Ring 2 Modifications



Compound	Ring 2	Ring 1	X	Rat PFT IC_{50}	*Tcruzi* EC_{50}
1			$-NH_2$	0.7	4
2			-OMe	>5000	0.6
3			-OMe	65	3.1
4			-OMe	3,260	0.7
5			-OMe	> 5,000	0.8
6			-OMe	343	1.1
7			-OMe	85	1.2
8			-OMe	1,320	12
9			-OMe	1,870	0.8
10			-OMe	329.8	0.8
11			-OMe	6035.0	0.82
12			-OMe	991	0.5
13			-OMe	410	2.0
14			-OMe	> 10,000	1.8
15			-OMe	>10,000	3.21
16			-OMe	>10,000	0.31
17			-OMe	470	1.4
18			-OMe	2,300	2.2
posaconazole				not determined	0.3

T. cruzi amastigotes are listed in Table 1. Compound **3** lacks the ortho methyl group but retains the NH_2 to OMe substitution. The compound is 100-fold less potent on protein farnesyltransferase compared to **1** and retains low nanomolar potency on *T. cruzi*. This result shows that the ortho methyl group and the OMe group of **2** act together to reduce the binding to protein farnesyltransferase. We also made compound **4**, which like **2** has the ortho methyl group and the NH_2-to-OMe change but lacks the 3-chloro group. The properties are very similar to those of **2**, showing that the 3-chloro group

Table 2. Tipifarnib Analogues with X Group Modifications



Compound	Ring 2	Ring 1	X	Rat PFT IC_{50}	Tcruzi EC_{50}
1			**NH2**	**0.7**	**4**
19			**OH**	**8**	**17**
2			**-OMe**	**>5000**	**0.6**
20			**-OH**	**796**	**112**
21			**-OEt**	**>10,000**	**27**
22			**-OPr**	**>5000**	**69**
23			**-NHMe**	**957**	**5**

is not required for potent inhibition of *T. cruzi* growth and that the ortho methyl group is important for reducing binding to protein farnesyltransferase. However, compound **4** still exists as a pair of stable rotamers, so it does not constitute the solution that we require. The same picture emerges with compound **5**, which has an ortho CF_3 instead of Me.

We made compounds that lack the ortho methyl group (and thus the rotamer problem) but contain replacements for 3-chloro group hoping to reduce binding to protein farnesyltransferase while retaining potency on *T. cruzi*. Replacing Cl with F, Me, or CF_3 reduced affinity to protein farnesyltransferase by ~100- to 2000-fold while retaining good potency on *T. cruzi* (see **6**−**8**, Table 1). This result shows that the Cl substituent gives an optimal fit in the active site of protein farnesyltransferase. This is apparent from the X-ray structure of **1** bound to protein farnesyltransferase.

Next we made compound **9**, which contains an ortho F instead of the ortho Me, hoping that the smaller F would not sterically interfere with the vinylic hydrogen. Compound **9** is similar to **2** in that it binds much more weakly to protein farnesyltransferase compared to **1** and is superior to **1** in its ability to kill *T. cruzi*. However, **9** was found to exist as stable rotamers that are distinguished in the ^{1}H NMR spectrum (not shown). The NMR peaks coalesce when the temperature is raised to 75 °C (not shown); however, the rotamers persist at physiological temperature.

We made compound **10**, which lacks an ortho substituent (so no rotamers are possible) and also lacks the 3-chloro group, which is important for binding to protein farnesyltransferase. This compound ranks among the most potent of our compounds against *T. cruzi* and displays an intermediate loss in affinity for protein farnesyltransferase (~500-fold).

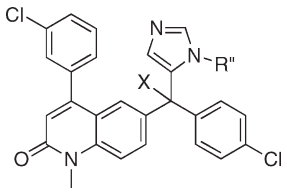
Compounds **11**−**13** lack ortho substituents and contain a single non-hydrogen substituent at the para position. All 3 compounds show good potency for killing *T. cruzi* and a substantial loss of binding to protein farnesyltransferase, with **11** showing the largest loss.

We also reasoned that addition of a non-hydrogen group to the ortho position is acceptable if both ortho positions are substituted, since the two rotamers are chemically identical in this case. Compound **14** contains a 2,6-dimethylphenyl ring, and like the 2-methylphenyl-containing compound **2**, it is devoid of protein farnesyltransferase inhibition activity and displays good potency for killing parasites. Compounds **15** and **16** display similar properties as **14**. The 2,6-difluorophenyl compound **16** is the most potent in the series against *T. cruzi* with an EC_{50} of 0.3 nM. This compound is as potent as posaconazole against *T. cruzi* in our in vitro amastigote killing assay. These are the most potent anti-*T. cruzi* compounds that we are aware of.

Compound **17** contains a 3,5-dimethyphenyl group. It is highly potent against parasites and displays a ~600-fold reduction in affinity for protein farnesyltransferase compared to **1**. In our previous study we showed that the tipifarnib analogue with a β-naphthyl replacing the 4-chlorophenyl group of **1** displayed ~20-fold less affinity to protein farnesyltransferase compared to **1** and displayed an EC_{50} against *T. cruzi* of 45 nM. Given the lowering of EC_{50} and the loss of protein farnesyltransferase affinity when the amino group of **1** is replaced with OMe, we prepared compound **18**. Indeed this compound now is a very weak inhibitor of protein farnesyltransferase, and the EC_{50} for killing *T. cruzi* drops to 2 nM.

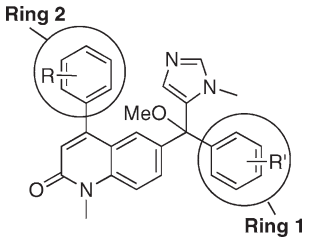
Table 2 shows the effect of a wider variation in substitution of the amino group of **1**. Replacing NH_2 with OH produces only a slight reduction in protein farnesyltransferase affinity. Presumably the OH group can still engage in the active site hydrogen bond network. Replacement of the NH_2 group with OMe, OEt, OPr, and NHMe has a much more dramatic effect. Modeling shows that the NH_2 group does not contact Tc-L14DM residues. It is quite likely that the improved

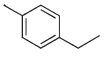
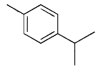
Table 3. Tipifarnib Analogues with Imidazole and X Group Modifications



Compound	Ring 2	Imidazole	X	Rat PFT IC_{50}	Tcruzi EC_{50}
1			-NH_2	0.7	4
24			-NH_2	28	118
25			-NHMe	66	100
26			-OMe	970	3
27			-OH	30	228

Table 4. Tipifarnib Analogues with Additional Ring 1 and Ring 2 Modifications



Compound	Ring 2	Ring 1	X	Tcruzi EC_{50}
2			-OMe	3
28			-OMe	3
29			-OMe	5
30			-OMe	10
31			-OMe	33
32			-OMe	320
33			-OMe	83

potency for killing *T. cruzi* when NH_2 is replaced with OMe is the result of better penetration of the more hydrophobic compound across host cell and parasite membranes. This was our motivation for preparing OEt, OPr and NHEt analogues. However, OMe remains as the best group in terms of EC_{50} values. We attempted to prepare the analogue containing $N(Me)_2$, but it was unstable presumably by breaking down in an S_N1 type reaction.

Table 3 shows data for compounds in which the imidazole *N*-Me is replaced with *N*-Et. Compound **26** is as potent against *T. cruzi* as the *N*-Me comparator, compound **3**, but is superior to **3** in that it binds ~1500-fold weaker to protein farnesyltransferase than **1**. Again, compounds with the OMe group are superior against *T. cruzi*. Compound **26** also lacks rotamers (no ortho substituent).

We made additional modifications to **1** to further test the validity of our homology model (Figure 2), and the results are summarized in Table 4. Modeling shows that the Cl of the 4-chlorophenyl group of **1** fills the active site well. It can be seen that replacement of this Cl with Me and CF_3 is tolerated, but the larger groups Et and *i*-Pr lead to less potent compounds against *T. cruzi*. Modeling also suggests that the Cl of

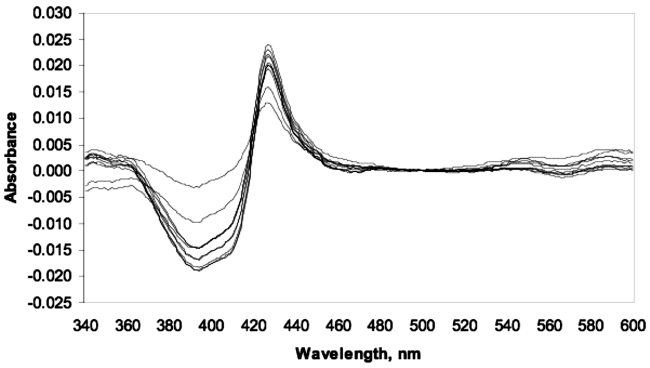


Figure 3. Difference spectra for the binding of **16** to recombinant Tc-14DM. Compound **16** was added at 200 nM to 2 μM with a Tc-14DM concentration of 1.4 μM.

Table 5. In Vitro Inhibition of Cytochrome P450 CYP3A4 Isoform

compd	IC_{50} (nM)	SEM (nM)
tipifarnib	4060	338.5
10	2345	847.5
11	923	212
12	1628	594
16	275	57
posaconazole	82	13
ketoconazole	11	0.5

the 3-chlorophenyl group fills the active site of Tc-L14DM well (Figure 2). Replacement of this Cl with larger groups, Ph and Bn, lead to a dramatic reduction in potency against *T. cruzi* parasites.

We tested our most potent anti-*T. cruzi* compound, **16**, for binding to recombinant Tc-L14DM in vitro. As shown in Figure 3, when 1.4 μM Tc-L14DM is titrated with 0.2−2 μM **16**, the visible absorption spectrum of the heme Soret band undergoes a spectral shift (as seen in the difference spectrum, Figure 3). The spectral features strongly suggest that the imidazole nitrogen of **16** coordinates directly to the heme iron. When the difference spectrum is quantified as a function of the equivalents of **16** added to the enzyme, it is found that the change in the spectrum ceases when 1 enzyme equivalent of inhibitor is added (not shown). This shows that the equilibrium dissociation constant for the enzyme−inhibitor complex, K_d, is much less than the enzyme concentration of 1.4 μM. From this result we can say that **16** binds tightly to Tc-L14DM, but we cannot determine the value of K_d precisely. It is for this reason that we prefer to rank our tipifarnib analogues based on values of EC_{50} for killing *T. cruzi* amastigotes (Tables 1−4). EC_{50} is the most important parameter for our drug discovery effort, since the compound not only has to bind to the target enzyme but also has to cross the host cell and parasite membranes.

As these tipifarnib analogues contain an imidazole ring, there is some concern that they may be potent inhibitors of hepatic cytochrome P450s. We tested some of our best compounds in the series for inhibition of the major drug metabolizing enzyme, cytochrome P450 CYP3A4 isoform, using an in vitro assay. The well established CYP3A4 inhibitor ketoconazole was a highly potent inhibitor with an IC_{50} measured at 11 nM (Table 5). We also tested posaconazole because it is being considered for clinical testing as an anti-Chagas disease drug. This compound was the next most potent inhibitor (IC_{50} = 82 nM). Tipifarnib was previously reported to be a weak inhibitor (>10000 nM) of P450 enzymes,[10] and we also observed relatively weak inhibition against CYP3A4 (IC_{50} = 4060 nM). The tipifarnib analogues designed in these studies had either approximately micromolar level IC_{50} values (**10**−**12**) or somewhat more potent activity as observed with **16** (Table 5). It is encouraging that the CYP3A4 inhibition by some of the tipifarnib analogues is considerably less than for the azole drugs. In future studies, it will be necessary to profile the compounds against additional liver microsomal enzymes to more fully establish their potential to cause drug−drug interactions.

Conclusions

In this continued study of analogues of the cancer drug clinical candidate tipifarnib, **1**, as inhibitors of Tc-L14DM and as anti-*T. cruzi* agents, we have developed 20 new compounds that display values of EC_{50} for killing *T. cruzi* of <10 nM and 7 new compounds that display values of EC_{50} < 1 nM. Many of these compounds either fail to bind to mammalian protein farnesyltransferase or bind with > 100-fold reduced affinity. In this study we have solved the rotamer problem that we encountered in our earlier study of tipifarnib analogues containing an ortho substituted phenyl group. The availability of a large set of highly potent anti-*T. cruzi* compounds sets the stage for the next steps of drug development which include pharmacokinetic, efficacy, and toxicology studies.

Experimental Section

Biological and Modeling Studies. Assays of rat protein farnesyltransferase to obtain the IC_{50} for inhibitors and of *T. cruzi* amastigote growth to obtain EC_{50} values for the inhibitors were carried out as described.[9] Binding of inhibitors to recombinant Tc-L14DM was carried out by difference optical spectroscopy as described.[11] Molecular modeling studies were carried out as described.[6] EC_{50} values reported in the tables have standard errors of less than 50% based on duplicate or triplicate independent determinations.

Inhibition of recombinant human CYP3A4 enzyme was determined using a commercial kit (CYP3A4/BFC high throughput inhibitor screening kit, GenTest, Inc.) following the manufacturer's instructions. The compounds were tested in serial dilutions in duplicate with the IC_{50} values calculated by nonlinear regression analysis using the Prism software (GraphPad Software, Inc.). The assay was performed twice, and average IC_{50} values are shown. Ketoconazole was the positive control and gave results within the expected range provided by the manufacturer.

Chemistry. Starting materials were purchased from Aldrich, Acros, Alfa-Aesar, EMD, Fisher, Lancaster, Mallinckrodt, TCI-America, or VWR and used without further purification unless otherwise specified. *N*-Methylimidazole (M50834) was purchased from Sigma-Aldrich and distilled at reduced pressure (10 mmHg, bp: 67−69 °C) after being stirred over sodium at room temperature overnight. Solvents were purified using a J.C. Meyer type solvent dispensing system utilizing Al_2O_3 and/or copper cartridges, depending on the particular solvent. *n*-BuLi was titrated with diphenylacetic acid prior to use. Nitrogen gas used in reactions requiring an inert atmosphere was house-supplied and run through Dri-Rite desiccant. Glassware for distillation and water sensitive reactions was flame-dried under vacuum or dried in an oven. Silica was EMD silica gel 60, 40−63 μm (11567-1). TLC plates were aluminum backed EMD silica gel 60 F_{254} (5554/7). ^{1}H NMR spectra were recorded on a Bruker Avance AV300. ESI-MS were recorded on a Bruker Esquire ion trap mass spectrometer. Purification of all final compounds was

by reverse phase HPLC utilizing an octadecylsilane stationary phase and a water-to-methanol gradient with 0.08% v/v trifluoroacetic acid, (TFA). HPLC was carried out on a Varian Pro-Star fitted with a Waters YMC Pack-ODS-A column (2 cm × 10 cm) running at 12 mL/min using a detector excitation wavelength of 254 nm. All target compounds possessed a purity of ≥95% as verified by HPLC.

Methanone Synthesis (Route 1). 4-Chloro-*N*-methoxy-*N*-methylbenzamide. An amount of 20.0 g (0.128 mols) of 4-chlorobenzoic acid (156.57 g/mol) was placed in a 500 mL round bottomed flask. Then 120 mL of thionyl chloride was added, and the mixture was refluxed overnight. Thionyl chloride was removed under reduced pressure to produce a red oil. Anhydrous toluene was added and then removed under reduced pressure two times. The crude product was dissolved in 200 mL of anhydrous CH_2Cl_2. An amount of 13.73 g (0.140 mol) of *N*,*O*-dimethylhydroxylamine·HCl (97.54 g/mol) was added. Then 52 mL (0.640 mol) of anhydrous pyridine was added over a period of 10 min. The mixture was stirred under nitrogen at room temperature overnight. Volatiles were removed under reduced pressure. The solid was partitioned between $CHCl_3$ and water. The organic phase was washed with brine, then collected and dried over anhydrous magnesium sulfate. The solvents were removed to produce a red oil which was purified on silica with 5% MeOH/CH_2Cl_2 as eluent. An amount of 22.9 g of product was produced, yield 90%. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.66 (m, 2H), 7.38 (m, 2H), 3.54 (s, 3H, -OMe), 3.36 (s, 3H, -NMe). ESI-MS m/z 200.4 $(M + H^+)^+$. MW: 199.63 g/mol.

(4-Chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methanone. A flame-dried 125 mL round-bottom flask was charged with a stir bar and overpressurized with dry nitrogen gas and 3.0 mL (37.6 mmol) of freshly distilled *N*-methylimidazole (82.11 g/mol, 1.035 g/mL). The flask was sealed with a new rubber septum, and 30 mL of anhydrous THF was added. The solution was stirred for about 10 min, and then the temperature was lowered to −78 °C and stirred for an additional 10 min. Then 16.2 mL (41.3 mmol) of freshly titrated *n*-BuLi (2.5 M in hexanes) was added dropwise through the septum over a period of 10 min under an overpressure of dry nitrogen. A slight color change to pale yellow was observed. The reaction mixture was allowed to stir at this temperature for 45 min. Then 6.3 mL (37.6 mmol) of 99% chlorotriethylsilane (Et_3SiCl) was added dropwise over 5 min. The mixture was allowed to stir for 1 h at −78 °C, at which point 15.0 mL (37.6 mmol) of freshly titrated *n*-BuLi (2.5 M in hexanes) was added dropwise through the septum over a period of 10 min and allowed to stir at −78 °C for an additional 45 min. A separate flask was flame-dried and charged with 5.0 g (25.1 mmol) 4-chloro-*N*-methoxy-*N*-methylbenzamide (199.63 g/mol) and sealed with a rubber septum. A total of 15 mL of anhydrous THF was added, and the mixture was stirred at room temperature for 10 min and then at the appropriate time transferred via cannula to the flask containing the in situ generated C-2 triethylsilyl protected *N*-methylimidazole at a slow rate to maintain low temperature as indicated by the slow sublimation of CO_2. The mixture was left to stir overnight and became deep red. The reaction was quenched by the addition of 1 M HCl until the pH of the aqueous phase was no longer basic as indicated by litmus paper, then allowed to stir for 1 h. The pH of the aqueous phase was adjusted to above 8 with 1.5 M NaOH, and the mixture was partitioned between $CHCl_3$ and water. The organic phase was washed with brine and dried with anhydrous $MgSO_4$. Solvents were removed under reduced pressure to produce a reddish solid. Product was purified by recrystallization from CH_2Cl_2 to produce 4.24 g of fluffy golden crystals, 76.6% yield. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.83 (d, J = 8.4 Hz, 2H), 7.68 (s, 1H), 7.59 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 4.03 (s, 1H). ESI-MS m/z 221.4 $(M + H^+)^+$. MW: 220.65 g/mol.

(4-Chlorophenyl)(1-ethyl-1*H*-imidazol-5-yl)methanone. The compound was prepared in a manner analogous to (4-chlorophenyl)-(1-methyl-1*H*-imidazol-5-yl)methanone. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.81 (m, 2H), 7.75 (s, 1H), 7.58 (s, 1H), 7.50 (m, 2H), 4.03 (s, 1H). ESI-MS m/z 221.4 $(M + H^+)^+$. MW: 234.68 g/mol.

Methanone Synthesis (Route 2). 1-Triphenylmethyl-4-imidazole Carboxaldehyde. To a 1 L three-necked round-bottomed flask with an addition funnel was added 3*H*-imidazole-4-carbaldehyde (12 g, 0.125 mol, Aldirch), trityl chloride (38.3 g, 0.137 mol) and acetonitrile (400 mL). The mixture was stirred at room temperature to give a slurry. Triethylamine (30 mL, 0.125 mol) was added dropwise over 20 min. After the addition was complete, the reaction mixture was stirred at room temperature for 20 h. Hexane (40 mL) and water (400 mL) were added. The slurry was stirred for 30 min and filtered. The cake was washed with water (3 × 100 mL) and dried in an oven at 50 °C for 20 h to give **2** as a white solid. (39.8 g, 94%). ^{1}H NMR ($CDCl_3$, δ): 9.81 (s, 1H), 7.54 (s, 1H), 7.46 (s, 1H), 7.20−7.29 (m, 10H), 7.09−7.04 (m, 5H). MS m/z 339.4 $(M + H)^+$. MW: 338.4.

***p*-Tolyl-(1-trityl-1-*H*-imidazol-4-yl)methanone.** An oven-dried 250 mL round-bottom flask fitted with reflux condenser was sealed with a rubber septum under argon atmosphere and charged with magnesium turnings (1.12 g, 46.7 mmol) and a pinch of iodine. Anhydrous ether (50 mL) was added, and the mixture was stirred for 5 min at room temperature. To this mixture *p*-bromotoluene (5 g, 29.2 mmol) was added dropwise in anhydrous ether (10 mL) slowly, at a rate to allow the ether to barely reflux. The mixture was then refluxed for 30 min and cooled to 0 °C. 1-Triphenylmethyl-4-imidazole carboxaldehyde (7.9 g 23.3 mmol) was dissolved in anhydrous ether (20 mL) and added dropwise with continuous stirring. The reaction mixture was stirred for 3 h at room temperature and then refluxed for 1 h. The reaction mixture was cooled and poured into 50 mL of ice cold 1 M HCl. The phases were separated, and the aqueous phase was extracted with ether (2 × 50 mL). The combined ether layers were washed with saturated $NaHCO_3$ solution, and the resulting ether layer was kept in an ice cold bath for 3 h and then filtered. The resulting white solid (9 g) was transferred to a 200 mL round bottomed flask fitted with a reflux condenser. The solid was suspended in 1,4-dioxane (50 mL) and stirred for 5 min, and then MnO_2 (9 g, 104 mmol) was added. The resulting mixture was refluxed for 3 h and cooled to room temperature and diluted with CH_2Cl_2 (50 mL) and then filtered through a Celite pad. Solvent was removed under reduced pressure to produce 8.45 g of product as a crispy solid, yield 94.4%. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.12 (d, J = 8.1 Hz, 2H), 7.69 (s, 1H), 7.54 (s, 1H), 7.43−7.34 (m, 10H), 7.25 (d, J = 8.1 Hz, 2H), 7.20−7.12 (m, 5H), 2.55 (s, 3H). ESI-MS m/z 429.2 $(M + H)^+$. MW: 428.56 g/mol.

(3-Methyl-3*H*-imidazol-4-yl)-*p*-tolylmethanone. A flask was charged with 5.0 g of the previous compound (11.6 mmol) under nitrogen atmosphere which was suspended in 40 mL of anhydrous CH_2Cl_2 and stirred rapidly for 10 min. A solution of methyltrifluoromethane sulfonate (1.95 mL, 17.5 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise over 10 min, and the reaction mixture was stirred at room temperature for 20 h. The volume of the mixture was reduced to about $^1/_3$ of its original volume, and to this was added 30 mL of hexane. The slurry was stirred for 30 min and filtered. The cake was washed with hexane and dissolved in 30 mL of 1:2 water/acetone mixture and stirred for 3 h. The reaction mixture was filtered to remove trityl alcohol, and the cake was washed with water (2 × 10 mL). The filtrate was concentrated under reduced pressure to remove acetone, and the resulting slurry was filtered again to remove traces of trityl alcohol and the cake washed with water (10 mL). The filtrate was washed with saturated $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 40 mL). Combined organic layers were dried with $MgSO_4$. Solvent was removed under reduced pressure to produce 2.09 g of product as a pulpy white solid, yield 89.6% ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.78 (d, J = 8.1 Hz, 2H), 7.64 (s, 1H), 7.59 (s, 1H), 7.31 (d, J = 8.1 Hz, 2H), 4.02 (s, 3H), 2.45(s, 3H). ESI-MS m/z 201.1 $(M + H)^+$. MW: 200.24 g/mol.

(3-Methyl-3*H*-imidazol-4-yl)(4-trifluoromethylphenyl)methanone. The compound was prepared in a manner analogous to the above methanone. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.95 (d, J = 8.7 Hz, 2H), 7.78 (d, J = 8.7 Hz, 2H), 7.69 (s, 1H), 7.58 (s, 1H), 4.03 (s, 3H). ESI-MS m/z 255.4 $(M + H)^+$. MW: 254.21 g/mol.

(4-Ethylphenyl)(3-methyl-3*H*-imidazol-4-yl)methanone. The compound was prepared in a manner analogous to the above methanone. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.80 (d, J = 9.0 Hz, 2H), 7.64 (s, 1H), 7.59 (s, 1H), 7.32 (d, J = 9.0 Hz, 2H), 4.01 (s, 3H), 2.75 (q, J = 3.3 Hz, 1.8 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H). ESI-MS m/z 215.1 $(M + H)^+$. MW: 214.26 g/mol.

(4-Isopropylphenyl)(3-methyl-3*H*-imidazol-4-yl)methanone. The compound was prepared in a manner analogous to the above methanone. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.82 (d, J = 8.6 Hz, 2H), 7.65 (s, 1H), 7.61 (s, 1H), 7.36 (d, J = 8.6 Hz, 2H), 4.02 (s, 3H), 3.0 (m, 1H), 1.33 (d, J = 6.9 Hz, 6H). ESI-MS m/z 229.1 $(M + H)^+$. MW: 228.29 g/mol.

2-Amino-5-bromo-*N*-methoxy-*N*-methylbenzamide. A 2 L flask was charged with 25.0 g (103.3 mmol) of 5-bromoisatoic anhydride (242.03 g/mol) and 15.1 g (155 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride (97.54 g/mol). The solids were suspended in 500 mL of anhydrous CH_2Cl_2 and stirred rapidly. Then 37.5 mL of pyridine (465 mmol) was added slowly, and the mixture was allowed to stir until all solids had dissolved, about 36 h. The crude mixture was partitioned between $CHCl_3$ and water. The organic phase was washed with brine and dried with anhydrous $MgSO_4$. Solvents were removed under reduced pressure to produce a gold oil which crystallized upon standing. Product was triturated with hexanes, filtered, then used without further purification. An amount of 23.9 g of a lightly colored crystalline product was produced, 89% yield. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.52 (d, J = 2.4 Hz, 1H), 7.28 (dd, J = 2.4 Hz, 8.1 Hz 1H), 6.61 (d, J = 8.7 Hz, 1H), 4.69 (s (broad), 2H), 3.61 (s, 3H), 3.36 (s, 3H). ESI-MS m/z 283.1 $(M + Na^+)^+$. MW: 259.10 g/mol.

(2-Amino-5-bromophenyl)(3-chloro-2-methylphenyl)methanone. A 250 mL flask was flame-dried and charged with a stir bar and a rubber septum. 2-Bromo-6-chlorotoluene (6 mL, 45.9 mmol) was added to the flask and dissolved in 60 mL of anhydrous THF under an atmosphere of dry nitrogen. The solution was stirred for about 5 min and then cooled to −78 °C and then stirred for about 10 min. An amount of 18 mL (45.9 mmol, 1 equiv) of *n*-BuLi (2.5 M in hexanes) was added dropwise at a rate such that temperature of the reaction remained close to −78 °C, as indicated by the slow sublimation of CO_2. The solution was allowed to stir for 20 min. Then 5.95 g (22.95 mmol, 0.5 equiv) of 2-amino-5-bromo-*N*-methoxy-*N*-methylbenzamide was added to a separate flask and dissolved in 60 mL of anhydrous THF. After being stirred for about 5 min, this solution was added dropwise by canula to the flask containing the in situ generated aryllithium. The solution was allowed to stir at this temperature for 2 h, at which time the cooling bath was removed allowing the flask to rise to room temperature. An amount of 50 mL of 1 M aqueous HCl was added, and the biphasic mixture was allowed to stir for 30 min. The mixture was partitioned between $CHCl_3$ and water. The organic phase was washed three times with saturated aqueous $NaHCO_3$, then separated and dried with $MgSO_4$. Solvents were removed under reduced pressure to produce an orange-brown oil. This was purified on silica with 20% EtOAc/hexanes to produce 6.3 g of yellow crystalline product, yield 85%. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.47 (d, J = 7.8 Hz, 1H), 7.36 (dd, J = 8.7 Hz, 2.1 Hz, 1H), 7.25 (d, J = 2.1 Hz 1H), 7.21 (m, 2H), 7.11 (d, J = 7.5 Hz 1H), 6.64 (d, J = 8.7 Hz, 1H), 6.49 (s (broad), 2H), 2.27 (s, 3H). ESI-MS m/z 324.3 $(M + H^+)^+$. MW: 324.60 g/mol.

6-Bromo-4-(3-chloro-2-methylphenyl)quinolin-2(1*H*)-one. A 250 mL flask was fitted with a stir bar, and 11.9 g of (2-amino-5-bromophenyl)(3-chloro-2-methylphenyl)methanone was added. A water condenser was attached, and then 50 mL of anhydrous toluene and 24.3 mL (257 mmol, 7 equiv) of acetic anhydride were added. The solution was heated to reflux for 6 h. Then volatiles were removed under reduced pressure. Approximately 50 mL of toluene was added and removed at reduced pressure two times. The crude product was set aside. A separate flask was fitted with a stir bar and a septum and loaded with 24.7 g (220 mmol, 6 equiv) of 95% *t*-BuOK powder. This was suspended in 120 mL of 1,2-dimethoxyethane and stirred for about 10 min. The temperature was lowered to 0 °C. The crude product set aside previously was dissolved in 45 mL of 1,2-dimethoxyethane and then transferred dropwise by cannula to the flask containing the *t*-BuOK suspension. The color of the solution changed to yellow, and the mixture was allowed to stir under an inert atmosphere overnight. At this point the volaties were removed under reduced pressure, and the resulting paste was suspended in ~300 mL of water. The solid was collected by filtration and used in the next step without purification. An amount of 8.4 g (24.10 mmol) of product was produced as a fluffy, white solid, yield 66%. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.62 (dd, J = 8.7 Hz, 1.8 Hz, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 7.30 (m, 1H), 7.21 (d, J = 1.8 Hz, 1H), 7.11 (d, J = 7.2 Hz, 1H), 6.62 (s, 1H), 2.17 (s, 3H). ESI-MS m/z 348.3 $(M + H^+)^+$. MW: 348.62 g/mol.

6-Bromo-4-(3-chloro-2-methylphenyl)-2-methoxyquinoline. A flame-dried 25 mL flask was fitted with a stir bar and charged with 500 mg (1.43 mmol) of 6-bromo-4-(3-chloro-2-methylphenyl)quinolin-2(1*H*)-one and 423 mg (2.86 mmol, 2 equiv) of BF_4OMe_3 and then sealed with a septum. The solids were suspended in 5.5 mL of anhydrous CH_2Cl_2 and stirred for 20 h, at which time 5.5 mL of 1 M aqueous NaOH was added. The mixture was stirred for about 3 h, then partitioned between $CHCl_3$ and water. The organic was washed three times with brine, then dried with $MgSO_4$. Solvents were removed under reduced pressure to produce a clear yellow oil which crystallized upon standing. This was purified on silica with 50:50 CH_2Cl_2/hexane to produce 329 mg of product as a flaky yellow-green solid, yield 63%. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.79 (d, J = 9.0 Hz, 1H), 7.69 (dd, J = 8.7 Hz, 2.3 Hz, 1H), 7.50 (dd, J = 7.8 Hz, 1.2 Hz, 1H), 7.40 (d, J = 2.1 Hz, 1H), 7.26 (m, 1H), 7.09 (dd, J = 7.5 Hz, 1.2 Hz, 1H), 6.77 (s, 1H), 4.10 (s, 3H), 2.08 (s, 3H). ESI-MS m/z 362.3 $(M + H^+)^+$. MW: 362.65 g/mol.

4-(3-Chloro-2-methylphenyl)-6-((4-chlorophenyl)(hydroxy)(1-methyl-1*H*-imidazol-5-yl)methyl)-2-methoxyquinoline. A flame-dried flask was charged with a stir bar and 4.2 g (11.58 mmol) of 6-bromo-4-(3-chloro-2-methylphenyl)-2-methoxyquinoline and sealed with a rubber septum. An amount of 20 mL of anhydrous THF was added and the solution stirred at room temperature for 10 min. The temperature was lowered to −78 °C, and the mixture was stirred for another 10 min. Then 5.0 mL (1.1 eq 12.7 mmol) of 2.5 M *n*-BuLi was added dropwise accompanied by a color shift to dark yellow-orange. This was allowed to stir for 20 min. A separate flask was flame-dried and charged with 2.8 g of (4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methanone (1.1 equiv, 12.7 mmol). This was dissolved in 55 mL of THF and added to the flask containing quinoline in three increments by syringe, rapidly dropwise over 10 min. The mixture was stirred overnight and allowed to warm slowly to room temperature, and the color shifted to gold. The reaction was quenched by addition of 1 volume of a saturated aqueous solution of NH_4Cl. This was partitioned between 1 M NH_4OH and $CHCl_3$. The organic phase was collected and solvents were removed under reduced pressure to produce a foamy, white semisolid. This was purified on silica with a mobile phase consisting of MeOH/CH_2Cl_2, 1:10 v/v, to produce 3.52 g (6.91 mmol) of product, 60% yield. TLC (CH_2Cl_2/MeOH, 9:1 v/v): R_f = 0.45. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.86 (m, 1H), 7.59 (m, 1H), 7.43 (m, 1H), 7.20 (m, 6H), 7.01 (m, 2H), 6.79 (s, 1H), 6.17 (m, 1H), 4.12 (s, 3H), 3.30 (m, 3H), 1.90 (m, 3H). ESI-MS m/z 504.3 $(M + H^+)^+$. MW: 504.41 g/mol.

4-(3-Chloro-2-methylphenyl)-6-((4-chlorophenyl)(hydroxy)(1-methyl-1*H*-imidazol-5-yl)methyl)quinolin-2(1*H*)-one. An amount of 3.5 g (6.91 mmol) of the previous compound was dissolved in

15 mL of THF. Then 30 mL of 6 N HCl (25 equiv) was added dropwise. The flask was fitted with a water-cooled condenser, and the mixture was stirred at 60 °C for 5 h. Most of the THF was removed by a stream of nitrogen, and the heterogeneous mixture that remained was made basic with excess aqueous 1 M NH_4OH and then partitioned between water and $CHCl_3$. The organic was dried with $MgSO_4$, and solvents were removed at reduced pressure. Product was purified on silica with a mobile phase consisting of MeOH/CH_2Cl_2, 1:10 v/v, to produce 2.1 g (4.28 mmol) of product as a white solid, 62% yield. TLC (CH_2Cl_2/MeOH, 9:1 v/v): $R_f = 0.30$. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.68 (m, 1H), 7.59 (m, 1H), 7.47 (m, 2H), 7.28 (m, 3H), 7.12 (m, 3H), 6.73 (m, 1H), 6.51 (m, 1H), 6.1 (m, 1H), 3.41 (m, 3H), 1.96 (m, 3H). ESI-MS m/z 490.4 $(M + H^+)^+$. MW: 490.38 g/mol.

4-(3-Chloro-2-methylphenyl)-6-((4-chlorophenyl)(hydroxy)(1-methyl-1*H*-imidazol-5-yl)methyl)-1-methylquinolin-2(1*H*)-one. An amount of 2.1 g (4.28 mmol) of the previous compound was added to a 100 mL flask and dissolved in 30 mL of THF. Then 487 mg (0.5 eq., 2.14 mmol) of benzyltriethylammonium chloride was added as a phase transfer catalyst. A total of 25.5 mL of 40% wt NaOH (120 equiv, 17.1 g) was added and the mixture allowed to stir for approximately 10 min. Then 375 μL (1.4 equiv, 6 mmol) of CH_3I was added, and the mixture was allowed to stir overnight. The THF was removed at reduced pressure, and the product was partitioned between $CHCl_3$ and 1 M NH_4OH. The product was purified on silica with a mobile phase consisting of MeOH/CH_2Cl_2, 1:10 v/v, to produce 2.0 g (3.97 mmol) of product as a colorless semisolid, 59% yield. TLC (CH_2Cl_2/MeOH, 9:1 v/v): R_f = 0.45. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.80 (m, 1H), 7.72 (m, 1H), 7.63 (m, 1H), 7.49 (m, 1H), 7.29 (m, 3H), 7.12 (m, 3H), 6.78 (m, 1H), 6.58 (m, 1H), 6.14 (m, 1H), 3.85 (s, 3H), 3.41 (m, 3H), 1.95 (m, 3H). ESI-MS m/z 504.3 $(M + H^+)^+$. MW: 504.41 g/mol.

4-(3-Chloro-2-methylphenyl)-6-((4-chlorophenyl)(ethoxy)(1-methyl-1*H*-imidazol-5-yl)methyl)-1-methylquinolin-2(1*H*)-one (21). A total of 10.0 mg (0.02 mmol) of the previous compound was dissolved in 10 mL of EtOH, and approximately 15 mg of tosic acid was added. The mixture was heated to reflux for 48 h. TLC analysis indicated only one major product and complete conversion of starting material. Solvents were removed under reduced pressure to produce a colorless, oily semisolid. Product was purified by HPLC using a water−methanol gradient with 0.08% v/v trifluoroacetic acid: 0−5 min 20% MeOH, 5−25 min 20−65% MeOH, 25−30 min 65−100% MeOH. Product elutes at 27.9 min, and 4.0 mg (0.0062 mmol) was produced as a mono-TFA salt. Yield 31%. TLC (CH_2Cl_2/MeOH, 9:1 v/v): $R_f = 0.55$. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.98 (s, 1H), 7.85 (m, 1H), 7.75 (m, 1H), 7.57 (m, 1H), 7.52 (m, 1H), 7.35 (m, 5H), 7.17 (m, 1H), 7.12 (m, 1H), 6.63 (m, 1H), 3.82 (m, 3H), 3.52 (m, 3H) 2.05 (s, 3H), 1.13 (m, 3H). ESI-MS m/z 533.6 $(M + H^+)^+$. MW: 532.46 g/mol. Mono-TFA salt FW: 646.45 g/mol.

4-(3-Chloro-2-methylphenyl)-6-((4-chlorophenyl)(propoxy)(1-methyl-1*H*-imidazol-5-yl)methyl)-1-methylquinolin-2(1*H*)-one (22). An amount of 10.0 mg (0.02 mmol) of 4-(3-chloro-2-methylphenyl)-6-((4-chlorophenyl)(hydroxy)(1-methyl-1*H*-imidazol-5-yl)-methyl)-1-methylquinolin-2(1*H*)-one was dissolved in 10 mL of PrOH, and approximately 15 mg of tosic acid was added. The mixture was heated to reflux for 48 h. TLC analysis indicated only one major product and complete conversion of starting material. Solvents were removed under reduced pressure to produce a colorless, oily semisolid. Product was purified by HPLC using a water−methanol gradient with 0.08% v/v trifluoroacetic acid: 0−5 min 20% MeOH, 5−25 min 20−65% MeOH, 25−30 min 65−100% MeOH. Product elutes at 28.6 min, and 3.9 mg (0.0059 mmol) was produced as a mono-TFA salt. Yield 30%. TLC (CH_2Cl_2/MeOH, 9:1 v/v): $R_f = 0.55$. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.97 (s, 1H), 7.76 (ddd, J = 9.0, 2.4 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.54 (m, 2H), 7.32 (m, 5H), 7.19 (dd, J = 2.4 Hz, 1H), 7.15 (m, 1H), 6.59 (m, 1H), 3.78 (s, 3H), 3.47 (m, 3H), 2.02 (m, 3H), 1.50 (m, 2H), 0.86 (m, 3H). ESI-MS m/z 546.6 $(M + H^+)^+$. MW: 546.49 g/mol. Mono-TFA salt FW: 660.51 g/mol.

4-(3-Chloro-2-methylphenyl)-6-((4-chlorophenyl)(methylamino)-(1-methyl-1*H*-imidazol-5-yl)methyl)-1-methylquinolin-2(1*H*)-one (23). An amount of 10.0 mg (0.02 mmol) of 4-(3-chloro-2-methylphenyl)-6-((4-chlorophenyl)(hydroxy)(1-methyl-1*H*-imidazol-5-yl)methyl)-1-methylquinolin-2(1*H*)-one was dissolved in 5 mL of $SOCl_2$. The flask was covered with aluminum foil, and the reaction mixture was stirred overnight. $SOCl_2$ was removed at reduced pressure to produce a whitish solid. A total of 10 mL of THF was added. Stirring was done with the flask open, and anhydrous methylamine was bubbled through the solution for a period of 30 min. Then the flask was sealed and stirred overnight under an overpressure of methylamine. Solvents were removed at reduced pressure, and the crude mixture was dissolved in 1 mL of MeOH and centrifuged. The supernatant was collected and injected onto the HPLC column. Product was purified using a water−methanol gradient with 0.08% v/v trifluoroacetic acid: 0−5 min 20% MeOH, 5−25 min 20−65% MeOH, 25−30 min 65−100% MeOH. Product elutes at 24.4 min, and 1.4 mg (0.0018 mmol) was produced as a bis-TFA salt. Yield 9%. TLC (CH_2Cl_2/MeOH, 9:1 v/v): $R_f = 0.55$. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.86 (m, 1H), 7.82 (m, 2H), 7.54 (m, 1H), 7.41−7.27 (m, 6H), 7.15 (m, 1H), 7.00 (m, 1H), 6.64 (s, 1H), 3.86 (m, 3H), 3.57 (m, 3H), 2.16 (m, 3H), 2.01 (m, 3H). ESI-MS m/z 517.5 $(M + H^+)^+$. MW: 517.45 g/mol. Bis-TFA salt FW: 745.5 g/mol.

4-(3-Chloro-2-methylphenyl)-6-((4-chlorophenyl)(hydroxy)(1-methyl-1*H*-imidazol-5-yl)methyl)-1-methylquinolin-2(1*H*)-one (20). The title compound was injected onto the HPLC column using a water−methanol gradient with 0.08% v/v trifluoroacetic acid: 0−5 min 20% MeOH, 5−25 min 20−65% MeOH, 25−30 min 65−100% MeOH. Product elutes at 23.9 min and was produced as a mono-TFA salt. TLC (CH_2Cl_2/MeOH, 9:1 v/v): $R_f = 0.55$. ^{1}H NMR (300 MHz, CD_3OD, δ): 8.94 (m, 1H), 7.86 (dd, J = 9.0, 2.1 Hz, 1H), 7.79 (m, 2H), 7.51 (m, 1H), 7.37 (m, 2H), 7.31−7.18 (m, 3H), 7.09 (m, 1H), 6.85−6.76 (m, 2H), 6.62 (m, 1H), 3.85 (s, 3H), 3.65 (m, 3H), 1.96 (m, 3H). ESI-MS m/z 504.6 $(M + H^+)^+$. MW: 504.41 g/mol. Mono-TFA salt FW: 618.43 g/mol.

6-Bromo-*N*-(*E*)-2,6-difluorocinnamoylanilide. An amount of 15.0 g (81.5 mmol) of (*E*)-2,6-difluorocinnamic acid was dissolved in 25 mL of $SOCl_2$, and the mixture was heated to reflux and stirred overnight. Thionyl chloride was removed at reduced pressure. Then anhydrous toluene was added and removed at reduced pressure two times to produce a flaky white solid. Crude product was triturated and transferred to a separate flame-dried flask, which was placed under vacuum overnight. An amount of 16.1 g (79.5 mmol) was produced and used without further purification. Yield, 97%. Then 6.50 g (37.8 mmol) of *p*-bromoaniline was placed in a separate 500 mL round-bottomed flask and dissolved in 100 mL of anhydrous CH_2Cl_2. A total of 13.2 mL (75.5 mmol, 2 equiv) of diisopropylethylamine was added, and the solution was allowed to stir for several minutes, at which time the temperature was lowered to 0 °C. Then 11.5 g (57.0 mmol, 1.5 equiv) of crude cinnamoyl chloride from above was dissolved in approximately 40 mL of CH_2Cl_2 and added rapidly, dropwise. This was allowed to stir overnight. The color became dark green. The crude mixture was partitioned between CH_2Cl_2 and water. The organic phase was collected and dried with $MgSO_4$. Then solvents were removed under reduced pressure to produce a solid which was recrystallized from $CHCl_3$ to produce 9.72 g (28.74 mmol) of long yellowish needles of product for a yield of 76%. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.87 (d, J = 15.9 Hz, 1H), 7.54 (m, 2H), 7.46 (m, 2H), 7.32 (m, 1H), 6.96 (m, 2H), 6.85 (d, J = 15.9 Hz, 1H). MW: 338.15 g/mol.

6-Bromo-4-(2,6-difluorophenyl)-2-oxotetrahydroquinoline. An amount of 4.35 g (12.9 mmol) of the previous compound was added to a 250 mL round bottomed flask, which was fitted with a reflux condenser and a stir bar. Then 45 mL of concentrated H_2SO_4 was added, and the mixture was heated to 105 °C for 4 h,

at which time the reaction was quenched by pouring the mixture into ice−water. A white precipitate formed and was collected by filtration to produce 3.42 g (10.1 mmol) of crude product, yield 79%. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.45 (m, 1H), 7.36 (dd, J = 8.4 Hz, 1.2 Hz, 1H), 7.09 (m, 2H), 7.07 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 3.00 (dd, J = 16.5 Hz, 12 Hz, 1H), 2.79 (dd, J = 16.5 Hz, 6.6 Hz, 1H). MW: 338.15 g/mol.

6-Bromo-4-(2,6-difluorophenyl)quinolin-2(1*H*)-one. A mixture of the previous compound (1.0 g, 2.95 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (4.03 g, 17.75 mmol) in dioxane (50 mL) was stirred under reflux for 48 h and concentrated in vacuo. The residue was dissolved in potassium carbonate solution (2.5%, 50 mL) and extracted with CH_2Cl_2/MeOH (20:1, 2 × 50 mL). The combined dried ($MgSO_4$) organic extracts were evaporated, and the residue was purified with flash chromatography over silica to produce 678 mg (2.02 mmol) of pure product, 68.4% yield. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.73 (dd, J = 9 Hz, 2.1 Hz, 1H), 7.65 (m, 1H), 7.40 (d, J = 8.7 Hz, 1H), 7.25 (m, 3H), 6.69 (s, 1H). MW: 336.13 g/mol.

6-Bromo-4-(2,6-difluorophenyl)-2-methoxyquinoline. A 50 mL round-bottomed flask was charged with 360 mg (1.07 mmol) of the previous compound. Then 15 mL of CH_2Cl_2 was added to the flask followed by 316 mg (2.14 mmol, 2 equiv) of BF_4OMe_3. The flask was sealed with a septum and the mixture stirred overnight with a slight overpressure of N_2 vented through a bubbler. The following day, several milliliters of 1.5 M NaOH was added and then allowed to stir for about an hour, at which time the mixture was partitioned between $CHCl_3$ and H_2O. The organic phase was collected, then washed with brine and dried with anhydrous $MgSO_4$. Solvents were removed under vacuum. Crude material was adsorbed onto silica, then purified using a mobile phase of hexanes/CH_2Cl_2, 1:1 (v/v), to produce 189 mg (0.54 mmol) of product, 50% yield. TLC (hexanes/CH_2Cl_2, 1:1 v/v): R_f = 0.50. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.82 (d, 7.36 (dd, J = 9 Hz, 1H), 1H), 7.73 (dd, J = 8.9 Hz, 2.1 Hz, 1H), 7.55 (d, J = 1.8 Hz, 1H), 7.50 (m, 1H), 7.28 (s, 1H), 7.11 (m, 2H), 6.95 (s, 1H), 4.13 (s, 3H). MW: 350.16 g/mol.

4-(2,6-Difluorophenyl)-6-((4-chlorophenyl)(hydroxy)(1-methyl-1*H*-imidazol-5-yl)methyl)-2-methoxyquinoline. A 25 mL round-bottomed flask was flame-dried, fitted with a magnetic stir bar, and charged with 100 mg of the previous compound. A total of 5 mL of THF was added, and mixture was stirred for 10 min, at which time the temperature was lowered to −78 °C and the mixture stirred for an additional 10 min. Then 125 μL (1.05 equiv, 0.3124 mmol) of 2.5 M *n*-BuLi was added dropwise accompanied by a color shift to dark yellow-orange. This was allowed to stir for approximately 5 min after the sublimation of CO_2 subsided as indicated by the evolution of gas from the dry ice bath. A separate flask was flame-dried and charged with 60 mg of **13** (0.9 equiv, 0.2678 mmol). This was dissolved in 55 mL of THF and added to the flask containing quinoline in three increments, rapidly dropwise over 10 min. Color shifted steadily to yellow-gold after stirring overnight and warming slowly to room temperature. The reaction was quenched by addition of 1 volume equivalent of a saturated aqueous solution of NH_4Cl. The biphasic mixture was partitioned between 1 M NH_4OH and $CHCl_3$. Organic phase was collected and solvents were removed under reduced pressure to produce a foamy, white semisolid. This was purified on silica with a mobile phase consisting of MeOH/CH_2Cl_2, 1:10 v/v, to produce 71.5 mg (0.1443 mmol) of product, 49% yield. TLC (CH_2Cl_2/MeOH, 9:1 v/v): R_f = 0.45. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.91 (d, 1H), 7.64 (dd, 1H), 7.41 (m, 1H), 7.23 (m, 4H), 7.14 (m, 1H), 6.98 (m, 3H), 4.13 (s, 3H), 3.50 (s, 3H), 3.35 (s, 3H). ESI-MS m/z 492.5 $(M + H^+)^+$. MW: 491.92 g/mol.

4-(2,6-Difluorophenyl)-6-((4-chlorophenyl)(hydroxy)(1-methyl-1*H*-imidazol-5-yl)methyl)quinolin-2(1*H*)-one. An amount of 71.5 mg (0.1453 mmol) of the previous compound was loaded into a 25 mL round-bottomed flask and dissolved in 5 mL of THF. Then 0.61 mL (3.63 mmol, 25 equiv) of 6 N aqueous HCl was added and mixture was refluxed for 4 h at which time reaction was neutralized with a 1 M NH_4OH in water. The mixture was partitioned between 1 M NH_4OH and $CHCl_3$. The aqueous was extracted 3 times with $CHCl_3$, and the organic fractions were combined and dried with anhydrous $MgSO_4$. Solvents were removed under vacuum. Crude product was purified on silica with a mobile phase consisting of MeOH/CH_2Cl_2, 1:10 v/v, to produce 71.5 mg (0.1443 mmol) of product, 78% yield. TLC (CH_2Cl_2/MeOH, 9:1 v/v): R_f = 0.35. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.91 (dd, J = 8.4 Hz, 1.8 Hz, 1H), 7.64 (dd, 1H), 7.41 (m, 1H), 7.23 (m, 4H), 7.14 (m, 1H), 6.98 (m, 3H), 4.13 (s, 3H), 3.50 (s, 3H), 3.35 (s, 3H). MW: 477.89 g/mol.

4-(2,6-Difluorophenyl)-6-((4-chlorophenyl)(hydroxy)(1-methyl-1*H*-imidazol-5-yl)methyl)-1-methylquinolin-2(1*H*)-one. An amount of 54 mg (0.11 mmol) of the previous compound was added to a 25 mL flask and dissolved in 5 mL of THF. Then 13 mg (0.5 equiv, 0.057 mmol) of benzyltriethylammonium chloride was added as a phase transfer catalyst. A total of 0.82 mL of 40% wt NaOH (120 equiv, 540 mg) was added and the mixture allowed to stir for approximately 10 min. Then 10 μL (1.4 equiv, 0.16 mmol) of CH_3I was added, and the mixture was allowed to stir overnight. The THF was removed at reduced pressure, and the residue was partitioned between $CHCl_3$ and 1 M NH_4OH. The product was purified on silica with a mobile phase consisting of MeOH/CH_2Cl_2, 1:10 v/v, to produce 27 mg (3.97 mmol) of product as a colorless semisolid, 48% yield. TLC (CH_2Cl_2/MeOH, 9:1 v/v): R_f = 0.45. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.77 (dd, 1H), 7.73 (d, 1H), 7.64 (s, 1H), 7.55 (m, 1H), 7.31 (m, 2H), 7.18 (m, 2H), 7.11 (m, 2H), 6.97 (d, 1H), 6.73 (s, 1H), 3.85 (s, 3H), 3.42 (m, 3H). MW: 491.92 g/mol.

4-(2,6-Difluorophenyl)-6-((4-chlorophenyl)(methoxy)(1-methyl-1*H*-imidazol-5-yl)methyl)-1-methylquinolin-2(1*H*)-one (16). An amount of 13 mg (0.027 mmol) of the previous compound was dissolved in 10 mL of MeOH, and approximately 7 mg of tosic acid was added. The mixture was heated to reflux for 48 h. TLC analysis indicated only one major product and complete conversion of starting material. Solvents were removed under reduced pressure to produce a colorless, oily semisolid. Product was purified by HPLC using a water−methanol gradient with 0.08% v/v trifluoroacetic acid: 30−100% over 20 min followed by 10 min at 100%. Product elutes at 12.2 min, and 6.7 mg (0.0893 mmol) was produced as a mono-TFA salt. Yield 59%. TLC (CH_2Cl_2/MeOH, 9:1 v/v): R_f = 0.55. ^{1}H NMR (300 MHz, CD_3OD, δ): 9.02 (s, 1H), 7.85 (dd, J = 9.0, 2.1 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.63 (m, 1H), 7.58 (d, J = 1.5 Hz, 1H), 7.38 (m, 4H), 7.20 (m, 3H), 6.78 (s, 1H), 6.73 (s, 1H), 3.83 (s, 3H), 3.55 (s, 3H), 3.21 (s, 3H). ESI-MS m/z 506.5 $(M + H^+)^+$. MW: 505.94 g/mol. Mono-TFA salt FW: 619.97 g/mol.

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Supporting Information Available: Additional synthesis information, analytical data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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