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D-piece modifications of the hemiasterlin analog HTI-286 produce potent tubulin inhibitors

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Abstract—Modifications of the D-piece carboxylic acid group of the hemiasterlin analog HTI-286 gave tubulin inhibitors which were potent cytotoxic agents in taxol resistant cell lines expressing P-glycoprotein. Amides derived from proline had potency comparable to HTI-286. Reduction of the carboxylic acid to ketones and alcohols or its conversion to acidic heterocycles also gave potent analogs. Synthetic modifications of the carboxylic acid could be carried out selectively using a wide range of synthetic reagents. Proline analog **3** was found to be effective in a human xenograft model in athymic mice.

Hemiasterlin[1] (**1**), a tripeptide isolated from marine sponges, and its synthetic analog HTI-286[2] (**2**), induce microtubule depolymerization, and mitotic arrest in cells (Fig. 1). These compounds contain highly unusual and sterically congested amino acids, which give rise to their stability and in vivo activity. Their relative structural simplicity allows for diverse modification via total synthesis.[3] In addition to its potent antitumor effects, HTI-286 has the advantage of circumventing the P-glycoprotein-mediated resistance that hampers the efficacy of other antimicrotubule agents such as paclitaxel and vincristine in animal models.[2] HTI-286 is presently in clinical trials.[4] Previously we described an in-depth study of the structure–activity relationships of HTI-286 analogs.[5] We now report that the carboxylic acid region of HTI-286 (D-piece) can be efficiently converted to a wide range of functional groups resulting in potent tubulin inhibitors.

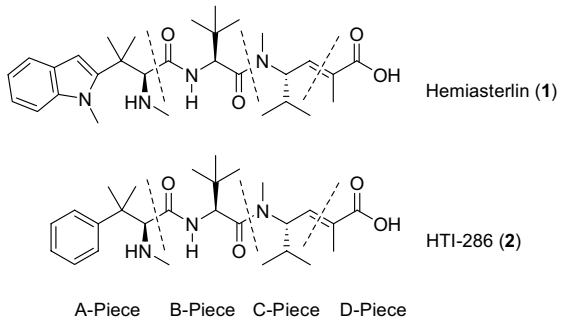

Figure 1. Hemiasterlin (**1**) and HTI-286 (**2**).

The carboxylic acid moiety of HTI-286 could be selectively derivatized via a variety of methods without affecting the other functional groups in the molecule. Preliminary activation of the carboxylic acid toward reaction with nucleophiles by treatment with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBT) was used in the synthesis of many analogs. Thus, activation followed by treatment with cyclic amino acid esters (Scheme 1) gave the corresponding tetrapeptides (**3**–**7**) (Table 1). Saponification of the ester groups in these amides with LiOH gave the acids **8**–**12**. Acid **8** was converted to amide **13** by coupling with phenethylamine under the coupling conditions described above. Use of HTI-286 analogs with modifications of the phenyl group in the A-piece similarly gave L-proline containing tetrapeptides (**14**–**20**) (Table 2).

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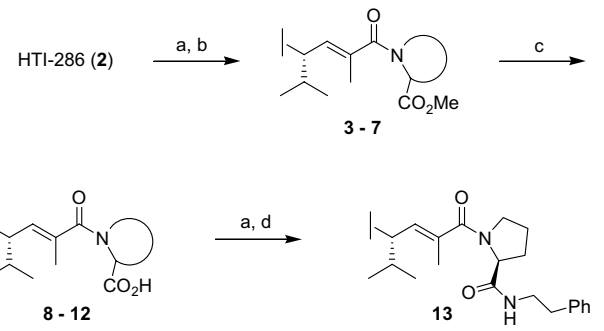


Scheme 1. Reagents and conditions: (a) EDC, HOBT, *i*-Pr_2NEt, DMF; (b) cyclic amino acid ester; (c) LiOH, MeOH, H_2O, THF; (d) $PhCH_2CH_2NH_2$.

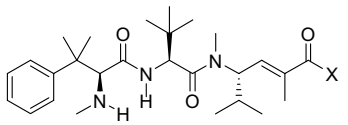
Reduction of the carboxylic acid in HTI-286 to the alcohol was effected by treatment with EDC in CH_3CN followed by addition of $NaBH_4$ to give analog **21** (Scheme 2). Oxidation of the alcohol in **21** with DMSO and oxalyl chloride[6] gave the corresponding aldehyde **22**. Aldehyde **22** could also be synthesized by conversion of the carboxylic acid in HTI-286 to the Weinreb amide (**23**), followed by reduction using $LiAlH_4$.

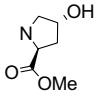
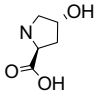
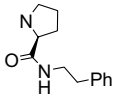
The Weinreb amide moiety could also be used for the preparation of ketones **24**–**26** by reaction with organometallic reagents (Scheme 3). For example, treatment of **23** with 3 equiv PhMgBr gave phenyl ketone **25**. The hydroxymethyl ketone analog **26** was prepared by treatment of **23** with $LiCH_2OSEM$ followed by removal of the SEM group with TFA.[7] The methyl ketone **27** was prepared by treatment of the ethyl ester of HTI-286 (**28**) with Tebbe reagent,[8] followed by acid hydrolysis. The aldehyde group in **22** could be used as a handle for further modification by treatment with organometallic reagents to give the corresponding alcohols (**29**–**32**) as epimeric mixtures. HPLC separation gave the phenyl alcohol diastereomers **31** and **32** whose stereochemistry was determined by NMR analysis. ROE correlations between protons on the CD portion of the molecule were consistent with the assigned stereochemistry for each isomer. Treatment of **22** with Wittig reagent $Ph_3PC(CH_3)CO_2Et$, gave diene **33** after saponification with LiOH.

Oxidation of the double bond in HTI-286 by ozonolysis gave intermediate **34**, which was used to efficiently effect D-piece transformations, including synthesis of two analogs not available through stepwise synthesis (Scheme 4). Thus, ozonolysis of HTI-286 followed by treatment with Me_2S cleaved the olefin to give aldehyde **34**. Treatment of **34** with Wittig reagents gave analogs **35**–**39**. Reaction with the hydantoins[9] **40** and **41** in the presence of LiOH gave **35** and **36**, respectively, as a mixture of isomers. Reaction with trifluoroethyl phosphonate[10] **42** gave the *Z* olefin isomer **37** after saponification with LiOH. Analog **37** could not be prepared in a stepwise fashion due to the propensity of *cis* vinylagous amino esters to cyclize to lactams.[11] Reaction of **34** with PPh_3CHCO_2Et gave **38** after saponification with LiOH. Analog **38** was not readily prepared in a stepwise synthesis due to reactivity of the disubstituted olefin during the repetitive coupling and deprotection steps required. Reaction of **34** with **43** gave **39**. Ozonolysis of HTI-286 followed by treatment with NaOCl cleaved the olefin to give acid **44**.

Four analogs (**45**–**48**) were synthesized using methods described above on C-piece, D-piece, or CD-Piece segments of HTI-286 (Scheme 5). The resulting segments

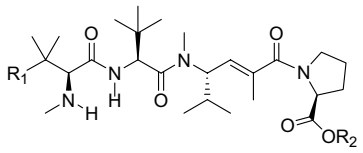
Table 1. Cyclic amino acid analogs



Compound	X	Tubulin[a]	KB-3-1[b]	KB-8-5[b]	KB-V1[b]
HTI-286 (**2**)		88[c]	0.96	2.3	77
3		82[d]	1.5	7.3	291
4		96	16	51	1099
5		77	5.2	17	150
6		94	3.5	17	272
7		93	3.5	116	>3000
8		97[d]	62	205	>3000
9		91	515	1577	>3000
10		89	64	270	>3000
11		90	58	184	>3000
12		96	184	1850	>3000
13		86[d]	6.4	21	1673

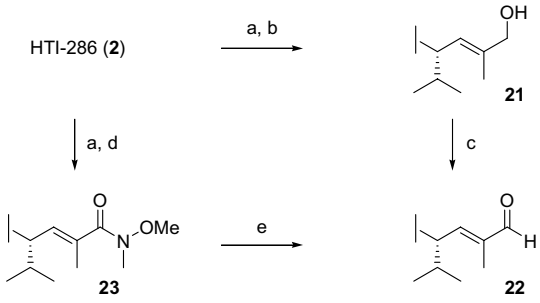
[a] %Inhibition of tubulin polymerization at 0.5 μM.
[b] IC_{50} (nM) in cells.
[c] Average over 10 runs.
[d] %Inhibition of tubulin polymerization at 0.3 μM.

Table 2. Proline amide derivatives

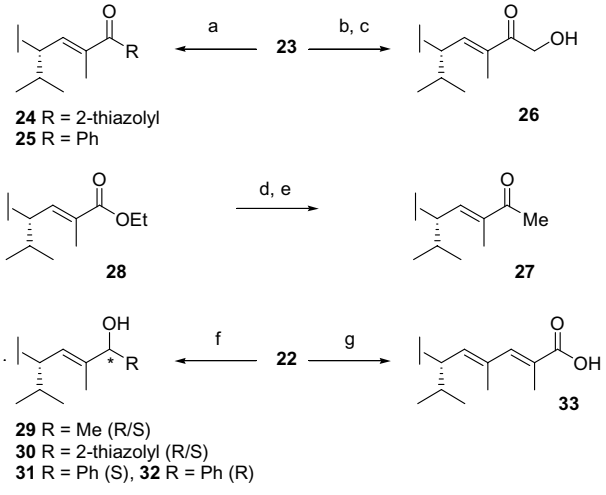


Compound	R_1	R_2	Tubulin[a]	KB-3-1[b]	KB-8-5[b]	KB-V1[b]
14	3-Tolyl	Me	89	1.6	6.2	275
15	3-Tolyl	H	95	70	599	>3000
16	3-Cl-Ph	Me	88	2.5	6.2	362
17	3-Cl-Ph	H	94	62	180	>3000
18	3,4-Xylyl	Me	71	1.9	15	363
19	3,4-Xylyl	H	76	74	519	>3000
20	C-hexyl	Me	88	3.7	16	493

[a] %Inhibition of tubulin polymerization at 0.5 μM.
[b] IC_{50} (nM) in cells.

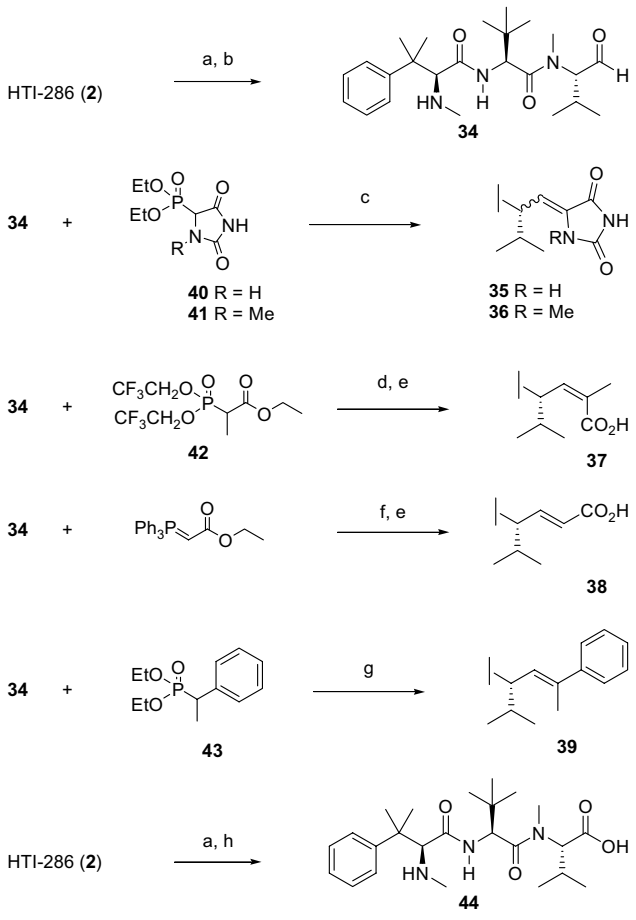


Scheme 2. Reagents and conditions: (a) EDC, HOBT, *i*-Pr_2NEt, CH_3CN; (b) $NaBH_4$; (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; (d) NHMeOMe; (e) $LiAlH_4$, Et_2O, −30 to 0 °C.



Scheme 3. Reagents and conditions: (a) THF, 0 °C **24**: 2-Li-thiazole, **25**: PhMgBr; (b) *n*-$BuSnCH_2OSEM$, *n*-BuLi, THF, −78 to −60 °C; (c) TFA, CH_2Cl_2: (d) (1) Tebbe reagent, THF, −40 to 25 °C; (2) aq NaOH; (e) 1 N aq HCl, THF; (f) THF, 0 °C, **29**: MeMgBr, **30**: 2-Li-thiazole, **31**/**32**: PhMgBr; (g) (1) $PPh_3C(Me)CO_2Et$; (2) LiOH, MeOH, H_2O.

were coupled to the remaining amino acids in a manner analogous to that reported in the literature.[3,5] Thus, the imidazole analog **45** was synthesized by treating the

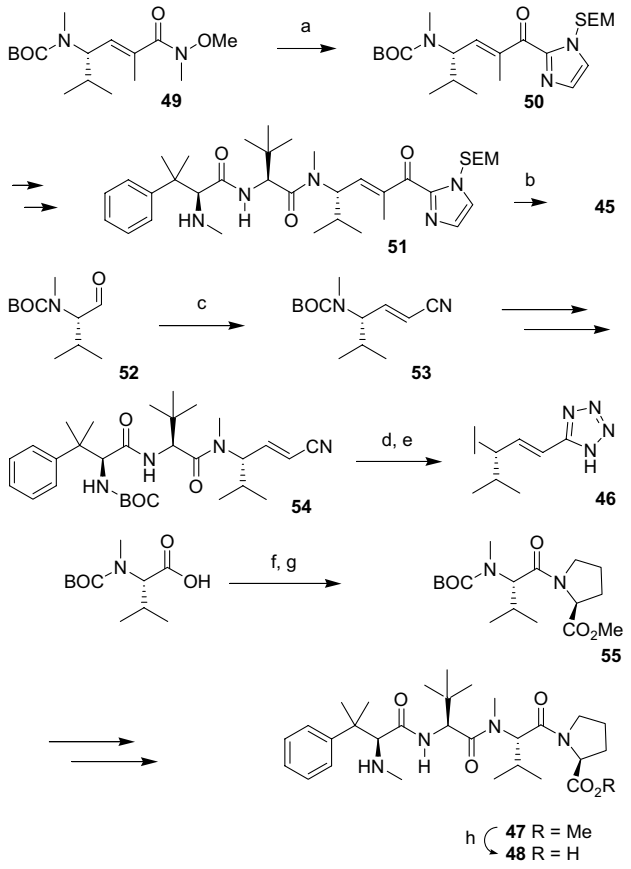


Scheme 4. Reagents and conditions: (a) O_3, MeOH, −78 °C; (b) Me_2S; (c) LiOH, EtOH, H_2O; (d) $KN(TMS)_2$, 18-C-6, THF; (e) LiOH, MeOH, H_2O; (f) CH_2Cl_2, 25 °C; (g) NaH, THF; (h) NaOCl.

Weinreb amide **49** with 2-Li-3-SEM-imidazole[12] to give **50**, followed by coupling to the A-piece to give **51** and removal of the SEM group with TFA. Tetrazole **46** was synthesized by treatment of **52** with PPh_3CHCN to give nitrile **53**, which was coupled, sequentially to the B-piece and A-piece to give Boc-protected intermediate **54**. Treatment with $TMSN_3$ and *n*-Bu_2SnO[13] followed by deprotection gave tetrazole **46**. Coupling of Boc-protected *N*-methyl-L-valine with proline gave **55**, which was coupled sequentially to the B-piece and A-piece to give ester **47**. Saponification of **47** with LiOH gave acid **48**.

Transformation of the D-piece carboxylic acid into a range of functional groups was carried out to evaluate the structural requirements of this region of HTI-286. Compounds were evaluated for their ability to inhibit cell-free tubulin polymerization.[2] Cytotoxicity was determined in paclitaxel sensitive KB-3-1 cells and in paclitaxel resistant KB-8-5 and KB-V1 cells expressing moderate and high levels of P-glycoprotein, respectively.[2] Functional group changes led to analogs with a wide range of potency including compounds with activity comparable to HTI-286.

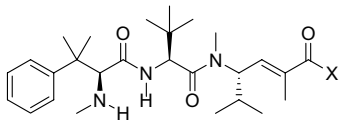
We had previously prepared amide analogs using simple cyclic and acyclic amines.[5] Although these compounds



Scheme 5. Reagents and conditions: (a) 2-Li-3-SEM-imidazole, THF, 0 °C; (b) TFA, CH_2Cl_2; (c) Ph_3CHCN, CH_2Cl_2; (d) $TMSN_3$, *n*-Bu_2SnO, toluene, 100 °C; (e) HCl, dioxane; (f) EDC, HOBT, *i*-Pr_2NEt, DMF; (g) L-proline methyl ester; (h) LiOH, MeOH, H_2O, THF.

were active, they were approximately one to three orders of magnitude less potent than the corresponding acids in the KB-3-1 cells. We now report that incorporation of cyclic amino acids gives analogs with dramatic increases in potency (Table 1). Thus, in the case of the L-proline ester analog **3**, the IC_{50} in KB-3-1 cells was 1.5 nM, comparable to the activity of HTI-286 ($IC_{50} = 0.96$ nM). It was also active in P-glycoprotein expressing cell lines (KB-8-5 and KB-V1) resistant to paclitaxel. The binding affinity (K_D) of **3** to tubulin was 0.9 μM, approximately threefold higher than that of HTI-286 ($K_D = 0.26$ nM).[2] The analog **4** made from D-proline ester was less potent (KB-3-1 $IC_{50} = 16$ nM). Keeping the L-amino acid configuration constant and expanding the ring size to cyclohexane (**5**), introducing unsaturation in the ring (**6**), or substituting the ring with a hydroxy group (**7**) gave potent analogs with IC_{50} values below 10 nM in the KB-3-1 cells. Relative to HTI-286 and analogs **3**–**6**, the hydroxyproline ester **7** was less effective in the resistant cell lines (KB-8-5, KB-V1) indicating that it was a better substrate for P-glycoprotein. The corresponding carboxylic acid of each of these analogs (**8**–**12**) was 10- to 50-fold less potent than the ester. The L-proline phenethyl amide moiety gave a potent analog **13** with an $IC_{50} = 6.4$ nM in the KB-3-1 cells. These proline analogs are structurally related to dolastatin-10 as hybrids of HTI-286 and the proline derived amine portion of dolastatin-10 yield potent tubulin inhibitors.[14] L-Proline amides with A-piece modifications where the phenyl ring was replaced with 3-tolyl, 3-Cl-phenyl, 3,4-xylyl, and cyclohexyl gave analogs (**14**–**20**) with comparable biological activities (Table 2).

Table 3. Ketone derivatives



Compound	X	Tubulin[a]	KB-3-1[b]	KB-8-5[b]	KB-V1[b]
22	H	71	454	447	1594
28	CH_3	69	403	664	2358
45	2-Imidazolyl	91[c]	218	1364	>3000
24	2-Thiazolyl	33	582	565	1787
25	Phenyl	70[c]	725	1326	1805
26	CH_2OH	76[c]	43	68	1134

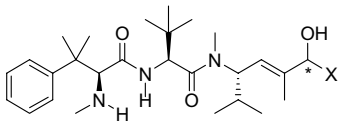
[a] %Inhibition of tubulin polymerization at 0.3 μM.
[b] IC_{50} (nM) in cells.
[c] %Inhibition of tubulin polymerization at 0.5 μM.

Conversion of the carboxylic acid to an aldehyde (**22**) or a methyl ketone (**28**) led to greater than two orders of magnitude decrease in potency in the KB-3-1 cells ($IC_{50} \sim 400$ nM) (Table 3). Efforts to increase potency by incorporation of other R groups (2-imidazolyl, 2-thiazolyl, phenyl) gave analogs (**45**, **24**, **25**, respectively) with similar activity. However, use of the α-hydroxymethyl ketone group, reported to serve as a carboxylic acid equivalent in other systems,[15] led to an analog (**26**), with a striking 10-fold increase in potency ($IC_{50} = 43$ nM), relative to **28** in the KB-3-1 cells.

Reduction of the carboxylic acid to a primary alcohol gave analog **21**, with greater than two orders of magnitude loss of potency in the KB-3-1 cells ($IC_{50} = 454$ nM). However, in contrast to the ketone analogs, addition of simple R groups led to dramatic increases in potency. Thus, the methyl alcohol analog **29** had an $IC_{50} = 63$ nM in the KB-3-1 cells. A further potency increase was achieved in the 2-thiazolyl containing analog **30** with an $IC_{50} = 13$ nM in the KB-3-1 cells. The configuration of the alcohol was revealed to be important for potency. Thus, in the pair of alcohol diastereomers incorporating a phenyl group (**31**, **32**), analog **31** with the *S* configuration at the carbon bearing the alcohol, was approximately eight times more potent than the epimer (**32**) in the KB-3-1 cells ($IC_{50} = 16$ nM). The alcohols **30** and **31** were also poorer substrates for P-glycoprotein than other analogs as indicated by their enhanced activity in the resistant KB-8-5 and KB-V1 cell lines relative to the non-P-glycoprotein expressing KB-3-1 cells (Table 4).

Incorporation of the carboxylic acid into an acidic heterocycle gave the potent hydantoin analog **36** (KB-3-1 cell $IC_{50} = 5.1$ nM). A decrease in potency was seen upon the demethylation of the hydantoin to give **35**. Weak activity was seen with the tetrazole carboxylic

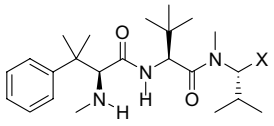
Table 4. Alcohol analogs

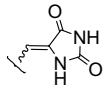
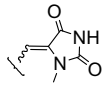
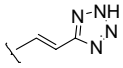
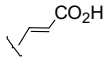
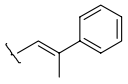
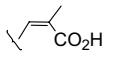
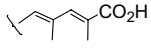
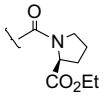
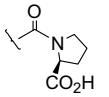


Compound	X	*	Tubulin	KB-3-1[a]	KB-8-5[a]	KB-V1[a]
21	H	—	71[b]	454	447	1594
29	CH_3	*R*/*S*	75[c]	63	172	1455
30	2-Thiazolyl	*R*/*S*	97[c]	13	19	364
31	Ph	*S*	63[b]	16	22	190
32	Ph	*R*	83[c]	124	186	632

[a] IC_{50} (nM) in cells.
[b] %Inhibition of tubulin polymerization at 0.3 μM.
[c] %Inhibition of tubulin polymerization at 0.5 μM.

Table 5. Carboxylic acid transformations and translations



Compound	X	Tubulin[a]	KB-3-1[b]	KB-8-5[b]	KB-V1[b]
35		59	1072	1738	>3000
36		95[c]	5.1	9.9	230
46		31	1148	1819	>3000
38		53	191	479	>3000
39		13	>3000	>3000	>3000
37		11	28	58	2630
33		90[c]	27	53	1582
44	$-CO_2H$	0[c]	>3000	>3000	>3000
47		19[c]	18	53	1533
48		27[c]	>3000	>3000	>3000

[a] %Inhibition of tubulin polymerization at 0.3 μM.
[b] IC_{50} (nM) in cells.
[c] %Inhibition of tubulin polymerization at 0.5 μM.

acid bioisostere **46**, although the lack of a methyl group on the olefin probably contributed to the low potency as in desmethyl analog **38**. Conversion of the carboxylic acid to a lipophilic phenyl ring (**39**), in contrast to the acidic tetrazole, led to a loss of potency at 3000 nM. Changing the orientation of the carboxylic acid through isomerization of the olefin to the *Z* configuration was tolerated giving analog **37**, with an IC_{50} value of 28 nM in the KB-3-1 cells. Moving the carboxylic acid longitudinally through elongation of the molecule, by adding a second olefin, gave **33** having an $IC_{50} = 27$ nM. However, truncation of the molecule gave carboxylic acid **44** with an $IC_{50} > 3000$ nM. Conversion of the acid in **44** to the proline ester gave analog **47**, having good potency in the KB-3-1 cells ($IC_{50} = 18$ nM). The five-membered ring may serve as a rigid scaffold placing the ester group in the proper orientation for tubulin binding. We had previously shown that the olefin in HTI-286 serves as a structural component as its hydrogenation led to a potent saturated analog.[5] Analog **47** bears a structural relationship to cemadotin as the hybrid of **44** with the proline containing amine portion of cemadotin produces a potent tubulin inhibitor.[14] The corresponding acid (**48**) had an $IC_{50} > 3000$ nM in the KB-3-1 cells (Table 5).

The above results indicate the need for a hydrogen bonding group in the D-piece of HTI-286 and a requirement for a correct spatial orientation of the group. In the series of cyclic amino acid amide analogs the additional polar carboethoxy group leads to increased potency over simple amides. In addition, the configuration at the carbon bearing the carboethoxy group is critical for optimum potency. For the ketone analogs, there is greatly reduced potency compared to analogous amides or esters,[5] perhaps due to the lower electron density on the carbonyl oxygen. However, adding a hydrogen bonding hydroxy group to the ketone (**26**) gives a sharp increase in potency. The alcohols were quite potent, with the orientation of the hydroxy group playing an important role in potency as seen in the enhanced potency of the *S* diastereomer (**31**). Replacing the olefin with a pyrrolidine ring (**47**) places the carboethoxy group in a defined orientation. There appears to be some flexibility in the location of the polar group as seen in **33** and **37** but not in **44**. Replacement of the carboxylic acid with a nonpolar phenyl group (**39**) leads to loss of potency in contrast to replacement with the acidic tetrazole ring (**46**). The tubulin polymerization assay results were not always consistent with the cellular cytotoxicity data. Cell permeability and concentration within cells[16] may play a role in cytotoxicity. The polymerization assay also measures the effects of inhibitors on microtubule formation but not their affinity to the tubulin heterodimer,[17] although it is unlikely that tubulin is not the target as photoaffinity probes specifically label alpha tubulin.[18] For analog **3**, the K_D value was consistent with the polymerization data.

In addition to having potent cellular activity, the L-proline analog **3** was active in a Lox melanoma human tumor xenograft model[2] in athymic mice. The minimum effective dose (MED) was 1 mpk administered

i.v. on a 1, 5, 9 day schedule ($p < 0.5$). HTI-286 (**2**) had an MED of 0.2 mpk in the xenograft model.

In summary, conversion of the carboxylic acid group in HTI-286 to other polar functionality gave potent tubulin inhibitors with activity in taxane resistant cell lines expressing P-glycoprotein. Potency was dependent on the nature of the functional group. The ability of the group to form hydrogen bonds and a correct spatial orientation were factors critical to activity. In vivo activity in a xenograft model in athymic mice was achieved with proline analog **3**.

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