Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 865–869

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

2-Arylindole-3-acetamides: FPP-Competitive Inhibitors of Farnesyl Protein Transferase

B. Wesley Trotter,[a,*] Amy G. Quigley,[a] William C. Lumma,[a] John T. Sisko,[a] Eileen S. Walsh,[b] Christian S. Hamann,[b] Ronald G. Robinson,[b] Hema Bhimnathwala,[b] D. Garrett Kolodin,[c] Wei Zheng,[c] Carolyn A. Buser,[b] Hans E. Huber,[b] Robert B. Lobell,[b] Nancy E. Kohl,[b] Theresa M. Williams,[a] Samuel L. Graham[a] and Christopher J. Dinsmore[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[b]*Department of Cancer Research, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Automated Biotechnology, Merck Research Laboratories, West Point, PA 19486, USA*

Received 1 December 2000; accepted 15 January 2001

Abstract—A series of 2-arylindole-3-acetamide farnesyl protein transferase inhibitors has been identified. The compounds inhibit the enzyme in a farnesyl pyrophosphate-competitive manner and are selective for farnesyl protein transferase over the related enzyme geranylgeranyltransferase-I. A representative member of this series of inhibitors demonstrates equal effectiveness against HDJ-2 and K-Ras farnesylation in a cell-based assay when geranylgeranylation is suppressed. © 2001 Published by Elsevier Science Ltd.

Inhibition of the cellular enzyme farnesyl protein transferase (FPTase) has emerged in recent years as a potentially effective strategy for cancer treatment. The observation that Ras prenylation, a primary function of FPTase, is essential to membrane localization of Ras and subsequent propagation of growth-promoting signals has prompted a number of investigators to design and synthesize selective, small molecule farnesyl protein transferase inhibitors (FTIs).[1] Further studies of FTIs and their biological activities have painted an increasingly complex picture of the effects of these compounds on cells.[2,3] Importantly, two of three Ras isoforms found in human cells can be alternatively prenylated by the enzyme geranylgeranyltransferase-I (GGPTase-I) in the absence of FPTase activity,[4] and non-Ras substrates for FPTase have been discovered.[5]

Despite such considerations, FTIs have shown promising early results as antitumor agents in human clinical trials.[6] FTIs reported to date can be broadly classified under three headings: (a) protein-competitive inhibitors, which occupy the FPTase site that normally accepts a C-terminal Ca_1a_2X peptide binding motif; (b) farnesyl pyrophosphate (FPP) competitive compounds, which displace the second FPTase substrate; and (c) bisubstrate inhibitors designed to occupy the peptide and FPP binding sites simultaneously.[1]

Given the existence of at least 18 FPTase protein substrates in mammalian cells,[2] inhibitors that compete only with FPP offer the potential advantage of protein substrate-independent enzyme inhibition. A number of small molecule FPP-competitive FTIs have been designed,[7] the majority by farnesylpyrophosphate mimicry[8] or by modification of previously identified inhibitors of the FPP-utilizing enzyme squalene synthase.[9] Here we report the identification of a unique series of FPP-competitive FTIs, 2-arylindole-3-acetamides,[10] which were developed from a high-throughput screen for FPTase inhibition.

Arylindole **1** is highly selective for inhibition of FPTase (IC_{50} 106 nM) over the related prenyltransferase GGPTase-I (IC_{50} GGPTase-I >20,000 nM). The mode of FPTase inhibition by **1** was qualitatively determined by observation of FPP- and CaaX-dependent modulations of inhibitory potency (Table 1). While variation of peptide substrate concentration had no effect on

*Corresponding author. Fax: +1-215-652-7310; e-mail: bwesley_trotter@merck.com

0960-894X/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0960-894X(01)00061-0

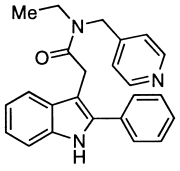
FPTase inhibition by **1**, increasing IC_{50} values were measured as the FPP concentration was raised from 20 to 500 nM.

In these experiments, we also observed a significant anion effect on inhibitory activity. For instance, while the mode of inhibition was anion-independent, consistently lower IC_{50} values were measured in the presence of 5 mM ATP (Table 1). This effect could be reproduced by the addition of various inorganic anions, including inorganic phosphate and sulfate.[11] A similar phenomenon has been observed previously in a structurally distinct class of FPP-competitive FPTase inhibitors.[7,12]

Structure–Activity Relationships: In Vitro Potency

Initial development of lead **1** focused on exploration of amide *N*-substituent structure–activity relationships. Rapid preparation of the appropriate compounds was possible via coupling reactions of commercially available acid **5** and various secondary amines (e.g., **4**, Scheme 1). The amines were obtained either from commercial sources or by reductive alkylation ($NaBH_4$, MeOH) of primary amines (**2** + **3**→**4**, Scheme 1).

Table 1. Mode of FPTase inhibition by **1**



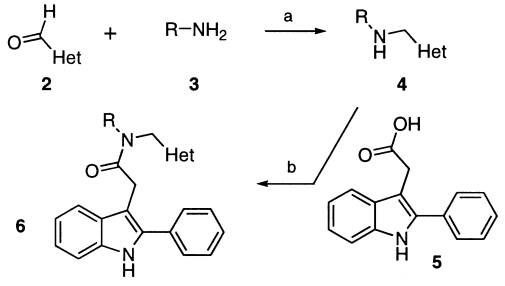
1

FPTase IC_{50} 106 nM[a]

GGTase-I IC_{50} > 20000 nM[b]

Peptide[c] (nM)	FPP (nM)	FPTase IC_{50} (nM)[d]	Peptide[c] (nM)	FPP (nM)	FPTase IC_{50} (nM)[d]
20	100	47 (230)	100	20	20 (54)
100	100	43 (250)	100	100	43 (250)
500	100	65 (230)	100	500	190 (4000)

[a]Concentration of compound required to reduce the human FPTase-catalyzed incorporation of ^3H FPP into recombinant Ras-CVIM by 50% in the presence of 5 mM ATP (ref 13).
[b]Concentration of compound required to reduce the human GGPTase-I-catalyzed incorporation of ^3H GGPP (100 nM) into a biotinylated K-Ras-derived peptide (1.6 μM, note c) by 50% (ref 14).
[c]Biotinylated peptide corresponding to the C-terminus of human K-Ras (b-GKKKKKKSKTKCVIM, Research Organics).
[d]Concentration of compound required to reduce the human FPTase-catalyzed incorporation of ^3H FPP into a biotinylated K-Ras-derived peptide (note c) by 50% in the presence of 5 mM ATP (ref 15); values in parentheses were obtained without addition of ATP.



Scheme 1. Conditions: (a) $NaBH_4$, MeOH; (b) PyBOP, iPr_2EtN, DMF.

Variation of the amide *N*-alkyl substituent was examined in the context of both 4- and 3-pyridylmethyl amides (Table 2).[16] Isopropyl amides **7a** and **7b** exhibited increased FPTase activity relative to **1**. Cyclopropyl and cyclobutyl substituents were well-tolerated in combination with the 3-pyridylmethyl substituent (**8b** and **9b**) but caused a drop in potency when combined with the 4-pyridylmethyl group (**8a** and **9a**).[17]

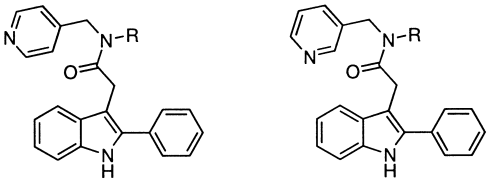
Larger substituents such as isobutyl and cyclopentyl (**10** and **11**) effected significant losses in potency. Bis(pyridylmethyl) *N*-substitution also resulted in decreased potency (**14**). *sec*-Butyl substituted enantiomers (*S*)-**12** and (*R*)-**13** exhibited a 50-fold difference in potency indicative of a stereospecific binding interaction for the *N*-alkyl substituent.

While 4- and 3-pyridylmethyl amides **7a** and **7b** were potent FPTase inhibitors, 2-pyridylmethyl isomer **7c** was an order of magnitude less active (Table 3). Other heterocyclic replacements, including pyrazine, furan, and pyrazole, were tolerated but exhibited somewhat reduced potencies. Replacement of the *N*-heteroarylmethyl substituent with nonaromatic groups was only successful in limited cases (vide infra).

Investigation of SAR in the 2-aryl region was accomplished using the synthesis strategy depicted in Scheme 2. Bromination[18] of 3-indolyl-acetonitrile was followed by Suzuki coupling with various boronic acids. Cyano hydrolysis and subsequent peptide coupling provided access to the desired compounds.

The 2-aryl region is largely intolerant to alteration (Table 4). Substitution at either the *para* or *meta* position of this aromatic ring was poorly tolerated (**20d**, **20e**).[19] In contrast, substitution at the *ortho* position of the 2-aryl ring was accommodated in certain cases. *ortho*-Chloro and *ortho*-methyl analogues **20a** and **20b** were as potent as the parent **7a**, but polar substitution at the *ortho*-position was not tolerated (**20c**, Table 4).

Table 2. Variation of the amide *N*-alkyl substituent



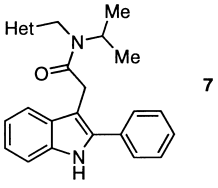
Compound	R	IC_{50} (nM)[a]	Compound	R	IC_{50} (nM)[a]
7a	Isopropyl	41	**7b**	Isopropyl	58
8a	Cyclopropyl	171	**8b**	Cyclopropyl	45
9a	Cyclobutyl	160	**9b**	Cyclobutyl	44
10a	Isobutyl	3900	**10b**	Isobutyl	2484
11a	Cyclopentyl	4004	**11b**	Cyclopentyl	11389
12	(*S*)*s*-Butyl	77	**14**	3-Py-Methyl	2733
13	(*R*)*s*-Butyl	4588	**15**	1-CN-Ethyl	380

[a]See footnote a in Table 1.

Removal of the 2-aryl moiety results in complete loss of potency (**21a**). This potency can be partially recovered by attachment of a benzyl group to the indole nitrogen (Table 4). Introduction of substituents on the benzyl group exerts significant effects on potency; the *ortho*-bromo substituted compound **21c** is the most active in this class. In FPTase-bound conformations, the *N*-benzyl group found in **21b–e** may therefore occupy the same space as the 2-aryl moiety common to **1–20**.

Substitution of the remaining positions on the indole nucleus was next examined. Methyl substitution at any of the 4–7 positions of the indole nucleus[20] resulted in substantial loss of FPTase potency. In contrast, alkylation of the indole nitrogen[21] (Table 4) provided *N*-methyl derivatives **22a** and **22b**, the most potent compounds synthesized to date in the 2-arylindole-3-acetamide series. Homologation to the *N*-ethyl derivative **22c** resulted in a dramatic decrease in potency, and higher homologues were less potent still.

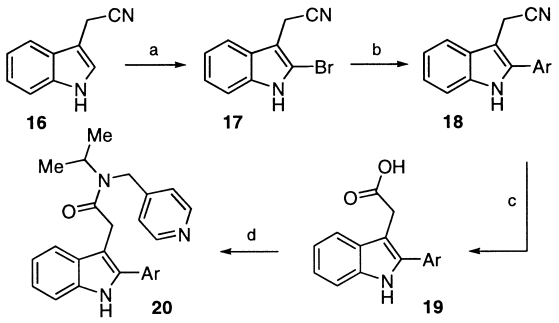
Table 3. FPTase inhibition by heterocyclic variants of **1**



7

Compound	Het	IC_{50} (nM)[a]	Compound	Het	IC_{50} (nM)[a]
7a		41	**7f**		232
7b		58	**7g**		400
7c		684	**7h**		245
7d		110	**7i**		527
7e		241	**7j**		568

[a]See footnote a in Table 1.



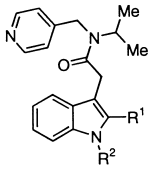
Scheme 2. Conditions: (a) *N*-bromosuccinimide, silica gel, CH_2Cl_2; (b) Ar-$B(OH)_2$, LiCl, Na_2CO_3, $Pd(PPh_3)_4$, toluene; (c) NaOH, MeOH/H_2O; (d) isopropyl 4-pyridylmethylamine, PyBOP, *i*Pr_2EtN, DMF.

N-Cyanoethyl-*N*-cyclopropyl amides **23** are among the few examples we have found of non-arylmethyl amides that retain in vitro potency against FPTase (Table 5). Comparison of the SAR delineated above with the dataset obtained for the cyanoethyl analogues **23** again indicates that the contributions to potency of different regions of the molecule are nonadditive. Methylation of the indole 1-position in this series does not increase potency (contrast **23a**/**23b** and **7a**/**22b**). Likewise, *ortho*-substitution of the 2-aryl group in this series is not well tolerated (**23c**,**d**). This tight interplay among substituent patterns may be a further indication of highly restrictive requirements for binding to FPTase.[22]

Inhibition of Protein Processing in Cell-Based Assays

Inhibitors **22a** and **22b** were selected for further evaluation in cell-based assays. Both compounds inhibited the

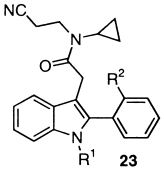
Table 4. Modifications of the 2-arylindole core



Compound	R^1	R^2	IC_{50} (nM)[a]
20a	2-Cl-Ph	H	46
20b	2-Me-Ph	H	31
20c	2-MeO-Ph	H	1372
20d	3-Cl-Ph	H	172
20e	4-Br-Ph	H	14,369
21a	H	H	>50,000
21b	H	Bn	8685
21c	H	2-Br-Bn	572
21d	H	3-Br-Bn	2150
21e	H	4-Br-Bn	1740
22a	2-Me-Ph	Me	12
22b	Ph	Me	15
22c	Ph	Et	3803
22d	Ph	*n*-Pr	29,863
22e	Ph	*n*-Bu	>50,000

[a]See footnote a in Table 1.

Table 5. Cyanoethyl replacement of the amide *N*-arylmethyl substituent



23

Compound	R^1	R^2	IC_{50} (nM)[a]
23a	H	H	123
23b	Me	H	182
23c	H	Me	712
23d	H	Cl	1628
23e	H	OMe	8641

[a]See footnote a in Table 1.

Table 6. Inhibition of HDJ-2 and K-Ras processing in PSN-1 cells[a]

Compound	GGTI[b] (nM)	HDJ-2 EC_{50} (nM)[c]	K-Ras EC_{50} (nM)[d]
22b	0	1980	>30,000
22b	100	1000	1800
CCFTI[a]	0	2.3	>3000
CCFTI[a]	100	—	78

[a]See ref 26.
[b]*N*-(1-Adamantyl)-4-{(1-(4-cyanobenzyl)-1*H*-imidazol-5-yl)-methyl}-piperazine-1-carboxamide, compound **1** in ref 14.
[c]See ref 24 (assay duration was 24 h).
[d]Concentration of compound required to inhibit prenylation of K-Ras in PSN-1 cells during a 24 h period by 50% (assay conditions analogous to ref 24).

farnesylation of the FPTase substrate HDJ-2[23] in PSN-1 cells with approximately equal potency (EC_{50} **22a** = 1064 nM, EC_{50} **22b** = 1332 nM).[24]

Given the ability of these compounds to inhibit protein prenylation in cells, an experiment was designed to investigate the possibility of protein substrate-independent inhibition of FPTase by **22b**. We chose to compare inhibition of HDJ-2 processing with that of K-Ras. Inhibition of K-Ras farnesylation by protein-competitive inhibitors is generally weaker than inhibition observed for other FPTase substrates due to the high affinity of FPTase for K-Ras.[4] However, an FPP-competitive inhibitor such as **22b** might inhibit farnesylation of K-Ras and other substrates with equal potency.

Complicating a direct comparison of HDJ-2 and K-Ras processing in cell culture is the fact that, while HDJ-2 is prenylated only by FPTase, K-Ras is a substrate for both FPTase and GGPTase-I and can therefore be alternatively geranylgeranylated by GGPTase-I when FPTase activity is inhibited.[25] Thus, **22b** alone does not inhibit processing of K-Ras (EC_{50} >30,000 nM, Table 6). However, when geranylgeranylation is suppressed by addition of a selective GGPTase-I inhibitor (**GGTI**, GGPTase-I IC_{50} 0.2 nM, FPTase IC_{50} 517 nM),[14] **22b** inhibits K-Ras processing with approximately the same potency as it does HDJ-2 processing (Table 6). In contrast, a Ca_1a_2X-competitive FPTase inhibitor (**CCFTI**, FPTase IC_{50} 0.1 nM, GGPTase-I IC_{50} 300 nM)[26] is 30-fold less potent against K-Ras than against HDJ-2 under the same conditions.

In conclusion, FPP-competitive farnesyltransferase inhibitors which are neither peptidomimetics nor farnesylpyrophosphate mimics have been identified. The 2-arylindole-3-acetamides surveyed here are selective for FPTase over the related enzyme GGPTase-I and appear to inhibit protein farnesylation in a protein substrate-independent manner. As our understanding of the cellular consequences of FPTase inhibition continues to evolve, this structurally unique class of FTIs may prove valuable. A more detailed examination of the biological effects of these compounds awaits the preparation of analogues with improved cell activity.

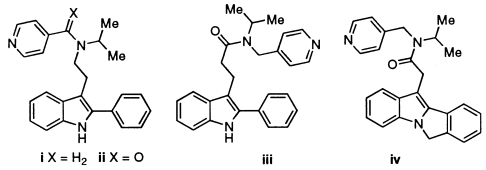
Acknowledgements

The authors would like to thank K. D. Anderson, P. A. Ciecko-Steck, A. B. Coddington, G. M. Smith, H. G. Ramjit, C. W. Ross, III, B.-L. Wan, and M. M. Zrada for analytical support.

References and Notes

1. Dinsmore, C. J. *Curr. Opin. Oncol. Endocr. Metabol. Invest. Drugs* **2000**, *2*, 26.
2. Oliff, A. *Biochim. Biophys. Acta*. **1999**, *C19*, 1423.
3. (a) Hill, B. T.; Perrin, D.; Kruczynski, A. *Crit. Rev. Oncol. Hematol.* **2000**, *33*, 7. (b) Prendergast, G. C. *Curr. Opin. Cell Biol.* **2000**, *12*, 166.
4. Zhang, F. L.; Kirschmeier, P.; Carr, D.; James, L.; Bond, R. W.; Wang, L.; Patton, R.; Windsor, W. T.; Syto, R.; Zhang, R.; Bishop, R. W. *J. Biol. Chem.* **1997**, *272*, 10232.
5. Lebowitz, P. F.; Prendergast, G. C. *Oncogene* **1998**, *17*, 1439.
6. (a) Zujewski, J.; Horak, I. D.; Bol, C. J. J. G.; Woestenborghs, R.; End, D.; Chiao, J.; Belly, R. T.; Kohler, D.; Chow, C.; Noone, M.; Hakim, F. T.; Larkin, G.; Gress, R. E.; Nussenblatt, R. B.; Kremer, A. B.; Cowan, K. H. *American Society of Clinical Oncology 35th Annual Meeting*. Atlanta, GA, 1999. (b) Adjei, A. A.; Erlichman, C.; Davis, J. N.; Cutler, D. L.; Sloan, J. A.; Marks, R. S.; Hanson, L. J.; Svingen, P. A.; Atherton, P.; Bishop, W. R.; Kirschmeier, P.; Kaufmann, S. H. *Cancer Res.* **2000**, *60*, 1871.
7. Leonard, D. M.; Shuler, K. R.; Poulter, C. J.; Eaton, S. R.; Sawyer, T. K.; Hodges, J. C.; Su, T.-Z.; Scholten, J. D.; Gowan, R. C.; Sebolt-Leopold, J. S.; Doherty, A. M. *J. Med. Chem.* **1997**, *40*, 192.
8. Gibbs, B. S.; Zahn, T. J.; Mu, Y.; Sebolt-Leopold, J. S.; Gibbs, R. A. *J. Med. Chem.* **1999**, *42*, 3800.
9. (a) Yonemoto, M.; Satoh, T.; Arakawa, H.; Suzuki-Takahashi, I.; Moden, Y.; Kodera, T.; Tanaka, K.; Aoyama, T.; Iwasawa, Y.; Kamei, T.; Nishimura, S.; Tomimoto, K. *Mol. Pharmacol.* **1998**, *54*, 1. (b) Tahir, S. K.; Gu, W. Z.; Zhang, H. C.; Leal, J.; Lee, J. Y.; Kovar, P.; Saeed, B.; Cherian, S. P.; Devine, E.; Cohen, J.; Warner, R.; Wang, Y. C.; Stout, D.; Arendsen, D. L.; Rosenberg, S.; Ng, S. C. *Eur. J. Cancer* **2000**, *36*, 1161.
10. For the synthesis and evaluation of related 2-arylindole-3-acetamides as mDRC ligands and a discussion of the conformational properties of these molecules, see: Kozikowski, A. P.; Ma, D.; Brewer, J.; Sun, S.; Costa, E.; Romeo, E.; Guidotti, A. *J. Med. Chem.* **1993**, *36*, 2908.
11. The anion survey was performed for **22b**. The rank order of anion effects (from lowest observed IC_{50} to highest) was: dithiophosphate (ca. 30-fold reduction in IC_{50} at 5 mM) < ATP < thiosulfate < phosphate < sulfate~glycerophosphate (ca. 3-fold reduction in IC_{50} at 5 mM).
12. Researchers at Parke-Davis have observed similar effects in a peptidic series of FPP-competitive FTIs and have presented evidence that ATP and other anions mimic the phosphate group of FPP, thereby enhancing the binding of FPP-competitive inhibitors that do not otherwise occupy the phosphate binding region. See: Scholten, J. D.; Zimmerman, K.; Oxender, M.; Sebolt-Leopold, J.; Gowan, R.; Leonard, D.; Hupe, D. *J. Bioorg. Med. Chem.* **1996**, *4*, 1537.
13. Graham, S. L.; deSolms, S. J.; Giuliani, E. A.; Kohl, N. E.; Mosser, S. D.; Oliff, A. I.; Pompliano, D. L.; Rands, E.; Breslin, M. J.; Deana, A. A.; Garsky, V. M.; Scholz, T. H.; Gibbs, J. B.; Smith, R. L. *J. Med. Chem.* **1994**, *37*, 725.
14. Huber, H. E.; Abrams, M.; Anthony, N.; Graham, S.; Hartman, G.; Lobell, R.; Lumma, W.; Nahas, D.; Robinson, R.; Sisko, J.; Heimbrook, D. C. *Proc. Am. Assoc. Cancer Res.* **2000**, *41*, Abstract 2838.

15. Bishop, W. R.; Bond, R.; Petrin, J.; Wang, L.; Patton, R.; Doll, R.; Njoroge, G.; Catino, J.; Schwartz, J.; Windson, W.; Syto, R.; Schwarz, J.; Carr, D.; James, L.; Kirschmeier, P. *J. Biol. Chem.* **1995**, *270*, 30611.
16. All compounds synthesized in this study exhibited no measurable inhibition of GGPTase-I (GGPTase-I IC_{50} >20,000 nM).
17. This nonadditive SAR was further highlighted by observations in the isobutyl series **10**. The 2-pyridyl-methyl analogue **10c** (not shown; FPTase IC_{50} 1500 nM) was more potent than either **10a** or **10b**, in contrast to the trend seen for other alkyl substituents (e.g., **7a**–**c**). The possibility exists that a change in binding mode accompanies the change in amide substituent size. It is interesting to note that NMR studies of representative inhibitors in aqueous solution reveal that both tertiary amide rotamers are equally populated. Thus, both rotamers are available for enzyme binding, and the preferentially bound rotamer may vary with the identities of the amide substituents.
18. Mistry, A. G.; Smith, K.; Bye, M. R. *Tetrahedron Lett.* **1986**, *27*, 1051.
19. Corresponding *para*-pyridyl and *meta*-pyridyl compounds were prepared; these analogues also exhibited greatly reduced activity.
20. Synthesis of these compounds was accomplished by Fischer indolization of the appropriate ketoamide tolylhydrazone precursors (see ref 10). FPTase IC_{50} values: 7-Me, 702 nM; 5-Me, 8181 nM; 3:1 mixture of 4-Me and 6-Me, 3859 nM.
21. Guida, W. C.; Mathre, D. J. *J. Org. Chem.* **1980**, *45*, 3172.
22. In this vein, it is worth noting that a variety of minor modifications to the 2-arylindole-3-acetamide scaffold were deleterious to potency. For instance, removal or relocation of the amide carbonyl obliterated inhibitory activity, as did homologation of the acetamide linkage (**i**–**iii**, FPTase IC_{50} >50,000 nM). Conformational restriction of the 2-aryl group was also deleterious (**iv**, FPTase IC_{50} 9353 nM).



23. (a) Adjei, A. A.; Davis, J. N.; Erlichman, C.; Svingen, P. A.; Kaufmann, S. H. *Clin. Cancer Res.* **2000**, *6*, 2318. (b) Soignet, S.; Yao, S.-L.; Britten, C.; Spriggs, D.; Pezzulli, S.; McCreery, H.; Mazina, K.; Deutsch, P.; Lee, Y.; Lobell, R.; Rosen, N.; Rowinsky, E. *Proc. Am. Assoc. Cancer Res.* **1999**, *40*, Abstract 3413.
24. EC_{50} = concentration of compound required to inhibit farnesylation of HDJ-2 in PSN-1 cells during a 7 h period by 50%. Following treatment with **22a** or **22b**, RIPA lysates of PSN-1 cells were prepared and analyzed by SDS-PAGE (25 μg/well) and immunoblotting (anti-HDJ-2, Neomarkers) to determine extent of prenylation. See ref 23.
25. (a) Rowell, C. A.; Kowalczyk, J. J.; Lewis, M. D.; Garcia, A. M. *J. Biol. Chem.* **1997**, *272*, 14093. (b) Whyte, D. B.; Kirschmeier, P.; Hockenberry, T. N.; Nunez-Oliva, I.; James, L.; Catino, J. J.; Bishop, R. B.; Pai, J.-K. *J. Biol. Chem.* **1997**, *272*, 14459.
26. Dinsmore, C. J.; Bogusky, M. J.; Culberson, J. C.; Bergman, J. M.; Homnick, C. F.; Zartman, C. B.; Mosser, S. D.; Schaber, M. D.; Robinson, R.; Koblan, K. S.; Huber, H. E.; Graham, S. L.; Hartman, G. D.; Huff, J. R.; Williams, T. M. *J. Am. Chem. Soc.* **2001**, in press.