# Structure−Activity Relationship of 3-Substituted *N*-(Pyridinylacetyl)-4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-piperidine Inhibitors of Farnesyl-Protein Transferase: Design and Synthesis of in Vivo Active Antitumor Compounds

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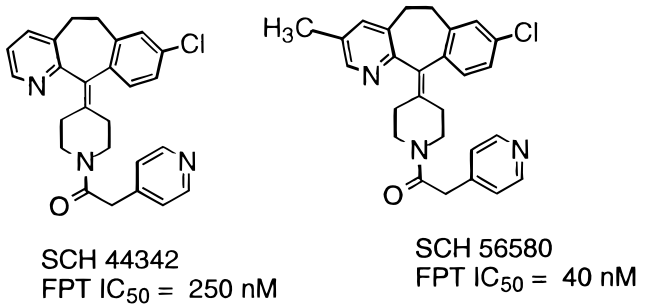
Novel tricyclic Ras farnesyl-protein transferase (FPT) inhibitors are described. A comprehensive structure−activity relationship (SAR) study of compounds arising from substitution at the 3-position of the tricyclic pyridine ring system has been explored. In the case of halogens, the chloro, bromo, and iodo analogues **19**, **22**, and **28** were found to be equipotent. However, the fluoro analogue **17** was an order of magnitude less active. Whereas a small alkyl substituent such as a methyl group resulted in a very potent FPT inhibitor (SCH 56580), introduction of bulky substituents such as *tert*-butyl, compound **33,** or a phenyl group, compound **29,** resulted in inactive FPT inhibitors. Polar groups at the 3-position such as amino **5**, alkylamino **6**, and hydroxyl **12** were less active. Whereas compound SCH 44342 did not show appreciable in vivo antitumor activity, the 3-bromo-substituted pyridyl *N*-oxide amide analogue **38** was a potent FPT inhibitor that reduced tumor growth by 81% when administered q.i.d. at 50 mpk and 52% at 10 mpk. These compounds are nonpeptidic and do not contain sulfhydryl groups. They selectively inhibit FPT and not geranylgeranyl-protein transferase-1 (GGPT-1). They also inhibit H-Ras processing in COS monkey kidney cells and soft agar growth of Ras-transformed cells.

Ras proteins are known to play a major role in controlling cell growth and differentiation.[1] Mutated Ras genes are found in 50% of lung and colorectal carcinomas and in up to 95% of pancreatic carcinomas. This observation has prompted considerable efforts at elucidating the pathways of Ras transformation and developing therapeutic agents which might interfere with this pathway.[2] To perform both its normal as well as its oncogenic functions, the Ras protein must be bound to the cell membrane. This occurs through a series of posttranslational modifications which include the farnesylation of the Ras protein using a farnesyl pyrophosphate donor and catalyzed by the enzyme farnesyl-protein transferase (FPT).[3] Inhibitors of FPT would therefore have potential as anticancer agents for tumors in which the Ras gene is mutated. A number of potent FPT inhibitors have been reported in the literature.[4−6] Some of these inhibitors have been shown to inhibit in vitro tumor cell growth[7] and have also shown activity in reducing tumor growth in animal models.[8] However, most of the reported FPT inhibitors are peptidic in nature or contain a sulfhydryl group. This laboratory recently reported a number of tricyclic compounds as novel nonsulfhydryl, nonpeptidic FPT inhibitors that also showed cellular activity.[9−11] One of these compounds, SCH 56580, a 3-methyl substituted analogue showed greatly enhanced activity in comparison to its unsubstituted analogue SCH 44342. It is for this reason that we decided to carry out an extensive study to investigate the effect of introducing other functionalities at the 3-position of the tricyclic pyridine ring system.




## Chemistry

Compounds prepared for this study are shown in Tables 1−5 and their synthetic routes are outlined in Schemes 1−7. Most of these compounds were prepared via carbodiimide-mediated coupling from appropriate tricyclic piperidine with either 3- or 4-pyridylacetic acid.[9] Chemistry for preparation of the 3-substituted analogues was greatly facilitated by our previous discovery that nitration of Loratadine[12] using tetrabutylammonium nitrate−trifluoroacetic anhydride nitrating system exclusively gave the 3-nitrosubstituted carbamate **2** (unpublished results). Hydrolysis of **2** in refluxing concentrated HCl gave amine **3** which was subsequently coupled with pyridineacetic acid to give target compound **4**. Reduction of **4** with iron powder in refluxing aqueous ethanol provided the 3-amino pyridylacetamide **5** (Scheme 1).

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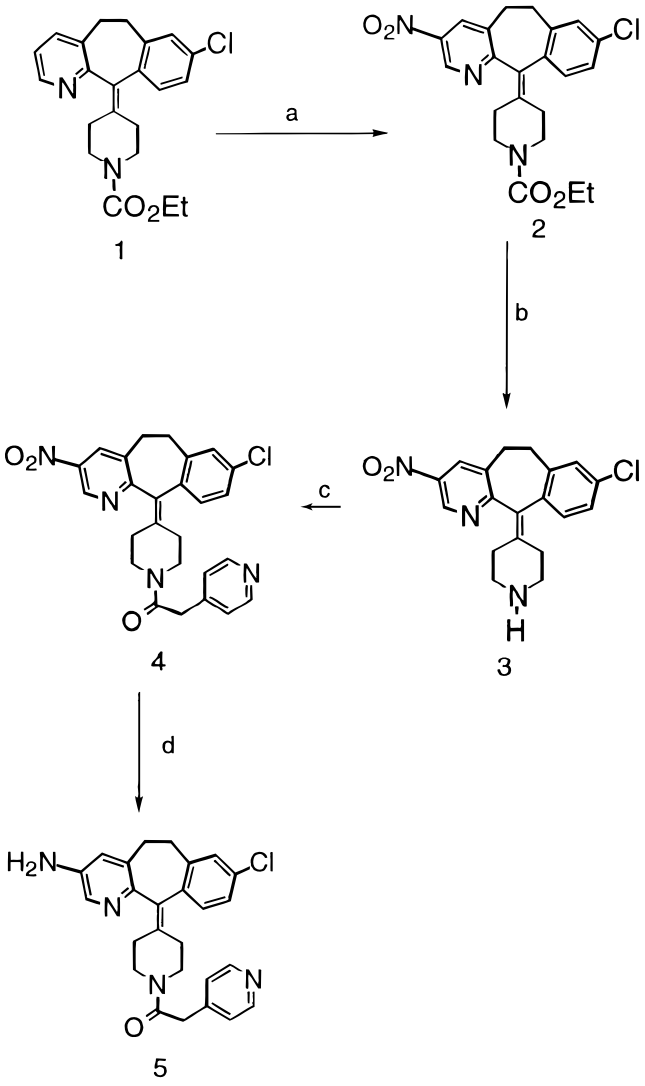
**Scheme 1**[a]



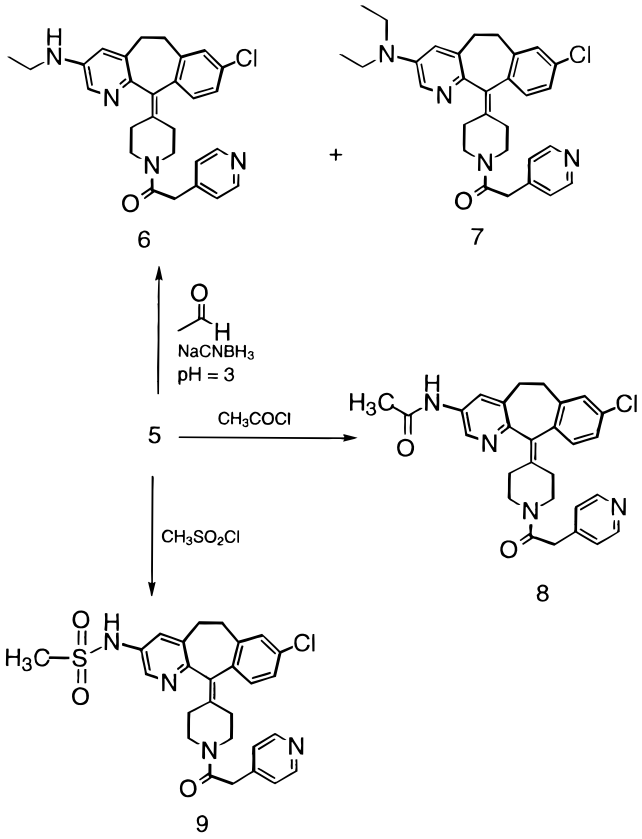

[a] (a) $Bu_4NNO_3$, TFAA; (b) concd HCl, reflux; (c) 4-pyridineacetic acid, DEC, HOBT, NMM; (d) iron fillings, $CaCl_2$.

Condensation of amine **5** with acetaldehyde followed by reduction with $NaBH_3CN$ at pH ~3 afforded the mono- and dialkylated amino carbamates **6** and **7**. While treatment of the amine **5** with acetyl chloride in the presence of triethylamine gave the 3-aminoacetyl compound **8**, reaction with methanesulfonyl chloride in the presence of potassium carbonate afforded the 3-aminosulfonyl derivative **9** (Scheme 2).

Diazotization of amine **5** using $NaNO_2$−HCl (HONO) followed by treatment with CuCN[13] gave the 3-cyano derivative **10**. On the other hand, treatment of the diazonium salt derived from amine **5** with CuSCN and KSCN according to the procedure of Burawoy et al.[14] gave the thiocyano compound **11.** In a similar manner diazotization of **5** followed by treatment with boiling $CuSO_4$ afforded the 3-hydroxyl compound **12**. Reaction of **12** with diazomethane gave the 3-methoxy analogue **13** (Scheme 3).

Methods of preparation of compounds **14**−**29** are as outlined in Scheme 4; thus, halogenations at the 3-position of the tricyclic ring system were conveniently effected through diazotization of amino carbamate **14** followed by treatment with the appropriate halogenating reagent. The latter is obtained from the reduction of the 3-nitro carbamate **2** using iron filings in refluxing

**Scheme 2**

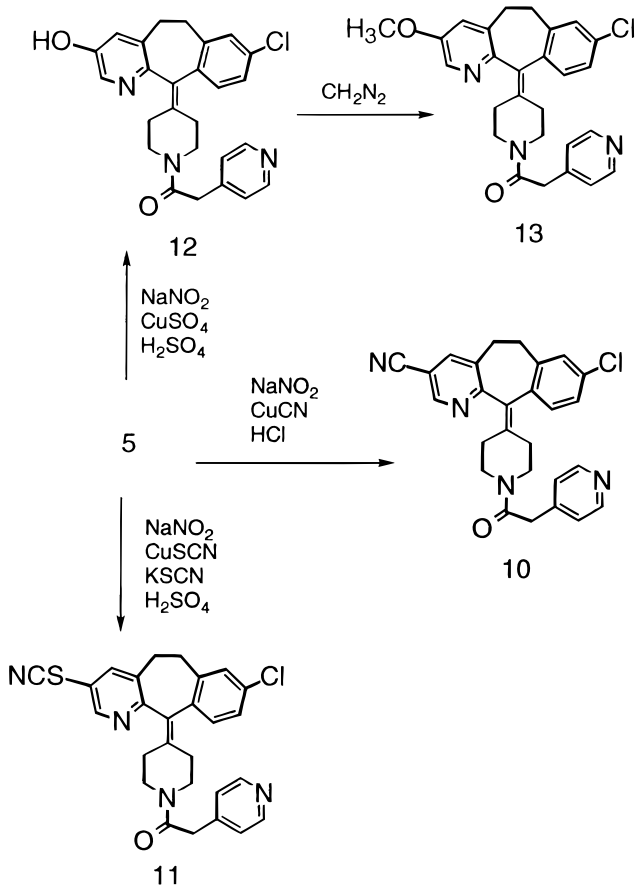



ethanol as previously described (Scheme 3). The 3-fluoro and 3-chloro carbamates **15** and **16,** respectively, were obtained from treatment of the amine **14** with nitrosonium tetrafluoroborate in dichloromethane/*o*-dichlorobenzene solvent system and heating the reaction mixture to 150 °C. Alternatively, the 3-chloro carbamate **16** could be prepared by treatment of the amino carbamate **14** with isoamyl nitrite in methylene chloride medium at refluxing temperatures. Carbamate **15** was hydrolyzed in refluxing concentrated HCl and subsequently coupled either to 4-pyridineacetic acid to give compound **17** or to 3-pyridineacetic acid to give compound **18**. In a similar manner the hydrolysate product of 3-chloro carbamate **16** was coupled with either 4- or 3-pyridylacetic acid to provide compound **19** or **20**, respectively (Scheme 4).

Preparation of the 3-bromo carbamate **21** was achieved by reacting the diazonium salt from amine **14** with $Br_2$ according to the method of Craig.[15] Again standard acid hydrolysis in refluxing HCl followed by standard DEC−HOBT coupling with either 4- or 3-pyridineacetic acid gave the desired 3-bromo target compound **22** or **23,** respectively. Reaction of 3-bromo carbamate **21** with sodium methylthiolate in the presence of strong UV light afforded the 3-thiomethyl carbamate **24**. The latter was acid-hydrolyzed and then coupled with 4-pyridineacetic acid to give the desired amide **25** (Scheme 4).

Finally, the 3-iodo and 3-phenyl substitutions were obtained by treatment of amine **14,** dissolved in benzene, with isoamyl nitrite in the presence of iodine. In this reaction both the 3-iodo and the 3-phenyl carbamates **26** and **27** were formed in a 2.6:1.0 ratio, respec-

**Scheme 3**




tively. It is possible that this reaction went through a free radical type of chemistry as previously described by Gokel et al.[16] The 3-iodo carbamate **26** and the 3-phenyl carbamate **27** were hydrolyzed and coupled to 4-pyridineacetic acid to give the target compounds **28** and **29**, respectively (Scheme 4).

Introduction of the trifluoromethyl moiety at the 3-position was accomplished by treatment of 3-iodo carbamate **26** with methyl fluorosulfonyldifluoroacetate in the presence of CuI according to the procedure described by Chen et al.[17] Since the trifluoromethyl group was labile toward acid hydrolysis,[18] transformation of the 3-trifluoromethyl carbamate **30** to the desired amine was carried out in aqueous potassium hydroxide. This reaction was rather sluggish; nevertheless, we obtained enough of the desired amine that was coupled with pyridineacetic acid to give the target 3-trifluoromethyl compound **31** (Scheme 5).

The 3-*tert*-butyl-substituted amide **33** was prepared from the coupling of the previously reported amine **32**[19] with 4-pyridineacetic acid through similar chemistry as described above. The 3-methyl-substituted 4-pyridylacetamide **35** was prepared in a similar manner from the previously reported amine **34**[20] (Scheme 6).

Preparation of 3-bromopyridine *N*-oxide acetamide **38** starts with the 3-bromo carbamate **21** which was hydrolyzed in refluxing concentrated HCl to give amine **36.** This amine was then coupled with 4-pyridineacetic acid *N*-oxide (**37**) (prepared by oxidation of ethyl 4-pyridylacetate with *m*-CPBA followed by base hydrolysis) to give the amide **38** (Scheme 7). Similarly coupling of amine **39** with 4-pyridineacetic acid *N*-oxide (**37)** provided target **40** (Scheme 7).

## Results and Discussion

Compounds prepared in this study were tested for their ability to inhibit the transfer of [$^3$H]farnesyl from farnesyl pyrophosphate to H-Ras-CVLS, a process that is mediated by FPT using conditions previously described.[21] Biological and pharmacokinetic data for these compounds are summarized in Tables 1−5.

In a previous report, we established the importance of having a pyridinylacetyl functionality, off the amino end of the piperidinyl moiety of the tricyclic system, in enhancement of FPT activity.[9] We also reported that introduction of a methyl group at the 3-position of the tricyclic pyridine gave SCH 56580, a compound with greatly enhanced FPT activity. We have now undertaken a study geared toward understanding the structure−activity relationship (SAR) at the 3-position of the tricyclic ring system. We also show with a few examples that the 4-pyridylacetyl group provides more potent compounds than the 3-pyridylacetyl derivatives in FPT inhibition.

Introduction of a bulky alkyl substituent such as the *tert*-butyl group at the 3-position of the tricyclic ring system was disadvantageous to FPT activity as demonstrated by compound **33** which did not inhibit this enzyme even at 4.0 $\mu$M. Similarly the 3-phenyl-substituted analogue **29** was also found to be inactive. These results suggested that the enzyme pocket at the 3-position of the tricyclic pyridine could only accommodate small groups such as methyl but not the bulky *tert*-butyl or phenyl groups. Interestingly, the trifluoromethyl-substituted analogue, compound **31** ($IC_{50}$ = 0.43 $\mu$M), was found to be 1 order of magnitude less active than the corresponding methyl analogue SCH 56580; since the size of the fluorine is considered to be similar in size to hydrogen, it is conceivable that some electronic factors might be responsible for this unexpected result.

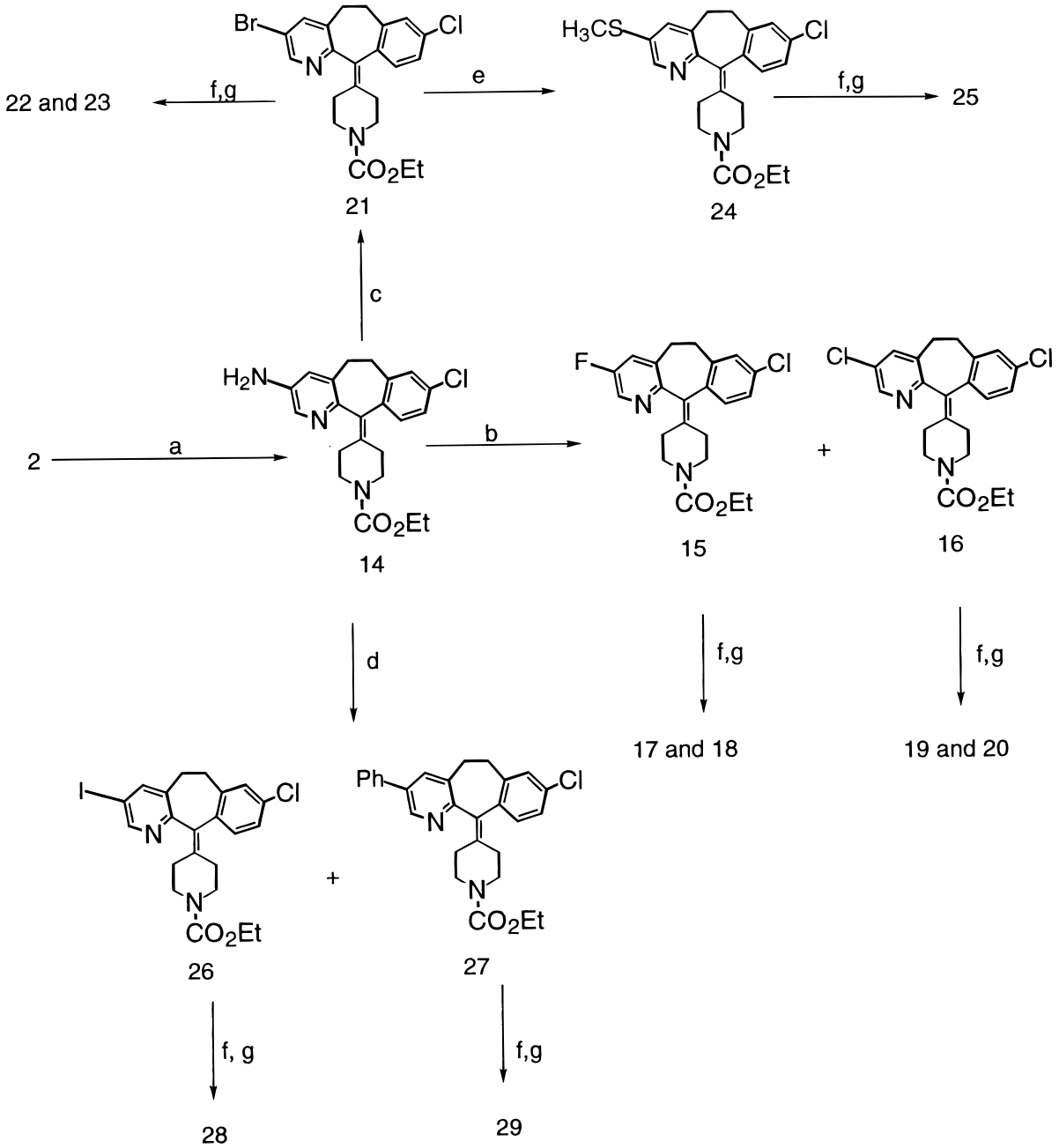
We then turned our attention to incorporating halogens at the 3-position. Whereas chloro, bromo, and iodo derivatives **19**, **22**, and **28**, respectively, were equipotent ($IC_{50} \sim 0.07$ $\mu$M), the fluoro compound **17** was 1 order of magnitude less potent ($IC_{50} = 0.65$ $\mu$M). This further indicated that both electronic as well as hydrophobic effects might be at play in the SAR of the 3-substituted tricyclic analogues.

We next investigated the influence of electron-withdrawing groups on FPT inhibitory activity. While the nitro derivative **4** ($IC_{50} = 0.57$ $\mu$M) was found to be 2-fold less active than the lead compound SCH 44342, the cyano compound **10** ($IC_{50}$ = 1.4 $\mu$M) was found to be 1 order of magnitude less active than SCH 44342.

Mixed results were obtained when polar electron-donating groups were introduced. The amino derivative, compound **5** ($IC_{50}$ = 1 $\mu$M), was substantially less active than the lead compound SCH 44342. Monoalkylation of the amine **5** to give compound **6** ($IC_{50}$ = 1.3 $\mu$M) did not affect the FPT activity of the parent amino compound. However, when the amino **5** was dialkylated to afford compound **7**, FPT activity was greatly reduced; thus, compound **7** inhibited FPT activity by only 22% at 4 $\mu$M.

Reducing the basicity of the 3-amino group by forming acetamide **8** resulted in greatly reduced activity, i.e., at 12 $\mu$M compound **8** inhibited FPT by only 15%. The

**Scheme 4**[a]




[a] (a) Iron fillings, $CaCl_2$; (b) $NOBF_4$, $CH_2Cl_2$, *o*-dichlorobenzene; (c) $NaNO_2$, $Br_2$−HBr; (d) isoamyl nitrite, $I_2$, $C_6H_6$; (e) $NaSCH_3$, *hν*; (f) concd HCl, reflux; (g) 3- or 4-pyridineacetic acid, DEC, HOBT, NMM.

sulfonamide **9** ($IC_{50}$ = 4.6 $\mu$M) was more potent than the acetamido compound **8** but less potent than the free amine **5**.

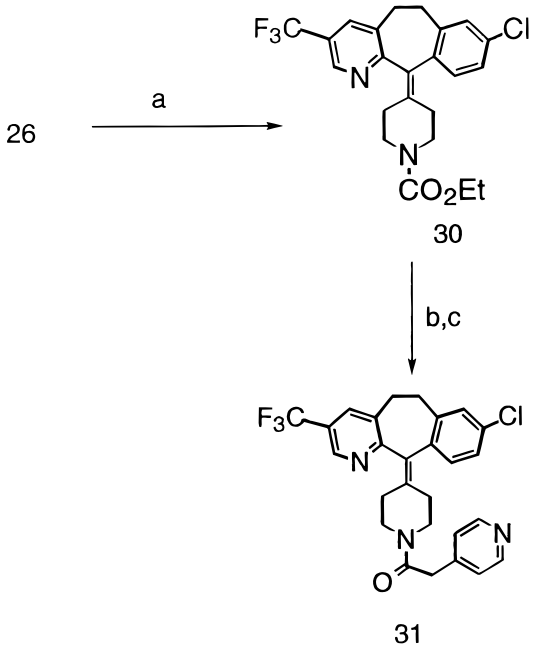
The hydroxyl analogue, compound **12** ($IC_{50}$ = 0.64 $\mu$M), was less active than the lead compound SCH 44342. Methylation of **12** gave compound **13** ($IC_{50}$ = 0.49 $\mu$M) that was also less active than the lead compound SCH 44342. The thiomethyl ether analogue **25** exhibited an $IC_{50}$ of 0.42 $\mu$M—one-half as active as SCH 44342.

In a previous publication,[9] we demonstrated that tricyclic compounds bearing a 4-pyridylacetyl moiety attached to the piperidine ring were more potent FPT inhibitors than their 3-pyridylacetamide counterparts. As shown in Table 2, a similar relationship was observed in the present study; thus analogues of 4-pyridylacetic acid were found to be more potent than those of 3-pyridylaceticpyridylacetic acid. For example, the 3-methyl-substituted compound **35** was 1 order of magnitude less potent than SCH 56580 ($IC_{50}$ = 0.55 $\mu$M), its 4-pyridylacetyl analogue. The fluoro analogue **18** ($IC_{50}$ = 3.80 $\mu$M) was also substantially less active than its 4-pyridylacetyl counterpart **17**.

**Inhibition of FPT versus GGPT-1.** In accordance with previous reports from this laboratory,[9−11] the tricyclic benzocycloheptapyridine compounds prepared in this series have good selectivity on inhibition of FPT versus the closely related enzyme GGPT-1 (geranylgeranyl-protein transferase-1). Thus compounds **19**, **22**, **23**, **28**, and **35** were found to be inactive in inhibition of GGPT-1 even at such high concentrations as 40 $\mu$M (Table 3).

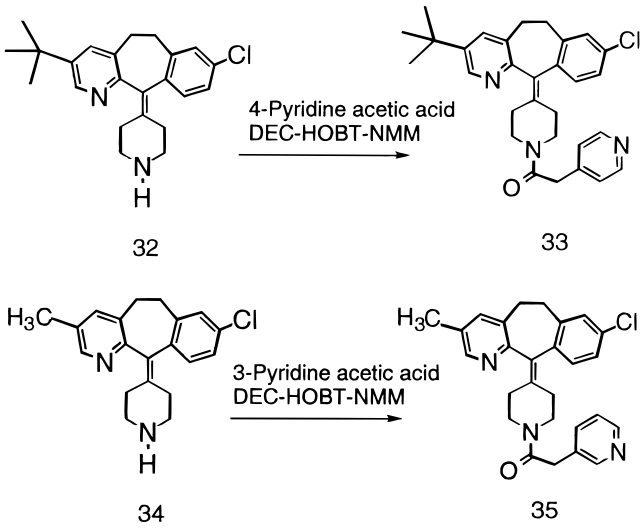
**COS Cell Inhibition.** Since Ras farnesylation is an intracellular event and the potential utility of Ras FPT

**Scheme 5**[a]




[a] (a) $FO_2SCF_2CO_2Me$, CuI, DMF; (b) 1 N KOH; (c) 4-pyridineacetic acid, DEC, HOBT, NMM.

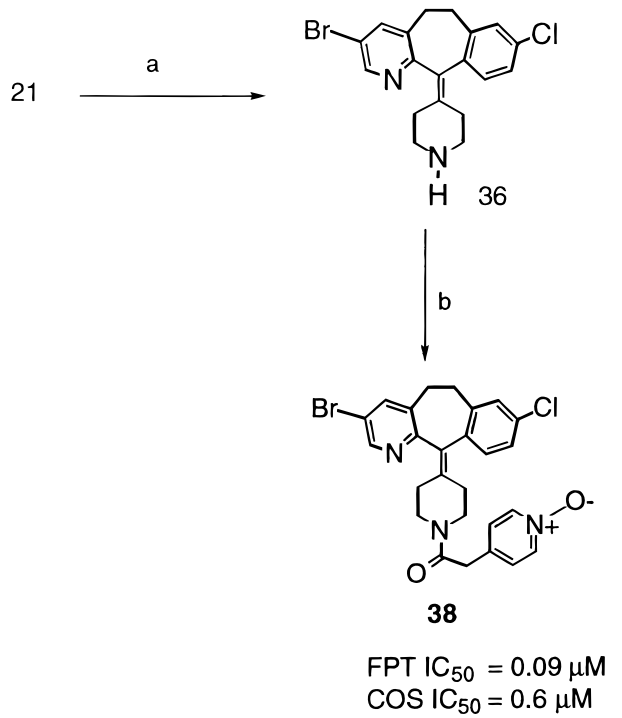
**Scheme 6**

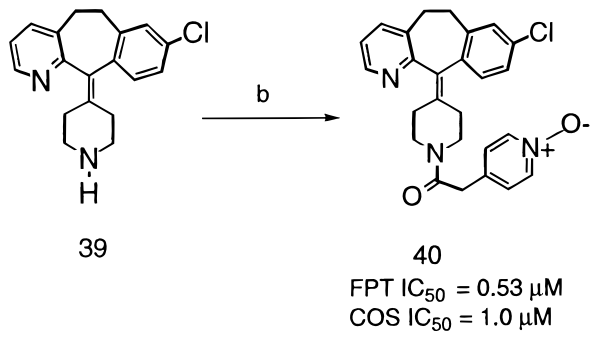



inhibitors in cancer therapy depends on their ability to penetrate the cell membrane and inhibit the posttranslational processing of Ras in vivo, it was necessary that compounds with good FPT activity be evaluated for their ability to inhibit the processing of Ras in intact cells. Compounds **19**, **20**, **22**, **23**, **28**, and **35** tested in monkey COS cells were shown to be active in the 1−4 $\mu$M range (Table 3).

**Pharmacokinetics.** We previously disclosed our findings that SCH 44342 was pharmacokinetically unstable in the mouse as evidenced by that fact that it had a half-life of less than 10 min and an AUC of 0.37 $\mu$g·h/mL.[11] Close examination of the pharmacokinetic profile of SCH 44342 indicated that the major metabolite of this compound was the pyridine *N*-oxide **40**. Compound **40** ($IC_{50}$ = 0.53 $\mu$M) was subsequently prepared and found to be slightly less active than SCH 44342, but the two were equipotent in the COS cell assay with an $IC_{50}$ of 1 $\mu$M. Whereas SCH 44342 had a short half-life of less than 10 min, compound **40** had

**Scheme 7**[a]



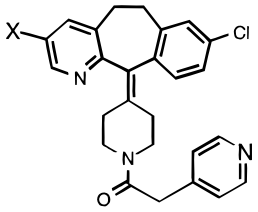




[a] (a) Concd HCl reflux; (b) pyridineacetic acid *N*-oxide (**37**), DEC, HOBT, NMM.

a half-life of 76 min with an AUC of 5.0 $\mu$g·h/mL and a $C_{max}$ of 8 $\mu$g/mL (Table 4). Examination of compound **38,** the *N*-oxide analogue of **22**, showed that it also had a relatively good half-life of 48 min, an AUC of 12.9 $\mu$g·h/mL, and a $C_{max}$ of 8.3 $\mu$g/mL (Table 4). Our next objective was to evaluate compounds that showed good pharmacokinetic profiles in in vivo antitumor models.

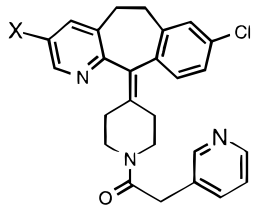
**In Vivo Activity.** To determine the effect of the tricyclic inhibitors in an animal tumor model, acetamide **38** was evaluated for its ability to block tumor growth in nude mice. The in vivo efficacy and specificity of **38** were evaluated using a panel of tumor models grown in nude mice (Table 5). The tumor models included PT-24 (BALB c/3T3 cells transfected with oncogenic *H-ras*), CVLS (NIH3T3 cells transfected with oncogenic *H-ras* with its native CVLS C-terminal sequence), CVLL (NIH3T3 cells transfected with oncogenic H-ras containing a CVLL C-terminal geranylgeranylation sequence), MSV-3T3 (NIH3T3 cells transfected with oncogenic *mos*), and human colon adenocarcinoma DLD-1 cells which expressed activated *K-ras*. As is seen in Table 5 and Figure 1, tricyclic pyridinylacetamide **38**, when

**Table 1.** SAR of 3-Substituted 4-Pyridinylacetyl Tricyclic FPT Inhibitors



| entry | X | FPT $IC_{50}$ ($\mu$M) |
|---|---|---|
| SCH 44342 | H | 0.25 |
| SCH 56580 | $CH_3$ | 0.04 |
| **4** | $NO_2$ | 0.57 |
| **5** | $NH_2$ | 1.0 |
| **6** | NHEt | 1.3 |
| **7** | $N(Et)_2$ | 22% @ 4 |
| **8** | $NCOCH_3$ | 15% @ 12 |
| **9** | $NSO_2CH_3$ | 4.6 |
| **10** | CN | 1.4 |
| **11** | SCN | 1.0 |
| **12** | OH | 0.64 |
| **13** | $OCH_3$ | 0.49 |
| **17** | F | 0.65 |
| **19** | Cl | 0.072 |
| **22** | Br | 0.06 |
| **25** | $SCH_3$ | 0.42 |
| **28** | I | 0.068 |
| **29** | Ph | 0% @12 |
| **31** | $CF_3$ | 0.43 |
| **33** | *t*-Bu | >4.0 |

**Table 2.** SAR of 3-Substituted 3-Pyridinylacetyl Tricyclic FPT Inhibitors



| entry | X | FPT $IC_{50}$ ($\mu$M) |
|---|---|---|
| SCH 44324 | H | 0.47 |
| **18** | F | 3.80 |
| **20** | Cl | 0.58 |
| **23** | Br | 0.16 |
| **35** | $CH_3$ | 0.55 |

**Table 3.** GGPTase and COS Cell Activity Results

| | $IC_{50}$ ($\mu$M) | |
|---|---|---|
| entry | GGPT | COS cell |
| SCH 44342 | >114 | 1.0 |
| SCH 56580 | >40 | 1.0 |
| SCH 44324 | >46 | 3.7 |
| **5** | ND | >10 |
| **19** | >42 | 1.0 |
| **20** | ND | 1.0 |
| **22** | >40 | 3.1 |
| **23** | >40 | 3.5 |
| **28** | >36 | 0.8 |
| **35** | >43 | 3.4 |

given orally at 10 and 50 mg/kg (four times a day, 7 days a week), significantly inhibited PT-24 and CVLS tumor growth in a dose-dependent manner; the inhibition was more than 80% at 50 mg/kg and more than 40% at 10 mg/kg. The rate of tumor growth was monitored and compared with vehicle control. The growth of CVLL and MSV-3T3, however, was inhibited only slightly by compound **38**. Compound **38** also significantly and dose-dependently inhibited the growth of human colon cancer DLD-1 xenografts. These results indicate that tricyclic acetamide **38** is an effective Ras farnesylation inhibitor and a potential anticancer agent when given orally.

**Table 4.** Pharmacokinetic Profile for FPT Compounds[a]

| compd | AUC (po) ($\mu$g·h/mL) | $C_{max}$ (po) ($\mu$g/mL) | AUC (iv) ($\mu$g·h/mL) | $t_{1/2}$ (iv) (min) |
|---|---|---|---|---|
| SCH 44342 | 0.37[b] | 1.02 | 1.75 | <10 |
| **38** | 12.9[c] | 8.30 | 17.3 | 48 |
| **40** | 5.0[d] | 8.00 | 11.9 | 76 |

[a] Compounds dosed at 25 mg/kg in mice as solutions of HCl salts. [b] AUC (0−1 h). [c] AUC (0−7 h). [d] AUC (0−24 h). Abbreviations: po, oral; iv, intravenous; AUC, area under the concentration−time curve.

**Table 5.** Average Inhibition of Tumor Growth on Various Tumor Models by Compound **38**

| | inhibition (%) at: | | | |
|---|---|---|---|---|
| | 5 mpk | 10 mpk | 20 mpk | 50 mpk |
| CVLL | | 18[c] | | 46[b] |
| CVLS | | 52[a] | | 81[a] |
| PT-24 | | 45[a] | | 81[a] |
| DLD-1 | | 28[c] | | 40[b] |
| MSV-3T3 | 0% | | 0% | 36[c] |
| CVIM | 20[c] | | 33[b] | 53[a] |

[a] $p \ll 0.0005$. [b] $p < 0.005$. [c] $0.1 < p < 0.25$.

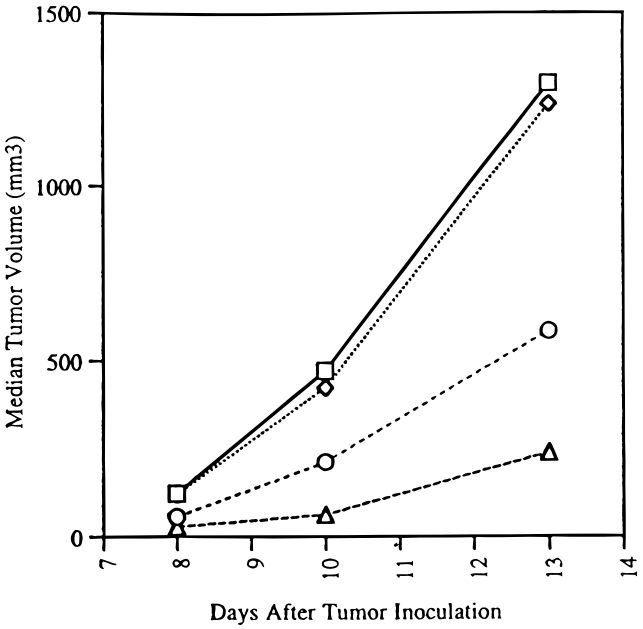



**Figure 1.** In vivo antitumor efficacy of compound **38** in CVLS model. Percent tumor growth inhibition is the average of percent change in tumor volume between the treated groups and the vehicle control group measured throughout the experiment period. Compound **38** has an average inhibition of 40% at 10 mg/kg per dosing versus 80% average inhibition at 50 mg/kg per dosing. Symbols: (□) no-treatment control, (◇) vehicle (20% HP$\beta$CD) control, (○) **38** at 10 mpk q.i.d., (△) **38** at 50 mpk q.i.d.

## Conclusion

We have investigated the effect of introducing a variety of substituents at the 3-position of the benzocycloheptapyridine tricyclic ring system. The need for a small aliphatic group such as a methyl is evident. Larger halogens such as chlorine, bromine, or iodine are

well-tolerated. However, introduction of fluorine seemed to hurt FPT activity. While very good in vitro potency was attained in this study, a number of compounds evaluated were found to be heavily metabolized as evidenced by their short half-lifes and low AUCs. We, however, found out that by having a pyridine *N*-oxide acetamide attached to the nitrogen of the piperidine, the pharmacokinetic properties of these compounds were greatly improved. Information obtained from our SAR studies that a bromine substitution at the 3-position elicited superior FPT potency, coupled to the fact that a pyridyl *N*-oxide group gives more pharmacokinetically stable compounds, led us to design **38**, a compound that incorporated both of these attributes. Compound **38** was a potent FPT inhibitor and showed in vivo efficacy. A key feature of the tricyclic compounds as FPT inhibitors is that they are nonpeptidic, do not have a sulfhydryl group, and are orally absorbed. On the basis of the in vivo data presented in this paper, these tricyclic inhibitors represent a promising class of potential cancer chemotherapeutics.

## Experimental Section

Melting points were determined with an Electrothermal digital melting point apparatus and are uncorrected. Elemental analyses were performed by the Physical-Analytical Chemistry Department, Schering-Plough Research Institute, on either a Leeman CE 440 or a FISONS EA 1108 elemental analyzer. FT-IR spectra were recorded using a BOMEN Michelson 120 spectrometer. Mass spectra were recorded using either EXTREL 401 (CI), JEOL, or MAT-90 (FAB), VG ZAB-SE (SIMS), or Finnigan MAT-CH-5 (EI), spectrometer. In general, structures of the compounds were determined by coupling constants, coupling information from the COSY spectra, and 1D NOE experiments. The $^1$H and $^{13}$C NMR spectra were obtained on either a Varian VXR-200 (200 MHz, $^1$H), Varian Gemini-300 (300 MHz, $^1$H; 75.5 MHz, $^{13}$C), or XL-400 (400 MHz, $^1$H; 100 MHz, $^{13}$C) spectrometer and are reported as ppm downfield from $Me_4Si$ with number of protons, multiplicities, and coupling constants in hertz indicated parenthetically. For $^{13}$C NMR, a Nalorac Quad nuclei probe was used. Preparation of SCH 44342, SCH 44324, and SCH 56580 has previously been reported.[9] Unless otherwise specified, all solvents and reagents were obtained from commercial suppliers and used without further purification.

**4-(8-Chloro-3-nitro-5,6-dihydro-1*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)piperidine (4).** Tricyclic carbamate **1** (5.69 g, 14.9 mmol) was dissolved in 35 mL of $CH_2Cl_2$ under $N_2$ atmosphere and stirred at ~0 °C. To this solution was added a mixture of $Bu_4NNO_3$ (4.98 g, 16.3 mmol) and trifluoroacetic anhydride (3.12 g, 2.1 mL, 14.9 mmol) dissolved in 20 mL of $CH_2Cl_2$ and cooled to 0 °C.[22] The reaction was stirred at 0 °C for 2 h and then allowed to come to room temperature overnight. It was then basified with saturated $NaHCO_3$ and extracted with $CH_2Cl_2$. Combined organic phase was dried over $MgSO_4$ and concentrated. Purification by flash chromatography eluting first with 10−20% EtOAc−hexanes afforded the nitro carbamate **2** in 44% yield: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.28 (t, $J$ = 7.5 Hz, 3H), 2.18−2.59 (m, 4H), 2.79−3.10 (m, 2H), 3.15−3.32 (m, 2H), 3.36−3.56 (m, 2H), 3.70−3.89 (m, 2H), 4.16 (q, $J$ = 7.5 Hz, 2H), 7.06−7.26 (m, 3H), 8.26 (d, $J$ = 2.5 Hz, 1H), 9.22 (d, $J$ = 2.5 Hz, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 14.57, 30.59, 30.72, 30.78, 30.935, 31.57, 44.62, 61.37, 126.59, 129.00, 130.63, 132.33, 132.69, 133.61, 134.48, 136.29, 138.84, 140.19, 141.86, 142.78, 155.31, 162.63; IR (film) $\upsilon_{max}$ 565, 813, 997, 1114, 1230, 1347, 1436, 1516, 1696, 2911, 2980, 3461 cm$^{-1}$; MS *m*/*z* (rel intensity) 382.3 (10.90), 427.0 (14.55), 428.0 (100, $MH^+$), 429.0 (34.36), 430.0 (36.95). Anal. ($C_{22}H_{22}N_3O_4Cl\cdot 0.2H_2O$) C, H, N.

To 250 mL of concentrated HCl was added 3-nitro carbamate **2** (10 g, 23.4 mmol). The reaction mixture was refluxed for 16 h. It was then cooled, poured into ice, and neutralized with concentrated $NH_4OH$. The aqueous phase was extracted with EtOAc. Concentration of the organic phase afforded 8.29 g (99.7% yield) of amine **3**. The latter was used for subsequent reaction without further purification: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.17−2.53 (m, 4H), 2.64−3.16 (m, 6H), 3.36−3.59 (m, 2H), 7.03−7.26 (m, 3H), 8.26 (d, $J$ = 2.5 Hz, 1H), 9.23 (d, $J$ = 2.5 Hz, 1H); MS *m*/*z* (rel intensity) 356 (100, $MH^+$).

To a solution of amine **3** (4.72 g, 13.26 mmol) in 40 mL of $CH_2Cl_2$ were added 4-pyridylacetic acid (2.73 g, 19.90 mmol), HOBT (3.58 g, 26.53 mmol), DEC (5.08, 26.53 mmol), and *N*-methylmorpholine (13.42 g, 14.6 mL, 132.65 mmol), and the mixture was stirred at room temperature for 16 h. The organic phase was washed with saturated $NaHCO_3$ and brine and then dried over $Na_2SO_4$. It was then concentrated and purified on silica gel eluting with 3% MeOH (saturated with ammonia)−$CH_2Cl_2$ to afford the amide **4** in 75% yield as a white solid:$^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.08−2.64 (m, 4H), 2.76−3.15 (m, 2H), 3.20−3.54 (m, 4H), 3.58−3.72 (m, 1H), 3.75 (s, 2H), 3.88−4.15 (m, 1H), 7.00−7.33 (m, 5H), 8.24 (br s, 1H), 8.49−8.68 (m, 2H), 9.22 (dd, $J$ = 5.0, 2.5 Hz, 1H); IR (film) $\upsilon_{max}$ 572, 810, 995, 1340, 1439, 1510, 1641, 2861, 2919, 3067 cm$^{-1}$; MS *m*/*z* (rel intensity) 475.2 (100, $MH^+$). Anal. ($C_{26}H_{23}N_4O_3Cl\cdot 0.5H_2O$) C, H, N.

**4-(3-Amino-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)piperidine (5).** 3-Nitro amide **4** (4.70 g, 9.90 mmol) was dissolved in 200 mL of 85% EtOH−$H_2O$. To this solution were added iron filings (4.96 g, 88.78 mmol) and $CaCl_2$ (0.49 g, 4.45 mmol), and the reaction mixture was refluxed for 16 h. The reaction mixture was filtered through Celite and extensively washed with hot EtOH. The organic solvents were removed, and the resulting semisolid material was purified on silica gel eluting with 3% MeOH (saturated with ammonia)−$CH_2Cl_2$ to afford the 3-amino compound **5** in 75% yield as a white solid: $^1$H NMR (200 MHz, DMSO) $\delta$ 2.01−2.36 (m, 4H), 2.58−2.83 (m, 2H), 3.04−3.46 (m, 4H), 3.38 (s, 2H), 3.62−3.89 (m, 2H), 5.28 (br s, 2H), 6.62−6.72 (m, 1H), 6.98−7.08 (m, 1H), 7.15−7.37 (m, 4H), 7.72 (br s, 1H), 8.42−8.54 (m, 2H); IR (film) $\upsilon_{max}$ 995, 1457, 1631, 2916, 3214, 3438 cm$^{-1}$; MS *m*/*z* (rel intensity) 445.3 (100, $MH^+$). Anal. ($C_{26}H_{25}N_4OCl$ 0.65·$H_2O$·0.35$CH_2Cl_2$) C, H, N.

**4-[8-Chloro-3-(ethylamino)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-(4-pyridinylacetyl)piperidine (6) and 4-[8-Chloro-3-(diethylamino)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-(4-pyridinylacetyl)piperidine (7).** Tricyclic amine **5** (1 g, 2.25 mmol) was dissolved in methanol (20 mL) and cooled in an ice−water bath. The pH of the solution was adjusted to 3 with the addition of 1 N HCl. Acetaldehyde (1.25 mL) was added followed by sodium cyanoborohydride (1.41 g, 22.4 mmol), and the solution was stirred for 1 h. Solvents were evaporated off under vacuum, and the residue was extracted with dichloromethane (100 mL). The organic extract was washed with 10% sodium bicarbonate (100 mL) and water (100 mL). The extract was dried over magnesium sulfate, and the solvent was evaporated under vacuum to give an oil. The oil was purified by silica gel column chromatography using a solution of 1.5% 10% ammonium hydroxide (in methanol) in dichoromethane to afford the monoethylamino compound **6** as the more polar compound (0.158 g, 15% yield): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.04−1.33 (m, 3H), 2.03−2.51 (m, 4H), 2.59−2.85 (m, 2H), 2.95−3.40 (m, 6H), 3.50−3.65 (m, 1H), 3.71 (s, 2H), 3.95−4.21 (m, 1H), 6.57 (br s, 1H), 6.90−7.22 (m, 5H), 7.70−7.86 (m, 1H), 8.40−8.62 (m, 2H); MS *m*/*z* (rel intensity) 473 ($MH^+$). Anal. ($C_{28}H_{29}N_4OCl\cdot 0.7H_2O$) C, H, N, Cl. The diethylamino compound **7** is the less polar compound (0.198 g, 18% yield): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 0.94−1.28 (m, 6H), 2.10−2.54 (m, 6H), 2.62−2.88 (m, 2H), 3.00−3.41 (m, 6H), 3.50−3.67 (m, 1H), 3.71 (s, 2H), 3.94−4.21 (m, 1H), 6.53−6.65 (m, 1H), 6.95−7.22 (m, 5H), 7.78−7.92 (m, 1H), 8.38−8.60 (m, 2H); MS *m*/*z* (rel intensity) 501 ($MH^+$). Anal. ($C_{30}H_{33}N_4OCl$) C, H, N, Cl.

***N*-[8-Chloro-6,11-dihydro-11-[1-[1-oxo-2-(4-pyridinyl)ethyl]-4-piperidinylidene]-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-3-yl]acetamide (8).** Tricyclic amine **5** (0.3 g, 0.67 mmol) was dissolved in 5 mL of pyridine and acetic anhydride

(0.102 g, 95 μL, 1.01 mmol). The reaction mixture was stirred at 60 °C for 16 h. It was then basified with 1 N aqueous NaOH to pH 11 and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ fraction was dried over $MgSO_4$ and concentrated. Purification on normal phase HPLC eluting with 8% MeOH (saturated with ammonia)−$CH_2Cl_2$ gave 0.22 g (0.45 mmol, 67% yield) of aminoacetyl compound **8**: $^1$H NMR (200 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.21−2.51 (m, 4H), 2.72−2.93 (m, 2H), 3.10−3.42 (m, 4H), 3.57−3.70 (m, 1H), 3.75 (s, 2H), 4.01−4.20 (m, 1H), 6.99−7.27 (m, 5H), 7.94 (d, $J$ = 2.5 Hz, 1H), 8.07 (s, 1H), 8.27 (d, $J$ = 7.5 Hz, 1H), 8.54 (d, $J$ = 2.5 Hz, 2H); IR (film) $\upsilon_{max}$ 995, 1272, 1395, 1455, 1527, 1598, 1631, 2915, 3028, 3079, 3169, 3249, 3295, 3431 cm$^{-1}$; MS *m/z* (rel intensity) 487.3 (100, $MH^+$); HRMS (FAB) cald for $C_{28}H_{27}N_4O_2Cl$ ($MH^+$) 487.1901, found 487.1903.

**4-(8-Chloro-5,6-dihydro-3-methanesulfonamido-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)piperidine (9).** Tricyclic amine **5** (0.3 g, 0.67 mmol) was dissolved in 5 mL of pyridine, and methanesulfonyl chloride (0.92 g, 62 μL, 0.8 mmol) was added. The reaction mixture was stirred at 60 °C for 20 h. It was then basified with 1 N aqueous NaOH to pH 10 and extracted with ethyl acetate−THF (50/50, v/v) mixture. The organic fraction was dried over $MgSO_4$ and concentrated. Purification on normal phase HPLC eluting with 8% MeOH (saturated with ammonia)−$CH_2Cl_2$ gave 0.32 g (0.61 mmol, 92% yield) of aminosulfonyl compound **9**: $^1$H NMR (200 MHz, $CDCl_3$) δ 2.16−2.45 (m, 4H), 2.72−2.94 (m, 2H), 3.03 (s, 3H), 3.15−3.44 (m, 4H), 3.55−3.70 (m, 1H), 3.77 (s, 2H), 3.98−4.18 (m, 1H), 7.00−7.27 (m, 5H), 7.42−7.55 (m, 1H), 8.23 (br s, 1H), 8.58 (br s, 2H); IR (film) $\upsilon_{max}$ 532, 970, 995, 1154, 1324, 1459, 1632, 2861, 2919, 3021, 3088, 3427 cm$^{-1}$; MS *m/z* (rel intensity) 523.2 (100, $MH^+$); Anal. ($C_{27}H_{27}N_4O_3ClS\cdot1.33H_2O$) C, H, N, S.

**4-(3-Cyano-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)piperidine (10).** Tricyclic amine **5** (0.5 g, 1.12 mmol) was dissolved in acetone (10 mL), and to this solution was added 230 μL of concentrated HCl. The reaction mixture was cooled to ∼−10 °C, and then a solution of $NaNO_2$ (0.085 g, 1.23 mmol dissolved in 4 mL of $H_2O$) was added. To this reaction mixture was added a solution of CuCN (freshly prepared from dissolving $CuSO_4$ (0.336 g, 1.34 mmol) in 2 mL of $H_2O$, then cooling the solution to ∼4 °C with ice, then adding KCN (0.365 g, 5.60 mmol) dissolved in 2 mL of $H_2O$, and heating to ∼60−70 °C) at temperatures between 60 and 70 °C for a period of 20 min. The reaction temperature was then raised to ∼70−80 °C, and heating was continued for 10 min to evaporate most of the acetone. The reaction mixture was cooled and further diluted with $H_2O$. It was exhaustively extracted with $CH_2Cl_2$ (4 × 100 mL). The organic phase was dried over $Na_2SO_4$ and concentrated. Purification on normal phase HPLC, eluting with 3% MeOH (saturated with ammonia)−$CH_2Cl_2$ afforded 0.25 g of the cyano compound **10** (50% yield): $^1$H NMR (200 MHz, $CDCl_3$) δ 2.08−2.60 (m, 4H), 2.72−3.04 (m, 2H), 3.16−3.50 (m, 4H), 3.54−3.73 (m, 1H), 3.78 (s, 2H), 3.89−4.16 (m, 1H), 6.98−7.33 (m, 5H), 7.74 (s, 1H), 8.48−8.59 (m, 2H), 8.62−8.72 (m, 1H); IR (film) $\upsilon_{max}$ 995, 1444, 1595, 1642, 2230, 2869, 2912, 3046, 3437 cm$^{-1}$; MS *m/z* (rel intensity) 455.2 (100, $MH^+$). Anal. ($C_{27}H_{23}N_4OCl\cdot0.7H_2O$) C, H, N.

**4-[8-Chloro-3-(thiocyano)-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-(4-pyridinylacetyl)piperidine (11).** Tricyclic amine **5** (0.55 g, 1.25 mmol) was dissolved in 50 mL of dilute $H_2SO_4$ (10%, v/v). The reaction mixture was then cooled to ∼0−5 °C for 15 min. To this reaction mixture were added $NaNO_2$ (0.092 g, 1.33 mmol dissolved in 10 mL of $H_2O$), KCN (0.46 g, 4.74 mmol), and CuSCN (0.3 g, 2.49 mmol) (both dissolved in 15 mL of $H_2O$). The reaction mixture was stirred for 0.5 h, heated to boiling for 15−30 min, and then cooled to room temperature. The pH of the reaction mixture was adjusted to 7, and then the mixture was extracted with $CH_2Cl_2$. The organic phase was dried over $MgSO_4$ and concentrated. Purification by flash chromatography eluting with 5% MeOH (saturated with ammonia)−$CH_2Cl_2$ afforded 0.19 g of the thiocyano compound **11** as a white solid (32% yield): mp 97−98 °C; $^1$H NMR (200 MHz, $CDCl_3$) δ 2.09−2.60 (m, 4H), 2.72−3.02 (m, 2H), 3.15−3.48 (m, 4H), 3.53−3.68 (m, 1H), 3.75 (s, 2H), 3.92−4.18 (m, 1H), 6.99−7.26 (m, 5H), 7.68 (br s, 1H), 8.44−8.62 (m, 3H); IR (film) $\upsilon_{max}$ 994, 1440, 1478, 1599, 1641, 2157, 2862, 2912, 3439 cm$^{-1}$; MS *m/z* (rel intensity) 487.1 (100, $MH^+$). Anal. ($C_{27}H_{23}N_4OClS\cdot1.3H_2O$) C, H, N.

**4-(8-Chloro-3-hydroxy-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)piperidine (12).** Tricyclic amine **5** (0.5 g, 1.12 mmol) was dissolved in 11 mL of dilute $H_2SO_4$ (10%, v/v) at room temperature. The reaction mixture was then cooled to ∼0−5 °C for 15 min. To this reaction mixture were added $NaNO_2$ (0.083 g, 1.20 mmol) dissolved in 10 mL of $H_2O$ and then a boiling solution of $CuSO_4\cdot5H_2O$ (1.13 g, 4.54 mmol) dissolved in 10 mL of $H_2O$. The reaction mixture was further boiled for 15 min and cooled to room temperature, and pH was adjusted to ∼11 using NaOH. It was extracted twice with $CH_2Cl_2$ (2 × 50 mL), and the pH of the aqueous phase was then adjusted to ∼7 using 1 N HCl. The aqueous phase was extracted with $CH_2Cl_2$. The $CH_2Cl_2$ fraction was dried over $MgSO_4$ and then concentrated. Purification by flash chromatography eluting with 5% MeOH (saturated with ammonia)−$CH_2Cl_2$ afforded 0.16 g of the hydroxy compound **12** as a light yellow solid (32% yield): mp 157−158 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 2.11−2.55 (m, 4H), 2.69−2.86 (m, 2H), 3.18−3.39 (m, 4H), 3.55−3.79 (m, 3H), 3.90−4.12 (m, 1H), 6.94−7.29 (m, 8H), 7.95−8.05 (m, 1H), 8.52 (br s, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 30.62, 31.89, 40.65, 40.79, 43.36, 47.09, 47.22, 126.12, 126.63, 129.37, 130.42, 133.42, 133.79, 134.28, 135.45, 138.17, 139.93, 144.93, 145.40, 14750, 149.73, 150.04, 154.11, 168.05; IR (film) $\upsilon_{max}$ 995, 1209, 1296, 1443, 1560, 1601, 1640, 2914, 3028, 3429 cm$^{-1}$; MS *m/z* (rel intensity) 327 (63), 446 (100, $MH^+$). Anal. ($C_{26}H_{24}N_3O_2Cl\cdot0.2H_2O\cdot0.2CH_2Cl_2$) C, H, N.

**4-(8-Chloro-3-methoxy-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)piperidine (13).** Tricyclic alcohol **12** (0.05 g, 0.11 mmol) was dissolved in 1 mL of $CH_2Cl_2$, and 4 mL of diazomethane solution in ether was added. After stirring for 72 h the reaction mixture was concentrated and purified on a preparative plate eluting with 10% MeOH (saturated with ammonia)−$CH_2Cl_2$ to provide 0.011 g of the methoxy compound **13** as a light yellow solid (22% yield): mp 93−94 °C; $^1$H NMR (200 MHz, $CDCl_3$) δ 2.14−2.54 (m, 4H), 2.68−2.95 (m, 2H), 3.09−3.44 (m, 4H), 3.53−3.79 (m, 3H), 3.83 (s, 3H), 3.97−4.21 (m, 1H), 6.88−7.30 (m, 6H), 8.11 (br s, 1H), 8.55 (br s, 2H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ 30.89, 31.43, 40.389, 40.46, 43.05, 43.09, 47.01, 55.62, 122.15, 124.06, 126.33, 128.76, 128.81, 130.13, 132.99, 133.87, 134.08, 134.53, 136.03, 139.58, 139.71, 144.20, 150.12, 154.67, 167.79 cm$^{-1}$; MS *m/z* (rel intensity) 341.0 (43), 460.0 (100), 462.0 (37); HRMS (FAB) calcd for $C_{27}H_{26}N_3O_2Cl$ ($MH^+$) 460.1787, found 460.1792.

**4-(3-Amino-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylic Acid Ethyl Ester (14).** Nitro carbamate **2** (5.99 g, 0.014 mmol) was dissolved in 300 mL of 85% EtOH−$H_2O$. To this solution were added iron filings (7.01 g, 0.125 mmol) and $CaCl_2$ (0.5 g, 0.006 mmol), and the reaction mixture was refluxed for 4 h. The reaction mixture was filtered through Celite and extensively washed with hot EtOH. It was then treated with decolorized charcoal and filtered, and the organic solvents were removed to give amine **14** in 100% yield: $^1$H NMR (200 MHz, DMSO) δ 1.16 (t, $J$ = 7.5 Hz, 3H), 2.04−2.36 (m, 4H), 2.56−2.82 (m, 2H), 3.02−3.21 (m, 4H), 3.53−3.70 (m, 2H), 4.04 (q, $J$ = 7.5 Hz, 2H), 6.69 (d, $J$ = 2.5 Hz, 1H), 7.04 (d, $J$ = 7.5 Hz, 1H), 7.21 (dd, $J$ = 7.5 Hz, 2.5 Hz, 1H), 7.31 (d, $J$ = 2.5 Hz, 1H), 7.73 (d, $J$ = 2.5 Hz, 1H); IR (film) $\upsilon_{max}$ 768, 998, 1117, 1232, 1440, 1479, 1681, 2919, 2979, 3222, 3350, 3434 cm$^{-1}$; MS *m/z* (rel intensity) 362 (17.65), 397 (21.45), 398 (100, $MH^+$), 399 (30.4), 400 (32.59).

**4-(8-Chloro-3-fluoro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylic Acid Ethyl Ester (15) and 4-(3,8-Dichloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylic Acid Ethyl Ester (16).** Amino carbamate **14** (16.2 g, 40.83 mmol) was introduced with stirring to a slurry of nitrosonium tetrafluoroborate (7.14 g, 61.11 mmol) in $CH_2Cl_2$ (100 mL), and the reaction mixture

stirred for 3 h. *o*-Dichlorobenzene (100 mL) was added to the reaction mixture, and the solution was heated for 5 h. $CH_2Cl_2$ was distilled off from the reaction mixture, and the solvents were then removed under reduced pressure to give rise to a dark brown oil. The crude product was dissolved in $CH_2Cl_2$ (200 mL) and washed with $H_2O$ (200 mL). The organic extract was dried over $MgSO_4$, and the organic solvents were removed to give a dark brown oil. Purification by flash chromatography eluting with 20% EtOAc−hexane afforded 4.01 g (25% yield) of 3-fluoro carbamate **15** as the more polar product: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.27 (t, $J$ = 7.5 Hz, 3H), 2.23−2.39 (m, 3H), 2.42−2.52 (m, 1H), 2.76−2.92 (m, 2H), 3.14−3.23 (m, 2H), 3.31−3.44 (m, 2H), 3.72−3.85 (m, 2H), 4.15 (q, $J$ = 7.5 Hz, 2H), 7.08−7.21 (m, 4H), 8.27 (d, $J$ = 2.5 Hz, 1H); MS *m/z* (rel intensity) 401 (100, $MH^+$). Also 4.1 g (24% yield) of the less polar 3-chloro carbamate **16** eluted as a white solid: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.23 (t, $J$ = 7.5 Hz, 3H), 2.17−2.54 (m, 4H), 2.69−2.93 (m, 2H), 3.03−3.21 (m, 2H), 3.22−3.50 (m, 2H), 3.65−3.89 (m, 2H), 4.12 (q, $J$ = 7.5 Hz, 2H), 7.00−7.20 (m, 3H), 7.44 (d, $J$ = 2.5 Hz, 1H), 8.34 (d, $J$ = 2.5 Hz, 1H); MS *m/z* (rel intensity) 418 (100, $MH^+$).

**4-(8-Chloro-3-fluoro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)-piperidine (17).** To 100 mL of concentrated HCl was added 3-fluoro carbamate **15** (3.40 g, 0.84 mmol). The reaction mixture was refluxed for 16 h. It was then cooled, poured into ice, and neutralized with 50% aqueous NaOH. The aqueous phase was extracted with $CH_2Cl_2$ (2 × 200 mL). Concentration of the organic phase afforded the hydrolyzed amine that was used for subsequent reaction without further purification: MS *m/z* (rel intensity) 329 (100, $MH^+$).

To a solution of amine obtained above (0.5 g, 1.25 mmol) in 15 mL of DMF were added 4-pyridylacetic acid (0.17 g, 1.2 mmol), HOBT (0.17 g, 1.87 mmol), DEC (0.36 g, 1.9 mmol), and *N*-methylmorpholine (0.63 g, 6.2 mmol), and the mixture was stirred at room temperature for 16 h. The organic phase was washed with saturated $NaHCO_3$ and brine and then dried over $Na_2SO_4$. It was then concentrated and purified by flash chromatography (silica gel) eluting with 1.5% MeOH (with ammonia)−$CH_2Cl_2$ to afford 3,10-dichloro pyridylacetamide **17** in 82% yield (0.456 g): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.05−2.36 (m, 4H), 2.76−2.92 (m, 2H), 3.12−3.38 (m, 4H), 3.62−3.90 (m, 2H), 3.28 (s, 2H), 7.09 (dd, $J$ = 7.5, 5.0 Hz, 1H), 7.20−7.27 (m, 3H), 7.34 (br s, 1H), 7.58 (dd, $J$ = 7.5, 5.0 Hz, 1H), 8.32−8.37 (m, 1H), 8.44−8.50 (m, 2H); MS *m/z* (rel intensity) $MH^+$ (448, 100). Anal. ($C_{26}H_{23}N_3OClF\cdot0.5H_2O$) C, H, N, Cl, F.

**4-(8-Chloro-3-fluoro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(3-pyridinylacetyl)-piperidine (18).** Reaction was carried out essentially in the same way as described for the preparation of compound **17** above replacing 4-pyridylacetic acid with 3-pyridylacetic acid to obtain the desired amide **18** in 94% yield: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.08−2.38 (m, 4H), 2.77−2.94 (m, 2H), 3.12−3.42 (m, 4H), 3.68−3.88 (m, 2H), 3.78 (s, 2H), 7.10 (d, $J$ = 7.5 Hz, 1H), 7.20−7.28 (m, 1H), 7.30−7.37 (m, 2H), 7.53−7.67 (m, 2H), 8.32−8.36 (m, 1H), 8.40−8.45 (m, 2H); IR (film) $\upsilon_{max}$ 713, 893, 996, 1206, 1272, 1445, 1592, 1641, 2862, 2909, 3020, 3046, 3438 cm$^{-1}$; MS *m/z* (rel intensity) 448.1 (100, $MH^+$). Anal. ($C_{26}H_{23}N_3OFCl\cdot0.5H_2O$) C, H, N.

**4-(3,8-Dichloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta-[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)piperidine (19).** Reaction was carried out essentially in the same way as described for the preparation of compound **17** above to obtain the desired amide **19** in 33% yield after purification on normal phase HPLC (silica gel) eluting with 5% MeOH (saturated with ammonia)−$CH_2Cl_2$: mp 113−114 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.10−2.50 (m, 4H), 2.70−2.95 (m, 2H), 3.15−3.40 (m, 4H), 3.50−3.70 (m, 1H), 3.80 (s, 2H), 3.95−4.15 (m, 1H), 7.00−7.30 (m, 5H), 745 (br s, 1H), 8.35 (m, 1H), 8.60 (m, 2H); MS *m/z* (rel intensity) 464 (60, $MH^+$), 466 (45). Anal. ($C_{26}H_{23}N_3OCl_2\cdot0.6H_2O$) C, H, N.

**4-(3,8-Dichloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta-[1,2-*b*]pyridin-11-ylidene)-1-(3-pyridinylacetyl)piperidine (20).** Reaction was carried out essentially in the same way as described for the preparation of compound **17** above replacing 4-pyridylacetic acid with 3-pyridylacetic acid to obtain the desired amide **20** in >95% yield: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.19−2.54 (m, 4H), 2.74−2.91 (m, 2H), 3.18−3.42 (m, 4H), 3.62−3.77 (m, 1H), 3.74 (s, 2H), 3.96−4.13 (m, 1H), 7.06 (dd, $J$ = 10.0, 7.5 Hz, 1H), 7.12−7.21 (m, 2H), 7.23−7.30 (m, 1H), 7.45 (d, $J$ = 2.5 Hz, 1H), 7.73 (d, $J$ = 7.5 Hz, 1H), 8.36 (dd, $J$ = 7.5, 2.5 Hz, 1H), 8.44−8.56 (m, 2H); IR (film) $\upsilon_{max}$ 718, 897, 994, 1135, 1206, 1436, 1479, 1641, 2860, 2908, 2995, 3036, 3432 cm$^{-1}$; MS *m/z* (rel intensity) 464 (100, $MH^+$), 465 (42), 466 (69). Anal. ($C_{26}H_{23}N_3OCl_2\cdot0.3H_2O$) C, H, N.

**4-(3-Bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylic Acid Ethyl Ester (21).** Amino carbamate **14** (0.1 g, 0.25 mmol) was dissolved in 2 mL of 48% HBr. The reaction mixture was then cooled to −5 °C, and molecular bromine (0.05 g, 0.72 mmol) was then added. The reaction mixture was stirred at that temperature for 15 min after which $NaNO_2$ (0.05 g, 0.72 mmol) dissolved in 5 mL of $H_2O$ was slowly added. The reaction mixture was stirred for 45 min and then neutralized with 40% NaOH. The aqueous phase was extracted with EtOAc (3 × 60 mL). Combined EtOAc fractions were dried over $Na_2SO_4$ and concentrated to give the 3-bromo carbamate **21** in 88% overall yield: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.24 (t, $J$ = 7.5 Hz, 3H), 2.22−2.52 (m, 4H), 2.71−2.89 (m, 2H), 3.06−3.20 (m, 2H), 3.25−3.43 (m, 2H), 3.68−3.88 (m, 2H), 4.14 (q, $J$ = 7.5 Hz, 2H), 7.04−7.20 (m, 3H), 7.58 (d, $J$ = 2.5 Hz, 1H), 8.44 (d, $J$ = 2.5 Hz, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 15.02, 30.88, 31.12, 31.60, 31.78, 32.05, 45.06, 61.69, 126.69, 129.25, 130.79, 133.43, 135.55, 137.68, 138.71, 139.57, 140.25, 147.86, 155.66, 155.75; IR (film) $\upsilon_{max}$ 997, 1114, 1229, 1435, 1473, 1698, 2865, 2905, 2979, 3448 cm$^{-1}$; MS *m/z* (rel intensity) 463 (100, $MH^+$).

**4-(3-Bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)-piperidine (22).** To 75 mL of concentrated HCl was added 3-bromo carbamate **21** (2.70 g, 5.83 mmol). The reaction mixture was refluxed for 16 h. It was then cooled, poured into ice, and neutralized with concentrated $NH_4OH$. The aqueous phase was extracted with EtOAc. Concentration of the organic phase afforded the hydrolyzed amine that was used for subsequent reaction without further purification: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.14−2.56 (m, 4H), 2.65−2.93 (m, 4H), 3.02−3.18 (m, 2H), 3.26−3.51 (m, 2H), 7.05−7.23 (m, 5H), 7.61 (d, $J$ = 2.5 Hz, 1H), 8.47 (d, $J$ = 2.5 Hz, 1H), 8.55 (d, $J$ = 5.0 Hz, 2H); MS *m/z* (rel intensity) 391.1 (100, $MH^+$).

To a solution of amine obtained above (0.5 g, 1.3 mmol) in 15 mL of DMF were added 4-pyridylacetic acid (0.178 g, 1.3 mmol), HOBT (0.17 g, 1.3 mmol), DEC (0.37 g, 1.9 mmol), and *N*-methylmorpholine (0.66 g, 0.71 mL, 6.5 mmol), and the mixture was stirred at room temperature for 16 h. The organic phase was washed with saturated $NaHCO_3$ and brine and then dried over $Na_2SO_4$. It was then concentrated and purified on normal phase HPLC (silica gel) eluting with 5% MeOH (saturated with ammonia)−$CH_2Cl_2$ gradient to afford tricyclic pyridylacetamide **22** in 93% yield as a white solid: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.14−2.60 (m, 4H), 2.69−2.96 (m, 2H), 3.15−3.46 (m, 4H), 3.55−3.73 (m, 1H), 3.81 (s, 1H), 3.94−4.19 (m, 1H), 6.98−7.26 (m, 5H), 7.62 (br s, 1H), 8.41−8.67 (m, 3H); $^{13}$C NMR (75.5 MHz, $CDCl_3$) $\delta$ 30.83, 31.28, 31.59, 31.91, 40.787, 43.39, 47.23, 119.43, 124.60, 126.92, 129.32, 130.21, 133.79, 134.29, 135.68, 137.53, 139.60, 140.52, 145.02, 147.92, 148.05, 150.05, 155.35, 168.05; IR (film) $\upsilon_{max}$ 574, 830, 897, 994, 1205, 1271, 1437, 1639, 2906, 3028 cm$^{-1}$; MS *m/z* (rel intensity) 510.1 (100, $MH^+$). Anal. ($C_{26}H_{23}N_3OBrCl\cdot0.5H_2O$) C, H, N.

**4-(3-Bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(3-pyridinylacetyl)-piperidine (23).** Reaction was carried out essentially in the same way as described for preparation of compound **22** above replacing 4-pyridylacetic acid with 3-pyridylacetic acid to obtain the desired amide **23** in 90% yield: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.14−2.51 (m, 4H), 2.69−2.94 (m, 2H), 3.12−3.44 (m, 4H), 3.57−3.70 (m, 1H), 3.75 (s, 2H), 3.92−4.18 (m, 1H), 6.99−7.27 (m, 4H), 7.53−7.70 (m, 2H), 8.37−8.60 (m, 3H); MS *m/z* (rel intensity) 510.1 (100, $MH^+$). Anal. ($C_{26}H_{23}N_3OBrCl\cdot0.3H_2O$) C, H, N.

**4-[8-Chloro-5,6-dihydro-3-(methylthio)-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (24).** 3-Bromo carbamate **21** was mixed with $CH_3SNa$ (5.0 g, 10.84 mmol), and then 50 mL of DMF was added. The reaction mixture was illuminated with a 200-W lamp for 72 h with stirring. The volatiles were then removed, and the resulting solid was partitioned between 1 N NaOH and $CH_2Cl_2$. The aqueous phase was extracted twice with $CH_2Cl_2$ (2 × 150 mL). Combined $CH_2Cl_2$ was dried over $MgSO_4$ and concentrated. Purification by flash chromatography on silica gel first eluting with 20−30% EtOAc−hexane yielded the 3-methylthio carbamate **24** in 52% yield: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.28 (t, $J$ = 7.5 Hz, 3H), 2.22−2.60 (m, 4H), 2.51 (s, 3H), 2.71−2.94 (m, 2H), 3.04−3.22 (m, 2H), 3.26−3.49 (m, 2H), 3.67−3.93 (m, 2H), 4.16 (q, $J$ = 7.5 Hz, 2H), 7.04−7.22 (m, 3H), 7.34 (d, $J$ = 2.5 Hz, 1H), 8.31 (d, $J$ = 2.5 Hz, 1H); IR (film) $\upsilon_{max}$ 998, 1115, 1233, 1435, 1463, 1479, 1696, 2925, 2975, 2987, 3444 cm$^{-1}$; MS $m/z$ (rel intensity) 429.1 (100, MH$^+$). Anal. ($C_{23}H_{25}N_2O_2ClS$) C, H, N, S.

**4-[8-Chloro-5,6-dihydro-3-(methylthio)-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-(4-pyridinylacetyl)-piperidine (25).** Reaction was carried out essentially in the same way as described for the preparation of compound **22** above but replacing 3-bromo carbamate **21** with the 3-methylthio carbamate **24**. Purification on normal phase HPLC (silica gel) eluting with 3% MeOH (saturated with ammonia)−$CH_2Cl_2$ afforded 3-iodo tricyclic pyridylacetamide **25** in 41% yield:$^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.19−2.45 (m, 1H), 2.62−2.91 (m, 2H), 3.15−3.41 (m, 6H), 3.57−3.78 (m, 4H), 3.96−4.18 (m, 1H), 7.02−7.36 (m, 8H), 8.27 (dd, $J$ = 7.5 Hz, 3.75 Hz, 1H); $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 15.78, 30.43, 30.91, 31.35, 40.35, 42.96, 43.00, 46.86, 126.34, 126.43, 128.88, 130.24, 133.34, 134.02, 136.17, 136.77, 137.49, 139.41, 144.25, 144.38, 144.84, 149.36, 152.93, 167.57; IR (film) $\upsilon_{max}$ 995, 1439, 1478, 1599, 1642, 2860, 2919, 3437 cm$^{-1}$; MS $m/z$ (rel intensity) 357 (90), 476 (100, MH$^+$). Anal. ($C_{27}H_{26}N_3OClS\cdot0.3H_2O$) C, H, N.

**4-(8-Chloro-5,6-dihydro-3-iodo-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylic Acid Ethyl Ester (26) and 4-(8-Chloro-5,6-dihydro-3-phenyl-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylic Acid Ethyl Ester (27).** Tricyclic amino carbamate **14** (6.0 g, 15.11 mmol) was suspended in 100 mL of benzene, and iodine (2.3 g) followed by isoamyl nitrite (2.7 g, 3.1 mL, 22.67 mmol) was added. The reaction mixture was refluxed for 3 h and then diluted with $CH_2Cl_2$ (100 mL). It was then washed with $NaHSO_3$ (100 mL) and 1 M NaOH. The organic phase was dried over $MgSO_4$ and concentrated. Purification by flash chromatography on silica gel first eluting with 20−40% EtOAc−hexanes yielded the 3-iodo carbamate **26** in 42% yield (3.2 g): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.26 (t, $J$ = 7.5 Hz, 3H), 2.21−2.57 (m, 4H), 2.71−2.91 (m, 2H), 3.07−3.24 (m, 2H), 3.26−3.48 (m, 2H), 3.71−3.91 (m, 2H), 4.15 (q, $J$ = 7.5 Hz, 2H), 7.05−7.22 (m, 3H), 7.78 (d, $J$ = 2.5 Hz, 1H), 8.61 (d, $J$ = 2.5 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 15.06, 30.93, 31.16, 31.64, 31.74, 45.10, 61.74, 91.74, 126.75, 129.30, 130.84, 133.54, 136.00, 137.69, 138.72, 139.62, 145.91, 152.85, 155.81, 156.06; IR (film) $\upsilon_{max}$ 996, 1114, 1228, 1434, 1478, 1696, 2860, 2908, 2978, 3447 cm$^{-1}$; MS $m/z$ (rel intensity) 509.0 (100, MH$^+$). Further elution with ethyl acetate only gave the 3-phenyl carbamate **27** in 16% yield (1.1 g): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.25 (t, $J$ = 7.5 Hz, 3H), 2.25−2.60 (m, 4H), 2.70−2.95 (m, 2H), 3.05−3.25 (m, 2H), 3.30−3.50 (m, 2H), 3.70−3.95 (m, 2H), 4.15 (q, $J$ = 7.5 Hz, 2H), 7.00−7.70 (m, 9H), 8.60 (d, $J$ = 2.5 Hz, 1H); MS $m/z$ (rel intensity) 459.3 (100, MH$^+$).

**4-(8-Chloro-3-iodo-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)-piperidine (28).** Reaction was carried out essentially in the same way as described for the preparation of compound **22** above but replacing 3-bromo carbamate **21** with the 3-iodo carbamate **26**. Purification on normal phase HPLC (silica gel) eluting with 8% MeOH (saturated with ammonia)−$CH_2Cl_2$ afforded 3-iodo tricyclic pyridylacetamide **28** in 66% yield: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.12−2.52 (m, 4H), 2.69−2.88 (m, 2H), 3.12−3.40 (m, 4H), 3.53−3.70 (m, 1H), 3.74 (s, 2H), 3.93−4.19 (m, 1H), 6.97−7.26 (m, 5H), 7.78 (br s, 1H), 8.42−8.69 (m, 3H); MS $m/z$ (rel intensity) 556.1 (100, MH$^+$). Anal. ($C_{26}H_{23}N_3OICl$) C, H, N.

**4-(8-Chloro-3-phenyl-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)-piperidine (29).** Reaction was carried out essentially in the same way as described for the preparation of compound **22** above but replacing 3-bromo carbamate **21** with the 3-phenyl carbamate **27**. Purification on normal phase HPLC (silica gel) eluting with 5% MeOH (saturated with ammonia)−$CH_2Cl_2$ afforded 3-iodo tricyclic pyridylacetamide **29** in 46% yield: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.20−2.61 (m, 4H), 2.74−3.06 (m, 2H), 3.12−3.52 (m, 4H), 3.58−3.72 (m, 1H), 3.79 (s, 1H), 4.01−4.28 (m, 1H), 7.05−7.26 (m, 5H), 7.35−7.61 (m, 5H), 7.64 (br s, 1H), 8.50−8.69 (m, 3H); MS $m/z$ (rel intensity) 506.2 (100, MH$^+$); HRMS (FAB) calcd for $C_{32}H_{28}N_3OCl$ (MH$^+$) 506.1999, found 506.2004.

**4-[8-Chloro-5,6-dihydro-3-(trifluoromethyl)-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylic Acid Ethyl Ester (30).** 3-Iodo carbamate **26** (1.01 g, 1.99 mmol) was dissolved in 30 mL of dry DMF at room temperature. To this solution were added methyl 2,2-difluoro-2-(fluorosulfonyl) acetate (1.33 g, 0.88 mL, 6.96 mmol), and CuI (0.76 g, 3.97 mmol), and the reaction mixture was heated to between 60 and 80 °C for 8 h. The reaction mixture was cooled to room temperature, and DMF was removed by rotary evaporation. It was then partitioned between $CH_2Cl_2$ and water. The aqueous phase was further extracted with $CH_2Cl_2$. The $CH_2Cl_2$ fraction was dried over $MgSO_4$ and concentrated. Purification by flash chromatography on silica gel first eluting with 30% EtOAc−hexanes and then with 10% MeOH (saturated with ammonia)−$CH_2Cl_2$ yielded 0.15 g of the 3-trifluoromethyl carbamate **30** (17% yield): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.30 (t, $J$ = 7.5 Hz, 3H), 2.20−2.60 (m, 4H), 2.70−3.01 (m, 2H), 3.05−3.30 (m, 2H), 3.35−3.55 (m, 2H), 3.70−3.90 (m, 2H), 4.20 (q, $J$ = 7.5 Hz, 2H), 7.05−7.25 (m, 3H), 7.70 (d, $J$ = 2.5 Hz, 1H), 8.70 (d, $J$ = 2.5 Hz, 1H); MS $m/z$ (rel intensity) 451.1 (100, MH$^+$); HRMS (FAB) calcd for $C_{23}H_{23}N_2F_3OCl$ (MH$^+$) 451.1400, found 451.1389.

**4-[8-Chloro-5,6-dihydro-3-(trifluoromethyl)-11*H*-benzo-[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-(4-pyridinylacetyl)piperidine (31).** 3-Trifluoromethyl carbamate **30** (0.14 g, 0.3 mmol) was dissolved in EtOH (20 mL). To this reaction mixture was added KOH (0.16 g, 2.7 mmol) dissolved in 10 mL of $H_2O$. The reaction mixture was heated to reflux for 16 h. It was then concentrated and partitioned between $CH_2Cl_2$ and water. The aqueous phase was further extracted with $CH_2Cl_2$. Combined $CH_2Cl_2$ was dried over $MgSO_4$ and concentrated. The resulting amine was used in the next reaction without further purification.

To the amine derived from hydrolysis of carbamate **30** above (0.07 g, 0.18 mmol) dissolved in 5 mL of DMF were added 4-pyridylacetic acid (0.05 g, 0.28 mmol), HOBT (0.05 g, 0.37 mmol), DEC (0.071 g, 0.37 mmol), and *N*-methyl morpholine (0.093 g, 0.1 mL, 6.5 mmol), and the mixture was stirred at room temperature for 16 h. The organic phase was washed with saturated $NaHCO_3$ and brine and then dried over $Na_2SO_4$. It was then concentrated and purified on normal phase flash chromatography eluting with 3% MeOH (saturated with ammonia)−$CH_2Cl_2$ gradient to afford 0.029 g of tricyclic pyridylacetamide **31** (32% yield): mp 93.6−94.1 °C; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.13−2.67 (m, 4H), 2.76−2.87 (m, 1H), 2.89−2.99 (m, 1H), 3.20−3.45 (m, 4H), 3.57−3.71 (m, 1H), 3.75 (s, 2H), 3.98−4.14 (m, 1H), 7.03−7.24 (m, 5H), 7.68 (s, 1H), 8.55 (d, $J$ = 5.0 Hz, 2H), 8.67 (d, $J$ = 10.0 Hz, 1H); MS $m/z$ (rel intensity) 498.16 (100, MH$^+$); HRMS (FAB) calcd for $C_{29}H_{23}N_3F_3OCl$ (MH$^+$) 498.1560, found 498.1551.

**4-(8-Chloro-3-*tert*-butyl-5,6-dihydro-11*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)-piperidine (33).** Coupling of amine **32**[19] with 4-pyridylacetic acid was accomplished in essentially the same manner as described in the preparation of compound **22** above. Purification by flash chromatography on silica gel first eluting with 3% MeOH (saturated with ammonia)−$CH_2Cl_2$ yielded the 3-*tert*-butyl tricyclic pyridylacetamide **33** in 52% yield: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.3 (s, 9H), 2.20−2.70 (m, 4H), 2.80−

2.95 (m, 2H), 3.20−3.45 (m, 4H), 3.60−3.75 (m, 1H), 3.80 (s, 2H), 4.05−4.25 (m, 1H), 7.10−7.30 (m, 5H), 7.45 (br s, 1H), 8.45−8.60 (m, 3H); MS *m/z* (rel intensity) 486.1 (100, $MH^+$); HRMS (EI) calcd for $C_{30}H_{32}N_3OCl$ ($M^+$) 485.2234, found 485.2229.

**4-(8-Chloro-3-methyl-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(3-pyridinylacetyl)-piperidine (35).** Coupling of amine **34**[20] with 3-pyridylacetic acid was accomplished in essentially the same manner as described in the preparation of compound **22** above. Purification by flash chromatography on silica gel first eluting with 4% MeOH (saturated with ammonia)−$CH_2Cl_2$ yielded the 3-methyl tricyclic pyridylacetamide **35** in 99% yield: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.20−2.52 (m, 4H), 2.28 (s, 3H), 2.69−2.90 (m, 2H), 3.07−3.45 (m, 4H), 3.62−3.79 (m, 1H), 3.72 (s, 2H), 3.99−4.20 (m, 1H), 7.02−7.32 (m, 5H), 7.58−7.67 (m, 1H), 8.23 (br s, 1H), 8.44−8.54 (m, 2H); IR (film) $\upsilon_{max}$ 713, 996, 1208, 1272, 1384, 1445, 1479, 1641, 2862, 2918, 3432 $cm^{-1}$; MS *m/z* (rel intensity) 443.25 (18), 444.20 (100, $MH^+$), 445.20 (33), 446.20 (36). Anal. ($C_{27}H_{26}N_3OCl\cdot1.2H_2O$) C, H, N.

**4-Pyridylacetic Acid *N*-Oxide (37).** Ethyl 4-pyridylacetate (6.23 g, 38 mmol) was dissolved in 50 mL of $CH_2Cl_2$ under $N_2$ atmosphere, and the reaction mixture was cooled to − 20 °C with stirring. *m*-Chloroperbenzoic acid (19.52 g, 110 mmol) was added to the reaction mixture over a period of 0.5 h. The reaction mixture was stirred for another 1.0 h and then at 25 °C for 16 h. It was further diluted with $CH_2Cl_2$ and washed with sodium bisulfite and 1 N NaOH. The organic phase was dried over $MgSO_4$ and concentrated. The resulting semisolid was purified on silica gel flash chromatography eluting with 10% EtOH−$CH_2Cl_2$ to afford 1.05 g of ethyl 4-pyridylacetate *N*-oxide (15% yield): $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.30 (t, $J$ = 7.5 Hz, 3H), 3.60 (s, 2H), 4.20 (q, $J$ = 7.5 Hz, 2H), 7.25 (d, $J$ = 6.0 Hz, 2H), 8.55 (d, $J$ = 6.0 Hz, 2H); MS *m/z* (rel intensity) 182 (100, $MH^+$).

Ethyl 4-pyridylacetate *N*-oxide (0.54 g, 3 mmol) was dissolved in 10 mL of EtOH under $N_2$ atmosphere. Lithium hydroxide (0.5 g, 12 mmol, dissolved in 12 mL of $H_2O$) was added, and the reaction mixture stirred at room temperature for 16 h. The organic solvents were then removed, and the resulting semisolid was neutralized with 20 mL of 1 N HCl. Volatiles were then removed in vacuo, and the resulting solid was washed with EtOH. Combined EtOH fractions were then concentrated to give 0.54 g of compound **37**: $^1$H NMR (200 MHz, DMSO) $\delta$ 3.50 (s, 2H), 7.35 (d, $J$ = 6.5 Hz, 2H), 8.20 (d, $J$ = 6.5 Hz, 2H).

**4-(3-Bromo-8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)-piperidine *N*$^1$-Oxide (38).** Reaction was carried out essentially in the same way as described for the preparation of compound **22** above but replacing pyridineacetic acid with pyridineacetic acid *N*-oxide (**37**). Purification on normal phase HPLC (silica gel) eluting with 3% MeOH (saturated with ammonia)−$CH_2Cl_2$ afforded 3-bromo tricyclic pyridylacetamide *N*-oxide **38** in 63% yield: $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.21−2.43 (m, 3H), 2.46−2.63 (m, 1H), 2.72−2.97 (m, 2H), 3.17−3.46 (m, 4H), 3.57−3.81 (m, 3H), 3.89−4.14 (m, 1H), 7.03−7.23 (m, 5H), 7.61 (d, $J$ = 2.5 Hz, 1H), 8.18 (d, $J$ = 7.5 Hz, 2H), 8.40−8.50 (m, 1H); IR (film) $\upsilon_{max}$ 807, 994, 1176, 1284, 1439, 1478, 1637 $cm^{-1}$; MS *m/z* (rel intensity) 526.6 (100, $MH^+$). Anal. ($C_{26}H_{23}N_3O_2BrCl\cdot0.6CH_2Cl_2\cdot2H_2O$) C, H, N.

**4-(8-Chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-(4-pyridinylacetyl)piperidine *N*$^1$-Oxide (40).** Reaction was carried out essentially in the same way as described for the preparation of compound **22** above by coupling amine **39**[20] with pyridineacetic acid *N*-oxide (**37**). Purification on normal phase (silica gel) eluting with 3−5% MeOH (saturated with ammonia)−$CH_2Cl_2$ afforded the acetamide pyridyl *N*-oxide **40** in 17% yield: mp 129−130 °C; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 2.22−2.45 (m, 4H), 2.46−2.64 (m, 1H), 2.72−2.98 (m, 2H), 3.16−3.47 (m, 4H), 3.57−3.78 (m, 2H), 3.92−4.16 (m, 1H), 7.06−7.24 (m, 6H), 7.41−7.52 (m, 1H), 8.15 (d, $J$ = 5.0 Hz, 2H), 8.36−8.48 (m, 1H); IR (film) $\upsilon_{max}$ 805, 994, 1172, 1249, 1437, 1640, 3438; MS *m/z* (rel intensity) 446.2 (100, $MH^+$). Anal. ($C_{26}H_{24}N_3O_2Cl\cdot0.5H_2O\cdot0.3CH_2Cl_2$) C, H, N.

**In Vitro Enzyme Assays.** FPT activity was determined by measuring transfer of [$^3$H]farnesyl from [$^3$H]farnesyl pyrophosphate to trichloroacetic acid-precipitable Ha-Ras-CVLS as previously described.[21] GGPT-1 activity was similarly determined using [$^3$H]geranylgeranyl diphosphate and Ha-Ras-CVLL as substrates.[21]

**Cellular Assays for Inhibition of Ha-Ras Processing and Transforming Function.** Inhibition of intracellular processing of H-Ras by inhibitors was measured in transfected COS cells as described previously.[21]

**Cell Lines for in Vivo Studies.** The PT-24 cell line is derived from BALB c/3T3 cells transfected with activated Ha-Ras-CVLS. NIH3T3 cells transfected with activated Ha-Ras containing its native C-terminal sequence (CVLS) or an altered C-terminal sequence (CVLL) were constructed by removing *H-ras* (the coding sequences) from the pSV Sport expression vectors by restriction digestion.[21] These fragments were incubated with the Klenow fragment of DNA polymerase I and subcloned into pOPRSVI (Stratagene) by standard methods.[23] The resulting pOPRSVI-H-ras-CVLS and pOPRSVI-H-ras-CVLL plasmids were transfected into NIH3T3 cells using Lipofectamine (GIBCO-BRL) under the conditions suggested by the manufacturer. G-418-resistant clones were isolated and screened for morphological transformation and their ability to grow in soft agar. NIH3T3 cells transfected with activated Ki-Ras containing its native C-terminal sequence of CVIM were similarly constructed. MSV-3T3 cells are NIH3T3 cells transfected with the *mos* oncogene. The human colon carcinoma DLD-1 cell line was obtained from American Type Culture Collection (Rockville, MD).

**In Vivo Efficacy Studies.** All animal studies were carried out in the animal facility of Schering-Plough Research Institute in accordance with institutional guidelines. All animals were maintained in accordance with the *National Institutes of Health Guide for the Care and Use of Laboratory Animals*. Experimental protocols were reviewed by and the experimental progress was supervised by the Schering Plough Animal Care and Use Committee. After 1 week of acclimation, 5−7-week-old female nude mice (Crl:Nu/Nu-nu Br; Charles River Laboratories, Wilmington, MA) were subcutaneously inoculated with various cell lines on day 0. The number of cells inoculated was $3.0 \times 10^5$ for NIH3T3 Ki-Ras-CVIM, $2 \times 10^6$ for NIH3T3 Ha-Ras-CVLL and CVLS, $3 \times 10^6$ for MSV-3T3, and $5 \times 10^6$ for DLD-1 and PT-24. Animals were randomly assigned to control and treatment groups (10 animals/group) before the first treatment. Drug treatment at either 10 or 50 mg/kg was initiated on day 1. Compound **38** was dissolved in 20% (w/v) hydroxypropyl-$\beta$-cyclodextrin (HP$\beta$CD). Vehicle controls received 20% HP$\beta$CD. Vehicle or drug solution (0.1 mL) was administered by oral gavage every 6 h (q.i.d.) for 14−21 days. A no-treatment control was always included along with the vehicle control to evaluate the influence of vehicle and of the q.i.d. gavage treatment. Once palpable, tumor volume was measured in three dimensions twice weekly and calculated with the formula of $V = {}^1/_6\pi LWT$, where $L$, $W$, and $T$ represent length, width, and thickness, respectively.[21] T/C value in percent was calculated for each measurement, where T and C are the median tumor volume of the treated and control groups, respectively. Average growth inhibition was used to compare efficacy of various treatments and was derived by subtracting the average T/C values of each treatment from 100. Single-tailed Student's *t*-test was used for statistical analysis.

**Pharmacokinetic Studies.** Nude mice were also used to study the pharmacokinetic properties of the tricyclic inhibitors. Blood samples were collected at nine time points (2 min, 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 7 h, and 24 h) after a single oral or intravenous (tail vein) dose of 25 mg/kg inhibitor in 20% HP$\beta$CD. Two mice were used for each time point, and samples were collected by cardiac puncture after euthanasia with carbon dioxide. After clotting on ice, serum was isolated by centrifugation. Quantitation of inhibitor serum levels was achieved using acetonitrile precipitation followed by high-performance liquid chromatography−atmospheric pressure chemical ionization (APCI) tandem mass spectrometry. A detailed description of the analytical methodology has been described for an earlier analogue in this series.[24]

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