# Non-Peptide Angiotensin II Receptor Antagonists. 2.[1] Design, Synthesis, and Biological Activity of N-Substituted (Phenylamino)phenylacetic Acids and Acyl Sulfonamides[2]

Daljit S. Dhanoa,*,§,† Scott W. Bagley,† Raymond S. L. Chang,‡ Victor J. Lotti,‡ Tsing-Bau Chen,‡ Salah D. Kivlighn,⊥ Gloria J. Zingaro,⊥ Peter K. S. Siegl,⊥ Arthur A. Patchett,† and William J. Greenlee†

*Merck Research Laboratories, Rahway, New Jersey 07065 and West Point, Pennsylvania 19486*

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The design, synthesis, and biological activity of a new class of highly potent non-peptide AII receptor antagonists derived from N-substituted (phenylamino)phenylacetic acids and acyl sulfonamides which exhibit a high selectivity for the $AT_1$ receptor are described. A series of N-substituted (phenylamino)phenylacetic acids (**9**) and acyl sulfonamides (**16**) and a tetrazole derivative (**19**) were synthesized and evaluated in the *in vitro* $AT_1$ (rabbit aorta) and $AT_2$ (rat midbrain) binding assay. The (phenylamino)phenylacetic acids **9c** ($AT_1$ $IC_{50}$ = 4 nM, $AT_2$ $IC_{50}$ = 0.74 μM), **9d** ($AT_1$ $IC_{50}$ = 5.3 nM, $AT_2$ $IC_{50}$ = 0.49 μM), and **9e** ($AT_1$ $IC_{50}$ = 5.3 nM, $AT_2$ $IC_{50}$ = 0.56 μM) were found to be the most potent $AT_1$-selective AII antagonists in the acid series. Incorporation of various substituents in the central and bottom phenyl rings led to a decrease in the $AT_1$ and $AT_2$ binding affinity of the resulting compounds. Replacement of the carboxylic acid ($CO_2H$) in **9c**, **9d**, and **9e** with the bioisostere acyl sulfonamide ($CONHSO_2Ph$) resulted in a (5–7)-fold increase in the $AT_1$ potency of **16a** ($AT_1$ $IC_{50}$ = 0.9 nM, $AT_2$ $IC_{50}$ = 0.2 μM), **16b** ($AT_1$ $IC_{50}$ = 1 nM, $AT_2$ $IC_{50}$ = 2.9 μM), and **16c** ($AT_1$ $IC_{50}$ = 0.8 nM, $AT_2$ $IC_{50}$ = 0.42 μM) and yielded acyl sulfonamides with subnanomolar $AT_1$ activity. Incorporation of the acyl sulfonamide ($CONHSO_2$-Ph) for the $CO_2H$ of **9c** not only enhanced the $AT_1$ potency but also effected a marked increase in the $AT_2$ potency of **16a** ($AT_2$ $IC_{50}$ = 0.74 μM of **9c** vs 0.2 μM of **16a**) and made it the most potent $AT_2$ antagonist in this study. Replacement of the $CO_2H$ of **9b** with the bioisostere tetrazole resulted in **19** ($AT_1$ $IC_{50}$ = 15 nM) with a 2-fold loss in the $AT_1$ and a complete loss in the $AT_2$ binding affinity. (Phenylamino)phenylacetic acid **9c** demonstrated good oral activity in AII-infused conscious normotensive rats at an oral dose of 1.0 mg/kg by inhibiting the pressor response for >6 h. Acyl sulfonamides **16a–c** displayed excellent *in vivo* activity by blocking the AII-induced pressor response for >6 h after oral administration in conscious rats at a 3.0 mg/kg dose level. Both acyl sulfonamides **16a** and **16c** exhibited superior *in vivo* activity in rats compared to that of (phenylamino)phenylacetic acid **9c**.

## Introduction

Inhibition of the renin–angiotensin system (RAS) by angiotensin II (AII) receptor antagonists continues to be the most active area of drug discovery for the treatment of hypertension and congestive heart failure.[3] Recently, we have described a new class of potent $AT_1$-selective AII receptor antagonists derived from N-substituted indoles and dihydroindoles.[4] In our continuing efforts to discover a structurally distinct class of AII antagonists, we became interested in exploring the possibility of replacing the 2,3-dihydroindole-5-methylene linker between the imidazopyridine and phenylacetic acid moieties by the ring-opened form of the dihydroindole unit at the $C_2$–$C_3$ bond. Herein, we report the design, synthesis, and biological activity of this new class of AII receptor antagonists derived from N-substituted (phenylamino)phenylacetic acids and acyl sulfonamides **1** (Figure 1), which display high potency with $AT_1$ selectivity and long duration of action in rats and offer considerable potential for a potent series of AII receptor antagonists with balanced $AT_1/AT_2$ activity.

## Chemistry

Various (phenylamino)phenylacetic acids (PAPAs) **9** described in this study (Tables I–III) were prepared as shown in Scheme I. 5,7-Dimethyl-2-ethyl-3*H*-imidazo-[4,5-*b*]pyridine (**2**)[5] was alkylated with 4-nitrobenzyl bromide (**3a**) ($R_1$ = H) and 3-methyl-4-nitrobenzyl bromide (**3b**) ($R_1$ = Me) using NaH in DMF to give the corresponding alkylated products **4** (**4a**, $R_1$ = H; **4b**, $R_1$ = Me). The aryl bromide **3b** was prepared from 3-methyl-4-nitrobenzoic acid (**10**) as described in scheme II. The substituted benzoic acid derivative **10** was reduced to alcohol **11** with a borane–dimethyl sulfide complex in THF followed by bromination with $Ph_3P/CBr_4$ in $CH_2Cl_2$ to provide the corresponding bromide **3b** (Scheme II). The alkylated intermediates **4** were reduced to the amino derivatives **5** which were alkylated with either methyl or ethyl α-bromophenylacetates **6** either by using NaH/DMF or by refluxing with $K_2CO_3$ in acetone to give **7**. Further alkylation of **7** with alkyl iodides ($R_3I$) using NaH/DMF or lithium hexamethyldisilyl azide (LiHMDS) in THF yielded the esters **8**. Although the use of LiHMDS in the alkylation of unhindered **7a** ($R_1$ = H) proved efficient, it failed to yield any alkylated product **8** in the case of the hindred 2-Me derivative **7b** ($R_1$ = Me). However, when **7a** and the hindered substrate **7b** were subjected to

* Author to whom correspondence should be addressed.
§ Current address: Synaptic Pharmaceutical Corp., 215 College Rd, Paramus, NJ 07652–1410.
† Department of Exploratory Chemistry, Merck Research Laboratories, Rahway, NJ.
‡ Department of New Lead Pharmacology, Merck Research Laboratories, West Point, PA.
⊥ Department of Pharmacology, Merck Research Laboratories, West Point, PA.
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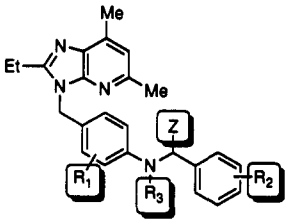
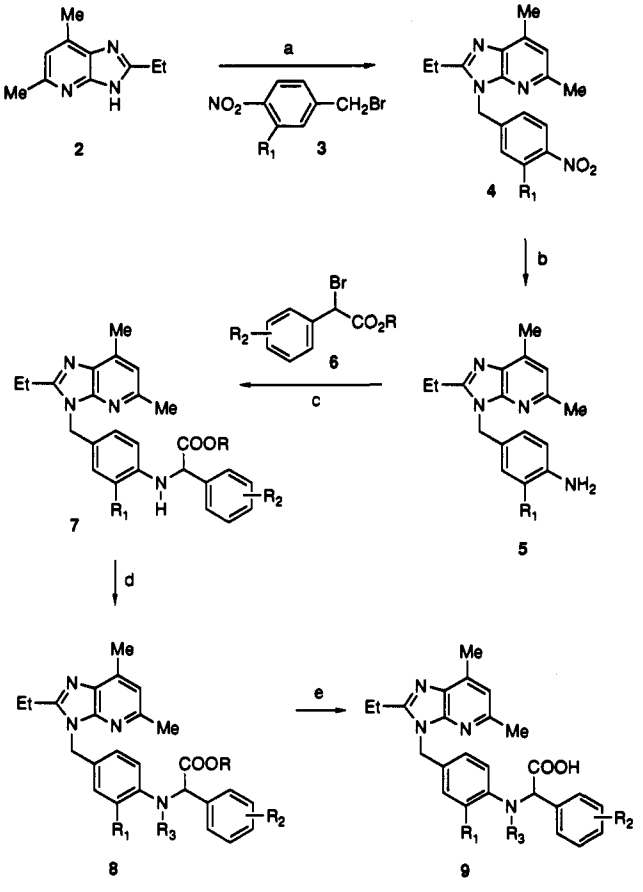


1: Z = COOH, $CONHSO_2Ar$, Tetrazol-5-yl
$R_1$, $R_3$ = Alkyl; $R_2$ = Alkyl, Halogen

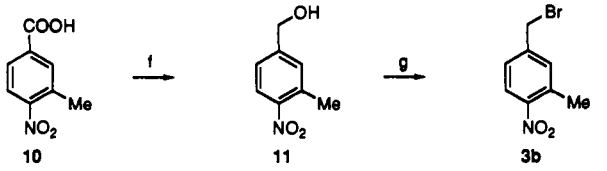
**Figure 1.** N-Substituted (phenylamino)phenylacetic-acid- and acyl-sulfonamide-based AII receptor antagonists.

**Scheme I.** Synthesis of N-Substituted PAPAs[a]



[a] Conditions: (a) NaH, DMF, **3**; (b) $H_2$, Pd/C, MeOH; (c) NaH, DMF, **6** or $K_2CO_3$, **6**, acetone, reflux; (d) NaH, DMF, $R_3I$ or $LiN(SiMe_3)_2$, THF, $R_3I$; (e) LiOH, $MeOH/H_2O$.

**Scheme II.** Preparation of 3-Methyl-4-nitrobenzyl Bromide **3b**[a]

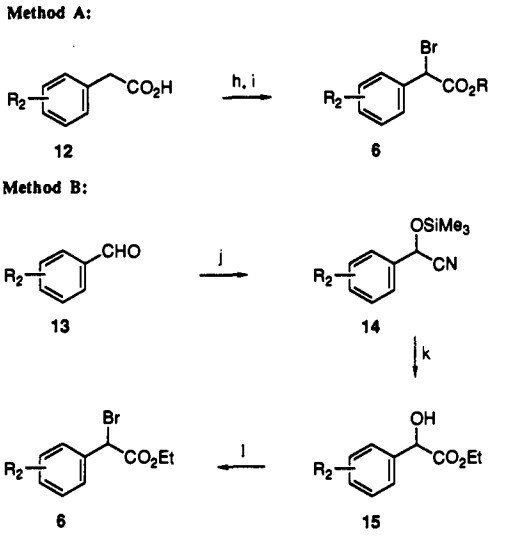


[a] Conditions: (f) $Me_2S{:}BH_3$, THF, 0 °C; (g) $Ph_3P$, $CBr_4$, $CH_2Cl_2$, 0 °C.

alkylation with **6** under NaH/DMF conditions, the desired esters **8** were obtained in good to excellent yields. Saponification of the esters **8** with aqueous LiOH in MeOH produced the desired N-substituted (phenylamino)phenylacetic acids **9**.

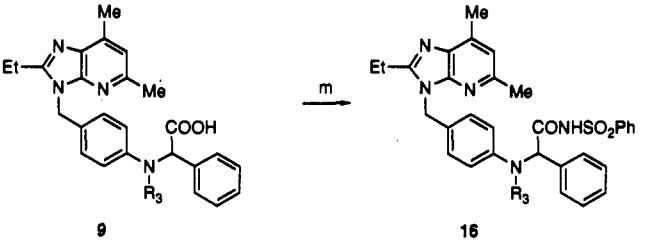
Methyl or ethyl α-bromophenylacetates **6** were prepared by two different methods as shown in scheme III. In method A, the substituted phenylacetic acids **12** were

**Scheme III.** Preparation of α-Bromo Esters **6**[a]



[a] Conditions: (h) ROH, $H_2SO_4$; (i) NBS, AIBN, $CCl_4$, reflux; (j) $Me_3SiCN$, KCN, catalytic 18-crown-6, $CH_2Cl_2$; (k) EtOH, HCl (g); (l) $Ph_3P$, $CBr_4$, $CH_2Cl_2$.

**Scheme IV.** Preparation of Acyl Sulfonamides **16**[a]



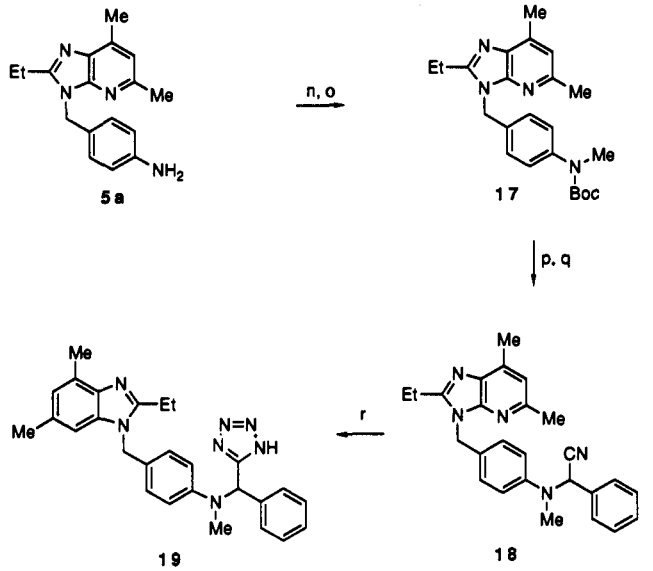
[a] Conditions: (m) 1,1′-Carbonyldiimidazole (CDI), THF, reflux, $PhSO_2NH_2$, DBU, THF, reflux.

converted to their corresponding esters by refluxing in MeOH or EtOH with a catalytic amount of $H_2SO_4$. These esters were brominated by refluxing with NBS/AIBN in $CCl_4$ to give the α-bromo esters **6**. In method B, the substituted aryl aldehydes **13** were treated with (trimethylsilyl)cyanide ($Me_3SiCN$) in $CH_2Cl_2$ with a trace amount of KCN and 18-crown-6 to afford trimethylsilyl ethers of the cyanohydrin adducts **14**. Exposure of **14** to HCl in EtOH afforded the ethyl α-hydroxyarylacetates **15**, which upon further treatment with $Ph_3P/CBr_4$ in $CH_2Cl_2$ yielded the corresponding ethyl α-bromoarylacetates **6** (Scheme III).

PAPAs **9** were converted to the corresponding acyl sulfonamides **16** via acylimidazoles generated *in situ* by refluxing **9** with 1,1′-carbonyldiimidazole (CDI) in THF, which were further refluxed with a mixture of $PhSO_2NH_2$ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give **16** (Scheme IV).

Tetrazole **19** was constructed from **5a** via the amino nitrile derivative **18**. The aniline intermediate **5a** was protected with a *t*-Boc group using $Boc_2/TEA/CH_2Cl_2$, which upon alkylation with $CH_3I$ in NaH/DMF provided the *t*-Boc-protected *N*-methyl aniline derivative **17**. Deprotection of **17** with trifluoroacetic acid in methylene chloride ($TFA/CH_2Cl_2$) followed by subsequent condensation with benzaldehyde under modified Strecker conditions[7] using PhCHO/KCN/AcOH/MeOH yielded amino nitrile **18**. Treatment of **18** with trimethyltin azide ($Me_3SnN_3$)[8] in refluxing toluene gave the tetrazole derivative **19**.

**Scheme V.** Preparation of Tetrazole 19[a]




[a] Conditions: (n) $Boc_2O$, $Et_3N$, $CH_2Cl_2$; (o) NaH, DMF, MeI; (p) TFA, $CH_2Cl_2$; (q) PhCHO, KCN, AcOH, MeOH; (r) $Me_3SnN_3$, $PhCH_3$, reflux.

## Biological Results and Discussion

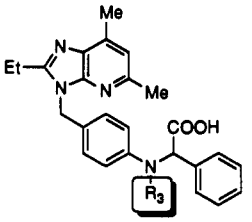
The *in vitro* $^{125}$I-[Sar$^1$,Ile$^8$]AII binding assays of the compounds reported here (Tables I–IV) were performed as described by Chang et al. using rabbit aorta and rat midbrain as receptor sources for the $AT_1$ and $AT_2$ receptors, respectively.[9] The relative potencies of the antagonists are expressed as the inhibitory concentration ($IC_{50}$ value) of the test compound required to completely displace 50% of the specifically bound $^{125}$I-[Sar$^1$,Ile$^8$]AII from the receptor.[9]

Results of the *in vitro* AII binding assay of the N-substituted PAPAs **9a–i** presented in Table I reveal that the presence of the *N*-alkyl group in **9** is essential for acquiring a high binding affinity to both $AT_1$ and $AT_2$ receptors. The unalkylated parent compound **9a** ($R_3$ = H) was found to be moderately active at the $AT_1$ subsite and extremely weakly active at the $AT_2$ subsite. N-Methylation of **9a** gave **9b** with a 25-fold increase in the $AT_1$ and a 6-fold improvement in the $AT_2$ binding affinity. Incorporation of longer side chains such as ethyl, allyl, and *n*-propyl in **9a** resulted in PAPAs **9c**, **9d**, and **9e** with an increase in $AT_1$ potency by 50- (N–Et), 38- (N–allyl), and 38-fold (N–Pr), respectively. In order to determine the optimal size of the *N*-alkyl side chain, PAPAs with larger primary and secondary *N*-alkyl groups including **9f** ($R_3$ = *n*-Bu), **9g** ($R_3$ = *i*-Bu), **9h** ($R_3$ = *sec*-Bu), and **9i** ($R_3$ = $CH_2$–cyclopropyl) were synthesized and evaluated in the *in vitro* $AT_1$ and $AT_2$ binding assays. Comparison of the $AT_1$ $IC_{50}$ values (Table I) demonstrated that the replacement of the Et group (**9c**) with *n*-Bu or *sec*-Bu resulted in the less-potent antagonists **9f** ($IC_{50}$ = 94 vs 4 nM) and **9h** ($IC_{50}$ = 80 vs 4 nM), respectively. The introduction of *i*-Bu and cyclopropylmethyl ($CH_2$–cyp) *N*-alkyl side chains gave the potent antagonists **9g** and **9i** but effected a 5.5-fold and a nearly 8-fold decrease in $AT_1$ binding as compared to that of the leading compound **9c** ($IC_{50}$ = 22 and 31 vs 4 nM).

The $AT_2$ receptor binding affinity of this series was markedly enhanced by 43-fold when the proton donor N–H linker in **9a** was replaced with an N–allyl side chain ($AT_2$ $IC_{50}$ = 0.49 vs 21 $\mu$M). Incorporation of Et, *n*-Pr and *n*-Bu side chains resulted in an increase of 28-, 38-, and 32-fold in the $AT_2$ potency of **9c**, **9e**, and **9f**, respectively. However, alkylation of **9a** by bulkier groups such as *i*-Bu, *sec*-Bu, and $CH_2$–cyp afforded the moderately potent $AT_2$ antagonists **9g**, **9h**, and **9i** with only 12-, 13-, and 10-fold improvement in their activity (Table I). The high $AT_1$ potency of PAPAs bearing N–Et, N–Pr, and N–allyl groups may be attributed to their favorable binding to one of the hydrophobic pockets of the $AT_1$ receptor (rabbit aorta).[10] The hydrophobic site which accommodates the Et, *n*-Pr, and N–allyl groups effectively is sensitive to the size of the side chain (N–$R_3$), as is indicated by the dramatic decrease in the $AT_1$ potency of the *n*-Bu- and *sec*-Bu-bearing analogs **9f** and **9h**. The increase in the $AT_2$ binding affinity of compounds **9b–f** obtained as a result of the incorporation of primary *N*-alkyl groups such as Et, *n*-Pr, allyl, and *n*-Bu may be attributed to favorable interactions of these *N*-alkyl side chains with the hydrophobic regions of the $AT_2$ receptor (rat midbrain) which accommodates the primary alkyl groups (Et, *n*-Pr, allyl, and *n*-Bu) more effectively than branched chains such as *i*-Bu, *sec*-Bu, and $CH_2$–cyp.

In order to determine the effect of the substitution of 2-Me in the central phenyl ring of PAPAs, the 2-Me analogs **9j–p** were synthesized and evaluated in the $AT_1$ and $AT_2$ binding assays (Table II). The results of this investigation demonstrate that **9j** is twice as potent as its desmethyl counterpart **9a** in the $AT_1$ and $AT_2$ binding assays. That the N–H of **9j** is partially shielded by the 2-Me group may account for its improved binding affinities. The $AT_1$ binding of **9o** is further improved by 4-fold when a 2-Me group is introduced into the bottom phenyl ring of **9j**. The shielding of the proton donor N–H bond by these 2-Me groups in **9o** seems to be only partially effective in providing a hydrophobic environment around it, which may account for its 7-fold increase in the $AT_1$ binding affinity ($AT_1$ $IC_{50}$ = 28 vs 200 nM, **9o** vs **9a**). N-Methylation of **9j** yielded **9k** which is slightly more potent (1.4-fold) than **9j** ($AT_1$ $IC_{50}$ = 70 vs 100 nM) but 2.5-fold less active than **9o** ($AT_1$ $IC_{50}$ = 70 vs 28 nM), which suggests that the unfavorable conformation acquired by **9k** for $AT_1$ binding is due to the steric congestion caused by the presence of two neighboring Me groups. On the other hand, the incorporation of N–Et and N–Pr groups for N–H in this 2-Me series resulted in

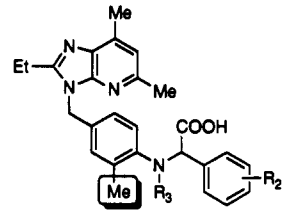
Table I. AII Antagonist Activity of N-Alkylated (Phenylamino)phenylacetic Acids **9**




| compd | $R_3$ | $IC_{50}$ ($\mu$M)[a] $AT_1$ | $AT_2$ |
|---|---|---|---|
| **9a** | H | 0.20 | 21.0 |
| **9b** | Me | 0.0082 | 3.40 |
| **9c** | Et | 0.004 | 0.74 |
| **9d** | allyl | 0.0053 | 0.49 |
| **9e** | *n*-Pr | 0.0053 | 0.56 |
| **9f** | *n*-Bu | 0.094 | 0.66 |
| **9g** | *i*-Bu | 0.022 | >0.3 |
| **9h** | *sec*-Bu | 0.08 | 1.6 |
| **9i** | $CH_2$–cyp | 0.031 | 2.2 |

[a] For racemic compounds.

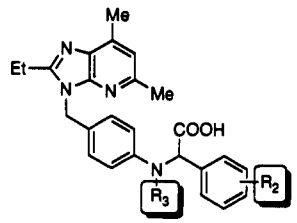
Table II. AII ($AT_1/AT_2$) Receptor Antagonist Activity of the 2-Methyl Analogs of 9



| compd | $R_2$ | $R_3$ | $IC_{50}$ ($\mu$M)[a] $AT_1$ | $AT_2$ |
|---|---|---|---|---|
| **9j** | H | H | 0.10 | 11.0 |
| **9k** | H | Me | 0.07 | 11.0 |
| **9l** | H | Et | 0.01 | 8.6 |
| **9m** | H | allyl | 0.034 | 4.3 |
| **9n** | H | *n*-Pr | 0.012 | 4.8 |
| **9o** | 2-Me | H | 0.028 | 19.0 |
| **9p** | 2-Me | allyl | 0.082 | 11.0 |

[a] For racemic compounds.

Table III. Effect of Substitution on the Phenylacetic Acid Moiety of Acids 9



| compd | $R_2$ | $R_3$ | $IC_{50}$ ($\mu$M)[a] $AT_1$ | $AT_2$ |
|---|---|---|---|---|
| **9q** | 3,5-bis-$CF_3$ | H | 0.86 | 6.0 |
| **9r** | 2,5-di-F | Me | >0.10 | >10 |
| **9s** | 2-Cl | Et | 0.38 | >10 |
| **9t** | 3-Me | Et | 0.066 | 2.1 |
| **9u** | 2,5-di-F | Et | 0.088 | >10 |
| **9v** | 3,5-bis-$CF_3$ | Et | 1.9 | 12 |
| **9w** | 2,5-di-F | allyl | 0.20 | 8.8 |

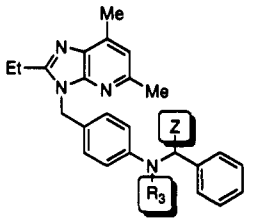
[a] For racemic compounds.

a noteworthy 10- and 8-fold increase in affinity for binding to the $AT_1$ receptor ($AT_1$ $IC_{50}$ = 10 and 12 vs 100 nM), suggesting that the Et and *n*-Pr side chains can extend beyond the reach of the N-Me group for better binding to the hydrophobic region of the $AT_1$ receptor. The N-allyl derivative **9m** was found to be 3-fold more active than **9j**. Incorporation of 2-Me in the central phenyl ring of PAPAs resulted in a decreased $AT_2$ binding affinity (Table II).

To examine the effect of substitution of the bottom phenyl ring of PAPAs on $AT_1$ and $AT_2$ binding, **9q–w** were synthesized and tested in the AII binding assay. The results shown in Table III demonstrate that the incorporation of large and hydrophobic substituents such as 3,5-bis(trifluoromethyl) led to a loss in $AT_1$ binding as observed in the case of **9q** and **9v**. Substitution by fluorine at C-2 and C-5 (2,5-di-F) of the bottom phenyl ring in **9r** ($R_3$ = Me), **9u** ($R_3$ = Et), and **9w** ($R_3$ = allyl) also resulted in decreased binding at the $AT_1$ receptor.

The PAPAs **9b–e** ($R_3$ = Me, Et, allyl, and *n*-Pr) were selected for the replacement of their terminal $CO_2H$ groups with carboxyl bioisosteres. Acyl sulfonamides **16a** ($R_3$ = Et), **16b** ($R_3$ = allyl), and **16c** ($R_3$ = *n*-Pr), and tetrazole **19** were synthesized, and their *in vitro* $AT_1$ and $AT_2$ binding affinities were evaluated (Table IV). From the data in Table IV, it is clear that the incorporation of the carboxylic acid bioisostere acyl sulfonamide ($CONHSO_2Ph$) in **16a**

Table IV. AII Antagonist Activity of Acyl Sulfonamides 16 and Tetrazole 19



| compd | $R_3$ | Z | $IC_{50}$ ($\mu$M)[a] $AT_1$ | $AT_2$ |
|---|---|---|---|---|
| **16a** | Et | $CONHSO_2Ph$ | 0.0009 | 0.20 |
| **16b** | allyl | $CONHSO_2Ph$ | 0.001 | 2.9 |
| **16c** | *n*-Pr | $CONHSO_2Ph$ | 0.0008 | 0.42 |
| **19** | Me | tetrazol-5-yl | 0.015 | >30 |
| **20** (DuP 753)[b] | | | 0.054 | >30 |
| **21** (L-158,809)[b] | | | 0.00054 | >10 |

[a] For racemic compounds. [b] Data from ref 9.

not only enhanced the binding affinity of the potent (phenylamino)phenylacetic acid **9c** ($AT_1$ $IC_{50}$ = 4 nM) by 4-fold to 0.9 nM at the $AT_1$ receptor but also effected a notable 4-fold increase in the binding affinity at the $AT_2$ receptor ($AT_2$ $IC_{50}$ = 0.2 $\mu$M). Similarly, replacement of the $CO_2H$ of **9e** by the bioisostere $CONHSO_2Ph$ resulted in **16c** with a remarkable 7-fold increase in its $AT_1$ binding ($AT_1$ $IC_{50}$ = 0.8 vs 5.3 nM) and a 1.3-fold increase in its $AT_2$ binding affinity ($AT_2$ $IC_{50}$ = 0.42 vs 0.56 $\mu$M). Replacement of $CO_2H$ of the N-allyl analog **9d** with $CONHSO_2Ph$ gave acyl sulfonamide **16b** ($AT_1$ $IC_{50}$ = 1 nM) with a 5-fold improved binding at the $AT_1$ receptor. Nearly a 6-fold loss was observed in the $AT_2$ binding of **16b**. Since carboxylic acid bioisostere tetrazole has been employed as an excellent $CO_2H$ replacement[8a] and generally results in improved binding affinity at the $AT_1$ receptor, we incorporated the tetrazole for $CO_2H$ in **9b** to produce **19**. The *in vitro* AII binding assay of **19** showed that although it is a potent $AT_1$ receptor antagonist, it is nearly 2-fold less potent than its carboxylic acid counterpart **9b** ($AT_1$ $IC_{50}$ = 15 vs 8.2 nM) and has no binding affinity for the $AT_2$ receptor at a concentration of 30 $\mu$M. A comparison of the acyl sulfonamides **16a–c** with **20** (DuP 753, Losartan; see ref 1 for structure) and **21** (L-158,809; see ref 1 for structure) shown in Table IV demonstrates that the AII antagonists **16a–c** are more potent than **20** and nearly equipotent to **21**.

The higher $AT_2$ potency attained by **16a** as a result of acyl sulfonamide (phenylsulfonyl carboxamide) replacement for the carboxyl of **9c** (Table IV) may in part be attributable to the favorable binding interactions of the $CONHSO_2Ph$ moiety with a hydrophobic region of the $AT_2$ receptor and the interaction of the acidic proton of $CONHSO_2Ph$ with the $AT_2$ receptor. This new finding offers considerable potential for further development of these compounds into a potent series of AII receptor antagonists with balanced $AT_1/AT_2$ activity.

The most potent PAPA **9c** and the acyl sulfonamides **16a**, **16b**, and **16c** were evaluated for their *in vivo* activity in conscious normotensive rats. The *in vivo* activity was determined by assessing the inhibition of the pressor response induced by 0.1 mg/kg iv infusion of AII in conscious normotensive rats.[11] All three acyl sulfonamides **16a** (N-Et), **16b** (N-allyl), and **16c** (N-Pr) showed excellent *in vivo* activity for >6-h duration of action in conscious rats after oral administration at a 3 mg/kg dose

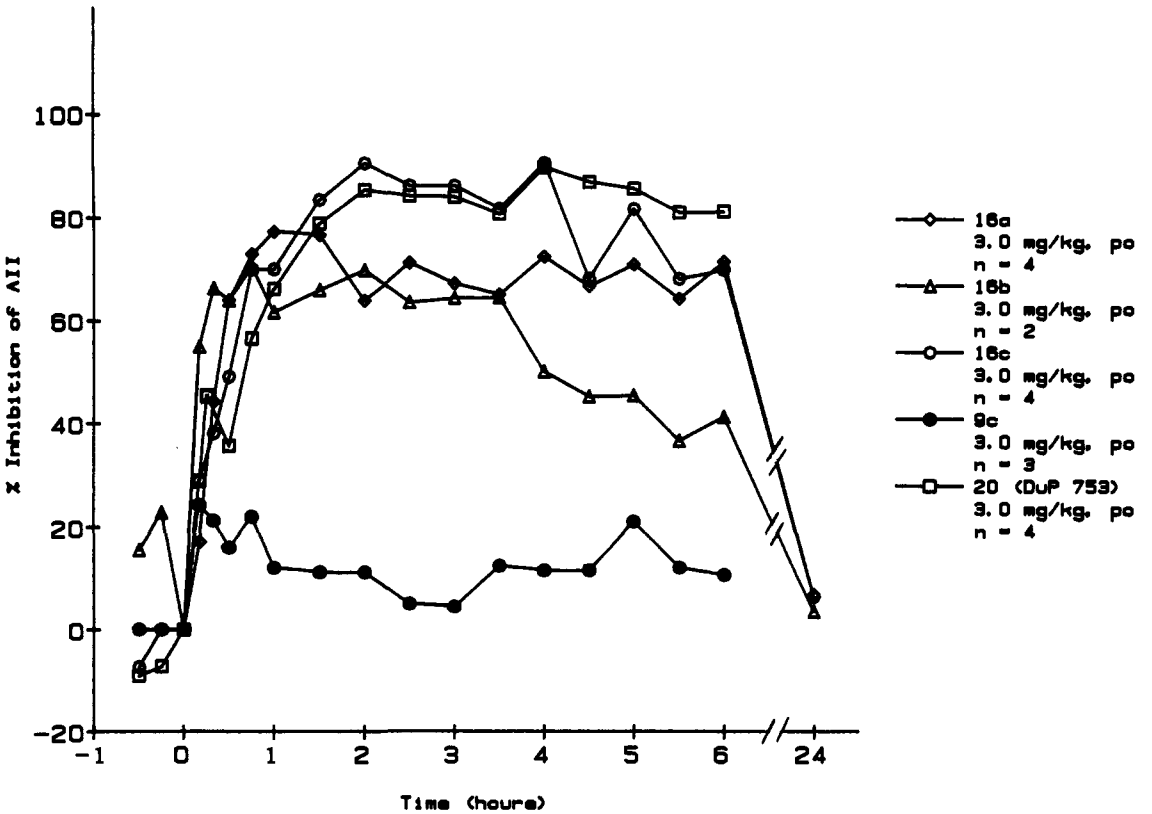



**Figure 2.** Inhibition of AII-induced (0.1 μg/kg) pressor response by **9c**, **16a–c**, and **20** after oral administration at 3.0 mg/kg in conscious normotensive rats. *n* is the number of animals tested.

(Figure 2). Superior *in vivo* potency of the acyl sulfonamides **16c** (N–Pr) and **16a** (N–Et) is evident from Figure 2 which shows a comparison of the inhibition of the AII-induced pressor response in conscious normotensive rats by PAPA **9c** and by acyl sulfonamides **16a**, **16b**, and **16c** at an oral dose of 3.0 mg/kg. The acyl sulfonamides **16a–c** exhibited higher *in vivo* activity than the indole-based AII antagonists (e.g., **24** in ref 1).[1] A comparison of the *in vivo* activity of **16a–c** and **9c** with **20** shows that the acyl sulfonamide **16c** has comparable *in vivo* activity to **20** (Figure 2).

## Conclusion

A new class of non-peptide AII receptor antagonists derived from the N-substituted (phenylamino)phenylacetic acids **9** and acyl sulfonamides **16** is described. These compounds are highly potent $AT_1$-selective antagonists ($AT_1$ $IC_{50} \leq 1$ nM). The size of the N-substitution is important for both the *in vitro* and *in vivo* potency of these compounds, N–Et and N–Pr being the most effective. Substitution of the central and bottom phenyl rings leads to a loss in $AT_1$ and $AT_2$ binding affinity. Bioisostere replacement of carboxyl ($CO_2H$) with acylsulfonamide ($CONHSO_2Ph$) in this series enhances both the *in vitro* and *in vivo* activity of these AII receptor antagonists.

In summary, it is demonstrated that the new structural design disclosed here, which incorporates a (phenylamino)-phenylacetic acid and an acyl sulfonamide as exemplified by **9c–e** and **16a–c**, respectively, is a highly efficient biphenyl tetrazole replacement for the exceptionally potent AII receptor antagonist **21**. This new class of AII antagonists, in particular the acyl sulfonamide **16a**, offers an appreciable opportunity to develop new series of AII antagonists with "balanced" $AT_1/AT_2$ activity.[12]

## Experimental Section

All air-sensitive reactions were conducted in flame- or oven-dried apparatus under a positive pressure of nitrogen. Analytical thin-layer chromatography (TLC) was performed using EM Reagents 0.25-mm silica gel 60-F plates. Flash column chromatography was performed with the use of silica gel 60 (230–400 mesh, EM Reagents). $^1H$ NMR spectra were recorded on Varian XL-300 and Varian XL-400 spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts for $^1H$ NMR signals are reported in ppm downfield from TMS (δ). Fast atom bombardment mass spectra (FABMS) were obtained using a MAT 731 spectrometer at 8 keV.

**Preparation of 3-Methyl-4-nitrobenzyl Bromide (3b). 3-Methyl-4-nitrobenzyl Alcohol** (11). To a solution of 3-methyl-4-nitrobenzoic acid (10.0 g, 55.2 mmol) in THF at 0 °C was added a borane–dimethyl sulfide complex (55.2 mL of 2.0 M in THF, 110.4 mmol, 2.0 equiv) in small portions over a period of 15 min. The mixture was stirred at 0 °C for 18 h. The reaction mixture was poured over 100 mL of ice in a 1-L Erlenmeyer flask. After 15 min, 200 mL of 1 N HCl was added and the mixture was extracted with ether (3 × 300 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated to yield 11 (9.10 g, 99%): $R_f$ = 0.42 (50% ethyl acetate/hexane); $^1H$ NMR ($CDCl_3$) δ 7.98 (d, 2H, *J* = 8.8 Hz), 7.34 (s, 1H), 7.28 (d, 2H, *J* = 7.8 Hz), 4.76 (d, 2H, *J* = 5.5 Hz), 2.61 (s, 3H), 1.95 (t, 1H, *J* = 5.8 Hz); FABMS *m/e* 168 (M + 1).

**3-Methyl-4-nitrobenzyl Bromide (3b).** To a solution of 11 (3.92 g, 23.46 mmol) in $CH_2Cl_2$ (30 mL) at 0 °C were added $Ph_3P$ (9.2 g, 35.2 mmol, 1.5 equiv) and $CBr_4$ (11.7 g, 35.2 mmol, 1.5 equiv). The resultant brown mixture was stirred for 18 h at 0 °C. The mixture was concentrated and purified by flash column chromatography with 30% EtOAc in hexane to give 5.01 g (93%): $R_f$ = 0.82 (25% ethyl acetate/hexane); $^1H$ NMR ($CDCl_3$) δ 7.96 (d, 1H, *J* = 8.9 Hz), 7.34–7.37 (m, 2H), 4.46 (s, 2H); 2.60 (s, 3H); FABMS *m/e* 230 (M + 1).

**5,7-Dimethyl-2-ethyl-3-[(4-nitrophenyl)methyl]-3*H*-imidazo[4,5-*b*]pyridine (4a) ($R_1$ = H).** To a solution of 5,7-dimethyl-2-ethylimidazo[4,5-*b*]pyridine (**2**)[5] (5.0 g, 28.6 mmol) in DMF (30 mL) was added NaH (1.37 g of a 60% dispersion in

mineral oil, 34.3 mmol). After the mixture was stirred for 5 min, 4-nitrobenzyl bromide (8.64 g, 40.0 mmol) was added and the resultant mixture was stirred for 2 h. The mixture was diluted with 1 L of $CH_2Cl_2$ and washed with 500 mL of $H_2O$ and 500 mL of a saturated aqueous solution of NaCl. The organic phase was dried over $MgSO_4$ and concentrated to a yellow oil. The oil was flash chromatographed with 1:1 ethyl acetate/hexane to give **4a** (6.81g, 77%): $R_f$ = 0.56 (100% ethyl acetate); $^1$H NMR ($CDCl_3$) $\delta$ 8.15 (d, 2H), 7.27 (d, 2H), 6.92 (s, 1H), 5.55 (s, 2H), 2.77 (q, 2H), 2.64 (s, 3H), 2.57 (s, 3H), 1.32 (t, 3H); FABMS *m/e* 325 (M + 1).

**5,7-Dimethyl-2-ethyl-3-[(3-methyl-4-nitrophenyl)methyl]-3*H*-imidazo[4,5-*b*]pyridine (4b) ($R_1$ = Me).** To a solution of **2** (3.82 g, 21.8 mmol) in DMF (30 mL) was added NaH (0.96 g of a 60% dispersion in mineral oil, 24.0 mmol) and the mixture stirred for 5 min. To this mixture was added **4b** (5.5 g, 24.0 mmol) and the resulting mixture stirred for 24 h. The reaction mixture was diluted with 500 mL of EtOAc and washed with $H_2O$ (200 mL) and brine (200 mL). The organic phase was dried over $Na_2SO_4$, filtered, and concentrated. The resultant brown oil was flash chromatographed with 2:1 EtOAc/hexane to yield **4b** (7.0 g, 99%): $R_f$ = 0.52 (100% ethyl acetate); $^1$H NMR ($CDCl_3$) $\delta$ 8.05 (d, 1H), 7.41 (s, 1H), 7.21 (s, 1H), 7.07 (s, 1H), 5.65 (s, 2H), 2.96 (q, 2H), 2.84 (s, 3H), 2.78 (s, 3H), 2.74 (s, 3H), 1.54 (t, 3H); FABMS *m/e* 325 (M + 1).

**5,7-Dimethyl-2-ethyl-3-[(4-aminophenyl)methyl]-3*H*-imidazo[4,5-*b*]pyridine (5a) ($R_1$ = H).** To a high-pressure reaction vessel charged with a solution of **4a** (6.81 g, 21.0 mmol) in MeOH (175 mL) was added 5% Pd on carbon (0.3 g). The resulting suspension was shaken under a 40 psi atmospheric pressure of $H_2$ for 2 h. The solution was filtered through Celite, and the crude material was flash chromatographed with 1:1 ethyl acetate/hexane and then 3% MeOH in EtOAc to yield **5a** (5.0 g, 85%): $R_f$ = 0.54 (100% ethyl acetate); $^1$H NMR ($CD_3OD$) $\delta$ 6.85 (s, 1H), 6.80 (d, 2H), 6.52 (d, 2H), 5.26 (s, 2H), 2.72 (q, 2H), 2.49 (s, 3H), 2.49 (s, 6H), 1.12 (t, 3H); FABMS *m/e* 281 (M + 1).

**5,7-Dimethyl-2-ethyl-3-[(3-methyl-4-aminophenyl)methyl]-3*H*-imidazo[4,5-*b*]pyridine (5b) ($R_1$ = Me).** To a solution of **4b** (7.0 g, 21.0 mmol) in MeOH (100 mL) in a high pressure reaction vessel was added 5% Pd on carbon (0.3 g). The resulting suspension was pressurized to 40 psi with $H_2$ and shaken for 24 h. The mixture was filtered through Celite, and then, the crude material was flash chromatographed with 1:1 EtOAc/hexane to afford **5b** (4.7 g, 74%): $R_f$ = 0.50 (100% ethyl acetate); $^1$H NMR ($CDCl_3$) $\delta$ 6.85 (s, 1H), 6.76–6.85 (m, 3H), 6.54 (d, 1H, $J$ = 7.9 Hz), 5.30 (s, 2H), 3.54 (br s, 2H) 2.76 (q, 2H, $J$ = 7.6 Hz), 2.60 (s, 3H), 2.57 (s, 3H), 2.06 (s, 3H), 1.27 (t, 3H, $J$ = 7.6 Hz); FABMS *m/e* 295 (M + 1).

**General Procedures for the Preparation of $\alpha$-Bromo Esters 6. Method A: From Phenylacetic Acids. Ethyl $\alpha$-Bromo-2,5-difluorophenylacetate (6) ($R_2$ = 2,5-di-F).** A solution of 2,5-difluorophenylacetic acid (12) (5.0 g, 29 mmol) was refluxed in EtOH (100 mL) with concentrated $H_2SO_4$ (5 mL) overnight. The ethanol was removed *in vacuo*, and the resulting residue was diluted with EtOAc and washed successively with water, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to give ethyl 2,5-difluorophenylacetate (5.6 g, 96%) as a white solid: $R_f$ = 0.74 (15% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.08–6.9 (m, 3H), 4.24–4.07 (q, 2H), 3.636 (s, 2H), 1.259 (t, 3H).

To a warm solution of ethyl 2,5-difluorophenylacetate (5.95 g, 29.75 mmol) in $CCl_4$ (30 mL) were added *N*-bromosuccinimide (NBS) (6.35 g, 35.7 mmol) and azobisisobutyronitrile (AIBN) (25 mg, 0.15 mmol), and the resulting mixture was refluxed for 4 h. The mixture was diluted with $CH_2Cl_2$ (600 mL), washed successively with water and brine, dried over $MgSO_4$, filtered, and concentrated to an oil. Flash column chromatography of the oil with 20% EtOAc in hexane gave the title compound **6** (4.84 g, 59%): $R_f$ = 0.81 (15% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.46 (m, 1H), 7.03 (dt, 2H, $J$ = 6.3, 1.7 Hz), 5.64 (s, 1H), 4.27 (q, 2H), 1.30 (t, 3H, $J$ = 7.3 Hz); FABMS *m/e* 279 (M + 1).

**Methyl $\alpha$-Bromo-3,5-bis(trifluoromethyl)phenylacetate (6) ($R_2$ = 3,5-bis-$CF_3$).** The title compound was obtained from 3,5-difluorophenylacetic acid by method A as described above: $R_f$ = 0.47 (15% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 8.03 (s, 2H), 7.87 (s, 1H), 5.42 (s, 1H), 3.84 (s, 3H); FABMS *m/e* 365 (M + 1) $^{79}$Br, 367 (M + 1) $^{81}$Br.

**Ethyl $\alpha$-Bromo-2-chlorophenylacetate (6) ($R_2$ = 2-Cl).** The title compound was prepared from 2-chlorophenylacetic acid by method A: $R_f$ = 0.46 (15% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.77 (dd, 1H, $J$ = 2.0, 7.6 Hz), 7.39 (dd, 1H, $J$ = 2.1, 7.3 Hz), 7.34–7.27 (m, 2H), 5.89 (s, 1H), 4.31–4.23 (m, 2H), 1.29 (t, 3H, $J$ = 7.1 Hz); FABMS *m/e* 277 (M + 1) $^{79}$Br, 279 (M + 1) $^{81}$Br.

**Method B: From Aldehydes. $\alpha$-[(Trimethylsilyl)oxy]-3-methylphenylacetonitrile (14) ($R_2$ = 3-Me).** A solution of *m*-tolualdehyde (1.22g, 10.15 mmol) in $CH_2Cl_2$ was treated with trimethylsilyl cyanide (1.354 mL, 1 equiv) for 16 h in the presence of trace amounts of KCN and 18-crown-6. The mixture was concentrated to an oil which after flash chromatography with 10% EtOAc in hexane gave 14 (2.0 g, 90%): $R_f$ = 0.38 (10% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.35–7.15 (m, 4H), 5.457 (s, 1H), 2.389 (s, 3H), 0.236 (s, 9H); FABMS *m/e* 219 ($M^+$), 204 (M – $CH_3$).

**Ethyl $\alpha$-Hydroxy-3-methylphenylacetate (15) ($R_2$ = 3-Me).** Anhydrous HCl gas was bubbled through a solution of 14 (2.0 g, 9.13 mmol) in EtOH (50 mL) at 0 °C for 0.5 h. The resulting mixture was allowed to warm to room temperature with stirring for 48 h in a well stoppered flask. The mixture was concentrated and dissolved in a mixture of EtOAc and $Et_2O$. The organic phase was washed with saturated aqueous NaHCO3, dried over MgSO4, filtered, and concentrated to an oil which after flash chromatography with 10% EtOAc in hexane gave 15 (1.663 g, 94%): $R_f$ = 0.25 (10% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.25∠7.15 (m, 3H), 7.114 (d, 1H, $J$ = 7.16 Hz), 5.097 (s, 1H), 4.3–4.2 (m, 1H), 4.2–4.1 (m, 1H), 3.42 (br s, 1H), 2.337 (s, 3H), 1.21 (t, 3H); FABMS *m/e* 194 ($M^+$).

**Ethyl $\alpha$-Bromo-3-methylphenylacetate (6) ($R_2$ = 3-Me).** To a solution of 15 (1.663 g, 8.57 mmol) in $CH_2Cl_2$ at 0 °C were added successively $CBr_4$ (4.3 g, 13 mmol) and $Ph_3P$ (3.4 g, 13 mmol). The resulting mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature and stirred overnight. The mixture was concentrated, and the residue was chromatographed with 5% EtOAc in hexane to yield **6t** (2.08 g, 95%): $R_f$ = 0.35 (5% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.4-7.33 (m, 2H), 7.258 (dd, 1H, $J$ = 7.6 Hz), 7.16 (d, 1H, $J$ = 7.32 Hz), 5.328 (s, 1H), 2.369 (s, 3H), 1.291 (t, 3H); FABMS *m/e* 257 (M + 1) $^{79}$Br, 259 (M + 1) $^{81}$Br.

**Ethyl $\alpha$-Bromo-2-methylphenylacetate (6) ($R_2$ = 2-Me).** The title compound was prepared from *o*-tolualdehyde using method B: $R_f$ = 0.38 (5% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.61 (m, 1H), 7.24 (m, 2H) 7.18 (m, 1H), 5.63 (s, 1H), 4.25 (m, 2H), 2.42 (s, 3H), 1.28 (t, 3H, $J$ = 7.1 Hz); FABMS *m/e* 257 (M + 1) $^{79}$Br, 259 (M + 1) $^{81}$Br.

**General Procedures for Alkylation of 5 with 6. Preparation of 3-[[4-[*N*-(Carbomethoxyphenylmethyl)amino]-phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (7a) ($R_1$ = H, $R_2$ =H, R = Me). Method A: Using NaH/DMF.** To a stirred solution of **5a** (0.50 g, 1.79 mmol) in 4.0 mL of DMF was added a 60% dispersion of NaH (86 mg, 2.15 mmol) in mineral oil. After 5 min, methyl $\alpha$-bromophenylacetate (0.52 mL, 2.685 mmol) was added. The mixture was stirred for 18 h. The DMF was removed *in vacuo*, and the resultant brown oil was flash chromatographed with 2:1 EtOAc/ hexane to yield **7a** (0.69 g, 90%): $R_f$ = 0.78 (100% ethyl acetate); $^1$H NMR ($CDCl_3$) $\delta$ 7.42 (d, 2H), 7.23–7.35 (m, 3H), 6.89 (d, 2H), 6.85 (s, 1H), 6.43 (d, 2H), 5.28 (s, 2H), 4.97–5.01 (m, 1H), 3.69 (s, 3H), 2.77 (q, 2H), 2.60 (s, 3H), 2.56 (s, 3H), 1.25 (t, 3H); FABMS *m/e* 429 (M + 1).

**Method B: Using $K_2CO_3$/Acetone.** A mixture of **5a** (0.50 g, 1.79 mmol), $K_2CO_3$ (0.495 g, 3.58 mmol), and methyl $\alpha$-bromophenylacetate (0.52 mL, 2.685 mmol) was refluxed in acetone (or MEK, methyl ethyl ketone) overnight. The mixture was filtered through Celite, and the filter cake was washed with acetone. The combined filtrate was concentrated to an oil which after flash chromatography with 2:1 EtOAc/hexane gave **7a** (0.65 g, 85%).

**3-[[4-[*N*-(Carbomethoxyphenylmethyl)amino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]-pyridine (7j) ($R_1$ = Me, $R_2$ = H, R = Me).** The title compound **7j** was prepared from **5b** by method A in 78% yield: $R_f$ = 0.77 (100% ethyl acetate); $^1$H NMR ($CDCl_3$) $\delta$ 7.45 (m, 2H), 7.36–7.29 (m, 3H), 6.87 (d, 2H, $J$ = 6.7 Hz), 6.72 (dd, 1H, $J$ = 1.5, 8.3 Hz), 6.20 (d, 2H, $J$ = 8.1 Hz), 5.28 (s, 2H), 5.05 (d, 1H, $J$ = 5.7 Hz),

4.86 (d, 1H, $J$ = 5.5 Hz), 3.72 (s, 3H), 2.76 (q, 2H, $J$ = 7.5 Hz), 2.61 (s, 3H), 2.58 (s, 3H), 2.20 (s, 3H), 1.27 (t, 3H, $J$ = 7.5 Hz); FABMS $m/e$ 443 (M + 1).

**3-[[4-[*N*-(Carbethoxy(2-methylphenyl)methyl)amino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (7o) ($R_1$ = Me, $R_2$ = 2-Me, R = Et).** The title compound **7o** was obtained from **5b** using method A in 60% yield: $R_f$ = 0.74 (100% ethyl acetate); $^1$H NMR ($CDCl_3$) $\delta$ 7.35 (d, 1H, $J$ = 7.2 Hz), 7.16 (m, 3H), 6.87 (s, 2H), 6.71 (d, 1H, $J$ = 7.0 Hz), 6.14 (d, 1H, $J$ = 8.3 Hz), 5.29 (s, 2H), 5.23 (d, 1H, $J$ = 5.7 Hz), 4.78 (d, 1H, $J$ = 5.7 Hz), 4.24–4.08 (m, 2H), 2.77 (q, 2H, $J$ = 7.4 Hz), 2.61 (s, 3H), 2.58 (s, 3H), 2.52 (s, 3H), 2.18 (s, 3H), 1.27 (t, 3H, $J$ = 7.5 Hz), 1.19 (t, 3H, $J$ = 7.1 Hz); FABMS $m/e$ 471 (M + 1).

**3-[[4-[*N*-[Carbomethoxy[3,5-bis(trifluoromethyl)phenyl]-methyl]amino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (7q) ($R_1$ = H, $R_2$ = 3,5-bis-$CF_3$, R = Me).** The compound **7q** was prepared from **5a** by method B in 52% yield: $R_f$ = 0.64 (100% ethyl acetate); $^1$H NMR ($CDCl_3$) $\delta$ 7.91 (s, 2H), 7.80 (s, 1H), 6.91 (d, 2H, $J$ = 8.6 Hz), 6.84 (s, 1H), 6.38 (d, 2H, $J$ = 8.4 Hz), 5.28 (s, 2H), 5.09 (m, 2H), 3.74 (s, 3H), 2.73 (q, 2H, $J$ = 7.6 Hz), 2.58 (s, 3H), 2.55 (s, 3H), 1.22 (t, 3H, $J$ = 7.5 Hz); FABMS $m/e$ 565 (M + 1).

**3-[[4-[*N*-(Carbethoxy(2,5-difluorophenyl)methyl)amino]-phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (7r) ($R_1$ = H, $R_2$ = 2,5-di-F, R = Et).** The compound **7r** was prepared by method A in 36% yield: $R_f$ = 0.62 (100% ethyl acetate); $^1$H NMR ($CDCl_3$) $\delta$ 7.09–7.01 (m, 2H), 6.95 (m, 1H), 6.90 (d, 2H, $J$ = 8.6 Hz), 6.85 (s, 1H), 6.44 (d, 2H, $J$ = 8.5 Hz), 5.29 (d, 1H, $J$ = 5.6 Hz), 5.28 (s, 2H), 4.98 (d, 1H, $J$ = 5.5 Hz), 4.25–4.07 (m, 2H) 2.74 (q, 2H, $J$ = 7.7 Hz), 2.59 (s, 3H), 2.56 (s, 3H), 1.24 (t, 3H, $J$ = 7.2 Hz), 1.17 (t, 3H, $J$ = 7.1 Hz); FABMS $m/e$ 479 (M + 1).

**3-[[4-[*N*-(Carbethoxy(2-chlorophenyl)methyl)amino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (7s) ($R_1$ = H, $R_2$ = 2-Cl, R = Et).** The compound **7s** was synthesized from **5a** by method B in 53% yield: $R_f$ = 0.73 (100% ethyl acetate); $^1$H NMR ($CDCl_3$) $\delta$ 7.38 (m, 2H), 7.19 (m, 2H), 6.91 (s, 1H), 6.89 (s, 2H), 6.43 (d, 2H, $J$ = 8.6 Hz), 5.51 (d, 1H, $J$ = 5.6 Hz), 5.28 (s, 2H), 5.06 (d, 1H, $J$ = 5.6 Hz), 4.15 (m, 2H), 2.80 (q, 2H, $J$ = 7.7 Hz), 2.62 (s, 3H), 2.57 (s, 3H), 1.25 (t, 3H, $J$ = 7.5 Hz), 1.16 (t, 3H, $J$ = 7.1 Hz); FABMS $m/e$ 477 (M + 1).

**3-[[4-[*N*-(Carbethoxy(3-methylphenyl)methyl)amino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (7t) ($R_1$ = H, $R_2$ = 3-Me, R = Et).** The title compound **7t** was prepared from **5a** by method B in 20% yield: $R_f$ = 0.78 (100% ethyl acetate); $^1$H NMR ($CDCl_3$) $\delta$ 7.21 (t, 3H, $J$ = 6.4 Hz), 7.07 (d, 1H, $J$ = 6.6 Hz), 6.89 (d, 2H, $J$ = 8.4 Hz), 6.84 (s, 1H), 6.43 (d, 2H, $J$ = 8.6 Hz), 5.27 (s, 2H), 4.93 (d, 1H, $J$ = 6.1 Hz), 4.89 (d, 1H, $J$ = 6.2 Hz), 4.14 (m, 2H), 2.74 (q, 2H, $J$ = 7.6 Hz), 2.59 (s, 3H), 2.57 (s, 3H), 2.30 (s, 3H), 1.24 (t, 3H, $J$ = 7.6 Hz), 1.17 (t, 3H, $J$ = 7.1 Hz); FABMS $m/e$ 456 (M + 1).

**General Procedures for Alkylation of 7 with Alkyl Iodides ($R_3$I). Preparation of 3-[[4-[*N*-Allyl-*N*-(carbomethoxyphenylmethyl)amino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8d) ($R_1$ = H, $R_2$ = H, $R_3$ = allyl, R = Me). Method A: Using NaH/DMF.** To a solution of **7a** (0.5 g, 1.17 mmol) in DMF (2 mL) was added a 60% dispersion of NaH (70 mg, 1.75 mmol) in mineral oil and the mixture stirred for 5 min. Allyl iodide (214 mL, 2.34 mmol) was added to the reaction mixture, and it was stirred overnight. EtOAc was added to the mixture, and the resulting solution was washed successively with water and brine. The organic phase was dried over $Na_2SO_4$, filtered, and concentrated to an oil which after flash chromatography with 2:1 hexane/EtOAc yielded **8d** (0.488 g, 89%): $R_f$ = 0.47 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.52 (d, 2H), 7.22–7.33 (m, 3H), 6.98 (s, 1H), 6.78 (d, 2H), 6.23 (d, 2H), 5.52–5.65 (ddd, 1H), 5.26 (s, 1H), 5.23 (s, 2H), 5.03 (dd, 1H), 4.96 (dd, 1H), 3.62 (s, 3H), 3.18 (d, 2H), 2.71 (q, 2H), 2.57 (s, 3H), 2.54 (s, 3H), 1.21 (t, 3H); FABMS $m/e$ 469 (M + 1).

**Method B: Using Lithium Hexamethyldisilyl Azide (LiN-($SiMe_3$)$_2$, LiHMDS).** To a solution of **7a** (0.30 g, 0.70 mmol) in 1.5 mL of THF was added LiHMDS (0.84 mL of 1 M in THF) and the resulting mixture stirred for 5 min. Allyl iodide (0.1 mL, 1.1 mmol) was added to the reaction mixture, and the yellow solution was stirred for 18 h. The solution was concentrated to a yellow oil which was flash chromatographed with 2:1 hexane/EtOAc to give the compound **8d** (0.173 g, 53%).

**3-[[4-[*N*-(Carbomethoxyphenylmethyl)-*N*-methylamino]-phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8b) ($R_1$ = H, $R_2$ = H, $R_3$ = Me, R = Me).** The compound **8b** was prepared from **7a** by method A in 73% yield: $R_f$ = 0.40 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.29–7.38 (m, 3H), 7.22 (d, 2H), 7.05 (d, 2H), 6.87 (s, 1H), 6.74 (d, 2H), 5.69 (s, 1H), 5.36 (s, 2H), 3.74 (s, 3H), 2.82 (q, 2H), 2.73 (s, 3H), 2.61 (s, 3H), 2.59 (s, 3H), 1.51 (t, 3H); FABMS $m/e$ 443 (M + 1).

**3-[[4-[*N*-(Carbomethoxyphenylmethyl)-*N*-ethylamino]-phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8c) ($R_1$ = H, $R_2$ = H, $R_3$ = Et, R = Me).** The title compound **8c** was prepared from **7a** by method A in 77% yield: $R_f$ = 0.41 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.24–7.40 (m 5H), 7.05 (d, 2H), 6.88 (s, 1H), 6.72 (d, 2H), 5.49 (s, 1H), 5.37 (s, 2H), 4.73 (s, 3H), 3.28 (q, 2H), 2.83 (q, 2H), 2.62 (s, 3H), 2.60 (s, 3H), 1.31 (t, 3H), 0.86 (t, 3H); FABMS $m/e$ 457 (M + 1).

**3-[[4-[*N*-(Carbomethoxyphenylmethyl)-*N*-propylamino]-phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8e) ($R_1$ = H, $R_2$ = H, $R_3$ = *n*-Pr, R = Me).** The title compound **8e** was prepared from **7a** by method A in 78% yield: $R_f$ = 0.46 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.22–7.38 (m, 5H), 7.04 (d, 2H), 6.88 (s, 1H), 6.70 (d, 2H), 5.49 (s, 1H), 5.37 (s, 2H), 3.72 (t, 2H), 2.83 (q, 2H), 2.62 (s, 3H), 2.60 (s, 3H), 1.44 (m, 2H), 1.33 (t, 3H), 0.89 (t, 3H); FABMS $m/e$ 471 (M + 1).

**3-[[4-[*N*-(Carbomethoxyphenylmethyl)-*N*-butylamino]-phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8f) ($R_1$ = H, $R_2$ = H, $R_3$ = *n*-Bu, R = Me).** The title compound **8e** was prepared from **7a** by method A in 56% yield: $R_f$ = 0.52 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.86 (d, 2H, $J$ = 7.4 Hz), 7.54–7.46 (m, 3H), 7.12 (d, 2H, $J$ = 8.2 Hz), 6.91 (s, 1H), 6.85 (d, 2H, $J$ = 8.2 Hz), 5.42 (s, 2H), 5.23 (s, 1H), 3.35 (s, 3H), 2.79 (q, 2H, $J$ = 7.2 Hz), 2.64 (s, 3H), 2.58 (s, 3H), 2.47 (m, 2H), 1.37 (qn, 2H, $J$ = 7.4 Hz), 1.32 (t, 3H, $J$ = 7.5 Hz), 1.11 (sx, 2H, $J$ = 7.4 Hz), 0.82 (t, 3H, $J$ = 7.3 Hz); FABMS $m/e$ 486 (M + 1).

**3-[[4-[*N*-(Carbomethoxyphenyimethyl)-*N*-isobutylamino]-phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8g) ($R_1$ = H, $R_2$ = H, $R_3$ = *i*-Bu, R = Me).** The title compound **8g** was prepared from **7a** by method B in 49% yield: $R_f$ = 0.54 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.49 (d, 2H), 7.18–7.30 (m, 3H), 6.83 (s, 1H), 6.77 (d, 2H), 6.20 (d, 2H), 5.49 (s, 1H), 5.22 (s, 2H), 3.61 (s, 3H), 2.70 (q, 2H), 2.57 (s, 3H), 2.54 (s, 3H), 2.45 (d, 2H), 1.63 (m(7), 1H), 1.18 (t, 3H), 0.81 (d, 3H), 0.75 (d, 3H); FABMS $m/e$ 485 (M + 1).

**3-[[4-[*N*-(Carbomethoxyphenylmethyl)-*N*-*sec*-butylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8h) ($R_1$ = H, $R_2$ = H, $R_3$ = *sec*-Bu, R = Me).** The title compound **8h** was prepared from **7a** by method B in 38% yield: $R_f$ = 0.54 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.53–7.59 (m, 3H), 7.20–7.30 (m, 2H), 6.82 (s, 1H), 6.79 (d, 2H), 6.24 (d, 2H), 5.23 (s, 2H), 4.36 (s, 1H), 3.55 (s, 3H), 2.72 (q, 2H), 2.58 (s, 3H), 2.55 (s, 3H), 2.10 (m, 1H), 1.20 (t, 3H), 0.82–0.90 (m, 5H), 0.80 (d, 3H); FABMS $m/e$ 485 (M + 1).

**3-[[4-[*N*-(Carbomethoxyphenylmethyl)-*N*-(cyclopropylmethyl)amino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8i) ($R_1$ = H, $R_2$ = H, $R_3$ = cyclopropyl-$CH_2$, R = Me).** The title compound **8i** was prepared from **7a** and cyclopropylmethyl bromide by method B in 38% yield: $R_f$ = 0.56 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.49 (d, 2H), 7.29 (t, 2H), 7.24 (d, 1H), 6.83 (s, 1H), 6.78 (d, 2H), 6.22 (d, 2H), 5.52 (s, 1H), 5.23 (s, 2H), 3.63 (s, 3H), 2.73 (q, 2H), 2.67 (dd, 1H), 2.57 (s, 3H), 2.55 (s, 3H), 2.09 (dd, 1H), 1.22 (t, 3H), 0.55–0.65 (m), 1H), 0.36 (dt, 2H), –0.06 (m, 2H); FABMS $m/e$ 483 (M + 1).

**3-[[4-[*N*-(Carbomethoxyphenylmethyl)-*N*-methylamino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8k) ($R_1$ = Me, $R_2$ = H, $R_3$ = Me, R = Me).** The title compound **8k** was prepared from **7j** by method A in 33% yield: $R_f$ = 0.46 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.50 (m, 2H), 7.32 (t, 2H, $J$ = 7.0 Hz), 7.26 (t, 1H, $J$

= 7.1 Hz), 6.89 (d, 1H, $J$ = 1.8 Hz), 6.85 (s, 1H), 6.56 (dd, 1H, $J$ = 2.0, 8.3 Hz), 5.91 (d, 1H, $J$ = 8.3 Hz), 5.25 (s, 2H), 5.24 (s, 1H), 3.67 (s, 3H), 2.75 (q, 2H, $J$ = 7.6 Hz), 2.60 (s, 3H), 2.57 (s, 3H), 2.21 (s, 3H), 1.95 (s, 3H), 1.26 (t, 3H, $J$ = 7.6 Hz); FABMS $m/e$ 457 (M + 1).

**3-[[4-[*N*-(Carbomethoxyphenylmethyl)-*N*-ethylamino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8l) ($R_1$ = Me, $R_2$ = H, $R_3$ = Et, R = Me).** The title compound **8l** was prepared from **7j** by method A in 97% yield: $R_f$ = 0.46 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.54 (s, 2H, $J$ = 7.3 Hz), 7.33–7.25 (m, 3H), 6.89 (d, 1H, $J$ = 1.5 Hz), 6.85 (s, 1H), 6.52 (dd, 1H, $J$ = 1.8, 8.4 Hz), 5.85 (d, 1H, $J$ = 8.3 Hz), 5.32 (s, 1H), 5.24 (s, 2H), 3.67 (s, 3H), 2.75 (q, 2H, $J$ = 7.5 Hz), 2.60 (s, 3H), 2.57 (s, 3H), 2.56 (m, 1H), 2.48 (m, 1H), 2.24 (s, 3H), 1.24 (t, 3H, $J$ = 7.5 Hz), 0.72 (t, 3H, $J$ = 7.2 Hz); FABMS $m/e$ 471 (M + 1).

**3-[[4-[*N*-Allyl-*N*-(carbomethoxyphenylmethyl)amino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8m) ($R_1$ = Me, $R_2$ = H, $R_3$ = allyl, R = Me).** The title compound **8m** was prepared from **7j** by method A in 53% yield: $R_f$ = 0.48 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.54 (d, 2H, $J$ = 7.7 Hz), 7.33 (t, 2H, $J$ = 7.6 Hz), 7.28 (m, 1H), 6.87 (s, 1H), 6.85 (s, 1H), 6.53 (d, 1H, $J$ = 8.1 Hz), 5.88 (d, 1H, $J$ = 8.4 Hz), 5.53 (m, 1H), 5.24 (s, 2H), 5.23 (s, 1H), 5.03 (d, 1H, $J$ = 9.9 Hz), 4.92 (d, 1H, $J$ = 17.2 Hz), 3.66 (s, 3H), 3.23 (m, 2H), 2.74 (q, 2H, $J$ = 7.5 Hz), 2.60 (s, 3H), 2.57 (s, 3H), 2.20 (s, 3H), 1.24 (t, 3H, $J$ = 7.7 Hz); FABMS $m/e$ 483 (M + 1).

**3-[[4-[*N*-(Carbomethoxyphenylmethyl)-*N*-propylamino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8n) ($R_1$ = Me, $R_2$ = H, $R_3$ = *n*-Pr, R = Me).** The title compound **8n** was prepared from **7j** by method A in 30% yield: $R_f$ = 0.49 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.53 (d, 2H, $J$ = 7.8 Hz), 7.30 (t, 2H, $J$ = 7.5 Hz), 7.24 (t, 1H, $J$ = 7.3 Hz), 6.88 (s, 1H), 6.85 (s, 1H), 6.51 (dd, 1H, $J$ = 8.5, 1.4 Hz), 5.86 (d, 1H, $J$ = 8.4 Hz), 5.33 (s, 1H), 5.24 (s, 2H), 4.01 (m, 2H), 2.74 (q, 2H, $J$ = 7.6 Hz), 2.60 (s, 3H), 2.58 (s, 3H), 2.46 (m, 2H), 2.23 (s, 3H), 1.52 (sx, 2H, $J$ = 7.1 Hz), 1.22 (t, 3H, $J$ = 7.6 Hz), 0.84 (t, 3H, $J$ = 7.3 Hz), 0.74 (t, 3H, $J$ = 7.4 Hz); FABMS $m/e$ 485 (M + 1).

**3-[[4-[*N*-Allyl-*N*-(carbomethoxy(2-methylphenyl)methyl)amino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8p) ($R_1$ = Me, $R_2$ = 2-Me, $R_3$ = allyl, R = Et).** The title compound **8p** was prepared from **7j** by method A in 72% yield: $R_f$ = 0.41 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.58 (d, 1H, $J$ = 7.7 Hz), 7.26 (m, 1H), 7.19 (dt, 1H, $J$ = 1.1, 7.4 Hz), 7.04 (d, 1H, $J$ = 6.6 Hz), 6.85 (s, 1H), 6.83 (s, 1H), 6.47 (dd, 1H, $J$ = 1.7, 8.4 Hz), 5.98 (d, 1H, $J$ = 8.4 Hz), 5.57 (m, 1H), 5.22 (s, 3H), 5.05 (d, 1H, $J$ = 10.1), 4.91 (d, 1H, $J$ = 16.8 Hz), 4.23 (m, 1H), 4.09 (m, 1H), 3.47 (m, 1H), 3.07 (m, 1H), 2.72 (q, 2H, $J$ = 7.6 Hz), 2.60 (s, 3H), 2.57 (s, 3H), 2.22 (s, 3H), 2.16 (s, 3H), 1.22 (t, 3H, $J$ = 7.5 Hz), 1.16 (t, 3H, $J$ = 7.1 Hz); FABMS $m/e$ 511 (M + 1).

**3-[[4-[*N*-(Carbethoxy(2,5-difluorophenyl)methyl)-*N*-methylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8r) ($R_1$ = H, $R_2$ = 2,5-di-F, $R_3$ = Me, R = Et).** The title compound **8r** was prepared from **7r** by method A in 53% yield: $R_f$ = 0.42 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.19 (dt, 1H, $J$ = 1.7, 7.8 Hz), 6.93 (t, 2H, $J$ = 6.4 Hz), 6.86 (s, 1H), 6.83 (d, 2H, $J$ = 7.0 Hz), 6.41 (d, 2H, $J$ = 7.8 Hz), 5.27 (s, 2H), 4.89 (d, 1H, $J$ = 4.8 Hz), 4.12 (m, 2H), 2.75 (q, 2H, $J$ = 7.5 Hz), 2.60 (s, 3H), 2.56 (s, 3H), 1.86 (s, 3H), 1.26 (t, 3H, $J$ = 7.6 Hz), 1.09 (t, 3H, $J$ = 7.1 Hz); FABMS $m/e$ 494 (M + 1).

**3-[[4-[*N*-(Carbethoxy(2-chlorophenyl)methyl)-*N*-ethylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8s) ($R_1$ = H, $R_2$ = 2-Cl, $R_3$ = Et, R = Et).** The title compound **8s** was prepared from **7s** by method A in 65% yield: $R_f$ = 0.38 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.65 (dd, 1H, $J$ = 1.2, 7.9 Hz), 7.27 (m, 2H), 7.19 (m, 1H), 6.83 (s, 1H), 6.73 (d, 2H, $J$ = 8.6 Hz), 6.30 (d, 2H, $J$ = 8.6 Hz), 5.26 (d, 1H, $J$ = 5.8 Hz), 5.21 (s, 2H), 4.16 (m, 2H), 2.70 (q, 2H, $J$ = 7.6 Hz), 2.66 (m, 1H), 2.58 (s, 3H), 2.55 (s, 3H), 2.22 (sx, 1H, $J$ = 6.8 Hz), 1.19 (t, 3H, $J$ = 7.6 Hz), 1.13 (t, 3H, $J$ = 7.1 Hz), 0.82 (t, 3H, $J$ = 7.3 Hz); FABMS $m/e$ 504 (M + 1).

**3-[[4-[*N*-(Carbethoxy(3-methylphenyl)methyl)-*N*-ethylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8t) ($R_1$ = H, $R_2$ = 3-Me, $R_3$ = Et, R = Et).** The title compound **8t** was prepared from **7t** by method A in 77% yield: $R_f$ = 0.44 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.32 (s, 1H), 7.31 (d, 1H, $J$ = 7.0 Hz), 7.17 (t, 1H, $J$ = 8.0 Hz), 7.03 (d, 1H, $J$ = 7.0 Hz), 6.83 (s, 1H), 6.78 (d, 2H, $J$ = 8.4 Hz), 6.24 (d, 2H, $J$ = 8.4 Hz), 5.33 (s, 1H), 5.23 (s, 2H), 4.08 (m, 2H), 2.74 (q, 2H, $J$ = 7.6 Hz), 2.58 (s, 3H), 2.55 (s, 3H), 2.52 (sx, 1H, $J$ = 7.0 Hz), 2.40 (sx, 1H, $J$ = 7.1 Hz), 2.28 (s, 3H), 1.22 (t, 3H, $J$ = 7.6 Hz), 1.10 (t, 3H, $J$ = 7.1 Hz), 0.75 (t, 3H, $J$ = 7.2 Hz); FABMS $m/e$ 485 (M + 1).

**3-[[4-[*N*-(Carboethoxy(2,5-difluorophenyl)methyl)-*N*-ethylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8u) ($R_1$ = H, $R_2$ = 2,5-di-F, $R_3$ = Et, R = Et).** The title compound **8u** was prepared from **7t** by method A in 48% yield: $R_f$ = 0.41 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.22 (m, 1H), 6.91 (m, 2H), 6.84 (s, 1H), 6.81 (d, 2H, $J$ = 8.4 Hz), 6.36 (d, 2H, $J$ = 8.7 Hz), 5.24 (s, 2H), 5.07 (s, 1H), 4.10 (q, 2H, $J$ = 7.1 Hz), 2.72 (q, 2H, $J$ = 7.6 Hz), 2.58 (s, 3H), 2.56 (s, 3H), 2.52 (sx, 1H, $J$ = 7.0 Hz), 2.27 (sx, 1H, $J$ = 7.0 Hz), 1.23 (t, 3H, $J$ = 7.1 Hz), 1.21 (t, 3H, $J$ = 7.5 Hz), 0.78 (t, 3H, $J$ = 7.3 Hz); FABMS $m/e$ 508 (M + 1).

**3-[[4-[*N*-[Carbethoxy[3,5-bis(trifluoromethyl)phenyl]methyl]-*N*-ethylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8v) ($R_1$ = H, $R_2$ = 3,5-bis-$CF_3$, $R_3$ = Et, R = Me).** The title compound **8v** was prepared from **7q** by method A in 65% yield: $R_f$ = 0.52 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 8.01 (s, 2H), 7.78 (s, 1H), 6.83 (s, 1H), 6.81 (d, 2H, $J$ = 8.4 Hz), 6.18 (d, 2H, $J$ = 8.5 Hz), 5.26 (s, 1H), 5.25 (s, 2H), 3.67 (s, 3H), 2.71 (q, 2H, $J$ = 7.6 Hz), 2.58 (s, 3H), 2.55 (s, 3H), 2.52–2.39 (m, 2H), 1.19 (t, 3H, $J$ = 7.5 Hz), 0.77 (t, 3H, $J$ = 7.3 Hz); FABMS $m/e$ 593 (M + 1).

**3-[[4-[*N*-Allyl-*N*-(carbethoxy(2,5-difluorophenyl)methyl)amino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (8w) ($R_1$ = H, $R_2$ = 2,5-di-F, $R_3$ = allyl, R = Et).** The title compound **8w** was prepared from **7r** by method A in 67% yield: $R_f$ = 0.46 (50% ethyl acetate/hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.18 (m, 1H), 6.94 (m, 2H), 6.85 (s, 1H), 6.82 (d, 2H, $J$ = 8.5 Hz), 6.38 (d, 2H, $J$ = 8.6 Hz), 5.59 (m, 1H), 5.26 (s, 2H), 5.07 (d, 1H, $J$ = 9.2 Hz), 5.06 (s, 1H), 5.00 (d, 1H, $J$ = 16.8 Hz), 4.12 (m, 2H), 3.25 (dd, 1H, $J$ = 5.9, 13.8 Hz), 2.98 (dd, 1H, $J$ = 8.4, 13.9 Hz), 2.76 (q, 2H, $J$ = 7.7 Hz), 2.59 (s, 3H), 2.56 (s, 3H), 1.21 (t, 3H, $J$ = 7.5 Hz), 1.10 (t, 3H, $J$ = 7.1 Hz); FABMS $m/e$ 519 (M + 1).

**General Procedure for Saponification of Esters 8 to Acids 9. 3-[[4-[*N*-Allyl-*N*-(carboxyphenylmethyl)amino]-phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (9d).** To a solution of methyl ester **8d** (0.488 g, 1.04 mmol) in MeOH (5 mL) was added an aqueous solution of 1 N LiOH (3 mL), and the resulting mixture was stirred overnight. The mixture was concentrated by removing the MeOH and water *in vacuo*. The product was purified by either flash column chromatography or preparative thin-layer chromatography (prep TLC) using $CHCl_3$/MeOH/$NH_4OH$ (90:10:1) or the developing solvent system (for the prep TLC) as the eluent to give the (phenylamino)phenylacetic acid **9d** (276 mg, 58%): $R_f$ = 0.40 (50% ethyl acetate/hexane); $R_f$ = 0.56 (80:20:2 chloroform/methanol/$NH_4OH$); $^1$H NMR ($CD_3OD$) $\delta$ 7.53 (d, 2H), 7.22 (t, 3H), 7.12 (t, 1H), 6.97 (s, 1H), 6.68 (d, 2H), 6.22 (d, 2H), 5.67–5.74 (m, 1H), 5.29 (s, 2H), 3.36 (dd, 1H), 3.07 (dd, 1H), 2.78 (q, 2H), 2.57 (s, 3H), 2.56 (s, 3H), 1.15 (t, 3H); FABMS $m/e$ 455 (M + 1).

**3-[[4-[*N*-(Carboxyphenylmethyl)amino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (9a).** The title compound **9a** was obtained from **7a** in 91% yield: $R_f$ = 0.47 (80:20:2 chloroform/methanol/$NH_4OH$); $^1$H NMR ($CDCl_3$) $\delta$ 7.48 (d, 2H), 7.40 (s, 1H), 7.20–7.34 (m, 4H), 6.91 (s, 1H), 6.87 (d, 2H), 5.31 (s, 2H), 4.89 (br s, 1H), 2.78 (q, 2H), 2.59 (s, 6H), 1.24 (t, 3H); FABMS $m/e$ 415 (M + 1).

**3-[[4-[*N*-(Carboxyphenylmethyl)-*N*-methylamino]-phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (9b).** The title compound **9b** was obtained from **8b** in 78% yield: $R_f$ = 0.52 (80:20:2 chloroform/methanol/$NH_4OH$); $^1$H NMR ($CDCl_3$) $\delta$ 7.00 (s, 5H), 6.77 (s, 1H), 6.70 (d, 2H), 6.43 (d, 2H), 5.15 (s, 1H), 5.12 (s, 2H), 2.68 (q, 2H), 2.57 (s, 3H), 2.40 (s, 6H), 1.20 (t, 3H); FABMS $m/e$ 429 (M + 1).

**3-[[4-[*N*-(Carboxyphenylmethyl)-*N*-ethylamino]phenyl]-methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (9c).** The title compound **9c** was obtained from **8c** in 92% yield: $R_f$

= 0.54 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.54 (d, 2H, $J$ = 7.2 Hz), 7.20 (t, 2H, $J$ = 7.7 Hz), 7.10 (t, 1H, $J$ = 7.3 Hz), 6.96 (s, 1H), 6.68 (d, 2H, $J$ = 8.7 Hz), 6.23 (d, 2H, $J$ = 8.6 Hz), 5.27 (s, 2H), 2.78 (q, 2H, $J$ = 7.6 Hz), 2.63 (sx, 1H, $J$ = 6.8 Hz), 2.56 (s, 3H), 2.55 (s, 3H), 2.30 (sx, 1H, $J$ = 6.8 Hz), 1.16 (t, 3H, $J$ = 7.6 Hz), 0.80 (t, 3H, $J$ = 7.2 Hz); FABMS $m/e$ 443 (M + 1).

**3-[[4-[*N*-(Carboxyphenylmethyl)-*N*-propylamino]-phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (9e).** The title compound **9e** was obtained from **8e** in 87% yield: $R_f$ = 0.54 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CDCl_3$) $\delta$ 7.20 (br s, 2H), 7.06 (br s, 3H), 6.78 (s, 1H), 6.73 (d, 2H), 6.52 (d, 2H), 5.11 (br s, 3H), 2.97 (m, 2H), 2.71 (q, 2H), 2.57 (s, 3H), 2.42 (s, 3H), 1.23 (t, 3H), 0.87 (m, 2H), 0.46 (t, 3H); FABMS $m/e$ 457 (M + 1).

**3-[[4-[*N*-(Carboxyphenylmethyl)-*N*-butylamino]-phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (9f).** The title compound **9f** was obtained from **8f** in 89% yield: $R_f$ = 0.59 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CDCl_3$) $\delta$ 7.21 (br s, 2H), 7.04 (br s, 3H), 6.75 (s, 1H), 6.73 (d, 2H), 6.55 (d, 2H), 5.09 (br s, 3H), 2.98 (m, 2H), 2.69 (q, 2H), 2.55 (s, 3H), 2.53 (s, 3H), 1.23 (t, 3H), 0.87 (m, 2H), 0.46 (m, 2H), 0.31 (t, 3H); FABMS $m/e$ 471 (M + 1).

**3-[[4-[*N*-(Carboxyphenylmethyl)-*N*-isobutylamino]-phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (9g).** The title compound **9g** was obtained from **8g** in 82% yield: $R_f$ = 0.57 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.49 (d, 2H), 7.17 (t, 2H), 7.08 (t, 1H), 6.96 (s, 1H), 6.68 (d, 2H), 6.21 (d, 2H), 5.27 (s, 2H), 2.76 (q, 2H), 2.57–2.63 (m, 1H), 2.56 (s, 3H), 2.55 (s, 3H), 2.31 (dd, 1H), 1.65–1.71 (m, 1H), 1.12 (t, 3H), 0.93 (d, 3H), 0.76 (d, 3H); FABMS $m/e$ 471 (M + 1).

**3-[[4-[*N*-(Carboxyphenylmethyl)-*N*-(cyclopropylmethyl)amino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo-[4,5-*b*]pyridine (9i).** The title compound **9i** was obtained from **8i** in 78% yield: $R_f$ = 0.58 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.53 (d, 2H, $J$ = 7.2 Hz), 7.28 (t, 2H, $J$ = 7.4 Hz), 7.22 (t, 1H, $J$ = 7.2 Hz), 7.01 (s, 1H), 6.76 (d, 2H, $J$ = 8.6 Hz), 6.30 (d, 2H, $J$ = 8.6 Hz), 5.33 (s, 2H), 2.83 (q, 2H, $J$ = 7.6 Hz), 2.58 (s, 3H): 2.57 (s, 3H), 2.56 (m, 1H), 2.27 (m, 1H), 1.18 (t, 3H, $J$ = 7.6 Hz), 0.67 (m, 1H), 0.40–0.28 (m, 2H), 0.11 (m, 1H), –0.07 (m, 1H); FABMS $m/e$ 485 (M + 1).

**3-[[4-[*N*-(Carboxyphenylmethyl)amino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (9j).** The title compound **9j** was obtained from **8i** in 56% yield: $R_f$ = 0.41 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.46 (d, 2H, $J$ = 7.3 Hz), 7.22 (t, 2H, $J$ = 7.3 Hz), 7.14 (t, 1H, $J$ = 7.4 Hz), 6.98 (s, 1H), 6.78 (s, 1H), 6.64 (d, 1H, $J$ = 8.2), 6.20 (d, 1H, $J$ = 8.3 Hz), 5.31 (s, 2H), 4.78 (s, 1H), 2.78 (q, 2H, $J$ = 7.6 Hz), 2.57 (s, 3H), 2.56 (s, 3H), 2.17 (s, 3H), 1.16 (t, 3H, $J$ = 7.6 Hz); FABMS $m/e$ 429 (M + 1).

**3-[[4-[*N*-(Carboxyphenylmethyl)-*N*-methylamino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]-pyridine (9k).** Compound **9k** was obtained from **8k** in 74% yield: $R_f$ = 0.45 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.47 (d, 2H, $J$ = 7.4 Hz), 7.23 (t, 2H, $J$ = 7.3 Hz), 7.14 (t, 1H, $J$ = 7.5 Hz), 6.97 (s, 1H), 6.77 (s, 1H), 6.45 (m, 1H), 5.89 (d, 1H, $J$ = 7.7 Hz), 5.28 (s, 2H), 2.78 (q, 2H, $J$ = 7.5 Hz), 2.57 (s, 3H), 2.56 (s, 3H), 2.17 (s, 3H), 1.91 (s, 3H), 1.16 (t, 3H, $J$ = 7.6 Hz); FABMS $m/e$ 443 (M + 1).

**3-[[4-[*N*-(Carboxyphenylmethyl)-*N*-ethylamino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo-[4,5-*b*]pyridine (9l).** The title compound **9l** was obtained by saponification of **8l** in 82% yield: $R_f$ = 0.46 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.52 (d, 2H, $J$ = 7.5 Hz), 7.20 (t, 2H, $J$ = 7.5 Hz), 7.10 (t, 1H, $J$ = 7.2 Hz), 6.95 (s, 1H), 6.77 (s, 1H), 6.42 (d, 1H, $J$ = 8.0 Hz), 5.83 (d, 1H, $J$ = 8.3 Hz), 5.26 (s, 2H), 2.77 (q, 2H, $J$ = 7.5 Hz), 2.64 (m, 1H), 2.57 (s, 3H), 2.56 (s, 3H), 2.36 (m, 1H), 2.20 (s, 3H), 1.16 (t, 3H, $J$ = 7.6 Hz); FABMS $m/e$ 457 (M + 1).

**3-[[4-[*N*-Allyl-*N*-(carboxyphenylmethyl)amino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo-[4,5-*b*]pyridine (9m).** The title compound **9m** was obtained from **8m** in 62% yield: $R_f$ = 0.47 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.53 (d, 2H, $J$ = 6.7 Hz), 7.25 (t, 2H, $J$ = 7.4 Hz), 7.15 (t, 1H, $J$ = 7.1 Hz), 6.97 (s, 1H), 6.76 (s, 1H), 6.46 (d, 1H, $J$ = 8.6 Hz), 5.88 (d, 1H, $J$ = 7.9 Hz), 5.63 (m, 1H), 5.29 (s, 2H), 3.36 (m, 1H), 3.14 (m, 1H), 2.77 (q, 2H, $J$ = 7.5 Hz), 2.57 (s, 3H), 2.56 (s, 3H), 2.15 (s, 3H), 1.14 (t, 3H, $J$ = 7.5 Hz); (FABMS $m/e$ 469 (M + 1).

**3-[[4-[*N*-(Carboxyphenylmethyl)-*N*-propylamino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]-pyridine (9n).** The title compound **9n** was obtained from **8n** in 68% yield: $R_f$ = 0.49 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.52 (d, 2H, $J$ = 7.6 Hz), 7.20 (t, 2H, $J$ = 7.5 Hz), 7.10 (t, 1H, $J$ = 6.7 Hz), 6.97 (s, 1H), 6.75 (s, 1H), 6.42 (d, 1H, $J$ = 8.0 Hz), 5.84 (d, 1H, $J$ = 8.2 Hz), 5.27 (s, 2H), 2.78 (q, 2H, $J$ = 7.5 Hz), 2.57 (s, 3H), 2.29 (m, 2H), 2.18 (s, 3H), 1.23 (m, 2H), 1.13 (t, 3H, $J$ = 7.6 Hz), 0.82 (t, 3H, $J$ = 7.3 Hz); FABMS $m/e$ 471 (M + 1).

**3-[[4-[*N*-(Carboxy(2-methylphenyl)methyl)amino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]-pyridine (9o).** The title compound **9o** was obtained from **7o** in 79% yield: $R_f$ = 0.46 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.34 (m, 1H), 7.10 (m, 3H), 6.98 (s, 1H), 6.80 (m, 1H), 6.66 (m, 1H), 6.16 (m, 1H), 5.33 (s, 2H), 5.09 (s, 1H), 2.78 (q, 2H, $J$ = 7.6 Hz), 2.57 (s, 3H), 2.56 (s, 3H), 2.52 (s, 3H), 2.16 (s, 3H), 1.17 (t, 3H, $J$ = 7.6 Hz); FABMS $m/e$ 443 (M + 1).

**3-[[4-[*N*-Allyl-*N*-(carboxy(2-methylphenyl)methyl)amino]-3-methylphenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (9p).** The title compound **9p** was obtained from **8p** in 74% yield: $R_f$ = 0.58 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.59 (d, 1H, $J$ = 7.5 Hz), 7.17 (t, 1H, $J$ = 7.9 Hz), 7.05 (t, 1H, $J$ = 7.5 Hz), 6.97 (s, 1H), 6.95 (d, 1H, $J$ = 7.7 Hz), 6.69 (s, 1H), 6.35 (d, 1H, $J$ = 7.3 Hz), 5.95 (d, 1H, $J$ = 8.4 Hz), 5.73 (m, 1H), 5.25 (s, 2H), 3.10 (m, 1H), 2.76 (q, 2H, $J$ = 7.5 Hz), 2.57 (s, 3H), 2.56 (s, 3H), 2.28 (s, 3H), 2.10 (s, 3H), 1.12 (t, 3H, $J$ = 7.6 Hz); FABMS $m/e$ 483 (M + 1).

**3-[[4-[*N*-(Carboxy[3,5-bis(trifluoromethyl)phenyl]-methyl)amino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (9q).** The title compound **9q** was obtained from the corresponding methyl ester **8** (R = Me, $R_1$, $R_3$ = H, $R_2$ = 3,5-bis-$CF_3$) in 82% yield: $R_f$ = 0.48 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 8.09 (s, 2H), 7.74 (s, 1H), 6.96 (s, 1H), 6.80 (d, 2H, $J$ = 8.3 Hz), 6.26 (d, 2H, $J$ = 8.3 Hz), 5.35 (s, 2H), 2.79 (q, 2H, $J$ = 7.6 Hz), 2.57 (s, 3H), 2.56 (s, 3H), 1.16 (t, 3H, $J$ = 7.6 Hz); FABMS $m/e$ 551 (M + 1).

**3-[[4-[*N*-(Carboxy(2,5-difluorophenyl)methyl)-*N*-methylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (9r).** The title compound **9r** was obtained from **8r** in 76% yield: $R_f$ = 0.52 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.27 (m, 1H), 6.97 (s, 1H), 6.87 (m, 2H), 6.73 (d, 2H, $J$ = 8.6 Hz), 6.38 (d, 2H, $J$ = 8.5 Hz), 5.30 (s, 2H), 2.77 (q, 2H, $J$ = 7.6 Hz), 2.57 (s, 3H), 2.56 (s, 3H), 1.86 (s, 3H), 1.15 (t, 3H, $J$ = 7.6 Hz); FABMS $m/e$ 465 (M + 1).

**3-[[4-[*N*-(Carboxy(2-chlorophenyl)methyl)-*N*-ethylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo-[4,5-*b*]pyridine (9s).** The title compound **9s** was obtained from **8s** in 81% yield: $R_f$ = 0.52 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.64 (dd, 2H, $J$ = 1.2, 7.9 Hz), 7.25–7.13 (m, 3H), 6.71 (d, 2H, $J$ = 8.5 Hz), 6.35 (d, 2H, $J$ = 8.6 Hz), 5.31 (s, 2H), 2.78 (q, 2H, $J$ = 7.6 Hz), 2.71 (m, 1H), 2..57 (s, 3H), 2.56 (s, 3H), 2.34 (m, 1H), 1.13 (t, 3H, $J$ = 7.5 Hz), 0.84 (t, 3H, $J$ = 7.3 Hz); FABMS $m/e$ 478 (M + 1).

**3-[[4-[*N*-(Carboxy(3-methylphenyl)methyl)-*N*-ethylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo-[4,5-*b*]pyridine (9t).** The title compound **9t** was obtained from **8t** in 83% yield: $R_f$ = 0.56 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.32 (s, 1H), 7.31 (d, 1H, $J$ = 8.0 Hz), 7.17 (t, 1H, $J$ = 7.9 Hz), 7.04 (d, 2H, $J$ = 8.0 Hz), 6.97 (s, 1H), 6.72 (d, 2H, $J$ = 8.2 Hz), 6.35 (d, 2H, $J$ = 8.2 Hz), 5.32 (s, 2H), 2.80 (q, 2H, $J$ = 7.6 Hz), 2.57 (s, 3H), 2.56 (s, 3H), 2.53 (m, 1H), 2.17 (s, 3H), 1.14 (t, 3H, $J$ = 7.5 Hz), 0.82 (t, 3H, $J$ = 7.2 Hz); FABMS $m/e$ 457 (M + 1).

**3-[[4-[*N*-(Carboxy(2,5-difluorophenyl)methyl)-*N*-ethylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo-[4,5-*b*]pyridine (9u).** The title compound **9u** was obtained from **8u** in 56% yield: $R_f$ = 0.52 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.32 (m, 1H), 6.97 (s, 1H), 6.86 (m, 2H), 6.71 (d, 2H, $J$ = 8.5 Hz), 6.34 (d, 2H, $J$ = 8.7 Hz), 5.29 (s, 2H), 2.77 (q, 2H, $J$ = 7.6 Hz), 2.57 (s, 3H), 2.56 (s, 3H), 2.47 (m, 1H),

2.34 (m, 1H), 1.14 (t, 3H, $J$ = 7.6 Hz), 0.85 (t, 3H, $J$ = 7.2 Hz); FABMS $m/e$ 479 (M + 1).

**3-[[4-[*N*-(Carboxy[3,5-bis(trifluoromethyl)phenyl]methyl)-*N*-ethylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (9v).** The title compound **9v** was obtained from **8v** in 67% yield: $R_f$ = 0.61 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 8.11 (s, 2H), 7.79 (s, 1H), 6.99 (s, 1H), 6.78 (d, 2H, $J$ = 8.4 Hz), 6.27 (d, 2H, $J$ = 8.4 Hz), 5.33 (s, 2H), 2.79 (q, 2H, $J$ = 7.6 Hz), 2.57 (s, 3H), 2.56 (s, 3H), 2.54 (m, 1H), 2.38 (m, 1H), 1.14 (t, 3H, $J$ = 7.6 Hz), 0.82 (t, 3H, $J$ = 7.2 Hz); FABMS $m/e$ 579 (M + 1).

**3-[[4-[*N*-Allyl-*N*-(carboxy(2,5-difluorophenyl)methyl)amino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (9w).** The title compound **9w** was obtained from **8w** in 83% yield: $R_f$ = 0.54 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.29 (m, 1H), 6.97 (s, 1H), 6.89 (m, 2H), 6.74 (d, 2H, $J$ = 8.2 Hz), 6.38 (d, 2H, $J$ = 8.3 Hz), 5.73 (m, 1H), 5.32 (s, 2H), 3.27 (m, 1H), 3.12 (m, 1H), 2.79 (q, 2H, $J$ = 7.6 Hz), 2.57 (s, 3H), 2.56 (s, 3H), 1.13 (t, 3H, $J$ = 7.6 Hz); FABMS $m/e$ 491 (M + 1).

**General Procedure for Conversion of (Phenylamino)phenylacetic Acids 9 to Acyl Sulfonamides 16. Preparation of 3-[[4-[*N*-(((Phenylsulfonyl)carbamoyl)phenylmethyl)-*N*-ethylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (16a).** To a solution of **9c** (0.2 g, 0.45 mmol) in THF (20 mL) was added 1,1'-carbonyldiimidazole (0.22 g, 1.36 mmol) and the resulting mixture stirred for 18 h. A mixture of DBU (0.102 mL, 0.68 mmol) and benzenesulfonamide (0.155 g, 0.9 mmol) in THF (1 mL) was added to the reaction mixture, and then, it was refluxed for 24 h. The mixture was diluted with $CH_2Cl_2$ (100 mL) and washed successively with a 5% aqueous citric acid solution, water, and brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by flash column chromatography with $CHCl_3$/MeOH/$NH_4OH$ (90:10:1) to give the title compound **16a** (0.156 g, 58%): $R_f$ = 0.71 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.646 (dd, 2H, $J$ = 7.24 Hz, 1.43 Hz), 7.455 (dd, 2H, $J$ = 7.05 Hz, 1.48 Hz), 7.375 (dd, 1H, $J$ = 7.38 Hz), 7.29–7.18 (m, 5H), 7.006 (s, 1H), 6.681 (dd, 2H, $J$ = 8.7 Hz), 6.26 (dd, 2H, $J$ = 8.66 Hz), 5.317 (s, 2H), 4.87 (s, 1H), 2.807 (q, 2H), 2.591 (s, 3H), 2.577 (s, 3H), 2.47–2.36 (m, 1H), 2.28–2.18 (m, 1H), 1.185 (t, 3H), 0.892 (t, 3H); FABMS $m/e$ 582 (M + 1).

**3-[[4-[*N*-Allyl-*N*-(((phenylsulfonyl)carbamoyl)phenylmethyl)amino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (16b).** The title acyl sulfonamide **16b** was prepared from the corresponding (phenylamino)phenylacetic acid **9d** as described above in 61% yield: $R_f$ = 0.74 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.89 (dd, 1H, $J$ = 6.87 Hz), 7.64 (d, 2H, $J$ = 7.42 Hz), 7.532 (d, 1H), 7.522 (dd, 1H, $J$ = 7.47 Hz), 7.455 (d, 2H, $J$ = 7.38 Hz), 7.366 (dd, 1H, $J$ = 7.37 Hz), 7.28 (dd, 1H, $J$ = 7.79 Hz), 7.212 (dd, 1H, $J$ = 7.79 Hz), 7.148 (dd, 1H, $J$ = 7.05 Hz), 6.968 (s, 1H), 6.67 (d, 2H, $J$ = 8.3 Hz), 6.2165 (d, 2H, $J$ = 8.3 Hz), 5.49 (ddd, 1H), 5.284 (s, 2H), 4.88 (s, 1H), 4.745 (dd, 1H, $J$ = 10.42 Hz), 4.705 (dd, 1H, $J$ = 17.25 Hz), 3.375–3.326 (m, 1H), 3.08–3.029 (m, 1H), 2.77 (q, 2H), 2.566 (s, 3H), 2.555 (s, 3H), 1.148 (t, 3H); FABMS $m/e$ 594 (M + 1).

**3-[[4-[*N*-(((phenylsulfonyl)carbamoyl)phenylmethyl)-*N*-propylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (16c).** The title compound **16c** was obtained from its acid counterpart **9e** in 47% yield: $R_f$ = 0.74 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.62 (d, 2H), 7.45 (d, 2H), 7.363 (dd, 1H), 7.265 (dd, 2H), 7.19 (dd, 2H), 7.1225 (dd, 1H), 6.962 (s, 1H), 6.66 (d, 2H), 6.22 (d, 2H), 5.27 (s, 2H), 4.9 (s, 1H), 2.77 (q, 2H), 2.63–2.53 (m, 1H), 2.57 (s, 3H), 2.55 (s, 3H), 2.25 (dt, 1H), 1.15 (t, 3H), 0.775 (t, 3H); FABMS $m/e$ 596 (M + 1).

**3-[[4-[*N*-(*tert*-Butoxycarbonyl)-*N*-methylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (17).** To a solution of **5a** (1.0 g, 3.57 mmol) in $CH_2Cl_2$ (100 mL) were added $Et_3N$ (0.75 mL, 5.36 mmol) and di-*tert*-butyldicarbonate (1.23 mL, 5.36 mmol). The resulting mixture was stirred for 18 h. The reaction mixture was diluted with $CH_2Cl_2$ (400 mL) and then washed with water, dried over $Na_2SO_4$, filtered, and concentrated to a pale yellow oil. Flash column chromatography of the oil with 1:1 EtOAc/hexane yielded the *N*-*tert*-Boc derivative of **5a** (3-[[4-[*N*-(*tert*-butoxycarbonyl)amino]phenyl]-methyl-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine) (0.45 g, 33%): $R_f$ = 0.75 (100% ethyl acetate); $^1H$ NMR ($CDCl_3$) $\delta$ 7.26 (d, 2H), 7.04 (d, 2H), 6.89 (s, 1H), 6.63 (br s, 1H), 5.39 (s, 2H), 2.77 (q, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 1.49 (s, 9H), 1.29 (t, 3H); FABMS $m/e$ 381 (M + 1).

To a solution of the *N*-*t*-Boc derivative of **5a** (100 mg, 0.26 mmol) in DMF (4 mL) was added a 60% dispersion of NaH (16 mg, 0.39 mmol) in mineral oil and the resulting mixture stirred for 5 min. Methyl iodide (74 mg, 0.52 mmol) was added to the mixture which was stirred for 18 h. The excess of NaH was quenched with the careful addition of MeOH. The mixture was concentrated *in vacuo* to a brown oil which after flash column chromatography with 1:1 EtOAc/hexane afforded the title compound **17** (75 mg, 72%): $R_f$ = 0.32 (50% ethyl acetate/hexane); $^1H$ NMR ($CDCl_3$) $\delta$ 7.12 (d, 2H), 7.04 (d, 2H), 6.87 (s, 1H), 5.40 (s, 2H), 3.18 (s, 3H), 2.77 (q, 2H), 2.60 (s, 3H), 2.56 (s, 3H), 1.49 (s, 9H), 1.27 (t, 3H); FABMS $m/e$ 395 (M + 1).

**3-[[4-[*N*-(Cyanophenylmethyl)-*N*-methylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (18).** Trifluoroacetic acid (2 mL) was added to a solution of **17** (75 mg, 0.19 mmol) in $CH_2Cl_2$ (4 mL) and the resulting mixture stirred for 3 h. Volatiles were removed *in vacuo*, and the residue was dissolved in MeOH. After the addition of saturated aqueous $NaHCO_3$ (2 mL), the methanol and water (as toluene/water azeotrope) were removed *in vacuo* and the residue was suspended in $CHCl_3$. The solution was filtered through Celite to remove $NaHCO_3$ to give deprotected **17** (5,7-dimethyl-2-ethyl-3-(4-(*N*-methylamino)benzyl)imidazo[4,5-*b*]pyridine) (53 mg, 94%): $R_f$ = 0.47 (66% ethyl acetate/hexane); $^1H$ NMR ($CDCl_3$) $\delta$ 6.97 (d, 2H), 6.85 (s, 1H), 6.48 (d, 2H), 5.32 (s, 2H), 3.73 (br s, 3H), 2.79 (q, 2H), 2.76 (s, 3H), 2.61 (s, 3H), 2.59 (s, 3H), 1.28 (t, 3H); FABMS $m/e$ 295 (M + 1).

Benzaldehyde (52 mL, 0.51 mmol) and KCN (25 mg, 0.38 mmol) were added to a solution of deprotected **17** (75 mg, 25.5 mmol) in MeOH (1 mL) and AcOH (1 mL), and the resulting mixture was stirred for 20 h. The reaction mixture was concentrated, and the residue was flash column chromatographed with 1:1 EtOAc/hexane to give **18** (101 mg, 97%): $R_f$ = 0.43 (50% ethyl acetate/hexane); $^1H$ NMR ($CDCl_3$) $\delta$ 7.40–7.32 (m, 3H), 7.24 (d, 2H, $J$ = 7.8 Hz), 7.08 (d, 2H, $J$ = 7.6 Hz), 6.90 (s, 1H), 6.75 (d, 2H, $J$ = 7.6 Hz), 5.65 (s, 1H), 5.35 (s, 2H), 2.88 (q, 2H, $J$ = 7.5 Hz), 2.62 (s, 3H), 2.58 (s, 3H), 1.50 (t, 3H, $J$ = 7.5 Hz); FABMS $m/e$ 410 (M + 1).

**3-[[4-[*N*-(Tetrazol-5-ylphenylmethyl)-*N*-methylamino]phenyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (19).** To a solution of **18** (101 mg, 0.25 mmol) in toluene (3 mL) was added trimethyltin azide (154 mg, 0.75 mmol) and the resulting mixture refluxed for 20 h. The product was purified by preparative thin-layer chromatography with $CHCl_3$/MeOH/$NH_4OH$ (80:20:2) to yield **19** (90 mg, 80%): $R_f$ = 0.34 (80:20:2 chloroform/methanol/$NH_4OH$); $^1H$ NMR ($CD_3OD$) $\delta$ 7.30–7.20 (m, 5H), 7.10 (d, 2H, $J$ = 7.6 Hz), 6.97 (s, 1H), 6.82 (d, 2H, $J$ = 7.6 Hz), 5.52 (s, 1H), 5.40 (s, 2H), 2.83 (q, 2H, $J$ = 7.7 Hz), 2.58 (s, 3H), 2.57 (s, 3H), 1.22 (t, 3H, $J$ = 7.6 Hz); FABMS $m/e$ 453 (M + 1).

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