

Non-Peptide Angiotensin II Receptor Antagonists. 1. Design, Synthesis, and Biological Activity of N-Substituted Indoles and Dihydroindoles^{1,2}

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A series of N-acylated indoles (12–18), N-alkylated indoles (19–24), N-acylated dihydroindoles (26–30), and N-alkylated dihydroindoles (31–34) were synthesized and evaluated in the *in vitro* AT₁ (rabbit aorta) and AT₂ (rat midbrain) binding assay. The carboxylic acid 3-[[N-(2-carboxy-3,6-dichlorobenzoyl)-5-indolyl]methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (14b) was found to be the most potent AT₁ (IC₅₀ = 0.8 nM) antagonist in the N-acylated indole series and displayed a 25-fold higher potency than the parent unsubstituted derivative 14a (AT₁ IC₅₀ = 20 nM) and a 22-fold greater potency than the corresponding dihydroindole analog 27 (AT₁ IC₅₀ = 18 nM). Replacement of the terminal carboxyl (COOH) of 14a with the bioisostere tetrazole in 16 (AT₁ IC₅₀ = 5 nM, AT₂ IC₅₀ = 130 nM) not only improved the AT₁ potency by 4-fold but also resulted in a 50-fold increase in AT₂ activity. In the N-alkylated indole series, the tetrazole 3-[[N-(2-tetrazol-5-yl-6-chlorobenzyl)-5-indolyl]methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (24) exhibited the highest AT₁ (IC₅₀ = 1 nM) activity, revealing a 230-fold increase in AT₁ activity as a result of the incorporation of the isosteric tetrazole for the carboxyl (COOH) of 20 and a nearly 9-fold increase over the corresponding deschloro analog 22 (AT₁ IC₅₀ = 8.7 nM). Tetrazole 34 was identified as the most potent (AT₁ IC₅₀ = 18 nM) AT₁ receptor antagonist in a structurally distinct series of compounds derived from N-alkylation of dihydroindole 25. A new class of highly potent (14b, AT₁ IC₅₀ = 0.8 nM; 24, AT₁ IC₅₀ = 1 nM) AT₁-selective non-peptide AII receptor antagonists derived from N-substituted indoles and dihydroindoles is disclosed. Tetrazole 24 of the N-alkylated indole series displayed good *in vivo* activity by blocking the AII-induced pressor response for 5.5 h after intravenous administration in conscious normotensive rats at a 1.0 mg/kg dose level.

Introduction

The renin-angiotensin system (RAS) is a proteolytic cascade essential to the regulation of normal blood pressure and in the maintenance of electrolyte and fluid balance.³ The first and rate-limiting step in this biochemical cascade is the cleavage of the precursor protein angiotensinogen by renin, an aspartic protease synthesized by the kidneys, to generate the decapeptide angiotensin I (AI). Further cleavage of angiotensin I by angiotensin-converting enzyme (ACE), a nonspecific carboxydipeptidase, produces the potent vasoconstrictor octapeptide angiotensin II (AII), which is responsible for the peripheral effects of the RAS.⁴ Biochemical responses of the active hormone AII, such as vasoconstriction, aldosterone release, renal reabsorption of sodium, and norepinephrine release, are thought to be mediated by the actions of membrane-bound specific receptors present on various tissues and organs such as the adrenal cortex, heart, kidney, arterioles, sympathetic nerve endings, and possibly others.⁵

Blockade of the RAS activity by renin inhibition, ACE inhibition, and AII receptor antagonism continues to attract enormous therapeutic interest for the treatment of hypertension and congestive heart failure.⁶ The ther-

apeutic and commercial success of the ACE inhibitors⁷ such as captopril, enalapril, and lisinopril has intensified the interest in the development of renin inhibitors⁸ and AII receptor antagonists^{6,9} as alternative pharmacological modes of inhibition of the renin-angiotensin system. Although ACE inhibitors are highly effective and widely used antihypertensives, these inhibitors increase bradykinin levels and potentiate the effects of bradykinin and Substance P, leading to adverse effects such as cough and angioedema.¹⁰ Renin inhibitors are thought to have superior pharmacological advantages over antihypertensive drugs with less specific modes of action such as ACE inhibitors because of the high substrate specificity of renin for angiotensinogen, its only known naturally occurring substrate. Although considerable progress has been made in the design of orally active renin inhibitors, the ultimate goal of discovering a renin inhibitor with adequate oral bioavailability has not yet been achieved.⁸

An alternate and more direct mode of selectively blocking the RAS is by antagonism of the effector hormone AII at the receptor level. This approach to inhibit the RAS is attractive because angiotensin II receptor antagonists would affect the RAS specifically and independently of the source of angiotensin II. Although a number of peptide analogs of AII (e.g., saralasin [Sar¹,Ala⁸]AII) have been reported^{6,11} to block the action of AII by binding to the AII receptor competitively, their usefulness as therapeutic agents and pharmacological tools has been hampered by their lack of oral absorption, short duration of action, rapid clearance, and partial agonist activity.¹²

The development of non-peptide AII receptor antagonists to resolve these problems associated with peptides

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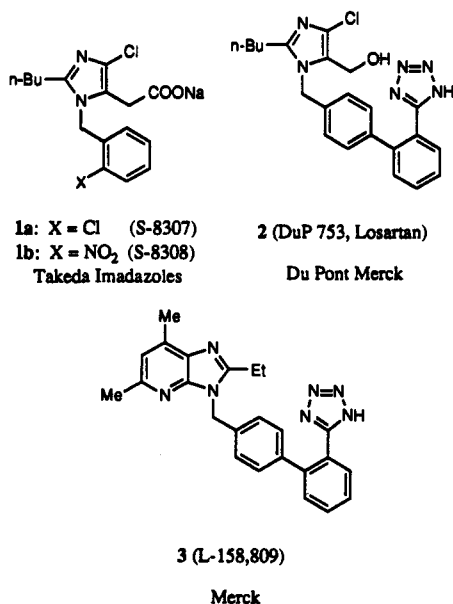


Figure 1. Non-peptide angiotensin II receptor antagonists.

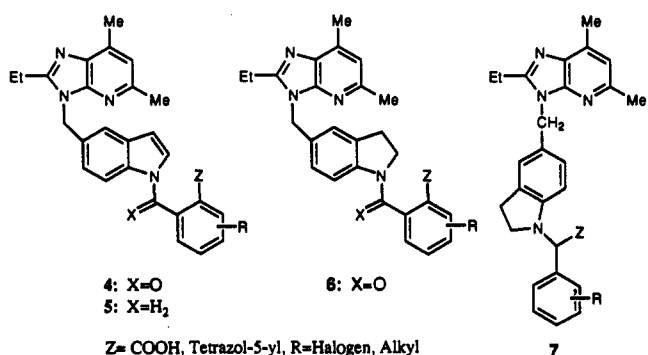


Figure 2. N-Substituted-indole- and -dihydroindole-based AII receptor antagonists.

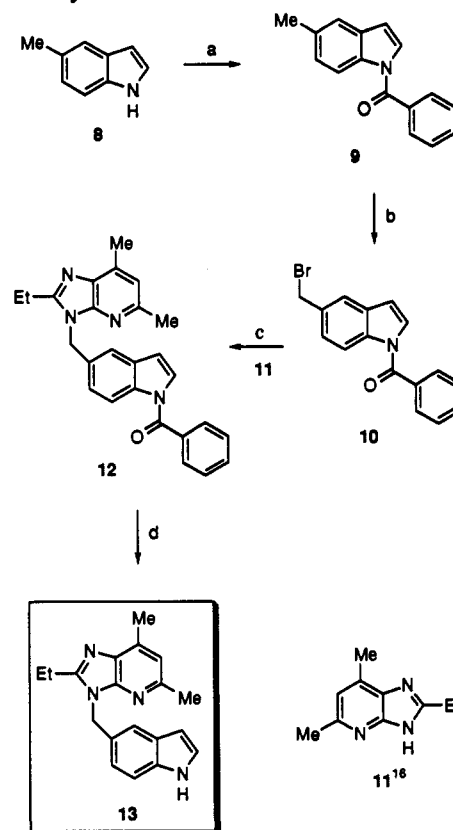
has attracted much current attention.^{6,9} The first report on the non-peptidic AII antagonists, of which benzyl-substituted imidazoles **1a** (S-8307) and **1b** (S-8308) are examples, was disclosed by Takeda.¹³ Structural modifications of the Takeda lead compounds by Du Pont have recently led to the discovery of the first potent and orally active non-peptide AII receptor antagonist 2-*n*-butyl-4-chloro-5-(hydroxymethyl)-1-[[2-(1*H*-tetrazol-5-yl)bi-phenyl-4'-yl]methyl]imidazole (**2**, DuP 753, Losartan, Figure 1)¹⁴ which is currently undergoing clinical trials for the treatment of hypertension.¹⁵ More recently, the highly potent, orally active, and longer acting AII antagonist 5,7-dimethyl-2-ethyl-3-[[2-(1*H*-tetrazol-5-yl)bi-phenyl-4'-yl]methyl]imidazo[4,5-*b*]pyridine (**3**, L-158,809, Figure 1) in which the imidazole of **2** is replaced with imidazopyridine has been reported by Merck.¹⁶ A number of new non-peptide AII receptor antagonists originating from structural designs of Takeda and Du Pont Merck compounds have recently been reported.^{6a,17}

Herein, we report on the design, synthesis, and biological activity of a novel class of highly potent non-peptide AT₁-selective AII receptor antagonists (**4**–**7**), in which the biphenyl tetrazole moiety of **3** is replaced with N-substituted indoles and dihydroindoles (Figure 2).

Chemistry

N-Substituted indoles and dihydroindoles described in this report (Tables I–IV) were synthesized according to

Scheme I. Synthesis of a Common Intermediate, **13**^a

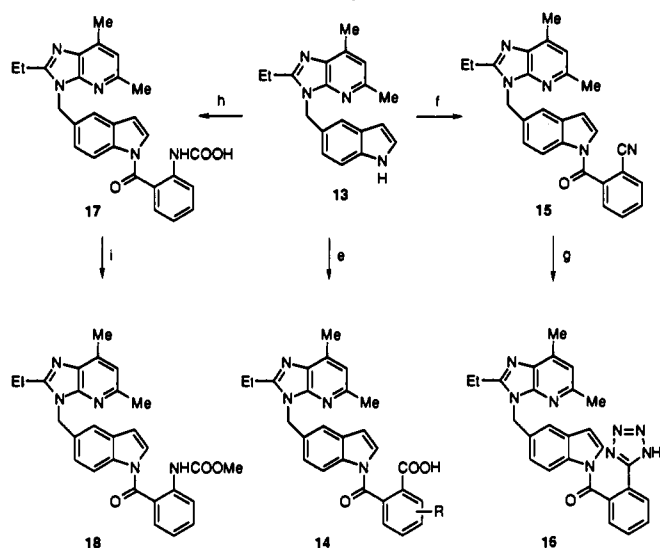


^a Conditions: (a) PhCOCl, Et₃N, DMAP, CH₂Cl₂ (96%); (b) NBS, AIBN, CCl₄, reflux (78%); (c) **11**, NaH, DMF (78%); (d) NaOH, MeOH (95%).

the routes described in the synthetic Schemes I–V. The N-acylated (**12**–**18**) and N-alkylated (**19**–**24**) indole and dihydroindole (**25**) derivatives were prepared from a common intermediate, **13**, which is linked to a heterocyclic moiety through a methylene group (Scheme I). The synthesis of **13** begins with the N-benzylation of 5-methylindole (**8**). Treatment of **8** with benzoyl chloride in methylene chloride in the presence of triethylamine and 4-(dimethylamino)pyridine (DMAP) gave N-benzoylated 5-methylindole **9** which was brominated to produce N-benzoyl-5-(bromomethyl)indole (**10**). Alkylation of 5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (**11**)¹⁶ with **10** using NaH in DMF yielded the alkylated product **12**. Deprotection of **12** in alkaline methanol (NaOH, MeOH/H₂O) provided the pivotal common intermediate **13** (Scheme I).

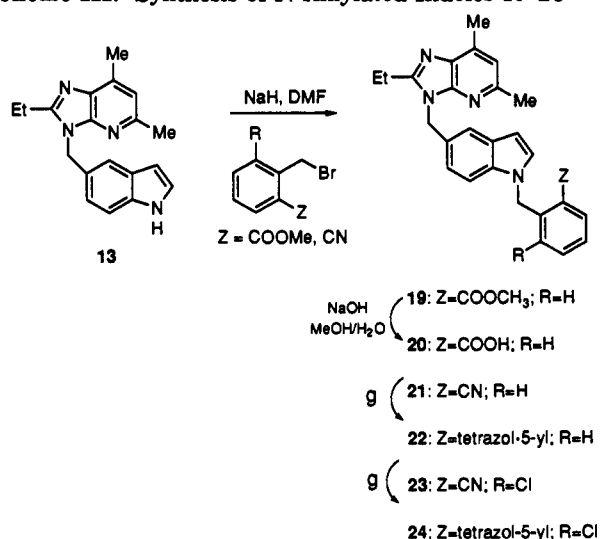
The indole intermediate **13** was treated with the appropriate phthalic anhydrides in NaH/DMF to give the *N*-(2-carboxybenzoyl)indole derivatives exemplified by **14** (Scheme II). Benzoylation of **13** with the appropriate acid chloride using NaH/DMF afforded the *N*-(2-cyanobenzoyl)indole derivative **15** which upon treatment with trimethyltin azide (Me₃SnN₃) in refluxing toluene gave the corresponding tetrazol-5-yl derivative **16**. The carbamic acid derivative *N*-(2-(carboxyamino)benzoyl)indole **17** was obtained by treating **13** with isatoic anhydride in NaH/DMF. Treatment of the carbamic acid **17** with (trimethylsilyl)diazomethane (TMSCHN₂) afforded methyl carbamate **18** (Scheme II).

The N-alkylated indoles **19**–**24** were prepared by alkylating **13** with the appropriately functionalized aryl bromide using NaH/DMF (Scheme III).

Scheme II. Synthesis of N-Acylated Indoles 14–18^a

^a Conditions: (e) NaH, DMF, phthalic anhydride (80%); (f) NaH, DMF, 2-cyanobenzoyl chloride (82%); (g) Me₃SnN₃, toluene, reflux (60%); (h) NaH, DMF, isatoic anhydride (76%); (i) Me₃SiCHN₂, toluene (92%).

Scheme III. Synthesis of N-Alkylated Indoles 19–24

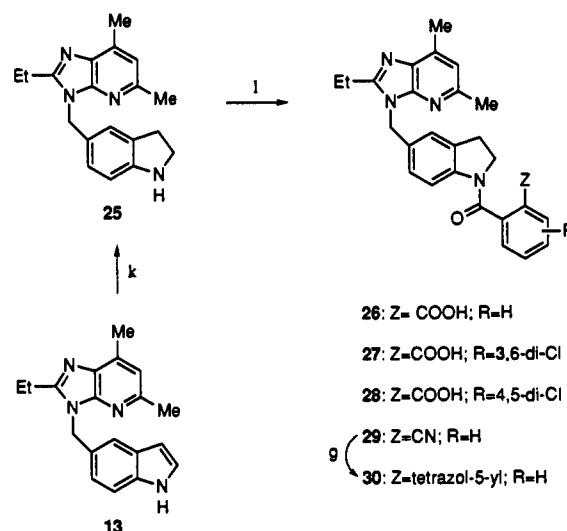


The intermediate 13 was reduced to the corresponding dihydroindole derivative 25 using NaCNBH₃ in AcOH. Acylation of dihydroindole 25 with acid chlorides or anhydrides yielded the corresponding N-acyl dihydroindoles 26–30 (Scheme IV). The tetrazole 30 was obtained from the nitrile derivative 29 which in turn was prepared from treatment of 25 with 2-cyanobenzoyl chloride in TEA/DMAP/CH₂Cl₂.

The dihydroindole derivative 25 was alkylated with methyl α-bromophenylacetate (PhCHBrCO₂Me) using NaH in DMF to produce 31, which was hydrolyzed to the carboxylic acid 32 (Scheme V). Treatment of 25 with arylaldehydes and KCN in AcOH and MeOH yielded the nitrile derivatives 33a–d. The nitrile 33a was converted to the tetrazole 34 by refluxing with trimethyltin azide (Me₃SnN₃)^{14c} in toluene (Scheme V).

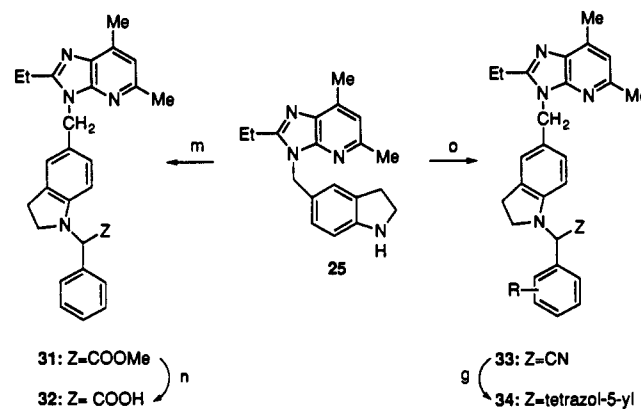
Biological Results and Discussion

The *in vitro* [¹²⁵I]-[Sar¹,Ile⁸]AII binding assays of compounds 12–34 reported in this study (Tables I–IV) were performed as described by Chang et al. using rabbit aorta

Scheme IV. Synthesis of N-Acylated Dihydroindoles 26–30^a

26: Z = COOH; R = H
 27: Z = COOH; R = 3,6-di-Cl
 28: Z = COOH; R = 4,5-di-Cl
 29: Z = CN; R = H
 30: Z = tetrazol-5-yl; R = H

^a Conditions: (k) NaCNBH₃, AcOH; (l) Et₃N, DMAP, acid anhydride or ArCOCl, CH₂Cl₂.

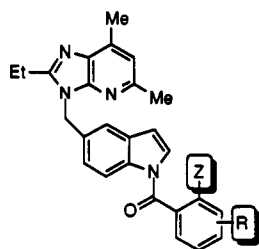
Scheme V. Synthesis of N-Alkylated Dihydroindoles 31–34^a

^a Conditions: (m) NaH, DMF, C₆H₅CHBrCO₂Me; (n) NaOH, MeOH/H₂O; (o) ArCHO, KCN, AcOH, MeOH; (g) Me₃SnN₃, toluene, reflux.

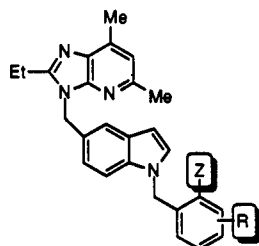
and rat midbrain as receptor sources for the AT₁ and AT₂ receptors, respectively.¹⁸ The relative potencies of the antagonists are expressed as the inhibitory concentration (IC₅₀ values) of the test compound required to completely displace 50% of the specifically bound [¹²⁵I]-[Sar¹,Ile⁸]AII from the receptor.¹⁸

Results of the *in vitro* AII (AT₁) binding assay of the N-benzoylated indoles shown in Table I demonstrate that the incorporation of nonacidic functional groups such as H, CN, and NHCO₂CH₃ in the ortho position of the benzoyl moiety of 4 affords AII antagonists with only moderate potency at the AT₁ receptor. However, the introduction of the acidic functional groups such as CO₂H and its bioisosteric tetrazol-5-yl results in potent AT₁-selective AII receptor antagonists 14a (AT₁ IC₅₀ = 20 nM) and 17 (AT₁ IC₅₀ = 5 nM). An antagonist with a marked (25-fold) increase in AT₁ potency was discovered when 3,6-dichloro substitution was incorporated into the unsubstituted carboxylic acid analog 14a to give 14b (IC₅₀ = 0.8 nM). The 4,5-dichloro analog was slightly more potent than 14a but nearly 19-fold less active than 14b at the AT₁ receptor.

The N-alkylated indole-based AII antagonists were synthesized to alleviate the potentially hydrolyzable amide

Table I. AII (AT₁/AT₂) Receptor Antagonist Activity of N-Acylated Indoles

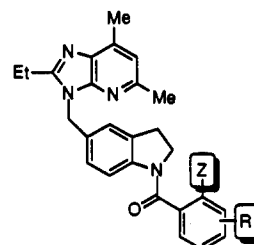
compd	R	Z	IC ₅₀ (μM)	
			AT ₁	AT ₂
12	H	H	0.24	8.9
14a	H	COOH	0.02	6.6
14b	3,6-di-Cl	COOH	0.0008	2.7
14c	4,5-di-Cl	COOH	0.015	1.9
14d	3-NO ₂	COOH	0.16	14
15	H	CN	0.25	>50
16	H	tetrazol-5-yl	0.005	0.13
17	H	NHCOOH	0.092	17
18	H	NHCOOMe	3.3	>30

Table II. AII (AT₁/AT₂) Receptor Antagonist Activity of N-Alkylated Indoles

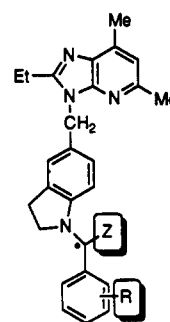
compd	R	Z	IC ₅₀ (μM)	
			AT ₁	AT ₂
19	H	COOMe	0.62	21
20	H	COOH	0.23	>30
21	H	CN	0.32	>30
22	H	tetrazol-5-yl	0.0087	>18
23	6-Cl	CN	0.12	>30
24	6-Cl	tetrazol-5-yl	0.001	12
2 (DuP 753)			0.054 ^a	>30
3 (L-158,809)			0.00054 ^a	>10

^a Data from ref 18.

bond present in the N-benzoylated series of AII receptor antagonists (12–18). Examination of the IC₅₀ values of the N-alkylated indole series (Table II) revealed that although the acid analog 20 was moderately active, the tetrazol-5-yl derivative 22 was nearly equipotent to its corresponding acylated analog 16. As it was observed in the N-acylated series that the incorporation of 3,6-dichloro substituents had a profound effect on the AT₁ potency enhancement, the introduction of only one *o*-chlorine (6-Cl) substituent caused nearly a 9-fold enhancement in the AT₁ potency of the tetrazol-5-yl analog 24 (AT₁ IC₅₀ = 1 nM) in the N-alkylated series of AII antagonists. A comparison of the indole-based AII antagonists with 2 and 3 shown in Table II reveals that both 14b and 24 are more potent than 2 and slightly less potent than 3 in the AT₁ binding assay. The increase in AT₁ potency observed for 14b and 24 by the incorporation of *o*-chloro substitution may be attributed to the favorable conformation acquired by 14b and 24 for maximal binding to the AT₁ receptor as a result of the *o*-chloro substitution, which orients the bottom phenyl ring bearing the 2-COOH or the 2-tetrazol-

Table III. AII (AT₁/AT₂) Receptor Antagonist Activity of N-Acylated Dihydroindoles

compd	R	Z	IC ₅₀ (μM)	
			AT ₁	AT ₂
26	H	COOH	0.048	10
27	3,6-di-Cl	COOH	0.018	6.5
28	4,5-di-Cl	COOH	0.170	1.0
29	H	CN	0.670	25
30	H	tetrazol-5-yl	0.078	>10

Table IV. AII (AT₁/AT₂) Receptor Antagonist Activity of N-Alkylated Dihydroindoles^a

compd	R	Z	IC ₅₀ (μM)	
			AT ₁	AT ₂
31	H	COOMe	0.170	16
32	H	COOH	0.082	14
33a	H	CN	0.350	11.5
33b	2-Me	CN	1.10	13
33c	3-Me	CN	1.60	10.5
33d	4-Me	CN	4.60	14
34	H	tetrazol-5-yl	0.018	>30

^a The asterisk on the structure refers to a racemic mixture (±).

5-yl in a nearly orthogonal plane to the amide bond which is coplanar with the top indole portion of 14b and 24.

A comparison of the IC₅₀ values of the N-acylated indoles (14a–c, 15, and 16; Table I) and dihydroindoles (26–30; Table III) shows that the indole series of AII antagonists is consistently more potent than the corresponding dihydroindole series at the AT₁ receptor subsite. The 3,6-dichloro-substituted dihydroindole compound 27 (AT₁ IC₅₀ = 18 nM) was found to be the most active AT₁ receptor antagonist in the dihydroindole series. The *in vitro* binding assay data described here suggest that the N-acylated and N-alkylated indole series of compounds are more effective biphenyl replacements for 3 than their corresponding dihydroindole analogs.

The *in vitro* binding affinities of 31–34, members of a structurally novel series of N-alkylated dihydroindoles, reveal that although the carboxylic acid analog 32 has shown moderate potency, the isosteric tetrazol-5-yl analog 34 (AT₁ IC₅₀ = 18 nM) is highly potent at the AT₁ receptor (Table IV). The SAR studies reported here strongly suggest that further modification of this distinct class of compounds by AT₁-potency-enhancing elements may also result in highly potent AII receptor antagonists.²⁰

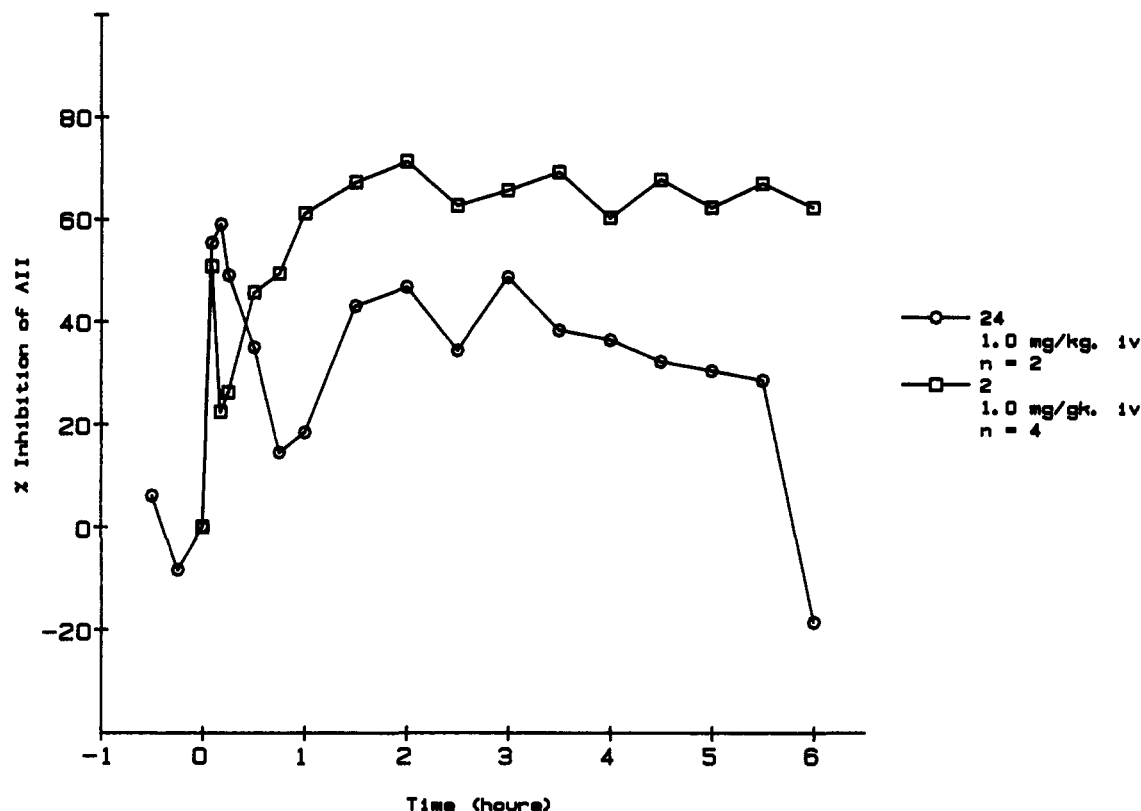


Figure 3. Comparison of the *in vivo* activity of 24 with 2 in conscious normotensive rats. Inhibition of AII-induced (0.1 $\mu\text{g}/\text{kg}$) pressor response after iv administration of 24 and 2 at a 1.0 mg/kg dose.

All the compounds reported here with the exception of 14c, 16, and 28 are AT_1 -selective AII receptor antagonists, since in the *in vitro* AT_2 receptor binding assay these compounds were found either very weakly active or completely inactive at concentrations $<20 \mu\text{M}$. Among the noteworthy AT_2 -active compounds 14c, 16, and 28, the tetrazole analog 16 ($\text{AT}_2 \text{IC}_{50} = 0.13 \mu\text{M}$) was found to be the most active AT_2 antagonist in both the indole and dihydroindole series. Comparison of the AT_2 (IC_{50}) potency of 14a with 14c in the indole series and that of 26 with 28 in the dihydroindole series reveals that the incorporation of 4,5-dichloro substitution in 14c and 28 results in a 4-fold increase in the AT_2 activity of 14c ($\text{IC}_{50} = 1.9 \mu\text{M}$) in the indole and a 10-fold increase in the AT_2 potency of 28 ($\text{IC}_{50} = 1 \mu\text{M}$) in the dihydroindole series of AII receptor antagonists. The improvement observed in the AT_2 potency of 28 as a result of the 4,5-dichloro substitution offers considerable potential for further development of these compounds (16 and 28) into a potent class of AT_2 -selective non-peptide AII receptor antagonists.¹⁹

The most potent compounds 14b ($\text{AT}_1 \text{IC}_{50} = 0.8 \text{ nM}$) and 24 ($\text{AT}_1 \text{IC}_{50} = 1 \text{ nM}$) were selected for *in vivo* evaluation. The *in vivo* activity was determined by measuring the inhibition of the pressor response to 0.1 $\mu\text{g}/\text{kg}$ iv infusion of AII in conscious normotensive rats.²⁰ While the AII antagonist 14b blocked the AII-induced pressor response for only 0.5 h (data not shown), 24 inhibited the AII-induced pressor response for 5.5 h after intravenous administration at 1.0 mg/kg to conscious normotensive rats (Figure 3). The longer duration of action displayed by the N-alkylated indole 24 may in part be due to the elimination of the labile amide bond present in the N-acylated indole 14b. In comparison with 2, 24 showed

slightly lower *in vivo* activity in conscious normotensive rats at 1.0 mg/kg iv (Figure 3).

Conclusion

We have developed a new class of non-peptide AII receptor antagonists which is derived from N-substituted indoles and dihydroindoles. These compounds (e.g., 14b and 24) are highly potent AII receptor antagonists and exhibit a high degree of selectivity for the AT_1 receptor. Incorporation of 3,6-dichloro substitution in the N-(2-carboxybenzoyl)indole series (14b) and 2-chloro substitution in the tetrazole-containing N-alkylated indole series (24) were the key potency-enhancing modifications. The carboxylic acid 14b ($\text{AT}_1 \text{IC}_{50} = 0.8 \text{ nM}$) and the tetrazole 24 ($\text{AT}_1 \text{IC}_{50} = 1 \text{ nM}$) were found to be the most potent AT_1 -selective AII antagonists in the N-substituted indole and dihydroindole series. In general, AII antagonists derived from N-substituted indoles exhibit higher *in vitro* AT_1 potency than their corresponding dihydroindole counterparts. N-alkylated indoles displayed better *in vivo* activity and longer duration of action in conscious normotensive rats than the N-acylated indoles (cf. 24 vs 14b).

In summary, we have demonstrated that N-substituted-indole- and dihydroindole-based moieties incorporated in 14, 16, 24, and 27 are efficient biphenyl tetrazole replacements for the potent AII receptor antagonist 3. This new class of compounds reported here offers a promising opportunity to design and develop a more potent and orally active series of AII receptor antagonists.^{21,22}

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 chro-

matography 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.

N-Benzoyl-5-methylindole (9) (Method A). To a solution of 5-methylindole (8) (1.0 g, 7.6 mmol) in 8 mL of CH_2Cl_2 were added 4-(dimethylamino)pyridine (DMAP) (0.186 g, 1.52 mmol), triethylamine (2.12 mL, 15.2 mmol), and benzoyl chloride (1 mL, 1.2 g, 8.6 mmol). The resulting solution was stirred for 16 h at room temperature. The solution was diluted with 500 mL of CH_2Cl_2 and washed with 200 mL of saturated aqueous NaHCO_3 solution and 200 mL of brine. The organic phase was dried over anhydrous MgSO_4 , filtered, and concentrated to a yellow oil. The resultant oil was flash chromatographed with 20% EtOAc in hexane yielding 1.73 g (96%) of 9: $R_f = 0.42$ (33% ethyl acetate/hexane); ^1H NMR (CDCl_3) δ 8.29 (d, 1H), 7.71 (d, 2H), 7.56 (d, 1H), 7.51 (d, 2H), 7.38 (s, 1H), 7.24 (d, 1H), 7.20 (d, 1H), 6.53 (d, 2H), 2.47 (s, 3H); FABMS m/e 236 ($M + 1$).

N-Benzoyl-5-(bromomethyl)indole (10). A suspension of 9 (5.5 g, 23.4 mmol) in 10 mL of CCl_4 was heated to reflux. *N*-Bromosuccinimide (4.6 g, 25.7 mmol) and azoisobutyronitrile (AIBN, 100 mg) were added to the refluxing CCl_4 solution of 9, and the resultant solution was stirred at reflux for 4 h. The solution was cooled, diluted with 1.5 L of CH_2Cl_2 , and washed with 400 mL of H_2O and 400 mL of brine. The organic phase was dried over MgSO_4 , filtered, and concentrated to a brown oil. The resultant oil was flash chromatographed with 10% EtOAc in hexane to afford 10 (5.6 g, 80%): $R_f = 0.47$ (20% ethyl acetate/hexane); ^1H NMR (CDCl_3) δ 8.35 (d, 1H), 7.73 (d, 2H), 7.63 (s, 1H), 7.61 (d, 1H), 7.55 (d, 2H), 7.41 (d, 1H), 7.33 (d, 1H), 7.33 (d, 1H), 6.60 (d, 1H), 4.66 (s, 2H); FABMS m/e 314 ($M + 1$).

3-[[N-(2-Benzoyl-5-indolyl)methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (12). To a solution of 5,7-dimethyl-2-ethyl-imidazo[4,5-b]pyridine (11)¹⁶ (1 g, 5.7 mmol) in 10 mL of DMF was added NaH (252 mg of a 60% dispersion in mineral oil, 6.3 mmol). After 5 min, 10 (2.33 g, 7.43 mmol) was added to the reaction mixture which was stirred for 2.5 h. DMF was removed *in vacuo* and the resultant brown oil was flash chromatographed with 65% EtOAc in hexane to yield 12 (1.74 g, 75%): $R_f = 0.52$ (100% ethyl acetate); ^1H NMR (CDCl_3) δ 8.31 (d, 1H), 7.70 (d, 2H), 7.58 (d, 1H), 7.52 (d, 2H), 7.28 (s, 1H), 7.26 (s, 1H), 7.22 (d, 1H), 6.90 (s, 1H), 6.49 (d, 1H), 5.59 (s, 2H), 2.80 (q, 2H), 2.65 (s, 3H), 2.61 (s, 3H), 1.30 (t, 3H); FABMS m/e 409 ($M + 1$).

3-[[5-Indolyl)methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (13). To a suspension of 12 (500 mg, 1.2 mmol) in 10 mL of MeOH was added 10 mL of 2 N NaOH, and the mixture was heated to 60 °C. After 18 h, MeOH was removed *in vacuo* and the reaction mixture was diluted with 150 mL of H_2O and then extracted with 3 \times 200 mL of CH_2Cl_2 . The combined extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated to yield 13 (377 mg, 100%) as a pale yellow powder: $R_f = 0.63$ (100% ethyl acetate); ^1H NMR (CD_3OD) δ 7.34 (d, 1H), 7.31 (s, 1H), 7.22 (d, 1H), 7.01 (s, 1H), 6.94 (d, 1H), 6.39 (d, 1H), 5.61 (s, 2H), 2.87 (q, 2H), 2.63 (s, 6H), 1.24 (t, 3H); FABMS m/e 305 ($M + 1$).

3-[[N-(2-Carboxybenzoyl)-5-indolyl)methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (14a) (Method B). To a solution of 13 (75 mg, 0.25 mmol) in 3 mL of DMF was added a 60% dispersion of NaH (11 mg, 0.27 mmol) in mineral oil followed by phthalic anhydride (45 mg, 0.30 mmol). This mixture was stirred for 16 h and the DMF removed *in vacuo*. The resultant oil was flash column chromatographed with 15% of a 10/1 mixture of MeOH/ NH_4OH in CHCl_3 to yield 14a (53 mg, 47%): $R_f = 0.35$ (80:20:2 chloroform/methanol/ NH_4OH); ^1H NMR (CD_3OD) δ 8.13 (d, 1H), 7.66–7.71 (m, 3H), 7.51 (d, 1H), 7.28 (s, 2H), 7.14–7.16 (m, 2H), 7.03 (s, 1H), 6.49 (d, 1H), 5.64 (s, 2H), 2.86 (q, 2H), 2.62 (s, 3H), 2.60 (s, 3H), 1.24 (t, 3H); FABMS m/e 453 ($M + 1$).

3-[[N-(2-Carboxy-3,6-dichlorobenzoyl)-5-indolyl)methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (14b). Carboxylic acid 14b was prepared in 64% yield from 13 and 3,6-dichlorophthalic anhydride using method B: $R_f = 0.24$ (85:15 chloroform/9:1 methanol/ NH_4OH); ^1H NMR (CD_3OD) δ 8.40 (d,

1H), 7.55 (d, 1H), 7.43 (d, 1H), 7.28 (s, 1H), 7.18 (d, 1H), 7.02 (s, 1H), 6.97 (d, 1H), 6.52 (d, 1H), 5.64 (s, 2H), 2.85 (q, 2H), 2.62 (s, 3H), 2.60 (s, 3H), 1.25 (t, 3H); FABMS m/e 521 ($M + 1$).

3-[[N-(2-Carboxy-4,5-dichlorobenzoyl)-5-indolyl)methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (14c). The title compound 14c was prepared in 59% yield from 13 and 4,5-dichlorophthalic anhydride by method B: $R_f = 0.28$ (85:15 chloroform/9:1 methanol/ NH_4OH); ^1H NMR (CD_3OD) δ 8.25 (s, 1H), 7.65 (s, 1H), 7.18 (d, 1H), 7.02 (s, 1H), 6.91 (m, 1H), 6.53 (d, 1H), 5.64 (s, 2H), 2.86 (q, 2H), 2.65 (s, 3H), 2.62 (s, 3H), 1.27 (t, 3H); FABMS m/e 521 ($M + 1$).

3-[[N-(2-Carboxy-3-nitrobenzoyl)-5-indolyl)methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (14d). 14d was prepared in 50% yield from 13 and 3-nitrophthalic anhydride according to method B: $R_f = 0.29$ (80:20:2 chloroform/methanol/ NH_4OH); ^1H NMR (CD_3OD) δ 8.46–8.51 (m, 3H), 7.89 (t, 3H), 7.31 (s, 1H), 7.24 (d, 1H), 7.06 (s, 1H), 6.92 (d, 1H), 6.50 (d, 1H), 5.68 (s, 2H), 2.91 (q, 2H), 2.63 (s, 3H), 2.62 (s, 3H), 1.29 (t, 3H); FABMS m/e 498 ($M + 1$).

3-[[N-(2-Cyanobenzoyl)-5-indolyl)methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (15) (Method C). To a solution of 13 (250 mg, 0.82 mmol) in 3 mL of DMF was added a 60% dispersion of NaH (39 mg, 1 mmol) in mineral oil and the mixture stirred for 5 min. 2-Cyanobenzoyl chloride (204 mg, 1.23 mmol) was added to the reaction mixture which was stirred for 16 h, and then, DMF was removed *in vacuo*. The resultant oil was flash chromatographed with 35% EtOAc in hexane to yield 15 (292 mg, 82%): $R_f = 0.46$ (5% methanol/ethyl acetate); ^1H NMR (CDCl_3) δ 8.30 (d, 1H), 7.84 (d, 1H), 7.64–7.73 (m, 3H), 7.23 (d, 2H), 6.99 (d, 1H), 6.89 (s, 1H), 6.52 (d, 1H), 5.56 (s, 2H), 2.78 (q, 2H), 2.63 (s, 3H), 2.58 (s, 3H), 1.29 (t, 3H); FABMS m/e 434 ($M + 1$).

3-[[N-(2-Tetrazol-5-ylbenzoyl)-5-indolyl)methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (16) (Method D). To a solution of 15 (75 mg, 0.17 mmol) in 5 mL of toluene was added Me_3SnN_3 (43 mg, 0.21 mmol). The mixture was heated at reflux for 18 h. Toluene was removed *in vacuo*, and the resultant oil was dissolved in 5 mL of THF and treated with 0.5 mL of 2.5 N HCl at 0 °C for 5 min. The volatiles were removed *in vacuo*, and the resultant oil was flash chromatographed with 15% of a 10/1 MeOH/ NH_4OH mixture in CHCl_3 to yield 16 (48 mg, 60%): $R_f = 0.21$ (80:20:2 chloroform/methanol/ NH_4OH); ^1H NMR (CD_3OD) δ 8.12 (br s, 1H), 7.96 (d, 1H), 7.55–7.70 (m, 3H), 7.20 (s, 1H), 7.08 (d, 1H), 6.98 (s, 1H), 6.87 (br s, 1H), 5.55 (s, 2H), 2.72 (q, 2H), 2.51 (s, 6H), 1.16 (t, 3H); FABMS m/e 477 ($M + 1$).

3-[[N-(2-(Carboxyamino)benzoyl)-5-indolyl)methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (17). The title compound 17 was prepared in 30% yield from 13 and isoic anhydride using method B: $R_f = 0.31$ (80:20:2 chloroform/methanol/ NH_4OH); ^1H NMR (CD_3OD) δ 8.47 (d, 1H), 8.31 (d, 1H), 8.10 (d, 1H), 7.86 (d, 1H), 7.42 (t, 1H), 7.29 (s, 1H), 7.13 (d, 1H), 7.08 (t, 1H), 7.03 (d, 1H), 6.62 (d, 1H), 5.63 (s, 2H), 2.86 (q, 2H), 2.61 (s, 3H), 2.57 (s, 3H), 1.24 (t, 3H); FABMS m/e 468 ($M + 1$).

3-[[N-(2-((Methoxycarbonyl)amino)benzoyl)-5-indolyl)methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (18). To a solution of 17 (12.2 mg, 0.026 mmol) in CH_2Cl_2 at 0 °C was added 0.2 mL of 10% (trimethylsilyl)diazomethane ($\text{Me}_3\text{SiCHN}_2$) and the mixture stirred for 0.25 h. Acetic acid (0.2 mL) was added, and the volatiles were removed *in vacuo*. Preparative TLC of the crude material using 50% ethyl acetate in hexane gave 18 (11.2 mg, 90%): $R_f = 0.76$ (100% ethyl acetate); ^1H NMR (CDCl_3) δ 11.80 (s, 1H), 8.71 (d, 1H), 8.37 (d, 1H), 8.19 (d, 1H), 7.73 (d, 1H), 7.62 (t, 1H), 7.23 (d, 1H), 7.17 (t, 1H), 6.94 (s, 1H), 6.62 (d, 1H), 5.52 (s, 2H), 3.98 (s, 3H), 2.84 (q, 2H), 2.62 (s, 3H), 2.59 (s, 3H), 1.27 (t, 3H); FABMS m/e 482 ($M + 1$).

3-[[N-(2-Carbomethoxybenzyl)-5-indolyl)methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (19). To a DMF solution of 13 (0.2 g, 0.66 mmol) was added NaH (29.5 mg, 0.73 mmol) as a 60% dispersion in mineral oil and the mixture stirred for 5 min. Methyl 2-(bromomethyl)benzoate (35) (0.182 g, 0.79 mmol) was added and the reaction mixture stirred for 18 h. The mixture was concentrated *in vacuo*, and the crude oil was flash chromatographed with 50% EtOAc in hexane to give 19 (0.275 g, 92%): $R_f = 0.67$ (100% ethyl acetate); ^1H NMR (CDCl_3) δ 8.02 (m, 1H), 7.39 (s, 1H), 7.24–7.33 (m, 2H), 7.10 (d, 1H), 7.08 (s, 1H),

6.99 (d, 1H), 6.89 (s, 1H), 6.50 (d, 2H), 6.42 (t, 1H), 5.74 (s, 2H), 5.57 (s, 2H), 3.92 (s, 3H), 2.82 (q, 2H), 2.63 (s, 3H), 2.59 (s, 3H), 1.32 (t, 3H); FABMS *m/e* 453 (M + 1).

Methyl 2-(Bromomethyl)benzoate (35). To a solution of methyl 2-methylbenzoate (2.3 g, 15.3 mmol) in 20 mL of refluxing CCl₄ were added NBS (3.0 g, 16.85 mmol) and 0.10 g of AIBN. After 2.5 h, the mixture was cooled, diluted with 500 mL of CH₂Cl₂, and washed with 200 mL of H₂O and 200 mL of brine. The organic phase was dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The resultant oil was flash chromatographed with 20% EtOAc in hexane to yield the title compound (2.56 g, 73%): *R*_f = 0.54 (15% ethyl acetate/hexane); ¹H NMR (CDCl₃) δ 7.97 (d, 1H), 7.51 (d, 1H), 7.48 (d, 1H), 7.39 (dd, 1H), 4.96 (s, 2H), 3.93 (s, 3H); FABMS *m/e* 230 (M + 1).

3-[[N-(2-Carboxybenzyl)-5-indolyl]methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (20). To a solution of 19 (75 mg, 0.17 mmol) in 3 mL of MeOH was added 2.0 mL of 1 N aqueous NaOH. The mixture was stirred for 16 h. The volatiles were removed *in vacuo*, and the remaining water was removed azeotropically with toluene. The clear oil was flash chromatographed with 85:15:1.5 CHCl₃/MeOH/NH₄OH to yield 20 (58 mg, 80%): *R*_f = 0.49 (80:20:2 chloroform/methanol/NH₄OH); ¹H NMR (CD₃OD) δ 7.89 (d, 1H), 7.31 (s, 1H), 7.17–7.25 (m, 4H), 7.00 (s, 1H), 6.93 (d, 1H), 6.44 (s, 1H), 6.43 (d, 1H), 5.74 (s, 2H), 5.60 (s, 2H), 2.86 (q, 2H), 2.61 (s, 3H), 2.60 (s, 3H), 1.21 (t, 3H); FABMS *m/e* 439 (M + 1).

3-[[N-(2-Cyanobenzyl)-5-indolyl]methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine 21 (Method E). To a solution of 13 (75 mg, 0.25 mmol) in 3 mL of DMF was added NaH (11 mg, 0.27 mmol) followed by α-bromo-*o*-tolunitrile (58 mg, 0.30 mmol). The mixture was stirred for 16 h and then concentrated *in vacuo*. The resultant oil was flash chromatographed with 50% EtOAc in hexane to yield 21 (98 mg, 95%): *R*_f = 0.64 (100% ethyl acetate); ¹H NMR (CDCl₃) δ 7.68 (d, 1H), 7.31–7.45 (m, 3H), 7.02 (d, 1H), 6.98 (s, 1H), 6.76 (d, 1H), 6.50 (d, 1H), 5.56 (s, 2H), 5.49 (s, 2H), 2.83 (q, 2H), 2.61 (s, 3H), 2.58 (s, 3H), 1.29 (t, 3H); FABMS *m/e* 420 (M + 1).

3-[[N-(2-Tetrazol-5-ylbenzyl)-5-indolyl]methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (22). The title tetrazole 22 was prepared in 55% yield from 21 using method D: *R*_f = 0.27 (80:20:2 chloroform/methanol/NH₄OH); ¹H NMR (CD₃OD) δ 7.76 (s, 1H), 7.73 (d, 1H), 7.39 (t, 1H), 7.32 (d, 1H), 7.12 (d, 1H), 7.10 (d, 1H), 7.01 (s, 1H), 6.92 (dd, 1H), 6.73 (d, 1H), 6.41 (d, 1H), 5.69 (s, 2H), 5.60 (s, 2H), 2.87 (q, 2H), 2.62 (s, 3H), 2.61 (s, 3H), 1.22 (t, 3H); FABMS *m/e* 463 (M + 1).

3-[[N-(2-Cyano-6-chlorobenzyl)-5-indolyl]methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (23). The title nitrile 23 was prepared in 87% yield by alkylation of 13 with 36 according to method E: *R*_f = 0.53 (100% ethyl acetate); ¹H NMR (CDCl₃) δ 7.63 (d, 2H), 7.40 (t, 1H), 7.34 (d, 1H), 7.31 (s, 1H), 7.01 (m, 2H), 6.87 (s, 1H), 6.40 (d, 1H), 5.52 (s, 2H), 2.78 (q, 2H), 2.61 (s, 3H), 2.58 (s, 3H), 1.26 (t, 3H); FABMS *m/e* 454 (M + 1).

2-Chloro-6-cyanobenzyl Bromide (36). To a refluxing solution of 3-chloro-2-methylbenzonitrile (2.0 g, 13.2 mmol) in 20 mL of CCl₄ were added NBS (2.6 g, 14.4 mmol) and 0.2 g of AIBN. The solution was refluxed for 3 h and then cooled, diluted with 500 mL of CH₂Cl₂, and washed with 200 mL of H₂O and 200 mL of brine. The organic phase was dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The resultant oil was flash chromatographed with 20% EtOAc in hexane to yield 36 (1.4 g, 46%) as a yellow oil: *R*_f = 0.56 (25% ethyl acetate/hexane); ¹H NMR (CDCl₃) δ 7.63 (dd, 1H), 7.58 (dd, 1H), 7.37 (t, 1H), 4.74 (s, 2H); FABMS *m/e* 230 (M + 1).

3-[[N-(2-Tetrazol-5-yl-6-chlorobenzyl)-5-indolyl]methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (24). The tetrazole 24 was prepared in 64% yield from 23 by method D: *R*_f = 0.24 (80:20:2 chloroform/methanol/NH₄OH); ¹H NMR (CD₃OD) δ 7.61 (d, 1H), 7.57 (d, 1H), 7.46 (t, 1H), 7.21 (s, 1H), 7.12 (d, 1H), 7.06 (s, 1H), 6.89 (dd, 1H), 6.72 (d, 1H), 6.18 (d, 1H), 5.69 (s, 2H), 5.58 (s, 2H), 2.87 (q, 2H), 2.61 (s, 3H), 2.59 (s, 3H), 1.19 (s, 3H); FABMS *m/e* 497 (M + 1).

3-[(2,3-Dihydroindol-5-yl)methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (25). To a solution of 13 (500 mg, 1.64 mmol) in 4 mL of AcOH was slowly added NaCNBH₃ (114 mg, 1.8 mmol). After 0.75 h, the reaction was diluted with 150 mL of H₂O and neutralized carefully with an aqueous solution

of saturated NaHCO₃. The pH of the mixture was adjusted to 9 with the addition of NaOH, and then, the mixture was extracted with 3 × 200 mL of CH₂Cl₂. The combined extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Flash column chromatography of the crude material with EtOAc gave 25 (377 mg, 75%) and the starting material 13 (115 mg, 23%). 25: *R*_f = 0.46 (100% ethyl acetate); ¹H NMR (CDCl₃) δ 6.88 (s, 2H), 6.83 (d, 1H), 6.52 (d, 1H), 5.34 (s, 2H), 3.75 (br s, 1H), 3.51 (t, 2H), 2.92 (t, 2H), 2.80 (q, 2H), 2.62 (s, 3H), 2.60 (s, 3H), 1.30 (t, 3H); FABMS *m/e* 307 (M + 1).

3-[[N-(2-Carboxybenzyl)-2,3-dihydroindol-5-yl]methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (26) (Method F). To a solution of 25 (153 mg, 0.5 mmol) in 10 mL of CH₂Cl₂ were added phthalic anhydride (112 mg, 0.75 mmol) and DMAP (62 mg, 0.5 mmol). The reaction mixture was stirred for 2 h and then concentrated *in vacuo*. The resultant oil was flash chromatographed with 85:15:1.5 CHCl₃/MeOH/NH₄OH to yield 26 (175 mg, 77%): *R*_f = 0.39 (80:20:2 chloroform/methanol/NH₄OH); ¹H NMR (CD₃OD) δ 8.10 (d, 1H), 7.62 (t, 2H), 7.46 (m, 2H), 7.31 (s, 1H), 6.89 (m, 2H), 5.42 (s, 2H), 3.57 (t, 2H), 2.88 (t, 2H), 2.77 (q, 2H), 2.56 (s, 3H), 2.51 (s, 3H), 1.27 (t, 3H); FABMS *m/e* 455 (M + 1).

3-[[N-(2-Carboxy-3,6-dichlorobenzyl)-2,3-dihydroindol-5-yl]methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (27). Treatment of 25 (150 mg, 0.49 mmol) with 3,6-dichlorophthalic anhydride (160 mg, 0.74 mmol) and DMAP (61 mg, 0.5 mmol) according to method F gave 27 (195 mg, 76%): *R*_f = 0.22 (85:15 chloroform/9:1 methanol/NH₄OH); ¹H NMR (CD₃OD) δ 8.12 (d, 1H), 7.70 (s, 1H), 7.55–7.37 (m, 2H), 7.05 (2 overlapping s, 2H), 5.50 (s, 2H), 4.05 (m, 1H), 3.82 (m, 1H), 3.10 (m, 2H), 2.875 (q, 2H), 2.64 (s, 3H), 2.605 (s, 3H), 1.30 (t, 3H); FABMS *m/e* 523 (M + 1).

3-[[N-(2-Carboxy-4,5-dichlorobenzyl)-2,3-dihydroindol-5-yl]methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (28). The title compound 28 was prepared in 72% yield from 25 and 4,5-dichlorophthalic anhydride according to method F: *R*_f = 0.20 (85:15 chloroform/9:1 methanol/NH₄OH); ¹H NMR (CD₃OD) δ 8.11 (m, 2H), 7.45 (s, 1H), 6.98 (d, 1H), 6.95 (s, 1H), 6.94 (d, 1H), 5.48 (s, 2H), 3.705 (t, 2H), 2.98 (t, 2H), 2.84 (q, 2H), 2.62 (s, 3H), 2.585 (s, 3H), 1.294 (t, 3H); FABMS *m/e* 523 (M + 1).

3-[[N-(2-Cyanobenzyl)-2,3-dihydroindol-5-yl]methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (29). To a solution of 25 (130 mg, 0.425 mmol) in 10 mL of CH₂Cl₂ were added 2-cyanobenzoyl chloride (110 mg, 0.665 mmol) and DMAP (52 mg, 0.425 mmol). The reaction mixture was stirred for 1 h and then diluted with 200 mL of CH₂Cl₂ and washed with 100 mL each of an aqueous saturated solution of NaHCO₃ and brine. The organic phase was dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*. The resultant oil was flash chromatographed with EtOAc to yield 29 (120 mg, 65%): *R*_f = 0.32 (100% ethyl acetate); ¹H NMR (CDCl₃) δ 8.20 (d, 1H), 7.65–7.78 (m, 2H), 7.64 (d, 2H), 7.13 (d, 1H), 6.88 (s, 2H), 5.46 (s, 2H), 3.87 (t, 2H), 3.17 (t, 2H), 2.79 (q, 2H), 2.63 (s, 3H), 2.58 (s, 3H), 1.28 (t, 3H); FABMS *m/e* 436 (M + 1).

3-[[N-(2-Tetrazol-5-ylbenzyl)-2,3-dihydroindol-5-yl]methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (30). The tetrazole 30 was prepared in 55% yield from 29 by method D: *R*_f = 0.29 (80:20:2 chloroform/methanol/NH₄OH); ¹H NMR (CD₃OD) δ 8.10 (d, 1H), 7.91–7.99 (m, 2H), 7.60–7.72 (m, 2H), 7.57 (d, 1H), 7.04 (s, 1H), 7.00 (s, 1H), 5.53 (s, 2H), 3.76 (t, 2H), 2.99 (t, 2H), 2.90 (q, 2H), 2.61 (s, 3H), 2.59 (s, 3H), 1.29 (t, 3H); FABMS *m/e* 479 (M + 1).

3-[[N-(Carbomethoxyphenyl)methyl]-2,3-dihydroindol-5-yl]methyl]-5,7-dimethyl-2-ethyl-3H-imidazo[4,5-b]pyridine (31). To a solution of 25 (147 mg, 0.48 mmol) in DMF was added NaH (23 mg of a 60% dispersion in oil, 0.57 mmol) and the mixture stirred for 15 min. Methyl 2-bromophenylacetate (165 mg, 0.72 mmol) was added to the reaction mixture, which was stirred for 24 h. The DMF was removed *in vacuo*, and the residue was flash chromatographed with 60% EtOAc in hexane to afford 31 (200 mg, 92%) as a racemic (R + S) mixture: *R*_f = 0.52 (33% ethyl acetate/hexane); ¹H NMR (CDCl₃) δ 7.35 (s, 5H), 6.86 (d, 1H), 6.34 (2 overlapping s, 2H), 6.31 (d, 1H), 5.33 (s, 2H), 5.225 (s, 1H), 3.73 (s, 3H), 3.13–3.04 (m, 1H), 2.88–2.75

(m, 1H), 2.8 (q, 2H), 2.73 (m, 2H), 2.63 (s, 3H), 2.6 (s, 3H), 1.3 (t, 3H); FABMS *m/e* 455 (M + 1).

3-[[*N*-(Carboxyphenylmethyl)-2,3-dihydroindol-5-yl]-methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (32). Methyl ester 31 (160 mg, 0.35 mmol) was treated with 1 N aqueous NaOH in MeOH for 24 h. The volatiles were removed *in vacuo*, and the residue was flash chromatographed with 15% of a 9/1 MeOH/NH₄OH mixture in CHCl₃ to give the racemic 32 (106 mg, 82%): *R_f* = 0.21 (85:15 chloroform/9:1 methanol/NH₄OH); ¹H NMR (CD₃OD) δ 7.73 (m), 7.63 (m), 7.5–7.27 (m), 7.2–6.96 (m), 6.35 (d), 6.2 (d), 5.65 (d), 3.69 (m, 2H), 3.58 (m, 2H), 2.89 (q, 2H), 2.66 (s, 3H), 2.65 (s, 3H), 1.32 (t, 3H); FABMS *m/e* 441 (M + 1).

3-[[*N*-(Cyanophenylmethyl)-2,3-dihydroindol-5-yl]-methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (33a) (Method G). A mixture of 25 (125 mg, 0.382 mmol), benzaldehyde (0.25 mL, 2.46 mmol), and KCN (185 mg, 1.14) in AcOH and MeOH was stirred for 72 h. The volatiles were removed *in vacuo*, and the resultant solid was flash chromatographed with 50% EtOAc in hexane to afford 33a (150 mg, 92%) as a racemate: *R_f* = 0.47 (50% ethyl acetate/hexane); ¹H NMR (CDCl₃) δ 7.58 (d, 2H), 7.427 (m, 3H), 6.94 (d, 1H), 6.902 (2 overlapping s, 2H), 6.533 (d, 1H), 5.697 (s, 1H), 5.381 (s, 2H), 3.33–3.14 (m, 2H), 2.98–2.3 (m, 2H), 2.85 (q, 2H), 2.62 (s, 3H), 2.602 (s, 3H), 1.307 (t, 3H); FABMS *m/e* 422 (M + 1).

3-[[*N*-(Cyano-*o*-tolylmethyl)-2,3-dihydroindol-5-yl]-methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (33b). The racemic nitrile 33b was prepared in 42% yield from 25 and *o*-tolualdehyde as described in method G: *R_f* = 0.42 (50% ethyl acetate/hexane); ¹H NMR (CDCl₃) δ 7.653 (d, 1H), 7.4–7.15 (m, 3H), 6.985 (d, 1H), 6.897 (2 overlapping s, 2H), 6.633 (d, 1H), 5.731 (s, 1H), 5.382 (s, 2H), 3.28–3.16 (m, 1H), 3.0 (dt, 1H), 2.95–2.7 (m, 2H), 2.8545 (q, 2H), 2.62 (s, 3H), 2.602 (s, 3H), 2.343 (s, 3H), 1.327 (t, 3H); FABMS *m/e* 436 (M + 1).

3-[[*N*-(Cyano-*m*-tolylmethyl)-2,3-dihydroindol-5-yl]-methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (33c). Nitrile 33c was prepared as a racemic mixture in 52% yield from 25 and *m*-tolualdehyde according to method G: *R_f* = 0.43 (50% ethyl acetate/hexane); ¹H NMR (CDCl₃) δ 7.35 (d, 1H), 7.285 (t, 1H), 7.18 (d, 1H), 6.92 (d, 1H), 6.87 (2 overlapping s, 2H), 6.5 (d, 1H), 5.63 (s, 1H), 5.36 (s, 2H), 3.26–3.13 (m, 2H), 2.92–2.85 (m, 2H), 2.825 (q, 2H), 2.62 (s, 3H), 2.585 (s, 3H), 2.37 (s, 3H), 1.3 (t, 3H); FABMS *m/e* 436 (M + 1).

3-[[*N*-(Cyano-*p*-tolylmethyl)-2,3-dihydroindol-5-yl]-methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (33d). The title compound 33d was prepared as a racemic mixture in 54% yield from 25 and *p*-tolualdehyde according to method G: *R_f* = 0.35 (50% ethyl acetate/hexane); ¹H NMR (CDCl₃) δ 7.425 (d, 2H), 7.21 (d, 2H), 6.915 (d, 1H), 6.86 (s, 2H), 6.52 (d, 1H), 5.63 (s, 1H), 5.36 (s, 2H), 3.26–3.1 (m, 2H), 2.93–2.83 (m, 2H), 2.78 (q, 2H), 2.61 (s, 3H), 2.57 (s, 3H), 2.35 (s, 3H), 1.3 (t, 3H); FABMS *m/e* 436 (M + 1).

3-[[*N*-(Tetrazol-5-ylphenylmethyl)-2,3-dihydroindol-5-yl]-methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (34). The tetrazole 34 was prepared as a racemic mixture from nitrile 33a in 52% yield according to method D: *R_f* = 0.19 (85:15 chloroform/9:1 methanol/NH₄OH); ¹H NMR (CDCl₃) δ 7.43–7.27 (m, 5H), 7.05 (s, 1H), 6.9 (s, 1H), 6.83 (d, 1H), 6.32 (d, 1H), 6.18 (s, 1H), 5.65 (s), 5.43 (s, 2H), 3.73–3.58 (m), 3.55–3.3 (m), 3.3–3.15 (m), 2.88 (q, 2H), 2.65 (s, 6H), 1.3 (t, 3H); FABMS *m/e* 465 (M + 1).

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