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* AT_1 (rabbit aorta) and AT_2 (rat midbrain) binding assay. The carboxylic acid 3-[[*N*-(2-carboxy-3,6-dichlorobenzoyl)-5-indolyl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (**14b**) was found to be the most potent AT_1 (IC_{50} = 0.8 nM) antagonist in the N-acylated indole series and displayed a 25-fold higher potency than the parent unsubstituted derivative **14a** (AT_1 IC_{50} = 20 nM) and a 22-fold greater potency than the corresponding dihydroindole analog **27** (AT_1 IC_{50} = 18 nM). Replacement of the terminal carboxyl (COOH) of **14a** with the bioisostere tetrazole in **16** (AT_1 IC_{50} = 5 nM, AT_2 IC_{50} = 130 nM) not only improved the AT_1 potency by 4-fold but also resulted in a 50-fold increase in AT_2 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-3*H*-imidazo[4,5-*b*]pyridine (**24**) exhibited the highest AT_1 (IC_{50} = 1 nM) activity, revealing a 230-fold increase in AT_1 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** (AT_1 IC_{50} = 8.7 nM). Tetrazole **34** was identified as the most potent (AT_1 IC_{50} = 18 nM) AT_1 receptor antagonist in a structurally distinct series of compounds derived from N-alkylation of dihydroindole **25**. A new class of highly potent (**14b**, AT_1 IC_{50} = 0.8 nM; **24**, AT_1 IC_{50} = 1 nM) AT_1-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 therapeutic and commercial success of the ACE inhibitors[7] such as captopril, enalapril, and lisinopril has intensified the interest in the development of renin inhibitors[8] 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 occuring 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 [Sar[1],Ala[8]]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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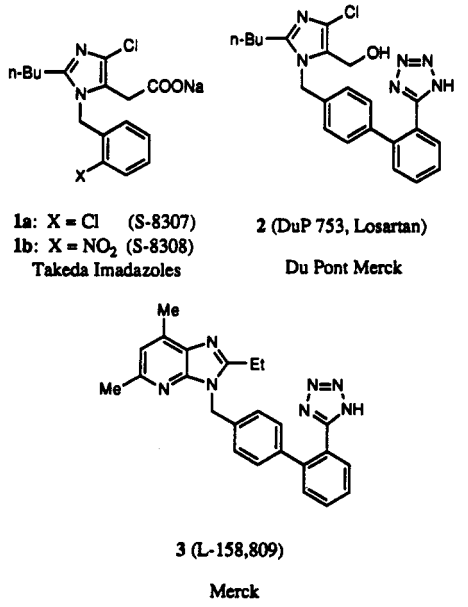


Figure 1. Non-peptide angiotensin II receptor antagonists.

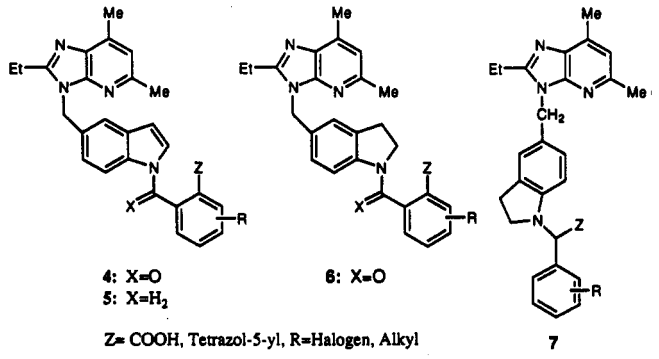


Figure 2. N-Substituted-indole- and -dihydroindole-based AII receptor antagonists.

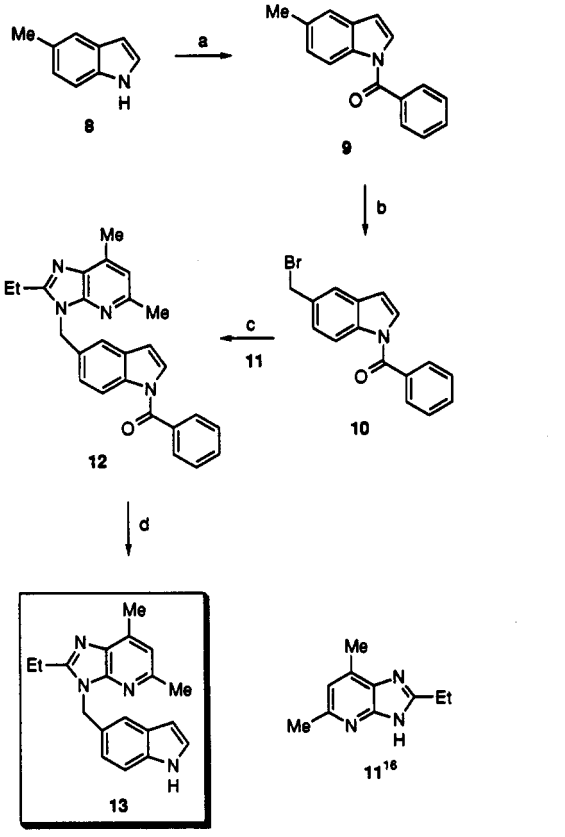
has attracted much current attention.[6,9] The first report on the non-peptidic AII antagonists, of which benzyl-substituted imidazoles **1a** (S-8307) and **1b** (S-8308) are examples, was disclosed by Takeda.[13] Structural modifications of the Takeda lead compounds by Du Pont have recently led to 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)biphenyl-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)biphenyl-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 AT_1-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 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-benzoylation 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/H_2O) provided the pivotal common intermediate **13** (Scheme I).

Scheme I. Synthesis of a Common Intermediate, **13**[a]

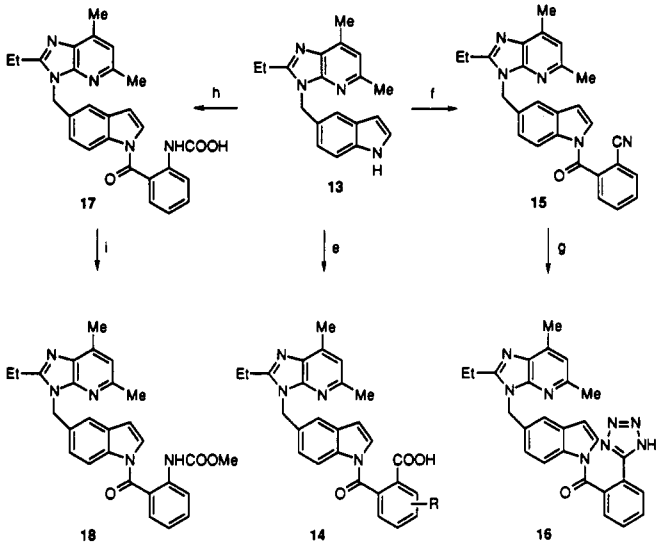


[a] Conditions: (a) PhCOCl, Et_3N, DMAP, CH_2Cl_2 (96%); (b) NBS, AIBN, CCl_4, reflux (78%); (c) **11**, NaH, DMF (78%); (d) NaOH, MeOH (95%).

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 (Me_3SnN_3) 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 ($TMSCHN_2$) afforded methyl carbamate **18** (Scheme II).

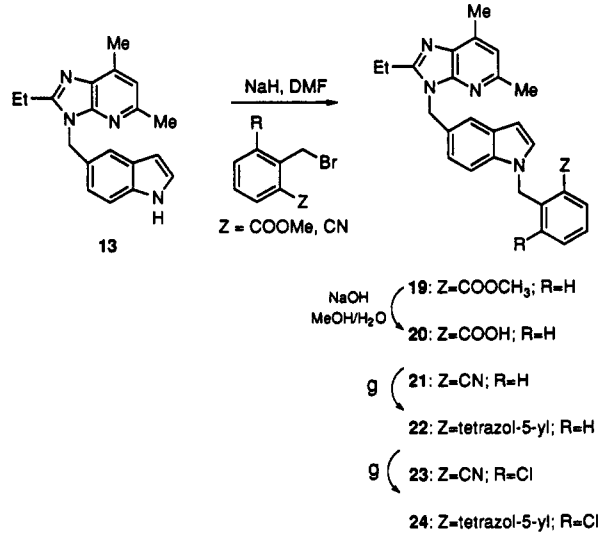
The N-alkylated indoles **19–24** were prepared by alkylating **13** with the appropriately functionalized aryl bromide using NaH/DMF (Scheme III).

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) Me_3SnN_3, toluene, reflux (60%); (h) NaH, DMF, isatoic anhydride (76%); (i) Me_3SiCHN_2, toluene (92%).

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



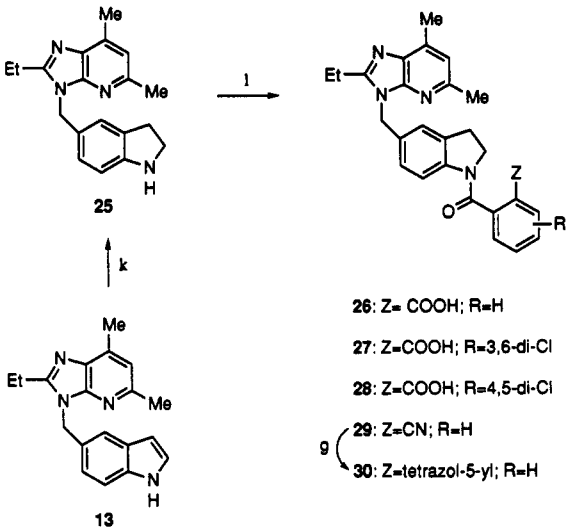
The intermediate **13** was reduced to the corresponding dihydroindole derivative **25** using $NaCNBH_3$ in AcOH. Acylation of dihydroindole **25** with acid chlorides or anhydrides yielded the corresponding *N*-acyl dihydroindoles **26–30** (Scheme IV). The tetrazole **30** was obtained from the nitrile derivative **29** which in turn was prepared by treatment of **25** with 2-cyanobenzoyl chloride in TEA/DMAP/CH_2Cl_2.

The dihydroindole derivative **25** was alkylated with methyl α-bromophenylacetate ($PhCHBrCO_2Me$) 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 (Me_3SnN_3)[14c] in toluene (Scheme V).

Biological Results and Discussion

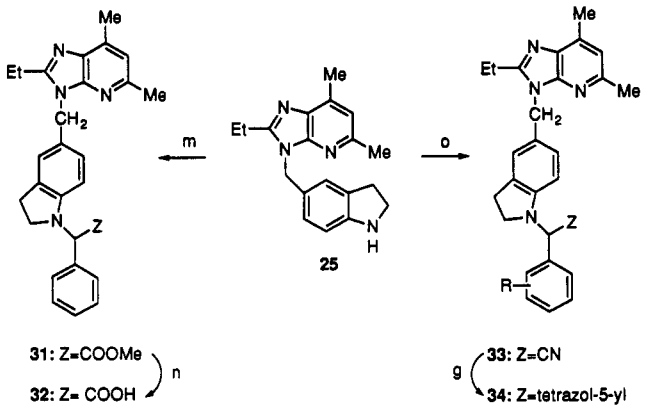
The *in vitro* ^{125}I-[Sar^1,Ile^8]AII binding assays of compounds **12–34** reported in this study (Tables I–IV) were performed as described by Chang et al. using rabbit aorta

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



[a] Conditions: (k) $NaCNBH_3$, AcOH; (l) Et_3N, DMAP, acid anhydride or ArCOCl, CH_2Cl_2.

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



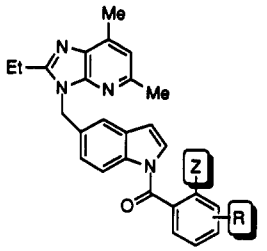
[a] Conditions: (m) NaH, DMF, $C_6H_5CHBrCO_2Me$; (n) NaOH, $MeOH/H_2O$; (o) ArCHO, KCN, AcOH, MeOH; (g) Me_3SnN_3, toluene, reflux.

and rat midbrain as receptor sources for the AT_1 and AT_2 receptors, respectively.[18] The relative potencies of the antagonists are expressed as the inhibitory concentration (IC_{50} values) of the test compound required to completely displace 50% of the specifically bound^{125}I-[Sar^1,Ile^8]AII from the receptor.[18]

Results of the *in vitro* AII (AT_1) binding assay of the N-benzoylated indoles shown in Table I demonstrate that the incorporation of nonacidic functional groups such as H, CN, and $NHCO_2CH_3$ in the ortho position of the benzoyl moiety of **4** affords AII antagonists with only moderate potency at the AT_1 receptor. However, the introduction of the acidic functional groups such as CO_2H and its bioisosteric tetrazol-5-yl results in potent AT_1-selective AII receptor antagonists **14a** (AT_1 IC_{50} = 20 nM) and **17** (AT_1 IC_{50} = 5 nM). An antagonist with a marked (25-fold) increase in AT_1 potency was discovered when 3,6-dichloro substitution was incorporated into the unsubstituted carboxylic acid analog **14a** to give **14b** (IC_{50} = 0.8 nM). The 4,5-dichloro analog was slightly more potent than **14a** but nearly 19-fold less active than **14b** at the AT_1 receptor.

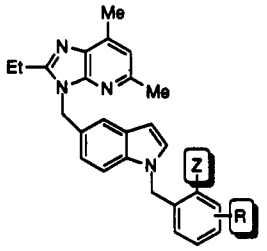
The N-alkylated indole-based AII antagonists were synthesized to alleviate the potentially hydrolyzable amide

Table I. AII (AT_1/AT_2) Receptor Antagonist Activity of N-Acylated Indoles



compd	R	Z	IC_{50} (μM) AT_1	IC_{50} (μM) 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 (AT_1/AT_2) Receptor Antagonist Activity of N-Alkylated Indoles

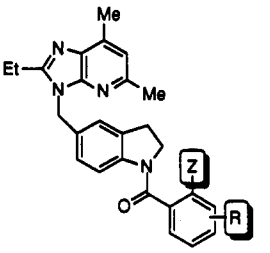


compd	R	Z	IC_{50} (μM) AT_1	IC_{50} (μM) AT_2
19	H	COOMe	0.62	21
20	H	COOH	0.23	>30
21	H	CN	0.32	>30
22	H	tetrazol-5-yl	0.0087	>18
23	6-Cl	CN	0.12	>30
24	6-Cl	tetrazol-5-yl	0.001	12
2 (DuP 753)			0.054[a]	>30
3 (L-158,809)			0.00054[a]	>10

[a] Data from ref 18.

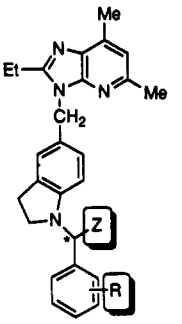
bond present in the N-benzoylated series of AII receptor antagonists (**12–18**). Examination of the IC_{50} values of the N-alkylated indole series (Table II) revealed that although the acid analog **20** was moderately active, the tetrazol-5-yl derivative **22** was nearly equipotent to its corresponding 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 AT_1 potency enhancement, the introduction of only one *o*-chlorine (6-Cl) substituent caused nearly a 9-fold enhancement in the AT_1 potency of the tetrazol-5-yl analog **24** (AT_1 IC_{50} = 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 AT_1 binding assay. The increase in AT_1 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 AT_1 receptor as a result of the *o*-chloro substitution, which orients the bottom phenyl ring bearing the 2-COOH or the 2-tetrazol-5-yl in a nearly orthogonal plane to the amide bond which is coplanar with the top indole portion of **14b** and **24**.

Table III. AII (AT_1/AT_2) Receptor Antagonist Activity of N-Acylated Dihydroindoles



compd	R	Z	IC_{50} (μM) AT_1	IC_{50} (μM) 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 (AT_1/AT_2) Receptor Antagonist Activity of N-Alkylated Dihydroindoles[a]



compd	R	Z	IC_{50} (μM) AT_1	IC_{50} (μM) 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 (±).

A comparison of the IC_{50} 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 AT_1 receptor subsite. The 3,6-dichloro-substituted dihydroindole compound **27** (AT_1 IC_{50} = 18 nM) was found to be the most active AT_1 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** (AT_1 IC_{50} = 18 nM) is highly potent at the AT_1 receptor (Table IV). The SAR studies reported here strongly suggest that further modification of this distinct class of compounds by AT_1-potency-enhancing elements may also result in highly potent AII receptor antagonists.[20]

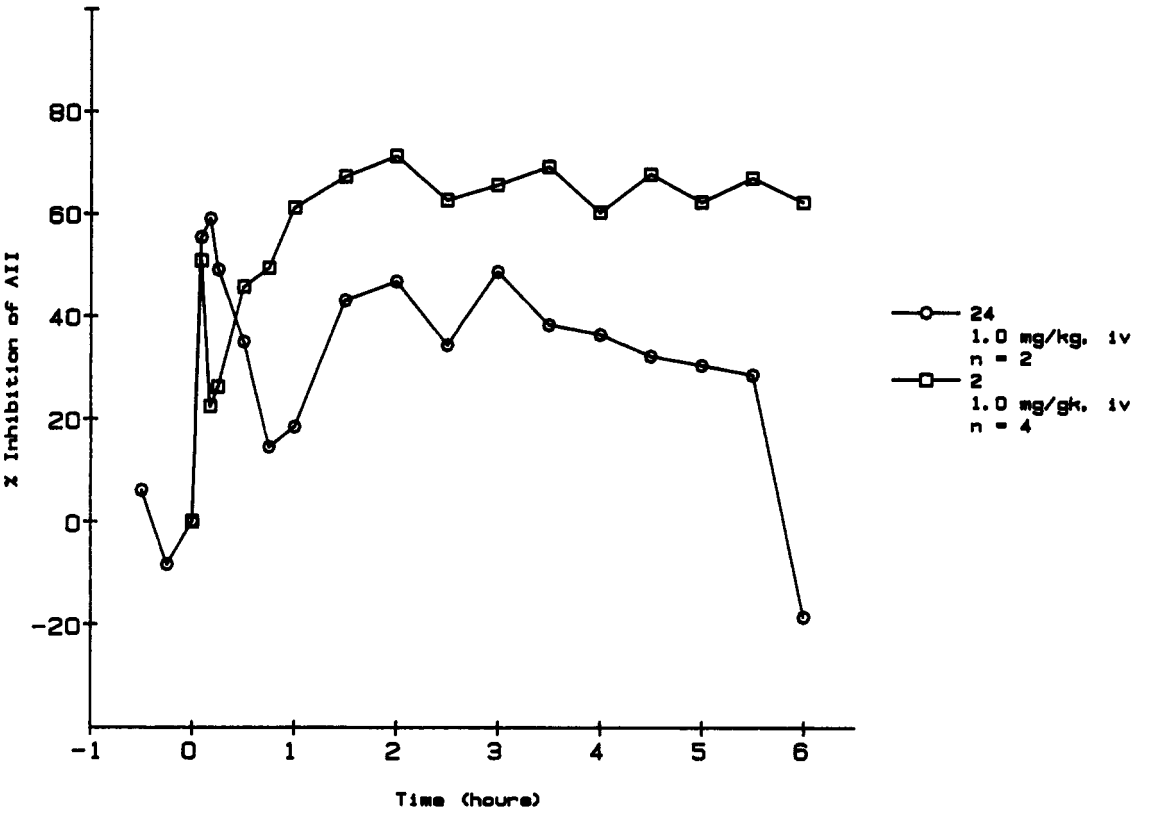


Figure 3. Comparison of the *in vivo* activity of **24** with **2** in conscious normotensive rats. Inhibition of AII-induced (0.1 μg/kg) pressor response after iv administration of **24** and **2** at a 1.0 mg/kg dose.

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 μM. Among the noteworthy AT_2-active compounds **14c**, **16**, and **28**, the tetrazole analog **16** (AT_2 IC_{50} = 0.13 μM) 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** (IC_{50} = 1.9 μM) in the indole and a 10-fold increase in the AT_2 potency of **28** (IC_{50} = 1 μM) 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** (AT_1 IC_{50} = 0.8 nM) and **24** (AT_1 IC_{50} = 1 nM) were selected for in *vivo* evaluation. The *in vivo* activity was determined by measuring the inhibition of the pressor response to 0.1 μg/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** (AT_1 IC_{50} = 0.8 nM) and the tetrazole **24** (AT_1 IC_{50} = 1 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). ^{1}H NMR spectra were recorded on Varian XL-300 and Varian XL-400 spectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts for ^{1}H 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); ^{1}H 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); ^{1}H 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*-Benzoyl-5-indolyl)methyl]-5,7-dimethyl-2-ethyl-3*H*-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); ^{1}H 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-3*H*-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 × 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); ^{1}H 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-3*H*-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); ^{1}H 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-3*H*-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); ^{1}H 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-3*H*-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); ^{1}H 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-3*H*-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); ^{1}H 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-3*H*-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); ^{1}H 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-3*H*-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); ^{1}H 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-3*H*-imidazo[4,5-*b*]pyridine (17). The title compound **17** was prepared in 30% yield from **13** and isatoic anhydride using method B: R_f = 0.31 (80:20:2 chloroform/methanol/NH_4OH); ^{1}H 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-3*H*-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 (Me_3SiCHN_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); ^{1}H 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-3*H*-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); ^{1}H 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 CCl_4 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 CH_2Cl_2, and washed with 200 mL of H_2O and 200 mL of brine. The organic phase was dried over anhdrous $MgSO_4$, 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); ^{1}H NMR ($CDCl_3$) 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-3*H*-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 $CHCl_3$/MeOH/NH_4OH to yield **20** (58 mg, 80%): R_f = 0.49 (80:20:2 chloroform/methanol/NH_4OH); ^{1}H NMR (CD_3OD) 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-3*H*-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); ^{1}H NMR ($CDCl_3$) 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-3*H*-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/NH_4OH); ^{1}H NMR (CD_3OD) 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-3*H*-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); ^{1}H NMR ($CDCl_3$) 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 CCl_4 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 CH_2Cl_2, and washed with 200 mL of H_2O and 200 mL of brine. The organic phase was dried over anhydrous $MgSO_4$, 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); ^{1}H NMR ($CDCl_3$) 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-3*H*-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/NH_4OH); ^{1}H NMR (CD_3OD) 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-3*H*-imidazo[4,5-*b*]pyridine (25). To a solution of **13** (500 mg, 1.64 mmol) in 4 mL of AcOH was slowly added $NaCNBH_3$ (114 mg, 1.8 mmol). After 0.75 h, the reaction was diluted with 150 mL of H_2O and neutralized carefully with an aqueous solution of saturated $NaHCO_3$. 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 CH_2Cl_2. The combined extracts were dried over Na_2SO_4, 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); ^{1}H NMR ($CDCl_3$) 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-Carboxybenzoyl)-2,3-dihydroindol-5-yl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (26) (Method F). To a solution of **25** (153 mg, 0.5 mmol) in 10 mL of CH_2Cl_2 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 $CHCl_3$/MeOH/NH_4OH to yield **26** (175 mg, 77%): R_f = 0.39 (80:20:2 chloroform/methanol/NH_4OH); ^{1}H NMR (CD_3OD) 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-dichlorobenzoyl)-2,3-dihydroindol-5-yl]methyl]-5,7-dimethyl-2-ethyl-3*H*-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/NH_4OH); ^{1}H NMR (CD_3OD) 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-dichlorobenzoyl)-2,3-dihydroindol-5-yl]methyl]-5,7-dimethyl-2-ethyl-3*H*-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/NH_4OH); ^{1}H NMR (CD_3OD) 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-Cyanobenzoyl)-2,3-dihydroindol-5-yl]methyl]-5,7-dimethyl-2-ethyl-3*H*-imidazo[4,5-*b*]pyridine (29). To a solution of **25** (130 mg, 0.425 mmol) in 10 mL of CH_2Cl_2 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 CH_2Cl_2 and washed with 100 mL each of an aqueous saturated solution of $NaHCO_3$ and brine. The organic phase was dried over anhydrous $MgSO_4$, 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); ^{1}H NMR ($CDCl_3$) 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-ylbenzoyl)-2,3-dihydroindol-5-yl]methyl]-5,7-dimethyl-2-ethyl-3*H*-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/NH_4OH); ^{1}H NMR (CD_3OD) 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*-(Carbomethoxyphenylmethyl)-2,3-dihydroindol-5-yl]methyl]-5,7-dimethyl-2-ethyl-3*H*-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); ^{1}H NMR ($CDCl_3$) 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/NH_4OH mixture in $CHCl_3$ to give the racemic **32** (106 mg, 82%): R_f = 0.21 (85:15 chloroform/9:1 methanol/NH_4OH); ^1H NMR (CD_3OD) 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 ($CDCl_3$) 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 ($CDCl_3$) 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 ($CDCl_3$) 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 ($CDCl_3$) 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/NH_4OH); ^1H NMR ($CDCl_3$) 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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