Non-Peptide Angiotensin II Receptor Antagonists: Synthesis and Biological Activity of a Series of Novel 4,5-Dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridine Derivatives†

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A series of novel non-peptide angiotensin II receptor antagonists containing a 2,3,5-trisubstituted 4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridine was prepared via several synthetic routes. Their affinity for angiotensin II receptors was established in a binding assay experiment and in an isolated-organ test. Molecules with small alkyl groups at C-2 and the (methylbiphenylyl)tetrazole moiety at N-3 were the preferred compounds with affinities and potencies in the nanomolar range. Variations at the N-5 position modulate the activity. Substitution at N-5 with various benzyl groups led to derivatives with in vitro potencies in the nanomolar range, which were equivalent to those of losartan in these assays. Replacement of the N-5 hydrogen with acetic acid esters or, in particular, acetamides gave molecules with increased activity. The most potent was 2-butyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-(*N*,*N*-diethylacetamide) (**14u**), which is superior to L-158,809 in vitro. Two prototypes were selected as their potassium salts for in vivo testing as antihypertensives. Compounds **14a** (EMD 61 650) and **14q** (EMD 66 684) reduced blood pressure dose dependently in spontaneously hypertensive rats when administered iv. In this assay, acetamide **14q** is superior to losartan.

Introduction

The renin–angiotensin system (RAS) plays a pivotal role in blood pressure homeostasis and water and electrolyte balance.[1] Its overactivity may contribute to the pathogenesis and maintenance of hypertension. In addition, several other diseases, such as heart failure and renal malfunction, appear also to be affected by the RAS.[2] The effector hormone angiotensin II (Ang II) is an octapeptide generated through a reaction cascade involving the enzymes renin and angiotensin converting enzyme (ACE) as well as peptide precursors.[1] The blockade of the Ang II synthesis by converting enzyme inhibitors (CEI) has become a well-established therapeutic application in the treatment of hypertension and heart failure.[3] The CEI, however, not only inhibits the generation of Ang II but also the degradation of the vasodilatory and inflammatory kinins, since ACE is identical with kininase II.[4] Whether this unspecificity contributes to the therapeutic and side-effect profiles of the CEI is disputed at this time.[5] Angiotensin II receptor antagonists will be a more specific attempt to inhibit the activity of the RAS; they ought to be free of dry cough, a common side effect of CEI.[6] Although peptide Ang II antagonists have been available for over 30 years, their therapeutic potential was strongly limited to acute intravenous applications due to their short half-life, low bioavailability, and partial agonistic activity.

Within the past decade, prototype *N*-benzylimidazole-5-acetic acid-based non-peptide Ang II antagonists were reported from Takeda laboratories.[7] Investigators at DuPont have developed this imidazole lead into a series of potent, selective, and orally active Ang II antagonists exemplified by losartan (DuP 753, **1a**) (Chart 1),[8] which is currently under development by DuPont Merck (phase III clinical trial) for treatment of hypertension.[9] Losartan is partially oxidized in vivo in rats[10] and humans[11] to the metabolic carboxylic acid EXP3174 (**1b**) (Chart 1), which is considerably more potent and longer acting compared with the parent drug.

The data available from literature indicated four main key structural requirements for good binding affinity in the imidazole derivatives: firstly, a biphenylyltetrazole moiety linked to the imidazole nucleus, secondly, a short lipophilic alkyl chain at the 2-position of this heterocycle, thirdly, a basic nitrogen acting as a hydrogen-bond acceptor in the 3-position especially in benzimidazoles,[12] and finally, polar substituents in the 5-position of imidazoles. Careful examination of this data provided the highly potent imidazo[4,5-*b*]pyridine antagonist L-158,809 (**2**) (Chart 1),[13] which shows good antihypertensive activity in animal models.

Looking for new series of Ang II antagonists, we focused our attention on the nature of the putative H-bonding substituents in the imidazole 5-position such as the hydroxymethyl in **1a** and the carboxylic acid in **1b**, respectively. Structural comparison of the previously reported imidazo[4,5-*b*]pyridines with EXP3174 (Scheme 1, path a) suggested that a cyclic amide functionality could also mimic the hydrogen-bonding interaction (formula **A**, Scheme 1, path b). These considerations resulted in the discovery of 4,5-dihydro-4-oxo-3*H*-imidazo[4,5-c]pyridines as potent angiotensin II receptor antagonists. In this publication, we describe their syntheses and biological properties.

Chemistry

The parent 4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridine heterocycles **6a–d**, key intermediates in the synthesis of a large number of analogs, were conveniently prepared

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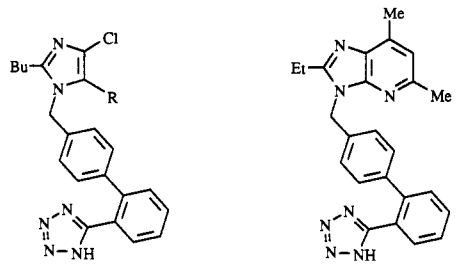
Chart 1

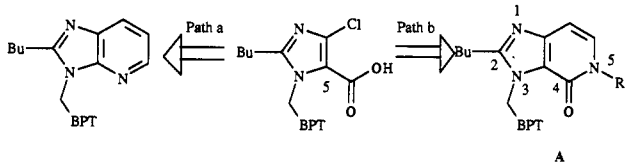


1a R = CH_2OH (K^+ salt); DuP 753

1b R = COOH; EXP3174

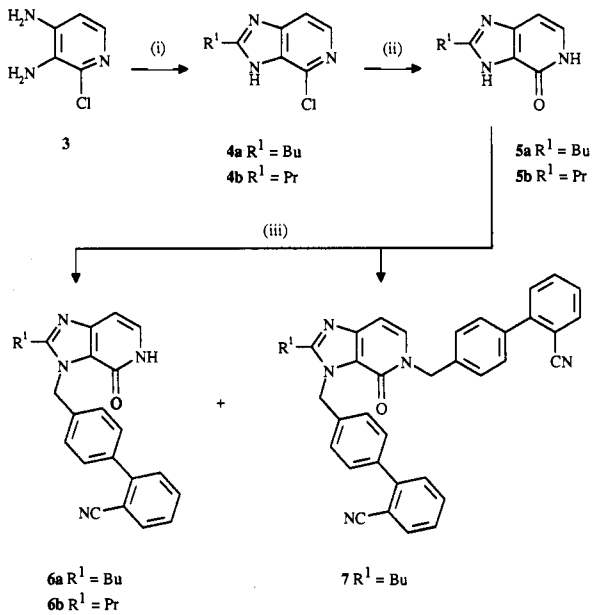
2 L-158,809

Scheme 1[a]



[a] BPT = biphenylyl-2-(1*H*-tetrazol-5-yl).

Scheme 2[a]



[a] Reagents: (i) R¹COOH, PPA, 80–90 °C; (ii) 15% HCl, DMF, reflux; (iii) K_2CO_3, 4′-(bromomethyl)biphenyl-2-carbonitrile, DMF.

on a large scale via the sequences in Scheme 2 and/or Scheme 3. 3,4-Diamino-2-chloropyridine (**3**)[14] was chosen as the starting material.

According to Scheme 2, pyridine **3** was condensed with an appropriate carboxylic acid in polyphosphoric acid at elevated temperature to give the 4-chloroimidazo[4,5-*c*]-pyridines **4a**[15] and **4b**, which on hydrolysis with HCl provided the 4-oxo derivatives **5a**[15] and **5b**. Alkylation of **5a** in dimethylformamide with 4′-(bromomethyl)biphenyl-2-carbonitrile[8] using potassium carbonate as a base gave, in addition to the desired 3*H* coupled product **6a**, the bisalkylated product **7** which was separated by silica gel chromatography. Via employing sodium methoxide in dimethylformamide in this alkylation step to **6a** and **7**, the 1*H* regioisomer of **6a** was prepared (data not shown). **6b** was synthesized from **5b** in an analogous manner.

The regiochemistry of the alkylation (**5** → **6**) could be verified by observation of nuclear Overhauser effects on

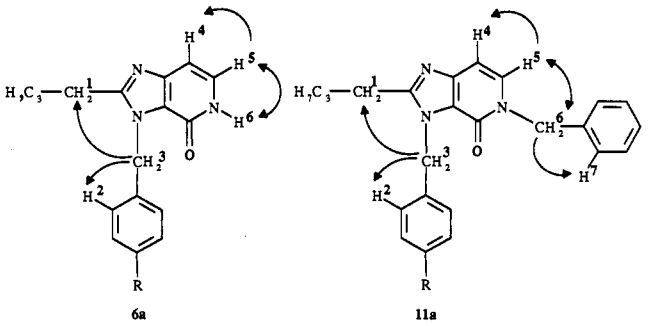


Figure 1. Observed NOE's for **6a** and **11a**. In the depicted isomers **6a** and **11a**, the arrows indicate the NOE's observed between the methylene protons 3 and/or 6 and the various protons in close spatial proximity. R = Ph(o-CN).

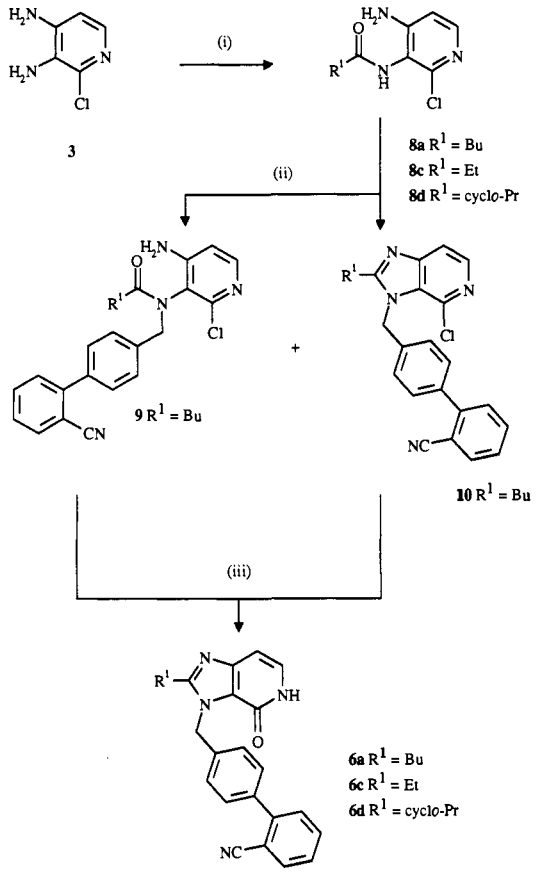
6a–d and their 1*H* regioisomers. For molecules of this type, it proved to be advantageous to record ROESY spectra.[16] The position of the biphenyl substituent on the heterocyclic ring is established by noting the NOE cross-peaks connecting the *N*-benzylic methylene group protons, the α-protons of the alkyl side chain, and the heterocyclic protons. For example, examination of the ROESY spectrum for **6a** reveals strong cross-peaks between H-3 and H-2, H-1, but the cross-peak between H-3 and H-4 is missing (Figure 1). Other NOE correlations support previous assignments. In the ROESY spectrum of the 1*H* regioisomer of **6a**, H-3 has significant cross-relaxation with H-2, H-1, and H-4. Moreover, imidazopyridines **6a–d** are also characterized in the solid state by a strong amide carbonyl absorption, supporting the assumption of 4-oxo derivatives.

In order to circumvent the bisalkylation problem, we sought a pathway which would be regiospecific and unequivocal. Acylation of pyridine **3** in THF with an acid anhydride of the suitable alkyl-chain length gave the amides **8a,c,d** (Scheme 3). The use of anhydrides in this reaction is essential to achieve a high degree of monoacylation. When using acid chlorides as acylation reagents, we observed considerable amounts of bisamides (data not shown). Subsequent alkylation of **8a** with 4′-(bromomethyl)biphenyl-2-carbonitrile[8] provided a mixture of **9** and **10** in a regiospecific manner. **9** and **10** can be identified after separation by chromatography on silica gel, but heating of this crude reaction mixture with hydrochloric acid afforded directly compound **6a**. The cyano group in the biphenyl moiety remained intact under these reaction conditions, obviously due to the steric hinderance of the biphenyl group. Conversion of amides **8c,d** to the intermediate products **6c,d** proceeded as described for **6a**. In conclusion, the anhydride approach was more appropriate for the regioselective introduction of the biphenyl substituent.

Schemes 4 and 5 describe the sequence of reactions which led to the preparation of the target molecules **12a–d**, **13**, **14a–x**, **16**, **19a–d**, and **20**.

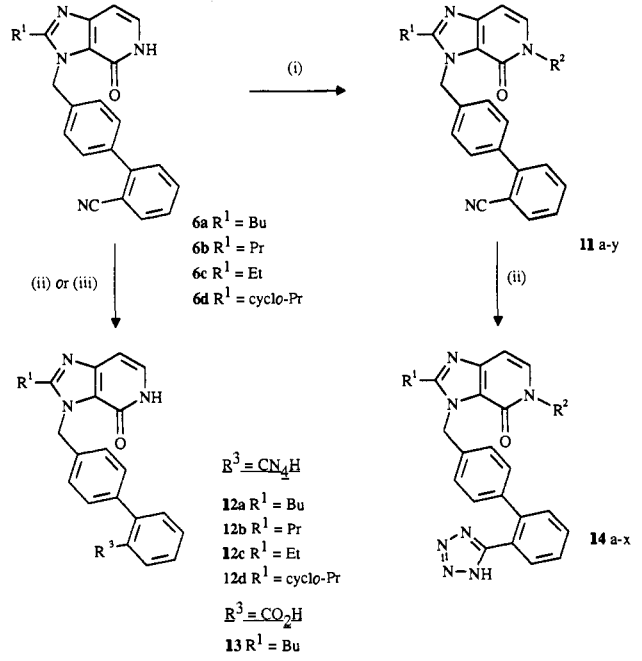
The compounds **6a–d** could be alkylated on the N-5 nitrogen under basic conditions with reactive halides. For example, treatment of **6a** with potassium *tert*-butoxide in dimethylformamide and reacting the anion with benzyl bromide resulted in formation of **11a** with high regioselectivity (Scheme 4). The corresponding 4-benzyloxy derivative obtainable from O-alkylation was only produced in traces. Again, the regiochemistry of this alkylation was confirmed on the basis of a ROESY spectrum (*e.g.*,

Scheme 3[a]



[a] Reagents: (i) $(R^1CO)_2O$, THF; (ii) KO*t*-Bu, 4′-(bromomethyl)-biphenyl-2-carbonitrile, NMP; (iii) HCl, reflux.

Scheme 4[a]

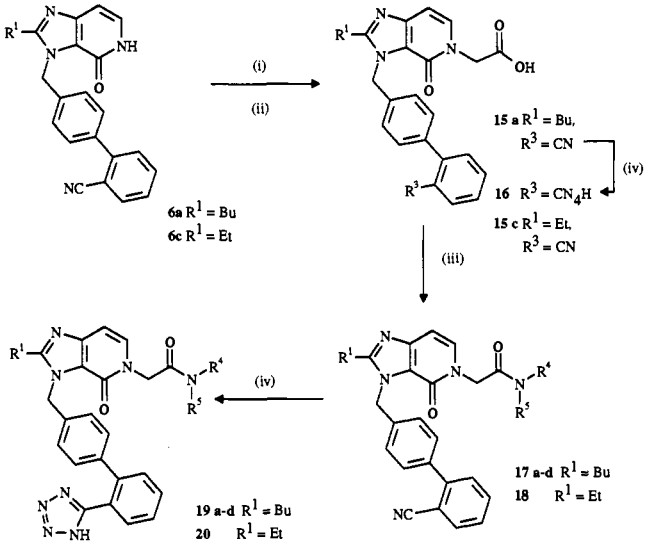


[a] Reagents: (i) KO*t*-Bu, R^2Br, DMF; (ii) Me_3SnN_3, toluene; HCl, MeOH; (iii) $HOCH_2CH_2OH$, KOH, 160 °C.

compound **6** in Figure 1). Replacement of the N-5 hydrogen in **6a–d** with other benzyl, alkyl, heteroaryl, and 2-oxoethyl substituents, acetates, and acetamides was accomplished as described above.

An alternative route was utilized for the synthesis of acetamides **17a–d** and **18** (Scheme 5). Treatment of **6a,c** with potassium *tert*-butoxide and ethyl bromoacetate gave the required adducts **11p,x**. These ester derivatives were hydrolyzed with aqueous sodium hydroxide to provide the carboxylic acids **15a,c** which were condensed under standard peptide-coupling conditions[17] to afford the acetamides **17a–d** and **18**.

Scheme 5[a]



[a] Reagents: (i) KO*t*-Bu, $BrCH_2CO_2Et$, DMF; (ii) NaOH, MeOH, THF; (iii) R^4R^5NH, HOBt, EDC, NMM, DMF; (iv) Me_3SnN_3, toluene; HCl, MeOH.

The biphenylnitrile intermediates **11a–y**, **17a–d**, and **18** prepared during the course of this work are listed in Tables 1 and 2.

The final biphenylyltetrazoles **12a–d**, **14a–x**, **16**, **19a–d**, and **20** in Tables 3, 4, and 5 were readily prepared from the corresponding nitriles[18] by employing trimethyltin azide.[19] For example, reaction of biphenylnitrile **11a** with trimethyltin azide in refluxing toluene followed by treatment with hydrochloric acid in methanol yielded the corresponding tetrazole **14a**. In the case of ethyl ester nitrile **11p**, we got a quantitative transesterification to methyl ester tetrazole **14p**.

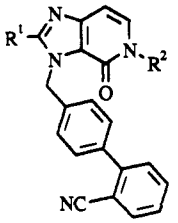
The biphenylcarboxylic acid **13** was synthesized by direct conversion of nitrile **6a** with potassium hydroxide in ethylene glycol at elevated temperature (Scheme 4).

Two analogs were not directly accessible under these convenient reaction conditions. Compound **22** having a methylaniline substituent at the imidazo[4,5-*c*]pyridine nucleus was prepared from the corresponding nitro precursor **14k** under hydrogenation conditions (Scheme 6), and alkaline hydrolysis of ethyl ester **14m** provided the target acid **21** (Scheme 7).

Results and Discussion

All compounds in Tables 3, 4, and 5 were evaluated for their binding affinities for the AT_1 subtype Ang II receptor (IC_{50}), determined in rat adrenal cortical membranes, and for antagonism of Ang II-induced contraction (IC_{50}), determined in the rabbit thoracic aortic ring. Compounds **1a,b** and **2** were used as reference standards in these assays. In binding, all compounds produced a biphasic dose–response curve indicating the presence of high-affinity AT_1- and low-affinity AT_2-binding sites. Correlation between high-affinity binding and functional antagonism was seen for most of the compounds with some exceptions discussed later.

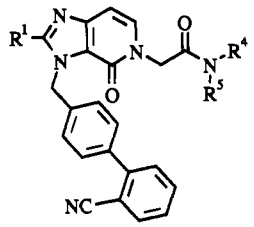
Table 1. Compound Numbering and Physical Data for 4-Oxo-3*H*-imidazo[4,5-*c*]pyridine Intermediates According to Scheme 4



no.	R^1	R^2	mp, °C	formula[a]
11a	Bu	CH_2Ph	131–132	$C_{31}H_{28}N_4O$
11b	Bu	2-thenyl	63–64	$C_{29}H_{28}N_4OS \cdot 0.15H_2O$
11c	Bu	Me	110–111	$C_{25}H_{24}N_4O$
11d	Bu	Et	oil	$C_{26}H_{26}N_4O \cdot 0.4H_2O$
11e	Bu	$CH_2Ph(p\text{-}Cl)$	124–125	$C_{31}H_{27}ClN_4O \cdot 0.2H_2O$
11f	Bu	$CH_2Ph(m\text{-}Cl)$	143–144	$C_{31}H_{27}ClN_4O$
11g	Bu	$CH_2Ph(o\text{-}Cl)$	138–139	$C_{31}H_{27}ClN_4O$
11h	Bu	$CH_2Ph(o\text{-}Br)$	141–142	$C_{31}H_{27}BrN_4O$
11i	Bu	$CH_2Ph(o\text{-}F)$	oil	$C_{31}H_{27}FN_4O \cdot 0.3H_2O$
11k	Bu	$CH_2Ph(o\text{-}NO_2)$	102–103	$C_{31}H_{27}N_5O_3 \cdot 0.25H_2O$
11m	Bu	$CH_2Ph(o\text{-}CO_2Et)$	138–139	$C_{34}H_{32}N_4O_3$
11n	Bu	CH_2COPh	167–168	$C_{32}H_{28}N_4O_2 \cdot 0.3H_2O$
11o	Bu	CH_2CO*t*-Bu	156–157	$C_{30}H_{32}N_4O_2 \cdot 0.45H_2O$
11p	Bu	CH_2CO_2Et	152–153	$C_{28}H_{28}N_4O_3$
11q	Bu	$CH_2CON(Me)_2$	189–190	$C_{28}H_{29}N_5O_2$
11r	Pr	$CH_2CON(Me)_2$	203–204	$C_{27}H_{27}N_5O_2 \cdot 0.6H_2O$
11s	Et	$CH_2CON(Me)_2$	234–235	$C_{26}H_{25}N_5O_2$
11t	cyclo-Pr	$CH_2CON(Me)_2$	178–179	$C_{27}H_{25}N_5O_2 \cdot 0.4H_2O$
11u	Bu	$CH_2CON(Et)_2$	169–170	$C_{30}H_{34}N_5O_2 \cdot 0.2H_2O$
11v	Et	$CH_2CON(Et)_2$	159–160	$C_{28}H_{29}N_5O_2$
11w	Bu	CH_2CONH*t*-Bu	132–133	$C_{30}H_{32}N_5O_2 \cdot 0.15H_2O$
11x	Et	CH_2CO_2Et	143–144	$C_{26}H_{24}N_4O_3$
11y	Bu	$CH_2CON(Ph)_2$	171–172	$C_{38}H_{33}N_5O_2 \cdot 0.2H_2O$

[a] Analyses for C, H, and N were correct within ±0.4% unless otherwise stated.

Table 2. Compound Numbering and Physical Data for 4-Oxo-3*H*-imidazo[4,5-*c*]pyridine Intermediates According to Scheme 5



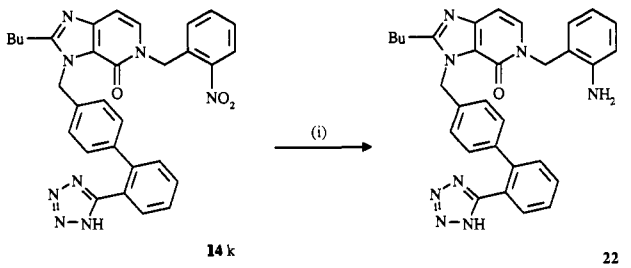
no.	R^1	R^4	R^5	mp, °C	formula[a]
17a	Bu	$-CH_2(CH_2)_2CH_2-$		166–167	$C_{30}H_{31}N_5O_2 \cdot 0.5H_2O$
17b	Bu	H	H	218–219	$C_{26}H_{25}N_5O_2$
17c	Bu	H	Ph	106–107	$C_{32}H_{29}N_5O_2 \cdot 0.4H_2O$
17d	Bu	CH_3	Ph	121–122	$C_{33}H_{31}N_5O_2 \cdot 0.6H_2O$
18	Et	$-CH_2(CH_2)_3CH_2-$		220–221	$C_{29}H_{29}N_5O_2$

[a] Analyses for C, H, and N were correct within ±0.4% unless otherwise stated.

For discussion of results, the imidazo[4,5-*c*]pyridine ring-numbering system as displayed in the general formula **A** (Scheme 1) is used.

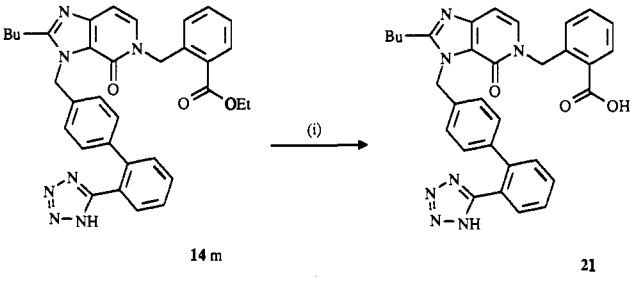
Initial work on the structure–affinity relationship demonstrated that attachment of the biphenyl substituent in the 3*H* position, as realized in the compounds **12a–d** or **13** (Table 3) was important in order to obtain good binding affinity. For example, the 1*H* derivative of **13** bound to the Ang II receptor with an affinity approximately 2 orders of magnitude lower than **13** (data for the 1*H* regioisomer not shown). On its part, the carboxylic acid **13** is much less potent than the corresponding tetrazole **12a** (IC_{50} = 20.0 nM versus 0.8 nM, functional assay), and therefore,

Scheme 6[a]



[a] Reagents: (i) catalytic Raney Ni, H_2, MeOH.

Scheme 7[a]



[a] Reagents: (i) NaOH, MeOH, THF; then HCl.

we decided to prepare further imidazopyridone derivatives with a tetrazole group on the biphenyl portion.

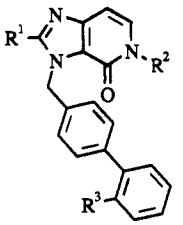
The structure–activity relationships (SAR) for substituents at the 2-position of the imidazopyridone is defined by the data for compounds **12a–d** in Table 3. In the alkyl-chain series, the substituent with the highest binding affinity is the propyl group in compound **12b** but a small ring like cyclopropyl is tolerated as well.

Compared with the binding affinity of losartan (**1a**), these preliminary results suggest that the carbonyl group in the 4-position of the imidazopyridone ring is located in the proximity of the receptor side where interactions with the receptor are strong. Because of these first results, further work was limited to making analogs of **12a–d**, but for a wide range of compounds, the butyl group at C-2, reported to be optimal for the imidazole series,[8] was kept constant throughout our in vitro studies.

Now, we turned our attention to the contribution of a substituent in the 5-position to the binding affinity and potency compared with the parent imidazopyridine **12a** (Table 3). Introducing a small alkyl group like methyl or ethyl, we were pleased to find that the biological activity was largely preserved in compounds **14c,d**, respectively. Replacement of the alkyl groups of **14c** or **14d** with benzyl **14a** led only to a small drop in functional potency (IC_{50} = 0.7 and 0.6 nM versus 1.0 nM), indicating that a larger group is still tolerated in the 5-position. The binding affinity of thiophene analog **14b** was altered little compared to that of **14a** (IC_{50} = 1.9 nM versus 1.7 nM).

Next, the role of substituents on the phenyl ring in **14a** was examined. These modifications are listed in Table 4. Regardless of the electronic properties of a given substituent, *para* substitution gave analogs of **14a** with decreased potencies. For example, the chloro derivatives **14f,g** were about 3 times as potent as the *para* product **14e** with a slight preference in binding affinity for the *ortho* derivative **14g**. Among the halogens in the *ortho* position, F was preferred to Br and Cl (**14i** versus **14h,g**). A variety of functional groups including nitro (**14k**), amino (**22**), and carbethoxy (**14m**) have been employed as *ortho* substituents with only minor variations in binding affinity

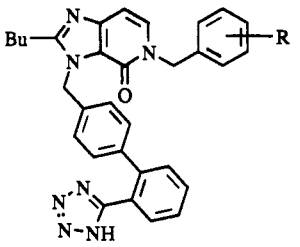
Table 3. Receptor Binding Activity, Inhibition of Ang II-Induced Contraction in Rabbit Aortic Rings, and Physical Data for Final Compounds



no.	R^1	R^2	R^3	binding IC_{50},[a] nM	rabbit aortic ring IC_{50},[a] nM	mp, °C	formula[b]
13	Bu	H	CO_2H	16.8	20.0	275–276	$C_{24}H_{23}N_3O_3 \cdot 0.35H_2O$
12a	Bu	H	CN_4H[c]	2.4	0.8	172–173	$C_{24}H_{23}N_7O \cdot 0.5H_2O$
12b	Pr	H	CN_4H	1.1	0.7	185–186	$C_{23}H_{21}N_7O \cdot 0.9H_2O$
12c	Et	H	CN_4H	3.8	2.0	195–196	$C_{22}H_{19}N_7O \cdot 1.0H_2O$
12d	cyclo-Pr	H	CN_4H	4.6	2.0	200–201	$C_{23}H_{19}N_7O \cdot 2.1H_2O$
14c	Bu	Me	CN_4H	2.3	0.7	194–195	$C_{25}H_{25}N_7O \cdot 0.45H_2O$
14d	Bu	Et	CN_4H	3.2	0.6	181–182	$C_{28}H_{27}N_7O \cdot 0.3H_2O$
14a	Bu	CH_2Ph	CN_4H	1.7	1.0	160–161	$C_{31}H_{29}N_7O \cdot 0.2H_2O$
14b	Bu	2-thenyl[d]	CN_4H	1.9	2.0	145–146	$C_{29}H_{27}N_7OS \cdot 2.5H_2O$
1a[e]				8.2	3.0		
1b[f]				7.5	0.3		
2[g]				2.1	0.1		

[a] For details, see the Experimental Section. [b] Analyses for C, H, and N were correct within ±0.4% unless otherwise stated. [c] 1*H*-Tetrazol-5-yl. [d] 2-Thienylmethyl. [e] Losartan. [f] EXP3174. [g] L-158,809.

Table 4. Effect of the Substituent at the N-5 Benzyl Moiety on Receptor Binding Activity, Inhibition of Ang II-Induced Contraction in Rabbit Aortic Rings, and Physical Data for Final Compounds



no.	position of phenyl subst	R	binding IC_{50},[a] nM	rabbit aortic ring IC_{50},[a] nM	mp, °C	formula[b]
14a	H	H	1.7	1.0	160–161	$C_{31}H_{29}N_7O \cdot 0.2H_2O$
14e	*para*	Cl	5.6	10.0	205–206	$C_{31}H_{28}ClN_7O \cdot 0.6H_2O$
14f	*meta*	Cl	5.7	3.0	187–188	$C_{31}H_{28}ClN_7O \cdot 0.2H_2O$
14g	*ortho*	Cl	3.5	3.0	126–127	$C_{31}H_{28}ClN_7O \cdot 1.4H_2O$
14h	*ortho*	Br	4.2	4.0	172–173	$C_{31}H_{28}BrN_7O \cdot 1.1H_2O$
14i	*ortho*	F	4.2	2.0	169–170	$C_{31}H_{28}FN_7O$
14k	*ortho*	NO_2	2.2	2.0	123–124	$C_{31}H_{28}N_8O_2 \cdot 0.3H_2O$
22	*ortho*	NH_2	4.3	2.0	198–199	$C_{31}H_{30}N_8O \cdot 0.4H_2O$
14m	*ortho*	CO_2Et	3.4	2.0	203–204	$C_{34}H_{33}N_7O_3 \cdot 0.1H_2O$
21	*ortho*	CO_2H	30.0	0.8	233–234	$C_{32}H_{29}N_7O_3 \cdot 1.0H_2O$

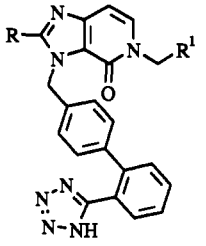
[a] For details, see the Experimental Section. [b] Analyses for C, H, and N were correct within ±0.4% unless otherwise stated.

and potency. With one exception, no compound gave an improvement in functional potency over the parent **14a**. This most effective substituent was the carboxyl group in **21**. This derivative shows an IC_{50} of 0.8 nM in the functional test. However, binding affinity dropped about 9-fold compared to that of the corresponding ethyl ester **14m** (IC_{50} = 30.0 nM).

In general, carboxylic acid and ester substituents in the 5-position of the imidazo nucleus displayed a distinct structure–activity pattern concerning the binding affinity studies, due to the absence or presence of bovine serum albumin (BSA) in the assay, which will be discussed later.

Modifications of functionality at the 5-position of imidazopyridone ring **12a** were next evaluated. As shown in Table 5, introduction of a functional group such as ketone **14n** does not have a significant adverse effect on binding and potency (IC_{50} = 4.6 and 4.0 nM), although it is less effective compared with the parent **14a**. However, replacement of the phenyl ring in **14n** by a bulky *tert*-butyl group surprisingly improved the biological activity. This modification led to the discovery of our first subnanomolar antagonist **14o** in this carbonyl series with an IC_{50} of 0.4 nM in the functional assay. A second improvement in activity was achieved with methyl acetate **14p** (IC_{50} = 0.2 nM, functional assay), which was significantly more active than either the unsubstituted compound **12a** or the benzyl derivatives **14a,e–k,m**, **21**, and **22**. The in vitro data were in the range of those of the potent antagonist L-158,809 (**2**). The carboxylic acid **16** retained functional antagonism but showed a dramatic decrease in binding affinity (IC_{50} = 56.0 nM). The introduction of amides as carboxylic acid derivatives led to a further increase in binding and potency. In contrast to the experience made with the free acid **16**, the unsubstituted acetamide **19b** (IC_{50} = 0.4 nM, functional test) was very similar in functional potency compared with the alkyl-

Table 5. Effect of the N-5 Substituent on Receptor Binding Activity, Inhibition of Ang II-Induced Contraction in Rabbit Aortic Rings, and Physical Data for Final Compounds



no.	R	R^1	binding IC_{50},[a] nM	rabbit aortic ring IC_{50},[a] nM	mp, °C	formula[b]
14n	Bu	COPh	4.60	4.00	148–149	$C_{32}H_{29}N_7O_2 \cdot 0.3H_2O$
14o	Bu	CO*t*-Bu	1.40	0.40	202–203	$C_{30}H_{33}N_7O_2 \cdot 0.75H_2O$
14p	Bu	CO_2Me	1.30	0.20	112–113	$C_{27}H_{27}N_7O_3 \cdot 0.6H_2O$
16	Bu	CO_2H	56.00	0.70	268–269	$C_{26}H_{25}N_7O_3 \cdot 0.5H_2O$
19b	Bu	$CONH_2$	1.30	0.40	218–219	$C_{26}H_{26}N_8O_2 \cdot 0.4H_2O$
14q	Bu	$CON(Me)_2$	0.70	0.20	256–257	$C_{28}H_{30}N_8O_2 \cdot 0.1H_2O$
14r	Pr	$CON(Me)_2$	0.80	0.10	149–150	$C_{27}H_{28}N_8O_2 \cdot 0.8H_2O$
14s	Et	$CON(Me)_2$	1.00	0.30	181–182	$C_{26}H_{26}N_8O_2$
14t	cyclo-Pr	$CON(Me)_2$	0.60	0.50	192–193	$C_{27}H_{26}N_8O_2 \cdot 1.55H_2O$
14u	Bu	$CON(Et)_2$	0.36	0.08	255–256	$C_{30}H_{34}N_8O_2 \cdot 2.0H_2O$
14v	Et	$CON(Et)_2$	0.70	0.30	191–192	$C_{28}H_{30}N_8O_2$
19a	Bu	COpyrrolidino	1.20	0.20	215–216	$C_{30}H_{32}N_8O_2 \cdot 0.4H_2O$
20	Et	COpiperidino	0.70	0.20	200–201	$C_{29}H_{30}N_8O_2 \cdot 2.0H_2O$
14w	Bu	CONH*t*-Bu	1.90	0.10	211–212	$C_{30}H_{34}N_8O_2 \cdot 2.3H_2O$
19c	Bu	CONHPh	6.00	1.00	156–157	$C_{32}H_{30}N_8O_2 \cdot 0.7H_2O$
19d	Bu	CONMePh	2.20	0.30	149–150	$C_{33}H_{32}N_8O_2 \cdot 1.0H_2O$
14x	Bu	$CON(Ph)_2$	5.70	7.00	211–212	$C_{38}H_{34}N_8O_2 \cdot 0.5H_2O$

[a] For details, see the Experimental Section. [b] Analyses for C, H, and N were correct within ±0.4% unless otherwise stated.

substituted derivatives **14q** or **14u**. The relative order of activity was $CON(Et)_2 > CON(Me)_2 > CONH_2$. Acetamides derived from replacement of the NH_2 moiety with pyrrolidine **19a** (IC_{50} = 0.2 nM) or piperidine **20** (IC_{50} = 0.2 nM) displayed similar biological data compared with those of dimethyl analog **14q**. The diethylacetamide **14u** was the most potent among these derivatives. This compound was 2-fold more active than the corresponding dimethyl analog **14q** in binding (IC_{50} = 0.36 nM versus 0.7 nM) as well as in functionality (IC_{50} = 0.08 nM versus 0.2 nM). Interestingly, the *tert*-butyl analog **14w** retained the high potency (IC_{50} = 0.1 nM), whereas the anilide derivative **19c** (IC_{50} = 1.0 nM) was less effective. This is comparable with the observation made in the ketone series. However, the loss in potency was regained by substitution of the remaining amide hydrogen with a methyl group in **19d** (IC_{50} = 0.3 nM). On the other hand, replacement of this hydrogen with an additional phenyl group produced a significantly less potent compound. Diphenylacetamide **14w** (IC_{50} = 7.0 nM, functional assay) was much less effective than the other acetamides, suggesting that the two phenyl rings force the carboxamide functionality into a less favorable orientation or distance to one receptor side. Dimethylacetamides **14q–t** showed the effect in changing the length of the 2-position alkyl chain. Both the propyl analog **14r** and the butyl analog **14q** were slightly more potent than the ethyl analog **14s** and the cyclopropyl analog **14t**. This is in accordance with the results obtained with the unsubstituted imidazo[4,5-*c*]pyridones **12a–d**.

While, in general, a good correlation between the binding affinities and the functional data is apparent, in some cases the binding affinities in rat adrenal cortex do not correlate with the aortic contractile response. It was already recognized by Chiu *et al.* that the presence of BSA could cause substantial shifts in the IC_{50} binding values[20] (the functional studies have been carried out in the absence of BSA). For this reason, binding affinity for several antagonists was determined in the presence of 0.01% BSA only (Table 6). With regard to the ester/carboxylic acid pairs **14m/21** and **14p/16**, it is apparent that the IC_{50} values of the carboxylic acids **21** and **16** are 10–20-fold higher than those of the corresponding esters **14m,p**, respectively. However, in accordance to investigations carried out with losartan (**1a**) and its corresponding metabolite **1b**, it could be shown that the decreased apparent affinity of the carboxylic acids **21** and **16** was dependent upon the concentration of BSA in the assay. Binding studies carried out with 0.01% BSA in the assay medium revealed that the IC_{50} values for the carboxylic acids **21** and **16** were decreased by a factor of 10 and 19, respectively, in comparison to those with 0.25% BSA; also, at 0.01% BSA, there was no difference between the IC_{50} values of the esters **14m,p** and their corresponding carboxylic acids **21** and **16**, respectively. No statistically significant difference was seen with the other investigated antagonists. For example, this is shown in Table 6 with amide **19b** and benzyl derivative **14a**.

Table 6. Binding Affinities of Selected Compounds in the Presence of Low or High Concentrations of BSA in the Assay Medium

no.	binding IC_{50},[a] nM	binding IC_{50},[b] nM	+BSA/−BSA
1a	8.2	1.5	5.5
1b	7.5	1.8	4.2
14m	3.4	5.3	0.6
21	30.0	3.0	10.0
14p	1.3	1.0	1.3
16	56.0	3.0	18.7
19b	1.3	1.1	1.2
14a	1.7	3.2	0.5

[a] Binding affinities in the presence of 0.25% BSA. [b] Binding affinities in the presence of 0.01% BSA.

All the antagonists in this study were assayed for AT_2-binding potency and demonstrated affinities of >1000 nM with one exception. *N,N*-Diphenylacetamide **14x** has a binding affinity to the AT_2 receptor (rat adrenal medulla)

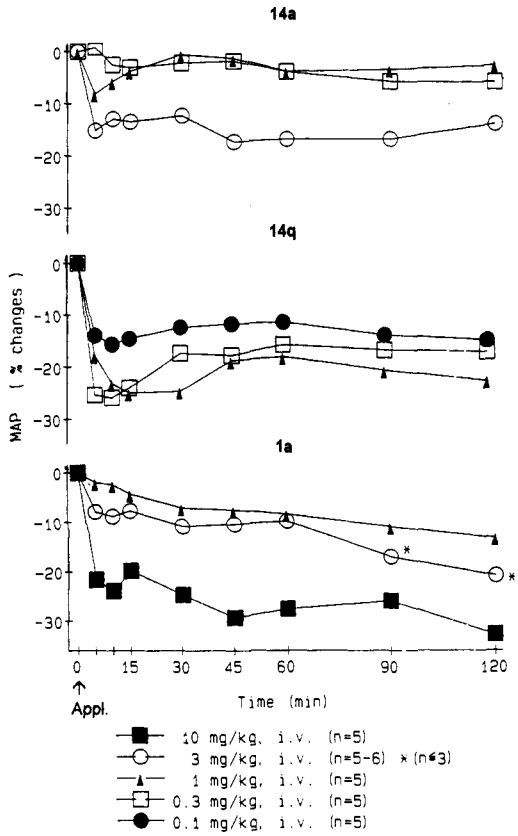


Figure 2. Antihypertensive effects of **14a** (on the top) and **14q** (in the middle) applied iv as potassium salts to conscious furosemide-treated SHR in comparison with those of losartan (**1a**) (at the bottom). The fall in mean arterial pressure (MAP) is presented as percent changes from pretreatment values (D %). For clarity, means are shown without SEM. There was a dose-related fall in blood pressure, which persisted over time of observation (2 h) after adequate dosing of the substances. The tested doses (0.1–10.0 mg/kg iv) are specified by the symbols given above. Identical symbols were used for identical doses; *n* = number of animals studied.

of 0.3 μM. This is in the range of the binding affinity of the previously reported BIBS39, a mixed AT_1/AT_2 antagonist.[21]

The refined hypothetical AT_1 receptor–ligand model of the DuPont group[8] can be transferred to imidazo[4,5-*c*]-pyridin-4-ones with slight modification of receptor interaction. The SAR obtained in this study suggests that the interactions of our compounds with the Ang II receptor can be divided into three different parts (*cf.* formula **A** in Scheme 1 for ring numbering and assignment of the substituents). These may be characterized as (i) hydrophobic associations between a lipophilic pocket and the aliphatic chain at C-2, the distal phenyl ring at N-3, and a phenyl or *tert*-butyl moiety at N-5, (ii) an ionic interaction between a cationic group on the receptor and the acidic tetrazole substituent on the biphenyl chain, and (iii) a hydrogen bond between a proton donor on the receptor and an oxygen as a proton acceptor at C-4 as well as at N-5 (*e.g.*, the acetamides) of the imidazopyridones.

Two representatives of this class of compounds were selected as their potassium salts for in vivo evaluation as an antihypertensive drug. As shown in Figure 2, EMD 61 650 (potassium salt of **14a**) and EMD 66 684 (potassium salt of **14q**) were examined in a furosemide-treated spontaneously hypertensive rat (FTSHR) model. For comparison, the effect of losartan (**1a**) in the same animal model is also shown. EMD 61 650 and EMD 66 684 caused a dose-related and long lasting fall in blood pressure. The dimethylacetamide EMD 66 684 was clearly more potent (~10 times) than the benzyl derivative EMD 61 650. The reference compound losartan (**1a**) was as effective as EMD 61 650 but less active than EMD 66 684.

Conclusions

This paper describes a novel series of potent, non-peptide Ang II receptor antagonists derived from substitution of an imidazo[4,5-*c*]pyridin-4-one nucleus with the well-known biphenylyltetrazole. With one exception, all compounds are selective ligands for the type I subclass of Ang II receptors. The position of the attachement of the biphenyl moiety is crucial for good binding affinity and in vitro potency. Only the 3*H* coupled products gave the expected biological results. Variation of the substitution pattern on the N-5 nitrogen of the imidazopyridone gave rise to further improvement in binding affinity and potency. Introduction of a diethylacetamide unit in the 5-position revealed, with compound **14u**, one of the most potent antagonists actually known related to in vitro properties. The H-, alkyl-, and benzyl-substituted derivatives have comparable affinity and potency to those of losartan but are less potent than L-158,809, whereas most of the acetamides were equipotent to L-158,809 in vitro. The same seems to be true in vivo, where acetamides, as shown for **14q**, were clearly more potent than losartan and the benzyl-substituted derivatives.

Experimental Section

Melting points were determined with a Mettler FP 62 melting point apparatus and are uncorrected. IR, NMR, and mass spectra are in agreement with the structures cited and were recorded on a Bruker 85 IFS 48 IR spectrophotometer, a Bruker AC 200, WM 250, or AM 500 spectrometer (TMS as internal standard), and a Fisons (formerly Vacuum Generator) 70-250SE spectrometer (fast atom bombardement, FAB) at 70 eV, respectively. Microanalyses were obtained with a Perkin-Elmer 240B CHN analyzer. Thin-layer chromatography (TLC) was carried out on precoated silica gel 60 F_{254} plates with a layer thickness of 0.25 mm, from E. Merck (Darmstadt, Germany). Visualization was done with UV and I_2. Yields are not optimized.

Chemistry. The following procedures are representative of the general methods that are described in the text.

2-Butyl-4-chloro-3*H*-imidazo[4,5-*c*]pyridine (4a). 3,4-Diamino-2-chloropyridine (**3**) (50.0 g, 0.35 mol), valeric acid (36.2 g, 0.35 mol), and polyphosphoric acid (700 g) were combined and stirred for 17 h at 80 °C. The reaction was poured into ice water (500 mL), and then, the pH was adjusted to 8 with NaOH and the aqueous layer extracted with ethyl acetate (3 × 300 mL). The organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo to give an oil. The purification by chromatography on silica gel with methylene chloride/methanol (90:10) afforded 46.3 g (63%) of pure **4a**: mp 119–120 °C; ^{1}H NMR (DMSO-d_6) δ 12.99 (brs, 1 H), 8.06 (d, J = 5.5 Hz, 1 H), 7.52 (d, J = 5.5 Hz, 1 H), 2.89 (t, J = 7.8 Hz, 2 H), 1.87–1.71 (m, 2 H), 1.47–1.27 (m, 2 H), 0.92 (t, J = 7.3 Hz, 3 H). Anal. ($C_{10}H_{12}ClN_3$) C, H, N.

The following was prepared analogously.

4-Chloro-2-propyl-3*H*-imidazo[4,5-*c*]pyridine (4b) was prepared from **3** (20 g, 0.14 mol) to give 15.2 g (61%) of **4b**: mp 137–138 °C; ^{1}H NMR (DMSO-d_6) δ 8.05 (d, J = 7.0 Hz, 1 H), 7.50 (d, J = 7.0 Hz, 1 H), 2.86 (t, J = 7.0 Hz, 2 H), 1.90–1.78 (m, 2 H), 0.97 (t, J = 7.0 Hz, 3 H). Anal. ($C_9H_{10}ClN_3$) C, H, N.

2-Butyl-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridine (5a). Compound **4a** (40 g, 0.19 mol) and a 1:1 mixture of 15% hydrochloric acid and dimethylformamide (500 mL) were mixed and refluxed for 24 h. The solvents were removed by rotary evaporation, and water (300 mL) was then added to the residue. After a few minutes, the product precipitated and was collected and dried to yield 19.0 g (52%) of **5a** as a white solid: mp 289–290 °C; ^{1}H NMR (DMSO-d_6) δ 12.60 (brs, 1 H), 11.10 (brs, 1 H),

7.05 (d, J = 6.9 Hz, 1 H), 6.45 (d, J = 6.9 Hz, 1 H), 2.74 (t, J = 7.0 Hz, 2 H), 1.78–1.63 (m, 2 H), 1.41–1.23 (m, 2 H), 0.90 (t, J = 7.0 Hz, 3 H). Anal. ($C_{10}H_{13}N_3O$) C, H, N.

The following was prepared analogously.

4,5-Dihydro-4-oxo-2-propyl-3*H*-imidazo[4,5-*c*]pyridine (5b) was prepared from **4a** (15.0 g, 76.6 mmol) and recrystallized from ethanol to give 7.0 g (52%) of **5b**: mp 282–283 °C; ^{1}H NMR (DMSO-d_6) δ 12.75 (brs, 1 H), 11.05 (brs, 1 H), 7.03 (d, J = 7.0 Hz, 1 H), 6.43 (d, J = 7.0 Hz, 1 H), 2.71 (t, J = 7.0 Hz, 2 H), 1.83–1.65 (m, 2 H), 0.91 (t, J = 7.0 Hz, 3 H). Anal. ($C_9H_{11}N_3O{\cdot}0.05H_2O$) C, H, N.

4′-[(2-Butyl-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (6a) and 3,5-Bis[(2′-cyano-4-biphenylyl)methyl]-2-butyl-4,5-dihydro-3*H*-imidazo-[4,5-*c*]pyridin-4-one (7). The solution of **5a** (191.2 g, 1.0 mol) in dimethylformamide (2500 mL) was treated with finely ground potassium carbonate (138.2 g, 1.0 mol) and 4′-(bromomethyl)-biphenyl-2-carbonitrile (272.2 g, 1.0 mol). The reaction mixture was allowed to stir at ambient temperature overnight. It was diluted with water (2500 mL) and extracted with ethyl acetate (3 × 1000 mL). After drying over anhydrous sodium sulfate, the solvent was evaporated to yield a yellow oil which was purified by flash chromatography on silica gel with ethyl acetate to provide 156.5 g (41%) of the monomer **6a** and 39.8 g (6.9%) of the bisadduct **7**.

6a: mp 179–180 °C; ^{1}H NMR (DMSO-d_6) δ 11.31 (brd, J = 2.8 Hz, 1 H), 7.93 (dd, J = 7.9 and 1.4 Hz, 1 H), 7.77 (td, J = 8.0 and 1.4 Hz, 1 H), 7.61–7.52 (m, 4 H), 7.32 (d, J = 8.3 Hz, 2 H), 7.13 (dd, J = 6.9 and 4.4 Hz, 1 H), 6.58 (d, J = 7.0 Hz, 1 H), 5.86 (s, 2 H), 2.74 (t, J = 7.2 Hz, 2 H), 1.70–1.54 (m, 2 H), 1.40–1.23 (m, 2 H), 0.82 (t, J = 7.3 Hz, 3 H); IR (KBr) 2220, 1656 cm^{-1}. Anal. ($C_{24}H_{22}N_4O$) C, H, N.

7: mp 87–88 °C; ^{1}H NMR (DMSO-d_6) δ 7.96–7.26 (m, 16 H), 7.62 (d, J = 7.2 Hz, 1 H), 6.69 (d, J = 7.2 Hz, 1 H), 5.87 (s, 2 H), 5.31 (s, 2 H), 2.75 (t, J = 7.7 Hz, 2 H), 1.70–1.54 (m, 2 H), 1.40–1.20 (m, 2 H), 0.82 (t, J = 7.3 Hz, 3 H). Anal. ($C_{38}H_{31}N_5O$) C, H, N.

The following was prepared analogously.

4′-[(4,5-Dihydro-4-oxo-2-propyl-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (6b) was prepared from **5b** (5.0 g, 28.0 mmol) and recrystallized from acetone to give 4.4 g (43%) of pure **6b**: mp 220–221 °C; ^{1}H NMR (DMSO-d_6) δ 11.26 (s, 1 H), 7.93 (dd, J = 7.3 and 0.7 Hz, 1 H), 7.77 (td, J = 7.7 and 1.0 Hz, 1 H), 7.58 (t, J = 7.7 Hz, 1 H), 7.56 (dd, J = 8.0 and 0.7 Hz, 1 H), 7.55 (d, J = 8.3 Hz, 2 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.10 (d, J = 7.0 Hz, 1 H), 6.56 (d, J = 7.0 Hz, 1 H), 5.84 (s, 2 H), 2.71 (t, J = 7.4 Hz, 2 H), 1.77–1.64 (m, 2 H), 0.89 (t, J = 7.4 Hz, 3 H); IR (KBr) 2220, 1654 cm^{-1}. Anal. ($C_{23}H_{20}N_4O{\cdot}0.9H_2O$) C, H, N.

***N*-(4-Amino-2-chloro-3-pyridyl)propionamide (8c).** To a solution of 3,4-diamino-2-chloropyridine (**3**) (5.0 g, 34.9 mmol) in tetrahydrofuran (50 mL) was added dropwise a solution of propionic anhydride (4.5 mL, 34.9 mmol) in tetrahydrofuran (10 mL). The reaction mixture was allowed to stir at ambient temperature over night. The resultant precipitate was filtered, dried, and recrystallized from hexane/*tert*-butyl methyl ether/ethyl acetate to yield 4.9 g (71%) of **8c** as a solid: mp 190–192 °C; ^{1}H NMR (DMSO-d_6) δ 9.02 (s, 1 H), 7.69 (d, J = 6.0 Hz, 1 H), 6.55 (d, J = 6.3 Hz, 1 H), 6.12 (s, 2 H), 2.32 (q, J = 7.5 Hz, 2 H), 1.07 (t, J = 7.5 Hz, 3 H). Anal. ($C_8H_{10}ClN_3O$) C, H, N, Cl.

The following were prepared analogously.

***N*-(4-Amino-2-chloro-3-pyridyl)pentanamide (8a)** was prepared from **3** (14.35 g, 0.1 mol) to give 15.8 g (69%) of pure **8a**: mp 161–162 °C; ^{1}H NMR (DMSO-d_6) δ 9.05 (brs, 1 H), 7.69 (d, J = 5.5 Hz, 1 H), 6.57 (d, J = 5.7 Hz, 1 H), 6.09 (brs, 2 H), 2.31 (t, J = 7.7 Hz, 2 H), 1.67–1.49 (m, 2 H), 1.45–1.25 (m, 2 H), 0.90 (t, J = 7.2 Hz, 3 H). Anal. ($C_{10}H_{14}ClN_3O$) C, H, N.

***N*-(4-Amino-2-chloro-3-pyridyl)cyclopropanecarboxamide (8d)** was prepared from **3** (17.0 g, 0.12 mol) to give 10.3 g (40%) of pure **8d**: mp 220–221 °C; ^{1}H NMR (DMSO-d_6) δ 9.38 (s, 1 H), 7.70 (d, J = 6.0 Hz, 1 H), 6.60 (d, J = 6.0 Hz, 1 H), 6.05 (s, 2 H), 1.89–1.73 (m, 1 H), 0.88–0.67 (m, 4 H). Anal. ($C_9H_{10}ClN_3O{\cdot}0.2H_2O$) C, H, N.

***N*-(4-Amino-2-chloro-3-pyridyl)-*N*-[(2′-cyano-4-biphenylyl)methyl]pentanamide (9), 4′-[(2-Butyl-4-chloro-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (10), and 4′-[(2-Butyl-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (6a).** To a solution of **8a** (227.7 g, 1.0 mol) in 1-methyl-2-pyrrolidinone (NMP, 1000 mL) was added a solution of potassium *tert*-butoxide (129.1 g, 1.15 mol) in NMP (400 mL) under a nitrogen atmosphere, and the reaction mixture was stirred for 1 h. A solution of 4′-(bromomethyl)biphenyl-2-carbonitrile (299.4 g, 1.10 mol) in NMP (750 mL) was added dropwise, and the reaction mixture was stirred for 5 h. For the identification of the intermediates **9** and **10**, a sample of the reaction mixture (25 mL) was poured into ice–water and extracted three times with *tert*-butyl methyl ether (300 mL). The combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography with *tert*-butyl methyl ether on silica gel yielded the faster eluting pentanamide **9** (1.8 g) and the slower eluting cyclic product **10** (2.3 g). The main reaction mixture was treated with hydrochloric acid (18%, 3100 mL) and heated at 105 °C for 40 h. The solution was cooled to 80 °C, and the pH was adjusted to 12.0 by addition of 3700 mL of 16% aqueous sodium hydroxide. It was cooled to ambient temperature, and the solid was filtered, washed with water, and dried under high vacuum to yield 446.0 g of a pale yellow powder. Recrystallization from ethanol yielded 312.0 g (82%) of **6a** as a white solid.

9: mp 191–192 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (dd, J = 8.2 Hz, 1 H), 7.77 (td, J = 7.7 and 1.4 Hz, 1 H), 7.71 (d, J = 5.6 Hz, 1 H), 7.56 (td, J = 8.0 and 1.3 Hz, 1 H), 7.56 (dd, J = 7.8 and 1.2 Hz, 1 H), 7.48–7.37 (m, 4 H), 6.60 (d, J = 5.7 Hz, 1 H), 6.45 (brs, 2 H), 4.91 (d, J = 14.0 Hz, 1 H), 4.50 (d, J = 14.0 Hz, 1 H), 2.11–1.86 (m, 2 H), 1.60–1.42 (m, 2 H), 1.32–1.12 (m, 2 H), 0.80 (t, J = 7.3 Hz, 3 H). Anal. ($C_{24}H_{23}ClN_4O$) C, H, N.

10: mp 136–137 °C; ^{1}H NMR (DMSO-d_6) δ 8.14 (d, J = 5.5 Hz, 1 H), 7.93 (dd, J = 8.1 and 1.3 Hz, 1 H), 7.78 (td, J = 6.9 and 1.4 Hz, 1 H), 1 H), 7.69 (d, J = 5.5 Hz, 1 H), 7.61–7.52 (m, 4 H), 7.16 (d, J = 8.3 Hz, 2 H), 5.90 (s, 2 H), 2.90 (t, J = 7.3 Hz, 2 H), 1.81–1.65 (m, 2 H), 1.45–1.26 (m, 2 H), 0.85 (t, J = 7.2 Hz, 3 H). Anal. ($C_{24}H_{21}ClN_4{\cdot}0.1H_2O$) C, H, N.

The following were prepared analogously.

4′-[(2-Ethyl-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (6c) was prepared from **8c** (47.0 g, 235.0 mmol) to give 34.0 g (41%) of **6c**: mp 230–231 °C; ^{1}H NMR (DMSO-d_6) δ 11.25 (brd, J = 5.3 Hz, 1 H), 7.92 (dd, J = 7.4 Hz, 1 H), 7.77 (td, J = 7.5 Hz, 1 H), 7.59 (brd, J = 7.8 Hz, 1 H), 7.56 (td, J = 7.8 Hz, 1 H), 7.55 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.2 Hz, 2 H), 7.09 (dd, J = 7.0 and 5.0 Hz, 2 H), 6.55 (d, J = 7.0 Hz, 1 H), 5.82 (s, 2 H), 2.74 (q, J = 7.5 Hz, 2 H), 1.21 (t, J = 7.5 Hz, 3 H); IR (KBr) 2220, 1659 cm^{-1}. Anal. ($C_{22}H_{18}N_4O$) C, H, N, O.

4′-[(2-Cyclopropyl-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]-pyridin-3-yl)methyl]biphenyl-2-carbonitrile (6d) was prepared from **8d** (5.1 g, 24.1 mmol) to give 1.87 g (21%) of **6d**: mp 206–207 °C; ^{1}H NMR (DMSO-d_6) δ 11.23 (brd, J = 5.5 Hz, 1 H), 7.83 (d, J = 7.0 Hz, 1 H), 7.84–7.68 (m, 1 H), 7.64–7.50 (m, 4 H), 7.40 (d, J = 7.7 Hz, 2 H), 7.07 (dd, J = 7.0 and 5.0 Hz, 1 H), 6.48 (d, J = 7.0 Hz, 1 H), 5.93 (s, 2 H), 2.27–2.08 (m, 1 H), 1.08–0.93 (m, 4 H); IR (KBr) 2210, 1658 cm^{-1}. Anal. ($C_{23}H_{18}N_4O{\cdot}1.2H_2O$) C, H, N.

4′-[(2-Butyl-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carboxylic Acid (13). A sample of **6a** (1.0 g, 2.6 mmol) was stirred in a mixture of 30 mL of ethylene glycol and 1.5 g of KOH for 12 h at 160 °C. The reaction mixture was poured on crushed ice and the pH adjusted to 5 with concentrated hydrochloric acid. The precipitate which was collected was dried and identified as the acid **13** (550 mg): mp 275–276 °C; ^{1}H NMR (DMSO-d_6) δ 12.70 (brs, 1 H), 11.25 (d, J = 5.8 Hz, 1 H), 7.55 (d, J = 7.2 Hz, 1 H), 7.38 (t, J = 6.0 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 2 H), 7.32 (t, J = 7.3 Hz, 1 H), 7.24 (d, J = 7.5 Hz, 1 H), 7.13 (d, J = 8.1 Hz, 2 H), 7.08 (dd, J = 6.9 and 5.8 Hz, 1 H), 6.53 (d, J = 6.9 Hz, 1 H), 5.77 (s, 2 H), 2.71 (t, J = 7.6 Hz, 2 H), 1.79–1.50 (m, 2 H), 1.42–1.20 (m, 2 H), 0.84 (t, J = 7.4 Hz, 3 H); IR (KBr) 1659 cm^{-1}. ($C_{24}H_{23}N_3O_3{\cdot}0.35H_2O$) C, H, N.

4′-[(5-Benzyl-2-butyl-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]-pyridin-3-yl)methyl]biphenyl-2-carbonitrile (11a). Under a nitrogen atmosphere, **6a** (14.5 g, 37.9 mmol) was dissolved in dry dimethylformamide (200 mL). At ambient temperature, potassium *tert*-butoxide (4.5 g, 40 mmol) was added to the solution. After the resulting mixture had been stirred at the

same temperature for 15 min, benzyl bromide (6.8 g, 40 mmol) was added at once. The reaction mixture was allowed to stir for 18 h at ambient temperature and concentrated in vacuo to an oil which was partitioned between water (250 mL) and ethyl acetate (250 mL). The organic extract was dried on Na_2SO_4, concentrated in vacuo, and chromatographed on silica gel with 50% ethyl acetate in hexane as eluent. Recrystallization from ethyl acetate provided 15.7 g (88%) of **11a** as a white solid: mp 131–132 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (d, J = 7.8 Hz, 1 H), 7.77 (td, J = 7.5 and 1.4 Hz, 1 H), 7.60–7.55 (m, 4 H), 7.53 (d, J = 7.2 Hz, 1 H), 7.37–7.22 (m, 7 H), 6.65 (d, J = 7.2 Hz, 1 H), 5.87 (s, 2 H), 5.22 (s, 2 H), 2.74 (t, J = 7.4 Hz, 2 H), 1.68–1.56 (m, 2 H), 1.37–1.23 (m, 2 H), 0.82 (t, J = 7.4 Hz, 3 H); IR (KBr) 2210, 1662 cm^{-1}. Anal. ($C_{31}H_{28}N_4O$) C, H, N.

The following were prepared analogously.

4′-[(2-Butyl-4,5-dihydro-4-oxo-5-(2-thenyl)-3*H*-imidazo-[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (11b) was prepared from **6a** (1.0 g, 2.6 mmol) to give 0.98 g (79%) of **11b**: mp 63–64 °C; ^{1}H NMR (DMSO-d_6) δ 7.93 (dd, J = 7.8 and 1.5 Hz, 1 H), 7.78 (td, J = 6.8 and 1.4 Hz, 1 H), 7.61–7.51 (m, 5 H), 7.42 (dd, J = 5.1 and 1.3 Hz, 1 H), 7.35–7.27 (m, 2 H), 7.17 (dd, J = 3.5 and 1.1 Hz, 1 H, 6.98 (dd, J = 5.1 and 3.4 Hz, 1 H), 6.64 (d, J = 7.2 Hz, 1 H), 5.87 (s, 2 H), 5.36 (s, 2 H), 2.74 (t, J = 7.5 Hz, 2 H), 1.68–1.51 (m, 2 H), 1.38–1.19 (m, 2 H), 0.81 (t, J = 7.3 Hz, 3 H). Anal. ($C_{29}H_{26}N_4OS$·0.15H_2O) C, H, N.

4′-[(2-Butyl-4,5-dihydro-5-methyl-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (11c) was prepared from **6a** (2.0 g, 5.2 mmol) to give 1.6 g (76%) of **11c**: mp 110–111 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (dd, J = 7.9 and 0.8 Hz, 1 H), 7.77 (td, J = 7.7 and 1.2 Hz, 1 H), 7.58 (d, J = 7.8 Hz, 1 H), 7.57 (td, J = 7.9 and 0.9 Hz, 1 H), 7.55 (d, J = 8.2 Hz, 2 H), 7.43 (d, J = 7.2 Hz, 1 H), 7.28 (d, J = 8.2 Hz, 2 H), 6.59 (d, J = 7.2 Hz, 1 H), 5.86 (s, 2 H), 3.52 (s, 3 H), 2.73 (t, J = 7.6 Hz, 2 H), 1.64–1.58 (m, 2 H), 1.33–1.25 (m, 2 H), 0.82 (t, J = 7.4 Hz, 3 H). Anal. ($C_{25}H_{24}N_4O$) C, H, N.

4′-[(2-Butyl-5-ethyl-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]-pyridin-3-yl)methyl]biphenyl-2-carbonitrile (11d) was prepared from **6a** (2.0 g, 5.2 mmol) to give 1.5 g (71%) of **11d** as a viscous oil: ^{1}H NMR (DMSO-d_6) δ 7.93 (dd, J = 7.8 and 1.5 Hz, 1 H), 7.78 (td, J = 8.0 and 1.5 Hz, 1 H), 7.61–7.51 (m, 4 H), 7.44 (d, J = 7.2 Hz, 1 H), 7.28 (m, 2 H), 6.61 (d, J = 7.2 Hz, 1 H), 5.86 (s, 2 H), 4.09–3.95 (m, 2 H), 2.72 (t, J = 7.2 Hz, 2 H), 1.69–1.51 (m, 2 H), 1.39–1.16 (m, 5 H), 0.81 (t, J = 7.2 Hz, 3 H); FAB MS m/e 411 (M^+ + H). Anal. ($C_{26}H_{26}N_4O$·0.4H_2O) C, H, N.

4′-[(2-Butyl-5-(4-chlorobenzyl)-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (11e) was prepared from **6a** (1.0 g, 2.6 mmol) to give 0.85 g (64%) of **11e**: mp 124–125 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (dd, J = 7.7 and 1.7 Hz, 1 H), 7.63 (dd, J = 8.2 and 1.4 Hz, 1 H), 7.54–7.38 (m, 4 H), 7.33–7.19 (m, 6 H), 7.11 (d, J = 7.2 Hz, 1 H), 6.69 (d, J = 7.2 Hz, 1 H), 5.87 (s, 2 H), 5.19 (s, 2 H), 2.77 (t, J = 7.3 Hz, 2 H), 1.84–1.69 (m, 2 H), 1.49–1.30 (m, 2 H), 0.91 (t, J = 7.3 Hz, 3 H). Anal. ($C_{31}H_{27}ClN_4O$·0.2H_2O) C, H, N.

4′-[(2-Butyl-5-(3-chlorobenzyl)-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (11f) was prepared from **6a** (1.0 g, 2.6 mmol) to give 0.80 g (61%) of **11f**: mp 143–144 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (dd, J = 7.9 and 1.8 Hz, 1 H), 7.63 (dd, J = 8.0 and 1.4 Hz, 1 H), 7.54–7.38 (m, 4 H), 7.29–7.14 (m, 6 H), 7.11 (d, J = 7.3 Hz, 1 H), 6.71 (d, J = 7.3 Hz, 1 H), 5.87 (s, 2 H), 5.20 (s, 2 H), 2.77 (t, J = 7.2 Hz, 2 H), 1.85–1.69 (m, 2 H), 1.49–1.30 (m, 2 H), 0.91 (t, J = 7.2 Hz, 3 H). Anal. ($C_{31}H_{27}ClN_4O$) C, H, N.

4-[(2-Butyl-5-(2-chlorobenzyl)-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (11g) was prepared from **6a** (5.0 g, 13.1 mmol) to give 4.2 g (64%) of **11g**: mp 138–139 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (dd, J = 8.0 and 1.5 Hz, 1 H), 7.62 (dd, J = 8.0 and 1.5 Hz, 1 H), 7.54–7.35 (m, 5 H), 7.29–7.06 (m, 6 H), 6.70 (d, J = 6.3 Hz, 1 H), 5.87 (s, 2 H), 5.35 (s, 2 H), 2.77 (t, J = 7.2 Hz, 2 H), 1.85–1.70 (m, 2 H), 1.50–1.30 (m, 2 H), 0.91 (t, J = 7.2 Hz, 3 H). Anal. ($C_{31}H_{27}ClN_4O$) C, H, N.

4′-[(5-(2-Bromobenzyl)-2-butyl-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (11h) was prepared from **6a** (1.0 g, 2.6 mmol) to give 1.2 g (83%) of **11h**: mp 141–142 °C; ^{1}H NMR (DMSO-d_6) δ 7.93 (dd, J = 8.3 and 1.6 Hz, 1 H), 7.77 (td, J = 8.0 and 1.5 Hz, 1 H), 7.67 (dd, J = 7.7 and 1.5 Hz, 1 H), 7.61–7.51 (m, 4 H), 7.49 (d, J = 7.3 Hz, 1 H), 7.38–7.18 (m, 4 H), 6.75 (dd, J = 7.7 and 1.9 Hz, 1 H), 6.72 (d, J = 7.3 Hz, 1 H), 5.84 (s, 2 H), 5.25 (s, 2 H), 2.76 (t, J = 7.2 Hz, 2 H), 1.71–1.54 (m, 2 H), 1.40–1.21 (m, 2 H), 0.83 (t, J = 7.3 Hz, 3 H). Anal. ($C_{31}H_{27}BrN_4O$) C, H, N.

4′-[(2-Butyl-5-(2-fluorobenzyl)-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (11i) was prepared from **6a** (1.5 g, 3.9 mmol) to give 1.69 g (88%) of **11i** as a viscous oil: ^{1}H NMR (DMSO-d_6) δ 7.77–7.01 (m, 13 H), 6.70 (d, J = 7.2 Hz, 1 H), 5.88 (s, 2 H), 5.29 (s, 2 H), 2.76 (t, J = 7.3 Hz, 2 H), 1.83–1.68 (m, 2 H), 1.48–1.29 (m, 2 H), 0.90 (t, J = 7.2 Hz, 3 Hz, 2 H); FAB MS m/e 491 (M^+ + H). Anal. ($C_{31}H_{27}FN_4O$·0.3H_2O) C, H, N.

4′-[(2-Butyl-4,5-dihydro-5-(2-nitrobenzyl)-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl] biphenyl-2-carbonitrile (11k) was prepared from **6a** (1.0 g, 2.6 mmol) to give 1.0 g (87%) of **11k**: mp 102–103 °C; ^{1}H NMR (DMSO-d_6) δ 8.13 (dd, J = 8.1 and 1.5 Hz, 1 H), 7.93 (dd, J = 8.3 and 1.6 Hz, 1 H), 7.78 (td, J = 7.8 and 1.4 Hz, 1 H), 7.68 (td, J = 7.6 and 1.5 Hz, 1 H), 7.62–7.49 (m, 6 H), 7.28 (m, 2 H), 6.89 (dd, J = 7.7 and 1.4 Hz, 1 H), 6.74 (d, J = 7.3 Hz, 1 H), 5.82 (s, 2 H), 5.55 (s, 2 H), 2.76 (t, J = 7.2 Hz, 2 H), 1.70–1.54 (m, 2 H), 1.40–1.21 (m, 2 H), 0.82 (t, J = 7.3 Hz, 3 H). Anal. ($C_{31}H_{27}N_5O_3$·0.25H_2O) C, H, N.

2-[[2-Butyl-3-[(2′-cyano-4-biphenylyl)methyl]-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-5-yl]methyl]benzoic acid, ethyl ester (11m) was prepared from **6a** (15.0 g, 39.2 mmol) to give 15.7 g (73%) of **11m**: mp 138–139 °C; ^{1}H NMR (DMSO-d_6) δ 7.95–7.91 (m, 2 H), 7.77 (td, J = 7.8 and 1.3 Hz, 1 H), 7.58–7.48 (m, 6 H), 7.40 (td, J = 7.3 and 1.5 Hz, 1 H), 7.28 (d, J = 8.2 Hz, 2 H), 6.77 (d, J = 7.8 Hz, 1 H), 6.70 (d, J = 7.2 Hz, 1 H), 5.83 (s, 2 H), 5.56 (s, 2 H), 4.34 (q, J = 7.1 Hz, 2 H), 2.76 (t, J = 7.5 Hz, 2 H), 1.66–1.59 (m, 2 H), 1.34 (t, J = 7.0 Hz, 3 H), 1.35–1.27 (m, 2 H), 0.83 (t, J = 7.3 Hz, 3 H). Anal. ($C_{34}H_{32}N_4O_3$) C, H, N, O.

4′-[(2-Butyl-4,5-dihydro-4-oxo-5-phenacyl-3*H*-imidazo-[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (11n) was prepared from **6a** (1.0 g, 2.6 mmol) to give 0.7 g (54%) of **11n**: mp 167–168 °C; ^{1}H NMR (DMSO-d_6) δ 8.10–8.05 (m, 2 H), 7.96–7.90 (m, 1 H), 7,82–7.50 (m, 8 H), 7.43 (d, J = 7.2 Hz, 1 H), 7.29–7.23 (m, 2 H), 6.67 (d, J = 7.2 Hz, 1 H), 5.82 (s, 2 H), 5.60 (s, 2 H), 2.75 (t, J = 7.7 Hz, 2 H), 1.71–1.55 (m, 2 H), 1.41–1.21 (m, 2 H), 0.83 (t, J = 7.3 Hz, 3 H). Anal. ($C_{32}H_{28}N_4O_2$·0.3H_2O) C, H, N.

4′-[(2-Butyl-4,5-dihydro-5-(3,3-dimethyl-2-oxobutyl)-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (11o) was prepared from **6a** (1.0 g, 2.6 mmol) to give 0.98 g (78%) of **11o**: mp 156–157 °C; ^{1}H NMR (DMSO-d_6) δ 7.93 (dd, J = 7.0 and 1.5 Hz, 1 H), 7.78 (td, J = 6.9 and 1.5 Hz, 1 H), 7.61–7.51 (m, 4 H), 7.31–7.22 (m, 3 H), 6.62 (d, J = 7.2 Hz, 1 H), 5.83 (s, 2 H), 5.10 (s, 2 H), 2.73 (t, J = 7.2 Hz, 2 H), 1.69–1.52 (m, 2 H), 1.39–1.22 (m, 2 H), 1.20 (s, 9 H), 0.82 (t, J = 7.3 Hz, 3 H). Anal. ($C_{30}H_{32}N_4O_2$·0.45H_2O) C, H, N.

2-Butyl-3-[(2′-cyano-4-biphenyl)methyl]-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridine-5-acetic acid, ethyl ester (11p) was prepared from **6a** (50.0 g, 0.13 mol) and recrystallized from ethyl acetate/hexane (95:5) to give 49.1 g (77%) of **11p**: mp 152–153 °C; ^{1}H NMR (DMSO-d_6) δ 7.96–7.89 (m, 1 H), 7.82–7.72 (m, 1 H), 7.61–7.52 (m, 4 H), 7.44 (d, J = 7.3 Hz, 1 H), 7.31–7.24 (m, 2 H), 6.65 (d, J = 7.3 Hz, 1 H), 5.82 (s, 2 H), 4.79 (s, 2 H), 4.14 (q, J = 7.1 Hz, 2 H), 2.74 (t, J = 7.4 Hz, 2 H), 1.71–1.54 (m, 2 H), 1.41–1.24 (m, 2 H), 1.20 (t, J = 7.1 Hz, 3 H), 0.83 (t, J = 7.2 Hz, 3 H). Anal. ($C_{28}H_{28}N_4O_3$) C, H, N.

4′-[[2-Butyl-4,5-dihydro-5-[(*N*,*N*-dimethylcarbamoyl)-methyl]-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl]methyl]biphenyl-2-carbonitrile (11q) was prepared from **6a** (2.0 g, 5.2 mmol) to give 1.95 g (81%) of **11q**: mp 189–190 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (dd, J = 7.5 and 0.9 Hz, 1 H), 7.76 (td, J = 7.6 and 1.2 Hz, 1 H), 7.58 (d, J = 7.4 Hz, 1 H), 7.56 (td, J = 7.3 and 1.0 Hz, 1 H), 7.54 (d, J = 8.1 Hz, 2 H), 7.29 (d, J = 7.3 Hz, 1 H), 7.27 (d, J = 8.2 Hz, 2 H), 6.60 (d, J = 7.2 Hz, 1 H), 5.84 (s, 2 H), 4.88 (s, 2 H), 3.07 (s, 3 H), 2.86 (s, 3 H), 2.74 (t, J = 7.6 Hz, 2 H), 1.66–1.59 (m, 2 H), 1.34–1.26 (m, 2 H), 0.82 (t, J = 7.4 Hz, 3 H). Anal. ($C_{28}H_{29}N_5O_2$) C, H, N.

4′-[[4,5-Dihydro-5-[(*N*,*N*-dimethylcarbamoyl)methyl]-4-oxo-2-propyl-3*H*-imidazo[4,5-*c*]pyridin-3-yl]methyl]biphenyl-2-carbonitrile (11r) was prepared from **6b** (0.4 g, 1.09 mmol)

to give 0.4 g (81%) of 11r: mp 203–204 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (dd, J = 1.4 and 7.9 Hz, 1 H), 7.82–7.72 (m, 1 H), 7.61–7.52 (m, 4 H), 7.31–7.24 (m, 3 H), 6.60 (d, J = 7.3 Hz, 1 H), 5.83 (s, 2 H), 4.87 (s, 2 H), 3.06 (s, 3 H), 2.85 (s, 3 H), 2.72 (q, J = 7.5 Hz, 2 H), 1.79–1.60 (m, 2 H), 0.90 (t, J = 7.5 Hz). Anal. ($C_{27}H_{27}N_5O_2 \cdot 0.6H_2O$) C, H, N.

4′-[[4,5-Dihydro-5-[(*N*,*N*-dimethylcarbamoyl)methyl]-2-ethyl-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl]methyl]biphenyl-2-carbonitrile (11s) was prepared from **6c** (1.4 g, 3.95 mmol) to give 1.2 g (71%) of 11s: mp 234–235 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (dd, J = 7.8 and 1.2 Hz, 1 H), 7.76 (td, J = 7.7 and 1.4 Hz, 1 H), 7.61–7.52 (m, 4 H), 7.30–7.25 (m, 3 H), 6.59 (d, J = 7.3 Hz, 1 H), 5.82 (s, 2 H), 4.87 (s, 2 H), 3.06 (s, 3 H), 2.85 (s, 3 H), 2.76 (q, J = 7.5 Hz, 2 H), 1.22 (t, J = 7.5 Hz, 3 H). Anal. ($C_{26}H_{25}N_5O_2$) C, H, N.

4′-[[2-Cyclopropyl-4,5-dihydro-5-[(*N*,*N*-dimethylcarbamoyl)methyl]-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl]methyl]biphenyl-2-carbonitrile (11t) was prepared from **6d** (430 mg, 1.2 mmol) to give 328 mg (60%) of 11t: mp 178–179 °C; ^{1}H NMR (DMSO-d_6) δ 7.93 (dd, J = 7.0 Hz, 1 H), 7.83–7.72 (m, 1 H), 7.65–7.51 (m, 2 H), 7.56 (d, J = 7.8 Hz, 2 H), 7.37 (d, J = 7.8 Hz, 2 H), 7.30 (d, J = 7.0 Hz, 1H), 6.54 (d, J = 7.0 Hz, 1 H), 5.94 (s, 2 H), 4.37 (s, 2 H), 3.08 (s, 3 H), 2.36 (s, 3 H), 2.32–2.19 (m, 1 H), 1.13–0.98 (m, 4 H). Anal. ($C_{27}H_{25}N_5O_2 \cdot 0.4H_2O$) C, H, N.

4′-[[2-Butyl-5-[(*N*,*N*-diethylcarbamoyl)methyl]-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl]methyl]biphenyl-2-carbonitrile (11u) was prepared from **6a** (2.0 g, 5.2 mmol) to give 1.3 g (50%) of 11u: mp 169–170 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (dd, J = 7.9 and 1.5 Hz, 1 H), 7.82–7.72 (m, 1 H), 7.61–7.52 (m, 4 H), 7.33 (d, J = 7.3 Hz, 1 H), 7.25 (d, J = 8.3 Hz, 1 H), 6.59 (d, J = 7.2 Hz, 1 H), 5.84 (s, 2 H), 4.86 (s, 2 H), 3.46–3.23 (m, 4 H), 2.72 (t, J = 7.2 Hz, 2 H), 1.70–1.53 (m, 2 H), 1.40–1.14 (m, 4 H), 1.04 (t, J = 7.1 Hz, 3 H), 0.82 (t, J = 7.2 Hz, 3 H). Anal. ($C_{30}H_{34}N_5O_2 \cdot 0.2H_2O$) C, H, N.

4′-[[5-[(*N*,*N*-Diethylcarbamoyl)methyl]-4,5-dihydro-2-ethyl-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl]methyl]biphenyl-2-carbonitrile (11v) was prepared from **6c** (1.4 g, 3.95 mmol) and recrystallized from ethyl acetate to give 1.3 g (72%) of 11v: mp 159–160 °C; ^{1}H NMR (DMSO-d_6) δ 7.93 (dd, J = 8.1 and 1.5 Hz, 1 H), 7.77 (td, J = 7.2 and 1.5 Hz, 1 H), 7.62–7.51 (m, 4 H), 7.33 (d, J = 7.3 Hz, 1 H), 7.26 (d, J = 8.3 Hz, 2 H), 6.60 (d, J = 7.2 Hz, 1 H), 5.83 (s, 2 H), 4.86 (s, 2 H), 3.40 (q, J = 7.2 Hz, 2 H), 3.28 (q, J = 7.2 Hz, 2 H), 1.22 (t, J = 7.4 Hz, 3 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.03 (t, J = 7.2 Hz, 3 H). Anal. ($C_{28}H_{29}N_5O_2$) C, H, N.

4′-[[2-Butyl-5-[(*N*-*tert*-butylcarbamoyl)methyl]-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl]methyl]biphenyl-2-carbonitrile (11w) was prepared from **6a** (2.0 g, 5.2 mmol) to give 2.1 g (75%) of 11w: mp 132–133 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (dd, J = 6.9 and 1.7 Hz, 1 H), 7.77 (td, J = 7.4 and 1.5 Hz, 1 H), 7.76 (brs, 1 H), 7.61–7.50 (m, 4 H), 7.33–7.25 (m, 3 H), 6.57 (d, J = 7.2 Hz, 1 H), 5.83 (s, 2 H), 4.55 (s, 2 H), 2.74 (t, J = 7.2 Hz, 2 H), 1.70–1.54 (m, 2 H), 1.40–1.20 (m, 2 H), 1.26 (s, 6 H), 0.82 (t, J = 7.2 Hz, 3 H). Anal. ($C_{30}H_{32}N_5O_2 \cdot 0.15H_2O$) C, H, N.

3-[(2′-Cyano-4-biphenylyl)methyl]-2-ethyl-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridine-5-acetic acid, ethyl ester (11x) was prepared from **6c** (10.0 g, 28.2 mmol) and recrystallized from ethyl acetate to give 9.2 g (74%) of 11x: mp 143–144 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (dd, J = 7.3 and 1.4 Hz, 1 H), 7.77 (td, J = 7.1 and 1.5 Hz, 1 H), 7.61–7.50 (m, 4 H), 7.44 (d, J = 7.3 Hz, 1 H), 7.31–7.24 (m, 2 H), 6.66 (d, J = 7.3 Hz, 1 H), 5.81 (s, 2 H), 4.80 (s, 2 H), 4.14 (q, J = 7.1 Hz, 2 H), 2.76 (q, J = 7.4 Hz, 2 H), 1.23 (t, J = 7.4 Hz, 3 H), 1.19 (t, J = 7.1 Hz, 3 H). Anal. ($C_{26}H_{24}N_4O_3$) C, H, N.

4′-[[2-Butyl-4,5-dihydro-5-[(*N*,*N*-diphenylcarbamoyl)methyl]-4-oxo-3*H*-imidazo[4,5-*c*]-pyridin-3-yl]methyl]biphenyl-2-carbonitrile (11y) was prepared from **6a** (1.0 g, 2.6 mmol) and recrystallized from acetone to give 0.93 g (60%) of 11y: mp 171–172 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (dd, J = 7.8 Hz, 1 H), 7.76 (td, J = 7.7 and 1.3 Hz, 1 H), 7.75–7.10 (m, 12 H), 7.53 (d, J = 8.3 Hz, 2 H), 7.38 (d, J = 7.3 Hz, 1 H), 7.26 (d, J = 8.3 Hz, 2 H), 6.60 (d, J = 7.2 Hz, 1 H), 5.85 (s, 2 H), 4.68 (s, 2 H), 2.73 (t, J = 7.5 Hz, 2 H), 1.63–1.56 (m, 2 H), 1.32–1.24 (m, 2 H), 0.80 (t, J = 7.3 Hz, 3 H). Anal. ($C_{38}H_{33}N_5O_2 \cdot 0.2H_2O$) C, H, N.

2-Butyl-3-[(2′-cyano-4-biphenylyl)methyl]-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridine-5-acetic Acid (15a). A solution of 11p (38.6 g, 82.5 mmol) in a 1:3 mixture of methanol and tetrahydrofuran (800 mL) and 400 mL of 10% aqueous sodium hydroxide solution was allowed to stir at ambient temperature overnight. The solution was concentrated to 600 mL, and this solution was adjusted to pH 3.0 with hydrochloric acid. The precipitated solids were recovered by filtration and recrystallized from ethyl acetate to provide 33.0 g (91%) of 15a: mp 221–222 °C; ^{1}H NMR (DMSO-d_6) δ 13.60 (brs, 1 H), 7.96–7.89 (m, 1 H), 7.82–7.72 (m, 1 H), 7.61–7.51 (m, 4 H), 7.43 (d, J = 7.3 Hz, 1 H), 7.32–7.25 (m, 2 H), 6.63 (d, J = 7.3 Hz, 1 H), 5.84 (s, 2 H), 4.71 (s, 2 H), 2.75 (t, J = 7.2 Hz, 2 H), 1.70–1.54 (m, 2 H), 1.39–1.21 (m, 2 H), 0.83 (t, J = 7.2 Hz, 3 H). Anal. ($C_{26}H_{24}N_4O_3 \cdot 0.7H_2O$) C, H, N.

The following were prepared analogously.

3-[(2′-Cyano-4-biphenylyl)methyl]-2-ethyl-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridine-5-acetic acid (15c) was prepared from 11w (9.2 g, 20.9 mmol) and recrystallized from ethyl acetate to give 6.0 g (70%) of 15c: mp 220–221 °C; ^{1}H NMR (DMSO-d_6) δ 7.93 (dd, J = 7.8 and 1.5 Hz, 1 H), 7.77 (td, J = 7.2 and 1.5 Hz, 1 H), 7.62–7.51 (m, 4 H), 7.43 (d, J = 7.3 Hz, 1 H), 7.32–7.25 (m, 2 H), 6.64 (d, J = 7.2 Hz, 1 H), 5.83 (s, 2 H), 4.72 (s, 2 H), 2.77 (q, J = 7.3 Hz, 2 H), 1.22 (t, J = 7.4 Hz, 3 H). Anal. ($C_{24}H_{20}N_4O_3$) C, H, N.

2-[[2-Butyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-5-yl]methyl]benzoic acid (21) was prepared from 14m (6.0 g, 10.2 mmol) to give 5.4 g (95%) of 21: mp 233–234 °C; ^{1}H NMR (DMSO-d_6) δ 13.05 (brs, 1 H), 7.96 (dd, J = 7.8 and 1.5 Hz, 1 H, 7.66 (dd, J = 7.5 and 1.4 Hz, 1 H), 7.64 (dd, J = 6.7 and 1.5 Hz, 1 H), 7.58–7.46 (m, 4 H), 7.38 (td, J = 7.4 and 0.8 Hz, 1 H), 7.10 (d, J = 8.3 Hz, 2 H), 7.04 (d, J = 8.3 Hz, 2 H), 6.72 (d, J = 7.8 Hz, 1 H), 6.69 (d, J = 7.2 Hz, 1 H), 5.75 (s, 2 H), 5.58 (s, 2 H), 2.70 (t, J = 7.5 Hz, 2 H), 1.63–1.56 (m, 2 H), 1.36–1.27 (m, 2 H), 0.84 (t, J = 7.4 Hz, 3 H). Anal. ($C_{32}H_{29}N_7O_3 \cdot 1.0H_2O$) C, H, N.

4′-[[2-Butyl-4,5-dihydro-5-[(2-oxo-2-pyrrolidino)ethyl]-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl]methyl]biphenyl-2-carbonitrile (17a). To compound 15a (1.0 g, 2.3 mmol) in dimethylformamide (20 mL) were added pyrrolidine (0.2 g, 2.3 mmol), 1-hydroxybenzotriazole (HOBt, 0.3 g, 2.3 mmol), *N*-methylmorpholine (NMM, 0.31 mL, 2.3 mmol), and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (EDC, 0.4 g, 2.3 mmol). After being stirred for 4 h at ambient temperature, the mixture was poured into saturated $NaHCO_3$ solution (100 mL) and extracted with ethyl acetate (3 × 100 mL) which was washed with water (50 mL) and brine (50 mL), and then dried and evaporated. Chromatography of the residue with 10% methanol in ethyl acetate afforded 0.92 g (83%) of 17a as a white solid: mp 166–167 °C; ^{1}H NMR (DMSO-d_6) δ 7.93 (d, J = 7.6 Hz, 1 H), 7.77 (td, J = 7.8 and 1.1 Hz, 1 H), 7.59–7.53 (m, 4 H), 7.33 (d, J = 7.3 Hz, 1 H), 7.27 (d, J = 8.2 Hz, 2 H), 6.60 (d, J = 7.3 Hz, 1 H), 5.83 (s, 2 H), 4.79 (s, 2 H), 3.52 (t, J = 6.9 Hz, 2 H), 3.31 (t, J = 6.9 Hz, 2 H), 2.74 (t, J = 7.5 Hz, 2 H), 1.97–1.90 (m, 2 H), 1.83–1.76 (m, 2 H), 1.65–1.56 (m, 2 H), 1.34–1.26 (m, 2 H), 0.83 (t, J = 7.4 Hz, 3 H). Anal. ($C_{30}H_{31}N_5O_2 \cdot 0.5H_2O$) C, H, N.

The following were prepared analogously.

4′-[(2-Butyl-5-(carbamoylmethyl)-4,5-dihydro-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl)methyl]biphenyl-2-carbonitrile (17b) was prepared from 15a (1.5 g, 3.4 mmol) to give 0.92 g (62%) of 17b: mp 218–219 °C; ^{1}H NMR (DMSO-d_6) δ 7.91 (dd, J = 7.9 and 0.8 Hz, 1 H), 7.79 (td, J = 7.0 and 1.5 Hz, 1 H), 7.61–7.50 (m, 5 H), 7.32 (d, J = 7.3 Hz, 1 H), 7.29 (m, 2 H), 7.11 (brs, 1 H), 6.59 (d, J = 7.2 Hz, 1H), 5.82 (s, 2 H), 4.59 (s, 2 H), 2.72 (t, J = 7.3 Hz, 2 H), 1.69–1.54 (m, 2 H), 1.39–1.20 (m, 2 H), 0.81 (t, J = 7.3 Hz, 3 H). Anal. ($C_{26}H_{25}N_5O_2$) C, H, N.

4′-[[2-Butyl-4,5-dihydro-4-oxo-5-[(*N*-phenylcarbamoyl)-methyl]-3*H*-imidazo[4,5-*c*]pyridin-3-yl]methyl]biphenyl-2-carbonitrile (17c) was prepared from 15a (1.0 g, 2.3 mmol) to give 0.45 g (38%) of 17c: mp 106–107 °C; ^{1}H NMR (DMSO-d_6) δ 10.30 (s, 1 H), 7.93 (dd, J = 8.0 and 0.8 Hz, 1 H), 7.77 (td, J = 8.0 and 1.1 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 2 H), 7.58 (t, J = 7.8 Hz, 2 H), 7.54 (d, J = 8.0 Hz, 2 H), 7.45 (d, J = 7.2 Hz, 1 H), 7.30 (t, J = 7.8 Hz, 1 H), 7.30 (d, J = 8.4 Hz, 1 H), 7.28 (d, J = 8.5 Hz, 2 H), 7.05 (t, J = 7.4 Hz, 1 H), 6.64 (d, J = 7.3 Hz, 1 H), 5.83 (s, 2 H), 4.83 (s, 2 H), 2.75 (t, J = 7.5 Hz, 2 H), 1.67–1.59 (m, 2 H), 1.37–1.24 (m, 2 H), 0.83 (t, J = 7.2 Hz, 3 H). Anal. ($C_{32}H_{29}N_5O_2 \cdot 0.4H_2O$) C, H, N.

4′-[[2-Butyl-4,5-dihydro-5-[(*N*-methyl-*N*-phenylcarbamoyl)methyl]-4-oxo-3*H*-imidazo[4,5-*c*]pyridin-3-yl]methyl]biphenyl-2-carbonitrile (17d) was prepared from **15a** (2.2 g, 5.0 mmol) to give 1.1 g (42%) of **17d**: mp 121–122 °C; ^{1}H NMR (DMSO-d_6) δ 7.92 (dd, J = 7.9 and 0.8 Hz, 1 H), 7.77 (td, J = 7.6 and 1.1 Hz, 1 H), 7.58 (d, J = 7.8 Hz, 1 H), 7.57 (d, J = 7.5 Hz, 1 H), 7.55–7.52 (m, 2 H), 7.53 (d, J = 8.2 Hz, 2 H), 7.49 (brm, 2 H), 7.42 (brm, 1 H), 7.32 (d, J = 7.3 Hz, 1 H), 7.23 (d, J = 8.1 Hz, 2 H), 6.59 (d, J = 7.3 Hz, 1 H), 5.82 (s, 2 H), 4.53 (s, 2 H), 3.20 (s, 3 H), 2.72 (t, J = 7.5 Hz, 2 H), 1.65–1.57 (m, 2 H), 1.34–1.24 (m, 2 H), 0.81 (t, J = 7.4 Hz, 3 H). Anal. ($C_{33}H_{31}N_5O_2$·0.6H_2O) C, H, N.

4′-[[2-Ethyl-4,5-dihydro-4-oxo-5-[(2-oxo-2-piperidino)ethyl]-3*H*-imidazo[4,5-*c*]pyridin-3-yl]methyl]biphenyl-2-carbonitrile (18) was prepared from **15c** (1.0 g, 2.43 mmol) and recrystallized from ethyl acetate/methanol (90:10) to give 0.6 g (52%) of 18: mp 220–221 °C; ^{1}H NMR (DMSO-d_6) δ 7.93 (dd, J = 7.8 and 1.2 Hz, 1 H), 7.77 (td, J = 7.9 and 1.5 Hz, 1 H), 7.62–7.50 (m, 4 H), 7.31 (d, J = 7.2 Hz, 1 H), 7.31–7.23 (m, 2 H), 6.60 (d, J = 7.2 Hz, 1 H), 5.82 (s, 2 H), 4.88 (s, 2 H), 3.52–3.35 (br, 4 H), 2.76 (q, J = 7.5 Hz, 2 H), 1.68–1.35 (br, 6 H), 1.22 (t, J = 7.3 Hz, 3 H). Anal. ($C_{29}H_{29}N_5O_2$) C, H, N.

5-Benzyl-2-butyl-4,5-dihydro-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (14a). Compound **11a** (15.0 g, 31.7 mmol) was allowed to reflux with trimethyltin azide (19.0 g, 95.1 mmol) in toluene (200 mL). The mixture was stirred for 48 h and concentrated in vacuo to an oil. The residue was taken up in 40 mL of ice-cold, dry methanol saturated with HCl gas. The resulting mixture was stirred for 15 min before it was concentrated in vacuo. Flash chromatography (10% methanol in ethyl acetate as eluent) and recrystallization from ethanol provided 7.6 g (47%) of pure tetrazole **14a**: mp 160–161 °C; ^{1}H NMR (DMSO-d_6) δ 7.66 (td, J = 7.0 and 1.1 Hz, 1 H), 7.65 (d, J = 7.6 Hz, 1 H), 7.56 (td, J = 7.4 and 0.9 Hz, 1 H), 7.52 (d, J = 7.3 Hz, 1 H), 7.50 (d, J = 7.7 Hz, 1 H), 7.33 (t, J = 7.4 Hz, 2 H), 7.28 (d, J = 7.6 Hz, 2 H), 7.27 (d, J = 7.8 Hz, 1 H), 7.08 (d, J = 8.3 Hz, 2 H), 7.05 (d, J = 8.3 Hz, 2 H), 6.63 (d, J = 7.2 Hz, 1 H), 5.77 (s, 2 H), 5.21 (s, 2 H), 2.67 (t, J = 7.4 Hz, 2 H), 1.61–1.54 (m, 2 H), 1.34–1.25 (m, 2 H), 0.82 (t, J = 7.4 Hz, 3 H). Anal. ($C_{31}H_{29}N_7O$·0.2H_2O) C, H, N.

The following were prepared analogously.

2-Butyl-4,5-dihydro-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (12a) was prepared from **6a** (0.86 g, 2.25 mmol) to give 0.3 g (31%) of **12a**: mp 172–173 °C; ^{1}H NMR (DMSO-d_6) δ 11.23 (d, J = 5.1 Hz, 1 H), 7.71–7.46 (m, 5 H), 7.10 (d, J = 8.6 Hz, 2 H), 7.05 (d, J = 8.6 Hz, 2 H), 6.53 (d, J = 6.9 Hz, 1 H), 5.74 (s, 2 H), 2.65 (t, J = 7.2 Hz, 2 H), 1.66–1.49 (m, 2 H), 1.39–1.19 (m, 2 H), 0.82 (t, J = 7.2 Hz, 3 H); IR (KBr) 1655 cm^{-1}. Anal. ($C_{24}H_{23}N_7O$·0.5H_2O) C, H, N.

4,5-Dihydro-2-propyl-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (12b) was prepared from **6b** (3.09 g, 8.3 mmol) and recrystallized from methanol to give 1.8 g (52%) of **12b**: mp 185–186 °C; ^{1}H NMR (DMSO-d_6) δ 16.25 (brs, 1 H), 11.24 (d, J = 5.8 Hz, 1 H), 7.69 (dd, J = 7.2 and 1.9 Hz, 1 H), 7.64–7.48 (m, 3 H), 7.14–7.02 (m, 5 H), 6.53 (dd, J = 7.0 and 0.7 Hz, 1 H), 5.74 (s, 2 H), 2.63 (t, J = 7.3 Hz, 2 H), 1.72–1.53 (m, 2 H), 0.86 (t, J = 7.3 Hz, 3 H); IR (KBr) 1660 cm^{-1}. Anal. ($C_{23}H_{21}N_7O$·0.9H_2O) C, H, N.

2-Ethyl-4,5-dihydro-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (12c) was prepared from **6c** (1.0 g, 2.8 mmol) and recrystallized from methanol/diethyl ether (80:20) to give 520 mg (46%) of **12c**: mp 195–196 °C; ^{1}H NMR (DMSO-d_6) δ 11.22 (d, J = 6.1 Hz, 1 H), 7.57 (dd, J = 7.2 and 1.7 Hz, 1 H), 7.46 (td, J = 7.2 and 1.8 Hz, 1 H), 7.41 (td, J = 7.5 and 1.8 Hz, 1 H), 7.36 (dd, J = 7.1 and 1.9 Hz, 1 H), 7.01–7.09 (m, 5 H), 6.52 (d, J = 6.2 Hz, 1 H), 5.71 (s, 2 H), 2.69 (q, J = 7.5 Hz, 2 H), 1.19 (t, J = 7.4 Hz, 3 H); IR (KBr) 1660 cm^{-1}. Anal. ($C_{22}H_{19}N_7O$·1.0H_2O) C, H, N.

2-Cyclopropyl-4,5-dihydro-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (12d) was prepared from **6d** (256 mg, 0.7 mmol) to give 113 mg (39%) of **12d**: mp 200–201 °C; ^{1}H NMR (DMSO-d_6) δ 11.19 (brd, J = 5.3 Hz, 1 H), 7.56–7.50 (m, 1 H), 7.38–7.23 (m, 3 H), 7.08 (s, 4 H), 7.05 (dd, J = 6.8 and 5.3 Hz, 1 H), 6.44 (d, J = 6.8 Hz, 1 H), 5.80 (s, 2 H), 2.22–2.05 (m, 1 H), 1.07–0.98 (m, 4 H); IR (KBr) 1659 cm^{-1}. Anal. ($C_{23}H_{19}N_7O$·2.1H_2O) C, H, N.

2-Butyl-4,5-dihydro-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-5-(2-thenyl)-3*H*-imidazo[4,5-*c*]pyridin-4-one (14b) was prepared from **11b** (2.1 g, 4.4 mmol) to give 2.2 g (96%) of **14b**: mp 145–146 °C; ^{1}H NMR (DMSO-d_6) δ 7.68–7.41 (m, 6 H), 7.19–6.95 (m, 6 H), 6.62 (d, J = 7.3 Hz, 1 H), 5.77 (s, 2 H), 5.36 (s, 2 H), 2.67 (t, J = 7.4 Hz, 2 H), 1.67–1.49 (m, 2 H), 1.37–1.18 (m, 2 H), 0.82 (t, J = 7.3 Hz, 3 H). Anal. ($C_{29}H_{27}N_7OS$·2.5H_2O) C, H, N.

2-Butyl-4,5-dihydro-5-methyl-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (14c) was prepared from **11c** (1.33 g, 3.34 mmol) and recrystallized from ether to give 0.76 g (57%) of **14c**: mp 194–195 °C; ^{1}H NMR (DMSO-d_6) δ 7.66–7.44 (m, 4 H), 7.42 (d, J = 6.2 Hz, 1 H), 7.07 (s, 4 H), 6.57 (d, J = 6.2 Hz, 1 H), 5.77 (s, 2 H), 3.52 (s, 3 H), 2.67 (t, J = 7.0 Hz, 2 H), 1.66–1.52 (m, 2 H), 1.36–1.23 (m, 2 H), 0.83 (t, J = 7.0 Hz, 3 H). Anal. ($C_{25}H_{25}N_7O$·0.45H_2O) C, H, N.

2-Butyl-5-ethyl-4,5-dihydro-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (14d) was prepared from **11d** (1.56 g, 3.8 mmol) to give 0.75 g (44%) of **14d**: mp 181–182 °C; ^{1}H NMR (DMSO-d_6) δ 7.64–7.39 (m, 5 H), 7.06 (s, 4 H), 6.58 (d, J = 6.0 Hz, 1 H), 5.72 (s, 2 H), 4.00 (q, J = 7.0 Hz, 2 H), 2.66 (t, J = 7.0 Hz, 2 H), 1.66–1.54 (m, 2 H), 1.36–1.22 (m, 2 H), 1.30 (t, J = 7.0 Hz, 3 H), 0.84 (t, J = 7.0 Hz, 3 H). Anal. ($C_{26}H_{27}N_7O$·0.3H_2O) C, H, N.

2-Butyl-5-(4-chlorobenzyl)-4,5-dihydro-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (14e) was prepared from **11e** (0.7 g, 1.4 mmol) to give 0.50 g (65%) of **14e**: mp 205–206 °C; ^{1}H NMR (DMSO-d_6) δ 7.69–7.45 (m, 5 H), 7.41–7.30 (m, 2 H), 7.21–7.11 (m, 2 H), 7.06 (s, 4 H), 6.63 (d, J = 7.3 Hz, 1 H), 5.76 (s, 2 H), 5.19 (s, 2 H), 2.67 (t, J = 7.3 Hz, 2 H), 1.65–1.50 (m, 2 H), 1.38–1.19 (m, 2 H), 0.82 (t, J = 7.3 Hz, 3 H). Anal. ($C_{31}H_{28}ClN_7O$·0.6H_2O) C, H, N.

2-Butyl-5-(3-chlorobenzyl)-4,5-dihydro-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (14f) was prepared from **11f** (0.6 g, 1.2 mmol) to give 0.47 g (71%) of **14f**: mp 187–188 °C; ^{1}H NMR (DMSO-d_6) δ 7.67–7.29 (m, 8 H), 7.24 (td, J = 6.5 and 2.0 Hz, 1 H), 7.11–7.01 (m, 4 H), 6.64 (d, J = 7.3 Hz, 1 H), 5.72 (s, 2 H), 5.21 (s, 2 H), 2.68 (t, J = 7.3 Hz, 2 H), 1.66–1.50 (m, 2 H), 1.39–1.20 (m, 2 H), 0.83 (t, J = 7.3 Hz, 3 H). Anal. ($C_{31}H_{28}ClN_7O$·0.2H_2O) C, H, N.

2-Butyl-5-(2-chlorobenzyl)-4,5-dihydro-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (14g) was prepared from **11g** (4.1 g, 8.1 mmol) to give 3.0 g (71%) of **14g**: mp 126–127 °C; ^{1}H NMR (DMSO-d_6) δ 7.69–7.45 (m, 6 H), 7.37–7.22 (m, 2 H), 7.06 (s, 4 H), 6.83 (dd, J = 7.2 and 2.2 Hz, 1 H), 6.68 (d, J = 7.3 Hz, 1 H), 5.74 (s, 2 H), 5.29 (s, 2 H), 2.69 (t, J = 7.2 Hz, 2 H), 1.68–1.52 (m, 2 H), 1.40–1.21 (m, 2 H), 0.83 (t, J = 7.2 Hz, 3 H). Anal. ($C_{31}H_{28}ClN_7O$·1.4H_2O) C, H, N.

5-(2-Bromobenzyl)-2-butyl-4,5-dihydro-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (14h) was prepared from **11h** (1.1 g, 2.0 mmol) to give 0.3 g (25%) of **14h**: mp 172–173 °C; ^{1}H NMR (DMSO-d_6) δ 7.67 (dd, J = 7.9 and 0.6 Hz, 1 H), 7.64 (td, J = 7.5 Hz, 1 H), 7.63 (d, J = 7.5 Hz, 1 H), 7.54 (td, J = 7.6 and 0.8 Hz, 1 H), 7.48 (d, J = 7.4 Hz, 1 H), 7.47 (d, J = 7.3 Hz, 1 H), 7.32 (td, J = 7.3 Hz, 1 H), 7.23 (td, J = 7.6 and 1.4 Hz, 1 H), 7.08 (d, J = 8.3 Hz, 2 H), 7.04 (d, J = 8.3 Hz, 2 H), 6.73 (dd, J = 7.8 and 0.9 Hz, 1 H), 6.69 (d, J = 7.3 Hz, 1 H), 5.74 (s, 2 H), 5.24 (s, 2 H), 2.68 (t, J = 7.4 Hz, 2 H), 1.63–1.56 (m, 2 H), 1.34–1.26 (m, 2 H), 0.84 (t, J = 7.4 Hz, 3 H). Anal. ($C_{31}H_{28}BrN_7O$·1.1H_2O) C, H, N.

2-Butyl-5-(2-fluorobenzyl)-4,5-dihydro-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (14i) was prepared from **11i** (1.4 g, 2.9 mmol) to give 0.84 g (54%) of **14i**: mp 169–170 °C; ^{1}H NMR (DMSO-d_6) δ 7.69–7.00 (m, 13 H), 6.66 (d, J = 7.2 Hz, 1 H), 5.74 (s, 2 H), 5.26 (s, 2 H), 2.67 (t, J = 7.2 Hz, 2 H), 1.67–1.50 (m, 2 H), 1.39–1.19 (m, 2 H), 0.83 (t, J = 7.3 Hz, 3 H). Anal. ($C_{31}H_{28}FN_7O$) C, H, N.

2-Butyl-4,5-dihydro-5-(2-nitrobenzyl)-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (14k) was prepared from **11k** (2.2 g, 4.1 mmol) to give 1.2 g (52%) of **14k**: mp 123–124 °C; ^{1}H NMR (DMSO-d_6) δ 8.12 (dd, J = 7.3 and 1.0 Hz, 1 H), 7.69–7.63 (m, 3 H), 7.58–7.55 (m, 2 H), 7.54 (d, J = 7.3 Hz, 1 H), 7.49 (d, J = 7.5 Hz, 1 H), 7.08 (d, J = 8.3 Hz, 2 H), 7.03 (d, J = 8.2 Hz, 2 H), 6.87 (d, J = 7.8 Hz, 1 H), 6.72 (d, J = 7.2 Hz, 1 H), 5.72 (s, 2 H), 5.54 (s, 2 H), 2.68 (t, J

= 7.5 Hz, 2 H), 1.62–1.55 (m, 2 H), 1.34–1.26 (m, 2 H), 0.83 (t, J = 7.4 Hz, 3 H). Anal. ($C_{31}H_{28}N_8O_2 \cdot 0.3H_2O$) C, H, N.

2-[[2-Butyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-5-yl]methyl]benzoic acid, ethyl ester (14m) was prepared from 11m (5.0 g, 9.2 mmol) and recrystallized from ethanol to give 2.35 g (44%) of pure 14m: mp 203–204 °C; ^{1}H NMR (DMSO-d_6) δ 16.25 (brs, 1 H), 7.93 (dd, J = 7.7 and 1.4 Hz, 1 H), 7.56 (dd, J = 7.4 and 1.7 Hz, 1 H), 7.52 (td, J = 7.8 and 1.5 Hz, 1 H), 7.46 (d, J = 7.2 Hz, 1 H), 7.44–7.37 (m, 3 H), 7.32 (dd, J = 7.6 and 1.5 Hz, 1 H), 7.06–6.98 (m, 4 H), 6.76 (d, J = 7.8 Hz, 1 H), 6.66 (d, J = 7.2 Hz, 1 H), 5.72 (s, 2 H), 5.54 (s, 2 H), 4.35 (q, J = 7.2 Hz, 2 H), 2.73–2.69 (m, 2 H), 1.66–1.59 (m, 2 H), 1.34 (t, J = 7.2 Hz, 3 H), 1.33–1.28 (m, 2 H), 0.85 (t, J = 7.4 Hz, 3 H). Anal. ($C_{34}H_{33}N_7O_3 \cdot 0.1H_2O$) C, H, N.

2-Butyl-4,5-dihydro-5-phenacyl-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (14n) was prepared from 11n (0.6 g, 1.2 mmol) to give 0.45 g (69%) of 14n: mp 148–149 °C; ^{1}H NMR (DMSO-d_6) δ 8.11–8.04 (m, 2 H), 7.93–7.77 (m, 8 H), 7.04 (m, 4 H), 6.64 (d, J = 7.6 Hz, 1 H), 5.71 (s, 2 H), 5.59 (s, 2 H), 2.69 (t, J = 7.7 Hz, 2 H), 1.70–1.53 (m, 2 H), 1.40–1.53 (m, 2 H), 0.84 (t, J = 7.3 Hz, 3 H). Anal. ($C_{32}H_{29}N_7O_2 \cdot 0.3H_2O$) C, H, N.

2-Butyl-4,5-dihydro-5-(3,3-dimethyl-2-oxobutyl)-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (14o) was prepared from 11o (6.5 g, 13.5 mmol) to give 4.6 g (65%) of 14o: mp 202–203 °C; ^{1}H NMR (DMSO-d_6) δ 7.62 (d, J = 7.6 Hz, 1 H), 7.60 (t, J = 7.6 Hz, 1 H), 7.52 (t, J = 7.5 Hz, 1 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.26 (d, J = 7.3 Hz, 1 H), 7.05 (d, J = 8.5 Hz, 2 H), 7.03 (d, J = 8.5 Hz, 2 H), 6.59 (d, J = 7.2 Hz, 1 H), 5.72 (s, 2 H), 5.09 (s, 2 H), 2.66 (t, J = 7.4 Hz, 2 H), 1.62–1.51 (m, 2 H), 1.33–1.26 (m, 2 H), 1.21 (s, 9 H), 0.83 (t, J = 7.4 Hz, 3 H). Anal. ($C_{30}H_{33}N_7O_2 \cdot 0.75H_2O$) C, H, N.

2-Butyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-acetic acid, methyl ester (14p) was prepared from 11p (2.0 g, 4.3 mmol) to give 0.47 g (22%) of 14p: mp 112–113 °C; ^{1}H NMR (DMSO-d_6) δ 7.67–7.63 (m, 2 H), 7.56–7.49 (m, 1 H), 7.43 (d, J = 7.3 Hz, 1 H), 7.08–7.04 (m, 4 H), 6.64 (d, J = 7.3 Hz, 1 H), 5.73 (s, 2 H), 4.81 (s, 2 H), 3.68 (s, 3 H), 2.67 (t, J = 7.5 Hz, 2 H), 1.64–1.56 (m, 2 H), 1.36–1.25 (m, 2 H), 0.83 (t, J = 7.4 Hz, 3 H). Anal. ($C_{27}H_{27}N_7O_3 \cdot 0.6H_2O$) C, H, N.

2-Butyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-(*N*,*N*-dimethylacetamide) (14q) was prepared from 11q (1.4 g, 2.6 mmol) to give 0.84 g (63%) of 14q: mp 256–257 °C; ^{1}H NMR (DMSO-d_6) δ 7.68–7.62 (m, 2 H), 7.57–7.53 (m, 1 H), 7.50 (d, J = 7.8 Hz, 1 H), 7.27 (d, J = 7.3 Hz, 1 H), 7.06 (q, J = 7.6 Hz, 4 H), 6.67 (d, J = 7.3 Hz, 1 H), 5.73 (s, 2 H), 4.86 (s, 2 H), 3.06 (s, 3 H), 2.85 (s, 3 H), 2.67 (t, J = 7.3 Hz, 2 H), 1.62–1.55 (m, 2 H), 1.33–1.25 (m, 2 H), 0.83 (t, J = 7.3 Hz, 3 H). Anal. ($C_{28}H_{30}N_8O_2 \cdot 0.1H_2O$) C, H, N.

4,5-Dihydro-4-oxo-2-propyl-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-(*N*,*N*-dimethylacetamide) (14r) was prepared from 11r (0.2 g, 0.44 mmol) to give 0.12 g (54%) of 14r: mp 149–150 °C; ^{1}H NMR (DMSO-d_6) δ 16.23 (brs, 1 H), 7.68–7.63 (m, 2 H), 7.57 (dd, J = 1.0 and 7.4 Hz, 1 H), 7.52 (td, J = 1.0 and 7.8 Hz, 1 H), 7.28 (d, J = 7.2 Hz, 1 H), 7.09 (d, J = 8.3 Hz, 2 H), 7.05 (d, J = 8.3 Hz, 2 H), 6.58 (d, J = 7.3 Hz, 1 H), 5.74 (s, 2 H), 4.87 (s, 2 H), 3.07 (s, 3 H), 2.86 (s, 3 H), 2.66 (q, J = 7.4 Hz, 2 H), 1.69–1.61 (m, 2 H), 0.88 (t, J = 7.4 Hz, 3 H). Anal. ($C_{27}H_{28}N_8O_2 \cdot 0.8H_2O$) C, H, N.

2-Ethyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-(*N*,*N*-dimethylacetamide) (14s) was prepared from 11s (1.0 g, 2.3 mmol) to give 1.0 g (91%) of 14s: mp 181–182 °C; ^{1}H NMR (DMSO-d_6) δ 7.60 (dd, J = 7.7 Hz, 1 H), 7.56 (td, J = 7.6 and 1.4 Hz, 1 H), 7.48 (td, J = 7.4 and 1.2 Hz, 1 H), 7.43 (dd, J = 7.5 Hz, 1 H), 7.27 (d, J = 7.3 Hz, 1 H), 7.05 (s, 4 H), 6.58 (d, J = 7.2 Hz, 1 H), 5.72 (s, 2 H), 4.87 (s, 2 H), 3.06 (s, 3 H), 2.85 (s, 3 H), 2.70 (q, J = 7.5 Hz, 2 H), 1.18 (t, J = 7.5 Hz, 3 H). Anal. ($C_{26}H_{26}N_8O_2$) C, H, N.

2-Cyclopropyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-(*N*,*N*-dimethylacetamide) (14t) was prepared from 11t (318 mg, 0.7 mmol) to give 332 mg (96%) of 14t: mp 192–193 °C; ^{1}H NMR (DMSO-d_6) δ 7.58–7.49 (m, 1 H), 7.42–7.26 (m, 3 H), 7.23 (d, J = 7.0 Hz, 1 H), 7.07 (s, 4 H), 6.48 (d, J = 7.0 Hz, 1 H), 5.79 (s, 2 H), 4.86 (s, 2 H), 3.07 (s, 3 H), 2.80 (s, 3 H), 2.23–2.06 (m, 2 H), 1.08–0.90 (m, 4 H). Anal. ($C_{27}H_{28}N_8O_2 \cdot 1.55H_2O$) C, H, N.

2-Butyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-(*N*,*N*-diethylacetamide) (14u) was prepared from 11u (0.5 g, 1.0 mmol) to give 187 mg (34%) of 14u: mp 255–256 °C; ^{1}H NMR (DMSO-d_6) δ 16.25 (brs, 1 H), 7.67–7.62 (m, 2 H), 7.55 (td, J = 7.8 and 0.9 Hz, 1 H), 7.50 (d, J = 7.7 Hz, 1 H), 7.31 (d, J = 7.3 Hz, 1 H), 7.07 (d, J = 8.6 Hz, 2 H), 7.04 (d, J = 8.6 Hz, 2 H), 6.57 (d, J = 7.2 Hz, 1 H), 5.74 (s, 2 H), 4.85 (s, 2 H), 3.41 (dd, J = 7.1 Hz, 2 H), 3.29 (dd, J = 7.2 Hz, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 1.62–1.55 (m, 2 H), 1.33–1.25 (m, 2 H), 1.21 (t, J = 7.1 Hz, 3 H), 1.03 (t, J = 7.1 Hz, 3 H), 0.83 (t, J = 7.3 Hz, 3 H). Anal. ($C_{30}H_{34}N_8O_2 \cdot 2.0H_2O$) C, H, N.

2-Ethyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-(*N*,*N*-diethylacetamide) (14v) was prepared from 11v (1.0 g, 2.1 mmol) to give 0.7 g (65%) of 14v: mp 191–192 °C; ^{1}H NMR (DMSO-d_6) δ 7.70–7.48 (m, 4 H), 7.32 (d, J = 7.3 Hz, 1 H), 7.11–7.01 (m, 4 H), 6.58 (d, J = 7.3 Hz, 1 H), 5.74 (s, 2 H), 4.86 (s, 2 H), 3.40 (q, J = 7.0 Hz, 2 H), 3.29 (q, J = 7.0 Hz, 2 H), 2.69 (q, J = 7.4 Hz, 2 H), 1.21 (t, J = 7.3 Hz, 3 H), 1.17 (t, J = 7.4 Hz, 3 H), 1.03 (t, J = 7.1 Hz, 3 H). Anal. ($C_{28}H_{30}N_8O_2$) C, H, N.

2-Butyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-(*N*-*tert*-butylacetamide) (14w) was prepared from 11w (1.5 g, 3.0 mmol) to give 0.86 g (53%) of 14w: mp 211–212 °C; ^{1}H NMR (DMSO-d_6) δ 7.78 (s, 1 H), 7.59 (dd, j = 7.7 and 1.3 Hz, 1 H), 7.54 (td, J = 7.6 and 1.8 Hz, 1 H), 7.47 (td, J = 7.6 and 1.8 Hz, 1 H), 7.41 (dd, J = 7.5 and 0.9 Hz, 1 H), 7.29 (d, J = 7.3 Hz, 1 H), 7.05 (s, 4 H), 6.55 (d, J = 7.3 Hz, 1 H), 5.72 (s, 2 H), 4.54 (s, 2 H), 2.69 (t, J = 7.4 Hz, 2 H), 1.64–1.56 (m, 2 H), 1.35–1.28 (m, 2 H), 0.84 (t, J = 7.4 Hz, 3 H). Anal. ($C_{30}H_{34}N_8O_2 \cdot 2.3H_2O$) C, H, N.

2-Butyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-(*N*,*N*-diphenylacetamide) (14x) was prepared from 11x (1.7 g, 2.9 mmol) to give 570 mg (31%) of 14x: mp 211–212 °C; ^{1}H NMR (DMSO-d_6) δ 16.20 (brs, 1 H), 7.77–7.10 (m, 15 H), 7.11–7.00 (m, 4 H), 6.58 (d, J = 7.3 Hz, 1 H), 5.75 (s, 2 H), 4.67 (s, 2 H), 2.65 (t, J = 7.2 Hz, 2 H), 1.65–1.49 (m, 2 H), 1.38–1.19 (m, 2 H), 0.82 (t, J = 7.3 Hz, 3 H). Anal. ($C_{38}H_{34}N_8O_2 \cdot 0.5H_2O$) C, H, N.

2-Butyl-4,5-dihydro-5-[(2-oxo-2-pyrrolidino)ethyl]-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (19a) was prepared from 17a (0.5 g, 1.0 mmol) to give 0.22 g (41%) of 19a: mp 215–216 °C; ^{1}H NMR (DMSO-d_6) δ 7.70–7.46 (m, 4 H), 7.30 (d, J = 7.3 Hz, 1 H), 7.11–7.01 (m, 4 H), 6.57 (d, J = 7.3 Hz, 1 H), 5.74 (s, 2 H), 4.78 (s, 2 H), 3.52 (t, J = 6.7 Hz, 2 H), 3.31 (t, J = 6.7 Hz, 2 H), 2.67 (t, J = 7.2 Hz, 2 H), 2.02–1.71 (m, 4 H), 1.67–1.51 (m, 2 H), 1.39–1.19 (m, 2 H), 0.83 (t, J = 7.2 Hz, 3 H). Anal. ($C_{30}H_{32}N_8O_2 \cdot 0.4H_2O$) C, H, N.

2-Butyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-acetamide (19b) was prepared from 17b (0.7 g, 1.45 mmol) to give 0.38 g (59%) of 19b: mp 218–219 °C; ^{1}H NMR (DMSO-d_6) δ 7.68–7.63 (m, 2 H), 7.57–7.53 (m, 2 H), 7.50 (d, J = 7.7 Hz, 1 H), 7.32 (d, J = 7.3 Hz, 1 H), 7.12 (brs, 1 H), 7.09 (d, J = 8.3 Hz, 2 H), 7.04 (d, J = 8.3 Hz, 2 H), 6.56 (d, J = 7.3 Hz, 1 H), 5.74 (s, 2 H), 4.57 (s, 2 H), 2.66 (t, J = 7.5 Hz, 2 H), 1.61–1.55 (m, 2 H), 1.33–1.25 (m, 2 H), 0.83 (t, J = 7.4 Hz, 3 H). Anal. ($C_{26}H_{26}N_8O_2 \cdot 0.4H_2O$) C, H, N.

2-Butyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-acetanilide (19c) was prepared from 17c (0.4 g, 0.8 mmol) to give 0.3 g (68%) of 19c: mp 156–157 °C; ^{1}H NMR (DMSO-d_6) δ 10.35 (s, 1 H), 7.59 (d, J = 8.0 Hz, 2 H), 7.56 (dd, J = 7.4 and 1.6 Hz, 1 H), 7.45 (td, J = 7.4 and 1.5 Hz, 1 H), 7.42 (d, J = 7.3 Hz, 1 H), 7.40 (td, J = 7.4 and 1.5 Hz, 1 H), 7.34 (dd, J = 7.5 and 1.2 Hz, 1 H), 7.30 (t, J = 8.0 Hz, 2 H), 7.05 (d, J = 8.1 Hz, 2 H), 7.03 (d, J = 8.2 Hz, 1 H), 7.01 (d, J = 8.2 Hz, 2 H), 6.61 (d, J = 7.2 Hz, 1 H), 5.71 (s, 2 H), 4.82 (s, 2 H), 2.70 (t, J = 7.5 Hz, 2 H), 1.66–1.59 (m, 2 H), 1.36–1.26 (m, 2 H), 0.85 (t, J = 7.3 Hz, 3 H). Anal. ($C_{32}H_{30}N_8O_2 \cdot 0.7H_2O$) C, H, N.

2-Butyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-(*N*-methylacetanilide) (19d) was prepared from **17d** (1.0 g, 1.9 mmol) to give 0.8 g (74%) of **19d**: mp 149–150 °C; ^{1}H NMR (DMSO-d_6) δ 7.58 (dd, J = 7.5 and 1.4 Hz, 1 H), 7.55–7.47 (m, 4 H), 7.50 (td, J = 7.5 and 1.4 Hz, 1 H), 7.44 (td, J = 7.4 and 1.2 Hz, 1 H), 7.44–7.39 (m, 1 H), 7.37 (dd, J = 7.4 and 1.1 Hz, 1 H), 7.30 (d, J = 7.3 Hz, 1 H), 7.04 (d, J = 8.1 Hz, 2 H), 6.98 (d, J = 8.1 Hz, 2 H), 6.56 (d, J = 7.3 Hz, 1 H), 5.71 (s, 2 H), 4.52 (brs, 2 H), 3.20 (s, 3 H), 2.66 (t, J = 7.5 Hz, 2 H), 1.64–1.56 (m, 2 H), 1.34–1.25 (m, 2 H), 0.82 (t, J = 7.3 Hz, 2 H). Anal. ($C_{33}H_{32}N_8O_2 \cdot 1.0H_2O$) C, H, N.

2-Ethyl-4,5-dihydro-5-[(2-oxo-2-piperidino)ethyl]-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (20) was prepared from 18 (0.5 g, 1.04 mmol) to give 0.4 g (74%) of **20**: mp 200–201 °C; ^{1}H NMR (DMSO-d_6) δ 7.69–7.46 (m, 4 H), 7.29 (d, J = 7.3 Hz, 1 H), 7.11–7.00 (m, 4 H), 6.57 (d, J = 7.2 Hz, 1 H), 5.73 (s, 2 H), 4.88 (s, 2 H), 3.55–3.35 (br, 4 H), 2.69 (q, J = 7.4 Hz, 2 H), 1.68–1.36 (br, 6 H), 1.18 (t, J = 7.5 Hz, 3 H). Anal. ($C_{29}H_{30}N_8O_2 \cdot 2.0H_2O$) C, H, N.

2-Butyl-4,5-dihydro-4-oxo-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenyl]methyl]-3*H*-imidazo[4,5-*c*]pyridine-5-acetic acid (16) was prepared from **15a** (2.0 g, 4.54 mmol) to give 1.3 g (59%) of **16**: mp 268–269 °C; ^{1}H NMR (DMSO-d_6) δ 13.00 (brs, 1 H), 7.68 (dd, J = 7.3 and 1.8 Hz, 1 H), 7.64–7.47 (m, 3 H), 7.41 (d, J = 7.2 Hz, 1 H), 7.12–7.11 (m, 4 H), 6.60 (d, J = 7.2 Hz, 1 H), 5.74 (s, 2 H), 4.70 (s, 2 H), 2.67 (t, J = 7.2 Hz, 2 H), 1.67–1.50 (m, 2 H), 1.39–1.19 (m, 2 H), 0.82 (t, J = 7.2 Hz, 3 H). Anal. ($C_{26}H_{25}N_7O_3 \cdot 0.5H_2O$) C, H, N.

5-(2-Aminobenzyl)-2-butyl-4,5-dihydro-3-[[2′-(1*H*-tetrazol-5-yl)-4-biphenylyl]methyl]-3*H*-imidazo[4,5-*c*]pyridin-4-one (22). A mixture of **14k** (0.9 g, 1.6 mmol), Raney Ni (0.9 g), and 50 mL of methanol was stirred at ambient temperature under hydrogen (1 atm) for 2 h. The reaction mixture was filtered through Celite, and the solvent was removed under vacuum to furnish 0.46 g (54%) of **22** as a white crystalline solid: mp 198–199 °C; ^{1}H NMR (DMSO-d_6) δ 7.67 (dd, J = 7.7 and 1.5 Hz, 1 H), 7.66–7.64 (m, 1 H), 7.56 (td, J = 7.7 and 0.8 Hz, 1 H), 7.51 (d, J = 7.6 Hz, 1 H), 7.44 (d, J = 7.3 Hz, 1 H), 7.11 (d, J = 8.3 Hz, 2 H), 7.08–7.03 (m, 3 H), 7.00 (td, J = 7.8 and 1.5 Hz, 1 H), 6.66–6.63 (m, 2 H), 6.53–6.49 (m, 1 H), 5.78 (s, 2 H), 5.07 (s, 2 H), 2.68 (t, J = 7.5 Hz, 2 H), 1.61–1.54 (m, 2 H), 1.32–1.24 (m, 2 H), 0.82 (t, J = 7.4 Hz, 3 H). Anal. ($C_{31}H_{30}N_8O \cdot 0.4H_2O$) C, H, N.

Biology. Ang II Receptor Binding. Wistar rats were killed by decapitation and the adrenal glands removed. By applying a slight positive pressure onto the glands, the capsular layer was separated from the medulla. All subsequent steps were carried out at 4 °C. The tissues were collected separately in 200 mM sucrose, 1.0 mM EDTA, and 10 mM Tris/HCl, pH 7.2. The glomerulosa cell layers were homogenized using a Polytron PT 10/35 followed by three strokes in a glass/Teflon homogenizer. The homogenate was centrifuged for 10 min at 3000*g*. The supernatant was filtered through gauze; the filtrate was centrifuged for 13 min at 12000*g*. The membrane vesicles contained in the supernatant were sedimented by centrifugation for 60 min at 102000*g*. The supernatant was discarded; the pellet was resuspended in 0.25% BSA, 5 mM $MgCl_2$, and 50 mM Tris/HCl, pH 7.2, and stored frozen in 1-2-mL aliquots in liquid N_2.

The binding assay was carried out in a total of 500 μL; 400 μL of the membrane suspension (appropriately diluted with 0.25% or 0.0067% BSA (to achieve 0.25% or 0.01% BSA in the membrane suspension), 5 mM $MgCl_2$, and 50 mM Tris/HCl, pH 7.2), 50 μL of [^{125}I]Ang II (concentration between 0.06 and 0.12 nM), and 50 μL of a 10% DMSO solution containing various amounts of unlabeled Ang II or competitors. Each concentration was determined in triplicate. The incubation was carried out for 60 min at room temperature. The incubation was terminated by rapidly filtering the incubation volume through Whatman GF/C filters which were rinsed immediately with 2 × 4 mL of ice-cold 0.9% NaCl solution. The radioactivity trapped on the filter was counted in a g-counter (Packard, Cobra 5010). Nonspecific binding was determined in the presence of 1 μM unlabeled Ang II. The effects of the competitors were determined by estimating the concentration at which they displayed the bound [^{125}I]Ang II half maximally.

Antagonism of Ang II-Contracted Rabbit Aortic Rings. New Zealand white rabbits were stunned by a blow to the head and exsanguinated. The aorta was excised and placed in an oxygenated (95% O_2/5% CO_2) physiological salt solution consisting of (mM) NaCl, 118.1; KCl, 4.7; $MgSO_4$, 1.2; KH_2PO_4, 1.2; $NaHCO_3$, 25; and glucose, 11.1.

The aorta was dissected free from fat and connective tissue and cut into rings of approximately 2 mm. The rings were mounted into 50-mL organ baths and allowed to equilibrate for 60–90 min under a resting tension of 2*g*. After equilibration, a cumulative concentration–contractile response curve for Ang II was obtained. After a wash-out period, the rings were contracted with Ang II in a concentration which induced 50% of the maximal response (3–8 nM). After a stable value was obtained, the preparations were washed three times and the tension was allowed to return to the base line. This procedure was repeated every 40 min for a total of three or four cycles. The level of the concentration observed during the last cycle was used as the control (predrug) value. Subsequent contractions were obtained in the presence of increasing concentrations of the test compound which was added 15 min prior to the agonist. One out of four vessel rings was exposed to the solvent without the test compound and served as time and solvent control in each experiment. The reduction in contractile force in the presence of the test compound was expressed as a percentage of the predrug value.

Data were expressed as mean values. IC_{50} values (concentrations required to inhibit predrug responses by 50%) were determined graphically.

Antihypertensive Effects in Conscious SHR. Male SHR were chronically instrumented with arterial and venous catheters for recording blood pressure and applying the test compounds, respectively. The renin–angiotensin system was stimulated by furosemide treatment (3 × 20 mg/kg iv, 24, 17, and 1 h prior to the experiment). The blood pressure-lowering effect of test compounds applied iv was measured and expressed as Δ percent change from pretreatment values.

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