Discovery and Biological Evaluation of Novel Cyanoguanidine $P2X_7$ Antagonists with Analgesic Activity in a Rat Model of Neuropathic Pain

Arturo Perez-Medrano,* Diana L. Donnelly-Roberts, Prisca Honore, Gin C. Hsieh, Marian T. Namovic, Sridhar Peddi, Qi Shuai, Ying Wang, Connie R. Faltynek, Michael F. Jarvis, and William A. Carroll

Abbott Laboratories, Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Park, Illinois 60064-6101

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We disclose the design of a novel series of cyanoguanidines that are potent ($IC_{50} \simeq 10-100$ nM) and selective (≥100-fold) $P2X_7$ receptor antagonists against the other P2 receptor subtypes such as the $P2Y_2$, $P2X_4$, and $P2X_3$. We also found that these $P2X_7$ antagonists effectively reduced nociception in a rat model of neuropathic pain (Chung model). Particularly, analogue **53** proved to be effective in the Chung model, with an ED_{50} of 38 μmol/kg after intraperitoneal administration. In addition compound **53** exhibited antiallodynic effects following oral administration and maintained its efficacy following repeated administration in the Chung model. These results suggest an important role of $P2X_7$ receptors in neuropathic pain and therefore a potential use of $P2X_7$ antagonists as novel therapeutic tools for the treatment of this type of pain.

Introduction

Ligand-gated ion channel P2X receptors are ionotropic receptors specifically activated by extracellular adenosine-5′-triphosphate (ATP[a]).[1] P2X receptors form a family of a least seven subtypes ($P2X_{1-7}$), containing 379 ($P2X_6$) to 595 ($P2X_7$) amino acids.[2] P2X receptors are under investigation as potential therapeutic targets for the alleviation of pain,[3,4] bone deterioration,[5] treatment of cancer of the reproductive system,[5] inflammation and immune disorders,[6] and cardiovascular pathologies.[7,8]

The $P2X_7$ receptor differs from some other members of the P2X family by its ability to form a pore permeable to large organic molecules upon prolonged or repeated agonist stimulation.[9] The $P2X_7$ receptor is expressed on antigen-presenting cells including macrophages, epidermal Langerhan's cells, microglial cells, and a number of tumor cell lines of varying origins.[10−14]

Activation of the $P2X_7$ receptor on cells of the immune system leads to the liberation of proinflammatory interleukin-1β (IL-1β),[15] giant cell formation, degranulation, and L-selectin shedding. $P2X_7$ antagonists have been proposed to be beneficial in various disease states and conditions, such as rheumatoid arthritis, osteoarthritis, psoriasis, and other chronic inflammatory diseases in which activation of the $P2X_7$ receptor may induce the release of IL-1β.[5] $P2X_7$ knockout mice showed a reduced inflammatory response in an experimental arthritis model, demonstrating a role of the $P2X_7$ receptor in inflammation.[16]

In addition, $P2X_7$ knockout mice showed a reduction in inflammatory thermal hyperalgesia and nerve injury induced mechanical allodynia as compared to matched wild type mice,[17] suggesting a role for $P2X_7$ in pain transmission. On glial cells in vitro, the $P2X_7$ receptor regulates the release of glutamate,[18] a neurotransmitter involved in pain transmission.[19] Hence, targeting $P2X_7$ receptors on glia cells under pathological conditions may culminate in the development of antagonists of $P2X_7$ that have therapeutic utility in the treatment of various pain states.[20] The presence and function of $P2X_7$ receptors on neurons remains controversial.[21] However, there is pharmacological evidence that neuronal $P2X_7$ receptors may play a role on presynaptic terminals in the central and peripheral nervous system.[15,22] This finding may indicate a role for the $P2X_7$ receptors in the process of neuronal synaptic transmission and therefore a potential use for $P2X_7$ antagonists as novel therapeutic tools to treat neuropathic pain. Neuropathic pain results from damage to or dysfunction in the nervous system. Once established, neuropathic pain frequently becomes a chronic condition that can be severe and extremely difficult to treat.[23] Further research into the development of newer drugs, such as selective $P2X_7$ compounds with targeted efficacy for neuropathic pain and improved side effect profiles, is clearly needed.

There have been an increasing number of $P2X_7$ antagonists described in the literature. KN-62 (**1**) has been reported to be a potent $P2X_7$ antagonist in human cells with an IC_{50} of 51 nM.[24] More potent derivatives of KN-62 have been developed such as MRS2306 (**2**)[25] and the fluorinated analogue **3**.[26] More recently, scientists at Astra Zeneca have described two novel series of noncompetitive $P2X_7$ antagonists exemplified by adamantane amide (**4**)[27] and cyclic imide **5**.[28] These compounds have been reported to be effective inhibitors in vitro of the $P2X_7$ receptor expressed endogenously on the human premonocytic cell line THP-1. From our own laboratories, a series of disubstituted tetrazoles, exemplified by **6**, were found to be potent in vitro $P2X_7$ antagonists. Moreover, **6** was found to possess in vivo activity in a model of neuropathic pain.[29]

Thiourea derivatives represented by **7** ($pIC_{50} = 6.81$) were identified as $P2X_7$ antagonists through high-throughput screening of our company compound collection (Figure 1). Because of concerns about the potential toxicity associated with the thiourea and the trichloromethyl groups, chemistry efforts were first directed toward finding suitable replacements for these two moieties. In this study, we describe the preparation and biological properties of cyanoguanidine derivatives. These new $P2X_7$ antagonists demonstrated in vivo activity in an animal model of neuropathic pain.

* To whom correspondence should be addressed. Phone: 847-937-9125. Fax: 847-935 5466. E-mail: arturo.perezmedrano@abbott.com.

[a] Abbreviations: ATP, adenosine-5′-triphosphate; IL-1β, interleukin-1β; FLIPR, fluorometric imaging plate reader technology; BzATP, 2′- and 3′-*O*-(4-benzoylbenzoyl)ATP; PEG, polyethylene glycol; SAR, structure−activity relationship; *F*, orally bioavailability; ip, intraperitoneal; TMS, tetramethylsilane.

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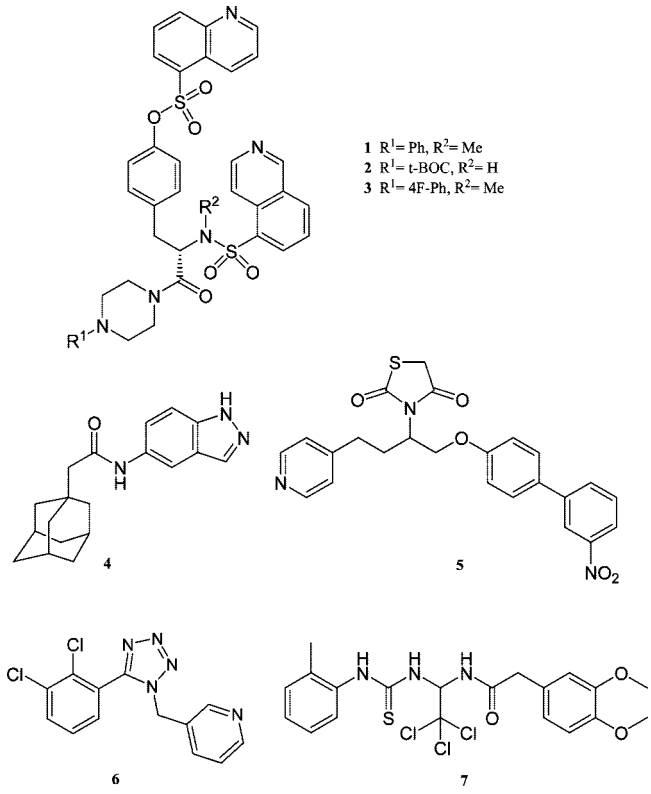
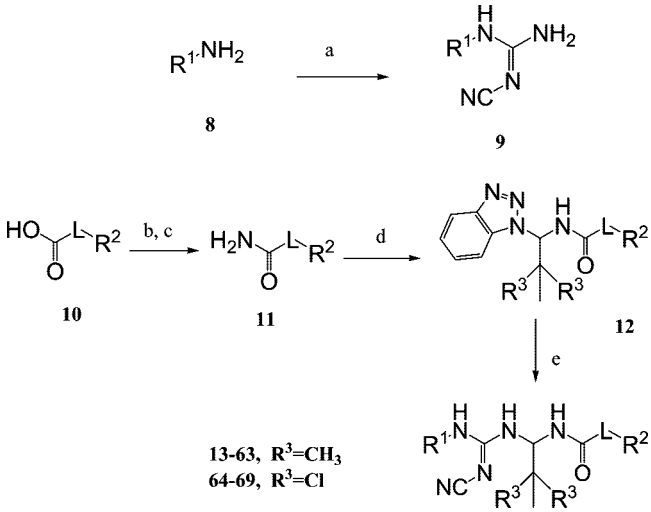


Figure 1. Structures of P2X$_7$ antagonists from the literature and high-throughput screening hit **7**.

Scheme 1[a]

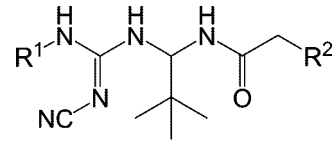


[a] Reagents and conditions: (a) $NaN(CN)_2$, HCl, H_2O, 60 °C; (b) $SOCl_2$, CH_2Cl_2, 22 °C; (c) NH_3, THF, 0 °C; (d) benzotriazole, 2,2-dimethylpropionaldehyde or 2,2-dichloropropionaldehyde, pTSOH, toluene, reflux, (d) **9**, Cs_2CO_3, CH_3CN, 20−60%.

Chemistry. *N*-arylcyanoguanidine fragments **9** were prepared from the corresponding arylamines **8** as illustrated in Scheme 1. Reaction of arylamines **8** with sodium dicyanamide in water in the presence of HCl[30] provided *N*-arylcyanoguanidines **9**. Unless available from commercial sources, phenylacetamides **11** were synthesized from the corresponding acids **10** by reaction with thionylchloride, followed by treatment of the acid chloride intermediate with ammonia in tetrahydrofuran.

The cyanoguanidine-aminals described in this report were assembled by a two-step sequence as depicted in Scheme 1. Reaction of amides **11** with 2,2-dimethylpropionaldehyde or 2,2-dichloropropionaldehyde[31] and benzotriazole in the presence of *p*-toluensulfonic acid[32] produced intermediates **12**, which were coupled with *N*-cyanoguanidines **9** to yield cyanoguanidine-aminals **13**−**69**. Although these compounds were obtained as single geometric isomers, the geometry of the double bond of the cyanoguanidine functionality was not established. However, *Z*-geometry has been reported for structurally similar compounds.[33,34]

Table 1. SAR of *tert*-Butylcyanoguanidine-aminals, Compounds **4**, **7**, **13**−**37**



compd	R^1	R^2	hP2X$_7$ pIC$_{50}$[a,c]	rP2X$_7$ pIC$_{50}$[a,c]
4			6.8 ± 0.1[b]	6.3 ± 0.1[b]
7			7.0 ± 0.2[b]	7.3 ± 0.1[b]
13	2-CH_3-C_6H_4	3,4-$(CH_3O)_2$-C_6H_3	6.9 ± 0.3[b]	7.9 ± 0.4[b]
13-(+)	2-CH_3-C_6H_4	3,4-$(CH_3O)_2$-C_6H_3	7.2 ± 0.3[b]	7.9 ± 0.2[b]
13-(−)	2-CH_3-C_6H_4	3,4-$(CH_3O)_2$-C_6H_3	5.3 ± 0.3[b]	6.3 ± 0.2[b]
14	2,6-$(CH_3O)_2$-3-pyridyl	3,4-$(CH_3O)_2$-C_6H_3	7.5 ± 0.3[b]	7.9 ± 0.3[b]
15	5-quinolyl	3,4-$(CH_3O)_2$-C_6H_3	7.4 ± 0.3[b]	7.7 ± 0.2[b]
16	2,5-$(CH_3)_2$-C_6H_3	3,4-$(CH_3O)_2$-C_6H_3	7.2 ± 0.3[b]	8.5 ± 0.3[b]
17	2-Cl-C_6H_4	3,4-$(CH_3O)_2$-C_6H_3	7.2 ± 0.6[b]	8.1 ± 0.5[b]
18	2-F-5-Cl-C_6H_3	3,4-$(CH_3O)_2$-C_6H_3	7.1 ± 0.3[b]	7.7 ± 0.2[b]
19	2,5-$(F)_2$-C_6H_3	3,4-$(CH_3O)_2$-C_6H_3	7.0 ± 0.2	7.7 ± 0.1
20	2,4,6-$(F)_3$-C_6H_2	3,4-$(CH_3O)_2$-C_6H_3	7.0 ± 0.3[b]	7.5 ± 0.2[b]
21	2-Cl-3-pyridyl	3,4-$(CH_3O)_2$-C_6H_3	7.1 ± 0.2[b]	7.4 ± 0.4[b]
22	2-CH_3O-3-pyridyl	3,4-$(CH_3O)_2$-C_6H_3	7.0 ± 0.2[b]	7.4 ± 0.2[b]
23	2-CH_3O-C_6H_4	3,4-$(CH_3O)_2$-C_6H_3	6.8 ± 0.2[b]	7.6 ± 0.1[b]
24	2-F-C_6H_4	3,4-$(CH_3O)_2$-C_6H_3	6.7 ± 0.2	7.9 ± 0.1
25	2,6-$(F)_2$-C_6H_3	3,4-$(CH_3O)_2$-C_6H_3	6.7 ± 0.1[b]	7.5 ± 0.3[b]
26	2,4-$(F)_2$-C_6H_3	3,4-$(CH_3O)_2$-C_6H_3	6.6 ± 0.1	8.0 ± 0.5
27	5-isoquinolyl	3,4-$(CH_3O)_2$-C_6H_3	6.6 ± 0.1[b]	7.5 ± 0.2
28	2-CH_3-3-pyridyl	3,4-$(CH_3O)_2$-C_6H_3	6.6 ± 0.1[b]	6.8 ± 0.2
29	4-F-C_6H_4	3,4-$(CH_3O)_2$-C_6H_3	6.5 ± 0.1	7.7 ± 0.1
30	2,3-$(F)_2$-C_6H_3	3,4-$(CH_3O)_2$-C_6H_3	6.5 ± 0.3[b]	7.0 ± 0.1[b]
31	3,5-$(F)_2$-C_6H_3	3,4-$(CH_3O)_2$-C_6H_3	6.4 ± 0.2[b]	6.5 ± 0.2[b]
32	2-Cl-$C_6H_4CH_2$−	3,4-$(CH_3O)_2$-C_6H_3	6.2 ± 0.1[b]	6.7 ± 0.3[b]
33	3,4-$(F)_2$-C_6H_3	3,4-$(CH_3O)_2$-C_6H_3	6.1 ± 0.1	7.3 ± 0.1
34	3-CH_3-C_6H_4	3,4-$(CH_3O)_2$-C_6H_3	6.0 ± 0.0	7.4 ± 0.0
35	4-CH_3-C_6H_4	3,4-$(CH_3O)_2$-C_6H_3	5.7 ± 0.3	7.7 ± 0.3[b]
36	8-quinolyl	3,4-$(CH_3O)_2$-C_6H_3	5.8 ± 0.1	6.8 ± 0.2
37	3-F-C_6H_4	3,4-$(CH_3O)_2$-C_6H_3	5.5 ± 0.3[b]	7.1 ± 0.2[b]

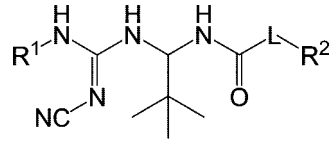
[a] pIC$_{50}$ values are the mean of two experiments unless otherwise indicated. [b] pIC$_{50}$ values are the mean of more than two experiments. [c] Standard deviation of measurement shown.

Results and Discussion

The cyanoguanidine analogues were assayed for human and rat functional P2X$_7$ activity by measuring the inhibition of Ca^{2+} flux in recombinant human or rat cell lines. Inhibition of Ca^{2+} was measured with a fluorometric imaging plate reader technology (FLIPR), using Fluo-4 as the calcium-sensing dye and the synthetic ATP analogue, benzoylbenzoic ATP (BzATP) as the agonist for the P2X$_7$ receptor as described previously.[35,36] In vitro data for compounds **4**, **7**, **13**−**69** is presented in Tables 1, 2, and 3.

Interestingly, replacement of the thiourea and trichloromethyl groups on compound **7** with the cyanoguanidine and *tert*-butyl groups, respectively, turned out to be well tolerated for in vitro potency as can be observed with analogue **13**. Preliminary examination of the effect of the stereochemistry in this series was performed with the chiral separation of the enantiomers of **13**. The dextrorotatory isomer **13**-(+) was more potent than its antipode **13**-(−). However, structure−activity relationship (SAR)

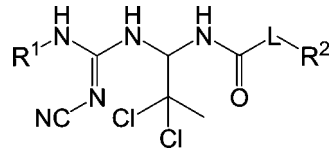
Table 2. SAR of *tert*-Butylcyanoguanidine-aminals, Compounds 38−63



compd	R^1	L	R^2	$hP2X_7$ pIC_{50}[a,c]	$rP2X_7$ pIC_{50}[a,c]
38	2-CH_3-C_6H_4	$-CH_2-$	4-CH_3S-C_6H_4	7.5 ± 0.2[b]	8.1 ± 0.3[b]
39	2-CH_3-C_6H_4	$-CH_2-$	3,4-(OCH_2O)-C_6H_3	7.3 ± 0.1[b]	7.4 ± 0.1[b]
40	2-CH_3-C_6H_4	$-CH_2-$	4-Cl-C_6H_4	7.2 ± 0.3[b]	7.7 ± 0.4[b]
41	2-CH_3-C_6H_4	$-CH-$	4-CH_3O-C_6H_4	7.2 ± 0.3[b]	7.5 ± 0.3[b]
42	2-CH_3-C_6H_4	$-CH_2-$	3,5-(CH_3O)$_2$-C_6H_3	6.6 ± 0.1[b]	7.2 ± 0.1[b]
43	2-CH_3-C_6H_4		$-(CH_2)_4$-CH_3	6.1 ± 0.3[b]	7.5 ± 0.6[b]
44	2-CH_3-C_6H_4	$-CH_2-$	$-C_6H_5$	4.5 ± 0.2	6.5 ± 0.0
45	2-CH_3-C_6H_4		3,5-(CH_3O)$_2$-C_6H_3	5.6 ± 0.1[b]	6.1 ± 0.3[b]
46	2-CH_3-C_6H_4		3,4-(CH_3O)$_2$-C_6H_3	5.3 ± 0.2	6.2 ± 0.0
47	2-CH_3-C_6H_4		4-CH_3O-C_6H_4	5.1 ± 0.1	5.6 ± 0.2
48	2-CH_3-C_6H_4	$-(CH_2)_2-$	3,4-(CH_3O)$_2$-C_6H_3	6.7 ± 0.1[b]	6.5 ± 0.2[b]
49	2-CH_3-C_6H_4	$-(CH_2)_2-$	4-CH_3O-C_6H_4	6.4 ± 0.3[b]	6.6 ± 0.3[b]
50	2-CH_3-C_6H_4	$-(CH_2)_3-$	4-CH_3O-C_6H_4	7.1 ± 0.2[b]	7.5 ± 0.2[b]
51	2-$CH_3-C_6H_4$	$-(CH_2)_3-$	$-C_6H_5$	7.1 ± 0.2[b]	7.6 ± 0.3[b]
52	2-CH_3-3-pyridyl	$-CH_2-$	4-CH_3S-C_6H_4	7.7 ± 0.1[b]	7.5 ± 0.2[b]
53	2-CH_3-3-pyridyl	$-CH_2-$	4-Cl-C_6H_4	7.5 ± 0.2[b]	7.4 ± 0.2[b]
54	2-CH_3-3-pyridyl	$-CH_2-$	4-CH_3-3-F-C_6H_3	7.2 ± 0.2	6.7 ± 0.0
55	2-CH_3-3-pyridyl	$-CH_2-$	4-F-C_6H_4	7.0 ± 0.1[b]	6.4 ± 0.2[b]
56	2-CH_3-3-pyridyl	$-(CH_2)_3-$	4-CH_3O-C_6H_4	7.3 ± 0.2	7.0 ± 0.1
57	2-CH_3-3-pyridyl	$-(CH_2)_4-$	$-C_6H_5$	7.2 ± 0.1	7.3 ± 0.1
58	5-quinolyl	$-CH_2-$	4-Cl-C_6H_4	8.0 ± 0.3[b]	8.2 ± 0.3[b]
59	5-quinolyl	$-CH_2-$	4-CH_3S-C_6H_4	8.0 ± 0.3[b]	8.1 ± 0.4[b]
60	5-quinolyl	$-CH_2-$	3,4-(OCH_2CH_2O)-C_6H_3	8.0 ± 0.3[b]	8.0 ± 0.2[b]
61	5-quinolyl	$-CH_2-$	1-naphthalenyl	7.5 ± 0.2[b]	7.5 ± 0.2[b]
62	5-quinolyl	$-CH_2-$	4-CN-C_6H_4	7.4 ± 0.1	8.2 ± 0.1[b]
63	5-quinolyl	$-(CH_2)_3-$	3-pyridyl	7.0 ± 0.0	7.4 ± 0.1[b]

[a] pIC_{50} values are the mean of two experiments, unless otherwise indicated. [b] pIC_{50} values are the mean of more than 2 experiments. [c] Standard deviation of measurement shown.

Table 3. SAR of Dichloroethylcyanoguanidine-aminals, Compounds 64−69



compd	R^1	L	R^2	$hP2X_7$ pIC_{50}[a,c]	$rP2X_7$ pIC_{50}[a,c]
64	2-CH_3O-3-pyridyl	$-CH_2-$	3,4-(CH_3O)$_2$-C_6H_3	7.5 ± 0.3[b]	8.1 ± 0.2[b]
65	2-CH_3O-3-pyridyl		3,5-(CH_3O)$_2$-C_6H_3	7.3 ± 0.3[b]	7.7 ± 0.5[b]
66	2-CH_3O-3-pyridyl		4-Cl-C_6H_4	7.2 ± 0.2[b]	7.3 ± 0.2[b]
67	2,6-(CH_3O)$_2$-3-pyridyl		4-Cl-C_6H_4	7.3 ± 0.1[b]	8.0 ± 0.4[b]
68	2-Cl-3-pyridyl		4-Cl-C_6H_4	7.2 ± 0.2[b]	6.9 ± 0.2[b]
69	2-CH_3-3-pyridyl		3,5-(CH_3O)$_2$-C_6H_3	6.7 ± 0.1[b]	6.0 ± 0.0

[a] pIC_{50} values are the mean of two experiments, unless otherwise indicated. [b] pIC_{50} values are the mean of more than 2 experiments. [c] Standard deviation of measurement shown.

studies were continued for practical reasons exclusively with racemic compounds. Our initial study was to investigate the substitution on the left hemisphere phenyl ring. A loss of activity was observed with the 3- and 4-methyl substituted analogues **34** and **35** at the human $P2X_7$ receptor, although these analogues showed comparable rat $P2X_7$ activities with compound **13**. Comparison of the $P2X_7$ activity of the three mono fluoro substituted analogues, 2-fluorophenyl (**24**), 3-fluorophenyl (**37**), and 4-fluorophenyl (**29**), confirmed that the 2-monosusbtitution is preferred. Similarly, the 2-chlorophenyl (**17**), 2-chloro-3-pyridyl (**21**), 2-methoxy-3-pyridyl (**22**), and 2-methoxyphenyl (**23**) analogues were potent $P2X_7$ antagonists. Examination of disubstitution and trisubstitution on the phenyl ring revealed a general trend toward higher $P2X_7$ antagonist potency for 2,5 disubstitutions and 2,4,6 trisubstitutions, as demonstrated with the 2,5-dimethylphenyl (**16**), 2-fluoro-5-chlorophenyl (**18**), 2,5-difluorophenyl (**19**), and 2,4,6-trifluorophenyl (**20**) analogues. Any other disubstitution such as the 2,6-, 2,4-, 2,3-, 3,5-, and 3,5-difluorophenyl analogues (**25**, **26**, **30**, **31**, and **33**) led to less active compounds.

Replacement of the 2-methylphenyl group by more polar aromatic rings such as 5-quinoline, 2-substituted pyridines and 2,6-disubstituted pyridines, generated potent antagonists (compounds **14**, **15**, **21**, and **22**) both at the human and rat $P2X_7$ receptors. However, the 5-isoquinoline (**27**), 2-methylpyridine (**28**), and 8-quinoline (**36**) analogues were less potent for the human $P2X_7$ receptor. Interestingly, insertion of a one-carbon

linker between the phenyl ring and the cyanoguanidine moiety, compound **32**, produced a decrease in potency.

Once established that 2-substitution or 2,5-disubstitution on the left-hand phenyl ring are optimal for activity, our next SAR study was focused on variations on the phenylacetamide moiety. We initiated this investigation having the 2-methylphenyl on the left-hand hemisphere of the cyanoguanidine pharmacophore, and results are outlined in Table 2. The analogues with 4-substitution and 3,4-disubstitution on the phenyl ring were in general more potent than any other substitutions, as shown by compounds **38**, **39**, **40**, and **41**. The unsubstituted phenyl, compound **44**, was significantly weaker at the $P2X_7$ human receptor than any other analogue in this SAR study. Replacement of the benzyl-type moiety with an *n*-pentyl group (**43**) was detrimental to human $P2X_7$ potency, but this analogue (**43**) retained good potency at the rat $P2X_7$ receptor. Elimination of the carbon linker between the carbonyl amide and the phenyl ring led to significantly less active analogues both at the human and rat $P2X_7$ receptors (analogues **45**, **46**, and **47**). Extension to a 2-carbon linker between the carbonyl and the phenyl ring produced a reduction of potency (analogues **48** and **49**). Antagonist potency is recovered when the linker is homologated to 3 carbons, as in analogue **50**. An interesting finding in this SAR study was that substitution on the phenyl ring in combination with the 3-carbon linker was unnecessary for $P2X_7$ activity, as demonstrated with the unsubstituted phenyl analogue **51**.

Because the aqueous solubility of this series of compounds was low, further exploration of the phenylacetamide substitution was done with the 2-methylpyridyl and 5-quinolyl groups fixed on the left-hand hemisphere. This study revealed comparable SAR between these two subsets, although the 2-methylpyridyl analogues (**52**−**57**) were generally less potent than the 5-quinolyl analogues (**58**−**63**). Compounds with 4-chloro substitution (**53** and **58**) and 4-thiomethyl substitution (**52** and **59**) on the phenylacetamide ring were the most potent in both subsets. Similar to the observations with **50** and **51**, the 2-methylpyridyl and 5-quinolyl compounds retained $P2X_7$ potency, with a 3- or 4-carbon linker between the carbonyl and a right-hand side phenyl or 4-methoxyphenyl (**56**, **57**). A pyridine ring was also tolerated with a three-carbon chain (**63**). Replacement of the *tert*-butyl group by the dichloroethyl group (**64**) resulted in an increase in $P2X_7$ activity, compared with the close analogue **22**. Unlike the analogues with a *tert*-butyl group (**45**−**47**), removal of the carbon linker between the carbonyl amide and the phenyl ring led to analogue **65** with equivalent in vitro potency. Additional SAR with the combination of the dichloroethyl group and 4-chlorobenzamide on the right side demonstrated consistent potency among a few analogues with substituted pyridines on the left side ring (**66**, **67**, and **68**). Nevertheless, a loss of activity was observed with a 2-methylpyridine on the left side ring (**69**). Compounds **66** and **68** have been reported previously as potassium channel openers.[34] However, **66** and **68** were approximately 100 times more potent for the $P2X_7$ receptor.

Compounds **13**, **15**, **16**, and **53** were evaluated for selectivity against the other P2 receptor subtypes such as $P2Y_2$, $P2X_4$, and $P2X_3$ and found to be inactive up to 10 μM. These results suggested that compounds from this series may serve as selective tools for in vivo studies. Thus, several analogues were chosen for advancement to pharmacokinetic studies. As shown in Table 4, the bioavailability (*F*) of compounds **13**, **15**, **53**, **55**, and **58**, after intraperitoneal (ip) administration, ranged from 54−90%. In view of these favorable results, these compounds were tested for effects on mechanical allodynia using von Frey testing in the L5−L6 spinal nerve ligation model of neuropathic pain (Chung model).[37,38] As indicated in Table 4, intraperitoneal administration of $P2X_7$ receptor antagonists **13**, **15**, **53**, **55**, and **58** reduced tactile allodynia. The 4-chloro analogue **53** proved to be highly effective in the Chung model with an ED_{50} of 38

Table 4. In Vivo Activity and Bioavailability (*F*) of Compounds **13**, **15**, **53**, **55**, and **58**[a]

compd	spinal nerve ligation (ip) ED_{50} (μmol/kg)[b]	*F* in rat (%)[c] ip
13	77 (59)	90
15	41 (65)	79
53	38 (82)	54
55	>300 (0)	52
58	55 (68)	66

[a] Values are the mean of six animals. [b] Maximum efficacy in parentheses as %. [c] Administered dose, 10 μmol/kg.

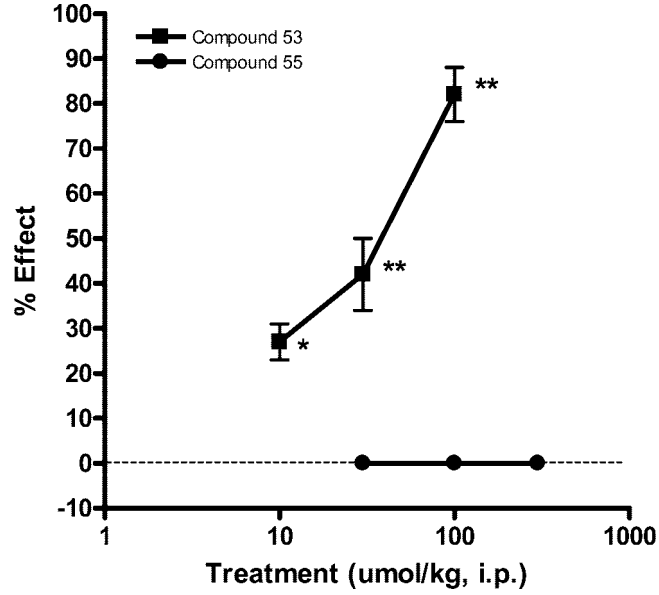


Figure 2. Effects of **53** and **55** on mechanical allodynia in the Chung model of neuropathic pain. Values are the mean of six animals.

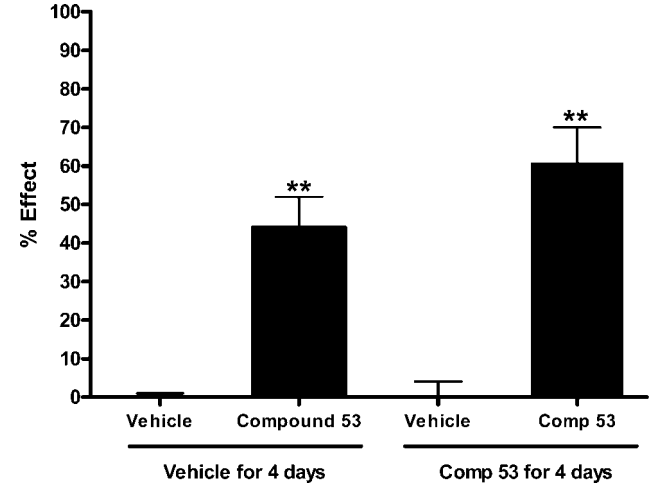


Figure 3. Effects of **53** on mechanical allodynia following a single oral dose and chronic oral administration in the Chung model of neuropathic pain. Vehicle (5% DMSO/PEG) or compound **53** (100 μmol/kg) were dosed orally twice a day for four days. On day 5, 1 h before behavioral testing for mechanical allodynia, animals received either vehicle or compound **53**. Data are expressed as % effect ± SEM. $^{**}P < 0.01$ vs respective vehicle group. $N = 6$ per group.

μmol/kg (Figure 2). The 4-F analogue **55**, which possessed weaker in vitro potency, did not show significant in vivo activity up to 300 μmol/kg despite having essentially equivalent pharmacokinetic properties to **53**. The superior in vivo effect of **53** compared to **55** (Figure 2) is consistent with its 10-fold greater potency for the rat $P2X_7$ receptor. These data provide substantial evidence that **53** and related analogues produce their antinociceptive effects via antagonism of the $P2X_7$ receptor.

Analogue **53**, which was orally bioavailable in rat ($F = 36\%$), exhibited antiallodynic effects following oral administration (45% @ 100 μmol/kg) in the Chung model. Following repeated administration in the Chung model, compound **53** retained antiallodynic efficacy (Figure 3). Vehicle or compound **53** were dosed orally twice a day for four days. On day 5, before behavioral testing for mechanical allodynia, animals received either vehicle or compound **53**. In animals that received chronic administration of vehicle, acute oral administration of compound **53** produced a 44% effect on mechanical allodynia. In animals that received analogue **53** for four days, on day 5, acute administration of **53** produced a 61% effect. The difference between the two compound **53** dose groups did not reach statistical significance ($p = 0.21$).

Conclusion

In summary, we have discovered a novel series of cyanoguanidines that are potent and selective $P2X_7$ receptor antagonists. In vitro potency of these novel cyanoguanidines is comparable or superior with our experimental data for compound **4**. The SAR studies conducted in this work revealed preferred substitution patterns for the *N*′-arylcyanoguanidine moiety. 2-Substituted and 2,5-disubstituted aryl groups produced potent $P2X_7$ receptor antagonists, as did the 5-quinoline ring system. We also found that these potent $P2X_7$ antagonists effectively reduce nociception in a model of neuropathic pain. This is manifested particularly by the dramatic differences in efficacies in the neuropathic pain model for analogues **53** and **55,** two structurally similar compounds with comparable pharmacokinetic profiles. Whereas **53** was effective in reducing neuropathic pain, the much weaker $P2X_7$ antagonist **55** was inactive. Moreover, compound **53** produces antiallodynic effects following oral administration and maintains its efficacy following repeated administration in the Chung model. These results suggest a role for $P2X_7$ receptors in neuropathic pain and therefore a potential use of $P2X_7$ receptor antagonists as novel therapeutic tools for the treatment of neuropathic pain.

Experimental Section

General Methods. Melting points were determined with a Thomas−Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were obtained in DMSO-d_6 with a Nicolet GE-300 (300 MHz) instrument using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS, and coupling constants (J) are reported in hertz (Hz). Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ, and results were within $\pm$0.4% of the theoretical values. Mass spectra were obtained with a Hewlett-Packard HP5985 spectrometer. Optical rotations were measured with an Autopol IV automatic polarimeter. Silica gel 60 (230−400 mesh) was used for flash chromatography, and thin-layer chromatography (TLC) was carried out on silica coated glass sheets (Merck silica gel 60 F-254). Preparative high-performance liquid chromatography (HPLC) purification was carried out on a Gilson HPLC.

General Procedure for the Synthesis of *N*″-cyano-*N*-arylguanidines (9). Two examples are given for the preparation of *N*″-cyano-*N*-arylguanidines **9**.

***N*″-Cyano-*N*-5-quinolinylguanidine (9a).** To a solution of 5-aminoquinoline (5.00 g, 34.7 mmol) in water was added 6 N HCl (7.00 mL, 41.6 mmol) and sodium dicyanamide (3.74 g, 41.6 mmol). The reaction was stirred overnight at 60 °C. The reaction mixture was cooled and the precipitate was collected and washed with water. The filtrate was dried at 60 °C for 24 h to provide 4.03 g (55%) of **9a**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.15 (s, 2 H), 7.57−7.64 (m, 2 H), 7.72−7.79 (m, 1 H), 7.93 (d, $J = 8.5$ Hz, 1 H), 8.33 (d, $J = 8.8$ Hz, 1 H), 8.94 (dd, $J = 4.4$, 1.7 Hz, 1 H), 9.25 (s, 1 H). MS (ESI$^+$) m/z 212 $(M + H)^+$.

***N*″-Cyano-*N*-(2-methyl-3-pyridinyl)guanidine (9b).** To a solution of 2-methyl-3-pyridinylamine (22.7 g, 0.21 mol) in water was added 6 N HCl (42 mL, 0.25 mol) and sodium dicyanamide (22.5 g, 0.25 mol). The reaction was stirred overnight at 60 °C. The reaction was continued for an additional 36 h with one more equivalent of both 6 N HCl and sodium dicyanamide added at the 12 and 24 h time points. The reaction mixture was cooled and the precipitate was collected and washed with water. The crude product was purified by Soxhlet extraction method using 5% MeOH/CH_2Cl_2, followed by flash chromatography (sequential elution with 2, 5, and 10% MeOH/CH_2Cl_2 to provide 11.3 g (30%) of compound **9b**. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.39 (s, 3 H), 7.12 (s, 2 H), 7.22 (dd, $J = 8.1$, 4.7 Hz, 1 H), 7.69 (dd, $J = 8.1$, 1.4 Hz, 1 H), 8.28 (dd, $J = 4.7$, 1.4 Hz, 1 H), 8.62 (s, 1 H). MS (ESI$^+$) m/z 176 $(M + H)^+$.

General Procedure for the Synthesis of Amide Intermediates (10). An example is given for the preparation of intermediates (**10**).

2-(3-Fluoro-4-methylphenyl)acetamide (10a). To a solution of 2-(3,4-difluorophenyl)acetic acid (5.1 g, 30.3 mmol) in 50 mL of anhydrous CH_2Cl_2 was added $SOCl_2$ (2.65 mL, 36.4 mmol) and a drop of dimethylformamide as catalyst. The mixture was stirred at room temperature for 2 h, and solvent and excess $SOCl_2$ were removed under reduced pressure. The crude product was dissolved in 50 mL of THF, cooled to 0 °C, and liquid NH_3 was added through a condenser dropwise for 20 min. The reaction mixture was concentrated, and the product was precipitated with 30 mL of water, filtered, and dried to afford 4.6 g (90%) of the title compound as a white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 2.26 (s, 3 H), 3.54 (s, 2 H), 5.39 (s, 2 H), 6.91−6.97 (m, 2 H), 7.17 (t, $J = 8.0$ Hz, 1 H). MS (ESI$^+$) m/z 168 $(M + H)^+$.

General Procedure for the Synthesis *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-(aryl)acetamides (12). An example is given for the preparation of intermediates (**12**).

***N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (12a).** A suspension of 2-(3,4-dimethoxyphenyl)acetamide (4.45 g, 22.8 mmol), trimethylacetaldehyde (4.15 g, 48.2 mmol), and 1*H*-1,2,3-benzotriazole (2.72 g, 22.8 mmol) in toluene (75 mL) was treated with *p*-TsOH (0.22 g, 1.14 mmol). The solution was heated at reflux under Dean−Stark conditions for 10 h, cooled gradually to ambient temperature, and further cooled at 5 °C. The white precipitate was collected by filtration and washed with 50% Et_2O/hexanes (100 mL) to provide 4.44 g (51%) of **12a** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 9 H), 3.48 (d, $J = 16.2$ Hz, 2 H), 3.59 (d, $J = 16.3$ Hz, 2 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 6.44 (d, $J = 9.9$ Hz, 1 H), 6.72 (d, $J = 2.0$ Hz, 1 H), 6.76−6.81 (m, 2 H), 6.86−6.90 (m, 1 H), 7.33−7.40 (m, 1 H), 7.46−7.53 (m, 1 H), 7.65 (d, $J = 8.3$ Hz, 1 H), 8.04 (d, $J = 8.3$ Hz, 1 H). MS (ESI$^+$) m/z 383 $(M + H)^+$.

General Procedure for the Synthesis of Compounds 13−69. *N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (13). A solution of *N*″-cyano-*N*-(2-methylphenyl)guanidine (99.3 mg, 0.57 mmol) and compound **12a** (218 mg, 0.57 mmol) in 5 mL of CH_3CN at 23 °C was treated with finely powdered Cs_2CO_3 (465 mg, 1.43 mmol). The reaction mixture was stirred for 10 h and then partitioned between EtOAc (15 mL) and water (10 mL). The aqueous layer was extracted with EtOAc (20 mL), and the combined organics were washed with water (2 × 15 mL) and brine (10 mL). The organic portions were dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (elution with 1% MeOH/CH_2Cl_2) provided 106 mg (43%) of **13** as a white solid; mp

156−157 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.88 (s, 9 H), 2.14 (s, 3 H), 3.39 (d, J = 5.8 Hz, 1 H), 3.43 (d, J = 5.8 Hz, 1 H), 3.72 (s, 6 H), 5.42 (dd, J = 9.2 Hz, 1 H), 6.26 (br s, 1 H), 6.74−6.79 (m, 1 H), 6.85−6.90 (m, 2 H), 7.05−7.10 (m, 1 H) 7.18−7.30 (m, 3 H), 8.15 (d, J = 8.5 Hz, 1 H), 9.04 (s, 1 H). MS (ESI$^+$) m/z 438 (M + H)$^+$. Anal. ($C_{24}H_{31}N_5O_3$) C, H, N.

(−)*N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (13-(−)). Compound **13** (2.4 g) was chromatographed over a Daicel Chiral Technologies Chiralcel AS chiral column (2.0 cm × 25 cm) eluting with 20% EtOAc/hexanes (rate 10 mL/min) to provide 837 mg (retention time = 14 min) of **13**-(−) as the less polar enantiomer; mp 156−157 °C; $[\alpha]_D^{23}$ −3.64° (c 0.60, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (s, 9 H), 2.14 (s, 3 H), 3.38 (d, J = 5.8 Hz, 1 H), 3.44 (d, J = 5.8 Hz, 1 H), 3.72 (s, 6 H), 5.42 (dd, J = 9.2 Hz, 1 H), 6.27 (br s, 1 H), 6.75−6.78 (m, 1 H), 6.86−6.89 (m, 2 H), 7.05−7.08(m, 1 H), 7.18−7.30 (m, 3 H), 8.15 (d, J = 8.5 Hz, 1 H), 9.04 (s, 1 H). MS (ESI$^+$) m/z 438 (M + H)$^+$. Anal. ($C_{24}H_{31}N_5O_3$) C, H, N.

(+)-*N*-[1-({(cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (13-(+)). Compound **13**-(+) was obtained as the more polar enantiomer (1.03 g; retention time = 24 min); mp 156−157 °C; $[\alpha]_D^{23}$ +3.56° (c 0.95, MeOH). ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.88 (s, 9 H), 2.14 (s, 3 H), 3.39 (d, J = 5.8 Hz, 1 H), 3.43 (d, J = 5.8 Hz, 1 H), 3.72 (s, 6 H), 5.42 (dd, J = 9.2 Hz, 1 H), 6.26 (br s, 1 H), 6.74−6.79 (m, 1 H), 6.85−6.90 (m, 2 H), 7.05−7.10 (m, 1 H) 7.18−7.30 (m, 3 H), 8.15 (d, J = 8.5 Hz, 1 H), 9.04 (s, 1 H). MS (ESI$^+$) m/z 438 (M + H)$^+$. Anal. ($C_{24}H_{31}N_5O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(2,6-dimethoxy-3-pyridinyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (14).** *N*″-cyano-*N*-(2,6-dimethoxy-3-pyridinyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **14**; mp 162−163 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.83 (s, 9 H), 3.35 (d, J = 4.4 Hz, 1 H), 3.39 (d, J = 4.4 Hz, 1 H), 3.71 (s, 3 H), 3.72 (s, 3 H,) 3.86 (s, 3 H), 3.88 (s, 3 H), 5.48 (dd, J = 8.8. 8.8 Hz, 1 H), 6.36−6.44 (m, 2 H), 6.75 (dd, J = 8.1, 2.0 Hz, 1 H), 6.82−6.91 (m, 2 H), 7.47 (d, J = 8.5 Hz, 1 H), 7.83 (d, J = 9.8 Hz, 1 H), 8.66 (s, 1 H). MS (ESI$^+$) m/z 485 (M + H)$^+$. Anal. ($C_{24}H_{32}N_6O_5$) C, H, N.

***N*-(1-{[(Cyanoimino)(5-quinolinylamino)methyl]amino}-2,2-dimethylpropyl)-2-(3,4-dimethoxyphenyl)acetamide (15).** *N*″-cyano-*N*-5-quinolinylguanidine and compound **12a** were processed as described for compound **13** to provide compound **15**; mp 128−129 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.90 (m, 9 H), 3.39 (d, J = 14.2 Hz, 1 H), 3.46 (d, J = 13.9 Hz, 1 H), 3.71 (d, J = 7.8 Hz, 6 H), 5.52 (dd, J = 8.8, 8.8 Hz, 1 H), 6.67 (br d, J = 8.1 Hz, 1 H), 6.77 (dd, J = 8.1, 1.7 Hz, 1 H), 6.88 (m, 2 H), 7.41 (dd, J = 7.5, 1.0 Hz, 1 H), 7.55 (dd, J = 8.5, 4.1 Hz, 1 H), 7.75 (m, 1 H), 7.97 (d, J = 8.5 Hz, 1 H), 8.06 (br d, J = 6.8 Hz, 1 H), 8.26 (d, J = 7.8 Hz, 1 H), 8.94 (dd, J = 4.4, 1.7 Hz, 1 H), 9.59 (br s, 1 H). MS (ESI$^+$) m/z 475 (M + H)$^+$. Anal. ($C_{26}H_{30}N_6O_3 \cdot 0.09CH_2Cl_2$) C, H, N.

***N*-[1-({(Cyanoimino)[(2,5-dimethylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (16).** *N*″-cyano-*N*-(2,5-dimethylphenyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **16**; mp 93−94 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.87 (s, 9 H), 2.08 (s, 3 H), 2.25 (s, 3 H), 3.38 (d, J = 13.9 Hz, 1 H), 3.44 (d, J = 13.9 Hz, 1 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 5.41 (dd, J = 9.2, 9.2 Hz, 1 H), 6.24 (br s, 1 H), 6.76 (dd, J = 8.5, 3.0 Hz, 1 H), 6.85−6.90 (m, 3 H), 7.01 (d, J = 8.1 Hz, 1 H), 7.14 (d, J = 7.8 Hz, 1 H), 8.15 (d, J = 8.1 Hz, 1 H), 8.99 (s, 1 H). MS (ESI$^+$) m/z 452 (M + H)$^+$. Anal. ($C_{25}H_{33}N_5O_3$) C, H, N.

***N*-(1-{[[(2-Chlorophenyl)amino](cyanoimino)methyl]amino}-2,2-dimethylpropyl)-2-(3,4-dimethoxyphenyl)acetamide (17).** *N*″-cyano-*N*-(2-chlorophenyl)guanidine[39] and compound **12a** were processed as described for compound **13** to provide compound **17**; mp 135−136 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 9 H), 3.39 (d J = 13.9 Hz, 1 H), 3.47 (d, J = 13.9 Hz, 1 H), 3.72 (s, 6H), 5.42 (dd, J = 8.7, 8.7 Hz, 1 H), 6.75−6.91 (m, 4 H), 7.24−7.40 (m, 3 H), 7.50−7.56 (m, 1 H), 8.17 (d, J = 8.1 Hz, 1 H), 9.22 (s, 1 H). MS (ESI$^+$) m/z 456 (M − H)$^+$. Anal. ($C_{23}H_{28}ClN_5O_3$) C, H, N.

***N*-(1-{[[(5-Chloro-2-fluorophenyl)amino](cyanoimino)methyl]amino}-2,2-dimethylpropyl)-2-(3,4-dimethoxyphenyl)acetamide (18).** *N*-(5-chloro-2-fluorophenyl)-*N*″-cyanoguanidine and compound **12a** were processed as described for compound **13** to provide compound **18**; mp 187−188 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.92 (s, 9 H), 3.40 (d, J = 14.2 Hz, 1 H), 3.50 (d, J = 14.2 Hz, 1 H), 3.71 (s, 6 H), 5.41 (dd, J = 9.2, 9.2 Hz, 1 H), 6.77 (dd, J = 8.1, 2.0 Hz, 1 H), 6.85−6.90 (m, 2 H), 7.13 (d, J = 8.8 Hz, 1 H), 7.29−45 (m, 3 H), 8.11 (d, J = 6.1 Hz, 1 H), 9.38 (m, 1 H). MS (ESI$^+$) m/z 476 (M + H)$^+$. Anal. ($C_{23}H_{27}ClFN_5O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(2,5-difluorophenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (19).** *N*″-cyano-*N*-(2,5-difluorophenyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **19**; mp 190−191 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.92 (s, 9 H), 3.40 (d, 1 H, J = 13.9 Hz), 3.50 (d, 1 H, J = 13.9 Hz), 3.71 (s, 6 H), 5.42 (dd, 1 H, J = 8.7 Hz), 6.77 (dd, 1 H, J = 2.0, 8.1 Hz), 6.86−6.88 (m, 2H), 7.06−7.14(m, 2H), 7.19−7.26 (m, 1H), 7.29−7.37 (m, 1H), 8.12 (d, 1 H, J = 7.1 Hz), 9.39 (s, 1 H). MS (ESI$^+$) m/z 460 (M + H)$^+$. Anal. ($C_{23}H_{27}F_2N_5O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(2,4,6-trifluorophenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (20).** *N*″-cyano-*N*-(2,4,6-trifluorophenyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **20**; mp 170−171 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 9 H), 3.40 (d, J = 13.9 Hz, 1 H), 3.49 (d, J = 13.9 Hz, 1 H), 3.72 (s, 6 H), 5.43 (dd, J = 9.2, 9.2 Hz, 2 H), 6.74−6.89 (m, 3 H), 7.11 (br s, 1 H), 7.32 (dd, J = 8.8, 8.8 Hz, 2 H), 8.02 (br s, 1 H), 8.99 (m, 1 H). MS (ESI$^+$) m/z 478 (M + H)$^+$. Anal. ($C_{23}H_{26}F_3N_5O_3$) C, H, N.

***N*-(1-{[[(2-Chloro-3-pyridinyl)amino](cyanoimino)methyl]amino}-2,2-dimethylpropyl)-2-(3,4-dimethoxyphenyl)acetamide (21).** *N*-(2-Chloro-3-pyridinyl)-*N*″-cyanoguanidine[34] and compound **12a** were processed as described for compound **13** to provide compound **21**; mp 149−150 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93 (s, 9 H), 3.40 (d, J = 13.9 Hz, 1 H), 3.50 (d, J = 13.6 Hz, 1 H), 3.73 (s, 6 H), 5.43 (dd, J = 8.0, 8.0 Hz, 1 H), 6.78 (dd, J = 8.3, 1.9 Hz, 1 H), 6.85−6.91 (m, 2 H), 7.16 (br s, 1 H), 7.39−7.46 (m, 1 H), 7.73 (d, J = 7.1 Hz, 1 H), 8.16 (br s, 1 H), 8.26 (s, 1 H), 9.32 (s, 1 H). MS (ESI$^+$) m/z 459 (M + H)$^+$. Anal. ($C_{22}H_{27}ClN_6O_3 \cdot 0.1CH_2Cl_2$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methoxy-3-pyridinyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (22).** *N*″-cyano-*N*-(2-methoxy-3-pyridinyl)guanidine[34] and compound **12a** were processed as described for compound **13** to provide compound **22**; mp 146−147 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.89 (s, 9 H), 3.37 (d, J = 13.9 Hz, 1 H), 3.46 (d, J = 13.9 Hz, 2 H), 3.71 (s, 6 H), 3.87 (m, 3 H), 5.46 (dd, J = 9.0, 9.0 Hz, 1 H), 6.73−6.89 (m, 4 H), 6.96−7.03 (m, 1 H), 7.59 (dd, J = 7.5, 1.7 Hz, 1 H), 7.96−8.05 (m, 2 H), 8.91 (s, 1 H). MS (ESI$^+$) m/z 455 (M + H)$^+$. Anal. ($C_{23}H_{30}N_6O_4$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methoxyphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (23).** *N*″-cyano-*N*-(2-methoxyphenyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **23**; mp 139−140 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.85 (s, 9 H), 3.33 (d, J = 14.0 Hz, 1 H), 3.45 (d, J = 13.9 Hz, 1 H), 3.71 (s, 3 H), 3.71 (s, 3 H), 3.78 (s, 3 H), 5.45 (dd, J = 9.2, 9.2 Hz, 1 H), 6.41 (d, J = 9.5 Hz, 1 H), 6.72−6.80 (m, 1 H), 6.84−6.89 (m, 2 H), 6.91−6.99 (m, 1 H), 7.08 (dd, J = 8.3, 1.2 Hz, 1 H), 7.17−7.30 (m, 2 H), 8.04 (d, J = 8.5 Hz, 1 H), 8.77 (s, 1 H). MS (ESI$^+$) m/z 454 (M + H)$^+$. Anal. ($C_{24}H_{31}N_5O_4$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-fluorophenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (24).** *N*″-cyano-*N*-(2-fluorophenyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **24**; mp 182−183 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.90 (s, 9 H), 3.39 (d, J = 14.2 Hz, 1 H), 3.47 (d, J = 14.2 Hz, 1 H), 3.71 (s, 3 H), 3.72 (s, 3 H), 5.44 (dd, J = 9.5, 9.5 Hz, 1 H), 6.75−6.80 (m, 1 H), 6.79−6.85

(m, 1 H), 6.85−6.90 (m, 2 H), 7.15−7.23 (m, 1 H), 7.24−7.34 (m, 3 H), 8.10 (d, J = 7.1 Hz, 1 H), 9.24 (s, 1 H). MS (ESI^+) m/z 442 $(M + H)^+$. Anal. ($C_{23}H_{28}FN_5O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(2,6-difluorophenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (25).** *N″*-cyano-*N*-(2,6-difluorophenyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **25**; mp 155−156 °C. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.90 (s, 9 H), 3.40 (d, J = 14.2 Hz, 1 H), 3.49 (d, J = 14.2 Hz, 1 H), 3.72 (s, 6 H), 5.43 (dd, J = 9.0, 9.0 Hz, 1 H), 6.74−6.81 (m, 1 H), 6.85−6.91 (m, 2 H), 7.05 (d, J = 9.2 Hz, 1 H), 7.18 (t, J = 8.5 Hz, 2 H), 7.33−7.46 (m, 1 H), 8.03−8.14 (m, 1 H), 9.11 (s, 1 H). MS (ESI^+) m/z 460 $(M + H)^+$. Anal. ($C_{23}H_{27}F_2N_5O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(2,4-difluorophenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (26).** *N″*-cyano-*N*-(2,4-difluorophenyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **26**; mp 172−173 °C. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.89 (s, 9 H), 3.38 (d, J = 14.2 Hz, 1 H), 3.47 (d, J = 14.2 Hz, 1 H), 3.71 (s, 3 H), 3.72 (s, 3 H), 5.43 (dd, J = 8.8, 8.8 Hz, 1 H), 6.74−6.80 (m, 1 H), 6.82 (d, J = 8.5 Hz, 1 H), 6.85−6.91 (m, 1 H), 7.03−7.14 (m, 1 H), 7.26−7.42 (m, 2 H), 8.03 (d, J = 7.5 Hz, 1 H), 9.15 (s, 1 H). MS (ESI^+) m/z 460 $(M + H)^+$. Anal. ($C_{23}H_{27}F_2N_5O_3$) C, H, N.

***N*-(1-{[(Cyanoimino)(5-isoquinolinylamino)methyl]amino}-2,2-dimethylpropyl)-2-(3,4-dimethoxyphenyl)acetamide (27).** *N″*-cyano-*N*-5-isoquinolinylguanidine and compound **12a** were processed as described for compound **13** to provide the title compound **27**; mp 131−132 °C. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.92 (s, 9 H), 3.42 (d, J = 13.9 Hz, 1 H), 3.48 (d, J = 13.9 Hz, 1 H), 3.70 (s, 3 H), 3.72 (s, 3 H), 5.52 (t, J = 8.6 Hz, 1 H), 6.71−6.84 (m, 2 H), 6.85−6.90 (m, 2 H), 7.57 (dd, J = 9.0, 1.0 Hz, 1 H), 7.66 (d, J = 8.1 Hz, 1 H), 7.69−7.79 (m, 1 H), 8.05 (d, J = 7.8 Hz, 1 H), 8.09−8.18 (m, 1 H), 8.51 (d, J = 6.1 Hz, 1 H), 9.36 (s, 1 H), 9.46−9.66 (m, 1 H). MS (ESI^+) m/z 475 $(M + H)^+$. Anal. ($C_{26}H_{30}N_6O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methyl-3-pyridinyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (28).** *N″*-cyano-*N*-(2-methyl-3-pyridinyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **28**; mp 102−103 °C. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.91 (s, 9 H), 2.33 (s, 3 H), 3.40 (d, J = 13.6 Hz, 1 H), 3.47 (d, J = 13.6 Hz, 1 H), 3.72 (s, 3 H), 3.72 (s, 3 H), 5.44 (dd, J = 9.2, 9.2 Hz, 1 H), 6.66−6.75 (m, 1 H), 6.78 (dd, J = 6.0, 2.0 Hz, 1 H), 6.85−6.90 (m, 2 H), 7.22 (dd, J = 7.8, 4.7 Hz, 1 H), 7.45 (dd, J = 7.8, 1.4 Hz, 1 H), 8.12 (d, J = 7.8 Hz, 1 H), 8.32 (d, J = 4.4 Hz, 1 H). MS (ESI^+) m/z 439 $(M + H)^+$. Anal. ($C_{26}H_{30}N_6O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(4-fluorophenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (29).** *N″*-cyano-*N*-(4-fluorophenyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **29**; mp 159−160 °C. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.92 (s, 9 H), 3.41 (d, J = 13.9 Hz, 1 H), 3.48 (d, J = 13.9 Hz, 1 H), 3.70 (s, 3 H), 3.72 (s, 3 H), 5.41 (dd, J = 9.0, 9.0 Hz, 1 H), 6.66 (d, J = 9.2 Hz, 1 H), 6.78 (dd, J = 9.0, 2.0 Hz, 1 H), 6.86 (d, J = 3.7 Hz, 1 H), 6.88 (d, J = 2.4 Hz, 1 H), 7.12−7.25 (m, 4 H), 8.15 (d, J = 8.1 Hz, 1 H), 9.38 (s, 1 H). MS (ESI^+) m/z 442 $(M + H)^+$. Anal. ($C_{23}H_{28}FN_5O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(2,3-difluorophenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (30).** *N″*-cyano-*N*-(2,3-difluorophenyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **30**; mp 180−181 °C. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.92 (s, 9 H), 3.41 (d, J = 14.1 Hz, 1 H), 3.49 (d, J = 14.1 Hz, 1 H), 3.72 (s, 3 H), 3.72 (s, 3 H), 5.43 (dd, J = 8.9, 8.9 Hz, 1 H), 6.78 (dd, J = 6.0, 2.1 Hz, 1 H), 6.87 (d, J = 4.3 Hz, 1 H), 6.88 (d, J = 1.5 Hz, 1 H), 7.05 (d, J = 8.6 Hz, 1 H), 7.10 (d, J = 6.4 Hz, 1 H), 7.14−7.22 (m, 1 H), 7.25−7.34 (m, 1 H), 8.09 (d, J = 8.3 Hz, 1 H), 9.41 (s, 1 H). MS (ESI^+) m/z 460 $(M + H)^+$. Anal. ($C_{23}H_{27}F_2N_5O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(3,5-difluorophenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (31).** *N″*-cyano-*N*-(3,5-difluorophenyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **31**; mp 198−199 °C. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.95 (s, 9 H), 3.42 (d, J = 13.9 Hz, 1 H), 3.54 (d, J = 13.9 Hz, 1 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 5.38 (dd, J = 8.6, 8.6 Hz, 1 H), 6.76−6.81 (m, 1 H), 6.83−6.97 (m, 4 H), 7.24 (d, J = 9.5 Hz, 1 H), 8.27 (d, J = 8.1 Hz, 1 H), 9.73 (s, 1 H). MS (ESI^+) m/z 460 $(M + H)^+$. Anal. ($C_{23}H_{27}F_2N_5O_3$) C, H, N.

***N*-(1-{[[(2-Chlorobenzyl)amino](cyanoimino)methyl]amino}-2,2-dimethylpropyl)-2-(3,4-dimethoxyphenyl)acetamide (32).** *N″*-cyano-*N*-(2-chlorobenzyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **32**; mp 158−160 °C. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.89 (s, 9 H), 3.39 (d, J = 13.9 Hz, 1 H), 3.48 (d, J = 13.9 Hz, 1 H), 3.70 (s, 3 H), 3.72 (s, 3 H), 4.43 (d, J = 5.4 Hz, 2 H), 5.34 (dd, J = 9.0, 9.0 Hz, 1 H), 6.60 (d, J = 10.2 Hz, 1 H), 6.77 (dd, J = 9.0, 2.0 Hz, 1 H), 6.84−6.90 (m, 2 H), 7.22−7.28 (m, 2 H), 7.28−7.33 (m, 1 H), 7.40−7.47 (m, 1 H), 7.85 (s, 1 H), 8.23 (d, J = 8.5 Hz, 1 H). MS (ESI^+) m/z 480 $(M + H)^+$. Anal. ($C_{24}H_{30}ClN_5O_3 \cdot 0.1CH_2Cl_2$) C, H, N.

***N*-[1-({(Cyanoimino)[(3,4-difluorophenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (33).** *N″*-cyano-*N*-(3,4-difluorophenyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **33**; mp 169−170 °C. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.93 (s, 9 H), 3.42 (d, J = 13.9 Hz, 1 H), 3.53 (d, J = 13.9 Hz, 1 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 5.39 (dd, J = 9.0, 9.0 Hz, 1 H), 6.78 (dd, J = 9.0, 1.7 Hz, 1 H), 6.85−6.88 (m, 2 H), 6.91 (d, J = 9.5 Hz, 1 H), 6.96−7.03 (m, 1 H), 7.25−7.43 (m, 2 H), 8.20 (d, J = 8.1 Hz, 1 H), 9.52 (s, 1 H). MS (ESI^+) m/z 460 $(M + H)^+$. Anal. ($C_{23}H_{27}F_2N_5O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(3-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (34).** *N″*-cyano-*N*-(3-methylphenyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **34**; mp 159−160 °C. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.92 (s, 9 H), 2.28 (s, 3 H), 3.41 (d, J = 13.9 Hz, 1 H), 3.48 (d, J = 13.9 Hz, 1 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 5.41 (dd, J = 9.0, 9.0 Hz, 1 H), 6.65 (d, J = 9.8 Hz, 1 H), 6.77 (dd, J = 8.5, 2.0 Hz, 1 H), 6.87 (d, J = 8.2 Hz, 2 H), 6.87 (d, J = 2.0 Hz, 1 H), 6.94−7.04 (m, 3 H), 7.20 (dd, J = 9.0, 7.5 Hz, 1 H), 8.18 (d, J = 7.1 Hz, 1 H), 9.38 (s, 1 H). MS (ESI^+) m/z 438 $(M + H)^+$. Anal. ($C_{24}H_{31}N_5O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(4-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (35).** *N″*-cyano-*N*-(4-methylphenyl)guanidine and compound **12a** were processed as described for compound **13** to provide compound **35**; mp 119−120 °C. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.89 (s, 9 H), 2.28 (s, 3 H), 3.39 (d, J = 13.9 Hz, 1 H), 3.46 (d, J = 13.9 Hz, 1 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 5.42 (t, J = 9.0 Hz, 1 H), 6.49 (d, J = 9.2 Hz, 1 H), 6.77 (dd, J = 9.0, 2.0 Hz, 1 H), 6.84−6.89 (m, 2 H), 7.08 (d, J = 8.5 Hz, 2 H), 7.15 (d, J = 8.5 Hz, 2 H), 8.13 (d, J = 8.5 Hz, 1 H), 9.31 (s, 1 H). MS (ESI^+) m/z 438 $(M + H)^+$. Anal. ($C_{24}H_{31}N_5O_3$) C, H, N.

***N*-(1-{[(Cyanoimino)(8-quinolinylamino)methyl]amino}-2,2-dimethylpropyl)-2-(3,4-dimethoxyphenyl)acetamide (36).** *N″*-cyano-*N*-8-quinolinylguanidine and compound **12a** were processed as described for compound **13** to provide compound **36**; mp 125−126 °C. ^1H NMR (300 MHz, DMSO-d_6) δ ppm 0.95 (s, 9 H), 3.40 (d, J = 13.9 Hz, 1 H), 3.49 (d, J = 13.9 Hz, 1 H), 3.69 (s, 3 H), 3.70 (s, 3 H), 5.61 (t, J = 9.0 Hz, 1 H), 6.78 (dd, J = 9.0, 1.7 Hz, 1 H), 6.84 (d, J = 8.1 Hz, 1 H), 6.88 (d, J = 1.7 Hz, 1 H), 7.46 (d, J = 10.2 Hz, 1 H), 7.58 (t, J = 7.8 Hz, 1 H), 7.63 (dd, J = 8.8, 4.7 Hz, 1 H), 7.72 (d, J = 7.1 Hz, 1 H), 7.81 (d, J = 8.1 Hz, 1 H), 8.14 (d, J = 8.1 Hz, 1 H), 8.42 (dd, J = 8.1, 1.7 Hz, 1 H), 8.91 (dd, J = 4.4, 1.7 Hz, 1 H), 9.63 (s, 1 H). MS (ESI^+) m/z 475 $(M + H)^+$. Anal. ($C_{26}H_{30}N_6O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(3-fluorophenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (37).** *N″*-cyano-*N*-(3-fluorophenyl)guanidine and compound **12a** were processed

as described for compound **13** to provide compound (**37**; mp 180−181 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.94 (s, 9 H), 3.43 (d, J = 13.9 Hz, 1 H), 3.52 (d, J = 13.9 Hz, 1 H), 3.70 (s, 3 H), 3.71 (s, 3 H), 5.40 (dd, J = 8.8, 8.8 Hz, 1 H), 6.78 (dd, J = 9.0, 1.7 Hz, 1 H), 6.84−6.93 (m, 2 H), 6.93−7.05 (m, 2 H), 7.05−7.14 (m, 1 H), 7.30−7.40 (m, 1 H), 8.23 (d, J = 8.8 Hz, 1 H), 9.61 (s, 1 H). MS (ESI$^+$) m/z 442 (M + H)$^+$. Anal. ($C_{23}H_{28}FN_5O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-[4-(methylthio)phenyl]acetamide (38).** *N*′′-Cyano-*N*-(2-methylphenyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-[4-(methylthio)phenyl]acetamide were processed as described for compound **13** to provide compound **38**; mp 151−152 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.87 (s, 9 H), 2.13 (s, 3 H), 3.42 (d, J = 13.9 Hz, 1 H), 3.48 (d, J = 13.9 Hz, 1 H), 5.41 (dd, J = 8.8, 8.8 Hz, 1 H), 6.23 (br s, 1 H), 7.01−7.32(m, 8 H), 8.20 (d, J = 8.8 Hz, 1 H), 9.01 (m, 1 H). MS (ESI$^+$) m/z 424 (M + H)$^+$. Anal. ($C_{23}H_{29}N_5OS\cdot 0.5H_2O$) C, H, N.

2-(1,3-Benzodioxol-5-yl)-*N*-[1-({(cyanoimino)[(2-methylphenyl)-amino]methyl}amino)-2,2-dimethylpropyl]acetamide (39). *N*′′-Cyano-*N*-(2-methylphenyl)guanidine and 2-(1,3-benzodioxol-5-yl)-*N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]acetamide were processed as described for compound **13** to provide compound **39**; mp 152−153 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.87 (s, 9 H), 2.14 (s, 3 H), 3.34 (d, J = 15.3 Hz, 1 H), 3.42 (d, J = 15.3 Hz, 1 H), 5.41 (dd, J = 9.2 Hz, 1 H), 5.98 (s, 2 H), 6.26 (br s, 1 H), 6.71 (dd, J = 7.8, 1.7 Hz, 1 H), 6.88−6.86 (m, 2 H), 7.05−7.11 (m, 1 H), 7.17−7.31 (m, 3 H), 8.15 (d, J = 8.8 Hz, 1 H), 9.02 (m, 1 H). MS (ESI$^+$) m/z 422 (M + H)$^+$. Anal. ($C_{23}H_{27}N_5O_3$) C, H, N.

2-(4-Chlorophenyl)-*N*-[1-({(cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]acetamide (40). *N*′′-cyano-*N*-(2-methylphenyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-(4-chlorophenyl)acetamide were processed as described for compound **13** to provide compound **40**; mp 181−182 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (s, 9 H), 2.13 (s, 3 H), 3.46 (d, J = 14.2 Hz, 1 H), 3.53 (d, J = 14.2 Hz, 1 H), 5.41 (dd, J = 9.2, 9.2 Hz, 1 H), 6.23 (br s, 1 H), 7.04−7.12 (m, 1 H), 7.18−7.31 (m, 5 H), 7.34−7.40 (m, 2 H), 8.23 (d, J = 8.8 Hz, 1 H), 8.99 (s, 1 H). MS (ESI$^+$) m/z 422 (M + H)$^+$. Anal. ($C_{22}H_{26}ClN_5O$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(4-methoxyphenyl)acetamide (41).** *N*′′-cyano-*N*-(2-methylphenyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-(4-methoxyphenyl)acetamide were processed as described for compound **13** to provide compound **41**; mp 173−174 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.86 (s, 9 H), 2.14 (s, 3 H), 3.38 (d, J = 13.9 Hz, 1 H), 3.44 (d, J = 14.2 Hz, 1 H), 3.72 (s, 3 H), 5.40 (dd, J = 9.2, 9.2 Hz, 1 H), 6.24 (br s, 1 H), 6.84−6.89 (m, 2 H), 7.03−7.30 (m, 6 H), 8.15 (d, J = 8.5 Hz, 1 H), 9.02 (m, 1 H). MS (ESI$^+$) m/z 408 (M + H)$^+$. Anal. ($C_{23}H_{29}N_5O_2$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3,5-dimethoxyphenyl)acetamide (42).** *N*′′-cyano-*N*-(2-methylphenyl)guanidine and *N*-[1-(1H-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-(3,5-dimethoxyphenyl)acetamide were processed as described for compound **13** to provide compound **42**; mp 154−155 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.87 (s, 9 H), 2.11−2.17 (m, 3 H), 3.38 (d, J = 14.2 Hz, 1 H), 3.45 (d, J = 13.6 Hz, 1 H), 3.71 (s, 6 H), 5.42 (dd, J = 8.8, 8.8 Hz, 1 H), 6.22−6.33 (m, 1 H), 6.37 (t, J = 2.2 Hz, 1 H), 6.43 (d, J = 2.0 Hz, 2 H), 7.05−7.10 (m, 2 H), 7.18−7.23 (m, 2 H), 7.24−7.30 (m, 1 H), 8.19 (d, J = 7.8 Hz, 1 H), 9.03 (s, 1 H). MS (ESI$^+$) m/z 438 (M + H)$^+$. Anal. ($C_{24}H_{31}N_5O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]hexanamide (43).** *N*′′-cyano-*N*-(2-methylphenyl)-guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-hexanamide were processed as described for compound **13** to provide compound **43**; mp 172−173 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.84 (t, J = 7.1 Hz, 3 H), 0.89 (s, 9 H), 1.18−1.34 (m, 4 H), 1.44−1.57 (m, 2 H), 2.15 (t, J = 6.5 Hz, 2 H), 2.19 (s, 3 H), 5.40 (dd, J = 9.0, 9.0 Hz, 1 H), 6.15−6.27 (m, 1 H), 7.08−7.15 (m, 1 H), 7.19−7.25 (m, 2 H), 7.26−7.32 (m, 1 H), 8.01 (d, J = 8.8 Hz, 1 H), 9.09 (s, 1 H). MS (ESI$^+$) m/z 358 (M + H)$^+$. Anal. ($C_{20}H_{31}N_5O$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(phenyl)acetamide (44).** *N*′′-cyano-*N*-(2-methylphenyl)guanidine and *N*-[1-(1H-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-(phenyl)acetamide were processed as described for compound **13** to provide compound **44**; mp 190−191 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.87 (s, 9 H), 2.14 (s, 3 H), 3.46 (d, J = 13.9 Hz, 1 H), 3.52 (d, J = 13.9 Hz, 1 H), 5.41 (dd, J = 9.0, 9.0 Hz, 1 H), 6.20−6.32 (m, 1 H), 7.05−7.11 (m, 1 H), 7.17−7.24 (m, 3 H), 7.23−7.35 (m, 5 H), 8.23 (d, J = 7.8 Hz, 1 H), 9.02 (s, 1 H). MS (ESI$^+$) m/z 378 (M + H)$^+$. Anal. ($C_{22}H_{27}N_5O$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-3,5-dimethoxybenzamide (45).** *N*′′-cyano-*N*-(2-methylphenyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-3,5-dimethoxybenzamide were processed as described for compound **13** to provide compound **45**; mp 164−165 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.89 (s, 9 H), 2.19 (s, 3 H), 3.79 (s, 6 H), 5.79 (t, J = 9.2 Hz, 1 H), 6.09 (d, J = 7.5 Hz, 1 H), 6.69 (t, J = 2.2 Hz, 1 H), 6.92 (d, J = 2.4 Hz, 2 H), 7.12−7.19 (m, 1 H), 7.23−7.36 (m, 2 H), 8.31 (d, J = 8.8 Hz, 1 H), 9.07 (s, 1 H). MS (ESI$^+$) m/z 424 (M + H)$^+$. Anal. ($C_{23}H_{29}N_5O_3\cdot 0.05CH_2Cl_2$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-3,4-dimethoxybenzamide (46).** *N*′′-cyano-*N*-(2-methylphenyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-3,4-dimethoxybenzamide were processed as described for compound **13** to provide compound **46**; mp 147−148 °C. ^{1}H NMR (500 MHz, MeOH-d_4) δ ppm 1.00 (s, 9 H), 2.27 (s, 3 H), 3.87 (s, 8 H), 3.88 (s, 6 H), 5.78 (s, 1 H), 7.01 (d, J = 8.4 Hz, 2 H), 7.20−7.35 (m, 4 H), 7.39−7.45 (m, 2 H), 8.29 (d, J = 7.8 Hz, 1 H). MS (ESI$^+$) m/z 424 (M + H)$^+$. Anal. ($C_{23}H_{29}N_5O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-4-methoxybenzamide (47).** *N*′′-cyano-*N*-(2-methylphenyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-4-methoxybenzamide were processed as described for compound **13** to provide compound **47**; mp 188−189 °C. ^{1}H NMR (500 MHz, MeOH-d_4) δ ppm 0.96 (s, 9 H), 2.23 (s, 3 H), 3.80 (s, 3 H), 5.73 (s, 1 H), 6.94 (d, J = 8.7 Hz, 2 H), 7.16−7.30 (m, 4 H), 7.72 (d, J = 8.7 Hz, 2 H), 8.22 (d, J = 8.4 Hz, 1 H). MS (ESI$^+$) m/z 394 (M + H)$^+$. Anal. ($C_{22}H_{27}N_5O_2$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-3-(3,4-dimethoxyphenyl)propanamide (48).** *N*′′-cyano-*N*-(2-methylphenyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-3-(3,4-dimethoxyphenyl)propanamide were processed as described for compound **13** to provide compound **48**; mp 168−169 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.84 (s, 9 H), 2.18 (s, 3 H), 2.43 (t, J = 7.2 Hz, 1 H), 2.76 (t, J = 7.3 Hz, 2 H), 3.70 (s, 3 H), 3.72 (s, 3 H), 5.41 (dd, J = 9.2, 9.2 Hz, 1 H), 6.15−6.30 (m, 1 H), 6.70 (dd, J = 9.0, 1.7 Hz, 1 H), 6.79−6.86 (m, 2 H), 7.06−7.13 (m, 1 H), 7.17−7.31 (m, 3 H), 8.03 (d, J = 7.8 Hz, 1 H), 9.08 (s, 1 H). MS (ESI$^+$) m/z 452 (M + H)$^+$. Anal. ($C_{25}H_{33}N_5O_3$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-3-(4-methoxyphenyl)propanamide (49).** *N*′′-cyano-*N*-(2-methylphenyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-3-(4-methoxyphenyl)propanamide were processed as described for compound **13** to provide compound **49**; mp 167−168 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.84 (s, 9 H), 2.18 (s, 3 H), 2.37−2.46 (m, 2 H), 2.76 (t, J = 7.5 Hz, 2 H), 3.70 (s, 3 H), 5.39 (dd, J = 9.0, 9.0 Hz, 1 H), 6.17−6.26 (m, 1 H), 6.82 (d, J = 8.5 Hz, 2 H), 7.07−7.10 (m, 1 H), 7.12 (d, J = 8.5 Hz, 2 H), 7.18−7.25 (m, 2 H), 7.25−7.31 (m, 1 H), 8.03 (d, J = 8.1 Hz, 1 H), 9.07 (s, 1 H). MS (ESI$^+$) m/z 422 (M + H)$^+$. Anal. ($C_{24}H_{31}N_5O_2$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-4-(4-methoxyphenyl)butanamide (50).** *N*′′-cyano-(2-methylphenyl)guanidine and *N*-(1-benzotriazol-1-yl-2,2-dimethylpropyl)-4-(4-methoxyphenyl)butanamide were processed as

described for compound **13** to provide compound **50**; mp 132−133 °C. ^{1}H NMR (500 MHz, MeOH-d_4) δ 0.95 (s, 9 H), 1.88 (m, 2 H), 2.24 (t, J = 7.49 Hz, 2 H), 2.27 (s, 3 H), 2.57 (t, J = 7.80 Hz, 2 H), 3.75 (s, 3 H), 5.47 (s, 1 H), 6.82 (d, J = 8.4 Hz, 2 H), 7.09 (d, J = 8.73 Hz, 2 H), 7.19 (m, 1 H), 7.25 (m, 2 H), 7.31 (m, 1 H). MS (ESI$^+$) m/z 436 (M + H)$^+$. Anal. ($C_{25}H_{33}N_5O_2$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methylphenyl)amino]methyl}amino)-2,2-dimethylpropyl]-4-phenylbutanamide (51).** *N*″-cyano-*N*-(2-methylphenyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-4-phenylbutanamide were processed as described for compound **13** to provide the title compound **51**; mp 153−154 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.89 (s, 9 H), 1.74−1.87 (m, 2 H), 2.12−2.22 (m, 5 H), 2.56 (t, J = 8.1 Hz, 2 H), 5.43 (dd, J = 9.0, 9.0 Hz, 1 H), 6.21 (br s, 1 H), 7.08−7.33 (m, 9 H), 8.03 (d, J = 7.5 Hz, 1 H), 9.09 (m, 1 H). MS (ESI$^+$) m/z 406 (M + H)$^+$. Anal. ($C_{24}H_{31}N_5O$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methyl-3-pyridinyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-[4-(methylthio)phenyl]acetamide (52).** *N*″-cyano-*N*-(2-methyl-3-pyridinyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-[4-(methylthio)phenyl]acetamide were processed as described for compound **13** to provide compound **52**; mp 172−173 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 9 H), 2.33 (s, 3 H), 2.45 (s, 3 H), 3.45 (d, J = 14.2 Hz, 1 H), 3.52 (d, J = 13.9 Hz, 1 H), 5.42 (dd, J = 9.0, 9.0 Hz, 1 H), 6.69 (d, J = 8.8 Hz, 1 H), 7.21 (s, 4 H), 7.24 (dd, J = 9.0, 5.1 Hz, 1 H), 7.46 (dd, J = 8.0, 1.5 Hz, 1 H), 8.17 (d, J = 7.5 Hz, 1 H), 8.34 (dd, J = 4.8, 1.4 Hz, 1 H), 9.11 (s, 1 H). MS (ESI$^+$) m/z 425 (M + H)$^+$. Anal. ($C_{22}H_{28}N_6OS$) C, H, N.

2-(4-Chlorophenyl)-*N*-[1-({(cyanoimino)[(2-methyl-3-pyridinyl)amino]methyl}amino)-2,2-dimethylpropyl]acetamide (53). *N*″-cyano-*N*-(2-methyl-3-pyridinyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-(4-chlorophenyl)acetamide were processed as described for compound **13** to provide compound **53**; mp 180−181 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 9 H), 2.32 (s, 3 H), 3.50 (d, J = 14.2 Hz, 1 H), 3.56 (d, J = 14.2 Hz, 1 H), 5.42 (dd, J = 8.8, 8.8 Hz, 1 H), 6.68 (d, J = 9.2 Hz, 1 H), 7.31 (m, 5 H), 7.47 (dd, J = 8.1, 1.4 Hz, 1 H), 8.21 (d, J = 8.1 Hz, 1 H), 8.34 (dd, J = 4.8, 1.4 Hz, 1 H), 9.09 (br s, 1 H). MS (ESI$^+$) m/z 413 (M + H)$^+$. Anal. ($C_{21}H_{25}ClN_6O$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methyl-3-pyridinyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(3-fluoro-4-methylphenyl)acetamide (54).** *N*″-cyano-*N*-(2-methyl-3-pyridinyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-(3-fluoro-4-methylphenyl)acetamide were processed as described for compound **13** to provide compound **54**; mp 75−77 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 9 H), 2.20 (d, J = 1.7 Hz, 3 H), 2.33 (s, 3 H), 3.47 (d, J = 14.6 Hz, 1 H), 3.53 (m, J = 13.9 Hz, 1 H), 5.42 (dd, J = 9.0, 9.0 Hz, 1 H), 6.69 (d, J = 8.5 Hz, 1 H), 7.06 (m, 2 H), 7.22 (m, 2 H), 7.47 (dd, J = 8.1, 1.7 Hz, 1 H), 8.18 (d, J = 7.8 Hz 1 H), 8.34 (dd, J = 4.8, 1.4 Hz, 1 H), 9.09 (br s, 1 H). MS (ESI$^+$) m/z 411 (M + H)$^+$. Anal. ($C_{22}H_{27}FN_6O\cdot 0.1CF_3COOH$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methyl-3-pyridinyl)amino]methyl}amino)-2,2-dimethylpropyl]-2-(4-fluorophenyl)acetamide (55).** *N*″-cyano-*N*-(2-methyl-3-pyridinyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-(4-fluorophenyl)acetamide were processed as described for compound **13** to provide compound **55**; mp 166−167 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 9 H), 2.32 (s, 3 H), 3.48 (d, J = 14.2 Hz, 1 H), 3.55 (d, J = 14.2 Hz, 1 H), 5.41 (dd, J = 9.0, 9.0 Hz, 1 H), 6.69 (d, J = 8.1 Hz, 1 H), 7.13 (m, 2 H), 7.23 (dd, J = 7.8, 4.8 Hz, 1 H), 7.31 (m, 2 H), 7.47 (dd, J = 8.0, 1.5 Hz, 1 H), 8.19 (d, J = 8.1, Hz 1 H), 8.34 (dd, J = 4.6, 1.2 Hz, 1 H), 9.10 (br s, 1 H). MS (ESI$^+$) m/z 397 (M + H)$^+$. Anal. ($C_{21}H_{25}FN_6O$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methyl-3-pyridinyl)amino]methyl}amino)-2,2-dimethylpropyl]-4-(4-methoxyphenyl)butanamide (56).** *N*″-cyano-*N*-(2-methyl-3-pyridinyl)guanidine and *N*-(1-benzotriazol-1-yl-2,2-dimethylpropyl)-4-(4-methoxyphenyl)butanamide were processed as described for compound **13** to provide compound **56**; mp 65−68 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.92 (s, 9 H), 1.77 (m, 2 H), 2.17 (t, J = 8.0 Hz, 2 H), 2.38 (s, 3 H), 2.49 (m, 2 H), 3.71 (s, 3 H), 5.43 (dd, J = 8.8, 8.8 Hz, 1 H), 6.63 (br m, 1 H), 6.84 (m, 2 H), 7.09 (m, 2 H), 7.24 (dd, J = 8.0, 4.9 Hz, 1 H), 7.51 (dd, J = 8.0, 1.5 Hz, 1 H), 7.99 (br d., J = 9.2, 1 H), 8.34 (dd, J = 4.8, 1.4 Hz, 1 H), 9.23 (br s, 1 H). MS (ESI$^+$) m/z 437 (M + H)$^+$. Anal. ($C_{24}H_{32}N_6O_2\cdot 0.3H_2O$) C, H, N.

***N*-[1-({(Cyanoimino)[(2-methyl-3-pyridinyl)amino]methyl}amino)-2,2-dimethylpropyl]-5-phenylpentanamide (57).** *N*″-cyano-*N*-(2-methyl-3-pyridinyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-5-phenylpentanamide were processed as described for compound **13** to provide compound **57**; mp 133−134 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.92 (s, 9 H), 1.55 (m, 4 H), 2.21 (m, 2 H), 2.36 (s, 3 H), 2.50 (m, 2 H), 2.58 (t, J = 7.1 Hz, 2 H), 5.42 (dd, J = 9.0, 9.0 Hz, 1 H), 7.21 (m, 7 H), 7.48 (d, J = 7.8 Hz, 1 H), 8.01 (br d, J = 7.8 Hz, 1 H 1 H), 8.34 (br m, 1 H), 9.24 (br s, 1 H). MS (ESI$^+$) m/z 421 (M + H)$^+$. Anal. ($C_{24}H_{32}N_6O\cdot 0.2H_2O$) C, H, N.

2-(4-Chlorophenyl)-*N*-(1-{[(cyanoimino(5-quinolinylamino)methyl]amino}-2,2-dimethylpropyl)acetamide (58). *N*″-cyano-*N*-5-quinolinylguanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-(4-chlorophenyl)acetamide were processed as described for compound **13** to provide compound **58**; mp 195−196 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.90 (s, 9 H), 3.48 (d, J = 14.2 Hz, 1 H), 3.55 (d, J = 14.6 Hz, 1 H), 5.50 (dd, J = 8.8, 8.8 Hz, 1 H), 6.66 (d, J = 8.1 Hz, 1 H), 7.28 (d, J = 8.8 Hz, 2 H), 7.37 (d, J = 8.8 Hz, 2 H), 7.40 (d, J = 7.1 Hz, 1 H), 7.55 (dd, J = 8.5, 4.1 Hz, 1 H), 7.75 (dd, J = 8.5, 7.8 Hz, 1 H), 7.97 (d, J = 8.8 Hz, 1 H), 8.15 (d, J = 8.5 Hz, 1 H), 8.26 (d, J = 8.5 Hz, 1 H), 8.94 (dd, J = 4.1, 1.7 Hz, 1 H), 9.55 (s, 1 H). MS (ESI$^+$) m/z 449 (M + H)$^+$. Anal. ($C_{24}H_{25}ClN_6O$) C, H, N.

***N*-(1-{[(Cyanoimino)(5-quinolinylamino)methyl]amino}-2,2-dimethylpropyl)-2-[4-(methylthio)phenyl]acetamide (59).** *N*″-cyano-*N*-5-quinolinylguanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-[4-(methylthio)phenyl]acetamide were processed as described for compound **13** to provide compound **59**; mp 188−189 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.90 (s, 9 H), 2.45 (s, 3 H), 3.50 (d, J = 12.6 Hz, 1 H), 3.44 (d, J = 12.6 Hz, 1 H), 5.51 (dd, J = 8.8, 8.8 Hz, 1 H), 6.67 (s, 1 H), 7.21 (s, 4 H), 7.40 (d, J = 7.5 Hz, 1 H), 7.55 (dd, J = 8.5, 4.07 Hz, 1 H), 7.74 (t, J = 7.5 Hz, 1 H), 7.97 (d, J = 8.5 Hz, 1 H), 8.12 (s, 1 H), 8.26 (d, J = 8.5 Hz, 1 H), 8.94 (dd, J = 4.1, 1.7 Hz, 1 H), 9.6 (s, 1 H). MS (ESI$^+$) m/z 461 (M + H)$^+$. Anal. ($C_{25}H_{28}N_6OS$) C, H, N.

***N*-(1-{[(Cyanoimino)(5-quinolinylamino)methyl]amino}-2,2-dimethylpropyl)-2-(2,3-dihydro-1,4-benzodioxin-6-yl)acetamide (60).** *N*″-cyano-*N*-5-quinolinylguanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-(2,3-dihydro-1,4-benzodioxin-6-yl)acetamide[40] were processed as described for compound **13** to provide compound **60**; mp 191−192 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 9 H), 3.35−3.44 (m, 2 H), 4.21 (s, 4 H), 5.50 (dd, J = 8.8, 8.8 Hz, 1 H), 6.64−6.73 (m, 2 H), 6.75−6.80 (m, 2 H), 7.42 (d, J = 7.5 Hz, 1 H), 7.53−7.59 (m, 1 H), 7.75 (dd, J = 7.5, 8.5 Hz, 1 H), 7.97 (d, J = 8.5 Hz, 1 H), 8.07 (br s, 1 H), 8.27 (d, J = 8.5 Hz, 1 H), 8.94 (dd, J = 1.7, 4.1 Hz, 1 H), 9.59 (s, 1 H). MS (ESI$^+$) m/z 473 (M + H)$^+$. Anal. ($C_{26}H_{28}N_6O_3$) C, H, N.

***N*-(1-{[(Cyanoimino)(5-quinolinylamino)methyl]amino}-2,2-dimethylpropyl)-2-(1-naphthyl)acetamide (61).** *N*″-cyano-*N*-5-quinolinylguanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-(1-naphthyl)acetamide were processed as described for compound **13** to provide compound **61**; mp 171−173 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 9 H), 3.97 (d, J = 15.3 Hz, 1 H), 4.04 (d, J = 15.3 Hz, 1 H), 5.54 (dd, J = 9.0, 9.0 Hz, 1 H), 6.74 (d, J = 9.5 Hz, 1 H), 7.37 (d, J = 7.5 Hz, 1 H), 7.45 (m, 3 H), 7.51 (m, 2 H), 7.73 (t, J = 7.8 Hz, 1 H), 7.84 (dd, J = 5.9, 3.6 Hz, 1 H), 7.95 (m, 1 H), 8.06 (m, 1 H), 8.19 (d, J = 8.8 Hz, 1 H), 8.26 (m, 1 H), 8.91 (dd, J = 4.2, 1.2 Hz, 1 H), 9.55 (s, 1 H). MS (ESI$^+$) m/z 465 (M + H)$^+$. Anal. ($C_{28}H_{28}N_6O$) C, H, N.

***N*-(1-{[(Cyanoimino)(5-quinolinylamino)methyl]amino}-2,2-dimethylpropyl)-2-(4-cyanophenyl)acetamide (62).** *N*″-cyano-*N*-5-quinolinylguanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-2-(4-cyanophenyl)acetamide were processed as described for compound **13** to provide compound **62**; mp 195−196

°C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.91 (s, 9 H), 3.59 (d, J = 14 Hz, 1 H), 3.66 (d, J = 14 Hz, 1 H), 5.50 (dd, J = 8.8, 8.8 Hz, 1 H), 6.66 (d, J = 9.2 Hz, 1 H), 7.38−7.49 (m, 3 H), 7.53−7.59 (m, 1 H), 7.71−7.81 (m, 3 H), 7.97 (d, J = 8.5 Hz, 1 H), 8.17−8.31 (m, 2 H), 8.95 (dd, J = 1.7, 5.8 Hz, 1 H), 9.53 (s, 1 H). MS (ESI$^+$) m/z 440 (M + H)$^+$. Anal. ($C_{25}H_{25}N_7O$) C, H, N.

***N*-(1-{[(Cyanoimino)(5-quinolinylamino)methyl]amino}-2,2-dimethylpropyl)-4-(3-pyridinyl)butanamide (63).** *N*″-cyano-*N*-5-quinolinylguanidine and example *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dimethylpropyl]-4-(3-pyridinyl)butanamide were processed as described for compound **13** to provide compound **63**; mp 181−182 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.93 (s, 9 H), 1.75−1.88 (m, 2 H), 2.17 (t, J = 7.1 Hz, 2 H), 2.59 (t, J = 7.5 Hz, 2 H), 5.52 (dd, J = 8.8, 8.8 Hz, 1 H), 6.59 (br s, 1 H), 7.27−7.34 (m, 1 H), 7.46 (dd, J = 1.0, 7.5, Hz, 1 H), 7.54−7.62 (m, 2 H), 7.76 (t, J = 19.7 Hz, 1 H), 7.89−8.02 (m, 2 H), 8.32 (d, J = 8.5 Hz, 1 H), 8.39−8.45 (m, 2 H), 8.94 (d, J = 5.8 Hz, 1 H), 9.64 (s, 1 H). MS (ESI$^+$) m/z 444 (M + H)$^+$. Anal. ($C_{25}H_{29}N_7O$) C, H, N.

***N*-[2,2-Dichloro-1-({(cyanoimino)[(2-methoxy-3-pyridinyl)amino]methyl}amino)propyl]-2-(3,4-dimethoxyphenyl)acetamide (64).** *N*″-cyano-N-(2-methoxy-3-pyridinyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dichloropropyl]-2-(3,4-dimethoxyphenyl)acetamide were processed as described for compound **13** to provide compound **64**; mp 188−190 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.07 (s, 3 H), 3.43 (d, J = 14.6 Hz, 1 H), 3.50 (d, J = 14.9 Hz, 1 H), 3.71 (s, 3 H), 3.72 (s, 3 H), 3.89 (s, 3 H), 6.25 (dd, J = 8.8, 8.8 Hz, 1 H), 6.77 (dd, J = 8.1, 2.0 Hz, 1 H), 6.86 (m, 2 H), 7.04 (dd, J = 7.5, 5.1 Hz, 2 H), 7.58 (dd, J = 7.8, 1.4 Hz, 1 H), 8.09 (dd, J = 4.9, 1.9 Hz, 1 H), 8.43 (d, J = 9.2 Hz, 1 H), 9.26 (s, 1 H). MS (ESI$^+$) m/z 496 (M + H)$^+$. Anal. ($C_{21}H_{24}Cl_2N_6O_4$) C, H, N.

***N*-[2,2-Dichloro-1-({(cyanoimino)[(2-methoxy-3-pyridinyl)amino]methyl}amino)propyl]-3,5-dimethoxybenzamide (65).** *N*″-cyano-*N*-(2-methoxy-3-pyridinyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dichloropropyl]-3,5-dimethoxybenzamide were processed as described for compound **13** to provide compound **65**; mp 198−199 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15 (s, 3 H), 3.80 (s, 6 H), 3.86 (s, 3 H), 6.48 (dd, J = 8.7, 8.7 Hz, 1 H), 6.74 (t, J = 2.2 Hz, 1 H), 6.79 (d, J = 8.8 Hz, 1 H), 6.95 (d, J = 2.4 Hz, 2 H), 7.07 (dd, J = 7.6, 4.9 Hz, 1 H), 7.63 (dd, J = 7.6, 1.5 Hz, 1 H), 8.14 (dd, J = 4.9, 1.9 Hz, 1 H), 8.65 (d, J = 8.1 Hz, 1 H), 9.53 (s, 1 H). MS (ESI$^+$) m/z 482 (M + H)$^+$. Anal. ($C_{20}H_{22}Cl_2N_6O_4$) C, H, N.

4-Chloro-*N*-[2,2-dichloro-1-({(cyanoimino)[(2-methoxy-3-pyridinyl)amino]methyl}amino)propyl]benzamide (66). *N*″-cyano-*N*-(2-methoxy-3-pyridinyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dichloropropyl]-4-chlorobenzamide were processed as described for compound **13** to provide compound **66**; mp 155−156 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.16 (s, 3 H), 3.86 (s, 3 H), 6.50 (dd, J = 8.7 Hz, 1 H), 6.82 (d, J = 8.8 Hz, 1 H), 7.07 (dd, J = 7.5, 5.1 Hz, 1 H), 7.63 (m, 3 H), 7.84 (d, J = 8.8 Hz, 2 H), 8.14 (dd, J = 5.1, 1.7 Hz, 1 H), 8.77 (d, J = 8.8 Hz, 1 H) 9.45 (s, 1 H). MS (ESI$^+$) m/z 457 (M + H)$^+$. Anal. ($C_{18}H_{17}Cl_3N_6O_2$) C, H, N.

4-Chloro-*N*-[2,2-dichloro-1-({(cyanoimino)[(2,6-dimethoxy-3-pyridinyl)amino]methyl}amino)propyl]benzamide (67). *N*″-cyano-*N*-(2,6-dimethoxy-3-pyridinyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dichloropropyl]-4-chlorobenzamide were processed as described for compound **13** to provide compound **67**; mp 162−163 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.14 (s, 3 H), 3.85 (s, 3 H), 3.89 (s, 3 H), 6.45 (d, J = 8.5 Hz, 1 H), 6.50 (dd, J = 8.5, 8.5 Hz, 1 H), 6.59 (d, J = 8.8 Hz, 1 H), 7.55 (d, J = 8.1 Hz, 1 H), 7.62 (d, J = 8.5 Hz, 2 H), 7.83 (d, J = 8.8 Hz, 2 H), 8.70 (d, J = 8.8 Hz, 1 H), 9.21 (s, 1 H). MS (ESI$^+$) m/z 486 (M + H)$^+$. Anal. ($C_{19}H_{19}Cl_3N_6O_3 \cdot 0.1C_6H_{14}$) C, H, N.

4-Chloro-*N*-(2,2-dichloro-1-{[[(2-chloro-3-pyridinyl)amino](cyanoimino)methyl]amino}propyl)benzamide (68). *N*-(2-chloro-3-pyridinyl)-*N*″-cyanoguanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dichloropropyl]-4-chlorobenzamide were processed as described or compound **13** to provide compound **68**; mp 135−137 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (s, 3 H), 6.50 (dd, J = 8.7, 8.7 Hz, 1 H), 7.16 (d, J = 8.5 Hz, 1 H), 7.52 (dd, J = 7.8, 4.8 Hz, 1 H), 7.63 (d, J = 8.8 Hz, 2 H), 7.86 (d, J = 8.5 Hz, 2 H), 7.90 (m, 1 H), 8.39 (dd, J = 4.8, 1.7 Hz, 1 H), 8.90 (d, J = 8.5 Hz, 1 H), 9.86 (s, 1 H). MS (ESI$^+$) m/z 461 (M + H)$^+$. Anal. ($C_{17}H_{14}Cl_4N_6O$) C, H, N.

***N*-[2,2-Dichloro-1-({(cyanoimino)[(2-methyl-3-pyridinyl)amino]methyl}amino)propyl]-3,5-dimethoxybenzamide (69).** *N*″-cyano-*N*-(2-methyl-3-pyridinyl)guanidine and *N*-[1-(1*H*-1,2,3-benzotriazol-1-yl)-2,2-dichloropropyl]-3,5-dimethoxybenzamide were processed as described for compound **13** to provide compound **69**; mp 203−204 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.12 (s, 3 H), 2.41 (s, 3 H), 3.80 (s, 6 H), 6.49 (dd, J = 9.0, 9.0 Hz, 1 H), 6.58−6.70 (m, 1 H), 6.74 (t, J = 2.4 Hz, 1 H), 6.94 (d, J = 2.4 Hz, 2 H), 7.28−7.38 (m, 1 H), 7.62 (d, J = 8.1 Hz, 1 H), 8.46 (s, 1 H), 8.68 (d, J = 8.5 Hz, 1 H), 9.62 (s, 1 H). MS (ESI$^+$) m/z 466 (M + H)$^+$. Anal. ($C_{24}H_{32}N_6O_5 \cdot 0.15H_2O$) C, H, N.

Supporting Information Available: Complete combustion analysis data for compounds **13**−**69**. This material is available free of charge via the Internet at http://pubs.acs.org.

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