Structure−Activity Studies of Novel Cyanoguanidine ATP-Sensitive Potassium Channel Openers for the Treatment of Overactive Bladder

Arturo Perez-Medrano,* Michael E. Brune, Steven A. Buckner, Michael J. Coghlan, Thomas A. Fey, Murali Gopalakrishnan, Robert J. Gregg, Michael E. Kort, Victoria E. Scott, James P. Sullivan, Kristi L. Whiteaker, and William A. Carroll

Abbott Laboratories, Neuroscience Research, Global Pharmaceutical Research and Development, Abbott Park, Illinois 60064-6104

Received August 15, 2007

A series of novel cyanoguanidine derivatives was designed and synthesized. Condensation of *N*-(1-benzotriazol-1-yl-2,2-dichloropropyl)-substituted benzamides with *N*-(substituted-pyridin-3-yl)-*N*′-cyanoguanidines furnished *N*-{2,2-dichloro-1-[*N*′-(substituted-pyridin-3-yl)-*N*″-cyanoguanidino]propyl}-substituted benzamide derivatives. These agents were glyburide-reversible potassium channel openers and hyperpolarized human bladder cells as assessed by the FLIPR membrane potential dye (K_{ATP}-FMP). These compounds were also potent full agonists in relaxing electrically stimulated pig bladder strips, an in vitro model of overactive bladder. The most active compound **9** was evaluated for in vivo efficacy and selectivity in a pig model of bladder instability. Preliminary pharmacokinetic studies in dog demonstrated excellent oral bioavailability and a $t_{1/2}$ of 15 h. The synthesis, SAR studies, and biological properties of these agents are discussed.

Introduction

Overactive bladder (OAB[a]) is a prevalent urinary disorder in humans, costly and yet vastly underreported. The symptoms of OAB can have a significant negative impact on the quality of life of the patient because of disturbed sleep, withdrawal from social activities, hygienic and toilet mapping, and loss of day time productivity. Establishing the actual prevalence of OAB is difficult because of the problems with definition, reporting bias, and other technical issues. It has been calculated[1] that the prevalence of OAB can be up to 37% among women in the US, almost 16% among men, and about 10−20% of the world population.[2,3] The prevalence of OAB increases with age, >50% of the elderly in nursing homes may be afflicted.[3]

Annual direct and indirect costs related with bladder overactivity for individuals in the US aged >65 years rose from $8.2 billion in 1984 to approximately $26.3 billion in 1995.[4] Pharmacotherapy, specifically muscarinic antagonists, has been widely used to treat OAB. The introduction of two muscarinic agents, tolterodine (Detrol) and oxybutynin (Ditropan XL), in recent years has driven an increase in drug therapy, although their usefulness is limited by antimuscarinic side effects such as dry mouth, constipation, and blurred vision, resulting in low patient compliance. Absorbent products still represent the largest segment of the OAB market.

OAB is characterized by the symptoms of increased urinary urgency, frequency, and incontinent episodes. Urinary urgency is defined as a sudden, precipitous urge to void and a feeling that micturition is imminent, accompanied by a fear of incontinence.[5] Persistent bladder instability causes chronic sensory urgency and involuntary loss of urine. The etiology of OAB can arise from various causes including myogenic, bladder hypertrophy associated with outlet obstruction or urinary infectious.

Normal bladder emptying is mediated by stimulation and contraction of the detrusor muscle. Symptoms of OAB occur because the detrusor muscle is overactive and contracts inappropriately during bladder filling. Although the cause of the overactive detrusor is unknown, it has been hypothesized to arise primarily from functional changes in detrusor smooth muscle structure and function (myogenic etiology). It has been suggested that supersensitivity to agonists, increase in gap junctions, and enhanced electrical coupling between smooth muscle cells could enable widespread dissemination of depolarization signals leading to spontaneous nonvoiding contractions.[6,7] ATP-sensitive potassium channels (K_{ATP} channels) present in bladder smooth muscle play a critical role in controlling myogenic tone and excitability. Compounds that selectively open these channels hyperpolarize cells, decrease cellular (hyper)excitability, and diminish smooth muscle cell activity, resulting in suppression of unstable bladder contractions.[7] Thus, K_{ATP} channel openers (KCOs) may be an attractive way of treating overactive bladder by inhibiting overactivity during the filling phase without affecting normal voiding contractions.

Several K_{ATP} openers such as cromakalim and pinacidil have been shown to relax in vitro bladder smooth muscle from humans, pigs, rats, or guinea pigs.[8,9] In vivo activity has also been showed with a number of K_{ATP} openers.[9−14] However, the clinical data for KCOs is restricted to a small pilot clinical study with cromakalim on patients with detrusor instability or detrusor hyperreflexia. In this study the nonselective KCO, cromakalim, demonstrated an improvement in the symptoms of bladder overactivity.[15] This agent has also shown, in a related study with patients with high spinal cord lesions, serious side effects on the cardiovascular system. Clinically, no beneficial effects were seen in the bladder at doses that were already hypotensive.[16] It is clear that more agents are needed that can be more selective for the bladder than for the cardiovascular system.

New KCOs have been developed recently;[17] among them ZD-6169 **1** has attracted high interest and demonstrated activation of bladder K_{ATP} channels in vitro. This compound selectively inhibited bladder function in two animal models[9,10] without apparent hypotensive effects. ZD-6169 advanced to phase II

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

[a] Abbreviations: FLIPR, fluorometric imaging plate reader; K_{ATP} channels, ATP-sensitive potassium channels; FMP, fast membrane potential; SAR, structure−activity relationship; OAB, overactive bladder, KCOs, K_{ATP} channel openers; LPD, Landrace pig detrusor; UBC, unstable bladder contractions.

10.1021/jm7010194 CCC: $37.00
Published on Web 10/31/2007

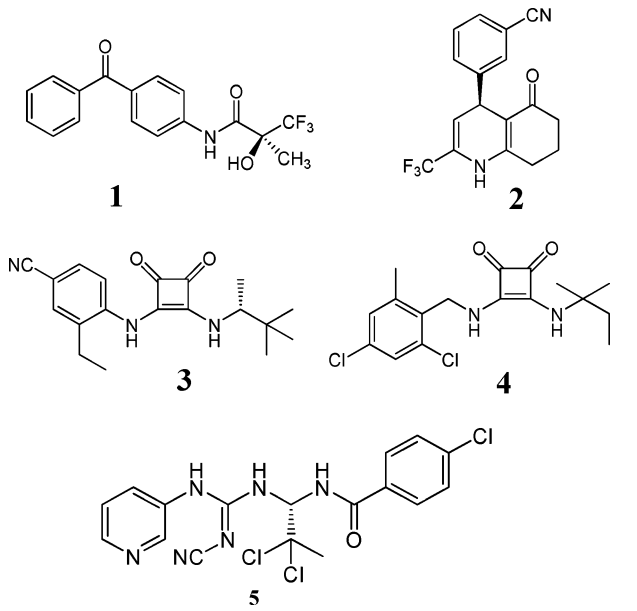
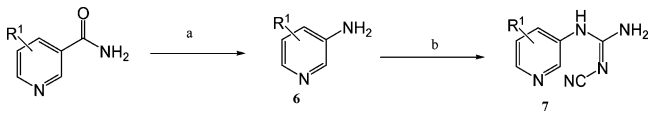


Figure 1. Structures of KCOs from literature and compound **5**.

Scheme 1[a]



[a] Reagents and conditions: (a) NaOH, Br_2, (b) $NaNH(CN)_2$, HCl, H_2O, 60 °C.

clinical trials for the treatment of OAB; however, it has since been replaced with a new compound ZD-0947 **2**.[18]

Researchers at Wyeth have recently described novel squarates as KCOs exemplified by WAY-133537 **3**[19] and WAY151616 **4**.[20] These compounds have been reported to be effective in vitro at relaxing rat bladder strips, and both compounds had in vivo bladder selectivity in conscious rats after oral dosing.

We have recently reported a series of novel cyanoguanidines that hyperpolarize human bladder K_{ATP} channels.[21] In our previous paper our group describes (*R*)-(−)-4-chloro-*N*-[2,2-dichloro-1-(*N*′-cyano-*N*″-pyridin-3-ylguanidino)propyl]benzamide **5** as a potent KCO that effectively relaxes pig detrusor strips (LPD) in vitro.[21] In an effort to enhance the potency of these cyanoguanidines, a large number of analogues were prepared. These new agents are also potent full agonists in relaxing pig bladder strips and demonstrate in vivo activity in an animal model. In this study, the preparation, SAR, and biological properties of these agents will be discussed.**Chemistry.** Structure−activity relationship (SAR) studies on the parent structure **5** entailed investigation of the pyridine substitution and phenyl ring patterns. 3-Pyridylcyanoguanidine fragments were prepared from the corresponding 3-aminopyridines **6** as illustrated in Scheme 1. Most of the 3-aminopyridines were commercially available and noncommercially available 3-aminopyridines were prepared from the corresponding nicotinamide by a Hoffmann rearrangement.[22] Reaction of 3-aminopyridines **6** with sodium dicyanamide in water in the presence of HCl[23] provided cyanoguanidines **7**.

The cyanoguanidine-aminals described in this report were assembled by a two-step sequence as depicted in Scheme 2. Reaction of substituted benzamides with 2,2-dichloropropionaldehyde[24] and benzotriazole in the presence of *p*-toluensulfonic acid[25] produced intermediates **8**, which were coupled with *N*-pyridylcyanoguanidines **7** to yield cyanoguanidine-aminals **9**−**61**. Resolution of the most potent compound **9** by preparative chiral HPLC with a Chiralcel AS column provided the levorotatory (*R*)-(−)-**9** and the dextrorotatory enantiomer (*S*)-(+)-**9**. The absolute stereochemistry of the enantiomer (*S*)-**9** was determined by X-ray crystallography. Additionally, with this X-ray analysis, the *Z*-geometry was established for the double bond of the cyanoguanidines.

Biological Assays. Human Bladder K_{ATP} Channels (K_{ATP}-FMP) Assay. Analogues were assayed for K_{ATP} activity in cells expressing human bladder K_{ATP} channels (SUR2B17-/Kir6.2)[26] (K_{ATP}-FMP). Membrane potential changes were measured with a fluorometric imaging plate reader (FLIPR) using the fast membrane potential (FMP) dye.[27] These effects were reversed upon addition of glyburide, a K_{ATP} channel inhibitor. Typically, addition of glyburide reversed 60−80% of the response, confirming a K_{ATP} mechanism. Potencies are expressed as the negative logarithm of the EC_{50} (pEC_{50}).

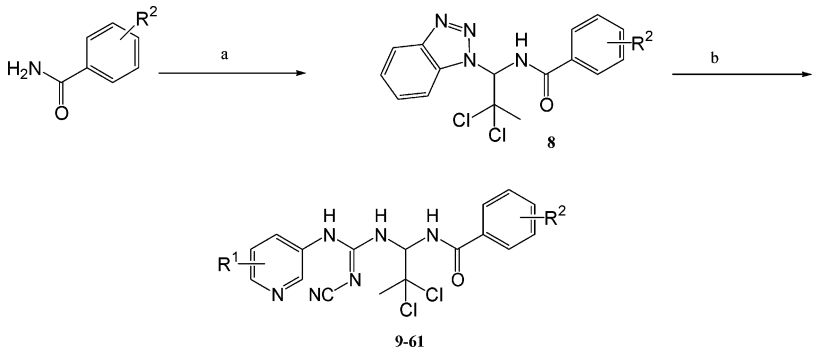
Landrace Pig Detrusor (LPD) Assay.[28] The most potent analogues were tested in spontaneously contracting bladder strips that were obtained from the area closer to the trigonal region of the bladder in Landrace pigs. The reduction of the area under the curve (AUC) by increasing concentrations of test agents was measured. These spontaneous contractions are purely of myogenic origin, have no cholinergic component, and thus are insensitive to the effects of muscarinic blockers like tolterodine. Concentration response curves were generated for each agent with the potency expressed as the pEC_{50}. Confirmation of a K_{ATP} mechanism was demonstrated for all compounds by reversal of the bladder relaxant effect following addition of glyburide at the end of each experiment.

Obstructed Pig Urodynamics.[29] The most active analogue **9** was evaluated in vivo in a disease model of overactive bladder. Female Landrace/Yorkshire swine (∼12 weeks old; 14−20 kg) were obstructed with a 7.5 mm silver omega ring placed around the proximal urethra. Seventeen to twenty weeks later, the pigs were equipped with telemetry transducer/transmitters for the measurement of carotid arterial pressure and intravesical (bladder) pressure. Animals were allowed to recover for 10 to 14 days before testing.

For urodynamic testing, pigs were anesthetized with telazol/xylazine, intubated, and maintained on isoflurane/oxygen in the supine position. Anesthesia level and bladder volume were adjusted to establish a regular pattern of unstable bladder contractions. The isoflurane/oxygen mixture inhibits normal parasympathetically mediated voiding contractions but not disease-related spontaneous contractions of myogenic origin. The anticholinergic tolterodine is not efficacious in this model. After a 30 min baseline data acquisition period, two increasing doses of test compounds were administered intravenously (3 min infusion) at 30 min intervals.[29] Blood samples were obtained from the opposite ear at 15 min after each dose for subsequent determination of plasma concentrations by liquid chromatography/mass spectroscopy. Bladder contraction AUC was averaged over each 30 min postdosing period and expressed as percent change from baseline. From the concentration−response relationship, an EC_{50} to inhibit bladder contractions was determined.

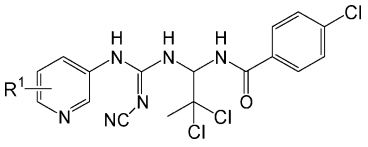
Conscious Pig Hemodynamics. For conscious mean arterial pressure (MAP) evaluation, pigs obstructed, and telemeterized as described above were placed into a stainless steel restraint cage, and 20 gauge venous catheters were placed in both ears to provide vascular access for dosing and blood sampling. Drug administration and plasma sampling were conducted as above. Arterial pressure data were averaged in 5 min bins for each 30

Scheme 2[a]



[a] Reagents and conditions: (a) Benzotriazole, 2,2-dichloropropionaldehyde, pTsOH, toluene, reflux, (b) **7**, Cs_2CO_3, CH_3CN, 25−60%.

Table 1. SAR of Pyridine Ring



compd	R^1	KATP-FMP (pEC_{50})[a]	LPD (pEC_{50})[b]
1	ZD-6169	6.36 ± 0.35	5.56 ± 0.13[8]
5	H	6.47 ± 0.01	5.26 ± 0.10
9	6-Cl	6.34 ± 0.29	6.13 ± 0.42[6]
10	5-Br	6.19 ± 0.06[b]	6.23 ± 0.22
11	5-CH_3	6.12[c]	
12	6-F	5.82 ± 0.14	5.87 ± 0.28
13	6-CF_3	5.79 ± 0.10	5.78 ± 0.47
14	6-CH_3	5.65 ± 0.02	
15	2-Cl	5.22 ± 0.54	6.16 ± 0.18
16	2-OCH_3	5.01 ± 0.32	6.60 ± 0.36
17	2- CH_3, 6-CF_3	5.02 ± 0.04	
18	6-OCH_3	4.98 ± 0.03	
19	2-F-phenyl[e]	4.92 ± 0.24[d]	5.98 ± 0.30[d]

[a] Values are the mean of two experiments, otherwise stated in cells expressing human bladder K_{ATP} channels (SUR2B17-/Kir6.2) (K_{ATP}-FMP). [b] Values are the mean of four experiments in tissue strips obtained from Landrace pig bladders (LPD). [c] Value is for one experiment. [d] Values are the mean of three experiments. [e] 3-Pyridyl was replaced with 2-fluorophenyl.

min postdosing period and expressed as percent change from baseline. Finally analogues **9** and **35** were selected for pharmacokinetic studies in dog.

Results and Discussion

Our initial efforts to enhance the activity of **5** were focused to investigate the substitution on the pyridine ring. Results are summarized in Table 1. For comparison purposes we have included the activity of **1** and our early lead **5**.[21] The effect of various halo substituents was particularly interesting. The 6-chloro and 5-bromo derivatives **9** and **10** were the most active. These analogues showed comparable K_{ATP}-FMP activities with compound **5**; however, they were superior in the functional assay (LPD) by approximately 10-fold. A general trend of higher potency was observed for 6-substituents except for the 6-methoxy derivative **18**. Strong electron-withdrawing groups such as the trifluoromethyl group in **13** had similar activity to that of the 6-fluoro analogue **12**. A loss of activity is observed with 2-substitution both for electron-withdrawing and electron-donating groups. Replacing the pyridine core with substituted phenyls led to a considerable decrease in potency.

Once established that 5 or 6 position electron-withdrawing groups on the pyridine ring are optimal for activity, our next SAR study centered on substituent variations on the benzamide moiety. We initiated this investigation having the 6-chloropyridine on the left-hand hemisphere of the cyanoguanidine pharmacophore, and results are outlined in Table 2. The 6-chloropyridine analogues with substitution at the 4 position of the benzamide ring were in general more potent than any other substitutions. The only compounds that were as potent as some of the 4-susbtituted derivatives were the 3,5-dichloro and 3,5-difluoro analogues **21** and **24**. No substantial differences in potency were observed with halides in 4 position such as 4-bromo **20**, 4-iodo **22**, and 4-fluoro **25**. Replacing the phenyl ring of the benzamide with a heterocyclic ring such as thienyl produced equivalent potency. However, the pyridyl analogue **33** was less potent that **26**.

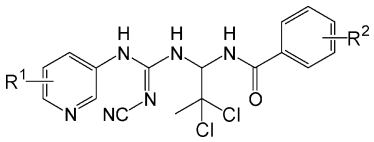
Examination of the substitution of the benzamide ring with 6-trifluoromethylpyridine on the left hemisphere displayed a different SAR than 6-chloropyridine analogues. Now the 3,5-difluoro substitution produced the most potent example, **35**. Interestingly the activities of **35** and the 6-chloropyridine **24** that also contains the 3,5-difluoro substitution were equivalent. However, the 4-iodo **43**, 4-trifluoromethyl **44**, and 4-bromo **45** derivatives were the weakest compounds in this subset.

Further exploration of the benzamide substitution having the 5-bromo or 6-fluoropyridine fixed on the left-hand hemisphere revealed differences in the SAR between all these four subsets. For the 5-bromopyridine subset, 3-chloro, 4-fluoro and 3,5-difluoro substitutions were especially effective, giving the potent derivatives **46**, **47**, and **48**. Meanwhile, the 3,5-dichloro (**54**) and 3-chloro (**55**) substitutions were the most effective for the 6-fluoropyridine subset. All of the results in Tables 1 and 2 indicate that the optimal susbstitutions on the pyridine ring are the 6-chloro and 5-bromo groups. On the other hand, the 4-chloro group is preferred on the benzamide ring. Preliminary examination of the effect of the absolute stereochemistry in this series was performed with the chiral separation of the enantiomers of **9**. However, the (*R*)-**9** isomer and its antipode (*S*)-**9** showed practically the same in vitro activity. Thus, the racemate **9** was selected for further in vivo studies.

Compound **9** was evaluated in a pig model of detrusor instability secondary to partial bladder outlet obstruction,[29] the results are summarized in Table 3. Intravenous administration of **9** produced a dose dependent inhibition of unstable bladder contractions (UBC) with 19.7% reduction in the frequency of spontaneous bladder contractions at 0.30 mg/kg and a significant 90.7% reduction at 1.00 mg/kg. The effect of **9** on MAP in conscious pigs was also evaluated. At 1.00 mg/kg, analogue **9** reduced blood pressure by 36%. Analogue **9** was also tested in vitro on rat portal vein tissue where pEC_{50} was 6.09.

Pharmacokinetic studies of **9** and the 6-trifluoromethylpyridine analogue **35** were also carried out and compared with the pharmacokinetic parameters also measured for ZD-6169. The

Table 2. SAR of Substituted Phenyls



compd	R^1	R^2	K_{ATP}-FMP (pEC_{50})[a]	LPD (pEC_{50})[b]
20	6-Cl	4-Br	6.27 ± 0.01	
21	6-Cl	3,5-Cl_2	6.09 ± 0.14	5.44 ± 0.11
22	6-Cl	4-I	6.05 ± 0.32	
23	6-Cl	4-CH_3	6.04 ± 0.01	
(*R*)-(−)-**9**	6-Cl	4-Cl	5.97 ± 0.38	
(*S*)-(+)-**9**	6-Cl	4-Cl	5.67 ± 0.14	
24	6-Cl	3,5-F_2	5.96 ± 0.26	
25	6-Cl	4-F	5.89 ± 0.53[c]	
26	6-Cl	4-H	5.69 ± 0.04	
27	6-Cl	3-Cl	5.78 ± 0.02	5.35 ± 0.10
28	6-Cl	3-CH_3	5.77 ± 0.15	5.42 ± 0.10
29	6-Cl	2-thienyl[e]	5.56 ± 0.34	
30	6-Cl	4-CF_3	5.30 ± 0.34	
31	6-Cl	3-F	5.27 ± 0.16[c]	5.68 ± 0.29
32	6-Cl	4-CF_3O	5.27 ± 0.02	
33	6-Cl	2-CH_3O-4-pyridyl[f]	5.18 ± 0.16	
34	6-Cl	3,5-$(CH_3O)_2$	5.05 ± 0.40	
35	6-CF_3	3,5-F_2	5.93 ± 0.04	5.54 ± 0.13
36	6-CF_3	2-thienyl[e]	5.76 ± 0.22	5.44 ± 0.28
37	6-CF_3	4-F	5.68 ± 0.06	6.02 ± 0.69
38	6-CF_3	3- CH_3	5.59 ± 0.02	5.94 ± 0.33
39	6-CF_3	3-F	5.64 ± 0.01	5.71 ± 0.13
40	6-CF_3	3,5-Cl_2	5.43 ± 0.42	5.70 ± 0.10
41	6-CF_3	4-CH_3	5.42 ± 0.27	5.15 ± 0.13
42	6-CF_3	3-Cl	5.17 ± 0.04	5.28 ± 0.28
43	6-CF_3	4-I	5.11 ± 0.02	
44	6-CF_3	4-CF_3	4.57 ± 0.17	5.65 ± 0.20[c]
45	6-CF_3	4-Br	<4.00[d]	
46	5-Br	3-Cl	6.11 ± 0.00	
47	5-Br	4-F	6.02[d]	
48	5-Br	3,5-F_2	5.96 ± 0.06	
49	5-Br	4-CH_3	5.88[d]	
50	5-Br	2-thienyl[e]	5.89 ± 0.06	
51	5-Br	3-CH_3	5.78[d]	
52	5-Br	3,5-Cl_2	5.58 ± 0.16	
53	5-Br	4-CF_3O	<4.00[d]	
54	6-F	3,5-Cl_2	5.69 ± 0.15	
55	6-F	3-Cl	5.64 ± 0.00	
56	6-F	2-thienyl[e]	5.34 ± 0.03	
57	6-F	4-CH_3	5.37 ± 0.05	
58	6-F	3-CH_3	5.37 ± 0.15	
59	6-F	3,5-F_2	5.37 ± 0.04	
60	6-F	4-CF_3O	5.05 ± 0.07	
61	6-F	4-F	4.93 ± 0.10	

[a] Values are the mean of two experiments, otherwise stated in cells expressing human bladder K_{ATP} channels (SUR2B17-/Kir6.2) (K_{ATP}-FMP). [b] Values are the mean of four experiments in tissue strips obtained from Landrace pig bladders (LPD). [c] Values are the mean of three experiments. [d] Values are for one experiment. [e] Phenyl was replaced with 2-thienyl. [f] Phenyl was replaced with 2-methoxy-4-pyridyl.

Table 3. In Vivo Effects of Compound **9** on Frequency of Spontaneous Bladder Contractions in a Pig Model of Detrusor Instability and Effect on MAP in Conscious Pigs (percent change from predrug value, $X \pm$ SE)

spontaneous bladder contractions			blood pressure		
dose (μmol/kg) iv	n[a]	frequency (% change)[b]	dose (μmol/kg) iv	n[a]	frequency (% change)
0.30	2	−19.7 ± 13.4	0.30	2	−1.40 ± 2.40
1.00	2	−90.7 ± 4.50	1.00	2	−36.0 ± 0.80

[a] Number of experiments in different animals.

results of intravenous and oral administration in dog are shown in Table 4. Intravenous administration of **9** gave a terminal-phase half-life of 9.9 h and a total plasma clearance of 0.13 L/h/kg. Compound **9** was well absorbed after oral administration, and then the plasma concentration was kept at a high level for 15 h. Maximum plasma concentrations were achieved at 0.4 h, and the calculated bioavailability was 100%.

Table 4. Pharmacokinetics of Compounds **9**, **35**, and ZD-6169 in Dog

		iv		po		
compd	dose, nmol/kg	$t_{1/2}$, h	Cl_p, L/h/kg	t_{max}, h	$t_{1/2}$, h	F, %
9	100	9.9	0.13	0.4	15	100
35	100	5.5	0.06	0.7	6.9	100
ZD-6169	10	1.9	0.67	0.4	1.6	43

[a] Values are the mean of two experiments.

In comparison with **9**, compound **35** possessed lower clearance (0.06 L/h/kg) and shorter oral half-live (6.9 h). Oral bioavailability for **35** was also extraordinarily high (100%). In general both compounds **9** and **35** had preferable pharmacokinetic profiles than ZD-6169.

Conclusion

A structurally novel series of K_{ATP} channel openers, possessing a cyanoguanidine unit attached to an aminal group were designed and synthesized. Chemical modifications of our early lead **5** showed a crucial role of the pyridine ring on the left-hand hemisphere and the substituents at the 6 or 5 positions of the pyridine ring for in vitro potency. Consequently, the 6-chloro and 5-bromo were recognized as the best substitutions for the pyridine ring. Further exploration of the benzamide moiety revealed differences in SAR in four different subsets in this cyanoguanidine-aminal series. This SAR study led to the identification of several potent in vitro K_{ATP} channel openers, which are also potent full agonists in relaxing pig bladder strips. Among these compounds, aminal **9** was selected for in vivo activity and pharmacokinetic evaluation. These studies demonstrated that derivative **9** suppresses in vivo unstable bladder contractions in a pig model of bladder instability and that **9** possesses excellent pharmacokinetic properties with an oral bioavailability of 100%. The relative in vivo selectivity of compound **9** is comparable to that of prototypical bladder selective agents.[29] However, it is unpredictable if the drop in blood pressure observed in animal model can be tolerated in humans. Although chemical stability was not tested for these novel cyanoguanidine-aminals, the pharmacokinetic profile of **9** and **35** demonstrated its biological stability.

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 ±0.4% of the theoretical values. Mass spectra were obtained with 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. X-ray crystal structure was obtained on a Bruker SMART diffractometer.

5-Bromopyridin-3-ylamine (6). Bromine (12.4 g, 80.7 mmol) was slowly added to a solution of 5% NaOH (215 mL) and 50 mL

of THF at 5 °C. 5-Bromonicotinamide (14.8 g, 73.4 mmol) was added portionwise for a period of 30 min at 5 °C. After the addition was complete, the mixture was heated at 70 °C for 2 h. The solution was cooled at 18 °C, and the product was extracted with CH_2Cl_2 (75 mL × 7). The combined extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (elution with 20% EtOAc/hexane) to afford 3.8 g of **6**; MS (ESI+) *m/z* 174 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.73 (m, 3 H), 7.84 (d, J = 2.03 Hz, 1 H), 7.87 (d, J = 1.70 Hz, 1 H).

General Procedure for the Synthesis of *N*-(3-Pyridyl)-*N′*-cyanoguanidines (7). Two examples are given for the preparation of *N*-(3-pyridyl)-*N′*-cyanoguanidines **7**. ***N*-(5-Bromopyridin-3-yl)-*N′*-cyanoguanidine.** 5-Bromopyridin-3-ylamine (460 mg, 2.66 mmol) was suspended in 10 mL of water and 6 N HCl (0.88 mL, 5.32 mmol). The mixture was stirred to dissolve all solids. Sodium dicyanamide (473 mg, 5.32 mmol) was added, and the mixture was heated at 45 °C for 12 h. One more equivalent of sodium dicyanamide (237 mg, 2.66 mmol) was added, and the mixture was heated at 45 °C for 8 h. The mixture was then cooled to 0 °C and stirred for 1 h, resulting in the formation of a precipitate. The solid was filtered and washed with cold water to provide 480 mg (75%) of *N*-(5-bromopyridin-3-yl)-*N′*-cyanoguanidine as a yellow-brown solid; MS (ESI+) *m/z* 241 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.34 (s, 2 H), 8.17 (t, J = 2.20 Hz, 1 H), 8.39 (d, J = 2.03 Hz, 1 H), 8.46 (d, J = 2.37 Hz, 1 H), 9.37 (s, 1 H).

***N*-(6-Chloropyridin-3-yl)-*N′*-cyanoguanidine**. 6-Chloropyridin-3-ylamine (5 g, 38.89 mmol) was suspended in 50 mL of water and 6N HCl (7.8 mL, 46.73 mmol). The mixture was stirred to dissolve all solids. Sodium dicyanamide (4.16 g, 46.73 mmol) was added, and the mixture was heated at 45 °C for 4 h. The mixture was then cooled to 0 °C and stirred for 1 h, resulting in the formation of a precipitate. The solid was filtered and washed with cold water to provide 6.51 g (86%) of *N*-(6-chloropyridin-3-yl)-*N′*-cyanoguanidine as a tan-white solid; MS (ESI+) *m/z* 196 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.29 (s, 2 H), 7.45 (d, J = 8.48 Hz, 1 H), 7.91 (dd, J = 8.65, 2.88 Hz, 1 H), 8.35 (d, J = 2.71 Hz, 1 H), 9.40 (s, 1 H).

General Procedure for the Synthesis *N*-(1-Benzotriazol-1-yl-2,2-dichloropropyl)benzamides (8). An example is given for the preparation of intermediates **8**. ***N*-(1-Benzotriazol-1-yl-2,2-dichloropropyl)-4-chlorobenzamide.** A suspension of 4-chlorobenzamide (4.31 g, 28.5 mmol), 2,2-dichloropropionaldehyde[24] (3.62 g, 28.5 mmol), and benzotriazole (3.39 g, 28.5 mmol) in toluene (100 mL) was treated with p-TsOH (267 mg, 1.4 mmol). The mixture was heated at reflux under Dean−Stark conditions for 10 h and cooled at 60 °C. The mixture was purified by flash chromatography (elution with 10% EtOAc/hexanes) to provide 2.2 g of *N*-(1-benzotriazol-1-yl-2,2-dichloropropyl)-4-chlorobenzamide as a white solid; MS (ESI+) *m/z* 384 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.46 (s, 3 H), 7.47 (m, 1 H), 7.53 (d, J = 8.81 Hz, 1 H,) 7.58 (d, J = 8.81 Hz, 2 H), 7.66 (m, 1 H), 7.89 (d, J = 8.81 Hz, 2 H), 8.12 (d, J = 8.48 Hz, 1 H), 8.20 (d, J = 8.48 Hz, 1 H), 10.18 (d, J = 9.15 Hz, 1 H).

General Procedure for the Synthesis of Compounds 9 to 61. 4-Chloro-*N*-{2,2-dichloro-1-[*N′*-(6-chloropyridin-3-yl)-*N″*-cyanoguanidino]propyl}benzamide (9). A suspension of *N*-(6-chloropyridin-3-yl)-*N′*-cyanoguanidine (**7**) (1.5 g, 7.67 mmol), *N*-(1-benzotriazol-1-yl-2,2-dichloropropyl)-4-chlorobenzamide (**8**) (1.96 g, 5.11 mmol), and Cs_2CO_3 (4.5 g, 12.78 mmol) in 10 mL of acetonitrile was stirred for 12 h at room temperature. The mixture was filtered through a pad of Celite, and the solvent was evaporated. The crude mixture was purified by flash chromatography (elution with 1 to 2% MeOH/CH_2Cl_2) to provide 1.35 g of product that was further recrystallized from EtOAc/hexane to provide 1.03 g (39%) of **9** as a white solid; mp 199−200 °C; MS (ESI+) *m/z* 460 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (s, 3 H), 6.54 (dd, J = 8.5, 8.8 Hz, 1 H), 7.29 (d, J = 9.1 Hz, 1 H), 7.59 (d, J = 8.5 Hz, 1 H), 7.61 (d, J = 8.8 Hz, 2 H), 7.76 (dd, J = 2.7, 8.5 Hz, 1 H), 7.84 (d, J = 8.8 Hz, 2 H), 8.35 (d, J = 2.7 Hz, 1 H), 8.73 (d, J = 8.5 Hz, 1 H), 9.98 (s, 1 H). Anal. ($C_{17}H_{14}Cl_4N_6O$) C, H, N.

(−)-4-Chloro-*N*-{(1*R*)-2,2-dichloro-1-[*N′*-(6-chloropyridin-3-yl)-*N″*-cyanoguanidino]propyl}benzamide (*R*)-(−)-(9). Compound **9** was chromatographed over a Daicel Chiral Technologies Chiralcel OD chiral column (2.0 cm × 25 cm) eluting with 5% ethanol/hexanes (flow rate = 10 mL/min) to provide (*R*)-**(9)** as the levorotatory enantiomer; $[\alpha]_D^{23}$ −31° (*c* 0.19, DMSO); mp 199−201 °C; MS (ESI+) *m/z* 460 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (s, 3 H), 6.54 (dd, J = 8.5, 8.8 Hz, 1 H), 7.29 (d, J = 9.1 Hz, 1 H), 7.59 (d, J = 8.5 Hz, 1 H), 7.61 (d, J = 8.8 Hz, 2 H), 7.76 (dd, J = 2.7, 8.5 Hz, 1 H), 7.84 (d, J = 8.8 Hz, 2 H), 8.35 (d, J = 2.7 Hz, 1 H), 8.73 (d, J = 8.5 Hz, 1 H), 9.98 (s, 1H). Anal. ($C_{17}H_{14}Cl_4N_6O$) C, H, N.

(+)-4-Chloro-*N*-{(1*S*)-2,2-dichloro-1-[*N′*-(6-chloropyridin-3-yl)-*N″*-cyanoguanidino]propyl}benzamide (*S*)-(+)-(9). Compound **9** was chromatographed over a Daicel Chiral Technologies Chiralcel OD chiral column (2.0 cm × 25 cm) eluting with 5% ethanol/hexanes (flow rate = 10 mL/min) to provide (*S*)-**(9)** as the dextrotatory enantiomer; $[\alpha]_D^{23}$ +30° (*c* 0.20, DMSO); mp 197−199 °C; MS (ESI+) *m/z* 460 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (s, 3 H), 6.54 (dd, J = 8.5, 8.8 Hz, 1 H), 7.29 (d, J = 9.1 Hz, 1 H), 7.60 (d, J = 8.5 Hz, 1 H), 7.63 (d, J = 8.8 Hz, 2 H), 7.76 (dd, J = 2.7, 8.5 Hz, 1 H), 7.84 (d, J = 8.8 Hz, 2 H), 8.35 (d, J = 2.7 Hz, 1 H), 8.73 (d, J = 8.5 Hz, 1 H), 9.98 (s, 1 H). Anal. ($C_{17}H_{14}Cl_4N_6O$·0.04C_6H_{14} (hexane)) C, H, N.

***N*-{1-[*N′*-(5-Bromopyridin-3-yl)-*N″*-cyanoguanidino]-2,2-dichloropropyl}-4 -chlorobenzamide (10).** mp 178−180 °C; MS (ESI+) *m/z* 505 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.19 (s, 3 H), 6.53 (t, J = 8.82 Hz, 1 H), 7.45 (d, J = 8.82 Hz, 1 H), 7.61 (d, J = 8.82 Hz, 2 H), 7.85 (d, J = 8.48 Hz, 2 H), 7.98 (t, J = 2.03 Hz, 1 H), 8.51 (d, J = 2.03 Hz, 1 H), 8.57 (d, J = 1.70 Hz, 1 H), 8.71 (d, J = 8.14 Hz, 1 H), 10.06 (s, 1 H). Anal. ($C_{17}H_{14}BrCl_3N_6O$) C, H, N.

4-Chloro-*N*-{2,2-dichloro-1-[*N′*-cyano-*N″*-(5-methylpyridin-3-yl)-guanidino]propyl}benzamide (11). mp 189−191 °C; MS (ESI+) *m/z* 440 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.17 (s, 3 H), 2.31 (s, 3 H), 6.53 (t, J = 8.8 Hz, 1 H), 7.13 (d, J = 9.1 Hz, 1 H), 7.52 (s, 1 H), 7.61 (d, J = 8.8 Hz, 2 H), 7.84 (d, J = 8.8 Hz, 2 H), 8.31 (m, 2 H), 8.72 (d, J = 8.4 Hz, 1 H), 9.89 (s, 1 H). Anal. ($C_{18}H_{17}Cl_3N_6O$) C, H, N.

4-Chloro-*N*-{2,2-dichloro-1-[*N′*-cyano-*N″*-(6-fluoropyridin-3-yl)guanidino]propyl}benzamide (12). mp 206−207 °C; MS (ESI+) *m/z* 443 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.15 (s, 3 H), 6.52 (t, J = 8.5 Hz, 1 H), 7.12 (br d, J = 8.6 Hz, 1 H), 7.28 (dd, J = 8.2, 2.3 Hz, 1 H), 7.60 (d, J = 8.7 Hz, 2 H), 7.83 (d, J = 8.7 Hz, 2 H), 7.92−7.84 (m, 1 H), 8.15 (d, J = 1.0 Hz, 1 H), 8.70 (br d, J = 8.5 Hz, 1 H), 9.87 (s, 1 H). Anal. ($C_{17}H_{14}Cl_3FN_6O$) C, H, N.

4-Chloro-*N*-{2,2-dichloro-1-[*N′*-cyano-*N″*-(6-trifluoromethylpyridin-3-yl}guanidino]propyl)benzamide (13). mp 204−205 °C; MS (ESI+) *m/z* 493 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.20 (s, 3 H), 6.58 (t, J = 9 Hz, 1 H), 7.61 (d, J = 8 Hz, 2 H), 7.65 (d, J = 10 Hz, 1 H), 8.68 (s, 1 H), 7.86 (d, J = 9 Hz, 2 H), 7.91−7.99 (m, 2 H), 8.73 (d, J = 8 Hz, 1 H), 10.25 (s, 1 H). Anal. ($C_{18}H_{14}Cl_3F_3N_6O$) C, H, N.

4-Chloro-*N*-{2,2-dichloro-1-[*N′*-cyano-*N″*-(6-methylpyridin-3-yl)-guanidino]propyl}benzamide (14). mp 142−144 °C; MS (ESI+) *m/z* 440 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.15 (s, 3 H), 2.48 (s, 3 H), 6.53 (t, J = 8.82 Hz, 1 H), 6.99 (d, J = 9.16 Hz, 1 H), 7.34 (d, J = 8.14 Hz, 1 H), 7.57 (m, 1 H), 7.61 (d, J = 8.48 Hz, 2 H), 7.83 (d, J = 8.48 Hz, 2 H), 8.37 (d, J = 2.71 Hz, 1 H), 8.71 (d, J = 8.48 Hz, 1 H), 9.81 (s, 1 H). Anal. ($C_{18}H_{17}Cl_3N_6O$) C, H, N.

4-Chloro-*N*-{2,2-dichloro-1-[*N′*-(2-fluoropyridin-3-yl)-*N″*-cyanoguanidino]propyl}benzamide (15). mp 200−201 °C; MS (ESI+) *m/z* 461 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (s, 3 H), 6.50 (t, J = 8.0 Hz, 1 H), 7.16 (d, J = 8.0 Hz, 1 H), 7.52 (dd, J = 8.0, 5.0 Hz, 1 H), 7.63 (d, J = 9.0 Hz, 2 H), 7.85−7.90 (m, 3 H), 8.66 (dd, J = 4, 2 Hz, 1 H), 8.90 (d, J = 8.0 Hz, 1 H), 9.86 (s, 1 H). Anal. ($C_{17}H_{14}Cl_4N_6O$) C, H, N.

4-Chloro-*N*-{2,2-dichloro-1-[*N′*-cyano-*N″*-(2-methoxypyridin-3-yl)guanidino]propyl}benzamide (16). mp 155−156 °C; MS

(ESI+) *m/z* 455 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.16 (s, 3H), 3.86 (s, 3 H), 6.50 (t, J = 8 Hz, 1 H), 6.82 (d, J = 9 Hz, 1 H), 7.07 (dd, J = 7, 5 Hz, 1 H), 7.60−7.64 (m, 3 H), 7.84 (d, J = 8 Hz, 2 H), 8.14 (dd, J = 5, 2 Hz, 1 H), 8.77 (d, J = 8 Hz, 1 H), 9.45 (s, 1 H). Anal. ($C_{18}H_{17}Cl_3N_6O_2$) C, H, N.

4-Chloro-*N*-{2,2-dichloro-1-[*N*′-cyano-*N*″-(2-methyl-6-(trifluoromethyl)-3-yl)guanidino]propyl}benzamide (17). mp 115−116 °C; MS (ESI+) *m/z* 507 (M + H)$^+$; ^{1}H NMR (300 Mz, DMSO-d_6) δ 2.17 (s, 3 H), 3.31 (s, *obscured*, 3 H), 6.16 (t, J = 8.0 Hz, 1 H), 7.13 (d, J = 8.0 Hz, 1 H), 7.62 (d, J = 8.0 Hz, 2 H), 7.86 (d, J = 9.0 Hz, 2 H), 7.81−7.90 (m, 2 H), 8.80 (d, J = 8.0 Hz, 1 H), 9.79 (s, 1 H). Anal. ($C_{19}H_{16}Cl_3F_3N_6O$) C, H, N.

4-Chloro-*N*-{2,2-dichloro-1-[*N*′-cyano-*N*″-(6-methoxypyridin-3-yl)guanidino]propyl}benzamide (18). mp 209−210 °C; MS (ESI+) *m/z* 456 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.14 (s, 3 H), 3.87 (s, 3 H), 6.51 (t, J = 8.65 Hz, 1 H), 6.81 (d, J = 8.81 Hz, 1 H), 6.92 (d, J = 8.81 Hz, 1 H), 7.63 (m, 3 H), 7.83 (d, J = 8.81 Hz, 2 H), 8.10 (d, J = 2.37 Hz, 1 H), 8.72 (d, J = 8.48 Hz, 1 H), 9.67 (s, 1 H). Anal. ($C_{18}H_{17}Cl_3N_6O_2$) C, H, N.

4-Chloro-*N*-{2,2-dichloro-1-[*N*′-cyano-*N*″-(2-fluorophenyl)-guanidino]propyl}benzamide (19). mp 216−217 °C; MS (ESI+) *m/z* 442 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.14 (s, 3 H), 6.52 (t, J = 8.65 Hz, 1 H), 6.88 (d, J = 8.82 Hz, 1 H), 7.28 (m, 1 H), 7.38 (m, 3 H), 7.61 (d, J = 8.48 Hz, 2 H), 7.85 (d, J = 8.48 Hz, 2 H), 8.84 (d, J = 8.48 Hz, 1 H), 9.68 (s, 1 H). Anal. ($C_{18}H_{15}Cl_3FN_5O$) C, H, N.

4-Bromo-*N*-{2,2-dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidino]propyl}benzamide (20). mp 215−216 °C; MS (ESI+) *m/z* 503 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.18 (s, 3 H), 6.54 (t, J = 8.65 Hz, 1 H), 7.31 (d, J = 8.82 Hz, 1 H), 7.60 (d, J = 8.48 Hz, 1 H), 7.76 (m, 4 H), 7.79 (d, J = 2.71 Hz, 1 H), 8.35 (d, J = 2.71 Hz, 1 H), 8.72 (d, J = 8.48 Hz, 1 H), 9.98 (s, 1 H). Anal. ($C_{17}H_{14}BrCl_3N_6O$) C, H, N.

3,5-Dichloro-*N*-{2,2-dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidine]propyl}benzamide (21). mp 138−140 °C; MS (ESI+) *m/z* 492 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.20 (s, 3H), 6.52 (t, J = 8.6 Hz, 1H), 7.31 (d, J = 8.7 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.77 (dd, J = 8.5, 2.9 Hz, 1H), 7.83 (app d, J = 1.7 Hz, 2H), 7.87−7.92 (m, 1H), 8.35 (d, J = 3.1 Hz, 1H), 8.90 (d, J = 8.6 Hz, 1H), 9.97 (br s, 1 H). Anal. ($C_{17}H_{13}Cl_5N_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidino]propyl}-4-iodobenzamide (22).** mp 222−224 °C; MS (ESI+) *m/z* 552 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.17 (s, 3 H), 6.53 (t, J = 8.65 Hz, 1 H), 7.31 (d, J = 8.82 Hz, 1 H), 7.60 (d, J = 8.14 Hz, 3 H), 7.77 (dd, J = 8.48, 2.71 Hz, 1 H), 7.93 (d, J = 8.14 Hz, 2 H), 8.35 (d, J = 2.71 Hz, 1 H), 8.69 (d, J = 8.48 Hz, 1 H), 9.98 (s, 1 H). Anal. ($C_{17}H_{14}Cl_3IN_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidino]propyl}-4-methylbenzamide (23).** mp 198−200 °C; MS (ESI+) *m/z* 439 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (s, 3 H), 2.37 (s, 3 H), 6.55 (dd, J = 8.8, 8.8 Hz, 1 H), 7.35 (d, J = 7.8 Hz, 3 H), 7.60 (d, J = 8.5 Hz, 1 H), 7.74 (d, J = 8.5 Hz, 2 H), 7.77 (dd, J = 2.7, 8.5 Hz, 1 H), 8.35 (d, J = 2.4 Hz, 1 H), 8.52 (d, J = 8.47 Hz, 1 H), 9.99 (s, 1 H). Anal. ($C_{18}H_{17}Cl_3N_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidino]propyl}-3,5-difluorobenzamide (24).** mp 195−196 °C; MS (ESI+) *m/z* 461 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.19 (s, 3 H), 6.52 (t, J = 8.6 Hz, 1 H), 7.30 (d, J = 8.5 Hz, 1 H), 7.77 (dd, J = 8.5, 2.7 Hz, 1 H), 7.52−7.63 (m, 4 H), 8.35 (d, J = 2.5 Hz, 1 H), 8.88 (d, J = 7.8 Hz, 1 H), 10.00 (br s, 1 H). Anal. ($C_{17}H_{13}Cl_3F_2N_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidino]propyl}-4-fluorobenzamide (25).** mp 197−198 °C; MS (ESI+) *m/z* 443 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (s, 3 H), 6.54 (t, J = 8.6 Hz, 1 H), 7.27 (br d, J = 8.0 Hz, 1 H), 7.37 (d, J = 8.8 Hz, 2 H), 7.59 (d, 8.8 Hz, 1 H), 7.77 (dd, J = 8.5, 2.7 Hz, 1 H), 7.91 (dd, J = 8.7, 5.3 Hz, 2 H), 8.34 (d, J = 2.5 Hz, 1 H), 8.66 (d, J = 7.8 Hz, 1 H), 9.96 (s, 1 H). Anal. ($C_{17}H_{14}Cl_3FN_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidino]propyl}benzamide (26).** mp 194−195 °C; MS (ESI+) *m/z* 426 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.18 (s, 3 H), 6.56 (t, J = 8.65 Hz, 1 H), 7.32 (d, J = 9.15 Hz, 1 H), 7.52 (m, 2 H), 7.60 (d, J = 7.12 Hz, 2 H), 7.77 (dd, J = 8.48, 2.71 Hz, 1 H), 7.82 (m, 2 H), 8.35 (d, J = 2.37 Hz, 1 H), 8.63 (d, J = 9.49 Hz, 1 H), 9.99 (s, 1 H). Anal. ($C_{17}H_{15}Cl_3N_6O$) C, H, N.

3-Chloro-*N*-{2,2-dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidine]propyl}benzamide (27). mp 138−140 °C; MS (ESI+) *m/z* 460 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.19 (s, 3H), 6.54 (dd, J = 8.8, 8.8 Hz, 1H), 7.32 (d, J = 9.2 Hz, 1H), 7.54 (d, J = 5.8 Hz, 1H), 7.61 (d, J = 5.8 Hz, 1H), 7.68 (m, 1H); 7.78 (m, 2H), 7.85 (m, 1H), 8.35 (d, J = 2.4 Hz, 1H), 8.80 (d, J = 8.1 Hz, 1H), 9.98 (s, 1H). Anal. ($C_{17}H_{14}Cl_4N_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidino]propyl}-3-methylbenzamide (28).** mp 145−146 °C; MS (ESI+) *m/z* 439 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (s, 3 H), 2.38 (s, 3H), 6.56 (dd, J = 8.5, 8.8 Hz, 1 H), 7.35 (d, J = 9.2 Hz, 1 H), 7.42 (m, 2 H), 7.50−7.64 (m, 3 H), 7.78 (dd, J = 2.7, 8.5 Hz, 1 H), 8.36 (d, J = 2.7 Hz, 1 H), 8.59 (d, J = 8.5 Hz, 1 H), 10.0 (s, 1 H). Anal. ($C_{18}H_{17}Cl_3N_6O$) C, H, N.

Thiophene-2-carboxylic Acid {2,2-Dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidino]propyl}amide (29). mp 201−203 °C; MS (ESI+) *m/z* 431 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (s, 3H); 6.49 (t, J = 8.5 Hz, 1H); 7.22 (dd, J = 5.1, 3.9 Hz, 1H), 7.30 (br d, J = 8.5 Hz, 1H); 7.60 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 8.7 Hz, 2H), 7.74−7.80 (m, 2H), 7.89 (dd, J = 4.8, 1.0 Hz, 1H), 8.35 (d, J = 2.7 Hz, 1H), 8.62 (br d, J = 8.5 Hz, 1H), 9.88 (s, 1H). Anal. ($C_{15}H_{13}Cl_3N_6OS$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidino]propyl}-4 -trifluoromethylbenzamide (30**). mp 210−211 °C; MS (ESI+) *m/z* 493 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.10 (s, 3H), 6.56 (t, J = 8.6 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.78 (dd, J = 8.5, 2.7 Hz, 1H), 7.92 (d, J = 8.9 Hz, 2H), 8.03 (d, J = 8.9 Hz, 2H), 8.35 (d, J = 2.5 Hz, 1H), 8.88 (d, 1H, J = 7.8 Hz, 1H), 9.97 (br s, 1H). Anal. ($C_{18}H_{14}Cl_3F_3N_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidino]propyl}-3-fluorobenzamide (31).** mp 191−192 °C; MS (ESI+) *m/z* 443 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.19 (s, 3H), 6.54 (dd, J = 8.5, 8.8 Hz, 1H), 7.30 (d, J = 8.8 Hz, 3H), 7.69−7.44 (m, 5H), 7.77 (dd, J = 2.7, 8.5 Hz, 1H), 8.35 (d, J = 2.7 Hz, 1H), 8.76 (d, J = 8.1 Hz, 1H), 9.98 (s, 1H). Anal. ($C_{17}H_{14}Cl_3FN_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidino]propyl}-4-trifluoromethoxybenzamide (32).** mp 198−199 °C; MS (ESI+) *m/z* 510 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 9.98 (s, 1 H), 8.76 (d, J = 8.14 Hz, 1 H), 8.35 (d, J = 2.37 Hz, 1 H), 7.96 (dd, J = 8.81, 2.71 Hz, 1 H), 7.60 (d, J = 8.48 Hz, 1 H), 7.53 (d, J = 7.80 Hz, 2 H), 7.31 (d, J = 8.81 Hz, 1 H), 6.54 (t, J = 8.65 Hz, 1 H), 2.19 (s, 3 H). Anal. ($C_{18}H_{14}Cl_3F_3N_6O_2$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidino]propyl}-2-methoxyisonicotinamide (33).** mp 172−173 °C; MS (ESI+) *m/z* 457 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.18 (s, 3 H), 3.90 (s, 3 H), 6.51 (t, J = 8.65 Hz, 1 H), 7.16 (s, 1 H), 7.27 (s, 1 H), 7.31 (dd, J = 5.43, 1.36 Hz, 1 H), 7.60 (d, J = 8.48 Hz, 1 H), 7.77 (dd, J = 8.82, 2.71 Hz, 1 H), 8.35 (d, J = 4.75 Hz, 2 H), 8.88 (d, J = 8.14 Hz, 1 H), 9.98 (s, 1 H). Anal. ($C_{17}H_{16}Cl_3N_7O_2$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-(6-chloropyridin-3-yl)-*N*″-cyanoguanidino]propyl}-3, 5-dimethoxybenzamide (34).** mp 193−195 °C; MS (ESI+) *m/z* 485 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.17 (s, 3H), 3.80 (s, 6H), 6.52 (t, J = 8.7 Hz1H), 6.75 (d, J = 1.3 Hz, 1H), 6.95 (d, J = 2.1 Hz, 2H), 7.27 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.78 (dd, J = 8.5, 2.7 Hz, 1H), 8.36 (d, J = 5.5 Hz, 1H), 8.59 (d, J = 8.6 Hz, 1H), 9.96 (br s, 1H). Anal. ($C_{19}H_{19}Cl_3N_6O_3$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-cyano-*N*″-(6-trifluoromethylpyridin-3-yl)-guanidino]propyl}-3,5-difluorobenzamide (35).** mp 202−

203 °C; MS (ESI+) *m/z* 495 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.22 (s, 3H), 6.57 (t, J = 8.0 Hz, 1H), 7.52−7.60 (m, 3H), 7.65 (d, J = 9.0 Hz, 1H), 7.90−7.98 (m, 2H), 8.68 (s, 1H), 8.89 (d, Hz, J = 8.0, 1H), 10.24 (s, 1H). Anal. ($C_{18}H_{13}Cl_2F_5N_6O$) C, H, N.

Thiophene-2-carboxylic Acid {2,2-Dichloro-1-[*N*′-cyano-*N*″-(6-trifluoromethylpyridin-3-yl)guanidino]propyl}amide (36). mp 207−208 °C; MS (ESI+) *m/z* 466 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.20 (s, 3 H), 6.53 (t, J = 8.48 Hz, 1 H), 7.21 (dd, J = 4.92, 3.90 Hz, 1 H), 7.65 (d, J = 8.14 Hz, 1 H), 7.80 (dd, J = 3.73, 1.02 Hz, 1 H), 7.89 (dd, J = 4.92, 1.19 Hz, 1 H), 7.96 (m, 2 H), 8.68 (m, 2 H), 10.25 (s, 1 H). Anal. ($C_{16}H_{13}Cl_2F_3N_6OS$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-cyano-*N*″-(6-trifluoromethylpyridin-3-yl)guanidino]propyl}-4-fluorobenzamide (37).** mp 205−206 °C; MS (ESI+) *m/z* 478 (M + H)$^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.21 (s, 3 H), 6.59 (t, J = 8.58 Hz, 1 H), 7.37 (t, J = 8.89 Hz, 2 H), 7.63 (d, J = 9.36 Hz, 1 H), 7.63 (m, 1 H), 7.93 (m, 3 H), 8.70 (m, 2 H), 10.23 (s, 1 H). Anal. ($C_{18}H_{14}Cl_2F_4N_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-cyano-*N*″-(6-trifluoromethylpyridin-3-yl)guanidino]propyl}-3-methylbenzamide (38).** mp 185−186 °C; MS (ESI+) *m/z* 474 (M + H)$^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.20 (s, 3 H), 2.38 (s, 3 H), 6.61 (t, J = 8.73 Hz, 1 H), 7.42 (m, 2 H), 7.65 (m, 3 H), 7.96 (m, 2 H), 8.61 (d, J = 7.18 Hz, 1 H), 8.69 (s, 1 H), 10.24 (s, 1 H). Anal. ($C_{19}H_{17}Cl_2F_3N_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-cyano-*N*″-(6-trifluoromethylpyridin-3-yl)guanidino]propyl}-3-fluorobenzamide (39).** mp 195−198 °C; MS (ESI+) *m/z* 478 (M + H)$^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.21 (s, 3 H), 6.59 (t, J = 8.58 Hz, 1 H), 7.47 (m, 1 H), 7.60 (m, 1 H), 7.64 (d, J = 8.73 Hz, 2 H), 7.70 (d, J = 7.80 Hz, 2 H), 7.96 (m, 2 H), 8.69 (d, J = 1.87 Hz, 1 H), 8.79 (d, J = 8.11 Hz, 1 H). Anal. ($C_{18}H_{14}Cl_2F_4N_6O$) C, H, N.

3,5-Dichloro-*N*-{2,2-dichloro-1-[*N*′-cyano-*N*″-(6-trifluoromethylpyridin-3-yl)guanidino]propyl}benzamide (40). mp 162−163 °C; MS (ESI+) m/529 (M + H)$^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H), 6.56 (t, J = 8.42 Hz, 1 H), 7.65 (d, J = 7.18 Hz, 1 H), 7.85 (d, J = 1.87 Hz, 2 H), 7.89 (t, J = 1.87 Hz, 1 H), 7.95 (m, 2 H), 8.68 (s, 1 H), 8.97 (d, J = 8.11 Hz, 1 H), 10.21 (s, 1 H). Anal. ($C_{18}H_{13}Cl_4F_3N_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-cyano-*N*″-(6-trifluoromethylpyridin-3-yl)guanidino]propyl}-4-methylbenzamide (41).** mp 184−186 °C; MS (ESI+) *m/z* 474 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.19 (s, 3 H), 2.37 (s, 3 H), 6.60 (t, J = 8.65 Hz, 1 H), 7.33 (d, J = 8.14 Hz, 2 H), 7.66 (d, J = 8.82 Hz, 1 H), 7.75 (d, J = 8.14 Hz, 2 H), 7.96 (m, 2 H), 8.57 (d, J = 8.14 Hz, 1 H), 8.69 (s, 1 H), 10.26 (s, 1 H). Anal. ($C_{19}H_{14}Cl_2F_3N_6O$) C, H, N.

3-Chloro-*N*-{2,2-dichloro-1-[*N*′-cyano-*N*″-(6-trifluoromethylpyridin-3-yl)guanidino]propyl}benzamide (42). mp 191−192 °C; MS (ESI+) *m/z* 493 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.21 (s, 3H), 6.58 (t, J = 8.0 Hz, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.71−7.65 (m, 2H), 7.81 (d, J = 8.0 Hz, 1H), 7.87 (t, J = 2.0 Hz, 1H), 7.98−7.92 (m, 2H), 8.68 (s, 1H), 8.84 (d, J = 8.0 Hz, 1H), 10.25 (s, 1H). Anal. ($C_{18}H_{14}Cl_3F_3N_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-cyano-*N*″-(6-trifluoromethylpyridin-3-yl)guanidino]propyl}-4-iodobenzamide (43).** mp 204−206 °C; MS (ESI+) *m/z* 586 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.20 (s, 3 H), 6.58 (t, J = 8.48 Hz, 1 H), 7.67 (m, 3 H), 7.84 (d, J = 8.48 Hz, 1 H), 7.94 (m, 3 H), 8.68 (s, 1 H), 8.74 (d, J = 8.48 Hz, 1 H), 10.25 (s, 1 H). Anal. ($C_{18}H_{14}Cl_2F_3IN_6O\cdot0.35C_6H_{14}$) C, H, N.

***N*-{2,2-Dichloro-1-[*N*′-cyano-*N*″-(6-trifluoromethylpyridin-3-yl)guanidino] propyl}-4-trifluoromethylbenzamide (44).** mp 221−222 °C; MS (ESI+) *m/z* 528 (M + H)$^+$; ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H), 6.60 (t, J = 8.58 Hz, 1 H), 7.68 (d, J = 6.86 Hz, 1 H), 7.92 (d, J = 8.42 Hz, 2 H), 7.95 (m, 2 H), 8.04 (d, J = 8.11 Hz, 2 H), 8.68 (s, 1 H), 8.94 (d, J = 7.49 Hz, 1 H), 10.23 (s, 1 H). Anal. ($C_{19}H_{14}Cl_2F_6N_6O$) C, H, N.

4-Bromo-*N*-{2,2-dichloro-1-[*N*′-cyano-*N*″-(6-trifluoromethylpyridin-3-yl)gu anidino]propyl}benzamide (45). mp 209−210 °C; MS (ESI+) *m/z* 539 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.20 (s, 3 H), 6.58 (t, J = 8.65 Hz, 1 H), 7.66 (d, J = 8.82 Hz, 1 H), 7.75 (d, J = 8.82 Hz, 2 H), 7.79 (d, J = 8.82 Hz, 2 H), 7.96 (m, 2 H), 8.69 (s, 1 H), 8.76 (d, J = 8.48 Hz, 1 H), 10.25 (s, 1 H). Anal. ($C_{18}H_{14}BrCl_2F_3N_6O$) C, H, N.

***N*-{1-[*N*′-(5-Bromopyridin-3-yl)-*N*″-cyanoguanidino]-2,2-dichloro-propyl}-3-chlorobenzamide (46).** mp 187−188 °C; MS (ESI+) *m/z* 505 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.20 (s, 3 H), 6.53 (t, J = 8.65 Hz, 1 H), 7.46 (d, J = 8.81 Hz, 1 H), 7.57 (t, J = 7.97 Hz, 1 H), 7.68 (m, 1 H), 7.79 (s, 1 H), 7.86 (t, J = 1.70 Hz, 1 H), 7.98 (t, J = 2.20 Hz, 1 H), 8.51 (d, J = 2.03 Hz, 1 H), 8.57 (d, J = 2.03 Hz, 1 H), 8.78 (d, J = 8.48 Hz, 1 H), 10.06 (s, 1 H). Anal. ($C_{17}H_{14}BrCl_3N_6O\cdot0.08C_6H_{14}$) C, H, N.

***N*-{1-[*N*′-(5-Bromopyridin-3-yl)-*N*″-cyanoguanidino]-2,2-dichloropropyl}-4 -fluorobenzamide (47).** mp 214−215 °C; MS (ESI+) *m/z* 489 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.19 (s, 3 H), 6.53 (t, J = 8.48 Hz, 1 H), 7.37 (t, J = 8.65 Hz, 2 H), 7.45 (d, J = 8.81 Hz, 1 H), 7.91 (m, 2 H), 7.98 (t, J = 2.20 Hz, 1 H), 8.51 (d, J = 2.37 Hz, 1 H), 8.57 (d, J = 1.69 Hz, 1 H), 8.65 (d, J = 7.80 Hz, 1 H), 10.06 (s, 1 H). Anal. ($C_{17}H_{14}BrCl_2FN_6O\cdot0.05C_6H_{14}$) C, H, N.

***N*-{1-[*N*′-(5-Bromopyridin-3-yl)-*N*″-cyanoguanidino]-2,2-dichloropropyl}-3 ,5-difluorobenzamide (48).** mp 176−177 °C; MS (ESI+) *m/z* 507 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.20 (s, 3 H), 6.51 (t, J = 8.82 Hz, 1 H), 7.44 (d, J = 9.15 Hz, 1 H), 7.56 (m, 3 H), 7.98 (t, J = 2.20 Hz, 1 H), 8.51 (d, J = 1.70 Hz, 1 H), 8.57 (d, J = 1.02 Hz, 1 H), 8.84 (d, J = 7.80 Hz, 1 H), 10.06 (s, 1 H). Anal. ($C_{17}H_{13}BrCl_2F_2N_6O$) C, H, N.

***N*-{1-[*N*′-(5-Bromopyridin-3-yl)-*N*″-cyanoguanidino]-2,2dichloropropyl}-4-methylbenzamide (49).** mp 203−204 °C; MS (ESI+) *m/z* 485 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.37 (s, 3 H), 6.55 (t, J = 8.65 Hz, 1 H), 7.33 (d, J = 7.80 Hz, 2 H), 7.47 (d, J = 8.82 Hz, 1 H), 7.74 (d, J = 8.48 Hz, 2 H), 7.98 (t, J = 2.03 Hz, 1 H), 8.52 (d, J = 2.03 Hz, 1 H), 8.53 (m, 1 H), 8.57 (d, J = 1.70 Hz, 1 H), 10.06 (s, 1 H). Anal. ($C_{18}H_{17}BrCl_2N_6O$) C, H, N.

Thiophene-2-carboxylic Acid {1-[*N*′-(5-Bromopyridin-3-yl)-*N*″-cyanoguanidino]-2,2-dichloropropyl}amide (50). mp 198−199 °C; MS (ESI+) *m/z* 477 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.18 (s, 3 H), 6.48 (t, J = 8.65 Hz, 1 H), 7.21 (dd, J = 4.92, 3.90 Hz, 1 H), 7.44 (d, J = 8.82 Hz, 1 H), 7.77 (dd, J = 3.73, 1.02 Hz, 1 H), 7.89 (dd, J = 4.92, 0.85 Hz, 1 H), 7.98 (t, J = 2.03 Hz, 1 H), 8.51 (d, J = 2.03 Hz, 1 H), 8.57 (d, J = 1.02 Hz, 1 H), 8.60 (d, J = 8.14 Hz, 1 H), 10.05 (s, 1 H). Anal. ($C_{15}H_{13}BrCl_2N_6OS\cdot0.1C_6H_{14}$) C, H, N.

***N*-{1-[*N*′-(5-Bromopyridin-3-yl)-*N*″-cyanoguanidino]-2,2-dichloropropyl}-3-methylbenzamide (51).** mp 203−204 °C; MS (ESI+) *m/z* 485 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.18 (s, 3 H), 6.56 (t, J = 8.81 Hz, 1 H), 7.42 (m, 2 H), 7.48 (d, J = 9.49 Hz, 1 H), 7.63 (m, 2 H), 7.98 (t, J = 2.03 Hz, 1 H), 8.51 (d, J = 1.70 Hz, 1 H), 8.55 (m, 1 H), 8.57 (d, J = 1.02 Hz, 1 H), 10.07 (s, 1 H). Anal. ($C_{18}H_{17}BrCl_2N_6O$) C, H, N.

***N*-{1-[*N*′-(5-Bromopyridin-3-yl)-*N*″-cyanoguanidino]-2,2-dichloropropyl}-3,5-dichlorobenzamide (52).** mp 204−205 °C; MS (ESI+) *m/z* 540 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.20 (s, 3 H), 6.51 (t, J = 8.48 Hz, 1 H), 7.46 (d, J = 8.82 Hz, 1 H), 7.84 (d, J = 1.70 Hz, 2 H), 7.90 (t, J = 1.87 Hz, 1 H), 7.97 (t, J = 2.20 Hz, 1 H), 8.51 (d, J = 2.03 Hz, 1 H), 8.56 (d, J = 2.03 Hz, 1 H), 8.92 (d, J = 8.48 Hz, 1 H), 10.04 (s, 1 H). Anal. ($C_{17}H_{13}BrCl_4N_6O$) C, H, N.

***N*-{1-[*N*′-(5-Bromopyridin-3-yl)-*N*″-cyanoguanidino]-2,2-dichloropropyl}-4-trifluoromethoxybenzamide (53).** mp 121−122 °C; MS (ESI+) *m/z* 555 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.20 (s, 3 H), 6.54 (t, J = 8.65 Hz, 1 H), 7.53 (m, 2 H), 7.96 (m, 4 H), 8.50 (m, 1 H), 8.56 (m, 1 H), 8.76 (d, J = 7.46 Hz, 1 H), 10.05 (s, 1 H). Anal. ($C_{18}H_{14}BrCl_{23}FN_6O_2\cdot0.1C_6H_{14}$) C, H, N.

3,5-Dichloro-*N*-{2,2-dichloro-1-[*N*′-cyano-*N*″-(6-fluoropyridin-3-yl)guanidino]propyl}benzamide (54). mp 209−210 °C; MS (ESI+) *m/z* 479 (M + H)$^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.18 (s, 3 H), 6.51 (t, J = 8.65 Hz, 1 H), 7.13 (d, J = 8.81 Hz, 1 H), 7.29 (dd, J = 8.65, 2.88 Hz, 1 H), 7.83 (d, J = 2.03 Hz,

2 H), 7.90 (s, 3 H), 8.18 (dd, J = 2.71, 1.02 Hz, 1 H), 8.91 (d, J = 8.82 Hz, 1 H), 9.88 (s, 1 H). Anal. ($C_{17}H_{13}Cl_4FN_6O \cdot 0.06C_6H_{14}$) C, H, N.

3-Chloro-*N*-{2,2-dichloro-1-[*N′*-cyano-*N″*-(6-fluoropyridin-3-yl)guanidino]propyl}benzamide (55). mp 124−125 °C; MS (ESI+) m/z 443 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.18 (s, 3H), 6.53 (t, J = 8.5 Hz, 1H), 7.13 (br d, J = 8.7 Hz, 1H), 7.29 (dd, J = 8.2, 2.6 Hz, 1H), 7.57 (t, 8.1 Hz, 1H), 7.66−7.73 (m, 1H), 7.80 (br d, J = 7.8 Hz, 1H), 7.85 (t, J = 1.1 Hz, 1H), 7.89−7.94 (m, 1H), 8.18 (d, J = 1.4 Hz, 1H), 8.79 (br d, J = 8.3 Hz, 1H), 9.88 (s, 1H). Anal. ($C_{17}H_{14}Cl_3FN_6O$) C, H, N.

Thiophene-2-carboxylic Acid {2,2-Dichloro-1-[*N′*-cyano-*N″*-(6-fluoropyridin-3-yl)guanidino]propyl}amide (56). mp 193−194 °C; MS (ESI+) m/z 416 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.16 (s, 3 H), 6.48 (t, J = 8.65 Hz, 1 H), 7.13 (d, J = 8.82 Hz, 1 H), 7.21 (dd, J = 5.09, 3.73 Hz, 1 H), 7.30 (dd, J = 8.82, 3.05 Hz, 1 H), 7.75 (dd, J = 3.73, 0.68 Hz, 1 H), 7.91 (m, 2 H), 8.18 (m, 1 H), 8.63 (d, J = 8.82 Hz, 1 H), 9.89 (s, 1 H). Anal. ($C_{15}H_{13}Cl_2FN_6OS$): C, H, N.

***N*-{2,2-Dichloro-1-[*N′*-cyano-*N″*-(6-fluoropyridin-3-yl)guanidino]propyl}-4-methylbenzamide (57).** mp 206−207 °C; MS (ESI+) m/z 424 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.16 (s, 3 H), 2.37 (s, 3 H), 6.54 (t, J = 8.65 Hz, 1 H), 7.14 (d, J = 8.81 Hz, 1 H), 7.29 (m, 1 H), 7.33 (d, J = 7.80 Hz, 2 H), 7.73 (d, J = 8.14 Hz, 2 H), 7.91 (m, 1 H), 8.17 (dd, J = 2.54, 1.19 Hz, 1 H), 8.54 (d, J = 8.81 Hz, 1 H), 9.89 (s, 2 H). Anal. ($C_{18}H_{17}Cl_2FN_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N′*-cyano-*N″*-(6-fluoroypyridin-3-yl)guanidino]propyl}-4-methylbenzamide (58).** mp 201−202 °C; MS (ESI+) m/z 424 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.17 (s, 3 H), 2.38 (s, 3 H), 6.55 (t, J = 8.65 Hz, 1 H), 7.17 (d, J = 8.82 Hz, 1 H), 7.30 (dd, J = 8.82, 3.05 Hz, 1 H), 7.42 (m, 2 H), 7.63 (m, 2 H), 7.91 (m, 1 H), 8.18 (m, 1 H), 8.58 (d, J = 8.48 Hz, 1 H), 9.89 (s, 1 H). Anal. ($C_{18}H_{17}Cl_2FN_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N′*-cyano-*N″*-(6-fluoropyridin-3-yl)guanidino]propyl}-3,5-difluorobenzamide (59).** mp 203−204 °C; MS (ESI+) m/z 446 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.18 (s, 3 H), 6.51 (t, J = 8.65 Hz, 1 H), 7.11 (d, J = 8.82 Hz, 1 H), 7.30 (dd, J = 8.65, 3.22 Hz, 1 H), 7.55 (m, 2 H), 7.90 (dd, J = 6.00, 2.71 Hz, 1 H), 7.93 (dd, J = 6.00, 3.05 Hz, 1 H), 8.18 (m, 1 H), 8.85 (d, J = 8.48 Hz, 1 H), 9.89 (s, 1 H). Anal. ($C_{17}H_{13}Cl_2F_3N_6O$) C, H, N.

***N*-{2,2-Dichloro-1-[*N′*-cyano-*N″*-(6-fluoropyridin-3-yl)guanidino]propyl}-4-trifluoromethoxybenzamide (60).** mp 207−208 °C; MS (ESI+) m/z 494 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.18 (s, 3 H), 6.53 (t, J = 8.65 Hz, 1 H,) 7.14 (d, J = 9.15 Hz, 1 H), 7.30 (dd, J = 8.65, 3.22 Hz, 1 H), 7.54 (m, J = 8.14 Hz, 2 H), 7.90 (m, 1 H), 7.96 (d, J = 8.81 Hz, 2 H), 8.17 (dd, J = 2.54, 1.19 Hz, 1 H), 8.77 (d, J = 8.14 Hz, 1 H), 9.89 (s, 1 H). Anal. ($C_{18}H_{14}Cl_2F_4N_6O_2$) C, H, N.

***N*-{2,2-Dichloro-1-[*N′*-cyano-*N″*-(6-fluoropyridin-3-yl)guanidino]propyl}-4-fluorobenzamide (61).** mp 182−183 °C; MS (ESI+) m/z 428 $(M + H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.17 (s, 3 H), 6.53 (t, J = 8.82 Hz, 1 H), 7.13 (d, J = 9.16 Hz, 1 H), 7.30 (dd, J = 8.82, 3.05 Hz, 1 H), 7.37 (t, J = 8.82 Hz, 2 H), 7.91 (m, 3 H), 8.18 (m, 1 H), 8.67 (d, J = 8.48 Hz, 1 H), 9.89 (m, 1 H). Anal. ($C_{17}H_{14}Cl_2F_2N_6O$) C, H, N.

Acknowledgment. The authors are grateful to Rodger Henry for carrying out X-ray crystal structure analysis.

Supporting Information Available: Crystallographic data for compound (*S*)-**9** and elemental analysis results. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Hampel, C.; Wienhold, D.; Benken, C. Eggersmann, C.; Thuroff, J. W. Definition of overactive bladder and epidemiology of urinary incontinence. *Urology* **1997**, *50* (Suppl. 6A), 4−14.
(2) Thomas, T. M.; Plymat, K. R.; Blannin, J.; Meade, T. W. Prevalence of urinary incontinence. *Br. Med. J.* **1980**, 1243−1245.
(3) Ouslander, J. G.; Kane, R. L.; Abrass, I. B. Urinary incontinence in elderly nursing home patients. *JAMA* **1982**, *248*, 1194−1198.
(4) Wagner, T. H.; Hu, T. W. Economic costs of urinary incontinence in 1995. *Urology* **1998**, *51*, 355−356.
(5) Payne, C. Epidemiology, phatophysiology and evaluation of urinary incontinence and overactive bladder. *Urology* **1998**, *51* (Suppl. 2A), 3−10.
(6) Brading, A. F. A Myogenic Basis for the Overactive Bladder. *Urology* **1997**, *50* (6A Suppl.), 57−73.
(7) Mills, I. W.; Greenland, J. E.; McMurray, G.; McCoy, R.; Ho, K. M.; Noble, J. G.; Brading, A. F. Studies of the Phatophysiology of Idiopathic Detrusor Instability: the Physiological Properties of the Detrusor Smooth Muscle and its Pattern of Innervation. *J. Urol.* **2000**, *163*, 646−651.
(8) (a) Chess-Williams, R.; Martin, S. W.; Korstanje, C.; Chapple, C. R. In vitro investigation of the bladder-vascular selectivity of levcromakalim and YM934 in human tissues. *BJU int.* **1999**, *83*, 1050−1054. (b) Zorografos, P.; Li, J. H.; Kau, S. T. Comparison of the in vitro Effects of K Channel Modulators on Detrusor and Portail Vein Strips from Guinea Pigs. *Pharmacology* **1992**, *45*, 216−230. (c) Martin, S. W.; Radley, S. C.; Chess-Williams, R.; Korstanje, C.; Chapple, C. R. Relaxant effects of potassium channel openers on normal and hyper-reflexic detrusor muscle. *Br. J. Urol.* **1997**, *80*, 405−413.
(9) Wojdan, A.; Freeden, C.; Woods, M.; Oshiro, G.; Spinelli, W.; Colatsky, T. J.; Sheldon, J. H.; Norton, N. W.; Warga, D.; Antane, M. M.; Antane, S. A.; Butera, J. A.; Argentieri, T. M.; Comparison of the potassium channel openers, WAY-133537, ZD6169 and Cellikalim on isolated bladder tissue and in vivo bladder instability. *J. Pharmacol. Exp. Ther.* **1999**, *289*, 1410−1418.
(10) Howe, B. B.; Halterman, T. J.; Youchim, C. L.; Do, M. L.; Pettinger, S. J.; Stow, R. B.; Ohnmacht, C. J.; Russell, K.; Empfield, J. R.; Trainor, D. A.; Brown, F. J.; Kau, S. T. ZENECA ZD6169: a novel K_{ATP} channel opener with in vivo selectivity for urinary bladder. *J. Pharmacol. Exp. Ther.* **1995**, *274*, 884−890.
(11) Malmgren, A.; Andersson, K. E.; Sjogren, C.; Andersson, P. O. Effects of pinacidil and cromakalim (BRL 34915) on bladder function in rats with detrusor instability. *J. Urol.* **1989**, *142*, 1134−1138.
(12) Li, J. H. Pharmacology of ZM244085: a Novel Bladder-Selective Dihydropyridine K_{ATP} Channel Activator. *Cardiovasc. Drug Rev.* **1997**, *15*, 220−231.
(13) Yu, Y.; de Groat, W. C. effects of ZD6169, a K_{ATP} channel opener, on bladder hyperactivity and spinal c-*fos* expression evoked by bladder irritation in rats. *Brain Res.* **1998**, *807*, 1−18.
(14) Yu, Y.; de Groat, W. C. effects of ZD6169, a K_{ATP} Channel Opener, on the Micturition Reflex in the Rat. *J. Pharmacol. Exp. Ther.* **1999**, *290*, 825−831.
(15) Nurse, D. E.; Restorick, J. M., Mundy, A. R. The effect of cromakalim on the normal and hyper-reflexic human detrusor muscle. *Br. J. Urol.* **1991**, *68*, 27.
(16) Komersova, K.; Rogerson, J. W; Conway, E L; Lim, T. C; Brown, D. J; Krum, H; Jackman, G. P; Murdoch, R; Louis, W. The effect of levcromakalim (BRL 38227) on bladder function in patients with high spinal cord lesions. *Br. J. Clin. Pharmacol.* **1995**, *39*, 207−9.
(17) Coghlan, M. J.; Carroll, W. A.; Gopalakrishnan, M. Recent Developments in the Biology and Medicinal Chemistry of Potassium Channel Modulators: Update from a Decade of Progress. *J. Med. Chem.* **2001**, *44*, 1628−1653.
(18) Steers, W. D. The future of direction of neuro-urology drug research. *Curr. Opin. Cent. Peripher. Nerv. Syst. Invest. Drugs* **2000**, *2*, 268−282. Pharmaprojects Database. Record 026988.
(19) Butera, J. A.; Antane, M. M.; Antane, S. A.; Argentieri, T. M.; Freeden, C.; Graceffa, R. F.; Hirth, B. H.; Jenkins, D.; Lennox, J. R.; Matelan, E.; Norton, N. W.; Quangliato, D.; Sheldon, J. H.; Spinelli, W.; Warga, D.; Wojdan, A.; Woods, M. Design and SAR of Novel Potassium Channel Openers Targeted for Urge Urinary Incontinence. 1. *N*-Cyanoguanidine Bioisosteres Possessing in Vivo Bladder Selectivity *J. Med. Chem.* **2000**, *43*, 1187−1202.
(20) Gilbert, A. M.; Antane, M. M.; Argentieri, T. M.; Butera, J. A.; Francisco, G. D.; Freeden, C.; Gundersen, E. G.; Graceffa, R. F.; Herbst, D.; Hirth, B. H.; Lennox, J. R.; McFarlane, G.; Norton, N. W.; Quagliato, D.; Sheldon, J. H.; Warga, D.; Wojdan, A.; Woods, M. Design and SAR of Novel Potassium Channel Openers Targeted for Urge Urinary Incontinence. 2. Selective and Potent Benzylamino Cyclobutenediones. *J. Med. Chem.* **2000**, *43*, 1203−1214.
(21) Perez-Medrano, A.; Buckner, S. A.; Coghlan, M. J.; Gregg, R. J.; Gopalakrishnan, M.; Kort, M. E.; Lynch, J. K.; Scott, V. E.; Sullivan, J. P.; Whiteaker, K. L.; Carroll, W. A. Design and Synthesis of Novel Cyanoguanidine ATP-Sensitive Potassium Channel Openers for the Treatment of Overactive Bladder *Bioorg. Med. Chem. Lett.* **2004**, *14*, 397−400.

(22) Kyba, E. P.; Liu, S. T.; Chockalingam, K.; Reddy, B. R. A General Synthesis of Substituted Fluorenones and Azafluorenones. *J. Org. Chem*. **1988**, *53*, 3513−21.
(23) Wu, M. T. Synthesis of Some N,1- and N′,1-Diary-1H-1,2,4-triazole-3,5-diamines. *J. Heterocycl. Chem.* **1977**, *13*, 443−444.
(24) De Buyck, L.; Verhe, R.; De Kimpe, N.; Courtheyn, D.; Schamp, N. 2,2-Dichloroaldehydes from aldehydes and alcohols by chlorination in dimethylformamide. *Bull. Soc. Chim. Belg*. **1980**, *89*, 441−458.
(25) Katritzky, A. R.; Drewniak, M. The Chemistry of Benzotriazole. Part 8. A Novel Two-step Procedure for the *N*-alkylation of Amides. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2339−2344.
(26) Scott, V. E.; Davis-Taber, R.; Silvia, C.; Hoogenboom, L.; Choi, W.; Kroger, P.; Whiteaker, K. L.; Gopalakrishnan, M. Characterization of Human Urinary Bladder KATP channels containing SUR2B Splice Variants Expressed in L-cells. *Eur. J. Pharmacol.* **2004**, *483*, 195−205.
(27) Baxter, D. F.; Kirk, M.; Garcia, A. F.; Raimondi, A.; Holmqvist, M. H.; Flint, K., K.; Bojanic, D.; Distefano, P. S.; Custis, R.; Xie, Y. A novel membrane potential-sensitive fluorescent dye improves cell-based assays for ion channels. *J. Biomol. Screen.* **2002**, *7*, 79−85.
(28) Buckner, S. A.; Milicic, I.; Daza, A.; Davis-Taber, R.; Scott, V. E. S.; Sullivan, J. P.; Brioni, J. D. Pharmacological and molecular analysis of ATP-sensitive K^+ channels in the pig and human detrusor. *Eur. J. Pharmacol.* **2000**, *400*, 287−295.
(29) Brune, M. E.; Fey, T. A.; Brioni, J. D; Sullivan, J. P.; Williams, M.; Carroll, W. A.; Coghlan, M. J; Gopalakrishna, M. (−)-(9S)-9-(3-Bromo-4-fluorophenyl)-2,3,5,6,7,9-hexahydrothieno[3,2-b]q uinolin-8(4H)-one 1,1-dioxide (A-278637): a novel ATP-sensitive potassium channel opener efficacious in suppressing urinary bladder contractions. II. in vivo characterization. *J. Pharmacol. Exp. Ther*. **2002**, *303*, 387−394.

JM7010194