

Brief Articles

Discovery and Structure–Activity Relationships of Trisubstituted Pyrimidines/Pyridines as Novel Calcium-Sensing Receptor Antagonists

Wu Yang,^{*,†} Zheming Ruan,^{*,‡} Yufeng Wang,[†] Katy Van Kirk,[‡] Zhengping Ma,[§] Brian J. Arey,[§] Christopher B. Cooper,[‡] Ramakrishna Seethala,[§] Jean H. M. Feyen,[§] and John K. Dickson, Jr.[†]

Discovery Chemistry, Early Discovery Chemistry, and Metabolic and Cardiovascular Drug Discovery, Bristol-Myers Squibb Pharmaceutical Research Institute, P.O. Box 5400, Princeton, New Jersey 08543-5400

Received September 18, 2008

The trisubstituted pyrimidine **1** was identified through high-throughput screening as a novel calcium-sensing receptor (CaSR) antagonist. Small molecule CaSR antagonists and/or negative allosteric modulators have the potential to act as an anabolic agent for the treatment of osteoporosis. The investigation of structure–activity relationships around **1** resulted in the identification of **18c** and **18d**, which showed efficacy at promoting PTH release in vivo and exhibited improved potency and solubility over the original lead **1**.

Introduction

Calcium is a key mediator of many important physiological functions including the regulation of bone anabolism and catabolism. One of the main sites of calcium-mediated bone metabolism is the parathyroid gland where calcium binds to the calcium-sensing receptor (CaSR^a).¹ The CaSR is a class 3 G-protein-coupled receptor expressed on the surface of parathyroid cells where it functions to mediate calcium effects on bone metabolism through the modulation of endogenous PTH release.² Plasma calcium concentrations are inversely related to plasma PTH levels.² These data suggest that the release of PTH from the parathyroid gland is tightly coupled to the prevailing plasma calcium concentration. The coupling of calcium concentration to PTH secretion is supported by observations that the range of normal calcium concentrations falls within a steeply cooperative region of the calcium dose–response curve for PTH release.³

Evidence suggests that physiologically relevant plasma levels of endogenous PTH are sufficient to elicit a bone anabolic response depending on the temporal exposure of elevated plasma PTH. Transient elevation of PTH leads to an overall net anabolic effect on bone metabolism, whereas chronic elevation leads to a net catabolic effect on bone turnover.⁴ This tight control of bone metabolism makes the CaSR an attractive target for the development of new therapies to treat bone-related diseases. Toward this end, Nemeth and colleagues have demonstrated that small molecules acting as CaSR negative allosteric modulators can act as orally available anabolic agents.⁵ **2** (NPS-2143) (Figure 1) was the first reported orally bioavailable small molecule calcilytic compound that stimulates the secretion of

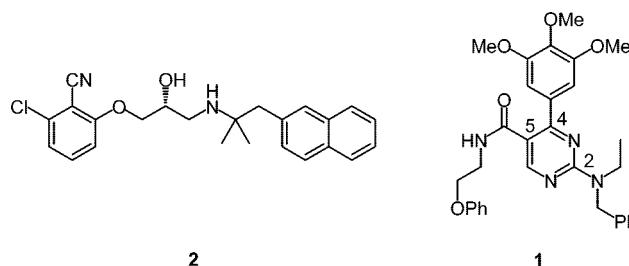


Figure 1. Compound **2** and HTS lead **1**.

endogenous PTH by negatively modulating the CaSR.⁵ The increase of endogenous circulating PTH in the presence of **2**, when coadministered with an antiresorptive agent 17 β -estradiol, resulted in the stimulation of new bone growth.⁶ Detailed pharmacological analyses of **2** revealed that when administered in vivo along with estradiol, this compound increased trabecular bone volume and bone mineral density to an extent comparable to that obtained by daily PTH injection. However, **2** suffers from a range of pharmacological liabilities (e.g., receptor specificity, cytochrome P₄₅₀ inhibition, long plasma half-life), thus precluding its use as a stand-alone agent. Toward that end, a number of other CaSR antagonists have been reported.⁷

To find alternative and proprietary chemotypes that have better pharmacological profiles, high-throughput screening of the BMS corporate compound collection was undertaken using an FLIPR assay.⁸ This assay measures the ability of compounds to affect mobilization of internal calcium stores in HEK-293 cells stably expressing the human CaSR following the addition of external calcium to the cell culture medium.⁸ From this effort, the substituted 2-amino-4-(3,4,5-trimethoxyphenyl)pyrimidine-5-carboxamide **1** was identified as a novel CaSR antagonist with an IC₅₀ of 190 nM using this assay (Figure 1). In this paper, we report the investigation of the SARs around **1** at the 2-, 4-, and 5-positions by substructure searches of the existing BMS compound collection and traditional exploratory medicinal chemistry including the use of solid-phase parallel synthesis. In addition, to improve the physical and pharmacological profile of the lead compound, we developed a novel PXPd₂-catalyzed regioselective Suzuki coupling methodology to efficiently

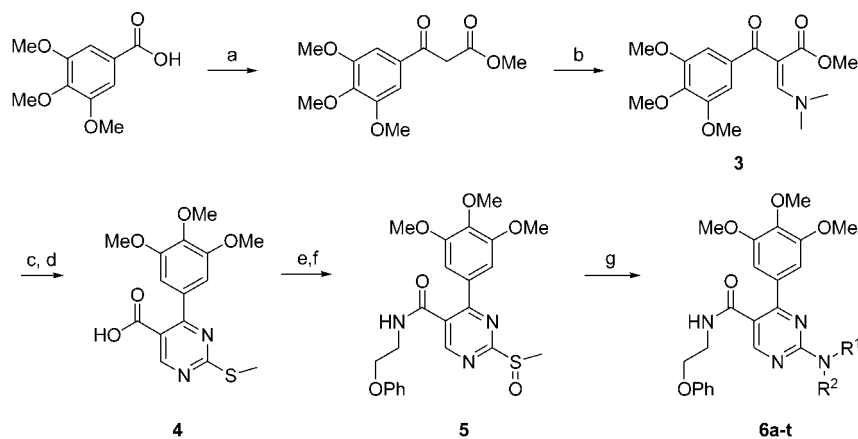
* To whom correspondence should be addressed. (W.Y.) Telephone: 609-818-6493. Fax: 609-818-3550. E-mail: Wu.Yang@bms.com. (Z.R.) Telephone: 609-252-3752. Fax: 609-252-7446. E-mail: zheming.ruan@bms.com.

[†] Discovery Chemistry.

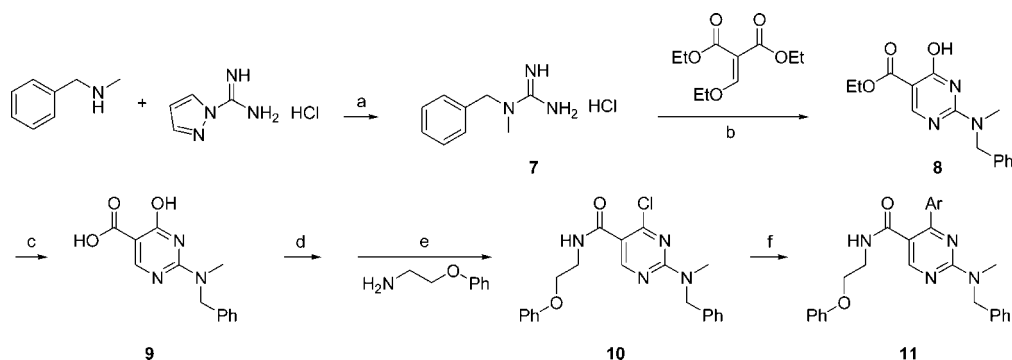
[‡] Early Discovery Chemistry.

[§] Metabolic and Cardiovascular Drug Discovery.

^a Abbreviations: CaSR, calcium-sensing receptor; PTH, parathyroid hormone; FLIPR, fluorescence imaging plate reader; PXPd₂, dichloro-(chloro-di-*tert*-butylphosphine)palladium(II) dimer (CAS No. 386706-33-8); POPd₂, dihydrogen di-*m*-chlorodichlorobis(di-*tert*-butylphosphinito-kP)dipalladate(2-) (CAS No. 386706-32-7).

Scheme 1. Synthesis of 2-Aminopyrimidine Analogues^a

^a Reagents and conditions: (a) i) carbonyl diimidazole, THF, room temp, 4 h; (ii) potassium methylmalonate, MgCl₂, 40 °C, 48 h, 58%; (b) dimethylformamide dimethyl acetal, 90 °C, 2 h; (c) 2-methyl-2-thiopseudourea, NaOAc, DMF, 80 °C, 16 h, 54% for two steps; (d) KOTMS, THF, room temp, 14 h, 91%; (e) (COCl)₂, DMF (cat.), 1.5 h, then phenoxyethylamine, TEA, 5 min, THF, 59%; (f) 2-benzenesulfonyl-3-phenyloxaziridine, CH₂Cl₂, room temp, 16 h, 80%; (g) NHR¹R², THF, 60 °C, 16 h.

Scheme 2. Synthesis of 4-Arylpyrimidine Analogues^a

^a Reagents and conditions: (a) DIEA, DMF, room temp, 16 h; (b) NaOEt, EtOH, reflux, overnight, 73% for two steps; (c) KOH, EtOH, reflux, overnight, 90%; (d) POCl₃, SOCl₂, 110 °C, 16 h; (e) TEA, THF, -78 °C, 1.5 h, 73% for two steps; (f) POPd2, K₂CO₃, THF, 80–140 °C, 16 h.

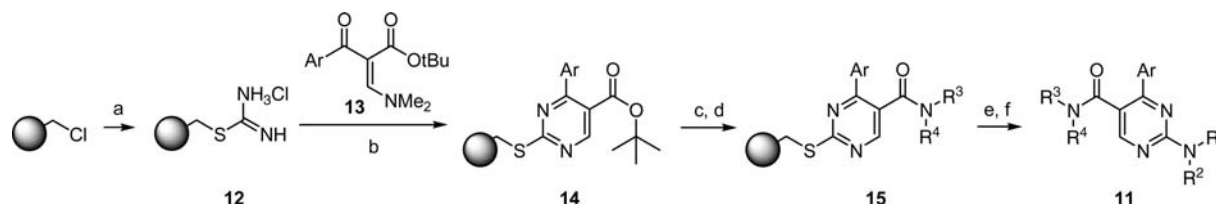
prepare analogues with a pyridine core in lieu of the original pyrimidine core.⁹ Analogues with a pyridine core were found to have *in vitro* activity comparable to those with a pyrimidine core. Selected analogues **18c** and **18d** were evaluated *in vivo* in an acute PTH release model and were found to have efficacy comparable to that of **2**. Interestingly, in a separate study via mutagenesis, **18c** was found to exhibit a binding mode different from **2**.¹⁰

Chemistry

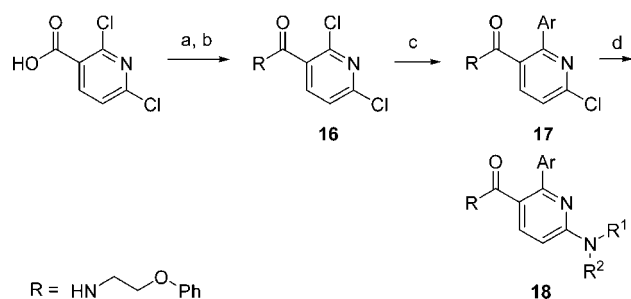
To explore the SAR around the amino substitution at the pyrimidine 2-position, a general procedure was used where a large number of diverse amines displaced an intermediate sulfoxide in the last step (Scheme 1). β -Ketoester was prepared from 3,4,5-trimethoxybenzoic acid by activation with carbonyl diimidazole, followed by treatment with potassium methylmalonate, generated through hydrolysis of dimethyl malonate with KOH.¹¹ The β -ketoester was converted to vinylogous carbamate **3** by treatment with *N,N*-dimethylformamide dimethyl acetal. Cyclization of **3** with 2-methyl-2-thiopseudourea afforded the pyrimidine methyl ester, which on hydrolysis provided acid **4**. Acid **4** was then coupled to phenoxyethylamine and oxidized to sulfoxide **5** by Davis' reagent¹² (the corresponding sulfone proved too unstable). Replacement of the sulfoxide by a variety of primary and secondary amines provided the final compounds **6a–t** in good yields (50–97%).

To explore the SAR around a broad range of 4-aryl/heteroaryl substituents on the pyrimidine, a convergent route was developed as shown in Scheme 2. Treatment of benzylmethylamine with pyrazole-1-carboxylidene¹³ afforded the *N*-benzyl-*N*-methylguanidine **7**. This material was next reacted with diethyl ethoxymethylene malonate (DEMME) to give the pyrimidine **8** in 73% combined yield for two steps. Upon hydrolysis, the 4-hydroxy acid **9** was treated with phosphoryl chloride and then reacted with phenoxyethylamine to provide the corresponding 4-chloro-5-carboxamide **10** in one pot. Suzuki coupling of this aryl chloride with various boronic acids using POPd2 as catalyst provided the final **11**.

The solid phase synthesis of a library of pyrimidine analogues to explore the SAR of amides at the 5-position with a limited number of 4-aryl groups is outlined in Scheme 3. Commercially available Merrifield resin was treated with thiourea to provide resin **12**. Pyrimidine-linked resins **14** were prepared by subjecting the resin **12** to enamines **13**, which were obtained in a similar fashion from the corresponding β -ketoesters as described previously for the synthesis of **3**. Standard deprotection of the *tert*-butyl ester with TFA followed by amide coupling afforded resins **15**. mCPBA-mediated oxidation of sulfides **15** followed by displacement of the resulting sulfones with a variety of amines provided the final products **11**. All final compounds were purified by preparative HPLC to afford ~5 mg of material from about 20 mg of starting resin (~1 mmol/1 g resin loading).

Scheme 3. Solid Phase Synthesis of **1** and Its Analogues^a

^a Reagents and conditions: (a) thiourea, 75 °C, 3 d; (b) ^tPrNEt₂, room temp, 3 d; (c) TFA/dichloroethane, room temp, overnight; (d) EDC, HOBT, ^tPrNEt₂, NMP, amines NHR³R⁴, room temp, 2 d; (e) mCPBA/DCM, room temp, overnight; (f) amines NHR¹R²/CH₃CN, 70 °C, 2 d.

Scheme 4. Synthesis of 2-Aryl-6-aminonicotinamide Analogues^a

^a Reagents and conditions: (a) SOCl₂, 90 °C, 2 h; (b) ^tPrNEt₂, 2-phenoxyethylamine, -78 °C, THF, 1.5 h, 82%; (c) arylboronic acids, PXPd2, K₂CO₃, MeOH, 80 °C, 16 h; (d) NHR¹R², neat, 130 °C, 8 h.

The synthesis of analogues with a pyridine core in lieu of the pyrimidine core of **11** was accomplished via a PXPd2-mediated regioselective Suzuki coupling, as previously reported from this laboratory (Scheme 4). 2,6-Dichloronicotinic acid was converted to its acid chloride, followed by treatment with 2-phenoxyethylamine at -78 °C to give the nicotinamide **16**. PXPd2-catalyzed regioselective Suzuki coupling of **16** with various arylboronic acids in reagent grade methanol provided the desired regioisomeric biaryl amides as the major products, which upon heating with different amines under neat conditions afforded final pyridyl analogues **18** in 30–60% yields.

Results and Discussion

2-Amino substituted pyrimidines from substructure searches of the BMS compound collection and directed synthesis exhibited a range of CaSR antagonist activities as shown in Table 1. While benzyl or phenethylamines were preferred in general, simple branched alkylamines such as **6a** also showed moderate activity. Alkylation of nitrogen on the benzylamine provided a stepwise improvement in potency from hydrogen (**6b**) to methyl (**6c**) to ethyl (**1**). Some general trends with regard to preferred substitution on the tethered phenyl ring of the benzylamine were also observed. In particular, while substitutions at the ortho- (**6d**, **6e**) or para-positions (**6g**) resulted in reduced potency compared with the unsubstituted parent compound (**6b**), substitution at the meta-position (**6f**, **6h**), as well as 3,4-methylenedioxy substitution (**6i**), improved in vitro potency by as much as 10-fold. In contrast, the more polar pyridyl analogues (**6j** and **6k**) completely abolished CaSR activity. The one carbon elongated phenethylamine analogue **6l** showed slightly improved activity compared with the benzyl analogue **6b**. However, in contrast to **6c**, methylation of **6l** to **6m** resulted in an almost 4-fold loss of activity. Also, unlike the benzylamine analogues, various substitutions on the phenyl ring of phenethylamine (**6n–p** and others not shown) did not provide additional improvements in potency. Replacement of the phenyl with pyridyl groups (**6q** and **6r**) was not tolerated

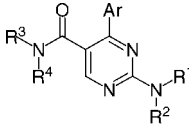
Table 1. Summary of SAR of Pyrimidine Analogues at the 2-Position



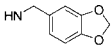


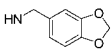
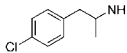

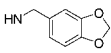
Compd	NR ¹ R ²	FLIPR IC ₅₀ (μM) ^a
1	NEtCH ₂ Ph	0.2
6a	NHCH ₂ CH ₂ CHMe ₂	2.2
6b	NHCH ₂ Ph	0.73
6c	NMeCH ₂ Ph	0.47
6d	NHCH ₂ (2-Cl)Ph	4.9
6e	NHCH ₂ (2-Me)Ph	10
6f	NHCH ₂ (3-Cl)Ph	0.07
6g	NHCH ₂ (4-OMe)Ph	3.1
6h	NHCH ₂ (3-OMe)Ph	0.34
6i		0.15
6j	NHCH ₂ (2-)Py	>30
6k	NHCH ₂ (3-)Py	>30
6l	NHCH ₂ CH ₂ Ph	0.4
6m	NMeCH ₂ CH ₂ Ph	1.5
6n	NHCH ₂ CH ₂ (2-OMe)Ph	0.34
6o	NHCH ₂ CH ₂ (3-OMe)Ph	1.0
6p	NHCH ₂ CH ₂ (4-OMe)Ph	2.8
6q	NHCH ₂ CH ₂ (2-Py)	>30
6r	NHCH ₂ CH ₂ (3-Py)	>30
6s		0.15
6t		>30

^a Average of two or more runs. Standard deviation of assay is less than ±10%.

in this homologated series either. Interestingly, the introduction of a polar hydroxymethyl group at the α-position of phenethylamine **6l** not only improved solubility but also provided a moderate increase in potency over the unsubstituted parent **6l**. This enhancement in activity upon substitution is stereospecific, with only the *S*-enantiomer being active against the CaSR (**6s** vs **6t**).

In contrast to the broad range of acceptable groups identified at the pyrimidine 2-position, there were far fewer potent alternatives identified at the 4- or 5-positions (Table 2). For example, replacing the trimethoxyphenyl group in compound **1** with phenyl (**11a**) or cyclohexyl (**11b**) resulted in the complete loss of CaSR antagonist activity, as did the one atom shortened phenylethylamide **11c**. The only other amides that showed even moderate activity were the phenylpropyl (**11d**) and phenylbutyl (**11e**) amides, both with similar, yet 10-fold weaker potencies compared with **1**.

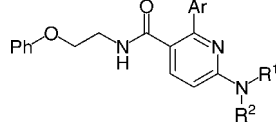
Table 2. Summary of SAR of Pyrimidine Analogues at the 4- and 5-Positions










Compd	NR ³ R ⁴	Ar	NR ¹ R ²	IC ₅₀ (μM) ^a
1	PhO-CH ₂ -NH	3,4,5-triMeOPh	NEtBn	0.2
11a	PhO-CH ₂ -NH	Ph	NEtBn	>30
11b	PhO-CH ₂ -NH	c-Hex.	NEtBn	>30
11c	Ph-CH ₂ -NH	3,4,5-triMeOPh	NEtBn	>30
11d	Ph-CH ₂ -NH	3,4,5-triMeOPh	NEtBn	2.1
11e	Ph-CH ₂ -NH	3,4,5-triMeOPh	NEtBn	1.8
11f	PhO-CH ₂ -NH	2-MeOPh	NMeBn	>30
11g	PhO-CH ₂ -NH	3-MeOPh	NMeBn	>30
11h	PhO-CH ₂ -NH	4-MeOPh	NMeBn	>30
11i	PhO-CH ₂ -NH	4-CF ₃ Ph	NMeBn	18.9
11j	PhO-CH ₂ -NH	3,4-diMeOPh	NMeBn	6.9
11k	PhO-CH ₂ -NH	3,5-diMeOPh	NMeBn	>30
11l	PhO-CH ₂ -NH		NEtBn	0.36
11m	PhO-CH ₂ -NH			0.22
11n				0.36
11o				0.15

^a Average of two or more runs. Standard deviation of assay is less than ±10%.

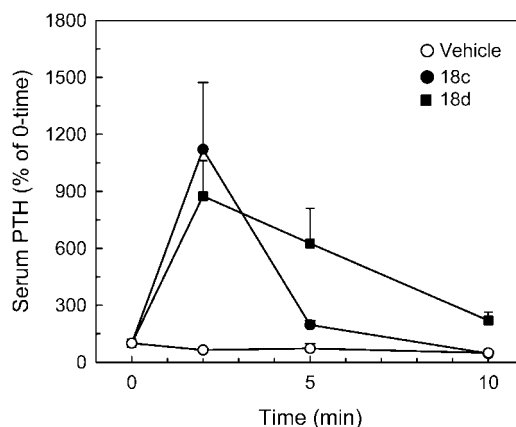
To explore further the SAR at the pyrimidine 4- and 5-positions, two concurrent approaches were undertaken. One approach focused on the SAR at the 4-position through a convergent synthesis by coupling 4-chloropyrimidine with a variety of arylboronic acids (Scheme 2). We were disappointed to find the SAR at the 4-position to be very narrow, with only 4-trifluoromethylphenyl (**11i**) and 3,4-dimethoxyphenyl (**11j**) showing measurable activities while close analogues **11f–h,k** were all considerably less potent. The second approach targeting the 5-amide position involved preparing a solid-phase library where the best amines at the 2-position from Table 1 were used in combination with a limited number of substituted aryl groups at the 4-position and a large number of amides at the 5-position (Scheme 3). Representative compounds from this library are provided in Table 2. Compound **11l**, which incorporates a 2,6-dimethoxypyridyl at the 4-position, exhibited potency similar to the lead compound **1**. Combining this new “top piece” with one of the best 2-position substituents (3,4-methylenedioxybenzylamino) resulted in the identification of several potent amide analogues. Most notable were the amides prepared from tetrahydroisoquinoline (**11n**) and α-methyl-4-chlorophenethylamine (**11o**), which showed activity comparable to the benchmark amide from phenoxyethylamine (**11m**).

In an attempt to improve some of the physicochemical properties of this series, the pyrimidine core was replaced with a more basic pyridine core. The two aryl groups (3,4,5-trimethoxyphenyl and 2,4-dimethoxypyridyl) were combined with the best amines from Table 1 to provide new analogues as shown in Table 3 (**18a–h**). The pyridine analogues in general

Table 3. Summary of in Vitro Potency of Pyridine Analogues


Compd	Ar	NR ¹ R ²	IC ₅₀ (μM) ^a
18a	3,4,5-triMeOPh		0.154
18b	2,6-dimethoxypyridin-3-yl		1.05
18c	3,4,5-triMeOPh		0.076
18d	2,6-dimethoxypyridin-3-yl		0.14
18e	3,4,5-triMeOPh		0.13
18f	2,6-dimethoxypyridin-3-yl		0.06
18g	3,4,5-triMeOPh		0.162
18h	2,6-dimethoxypyridin-3-yl		0.197

^a Average of two or more runs. Standard deviation of assay is less than ±10%.

**Figure 2.** In vivo activity of **18c** and **18d**.

showed similar or slightly improved potency compared with the corresponding pyrimidine compounds with the exception of **18b**, with **18f** being the most potent analogue (IC₅₀ = 60 nM). In addition, **18d** showed improved aqueous solubility (11 μg/mL at pH 6.5; 36 μg/mL at pH 4.5) compared to the HTS lead **1** (<1 μg/mL at pH 6.5 and 4.5). Compounds **18c** and **18d** were chosen to be evaluated in vivo on the basis of their potency (IC₅₀ = 0.076 and 0.14 μM, respectively) and improved solubility. They were able to stimulate parathyroid hormone secretion in vivo when administered intravenously (**18c**, 7 μmol/kg; **18d**, 6 μmol/kg) in a PTH release model (Figure 2). More importantly, the stimulation observed was rapid and transient, which is the necessary profile for an anabolic calcium-sensing receptor negative modulator.

Conclusion

From high-throughput screening, we have discovered a novel series of trisubstituted pyrimidines as exemplified by **1** that act as calcium-sensing receptor antagonists. The investigation of structure–activity relationships of **1** by solid phase library synthesis in conjunction with traditional medicinal chemistry led to the identification of novel, pyridyl-based analogue **18d**, which has shown improvements in intrinsic potency and physical properties relative to the original lead. Compounds **18c** and **18d** also demonstrated a desired in vivo activity profile by stimulat-

ing PTH release in a rapid and transient manner. Results from further chemical and biological investigations of these active series will be forthcoming.

Acknowledgment. We thank Dharmopal Dodd and Rogelio Martinez for their original contributions to the preparation of 2-aminopyrimidine-5-carboxamides via solid-phase synthetic chemistry routes.

Supporting Information Available: Detailed experimental information on synthetic preparation and analytical data of **6a–t**, **11a–o**, and **18a–h**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) (a) Brown, E. M.; Gamba, G.; Riccardi, D.; Lombardi, M.; Butters, R.; Kifor, O.; Sun, A.; Hediger, M. A.; Lytton, J.; Hebert, S. C. Cloning and characterization of an extracellular Ca^{2+} -sensing receptor from bovine parathyroid. *Nature* **1993**, *366*, 575–80. (b) Brown, E. M.; Pollak, M.; Riccardi, D.; Hebert, S. C. Cloning and characterization of an extracellular Ca^{2+} -sensing receptor from parathyroid and kidney: new insights into the physiology and pathophysiology of calcium metabolism. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association. *Eur. Renal Assoc.* **1994**, *9*, 1703–6.
- (2) Brown, E. M.; MacLeod, R. J. Extracellular calcium sensing and extracellular calcium signaling. *Physiol. Rev.* **2001**, *81*, 239–297.
- (3) Bai, M.; Quinn, S.; Trivedi, S.; Kifor, O.; Pearce, S. H.; Pollak, M. R.; Krapcho, K.; Hebert, S. C.; Brown, E. M. Expression and characterization of inactivating and activating mutations in the human Ca^{2+} -sensing receptor. *J. Biol. Chem.* **1996**, *271*, 19537–19545.
- (4) (a) Dempster, D. W.; Cosman, F.; Parisien, M.; Shen, V.; Lindsay, R. Anabolic actions of parathyroid hormone on bone. *Endocr. Rev.* **1993**, *14*, 690–709. (b) Kimmel, D. B.; Bozzato, R. P.; Kronis, K. A.; Coble, T.; Sindrey, D.; Kwong, P.; Recker, R. R. The effect of recombinant human (1–84) or synthetic human (1–34) parathyroid hormone on the skeleton of adult osteopenic ovariectomized rats. *Endocrinology* **1993**, *132*, 1577–1584.
- (5) (a) Nemeth, E. F. Pharmacological regulation of parathyroid hormone secretion. *Curr. Pharm. Des.* **2002**, *8*, 2077–2087. (b) Nemeth, E. F.; Delmar, E. G.; Heaton, W. L.; Miller, M. A.; Lambert, L. D.; Conklin, R. L.; Gowen, M.; Gleason, J. G.; Bhatnagar, P. K.; Fox, J. Calcilytic compounds: potent and selective Ca^{2+} receptor antagonists that stimulate secretion of parathyroid hormone. *J. Pharmacol. Exp. Ther.* **2001**, *299*, 323–331.
- (6) Gowen, M.; Stroup, G. B.; Dodds, R. A.; James, I. E.; Votta, B. J.; Smith, B. R.; Bhatnagar, P. K.; Lago, A. M.; Callahan, J. F.; DelMar, E. G.; Miller, M. A.; Nemeth, E. F.; Fox, J. Antagonizing the parathyroid calcium receptor stimulates parathyroid hormone secretion and bone formation in osteopenic rats. *J. Clin. Invest.* **2000**, *105*, 1595–1604.
- (7) (a) Yang, W.; Wang, Y.; Roberge, J. Y.; Ma, Z.; Liu, Y.; Lawrence, R. M.; Rotella, D. P.; Seethala, R.; Feyen, J. H. M.; Dickson, J. K., Jr. Discovery and structure–activity relationships of 2-benzylpyrrolidine-substituted aryloxypropanols as calcium-sensing receptor antagonists. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1225–1228. (b) Shcherbakova, I.; Balandrin, M. F.; Fox, J.; Ghatak, A.; Heaton, W. L.; Conklin, R. L. 3H-Quinazolin-4-ones as a new calcilytic template for the potential treatment of osteoporosis. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1557–1560. (c) Shcherbakova, I.; Huang, G.; Geoffroy, O. J.; Nair, S. K.; Swierczek, K.; Balandrin, M. F.; Fox, J.; Heaton, W. L.; Conklin, R. L. Design, new synthesis, and calcilytic activity of substituted 3H-pyrimidin-4-ones. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2537–2540. (d) Gavai, A. V.; Vaz, R. J.; Mikkilineni, A. B.; Roberge, J. Y.; Liu, Y.; Lawrence, R. M.; Corte, J. R.; Yang, W.; Bednarz, M.; Dickson, J. K.; Ma, Z.; Seethala, R.; Feyen, J. H. M. Discovery of novel 1-aryl-methylpyrrolidin-2-ylethanolamines as calcium-sensing receptor antagonists. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5478–5482. (e) Kessler, A.; Faure, H.; Petrel, C.; Rognan, D.; Cesario, M.; Ruat, M.; Dauban, P.; Dodd, R. H. N1-Benzoyl-N2-[1-(1-naphthyl)ethyl]-*trans*-1,2-diaminocyclohexanes: development of 4-chlorophenylcarboxamide (Calhex 231) as a new calcium sensing receptor ligand demonstrating potent calcilytic activity. *J. Med. Chem.* **2006**, *49*, 5119–5128.
- (8) Arey, B. J.; Seethala, R.; Ma, Z.; Fura, F.; Morin, J.; Swartz, J.; Vyas, V.; Yang, W.; Dickson, J. K., Jr.; Feyen, J. H. M. A novel calcium-sensing receptor antagonist transiently stimulates parathyroid hormone secretion. *In Vivo Endocrinol.* **2005**, *146*, 2015.
- (9) Yang, W.; Wang, Y.; Corte, J. R. An efficient synthesis of 2-aryl-6-chloronicotinamides via PXPd2 catalyzed regioselective Suzuki coupling. *Org. Lett.* **2003**, *5*, 3131–3134.
- (10) Hu, J.; Jiang, J.; Costanzi, S.; Thomas, C.; Yang, W.; Feyen, J. H. M.; Jacobson, K. A.; Spiegel, A. M. A missense mutation in the seven-transmembrane domain of the human Ca^{2+} receptor converts a negative allosteric modulator into a positive allosteric modulator. *J. Biol. Chem.* **2006**, *281*, 21558–21565.
- (11) Clay, R. J.; Collom, T. A.; Karrick, G. L.; Wemple, J. A safe, economical method for the preparation of β -oxo esters. *Synthesis* **1993**, *3*, 290–292.
- (12) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. Chemistry of oxaziridines. 9. Synthesis of 2-sulfonyl- and 2-sulfamylloxaziridines using potassium peroxymonosulfate (Oxone). *J. Org. Chem.* **1988**, *53*, 2087–2089.
- (13) Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. 1H-Pyrazole-1-carboxamide hydrochloride an attractive reagent for guanylation of amines and its application to peptide synthesis. *J. Org. Chem.* **1992**, *57*, 2497–2502.

JM801178C