Brief Articles

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

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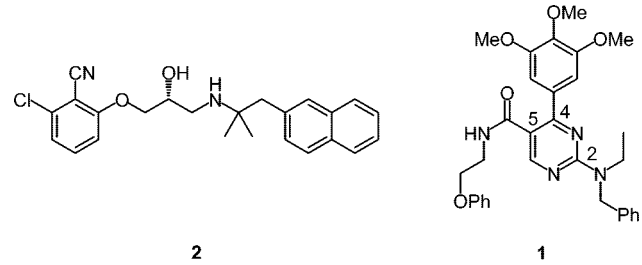
The trisubstituted pyrimidine **1** was identified through high-throughput screening as a novel calcium-sensing receptor (CaSR) antagonist. Small molecule CaSR antagonists and/or negative allosteric modulators have the potential to act as an anabolic agent for the treatment of osteoporosis. The investigation 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 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 17β-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 P_{450} 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]



2 **1**

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

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 IC_{50} 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

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[a] Abbreviations: CaSR, calcium-sensing receptor; PTH, parathyroid hormone; FLIPR, fluororescence 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-*k*P)dipalladate(2−) (CAS No. 386706-32-7).

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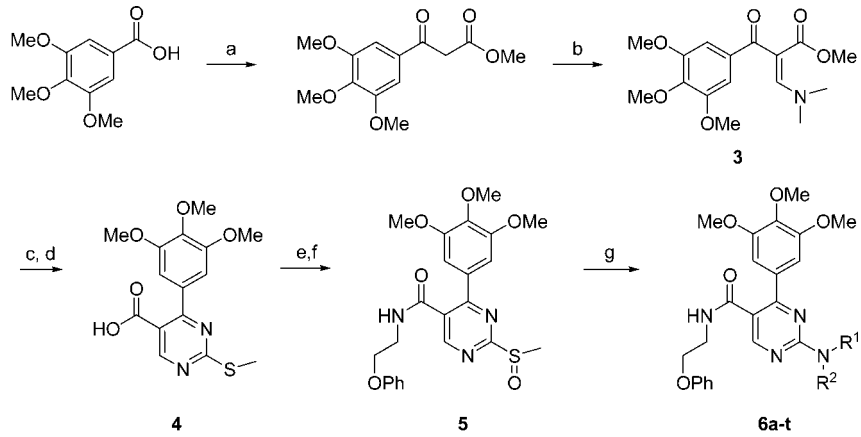
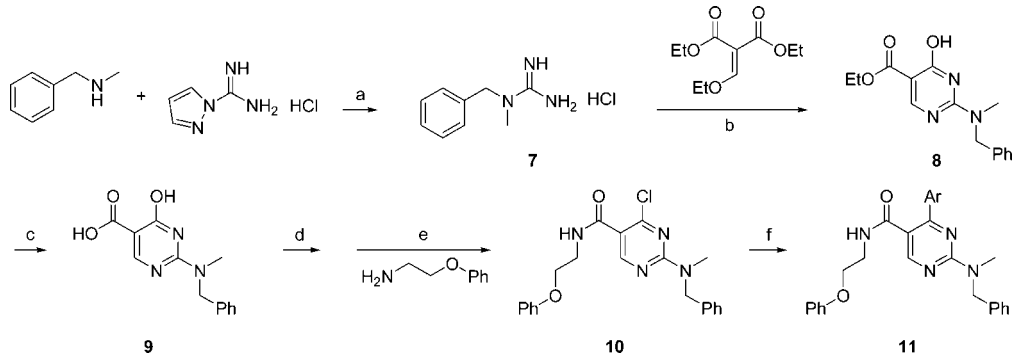
Scheme 1. Synthesis of 2-Aminopyrimidine Analogues[a]



[a] Reagents and conditions: (a) i) carbonyl diimidazole, THF, room temp, 4 h; (ii) potassium methylmalonate, $MgCl_2$, 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, CH_2Cl_2, room temp, 16 h, 80%; (g) NHR^1R^2, 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) $POCl_3$, $SOCl_2$, 110 °C, 16 h; (e) TEA, THF, −78 °C, 1.5 h, 73% for two steps; (f) POPd2, K_2CO_3, 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]

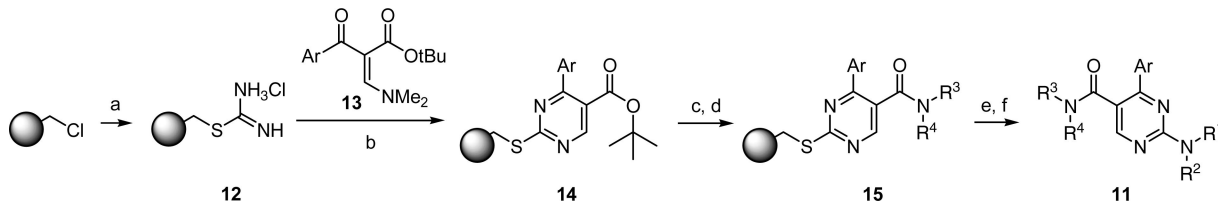
Chemistry

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' reagent[12] (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-carboxylimidine[13] afforded the *N*-benzyl-*N*-methylguanidine **7**. This material was next reacted with diethyl ethoxymethylene malonate (DEMM) 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**.

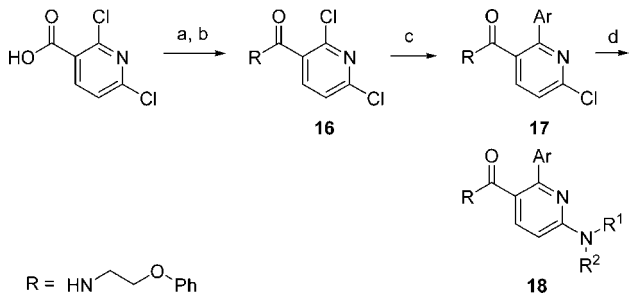
The solid phase synthesis of a library of pyrimidine analogues to explore the SAR of amides at the 5-position with a limited number of 4-aryl groups is outlined in Scheme 3. Commercially available Merrifield resin was treated with thiourea to provide resin **12**. Pyrimidine-linked resins **14** were 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) ^{i}PrNEt$_2$, room temp, 3 d; (c) TFA/dichloroethane, room temp, overnight; (d) EDC, HOBt, ^{i}PrNEt$_2$, NMP, amines NHR^{3}R^4, room temp, 2 d; (e) mCPBA/DCM, room temp, overnight; (f) amines NHR^{1}R^2/CH$_3$CN, 70 °C, 2 d.

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



[a] Reagents and conditions: (a) $SOCl_2$, 90 °C, 2 h; (b) ^{i}PrNEt$_2$, 2-phenoxyethylamine, −78 °C, THF, 1.5 h, 82%; (c) arylboronic acids, PXPd2, K_2CO_3, MeOH, 80 °C, 16 h; (d) NHR^{1}R^2, neat, 130 °C, 8 h.

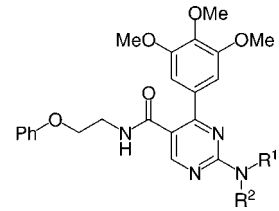
The synthesis of analogues with a pyridine core in lieu of the pyrimidine core of **11** was accomplished via a PXPd2-mediated regioselective Suzuki coupling, as previously reported from this laboratory (Scheme 4). 2,6-Dichloronicotinic acid was converted to its acid chloride, followed by treatment with 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 biarylamides as the major products, which upon heating with different amines under neat conditions afforded final pyridyl analogues **18** in 30−60% yields.

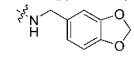
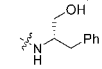
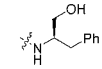
Results and Discussion

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 in this homolongated series either. Interestingly, the introduction of a polar hydroxylmethyl 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**.

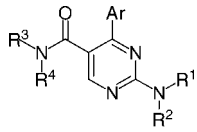
Table 1. Summary of SAR of Pyrimidine Analogues at the 2-Position

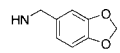
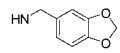
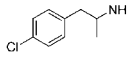
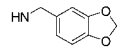


Compd	NR^1 R^2	FLIPR IC$_{50}$ (μM)[a]
1	NEtCH$_2$Ph	0.2
6a	NHCH$_2$CH$_2$CHMe$_2$	2.2
6b	NHCH$_2$Ph	0.73
6c	NMeCH$_2$Ph	0.47
6d	NHCH$_2$(2-Cl) Ph	4.9
6e	NHCH$_2$(2-Me) Ph	10
6f	NHCH$_2$(3-Cl) Ph	0.07
6g	NHCH$_2$(4-OMe) Ph	3.1
6h	NHCH$_2$(3-OMe) Ph	0.34
6i		0.15
6j	NHCH$_2$(2-)Py	>30
6k	NHCH$_2$(3-)Py	>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%.

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



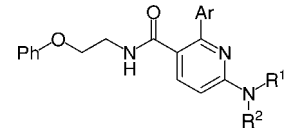
Compd	NR^3R^4	Ar	NR^1R^2	IC_{50} (μM)[a]
1		3,4,5-triMeOPh	NEtBn	0.2
11a		Ph	NEtBn	>30
11b		c-Hex.	NEtBn	>30
11c		3,4,5-triMeOPh	NEtBn	>30
11d		3,4,5-triMeOPh	NEtBn	2.1
11e		3,4,5-triMeOPh	NEtBn	1.8
11f		2-MeOPh	NMeBn	>30
11g		3-MeOPh	NMeBn	>30
11h		4-MeOPh	NMeBn	>30
11i		4-CF_3Ph	NMeBn	18.9
11j		3,4-diMeOPh	NMeBn	6.9
11k		3,5-diMeOPh	NMeBn	>30
11l			NEtBn	0.36
11m				0.22
11n				0.36
11o				0.15

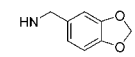
[a] Average of two or more runs. Standard deviation of assay is less than ±10%.

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-methylenedioxanebenzylamino) 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 showed similar or slightly improved potency compared with the corresponding pyrimidine compounds with the exception of **18b**, with **18f** being the most potent analogue (IC_{50} = 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 (IC_{50} = 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.

Table 3. Summary of in Vitro Potency of Pyridine Analogues



Compd	Ar	NR^1R^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%.

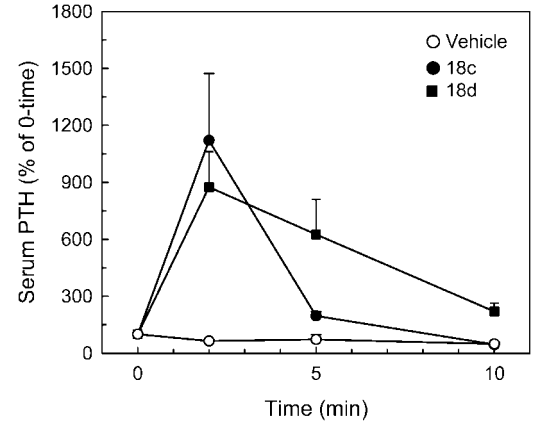


Figure 2. In vivo activity of **18c** and **18d**.

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 Dharmpal 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.

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