Exploration of Novel 2-Alkylimino-1,3-thiazolines: T-Type Calcium Channel Inhibitory Activity

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We have developed combinatorial libraries of new 2-alkylimino-1,3-thiazolines with four diversity points, consisting of more than 500 compounds, in a parallel synthetic fashion. The synthetic strategy was based on the construction of a large library aimed at the discovery of new compounds with T-type calcium channel inhibitory activity through structure modifications of hit compound **2**. The syntheses of the compounds of Chemset A with four diversity points were accomplished by the condensation of thioureas **5** with α-haloketones **6**{*1*−*66*} having two diversity points each. A library of phthalimidyl 1,3-thiazolines **24** was synthesized to provide Chemset B, which allowed the introduction of other diversity points through the nucleophilic character of the amino nitrogen. A sublibrary, Chemset C, was constructed from the libraries of Chemset A and Chemset B by functionalization of the C-4 position of the 1,3-thiazoline ring. The products containing ester or acid groups at the C-4 position of the 1,3-thiazoline ring were used in amide synthesis to give a new sublibrary within Chemset C. Deprotection of the phthalimidyl moiety of **24** followed by the reaction with benzoyl chloride gave the corresponding sublibrary in Chemset C. Another sublibrary which includes secondary amino derivatives was obtained by reduction of the amide moiety or reductive amination of **23** with phenyl aldehyde. The selected compounds from the generated libraries were evaluated with respect to inhibition of T-type calcium channels, where some of them have exhibited promising activity.

Introduction

Combinatorial chemistry serves as a powerful tool in lead discovery and lead optimization by allowing rapid generation of potential candidates for screening. Introduction of high-throughput biological screening has increased the demand for the preparation of large numbers of compounds. Among the broad range of templates, heterocyclic scaffolds represent the most promising molecules as leading structures for the discovery of novel synthetic drugs. In particular, 2-imino-1,3-thiazoline derivatives have been the focus of great interest because of their remarkable biological properties. For instance, β-turn mimic 2-acylimino-1,3-thiazolines exhibited GPIIb/IIIa antagonist activities[1] and 3-hydroxy-1,3-thiazolines exhibited PHD2 antagonistic activitiy.[2] This scaffold has received more attention recently as a potent CB2 cannabinoid receptor agonist[3,4] and KCNQ2/Q3 agonist for treatment of neuropathic pain.[5]

Calcium channels play a number of critical roles in nervous system function, including controlling pacemaker activities in the heart, sleep, hormone secretion, mechanosensation, and epilepsy.[6] Low-voltage-activated calcium channels were classified as T-type, defined by activation at low membrane potentials. While several classes of T-type calcium channel blockers, including mibefradil (withdrawn from the market because of the toxicity induced by drug−drug interaction),[7] amiloride,[8] diphenylpiperidine derivatives,[9] succinimide derivatives,[10] fluoxetine, NNC 55-0396,[11] 3,4-dihydroquinazolines,[12] and dioxoquinazoline carboxamides, were reported, there is no subtype-specific drug yet available. The development of an antagonist that acts selectively on T-type calcium channels would be a key in understanding its function in many physiological processes.[13]

To identify new small molecule blockers against T-type calcium channels, we screened a limited set of selected compounds from our in-house indigenous chemical library. The compounds were evaluated against HEK293 cells which stably express both T-type calcium channel $Ca_V3.1$ with an a_1G subunit and potassium channel Kir2.1. Primary screening was conducted with an FDSS6000 assay system which was developed for high-throughput screening. From the primary screening, we identified 2-cyclohexylimino-1,3-thiazolines **2** which showed 54% inhibitory activity at a concentration of 10 μM, while the phenylimino-1,3-thiazolines **1** showed much weaker activity (−8 to 36%) at the same concentration (Figure 1).[14] With these initial data, we decided to synthesize analogues of compound **2** for lead optimization.

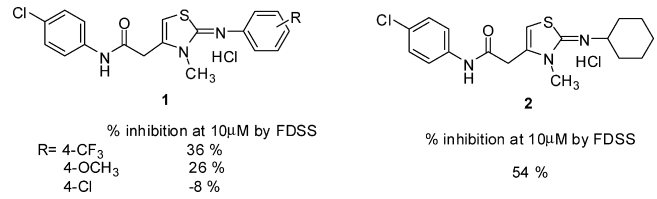

Figure 1. T-Type Ca^{2+} channel inhibitory activity of 2-imino-1,3-thiazolines.

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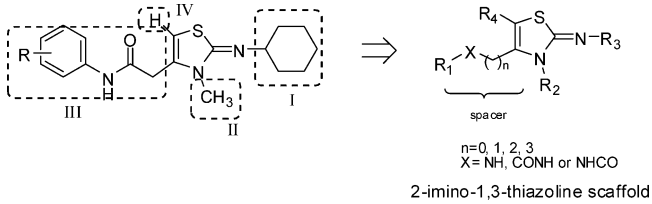


Figure 2. Fragment analysis of the structure of 2-cyclohexylimino-1,3-thiazoline and targeted libraries of the analogues of the scaffold 2-imino-1,3-thiazoline.

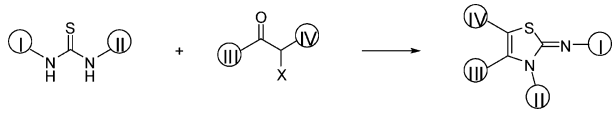


Figure 3. 2-Imino-1,3-thiazoline core with four diversity points.

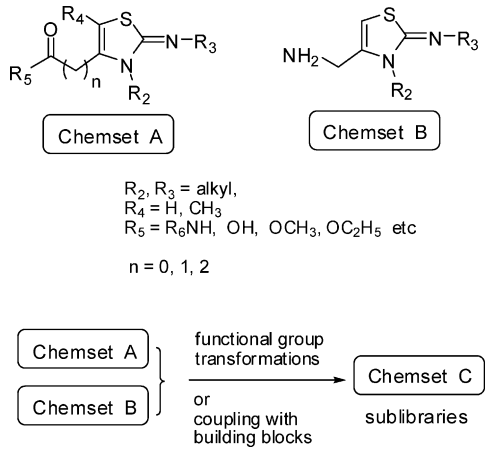


Figure 4. Chemset A and Chemset B as key compounds for lead optimization and Chemset C sublibraries thereof.

Results and Discussion

Compound Design and Strategy. Considering the structures and activities of compounds **1** and **2** (see Figure 1), one could speculate that the substituent at the 2-imino moiety would play a critical role in their biological activities. Therefore, we elaborated a strategy for the construction of a focused chemical library of alkyl (or cycloalkyl) substituents at the imino nitrogen (R_3) on the 2-imino-1,3-thiazolines. To increase the chemical diversity at the 2-cyclohexylimino-1,3-thiazoline nucleus using combinatorial strategies, we planned to modify the four points (I−IV) shown in Figure 2. It seems that the spacer from R_1 to the core of 2-imino-1,3-thiazoline plays an important role in the activity.

The synthetic strategy for the preparation of the core structure 2-alkylimino-1,3-thiazolines with four diversity points was based on condensations of α-haloketones with thioureas (Figure 3).[14] Reactions of thioureas **3** and α-haloketones **4** with two diversity points in each afforded 2-imino-1,3-thiazolines bearing four diversity points (I−IV) in one molecule.

We hypothesized that our previously described construction of the 2-alkylimino-1,3-thiazoline core structure[14] should readily afford a library of Chemset A and Chemset B (Figure 4). Also, numerous analogues of the libraries should be readily prepared through various coupling reactions with a suitable building block collection and subsequent functionalization at the C-4 position of the 1,3-thiazoline core to give sublibrary C. In the case of Chemset B, the nucleophilic character of the nitrogen of the 4-amino moiety would allow the diversity of the library to afford an additional sublibrary within Chemset C.

Syntheses of Building Blocks 3{*1*−*20*} and 4{*1*−*66*}. The building blocks thioureas **3** and α-haloketones **4** used in this study are listed in Figures 5 and 6, respectively. The building blocks thioureas **3** were easily prepared in quantitative yields by the reaction of the commercially available primary amines with isothiocyanates in refluxing ethanol.

The other building blocks, γ-chloroacetoacetanilide derivatives **4**{*1*−*47*}, were prepared by the previously reported method.[14] The preparation of α-haloketones is summarized in Scheme 1. New γ-chloroacetoacetamides **4**{*48*−*61*} were prepared in 25−82% yields (see the Supporting Information

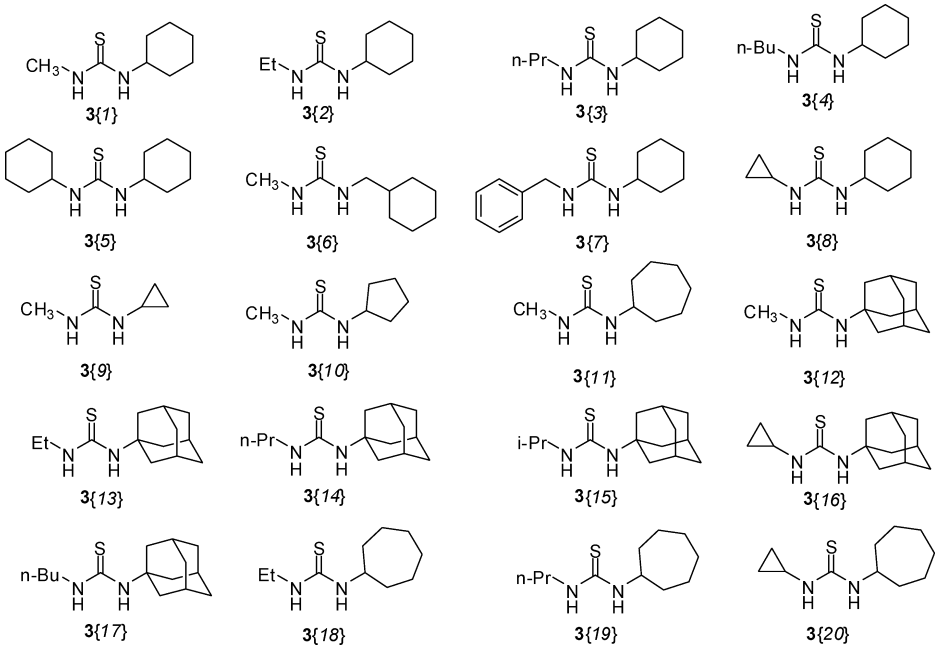


Figure 5. Thiourea building blocks **3**{*1*−*20*} used in this study.

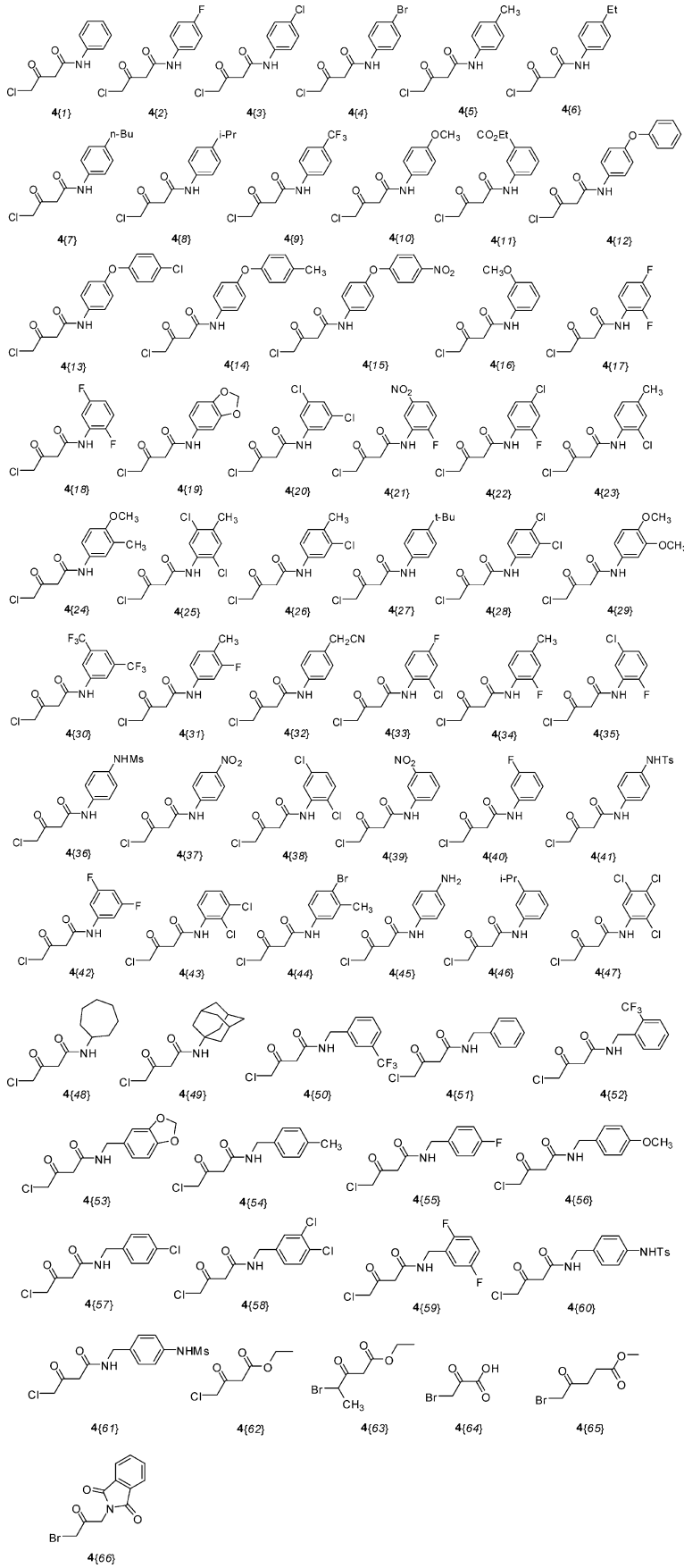
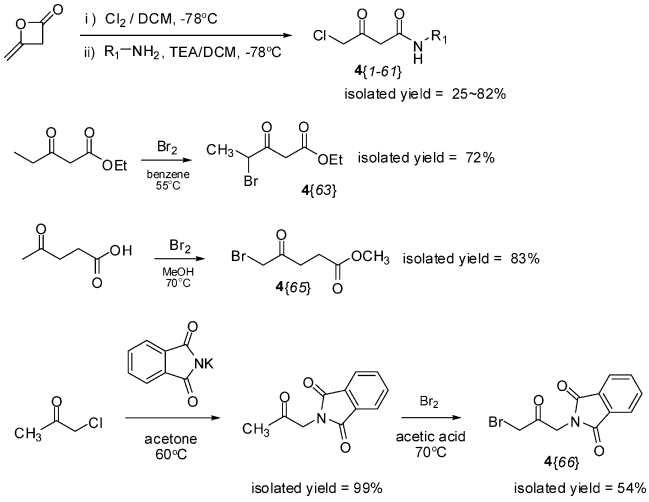


Figure 6. γ-Chloroacetoacetamides and α-haloketone building blocks **4**{*1*−*66*} used in this study.

for the yields and melting points) by dropwise addition of either aliphatic amines or benzylamine derivatives to a −78 °C solution of γ-chloroacetoacetyl chloride (1.1 molar equiv) in methylene chloride in the presence of triethylamine (1.1 molar equiv) (Scheme 1). These solid products were isolated by simple filtration and were used for the subsequent

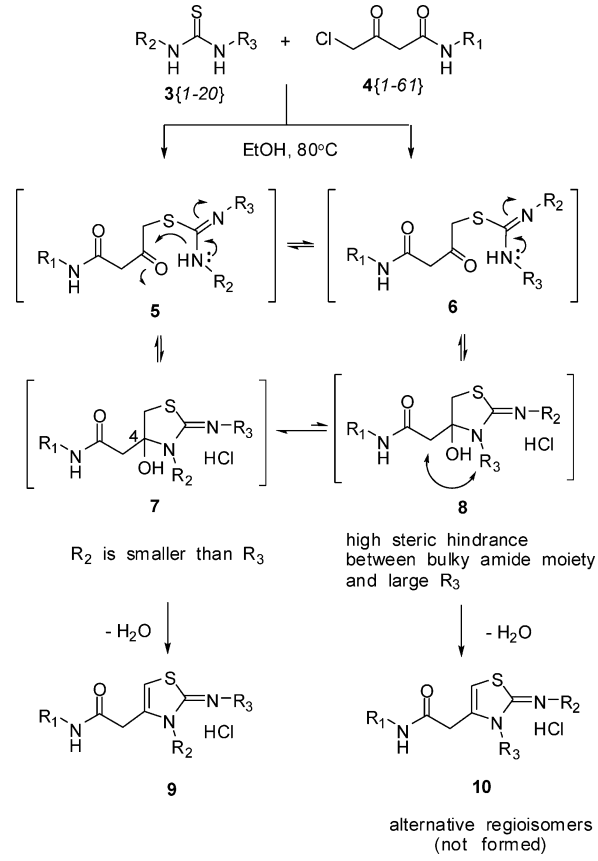
Scheme 1. Preparation of the Building Blocks α-Haloketones **4** Used in This Study



reactions without further purification. The structures of the new derivatives **4**{*47*−*61*} were confirmed by their ^{1}H NMR spectroscopy. Building blocks **4**{*62,64*} are commercially available, and building blocks **4**{*63,65,66*} were prepared by bromination of the corresponding ketones (see the Experimental Section for the reaction conditions).[15]

Syntheses of Chemset A. A synthetic route to 2-alkylimino-1,3-thiazoline-4-acetamide derivatives **9** by a parallel combinatorial method is shown in Scheme 2. The reaction of the prepared building block γ-chloroacetoacetamides **4**{*1*−*61*} with thioureas **3**{*1*−*20*} in refluxing ethanol gave the corresponding 2-alkylimino-1,3-thiazoline-4-acetamides in quantitative yields. With regard to the regiochemistry of the product, there are two regioisomers (**9** or **10**) depending on the spatial arrangement of the two substituents (R_2 and R_3) at the 1,3-thiazoline scaffold. The Hantzsch thiazole synthesis from the condensation of α-haloketones with mono-N-substituted thioamides produced 2-aminothiazoles and/or 2-iminothiazolines depending on the acidity of the reaction medium.[16] In case of the reaction of α-haloketones with N,N-disubstituted thioureas to form 2-imino-1,3-thiazoline, the regiochemistry of the product is likely dependent on the relative bulkiness of the two substituents at thiourea nitrogens. Presumably, the steric repulsion between the bulky amide group at C-4 and the substituent at C-3 of the intermediate 1,3-thiazolidine would be a critical factor that affects the regiochemistry of the product. Thus, the reaction of **4** with thioureas **3** provides initially either imino sulfide **5** or **6**, by attack of the sulfur in thiourea on the carbon neighboring chlorine. Intermediates **5**−**8** are in equilibrium as shown in Scheme 2. When R_2 is smaller than R_3, **7** is a more favorable conformation than **8**, because of the possible steric repulsion between the bulky amide group at C-4 ($R_1NHCOCH_2$) and R_3 of the 1,3-thiazolidine scaffold in conformation **8**. Accordingly, we concluded that the structures of the resulting 2-alkylimino-1,3-thiazoline derivatives would contain the bulkier group at the imino nitrogen and the smaller group at the C-3 nitrogen. For example, the reaction of γ-chloroacetoacetanilide(*p*-phenoxy) **4**{*12*} with *N*-cyclopropyl-*N*′-adamantylthiourea **3**{*16*} afforded the corresponding 2-imino-1,3-thiazoline **9**{*16,12*} in which the

Scheme 2. Synthetic Route of 2-Imino-1,3-thiazolines and Regiochemistry



bulky adamantyl group was substituted at the imino nitrogen and the smaller cyclopropyl group was substituted at C-3 of the 1,3-thiazolidine scaffold. Further proof of the structure was established by means of an X-ray crystallographic analysis (Figure 7) of compound **9**{*16,12*} (see the Supporting Information for X-ray crystallographic analysis of additional compound **9**{*7,3*}).

After the completion of the reaction, the desired products, 2-alkylimino-1,3-thiazolines, were isolated by filtration from the reaction mixture. The obtained solids were the corresponding hydrogen chloride salts of 2-alkylimino-1,3-thiazolines, which could be used directly for T-type calcium channel inhibitory activity screening. We have constructed a library of 308 compounds in this manner using Carousel Reaction Stations in a parallel synthetic fashion without isolating intermediates **7**. The isolated yields ranged from 8 to 99% for the final step.

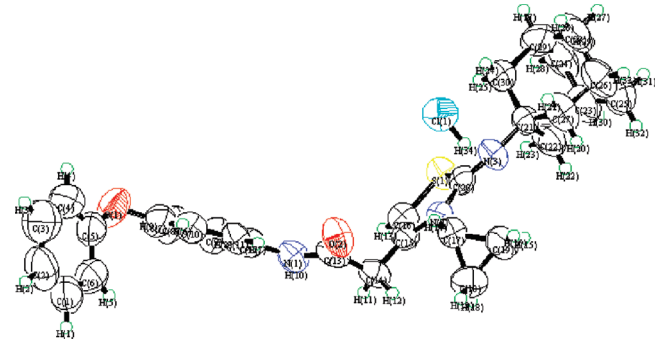
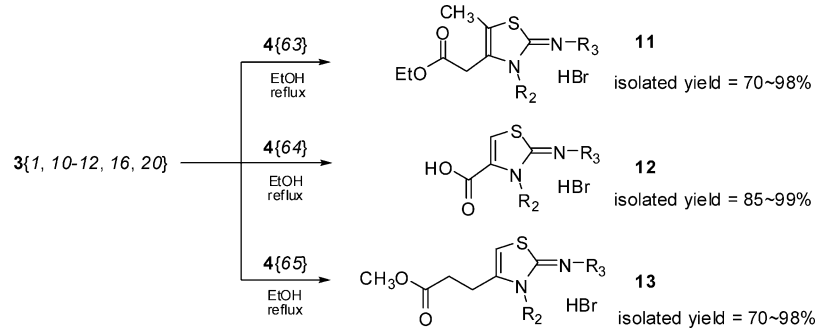


Figure 7. ORTEP plots of 2-adamantylimino-1,3-thiazoline **9**{*16,12*}.

Scheme 3. Preparation of 2-Imino-1,3-thiazoline Derivatives **11**−**13**



Along with the syntheses of 2-alkylimino-1,3-thiazoline-4-acetamides **9**, we prepared analogues **11**−**13** from the reaction of thioureas **5** with building blocks **6**{*63*−*65*} by the same method described above to give the corresponding 2-alkylimino-1,3-thiazolines **11**−**13** (Scheme 3).

Figure 8 provides representative structures of the prepared 2-alkylimino-1,3-thiazolines **9** and **11**−**13**, and Table 1 lists yields and HRMS data. The acid or ester functions in molecules **11**−**13** were further used for preparation of an amide library to increase the chemical diversity of the synthesized libraries. We synthesized nine compounds as key intermediates, which were used for the construction of additional sublibraries within Chemset C through various coupling reactions and subsequent functionalization at the C-4 position of the 1,3-thiazoline core. Figure 7 provides representative structures of the prepared 2-alkylimino-1,3-thiazolines of Chemset A, and Table 1 lists the yields and MS data.

Syntheses of Chemset B. To increase the diversity, we have synthesized 4-aminomethyl-1,3-thiazoline **15** (see Scheme 4), a key intermediate for the preparation of new 2-imino-1,3-thiazoline derivatives, by using the nucleophilic character of its 4-amino moiety. The reaction

Table 1. Yields, Purities, and Molecular Weights of Representative 2-Alkylimino-1,3-thiazoline-4-acetamides **9** and Their Analogues

entry	compound	yield[a]	MW (found)[b]	purity[c]
1	**9**{*1,30*}	80	466.13857 (MH^+)	89
2	**9**{*2,7*}	57	400.23989 (MH^+)	86
3	**9**{*3,12*}	80	450.21934 (MH^+)	85
4	**9**{*4,26*}	74	420.18538 (MH^+)	50
5	**9**{*5,6*}	80	426.25656 (MH^+)	100
6	**9**{*7,6*}	87	434.22686 (MH^+)	61
7	**9**{*9,12*}	84	380.14093 (MH^+)	100
8	**9**{*10,1*}	66	316.15252 (MH^+)	70
9	**9**{*11,12*}	86	436.20458 (MH^+)	88
10	**9**{*9,56*}	78	332.14342 (MH^+)	62
11	**9**{*12,7*}	76	438.25544 (MH^+)	98
12	**9**{*13,6*}	19	424.24122 (MH^+)	92
13	**9**{*16,8*}	74	450.25715 (MH^+)	96
14	**9**{*20,12*}	83	462.22103 (MH^+)	93
15	**9**{*12,48*}	69	402.25659 (MH^+)	87
16	**9**{*16,49*}	93	466.28870 (MH^+)	98
17	**9**{*14,62*}	96	363.21128[d] [$(M - Br)^+$]	88
19	**12**{*12,64*}	97	293.13328[d] [$(M - Br)^+$]	92

[a] Yields (percent) were calculated on the basis of the weight of the solid obtained by filtration of the reaction mixture. [b] Molecular ions were determined by mass spectrometry (ESI) after removal of the HCl salt by the treatment of triethylamine. [c] Purities (percent) were determined by HPLC at 210 nm. [d] Molecular ions were determined by mass spectrometry (ESI) without removal of the HX salt (X = Cl or Br).

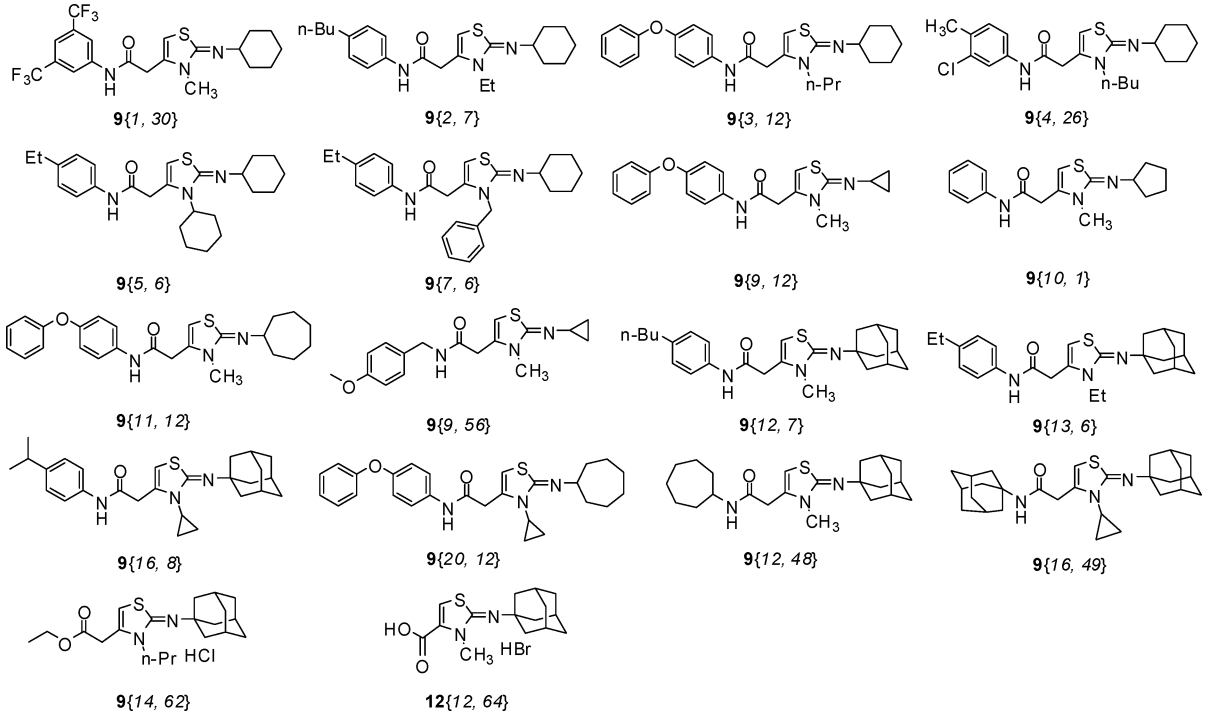


Figure 8. Representative structures of the prepared 2-alkylimino-1,3-thiazolines of Chemset A.

Scheme 4. Synthetic Route of 4-Aminomethyl-2-imino-1,3-thiazolines **15**

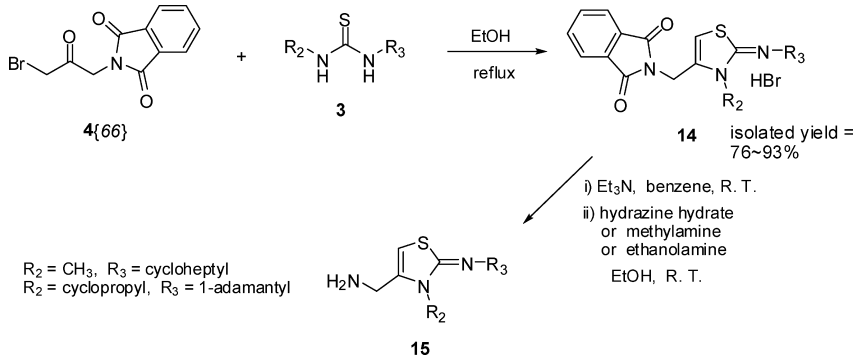


Table 2. Yields, Purities, and Molecular Weights of Representative Phthalimidyl 2-Imino-1,3-thiazolines **14**

entry	compound	yield[a]	MW (found)[b]	purity[c]
1	**14**{*1,66*}	90	356.14416 [(M − Br)$^+$]	84
2	**14**{*2,66*}	94	370.15966 [(M − Br)$^+$]	89
3	**14**{*3,66*}	83	384.17491 [(M − Br)$^+$]	82
4	**14**{*8,66*}	78	382.15853[d] (MH$^+$)	93
5	**14**{*11,66*}	87	370.15900 [(M − Br)$^+$]	76
6	**14**{*18,66*}	82	384.17586 [(M − Br)$^+$]	87
7	**14**{*19,66*}	78	398.19069 [(M − Br)$^+$]	90
8	**14**{*20,66*}	71	−[e]	81
9	**14**{*12,66*}	94	400.17383 [(M − Br)$^+$]	85
10	**14**{*13,66*}	81	422.18996 [(M − Br)$^+$]	87
11	**14**{*14,66*}	79	436.20564 [(M − Br)$^+$]	88
12	**14**{*16,66*}	79	434.18997 [(M − Br)$^+$]	87

[a] Yields (percent) were calculated on the basis of the weight of the solid obtained by filtration of the reaction mixture. [b] Molecular ions were determined by mass spectrometry (ESI) without removal of the HX salt (X = Cl or Br). [c] Purities (percent) were determined by HPLC at 210 nm. [d] The molecular ion was determined by mass spectrometry (ESI) after removal of the HBr salt by the treatment of triethylamine. [e] Molecular ion could not be obtained.

of **4**{*66*} with thiourea **3** in refluxing ethanol afforded 2-imino-1,3-thiazoline hydrogen bromide salt **14** in quantitative yield. We have synthesized a library of 12 compounds of phthalimidyl 1,3-thiazolines **14**, which were precursors of **15**.[17] Treatment of **14** with triethylamine in benzene followed by addition of hydrazine hydrate (or methylamine or ethanolamine) in ethanol at room temperature gave 4-aminomethyl-1,3-thiazoline **15** in moderate yields (42−65%). Product **15** was confirmed as a single compound by TLC (8:2 methanol/chloroform), and its structure was confirmed by the appearance of a broad singlet peak at 1.37 ppm with the disappearance of the multiplet peak at 7.70−7.90 ppm, which corresponds to the phthalimidyl protons, in the ^{1}H NMR spectrum. Since 4-aminomethyl-1,3-thiazoline **15** was unstable at room temperature, it was used for the subsequent reaction without purification. Figure 9 provides representative structures of the prepared phthalimidyl 1,3-thiazolines, Chemset B, and Table 2 lists the yields and HRMS data.

Syntheses of Sublibrary Chemset C. Lead optimization involves structural modifications of a hit compound to lead compound that has demonstrated desired biological or pharmacological activities, often using an in vivo and in vitro assay system. We synthesized **11**−**13** as shown in Scheme 3 along with the library of 300 compounds of 2-alkylimino-1,3-thiazoline-4-acetamides **9**. The acid or ester functions in molecules **11**−**13** were used for the preparation of an amide library to increase the chemical diversity of the synthesized libraries. Intermediate ethyl ester **11** and methyl ester **13** were transformed into the corresponding acids **16** and **17**, respectively, via hydrolysis with an aqueous potassium hydroxide solution at ambient temperature in ∼70% yield (Scheme 5). An interesting phenomenon was observed for hydrolysis of **11**. Refluxing of **11** in an aqueous potassium hydroxide solution gave 4,5-dimethyl-2-cyclohexylimino-1,3-thiazoline, presumably resulting from further decarboxylation of **16** (see the

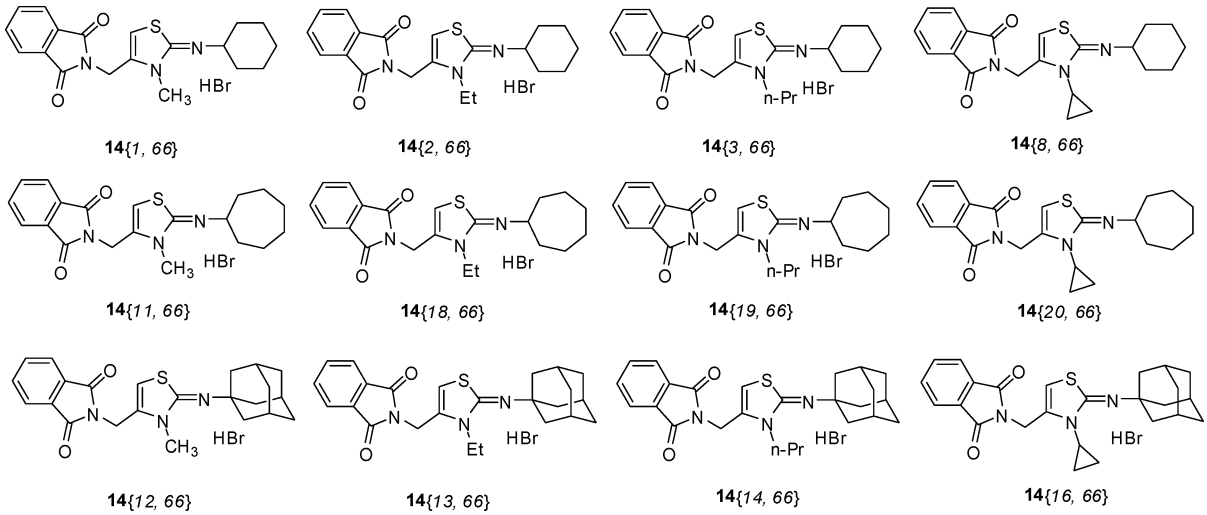
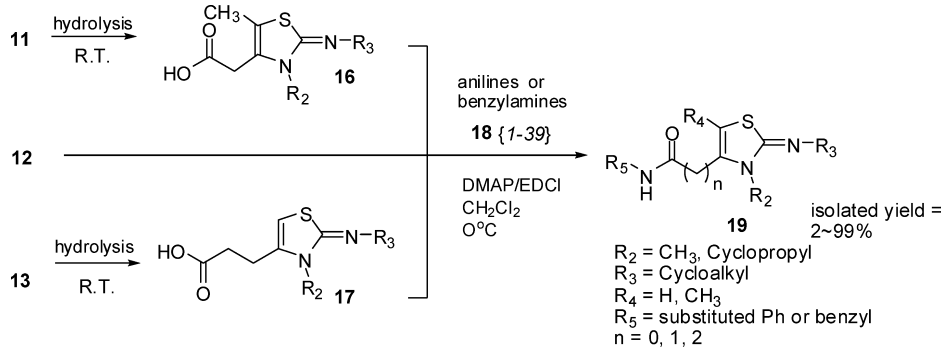


Figure 9. Representative structures of the prepared phthalimidyl 2-imino-1,3-thiazolines **14** of Chemset B.

Scheme 5. Preparation of Amide Compounds for Increasing the Chemical Diversity of the Library



Supporting Information). Successful results were obtained when the hydrolysis reaction conducted for a short reaction time at room temperature (2 h) afforded **16** and **17** in 65−75% yield. The amide coupling of carboxylic acids **12**, **16**, and **17** with either anilines or benzylamines was performed in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) as a condensing agent and *N*,*N*-dimethylaminopyridine (DMAP) in a methylene chloride solution at 0 °C to give corresponding amides **19**.[18] The used aniline or benzylamine **18** building blocks in these reactions are shown in Figure 10.

We have constructed a sublibrary of 80 compounds in this manner using Carousel Reaction Stations in a parallel synthetic fashion. The structures of compounds **19** were confirmed by ^{1}H NMR spectroscopy. The yields obtained ranged from 15 to 99% for the final step. Figure 11 provides representative structures of the prepared 2-alkylimino-1,3-thiazolines **19**, and Table 3 lists yields and HRMS data.

The next approach to increasing the diversity of the library involved reduction of the amide moiety of prepared compounds **9** and **19**. Generally, hydrogen bonds affect drug−target interactions in biological systems.[19] Nitrogen and oxygen are the most common atoms involved as hydrogen bond acceptors. The nitrogen atom of an aliphatic tertiary amine is a better hydrogen bond acceptor than that of an amide.[20] In the latter cases, the lone pair of the nitrogen can interact with neighboring π systems to form various resonance structures, resulting in a nitrogen that is less likely to participate in hydrogen bonding. For this reason, we transformed the amide moiety to the secondary amine by reduction (Scheme 6). Reduction of compounds **9** and **19** with lithium aluminum hydride (LAH) in refluxing tetrahydrofuran afforded corresponding secondary amine **20** smoothly in moderate to high yield (11−82%). We have constructed a sublibrary of 76 compounds in this manner using Carousel Reaction Stations in a parallel synthetic fashion. Figure 11 provides representative structures of the prepared 2-alky-

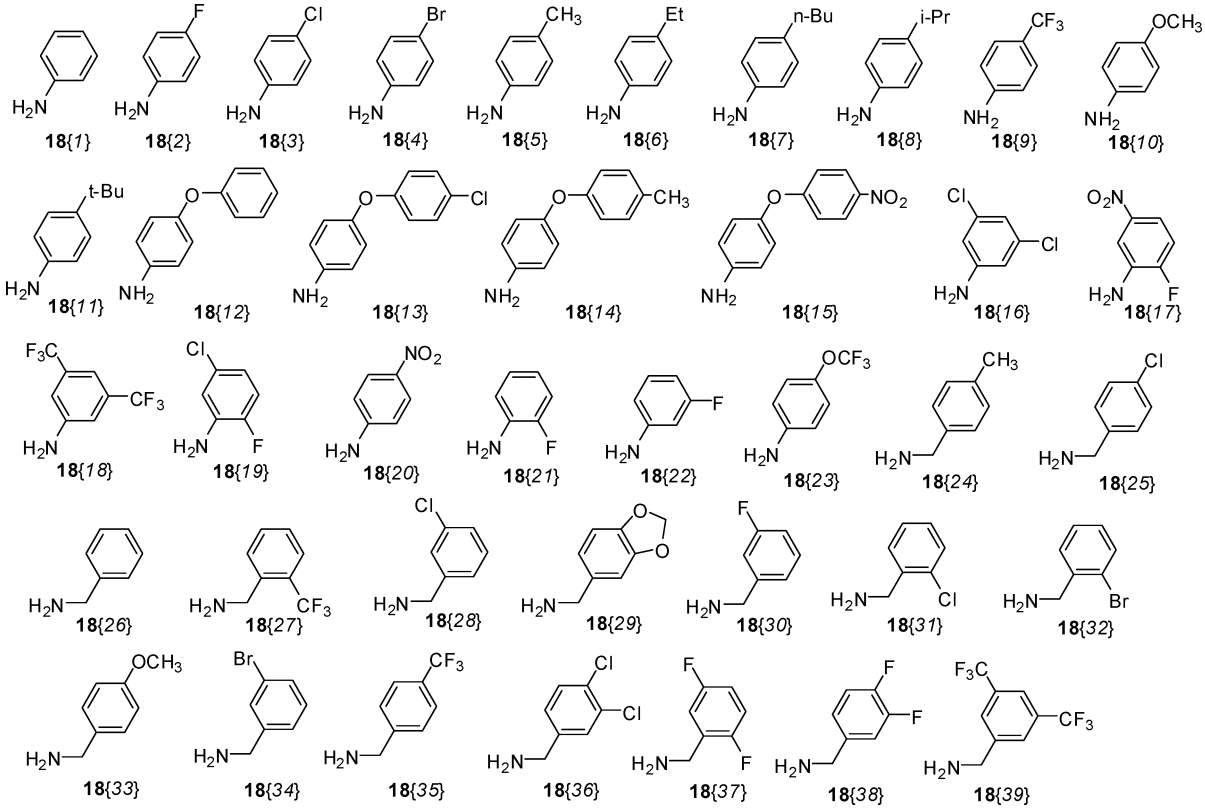


Figure 10. Building blocks anilines or benzylamines **18**{*1*−*39*} used in the reactions.

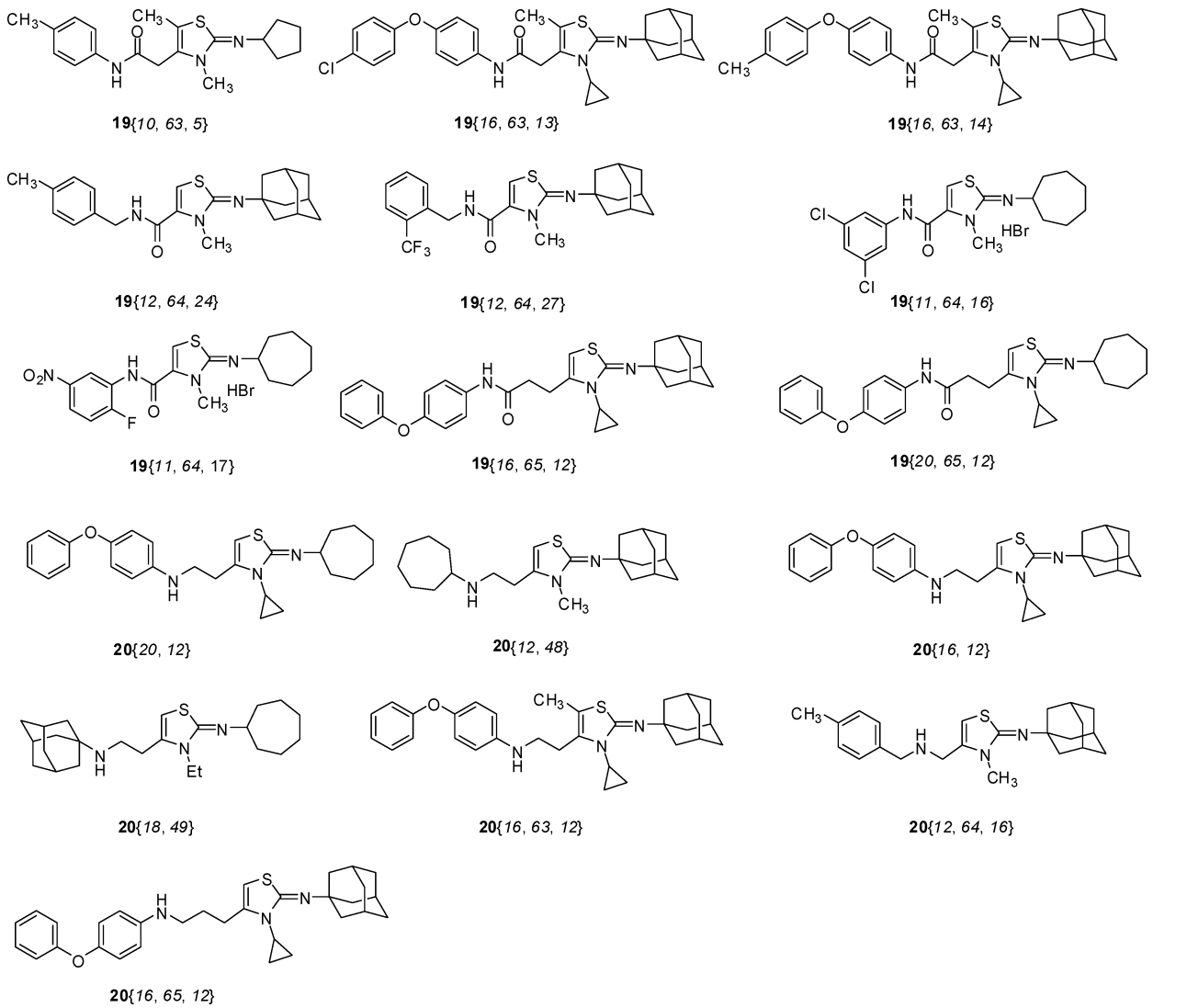


Figure 11. Representative structures of the prepared 2-alkylimino-1,3-thiazolines of 2-alkylimino-1,3-thiazolines **19** and **20**.

Table 3. Yields, Purities, and Molecular Weights of Representative 2-Alkylimino-1,3-thiazolines **19**

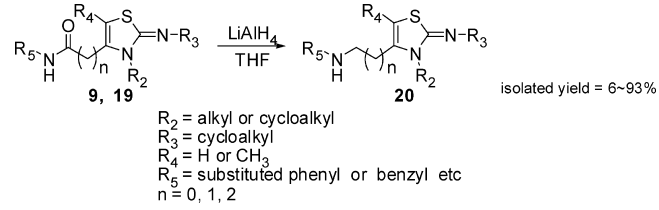
entry	compound	*n*	yield[a]	MW (found)[b]	purity[c]
1	**19**{*10,63,5*}	1	66	344.18017 (MH^+)	82
2	**19**{*16,63,13*}	1	60	548.21405 (MH^+)	97
3	**19**{*16,63,14*}	1	51	528.26872 (MH^+)	90
4	**19**{*12,64,24*}	0	32	396.21038 (MH^+)	98
5	**19**{*12,64,27*}	0	42	450.18335 (MH^+)	95
6	**19**{*11,64,16*}	0	83	398.08522[d] [$(M - Br)^+$]	98
7	**19**{*11,64,17*}	0	49	393.13904[d] [$(M - Br)^+$]	75
8	**19**{*16,65,12*}	2	28	514.25467 (MH^+)	88
9	**19**{*20,65,12*}	2	21	476.23763 (MH^+)	89

[a] Yields (percent) were calculated on the basis of the weight of the solid obtained by filtration of the reaction mixture. [b] Molecular ions were determined by mass spectrometry (ESI) after removal of the HCl salt by the treatment of triethylamine. [c] Purities (percent) were determined by HPLC at 210 nm. [d] Molecular ions were determined by mass spectrometry (ESI) without removal of the HX salt (X = Cl or Br).

limino-1,3-thiazolines-4-ethylamine **20**, and Table 4 lists yields and HRMS data.

The third synthetic approach for expanding the library was the functionalization of the side chains starting with 2-aminomethyl-1,3-thiazolines **15**. After deprotection of the phthalimimdyl moiety, the amino function of **15** was used for

Scheme 6. Reduction of the Amide Moiety to Amine, Resulting in an Increase in Diversity



the preparation of amides and secondary amines through coupling with acyl chlorides and reductive amination (Scheme 7).[21]

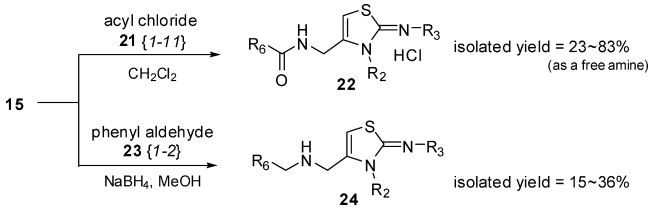
Treatment of **15** with acyl chlorides **21**{*1*−*11*} gave the corresponding 1,3-thiazolines **22**. Since the structures of these compounds have NH and CO moieties in positions analogous to the positions of those in **9** (see Scheme 1), the comparison of the biological activities of both compounds **9** and **22** would contribute to the elucidation of the structure−activity relationship of these series. To further increase the versatility using intermediate **15**, another reaction was employed through reductive amination, to generate secondary amines **24** by the reaction with phenyl aldehydes **23**{*1,2*} in the presence of sodium borohydride in methanol. The acyl

Table 4. Yields, Purities, and Molecular Weights of Representative 2-Alkylimino-1,3-thiazolines **20**

entry	compound	*n*	yield[a]	MW (found)[b]	purity[c]
1	**20**{*20,12*}	1	78	448.24123 (MH^+)	99
2	**20**{*16,12*}	1	59	486.25703 (MH^+)	99
3	**20**{*12,48*}	1	32	388.27852 (MH^+)	–[d]
4	**20**{*18,49*}	1	39	402.29360 (MH^+)	–[d]
5	**20**{*16,63,12*}	1	93	500.27359 (MH^+)	88
6	**20**{*12,64,16*}	0	75	382.23022 (MH^+)	67
7	**20**{*16,65,12*}	2	43	500.27316 (MH^+)	98

[a] Yields (percent) were calculated on the basis of the weight of the solid obtained by filtration of the reaction mixture. [b] Molecular ions (MH^+) were determined by mass spectrometry (ESI) after removal of the HCl salt by the treatment of triethylamine. [c] Purities (percent) were determined by HPLC at 210 nm. [d] The purity could not be determined due to a lack of the sample.

Scheme 7. Preparation of Sublibraries **22** and **24** from Aminomethyl-1,3-thiazolines



chloride and phenyl aldehyde building blocks used in this study are shown in Figure 12.

We constructed a library of 35 compounds in this manner using Carousel Reaction Stations in a parallel synthetic fashion. Figure 13 provides representative structures of the prepared 2-imino-1,3-thiazolines, and Table 5 lists yields and MS data.

Biological Screening

The biological activities of the synthesized compounds were evaluated against HEK293 cells which stably express both T-type calcium channel $Ca_v3.1$ with an a_{1G} subunit and potassium channel Kir2.1. The percent inhibition of the Ca^{2+} current was measured at certain molar concentrations of the synthesized compounds. For this purpose, two assay methods were employed: FDSS6000 assay and patch-clamp assay using a single cell. The FDSS6000 assay is developed for high-throughput screening and applied to the whole small molecule library. The patch-clamp assay is more accurate and sensitive but measures Ca^{2+} current one by one. All the synthesized compounds were first screened by the FDSS6000 assay, and selected compounds with potent activity were further screened by the patch-clamp assay, yielding IC_{50} values.[22]

Primary screening results of the FDSS6000 assay system and IC_{50} values from the patch-clamp assay of a portion of the synthesized compounds are summarized in Table 6.

In summary, combinatorial libraries of new 2-alkylimino-1,3-thiazolines with four diversity points consisting of more than 500 compounds were constructed in a parallel synthetic fashion. The synthetic strategy was a lead optimization method of compounds with T-type calcium channel inhibitory activity, designed through structural modifications of hit compound **2**. The compounds of Chemset A were synthesized by the condensation of thioureas **5** with α-haloketones **6**{*1*−*66*}. The libraries included intermediates 4-aminomethyl-1,3-thiazoline **15** and 1,3-thiazolinecarboxylic acids **12**, **16**, and **17**, which gave sublibrary C through various coupling reactions with suitable building block collection and subsequent functionalization at the C-4 position of the 1,3-thiazoline core. The selected compounds from the generated library were evaluated against a T-type calcium channel, and some of them have exhibited promising inhibitory activity.

Experimental Section

Synthesis of Thiourea 3 (general procedure). To a solution of isothiocyanate (1.5 mmol) in ethanol (5 mL) was added amine (1.5 mmol), and the mixture was stirred at room temperature for 12 h. The reaction mixture was cooled to room temperature, and the precipitates were filtered, washed with cold ethyl ether, and then dried in air to afford the corresponding alkylthiourea.

Synthesis of γ-Chloroacetoacetanilide 4{*1*−*61*} (general procedure). To a solution of distilled diketene (49 mmol) in dried methylene chloride (50 mL) at −78 °C under a dry ice/acetone cooling bath was added slowly a solution of chlorine in dried methylene chloride (100 mL). The reaction mixture was stirred for 30 min at the same

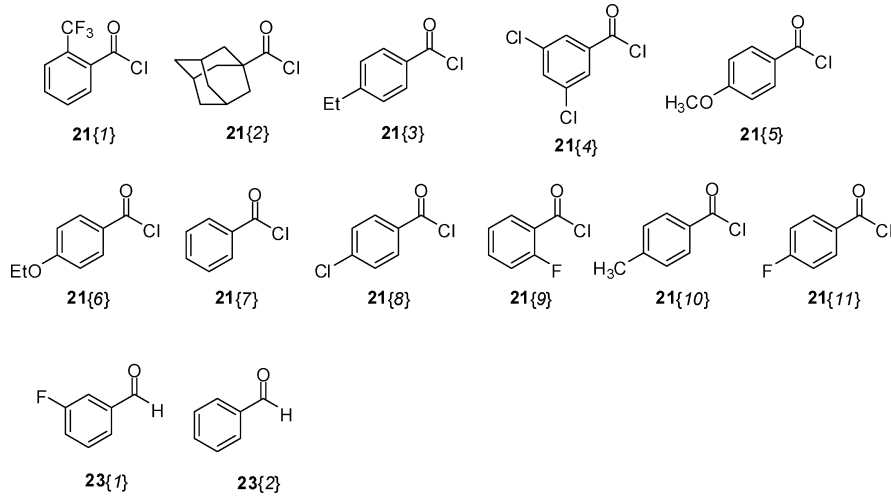


Figure 12. Building blocks acyl chlorides **21**{*1*−*11*} and phenyl aldehydes **23**{*1,2*} used in the reactions.

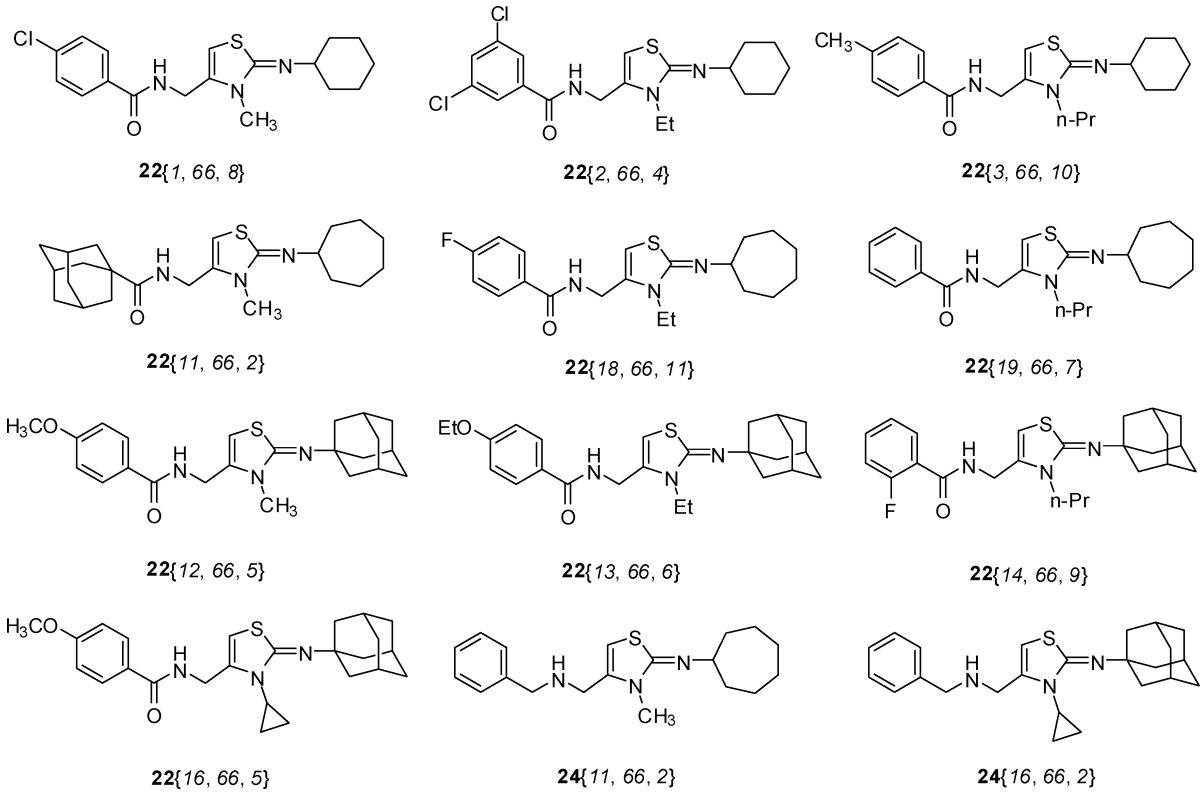


Figure 13. Representative structures of the prepared 2-alkylimino-1,3-thiazolines of 2-alkylimino-1,3-thiazolines **22** and **24**.

Table 5. Yields, Purities, and Molecular Weights of Representative 2-Alkylimino-1,3-thiazolines **21** and **23**

entry	compound	yield[a]	MW (found)[b]	purity[c]
1	**22**{*1,66,8*}	47	364.12450 (MH^+)	73
2	**22**{*2,66,4*}	35	412.10069 (MH^+)	94
3	**22**{*3,66,10*}	43	372.21219 (MH^+)	86
4	**22**{*11,66,2*}	57	402.25788 (MH^+)	86
5	**22**{*18,66,11*}	62	376.18616 (MH^+)	78
6	**22**{*19,66,7*}	63	372.21120 (MH^+)	95
7	**22**{*12,66,5*}	62	412.20572 (MH^+)	81
8	**22**{*13,66,6*}	49	440.23710 (MH^+)	90
9	**22**{*14,66,9*}	59	428.21689 (MH^+)	100
10	**22**{*16,66,5*}	64	438.22170 (MH^+)	95
11	**24**{*11,66,2*}	21	—[d]	—[e]
12	**24**{*16,66,2*}	29	—[d]	—[e]

[a] Yields (percent) were calculated on the basis of the weight of the solid obtained by filtration of the reaction mixture. [b] Molecular ions (MH^+) were determined by mass spectrometry (ESI) after removal of the HCl salt by the treatment of triethylamine. [c] Purities (percent) were determined by HPLC at 210 nm. [d] Molecular ion could not be obtained. [e] The purity could not be determined due to a lack of the sample.

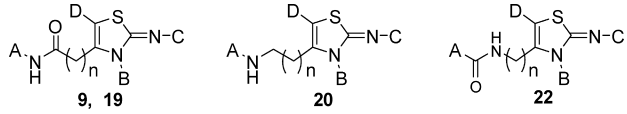
temperature. To the reaction mixture was added dropwise a mixture of triethylamine (0.75 mL, 54 mmol) and the appropriate amine or aniline (49 mmol) dissolved in methylene chloride (100 mL) cooled to −78 °C under an acetone/dry ice cooling bath. The rection mixture was stirred for 1 h at the same temperature and allowed to warm to room temperature. The mixture was then washed with a 0.1 N HCl solution, a saturated aqueous $NaHCO_3$ solution, and then H_2O. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The resulting solid was collected by filtration, washed with cold ethyl ether, and then dried in air to afford γ-chloroacetoacetanilide **4**{*1*−*61*} (25−82% yield).

Synthesis of Ethyl 4-Bromo-3-oxopentanoate 4{*63*}. To a stirred and heated (55 °C) solution of ethyl 3-oxopentanoate (23.0 g, 0.16 mol) dissolved in benzene (500 mL) under an oil bath was added a solution of Br_2 (8.24 mL, 0.16 mol) dissolved in benzene (200 mL) over 40 min, and stirring was continued for 30 min. The solvent was removed by evaporation to afford 4-bromo-3-oxopentanoate **4**{*63*} (light brown oil, 72% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.55 (q, 1H, J = 6.8 Hz, $\underline{CH}$Br), 4.20 (q, 2H, J = 7.1 Hz, $\underline{CH_2}CH_3$), 3.74 (q, 2H, J = 6.1 Hz, $\underline{CH_2}$), 1.76 (d, 3H, J = 6.8 Hz, BrCH$\underline{CH_3}$), 1.27 (t, 3H, J = 7.1 Hz, $CH_2\underline{CH_3}$).

Synthesis of Methyl 5-Bromo-4-oxopentanoate 4{*65*}. To a stirred and heated (70 °C) solution of 4-oxopentanoic acid (8.1 g, 70 mmol) dissolved in methanol (90 mL) was added a solution of Br_2 (3.6 mL, 70 mmol) dissolved in methanol (20 mL) over 10 min, and stirring was continued for 2 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was diluted with methylene chloride (50 mL) and washed with a saturated $NaHCO_3$ solution three times and then with water. The organic layer was dried with $MgSO_4$. The solvent was removed to afford methyl 5-bromo-4-oxopentanoate **4**{*65*} (light brown oil, 83% yield): ^{1}H NMR (400 MHz, CDCl3) δ 3.97 (s, 2H, $\underline{CH_2}$Br), 3.68 (s, 3H, $\underline{OCH_3}$), 2.97−2.94 (t, 2H, J = 6.6 Hz, $COCH_2\underline{CH_2}CO_2CH_3$), 2.67−2.65 (t, 2H, J = 6.2 Hz, $CO\underline{CH_2}CH_2CO_2CH_3$).

Synthesis of α-Bromo-α′-phthaimidyl Acetone 4{*66*}. To a mechanically stirred solution of chloroacetone (10.0 mL, 0.126 mol) dissolved in acetone (150 mL) was added phthalimide potassuium salt (25.5 g, 0.138 mol), and the

Table 6. Primary Screening Results and IC_{50} Values of a Portion of the Synthesized Compounds



entry	compound	*n*	A	B	C	D	% inhibition[a]	IC_{50}[b] (μM)
1	**9**{*1,5*}	1	C_6H_4(4-CH_3)	methyl	cyclohexyl	H	46	−
2	**9**{*3,9*}	1	C_6H_4(4-CF_3)	*n*-propyl	cyclohexyl	H	68	−
3	**9**{*8,7*}	1	C_6H_4(4-C_4H_9)	cyclopropyl	cyclohexyl	H	62	−
4	**9**{*18,12*}	1	C_6H_4(4-OC_6H_5)	ethyl	cycloheptyl	H	82	−
5	**9**{*20,12*}	1	C_6H_4(4-OC_6H_5)	cyclopropyl	cycloheptyl	H	81	−
6	**9**{*11,7*}	1	C_6H_4(4-C_4H_9)	methyl	cycloheptyl	H	75	−
7	**9**{*12,8*}	1	C_6H_4[4- $CH(CH_3)_2$]	methyl	1-adamantyl	H	73	0.05 ± 0.01
8	**9**{*12,12*}	1	C_6H_4(4-OC_6H_5)	methyl	1-adamantyl	H	77	0.92 ± 0.08
9	**9**{*12,5*}	1	C_6H_4(4-CH_3)	methyl	1-adamantyl	H	61	1.17 ± 0.08
10	**9**{*12,2*}	1	C_6H_4(4-F)	methyl	1-adamantyl	H	74	0.77 ± 0.03
11	**9**{*12,4*}	1	C_6H_4(4-Br)	methyl	1-adamantyl	H	69	0.61 ± 0.07
12	**9**{*16,8*}	1	C_6H_4[4-$CH(CH_3)_2$]	cyclopropyl	1-adamantyl	H	75	0.31 ± 0.02
13	**9**{*16,7*}	1	C_6H_4(4-C_4H_9)	cyclopropyl	1-adamantyl	H	82	0.19 ± 0.02
14	**9**{*16,12*}	1	C_6H_4(4-OC_6H_5)	cyclopropyl	1-adamantyl	H	83	0.43 ± 0.07
15	**9**{*14,2*}	1	C_6H_4(4-F)	*n*-propyl	1-adamantyl	H	73	0.60 ± 0.04
16	**9**{*14,6*}	1	C_6H_4(4-C_2H_5)	*n*-propyl	1-adamantyl	H	76	0.30 ± 0.01
17	**9**{*13,6*}	1	C_6H_4(4-C_2H_5)	ethyl	1-adamantyl	H	75	0.35 ± 0.01
18	**19**{*16,63,12*}	1	C_6H_4(4-OC_6H_5)	cyclopropyl	1-adamantyl	CH_3	76	−
19	**19**{*12,63,14*}	1	C_6H_4[4-OC_6H_4(4-CH_3)]	methyl	1-adamantyl	CH_3	51	−
20	**19**{*12,63,13*}	1	C_6H_4[4-OC_6H_4(4-Cl)]	methyl	1-adamantyl	CH_3	60	−
21	**19**{*12,64,35*}	0	$CH_2C_6H_4$(4-CF_3)	methyl	1-adamantyl	H	72	0.14 ± 0.02
22	**19**{*12,64,28*}	0	$CH_2C_6H_4$(3-Cl)	methyl	1-adamantyl	H	78	0.16 ± 0.02
23	**19**{*12,64,27*}	0	$CH_2C_6H_4$(2-CF_3)	methyl	1-adamantyl	H	63	0.37 ± 0.04
24	**19**{*16,65,12*}	2	$CH_2C_6H_4$(4-OC_6H_5)	cyclopropyl	1-adamantyl	H	73	−
25	**19**{*16,65,14*}	2	C_6H_4[4-OC_6H_4(4-CH_3)]	cyclopropyl	1-adamantyl	H	68	−
26	**19**{*16,65,13*}	2	C_6H_4[4-OC_6H_4(4-Cl)]	cyclopropyl	1-adamantyl	H	60	−
27	**20**{*12,8*}	1	C_6H_4[4-$CH(CH_3)_2$]	methyl	1-adamantyl	H	25	0.72 ± 0.07
28	**20**{*12,12*}	1	C_6H_4(4-OC_6H_5)	methyl	1-adamantyl	H	64	0.60 ± 0.04
29	**20**{*12,5*}	1	C_6H_4(4-CH_3)	methyl	1-adamantyl	H	65	0.21 ± 0.05
30	**20**{*12,2*}	1	C_6H_4(4-F)	methyl	1-adamantyl	H	70	1.09 ± 0.81
31	**20**{*12,4*}	1	C_6H_4(4-Br)	methyl	1-adamantyl	H	65	0.38 ± 0.11
32	**20**{*16,8*}	1	C_6H_4[4-$CH(CH_3)_2$]	cyclopropyl	1-adamantyl	H	73	0.18 ± 0.06
33	**20**{*16,7*}	1	C_6H_4(4-C_4H_9)	cyclopropyl	1-adamantyl	H	69	1.53 ± 0.83
34	**20**{*16,12*}	1	C_6H_4(4-OC_6H_5)	cyclopropyl	1-adamantyl	H	77	0.31 ± 0.09
35	**20**{*14,2*}	1	C_6H_4(4-F)	*n*-propyl	1-adamantyl	H	77	0.43 ± 0.08
36	**20**{*14,6*}	1	C_6H_4(4-C_2H_5)	*n*-propyl	1-adamantyl	H	55	1.43 ± 0.38
37	**20**{*13,6*}	1	C_6H_4(4-C_2H_5)	ethyl	1-adamantyl	H	63	2.00 ± 0.67
38	**22**{*12,66,5*}	1	C_6H_4(4-OCH_3)	methyl	1-adamantyl	H	55	−
39	**22**{*13,66,4*}	1	C_6H_3(3,5-di-Cl)	ethyl	1-adamantyl	H	78	−
40	**22**{*16,66,5*}	1	C_6H_4(4-OCH_3)	cyclopropyl	1-adamantyl	H	53	−

[a] Percent inhibition values were obtained with the FDSS6000 assay system. [b] IC_{50} values were determined from the dose−response curve, obtained by the patch-clamp method.

mixture was heated to reflux over 20 h. The reaction mixture was cooled to room temperature, and the solvent was removed by evaporation. The residue was diluted with methylene chloride (200 mL), washed with water, and then dried with $MgSO_4$. The solvent was removed in vacuo, and the resulting solid was filtered, washed with cold ethyl ether, and then dried in air to afford α-phthaimidyl acetone as a white solid. To a stirred and heated (70 °C) solution of α-phthaimidyl acetone (1.01 g, 5 mmol) in acetic acid (20 mL) was added a solution of Br_2 (0.3 mL, 6 mmol) dissolved in acetic acid (5 mL) over 10 min. After the reaction mixture had been stirred for 1 h and cooled to room temperature, the solvent was removed under reduced pressure. The residue was diluted with methylene chloride (50 mL), washed with a saturated aqueous $NaHCO_3$ solution five times and water, and then dried with $MgSO_4$. The solvent was removed by evaporation, and the resulting solid was collected by filtration, washed with isopropyl ether, and then dried in air to afford 2-(3-bromo-2-oxopropyl)isoindoline-1,3-dione **4**{*66*} (white solid, 54% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.74 (m, 4H, *ArH*), 4.78 (s, 2H, N*CH*$_2$), 4.01 (s, 3H, *CH*$_2$Br).

Synthesis of 2-Alkylimino-1,3-thiazoline 9 (general procedure). The syntheses of 2-alkylimino-1,3-thiazoline **9** was accomplished using a parallel synthesizer Carousel 12-place reaction station (Radleys Discovery Technologies). To a solution of alkylthiourea **3** (0.01 mol) in ethanol (5 mL) was added γ-chloroacetoacetanilide **4**{*1*−*62*} (0.01 mol). The reaction mixture was heated to reflux for 12 h. The reaction mixture was cooled to room temperature, and the precipitates were filtered, washed with cold ethyl ether (or isopropyl ether), and then dried in air to afford **9** (solid, 8−99% yield).

Synthesis of 2-Alkylimino-1,3-thiazoline Ester 11 (general procedure). To a solution of ethyl 4-bromo-3-oxopentanoate **4**{*63*} (1.1 g, 5 mmol) dissolved in ethanol (40 mL) was added alkylthiourea **3** (5 mmol), and the mixture was heated to reflux over 5 h. The reaction mixture was cooled to room temperature, and the solvent was removed under

reduced pressure; the resulting solid was filtered, washed with cold ethyl ether (or isopropyl ether), and then dried in air to afford **11** (solid, 70−98% yield).

Synthesis of 2-Alkylimino-1,3-thiazoline Acid 12 (general procedure). To a solution of ethyl 3-bromopyruvic acid **4**{*64*} (1.01 g, 6 mmol) dissolved in ethanol (10 mL) was added alkylthiourea **3** (6 mmol), and the mixture was heated to reflux over 2 h. The reaction mixture was cooled to room temperature, and the solvent was removed by evaporation; the resulting solid was filtered, washed with cold ethyl ether (or isopropyl ether), and then dried in air to afford **12** (solid, 85−99% yield).

Synthesis of 2-Alkylimino-1,3-thiazoline Ester 13 (general procedure). To a solution of methyl 5-bromo-4-oxopentanoate **4**{*65*} (1.7 g, 8 mmol) dissolved in ethanol (20 mL) was added alkylthiourea **3** (8 mmol), and the mixture was heated to reflux over 3 h. The reaction mixture was cooled to room temperature, and the solvent was removed by evaporation; the resulting solid was filtered, washed with cold ethyl ether (or isopropyl ether), and then dried in air to afford **13** (solid, 70−98% yield).

Synthesis of Phthalimidyl 1,3-Thiazoline 14 (general procedure). To a solution of **4**{*66*} (5.6 g, 20 mmol) dissolved in ethanol (60 mL) was added alkylthiourea **3** (20 mmol), and the mixture was heated to reflux over 2 h. The reaction mixture was cooled to room temperature, and the solvent was removed by evaporation; the resulting solid was filtered, washed with cold ethyl ether, and then dried in air to afford **14** (solid, 76−93% yield).

Synthesis of 4-Aminomethyl-2-imino-1,3-thiazoline 15 (general procedure). To a solution of **14** (4 mmol) dissolved in benzene (30 mL) was added triethylamine (0.61 mL, 4 mmol), and the reaction mixture was stirred for 2 h at room temperature. The produced precipitates were filtered out, and the solvent was removed under reduced pressure. The residue was diluted with ethanol (50 mL) and added hydrazine monohydrate (0.39 mL, 8 mmol) and the mixture stirred at ambient temperature for 10 h. The resulting solid was then filtered off and washed with methylene chloride. The filtrate was concentrated in vacuo to yield **15** (oil, 42−65% yield).

Synthesis of 2-Alkylimino-1,3-thiazoline Acids 16 and 17 (general procedure). To a solution of **11** (or **13**) (5 mmol) dissolved in methanol (3.3 mL/g) was added KOH (15 mmol). The reaction mixture was stirred for 2 h, and the solvent was removed under reduced pressure. The reaction mixture was poured onto water (30 mL/g) and stirred for 1 h. The mixture was washed with methylene chloride, and the aqueous layer was acidified (pH 2−3) by addition of concentrated HCl. The reaction mixture was evaporated, and the produced residue was filtered off using acetone and methylene chloride. The filtrate was dried with anhydrous $MgSO_4$, and the solvent was removed by evaporation to afford the corresponding **16** (or **17**) (solid, 65−75% yield).

Synthesis of 2-Alkylimino-1,3-thiazoline 19 (general procedure). To a suspension of **12** (or **16** or **17**) (1 mmol) dissolved in methylene chloride (10 mL) at 0 °C were added DMAP (0.25 g, 2 mmol) and EDCI (0.20 g, 1 mmol) sequentially. The resulting mixture was stirred for 30 min, and the corresponding amine or aniline **18** (2 mmol) was added to the reaction mixture while it was being stirred. The reaction mixture was allowed to warm to room temperature over 5−10 h. The reaction mixture was diluted with methylene chloride, washed sequentially with 0.1 N HCl, a saturated aqueous $NaHCO_3$ solution, and water, and then dried with anhydrous $MgSO_4$. The solvent was removed by evaporation, and the residue was purified by flash chromatography on silica gel to yield the corresponding **19** (solid, 2−99% yield).

Synthesis of 2-Alkylimino-1,3-thiazoline-4-ethylamine 20 (general procedure). To a solution of **9** (or **19**) (0.4 mmol) in tetrahydrofuran (10 mL) was added $LiAlH_4$ (76 mg, 2 mmol). The reaction mixture was heated to reflux over 7−20 h. The reaction progress was monitored by TLC. Glauber's salt (67 mg, 0.2 mmol) was added to destroy excess $LiAlH_4$ while the mixture was being stirred for 1 h at room temperature. The precipitates were removed by filtration through Celite. The solvent was removed by evaporation, and the residue was separated by flash chromatography using silica gel to give **20** (solid, 6−93% yield).

Synthesis of 2-Alkylimino-1,3-thiazoline Hydrochloride 22 (general procedure). To a solution of **15** (0.3 mmol) dissolved in methylene chloride (10 mL) was added acyl chloride **21** (0.3 mmol). The reaction mixture was stirred at room temperature for 5 h. The precipitates were filtered, washed with methylene chloride, and then dried in air to afford **22**. To obtain the free amine of **22**, the reaction mixture was treated with triethylamine (42 μL, 0.3 mol) at room temperature while being stirred for 30 min. The solvent was removed by evaporation, and the residue was purified by flash chromatography using silica gel and a mixture of ethyl acetate and *n*-hexane (1:1) to afford the free amine of **22** (23−83% yield).

Synthesis of 2-Alkylimino-1,3-thiazoline 24 (general procedure). A solution of **15** (0.5 mol) in methanol (5 mL) and aldehyde **23** (0.5 mol) was stirred at room temperature for 5 h. To the reaction mixture was added $NaBH_4$ (38 mg, 1 mol), and stirring was continued at the same temperature for 10 h. To the resulting reaction mixture was added a 1 N NaOH aqueous solution to destroy excess $NaBH_4$. This mixture was extracted with methylene chloride, and the organic extract was dried with anhydrous $MgSO_4$. The solvent was removed by evaporation, and the crude product was purified by flash chromatography on silica gel to yield **24** (15−36% yield).

Acknowledgment. We thank Prof. H. Mah, Prof. S. H. Cheon, and Mr. I. M. El-Deeb for assistance in preparation of the manuscript.

Supporting Information Available. Yields, melting points, and ^{1}H NMR data for all the compounds, mass and HPLC data for the representative compounds, and X-ray crystallographic data for **9**{*7,3*} and **9**{*16,12*} (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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