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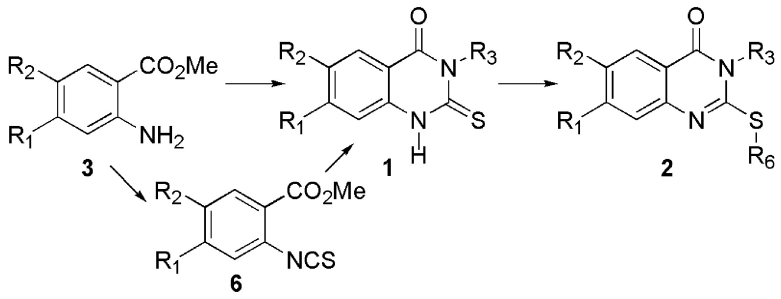

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Synthesis of Substituted 4-Oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines and 4-Oxo-3,4-dihydroquinazoline-2-thioles

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We have developed a liquid-phase synthesis of combinatorial libraries of new disubstituted 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines and trisubstituted 4-oxo-3,4-dihydroquinazoline-2-thioles. The former were prepared using two general procedures: (i) cyclization of substituted methyl anthranilates with isothiocyanates, or (ii) cyclization of substituted 2-(methylcarboxy)benzeneisothiocyanates with primary amines or hydrazines. 4-Oxo-3,4-dihydroquinazoline-2-thioles were prepared by S-alkylation of disubstituted 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines with alkyl or aryl halides. The hydrolysis of methyl benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thione-3-carboxylate led to the corresponding acid. This acid was utilized in the synthesis of new benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thione-3-carboxamide and S-substituted 6-mecaptobenzimidazo[1,2-*c*]quinazoline-3-carboxamide libraries.

Introduction

A large number of quinazoline derivatives, which contain the 4-oxo-2-thioxo-1,2,3,4-pyrimidine or 4-oxo-3,4-dihydropyrimidine-2-thiole structural motifs in their heterocyclic rings, possess a wide range of biological activities and provide an incentive for further exploration of this class of compounds as potential drug precursors.[1−8] The synthetic methods leading to these quinazoline derivatives are well-established and include the cyclization of *N*,*N*′-disubstituted thioureas into 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines (**1**). The *N*,*N*′-disubstituted thioureas used are generated in situ by reacting alkyl anthranilates with isothiocyanates or by reacting 2-(methylcarboxy)benzeneisothiocyanates with primary amines. S-Alkylation of **1** leads to the corresponding S-substituted 4-oxo-3,4-dihydroquinazoline-2-thioles (**2**).[9−12] The preparation of 2-thioxoquinazoline-4-one libraries by solid-phase synthesis has recently been reported.[13,14]

Recognizing the considerable interest in these classes of compounds, we have prepared libraries of 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines **1**{*1*−*4*} 4-oxo-3,4-dihydroquinazoline-2-thioles **2**{*1*−*4*} benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thione-3-carboxamides (**20**), and S-substituted 6-mercaptobenzimidazo[1,2-*c*]quinazoline-3-carboxamides (**21**) (Figure 1) by solution-phase parallel syntheses that were carried out in the proprietary reactor CombiSyn-012-3000.[15] These libraries are either previously unreported **1**{*3*,*4*} **2**{*3*,*4*} **20**, and **21**, or contain a majority of new 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines **1**{*1*,*2*} and 4-oxo-3,4-dihydroquinazoline-2-thioles **2**{*1*,*2*}.

Results and Discussion

We investigated two approaches for the solution-phase parallel synthesis of library members of **1**{*1*} and **1**{*2*}. The first approach is based on the reaction of methyl anthranilates **3** with isothiocyanates **4** in refluxing pyridine or dimethylformamide. This reaction generates 2-thioxoquinazoline-4-ones (**1**) through the intermediacy of *N*,*N*′-disubstituted thioureas (**5**), which are not isolated.

A wide variety of methyl anthranilates **3**{*1*−*13*} (Figure 2) and arylisothiocyanates **4**{*1*−*25*} (Figure 3) gave rise to satisfactory yields (45−90%). The exceptions were arylisothiocyanates possessing a large ortho substituent (such as Br or CF_3) or a strong electron-withdrawing group (such as NO_2), as well as alkyl-, **4**{*26*,*27*}; cycloalkyl-, **4**{*28*}; and benzylisothiocyanates, **4**{*29*}. In these cases, the reaction times increased by up to 10 h, and the yields of the target compounds, **1**, did not exceed 30%. For example, we failed to obtain methyl 3-cyclohexyl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate, **1**{*2*(*1*)}, by reacting methyl anthranilate **3**{*3*} with cyclohexylisothiocyanate, **4**{*28*} in pyridine, even after 10 h of heating at reflux.

The second approach proved to be more versatile in the solution-phase parallel synthesis of library members of **1**{*1*} and **1**{*2*}. It involved briefly heating 2-(methylcarboxy)-benzeneisothiocyanates **6**{*1*−*5*} (Figure 4) in isopropyl alcohol with a wide variety of primary aliphatic amines, **7**{*1*−*73*} (Figure 5); primary aromatic amines, **8**{*1*−*10*} (Figure 6); amino acids, **9**{*1*−*11*} (Figure 7); hydrazines, **10**{*1*−*7*}; hydrazides, **10**{*8*−*30*}; sulfohydrazides, **10**{*31*−*34*}; or thiosemicarbazides, **10**{*35*,*36*} (Figure 8).

This second approach led in many cases to the desired products in high yields, reaching 95%. In particular, members of chemset **1**{*2*}, which could not be synthesized using the first approach (**3** → **1**), namely, those possessing a 3-alkyl, 3-benzyl, or 3-cyclohexyl substituent, were obtained in good-to-high yields: **1**{*2*(*1*)}, 85%; **1**{*2*(*2*)}, 92%; and **1**{*2*(*3*)}, 95%. Moreover, we observed that the yields of products

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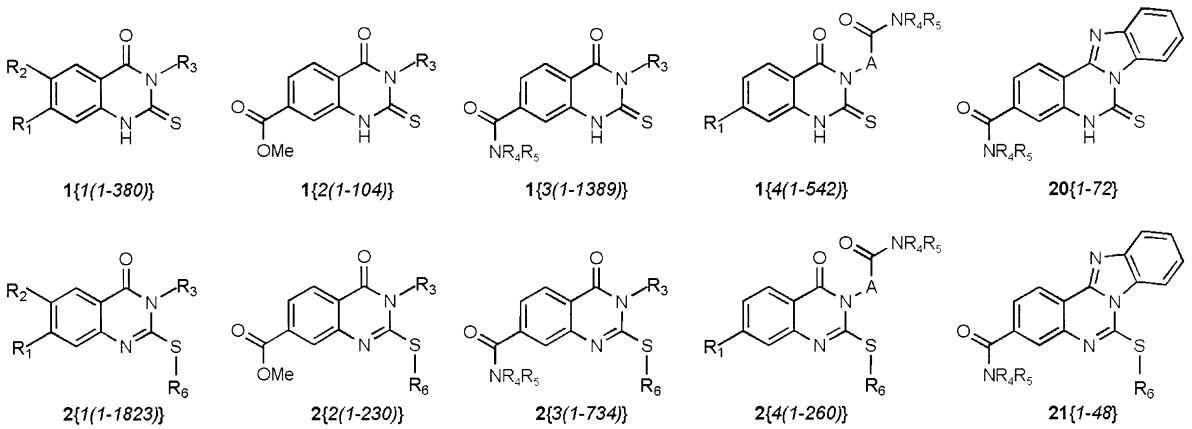


Figure 1. 4-Oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines, **1**{*1*−*4*}; 4-oxo-3,4-dihydroquinazoline-2-thioles, **2**{*1*−*4*}; benzimidazo[1,2-*c*]-quinazoline-6(5*H*)-thione-3-carboxamides (**20**); and S-substituted 6-mercaptobenzimidazo[1,2-*c*]quinazoline-3-carboxamides (**21**).

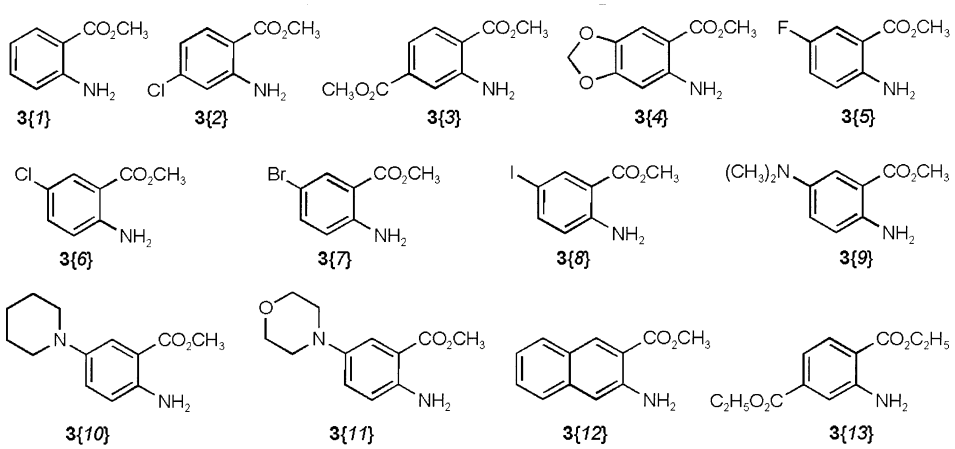


Figure 2. Diversity methyl anthranilates, **3**{*1*−*13*}.

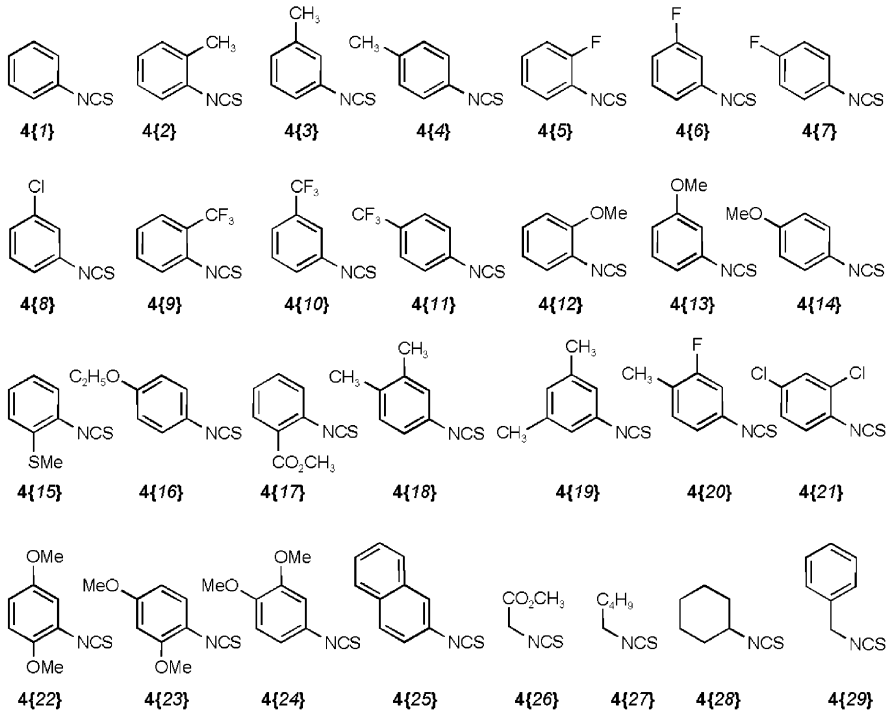


Figure 3. Diversity isothiocyanates, **4**{*1*−*29*}.

1{*1*,*2*} by this second approach decreased when the aromatic amine contained electronegative substituents. In addition, weakly basic amines, such as nitroanilines or aminopyridazine, did not react with benzeneisothiocyanates **6**{*1*−*5*}. Steric hindrance at the nitrogen atom of the amine (such as in 1-aminoadamantane) also caused the reaction to fail.

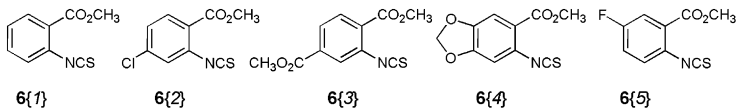


Figure 4. Diversity 2-(methylcarboxy)benzeneisothiocyanates, **6**{*1*−*5*}.

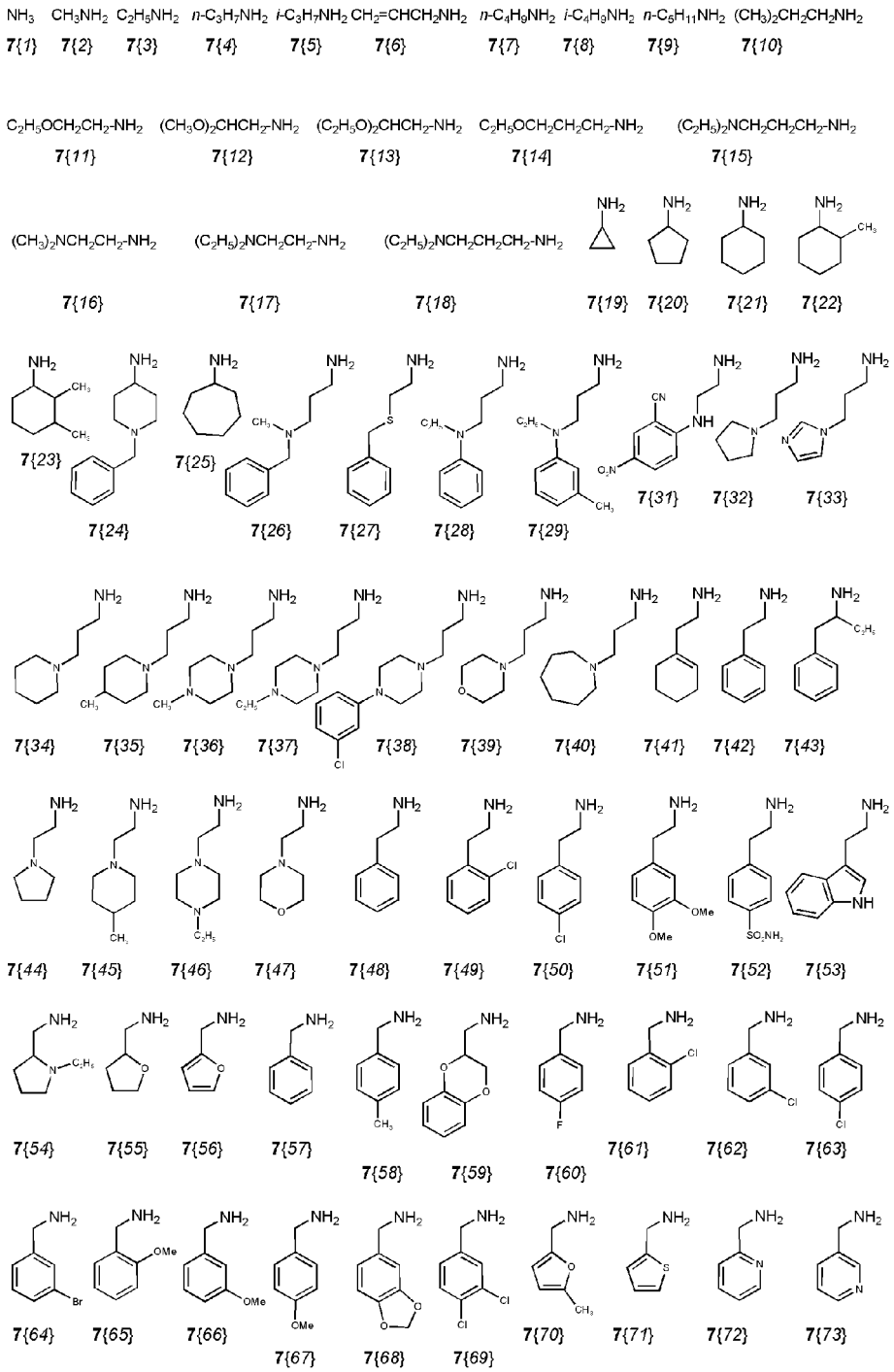


Figure 5. Diversity primary aliphatic amines, **7**{*1*−*73*}.

It is worth noting that although both approaches were applicable to the solution phase, parallel synthesis of chemsets **1**{*1,2*} the choice of which approach to use in a specific case was dictated by the availability of the starting isothiocyanates, **4** or **6**. By implementing the two approaches, a 380-compound library of disubstituted 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines, **1**{*1*}, and a 104-compound library of alkyl 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylates, **1**{*2*}, were synthesized. The majority of these compounds are new entities; some of the more interesting ones are shown in Figure 9.

Alkaline hydrolysis of methyl 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylates, **1**{*2*}, led to the corresponding 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic acids, **11**{*1*−*24*} (Figure 10). Reacting acids **11**{*1*−*24*} with carbodiimidazole and various amines resulted

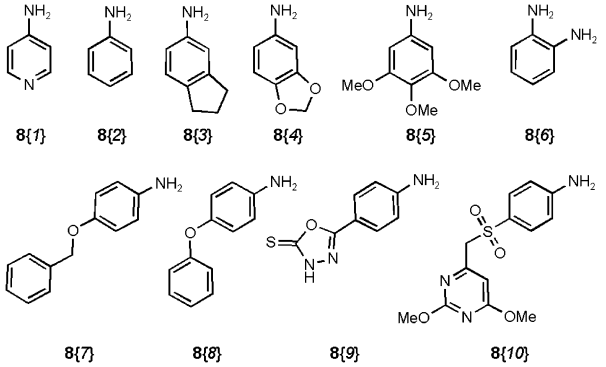


Figure 6. Diversity primary aromatic amines, **8**{*1*−*10*}.

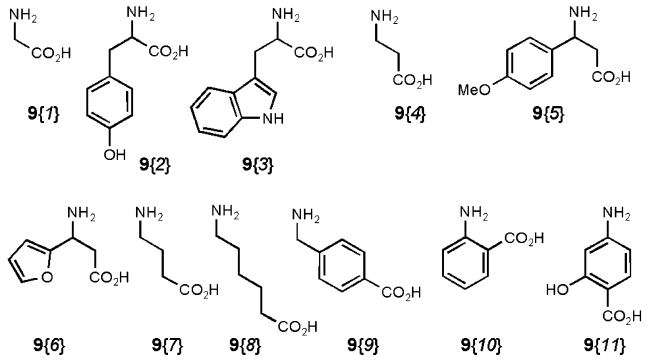


Figure 7. Diversity amino acids, **9**{*1*−*11*}.

in a new 1389-compound library of 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxamides, **1**{*3*}. A couple of the compounds from this library are illustrated in Figure 9. Using acids **1**{*1*} under analogous conditions, a new 542-compound library of amides, **1**{*4*(*1*−*542*)}, was obtained. Some of these amides are shown in Figure 9. For the synthesis of libraries **1**{*3,4*}, 104 primary amines, **7**{*4*−*10,12,14*−*18,20*−*29,32,41,44*−*48,50*−*63,65,67*−*69,71*−*73*} (Figure 5), **8**{*3,5,8*} (Figure 6), **7**{*74*−*90*} (Figure 11), **8**{*11*−*3*} (Figure 12), and 40 secondary amines, **12**{*1*−*40*}, (Figure 13) were used.

The new trisubstituted 4-oxo-3,4-dihydroquinazoline-2-thiole library, **2**{*1*−*4*}, was obtained by the S-alkylation or S-arylation of the corresponding thioxo compounds **1**{*1*−*4*} with alkyl halides **13**{*1*−*64*}, 2,4-dinitrochlorobenzene **13**{*65*}, and chloronitrobenzothiadiazoles **13**{*66,67*} (Figure 14); with α-chloroketones **14**{*1*−*15*} (Figure 15); with chloroacetic **15**{*1*}, α-chloropropionic acid **15**{*2*}, related alkyl esters **15**{3−6}, and amides **15**{*7*−*76*} (Figure 16); with *N,N*-disubstituted 2-chloroacylamides **16**{*1*−*25*} (Figure 17); and with 2-chloroacethydrazides **17**{*1*−*12*} (Figure 18). The S-alkylation/arylation reaction was carried out in DMF in the presence of triethylamine. Yields of target products reached 90%. Library **2**{*1*−*4*} includes 3056 variously substituted 4-oxo-3,4-dihydroquinazoline-2-thioles **2**, some of which are illustrated in Figure 19.

We have recently reported[16] the unusual intramolecular cyclization of 3-(2-aminophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines (obtained using approach 2 (vide supra) by reacting **6**{*1,3*} with phenylenediamine, **8**{*6*}) into methyl benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thione-3-carboxylates, which are of great interest as potentially biologically active substances.[17,18] In particular, the parent ester, methyl benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thione-3-carboxylate (**18**), was hydrolyzed into benzimidazo[1,2-*c*]-quinazoline-6(5*H*)-thione-3-carboxylic acid (**19**). Acid **19** was then employed in the synthesis of a new benzimidazo-[1,2-*c*]quinazoline-6(5*H*)-thione-3-carboxamide library, **20**,[1−72]

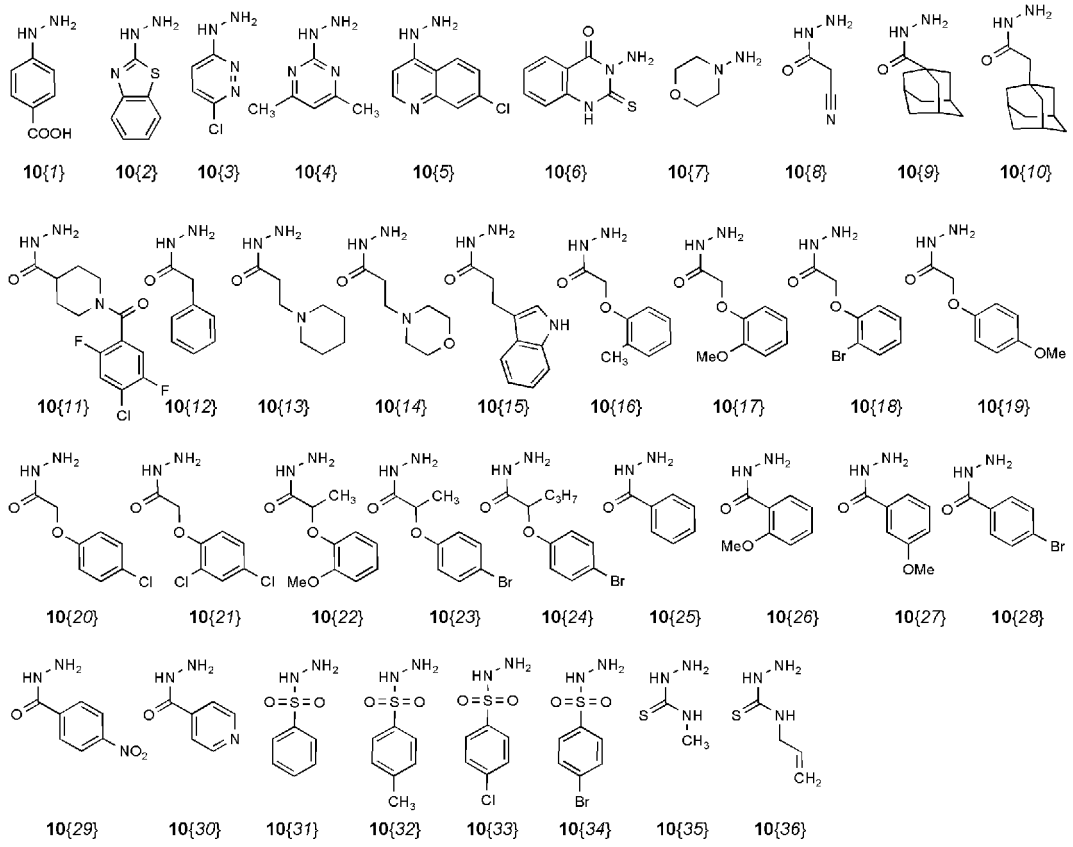


Figure 8. Diversity hydrazines, **10**{1−7}; hydrazides, **10**{*8*−*30*}; sulfohydrazides, **10**{*31*−*34*}; and thiosemicarbazides, **10**{*35,36*}.

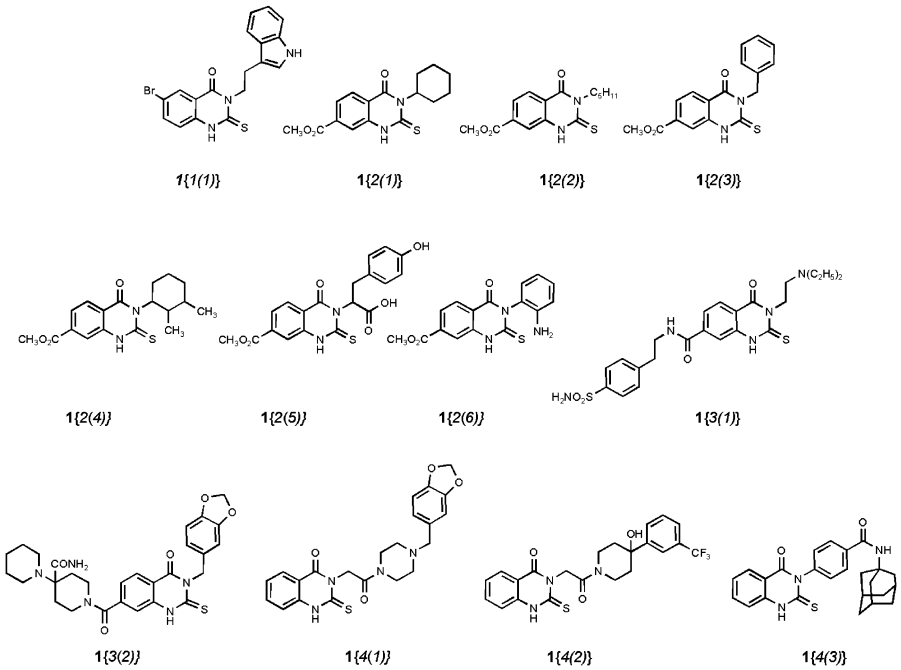


Figure 9. Examples of 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines synthesized, **1**{*1*−*4*}.

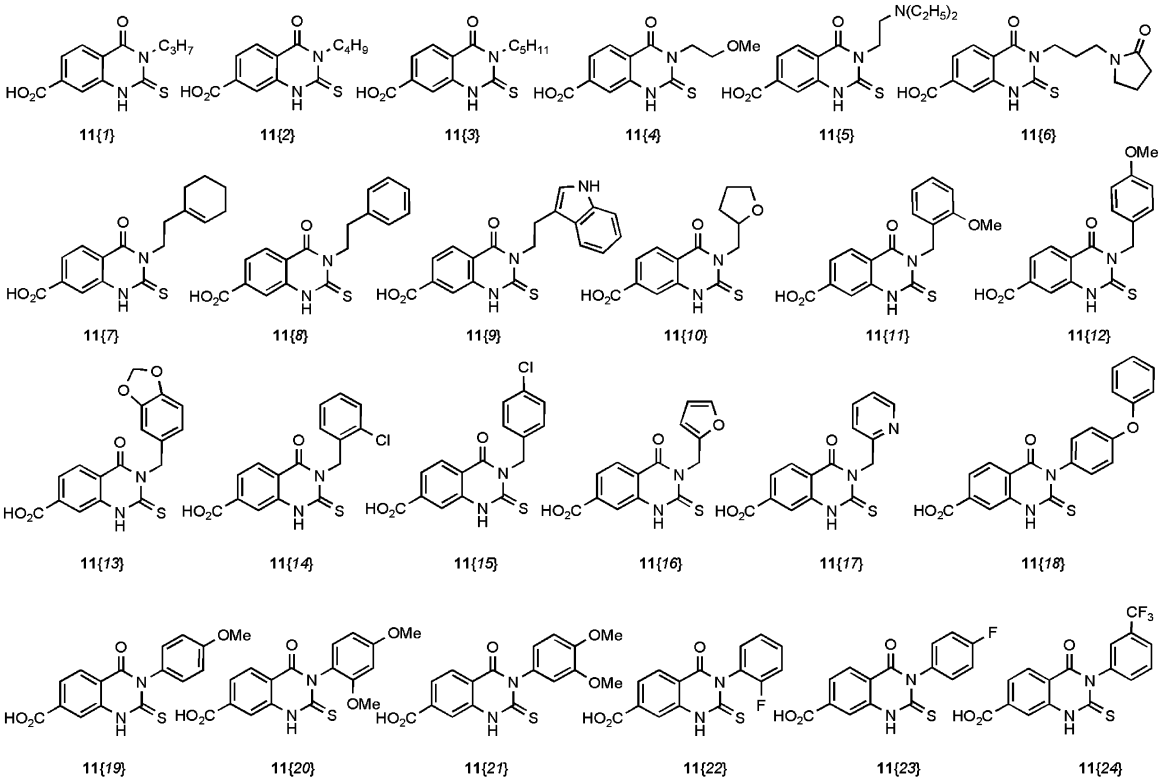


Figure 10. All the 4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic acids synthesized, **11**{*1*−*24*}.

and S-substituted 6-mercaptobenzimidazo[1,2-*c*]quinazoline-3-carboxamide library, **21**{*1*−*48*}. Library **20** was obtained by parallel synthesis from acid **19** and various primary, **7**, and secondary, **12**, amines by the carbonyldiimidazole method. Library **21** was obtained by alkylation of chemset **20** with various alkyl halides, **13**−**15**. Figure 20 illustrates a couple of examples from libraries **20** and **21**.

Conclusions

The present study has demonstrated the viability and utility of solution-phase parallel synthesis for the preparation of libraries of quinazoline derivatives that include hundreds of new and versatile members. These heterocyclic compounds are of interest because of their potential biological activity, in analogy to the 5HT-receptor antagonist,[1,2] α-1-adrenoceptor antagonists,[3,4] IL-1 inhibitors, and antiarthritic drugs.[5]

Experimental Section

General Information. The synthesis, isolation, and purification of the compounds reported were carried out using a proprietary technology platform, which includes all the equipment required for parallel synthesis.[15,19] All solvents

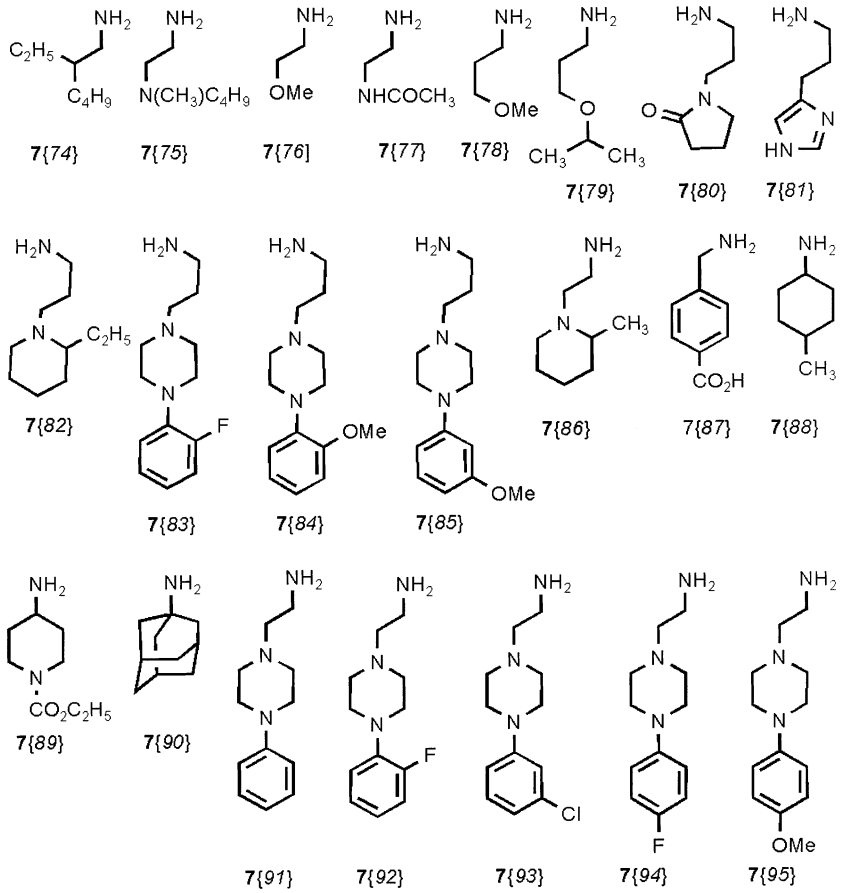


Figure 11. Additional diversity primary aliphatic amines, **7**{*74*−*95*}.

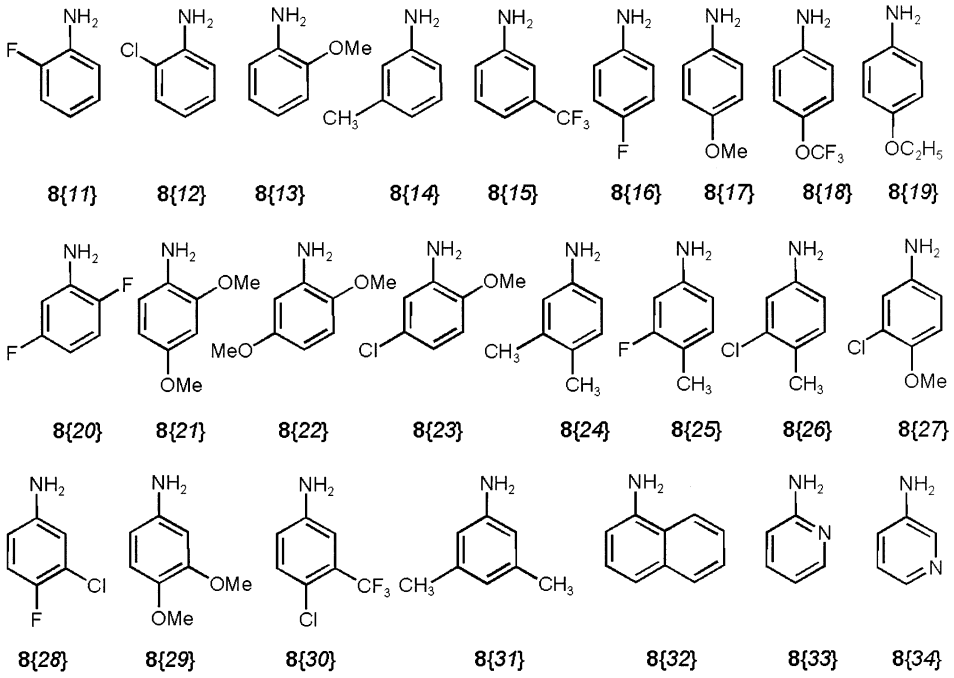


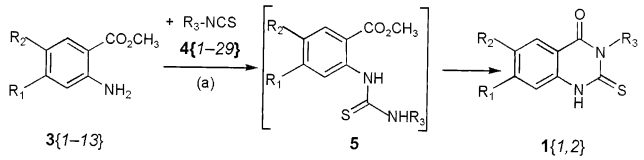
Figure 12. Additional diversity primary aromatic amines, **8**{*11*−*34*}.

and reagents were obtained from commercial sources and used without further purification. Diversity reagents **3** were obtained from Acros Organics, Aldrich, or ChemDiv, Inc.

Melting points (mp) were measured with a Koeffler melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60 F-254). ^{1}H NMR spectra were recorded on a Bruker AMX-400 spectrometer in DMSO-d_6 using TMS as an internal standard (chemical shifts in ppm). LC/MS spectra were obtained with PE SCIEX API 150EX liquid chromatograph equipped with a UV detector (λ_{max} 215 and 254 nm) and using a C_{18} column

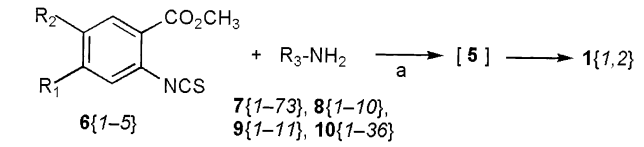
(100 × 4 mm). Elution started with water and ended with acetonitrile/water (95:5, v/v) and used a linear gradient at a flow rate of 0.15 mL/min and an analysis cycle time of 25 min. According to the LC/MS data, all the synthesized compounds were more than 95% pure at 254 nm.

General Procedure for the Synthesis of 4-Oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines, 1. Method A (3 → 1). A solution of 5 mmol of alkyl anthranilate **3**{*1*−*13*} and 5.5 mmol of isothiocyanate **4**{*1*−*29*} in 10 mL of pyridine or dimethylformamide was heated at reflux from 3 to 10 h, depending on the reactivity of the isothiocyanate. After cooling, the reaction mixture was diluted with 20 mL of water, and the precipitate was filtered and recrystallized from 2-propanol, dimethylformamide, or a mixture of the two.



(a) Heated at reflux for 3–10 h in pyridine or DMF

Method B (6 → 1). A 1.0-mmol portion of the desired primary amine, **7**{*1*−*73*} or **8**{*1*−*10*}, was added to a warm solution of 0.25 g (1.00 mmol) of 2,5-di(methylcarboxy)-benzeneisothiocyanate, **6**{3}, in 5 mL of 2-propanol. The reaction mixture was stirred and heated at reflux from 1 to 30 min, depending on the reactivity of the amine. After cooling, the mixture was diluted with 20 mL of water, and the precipitate was filtered and recrystallized from 2-propanol, dimethylformamide, or a mixture of the two.



(a) heated at reflux for 15–30 min in *i*-PrOH or *i*-PrOH–H_2O.

Method C (6 → 1). A 100-mmol portion of 2-(methylcarboxy)benzeneisothiocyanate **6**{*1*−*5*} was added with stirring to 150 mL of a warm solution (2-propanol/water, 1:1) of the triethylamine salt of amino acid **9**{*1*−*11*} [100 mmol of acid and 15.4 mL (110 mmol) of triethylamine]. The reaction mixture was heated at reflux for ∼1 h. After cooling, the mixture was acidified with hydrochloric acid to pH 2.5−3.0, and the resulting precipitate was filtered and crystallized from dimethylformamide.

In the examples of chemsets **1**{*1*,*2*} below, the relevant experimental information is provided in the following order: name, yield, mp, recrystallization solvent, and ^{1}H NMR data.

6-Bromo-3-[2-(1*H*-indol-3-yl)ethyl]-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline, 1{***1(1)***}**.** Yield 89%; mp 249−250 °C; DMF/*i*-PrOH; ^{1}H NMR δ 3.12 (t, J = 7.4 Hz, 2H), 4.61 (t, J = 7.4 Hz, 2H), 6.96 (t, J = 7.6 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 1.0 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 8.09 (d, J = 1.0 Hz, 1H), 10.6 (s, 1H), 12.90 (s, 1H).

Methyl 3-Cyclohexyl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate, 1{***2(1)***}**. Yield 85%; mp 250 °C (dec); DMF; ^{1}H NMR δ 1.65−1.75 (m, 2H), 1.85−1.95 (m, 2H), 2.85−2.95 (m, 2H), 3.95 (s, 3H), 5.70 (q, J = 6.7 Hz, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.93 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H), 12.80 (s, 1H).

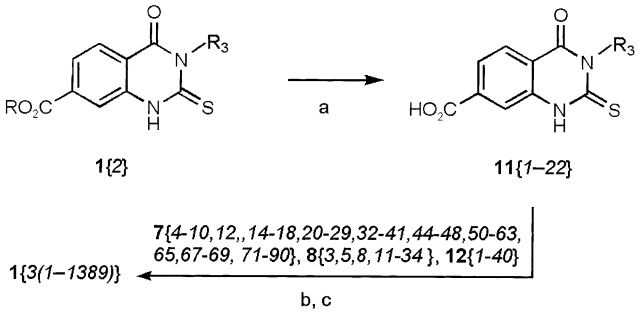
Methyl 4-Oxo-3-pentyl-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate, 1{***2(2)***}**. Yield 92%; mp 209 °C (dec); DMF; ^{1}H NMR δ 1.03 (t, J = 7.4 Hz, 3H), 1.37−1.49 (m, 4H), 1.77−1.89 (q, J = 6.9 Hz, 2H), 3.95 (s, 3H), 4.42 (t, J = 7.4 Hz, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.93 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H), 12.80 (s, 1H).

Methyl 3-Benzyl-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate, **1**{***2(3)***}**. Yield 95%; mp 237 °C (dec); DMF; ^{1}H NMR δ 3.95 (s, 3H), 5.80 (s, 2H), 7.20−7.30 (m, 3H), 7.40−7.44 (m, 2H), 7.83 (d, J = 7.6 Hz, 1H), 8.03 (m, 2H), 12.80 (s, 1H).

Methyl 3-(2,3-Dimethylcyclohexyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylate, 1{***2(4)***}**. Yield 56%; mp 207−208 °C (dec); DMF/*i*-PrOH; ^{1}H NMR δ 0.80−1.00 (m, 6H), 1.20−1.70 (m, 6H), 2.00 (m, 1H), 2.35 (m, 1H), 3.95 (s, 3H), 5.52 (q, J = 6.6 Hz, 0.55H 1a−H of cyclohexane ring), −5.85 (q, J = 6.6 Hz, 0.46H 1e−H of cyclohexane ring), 7.83 (d, J = 7.6 Hz, 1H), 7.93 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H), 12.80 (s, 1H).

3-(4-Hydroxyphenyl)-2-[7-(methoxycarbonyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolin-3(2*H*)-yl]propanoic Acid, 1{***2(5)***}**. Yield 44%; mp 242−243 °C; DMF/*i*-PrOH; ^{1}H NMR δ 3.12 (t, J = 6.9 Hz, 1H), 3.42 (t, J = 6.9 Hz, 1H), 3.95 (s, 3H), 6.50−6.55 (m, 2H), 6.74 (t, J = 6.9 Hz, 1H), 7.08−6.95 (m, 2H), 7.78 (d, J = 7.6 Hz, 1H), 7.95 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H), 9.8 (s, 1H), 13.00 (s, 1H).

General Procedure for the Synthesis of 4-Oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic Acids, 11. A 50-mL portion of a 20% aqueous solution of NaOH was added to an agitated suspension of 100 mmol of methyl ester **1**{*2*} in 300 mL of methanol. The mixture was heated at reflux for 3 h, diluted with water, and neutralized with 30 mL of 10% hydrochloric acid. The precipitate was filtered and recrystallized from DMF.



(a) heated at reflux for 3 h in MeOH–H_2O solution of NaOH. (b) CDI, 90 °C, 2 h in dioxane. (c) heated at reflux for 1–15 h in dioxane.

Experimental information for a few members of chemset **11** is provided in the following order: name, yield, mp, recrystallization solvent, and ^{1}H NMR data.

3-(Diethylaminoethyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic Acid, 11{***5***}**. Yield 72%; mp

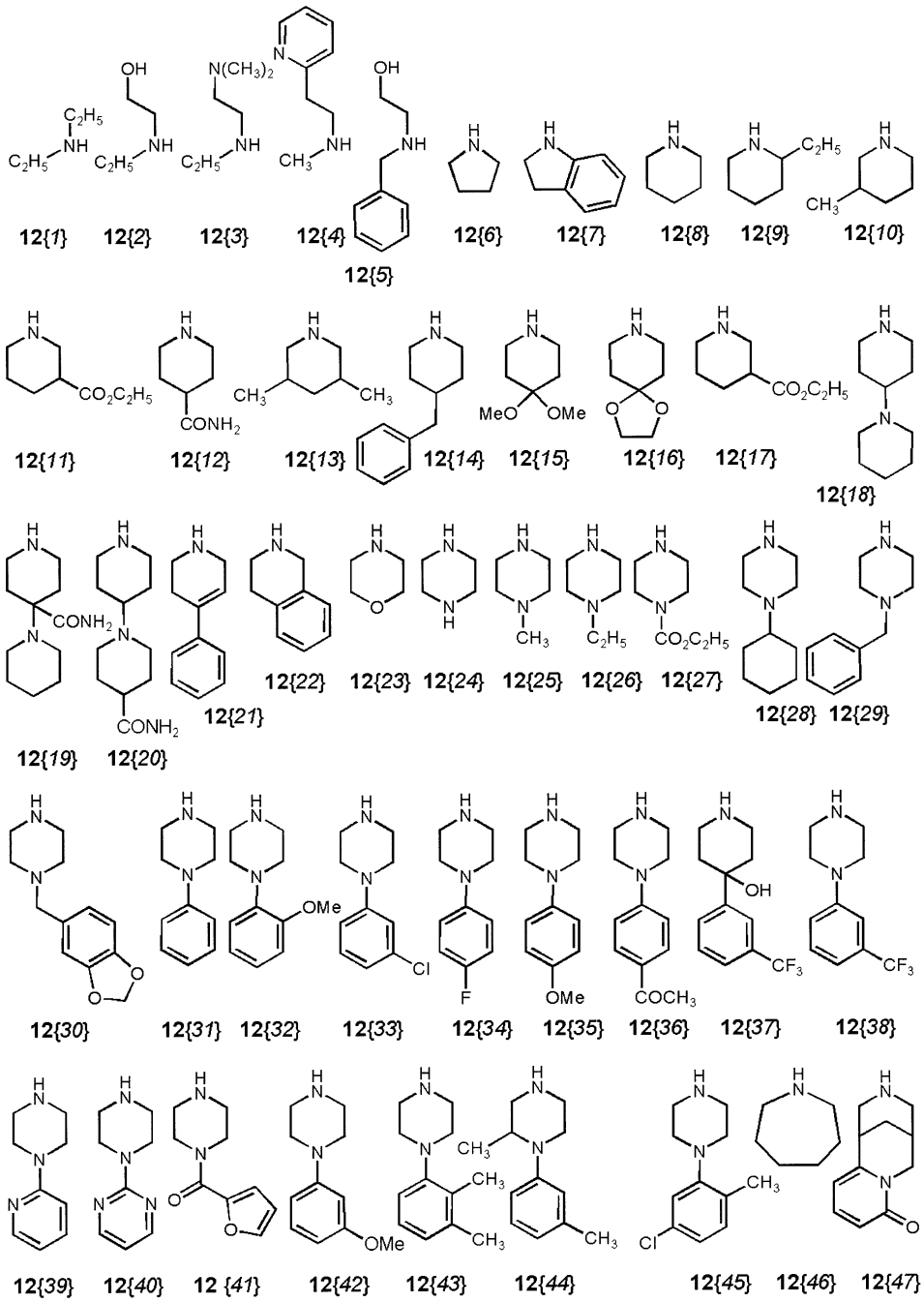


Figure 13. Diversity secondary aliphatic amines, **12**{*1*−*47*}.

292 °C (dec); DMF; ^{1}H NMR δ 1.05 (t, J = 7.4 Hz, 6H), 2.85 (q, J = 7.4 Hz, 4H), 3.22 (t, J = 7.4 Hz, 2H), 4.64 (t, J = 7.4 Hz, 2H), 7.78 (d, J = 7.6 Hz, 1H), 7.95 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H), 13.00 (s, 1H)).

4-Oxo-3-[3-(2-pyrrolidon-1-yl)propyl]-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic Acid, 11{*6*}**.** Yield 72%; mp 335 °C (dec); DMF; ^{1}H NMR δ 1.92−1.97 (m, 2H), 2.02−2.09 (m, 2H), 2.22−2.29 (m, 2H), 3.33 (t, J = 7.4 Hz, 2H), 3.48 (t, J = 7.4 Hz, 2H), 4.34 (t, J = 7.4 Hz, 2H), 7.78 (d, J = 7.6 Hz, 1H), 7.95 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H), 13.00 (s, 1H).

3-[(3,4-Methylenedioxy)benzyl]-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic Acid, 11{*13*}**.** Yield 81%; mp >360 °C; DMF; ^{1}H NMR δ 5.60 (s, 2H), 5.90 (s, 2H), 6.75 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 7.20 (s, 1H), 7.78 (d.d, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.95 (d, J = 0.8 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), 13.00 (s, 1H).

3-(2-Furanylmethyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic Acid, 11{*16*}**.** Yield 80%; mp 298 °C (dec); DMF; ^{1}H NMR δ 5.67 (s, 2H), 6.27 (d, J = 6.6 Hz, 1H), 6.35 (t, J = 6.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 6.6 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.95 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H), 13.00 (s, 1H).

4-Oxo-3-(4-phenyloxyphenyl)-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxylic Acid, 11{*18*}**.** Yield 68%; mp

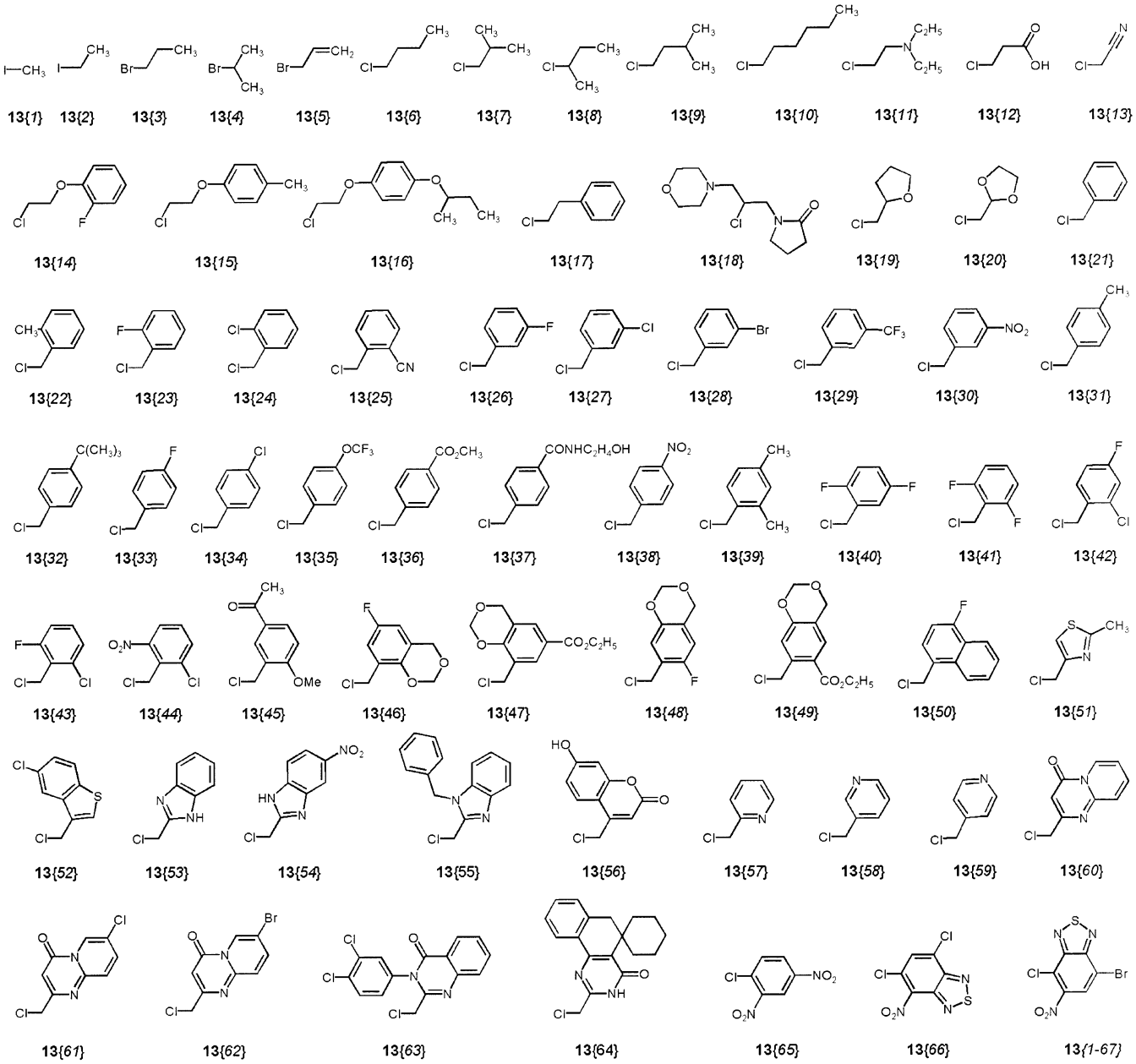
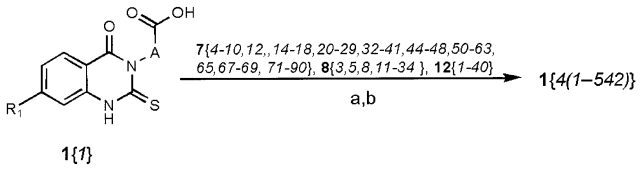


Figure 14. Diversity alkyl halides, **13**{*1*−*64*}; 2,4-dinitrochlorobenzene, **13**{*65*}; and chloronitro-2,1,3-benzothiadiazoles, **13**{*66*,*67*}.

321 °C (dec); DMF; ^{1}H NMR δ 7.02−7.15 (m, 7H), 7.35 (d, J = 7.6 Hz, 2H), 7.78 (d, J = 7.6 Hz, 1H), 7.95 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H), 13.00 (s, 1H).

General Procedure for the Synthesis of 4-Oxo-2-thioxo-1,2,3,4-tetrahydroquinazolines 1{***3,4***}**.** A 0.18-g (1.1 mmol) portion of 1,1′-carbonyldiimidazole was added to an agitated suspension of 1 mmol of acid **1**{*1*} or **11**{*1*−*22*} in 5 mL of anhydrous dioxane at 90 °C. The suspension was heated at reflux for 2 h, and 1.2 mmol of amine **7**, **8**, or **12** was then added. The resulting reaction mixture was heated at reflux from 1 to 15 h, depending on the reactivity of the amine. After cooling, the mixture was diluted with 20 mL of water and allowed to stand at room temperature for 1−3 days to form the precipitate of the amide product. The precipitate was filtered and recrystallized from *i*-PrOH, DMF, or a mixture of the two.

Experimental information for a few members of chemsets **1**{*3*,*4*} is provided in the following order: name, yield, mp, recrystallization solvent, and ^{1}H NMR data.



(a) CDI , 90 °C, 2 h in dioxane. (b) heated at reflux for 1–15 h in dioxane.

N*-(2-(4-(Aminosulfonyl)phenyl)ethyl)-3-(2-(dimethylamino)ethyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline-7-carboxamide, 1**{3(1)***}**. Yield 38%; mp 296−297 °C; DMF/*i*-PrOH; ^{1}H NMR δ 1.05 (t, J = 7.4 Hz, 6H), 2.85 (q, J = 7.4 Hz, 4H), 3.06 (t, J = 7.4 Hz, 2H), 3.22 (t, J = 7.4 Hz, 2H), 3.63 (t, J = 7.4 Hz, 2H), 4.54 (t, J = 7.4 Hz, 2H),

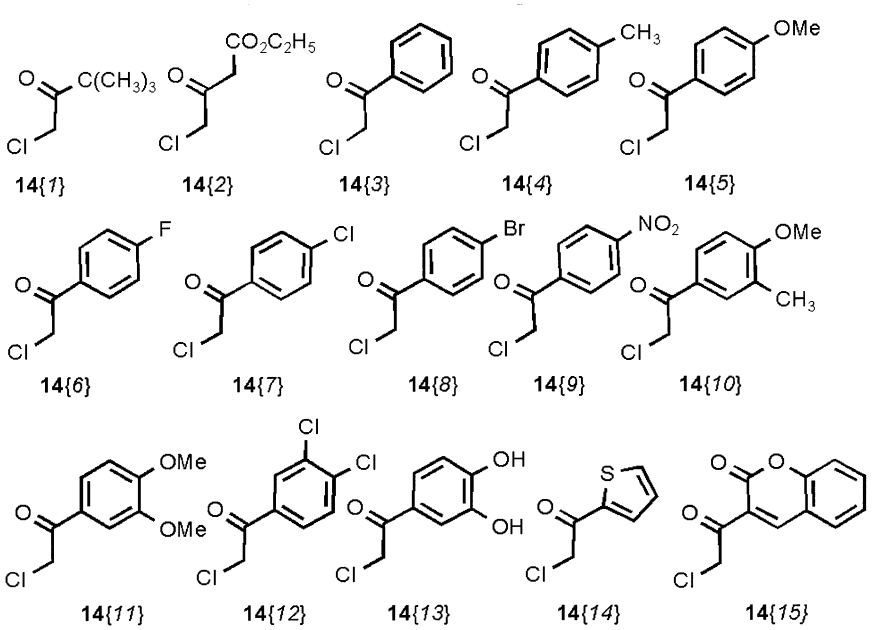


Figure 15. Diversity α-chloroketones, **14**{*1*−*15*}.

7.13 (d, J = 7.6 Hz, 2H), 7.42 (d, J = 7.6 Hz, 2H), 7.60 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.93 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H), 8.70 (s, 1H), 12.90 (s, 1H).

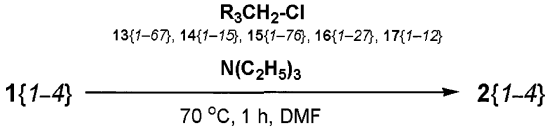
1′-((3-(1,3-Benzodioxol-5-ylmethyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolin-7-yl)carbonyl)-1,4′-bipiperidine-4′-carboxamide, 1{***3*(*2*)**}.** Yield 73%; mp 198−199 °C; DMF/*i*-PrOH; ^{1}H NMR δ 1.50−1.90 (m, 10H), 2.30−2.50 (m, 4H), 3.30−3.45 (m, 3H), 3.95−4.05 (m, 1H), 5.60 (s, 2H), 5.90 (s, 2H), 6.76 (d, J = 7.6 Hz, 1H), 7.00 (s, 2H), 7.08 (d, J = 7.6 Hz, 1H), 7.20 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.93 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H), 12.90 (s, 1H).

3-(2-(4-(1,3-Benzodioxol-5-ylmethyl)piperazin-1-yl)-2-oxoethyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline, 1{***4*-(*1*)**}.** Yield 70%; mp 209−210 °C; DMF/*i*-PrOH; ^{1}H NMR δ 3.00−3.10 (m, 8H), 5.60 (s, 2H), 5.90 (s, 2H), 6.20 (s, 2H), 6.73 (d, J = 7.6 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 7.20 (s, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 12.80 (s, 1H).

3-(2-(4-Hydroxy-4-[3-(trifluoromethyl)phenyl)piperidin-1-yl)-2-oxoethyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazoline, 1{***4*(*2*)**}.** Yield 63%; mp 234−235 °C; DMF/*i*-PrOH; ^{1}H NMR δ 1.70−1.85 (m, 3H), 2.15−2.25 (m, 1H), 3.55−3.65 (m, 1H), 3.85−3.95 (m, 1H), 4.20−4.30 (m, 1H), 5.30 (s, 1H), 5.40 (s, 2H), 7.33 (t, J = 7.6 Hz, 1H), 7.46−7.54 (m, 2H), 7.60−7.70 (m, 2H), 7.80 (s, 1H), 7.97 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 7.6 Hz, 1H), 12.80 (s, 1H).

N*-(1-Adamantyl)-4-(4-oxo-2-thioxo-1,2,3,4-tetrahydroquinazolin-3(2*H*)-yl)benzamide, 1**{4*(*3*)**}.** Yield 46%; mp 326−327 °C; DMF/*i*-PrOH; ^{1}H NMR δ 1.60−1.70 (m, 6H), 1.75−1.85 (m, 6H), 2.15−2.25 (m, 3H), 7.13 (d, J = 7.6 Hz, 2H), 7.25 (t, J = 7.6 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.96 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 7.6 Hz, 2H), 8.70 (s, 1H), 12.80 (s, 1H).

General Procedure for the Synthesis of Amides Possessing an S-Substituted (4-Oxo-3,4-dihydroquinazolin-2-yl)thiole Moiety, 2{***1*−*4*}**.** A 1.5 mmol portion of triethylamine and 1.2 mmol of alkylating agent **13**−**17** were added to a warm (65−70 °C) solution of 1 mmol of thione **1**{*1*−*4*} in 5 mL of DMF. The reaction mixture was stirred at 70 °C for ∼1 h. After cooling, the mixture was diluted with 10 mL of water, and the precipitate was filtered, washed with water and methanol, and then recrystallized from DMF, *i*-PrOH, or other solvents.



Experimental information for a few members of chemsets **2**{*1*−*4*} is provided in the following order: name, yield, mp, recrystallization solvent, and ^{1}H NMR data.

2-((6-Bromo-3-(2-methoxybenzyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio)-*N*-cyclohexylacetamide, 2{***1*(*1*)**}.** Yield 68%; mp 202−203 °C; DMF; ^{1}H NMR δ 1.25−1.35 (m, 5H), 1.65−1.75 (m, 5H), 3.45−3.55 (q, J = 6.9 Hz, 1H), 3.90 (s, 2H), 3.95 (s, 3H), 5.30 (s, 2H), 6.72 (d, J = 7.6 Hz, 1H), 6.83 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.85−7.95 (m, 2H), 8.30 (s, 1H).

2-((5-Acetyl-2-methoxybenzyl)thio)-3-((1-ethylpyrrolidin-2-yl)methyl)quinazolin-4(3*H*)-one, 2{***1*(*2*)**}.** Yield 74%; mp 108−109 °C; $CHCl_3$/hexane; ^{1}H NMR δ 1.00 (t, J = 7.4 Hz, 3H), 1.65−1.75 (m, 2H), 1.85−1.95 (m, 2H), 2.30 (s, 3H), 3.00−3.10 (m, 4H), 3.75−3.85, (m, 1H), 3.95 (s, 3H), 4.00 (d, J = 7.4 Hz, 2H), 4.50 (s, 2H), 7.00 (d, J = 7.6 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.85 (d.d, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 8.06 (d, J = 7.6 Hz, 1H), 8.19 (d, J = 0.8 Hz, 1H).

Ethyl 8-(((3-(1,3-Benzodioxol-5-ylmethyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio)methyl)-4*H*-1,3-benzodioxine-6-carboxylate, 2{***1*(*3*)**}.** Yield 65%; mp 177−178 °C; *i*-PrOH; ^{1}H NMR δ 1.33 (t, J = 7.4 Hz, 3H), 4.25 (q, J =

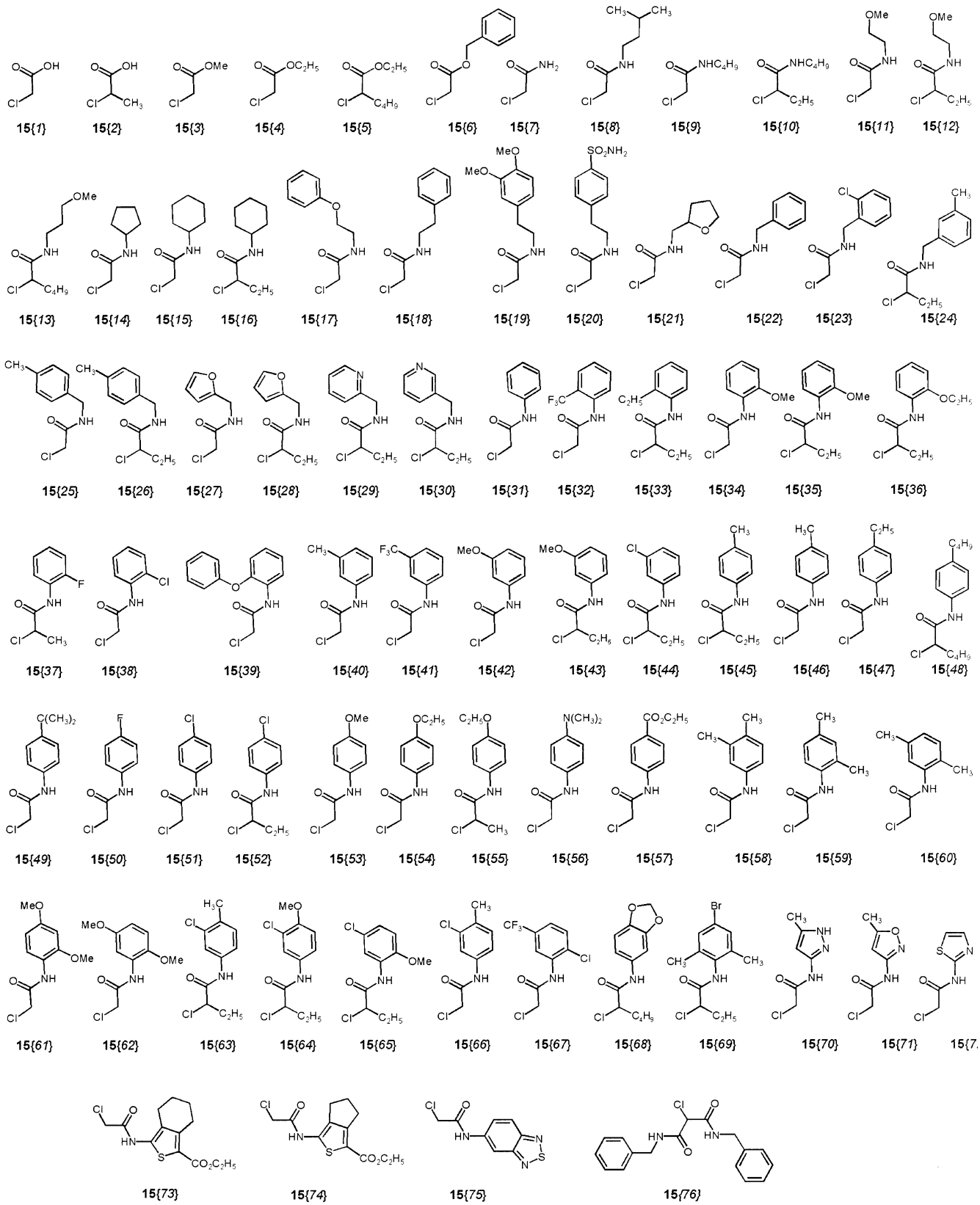


Figure 16. Diversity chloroacetic acid, **15**{*1*}; α-chloropropionic acid, **15**{*2*}; and related alkyl esters, **15**{*3*−*6*}, and amides, **15**{*7*−*76*}.

7.4 Hz, 2H), 4.45 (s, 2H), 4.90 (s, 2H), 5.15 (s, 2H), 5.35 (s, 2H), 5.90 (s, 2H), 6.68 (d, J = 7.6 Hz, 1H), 6.80 (t, J = 7.6 Hz, 1H), 6.82 (s, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.57 (s, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 8.13 (d, J = 7.6 Hz, 1H), 8.15 (s, 1H).

2-(((5-Chloro-1-benzothien-3-yl)methyl)thio)-*N*-(2-furylmethyl)-4-oxo-3-(tetrahydrofuran-2-ylmethyl)-3,4-dihydroquinazoline-7-carboxylate, 2{**3*(1)*}.** Yield 66%; mp 132−133 °C; DMF/*i*-PrOH; ^{1}H NMR δ 1.70−2.00 (m, 4H), 3.61−3.66 (m, 1H), 3.82−3.86 (m, 1H), 4.10 (d, J = 6.8

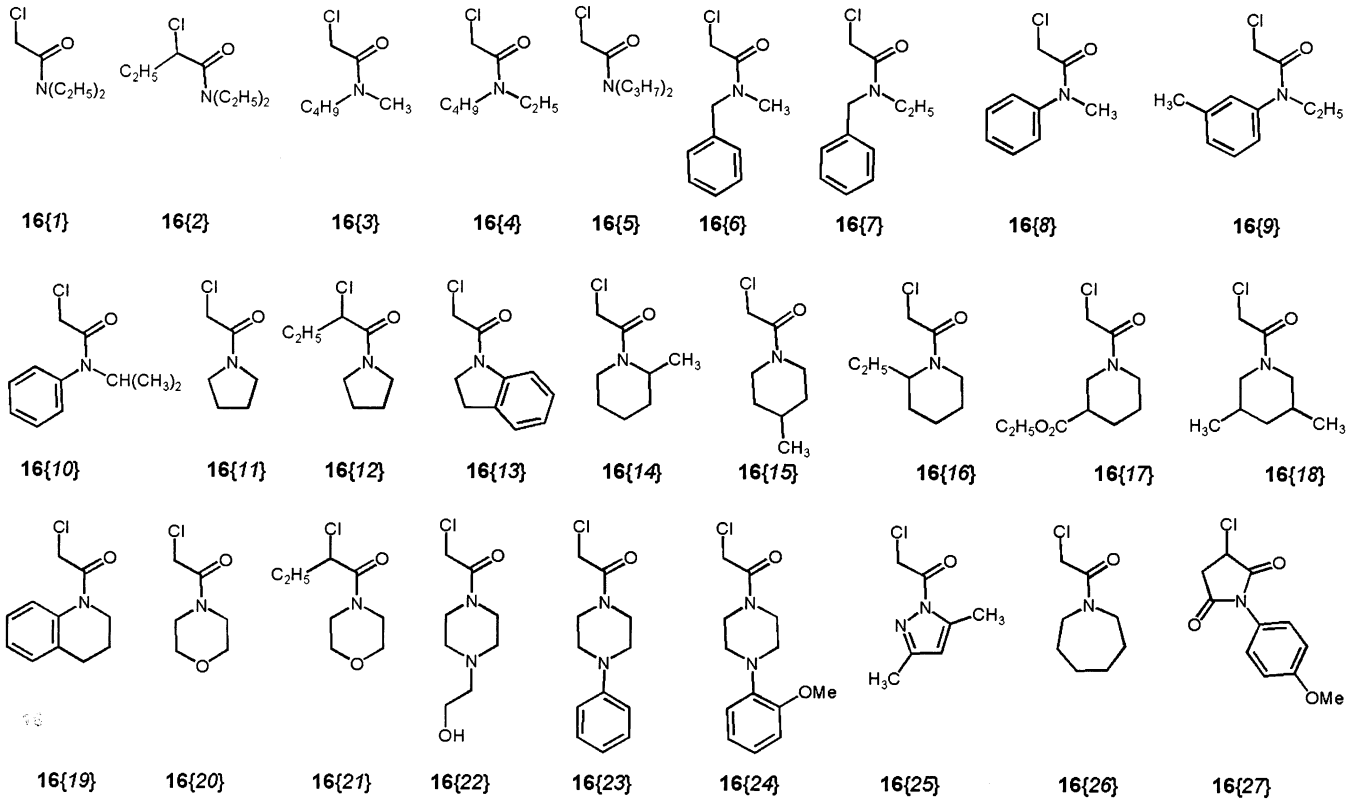


Figure 17. Diversity *N*,*N*-disubstituted α-chloroacylamides, **16**{*1*−*25*}.

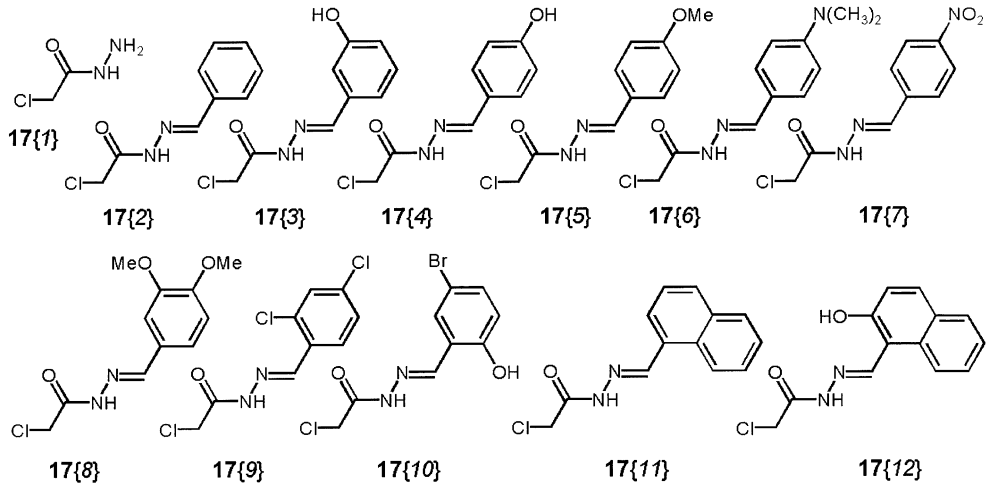


Figure 18. Diversity α-chloroacethydrazides, **17**{*1*−*12*}.

Hz, 2H), 4.20−4.30 (q, J = 6.8 Hz, 1H), 4.50 (s, 2H), 4.81 (d, J = 7.8 Hz, 2H), 6.23 (d, J = 7.6 Hz, 1H), 6.37 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.40 (s, 1H), 7.80−7.90 (m, 3H), 7.95 (s, 1H), 8.11 (d, J = 7.6 Hz, 1H), 8.18 (s, 1H) 9.13 (t, J = 7.6 Hz, 1H).

1-((3-Cyclohexyl-2-([2-(3,4-dihydroquinolin-1(2*H*)-yl)-2-oxoethyl)thio)-4-oxo-3,4-dihydroquinazolin-7-yl)carbonyl)piperidine-4-carboxamide, 2{***3*(*2*)**}.** Yield 72%; mp 231−232 °C; DMF; ^{1}H NMR δ 1.50−1.80 (m, 14H), 2.50−2.60 (m, 3H), 2.85 (t, J = 6.8 Hz, 2H), 3.55 (q, J = 6.8 Hz, 1H), 3.83 (t, J = 6.8 Hz, 2H), 4.25 (q, J = 6.9 Hz, 1H), 4.40 (s, 2H), 4.55 (q, J = 6.8 Hz, 1H), 6.50 (s, 2H), 7.02 (d, J = 7.6 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.20−7.26 (m, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.93 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H).

2-((7-((4-(Aminocarbonyl)piperidin-1-yl)carbonyl)-4-oxo-3-pentyl-3,4-dihydroquinazolin-2-yl)thio)-*N*,*N*-dibenzylmalonamide, 2{***3*(*3*)**}.** Yield 64%; mp 141−142 °C; DMF/*i*-PrOH; ^{1}H NMR δ 1.00 (t, J = 7.4 Hz, 3H), 1.35−1.45(m, 7H), 1.65−1.75 (m, 3H), 2.70−2.90 (m, 4H), 3.52 (q, J = 6.8 Hz, 1H), 4.11 (t, J = 6.8 Hz, 2H), 4.37 (d, J = 6.8 Hz, 4H), 5.40 (s, 1H), 6.70 (s, 1H), 7.20−7.25 (m, 10H), 7.43 (d, J = 7.6 Hz, 1H), 7.93 (s, 1H), 8.11 (d, J = 7.6 Hz, 1H), 8.7 (s, 2H).

3-[4-(Morpholin-4-ylcarbonyl)phenyl]-2-[(pyridin-4-ylmethyl)thio]quinazolin-4(3*H*)-one, 2{***4*(*1*)**}.** Yield 35%; mp 164−165 °C; DMF/*i*-PrOH; ^{1}H NMR δ 3.60−3.75 (m, 8H), 4.40 (s, 2H), 7.36−7.44 (m, 5H), 7.57 (d, J = 7.6 Hz, 2H), 7.63 (d, J = 7.6 Hz, 1H), 7.78 (t, J = 7.6 Hz, 1H), 8.10 (d, J = 7.6 Hz, 2H), 8.40 (d, J = 7.6 Hz, 1H).

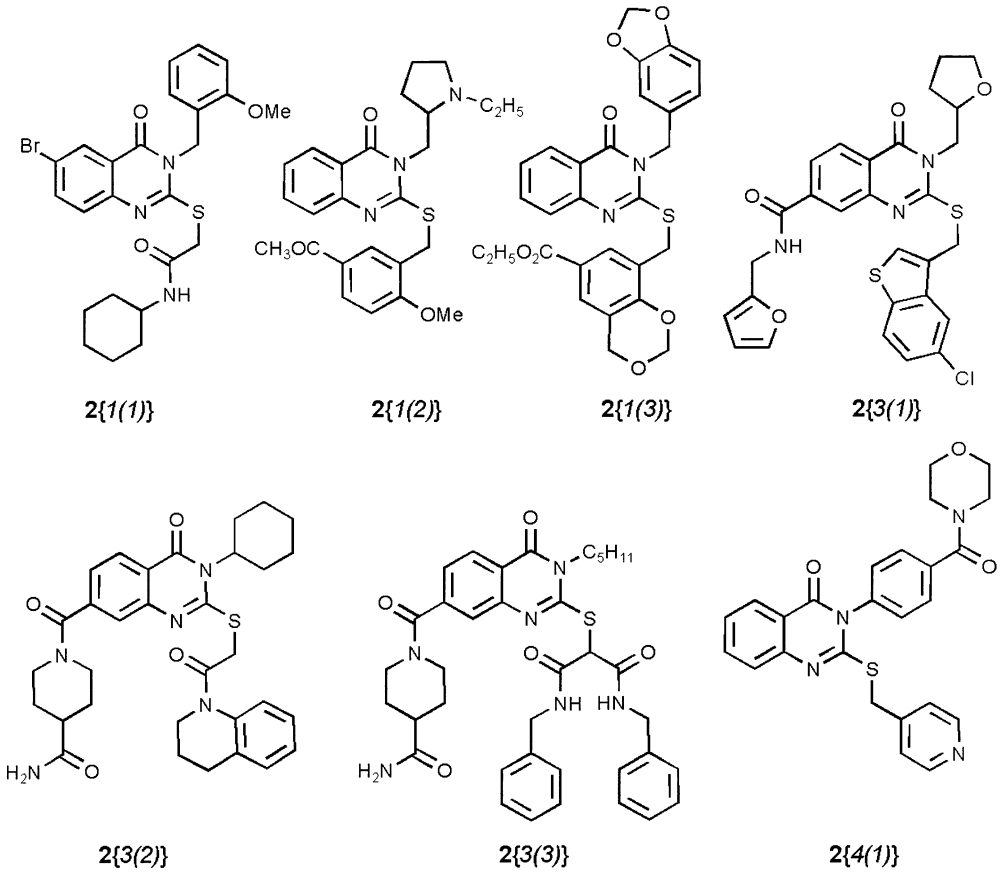


Figure 19. Examples of substituted 4-oxo-3,4-dihydroquinazoline-2-thioles, **2**{*1*−*4*}, synthesized.

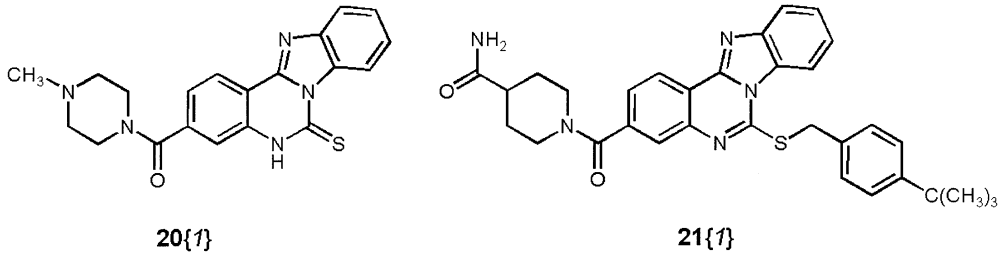
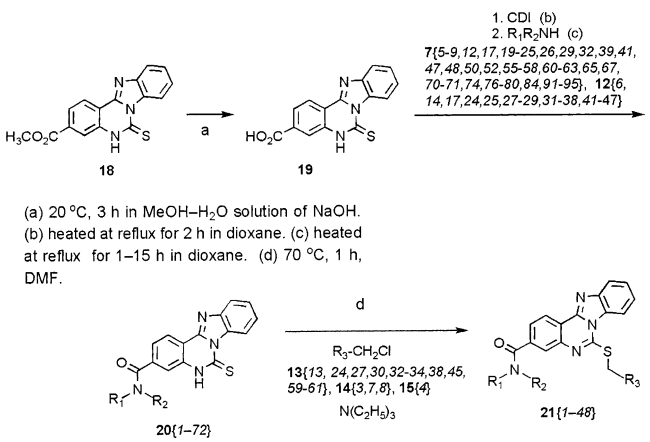


Figure 20. Examples from the synthesized benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thione-3-carboxamide library (**20**) and from the S-substituted 6-mercaptobenzimidazo[1,2-*c*]quinazoline-3-carboxamide library (**21**).

Benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thione-3-carboxylic Acid, 19. A 50-mL portion of a 20% aqueous solution of NaOH was added to an agitated suspension of 30.9 g (100 mmol) of methyl benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thione-3-carboxylate (**18**)[16] in 300 mL of methanol. The mixture was heated at reflux for 3 h, diluted with water, and neutralized with 30 mL of 10% hydrochloric acid. The precipitate was filtered and recrystallized from 300 mL of dimethylformamide, yielding 20.9 g (72%) of **19**; mp >360 °C; ^{1}H NMR δ 7.48 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.90 (d, J = 7.6 Hz, 1H), 8.00 (d, J = 7.6 Hz, 1H), 8.22 (s, 1H), 8.46 (d, J = 7.6 Hz, 1H), 9.40 (d, J = 7.6 Hz, 1H), 13.20 (s, 1H), 13.50 (s, 1H).

General Procedure for the Synthesis of Benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thione-3-carboxamides 20{*1*−*72*}. A 0.18-g (1.1 mmol) portion of 1,1′-carbonyldiimidazole was added to an agitated suspension of acid **19** (1 mmol) in 5 mL of anhydrous dioxane at 90 °C. The suspension was heated at reflux for 2 h, and 1.2 mmol of amine **7** or **12** was then added. The reaction mixture was heated at reflux from 1 to 15 h, depending on the reactivity of the amine. After cooling, the mixture was diluted with 20 mL of water and allowed to stand for 1−3 days to form the precipitate of amide **20**. The precipitate was filtered and recrystallized from *i*-PrOH, DMF, or a mixture of the two.



3-((4-Methylpiperazin-1-yl)carbonyl)benzimidazo[1,2-*c*]quinazoline-6(5*H*)-thione 20{*1*}. Yield 59%; mp 294 °C (dec); DMF/*i*-PrOH; ^{1}H NMR δ 2.20 (s, 3H), 2.30−2.45 (m, 4H), 3.35−3.45 (m, 2H), 3.75−3.85 (m, 2H), 7.36−7.44 (m, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.60 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 8.44 (d, J = 7.6 Hz, 1H), 9.36 (d, J = 7.6 Hz, 1H), 13.50 (s, 1H).

General Procedure for the Synthesis of S-Substituted 6-Mercaptobenzimidazo[1,2-*c*]quinazoline-3-carboxamides 21{1−48}. A 1.5-mmol portion of triethylamine and 1.2 mmol of alkylating agent **13**, **14**, or **15** were added to a warm (65−70 °C) solution of 1.0 mmol of benzimidazo-[1,2-*c*]quinazoline-6(5*H*)-thione (**20)** in 5 mL of DMF. The reaction mixture was stirred at 70 °C for ∼1 h. After cooling, the mixture was diluted with 10 mL of water, and the precipitate was filtered and washed with water and methanol and then recrystallized from a mixture of DMF and *i*-PrOH.

1-((6-((4-Isopropylbenzyl)thio)benzimidazo[1,2-*c*]quinazolin-3-yl)carbonyl)piperidine-4-carboxamide 21{*1*}. Yield 76%; mp 242 °C (dec); DMF/*i*-PrOH; ^{1}H NMR δ 1.30 (s, 9H), 1.70−1.85 (m, 3H), 2.35−2.45 (m, 5H), 3.45−3.53 (m, 1H), 4.70 (s, 2H), 6.70 (s, 1H), 7.20 (s, 1H), 7.34 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 7.6 Hz, 1H), 7.56 (d, J = 7.6 Hz, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.87 (s, 1H), 7.96 (d, J = 7.6 Hz, 1H), 8.45 (d, J = 7.6 Hz, 1H), 8.58 (d, J = 7.6 Hz, 1H).

Supporting Information Available. ^{1}H NMR spectra of synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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