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Quinoxalin-2(1*H*)-One Derivatives As Inhibitors Against Hepatitis C Virus

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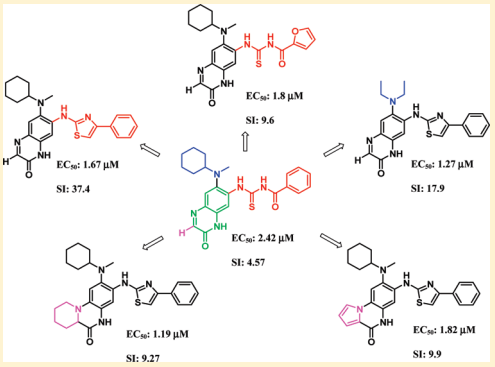
Supporting Information

ABSTRACT: Hepatitis C virus (HCV) infection is a serious problem worldwide, but no effective drugs are currently available. Through screening of our privileged structure library, quinoxalin-2(1*H*)-one derivative *N*-(7-(cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylcarbamothioyl)benzamide (compound **1**) was identified as potent HCV inhibitor in vitro. Subsequently, a structure−activity relationship analysis was carried out that showed *N*-(7-(cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylcarbamothioyl)-furan-2-carboxamide (compound **11**, EC_{50} = 1.8 μM, SI = 9.6), 6-(cyclohexyl(methyl)amino)-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1*H*)-one (compound **33**, EC_{50} = 1.67 μM, SI = 37.4), 2-(cyclohexyl(methyl)amino)-3-(4-phenylthiazol-2-ylamino)-7,8,9,10-tetrahydro-5*H*-pyrido[1,2-*a*]quinoxalin-6(6a*H*)-one (compound **60**, EC_{50} = 1.19 μM, SI = 9.27), 8-(cyclohexyl(methyl)amino)-7-(4-phenylthiazol-2-ylamino)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (compound **65**, EC_{50} = 1.82 μM, SI = 9.9), and 6-(diethylamino)-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1*H*)-one (compound **78**, EC_{50} = 1.27 μM, SI = 17.9) acted against HCV. The data from the structure−activity relationship study suggests that quinoxalin-2(1*H*)-one derivatives exhibited potent activity against HCV.



INTRODUCTION

Hepatitis C virus (HCV) belongs to the *flaviviridae* family and is a positive single-stranded RNA virus.[1] It was first identified in 1989 as the pathogen responsible for non-A and non-B hepatitis.[2] Currently, HCV infection is a significant health problem worldwide. An estimated 3% of the world's population (i.e., more than 170 million people) is infected by HCV, with 3−4 million new cases being reported each year.[3] Approximately 60−80% of these infections lead to the chronic form of hepatitis C virus that may lead to fibrosis, cirrhosis, and hepatocellular carcinoma. Unfortunately, there is no vaccine or specific antiviral drugs available against HCV. Interferon-based therapy was the main strategy for treatment of this disease for more than two decades.[4] Treatment with interferon α or PEG-interferon α, either alone or in combination with a broad spectrum antiviral ribavirin, is the current standard of care. However, this treatment regimen is only effective for 40−60% of people infected with HCV genotype-1, which accounts for the majority of infections in the U.S., Europe, and Asia.[5,6] Meanwhile, serious adverse effects, such as depression and flu-like symptoms, also limit its application. Recently, much effort has been devoted toward developing drugs that inhibit viral replication. The most promising agents under development are viral protease and polymerase inhibitors. Several small-molecule inhibitors of NS3/4A protease are currently in preclinical or clinical studies, such as ITMN-191, telaprevir, and boceprevir[a] (Figure 1).[7] HCV NS5B polymerase is another attractive target for antiviral therapy. The inhibitors of NS5B polymerase include nucleoside (such as NM-283 and R7128) and nonnucleoside polymerase inhibitors (such as PF-00868554 and VCH-916) (Figure 1).[8] However, the emergence of drug resistance is the major limitation for anti-HCV therapies targeted at viral protease or viral polymerase.[9] Therefore, there is an urgent need to develop new classes of antiviral agents for the treatment of HCV infection.

Antiviral screening of our privileged structure library was carried out, and compound **1**, *N*-(7-(cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylcarbamothioyl)benzamide (Figure 2), was identified as a potent HCV inhibitor in vitro. Quinoxalinone is an important subunit in drugs with many biological activities, such as antitumor, antimicrobial, and antithrombotic functions.[10] However, as one type of small molecular heterocyclic compound, quinoxalin-2(1*H*)-one has not been reported for its anti-HCV activity. As the compound

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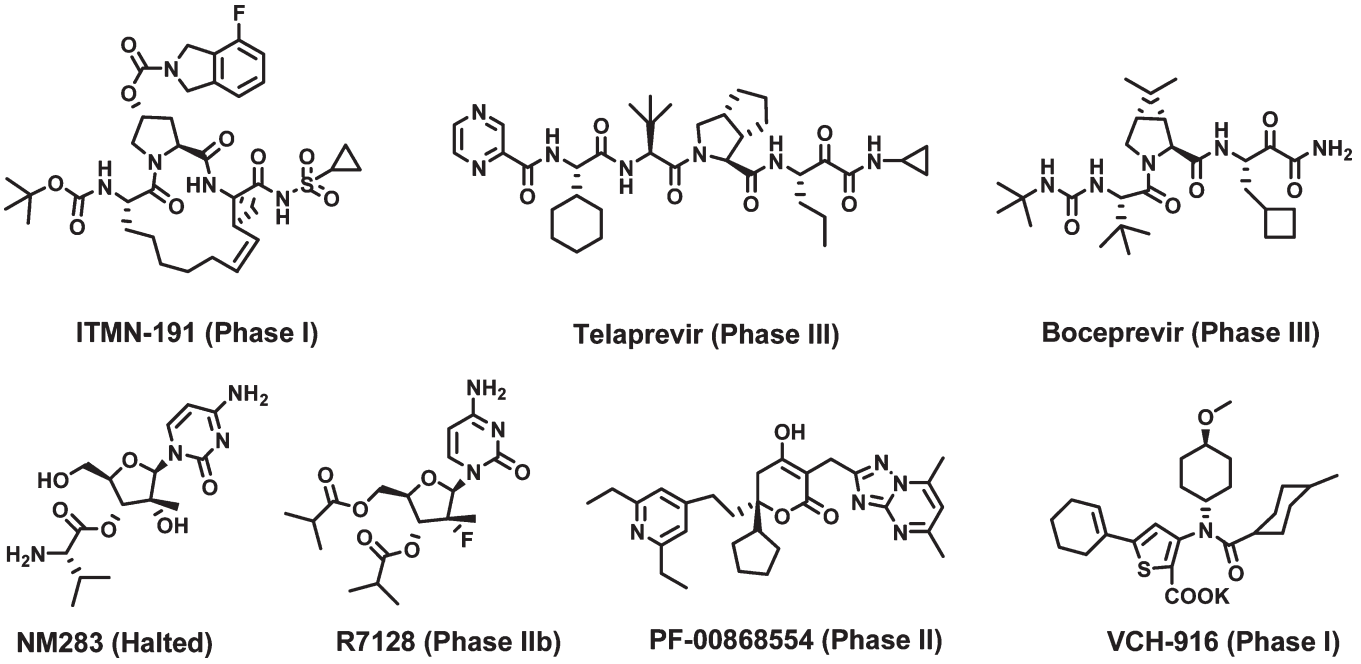

Figure 1. Candidate drugs under development for treatment of hepatitis C virus infection.

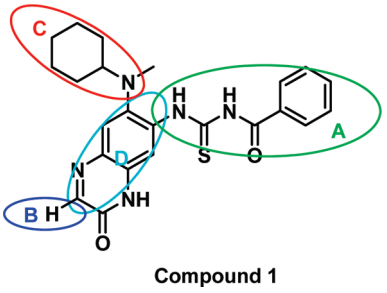

Figure 2. Structure of compound **1**.

contains a unique quinoxalin-2(1*H*)-one scaffold amenable to chemical modification, we carried out a structure−activity relationship (SAR) investigation of compound **1** with the goal to develop compounds with improved efficacy against HCV and lower cytotoxicity properties. The results are reported in this article.

RESULTS AND DISCUSSION

Chemistry. To facilitate the synthesis and subsequent SAR analysis, compound **1** was characterized from the four major segments indicated in Figure 2. To modify segment A, the core structure **4** was synthesized according to our previous report (Scheme 1).[11] In the presence of diisopropylethylamine (DIPEA), two fluoro atoms of 1,5-difluoro-2,4-dinitrobenzene (DFDNB) were substituted by an equivalent methyl 2-aminoacetate hydrochlorate and subsequently *N*-methylcyclohexanamine to give compounds **2** and **3**. After reduction of the two nitro groups using 10% palladium on activated carbon, followed by a self-cyclization, the key intermediate **4** was obtained in total yield of 68%.

Segment A Modifications (Schemes 2−5). To investigate the medicinal potential, a series of compounds with modifications of segment A were considered from its three pharmacophores, including phenyl, thiourea, and acyl groups. To examine the effect of the phenyl group for antiviral activity, compound **4** was reacted with various acyl isothiocyanates with different R_1 groups, including electron-withdrawing, electron-donating, and large aromatic hydrocarbon groups, to provide compounds **5**−**13** (Scheme 2). The selection of various acyl isothiocyanates was further considered, including halogenations, aromatic heterocycles, and double bonds, for their substituent influence on the benzoyl group of segment A. Second, the acyl thiourea was replaced by thiourea (compounds **14**−**17**) or urea (compounds **18**−**19**) through the reaction of **4** with isothiocyanates or isocyanates to simplify the acyl thiourea group. The guanidino group, a classic bioisostere of the thiourea group, is an important pharmacophore in many drugs. Therefore, the acyl thiourea group was replaced by a guanidino group mimicking thiourea and urea. As illustrated in Scheme 3i, the key intermediate cyanamide **20** was predicted to form from the reaction of cyanogen bromide with compound **4**. However, the reactivity of the 7-amino group of compound **4** was too weak to obtain the target compound, so the alternative Scheme 3ii was designed and was successfully performed. Compound **1** was first converted into the free thiourea compound **21** in the presence of K_2CO_3. The reaction of **21** with CH_3I in ethanol afforded the methylated compound **22** that offered a route to compounds **24**−**30** by refluxing **22** with primary amines in pyridine.[12] However, when intermediate **22** was reacted with aniline, compound **23** did not form, even in the presence of $HgCl_2$.[13] A thiohydantoin group was introduced to block the NH group H-bonding donor of the thiourea moiety and to fix the steric configuration. As shown in Scheme 4i, from the reaction of compound **14** with 2-chloroacetyl chloride in the presence of Et_3N, a compound with four possible structures, **31**, **31′**, **31″**, or **31‴**, was obtained.[14] From the ^{1}H NMR spectra obtained, the two H atoms of the methylene group of thiohydantoin showed geminal coupling 4.11 (d, 1H, J = 17.4 Hz) and 4.19 (d, 1H, J = 17.4 Hz), indicating that the

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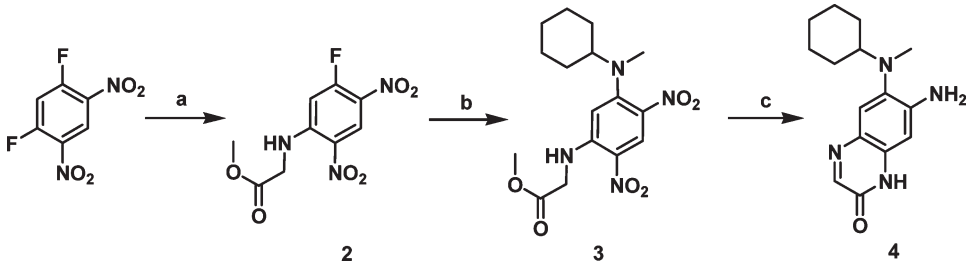
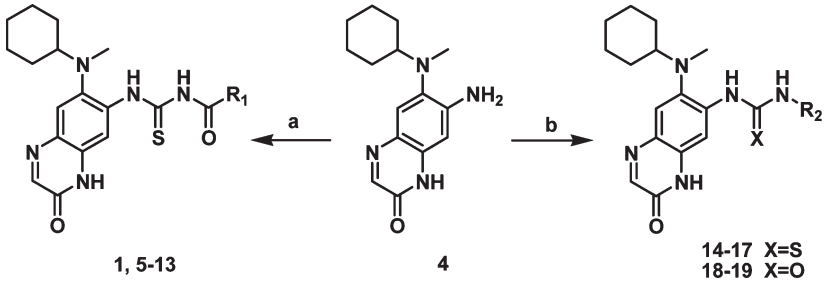
Scheme 1[a]



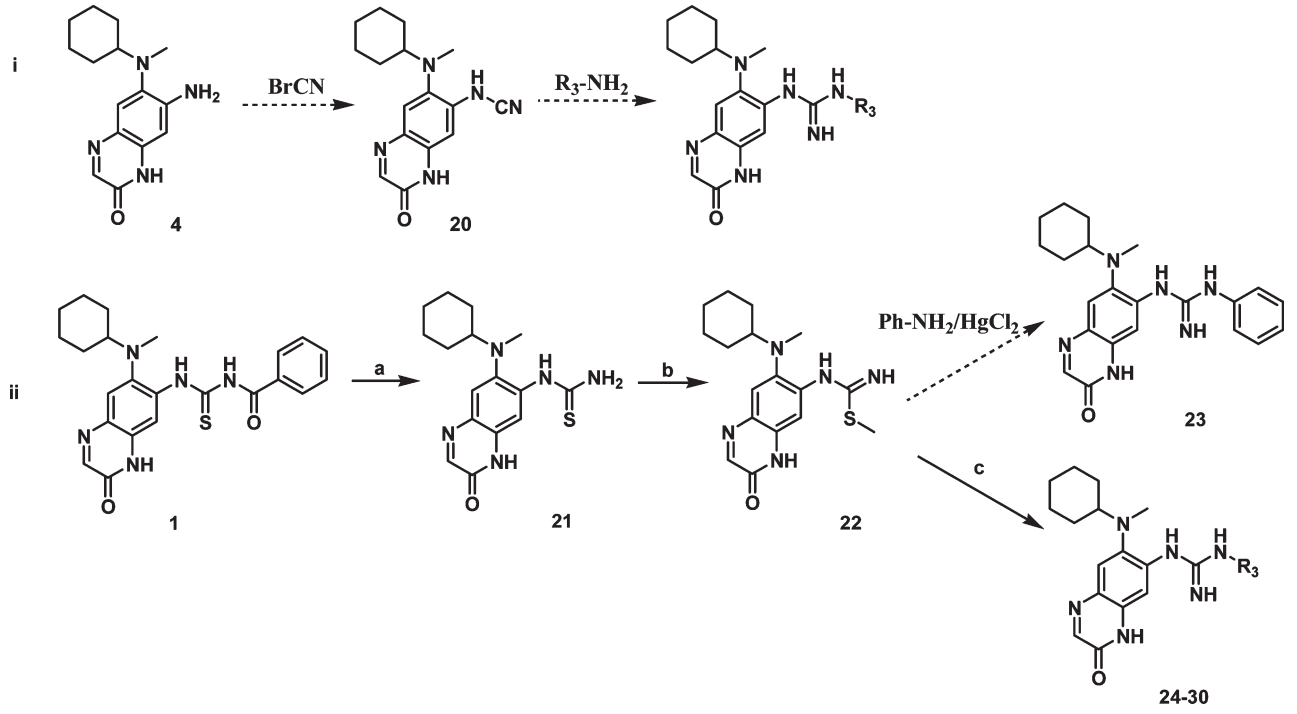
[a] Reagents and conditions used: (a) $NH_2CH_2COOCH_3 \cdot HCl$, DIPEA, THF, room temperature; (b) *N*-methylcyclohexanamine, DIPEA, THF, reflux; (c) 10% Pd/C, NH_4COOH, THF/CH_3CH_2OH, room temperature.

Scheme 2[a]



[a] Reagents and conditions used: (a) R_1CONCS, acetone, reflux; (b) R_2NCX, THF, reflux.

Scheme 3[a]



[a] Reagents and conditions used: (a) K_2CO_3, CH_3OH/H_2O, 75 °C; (b) CH_3I, CH_3CH_2OH, 50 °C; (c) R_3-NH_2, pyridine, reflux.

methylene group of the thiohydantoin was adjacent to a stereo 7-*N* atom. This observation excluded the possibility of compounds **31**″ and **31**‴. Further structural identification using nuclear Overhauser effect spectroscopy (NOESY) revealed that the methylene group correlated with 6-*N*-methylcyclohexanamine, but not with a phenyl group (Figure 3, **31**, the NOESY is

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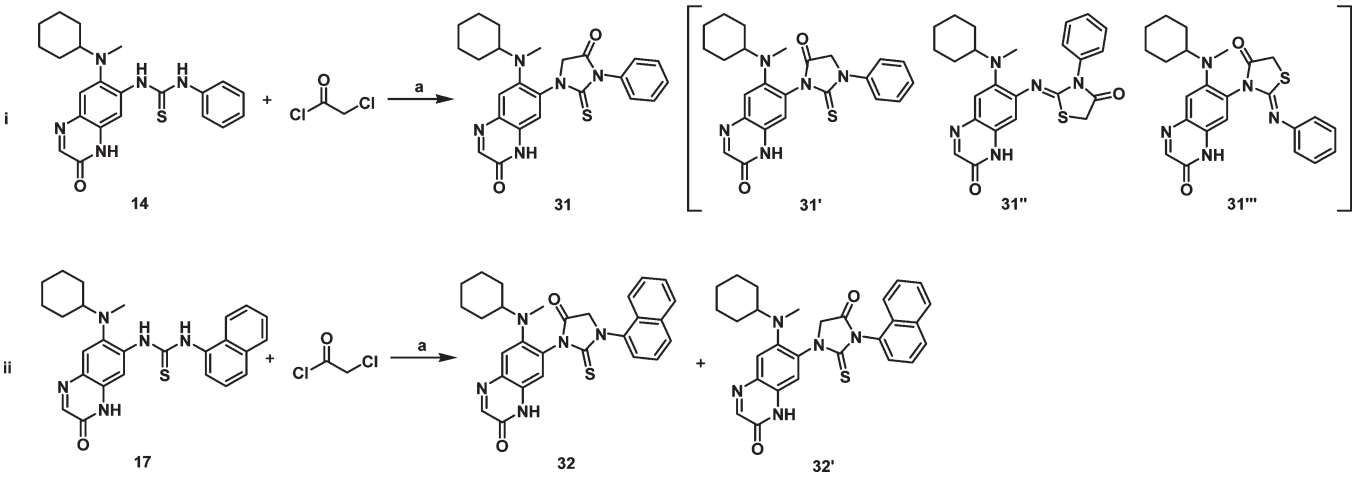
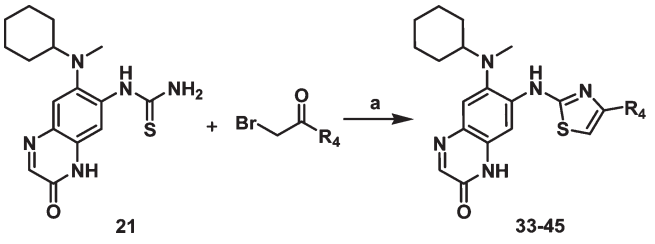
Scheme 4[a]



[a] Reagents and conditions used: (a) Et_3N, 1,4-dioxane, reflux.

Scheme 5[a]



[a] Reagents and conditions used: (a) CH_3CH_2OH, reflux.

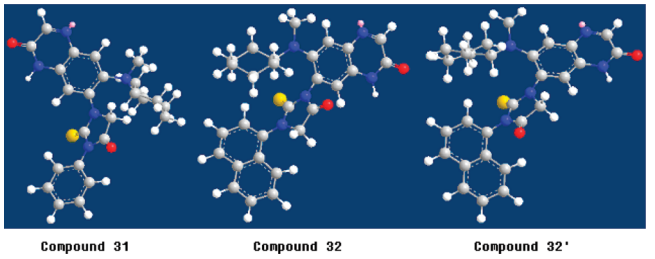


Figure 3. Three dimensional structures of compounds **31**, **32**, and **32′** plotted using the Chem3D software package.

shown in the Supporting Information). Taking all this information together, the final compound was determined to be compound **31**. However, in the reaction of compound **17** with 2-chloroacetyl chloride, two final products were obtained in yields of 59% (**32**) and 34% (**32′**) (Scheme 4ii). Interestingly, NOE data was not indicated in NOESY experiments on **32** and **32′**. The difference in the ^{1}H NMR spectra arises from the chemical shift of the methylene group of thiohydantoin **32** 4.31 (d, 1H, J = 17.1 Hz) and 4.51 (d, 1H, J = 17.1 Hz), which is shifted to a lower field compared to **32′** 4.14 (d, 1H, J = 17.1 Hz) and 4.23 (d, 1H, J = 17.1 Hz). It is thought that the naphthalene group deshields the methylene group of thiohydantoin **32**, and so it is concluded that the methylene group of compound **32**, but not compound **32′**, is closed to the naphthalene group (Figure 3).

The thiocarbonyl group is a reactive group that can have potential adverse effects on patients who take the drug over a long period of time. Therefore, we further cyclized it into a thiazole moiety. Compounds **33**−**45** were prepared from the reaction of **21** with various commercially available α-bromo substituted ketones that offer thiazole analogues of compound **1** (Scheme 5).

Segment B Modifications (Schemes 6−8). Segment B was studied because it is located directly in the quinoxalin-2(1*H*)-one core structure. Alkyl, aryl, or thioether groups were introduced to examine the effect of steric hindrance, $\pi-\pi$ interactivity, and the change in hydrophobicity (compounds **51**−**55**, Scheme 6). Intermediates **48a**−**48d** were synthesized according to a procedure similar to Scheme 1, where the R_5 group was introduced using different amino acid alkyl esters. The difference was that compound **48e** was obtained from a reduction reaction via $SnCl_2$/HCl. Accordingly, **49a**−**49e** were obtained after reaction of benzoyl isothiocyanate, which further afforded free thiourea compounds **50a**−**50e** after treatment with K_2CO_3. On cyclization of **50a**−**50e** with 2-bromo-1-phenylethanone, compounds **51**−**55** were obtained.

Notably, two tricyclic compounds **60** and **65** were constructed (Schemes 7 and 8), which provided a large hydrophobic region and a mimic of the 3,4-double bond of segment B. As illustrated in Scheme 7, starting from **46**, methyl piperidine-2-carboxylate was used to prepare the disubstituted compound **56**, which was subsequently reduced via catalytic hydrogenation to obtain compound **57**. Condensation of **57** with benzoyl isothiocyanate was followed by hydrolysis of the resulting compound **58** and subsequent cyclization of **59** with 2-bromo-1-phenylethanone to give the desired compound **60**.

While attempting to prepare the anticipated compound **65′**, intermediate **62′** could not be obtained. Further investigation showed that **62′** was converted into **62** under the experimental conditions used,[15] which allowed the synthesis of compound **65** (Scheme 8).

Segment C Modifications (Scheme 9). The significance of the *N*-methylcyclohexanamine moiety for anti-HCV activity was examined using segment C. The role of any electronic effect was explained by introducing an *N*-methylbenzenamine group (**70**). Steric hindrance and the necessity of the *N*-methyl moiety on the

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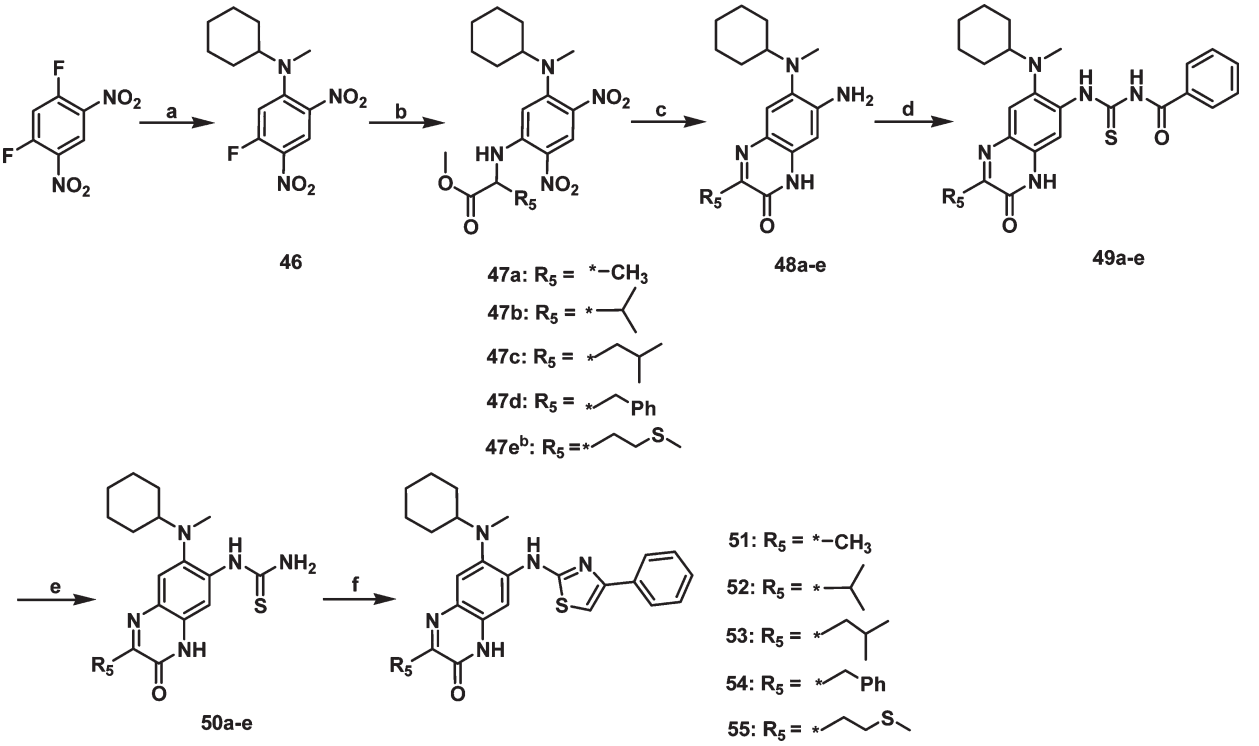
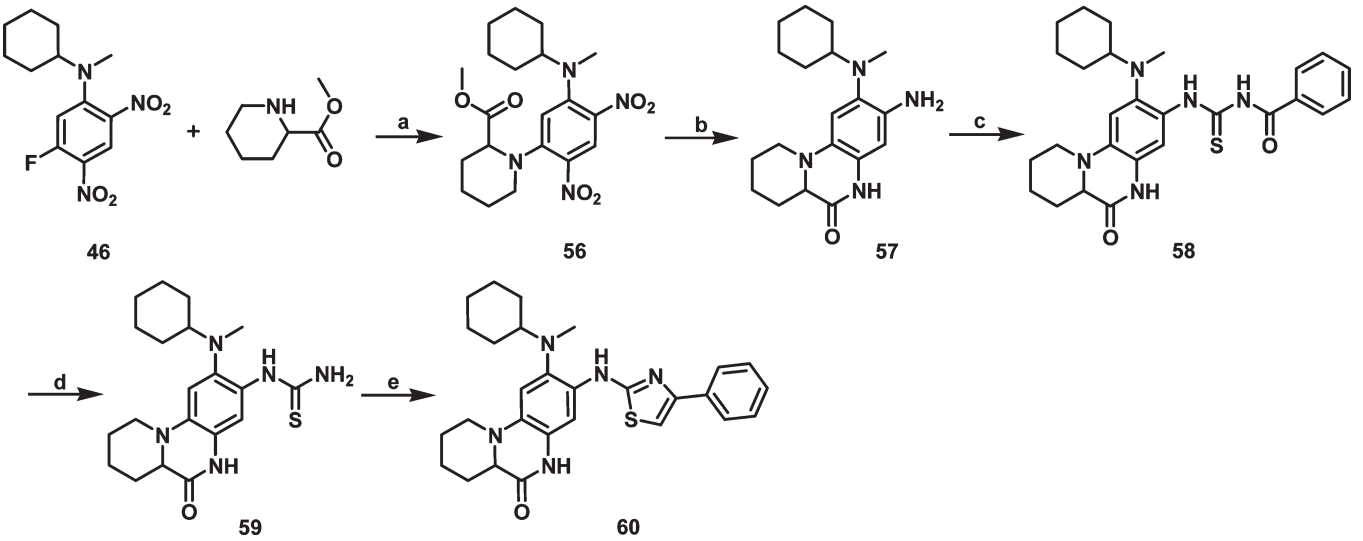
Scheme 6[a]



[a] Reagents and conditions used: (a) *N*-methylcyclohexanamine, DIPEA, THF, room temperature; (b) $R_5CH(NH_2)COOCH_3 \cdot HCl$, DIPEA, THF, reflux; (c) 10% Pd/C, NH_4COOH, THF/CH_3CH_2OH, room temperature; (d) PhCONCS, acetone, reflux; (e) K_2CO_3, CH_3OH/H_2O, 75 °C; (f) $PhCOCH_2Br$, CH_3CH_2OH, reflux. [b] Reagents and conditions used: (c) $SnCl_2 \cdot 2H_2O$, 36% HCl, CH_3CH_2OH, reflux.

Scheme 7[a]



[a] Reagents and conditions used: (a) DIPEA, THF, reflux; (b) 10% Pd/C, NH_4COOH, THF/CH_3CH_2OH, room temperature; (c) PhCONCS, acetone, reflux; (d) K_2CO_3, CH_3OH/H_2O, 75 °C; (e) $PhCOCH_2Br$, CH_3CH_2OH, reflux.

N-methylcyclohexanamine group were investigated by introducing an *N*-ethylcyclohexanamine group (**71**). Considering the drug-like properties of the entire molecule, the *N*-methylcyclohexanamine group was replaced by various six-member rings, such as piperidine, morpholine, and 1-methylpiperazine (**72**−**76**). Mimicking *N*-cyclohexanamine using a chain alkyl amine was also investigated (**77**−**79**). When the N atom was replaced by an O atom, a substituent of cyclohexanol could be introduced (**80**).

As shown in Scheme 9, the reaction of methyl-2-(5-fluoro-2,4-dinitrophenylamino)acetate (**2**) with various commercially

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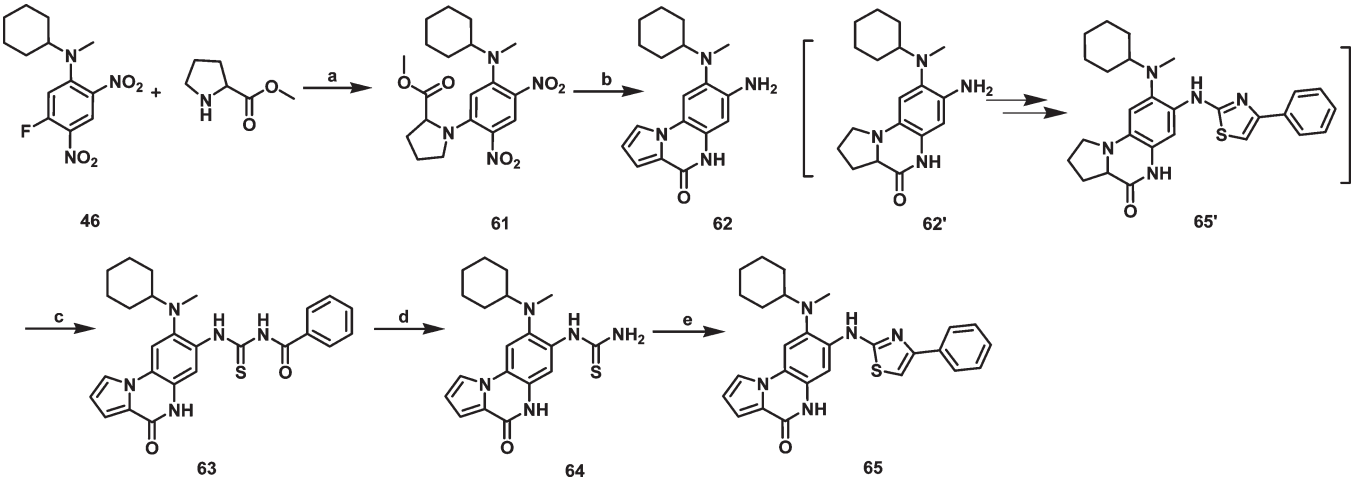
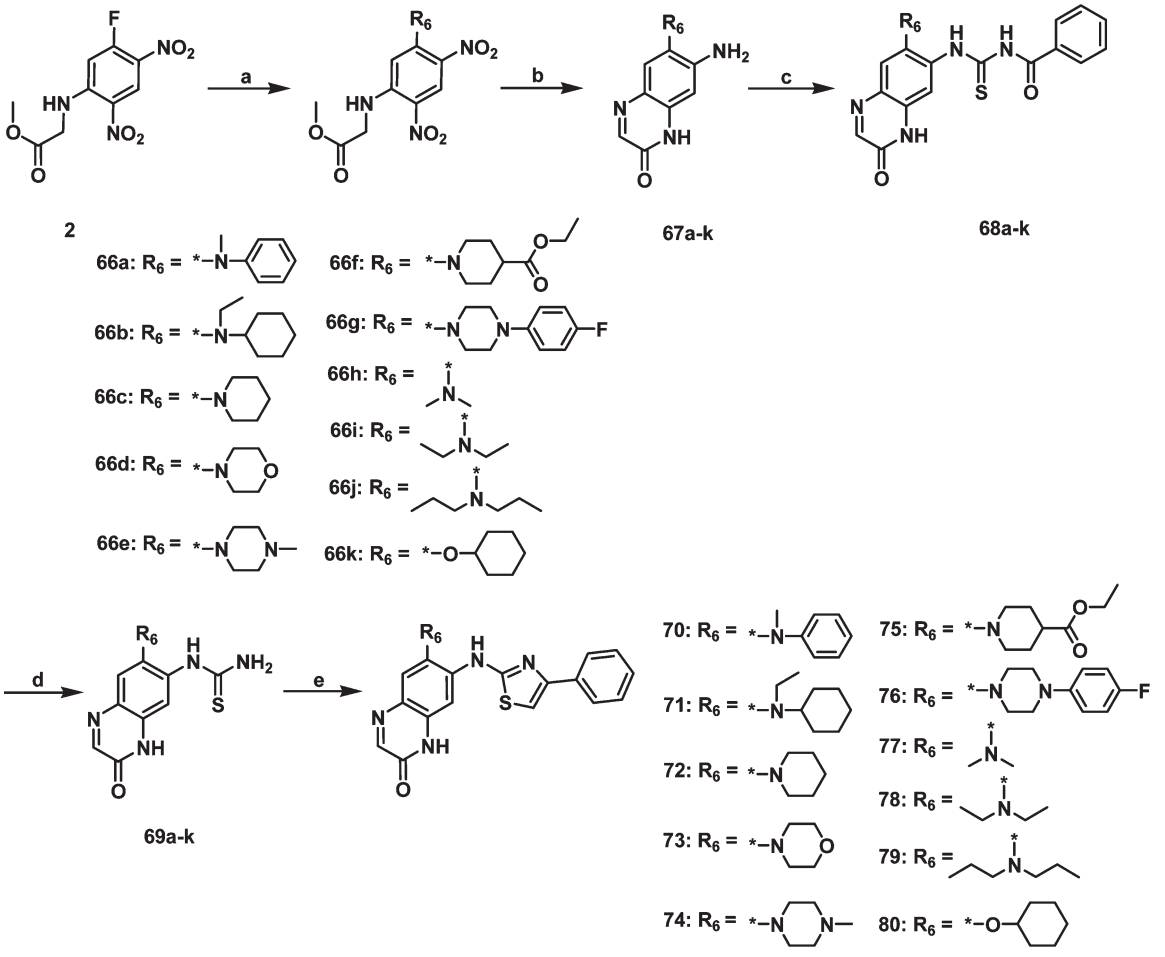
Scheme 8[a]



[a] Reagents and conditions used: (a) DIPEA, THF, reflux; (b) 10% Pd/C, cyclohexene, reflux; (c) PhCONCS, acetone, reflux; (d) K_2CO_3, CH_3OH/H_2O, 75 °C; (e) $PhCOCH_2Br$, CH_3CH_2OH, reflux.

Scheme 9[a]



[a] Reagents and conditions used: (a) secondary amine or sodium cyclohexanolate, DIPEA, THF, reflux; (b) 10% Pd/C, NH_4COOH, THF/CH_3CH_2OH, room temperature; (c) PhCONCS, acetone, reflux; (d) K_2CO_3, CH_3OH/H_2O, 75 °C; (e) $PhCOCH_2Br$, CH_3CH_2OH, reflux.

available secondary amines or sodium alcoholate in the presence of a base gave the corresponding intermediates **66a**−**66k**, followed by a reduction and then self-cyclization to afford the key structures **67a**−**67k**. Similar to the previous schemes shown,

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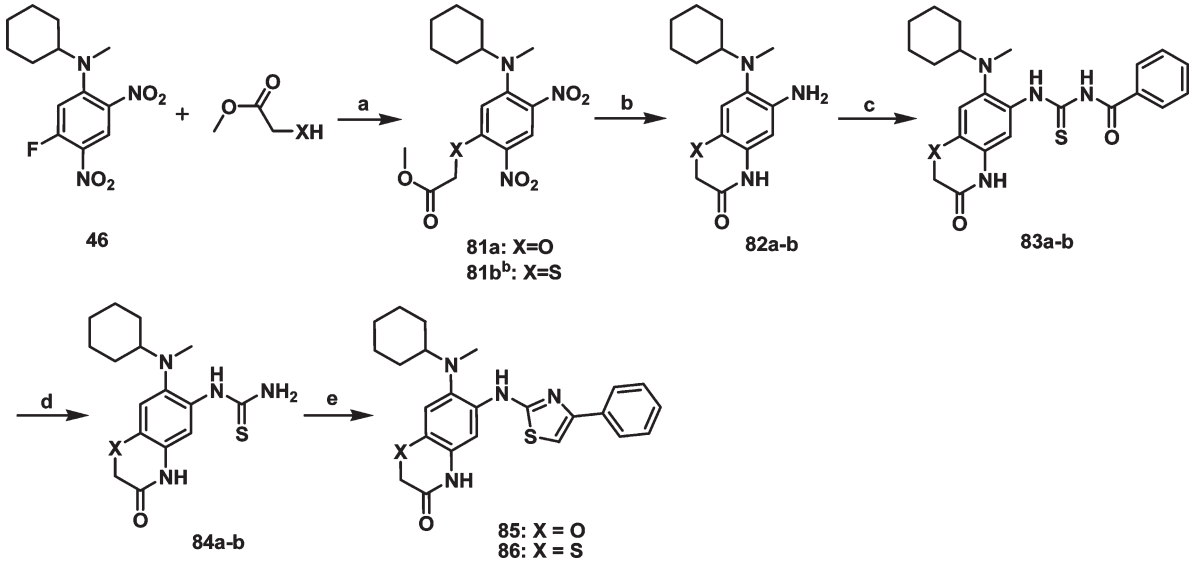
Scheme 10[a]



[a] Reagents and conditions used: (a) $HOCH_2COOCH_3$ or $HSCH_2COOCH_3$, DIPEA, THF, reflux; (b) 10% Pd/C, NH_4COOH, THF/CH_3CH_2OH, room temperature; (c) PhCONCS, acetone, reflux; (d) K_2CO_3, CH_3OH/H_2O, 75 °C; (e) $PhCOCH_2Br$, CH_3CH_2OH, reflux. [b] Reagents and conditions used: (b) $SnCl_2 \cdot 2H_2O$, 36% HCl, CH_3CH_2OH, reflux.

67a−**67k** were condensed with benzoyl isothiocyanate, followed by hydrolysis and subsequent cyclization with 2-bromo-1-phenylethanone, to prepare the target compounds **70**−**80**.

Segment D Modifications (Scheme 10). When we fixed the substituent on segments A−C, the role of the quinoxalin-2(1*H*)-one core structure was then elucidated by replacing it with other structures. In the presence of DIPEA in THF, the intermediates **81a** and **81b** were prepared by coupling **46** with methyl 2-hydroxyacetate or methyl 2-mercaptoacetate, respectively. The reduction of the nitro groups of **81a** and **81b** with Pd/C or $SnCl_2$, and then self-cyclization, gave compounds **82a** and **82b**, respectively. The target compounds **85** and **86** were obtained following reaction steps c−e in Scheme 9.

Anti-HCV Activity in Vitro. All the synthesized compounds were evaluated for anti-HCV activity and cytotoxicity in the HCV RNA replicon assay in Huh 7 ET cells, as described in a previous publication.[16] The results are summarized in Tables 1−8. Briefly, the concentration of compound inhibiting HCV RNA replication activity by 50% (EC_{50}), the concentration of compound decreasing cell viability by 50% (IC_{50}), and the selective index (SI) is presented.

Our initial effort to outline the SAR values of segment A focused on the replacement of substituents of the phenyl group (Table 1). On replacement of the phenyl group by a 4-fluorophenyl group (**5**, EC_{50} = 2.97 μM), the potency against the HCV replicon was retained, compared to compound **1**. Similar results were observed for a 4-CF_3O-phenyl group (**6**) with an EC_{50} value of 2.33 μM. In the case of a 3-CF_3-phenyl group (**7**), a significant reduction in cytotoxicity was observed, however, anti-HCV activity was lost. Introduction of an electron-donating substituent (CH_3O−, **8**) or π−π interactions (**9** and **10**) also decreased the antiviral activity. Mimicking the phenyl group using different heterocycles gave variable results. The furan analogue **11** exhibited the most potent antiviral activity in the series, with an EC_{50} value of 1.8 μM and low cytotoxicity (17.28 μM), resulting in a selectivity index approaching 10-fold (SI = 9.6). Other mimicking analogues **12** and **13** did not show an improved antiviral inhibitory potency compared to compound **1**. None of the other compounds had a significant selection index.

Further modifications of segment A are summarized in Tables 2−5. Removal of the carbonyl group from **1** gave the thiourea analogue **14**, which showed a greatly reduced activity against HCV. Introduction of the electron-withdrawing group 4-fluoro-phenyl **15**, 3-CF_3-phenyl **16**, or large aryl group naphthyl **17** also resulted in inactive compounds (Table 2). These results imply that simplifying the acyl thiourea moiety into a thiourea group is not appropriate for anti-HCV activity. Changing the thiourea moiety to a bioisostere urea group gave compounds **18** and **19**, which had a higher toxicity to the virus host cells. The effect on the anti-HCV activity of the guanidino group is shown in Table 3. Compound **24**, which changed the benzoylthiourea group to a benzylguanidino group, exhibited an EC_{50} value of 11.44 μM. Furthermore, neither the introduction of an electron-withdrawing group (F^- **25**, Cl^- **26**, CF_3^- **27**, and CF_3O^- **28**) nor an electron-donating group (CH_3O^- **29**) provided an obvious potency or improvement in the selectivity index. A pyridine mimic of the phenyl moiety was also disadvantageous (**30**). All of these suboptimal results suggest that the introduction of a urea moiety or an H-bond donor (i.e., the NH group of the guanidino group) contributed a reduction in potency. Introduction of a thiohydantoin group (**31** and **32**) was also unfavorable for the antiviral potency (Table 4).

Cyclization of the thiourea moiety to a thiazole ring provided compound **33**, which had a significantly reduced cytotoxicity compared to compound **1** (Table 5, **33**, EC_{50} = 1.67 μM, IC_{50} = 62.47 μM, SI = 37.4). Various groups were tested to identify the optimal substituent for the R_4 group. The 4-fluoro-phenyl substitutive compound **34** had an EC_{50} value of 5.26 μM, and the 4-chloro-phenyl substitutive compound **35** (EC_{50} = 5.39 μM) had a reduced antiviral activity and selection index. These results show that halogen substituents for R_4 may be harmful to the anti-HCV potency. The same trend was observed for a cyano group,

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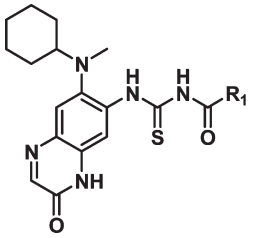
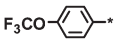
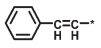
Table 1. Inhibitory Effects of Quinoxalin-2(1*H*)-one Derivatives on HCV Replication in Huh 7 Cells (Modification of the Phenyl Group)



Compound	R_1	Anti-HCV activity EC_{50} (μM)	Cytotoxicity IC_{50} (μM)	SI[a]
1		2.42	11.05	4.57
5		2.97	11.38	3.8
6		2.33	6.47	2.78
7		4.08	31.51	7.5
8		5.16	15.89	3.1
9		6.77	10.96	1.6
10		5.48	9.98	1.82
11		1.8	17.28	9.6
12		3.27	12.56	3.84
13		16.4	34.49	2.1
rIFNα-2b		0.06 IU/mL	> 2 IU/mL	> 33.3

[a] SI calculated as IC_{50}/EC_{50}.

which is the bioisostere of the chloro atom (**36**, $EC_{50} = 6.07\ \mu M$). Adding electron density to the phenyl group by the addition of an electron-donating moiety yielded compounds **37** and **38**. Both of these compounds were devoid of antiviral activity. Furthermore, the replacement of the phenyl group of **33** with a naphthyl moiety resulted in **39**, which exhibited comparable cytotoxicity but had a lower selectivity index than compound **33**. The biphenyl analogue **40** had no measurable potency against HCV but with lower cell toxicity. We hypothesized that the larger aryl substituent may reduce the inhibitory activity by increasing the $\pi-\pi$ interactions between the compound and the target. Therefore, the compounds were tested with further modification of the phenyl group into its bioisosteres, such as furan **41**, thiophene **42**, and pyridine **43**. None of these analogues showed an improved potency. The necessity of a phenyl group in R_4 was further supported by changing it into a CF_3 group, which also led to a loss in anti-HCV activity (**44**). Fixation of the steric configuration between the thiazole group and the phenyl moiety on **33** by a methylene group yielded compound **45**, which exhibited a marked cytotoxicity. All of the data in Table 5 supports the conclusion that the thiazole−phenyl moiety was favorable for anti-HCV potency as well as having lower cytotoxicity.

Next, modifications of segment B (R_5) were investigated in detail (Table 6) when segment A was maintained as the thiazole−phenyl moiety. In principle, lower alkyl groups can improve the liposolubility of small molecules and block

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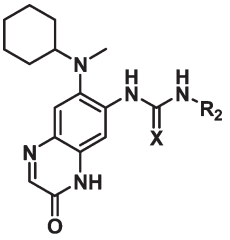
Table 2. Inhibitory Effects of Quinoxalin-2(1*H*)-one Derivatives on HCV Replication in Huh 7 Cells (Replacement of the Aromatic Acyl Thiourea Group by a Thiourea and Urea Group)



Compound	X	R_2	Anti-HCV activity EC_{50} (μM)	Cytotoxicity IC_{50} (μM)	SI[a]
14	S		> 20	49.56	<2.8
15	S		> 20	64.31	<3.2
16	S		> 20	78.43	<3.9
17	S		> 20	43.64	<2.2
18	O		11.38	5.52	0.5
19	O		9.84	5.33	0.5
rIFNα-2b			0.06 IU/mL	> 2 IU/mL	>33.3

[a] SI calculated as IC_{50}/EC_{50}.

metabolism sites. However, methyl (**51**), isopropyl (**52**), and isobutyl (**53**) group R_5 substituents demonstrated lower in vitro potency than an H atom did (**33**). The replacement of the R_5 group with an aromatic group (benzyl, **54**) also made the compound inactive. Similarly, introducing a thioether group on R_5 also completely removed the activity (compound **55**). Cyclization at the 3- and 4- positions of **33** with a six-member ring yielded compound **60**, which improved the anti-HCV activity and had a good selectivity index (EC_{50} = 1.19 μM, IC_{50} = 11.03 μM). Another tricyclic compound **65** also had a good antiviral potency and an acceptable cytotoxicity (EC_{50} = 1.82 μM, IC_{50} = 18.01 μM). From multiple modifications and the corresponding anti-HCV results, we concluded that substitution of the R_5 group may be prevented by steric limitations, but the 3,4-double bond could be mimicked by a cycloalkyl group.

In an effort to obtain an increased potency, we studied the effect of R_6 substitutions (segment C, Table 7). Compounds **70**−**80** were initially assessed at a single concentration of 20 μM. All potentially active or cytotoxic compounds in the primary assay were then evaluated further in a dose−response assay. Replacement of R_6 with *N*-methylbenzenamine (**70**) reduced the compound's activity. We proposed that introducing π−π interactions from an aromatic group may be harmful for the anti-HCV potency. Changing the *N*-methylcyclohexanamine group of compound **33** to *N*-ethylcyclohexanamine provided compound **71**, which showed no activity in the initial single dose screening. This may be because of steric hindrance at this position. Moving the N atom of the R_6 substituent to various heterocyclic aliphatics also did not improve the activity against HCV. For example, compound **72**, with a piperidine substitution on R_6, showed only a 9% inhibition under the test conditions. Introducing an ethyl ester (**75**) to compound **72** did not significantly change the activity of the compound. Morpholine substitution (**73**) resulted in a cytotoxicity value (IC_{50}) of 58.32 μM but resulted in a near 3-fold loss of inhibitory activity against HCV compared with compound **33**. Moreover, introduction of piperazine analogues yielded a lower activity of **74** and an inactive **76** under the test conditions. An alternative strategy to modify R_6 with a chain alkyl amine gave different results. Replacement of R_6 with dimethylamine (**77**) led to a complete loss of anti-HCV activity. It is interesting to note that similar antiviral potency but higher cytotoxicity of compound **78** (EC_{50} = 1.27 μM, IC_{50} = 22.78 μM, SI = 17.9) with a diethylamine group at R_6 was achieved compared to the R_6 with *N*-methylcyclohexanamine of compound **33**. However, further extension of the alkyl chain of a dipropylamine group (**79**) was disadvantageous with EC_{50} = 3.81 μM. Taking all

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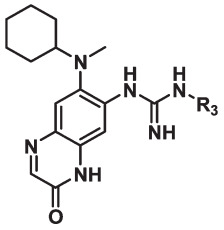
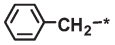
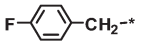
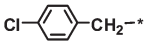
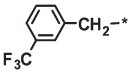
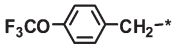
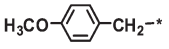
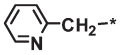
Table 3. Inhibitory Effects of Quinoxalin-2(1*H*)-one Derivatives on HCV Replication in Huh 7 Cells (Replacement of the Aromatic Acyl Thiourea Group by a Guanidino Group)



Compound	R_3	Anti-HCV activity EC_{50} (μM)	Cytotoxicity IC_{50} (μM)	SI[a]
24		11.44	9.94	0.87
25		12.75	10.22	0.8
26		3.94	4.4	1.12
27		> 20	53.98	<2.7
28		3.97	3.70	0.9
29		> 20	19.54	<0.98
30		> 20	48.62	<2.4
rIFNα-2b		0.08 IU/mL	> 2 IU/mL	> 25

[a] SI calculated as IC_{50}/EC_{50}.

these results into account, mimicking the *N*-methylcyclohexanamine group at the R_6 position with a proper length alkyl chain and the steric conformation of a lipophilic group may be promising for improved anti-HCV activity. Further investigation of substitution of the N atom at the R_6 position was also carried out. Replacement of R_6 with cyclohexanol (**80**) resulted in a loss of activity.

Finally, two mimics of the quinoxalin-2(1*H*)-one core structure were synthesized and evaluated for their anti-HCV activity (segment **D**, Table 8). Changing the N atom at the 4- position of compound **33** by its bioisostere O or S atom gave compounds **85** and **86**, respectively. However, both of these compounds had no potency against HCV. As a result, quinoxalin-2(1*H*)-one was considered as the optimal core structure for anti-HCV activity.

CONCLUSIONS

This study has identified new quinoxalin-2(1*H*)-one derivatives as inhibitors of HCV. Compound **1** was first identified for its anti-HCV activity by screening a library of compounds using the HCV replicon and cytotoxicity assays. A series of modifications of compound **1** were carried out in an effort to improve anti-HCV potency and decrease cytotoxic effects. Five compounds, **11**, **33**, **60**, **65**, and **78**, showed high antiviral potency and an acceptable selectivity index, with EC_{50} = 1.8 μM and SI = 9.6, EC_{50} = 1.67 μM and SI = 37.4, EC_{50} = 1.19 μM and SI = 9.27, EC_{50} = 1.82 μM and SI = 9.9 μM, and EC_{50} = 1.27 μM and SI =17.9, respectively.

To elucidate the action mechanism of the compound, biochemical assays were carried out essentially as previously described.[17] The results indicated that the compound **33** did not exhibit any inhibitory effects on HCV protease, helicase, and NS5B polymerase (data not show herein). It was concluded that that **33** are acting on other virus-encoded and/or cellular targets that need to be further investigated.

In conclusion, quinoxalin-2(1*H*)-one with a thiazole−phenyl moiety is optimal for anti-HCV activity; there may be a steric limitation at 3- position of quinoxalin-2(1*H*)-one, however, the 3,4-double bond was mimicked by a cycloalkyl group and a hydrophobic group with proper alkyl chain and steric conformation at 6- position is necessary for the anti-HCV activity. Although the mechanism underlying how these compounds inhibit HCV is unknown, further SAR analysis and mechanistic studies on this class of compounds against HCV are currently being investigated.

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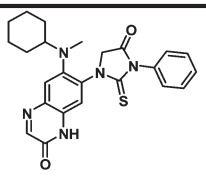
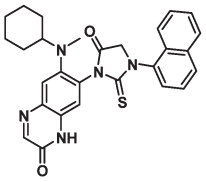
Table 4. Inhibitory Effects of Quinoxalin-2(1*H*)-one Derivatives on HCV Replication in Huh 7 Cells (Replacement of the Aromatic Acyl Thiourea Group by a Thiohydantoin Group)

Compound	Structure	Anti-HCV activity EC_{50} (μM)	Cytotoxicity IC_{50} (μM)	SI[a]
31		2.21	2.99	1.4
32		13.08	11.15	0.85
rIFNα-2b		0.08 IU/mL	> 2 IU/mL	> 25

[a] SI calculated as IC_{50}/EC_{50}.

EXPERIMENTAL SECTION

Chemistry. Unless otherwise noted, all materials were obtained from commercial suppliers and used without purification. All NMR experiments were carried out on a Varian Mercury 300 or 400 or 500 MHz NMR spectrometer using DMSO-d_6 as the solvent. Chemical shifts were reported in ppm (δ) relative to the solvent, and coupling constants (J) were reported in Hz. Melting points were determined without correction with a Yanaco micromelting point apparatus. Automatic HPLC-MS analysis was performed on a Thermo Finnigan LCQ-Advantage mass spectrometer equipped with an Agilent pump, an Agilent detector, an Agilent liquid handler, and a fluent splitter. The column used was a Kromasil C18 column (4.6 μm, 4.6 mm × 50 mm) from DIKMA for analysis. The eluent was a mixture of acetonitrile and water containing 0.05% HCOOH with a linear gradient from 5:95 (v/v) to 95:5 (v/v) of acetonitrile−H_2O within 5 min at a 1 mL/min flow rate for analysis. The UV detection was carried out at a UV wavelength of 254 nm. The 5% of the eluent was split into the MS system. Mass spectra were recorded in either positive or negative ion mode using electrospray ionization (ESI). High resolution LC-MS was carried out by Agilent LC/MSD TOF using a column of Agilent ZORBAX SB-C18 (rapid resolution, 3.5 μm, 2.1 mm × 30 mm) at a flow of 0.40 mL/min. The solvent is methanol/water = 75:25 (v/v) containing 5 mmol/L ammonium formate. The ion source is electrospray ionization (ESI). Flash column chromatography was performed with silica gel 60 (200−300 mesh) from Qingdao Haiyang Chemical Factory. All tested compounds were purified until the purity was ≥95%, detected by HPLC under UV 254 nm wavelength, NMR, melting point, and HRLC-MS.

Preparation of the Key Intermediate Compound 4. To a stirred solution of 1,5-difluoro-2,4-dinitrobenzene (DFDNB, 2.04 g, 10 mmol) in THF (50 mL) was added DIPEA (20 mmol) and $NH_2CH_2COOCH_3 \cdot HCl$ (10 mmol). After vigorously stirring at room temperature until the total disappearance of DFDNB, compound **2** was obtained without purification. Then, *N*-methylcyclohexanamine (10 mmol) and DIPEA (10 mmol) were added and stirred under reflux for 8 h. The solvent was removed under reduced pressure to give compound **3**, which was used directly. The above two reactions were traced by a fast LC-MS system until all of the starting material was changed to the anticipated compound. Compound **3** (1 g) was dissolved in a mixed solvent of THF (30 mL) and EtOH (30 mL), followed by the addition of 10% Pd/C (1 g) and $HCOONH_4$ (2 g). The mixture was stirred at room temperature for 3 h. The residue solid was filtered off, and the filtrate was concentrated in vacuo. Water (50 mL) was added to the resulting product and was further extracted by CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and evaporated in vacuo. Intermediate **4** was obtained as a yellow solid after chromatography through silica gel eluting with $CHCl_3$−CH_3OH (30:1, v/v). Yield 68%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03−1.26 (m, 3H), 1.29−1.37 (m, 2H), 1.54 (m, 1H), 1.68−1.77 (m, 4H), 2.55 (s, 3H), 2.65−2.72 (m, 1H), 5.71 (s, 2H), 6.45 (s, 1H), 7.22 (s, 1H), 7.67 (s, 1H), 11.97 (s, 1H). HRMS calcd for $C_{15}H_{21}N_4O$ ($M + H^+$) 273.1710; found 273.1704.

General Procedure for the Synthesis of Compounds 1, 5−13. To a stirred solution of **4** (0.5 mmol) in 20 mL of dried acetone, various aroyl isothiocyanates (0.5 mmol) were added. The reaction mixture was refluxed for 4 h. After the reaction was completed, the solvent was evaporated in vacuo. The final products were characterized after purification by silica gel column chromatography.

***N*-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylcarbamothioyl)benzamide (1).** Yellow powder in 88% yield; mp 190−191 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00−1.36 (m, 5H), 1.49−1.52 (m, 1H), 1.65−1.69 (m, 2H), 1.76−1.80 (m, 2H), 2.65 (s, 3H), 2.78 (m, 1H), 7.51−7.56 (m, 2H), 7.63−7.69 (m, 2H), 7.95 (d, 2H, J = 7.2 Hz), 8.09 (s, 1H), 8.93 (s, 1H), 11.60 (s, 1H), 12.42 (s, 1H), 13.44 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 24.8, 25.4, 29.1, 37.5, 61.7, 108.2, 122.6, 128.4, 128.6, 129.6, 132.1, 133.1, 137.0, 140.3, 150.6, 154.9, 167.7, 177.6. HRMS calcd for $C_{23}H_{26}N_5O_2S$ ($M + H^+$) 436.1801; found 436.1815.

***N*-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylcarbamothioyl)-4-fluorobenzamide (5).** Light-yellow powder in 85% yield; mp 214−215 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02−1.14 (m, 3H), 1.19−1.33 (m, 2H), 1.50−1.53 (m, 1H), 1.67−1.70 (m, 2H), 1.77−1.81 (m, 2H), 2.65 (s, 3H), 2.75−2.82 (m, 1H), 7.36−7.41 (m, 2H), 7.65 (s, 1H), 8.05−8.10 (m, 3H),

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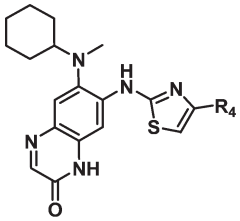
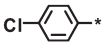
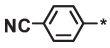
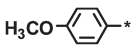
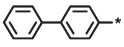
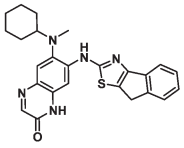
Table 5. Inhibitory Effects of Quinoxalin-2(1*H*)-one Derivatives on HCV Replication in Huh 7 Cells (Cyclization of the Thiourea Moiety to a Thiazole Ring)



Compound	R_4	Anti-HCV activity EC_{50} (μM)	Cytotoxicity IC_{50} (μM)	SI[a]
33		1.67	62.47	37.4
34		5.26	9.92	1.9
35		5.39	16.71	3.1
36		6.07	18.10	2.98
37		> 20	15	<0.75
38		> 20	61.17	<3.1
39		6.80	57.44	8.4
40		> 20	82.04	<4.1
41		12.18	11.91	1
42		> 20	71.26	<3.6
43		5.49	11.46	2.09
44	CF_3	8.12	37.38	4.6
45[b]		4.57	10.94	2.39
rIFNα-2b		0.08 IU/mL	> 2 IU/mL	> 25

[a] SI calculated as IC_{50}/EC_{50}. [b] The structure of compound **45**.

8.96 (s, 1H), 11.67 (s, 1H), 12.43 (s, 1H), 13.43 (s, 1H). HRMS calcd for $C_{23}H_{25}N_5O_2FS$ (M + H^+) 454.1707; found 454.1723.

***N*-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylcarbamothioyl)-4-(trifluoromethoxy)benzamide (6).** Yellow powder in 87% yield; mp 176−178 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.99−1.33 (m, 5H), 1.47−1.50 (m, 1H), 1.64−1.67 (m, 2H), 1.75−1.79 (m, 2H), 2.63 (s, 3H), 2.77 (m, 1H), 7.50 (d, 2H, *J* = 8.1 Hz), 7.63 (s, 1H), 8.07−8.10 (m, 3H), 8.97 (s, 1H), 11.75 (s, 1H), 12.43 (s, 1H), 13.40 (s, 1H). HRMS calcd for $C_{24}H_{25}N_5O_3F_3S$ (M + H^+) 520.1624; found 520.1645.

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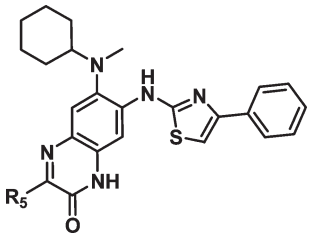
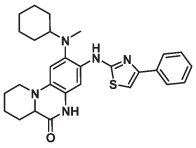
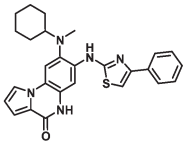
Table 6. Inhibitory Effects of Quinoxalin-2(1*H*)-one Derivatives on HCV Replication in Huh 7 Cells (Modification of Segment B)



Compound	R_5	Anti-HCV activity EC_{50} (μM)	Cytotoxicity IC_{50} (μM)	SI[a]
51	CH_3–*	3.91	12.32	3.15
52	*	8.62	67.42	7.8
53	*	4.19	33.28	7.9
54	*	> 20	41.98	<2.1
55	S *	> 20	85.97	<4.3
60[b]		1.19	11.03	9.27
65[b]		1.82	18.01	9.9
rIFNα-2b		0.14 IU/mL	> 2 IU/mL	> 14.3

[a] SI calculated as IC_{50}/EC_{50}. [b] The structure of compounds **60** and **65**.

***N*-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylcarbamothioyl)-3-(trifluoromethyl)benzamide (7).** Pale-yellow solid in 85% yield; mp 187−189 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07−1.28 (m, 5H), 1.51 (m, 1H), 1.66−1.77 (m, 4H), 2.64 (s, 3H), 2.78 (m, 1H), 7.65 (s, 1H), 7.78 (m, 1H), 8.00−8.09 (m, 2H), 8.21−8.31 (m, 2H), 8.98 (s, 1H), 11.96 (s, 1H), 12.43 (s, 1H), 13.40 (s, 1H). HRMS calcd for $C_{24}H_{25}N_5O_2F_3S$ (M + H^+) 504.1687; found 504.1675.

***N*-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylcarbamothioyl)-3,4,5-trimethoxybenzamide (8).** Pale-yellow powder in 74% yield; mp 110−111 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.09−1.32 (m, 5H), 1.52−1.79 (m, 5H), 2.66 (s, 3H), 2.76 (m, 1H), 3.71−3.88 (m, 9H), 7.22 (s, 1H), 7.35 (s, 1H), 7.62 (s, 1H), 8.10 (s, 1H), 8.83 (s, 1H), 11.61 (s, 1H), 12.41 (s, 1H), 13.39 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 24.9, 25.4, 28.9, 37.1, 55.8, 56.1, 60.1, 61.8, 106.3, 106.5, 108.8, 122.4, 125.8, 126.7, 128.2, 129.6, 136.7, 140.5, 141.6, 150.7, 152.5, 154.8, 166.8, 177.8. HRMS calcd for $C_{26}H_{32}N_5O_5S$ (M + H^+) 526.2118; found 526.2140.

***N*-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylcarbamothioyl)-3-phenylacrylamide (9).** Light-yellow powder in 89% yield; mp 232−233 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07−1.34 (m, 5H), 1.53−1.81 (m, 5H), 2.64 (s, 3H), 2.72−2.74 (m, 1H), 7.08 (d, 1H, J = 15.9 Hz), 7.46−7.48 (m, 3H), 7.63−7.67 (m, 3H), 7.76 (d, 1H, J = 15.9 Hz), 8.08 (d, 1H, J = 1.8 Hz), 8.92 (s, 1H), 11.57 (s, 1H), 12.42 (s, 1H), 13.38 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.9, 25.4, 29.1, 37.5, 61.9, 108.0, 119.9, 122.7, 128.2, 128.4, 129.1, 130.7, 134.0, 137.0, 140.2, 144.4, 150.6, 154.9, 165.3, 177.5. HRMS calcd for $C_{25}H_{28}N_5O_2S$ (M + H^+) 462.1958; found 462.1949.

***N*-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylcarbamothioyl)-1-naphthamide (10).** Yellow powder in 80% yield; mp 169−170 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.06−1.21 (m, 3H), 1.33−1.43 (m, 2H), 1.53−1.57 (m, 1H), 1.71−1.75 (m, 2H), 1.82−1.86 (m, 2H), 2.69 (s, 3H), 2.84−2.87 (m, 1H), 7.59−7.66 (m, 4H), 7.80−7.82 (m, 1H), 8.04−8.06 (m, 1H), 8.10−8.15 (m, 3H), 8.96 (s, 1H), 12.03 (s, 1H), 12.45 (s, 1H), 13.49

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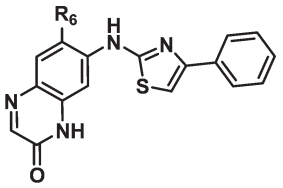
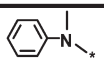
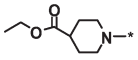
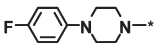
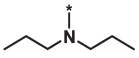
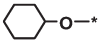
Table 7. Inhibitory Effects of Quinoxalin-2(1*H*)-one Derivatives on HCV Replication in Huh 7 Cells (Modification of Segment C)



Compound	R_6	Anti-HCV activity EC_{50} (μM)	Cytotoxicity IC_{50} (μM)	SI[a]
70		4.61	15.89	3.4
71[b]		35%	58%	ND[c]
72[b]		9%	95.1%	ND[c]
73		5.19	58.32	11.2
74		4.59	10.22	2.2
75[b]		37.6%	59.6%	ND[c]
76[b]		35%	84.3%	ND[c]
77		> 20	57.48	<2.9
78		1.27	22.78	17.9
79		3.81	31.63	8.3
80[b]		4.9%	74.4%	ND[c]
rIFNα-2b		0.14 IU/mL	2 IU/mL	> 14.3

[a] SI calculated as IC_{50}/EC_{50}. [b] Compounds assessed at a single-concentration of 20 μM with the percentage donating inhibition level compared to the control cell. [c] ND = not detected.

(s, 1H). HRMS calcd for $C_{27}H_{28}N_5O_2S$ ($M + H^+$) 486.1958; found 486.1968.

***N*-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylcarbamothioyl)furan-2-carboxamide (11).** Yellow powder in 81% yield; mp 202−204 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00−1.32 (m, 5H), 1.49−1.52 (m, 1H), 1.65−1.69 (m, 2H), 1.76−1.80 (m, 2H), 2.63 (s, 3H), 2.72−2.80 (m, 1H), 6.75−6.77 (m, 1H), 7.64 (s, 1H), 7.87−7.88 (m, 1H), 8.07−8.09 (m, 2H), 8.96 (s, 1H), 11.28 (s, 1H), 12.42 (s, 1H), 13.29 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.3, 24.9, 28.7, 37.4, 61.2, 107.3, 112.1, 118.3, 122.3, 128.0, 129.0, 136.6, 139.6, 144.0, 147.9, 150.1, 154.4, 156.4, 176.6. HRMS calcd for $C_{21}H_{24}N_5O_3S$ ($M + H^+$) 426.1594; found 426.1605.

***N*-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylcarbamothioyl)-3-methylthiophene-2-carboxamide (12).** Pale-yellow powder in 85% yield; mp 182−184 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07−1.32 (m, 5H), 1.52−1.78 (m, 5H), 2.51 (s, 3H), 2.63 (s, 3H), 2.76 (m, 1H), 7.07 (d, 1H, J = 4.8 Hz), 7.63 (s, 1H), 7.84 (d, 1H, J = 4.8 Hz), 8.09 (s, 1H), 8.89 (s, 1H), 11.06 (s, 1H), 12.42 (s, 1H), 13.17 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 15.5, 24.8, 25.4, 29.0, 37.5, 61.7, 108.1, 122.6, 128.4, 128.9, 129.6, 131.1, 131.9, 136.9, 140.3, 143.9, 150.7, 154.9, 162.5, 177.0. HRMS calcd for $C_{22}H_{26}N_5O_2S_2$ ($M + H^+$) 456.1522; found 456.1523.

6-Chloro-*N*-(7-(cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylcarbamothioyl)nicotinamide (13). Yellow powder in 84% yield; mp 215−217 °C. ^{1}H NMR (300 MHz,

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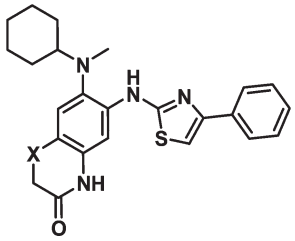
Table 8. Inhibitory Effects of Quinoxalin-2(1*H*)-one Derivatives on HCV Replication in Huh 7 Cells (Modification of Segment D)



compd	X	anti-HCV activity EC_{50} (μM)	cytotoxicity IC_{50} (μM)	SI[a]
85	O	15.36	17.53	1.1
86	S	>20	13.85	<0.69
rIFNα-2b		0.14 IU/mL	>2 IU/mL	>14.3

[a] SI calculated as IC_{50}/EC_{50}.

DMSO-d_6): δ 1.07−1.24 (m, 5H), 1.49−1.51 (m, 1H), 1.65−1.68 (m, 2H), 1.77−1.80 (m, 2H), 2.63 (s, 3H), 2.77 (m, 1H), 7.65−7.70 (m, 2H), 8.09 (s, 1H), 8.31−8.34 (m, 1H), 8.90 (s, 1H), 9.01 (s, 1H), 11.96 (s, 1H), 12.44 (s, 1H), 13.36 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.8, 25.4, 29.2, 38.0, 61.8, 107.7, 122.9, 124.0, 127.9, 128.5, 129.6, 137.0, 140.0, 140.1, 150.1, 150.7, 153.8, 154.9, 165.4, 177.1. HRMS calcd for $C_{22}H_{24}N_6O_2SCl$ (M + H^+) 471.1364; found 471.1369.

General Procedure for the Synthesis of Compounds 14−17. Intermediate **4** (0.2 mmol) was dissolved in dried THF (5 mL). Various isothiocyanates (1 mmol) were added and the solution was heated at 65 °C for 24 h. After the reaction was completed, the solvent was evaporated in vacuo. The final products were characterized after purification by silica gel column chromatography.

1-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-yl)-3-phenylthiourea (14). Light-yellow powder in 84% yield; mp 131−132 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.82−1.02 (m, 5H), 1.22 (m, 1H), 1.48−1.58 (m, 4H), 2.49 (s, 3H), 2.58 (m, 1H), 7.26−7.30 (m, 1H), 7.44−7.45 (m, 4H), 7.54 (s, 1H), 8.01 (d, 1H, J = 2.4 Hz), 8.74 (s, 1H), 9.74 (s, 1H), 10.44 (s, 1H), 12.35 (s, 1H). HRMS calcd for $C_{22}H_{26}N_5OS$ (M + H^+) 408.1853; found 408.1859.

1-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-yl)-3-(4-fluorophenyl)thiourea (15). Yellow powder in 85% yield; mp 137−138 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.01−1.09 (m, 5H), 1.48−1.60 (m, 5H), 2.51 (s, 3H), 2.61 (m, 1H), 7.25−7.30 (m, 2H), 7.45−7.50 (m, 2H), 7.54 (m, 1H), 8.02 (s, 1H), 8.69 (s, 1H), 9.67 (s, 1H), 10.40 (s, 1H), 12.35 (s, 1H). HRMS calcd for $C_{22}H_{25}FN_5OS$ (M + H^+) 426.1758; found 426.1762.

1-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)phenyl)thiourea (16). Yellow powder in 79% yield; mp 127−129 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.01−1.34 (m, 5H), 1.47−1.66 (m, 5H), 2.58 (s, 3H), 2.64 (m, 1H), 7.54−7.58 (m, 2H), 7.62−7.67 (m, 1H), 7.78−7.81 (m, 1H), 7.98 (s, 1H), 8.04 (s, 1H), 8.44 (s, 1H), 9.70 (s, 1H), 10.66 (s, 1H), 12.35 (s, 1H). HRMS calcd for $C_{23}H_{25}F_3N_5OS$ (M + H^+) 476.1726; found 476.1731.

1-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-yl)-3-(naphthalen-1-yl)thiourea (17). Yellow powder in 82% yield; mp 233−235 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.20 (m, 2H), 0.67 (m, 1H), 0.82−0.88 (m, 2H), 1.23−1.35 (m, 5H), 2.00 (s, 3H), 2.32 (m, 1H), 7.45 (s, 1H), 7.59−7.65 (m, 4H), 7.88−7.91 (m, 1H), 7.97 (s, 1H), 8.01−8.04 (m, 2H), 9.12 (s, 1H), 9.72 (s, 1H), 10.57 (s, 1H), 12.39 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.3, 24.9, 29.2, 38.4, 61.1, 122.5, 122.8, 125.9, 126.0, 126.8, 127.0, 128.1, 129.3, 130.0, 133.1, 134.3, 138.2, 138.3, 149.1, 156.0, 178.8. HRMS calcd for $C_{26}H_{28}N_5OS$ (M + H^+) 458.2009; found 458.1993.

General Procedure for the Synthesis of Compounds 18 and 19. To a stirred solution of **4** (0.2 mmol) in 5 mL of dried THF, various isocyanates (1.0 mmol) were added and the reaction mixture was refluxed for 10 h. After the reaction was completed, the solvent was evaporated in vacuo. The final products were characterized after purification by silica gel column chromatography.

1-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-yl)-3-phenylurea (18). Pale-yellow powder in 89% yield; mp 150−152 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02−1.23 (m, 5H), 1.51−1.55 (m, 1H), 1.67−1.70 (m, 2H), 1.87−1.90 (m, 2H), 2.64 (m, 4H), 6.97−7.02 (m, 1H), 7.27−7.33 (m, 2H), 7.49- 7.52 (m, 2H), 7.57 (s, 1H), 7.95 (s, 1H), 8.24 (s, 1H), 8.81 (s, 1H), 9.76 (s, 1H), 12.26 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.9, 25.4, 29.2, 38.8, 62.2, 102.6, 118.1, 118.4, 122.1, 123.5, 127.1, 128.7, 128.8, 130.0, 136.8, 139.3, 139.5, 148.0, 152.0, 155.2. HRMS calcd for $C_{22}H_{26}N_5O_2$ (M + H^+) 392.2081; found 392.2090.

1-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-yl)-3-(naphthalen-1-yl)urea (19). Pale-yellow powder in 79% yield; mp 226−228 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.97−1.22 (m, 5H), 1.46−1.50 (m, 1H), 1.60−1.77 (m, 4H), 2.55 (s, 3H), 2.63 (m, 1H), 7.47−7.63 (m, 4H), 7.74 (d, 1H, J = 8.1 Hz), 7.80 (d, 1H, J = 7.2 Hz), 7.94 (d, 1H, J = 1.8 Hz), 7.97(s, 1H), 8.13 (d, 1H, J = 8.1 Hz), 8.21 (s, 1H), 8.98 (s, 1H), 9.61 (s, 1H), 12.27 (s, 1H). HRMS calcd for $C_{26}H_{28}N_5O_2$ (M + H^+) 442.2243; found 442.2240.

General Procedure for the Synthesis of Compounds 24−30. Compound **1** (1 mmol) and K_2CO_3 (1.5 mmol) were dissolved in a mixed solvent of CH_3OH (20 mL) and H_2O (5 mL). The reaction mixture was refluxed with stirring for 1 h. After evaporation of the solvent in vacuo, compound **21** was obtained as a yellow solid after chromatography through silica gel. The yield was 84%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.01−1.18 (m, 3H), 1.22−1.31 (m, 2H), 1.55 (m, 1H), 1.68−1.79 (m, 4H), 2.62 (s, 3H), 2.65 (s, 1H), 7.47 (s, 1H), 7.99−8.01 (m, 3H), 8.25 (s, 1H), 9.14 (s, 1H), 12.29 (s, 1H). HRMS calcd for $C_{16}H_{22}N_5OS$ (M + H^+) 332.1540; found 332.1542.

To a solution of compound **21** (1 mmol) in ethanol (30 mL) was added methyl iodide (2 mmol). The mixture was heated at 45 °C for 5 h and then purified by silica gel column chromatography. Compound **22** was obtained as a yellow powder in 88% yield. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03−1.22 (m, 4H), 1.31−1.38 (m, 2H), 1.52−1.61 (m, 2H), 1.69−1.72 (m, 2H), 2.36 (s, 3H), 2.60 (s, 3H), 3.11 (m, 1H), 6.39 (s, 2H), 6.53 (s, 1H), 7.13 (s, 1H), 7.92 (s, 1H), 12.11 (s, 1H). HRMS calcd for $C_{17}H_{24}N_5OS$ (M + H^+) 346.1696; found 346.1684.

Compound **22** (0.5 mmol) was dissolved in pyridine (20 mL). Various amines (0.75 mmol) was added, and the solution was refluxed. After the reaction was completed, the solution was evaporated in vacuo. The residue was neutralized with 10% HCl. The mixture was partitioned between $CHCl_3$ and water. The organic phase was then dried with anhydrous magnesium sulfate and evaporated in vacuo. The final products **24**−**30** were characterized after purification by silica gel column chromatography.

1-Benzyl-3-(7-(cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-yl)guanidine (24). Orange powder in 43% yield; mp 235−237 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.06−1.36 (m, 5H), 1.55−1.69 (m, 5H), 2.63 (s, 3H), 2.70 (m, 1H), 4.49 (d, 2H, J = 5.4 Hz), 7.16 (s, 1H), 7.32−7.43 (m, 5H), 7.53 (s, 1H), 7.99 (s, 1H), 8.14 (s, 1H), 8.39 (m, 1H), 9.02 (s, 1H), 12.45 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.4, 28.5, 34.2, 44.4, 61.8, 111.7, 121.9, 127.2, 127.6, 128.0, 128.5, 130.5, 133.1, 136.7, 142.8, 151.2, 154.5, 154.6. HRMS calcd for $C_{23}H_{29}N_6O$ (M + H^+) 405.2397; found 405.2402.

1-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-yl)-3-(4-fluorobenzyl)guanidine (25). Yellow powder in

48% yield; mp 151−153 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.04−1.22 (m, 3H), 1.30−1.34 (m, 3H), 1.52−1.64 (m, 4H), 2.59 (s, 3H), 3.00 (m, 1H), 3.94 (s, 2H), 4.43 (s, 2H), 6.87 (s, 1H), 7.16−7.29 (m, 4H), 7.37−7.49 (m, 3H), 7.98 (s, 1H). HRMS calcd for $C_{23}H_{28}N_6OF$ (M + H$^+$) 423.2303; found 423.2310.

1-(4-Chlorobenzyl)-3-(7-(cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-yl)guanidine (26). Yellow powder in 43% yield; mp 165−167 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.04−1.13 (m, 3H), 1.22−1.34 (m, 3H), 1.54−1.75 (m, 4H), 2.62 (s, 3H), 2.68 (m, 1H), 4.47 (d, 2H, *J* = 6.0 Hz), 7.14 (s, 1H), 7.37 (d, 2H, *J* = 8.4 Hz), 7.45 (d, 2H, *J* = 8.4 Hz), 7.52 (s, 1H), 7.98 (s, 1H), 8.14 (s, 1H), 8.36 (m, 1H), 9.07 (s, 1H), 12.45 (s, 1H). HRMS calcd for $C_{23}H_{28}N_6OCl$ (M + H$^+$) 439.2007; found 439.2006.

1-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-yl)-3-(3-(trifluoromethyl)benzyl)guanidine (27). Yellow powder in 47% yield; mp 199−200 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.01−1.13 (m, 3H), 1.22−1.28 (m, 3H), 1.50−1.64 (m, 4H), 2.60 (s, 3H), 2.71 (m, 1H), 4.58 (d, 2H, *J* = 5.1 Hz), 7.15 (s, 1H), 7.49 (s, 1H), 7.61−7.73 (m, 4H), 8.00 (s, 1H), 8.14 (s, 1H), 8.39 (m, 1H), 9.08 (s, 1H), 12.45 (s, 1H). HRMS calcd for $C_{24}H_{28}N_6OF_3$ (M + H$^+$) 473.2271; found 473.2279.

1-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-yl)-3-(4-(trifluoromethoxy)benzyl)guanidine (28). Yellow powder in 47% yield; mp 199−200 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03−1.13 (m, 3H), 1.22−1.33 (m, 3H), 1.51−1.65 (m, 4H), 2.61 (s, 3H), 2.71 (m, 1H), 4.51 (d, 2H, *J* = 5.4 Hz), 7.15 (s, 1H), 7.39 (d, 2H, *J* = 8.4 Hz), 7.48−7.52 (m, 3H), 7.98 (s, 1H), 8.14 (s, 1H), 8.38 (m, 1H), 9.08 (s, 1H), 12.46 (s, 1H). HRMS calcd for $C_{24}H_{28}N_6O_2F_3$ (M + H$^+$) 489.2220; found 489.2223.

1-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-yl)-3-(4-methoxybenzyl)guanidine (29). Light-yellow powder in 53% yield; mp 177−179 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03−1.05 (m, 3H), 1.22−1.34 (m, 3H), 1.53−1.67 (m, 4H), 2.61 (s, 3H), 2.69 (m, 1H), 3.74 (s, 3H), 4.41 (d, 2H, *J* = 3.6 Hz), 6.93 (d, 2H, *J* = 8.4 Hz), 7.14 (s, 1H), 7.28 (d, 2H, *J* = 8.4 Hz), 7.51 (s, 1H), 7.99 (s, 1H), 8.13 (s, 1H), 8.39 (s, 1H), 9.05 (s, 1H), 12.46 (s, 1H). HRMS calcd for $C_{24}H_{31}N_6O_2$ (M + H$^+$) 435.2503; found 435.2515.

1-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-yl)-3-(pyridin-2-ylmethyl)guanidine (30). Yellow powder in 44% yield; mp 199−201 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.06−1.11 (m, 3H), 1.22−1.35 (m, 2H), 1.54−1.70 (m, 5H), 2.64 (s, 3H), 2.73 (m, 1H), 4.61 (d, 2H, *J* = 5.1 Hz), 7.20 (s, 1H), 7.36−7.42 (m, 2H), 7.54 (s, 1H), 7.83−7.89 (m, 1H), 8.05 (s, 1H), 8.13 (s, 1H), 8.44 (m, 1H), 8.59 (d, 1H, *J* = 4.8 Hz), 9.27 (s, 1H), 12.43 (s, 1H). HRMS calcd for $C_{22}H_{28}N_7O$ (M + H$^+$) 406.2349; found 406.2354.

6-(Cyclohexyl(methyl)amino)-7-(4-oxo-3-phenyl-2-thioxoimidazolidin-1-yl)quinoxalin-2(1*H*)-one (31). To a stirred solution of compound **14** (1 mmol) in 1,4-dioxane (50 mL) was added Et_3N (2 mmol) and 2-chloroacetyl chloride (1 mmol). The mixture was refluxed for 8 h. After the reaction was completed, the solution was evaporated in vacuo. The final product **31** was obtained as a yellow powder after purification by silica gel column chromatography eluting with $CHCl_3$−CH_3OH (40:1, v/v). Yield 51%; mp 140−142 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07−1.23 (m, 5H), 1.56−1.70 (m, 5H), 2.60 (s, 3H), 2.74 (m, 1H), 4.11 (d, 1H, *J* = 17.4 Hz), 4.19 (d, 1H, *J* = 17.4 Hz), 6.83−6.85 (m, 2H), 7.07−7.12 (m, 1H), 7.25 (s, 1H), 7.32−7.37 (m, 2H), 7.57 (s, 1H), 8.19 (s, 1H), 12.47 (s, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.3, 25.6, 25.7, 28.6, 29.8, 32.9, 33.5, 62.2, 117.2, 120.4, 121.9, 124.2, 127.3, 129.3, 132.9, 145.9, 147.9, 152.6, 154.4, 155.2, 170.9. HRMS calcd for $C_{24}H_{26}N_5O_2S$ (M + H$^+$) 448.1802; found 448.1804.

6-(Cyclohexyl(methyl)amino)-7-(3-(naphthalen-1-yl)-5-oxo-2-thioxoimidazolidin-1-yl)quinoxalin-2(1*H*)-one (32). To a stirred solution of compound **17** (1 mmol) in 1,4-dioxane (50 mL) was added Et_3N (2 mmol) and 2-chloroacetyl chloride (1 mmol). The mixture was refluxed for 8 h. After the reaction was completed, the solution was evaporated in vacuo. The final product **32** and **32′** were obtained as yellow powders after purification by silica gel column chromatography eluting with $CHCl_3$−CH_3OH (40:1, v/v).

32: Yield 59%; mp 210−211 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.53−0.86 (m, 3H), 1.09−1.22 (m, 4H), 1.37−1.62 (m, 3H), 2.39 (s, 3H), 2.66 (m, 1H), 4.31 (d, 1H, *J* = 17.1 Hz), 4.51 (d, 1H, *J* = 17.1 Hz), 6.68 (s, 1H), 7.19 (s, 1H), 7.55−7.70 (m, 4H), 7.79−7.82 (m, 1H), 8.00 (s, 1H), 8.05−8.11 (m, 2H), 12.22 (s, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 25.2, 25.4, 25.5, 28.0, 28.6, 33.0, 33.1, 41.4, 59.5, 106.5, 119.5, 122.3, 125.7, 126.5, 127.0, 127.2, 128.4, 129.3, 129.5, 131.7, 133.9, 141.3, 145.4, 149.4, 154.7, 156.0, 168.5, 171.9. HRMS calcd for $C_{28}H_{28}N_5O_2S$ (M + H$^+$) 498.1963; found 498.1955.

32′: Yield 34%; mp 207−209 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.10−1.34 (m, 5H), 1.41−1.76 (m, 5H), 2.70 (s, 3H), 2.82 (m, 1H), 4.14 (d, 1H, *J* = 17.1 Hz), 4.23 (d, 1H, *J* = 17.1 Hz), 6.94 (d, 1H, *J* = 7.5 Hz), 7.42−7.54 (m, 4H), 7.60 (s, 1H), 7.65 (d, 1H, *J* = 8.4 Hz), 7.87−7.92 (m, 2H), 8.20 (s, 1H), 12.58 (s, 1H). HRMS calcd for $C_{28}H_{28}N_5O_2S$ (M + H$^+$) 498.1963; found 498.1953.

General Procedure for the Synthesis of Compounds 33−45. Compound **21** (1 mmol) and various α-bromo substituted ketones (1 mmol) were dissolved in EtOH (30 mL) and refluxed for 2 h. The mixture was concentrated and the final products **33**−**45** were characterized after purification by silica gel column chromatography.

6-(Cyclohexyl(methyl)amino)-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1*H*)-one (33). Yellow powder in 80% yield; mp 226−228 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08−1.31 (m, 5H), 1.50−1.54 (m, 1H), 1.66−1.70 (m, 2H), 1.84−1.88 (m, 2H), 2.65 (s, 3H), 2.72 (m, 1H), 7.31−7.36 (m, 1H), 7.43−7.48 (m, 3H), 7.58 (s, 1H), 7.96 (s, 1H), 8.08 (d, 2H, *J* = 7.2 Hz), 8.58 (s, 1H), 9.75 (s, 1H), 12.72 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.9, 25.4, 29.1, 38.4, 62.0, 101.4, 104.8, 123.3, 126.0, 127.0, 127.6, 128.5, 130.2, 134.2, 136.8, 139.8, 147.4, 150.1, 155.5, 162.0. HRMS calcd for $C_{24}H_{26}N_5OS$ (M + H$^+$) 432.1858; found 432.1841.

6-(Cyclohexyl(methyl)amino)-7-(4-(4-fluorophenyl)thiazol-2-ylamino)quinoxalin-2(1*H*)-one (34). Pale-yellow powder in 83% yield; mp 245−247 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08−1.26 (m, 5H), 1.50−1.53 (m, 1H), 1.66−1.69 (m, 2H), 1.84−1.88 (m, 2H), 2.65 (s, 3H), 2.71 (m, 1H), 7.23−7.29 (m, 2H), 7.46 (s, 1H), 7.57 (s, 1H), 7.96 (s, 1H), 8.12−8.16 (m, 2H), 8.59 (s, 1H), 9.78 (s, 1H), 12.73 (s, 1H). HRMS calcd for $C_{24}H_{25}FN_5OS$ (M + H$^+$) 450.1758; found 450.1759.

7-(4-(4-Chlorophenyl)thiazol-2-ylamino)-6-(cyclohexyl(methyl)amino)quinoxalin-2(1*H*)-one (35). Pale-yellow powder in 87% yield; mp 278−280 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08−1.27 (m, 5H), 1.50−1.54 (m, 1H), 1.66−1.70 (m, 2H), 1.85−1.88 (m, 2H), 2.65 (s, 3H), 2.72 (m, 1H), 7.48 (d, 2H, *J* = 8.4 Hz), 7.55 (m, 2H), 7.57 (s, 1H), 8.11 (d, 2H, *J* = 8.4 Hz), 8.58 (s, 1H), 9.81 (s, 1H), 12.74 (s, 1H). HRMS calcd for $C_{24}H_{25}ClN_5OS$ (M + H$^+$) 466.1463; found 466.1455.

4-(2-(7-(Cyclohexyl(methyl)amino)-3-oxo-3,4-dihydroquinoxalin-6-ylamino)thiazol-4-yl)benzonitrile (36). Light-yellow powder in 85% yield; mp 261−263 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07−1.26 (m, 5H), 1.53 (m, 1H), 1.66−1.69 (m, 2H), 1.85−1.88 (m, 2H), 2.65 (s, 3H), 2.72 (m, 1H), 7.58 (s, 1H), 7.78(s, 1H), 7.88 (d, 2H, *J* = 8.4 Hz), 7.97 (s, 1H), 8.28 (d, 2H, *J* = 8.4 Hz), 8.61 (s, 1H), 9.91 (s, 1H), 12.77 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.9, 25.5, 29.1, 38.5, 62.1, 101.7, 108.9, 109.6, 119.0, 123.4, 126.6, 127.1, 130.1, 132.6, 136.9, 138.3, 139.7, 147.6, 148.3, 155.5, 162.4. HRMS calcd for $C_{25}H_{25}N_6OS$ (M + H$^+$) 457.1810; found 457.1792.

6-(Cyclohexyl(methyl)amino)-7-(4-(4-methoxyphenyl)thiazol-2-ylamino)quinoxalin-2(1*H*)-one (37). Yellow powder in 83% yield; mp 226−228 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.09−1.27 (m, 5H), 1.50−1.54 (m, 1H), 1.66−1.88 (m, 4H), 2.65 (s, 3H), 2.72

(m, 1H), 3.80 (s, 3H), 6.99 (d, 2H, J = 8.4 Hz), 7.30 (s, 1H), 7.57 (s, 1H), 7.95 (s, 1H), 8.01 (d, 2H, J = 8.4 Hz), 8.57 (s, 1H), 9.71 (s, 1H), 12.71 (s, 1H). HRMS calcd for $C_{25}H_{28}N_5O_2S$ (M + H^+) 462.1958; found 492.1961.

7-(4-(Benzo[*d*][1,3]dioxol-5-yl)thiazol-2-ylamino)-6-(cyclohexyl(methyl)amino)quinoxalin-2(1*H*)-one (38). Yellow powder in 70% yield; mp 209−210 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08−1.27 (m, 5H), 1.50−1.53 (m, 1H), 1.66−1.88 (m, 4H), 2.65 (s, 3H), 2.71 (m, 1H), 6.06 (s, 2H), 6.96 (d, 1H, J = 7.8 Hz), 7.34 (s, 1H), 7.57 (s, 1H), 7.63−7.66 (m, 2H), 7.95 (d, 1H, J = 2.1 Hz), 8.53 (s, 1H), 9.71 (s, 1H), 12.74 (s, 1H). HRMS calcd for $C_{25}H_{26}N_5O_3S$ (M + H^+) 476.1751; found 476.1769.

6-(Cyclohexyl(methyl)amino)-7-(4-(naphthalen-1-yl)thiazol-2-ylamino)quinoxalin-2(1*H*)-one (39). Yellow powder in 82% yield; mp 247−249 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.10−1.31 (m, 5H), 1.52−1.55 (m, 1H), 1.69−1.72 (m, 2H), 1.86−1.90 (m, 2H), 2.67 (s, 3H), 2.76 (m, 1H), 7.27 (s, 1H), 7.54−7.63 (m, 4H), 7.87−7.98 (m, 4H), 8.29 (s, 1H), 8.37−8.40 (m, 1H), 9.73 (s, 1H), 12.43 (s, 1H). HRMS calcd for $C_{28}H_{28}N_5OS$ (M + H^+) 482.2009; found 482.1955.

7-(4-(Biphenyl-4-yl)thiazol-2-ylamino)-6-(cyclohexyl(methyl)amino)quinoxalin-2(1*H*)-one (40). Yellow powder in 85% yield; mp 232−234 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.06−1.28 (m, 5H), 1.50−1.54 (m, 1H), 1.67−1.71 (m, 2H), 1.86−1.90 (m, 2H), 2.66 (s, 3H), 2.73 (m, 1H), 7.35−7.40 (m, 1H), 7.47−7.52 (m, 2H), 7.55 (s, 1H), 7.58 (s, 1H), 7.72−7.77 (m, 4H), 7.96 (d, 1H, J = 1.5 Hz), 8.18 (d, 2H, J = 8.7 Hz), 8.63 (s, 1H), 9.79 (s, 1H), 12.76 (s, 1H). HRMS calcd for $C_{30}H_{30}N_5OS$ (M + H^+) 508.2165; found 508.2188.

6-(Cyclohexyl(methyl)amino)-7-(4-(furan-2-yl)thiazol-2-ylamino)quinoxalin-2(1*H*)-one (41). Yellow powder in 77% yield; mp 196−197 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08−1.25 (m, 5H), 1.50−1.53 (m, 1H), 1.66−1.70 (m, 2H), 1.84−1.88 (m, 2H), 2.64 (s, 3H), 2.72 (m, 1H), 6.63 (dd, 1H, J_1 = 1.5 Hz, J_2 = 2.7 Hz), 7.11 (s, 1H), 7.14 (d, 1H, J = 2.7 Hz), 7.57 (s, 1H), 7.72 (s, 1H), 7.95 (d, 1H, J = 1.5 Hz), 8.63 (s, 1H), 9.85 (s, 1H), 12.61 (s, 1H). HRMS calcd for $C_{22}H_{24}N_5O_2S$ (M + H^+) 422.1645; found 422.1666.

6-(Cyclohexyl(methyl)amino)-7-(4-(thiophen-2-yl)thiazol-2-ylamino)quinoxalin-2(1*H*)-one (42). Yellow powder in 75% yield; mp 196−197 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08−1.26 (m, 5H), 1.50−1.54 (m, 1H), 1.66−1.70 (m, 2H), 1.84−1.88 (m, 2H), 2.65 (s, 3H), 2.72 (m, 1H), 7.11−7.14 (m, 1H), 7.22 (s, 1H), 7.49−7.51 (m, 1H), 7.57 (s, 1H), 7.70−7.71 (m, 1H), 7.95 (s, 1H), 8.43 (s, 1H), 9.75 (s, 1H), 12.63 (s, 1H). HRMS calcd for $C_{22}H_{24}N_5OS_2$ (M + H^+) 438.1417; found 438.1408.

6-(Cyclohexyl(methyl)amino)-7-(4-(pyridin-3-yl)thiazol-2-ylamino)quinoxalin-2(1*H*)-one (43). Yellow powder in 73% yield; mp 156−158 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.01−1.27 (m, 5H), 1.50−1.53 (m, 1H), 1.66−1.70 (m, 2H), 1.85−1.88 (m, 2H), 2.65 (s, 3H), 2.72 (m, 1H), 7.46−7.50 (m, 1H), 7.58 (s, 1H), 7.66 (s, 1H), 7.96 (s, 1H), 8.43−8.45 (m, 1H), 8.54−8.55 (m, 1H), 8.63 (s, 1H), 9.32 (d, 1H, J = 1.5 Hz), 9.87 (s, 1H), 12.74 (s, 1H). HRMS calcd for $C_{23}H_{25}N_6OS$ (M + H^+) 433.1805; found 433.1819.

6-(Cyclohexyl(methyl)amino)-7-(4-(trifluoromethyl)thiazol-2-ylamino)quinoxalin-2(1*H*)-one (44). Yellow powder in 81% yield; mp 225−227 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.06−1.25 (m, 5H), 1.52−1.84 (m, 5H), 2.63 (s, 3H), 2.70 (m, 1H), 7.56 (s, 1H), 7.74 (s, 1H), 7.96 (s, 1H), 8.25 (s, 1H), 10.04 (s, 1H), 12.56 (s, 1H). HRMS calcd for $C_{19}H_{21}N_5OF_3S$ (M + H^+) 424.1418; found 424.1424.

7-(8*H*-Indeno[1,2-*d*]thiazol-2-ylamino)-6-(cyclohexyl(methyl)amino)quinoxalin-2(1*H*)-one (45). Light-yellow powder in 73% yield; mp 262−264 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.01−1.31 (m, 5H), 1.50−1.53 (m, 1H), 1.66−1.70 (m, 2H), 1.86−1.89 (m, 2H), 2.66 (s, 3H), 2.73 (m, 1H), 3.86 (s, 2H), 7.20−7.25 (m, 1H), 7.36−7.40 (m, 1H), 7.54 (d, 1H, J = 7.5 Hz), 7.57 (s, 1H), 7.67 (d, 1H, J = 7.5 Hz), 7.95 (s, 1H), 8.67 (s, 1H), 9.81 (s, 1H), 12.46 (s, 1H). HRMS calcd for $C_{25}H_{26}N_5OS$ (M + H^+) 444.1853; found 444.1851.

6-(Cyclohexyl(methyl)amino)-3-methyl-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1*H*)-one (51). To a stirred solution of 1,5-difluoro-2,4-dinitrobenzene (DFDNB, 2.04 g, 10 mmol) in THF (50 mL) was added DIPEA (10 mmol) and *N*-methylcyclohexanamine (10 mmol). After vigorously stirring at room temperature until the total disappearance of DFDNB, compound **46** was obtained without purification. Then, $NH_2CH(CH_3)COOCH_3 \cdot HCl$ (10 mmol) and DIPEA (20 mmol) were added and stirred under reflux for 8 h. The solvent was removed under reduced pressure to give compound **47a** that was used directly. The above two reactions were traced by a fast LC-MS system until all of the starting material was changed into the anticipated compound. Compound **47a** (1 g) was dissolved in a mixed solvent of THF (30 mL) and EtOH (30 mL), followed by the addition of 10% Pd/C (1 g) and $HCOONH_4$ (2 g). The mixture was stirred at room temperature for 3 h. The residue solid was filtered off, and the filtrate was concentrated in vacuo. Water (50 mL) was added to the resulting product and then was extracted by CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and evaporated in vacuo. Intermediate **48a** was obtained as a yellow solid after chromatography through silica gel eluting with $CHCl_3$−CH_3OH (30:1, v/v). Yield 70%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03−1.25 (m, 3H), 1.28−1.36 (m, 2H), 1.54 (m, 1H), 1.67−1.74 (m, 4H), 2.26 (s, 3H), 2.54 (s, 3H), 2.65−2.72 (m, 1H), 5.49 (s, 2H), 6.44 (s, 1H), 7.25 (s, 1H), 11.88 (s, 1H). HRMS calcd for $C_{16}H_{23}N_4O$ (M + H^+) 287.1866; found 287.1856.

Intermediate **48a** (1 mmol) and benzoyl isothiocyanate (1 mmol) were dissolved in dried acetone (30 mL). The reaction mixture was refluxed with stirring for 4 h and then concentrated in vacuo to give compound **49a** without purification. Intermediate **49a** (1 mmol) and K_2CO_3 (1.5 mmol) in CH_3OH (20 mL)/H_2O (5 mL) were heated to reflux for 1 h. After evaporation of the solvent in vacuo, compound **50a** was obtained as a yellow solid after chromatography through silica gel eluting with $CHCl_3$−CH_3OH (30:1, v/v). Yield 75%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07−1.34 (m, 3H), 1.22−1.30 (m, 2H), 1.55 (m, 1H), 1.68−1.79 (m, 4H), 2.35 (s, 3H), 2.61 (s, 3H), 2.65−2.68 (m, 1H), 7.40 (s, 1H), 7.91 (s, 2H), 8.14 (s, 1H), 9.08 (s, 1H), 12.16 (s, 1H). HRMS calcd for $C_{17}H_{24}N_5OS$ (M + H^+) 346.1696; found 346.1680.

50a (0.5 mmol) and 2-bromo-1-phenylethanone (0.5 mmol) were dissolved in EtOH (30 mL) and refluxed for 2 h. After the reaction was completed, the solvent was evaporated in vacuo. The final product **51** was obtained as a yellow powder after purification by silica gel column chromatography eluting with $CHCl_3$−CH_3OH (80:1, v/v). Yield 84%; mp 229−231 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08−1.26 (m, 5H), 1.50−1.53 (m, 1H), 1.66−1.70 (m, 2H), 1.84−1.88 (m, 2H), 2.36 (s, 3H), 2.64 (s, 3H), 2.71 (m, 1H), 7.33−7.35 (m, 1H), 7.43−7.48 (m, 3H), 7.51 (s, 1H), 8.08 (d, 2H, J = 7.2 Hz), 8.55 (s, 1H), 9.68 (s, 1H), 12.62 (s, 1H). HRMS calcd for $C_{25}H_{28}N_5OS$ (M + H^+) 446.2009; found 446.1987.

6-(Cyclohexyl(methyl)amino)-3-isopropyl-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1*H*)-one (52). Compound **52** was prepared in a similar manner to the synthesis of compound **51**, substituting $NH_2CH(CH(CH_3)_2)COOCH_3 \cdot HCl$ for $NH_2CH(CH_3)COOCH_3 \cdot HCl$. The final product **52** was obtained as a yellow solid after purification by silica gel column chromatography. Yield 86% (the last step); mp 208−210 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.05−1.27 (m, 11H), 1.50−1.53 (m, 1H), 1.66−1.69 (m, 2H), 1.84−1.88 (m, 2H), 2.65 (s, 3H), 2.72 (m, 1H), 3.41−3.46 (m, 1H), 7.33−7.35 (m, 1H), 7.43−7.48 (m, 3H), 7.52 (s, 1H), 8.08 (d, 2H, J = 7.2 Hz), 8.55 (s, 1H), 9.68 (s, 1H), 12.62 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 20.1, 24.9, 25.5, 29.2, 29.5, 38.6, 62.1, 101.3, 104.5, 122.8, 126.0, 126.4, 127.5, 128.5, 129.8, 134.2, 136.5, 138.6, 150.1, 154.7, 161.8, 162.1. HRMS calcd for $C_{27}H_{32}N_5OS$ (M + H^+) 474.2322; found 474.2349.

6-(Cyclohexyl(methyl)amino)-3-isobutyl-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1*H*)-one (53). Compound **53** was prepared in a similar manner to the synthesis of compound **51**, substituting $NH_2CH(CH_2CH(CH_3)_2)COOCH_3 \cdot HCl$ for $NH_2CH(CH_3)COOCH_3 \cdot HCl$. The final product **53** was obtained as a pale-yellow powder after purification by silica gel column chromatography. Yield 77% (the last step); mp 223−224 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.92 (d, 6H, J = 6.3 Hz), 1.08−1.27 (m, 5H), 1.49−1.53 (m, 1H), 1.66−1.70 (m, 2H), 1.84−1.88 (m, 2H), 2.19−2.24 (m, 1H), 2.61 (d, 2H, J = 7.5 Hz), 2.65 (s, 3H), 2.71 (m, 1H), 7.30−7.35 (m, 1H), 7.42−7.48 (m, 3H), 7.53 (s, 1H), 8.07 (d, 2H, J = 7.2 Hz), 8.54 (s, 1H), 9.67 (s, 1H), 12.61 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 22.6, 24.9, 25.5, 26.3, 29.2, 38.4, 41.3, 62.0, 101.3, 104.5, 122.7, 126.0, 126.6, 127.5, 128.5, 129.8, 134.2, 136.5, 138.6, 150.1, 155.4, 157.4, 162.1. HRMS calcd for $C_{28}H_{34}N_5OS$ (M + H$^+$) 488.2479; found 488.2502.

3-Benzyl-6-(cyclohexyl(methyl)amino)-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1*H*)-one (54). Compound **54** was prepared in a similar manner to the synthesis of compound **51**, substituting $NH_2CH(CH_2Ph)COOCH_3 \cdot HCl$ for $NH_2CH(CH_3)COOCH_3 \cdot HCl$. The final product **54** was obtained as a pale-yellow powder after purification by silica gel column chromatography. Yield 71% (the last step); mp 239−241 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07−1.26 (m, 5H), 1.49−1.52 (m, 1H), 1.65−1.87 (m, 4H), 2.64 (s, 3H), 2.70 (m, 1H), 4.08 (s, 2H), 7.19−7.22 (m, 1H), 7.26−7.35 (m, 5H), 7.42−7.47 (m, 3H), 7.51 (s, 1H), 8.07 (d, 2H, J = 7.2 Hz), 8.55 (s, 1H), 9.70 (s, 1H), 12.70 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.9, 25.4, 29.2, 38.4, 62.0, 101.3, 104.5, 122.8, 126.0, 126.1, 126.5, 127.5, 128.2, 128.5, 129.0, 130.1, 134.2, 136.7, 138.0, 138.9, 150.1, 155.1, 156.4, 162.1. HRMS calcd for $C_{31}H_{32}N_5OS$ (M + H$^+$) 522.2322; found 522.2345.

6-(Cyclohexyl(methyl)amino)-3-(2-(methylthio)ethyl)-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1*H*)-one (55). To a stirred solution of compound **46** (10 mmol) in THF (50 mL) was added DIPEA (20 mmol) and $NH_2CH((CH_2)_2SCH_3)COOCH_3 \cdot HCl$ (10 mmol). After vigorously stirring at 65 °C until the total disappearance of the starting materials, compound **47e** was obtained without purification. Compound **47e** (5 mmol) and $SnCl_2 \cdot 2H_2O$ (75 mmol) were dissolved in ethanol (75 mL). Then 15 equiv of 12 mol/L hydrochloric acid was added and the mixture was stirred under reflux for 3 h. The solvent was then evaporated. The residue was neutralized with 40% NaOH until the pH reached 8. The mixture was filtered, and the filtrate was extracted with 100 mL of $CHCl_3$ twice. The organic solvent was washed with brine, dried over anhydrous sodium sulfate, and evaporated in vacuo. The intermediate **48e** was obtained as a yellow solid after purification by silica gel column chromatography. Yield 51%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.03−1.19 (m, 3H), 1.26−1.36 (m, 2H), 1.54 (m, 1H), 1.67−1.76 (m, 4H), 2.08 (s, 3H), 2.55 (s, 3H), 2.65−2.72 (m, 1H), 2.78−2.84 (m, 2H), 2.89−2.95 (m, 2H), 5.56 (s, 2H), 6.44 (s, 1H), 7.20 (s, 1H), 11.92 (s, 1H). HRMS calcd for $C_{18}H_{27}N_4OS$ (M + H$^+$) 347.1900; found 347.1889.

Intermediate **48e** (1 mmol) and benzoyl isothiocyanate (1 mmol) were dissolved in dried acetone (30 mL). The reaction mixture was refluxed with stirring for 4 h and then concentrated to give compound **49e** without purification. Intermediate **49e** (1 mmol) and K_2CO_3 (1.5 mmol) in CH_3OH (20 mL)/H_2O (5 mL) were heated to reflux for 1 h. After evaporation of the solvent in vacuo, compound **50e** was obtained as a yellow solid after chromatography through silica gel eluting with $CHCl_3-CH_3OH$ (10:1, v/v). Yield 66%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07−1.13 (m, 3H), 1.27−1.31 (m, 2H), 1.55 (m, 1H), 1.68−1.79 (m, 4H), 2.09 (s, 3H), 2.59 (s, 3H), 2.62−2.65 (m, 1H), 2.83−2.88 (m, 2H), 3.00−3.04 (m, 2H), 7.42 (s, 1H), 7.92 (s, 2H), 8.17 (s, 1H), 9.10 (s, 1H), 12.22 (s, 1H). HRMS calcd for $C_{19}H_{28}N_5OS_2$ (M + H$^+$) 406.1730; found 406.1716.

50e (0.5 mmol) and 2-bromo-1-phenylethanone (0.5 mmol) were dissolved in EtOH (30 mL) and refluxed for 2 h. After the reaction was completed, the solvent was evaporated in vacuo. The final product **55** was obtained as a yellow powder after purification by silica gel column chromatography eluting with $CHCl_3-CH_3OH$ (50:1, v/v). Yield 75%; mp 130−131 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.15−1.31 (m, 5H), 1.59−1.63 (m, 1H), 1.71−1.91 (m, 4H), 2.09 (s, 3H), 2.80−2.85 (m, 2H), 2.94−2.99 (m, 2H), 3.23 (m, 1H), 3.40 (s, 3H), 5.58 (d, 1H, J = 8.1 Hz), 6.52 (s, 1H), 7.17 (s, 1H), 7.26−7.31 (m, 1H), 7.36−7.43 (m, 2H), 7.57 (s, 1H), 7.88 (d, 2H, J = 7.2 Hz), 11.97 (s, 1H). HRMS calcd for $C_{27}H_{32}N_5OS_2$ (M + H$^+$) 506.2043; found 506.2064.

2-(Cyclohexyl(methyl)amino)-3-(4-phenylthiazol-2-ylamino)-7,8,9,10-tetrahydro-5*H*-pyrido[1,2-*a*]quinoxalin-6(6a*H*)-one (60). To a stirred solution of compound **46** (10 mmol) in THF (50 mL), DIPEA (10 mmol) and ethyl piperidine-2-carboxylate (10 mmol) was added. After vigorously stirring at 65 °C until the total disappearance of the starting materials, compound **56** was obtained without purification. Compound **56** (1 g) was dissolved in a mixed solvent of THF (30 mL) and EtOH (30 mL), followed by the addition of 10% Pd/C (1 g) and $HCOONH_4$ (2 g). The mixture was stirred at room temperature for 3 h. The residue solid was filtered off, and the filtrate was concentrated in vacuo. Water (50 mL) was added to the resulting product and then was extracted by CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and evaporated in vacuo. The intermediate **57** was obtained as a white solid after purification by silica gel column chromatography with a yield of 68%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.00−1.53 (m, 9H), 1.66−1.79 (m, 6H), 2.00−2.03 (m, 1H), 2.40−2.43 (m, 1H), 2.53 (s, 3H), 2.60−2.66 (m, 1H), 3.09−3.13 (m, 1H), 3.50−3.54 (m, 1H), 4.35 (s, 2H), 6.22 (s, 1H), 6.46 (s, 1H), 10.08 (s, 1H). HRMS calcd for $C_{19}H_{29}N_4O$ (M + H$^+$) 329.2336; found 329.2320.

Intermediate **57** (1 mmol) and benzoyl isothiocyanate (1 mmol) were dissolved in dried acetone (30 mL). The reaction mixture was refluxed with stirring for 4 h and then concentrated to give compound **58** without purification. Intermediate **58** (1 mmol) and K_2CO_3 (1.5 mmol) in CH_3OH (20 mL)/H_2O (5 mL) were heated to reflux for 1 h. Compound **59** was obtained as a white solid after evaporation of the solvent in vacuo and chromatography through silica gel eluting with $CHCl_3-CH_3OH$ (40:1, v/v). Yield 69%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.99−1.17 (m, 4H), 1.29−1.54 (m, 6H), 1.67−1.70 (m, 4H), 1.76−1.80 (m, 2H), 2.00−2.03 (m, 1H), 2.55 (s, 3H), 2.67−2.74 (m, 1H), 3.35−3.39 (m, 1H), 3.68−3.72 (m, 1H), 6.51 (s, 1H), 7.06 (s, 1H), 7.34 (s, 2H), 8.61 (s, 1H), 10.24 (s, 1H). HRMS calcd for $C_{20}H_{30}N_5OS$ (M + H$^+$) 388.2166; found 388.2157.

Compound **59** (0.5 mmol) and 2-bromo-1-phenylethanone (0.5 mmol) were dissolved in ethanol (30 mL) and refluxed for 2 h. After the reaction was completed, the solvent was evaporated in vacuo. The final product **60** was obtained as a white solid after purification by silica gel column chromatography eluting with $CHCl_3-CH_3OH$ (50:1, v/v). Yield 73%; mp 200−202 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07−1.24 (m, 6H), 1.41−1.48 (m, 4H), 1.64−1.68 (m, 2H), 1.74−1.79 (m, 3H), 2.05 (m, 1H), 2.58 (s, 3H), 2.68 (m, 1H), 3.30 (s, 1H), 3.31−3.35 (m, 1H), 3.67−3.71 (m, 1H), 6.67 (s, 1H), 7.23 (s, 1H), 7.26−7.31 (m, 1H), 7.38−7.43 (m, 2H), 7.80 (s, 1H), 7.96 (d, 2H, J = 7.8 Hz), 8.94 (s, 1H), 10.59 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.0, 23.3, 25.0, 25.5, 26.5, 29.3, 29.6, 37.6, 46.3, 58.7, 61.9, 102.4, 106.1, 107.5, 123.5, 125.9, 127.3, 128.4, 129.3, 130.7, 134.6, 136.3, 150.0, 163.9, 168.0. HRMS calcd for $C_{28}H_{34}N_5OS$ (M + H$^+$) 488.2479; found 488.2495.

8-(Cyclohexyl(methyl)amino)-7-(4-phenylthiazol-2-ylamino)-pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (65). To a stirred solution of compound **46** (10 mmol) in THF (50 mL) was added DIPEA (10 mmol) and methyl pyrrolidine-2-carboxylate (10 mmol). After vigorously stirring at 65 °C until the total disappearance of the starting materials, compound **61** was obtained without purification. Compound **61** (5 mmol) and 10% Pd/C (5 g) were dissolved in ethanol (50 mL). Then cyclohexene (5 mmol) was added, and the mixture was stirred under reflux for 2 h. The mixture was filtered, and the filtrate was evaporated in vacuo. The intermediate **62** was obtained as a white solid after purification by silica gel

column chromatography. Yield 68%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.12−1.21 (m, 3H), 1.27−1.37 (m, 2H), 1.55 (m, 1H), 1.68−1.78 (m, 4H), 2.60 (s, 3H), 2.72−2.79 (m, 1H), 4.98 (s, 2H), 6.53−6.55 (m, 2H), 6.87−6.88 (m, 1H), 7.57 (s, 1H), 8.04 (m, 1H), 10.89 (s, 1H). HRMS calcd for $C_{18}H_{23}N_4O$ (M + H$^+$) 311.1866; found 311.1864.

Intermediate **62** (1 mmol) and benzoyl isothiocyanate (1 mmol) were dissolved in dried acetone (30 mL). The reaction mixture was refluxed with stirring for 4 h and then concentrated to give compound **63** without purification. Intermediate **63** (1 mmol) and K_2CO_3 (1.5 mmol) in CH_3OH (20 mL)/H_2O (5 mL) were heated to reflux for 1 h. Compound **64** was obtained as a white solid after evaporation of the solvent and chromatography through silica gel eluting with $CHCl_3$−CH_3OH (40:1, v/v). Yield 69%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.08−1.16 (m, 3H), 1.31−1.35 (m, 2H), 1.55 (m, 1H), 1.68−1.79 (m, 4H), 2.66 (s, 3H), 2.77 (m, 1H), 6.64−6.65 (m, 1H), 6.97−6.98 (m, 1H), 7.69 (m, 3H), 7.78 (s, 1H), 8.21 (s, 1H), 8.89 (s, 1H), 11.10 (s, 1H). HRMS calcd for $C_{19}H_{24}N_5OS$ (M + H$^+$) 370.1696; found 370.1693.

Compound **64** (0.5 mmol) and 2-bromo-1-phenylethanone (0.5 mmol) were dissolved in ethanol (30 mL) and refluxed for 2 h. After the reaction was completed, the solvent was evaporated in vacuo. The final product **65** was obtained as a white powder after purification by silica gel column chromatography eluting with $CHCl_3$−CH_3OH (50:1, v/v). Yield 70%; mp 248−250 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02−1.32 (m, 5H), 1.50−1.53 (m, 1H), 1.67−1.71 (m, 2H), 1.85−1.88 (m, 2H), 2.69 (s, 3H), 2.74−2.81 (m, 1H), 6.63−6.65 (m, 1H), 6.97−6.99 (m, 1H), 7.29−7.34 (m, 1H), 7.37 (s, 1H), 7.42−7.47 (m, 2H), 7.92 (s, 1H), 8.07−8.09 (m, 2H), 8.20−8.21 (m, 1H), 8.48 (s, 1H), 9.39 (s, 1H), 11.55 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.9, 25.5, 29.4, 38.3, 62.0, 103.7, 104.5, 110.6, 110.7, 112.1, 116.8, 117.7, 122.8, 125.4, 126.0, 127.4, 128.5, 134.4, 135.2, 136.0, 150.1, 155.3, 162.7. HRMS calcd for $C_{27}H_{28}N_5OS$ (M + H$^+$) 470.2009; found 470.2028.

6-(Methyl(phenyl)amino)-7-(4-phenylthiazol-2-ylamino)-quinoxalin-2(1*H*)-one (70). To a stirred solution of compound **2** (10 mmol) in THF (50 mL) was added K_2CO_3 (10 mmol) and *N*-methylaniline (10 mmol). The mixture was stirred under reflux for 8 h. The solvent was removed under reduced pressure to give compound **66a** that was used directly. Compound **66a** (1 g) was dissolved in a mixed solvent of THF (30 mL) and ethanol (30 mL), followed by the addition of 10% Pd/C (1 g) and $HCOONH_4$ (2 g). The mixture was stirred at room temperature for 3 h. The residue solid was filtered off, and the filtrate was concentrated in vacuo. Water (50 mL) was added to the resulting product and then was extracted by CH_2Cl_2 (3 × 50 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, and evaporated in vacuo. Intermediate **67a** was obtained as a yellow solid after chromatography through silica gel eluting with $CHCl_3$−CH_3OH (30:1, v/v). Yield 68%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.11 (s, 3H), 5.85 (s, 2H), 6.56−6.58 (m, 3H), 6.64−6.69 (m, 1H), 7.10−7.15 (m, 2H), 7.25 (s, 1H), 7.69 (s, 1H), 12.08 (s, 1H). HRMS calcd for $C_{15}H_{15}N_4O$ (M + H$^+$) 267.1240; found 267.1230.

Intermediate **67a** (1 mmol) and benzoyl isothiocyanate (1 mmol) were dissolved in dried acetone (30 mL). The reaction mixture was refluxed with stirring for 4 h and then concentrated to give compound **68a** without purification. Intermediate **68a** (1 mmol) and K_2CO_3 (1.5 mmol) in CH_3OH (20 mL)/H_2O (5 mL) were heated to reflux for 1 h. Compound **69a** was obtained as a yellow solid after evaporation of the solvent and chromatography through silica gel eluting with $CHCl_3$−CH_3OH (40:1, v/v). Yield 84%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.07 (s, 3H), 6.65−6.67 (m, 2H), 6.73−6.78 (m, 1H), 7.14−7.19 (m, 2H), 7.47 (s, 1H), 7.87 (s, 2H), 8.02 (s, 1H), 8.52 (s, 1H), 9.23 (s, 1H), 12.42 (s, 1H). HRMS calcd for $C_{16}H_{16}N_5OS$ (M + H$^+$) 326.1070; found 326.1055.

Compound **69a** (0.5 mmol) and 2-bromo-1-phenylethanone (0.5 mmol) were dissolved in ethanol (30 mL) and refluxed for 2 h. After the reaction was completed, the solvent was evaporated in vacuo. The final product **70** was obtained as a light-yellow powder after purification by silica gel column chromatography eluting with $CHCl_3$−CH_3OH (50:1, v/v). Yield 70%; mp 262−264 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.15 (s, 3H), 6.62 (d, 2H, J = 7.8 Hz), 6.71−6.76 (m, 1H), 7.14−7.20 (m, 2H), 7.31−7.36 (m, 1H), 7.44−7.49 (m, 4H), 7.96 (d, 1H, J = 1.8 Hz), 8.11 (d, 2H, J = 7.2 Hz), 8.89 (s, 1H), 10.14 (s, 1H), 12.89 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 39.3, 102.3, 105.3, 114.0, 117.6, 126.1, 127.5, 127.6, 128.6, 128.7, 131.8, 133.4, 134.2, 140.7, 147.9, 149.5, 149.9, 155.6, 162.2. HRMS calcd for $C_{24}H_{20}N_5OS$ (M + H$^+$) 426.1383; found 426.1361.

6-(Cyclohexyl(ethyl)amino)-7-(4-phenylthiazol-2-ylamino)-quinoxalin-2(1*H*)-one (71). Compound **71** was prepared in a similar manner to the synthesis of compound **70**, substituting *N*-ethylcyclohexanamine for *N*-methylaniline and DIPEA for K_2CO_3, respectively. The final product **71** was obtained as a yellow powder after purification by silica gel column chromatography. Yield 82% (the last step); mp 247−249 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.85 (t, 3H, J = 6.6 Hz), 1.00−1.19 (m, 5H), 1.49−1.52 (m, 1H), 1.66 (m, 2H), 1.91 (m, 2H), 2.80 (m, 1H), 3.07 (q, 2H, J = 6.6 Hz), 7.31−7.36 (m, 1H), 7.43−7.49 (m, 3H), 7.58 (s, 1H), 7.96 (s, 1H), 8.09 (d, 2H, J = 7.8 Hz), 8.60 (s, 1H), 9.84 (s, 1H), 12.77 (s, 1H). HRMS calcd for $C_{25}H_{28}N_5OS$ (M + H$^+$) 446.2009; found 446.2026.

7-(4-Phenylthiazol-2-ylamino)-6-(piperidin-1-yl)quinoxalin-2(1*H*)-one (72). Compound **72** was prepared in a similar manner to the synthesis of compound **71**, substituting piperidine for *N*-ethylcyclohexanamine. The final product **72** was obtained as a yellow powder after purification by silica gel column chromatography. Yield 79% (the last step); mp 248−250 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.55 (m, 2H), 1.78 (m, 4H), 2.81 (m, 4H), 7.33−7.35 (m, 1H), 7.43−7.49 (m, 4H), 7.96 (s, 1H), 8.06 (d, 2H, J = 7.2 Hz), 8.54 (s, 1H), 9.52 (s, 1H), 12.71 (s, 1H). HRMS calcd for $C_{22}H_{22}N_5OS$ (M + H$^+$) 404.1540; found 404.1549.

6-Morpholino-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1*H*)-one (73). Compound **73** was prepared in a similar manner to the synthesis of compound **71**, substituting morpholine for *N*-ethylcyclohexanamine. The final product **73** was obtained as a yellow powder after purification by silica gel column chromatography. Yield 75% (the last step); mp 234−236 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.86 (br s, 4H), 3.87 (br s, 4H), 7.30−7.35 (m, 1H), 7.43−7.48 (m, 2H), 7.50 (s, 1H), 7.54 (s, 1H), 7.97 (s, 1H), 8.07 (d, 2H, J = 7.2 Hz), 8.60 (s, 1H), 9.66 (s, 1H), 12.73 (s, 1H). HRMS calcd for $C_{21}H_{20}N_5O_2S$ (M + H$^+$) 406.1332; found 406.1329.

6-(4-Methylpiperazin-1-yl)-7-(4-phenylthiazol-2-ylamino)-quinoxalin-2(1*H*)-one (74). Compound **74** was prepared in a similar manner to the synthesis of compound **71**, substituting 1-methylpiperazine for *N*-ethylcyclohexanamine. The final product **74** was obtained as a yellow powder after purification by silica gel column chromatography. Yield 75% (the last step); mp 223−225 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.89 (s, 3H), 3.15 (br s, 4H), 3.47 (br s, 4H), 7.34−7.36 (m, 1H), 7.43−7.48 (m, 2H), 7.53 (s, 1H), 7.58 (s, 1H), 7.99 (s, 1H), 8.08 (d, 2H, J = 7.2 Hz), 8.64 (s, 1H), 9.59 (s, 1H), 12.79 (s, 1H). HRMS calcd for $C_{22}H_{23}N_6OS$ (M + H$^+$) 419.1649; found 419.1670.

Ethyl-1-(2-oxo-7-(4-phenylthiazol-2-ylamino)-1,2-dihydro-quinoxalin-6-yl)-piperidine-4-carboxylate (75). Compound **75** was prepared in a similar manner to the synthesis of compound **71**, substituting ethyl piperidine-4-carboxylate for *N*-ethylcyclohexanamine. The final product **75** was obtained as a yellow powder after purification by silica gel column chromatography. Yield 71% (the last step); mp 259−261 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.21 (t, 3H, J = 7.5 Hz), 1.89−1.93 (m, 2H), 2.01−2.12 (m, 2H), 2.43 (m, 1H), 2.68−2.75 (m, 2H), 2.98−3.01 (m, 2H), 4.10 (q, 2H, J = 7.5 Hz), 7.30−7.35 (m, 1H), 7.42−7.45 (m, 2H), 7.48−7.49 (m, 2H), 7.96 (s, 1H), 8.06 (d, 2H, J = 7.5 Hz), 8.59 (s, 1H), 9.61 (s, 1H), 12.72 (s, 1H). HRMS calcd for $C_{25}H_{26}N_5O_3S$ (M + H$^+$) 476.1751; found 476.1772.

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6-(4-(4-Fluorophenyl)piperazin-1-yl)-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1H)-one (76). Compound **76** was prepared in a similar manner to the synthesis of compound **71**, substituting 1-(4-fluorophenyl)piperazine for *N*-ethylcyclohexanamine. The final product **76** was obtained as a yellow powder after purification by silica gel column chromatography. Yield 77% (the last step); mp 245−247 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.02 (br s, 4H), 3.39 (br s, 4H), 7.00−7.08 (m, 4H), 7.33−7.36 (m, 1H), 7.43−7.48 (m, 2H), 7.50 (s, 1H), 7.57 (s, 1H), 7.98 (s, 1H), 8.07 (d, 2H, J = 7.5 Hz), 8.61 (s, 1H), 9.65 (s, 1H), 12.75 (s, 1H). HRMS calcd for $C_{27}H_{24}FN_6OS$ (M + H$^+$) 499.1711; found 499.1735.

6-(Dimethylamino)-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1*H*)-one (77). Compound **77** was prepared in a similar manner to the synthesis of compound **71**, substituting dimethylamine for *N*-ethylcyclohexanamine. The final product **77** was obtained as a yellow powder after purification by silica gel column chromatography. Yield 80% (the last step); mp 221−223 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.66 (s, 6H), 7.30−7.35 (m, 1H), 7.43−7.47 (m, 3H), 7.51 (s, 1H), 7.95 (s, 1H), 8.08 (d, 2H, J = 7.5 Hz), 8.68 (s, 1H), 9.99 (s, 1H), 12.74 (s, 1H). HRMS calcd for $C_{19}H_{18}N_5OS$ (M + H$^+$) 364.1227; found 364.1225.

6-(Diethylamino)-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1*H*)-one (78). Compound **78** was prepared in a similar manner to the synthesis of compound **71**, substituting diethylamine for *N*-ethylcyclohexanamine. The final product **78** was obtained as a yellow powder after purification by silica gel column chromatography. Yield 82% (the last step); mp 238−240 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.92 (t, 6H, J = 6.9 Hz), 2.98 (q, 4H, J = 6.9 Hz), 7.31−7.36 (m, 1H), 7.43−7.47 (m, 3H), 7.57 (s, 1H), 7.95 (d, 1H, J = 1.8 Hz), 8.09 (d, 2H, J = 7.5 Hz), 8.64 (s, 1H), 9.95 (s, 1H), 12.77 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 11.8, 48.7, 101.2, 104.9, 123.0, 126.0, 127.1, 127.5, 128.5, 130.4, 134.2, 134.3, 141.0, 147.4, 150.0, 155.6, 162.0. HRMS calcd for $C_{21}H_{22}N_5OS$ (M + H$^+$) 392.1540; found 392.1557.

6-(Dipropylamino)-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1*H*)-one (79). Compound **79** was prepared in a similar manner to the synthesis of compound **71**, substituting dipropylamine for *N*-ethylcyclohexanamine. The final product **79** was obtained as a yellow powder after purification by silica gel column chromatography. Yield 69% (the last step); mp 215−217 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.81 (t, 6H, J = 7.5 Hz), 1.30−1.42 (m, 4H), 2.89 (t, 4H, J = 7.5 Hz), 7.31−7.36 (m, 1H), 7.43−7.49 (m, 3H), 7.61 (s, 1H), 7.95 (d, 1H, J = 2.1 Hz), 8.08 (d, 2H, J = 7.2 Hz), 8.59 (s, 1H), 9.79 (s, 1H), 12.75 (s, 1H). HRMS calcd for $C_{23}H_{26}N_5OS$ (M + H$^+$) 420.1853; found 420.1872.

6-(Cyclohexyloxy)-7-(4-phenylthiazol-2-ylamino)quinoxalin-2(1*H*)-one (80). Compound **80** was prepared in a similar manner to the synthesis of compound **71**, substituting sodium cyclohexanolate for *N*-ethylcyclohexanamine. The final product **80** was obtained as a pale-yellow solid after purification by silica gel column chromatography. Yield 78% (the last step); mp 215−216 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.22−1.44 (m, 4H), 1.53−1.60 (m, 2H), 1.76−1.80 (m, 2H), 2.02−2.05 (m, 2H), 4.47 (m, 1H), 7.30−7.36 (m, 2H), 7.43−7.51 (m, 2H), 7.85−7.87 (m, 1H), 7.96 (s, 1H), 8.08 (d, 2H, J = 7.5 Hz), 8.73 (s, 1H), 9.76 (s, 1H), 12.75 (s, 1H). HRMS calcd for $C_{23}H_{23}N_4O_2S$ (M + H$^+$) 419.1536; found 419.1553.

7-(Cyclohexyl(methyl)amino)-6-(4-phenylthiazol-2-ylamino)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (85). Compound **85** was prepared in a similar manner to the synthesis of compound **51**, substituting $HOCH_2COOCH_3$ for $NH_2CH(CH_3)COOCH_3$·HCl. The final product **85** was obtained as a light-yellow powder after purification by silica gel column chromatography. Yield 86% (the last step); mp 205−206 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.07−1.24 (m, 5H), 1.53−1.80 (m, 5H), 2.54 (s, 3H), 2.61 (m, 1H), 4.52 (s, 2H), 6.84 (s, 1H), 7.28−7.32 (m, 2H), 7.39−7.44 (m, 2H), 7.97−8.01 (m, 3H), 9.09 (s, 1H), 10.90 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.0, 25.5, 29.3, 37.6, 61.8, 66.8, 103.0, 106.0, 111.3, 123.4, 125.9, 127.4, 128.4, 131.9, 134.5, 136.0, 137.7, 149.9, 163.4, 165.0. HRMS calcd for $C_{24}H_{27}N_4O_2S$ (M + H$^+$) 435.1849; found 435.1868.

7-(Cyclohexyl(methyl)amino)-6-(4-phenylthiazol-2-ylamino)-2*H*-benzo[*b*][1,4]thiazin-3(4*H*)-one (86). To a stirred solution of compound **46** (10 mmol) in THF (50 mL) was added DIPEA (10 mmol) and $HSCH_2COOCH_3$ (10 mmol). After vigorously stirring at 65 °C until the total disappearance of the starting materials, compound **81b** was obtained without purification. Compound **81b** (5 mmol) and $SnCl_2 \cdot 2H_2O$ (75 mmol) were dissolved in ethanol (75 mL). Then 15 equiv of 12 mol/L hydrochloric acid was added and the mixture was stirred under reflux for 3 h. The solvent was then evaporated. The residue was neutralized with 40% NaOH until the pH reached 8. The mixture was filtered, and the filtrate was extracted with 100 mL of $CHCl_3$ twice. The organic solvent was washed with brine, dried over anhydrous sodium sulfate, and evaporated in vacuo. The intermediate **82b** was obtained as a white solid after purification by silica gel column chromatography. Yield 49%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.11−1.18 (m, 3H), 1.21−1.28 (m, 2H), 1.53 (m, 1H), 1.67−1.70 (m, 4H), 2.48 (s, 3H), 2.61−2.64 (m, 1H), 4.86 (s, 2H), 6.32 (s, 1H), 6.81 (s, 1H), 10.20 (s, 1H). HRMS calcd for $C_{15}H_{22}N_3OS$ (M + H$^+$) 292.1478; found 292.1472.

Intermediate **82b** (1 mmol) and benzoyl isothiocyanate (1 mmol) were dissolved in dried acetone (30 mL). The reaction mixture was refluxed with stirring for 4 h and then concentrated to give compound **83b** without purification. Intermediate **83b** (1 mmol) and K_2CO_3 (1.5 mmol) in CH_3OH (20 mL)/H_2O (5 mL) were heated to reflux for 1 h. After evaporation of the solvent in vacuo, compound **84b** was obtained as a white solid after chromatography through silica gel eluting with $CHCl_3$−CH_3OH (20:1, v/v). Yield 60%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.06−1.18 (m, 3H), 1.23−1.34 (m, 2H), 1.51−1.54 (m, 1H), 1.68−1.71 (m, 4H), 2.53 (s, 3H), 2.62−2.65 (m, 1H), 3.42 (s, 2H), 7.00 (s, 1H), 7.46 (s, 1H), 7.60 (s, 2H), 8.78 (s, 1H), 10.40 (s, 1H). HRMS calcd for $C_{16}H_{23}N_4O_2S$ (M + H$^+$) 351.1308; found 292.1294.

84b (0.5 mmol) and 2-bromo-1-phenylethanone (0.5 mmol) were dissolved in ethanol (30 mL) and refluxed for 2 h. After the reaction was completed, the solvent was evaporated in vacuo. The final product **86** was obtained as a yellow powder after purification by silica gel column chromatography eluting with $CHCl_3$−CH_3OH (40:1, v/v). Yield 81%; mp 249−250 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.06−1.24 (m, 5H), 1.49−1.52 (m, 1H), 1.65−1.69 (m, 2H), 1.78−1.82 (m, 2H), 2.56 (s, 3H), 2.64 (m, 1H), 3.43 (s, 2H), 7.15 (s, 1H), 7.28−7.34 (m, 2H), 7.40−7.45 (m, 2H), 7.99 (d, 2H, J = 7.5 Hz), 8.13 (s, 1H), 9.24 (s, 1H), 10.75 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.9, 25.4, 29.2, 29.3, 37.9, 61.8, 103.6, 106.5, 110.3, 122.2, 125.9, 127.4, 128.4, 134.3, 134.4, 135.7, 136.1, 150.1, 162.7, 165.4. HRMS calcd for $C_{24}H_{27}N_4OS_2$ (M + H$^+$) 451.1621; found 451.1643.

HCV Antiviral Assay. The Huh7 ET (luc-ubi-neo/ET) cell line which harbors a dicistronic self-replicating HCV RNA replicon with a firefly luciferase gene was used for antiviral evaluation.[18] The activity of the luciferase reporter is proportional to HCV RNA levels. Briefly, the replicon cells were seeded into two identical sets of 96-well plates at a density of 5000/well in 100 μL of DMEM without G418 overnight. Compounds were solubilized in DMSO and then dilutions prepared in DMEM and added to the wells. Following 72 h incubation, one set of the cells was processed to assess the replicon-derived luciferase activity with the Steady-Glo luciferase assay system (Promega, Madison, WI) according to manufacturer's instruction. Another set of the plates was used to determine cytotoxicity of the compounds using a tetrazolium-based CytoTox-1 cell proliferation assay (Promega, Madison WI). Each data point represents an average of four replicates to derive EC_{50} (concentration inhibiting HCV RNA replication activity by 50%), IC_{50} (concentration decreasing cell viability by 50%), and SI_{50} (selective index which is calculated by IC_{50}/EC_{50}) values.

■ ASSOCIATED CONTENT

Supporting Information. The general procedure for the synthesis of intermediates **50b**−**d**, **69b**−**k**, and **84a**. NMR spectra and HPLC analysis results of all the final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

HCV, hepatitis C virus; DFDNB, 1,5-difluoro-2,4-dinitrobenzene; DIPEA, diisopropylethylamine; NOESY, nuclear Overhauser effect spectroscopy; THF, tetrahydrofuran; EC_{50}, concentration of compound inhibiting HCV replicon by 50%; IC_{50}, concentration of compound decreasing cell viability by 50%; SI, selectivity index; SAR, structure−activity relationship

■ ADDITIONAL NOTE

[a] Telaprevir and boceprevir were approved by USA FDA recently for treatment of HCV infection.

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