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A novel class of sodium/calcium exchanger inhibitor: design, synthesis, and structure–activity relationships of 3,4-dihydro-2(1*H*)-quinazolinone derivatives

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Abstract—Design, synthesis, and structure–activity relationships of 3,4-dihydro-2(1*H*)-quinazolinone derivatives as inhibitors of the sodium/calcium (Na^+/Ca^{2+}) exchanger are discussed. These studies, based on a lead compound **9a**, which was identified in our library, involved systematic modification of three regions and revealed that (1) the 3,4-dihydro-2(1*H*)-quinazolinone having a tertiary amino alkyl side chain at the 3-position is essential for activity, (2) a nonsubstituted phenyl ring is most suitable for high activity, and (3) introduction of a 4-substituted piperidine moiety enhanced the activity, in particular 4-benzylpiperidin-1-yl showed strong inhibitory activity. Based on these SAR studies, a structurally novel and highly potent inhibitor against the Na^+/Ca^{2+} exchanger, **12g** (**SM-15811**), was discovered. In particular, **SM-15811** directly inhibited the Na^+-dependent Ca^{2+} influx via the Na^+/Ca^{2+} exchanger in cardiomyocytes with a high potency. The activity was almost two orders more potent than the lead compound **9a** and **SM-15811** exerted a protective effect against myocardial ischemic reperfusion injury. These Na^+/Ca^{2+} inhibitors could have a therapeutic potential for the treatment of ischemic reperfusion injury.

1. Introduction

Recently, several invasive procedures such as intracoronary thrombolysis, percutaneous coronary angioplasty, and coronary bypass surgery for patients with acute myocardial infarction are performed to salvage jeopardized myocardium and beneficial effects of these procedures have been confirmed. Although these procedures are necessary to reduce the amount of necrotic myocardium, it has been known that restortion of coronary blood flow caused reperfusion injury.[1] It is well known that reperfusion injury is associated with a large increase in intracelluar Ca^{2+} content.[2] Therefore inhibition of this Ca^{2+} overload is considered one of the pharmacological intervention to prevent reperfusion injury. It is proposed that the sodium/calcium (Na^+/Ca^{2+}) exchanger plays an important role when Ca^{2+} overload occurs.[3,4] We considered that inhibitors of the Na^+/Ca^{2+} exchanger would inhibit Ca^{2+} overload during reperfusion and then prevent reperfusion injury. Therefore we started this study to develop inhibitor(s) of the Na^+/Ca^{2+} exchanger with high potency and selectivity.

To date, a number of inhibitors against the Na^+/Ca^{2+} exchanger have been reported, most of them, however, being weak and nonselective inhibitors.[1] Recently, Val-Met-Arg-Phe-NH_2 (**1**) with an IC_{50} value of 1.5 μM has been reported, which is a peptidic inhibitor.[5] As a nonpeptidic inhibitor, an aroylguanidine derivative (**3**) with an IC_{50} value of 3.4 μM has been reported, which is a modified amiloride derivative as is dimethylamiloride (**2**).[6] Furthermore, KB-R7943 (**4**)[7] and SEA0400 (**5**)[8] have also been reported as nonpeptidic inhibitors. SEA0400 shows more than 80% inhibition at 1 μM against the Na^+/Ca^{2+} exchanger, which is a 10-fold higher potency than that of KB-R7943. Very recently, phenoxypyridine derivatives (**6** and **7**) and SN-6 (**8**) have been reported.[9,10] (Fig. 1).

Keywords: Sodium/calcium exchanger; Na^+/Ca^{2+} exchanger; 3,4-Dihydro-2(1*H*)-quinazolinone derivative; Ischemic reperfusion injury.
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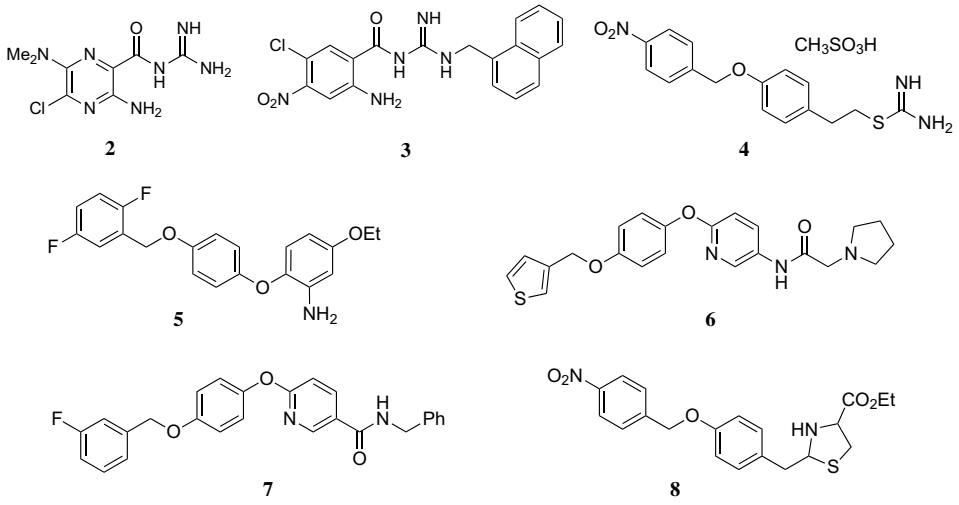


Figure 1. Chemical structures of nonpeptidic inhibitor of the Na^+/Ca^{2+} exchanger: (**2**) dimethylamiloride; (**3**) aroylguanidine analogue; (**4**) KB-R7943; (**5**) SEA0400; (**6**) and (**7**) phenoxypyridine analogue; (**8**) SN-6.

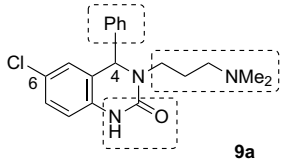


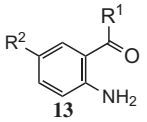
Figure 2. Chemical structure of 3,4-dihydro-2(1*H*)-quinazolinone derivatives **9a**.

In our research, we identified that 3,4-dihydro-2(1*H*)-quinazolinone derivative **9a** in our chemical library, through a random screening, had a moderately potent inhibitory activity against the Na^+/Ca^{2+} exchanger. Since **9a** has a nonpeptidic, structurally novel, and quite different skeleton from other inhibitors, we therefore used **9a** as a lead compound and synthesized derivatives to find a more potent compound evaluating the structure–activity relationships (SARs) in three parts systematically (boxed regions in Fig. 2). These studies lead to the discovery of a structurally novel and highly potent inhibitor against the Na^+/Ca^{2+} exchanger **12g** (**SM-15811**). Herein, we wish to report and present these studies in full detail.

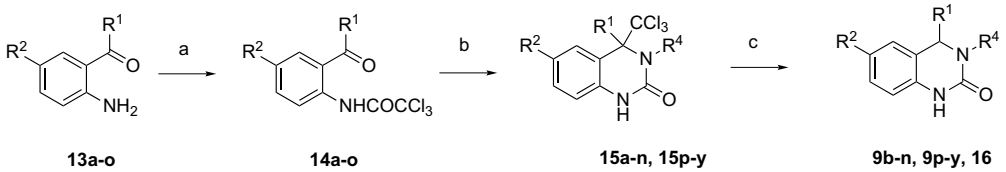
2. Chemistry

Compounds **9a**–**m**, **9o**–**y** having a straight side chain at the 3-position (Tables 4–6) of the 3,4-dihydro-2(1*H*)-quinazolinone were synthesized using Yamamoto's procedure.[11] Trichloroacetylation of 2-acylaniline derivatives **13a**–**o**[12] with trichloroacetyl chloride, followed by treatment with primary amines in DMSO gave directly cyclized products **15a**–**n**, **15p**–**y**, with accompanying rearrangement of the trichloromethyl group. Removal of the trichloromethyl group leading to the 3,4-dihydro-2(1*H*)-quinazolinones **9b**–**n**, **9p**–**y**, and **16** was effected by $NaBH_4$ in DMF (Scheme 1). The starting materials and intermediates for the synthesis of **9b**–**y**, and **16** are listed in Tables 1–3. The citric acid salt of

Table 1. Chemical structure of **13a**–**o**

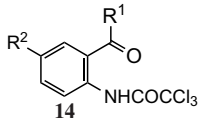


Compound	R^1	R^2
13a	Ph	Cl
13b	Ph	H
13c	2-Furyl	Cl
13d	2-Thienyl	H
13e	2-Pyridyl	H
13f	Me	H
13g	*i*-Pr	H
13h	Cyclohexyl	H
13i	Benzyl	H
13j	2-Naphthyl	H
13k	3-Me–Ph	H
13l	4-Me–Ph	H
13m	3-MeO–Ph	H
13n	3-BnO–Ph	H
13o	3-Cl–Ph	H



Scheme 1. Reagents: (a) CCl_3COCl, Et_3N, THF; (b) R^4–NH_2, DMSO; (c) $NaBH_4$, DMF.

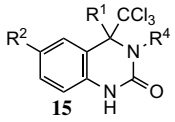
Table 2. Chemical structure of intermediate **14a–o**



14

Compound	R^1	R^2
14a	Ph	Cl
14b	Ph	H
14c	2-Furyl	Cl
14d	2-Thienyl	H
14e	2-Pyridyl	H
14f	Me	H
14g	*i*-Pr	H
14h	Cyclohexyl	H
14i	Benzyl	H
14j	2-Naphthyl	H
14k	3-Me–Ph	H
14l	4-Me–Ph	H
14m	3-MeO–Ph	H
14n	3-BnO–Ph	H
14o	3-Cl–Ph	H

Table 3. Chemical structure of intermediate **15a–n**, **15p–y**

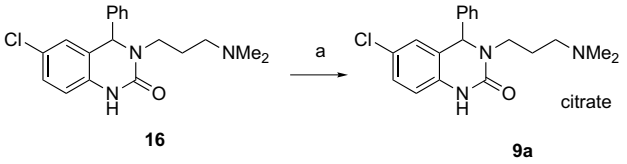


15

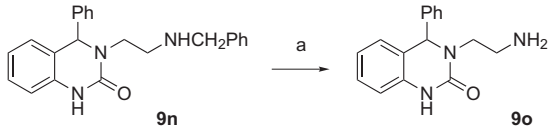
Compound[a]	R^1	R^2	R^4
15a	Ph	Cl	$(CH_2)_3NMe_2$
15b	Ph	H	$(CH_2)_3NMe_2$
15c	2-Furyl	Cl	$(CH_2)_3NMe_2$
15d	2-Thienyl	H	$(CH_2)_3NMe_2$
15e	2-Pyridyl	H	$(CH_2)_3NMe_2$
15f	Me	H	$(CH_2)_3NMe_2$
15g	*i*-Pr	H	$(CH_2)_3NMe_2$
15h	Cyclohexyl	H	$(CH_2)_3NMe_2$
15i	Benzyl	H	$(CH_2)_3NMe_2$
15j	2-Naphthyl	H	$(CH_2)_3NMe_2$
15k	Ph	H	$(CH_2)_3CH(Me)_2$
15l	Ph	H	$(CH_2)_2OEt$
15m	Ph	H	CH_2CONEt_2
15n	Ph	H	$(CH_2)_2NHCH_2Ph$
15p	Ph	H	$(CH_2)_2NHEt$
15q	Ph	H	$(CH_2)_2NEt_2$
15r	Ph	H	$(CH_2)_3NEt_2$
15s	Ph	H	$(CH_2)_4NEt_2$
15t	Ph	H	$(CH_2)_2N(i\text{-}Pr)_2$
15u	3-Me–Ph	H	$(CH_2)_2NEt_2$
15v	4-Me–Ph	H	$(CH_2)_2NEt_2$
15w	3-MeO–Ph	H	$(CH_2)_2NEt_2$
15x	3-BnO–Ph	H	$(CH_2)_2NEt_2$
15y	3-Cl–Ph	H	$(CH_2)_2NEt_2$

[a] All the compounds were racemic.

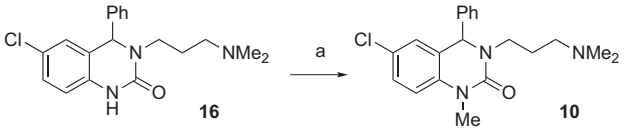
16 was prepared by treating **16** with citric acid in EtOH to give **9a** (Scheme 2). Primary amine **9o** was prepared by debenzylation of **9n** with ammonium formate in the presence of Pd/C in MeOH (Scheme 3). 1-Methylated 3,4-dihydro-2(1*H*)-quinazolinone analogue **10** was prepared from **16** by reaction with NaH followed by iodomethane (Scheme 4). Thiocarbonyl analogue **11**



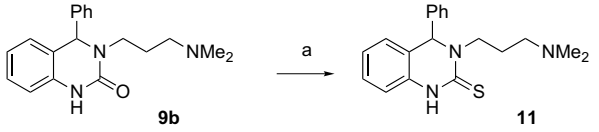
Scheme 2. Reagents: (a) citric acid, EtOH.



Scheme 3. Reagents: (a) HCO_2NH_4, Pd/C, MeOH.



Scheme 4. Reagents: (a) NaH, MeI, DMF.



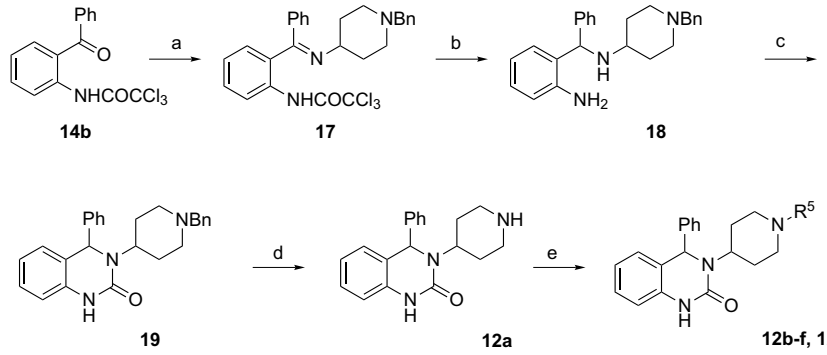
Scheme 5. Reagents: (a) P_2S_5, xylene, reflux.

was prepared by treating **9b** with P_2S_5 in xylene (Scheme 5).

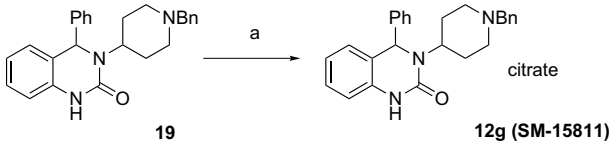
In order to synthesize 4-phenyl-3-(4-piperidinyl)-3,4-dihydro-2(1*H*)-quinazolinone derivatives having cyclic amines **12a–h** (Table 7), we developed a more versatile procedure (Scheme 6). Treatment of trichloroacetylamide **14b** with 4-amino-1-benzylpiperidine in DMSO gave imine **17**. Reduction of this imine and removal of the trichloroacetyl moiety with $NaBH_4$ gave diamine **18**. Treatment of diamine **18** with 1,1′-carbonyldiimidazole lead to cyclization to afford 3-[4-(1-benzyl)piperidinyl]-4-phenyl-3,4-dihydro-2(1*H*)-quinazolinone **19**, which was then converted into the mono citric acid salt **12g (SM–15811)** by treating **19** with citric acid in EtOH (Scheme 7). Debenzylation of **19** gave **12a**, which was subsequently alkylated or reductively alkylated to afford **12b–f**, **12h** (Scheme 6).[17]

3. Pharmacological results and discussion

In cardiomyocytes, fura 2 fluorescence ratio (an index of $[Ca^{2+}]_i$) increases by Na^+-dependent Ca^{2+} influx via the Na^+/Ca^{2+} exchanger after Na^+-free treatment. The lead compound **9a** concentration-dependently attenuated the increase in the Na^+-free-induced fura 2 fluorescence ratio (Fig. 3).[18] It is well known that an increase in the



Scheme 6. Reagents: (a) 4-amino-1-benzylpiperidine, DMSO; (b) $NaBH_4$, EtOH; (c) 1,1′-carbonyldiimidazole, THF, reflux; (d) HCO_2NH_4, Pd/C, MeOH, reflux; (e) R^5–X^2, K_2CO_3, DMF (X^2 = Br, I) or aldehyde, $NaBH_3CN$, HCl, MeOH.



Scheme 7. Reagents: (a) citric acid, EtOH.

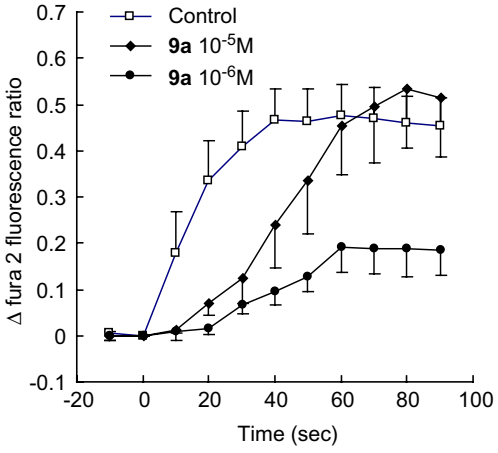
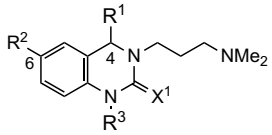


Figure 3. Effect of **9a** on the Na^+/Ca^{2+} exchange activity in rat cardiomyocytes. The Na^+/Ca^{2+} exchange activity was estimated as the increase in fura 2 fluorescence ratio induced by exposing to the Na^+-free HEPES-based buffer using a Ca^{2+} sensitive fluorescent indicator fura 2. Each point represents the mean ± SEM of five experiments.

$[Ca^{2+}]_i$ is correlated with the development of cardiac contractile force. Therefore, we evaluated the inhibitory activity against Na^+- and K^+-free contracture after 30 min of K^+ free incubation in isolated left atria from guinea pigs.[19] The inhibitory activities were calculated as IC_{30} values. In this evaluation system, Val-Met-Arg-Phe-NH_2 (**1**) and dimethylamiloride (**2**) showed inhibitory activities with IC_{30} values of 10 and 30 μM, respectively.

The lead compound **9a** showed an inhibitory activity with an IC_{30} value of 0.46 μM. We first examined the 3,4-dihydro-2(1*H*)-quinazolinone of **9a** (Table 4). Removal of the chlorine atom at the 6-position did not affect the activity (**9b** vs **9a**), although introduction of a methyl group at the 1-position (**10** vs **9a**) reduced the activity markedly. The conversion of the cyclic urea to cyclic thiourea (**11** vs **9b**) caused a 10-fold reduction in the activity. Therefore these results suggested that the 3,4-dihydro-2(1*H*)-quinazolinone was essential for activity.

Table 4. Inhibitory activity of 3,4-dihydro-2(1*H*)-quinazolinones against the Na^+/Ca^{2+} exchanger



Compound[a]	R^1	R^2	R^3	X^1	IC_{30} (μM)
1 (Val-Met-Arg-Phe-NH_2)					10
2 (Dimethylamiloride)					30
9a[b]	Ph	Cl	H	O	0.46
9b	Ph	H	H	O	0.35
10	Ph	Cl	Me	O	>10
11[c]	Ph	H	H	S	3.8
9c	2-Furyl	Cl	H	O	0.69
9d	2-Thienyl	H	H	O	0.72
9e	2-Pyridyl	H	H	O	0.51
9f	Me	H	H	O	5.3
9g	*i*-Pr	H	H	O	8.5
9h	Cyclohexyl	H	H	O	0.57
9i	Benzyl	H	H	O	>10
9j	2-Naphthyl	H	H	O	>10

[a] All the compounds tested were racemic.
[b] Compound tested as the citrate.
[c] Compound tested as the hydrochloride.

Next we replaced the phenyl group at the 4-position (i.e., R^1, Table 4). Replacement of the phenyl group with heteroaryl groups such as 2-furyl **9c**, 2-thienyl **9d**, and 2-pyridyl **9e**, which are comparable to the phenyl ring in bulkiness, reduced the activity slightly. Introduction of a methyl group **9f** or isopropyl group **9g** resulted in a drop in inhibitory activity by almost 20-fold (**9f** and **9g** vs **9b**), although the cyclohexyl **9h** had only a slightly reduced activity. A larger group such as benzyl **9i** or 2-naphthyl **9j** abolished the activity. These results sug-

gested that the hydrophobic pocket at the 4-position was not very large. The phenyl group was the most suitable substituent for high activity.

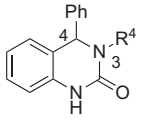
For further exploration of the SARs, modifications of the side chain at the 3-position were carried out (i.e., R^4, Table 5). Replacement of a nitrogen atom with a carbon atom (**9k** vs **9b**) or oxygen atom (**9l** vs **9q**) resulted in complete loss in activity, showing that the nitrogen atom is essential. Furthermore, the amide derivative also had diminished activity (**9m** vs **9q**). Hence a basic nitrogen atom was essential for activity. Actually, the calculated pK_a values of the amino group of the side chain in **9m** and **9q** were −0.58 and 10.23, respectively, which means that 3,4-dihydro-2(1*H*)-quinazolinones show activities in the protonated form.[21]

The secondary amino group showed stronger activity than the primary amino group, but the tertiary amino group showed the strongest activity (**9o** and **9p** vs **9q**), suggesting that the tertiary amino group was preferred. In terms of the length between nitrogen atom in the side chain and nitrogen atom at the 3-position of the 3,4-dihydro-2(1*H*)-quinazolinone, two carbon atoms **9q** and three carbon atoms **9r** showed strong activity, but four carbon atoms **9s** reduced the activity, suggesting either two or three carbon atoms were preferred. These results suggested that the amine at the 3-position was very important and that a tertiary amine with either a length of 2 or 3 carbons were preferred. In terms of bulkiness of the amino group, *N*,*N*-diisopropylamino group **9t** reduced the activity, suggesting ethyl is preferred for activity.

In order to evaluate SARs at the 4-position further, some substituents were introduced on the phenyl group (i.e., Y^1, Table 6). The introduction of a methyl group at the 3- and 4-positions reduced the activity (**9u** and **9v** vs **9q**), but **9u** was slightly stronger than **9v**. We, therefore, introduced the electron donating methoxy group and the more sterically large electron donating benzyloxy group at the 3-position (**9w** and **9x**), but only the methoxy group **9w** maintained the activity. On the other hand, introduction of the electron withdrawing chlorine atom at the 3-postion enhanced the activity in contrast to the electron donating group (**9y** vs **9w**), but its activity was weaker than nonsubstituted phenyl ring. These results suggested that introduction of substitutents at the either 3- or 4-position on the phenyl group was not preferred, indicating hydrophobic pocket toward the 3- or 4-position was not so large.

We next introduced a cyclic amine into the side chain at the 3-position of this derivative so as to increase the activity. Table 7 summarizes our results in introducing the 4-piperidinyl as the cyclic amine. We synthesized the nonsubstituted **12a** and various substituted piperidine derivatives **12b–h**. Nonsubstituted **12a** was weaker than **12b**. But introduction of chain alkyl groups enhanced the activities (**12b–d**). Further introduction of a bulky alkyl group such as isopropyl **12e** or cyclohexylmethyl **12f** reduced the inhibitory activity. In contrast to cyclohexylmethyl **12f**, the benzyl group **12g**

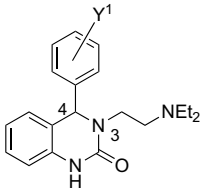
Table 5. Inhibitory activity of 3,4-dihydro-2(1*H*)-quinazolinones against the Na^+/Ca^{2+} exchanger



Compound[a]	R^4	IC_{30} (μM)
9k	$(CH_2)_3CH(Me)_2$	>10
9l	$(CH_2)_2OEt$	>10
9m	CH_2CONEt_2	>10
9o	$(CH_2)_2NH_2$	>10
9p	$(CH_2)_2NHEt$	0.58
9q	$(CH_2)_2NEt_2$	0.069
9r	$(CH_2)_3NEt_2$	0.04
9s	$(CH_2)_4NEt_2$	1.9
9t	$(CH_2)_2N(i\text{-}Pr)_2$	0.65

[a] All the compounds tested were racemic.

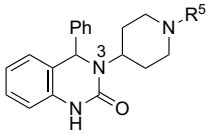
Table 6. Inhibitory activity of 3,4-dihydro-2(1*H*)-quinazolinones against the Na^+/Ca^{2+} exchanger



Compound[a]	Y^1	IC_{30} (μM)
9u	3-Me	0.19
9v	4-Me	0.81
9w[b]	3-OMe	0.44
9x	3-OBn	>10
9y	3-Cl	0.09

[a] All the compounds tested were racemic.
[b] Compound tested as the hydrochloride.

Table 7. Inhibitory activity of 3,4-dihydro-2(1*H*)-quinazolinones against the Na^+/Ca^{2+}exchanger



Compound[a]	R^5	IC_{30} (μM)
12a	H	1.1
12b[d]	Me	0.087
12c[c,d]	Et	0.053
12d[c,e]	*n*-Pr	0.093
12e	*i*-Pr	0.21
12f[c,f]	Cyclohexylmethyl	4.0
12g (SM-15811)[b]	$PhCH_2$–	0.017
12h[c,f]	$Ph(CH_2)_2$–	3.6

[a] All the compounds tested were racemic.
[b] Compound tested as the citrate.
[c] Compounds tested as the hydrochloride.
[d] Corresponding alkyl iodides were used for *N*-alkylation.
[e] *n*-PrBr was used for *N*-alkylation.
[f] Corresponding aldehydes were used for *N*-alkylation.

(**SM-15811**) showed strong activity, with an IC_{30} value of 0.017 μM, suggesting in this case there may be a π–π interaction between the inhibitor and the binding site. However, phenylethyl group **12h** decreased the activity drastically, suggesting location of the phenyl ring was important for activity (**12g** vs **12h**).

We found that **12g** (**SM-15811**) had strong inhibitory activity against Na^+- and K^+-free contracture after 30 min of K^+ free incubation in isolated left atria from guinea pigs. Moreover, we evaluated **SM-15811** by fura 2 fluorescence ratio (an index of $[Ca^{2+}]_i$) increased by Na^+-dependent Ca^{2+} influx via Na^+/Ca^{2+} exchanger after Na^+-free treatment in cardiomyocytes.[18] Figure 4 shows the results. **SM-15811** concentration-dependently attenuated the increase in Na^+-free induced fura 2 fluorescence ratio, indicating **SM-15811** discovered by our systematic modification of **9a** directly inhibited the Na^+-dependent Ca^{2+} influx via Na^+/Ca^{2+} exchanger after Na^+-free treatment in cardiomyocytes. The inhibitory activity of **SM-15811** was almost 2 orders stronger than the lead compound **9a** (Fig. 3 vs Fig. 4). These results suggested that **SM-15811** found by our systematic SARs studies showed strong inhibitory activity against the Na^+/Ca^{2+} exchanger.

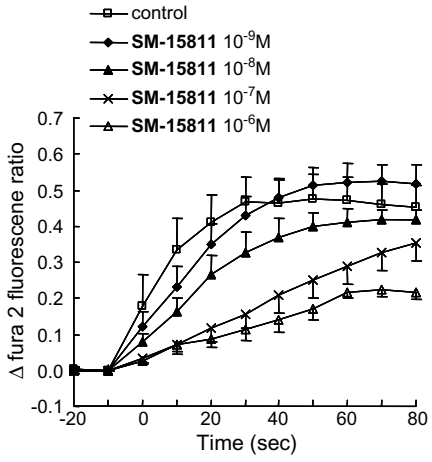


Figure 4. Effect of (**12g**) **SM-15811** on the Na^+/Ca^{2+} exchange activity in rat cardiomyocytes. The Na^+/Ca^{2+} exchange activity was estimated as the increase in fura 2 fluorescence ratio induced by exposing to the Na^+-free HEPES-based buffer using a Ca^{2+} sensitive fluorescent indicator fura 2. Each point represents the mean ± SEM of 5 experiments.

The Na^+/Ca^{2+} exchanger is involved in regulation of intracellular Ca^{2+} concentration via the forward mode (Ca^{2+} extrusion) and/or the reverse mode (Ca^{2+} influx).[22] On the other hand, it has been reported that KB-R7943 selectively inhibits the reverse mode of Na^+/Ca^{2+} exchanger and prevents Ca^{2+} overload induced by Ca^{2+} paradox.[7] In our preliminary study, however, we did not evaluate the effect of **SM-15811** on Na^+-dependent Ca^{2+} efflux via the Na^+/Ca^{2+} exchanger. Further investigation is necessary to examine against the forward mode of Na^+/Ca^{2+} exchanger.

Furthermore, we investigated the cardioprotective effects of **SM-15811** on ischemic reperfusion injury in isolated perfused rat hearts (Fig. 5). **SM-15811** significantly reduced the elevation of left ventricular end-diastolic pressure after reperfusion, improved the post-ischemic recovery of developed pressure, and prevented the abnormal gain of tissue Ca^{2+} at the end of reperfusion.[18] These results suggested that **SM-15811**, a highly potent Na^+/Ca^{2+} exchange inhibitor, exerts a protective effect against myocardial ischemia and reperfusion injury.

4. Conclusion

In summary, we found that 3,4-dihydro-2(1*H*)-quinazolinone derivative **9a** in our library concentration-dependently attenuated the increase in Na^+-free-induced fura 2 fluorescence ratio and exhibited inhibitory activity against the Na^+/Ca^{2+} exchanger with an IC_{30} value of 0.46 μM. We disclosed the SARs of lead compound **9a** by systematic modification in three parts. The results of the SARs studies are as follows: (1) Removal of

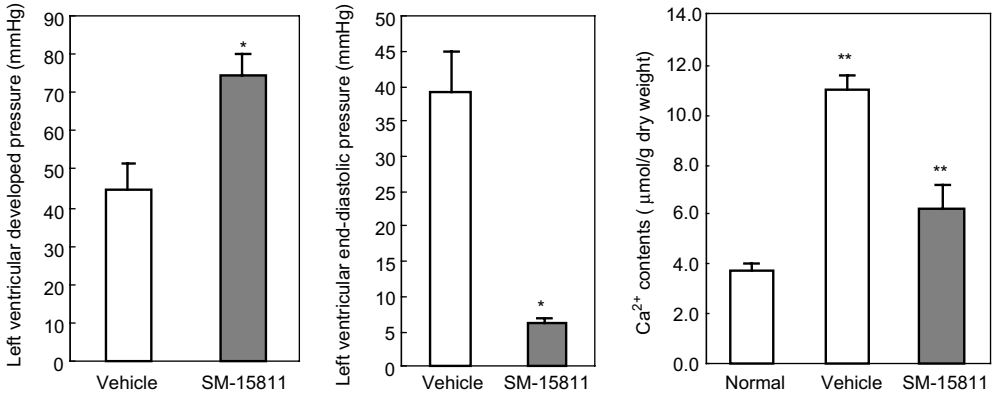


Figure 5. Effects of **SM-15811** on left ventricular developed pressure, left ventricular end-diastolic pressure and tissue Ca^{2+} contents at end of ischemic reperfusion in isolated perfused rat hearts. Hearts were subjected to 40 min of global ischemia and 20 min of reperfusion. **SM-15811** (0.3 μM) or vehicle was administered for 5 min before ischemia and 20 min throughout the reperfusion period. Tissue Ca^{2+} contents were measured by atomic spectrophotometer. Each column is mean ± SEM of 4–5 hearts. $^*P < 0.05$, $^{**}P < 0.01$ versus vehicle by *t*-test. $^{**}P < 0.01$ versus vehicle by *t*-test.

chlorine atom at the 6-position of the 3,4-dihydro-2(1*H*)-quinazolinone did not affect the activity. (2) The 3,4-dihydro-2(1*H*)-quinazolinone was essential for activity. (3) A phenyl group at the 4-position of the 3,4-dihydro-2(1*H*)-quinazolinone was preferred and its hydrophobic pocket toward the 3- or 4-position was not so large. (4) An amine at the 3-position of the 3,4-dihydro-2(1*H*)-quinazolinone was very important and a tertiary amine with either 2 or 3 carbon chain length were preferred. (5) Introduction of *N*-alkyl-4-piperidines at the 3-position of the 3,4-dihydro-2(1*H*)-quinazolinone further enhanced the activity. (6) Introduction of a benzyl group, which possibly interacted in a π–π manner at the 1-position on the 4-piperidine improved the activity and gave the highly potent inhibitor of the Na^+/Ca^{2+} exchanger **SM-15811** with an IC_{30} value of 0.017 μM. (7) The location of phenyl ring is important for activity.

SM-15811 discovered by these SARs studies concentration-dependently attenuated the increase in Na^+-free induced fura 2 fluorescence ratio, indicating **SM-15811** directly inhibited the Na^+-dependent Ca^{2+} influx via the Na^+/Ca^{2+} exchanger in cardiomyocytes, the activity of which was almost 2 orders stronger than the lead compound **9a** and exerted the protective effect against myocardial ischemic reperfusion injury.

Thus we discovered the structurally novel 3,4-dihydro-2(1*H*)-quinazolinone derivatives as highly potent inhibitors of the Na^+/Ca^{2+} exchanger. In particular, **SM-15811** could have therapeutic potential in the treatment of ischemic reperfusion injury as well as a powerful tool for further studies on the role of the Na^+/Ca^{2+} exchanger in the heart.

5. Experimental

Melting points were measured on a Thomas–Hoover melting point apparatus and uncorrected. ^{1}H NMR spectra were recorded on a JEOL GX270 or JEOL JNM-LA300 spectrometers in the stated solvents using tetramethylsilane as an internal standard. LC mass spectra (low-resolution ESI) were obtained on a PE SCIEX API 150 EX spectrometer. Elemental analyses, low-resolution mass spectra (EI or FAB) and high-resolution mass spectra (EI, ESI or FAB) were obtained from Sumitomo Analytical Center Inc. Thin layer chromatography and flash column chromatography were performed on silica gel glass-backed plates (5719, Merck & Co.) and silica gel 60 (230–400 or 70–230 mesh, Merck & Co.), respectively. Unless otherwise noted, all the materials were obtained from commercial suppliers and used without further purification. All solvents were commercially available grade. All reactions were carried out under a nitrogen atmosphere unless otherwise mentioned.

5.1. Representative example of the synthesis of 14a–h

5.1.1. Synthesis of 5-chloro-2-trichloroacetylaminobenzophenone (14a). To a stirred THF solution (200 mL) of 2-amino-5-chlorobenzophenone (**13a**) (23.2 g, 100 mmol) and triethylamine (11.0 g, 110 mmol) was added trichloroacetyl chloride (20.0 g, 110 mmol) dropwise at 0 °C. The mixture was stirred at ambient temperature for 3 h. The mixture was poured into ice/water and the resultant mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to give a residue. The residue was crystallized from EtOH to give **14a** (33.8 g, yield 90 %) as a white powder. mp 91–92 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 12.14 (br s, 1H), 8.61 (d, J = 9.9 Hz, 1H), 7.51–7.85 (m, 7H); MS (ESI) *m*/*z* 376.2 (M+1).

The following compounds (**14b–o**) were prepared by a similar method described above for the synthesis of **14a** using the appropriate starting material(s).

5.1.2. *N*-(2-Benzoylphenyl)-2,2,2-trichloroacetamide (14b). The title compound was prepared from 2-aminobenzophenone (**13b**) to give **14b** as a white powder in 89% yield (crystallization from EtOH). mp 99–100 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 12.34 (br s, 1H), 8.65 (m, 1H), 7.60–7.75 (m, 5H), 7.51 (m, 2H), 7.23 (m, 1H); MS (FAB) *m*/*z* 342 (M+1).

5.1.3. 2,2,2-Trichloro-*N*-[4-chloro-2-(2-furoyl)phenyl]acetamide (14c). The title compound was prepared from (2-amino-5-chlorophenyl)(2-furyl)methanone (**13c**) to give **14c** in 97% yield as a white solid. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 11.95 (br s, 1H), 8.56 (d, J = 8.9 Hz, 1H), 8.06 (d, J = 2.6 Hz, 1H), 7.80 (d, J = 1.0 Hz, 1H), 7.63 (dd, J = 2.6, 8.9 Hz, 1H), 7.36 (d, J = 3.6 Hz, 1H), 8.69 (dd, J = 1.7, 3.6 Hz, 1H); MS (FAB) *m*/*z* 366 (M+1).

5.1.4. 2,2,2-Trichloro-*N*-[2-(2-thienylcarbonyl)phenyl]acetamide (14d). The title compound was prepared from (2-aminophenyl)(thien-2-yl)methanone (**13d**) to give **14d** in 96% yield as a white solid. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 11.81 (br s, 1H), 8.57 (m, 1H), 7.94 (m, 1H), 7.80 (m, 1H), 7.63–7.71 (m, 2H), 7.30 (m, 2H), 7.20 (m, 1H); MS (FAB) *m*/*z* 348 (M+1).

5.1.5. 2,2,2-Trichloro-*N*-[2-(2-pyridylcarbonyl)phenyl]acetamide (14e). The title compound was prepared from (2-aminophenyl)(pyridin-2-yl)methanone (**13e**) to give **14e** in 99% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 12.48 (br s, 1H), 8.74 (m, 1H), 8.65 (m, 1H), 7.91–7.99 (m, 3H), 7.68 (m, 1H), 7.53 (m, 1H), 7.25 (m, 1H); MS (FAB) *m*/*z* 343 (M+1).

5.1.6. *N*-(2-Acetylphenyl)-2,2,2-trichloroacetamide (14f). The title compound was prepared from 2-aminoacetophenone (**13f**) to give **14f** in 81% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 13.13 (br s, 1H), 8.69–8.73 (m, 1H), 7.98–8.01 (m, 1H), 7.63–7.69 (m, 1H), 7.25–7.31 (m, 1H), 2.73 (s, 3H); MS (FAB) *m*/*z* 280 (M+1).

5.1.7. 2,2,2-Trichloro-*N*-[2-(isopropylcarbonyl)phenyl]acetamide (14g). The title compound was prepared from (2-aminophenyl)(isopropyl)methanone (**13g**) to give **14g** in 99% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.71 (dd, J = 1.3, 8.2 Hz, 1H), 8.21 (dd, J = 1.3, 8.2 Hz, 1H), 7.64 (m, 1H), 7.27 (m, 1H), 3.69 (m, 1H), 1.26 (d, J = 6.9 Hz, 6H); MS (FAB) *m*/*z* 308 (M+1).

5.1.8. 2,2,2-Trichloro-*N*-[2-(cyclohexylcarbonyl)phenyl]-acetamide (14h). The title compound was prepared from (2-aminophenyl)(cyclohexyl)methanone (**13h**) to give **14h** in 73% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 13.15 (br s, 1H), 8.69 (dd, J = 1.0, 8.3 Hz, 1H), 8.01 (dd, J = 1.7, 8.3 Hz, 1H), 7.59–7.66 (m, 1H), 7.23–7.29 (m, 1H), 3.36 (m, 1H), 1.19–1.91 (m, 10H); MS (FAB) *m*/*z* 348 (M+1).

5.1.9. 2,2,2-Trichloro-*N*-[2-(benzylcarbonyl)phenyl]acetamide (14i). The title compound was prepared from (2-aminophenyl)(benzyl)methanone (**13i**) to give **14i** in 80% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 13.02 (br s, 1H), 8.71 (dd, J = 1.0, 9.0 Hz, 1H), 8.10 (dd, J = 1.0, 8.0 Hz, 1H), 7.64 (m, 1H), 7.22–7.39 (m, 6H), 4.36 (s, 2H); MS (FAB) *m*/*z* 356 (M+1).

5.1.10. 2,2,2-Trichloro-*N*-[2-(2-naphthylcarbonyl)phenyl]-acetamide (14j). The title compound was prepared from (2-aminophenyl)(naphthalene-2-yl)methanone (**13j**) to give **14j** in 98% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 12.31 (m, 1H), 8.66 (m, 1H), 8.20 (m, 1H), 7.56–7.79 (m, 8H), 7.26 (m, 1H); MS (FAB) *m*/*z* 392 (M+1).

5.1.11. 2,2,2-Trichloro-*N*-[2-(3-methylbenzoyl)phenyl]acetamide (14k). The title compound was prepared from (2-aminophenyl)(3-methylphenyl)methanone (**13k**) to give **14k** in 98% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.63 (dd, J = 8.9, 1.0 Hz, 1H), 7.64–7.70 (m, 2H), 7.56 (d, J = 0.7 Hz, 1H), 7.35–7.51 (m, 3H), 7.21 (dd, J = 7.6, 1.0 Hz, 1H), 2.43 (s, 3H); MS (FAB) *m*/*z* 356 (M+1).

5.1.12. 2,2,2-Trichloro-*N*-[2-(4-methylbenzoyl)phenyl]-acetamide (14l). The title compound was prepared from (2-aminophenyl)(4-methylphenyl)methanone (**13l**) to give **14l** in 91% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 12.26 (br s, 1H), 8.61 (dd, J = 7.6 Hz, 1H), 7.63–7.69 (m, 4H), 7.20–7.33 (m, 3H), 2.46 (s, 3H); MS (FAB) *m*/*z* 356 (M+1).

5.1.13. 2,2,2-Trichloro-*N*-[2-(3-methoxybenzoyl)phenyl]-acetamide (14m). The title compound was prepared from (2-aminophenyl)(3-methoxylphenyl)methanone (**13m**) to give **14m** in 93% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 12.30 (br s, 1H), 8.63 (d, J = 8.3 Hz, 1H), 7.65–7.71 (m, 2H), 7.38–7.44 (m, 1H), 7.14–7.27 (m, 4H), 3.87 (s, 3H); MS (FAB) *m*/*z* 372 (M+1).

5.1.14. 2,2,2-Trichloro-*N*-[2-(3-benzyloxybenzoyl)phenyl]-acetamide (14n). The title compound was prepared from (2-aminophenyl)(3-benzyloxyphenyl)methanone (**13n**) to give **14n** in 98% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 12.29 (br s, 1H), 8.62 (d, J = 7.9 Hz, 1H) 7.64–7.70 (m, 2H), 7.17–7.45 (m, 10H), 5.12 (s, 2H); MS (FAB) *m*/*z* 448 (M+1).

5.1.15. 2,2,2-Trichloro-*N*-[2-(3-chlorobenzoyl)phenyl]acetamide (14o). The title compound was prepared from (2-aminophenyl)(3-chlorophenyl)methanone (**13o**) to give **14o** in 89% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 12.25 (br s, 1H), 8.65 (dd, J = 8.3, 1.0 Hz, 1H), 7.57–7.74 (m, 5H), 7.43–7.48 (m, 1H), 7.23–7.29 (m, 1H); MS (ESI) *m*/*z* 376.2 (M+1).

5.2. Representative example of the synthesis of 15a–q

5.2.1. Synthesis of 6-chloro-3-[3-(dimethylamino)propyl]-4-phenyl-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15a). To a stirred DMSO solution (50 mL) of **14a** (3.77 g, 10.0 mmol) at room temperature was added 3-dimethylaminopropylamine (1.23 g, 12.0 mmol), and the mixture was stirred at room temperature for 24 h. The reaction mixture was poured into ice/water, and the solid was collected by filtration. The resulting crude solid was crystallized from a mixed solvent of $CHCl_3$ and DMF to give **15a** (3.97 g, yield 86%) as a white powder. mp 204–205 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.35 (br s, 1H), 8.21 (m, 1H), 7.39–7.55 (m, 3H), 7.34 (dd, J = 2.4, 8.6 Hz, 1H), 7.20 (m, 1H), 6.92 (d, J = 8.6 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 3.57 (m, 1H), 2.93 (m, 1H), 1.80 (s, 6H), 1.72–1.92 (m, 3H), 1.04 (m, 1H); MS (FAB) *m*/*z* 460 (M+1); HRMS (FAB) $(M+1)^+$ calcd for $C_{20}H_{22}Cl_4N_3O$, 460.0517; found 460.0520.

The following compounds (**15b**–**n**, **15p**–**y**) were prepared by a similar method described above for the synthesis of **15a** using the appropriate starting material(s).

5.2.2. 3-[3-(Dimethylamino)propyl]-4-phenyl-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15b). The title compound was prepared from **14b** to give **15b** as a white powder in 81% yield. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.16 (br s, 1H), 8.21 (m, 1H), 7.49 (m, 1H), 7.36 (m, 2H), 7.23 (t, J = 7.5 Hz, 1H), 7.15 (m, 1H), 6.87 (d, J = 7.5 Hz, 1H), 6.76 (t, J = 7.5 Hz, 1H), 6.62 (d, J = 7.5 Hz, 1H), 3.57 (m, 1H), 2.93 (m, 1H), 1.72–1.94 (m, 3H), 1.81 (s, 6H), 1.04 (m, 1H); MS (ESI) *m*/*z* 426.1 (M+1).

5.2.3. 6-Chloro-3-[3-(dimethylamino)propyl]-4-(2-furyl)-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15c). The title compound was prepared from **14c** to give **15c** in 54%. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.12 (br s, 1H), 7.46 (dd, J = 0.7, 2.0 Hz, 1H), 7.28 (dd, J = 2.2, 8.6 Hz, 1H), 7.09 (br d, J = 3.3 Hz, 1H), 6.80 (d, J = 2.3 Hz, 1H), 6.74 (d, J = 8.6 Hz, 1H), 6.52 (dd, J = 2.0, 3.6 Hz, 1H), 3.89 (m, 1H), 3.18 (m, 1H), 2.10 (s, 6H), 2.10 (m, 2H), 1.63 (m, 1H), 1.33 (m, 1H); MS (FAB) *m*/*z* 450 (M+1).

5.2.4. 3-[3-(Dimethylamino)propyl]-4-(2-thienyl)-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15d). The title compound was prepared from **14d** to give **15d** in 60%. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.99 (br s, 1H), 7.89 (d, J = 3.3 Hz, 1H), 6.73–7.41 (m, 6H), 3.79 (m, 1H), 3.31 (m, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 1.48–2.04 (m, 4H); MS (FAB) *m*/*z* 432 (M+1).

5.2.5. 3-[3-(Dimethylamino)propyl]-4-(2-pyridyl)-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15e). The title compound was prepared from **14e** to give **15e** as racemic of two atropisomers in 73%. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.70 (m, 0.7H), 8.39 (m, 0.3H), 7.70 (m, 0.3H), 7.68 (m, 0.7H), 7.65 (br s, 0.7H), 7.53 (br s, 0.3H), 7.21–7.35 (m, 3H), 6.54–6.87 (m, 3H), 3.71–3.88 (m, 1H), 2.87–3.07 (m, 1H), 2.01 (s, 4.2H), 1.98 (s,

1.8H), 1.84–2.09 (m, 3H), 1.05–1.35 (m, 1H); MS (FAB) *m/z* 427 (M+1).

5.2.6. 3-[3-(Dimethylamino)propyl]-4-methyl-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15f). The title compound was prepared from **14f** to give **15f** in 73% yield. mp 161–162 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.42 (br s, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.26–7.35 (m, 1H), 7.00–7.06 (m, 1H), 6.77–6.80 (m, 1H), 4.11–4.23 (m, 1H), 3.72–3.83 (m, 1H), 2.22 (s, 2H), 1.94–2.00 (m, 1H), 1.49–1.56 (m, 1H); MS (FAB) *m/z* 364 (M+1).

5.2.7. 3-[3-(Dimethylamino)propyl]-4-isopropyl-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15g). The title compound was prepared from **14g** to give **15g** in 46% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.75 (br s, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.25 (m, 1H), 6.90 (m, 1H), 6.74 (m, 1H), 4.02 (m, 2H), 3.19 (m, 1H), 2.34 (m, 2H), 2.25 (s, 6H), 1.70 (m, 2H); MS (FAB) *m/z* 392 (M+1).

5.2.8. 4-Cyclohexyl-3-[3-(dimethylamino)propyl]-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15h). The title compound was prepared from **14h** to give **15h** in 69%. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.50 (br s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.25 (m, 1H), 6.94 (m, 1H), 6.71 (dd, J = 1.3, 7.9 Hz, 1H), 4.11 (br s, 1H), 3.97 (m, 1H), 2.26 (s, 6H), 1.50–2.80 (m, 13H), 1.28 (m, 2H); MS (FAB) *m/z* 432 (M+1).

5.2.9. 4-Benzyl-3-[3-(dimethylamino)propyl]-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15i). The title compound was prepared from **14i** to give **15i** in 20%. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.31 (br s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.32 (m, 1H), 7.14 (m, 3H), 6.85–7.00 (m, 4H), 4.43 (ABq, J = 18.0 Hz, 1H), 3.94 (ABq, J = 18.0 Hz, 1H), 3.81 (m, 1H), 3.38 (m, 1H), 2.00 (s, 6H), 1.71–2.12 (m, 4H); MS (FAB) *m/z* 440 (M+1).

5.2.10. 3-[3-(Dimethylamino)propyl]-4-(2-naphthyl)-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15j). The title compound was prepared from **14j** to give **15j** in 43% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.46 (br s, 1H), 8.78 (d, J = 1.0 Hz, 1H), 7.72–8.00 (m, 3H), 7.58 (m, 2H), 7.26 (m, 2H), 6.88 (d, J = 8.0 Hz, 1H), 6.75 (d, J = 4.0 Hz, 1H), 3.83 (m, 1H), 3.19 (m, 1H), 1.99 (m, 1H), 1.90 (s, 6H), 1.90 (m, 2H), 1.27 (m, 1H); MS (FAB) *m/z* 476 (M+1).

5.2.11. 3-(4-Methylpentyl)-4-phenyl-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15k). The title compound was prepared from **14b** and 4-methylpentylamine to give **15k** in 48% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.76 (br s, 1H), 8.33 (m, 1H), 7.22–7.44 (m, 5H), 6.80 (m, 2H), 3.78 (m, 1H), 2.96 (m, 1H), 1.88 (m, 1H), 1.26 (m, 1H), 0.95 (m, 2H), 0.70 (d, J = 11.6 Hz, 3H), 0.68 (d, J = 11.6 Hz, 3H), 0.60–0.72 (m, 1H); MS (FAB) *m/z* 425 (M+1).

5.2.12. 3-(2-Ethoxyethyl)-4-phenyl-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15l). The title compound was prepared from **14b** and 2-ethoxylethylamine to give **15l** in 94%. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.15 (br s, 1H), 8.35 (m, 1H), 7.16–7.76 (m, 6H), 6.76–6.84 (m, 3H), 4.01 (m, 1H), 3.74 (m, 1H), 3.08–3.38 (m, 4H), 1.04 (t, J = 7.0 Hz, 3H); MS (FAB) *m/z* 413 (M+1).

5.2.13. *N,N*-Diethyl-2-[2-oxo-4-phenyl-4-(trichloromethyl)-1,4-dihydroquinazolin-3(2*H*)-yl]acetamide (15m). The title compound was prepared from **14b** and glycine diethylamide to give **15m** in 59%. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.87 (br s, 1H), 8.27 (m, 1H), 7.09–7.37 (m, 5H), 6.75–6.86 (m, 3H), 4.73 (Abq, J = 16.0 Hz, 1H), 3.69 (ABq, J = 16.0 Hz, 1H), 3.34 (m, 2H), 3.13 (m, 2H), 0.99 (t, J = 7.0 Hz, 3H), 0.83 (t, J = 7.0 Hz, 3H); MS (FAB) *m/z* 454 (M+1).

5.2.14. 3-[2-(Benzylamino)ethyl]-4-phenyl-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15n). The title compound was prepared from **14b** and *N*-benzylethylenediamine to give **15n** in 99% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.22 (br s, 1H), 8.31 (m, 1H), 7.11–7.46 (m, 9H), 6.78–6.84 (m, 4H), 3.94 (m, 1H), 3.55 (dd, J = 13.0, 24.0 Hz, 2H), 3.25 (m, 1H), 2.99 (m, 1H), 2.32 (m, 1H); MS (FAB) *m/z* 474 (M+1).

5.2.15. 3-[2-(Ethylamino)ethyl]-4-phenyl-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15p). The title compound was prepared from **14b** and *N*-ethylethylenediamine to give **15p** in 59% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.32 (br s, 1H), 8.33 (m, 1H), 7.19–7.45 (m, 5H), 6.79 (m, 3H), 3.88 (m, 1H), 3.21 (m, 1H), 2.97 (m, 1H), 2.38 (m, 2H), 2.34 (m, 1H), 0.95 (t, J = 7.0 Hz, 3H); MS (FAB) *m/z* 412 (M+1).

5.2.16. 3-[2-(Diethylamino)ethyl]-4-phenyl-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15q). The title compound was prepared from **14b** and *N,N*-diethylethylenediamine to give **15q** in 76% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.48 (br s, 1H), 8.35 (m, 1H), 7.19–7.44 (m, 5H), 6.77–6.87 (m, 3H), 3.97 (m, 1H), 3.20 (m, 1H), 2.80 (m, 1H), 2.28 (m, 4H), 1.98 (m, 1H), 0.81 (t, J = 7.0 Hz, 6H); MS (FAB) *m/z* 440 (M+1).

5.2.17. 3-[3-(Diethylamino)propyl]-4-phenyl-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15r). The title compound was prepared from **14b** and *N,N*-diethyl-1,3-propanediamine to give **15r** in 75% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.30 (br s, 1H), 8.33 (m, 1H), 7.19–7.46 (m, 5H), 6.76–6.85 (m, 3H), 3.78 (m, 1H), 3.06 (m, 1H), 1.92–2.62 (m, 7H), 1.16 (m, 1H), 0.86 (t, J = 7.0 Hz, 6H); MS (FAB) *m/z* 454 (M+1).

5.2.18. 3-[4-(Diethylamino)butyl]-4-phenyl-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15s). The title compound was prepared from **14b** and 4-(diethylamino)butylamine to give **15s** in 80% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.62 (m, 1H), 8.33 (m, 1H), 7.19–7.49 (m, 6H), 6.78–6.87 (m, 3H), 3.82 (m, 1H), 3.05 (m, 1H), 2.45 (q, J = 7.0 Hz, 4H), 2.19 (m, 2H), 1.90 (m, 1H), 1.27 (m, 1H), 0.96 (t, J = 7.0 Hz, 6H); MS (FAB) *m/z* 468 (M+1).

5.2.19. 3-[2-(Diisopropylamino)ethyl]-4-phenyl-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15t). The title compound was prepared from **14b** and *N*,

N-diethylethylenediamine to give **15t** in 12% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 10.09 (br s, 1H), 8.22–8.29 (m, 1H), 6.59–7.48 (m, 8H), 3.20–3.62 (m, 1H), 2.85–2.96 (m, 1H), 2.49–2.69 (m, 3H), 1.73–1.84 (m, 1H), 0.71 (d, J = 7.0 Hz, 6H), 0.59 (d, J = 7.0 Hz, 6H); MS (FAB) *m*/*z* 468 (M+1).

5.2.20. 3-[2-(Diethylamino)ethyl]-4-(3-methylphenyl)-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15u). The title compound was prepared from **14k** and *N*,*N*-diethylethylenediamine to give **15u** as racemic of two atropisomers in 89% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.33 (s, 0.7H), 0.26 (s, 0.3H), 8.16 (s, 0.7H), 8.13 (s, 0.3H), 7.14–7.32 (m, H), 6.98 (s, 0.7H), 6.96 (s, 0.3H), 6.77–6.86 (m, 4H), 3.90–4.00 (m, 1H), 3.13–3.25 (m, 1H), 2.74–2.91 (m, 1H), 2.45 (s, 3H), 2.22–2.39 (m, 8H), 1.93–2.04 (m, 1H), 0.83 (t, J = 7.3 Hz, 6H); MS (FAB) *m*/*z* 454 (M+1).

5.2.21. 3-[2-(Diethylamino)ethyl]-4-(4-methylphenyl)-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15v). The title compound was prepared from **14l** and *N*,*N*-diethylethylenediamine to give **15v** in 88% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.38 (br s, 1H), 8.22 (dd, J = 8.3, 2.3 Hz, 1H), 7.04–7.27 (m, 5H), 6.76–6.85 (m, 3H), 3.89–3.99 (m, 1H), 3.14–3.23 (m, 1H), 1.92–2.05 (m, 1H), 0.80 (t, J = 7.3 Hz, 6H); MS (FAB) *m*/*z* 454 (M+1).

5.2.22. 3-[2-(Diethylamino)ethyl]-4-(3-methoxyphenyl)-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15w). The title compound was prepared from **14m** and *N*,*N*-diethylethylenediamine to give **15w** as racemic of two atropisomers in 85% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.40 (br s, 0.5H), 8.38 (br s, 0.5H), 7.93–7.97 (m, 1H), 7.20–7.36 (m, 3H), 6.67–6.92 (m, 4H), 3.89–4.00 (m, 1H), 3.87 (s, 1.5H), 3.68 (s, 1.5H), 3.14–3.27 (m, 1H), 2.74–2.87 (m, 1H), 2.22–2.40 (m, 4H), 2.01–2.12 (m, 1H), 0.81–0.85 (m, 6H); MS (FAB) *m*/*z* 470 (M+1).

5.2.23. 3-[2-(Diethylamino)ethyl]-4-(3-benzyloxyphenyl)-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15x). The title compound was prepared from **14n** and *N*,*N*-diethylethylenediamine to give **15x** as racemic of two atropisomers in 94% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.45 (br s, 1H), 7.94–7.99 (m, 1H), 7.18–7.49 (m, 7H), 6.91–7.00 (m, 1H), 6.74–6.85 (m, 4H), 5.12 (s, 2H), 4.90 (ABq, J = 11.6, 17.2 Hz, 0.5H), 3.90–3.98 (m, 1H), 3.14–3.25 (m, 1H), 2.75–2.83 (m, 1H), 2.22–2.38 (m, 4H), 1.98–2.07 (m, 1H), 0.84 (t, J = 7.3 Hz, 3H), 0.83 (t, J = 7.3 Hz, 3H); MS (FAB) *m*/*z* 546 (M+1).

5.2.24. 3-[2-(Diethylamino)ethyl]-4-(3-chlorophenyl)-4-(trichloromethyl)-3,4-dihydroquinazolin-2(1*H*)-one (15y). The title compound was prepared from **14o** and *N*,*N*-diethylethylenediamine to give **15y** as racemic of two atropisomers in 39% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.70 (s, 0.6H), 8.62 (s, 0.4H), 8.37 (t, J = 2.0 Hz, 0.4H), 8.27 (dt, J = 2.0, 6.9 Hz, 0.6H), 7.10–7.41 (m, 4H), 6.77–6.88 (m, 3H), 3.93–4.02 (m, 1H), 3.07–3.21 (m, 1H), 2.77–2.89 (m, 1H), 2.23–2.41 (m, 4H), 1.97–2.07 (m, 1H), 0.86 (t, J = 7.3 Hz, 3.6H), 0.84 (t, J = 7.3 Hz, 2.4H); MS (FAB) *m*/*z* 474 (M+1).

5.3. Representative example of the synthesis of 9a–n, 9p–y

5.3.1. Synthesis of 6-chloro-3-[3-(dimethylamino)propyl]-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (16) and 6-chloro-3-[3-(dimethylamino)propyl]-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one monocitrate (9a). To a stirred DMF solution (80 mL) of **15a** (3.69 g, 8.00 mmol) at 0 °C was added sodium borohydride (60 mg, 16.0 mmol), and the mixture was stirred at 0 °C for 3 h. The reaction mixture was poured into ice/water, and the resultant mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give a residue. The residue was dissolved in EtOH and heated under reflux for 2 h. After concentration of the mixture, purification was carried out by silica gel column chromatography ($MeOH/CHCl_3$ 1:9), followed by crystallization from EtOH to give **16** (1.67 g, 81%) as a white powder. mp 176–177 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.49 (br s, 1H), 7.26–7.30 (m, 5H), 7.07 (dd, J = 2.3, 8.6 Hz, 1H), 6.95 (d, J = 2.3 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 5.58 (s, 1H), 3.85 (m, 1H), 2.95 (m, 1H), 1.86–2.44 (m, 2H), 2.19 (s, 6H), 1.63–1.86 (m, 2H); MS (FAB) *m*/*z* 344 (M+1). Anal. Calcd for $C_{19}H_{22}ClN_3O{\cdot}1/3H_2O$: C, 65.23; H, 6.53; Cl, 10.13; N, 12.01. Found: C, 65.13; H, 6.51; Cl, 10.52; N, 11.81.

To a stirred solution of **16** (1.72 g, 5.00 mmol) in EtOH (30 mL) at ambient temperature was added citric acid monohydrate (1.05 g, 5.00 mmol), and the mixture was stirred at ambient temperature for 1 h. The mixture was concentrated to dryness, and the resultant solid was recrystallized from EtOH to give **9a** as a white powder. mp 157–159 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.68 (br s, 1H), 7.27–7.41 (m, 5H), 7.16–7.22 (m, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.70 (s, 1H), 3.65–3.74 (m, 1H), 2.77–2.86 (m, 3H), 2.61 (s, 6H), 2.56 (s, 2H), 2.53 (s, 2H), 1.80 (m, 2H); Anal. Calcd for $C_{25}H_{30}ClN_3O_8$: C, 56.03; H, 5.64; N, 7.84. Found: C, 55.86; H, 5.68; N, 7.80.

The following compounds (**9b**–**n**, **9q**–**y**) were prepared by a similar method described above for the synthesis of **9a** using the appropriate starting material(s).

5.3.2. 3-[3-(Dimethylamino)propyl]-4-phenyl-3,4-dihydroquinazolin- 2(1*H*)-one (9b). The title compound was prepared from **15b** to give **9b** as a white powder in 60% yield. mp 128–129 °C (from diethyl ether/EtOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.24–7.37 (m, 5H), 7.14 (dt, J = 1.3, 7.6 Hz, 1H), 7.01 (dd, J = 1.9, 6.6 Hz, 1H), 6.88 (dt, J = 1.0, 7.3 Hz, 1H), 6.71 (dd, J = 1.0, 7.9 Hz, 1H), 5.53 (s, 1H), 3.83 (m, 1H), 3.06 (m, 1H), 2.37–2.54 (m, 2H), 2.93 (s, 6H), 1.75–1.89 (m, 2H); Anal. Calcd for $C_{19}H_{23}N_3{\cdot}6/5H_2O$: C, 69.84; H, 7.73; N, 12.69. Found: C, 69.17; H, 8.07; N, 12.67.

5.3.3. 6-Chloro-3-[3-(dimethylamino)propyl]-4-(2-furyl)-3,4-dihydroquinazolin-2(1*H*)-one (9c). The title compound was prepared from **15c** to give **9c** as a white

powder in 73% yield. mp 130–132 °C (from diethyl ether); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.86 (br s, 1H), 7.33 (m, 1H), 7.15 (dd, J = 2.0, 8.3 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 6.29 (dd, J = 2.0, 3.0 Hz, 1H), 6.17 (d, J = 3.3 Hz, 1H), 5.59 (s, 1H), 3.84 (m, 1H), 3.15 (m, 1H), 2.27–2.48 (m, 2H), 2.23 (s, 6H), 1.84–2.01 (m, 2H); Anal. Calcd for $C_{17}H_{20}N_3O_2Cl{\cdot}1/3H_2O$: C, 60.09; H, 6.13; N, 12.37. Found: C, 59.94; H, 6.05; N, 12.33.

5.3.4. 3-[3-(Dimethylamino)propyl]-4-(2-thienyl)-3,4-dihydroquinazolin-2(1*H*)-one (9d). The title compound was prepared from **15d** to give **9d** as a white powder in 54% yield. mp 144–146 °C (from diethyl ether/$CHCl_3$); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.45 (br s, 1H), 7.16–7.24 (m, 2H), 7.08 (m, 1H), 6.90–7.02 (m, 3H), 6.76 (d, J = 7.9 Hz, 1H), 5.79 (s, 1H), 3.84 (m, 1H), 3.15 (m, 1H), 2.75 (m, 2H), 2.54 (s, 3H), 2.52 (s, 3H), 1.95–2.11 (m, 2H); Anal. Calcd for $C_{17}H_{21}N_3OS{\cdot}1/5H_2O$: C, 64.00; H, 6.76; N, 13.17. Found: C, 64.27; H, 6.76; N, 13.16.

5.3.5. 3-[3-(Dimethylamino)propyl]-4-(2-pyridyl)-3,4-dihydroquinazolin-2(1*H*)-one (9e). The title compound was prepared from **15e** to give **9e** as a white powder in 53% yield. mp 128–129 °C (from CH_2Cl_2/diethyl ether); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.54 (m, 1H), 7.91 (m, 1H), 7.63 (m, 1H), 7.12–7.32 (m, 4H), 6.90 (m, 1H), 6.77 (m, 1H), 5.71 (s, 1H), 3.92 (m, 1H), 3.00 (m, 1H), 2.33 (m, 2H), 2.24 (m, 6H), 1.87 (m, 2H); Anal. Calcd for $C_{18}H_{22}N_4O{\cdot}1/4H_2O$: C, 68.66; H, 7.20; N, 17.79. Found: C, 68.41; H, 7.17; N, 17.68.

5.3.6. 3-[3-(Dimethylamino)propyl]-4-methyl-3,4-dihydroquinazolin-2(1*H*)-one (9f). The title compound was prepared from **15f** to give **9f** as a white powder in 84% yield. mp 79–81 °C (from diethyl ether/hexane); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.17 (s, 1H), 7.07–7.13 (m, 2H), 6.86 (dt, J = 0.9, 7.5 Hz, 1H), 6.78 (d, J = 7.5 Hz, 1H), 4.55 (q, J = 6.4 Hz, 1H), 3.64–3.74 (m, 1H), 2.90–2.99 (m, 1H), 2.16–2.28 (m, 2H), 2.13 (s, 6H), 1.57–1.70 (m, 2H), 1.22 (d, J = 6.4 Hz, 3H); Anal. Calcd for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56; N, 16.99. Found: C, 67.58; H, 8.55; N, 16.98.

5.3.7. 4-Isopropyl-3-[3-(dimethylamino)propyl]-3,4-dihydroquinazolin-2(1*H*)-one (9g). The title compound was prepared from **15g** to give **9g** as an oil in 76% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.33 (br s, 1H), 7.17 (m, 1H), 6.96 (m, 2H), 6.70 (m, 1H), 4.20 (d, J = 5.0 Hz, 1H), 4.03 (m, 1H), 3.09 (m, 1H), 2.18 (s, 6H), 2.10–2.31 (m, 3H), 1.76 (m, 2H), 0.94 (d, J = 7.0 Hz, 1H), 0.78 (d, J = 7.0 Hz, 3H); HRMS (EI) M^+ calcd for $C_{16}H_{25}N_3O_2$ 275.1997, found 275.1987.

5.3.8. 4-Cyclohexyl-3-[3-(dimethylamino)propyl]-3,4-dihydroquinazolin-2(1*H*)-one (9h). The title compound was prepared from **15h** to give **9h** as a white powder in 11% yield. mp 124–125 °C (from EtOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.65 (br s, 1H), 7.17 (m, 1H), 6.94 (m, 2H), 6.73 (m, 1H), 4.16 (d, J = 5.0 Hz, 1H), 4.04 (m, 1H), 3.02 (m, 1H), 2.28 (m, 2H), 2.17 (s, 6H), 1.72 (m, 7H), 1.04 (m, 5H), 0.80 (m, 1H); Anal. Calcd for $C_{19}H_{29}N_3O$: C, 72.34; H, 9.26; N, 13.32. Found: C, 72.19; H, 9.19; N, 13.22.

5.3.9. 4-Benzyl-3-[3-(dimethylamino)propyl]-3,4-dihydroquinazolin-2(1*H*)-one (9i). The title compound was prepared from **15i** to give **9i** as a white powder in 77%. mp 122–124 °C (from diethyl ether); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.11–7.22 (m, 4H), 6.79–6.90 (m, 3H), 6.59–6.64 (m, 3H), 4.62 (dd, J = 5.0, 7.0 Hz, 1H), 3.99 (qn, J = 7.0 Hz, 1H), 2.94 (m, 3H), 2.18 (s, 6H), 2.15–2.35 (m, 2H), 1.74 (m, 2H); Anal. Calcd for $C_{20}H_{25}N_3O{\cdot}1/10H_2O$: C, 73.86; H, 7.81; N, 12.92. Found: C, 73.81; H, 7.77; N, 12.88.

5.3.10. 3-[3-(Dimethylamino)propyl]-4-(2-naphthyl)-3,4-dihydroquinazolin-2(1*H*)-one (9j). The title compound was prepared from **15j** to give **9j** as a solid in 75% yield. ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.95 (br s, 1H), 7.75–7.85 (m, 4H), 7.47 (m, 3H), 7.12 (m, 1H), 7.02 (br d, J = 7.0 Hz, 1H), 6.76–6.88 (m, 2H), 5.72 (s, 1H), 3.90 (m, 1H), 2.98 (m, 1H), 2.17–2.32 (2H, m), 2.17 (m, 6H), 1.66–1.88 (m, 2H); HRMS (EI) M^+ calcd for $C_{23}H_{25}N_3O$ 359.1997, found 359.1981.

5.3.11. 3-(4-Methylpentyl)-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (9k). The title compound was prepared from **15k** to give **9k** as a white solid in 91% yield. mp 148–151 °C (diethyl ether/hexane); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.23–7.35 (m, 5H), 7.10–7.16 (m, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.85–6.91 (m, 1H), 6.68–6.72 (m, 1H), 5.47 (s, 1H), 3.79–3.90 (m, 1H), 2.74–2.85 (m, 1H), 1.44–1.65 (m, 4H), 1.13–1.17 (m, 1H), 0.84 (d, J = 6.6 Hz, 6H); Anal. Calcd for $C_{20}H_{24}N_2O{\cdot}1/5H_2O$: C, 76.99; H, 7.88; N, 8.98. Found: C, 77.18; H, 7.84; N, 8.95.

5.3.12. 3-(2-Ethoxyethyl)-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (9l). The title compound was prepared from **15l** to give **9l** as a white powder in 64% yield. mp 118–119 °C (from diethyl ether/hexane); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.11 (br s, 1H), 7.22–7.52 (m, 5H), 6.73–7.15 (m, 4H), 5.73 (s, 1H), 4.02 (m, 1H), 3.41–3.70 (m, 4H), 3.08 (m, 1H), 1.16 (t, J = 7.0 Hz, 3H); Anal. Calcd for $C_{18}H_{20}N_2O_2{\cdot}1/5H_2O$: C, 72.07; H, 6.85; N, 9.34. Found: C, 72.30; H, 6.76; N, 9.41.

5.3.13. *N*,*N*-Diethyl-2-(2-oxo-4-phenyl-1,4-dihydroquinazolin-3(2*H*)-yl)acetamide (9m). The title compound was prepared from **15m** to give **9m** as a white powder in 86% yield. mp 142–144 °C (from EtOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.60 (br s, 1H), 7.26–7.38 (m, 5H), 7.06–7.13 (m, 1H), 6.82–6.86 (m, 4H), 6.70 (m, 1H), 5.83 (s, 1H), 4.94 (ABq, J = 16.0 Hz, 1H), 3.29 (ABq, J = 16.0 Hz, 1H), 3.12–3.42 (m, 4H), 1.13 (t, J = 7.0 Hz, 3H), 1.08 (t, J = 7.0 Hz, 3H); Anal. Calcd for $C_{20}H_{23}N_3O_2{\cdot}1/5H_2O$: C, 70.44; H, 6.92; N, 12.32. Found: C, 70.73; H, 6.84; N, 12.31.

5.3.14. 3-[2-(Benzylamino)ethyl]-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (9n). The title compound was prepared from **15n** to give **9n** as a white powder in 47% yield. mp 102–104 °C (from diethyl ether/EtOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.63 (br s, 1H), 7.21–7.34 (m,

10H), 6.71–7.19 (m, 4H), 5.54 (s, 1H), 3.98 (m, 1H), 3.77 (dd, J = 13.0, 17.0 Hz, 2H), 3.04 (m, 1H), 2.82 (m, 2H); Anal. Calcd for $C_{23}H_{23}N_3O\cdot 1/5H_2O$: C, 76.51; H, 6.53; N, 11.64. Found: C, 76.82; H, 6.41; N, 11.68.

5.3.15. 3-[2-(Ethylamino)ethyl]-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (9p). The title compound was prepared from **15p** to give **9p** as a white powder in 43% yield. mp 144–146 °C (from EtOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 9.07 (br s, 1H), 7.21–7.37 (m, 5H), 6.81–7.13 (m, 4H), 5.56 (s, 1H), 3.90 (m, 1H), 3.15 (m, 1H), 2.63–2.91 (m, 5H), 1.09 (t, J = 7.0 Hz, 3H); Anal. Calcd for $C_{18}H_{21}N_3O\cdot 6/5H_2O$: C, 68.20; H, 7.44; N, 13.26. Found: C, 67.99; H, 7.26; N, 13.51.

5.3.16. 3-[2-(Diethylamino)ethyl]-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (9q). The title compound was prepared from **15q** to give **9q** as a white powder in 97% yield. mp 137–139 °C (from EtOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.70 (br s, 1H), 7.22–7.39 (m, 5H), 6.71–7.14 (m, 4H), 5.66 (s, 1H), 3.82 (m, 1H), 3.02 (m, 1H), 2.73 (m, 1H), 2.51 (m, 5H), 0.98 (t, J = 7.0 Hz, 6H); Anal. Calcd for $C_{20}H_{25}N_3O$: C, 74.27; H, 7.79; N, 12.99. Found: C, 74.38; H, 8.13; N, 13.15.

5.3.17. 3-[3-(Diethylamino)propyl]-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (9r). The title compound was prepared from **15r** to give **9r** as a white powder in 67% yield. mp > 250 °C (from EtOAc); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.47 (br s, 1H), 9.54 (s, 1H), 7.23–7.36 (m, 5H), 7.11 (m, 2H), 6.34 (m, 2H), 5.75 (s, 1H), 3.70–3.79 (m, 1H), 1.86–1.93 (m, 2H), 1.14 (t, J = 7.1 Hz, 6H); HRMS (EI) calcd for $C_{21}H_{27}N_3O$ 337.2154; found 337.2147.

5.3.18. 3-[4-(Diethylamino)butyl]-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (9s). The title compound was prepared from **15s** to give **9s** as a white powder in 98% yield. mp 88–90 °C (from diethyl ether/EtOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.23–7.38 (m, 5H), 6.68–7.17 (m, 4H), 5.48 (s, 1H), 3.90 (m, 1H), 2.82 (m, 1H), 2.36–2.53 (m, 6H), 1.40–1.72 (m, 4H), 0.98 (t, J = 7.0 Hz, 6H); Anal. Calcd for $C_{22}H_{29}N_3O\cdot 1/10H_2O$: C, 74.79; H, 8.33; N, 11.89. Found: C, 74.77; H, 8.23; N, 11.86.

5.3.19. 3-[2-(Diisopropylamino)ethyl]-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (9t). The title compound was prepared from **15t** to give **9t** as a white powder in 96% yield. mp 173–175 °C (from EtOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 8.47 (br s, 1H), 7.22–7.38 (m, 5H), 7.06–7.13 (m, 1H), 6.75–6.95 (m, 3H), 5.65 (s, 1H), 3.59–3.69 (m, 1H), 2.68–3.10 (m, 4H), 2.40–2.50 (m, 1H), 0.98 (m, 12H); Anal. Calcd for $C_{22}H_{29}N_3O$: C, 75.18; H, 8.31; N, 11.96. Found: C, 74.87; H, 8.21; N, 11.93.

5.3.20. 3-[2-(Diethylamino)ethyl]-4-(3-methylphenyl)-3,4-dihydroquinazolin-2(1*H*)-one (9u). The title compound was prepared from **15u** to give **9u** as a white powder in 98% yield. mp 117–119 °C (from hexane/diethyl ether); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.00–7.23 (m, 6H), 6.98 (d, J = 6.9 Hz, 1H), 5.62 (s, 1H), 3.76–3.87 (m, 1H), 2.94–3.05 (m, 1H), 2.61–2.75 (m, 1H), 2.41–2.58 (m, 5H), 2.31 (s, 3H), 0.98 (t, J = 7.3 Hz, 6H); Anal. Calcd for $C_{21}H_{27}N_3O$: C, 74.74; H, 8.07; N, 12.45. Found: C, 74.61; H, 7.98; N, 12.45.

5.3.21. 3-[2-(Diethylamino)ethyl]-4-(4-methylphenyl)-3,4-dihydroquinazolin-2(1*H*)-one (9v). The title compound was prepared from **15v** to give **9v** as a white powder in 48% yield. mp 140–142 °C (from EtOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.21–7.27 (m, 3H), 7.07–7.13 (m, 3H), 6.96 (d, J = 6.9 Hz, 1H), 6.82–6.88 (m, 1H), 6.69 (d, J = 7.9 Hz, 1H), 5.63 (s, 1H), 3.77–3.87 (m, 1H), 2.94–3.04 (m, 1H), 2.64–2.75 (m, 1H), 2.43–2.57 (m, 5H), 2.30 (s, 3H), 0.98 (t, J = 7.3 Hz, 6H); Anal. Calcd for $C_{21}H_{27}N_3O$: C, 74.74; H, 8.07; N, 12.45. Found: C, 74.54; H, 8.11; N, 12.51.

5.3.22. 3-[2-(Diethylamino)ethyl]-4-(3-methoxylphenyl)-3,4-dihydroquinazolin-2(1*H*)-one hydrochloride (9w). The title compound was prepared from **15w** to give **9w** as a white powder in 51% yield. mp 182–184 °C (from EtOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.16 (br s, 1H), 9.68 (s, 1H), 7.28 (t, J = 7.7 Hz, 1H), 7.08–7.15 (m, 2H), 6.83–6.94 (m, 5H), 5.76 (s, 1H), 3.92–3.98 (m, 1H), 3.74 (s, 3H), 3.09–3.34 (m, 7H), 1.17 (t, J = 7.3 Hz, 6H); Anal. Calcd for $C_{21}H_{27}N_3O_2\cdot HCl$: C, 64.68; H, 7.24; N, 10.78; Cl, 9.09. Found: C, 64.30; H, 7.23; N, 10.49; Cl, 9.10.

5.3.23. 4-(3-Benzyloxyphenyl)-3-[2-(diethylamino)ethyl]-3,4-dihydroquinazolin-2(1*H*)-one (9x). The title compound was prepared from **15x** to give **9x** as a white powder in 65% yield. mp 128–129 °C (from EtOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.29–7.43 (m, 5H), 7.22 (m, 1H), 7.12 (m, 1H), 6.83–6.97 (m, 6H), 6.66 (dd, J = 7.9, 1.0 Hz, 1H), 5.63 (s, 1H), 5.01 (s, 2H), 3.77–3.87 (m, 1H), 2.93–3.03 (m, 1H), 2.54–2.71 (m, 1H), 2.39–2.52 (m, 5H), 0.97 (t, J = 7.3 Hz, 6H); Anal. Calcd for $C_{27}H_{31}N_3O_2$: C, 75.49; H, 7.27; N, 9.78. Found: C, 75.15; H, 7.32; N, 9.69.

5.3.24. 4-(3-Chlorophenyl)-3-[2-(diethylamino)ethyl]-3,4-dihydroquinazolin-2(1*H*)-one (9y). The title compound was prepared from **15y** to give **9y** as a white powder in 94% yield. mp 133–135 °C (from EtOH); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.53 (br s, 1H), 7.32 (s, 1H), 7.22–7.29 (m, 3H), 7.15 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 6.97 (d, J = 6.9 Hz, 1H), 6.89 (ddd, J = 7.6, 7.3, 1.0 Hz, 1H), 6.72 (dd, J = 7.2, 0.7 Hz, 1H), 5.69 (s, 1H), 3.81–3.89 (m, 1H), 2.91–3.01 (m, 1H), 2.66–2.73 (m, 1H), 2.40–2.59 (m, 5H), 0.99 (t, J = 7.3 Hz, 6H); Anal. Calcd for $C_{20}H_{24}N_3OCl$: C, 67.12; H, 6.76; N, 11.74; Cl, 9.91. Found: C, 67.03; H, 6.81; N, 11.68; Cl, 10.01.

5.3.25. 3-[2-Aminoethyl]-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (9o). To a stirred MeOH solution (50 mL) of **9n** (330 mg, 0.923 mmol) and HCO_2NH_4 (294 mg, 4.62 mmol) was added 10% Pd/C (30 mg) and the mixture was heated under reflux for 8 h. After being cooled to room temperature, the mixture was filtered through Celite, and the filtrate was concentrated to dryness. Water was added to the residue and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to

dryness. The residue was purified by silica gel column chromatography with ($MeOH/CHCl_3/NH_3$ aq 10:90:1) to give **9o** (207 mg, yield 84%) as a white powder (crystallization from diethyl ether/EtOH). mp 146–148 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 8.04 (br s, 1H), 7.22–7.36 (m, 5H), 6.77–7.16 (m, 4H), 5.53 (s, 1H), 3.86 (m, 1H), 2.81–3.07 (m, 3H); Anal. Calcd for $C_{16}H_{17}N_3O\cdot 3/5H_2O$: C, 69.09; H, 6.59; N, 15.11. Found: C, 69.38; H, 6.52; N, 14.89.

5.3.26. 3-[3-(Dimethylamino)propyl]-1-methyl-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (10). To a stirred DMF solution (10 mL) of **16** (100 mg, 0.291 mmol) at 0 °C was added NaH in 60% mineral oil (24 mg, 0.600 mmol), and stirred at 0 °C for 30 min. Iodomethane (48 μL, 0.600 mmol) was added and the mixture was stirred at ambient temperature for 3 h. The mixture was poured into ice/water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give the residue. The residue was purified by silica gel column chromatography ($MeOH/CHCl_3$ 1:9) to give **10** (98mg, yield 94%) as a white powder (crystallization from $CHCl_3$/diethyl ether). mp 235–237 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.23–7.35 (m, 5H), 7.18 (dd, J = 2.3, 8.6 Hz, 1H), 7.06 (d, J = 2.3 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 5.44 (s, 1H), 3.87 (m, 1H), 3.35 (s, 3H), 2.96 (m, 1H), 2.20–2.28 (m, 2H), 2.17 (s, 6H), 1.69 (m, 2H); Anal. Calcd for $C_{20}H_{24}ClN_3O\cdot 1/5H_2O$: C, 66.45; H, 6.80; N, 11.62; Cl, 9.81. Found: C, 66.43; H, 6.71; N, 11.64; Cl, 10.18.

5.3.27. 3-[3-(Dimethylamino)propyl]-4-phenyl-3,4-dihydroquinazoline-2(1*H*)-thione hydrochloride (11). A mixture of **9b** (2.80 g, 9.05 mmol) and P_2S_5 (4.20 g, 9.05 mmol) in xylene (100 mL) was heated under reflux for 10 h. After being cooled to room temperature, the mixture was poured into aqueous 28% NH_3 and the resultant mixture was heated at 80 °C for 1 h. The mixture was extracted with $CHCl_3$, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give the residue. The residue was purified by silica gel column chromatography ($MeOH/CHCl_3$ 1:9), followed by treatment with HCl/*i*-PrOH and crystallization from *i*-PrOH to afford **11** (1.05 g, yield 36 %) as a white powder. mp 122–125 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 10.88 (s, 1H), 10.15 (br s, 1H), 7.26–7.40 (m, 5H), 7.15–7.23 (m, 2H), 6.94–7.03 (m, 2H), 5.96 (s, 1H), 4.43–4.53 (m, 1H), 3.18 (m, 1H), 3.00–3.07 (m, 2H), 2.72 (s, 3H), 2.01–2.08 (m, 2H); Anal. Calcd for $C_{20}H_{23}N_3S\cdot HCl$: C, 63.05; H, 6.68; N, 11.61. Found: C, 62.85; H, 6.79; N, 11.33.

5.3.28. 3-(1-Benzylpiperidin-4-yl)-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one monocitrate (12g) (SM-15811)

5.3.28.1. *N*-{2-[[(1-benzylpiperidin-4-yl)imino](phenyl)methyl]phenyl}-2,2,2-trichloroacetamide (17). To a stirred DMSO solution (300 mL) of **14b** (40.8 g, 119 mmol) at room temperature was added 4-amino-1-benzylpiperidine (25.0 g, 131 mmol), and the mixture was stirred at 40 °C for 15 h. The mixture was poured into ice/water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness to give the residue. The residue was crystallized from EtOAc to give **17** (44.8 g, yield 73 %). mp 151–152 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 8.73 (m, 1H), 7.22–7.54 (m, 9H), 7.12–7.16 (m, 2H), 6.88–6.99 (m, 2H), 3.44 (s, 2H), 3.06–3.17 (m, 1H), 2.82–2.86 (m, 2H), 1.96–2.11 (m, 2H), 1.72–1.82 (m, 2H), 1.50–1.58 (m, 2H); MS (FAB) *m*/*z* 514 (M+1); HRMS (FAB) $(M+H)^+$ calcd for $C_{27}H_{27}Cl_3N_3O_4$ 514.1220, found 514.1216.

5.3.28.2. *N*-[(2-Aminophenyl)(phenyl)methyl]-1-benzylpiperidin-4-amine (18). To a stirred EtOH solution (150 mL) of **17** (44.7 g, 86.8 mmol) at 5 °C was added $NaBH_4$ (3.28 g, 86.8 mmol). The mixture was stirred at ambient temperature for 2 h. The mixture was cooled to 5 °C. $NaBH_4$ (3.28 g, 86.8 mmol) was added at 5 °C, and the mixture was then stirred at ambient temperature for 10 h. The reaction mixture was diluted with water, and EtOH was removed by evaporation. The residual mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography (EtOAc) to give **18** (27.7 g, yield 86%). ^1H NMR ($CDCl_3$, 270 MHz) δ 7.21–7.35 (m, 10H), 7.01–7.07 (m, 1H), 6.84–6.88 (m, 1H), 6.60–6.65 (m, 2H), 5.08 (s, 1H), 4.74 (br s, 1H), 3.46 (s, 2H), 2.79 (d, J = 11.1 Hz, 2H), 2.44–2.52 (m, 1H), 1.86–2.00 (m, 4H), 1.65 (br s, 2H), 1.46–1.60 (m, 2H); MS (FAB) *m*/*z* 372 (M+1); HRMS (FAB) $(M+H)^+$ calcd for $C_{25}H_{30}N_3O$ 372.2440, found 372.2452.

5.3.28.3. 3-(1-Benzylpiperidin-4-yl)-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (19). To a stirred THF solution (300 mL) of **18** (27.6 g, 74.4 mmol) was added 1,1′-carbonyldiimidazole (12.1 g, 74.5 mmol) and the mixture was heated under reflux for 8 h. The mixture was concentrated to dryness. The residue was purified by silica gel column chromatography ($MeOH/CHCl_3$ 1:9) to give **19** (24.0 g, yield 81%) as a white powder (crystallization from EtOH). mp 199–200 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 7.11–7.40 (m, 12H), 6.91 (dt, J = 1.0, 7.6 Hz, 1H), 6.83 (s, 1H), 6.66 (d, J = 7.6 Hz, 1H), 5.56 (s, 1H), 4.33–4.45 (m, 1H), 3.45 (s, 1H), 2.90–2.97 (m, 1H), 2.74–2.81 (m, 1H), 1.91–2.14 (m, 2H), 1.42–1.65 (m, 2H); MS (FAB) *m*/*z* 398 (M+1); HRMS (FAB) $(M+1)^+$ calcd for $C_{26}H_{28}N_3O$ 398.2232, found 398.2236.

5.3.28.4. 3-(1-Benzylpiperidin-4-yl)-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one monocitrate (12g). The title compound was prepared from **19** using the procedure described above for **9a** to give **12g** (**SM-15811**) as a white powder. mp 159–161 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 9.41 (br s, 1H), 7.17–7.41 (m, 1H), 7.06 (m, 1H), 6.76–6.84 (m, 2H), 5.72 (s, 1H), 4.10 (m, 1H), 3.67 (m, 2H), 2.87–2.96 (m, 2H), 2.62 (ABq, J = 15.2, 29.5 Hz, 4H), 2.16–2.27 (m, 3H), 1.47 (m, 3H); Anal. Calcd for $C_{26}H_{27}N_3O\cdot C_6H_8O_7$: C, 65.18; H, 5.98; N, 7.13. Found: C, 64.90; H, 6.12; N, 7.22.

5.3.29. 4-Phenyl-3-piperidin-4-yl-3,4-dihydroquinazolin-2(1*H*)-one (12a). To a stirred MeOH solution (50 mL) of **19** (2.50 g, 6.29 mmol) and HCO_2NH_4 (1.59 g,

25.0 mmol) was added 10% Pd/C (300 mg) and the mixture was heated under reflux for 8 h. After being cooled to room temperature, the mixture was filtered through Celite, and the filtrate was concentrated to dryness. Water was added to the residue and extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography with (MeOH/$CHCl_3$ 1:9) to give **12a** (1.62 g, yield 84%) as a white powder (crystallization from diethyl ether/EtOH). mp 213–215 °C; ^{1}H NMR ($CDCl_3$) δ 7.37–7.41 (m, 2H), 7.09–7.31 (m, 5H), 6.90 (dt, J = 1.1, 7.3 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 5.56 (s, 1H), 4.36 (m, 1H), 3.13 (m, 1H), 2.99 (m, 1H), 2.55–2.73 (m, 2H), 1.87–2.02 (m, 1H), 1.56–1.76 (m, 2H), 1.29–1.45 (m, 1H); MS (ESI) m/z 308.4 (M+1); Anal. Calcd for $C_{19}H_{21}N_3O{\cdot}H_2O$: C, 70.13; H, 7.12; N, 12.91, Found: C, 70.53; H, 7.50; N, 12.55.

5.4. Representative example of the synthesis of 12b–d

5.4.1. 3-(1-Methylpiperidin-4-yl)-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (12b). To a stirred DMF solution (10 mL) of **12a** (315 mg, 1.02 mmol) and K_2CO_3 (282 mg, 2.04 mmol) was added iodomethane (76 μL, 1.22 mmol) and the mixture was stirred at room temperature for 8 h. The mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography with MeOH/$CHCl_3$/NH_3 aq (3:97:1) to give **12b** (197 mg, yield 60%) as a white powder (crystallization from diethyl ether/EtOH). mp 252–254 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.54 (br s, 1H), 7.08–7.43 (m, 7H), 6.90 (m, 1H), 6.72 (m, 1H), 5.55 (s, 1H), 4.40 (m, 1H), 2.91 (m, 1H), 2.73 (m, 1H), 3.23 (s, 3H), 1.93–2.12 (m, 3H), 1.46–1.69 (m, 3H); Anal. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.65; H, 7.23; N, 12.99.

The following compounds (**12c**, **12d**) were prepared by a similar method described above for the synthesis of **12b** using the appropriate starting material(s).

5.4.2. 3-(1-Ethylpiperidin-4-yl)-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one hydrochloride (12c). The title compound was prepared from **12a** and iodoethane, followed by treatment with 1 M HCl/diethyl ether in EtOH at room temperature to give **12c** as a white powder in 60%. mp 195–196 °C yield (from diethyl ether/EtOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.58–9.76 (br s, 1H), 9.54 (s, 1H), 7.18–7.45 (m, 6H), 7.09 (dd, J = 8.1, 1.5 Hz, 1H), 6.77–6.89 (m, 2H), 5.64 (s, 1H), 4.13–4.30 (m, 1H), 3.21–3.50 (m, 2H), 2.72–3.09 (m, 4H), 2.30–2.59 (m, 1H, m), 1.75–1.99 (m, 1H), 1.50–1.72 (m, 2H), 1.16 (t, J = 7.3 Hz, 3H); Anal. Calcd for $C_{21}H_{25}N_3O{\cdot}HCl{\cdot}1/5H_2O$: C, 67.17; H, 7.09; N, 11.19. Found: C, 67.41; H, 7.33; N, 11.10.

5.4.3. 4-Phenyl-3-(1-*n*-propylpiperidin-4-yl)-3,4-dihydroquinazolin-2(1*H*)-one hydrochloride (12d). The title compound was prepared from **12a** and *n*-propylbromide to give **12d** as a white powder in 62% yield. mp > 250 °C yield (from diethyl ether/EtOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.54 (br s, 1H), 7.20–7.42 (m, 6H), 7.06–7.12 (m, 1H), 6.83 (m, 1H), 5.64 (s, 1H), 4.29 (m, 1H), 3.40 (m, 2H), 2.84–3.02 (m, 4H), 2.41–2.54 (m, 1H), 1.87–1.97 (m, 1H), 1.62 (m, 4H), 0.86 (t, J = 7.3 Hz, 3H); Anal. Calcd for $C_{22}H_{27}N_3O{\cdot}HCl$: C, 68.47; H, 7.31; N, 10.89; Cl, 9.19. Found: C, 68.16; H, 7.28; N, 10.72; Cl, 9.11.

5.5. Representative example of the synthesis of 12e, 12f, 12h

5.5.1. Synthesis of 3-[1-(cyclohexylmethyl)piperidin-4-yl]-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one hydrochloride (12f). To a stirred MeOH solution (10 mL) of the HCl salt of **12a** (344 mg, 1.00 mmol) and cyclohexylcarboxaldehyde (449 mg, 4.00 mmol) at 0 °C was added $NaBH_3CN$ (251 mg, 4.00 mmol). The cooling bath was removed and the mixture was stirred at ambient temperature for 12 h. The mixture was made basic to pH 9 by the addition of saturated $NaHCO_3$, then MeOH was removed by evaporation. The residue was extracted with $CHCl_3$. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by silica gel column chromatography with MeOH/$CHCl_3$ 1:50, followed by treatment with 1 M HCl/diethyl ether in EtOH at room temperature to give **12f** (242 mg, yield 55%) as a white powder (crystallization from diethyl ether/EtOH). mp 194–196 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 9.88 (br s, 1H), 9.55 (s, 1H), 7.41 (d, J = 7.5 Hz, 1H), 7.19–7.33 (m, 4H), 7.09 (t, J = 7.5 Hz, 1H), 6.81–6.87 (m, 2H), 5.68 (s, 1H), 4.39 (m, 1H), 3.43 (m, 2H), 2.79–3.00 (m, 4H), 2.46–2.63 (m, 1H), 2.10 (m, 1H), 1.49–1.77 (m, 7H), 1.12–1.23 (m, 2H), 0.88–0.96 (m, 2H); Anal. Calcd for $C_{26}H_{33}N_3O{\cdot}HCl{\cdot}3H_2O$: C, 63.21; H, 8.16; N, 8.50; Cl, 7.18. Found: C, 63.09; H, 8.16; N, 8.36; Cl, 7.28.

The following compounds (**12e, 12h**) were prepared by a similar method described above for the synthesis of **12f** using the appropriate starting material(s).

5.5.2. 3-[1-(Isopropyl)piperidin-4-yl]-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (12e). The title compound was prepared from **12a** and acetone to give **12e** as a white powder in 99% yield. mp 219–221 °C (from EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75 (br s, 1H), 7.36–7.40 (m, 2H), 7.08–7.29 (m, 5H), 6.87–6.93 (m, 2H), 6.72–6.74 (m, 2H), 5.60 (s, 1H), 4.38–4.50 (m, 1H), 2.64–2.94 (m, 3H), 1.89–2.32 (m, 3H), 1.00 (d, J = 7.3 Hz, 6H); Anal. Calcd for $C_{22}H_{27}N_3O$: C, 75.61; H, 7.79; N, 12.02. Found: C, 75.39; H, 7.78; N, 11.92.

5.5.3. 4-Phenyl-3-[1-(2-phenylethyl)piperidin-4-yl]-3,4-dihydroquinazolin-2(1*H*)-one hydrochloride (12h). The title compound was prepared from **12a** and phenylacetaldehyde to give **12h** as a white powder in 36% yield. mp > 250 °C (from diethyl ether/EtOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 10.08 (br s, 1H), 9.55 (s, 1H), 7.23–7.43 (m, 11H), 7.10 (t, J = 7.5 Hz, 1H), 6.84 (m, 2H), 5.66 (s, 1H), 4.24 (m, 1H), 3.53 (m, 2H), 3.17 (m, 2H), 2.99 (m, 4H), 2.49–2.51 (m, 1H), 1.94 (m, 1H),

1.64 (m, 2H); Anal. Calcd for $C_{27}H_{29}N_3O{\cdot}HCl{\cdot}H_2O$: C, 69.59; H, 6.92; N, 9.02; Cl, 7.61. Found: C, 69.41; H, 6.94; N, 8.87; Cl, 7.71.

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