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Discovery and structure–activity relationships of 4-aminoquinazoline derivatives, a novel class of opioid receptor like-1 (ORL1) antagonists

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ABSTRACT

Synthesis and structure–activity relationship studies of a series of 4-aminoquinazoline derivatives led to the identification of (**1*R*,2*S*)-17**, *N*-[(1*R*,2*S*)-2-({2-[(4-chlorophenyl)carbonyl]amino-6-methylquinazolin-4-yl}amino)cyclohexyl]guanidine dihydrochloride, as a highly potent ORL1 antagonist with up to 3000-fold selectivity over the μ, δ, and κ opioid receptors. Molecular modeling clarified the structural factors contributing to the high affinity and selectivity of (**1*R*,2*S*)-17**.

1. Introduction

Opioid receptor like-1 (ORL1) was first identified as an orphan opioid receptor in 1994 by homology screening of the opioid receptor.[1] ORL1 is a member of the G-protein-coupled receptor superfamily and it shows high amino-acid-sequence similarity to the other opioid receptors μ, δ, and κ. However, ORL1 does not bind opioid peptides or ligands for the μ, δ, or κ opioid receptors. An endogenous ligand for ORL1, the 17-amino-acid neuropeptide nociceptin or orphanin FQ (N/OFQ), was simultaneously identified by two groups.[2] Pharmacological studies have shown that the N/OFQ-ORL1 system is implicated in morphine tolerance,[3] the pain response,[4] learning and memory,[5] the control of food intake,[6] anxiety,[7] and locomotion.[8] These findings suggest that the N/OFQ-ORL1 system might be an important new molecular target for the treatment of various human disorders, so researchers have been motivated to identify potent and selective ORL1 agonists and antagonists.

Several small-molecule ligands with high affinity and selectivity for ORL1 have recently been reported.[9] For example, J-113397, which was reported as the first small-molecule ORL1 antagonist, inhibits the hyperalgesia produced by intracerebroventricular administration of nociceptin[10] while JTC-801 antagonizes nociceptin-induced allodynia in mice and shows an analgesic effect in a hot-plate test with mice and in a formalin test with rats.[11] In addition, Ro 64-6198 is reported to be a highly potent and selective agonist that exhibits anxiolytic-like properties in vivo.[12]

With these points as background, we developed an interest in this new opioid receptor and carried out high-throughput screening to find an original ORL1 ligand lead compound in our chemical library. From the hit compounds, we selected benzo[*g*]quinazoline derivative **1** as a lead compound because of its chemical stability and ease of chemical modification (Fig. 1). Compound **1** itself showed moderate affinity for ORL1, with a K_i value of 133 nM, but poor selectivity for ORL1 over the μ opioid receptor.

Our goals were to investigate the structure–activity relationships (SAR) of ORL1 antagonists based on the structure of **1** and to identify highly potent ORL1 antagonists with high selectivity over the other opioid receptors. We devised three strategies for

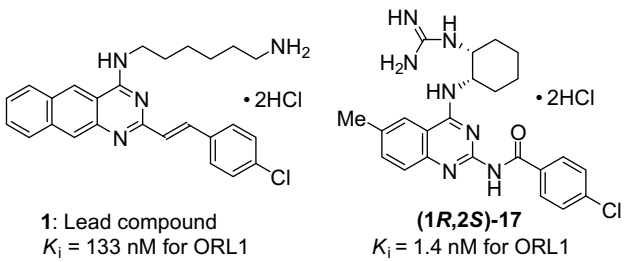

Figure 1. Chemical structures of ORL1 antagonists **1** and (**1*R*,2*S*)-17**.

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the optimization of the ORL1-antagonist activity of **1**: (1) replacement of the tricyclic ring system of benzo[*g*]quinazoline **1** with the bicyclic quinazoline ring system followed by exploration of substituent effects on the benzene ring of the quinazoline scaffold, (2) modification of the amino side chain at the 4-position of the quinazoline scaffold, and (3) replacement of the ethenylene group at the 2-position of the quinazoline with an amide group.

In the present paper, we report on the synthesis and structure–activity relationships of 4-aminoquinazoline derivatives as a novel class of ORL1 antagonists. We identify optically active (**1*R*,2*S*)-17** as the most potent ORL1 antagonist with the highest selectivity over the other opioid receptors among the compounds tested, and a 3D docking study of ORL1 and (**1*R*,2*S*)-17** helps explain the high affinity and selectivity of this compound.

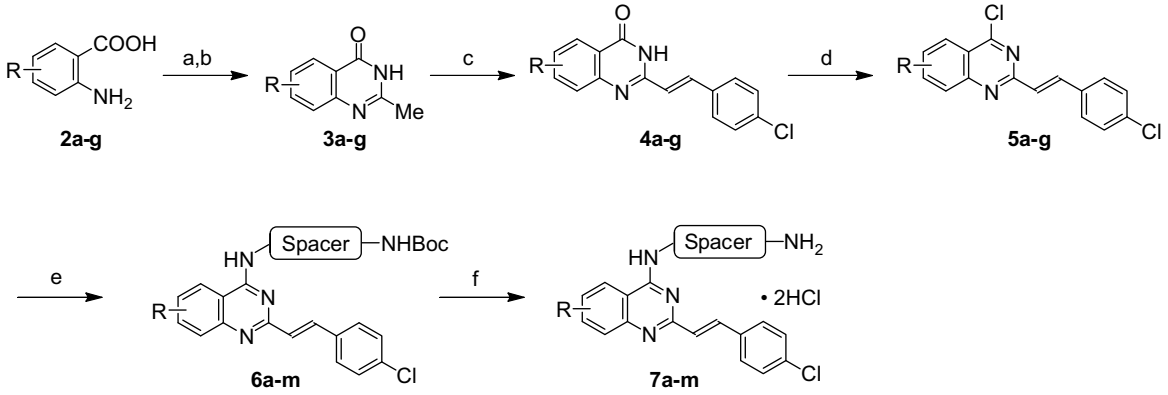
2. Chemistry

Various substituted quinazoline derivatives related to **7a**–**m**, which all have terminal amino groups at the 4-position of the quinazoline scaffold, were synthesized as shown in Scheme 1. 2-Aminobenzoic acid derivatives **2a**–**g** were treated with acetic anhydride and then with aqueous ammonia to afford 2-methylquinazolin-4-one derivatives **3a**–**g**. These derivatives were condensed with 4-chlorobenzaldehyde in acetic acid to afford the 2-styrylquinazoline-4-ones **4a**–**g**, which in turn were treated with phosphorus oxychloride to give the chlorides **5a**–**g**. Coupling of **5a**–**g** under basic conditions with various diamines monoprotected with the *tert*-butoxycarbonyl (Boc) group provided compounds **6a**–**m**. Finally, removal of the Boc group of **6a**–**m** with 4 N HCl in ethyl acetate yielded the desired 4-aminoquinazoline derivatives **7a**–**m** as the hydrochlorides.

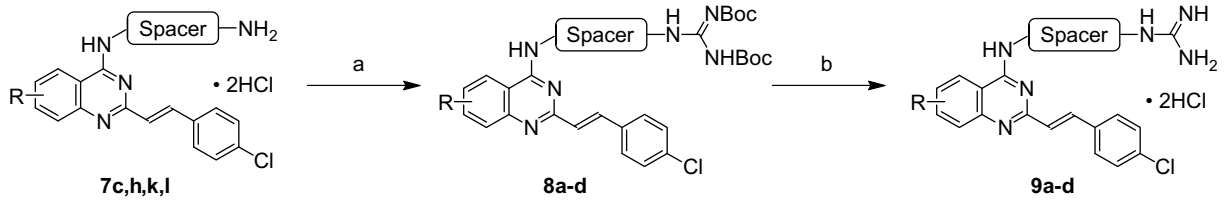
The terminal guanidine derivatives **9a**–**d** were prepared from the appropriate compounds **7c**, **7h**, **7k** and **7l**, as shown in Scheme 2. Compounds **7c**, **7h**, **7k**, and **7l** were reacted with *N*,*N*′-bis-Boc-1*H*-pyrazole-1-carboxamidine[13] in the presence of triethylamine to provide the corresponding diprotected guanidine derivatives **8a**–**d**. Subsequent deprotection of **8a**–**d** by treatment with 4 N HCl in ethyl acetate yielded the desired compounds **9a**–**d**.

2-Benzoylaminoquinazoline derivative **17**, meanwhile, was synthesized from **2c** as shown in Scheme 3. 2,4-Dichloro-6-methylquinazoline **11** was synthesized from **2c** by a known procedure.[14] Compound **2c** was reacted with potassium cyanate in aqueous acetic acid to give **10**, followed by chlorination with phosphorus oxychloride in the presence of *N*,*N*-dimethylaniline to afford the dichloride **11**. Selective displacement of chloride at the 4-position[15] of **11** with monoprotected *cis*-1,2-diaminocyclohexane was readily carried out to afford **12**. However, direct amination at the 2-position of quinazoline **12** with ammonia in EtOH[16] produced the 2-amino compound in only modest yield (<30%). To improve the yield, we tried another stepwise synthetic approach. Compound **12** was treated with 4-methoxybenzylamine, which is more reactive than ammonia, in *N*-methyl-2-pyrrolidone (NMP) at 90 °C for 15 h to afford **13** in 91% yield. The Boc group and the 4-methoxybenzyl group were simultaneously removed by treatment with trifluoroacetic acid (TFA) to give **14**, which was then selectively amidinated at the more reactive cyclohexylamino group at the 4-position of quinazoline to give the diprotected guanidine **15**. The amino group at the 2-position of **15** was then benzoylated with 4-chlorobenzoyl chloride in the presence of 4-dimethylaminopyridine to give the 2-benzoylamino quinazoline derivative **16**. The target compound **17** was obtained by acidic deprotection of the di-Boc compound **16**. Optically active (**1*R*,2*S*)-17** and (**1*S*,2*R*)-17** were synthesized from chiral monoprotected *cis*-1,2-diaminocyclohexane in the same manner as racemic **17**. Their optical purity was confirmed by HPLC on a Chiralpak AD chiral column with hexane/EtOH/Et_2NH (95:5:0.2) as the eluent. Both optical isomers **12** showed an enantiomeric excess greater than 99%.

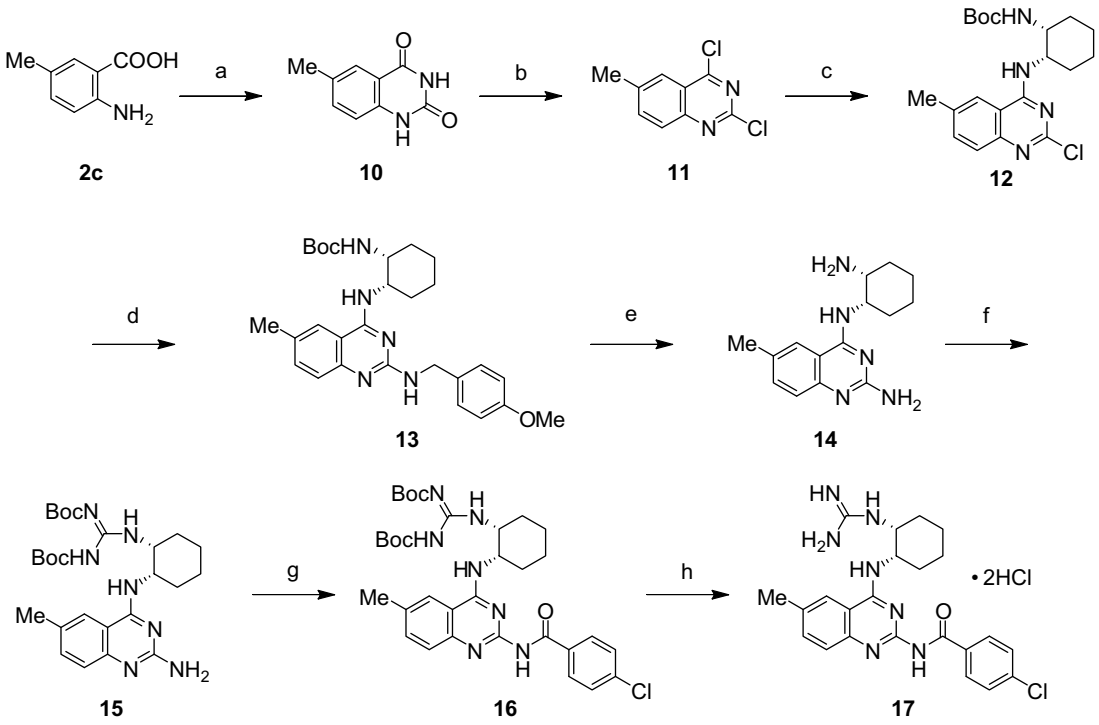
The synthesis of chiral mono-Boc-protected *cis*-1,2-diaminocyclohexane is shown in Scheme 4. (**1*R*,2*S*)-22** was prepared from the commercially available compound (1*R*,2*R*)-2-benzyloxycyclo-



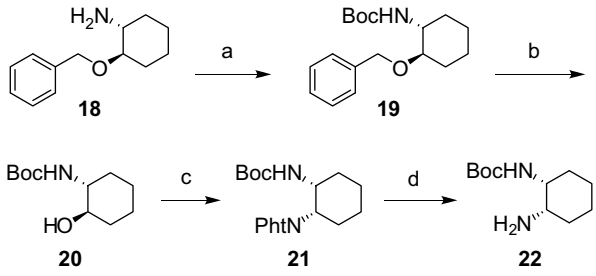
Scheme 1. Reagents: (a) Ac_2O; (b) 28% aq NH_3; (c) 4-chlorobenzaldehyde, AcOH; (d) $POCl_3$, *N*,*N*-dimethylaniline, toluene; (e) H_2N–Spacer–NHBoc, Et_3N, 4-dimethylaminopyridine (DMAP), toluene; (f) 4 N HCl in EtOAc.



Scheme 2. Reagents: (a) *N*,*N*′-bis-Boc-1*H*-pyrazole-1-carboxamidine, Et_3N, CH_2Cl_2; (b) 4 N HCl in EtOAc, MeOH.



Scheme 3. Reagents: (a) KOCN, AcOH, H_2O; (b) $POCl_3$, *N*,*N*-dimethylaniline; (c) *tert*-butyl (*cis*-2-aminocyclohexyl)carbamate, Et_3N, CH_2Cl_2; (d) 4-methoxybenzylamine, DMAP, NMP; (e) TFA; (f) *N*,*N*′-bis-Boc-1*H*-pyrazole-1-carboxamidine, CH_2Cl_2; (g) 4-chlorobenzoyl chloride, *N*,*N*-diisopropylethylamine, DMAP, CH_2Cl_2; (h) 4 N HCl in EtOAc, MeOH, $CHCl_3$.



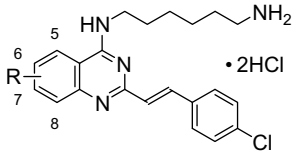
Scheme 4. Reagents: (a) $(Boc)_2O$, $CHCl_3$; (b) H_2, 10% Pd–C, MeOH; (c) phthalimide, PPh_3, diethyl azodicarboxylate, THF; (d) NH_2NH_2, EtOH.

hexylamine **18**. The amino group of **18** was protected with the Boc group, then the benzyl group was removed by hydrogenation in the presence of palladium on carbon to give the secondary alcohol **20**. To introduce an amino group at the secondary alcohol position with inversion of configuration, **20** was reacted with phthalimide under Mitsunobu conditions[17] followed by treatment with hydrazine to give **22**. The enantiomer of **22** was similarly synthesized from (1*S*,2*S*)-2-benzoyloxycyclohexylamine.

3. Biological results and discussion

The binding affinities of compounds **7a**–**m** and **9a**–**d**, synthesized as described above, were evaluated for human ORL1 and the rat μ opioid receptor (Tables 1–3) and the binding affinities of compounds **17** [(**1*R*,2*S*)-17** and (**1*S*,2*R*)-17**] were evaluated for human ORL1 and the human μ, rat δ, and rat κ opioid receptors (Table 4). Competition binding experiments were performed with membranes prepared from CHO-K1 cells stably expressing human ORL1 or the human or rat μ, rat δ, or rat κ opioid receptor with the radioligand leucyl-[^{3}H]nociceptin (for ORL1) or [^{3}H]diprenorphine

Table 1
Effects of quinazoline ring substituents on affinity and selectivity for ORL1



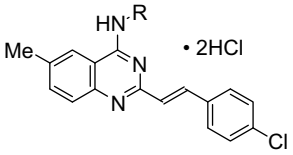
Compound	R	K_i (nM)		Selectivity
		ORL1[a]	μ[b]	μ/ORL1
1	6,7-CH=CH-CH=CH	133	410	3.08
7a	H	383	180	0.47
7b	5-Me	808	170	0.21
7c	6-Me	232	120	0.51
7d	7-Me	420	200	0.48
7e	8-Me	653	930	1.42
7f	6-*t*-Bu	292	380	1.30
7g	6-Cl	294	380	1.29

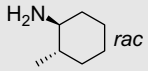
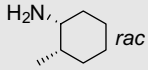
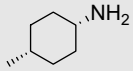
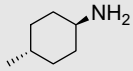
[a] Using membranes from CHO-K1 cells expressing human ORL1.
[b] Using membranes from CHO-K1 cells expressing the rat μ opioid receptor.

(for the μ, δ, and κ opioid receptors). Results are given as K_i values calculated according to the method of Cheng and Prusoff.[18]

The effect of substituents on the benzene ring of the quinazoline scaffold are shown in Table 1. We first changed the tricyclic benzo[*g*]quinazoline scaffold to a bicyclic quinazoline one because of the high lipophilicity ($c\log P = 6.820$) shown by lead compound **1**. Lipinski's rule of five, which is commonly used as an indicator of the drug-likeness of molecules, indicates that highly lipophilic compounds ($c\log P > 5$) may be poorly absorbed and distributed in humans.[19] Bicyclic quinazoline **7a** showed decreased affinity for ORL1 compared with **1**, and the introduction of a methyl group at the 5-position (as in **7b**) or the 8-position (as in **7e**) of the quinazoline scaffold resulted in further loss of affinity for ORL1. In contrast, when a methyl group was introduced at the 6-position of the

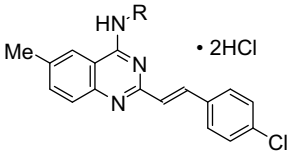
Table 2
Effects of substituents at the 4-position of the quinazoline ring system on affinity and selectivity for ORL1

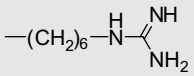
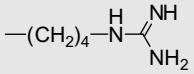
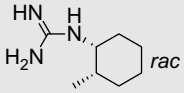
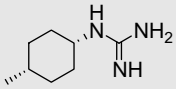


Compound	R	K_i (nM)		Selectivity
		ORL1[a]	μ[b]	μ/ORL1
7c	$-(CH_2)_6-NH_2$	232	120	0.51
7h	$-(CH_2)_4-NH_2$	194	250	1.29
7i	$-(CH_2)_2-NH_2$	972	240	0.25
7j		538	180	0.33
7k		200	150	0.75
7l		162	410	2.53
7m		795	300	0.37

[a,b] See corresponding footnotes to Table 1.

Table 3
Effect of terminal guanidine substitution at the 4-position of the quinazoline ring system on affinity and selectivity for ORL1



Compound	R	K_i (nM)		Selectivity
		ORL1[a]	μ[b]	μ/ORL1
9a		89	300	3.37
9b		160	2300	14.38
9c		43	220	5.11
9d		152	60	0.39

[a,b] See corresponding footnotes to Table 1.

quinazoline scaffold (as in **7c**), the affinity for ORL1 was moderately increased compared with **7a**, but the introduction of more-bulky substituents such as 6-*tert*-butyl (as in **7f**) or 6-chloro (as in **7g**) resulted in a slight decrease in the affinity compared with **7c**. In the light of these results, we judged that replacement of the substituents on the quinazoline scaffold would be unlikely to dramatically increase the affinity, and we selected 6-methylquinazoline **7c** as the basic scaffold for further study.

We next investigated the effects of the length and rigidity of the conformationally flexible alkylene spacer at the 4-position of **7c**. The location of the amino group at the end of this spacer is thought to be an important determinant of the affinity of ligands for opioid receptors.[20] We expected that modification of the substituent at the 4-position by reducing the length of the alkylene spacer or fixing the position of the terminal amino group by cyclization would considerably increase the affinity for ORL1. The effects of the spacer at the 4-position of the quinazoline scaffold are shown in Table 2. Reducing the length of the alkylene spacer of **7c** by two methylene units produced a compound **7h** with slightly greater affinity than **7c**. Compound **7i**, with four fewer methylene units than **7c**, showed 4-fold less affinity than **7c**. Among compounds whose spacer was rigidified by cyclization, those with a 1,2-*cis*- or a 1,4-*cis*-cyclohexyl spacer (**7k** and **7l**) showed slightly higher affinity than **7c.** In contrast, those with a 1,2-*trans*- or a 1,4-*trans*-cyclohexyl spacer (**7j** and **7m**) showed 2- to 3-fold lower affinity than **7c**.

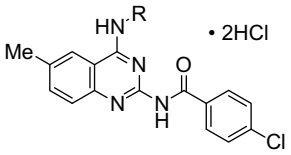
Bearing in mind the structure of nociceptin, we then considered attaching substituents to the terminal amino group at the 4-position of the quinazoline scaffold. Because nociceptin has two arginine residues at the ligand-binding site, we decided to try to mimic the arginine residues by attaching an amidino group to the terminal amino group at the 4-position of the relatively active compounds **7c**, **7h**, **7k** and **7l**. The binding affinities of the corresponding guanidine derivatives **9a**–**d** for the ORL1 and μ receptor are shown in Table 3. The guanidine derivatives all had increased binding affinity for ORL1 compared to the respective original amino compounds **7c**, **7h**, **7k** and **7l**. Racemate **9c** displayed particularly high affinity for ORL1 (K_i = 43 nM). However, the selectivity of **9c** for ORL1 over the μ receptor was only 5-fold. Because it was clear that compounds having a guanidino group at the end of the spacer at the 4-position of the quinazoline scaffold showed high affinity for ORL1, we decided to retain this feature. In addition, we tried replacing the ethenylene moiety of **9c** by an amide group. The ethenylene moiety and amide group are equivalent in size, but the amide group offers the possibility of additional hydrogen bonding, which may further increase the affinity.

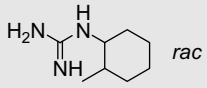
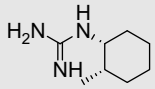
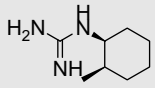
The affinities of the racemic amide derivatives **17** and the enantiomers (**1*R*,2*S*)-17** and (**1*S*,2*R*)-17** for ORL1 and the μ, δ, and κ opioid receptors is shown in Table 4. The affinity for ORL1 of amide **17** was 20-fold greater than that of the corresponding 2-ethenyl compound **9c**. In particular, it is clear that compound (**1*R*,2*S*)-17** showed very high affinity for ORL1, with a K_i value of 1.4 nM; furthermore, its selectivity over the other opioid receptors was as high as 240- to 3100-fold. To evaluate the functionality of (**1*R*,2*S*)-17**, we assayed forskolin-stimulated cyclic AMP (cAMP) in CHO cells expressing human ORL1. Compound (**1*R*,2*S*)-17** did not inhibit forskolin-stimulated cAMP accumulation in these cells, but it did block nociceptin-induced inhibition of cAMP accumulation with an IC_{50} value of 17 nM (Fig. 2). These results demonstrate that (**1*R*,2*S*)-17** is a potent antagonist of ORL1.

4. Molecular modeling studies

To elucidate the structural factors contributing to the high affinity and selectivity of (**1*R*,2*S*)-17** for ORL1, we docked (**1*R*,2*S*)-17** into the binding site of a homology-modeled structure of ORL1. Figure 3a shows the entire docked model, in which ORL1 is represented as seven transmembrane (TM) helices and some of the important amino acids are depicted. The amino acids in parentheses correspond to those at the equivalent positions in the μ, δ, and κ opioid receptors, respectively. Compound (**1*R*,2*S*)-17** interacts mainly with helices TM3, TM4, TM5, TM6 and TM7. Figure 3b is a close-up view of the occupied binding site, in which hydrophobic amino acids are shown in white and hydrogen-bonding interactions are shown as broken lines. A hydrophobic pocket formed by amino acids Met134, Phe135, Phe272, Trp276 and Val279

Table 4
Affinity and selectivity of 2-benzoylquinazoline analogues for ORL1



Compound	R	K_i (nM)				Selectivity		
		ORL-1[a]	μ[b]	δ[c]	κ[d]	μ/ORL1	δ/ORL1	κ/ORL1
17	 *rac*	2.1	310	4000	1200	148	1904	571
(**1*R*,2*S*)-17**		1.4	330	4300	510	236	3071	364
(**1*R*,2*S*)-17**		140	270	3600	2400	1.9	26	17

[a,b] Using membranes from CHO-K1 cells expressing human ORL1 or the human μ opioid receptor.
[c,d] Using membranes from CHO-K1 cells expressing the rat δ or κ opioid receptor.

accommodates well the methylbenzene and cyclohexyl moieties of (**1*R*,2*S*)-17**, and van der Waals interactions between the hydrophobic moieties are facilitated. Two hydrophobic amino acids, Ile204 and Val283, are located near the chlorobenzene moiety, and the carboxyl group of Asp130 is well placed for electrostatic interaction with the guanidino group. Such an electrostatic interaction has been reported to be critical for ligand binding to the μ, δ, and κ opioid receptors.[21] The biological data for **7k** and **9c** indicate that the replacement of an amino by a guanidino group increased their affinity for ORL1. In addition to its electrostatic interaction with Asp130, the guanidino group can hydrogen-bond to the side-chain oxygen of Thr305 (Fig. 3b). Because the corresponding amino acid for the μ, δ, and κ opioid receptors at this position is Ile (Fig. 3a), a hydrogen-bonding interaction between the guanidino group and the side-chain oxygen of Thr305 could contribute to the increased affinity and selectivity of (**1*R*,2*S*)-17** for ORL1. The biological data for **9c** and **17** show that replacement of the ethenylene group by an amide group greatly increased their affinity for ORL1, and chiral (**1*R*,2*S*)-17** was more active than racemic **17**. The oxygen atom of the amide group is well placed for hydrogen bonding to the side-chain NH_2 of Gln280 (Fig. 3b). The amino acid at this position in the μ, δ, and κ opioid receptors is His (Fig. 3a), so that Gln280 could play an important role in determining the affinity of (**1*R*,2*S*)-17** for ORL1 and its selectivity for ORL1 over other opioid receptors. It is not fully understood why His at position 280 would decrease the affinity of (**1*R*,2*S*)-17** for the μ, δ, and κ opioid receptors, but molecular modeling suggests that steric clash between His and the amide moiety is likely to be responsible because His is more bulky than Gln. (**1*S*,2*R*)-17**, whose configuration is the opposite of that of (**1*R*,2*S*)-17**, was much less active than (**1*R*,2*S*)-17** (Table 4). In accordance with its observed relatively low activity, (**1*S*,2*R*)-17** could not be docked well into the ORL1 binding site owing to steric clash between its (1*S*,2*R*)-cyclohexyl moiety and amino acids within the hydrophobic pocket (Fig. 3b).

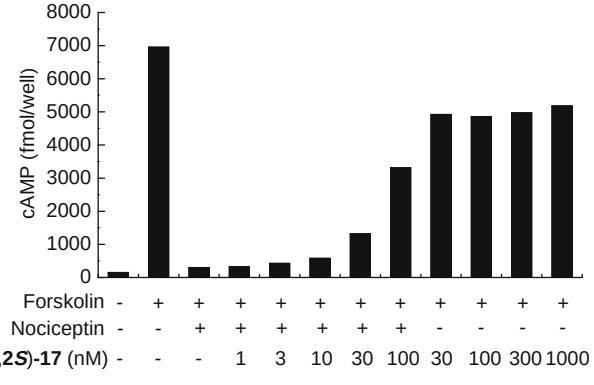


Figure 2. Effect of (**1*R*,2*S*)-17** on nociceptin-induced inhibition of forskolin-stimulated cAMP accumulation in CHO-K1 cells expressing human ORL1.

5. Conclusion

Starting from lead compound **1** in our compound library, we developed an ORL1 antagonist (**1*R*,2*S*)-17** which possesses a new and unique structure. (**1*R*,2*S*)-17** displayed high affinity for ORL1 (K_i = 1.4 nM), and exhibited 270- to 3100-fold selectivity for ORL1 over the other opioid receptors. We also performed a docking study of (**1*R*,2*S*)-17** with a homology-modeled ORL1 structure and showed how the introduction of a guanidino group at the (**1*R*,2*S*)-**cyclohexyl spacer at the 4-position and an amide group at the 2-position of the quinazoline scaffold of (**1*R*,2*S*)-17** could contribute to the high affinity and selectivity of this compound for ORL1.

6. Experimental

6.1. Chemistry

6.1.1. General methods

Reagents and solvents were used as obtained from the supplier without further purification. Melting points were determined on a Büchi B–545 melting-point apparatus, and are uncorrected. Column chromatography was carried out on a silica gel column (Wako Wakogel® C-200 or Fuji Silysia PSQ-100B) and analytical TLC on Merck TLC aluminum sheets silica gel 60 F_{254}. Synthetic yields of compounds were not optimized. ^{1}H NMR spectra were recorded on a Varian Gemini 2000 (200 MHz) or a Varian UnityPlus 300 (300 MHz) spectrometer. Chemical shifts (δ) are given in ppm from the internal standard, tetramethylsilane, and coupling constants in Hertz (Hz). Mass spectra were recorded on a JEOL JMS-700 mass spectrometer. Optical rotations were determined on a Horiba SEPA-200 high-sensitivity polarimeter in a 5-cm-path-length cell,

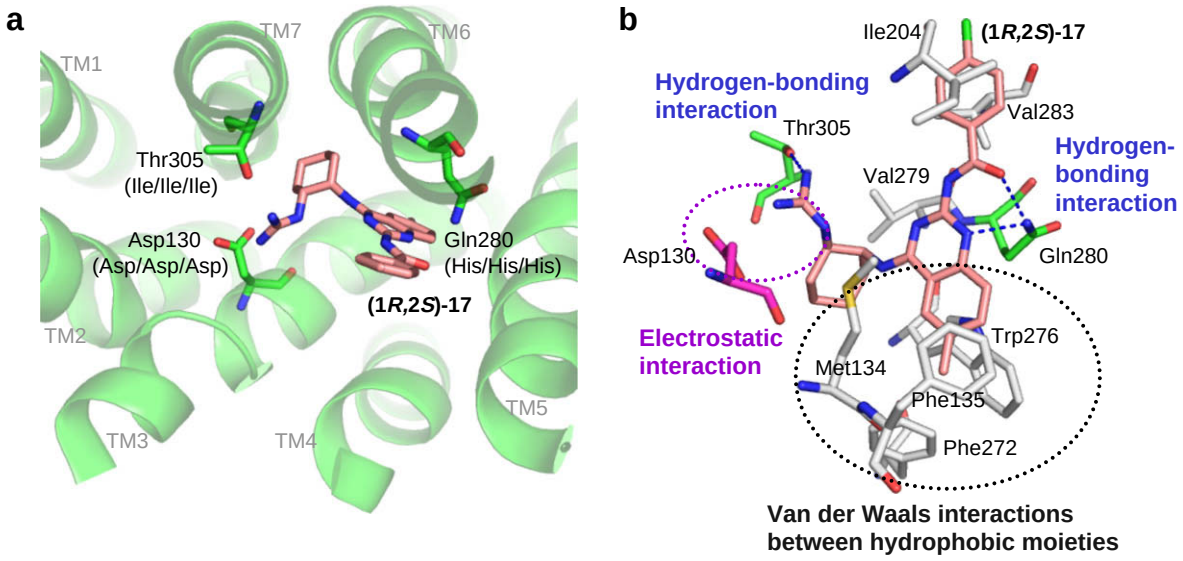


Figure 3. Docking models of the homology-modeled ORL1 in complex with (**1*R*,2*S*)-17**. Hydrophobic amino acids are shown in white and hydrogen-bonding interactions are shown as broken lines.

and elemental analyses were performed on a J-Science Lab Micro Corder JM 10 elemental analyzer.

6.1.2. General procedure for the synthesis of 3a–g: 2,6-dimethylquinazolin-4(3*H*)-one (3c)

A solution of benzoic acid **2c** (5.0 g, 33.1 mmol) in acetic anhydride (20 mL) was heated at 120 °C for 3 h and the reaction mixture was evaporated to dryness. Ammonia solution (28%; 40 mL) was added and the mixture was heated at reflux for 4 h and cooled to room temperature. The precipitate that formed was collected by filtration, washed successively with water and methanol, and dried under reduced pressure, to give **3c** (2.53 g, 43.9%) as pale yellow crystals. Mp 252–253 °C. Fast atom bombardment mass spectrometry (FAB-MS) *m*/*z* 175 $[MH]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.26 (3H, s), 2.35 (3H, s), 7.41 (1H, d, *J* = 8.3 Hz), 7.52 (1H, d, *J* = 8.3 Hz), 7.80 (1H, s), 12.0 (1H, br s). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.86; H, 5.52; N, 16.17.

6.1.3. 2-Methylquinazolin-4(3*H*)-one (3a)

Compound **3a** was prepared from **2a** in a manner similar to that described for **3c**. Yield 29.8%, pale yellow crystals. Mp 230–232 °C FAB-MS *m*/*z* 161 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.28 (3H, s), 7.17 (1H, t, *J* = 7.6 Hz), 7.55–7.75 (2H, m), 8.41 (2H, d, *J* = 8.6 Hz), 10.20 (1H, br s). Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.40; H, 5.20; N, 17.67.

6.1.4. 2,5-Dimethylquinazolin-4(3*H*)-one (3b)

Compound **3b** was prepared from **2b** in a manner similar to that described for **3c**. Yield 52.2%, colorless crystals. Mp 257–258 °C. FAB-MS *m*/*z* 175 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.31 (3H, s), 2.76 (3H, s) 7.17 (1H, d, *J* = 6.8 Hz), 7.37 (1H, d, *J* = 8.2 Hz), 7.58 (1H, dd, *J* = 8.2, 6.8 Hz), 12.0 (1H, br s). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.98; H, 5.70; N, 16.07.

6.1.5. 2,7-Dimethylquinazolin-4(3*H*)-one (3d)

Compound **3d** was prepared from **2d** in a manner similar to that described for **3c**. Yield 49.3%, colorless crystals. Mp 263–264 °C. FAB-MS *m*/*z* 175 $[MH]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.33 (3H, s), 2.43 (3H, s), 7.26 (1H, d, *J* = 8.1 Hz), 7.36 (1H, s), 7.95 (1H, d, *J* = 8.1 Hz), 12.1 (1H, br s). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.03; H, 5.63; N, 16.12.

6.1.6. 2,8-Dimethylquinazolin-4(3*H*)-one (3e)

Compound **3e** was prepared from **2e** in a manner similar to that described for **3c**. Yield 67.5%, colorless crystals. Mp 252–253 °C. FAB-MS *m*/*z* 175 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.38 (3H, s), 2.50 (3H, s), 7.32 (1H, dd, *J* = 7.6, 7.4 Hz), 7.77 (1H, d, *J* = 7.4 Hz), 7.92 (1H, d, *J* = 7.6 Hz), 12.2 (1H, br s). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.94; H, 5.53; N, 16.13.

6.1.7. 6-*tert*-Butyl-2-methylquinazolin-4(3*H*)-one (3f)

Compound **3f** was prepared from **2f** in a manner similar to that described for **3c**. Yield 63.0%, colorless crystals. Mp 230–231 °C. FAB-MS *m*/*z* 217 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.34 (9H, s), 2.33 (3H, s), 7.52 (1H, d, *J* = 8.8 Hz), 7.87 (1H, dd, *J* = 8.8, 2.2 Hz), 8.01 (1H, d, *J* = 2.2 Hz), 12.2 (1H, br s). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 71.91; H, 7.38; N, 13.00.

6.1.8. 6-Chloro-2-methylquinazolin-4(3*H*)-one (3g)

Compound **3g** was prepared from **2g** in a manner similar to that described for **3c**. Yield 82.2%, colorless crystals. Mp 289–291 °C. FAB-MS *m*/*z* 195 $[MH]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.28 (3H, s), 7.59 (1H, d, *J* = 8.7 Hz), 7.72 (1H, dd, *J* = 8.7, 2.6 Hz), 8.31 (1H, d, *J* = 2.6 Hz), 12.3 (1H, br s). Anal. Calcd for $C_9H_7ClN_2O$: C, 55.24; H, 3.63; N, 14.39. Found: C, 55.25; H, 3.36; N, 14.37.

6.1.9. General procedure for the synthesis of 4a–g: 2-[(*E*)-2-(4-chlorophenyl)ethenyl]-6-methylquinazolin-4(3*H*)-one (4c)

A solution of **3c** (500 mg, 2.87 mmol) and 4-chlorobenzaldehyde (403 mg, 2.87 mmol) in acetic acid (3 mL) was heated at 120 °C for 12 h. The reaction mixture was cooled to room temperature and the resulting precipitate was collected by filtration, washed with methanol and dried under reduced pressure to give **4c** (790 mg, 92.8%) as pale yellow crystals. Mp 329–330 °C. FAB-MS *m*/*z* 297 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.45 (3H, s), 7.00 (1H, d, *J* = 15.4 Hz), 7.52 (2H, d, *J* = 8.4 Hz), 7.53–7.74 (2H, m), 7.68 (2H, d, *J* = 8.4 Hz), 7.90 (1H, d, *J* = 15.4 Hz), 7.91 (1H, s),

12.3 (1H, br s). Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; N, 9.44. Found: C, 68.46; H, 4.59; N, 9.46.

6.1.10. 2-[(*E*)-2-(4-Chlorophenyl)ethenyl]quinazolin-4(3*H*)-one (4a)

Compound **4a** was prepared from **3a** in a manner similar to that described for **4c**. Yield 22.2%, yellow crystals. Mp 303–305 °C. FAB-MS *m*/*z* 283 $[MH]^+$. ^1H NMR (200 MHz, DMSO-d_6) δ: 7.22 (1H, d, *J* = 16.0 Hz), 7.50 (1H, ddd, *J* = 7.6, 6.6, 1.4 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 7.68 (1H, dd, *J* = 8.4, 1.4 Hz), 7.70 (2H, d, *J* = 8.4 Hz), 7.82 (1H, ddd, *J* = 8.4, 6.6, 1.4 Hz), 7.94 (1H, d, *J* = 16.0 Hz), 8.12 (1H, dd, *J* = 7.6, 1.4 Hz), 12.4 (1H, br s). Anal. Calcd for $C_{16}H_{11}ClN_2O$: C, 67.97; H, 3.92; N, 9.91. Found: C, 67.59; H, 3.64; N, 9.93.

6.1.11. 2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-5-methylquinazolin-4(3*H*)-one (4b)

Compound **4b** was prepared from **3b** in a manner similar to that described for **4c**. Yield 91.7%, pale yellow crystals. Mp 331–332 °C. FAB-MS *m*/*z* 297 $[MH]^+$. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.79 (3H, s), 6.99 (1H, d, *J* = 16.4 Hz), 7.22 (1H, d, *J* = 7.6 Hz), 7.45–7.58 (1H, m), 7.52 (2H, d, *J* = 8.5 Hz), 7.61 (1H, d, *J* = 7.4 Hz), 7.69 (2H, d, *J* = 8.5 Hz), 7.91 (1H, d, *J* = 16.4 Hz), 12.1 (1H, br s). Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; N, 9.44. Found: C, 68.77; H, 4.34; N, 9.49.

6.1.12. 2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-7-methylquinazolin-4(3*H*)-one (4d)

Compound **4d** was prepared from **3d** in a manner similar to that described for **4c**. Yield 97.5%, pale yellow crystals. Mp 332–333 °C. FAB-MS *m*/*z* 297 $[MH]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 2.50 (3H, s), 7.00 (1H, d, *J* = 16.2 Hz), 7.32 (1H, d, *J* = 8.1 Hz), 7.49 (1H, s), 7.52 (2H, d, *J* = 8.5 Hz), 7.68 (2H, d, *J* = 8.5 Hz), 7.91 (1H, d, *J* = 16.2 Hz), 8.00 (1H, d, *J* = 8.1 Hz), 12.4 (1H, br s). Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; N, 9.44. Found: C, 68.75; H, 4.22; N, 9.50.

6.1.13. 2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-8-methylquinazolin-4(3*H*)-one (4e)

Compound **4e** was prepared from **3e** in a manner similar to that described for **4c**. Yield 90.5%, pale yellow crystals. Mp 302–303 °C. FAB-MS *m*/*z* 297 $[MH]^+$. ^1H NMR (200 MHz, DMSO-d_6) δ: 2.69 (3H, s), 7.01 (1H, d, *J* = 16.2 Hz), 7.37 (1H, t, *J* = 7.6 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 7.63–7.72 (1H, m), 7.70 (2H, d, *J* = 8.4 Hz), 7.92–7.99 (1H, m), 7.94 (1H, d, *J* = 16.2 Hz), 12.3 (1H, br s). Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; N, 9.44. Found: C, 68.75; H, 4.30; N, 9.38.

6.1.14. 6-*tert*-Butyl-2-[(*E*)-2-(4-chlorophenyl)ethenyl]quinazolin-4(3*H*)-one (4f)

Compound **4f** was prepared from **3f** in a manner similar to that described for **4c**. Yield 68.6%, pale yellow crystals. Mp 313–314 °C. FAB-MS *m*/*z* 339 $[MH]^+$. ^1H NMR (200 MHz, DMSO-d_6) δ: 1.36 (9H, s), 7.00 (1H, d, *J* = 16.3 Hz), 7.53 (2H, d, *J* = 8.8 Hz), 7.64 (1H, d, *J* = 8.8 Hz), 7.69 (2H, d, *J* = 8.8 Hz), 7.92 (1H, d, *J* = 16.3 Hz), 7.92 (1H, dd, *J* = 8.8, 2.2 Hz), 8.06 (1H, d, *J* = 2.2 Hz), 12.3 (1H, br s). Anal. Calcd for $C_{20}H_{19}ClN_2O{\cdot}0.25H_2O$: C, 69.96; H, 5.72; N, 8.16. Found: C, 69.90; H, 5.39; N, 8.21.

6.1.15. 6-Chloro-2-[(*E*)-2-(4-chlorophenyl)ethenyl]quinazolin-4(3*H*)-one (4g)

Compound **4g** was prepared from **3g** in a manner similar to that described for **4c**. Yield 85.9%, pale yellow crystals. Mp 374–375 °C. FAB-MS *m*/*z* 317 $[MH]^+$. ^1H NMR (200 MHz, DMSO-d_6) δ: 7.01 (1H, d, *J* = 16.2 Hz), 7.53 (2H, d, *J* = 8.4 Hz), 7.69 (2H, d, *J* = 8.4 Hz), 7.70 (1H, d, *J* = 8.6 Hz), 7.83 (1H, dd, *J* = 8.6, 2.6 Hz), 7.94 (1H, d, *J* = 16.2 Hz), 8.04 (1H, d, *J* = 2.6 Hz), 12.3 (1H, br s). Anal. Calcd for $C_{16}H_{10}Cl_2N_2O$: C, 60.59; H, 3.18; N, 8.83. Found: C, 60.29; H, 3.01; N, 8.88.

6.1.16. General procedure for the synthesis of 5a–g: 4-chloro-2-[(*E*)-2-(4-chlorophenyl)ethenyl]-6-methylquinazoline (5c)

A solution of **4c** (780 mg, 2.63 mmol), phosphorus oxychloride (807 mg, 5.26 mmol) and *N*,*N*-dimethylaniline (642 mg, 5.26 mmol) in toluene (10 mL) was heated at reflux for 5 h and the reaction mixture was evaporated to dryness. $CHCl_3$ was added to the residue and washed with water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give **5c** (3.53 g, 96.6%) as pale yellow crystals. Mp 166–168 °C. FAB-MS *m*/*z* 315 $[MH]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.55 (3H, s), 7.23 (1H, d, *J* = 15.9 Hz), 7.34 (2H, d, *J* = 8.5 Hz), 7.54 (2H, d, *J* = 8.5 Hz), 7.71 (1H, d, *J* = 8.6 Hz), 7.86 (1H, d, *J* = 8.6 Hz), 7.95 (1H, s), 8.01 (1H, d, *J* = 15.9 Hz). Anal. Calcd for $C_{17}H_{12}Cl_2N_2{\cdot}0.2H_2O$: C, 64.05; H, 3.92; N, 8.79. Found: C, 64.27; H, 3.78; N, 8.69.

6.1.17. 4-Chloro-2-[(*E*)-2-(4-chlorophenyl)ethenyl]quinazoline (5a)

Compound **5a** was prepared from **4a** in a manner similar to that described for **5c**. Yield 84.6%, pale yellow crystals. Mp 178–179 °C. FAB-MS *m*/*z* 301 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.29 (1H, d, *J* = 15.8 Hz), 7.39 (2H, d, *J* = 8.6 Hz), 7.60 (2H, d, *J* = 8.6 Hz), 7.66 (1H, ddd, *J* = 7.8, 6.6, 1.4 Hz), 7.93 (1H, ddd, *J* = 8.8, 6.6, 1.0 Hz), 8.01 (1H, dd, *J* = 7.8, 1.0 Hz), 8.09 (1H, d, *J* = 15.8 Hz), 8.24 (1H, dd, *J* = 8.8, 1.4 Hz). Anal. Calcd for $C_{16}H_{10}Cl_2N_2$: C, 63.81; H, 3.35; N, 9.30. Found: C, 63.73; H, 3.15; N, 9.30.

6.1.18. 4-Chloro-2-[(*E*)-2-(4-chlorophenyl)ethenyl]-5-methylquinazoline (5b)

Compound **5b** was prepared from **4b** in a manner similar to that described for **5c**. Yield 67.6%, colorless crystals. Mp 193–195 °C. FAB-MS *m*/*z* 315 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 3.05 (3H, s), 7.27 (1H, d, *J* = 15.9 Hz), 7.40 (2H, d, *J* = 8.5 Hz), 7.44 (1H, d, *J* = 7.2 Hz), 7.61 (2H, d, *J* = 8.5 Hz), 7.76 (1H, dd, *J* = 8.4, 7.2 Hz), 7.89 (1H, d, *J* = 8.4 Hz), 8.07 (1H, d, *J* = 15.9 Hz). Anal. Calcd for $C_{17}H_{12}Cl_2N_2$: C, 64.78; H, 3.84; N, 8.89. Found: C, 64.61; H, 3.61; N, 8.89.

6.1.19. 4-Chloro-2-[(*E*)-2-(4-chlorophenyl)ethenyl]-7-methylquinazoline (5d)

Compound **5d** was prepared from **4d** in a manner similar to that described for **5c**. Yield 60.8%, pale yellow crystals. Mp 188–189 °C. FAB-MS *m*/*z* 315 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.60 (3H, s), 7.26 (1H, d, *J* = 16.0 Hz), 7.37 (2H, d, *J* = 8.8 Hz), 7.46 (1H, d, *J* = 8.6 Hz), 7.58 (2H, d, *J* = 16.0 Hz), 7.77 (1H, s), 8.06 (1H, d, *J* = 16.0 Hz), 8.10 (1H, d, *J* = 8.6 Hz). Anal. Calcd for $C_{17}H_{12}Cl_2N_2$: C, 64.78; H, 3.84; N, 8.89. Found: C, 64.44; H, 3.66; N, 8.89.

6.1.20. 4-Chloro-2-[(*E*)-2-(4-chlorophenyl)ethenyl]-8-methylquinazoline (5e)

Compound **5e** was prepared from **4e** in a manner similar to that described for **5c**. Yield 80.5%, colorless crystals. Mp 165–166 °C. FAB-MS *m*/*z* 315 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.79 (3H, s), 7.31 (1H, d, *J* = 16.0 Hz), 7.38 (2H, d, *J* = 8.4 Hz), 7.43 (1H, dd, *J* = 8.3, 7.1 Hz), 7.60 (2H, d, *J* = 8.4 Hz), 7.75 (1H, d, *J* = 7.1 Hz), 8.07 (1H, d, *J* = 16.0 Hz), 8.07 (1H, d, *J* = 8.3 Hz). Anal. Calcd for $C_{17}H_{12}Cl_2N_2$: C, 64.78; H, 3.84; N, 8.89. Found: C, 64.58; H, 3.57; N, 8.90.

6.1.21. 6-*tert*-Butyl-4-chloro-2-[(*E*)-2-(4-chlorophenyl)ethenyl]-quinazoline (5f)

Compound **5f** was prepared from **4f** in a manner similar to that described for **5c**. Yield 99.0%, colorless crystals. Mp 125–126 °C. FAB-MS *m*/*z* 357 $[MH]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.47 (9H,

s), 7.30 (1H, d, J = 15.5 Hz), 7.40 (2H, d, J = 8.5 Hz), 7.61 (2H, d, J = 8.5 Hz), 7.96 (1H, d, J = 8.9 Hz), 8.03–8.07 (2H, m), 8.13 (1H, d, J = 15.5 Hz). Anal. Calcd for $C_{20}H_{18}Cl_2N_2$: C, 67.23; H, 5.08; N, 7.84. Found: C, 67.28; H, 4.97; N, 7.77.

6.1.22. 4,6-Dichloro-2-[(*E*)-2-(4-chlorophenyl)ethenyl]quinazoline (5g)

Compound **5g** was prepared from **4g** in a manner similar to that described for **5c**. Yield 61.6%, pale yellow crystals. Mp 203–204 °C. FAB-MS m/z 335 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 7.24 (1H, d, J = 15.8 Hz), 7.38 (2H, d, J = 8.5 Hz), 7.58 (2H, d, J = 8.5 Hz), 7.84 (1H, dd, J = 12.8, 2.2 Hz), 7.94 (1H, d, J = 8.8 Hz), 8.08 (1H, d, J = 15.8 Hz), 8.20 (1H, d, J = 2.2 Hz). Anal. Calcd for $C_{16}H_9Cl_3N_2$: C, 57.26; H, 2.70; N, 8.35. Found: C, 57.24; H, 2.69; N, 8.33.

6.1.23. General procedure for the synthesis of 6a–m: *tert*-butyl [6-({2-[(*E*)-2-(4-chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}amino)hexyl]carbamate (6c)

A solution of **5c** (350 mg, 1.11 mmol), *N*-Boc-1,6-hexanediamine (240 mg, 1.11 mmol), triethylamine (225 mg, 2.22 mmol), and 4-dimethylaminopyridine (14 mg 0.111 mmol) in toluene (15 mL) was heated at reflux for 15 h. The mixture was then diluted with water and extracted with $CHCl_3$. The organic layer was washed with water and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel with $CHCl_3$/MeOH (30:1) as the eluent to give **6c** (491 mg, 89.3%) as pale yellow crystals. Mp 110–113 °C. FAB-MS m/z 495 $[MH]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.46 (9H, s), 1.46–1.58 (4H, m), 1.65–1.72 (2H, m), 1.72–1.88 (2H, m), 2.52 (3H, s), 3.09–3.24 (2H, m), 3.77 (2H, dd, J = 12.5, 6.8 Hz), 4.56 (1H, br s), 5.91 (1H, br s), 7.20 (1H, d, J = 15.8 Hz), 7.37 (2H, d, J = 8.5 Hz), 7.48–7.62 (4H, m), 7.74 (1H, d, J = 8.8 Hz), 7.94 (1H, d, J = 15.8 Hz). Anal. Calcd for $C_{28}H_{35}ClN_4O_2$: C, 67.93; H, 7.13; N, 11.32. Found: C, 67.70; H, 7.11; N, 11.18.

6.1.24. *tert*-Butyl [6-({2-[(*E*)-2-(4-chlorophenyl)ethenyl]quinazolin-4-yl}amino)hexyl]carbamate (6a)

Compound **6a** was prepared from **5a** and *N*-Boc-1,6-hexanediamine in a manner similar to that described for **6c**. Yield 80.3%, colorless crystals. Mp 120–122 °C. FAB-MS m/z 481 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.37–1.77 (6H, m), 1.45 (9H, s), 1.64–1.92 (2H, m), 3.02–3.25 (2H, m), 3.76 (2H, dd, J = 12.4, 6.6 Hz), 4.55 (1H, br s), 6.10 (1H, br s), 7.19 (1H, d, J = 15.6 Hz), 7.36 (2H, d, J = 8.4 Hz), 7.39–7.46 (1H, m), 7.57 (2H, d, J = 8.4 Hz), 7.66–7.85 (3H, m), 7.95 (1H, d, J = 15.6 Hz). Anal. Calcd for $C_{27}H_{33}ClN_4O_2$: C, 67.42; H, 6.91; N, 11.65. Found: C, 67.32; H, 6.90; N, 11.68.

6.1.25. *tert*-Butyl [6-({2-[(*E*)-2-(4-chlorophenyl)ethenyl]-5-methylquinazolin-4-yl}amino)hexyl]carbamate (6b)

Compound **6b** was prepared from **5b** and *N*-Boc-1,6-hexanediamine in a manner similar to that described for **6c**. Yield 84.1%, colorless crystals. Mp 126–127 °C. FAB-MS m/z 495 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.43 (9H, s), 1.36–1.65 (6H, m), 1.64–1.92 (2H, m), 2.87 (3H, s), 3.13 (2H, dd, J = 12.0, 6.6 Hz), 3.72 (2H, dd, J = 12.2, 6.9 Hz), 4.52 (1H, br s), 6.15 (1H, br s), 7.14 (1H, d, J = 7.0 Hz), 7.15 (1H, d, J = 15.6 Hz), 7.31 (2H, d, J = 19.4 Hz), 7.37–7.56 (3H, m), 7.66 (1H, d, J = 7.4 Hz), 7.91 (1H, d, J = 15.6 Hz). Anal. Calcd for $C_{28}H_{35}ClN_4O_2$: C, 67.93; H, 7.13; N, 11.32. Found: C, 67.82; H, 7.30; N, 11.23.

6.1.26. *tert*-Butyl [6-({2-[(*E*)-2-(4-chlorophenyl)ethenyl]-7-methylquinazolin-4-yl}amino)hexyl]carbamate (6d)

Compound **6d** was prepared from **5d** and *N*-Boc-1,6-hexanediamine in a manner similar to that described for **6c**. Yield 70.1%, pale yellow crystals. Mp 162–163 °C. FAB-MS m/z 495 $[MH]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.25–1.59 (4H, m), 1.37 (9H, s), 1.37–1.66 (2H, m), 1.66–1.83 (2H, m), 2.43 (3H, s), 2.95–3.12 (2H, m), 3.68 (2H, dd, J = 12.4, 6.8 Hz), 4.47 (1H, br s), 5.89 (1H, br s), 7.11 (1H, d, J = 15.8 Hz), 7.16 (1H, d, J = 8.7 Hz), 7.28 (2H, d, J = 8.5 Hz), 7.50 (2H, d, J = 8.5 Hz), 7.53 (1H, s), 7.60 (1H, d, J = 8.7 Hz), 7.87 (1H, d, J = 15.8 Hz). Anal. Calcd for $C_{28}H_{35}ClN_4O_2 \cdot 0.5H_2O$: C, 66.72; H, 7.20; N, 11.11. Found: C, 66.58; H, 7.17; N, 11.10.

6.1.27. *tert*-Butyl [6-({2-[(*E*)-2-(4-chlorophenyl)ethenyl]-8-methylquinazolin-4-yl}amino)hexyl]carbamate (6e)

Compound **6e** was prepared from **5e** and *N*-Boc-1,6-hexanediamine in a manner similar to that described for **6c**. Yield 87.0%, colorless crystals. Mp 118–119 °C. FAB-MS m/z 495 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.38–1.65 (6H, m), 1.44 (9H, s), 1.66–1.83 (2H, m), 2.72 (3H, s), 3.12–3.44 (2H, m), 3.74 (2H, dd, J = 12.0, 6.6 Hz), 4.54 (1H, br s), 5.91 (1H, br s), 7.22 (1H, d, J = 15.8 Hz), 7.20–7.41 (3H, m), 7.55–7.63 (4H, m), 7.96 (1H, d, J = 15.6 Hz). Anal. Calcd for $C_{28}H_{35}ClN_4O_2$: C, 67.93; H, 7.13; N, 11.32. Found: C, 67.77; H, 7.25; N, 11.28.

6.1.28. *tert*-Butyl [6-({6-*tert*-butyl-2-[(*E*)-2-(4-chlorophenyl)-ethenyl]quinazolin-4-yl}amino)hexyl]carbamate (6f)

Compound **6f** was prepared from **5f** and *N*-Boc-1,6-hexanediamine in a manner similar to that described for **6c**. Yield 74.0%, pale yellow crystals. Mp 129–130 °C. FAB-MS m/z 537 $[MH]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.43 (9H, s), 1.46 (9H, s), 1.49–1.90 (8H, m), 3.10–3.30 (2H, m), 3.79 (2H, dd, J = 12.7, 6.7 Hz), 4.56 (1H, br s), 7.22 (1H, d, J = 15.7 Hz), 7.37 (2H, d, J = 8.5 Hz), 7.57–7.60 (3H, m), 7.68 (1H, br s), 7.78–7.85 (2H, m), 7.95 (1H, d, J = 15.7 Hz). Anal. Calcd for $C_{31}H_{41}ClN_4O_2$: C, 69.32; H, 7.69; N, 10.43. Found: C, 69.10; H, 7.68; N, 10.45.

6.1.29. *tert*-Butyl [6-({6-chloro-2-[(*E*)-2-(4-chlorophenyl)-ethenyl]quinazolin-4-yl}amino)hexyl]carbamate (6g)

Compound **6g** was prepared from **5g** and *N*-Boc-1,6-hexanediamine in a manner similar to that described for **6c**. Yield 77.9%, pale yellow crystals. Mp 119–120 °C. FAB-MS m/z 515 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.35–1.63 (6H, m), 1.45 (9H, s), 1.65–1.83 (2H, m), 2.97–3.28 (2H, m), 3.74 (2H, dd, J = 12.0, 6.6 Hz), 4.57 (1H, br s), 6.27 (1H, br s), 7.15 (1H, d, J = 15.6 Hz), 7.35 (2H, d, J = 8.4 Hz), 7.56 (2H, d, J = 8.4 Hz), 7.62 (1H, dd, J = 8.8, 2.2 Hz), 7.74 (1H, d, J = 8.8 Hz), 7.87 (1H, d, J = 2.2 Hz), 7.94 (1H, d, J = 15.6 Hz). Anal. Calcd for $C_{27}H_{32}Cl_2N_4O_2$: C, 62.91; H, 6.26; N, 10.87. Found: C, 62.87; H, 6.25; N, 10.73.

6.1.30. *tert*-Butyl [4-({2-[(*E*)-2-(4-chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}amino)butyl]carbamate (6h)

Compound **6h** was prepared from **5c** and *N*-Boc-1,4-butanediamine in a manner similar to that described for **6c**. Yield 87.4%, colorless crystals. Mp 191–192 °C. FAB-MS m/z 467 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.46 (9H, s), 1.62–1.89 (4H, m), 2.50 (3H, s), 3.25 (2H, dd, J = 12.8, 6.6 Hz), 3.81 (2H, dd, J = 12.0, 6.2 Hz), 4.69 (1H, br s), 6.19 (1H, br s), 7.18 (1H, d, J = 15.6 Hz), 7.34 (2H, d, J = 8.4 Hz), 7.48–7.66 (3H, m), 7.57 (1H, d, J = 8.6 Hz), 7.72 (1H, d, J = 8.6 Hz), 7.92 (1H, d, J = 15.6 Hz). Anal. Calcd for $C_{26}H_{31}ClN_4O_2 \cdot 0.6H_2O$: C, 65.36; H, 6.79; N, 11.73. Found: C, 65.36; H, 6.46; N, 11.73.

6.1.31. *tert*-Butyl [2-({2-[(*E*)-2-(4-chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}amino)ethyl]carbamate (6i)

Compound **6i** was prepared from **5c** and *N*-Boc-1,2-ethanediamine in a manner similar to that described for **6c**. Yield 85.1%, col-

orless crystals. Mp 203−204 °C. FAB-MS *m*/*z* 439 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.44 (9H, s), 2.49 (3H, s), 3.50–3.65 (2H, m), 3.68–3.80 (2H, m), 5.22 (1H, br s), 6.95 (1H, br s), 7.17 (1H, d, *J* = 15.7 Hz), 7.34 (2H, d, *J* = 8.4 Hz), 7.50–7.62 (4H, m), 7.71 (1H, d, *J* = 8.8 Hz), 7.92 (1H, d, *J* = 15.7 Hz). Anal. Calcd for $C_{24}H_{27}ClN_4O_2{\cdot}0.3H_2O$: C, 64.87; H, 6.26; N, 12.61. Found: C, 64.96; H, 6.10; N, 12.62.

6.1.32. *tert*-Butyl (1*RS*,2*RS*)-[2-({2-[(*E*)-2-(4-chlorophenyl)-ethenyl]-6-methylquinazolin-4-yl}amino)cyclohexyl]-carbamate (6j)

Compound **6j** was prepared from **5c** and *tert*-butyl (*trans*-2-aminocyclohexyl)carbamate in a manner similar to that described for **6c**. Yield 73.4%, colorless crystals. Mp 248−250 °C. FAB-MS *m*/*z* 493 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.01–1.65 (4H, m), 1.34 (9H, s), 1.61–2.00 (2H, m), 2.00–2.24 (1H, m), 2.47 (3H, s), 2.58–2.61 (1H, m), 3.58–3.81 (1H, m), 3.95–4.15 (1H, m), 4.81 (1H, d, *J* = 8.4 Hz), 7.04 (1H, d, *J* = 6.2 Hz), 7.17 (1H, d, *J* = 15.8 Hz), 7.32 (2H, d, *J* = 8.4 Hz), 7.47–7.63 (2H, m), 7.55 (2H, d, *J* = 8.4 Hz), 7.68 (1H, d, *J* = 8.4 Hz), 7.87 (1H, d, *J* = 15.8 Hz). Anal. Calcd for $C_{28}H_{33}ClN_4O_2{\cdot}0.2H_2O$: C, 67.72; H, 6.78; N, 11.28. Found: C, 67.72; H, 6.67; N, 11.10.

6.1.33. *tert*-Butyl (1*RS*,2*SR*)-[2-({2-[(*E*)-2-(4-chlorophenyl)-ethenyl]-6-methylquinazolin-4-yl}amino)cyclohexyl]carbamate (6k)

Compound **6k** was prepared from **5c** and *tert*-butyl (*cis*-2-aminocyclohexyl)carbamate in a manner similar to that described for **6c**. Yield 88.1%, pale yellow crystals. Mp 221–223 °C. FAB-MS *m*/*z* 493 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.30–2.18 (7H, m), 1.51 (9H, s), 2.29–2.52 (1H, m), 2.49 (3H, s), 4.07–4.14 (1H, m), 4.32–4.50 (1H, m), 5.23 (1H, br s), 7.17 (1H, d, *J* = 15.8 Hz), 7.33 (1H, br s), 7.35 (2H, d, *J* = 8.4 Hz), 7.49–7.61 (4H, m), 7.70 (1H, d, *J* = 8.4 Hz), 7.88 (1H, d, *J* = 15.8 Hz). Anal. Calcd for $C_{28}H_{33}ClN_4O_2{\cdot}\ 0.2H_2O$: C, 67.72; H, 6.78; N, 11.28. Found: C, 67.74; H, 6.60; N, 11.27.

6.1.34. *tert*-Butyl *cis*-[4-({2-[(*E*)-2-(4-chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}amino)cyclohexyl]carbamate (6l)

Compound **6l** was prepared from **5c** and *tert*-butyl (*cis*-4-aminocyclohexyl)carbamate in a manner similar to that described for **6c**. Yield 80.6%, pale yellow crystals. Mp 201–202 °C. FAB-MS *m*/*z* 493 $[MH]^+$. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.38 (9H, s), 1.54–1.93 (8H, m), 2.43 (3H, s), 3.60–3.74 (1H, m), 4.35–4.60 (2H, m), 5.44 (1H, d, *J* = 6.9 Hz), 7.08 (1H, d, *J* = 15.8 Hz), 7.26 (2H, d, *J* = 8.5 Hz), 7.31 (1H, s), 7.44–7.52 (1H, m), 7.46 (2H, d, *J* = 8.5 Hz), 7.64 (1H, d, *J* = 8.5 Hz), 7.79 (1H, d, *J* = 15.8 Hz). Anal. Calcd for $C_{28}H_{33}ClN_4O_2$: C, 68.21; H, 6.75; N, 11.36. Found: C, 67.91; H, 6.56; N, 11.17.

6.1.35. *tert*-Butyl *trans*-[4-({2-[(*E*)-2-(4-chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}amino)cyclohexyl]carbamate (6m)

Compound **6m** was prepared from **5c** and *tert*-butyl (*trans*-4-aminocyclohexyl)carbamate in a manner similar to that described for **6c**. Yield 61.6%, pale brown crystals. Mp 242−243 °C. FAB-MS *m*/*z* 493 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.22–1.60 (4H, m), 1.47 (9H, s), 2.05–2.45 (4H, m), 2.50 (3H, s), 3.40–3.75 (1H, m), 4.20–4.58 (2H, m), 5.45 (1H, d, *J* = 7.0 Hz), 7.17 (1H, d, *J* = 16.0 Hz), 7.35 (2H, d, *J* = 8.4 Hz), 7.43 (1H, s), 7.48–7.60 (1H, m), 7.54 (2H, d, *J* = 8.4 Hz), 7.72 (1H, d, *J* = 8.4 Hz), 7.68 (1H, d, *J* = 16.0 Hz). Anal. Calcd for $C_{28}H_{33}ClN_4O_2{\cdot}0.5H_2O$: C, 66.99; H, 6.83; N, 11.16. Found: C, 67.29; H, 6.83; N, 10.95.

6.1.36. General procedure for the synthesis of 7a–m: *N*-{2-[(*E*)-2-(4-chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}hexane-1,6-diamine dihydrochloride (7c)

To a solution of **6c** (65 mg, 0.131 mmol) in EtOAc (2 mL) was added 4 N HCl in EtOAc (5 mL) and the mixture was stirred at room temperature for 15 h. The precipitate that formed was collected by filtration, washed with EtOAc and dried under reduced pressure to give **7c** (50 mg, 82.0%) as a pale yellow powder. Mp 323–325 °C. FAB-MS *m*/*z* 395 $[MH]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.31–1.48 (4H, m), 1.48–1.62 (2H, m), 1.62–1.80 (2H, m), 2.50 (3H, s), 2.62–2.80 (2H, m), 3.78–3.85 (2H, m), 7.37 (1H, d, *J* = 15.8 Hz), 7.59 (2H, d, *J* = 8.5 Hz), 7.77–7.87 (4H, m), 7.78 (2H, d, *J* = 8.5 Hz), 8.13 (2H, br s), 8.22 (1H, d, *J* = 15.8 Hz), 8.46 (1H, s), 10.1 (1H, br s). Anal. Calcd for $C_{23}H_{27}ClN_4{\cdot}2HCl{\cdot}2.6H_2O$: C, 53.67; H, 6.70; N, 10.89. Found: C, 53.36; H, 6.32; N, 10.87.

6.1.37. *N*-{2-[(*E*)-2-(4-Chlorophenyl)ethenyl]quinazolin-4-yl} hexane-1,6-diamine dihydrochloride (7a)

Compound **7a** was prepared from **6a** in a manner similar to that described for **7c**. Yield 80.5%, colorless powder. Mp 322–323 °C. FAB-MS *m*/*z* 381 $[MH]^+$. ^1H NMR (200 MHz, DMSO-d_6) δ: 1.20–1.85 (8H, m), 2.60–2.90 (2H, m), 3.68–3.90 (2H, m), 7.40 (1H, d, *J* = 15.8 Hz), 7.60 (2H, d, *J* = 8.5 Hz), 7.64–7.78 (1H, m), 7.75–7.85 (1H, m), 7.80 (2H, d, *J* = 8.5 Hz), 7.88–8.18 (5H, m), 8.25 (1H, d, 15.8 Hz), 8.67 (1H, d, *J* = 8.0 Hz), 10.3 (1H, br s). Anal. Calcd for $C_{22}H_{25}ClN_4{\cdot}2HCl{\cdot}1.5H_2O$: C, 54.95; H, 6.29; N, 11.65. Found: C, 55.03; H, 5.99; N, 11.55.

6.1.38. *N*-{2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-5-methyl-quinazolin-4-yl}hexane-1,6-diamine dihydrochloride (7b)

Compound **7b** was prepared from **6b** in a manner similar to that described for **7c**. Yield 84.2%, colorless powder. Mp 202–203 °C. FAB-MS *m*/*z* 395 $[MH]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.27–1.48 (4H, m), 1.48–1.65 (2H, m), 1.65–1.80 (2H, m), 2.64–2.79 (2H, m), 2.86 (3H, s), 3.76–3.88 (2H, m), 7.33 (1H, d, *J* = 15.8 Hz), 7.47 (1H, d, *J* = 7.3 Hz), 7.57 (2H, d, *J* = 8.4 Hz), 7.74–7.92 (6H, m), 7.75 (2H, d, *J* = 8.4 Hz), 8.18 (1H, d, *J* = 15.8 Hz), 8.59 (1H, br s). Anal. Calcd for $C_{23}H_{27}ClN_4{\cdot}2HCl{\cdot}2.9H_2O$: C, 53.11; H, 6.74; N, 10.77. Found: C, 53.36; H, 6.41; N, 10.70.

6.1.39. *N*-{2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-7-methyl-quinazolin-4-yl}hexane-1,6-diamine dihydrochloride (7d)

Compound **7d** was prepared from **6d** in a manner similar to that described for **7c**. Yield 75.8%, pale brown powder. Mp 320–323 °C. FAB-MS *m*/*z* 395 $[MH]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.50–1.68 (4H, m), 1.68–1.82 (2H, m), 1.82–2.00 (2H, m), 2.50 (3H, s), 2.88–3.01 (2H, m), 4.03 (2H, dd, *J* = 6.5, 12.5 Hz), 7.62 (1H, d, *J* = 15.8 Hz), 7.77 (1H, d, *J* = 8.6 Hz), 7.81 (2H, d, *J* = 8.5 Hz), 7.93 (1H, s), 8.00 (2H, d, *J* = 8.5 Hz), 8.19 (3H, br s), 8.45 (1H, d, *J* = 15.8 Hz), 8.74 (1H, d, *J* = 8.6 Hz), 10.4 (1H, br s), 15.2 (1H, br s). Anal. Calcd for $C_{23}H_{27}ClN_4{\cdot}2HCl{\cdot}1.5H_2O$: C, 55.82; H, 6.52; N, 11.32. Found: C, 56.09; H, 6.59; N, 11.13.

6.1.40. *N*-{2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-8-methyl-quinazolin-4-yl}hexane-1,6-diamine dihydrochloride (7e)

Compound **7e** was prepared from **6e** in a manner similar to that described for **7c**. Yield 96.2%, colorless powder. Mp 317–318 °C. FAB-MS *m*/*z* 395 $[MH]^+$. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.36–1.48 (4H, m), 1.48–1.65 (2H, m), 1.65–1.82 (2H, m), 2.70 (3H, s), 2.68–2.92 (2H, m), 3.86 (2H, dd, *J* = 12.0, 6.0 Hz), 7.45–7.58 (3H, m), 7.62–7.89 (3H, m), 7.95–8.30 (4H, m), 8.04 (1H, d, *J* = 15.7 Hz), 8.19 (1H, d, *J* = 15.7 Hz), 8.51 (1H, d, *J* = 8.2 Hz), 10.4 (1H, br s). Anal. Calcd for $C_{23}H_{27}ClN_4{\cdot}2HCl{\cdot}1.5H_2O$: C, 55.82; H, 6.52; N, 11.32. Found: C, 55.55; H, 6.42; N, 11.08.

6.1.41. *N*-{6-*tert*-Butyl-2-[(*E*)-2-(4-chlorophenyl)ethenyl]-quinazolin-4-yl}hexane-1,6-diamine dihydrochloride (7f)

Compound **7f** was prepared from **6f** in a manner similar to that described for **7c**. Yield 99.0%, colorless powder. Mp 195–197 °C. FAB-MS *m*/*z* 437 $[MH]^+$. ^1H NMR (200 MHz, DMSO-d_6) δ: 1.31–1.88 (8H, m), 1.39 (9H, s), 2.66–2.88 (2H, m), 3.75–3.94 (2H, m),

7.34 (1H, d, J = 15.7 Hz), 7.60 (2H, d, J = 8.6 Hz), 7.76–8.08 (5H, m), 7.80 (2H, d, J = 8.6 Hz), 8.10 (1H, d, J = 8.4 Hz), 8.23 (1H, d, J = 15.7 Hz), 8.55 (1H, s), 10.3 (1H, br s). Anal. Calcd for $C_{26}H_{33}ClN_4{\cdot}2HCl{\cdot}1.8H_2O$: C, 57.58; H, 7.17; N, 10.33. Found: C, 57.49; H, 6.80; N, 10.25.

6.1.42. *N*-{6-Chloro-2-[(*E*)-2-(4-chlorophenyl)ethenyl]quinazolin-4-yl}hexane-1,6-diamine dihydrochloride (7g)

Compound **7g** was prepared from **6g** in a manner similar to that described for **7c**. Yield 67.7%, colorless powder. Mp 334–335 °C. FAB-MS m/z 415 $[MH]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.25–1.45 (4H, m), 1.45–1.65 (2H, m), 1.65–1.78 (2H, m), 2.48–2.90 (2H, m), 3.76 (2H, dd, J = 12.0, 5.6 Hz), 7.28 (1H, d, J = 16.0 Hz), 7.53 (2H, d, J = 8.5 Hz), 7.73 (2H, d, J = 8.5 Hz), 7.75–8.07 (6H, m), 8.23 (1H, d, J = 16.0 Hz), 8.74 (1H, s), 10.1 (1H, br s). Anal. Calcd for $C_{22}H_{24}Cl_2N_4{\cdot}2HCl{\cdot}0.5H_2O$: C, 53.14; H, 5.47; N, 11.27. Found: C, 53.12; H, 5.25; N, 11.17.

6.1.43. *N*-{2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}butane-1,4-diamine dihydrochloride (7h)

Compound **7h** was prepared from **6h** in a manner similar to that described for **7c**. Yield 78.5%, colorless powder. Mp 330–332 °C. FAB-MS m/z 367 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.58–1.90 (4H, m), 2.50 (3H, m), 2.70–2.95 (2H, m), 3.79–3.95 (2H, m), 7.22–7.50 (2H, m), 7.60 (2H, d, J = 8.0 Hz), 7.76–8.14 (5H, m), 7.82 (2H, d, J = 8.0 Hz), 8.25 (1H, d, J = 15.6 Hz), 8.48 (1H, s), 10.1 (1H, br s). Anal. Calcd for $C_{21}H_{23}ClN_4{\cdot}2HCl{\cdot}H_2O$: C, 55.09; H, 5.94; N, 12.24. Found: C, 54.96; H, 5.64; N, 11.96.

6.1.44. *N*-{2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}ethane-1,2-diamine dihydrochloride (7i)

Compound **7i** was prepared from **6i** in a manner similar to that described for **7c**. Yield 90.5%, colorless powder. Mp 298–300 °C. FAB-MS m/z 339 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.50 (3H, m), 3.06–3.32 (2H, m), 4.02–4.20 (2H, m), 7.33 (1H, d, J = 15.8 Hz), 7.60 (2H, d, J = 8.0 Hz), 7.78–7.96 (5H, m), 8.28 (3H, br s), 8.38–8.56 (2H, m), 10.2 (1H, br s). Anal. Calcd for $C_{19}H_{19}ClN_4{\cdot}2HCl{\cdot}0.5H_2O$: C, 54.24; H, 5.27; N, 13.32. Found: C, 54.14; H, 5.08; N, 13.19.

6.1.45. (1*RS*,2*RS*)-*N*-{2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}cyclohexane-1,2-diamine dihydrochloride (7j)

Compound **7j** was prepared from **6j** in a manner similar to that described for **7c**. Yield 95.8%, pale yellow crystals. Mp 344–345 °C. FAB-MS m/z 393 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.21–2.32 (8H, m), 2.50 (3H, m), 3.40–3.72 (1H, m), 4.68–4.90 (1H, m), 7.37 (1H, d, J = 15.8 Hz), 7.60 (2H, d, J = 8.0 Hz), 7.78–7.90 (4H, m), 8.35 (4H, br s), 8.46 (1H, d, J = 15.8 Hz), 8.59 (1H, s), 9.97 (1H, br s). Anal. Calcd for $C_{23}H_{25}ClN_4{\cdot}2HCl{\cdot}0.2H_2O$: C, 58.85; H, 5.88; N, 11.93. Found: C, 58.62; H, 5.67; N, 11.90.

6.1.46. (1*RS*,2*SR*)-*N*-{2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}cyclohexane-1,2-diamine dihydrochloride (7k)

Compound **7k** was prepared from **6k** in a manner similar to that described for **7c**. Yield 85.6%, pale yellow crystals. Mp 245–247 °C. FAB-MS m/z 393 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.26–2.08 (8H, m), 2.50 (3H, s), 3.50–3.69 (1H, m), 4.68–4.85 (1H, m), 7.25 (1H, d, J = 15.8 Hz), 7.40 (2H, d, J = 8.4 Hz), 7.62 (2H, d, J = 8.4 Hz), 7.76–7.79 (2H, m), 8.12 (1H, d, J = 15.8 Hz), 8.20 (4H, br s), 8.60 (1H, s), 9.24 (1H, d, J = 6.8 Hz). Anal. Calcd for $C_{23}H_{25}ClN_4{\cdot}2HCl{\cdot}2.5H_2O$: C, 54.07; H, 6.31; N, 10.97. Found: C, 54.47; H, 5.92; N, 10.97.

6.1.47. *cis*-*N*-{2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}cyclohexane-1,4-diamine dihydrochloride (7l)

Compound **7l** was prepared from **6l** in a manner similar to that described for **7c**. Yield 66.5%, pale yellow crystals. Mp 258–261 °C. FAB-MS m/z 393 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.70–2.30 (9H, m), 2.50 (3H, s), 4.40–4.62 (1H, m), 7.36 (1H, d, J = 15.4 Hz), 7.66 (2H, d, J = 8.4 Hz), 7.77–7.86 (5H, m), 8.00–8.23 (4H, m), 8.63 (1H, s), 9.23 (1H, br s). Anal. Calcd for $C_{23}H_{25}ClN_4{\cdot}2HCl{\cdot}1.3H_2O$: C, 56.46; H, 6.10; N, 11.45. Found: C, 56.15; H, 5.73; N, 11.25.

6.1.48. *trans*-*N*-{2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}cyclohexane-1,4-diamine dihydrochloride (7m)

Compound **7m** was prepared from **6m** in a manner similar to that described for **7c**. Yield 94.7%, pale yellow powder. Mp 339–341 °C. FAB-MS m/z 393 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.21–1.58 (4H, m), 1.72–1.92 (4H, m), 2.70–3.00 (1H, m), 4.00–4.30 (1H, m), 6.90–7.05 (1H, m), 6.98 (1H, d, J = 15.4 Hz), 7.15–7.38 (1H, m), 7.31 (2H, d, J = 8.4 Hz), 7.46–7.57 (5H, m), 7.65–7.90 (4H, m), 7.86 (1H, d, J = 15.4 Hz), 8.12 (1H, s), 9.24 (1H, br s). Anal. Calcd for $C_{23}H_{25}ClN_4{\cdot}2HCl{\cdot}3.7H_2O$: C, 51.88; H, 6.51; N, 10.52. Found: C, 51.90; H, 6.61; N, 10.50.

6.1.49. General procedure for the synthesis of 8a–d: *N*-[6-({2-[(*E*)-2-(4-chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}amino)hexyl]-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidine (8a)

To a suspension of **7c** (170 mg, 0.363 mol) in CH_2Cl_2 (5 mL) was added triethylamine (110 mg, 1.09 mol) and *N*,*N*′-bis-Boc-1*H*-pyrazole-1-carboxamidine (124 mg, 0.400 mol), and the mixture was stirred at room temperature for 15 h. The mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with hexane/EtOAc (2:1) as the eluent to give **8a** (187 mg, 81.0%) as colorless crystals. Mp 165–167 °C. FAB-MS m/z 637 $[MH]^+$. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.40–1.90 (8H, m), 1.49 (9H, s), 1.49 (9H, s), 2.50 (3H, s), 3.43 (2H, d, J = 12.4 Hz), 3.76 (2H, dd, J = 12.6, 6.9 Hz), 5.76 (1H, br s), 7.18 (1H, d, J = 15.8 Hz), 7.35 (2H, d, J = 8.4 Hz), 7.45–7.64 (4H, m), 7.72 (1H, d, J = 8.6 Hz), 7.92 (1H, d, J = 15.8 Hz), 8.36 (1H, br s), 11.5 (1H, br s). Anal. Calcd for $C_{34}H_{45}ClN_6O_4$: C, 64.09; H, 7.21; N, 13.19. Found: C, 64.07; H, 7.13; N, 13.24.

6.1.50. *N*-[4-({2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}amino)butyl]-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidine (8b)

Compound **8b** was prepared from **7h** in a manner similar to that described for **8a**. Yield 89.7%, colorless crystals. Mp 151–153 °C. FAB-MS m/z 609 $[MH]^+$. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.44 (9H, s), 1.49 (9H, s), 1.64–1.94 (4H, m), 2.50 (3H, s), 3.46–3.64 (2H, m), 3.75–3.94 (2H, m), 6.39 (1H, br s), 7.18 (1H, d, J = 15.8 Hz), 7.35 (2H, d, J = 8.4 Hz), 7.48–7.64 (4H, m), 7.72 (1H, d, J = 8.4 Hz), 7.92 (1H, d, J = 15.8 Hz), 8.46 (1H, br s), 11.5 (1H, br s). Anal. Calcd for $C_{32}H_{41}ClN_6O_4$: C, 63.09; H, 6.78; N, 13.80. Found: C, 62.87; H, 6.61; N, 13.87.

6.1.51. (1*RS*,2*SR*)-*N*-[2-({2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}amino)cyclohexyl]-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidine (8c)

Compound **8c** was prepared from **7k** in a manner similar to that described for **8a**. Yield 85.6%, pale yellow crystals. Mp 231–233 °C. FAB-MS m/z 635 $[MH]^+$. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.40–2.00 (25H, m), 2.37–2.45 (1H, m), 2.51 (3H, s), 4.50–4.81 (2H, m), 6.69 (1H, d, J = 5.0 Hz), 7.15 (1H, d, J = 15.8 Hz), 7.34 (2H, d, J = 8.6 Hz), 7.37 (1H, d, J = 8.4 Hz), 7.51 (2H, d, J = 8.6 Hz), 7.58 (1H, s), 7.70 (1H, d, J = 8.4 Hz), 7.86 (1H, d, J = 15.8 Hz), 8.91 (1H, d, J = 8.4 Hz),

11.5 (1H, br s). Anal. Calcd for $C_{34}H_{43}ClN_6O_4{\cdot}0.5H_2O$: C, 63.39; H, 6.88; N, 13.05. Found: C, 63.57; H, 6.85; N, 12.90.

6.1.52. *N*-[*cis*-4-({2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}amino)cyclohexyl]-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidine (8d)

Compound **8d** was prepared from **7l** in a manner similar to that described for **8a**. Yield 83.7%, colorless crystals. Mp 240–241 °C. FAB-MS *m*/*z* 635 $[MH]^+$. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.19–1.35 (4H, m), 1.52 (9H, s), 1.56 (9H, s), 1.65–2.18 (5H, m), 2.56 (3H, s), 4.30–4.62 (2H, m), 5.61 (1H, d, *J* = 7.0 Hz), 7.19 (1H, d, *J* = 15.8 Hz), 7.37 (2H, d, *J* = 8.5 Hz), 7.50 (1H, s), 7.57 (2H, d, *J* = 8.5 Hz), 7.57 (1H, d, *J* = 8.4 Hz), 7.75 (1H, d, *J* = 8.4 Hz), 7.90 (1H, d, *J* = 15.8 Hz), 8.63 (1H, d, *J* = 8.1 Hz). Anal. Calcd for $C_{34}H_{43}ClN_6O_4{\cdot}0.5H_2O$: C, 63.39; H, 6.88; N, 13.05. Found: C, 63.08; H, 6.82; N, 12.75.

6.1.53. General procedure for the synthesis of 9a–d: *N*-[6-({2-[(*E*)-2-(4-chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}amino)hexyl]guanidine dihydrochloride (9a)

To a stirred solution of **8a** (120 mg, 0.188 mmol) in EtOAc (2 mL) and MeOH (2 mL) was added 4 N HCl in EtOAc solution (2 mL), and the mixture was heated at 50 °C for 15 h. The precipitate that formed was collected by filtration, washed with EtOAc and dried under reduced pressure to give **9a** (91 mg, 94.8%) as colorless crystals. Mp 298–300 °C. FAB-MS *m*/*z* 437 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.24–1.62 (6H, m), 1.63–1.90 (2H, m), 2.50 (3H, s), 2.97–3.21 (2H, m), 3.72–3.95 (2H, m), 7.21 (5H, br s), 7.35 (1H, d, *J* = 15.8 Hz), 7.60 (2H, d, *J* = 8.4 Hz), 7.73–7.92 (3H, m), 7.80 (2H, d, *J* = 8.4 Hz), 8.22 (1H, d, *J* = 15.8 Hz), 8.44 (1H, s), 10.1 (1H, br s). Anal. Calcd for $C_{24}H_{29}ClN_6{\cdot}2HCl$: C, 56.53; H, 6.13; N, 16.48. Found: C, 56.21; H, 5.86; N, 16.35.

6.1.54. *N*-[4-({2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}amino)butyl]guanidine dihydrochloride (9b)

Compound **9b** was prepared from **8b** in a manner similar to that described for **9a**. Yield 94.4%, pale yellow powder. Mp 346–348 °C. FAB-MS *m*/*z* 409 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 1.53–1.89 (4H, m), 2.50 (3H, s), 3.13–3.25 (2H, m), 3.75–3.97 (2H, m), 7.08 (5H, br s), 7.30 (1H, d, *J* = 16.0 Hz), 7.61 (2H, d, *J* = 8.4 Hz), 7.65–7.92 (5H, m), 8.24 (1H, d, *J* = 16.0 Hz), 8.42 (1H, s), 10.0 (1H, br s). Anal. Calcd for $C_{22}H_{25}ClN_6{\cdot}2HCl{\cdot}0.5H_2O$: C, 53.83; H, 5.75; N, 17.12. Found: C, 54.16; H, 5.73; N, 16.76.

6.1.55. (1*RS*,2*SR*)-*N*-[2-({2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}amino)cyclohexyl]guanidine dihydrochloride (9c)

Compound **9c** was prepared from **8c** in a manner similar to that described for **9a**. Yield 87.5%, pale yellow crystals. Mp 311–313 °C. FAB-MS *m*/*z* 435 $[MH]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.32–2.19 (8H, m), 2.50 (3H, s), 3.98–4.19 (1H, m), 4.97–5.11 (1H, m), 7.25 (5H, br s), 7.39 (1H, d, *J* = 15.8 Hz), 7.61 (2H, d, *J* = 8.5 Hz), 7.81 (2H, d, *J* = 8.5 Hz), 7.90 (1H, d, *J* = 9.0 Hz), 8.04 (1H, d, *J* = 9.0 Hz), 8.28 (1H, d, *J* = 15.8 Hz), 8.69 (1H, s), 9.27 (1H, d, *J* = 9.0 Hz), 15.4 (1H, br s). Anal. Calcd for $C_{24}H_{27}ClN_6{\cdot}2HCl{\cdot}2.1H_2O$: C, 52.82; H, 6.13; N, 15.40. Found: C, 52.60; H, 5.73; N, 15.77.

6.1.56. *N*-[*cis*-4-({2-[(*E*)-2-(4-Chlorophenyl)ethenyl]-6-methylquinazolin-4-yl}amino)cyclohexyl]guanidine dihydrochloride (9d)

Compound **9d** was prepared from **8d** in a manner similar to that described for **9a**. Yield 91.8%, pale yellow crystals. Mp 265–268 °C. FAB-MS *m*/*z* 435 $[MH]^+$. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.62–2.15 (6H, m), 2.50 (3H, s), 3.22–3.65 (2H, m), 3.65–3.82 (1H, m), 4.45–4.72 (1H, m), 7.19 (5H, br s), 7.37 (1H, d, *J* = 15.6 Hz), 7.60 (2H, d, *J* = 8.6 Hz), 7.75–7.84 (3H, m), 7.80 (2H, d, *J* = 8.6 Hz), 8.22 (1H, d, *J* = 15.6 Hz), 8.56 (1H, s), 9.52 (1H, br s). Anal. Calcd for $C_{24}H_{27}ClN_6{\cdot}2HCl{\cdot}1.75H_2O$: C, 53.44; H, 6.07; N, 15.58. Found: C, 53.60; H, 5.90; N, 15.36.

6.1.57. 6-Methylquinazoline-2,4(1*H*,3*H*)-dione (10)

To a solution of **2c** (21.5 g, 0.142 mol) in H_2O (765 mL) and AcOH (17 mL) was added dropwise a solution of KOCN (26.0 g, 0.32 mol) at 30 °C over a period of 1 h. The reaction mixture was refluxed for 1.5 h and cooled to room temperature. NaOH (175 g, 4.36 mol) was added to the reaction mixture in several portions and the mixture was heated at 90 °C for 1 h. The reaction mixture was cooled to 0 °C and acidified by the addition of concd HCl. The precipitate that formed was collected by filtration, washed with water and dried under reduced pressure to give **10** (22.0 g, 87.8%) as pale yellow crystals. Mp 310–313 °C. FAB-MS *m*/*z* 177 $[MH]^+$. ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.32 (3H, s), 7.07 (1H, d, *J* = 8.4 Hz), 7.46 (1H, dd, *J* = 8.4, 1.8 Hz), 7.69 (1H, d, *J* = 1.8 Hz), 11.1 (1H, s), 11.2 (1H, s). Anal. Calcd for $C_9H_8N_2O_2{\cdot}0.1H_2O$: C, 60.74; H, 4.64; N, 15.74. Found: C, 60.68; H, 4.90; N, 15.75.

6.1.58. 2,4-Dichloro-6-methylquinazoline (11)

A solution of **10** (10.0 g, 56.8 mmol), phosphorus oxychloride (52.9 mL, 568 mmol) and *N*,*N*-dimethylaniline (3.6 mL, 28.4 mmol) was refluxed for 6 h and the reaction mixture was concentrated in vacuo. $CHCl_3$ was added to the residue and the mixture was washed with water. The extract was then dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography on silica gel with $CHCl_3$ as the eluent to give **11** (11.1 g, 91.7%) as colorless crystals. Mp 140–141 °C (lit. mp 138–140 °C[14b]). FAB-MS *m*/*z* 212 $[MH]^+$. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.62 (3H, s), 7.83 (1H, dd, *J* = 7.4, 1.0 Hz), 7.91 (1H, d, *J* = 7.4, Hz), 8.02 (1H, d, *J* = 1.0 Hz). Anal. Calcd for $C_9H_6Cl_2N_2$: C, 50.73; H, 2.84; N, 13.15. Found: C, 50.76; H, 2.76; N, 13.18.

6.1.59. *tert*-Butyl {(1*RS*,2*SR*)-2-[(2-chloro-6-methylquinazolin-4-yl)amino]cyclohexyl}carbamate (12)

To a solution of **11** (4.80 g, 22.5 mmol) in CH_2Cl_2 (100 mL) was added triethylamine (4.56 g, 45.1 mmol) and *cis*-2-(Boc-amino)cyclohexylamine (5.31 g, 24.8 mmol). The mixture was stirred at room temperature for 24 h and then concentrated in vacuo. The residue was combined with water, extracted with CH_2Cl_2 and dried over $MgSO_4$. Removal of solvent and purification by column chromatography on silica gel with $CHCl_3$/MeOH (30:1) as the eluent gave **12** (8.30 g, 99.2%) as colorless crystals. Mp 194–196 °C. FAB-MS *m*/*z* 391 $[MH]^+$. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.18–1.95 (7H, m), 1.52 (9H, s), 2.23–2.41 (1H, m), 2.43 (3H, s), 4.09 (2H, br s), 4.98 (1H, d, *J* = 6.6 Hz), 7.48 (1H, dd, *J* = 8.4, 1.8 Hz), 7.55 (1H, br s), 7.59 (1H, d, *J* = 8.4 Hz), 7.94 (1H, br s). Anal. Calcd for $C_{20}H_{27}ClN_4O_2{\cdot}0.2H_2O$: C, 60.89; H, 7.00; N, 14.20. Found: C, 60.91; H, 6.89; N, 14.14.

6.1.60. *tert*-Butyl {(1*R*,2*S*)-2-[(2-chloro-6-methylquinazolin-4-yl)amino]cyclohexyl}carbamate ((1*R*,2*S*)-12)

Compound (**1*R*,2*S*)-12** was prepared from **11** and (**1*R*,2*S*)-22** in a manner similar to that described for **12**. $[\alpha]_D^{20}$, +3.60 (*c* 0.50, MeOH).

6.1.61. *tert*-Butyl {(1*S*,2*R*)-2-[(2-chloro-6-methylquinazolin-4-yl)amino]cyclohexyl}carbamate ((1*S*,2*R*)-12)

Compound (**1*S*,2*R*)-12** was prepared from **11** and (**1*S*,2*R*)-22** in a manner similar to that described for **12**. $[\alpha]_D^{20}$, −3.60 (*c* 0.50, MeOH).

6.1.62. *tert*-Butyl [(1*RS*,2*SR*)-2-({2-[(4-methoxybenzyl)amino]-6-methylquinazolin-4-yl}amino)cyclohexyl]carbamate (13)

To a solution of **12** (8.0 g, 21.5 mmol) and 4-methoxybenzylamine (8.86 g, 64.2 mmol) in *N*-methyl-2-pyrrolidone (10 mL)

was added 4-dimethylaminopyridine (263 mg, 2.15 mmol), and the mixture was heated at 110 °C for 24 h. The mixture was diluted with 5% acetic acid solution and extracted with EtOAc. The organic layer was washed successively with water and brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel with $CHCl_3$/MeOH (20:1–10:1), followed by crystallization from *i*-Pr_2O to give **13** (9.63 g, 90.9%) as colorless crystals. Mp 170–171 °C. FAB-MS *m*/*z* 492 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.10–1.98 (7H, m), 1.51 (9H, s), 2.02–2.25 (1H, m), 2.38 (3H, s), 3.79 (3H, s), 3.96–4.27 (2H, m), 4.53 (1H, dd, *J* = 14.8, 6.0 Hz), 4.66 (1H, dd, *J* = 14.8, 6.0 Hz), 4.99–5.24 (2H, m), 6.85 (2H, d, *J* = 8.8 Hz), 6.95 (1H, br s), 7.31 (2H, d, *J* = 8.8 Hz), 7.33–7.45 (3H, m). Anal. Calcd for $C_{28}H_{37}N_5O_3$: C, 68.41; H, 7.59; N, 14.25. Found: C, 68.13; H, 7.60; N, 14.26.

6.1.63. *tert*-Butyl [(1*R*,2*S*)-2-({2-[(4-methoxybenzyl)amino]-6-methylquinazolin-4-yl}amino)cyclohexyl]carbamate ((1*R*,2*S*)-13)

Compound (**1*R*,2*S*)-13** was prepared from (**1*R*,2*S*)-12** in a manner similar to that described for **13**. $[\alpha]_D^{20}$, −23.60 (*c* 0.50, MeOH).

6.1.64. *tert*-Butyl [(1*S*,2*R*)-2-({2-[(4-methoxybenzyl)amino]-6-methylquinazolin-4-yl}amino)cyclohexyl]carbamate ((1*S*,2*R*)-13)

Compound (**1*S*,2*R*)-13** was prepared from (**1*S*,2*R*)-12** in a manner similar to that described for **13**. $[\alpha]_D^{20}$, +23.60 (*c* 0.50, MeOH).

6.1.65. (1*RS*,2*SR*)-2-[(2-Amino-6-methylquinazolin-4-yl)amino]-cyclohexylamine (14)

A mixture of **13** (9.37 g, 19.1 mmol) in trifluoroacetic acid (95 mL) was stirred at room temperature for 72 h and then concentrated in vacuo. Sat. $NaHCO_3$ solution was added to the residue and the mixture was extracted with $CHCl_3$/MeOH (30:1) and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on Fuji Silysia NH silica gel with $CHCl_3$ as the eluent and crystallized from EtOAc to give **14** (4.60 g, 89.0%) as colorless crystals. Mp 149–150 °C. FAB-MS *m*/*z* 272 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.10–1.95 (10H, m), 2.42 (3H, s), 3.13–3.22 (1H, m), 4.16–4.32 (1H, m), 4.72 (2H, br s), 6.46 (1H, d, *J* = 8.4 Hz), 7.28–7.42 (3H, m). Anal. Calcd for $C_{15}H_{21}N_5 \cdot 0.23H_2O$: C, 65.39; H, 7.85; N, 25.42. Found: C, 65.71; H, 7.76; N, 25.05.

6.1.66. (1*R*,2*S*)-2-[(2-Amino-6-methylquinazolin-4-yl)amino]-cyclohexylamine ((1*R*,2*S*)-14)

Compound (**1*R*,2*S*)-14** was prepared from (**1*R*,2*S*)-13** in a manner similar to that described for **14**. $[\alpha]_D^{20}$, −7.59 (*c* 0.50, MeOH).

6.1.67. (1*S*,2*R*)-2-[(2-Amino-6-methylquinazolin-4-yl)amino]-cyclohexylamine ((1*S*,2*R*)-14)

Compound (**1*S*,2*R*)-14** was prepared from (**1*S*,2*R*)-13** in a manner similar to that described for **14**. $[\alpha]_D^{20}$, +7.59 (*c* 0.50, MeOH).

6.1.68. *N*-{(1*RS*,2*SR*)-2-[(2-Amino-6-methylquinazolin-4-yl)-amino]cyclohexyl}-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidine (15)

To a solution of **14** (4.53 g, 16.7 mmol) in CH_2Cl_2 (90 mL) was added *N*,*N*′-bis-Boc-1*H*-pyrazole-1-carboxyamidine (5.18 g, 16.7 mmol), and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with water, extracted with CH_2Cl_2 and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on Fuji Silysia NH silica gel with $CHCl_3$ as the eluent and crystallized from *i*-Pr_2O–hexane to give **15** (8.50 g, 99.2%) as colorless crystals. Mp 175–178 °C. FAB-MS *m*/*z* 513 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.30–1.86 (7H, m), 1.44 (9H, s), 1.47 (9H, s), 2.02–2.23 (1H, m), 2.42 (3H, s), 4.44–4.68 (2H, m), 4.81 (2H, br s), 6.32 (1H, d, *J* = 5.8 Hz), 7.23 (1H, s), 7.31 (1H, d, *J* = 8.6 Hz), 7.37 (1H, dd, *J* = 8.6, 1.4 Hz), 8.74 (1H, d, *J* = 8.0 Hz), 11.4 (1H, br s). Anal. Calcd for $C_{26}H_{39}N_7O_4 \cdot 0.3H_2O$: C, 60.17; H, 7.69; N, 18.89. Found: C, 60.11; H, 7.53; N, 19.06.

6.1.69. *N*-{(1*R*,2*S*)-2-[(2-Amino-6-methylquinazolin-4-yl)-amino]cyclohexyl}-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidine ((1*R*,2*S*)-15)

Compound (**1*R*,2*S*)-15** was prepared from (**1*R*,2*S*)-14** in a manner similar to that described for **15**. $[\alpha]_D^{20}$, −12.80 (*c* 0.50, MeOH).

6.1.70. *N*-{(1*S*,2*R*)-2-[(2-Amino-6-methylquinazolin-4-yl)-amino]cyclohexyl}-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidine ((1*S*,2*R*)-15)

Compound (**1*S*,2*R*)-15** was prepared from (**1*S*,2*R*)-14** in a manner similar to that described for **15**. $[\alpha]_D^{20}$, +12.40 (*c* 0.50, MeOH).

6.1.71. *N*-[(1*RS*,2*SR*)-2-({2-[(4-Chlorophenyl)carbonyl]amino-6-methylquinazolin-4-yl}amino)cyclohexyl]-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidine (16)

To a solution of *N*,*N*-diisopropylethylamine (8.70 mL, 50.0 mmol) in CH_2Cl_2 (40 mL) was added 4-dimethylaminopyridine (407 mg, 3.33 mmol) and 4-chlorobenzoyl chloride (4.21 mL, 33.1 mmol), and the mixture was stirred at room temperature for 0.5 h. A solution of **15** (8.50 g, 16.7 mmol) in CH_2Cl_2 (50 mL) was added dropwise and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with water, extracted with CH_2Cl_2 and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on Fuji Silysia NH silica gel with hexane/EtOAc (2:1) as the eluent. The resulting amorphous residue was crystallized from *i*-Pr_2O, collected by filtration, and dried in vacuo to give **16** (9.68 g, 89.0%) as colorless crystals. Mp 213−215 °C. FAB-MS *m*/*z* 652 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.12–1.94 (7H, m), 1.42 (9H, s), 1.48 (9H, s), 2.16–2.35 (1H, m), 2.47 (3H, s), 4.34–4.51 (1H, m), 4.57–4.72 (1H, m), 6.69 (1H, br s), 7.35 (1H, s), 7.44 (2H, d, *J* = 10.0 Hz), 7.42–7.65 (3H, m), 8.02 (2H, d, *J* = 10.0 Hz), 8.86 (1H, d, *J* = 8.0 Hz), 11.4 (1H, br s). Anal. Calcd for $C_{33}H_{42}ClN_7O_5 \cdot 0.25i\text{-}Pr_2O$: C, 61.14; H, 6.77; N, 14.13. Found: C, 60.99; H, 6.79; N, 14.47.

6.1.72. *N*-[(1*R*,2*S*)-2-({2-[(4-Chlorophenyl)carbonyl]amino-6-methylquinazolin-4-yl}amino)cyclohexyl]-*N*′,*N*″-bis(*tert*butoxycarbonyl)guanidine ((1*R*,2*S*)-16)

Compound (**1*R*,2*S*)-16** was prepared from (**1*R*,2*S*)-15** in a manner similar to that described for **16**. $[\alpha]_D^{20}$, −16.39 (*c* 0.50, MeOH).

6.1.73. *N*-[(1*S*,2*R*)-2-({2-[(4-Chlorophenyl)carbonyl]amino-6-methylquinazolin-4-yl}amino)cyclohexyl]-*N*′,*N*″-bis(*tert*-butoxycarbonyl)guanidine ((1*S*,2*R*)-16)

Compound (**1*S*,2*R*)-16** was prepared from (**1*S*,2*R*)-15** in a manner similar to that described for **16**. $[\alpha]_D^{20}$, +16.80 (*c* 0.50, MeOH).

6.1.74. *N*-[(1*RS*,2*SR*)-2-({2-[(4-Chlorophenyl)carbonyl]amino-6-methylquinazolin-4-yl}amino)cyclohexyl]guanidine dihydrochloride (17)

To a solution of **16** (9.50 g, 14.6 mmol) in MeOH (40 mL) and $CHCl_3$ (30 mL) was added 4 N HCl in EtOAc (95 mL), and the mixture was heated at 50 °C for 24 h. The resulting precipitate was collected by filtration, washed successively with *i*-PrOH and Et_2O, and dried under reduced pressure, to give **17** (4.20 g, 54.9%) as colorless crystals. Mp 235–238 °C. FAB-MS *m*/*z* 452 $[MH]^+$. ^1H NMR (200 MHz, DMSO-d_6) δ: 1.36–1.99 (7H, m), 2.03–2.31 (1H, m), 2.51 (3H, s), 4.41–4.78 (1H, m), 4.51–4.55 (1H, m), 7.28 (5H, br s), 7.72 (2H, d, *J* = 8.8 Hz), 7.82 (1H, d, *J* = 8.4 Hz), 8.04 (1H, d, *J* = 8.4 Hz), 8.20 (2H, d, *J* = 8.8 Hz), 8.33 (1H, d, *J* = 9.2 Hz), 8.68 (1H, s), 9.57 (1H, d, *J* = 7.4 Hz), 12.4 (1H, br s). Anal. Calcd for

$C_{23}H_{26}ClN_7O{\cdot}2HCl{\cdot}H_2O$: C, 50.89; H, 5.57; N, 18.06. Found: C, 50.74; H, 5.76; N, 18.07.

6.1.75. *N*-[(1*R*,2*S*)-2-({2-[(4-Chlorophenyl)carbonyl]amino-6-methylquinazolin-4-yl}amino)cyclohexyl]guanidine dihydrochloride ((1*R*,2*S*)-17)

Compound (**1*R*,2*S*)-17** was prepared from (**1*R*,2*S*)-16** in a manner similar to that described for **17**. $[\alpha]_D^{20}$, −51.20 (*c* 0.50, MeOH).

6.1.76. *N*-[(1*S*,2*R*)-2-({2-[(4-Chlorophenyl)carbonyl]amino-6-methylquinazolin-4-yl}amino)cyclohexyl]guanidine dihydrochloride ((1*S*,2*R*)-17)

Compound (**1*S*,2*R*)-17** was prepared from (**1*S*,2*R*)-16** in a manner similar to that described for **17**. $[\alpha]_D^{20}$, +51.20 (*c* 0.50, MeOH).

6.1.77. *tert*-Butyl [(1*R*,2*R*)-2-(benzyloxy)cyclohexyl]carbamate ((1*R*,2*R*)-19)

To a solution of (**1*R*,2*R*)-18** (19.4 g, 94.5 mmol) in $CHCl_3$ (200 mL) was added di-*tert*-butyl dicarbonate (20.6 g, 94.5 mmol) in $CHCl_3$ (100 mL) dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 15 h. After concentration under reduced pressure, the residue was purified by silica gel column chromatography with hexane/EtOAc (3:1) as the eluent to give (**1*R*,2*R*)-19** (28.0 g, 96.7%) as colorless crystals. Mp 115–116 °C. FAB-MS *m*/*z* 306 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.06–1.52 (4H, m), 1.45 (9H, s), 1.54–1.82 (2H, m), 2.00–2.18 (2H, m), 3.15 (1H, dt, *J* = 9.0, 4.0 Hz), 3.21–3.60 (1H, m), 4.46 (1H, d, *J* = 12.2 Hz), 4.48 (1H, br s), 4.59 (1H, d, *J* = 12.2 Hz), 7.21–7.42 (5H, m). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.68; H, 8.78; N, 4.66. $[\alpha]_D^{20}$, −11.20 (*c* 0.50, MeOH).

6.1.78. *tert*-Butyl [(1*S*,2*S*)-2-(benzyloxy)cyclohexyl]carbamate ((1*S*,2*S*)-19)

Compound (**1*S*,2*S*)-19** was prepared from (**1*S*,2*S*)-18** in a manner similar to that described for (**1*R*,2*R*)-19**. $[\alpha]_D^{20}$, +11.60 (*c* 0.50, MeOH).

6.1.79. *tert*-Butyl [(1*R*,2*R*)-2-hydroxycyclohexyl]carbamate ((1*R*,2*R*)-20)

A mixture of (**1*R*,2*R*)-19** (28.0 g 91.7 mmol) and 10% palladium on carbon (water 50%, 6.0 g) in MeOH (300 mL) was stirred under 4 atm of hydrogen at room temperature for 48 h. The catalyst was filtered through a pad of Celite and the filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/EtOAc (2:1) as the eluent to give (**1*R*,2*R*)-20** (17.2 g, 87.1%) as colorless crystals. Mp 111–112 °C. FAB-MS *m*/*z* 216 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.02–1.42 (4H, m), 1.44 (9H, s), 1.61–1.77 (2H, m), 1.86–2.10 (2H, m), 3.29 (3H, br s), 4.60 (1H, br s). Anal. Calcd for $C_{11}H_{21}NO_3$: C, 61.37; H, 9.83; N, 6.51. Found: C, 61.20; H, 9.80; N, 6.53. $[\alpha]_D^{20}$, –19.19 (*c* 0.50, MeOH).

6.1.80. *tert*-Butyl [(1*S*,2*S*)-2-hydroxycyclohexyl]carbamate ((1*S*,2*S*)-20)

Compound (**1*S*,2*S*)-20** was prepared from (**1*S*,2*S*)-19** in a manner similar to that described for (**1*R*,2*R*)-20**. $[\alpha]_D^{20}$, +19.19 (*c* 0.50, MeOH).

6.1.81. *tert*-Butyl [(1*R*,2*S*)-2-(phthalimidoyl)cyclohexyl]-carbamate ((1*R*,2*S*)-21)

To a stirred solution of (**1*R*,2*R*)-20** (13.5 g, 62.7 mmol), phthalimide (13.8 g, 94.1 mmol) and triphenylphosphine (24.7 g, 94.1 mmol) in tetrahydrofuran (THF; 300 mL) was added diethyl azodicarboxylate (40% in toluene; 14.8 mL, 94.1 mmol) dropwise at 0 °C under an argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 3 h. The solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel with hexane/EtOAc (4:1) as the eluent to give (**1*R*,2*S*)-21** (13.1 g, 60.6%) as colorless crystals. Mp 132–133 °C. FAB-MS *m*/*z* 345 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.12–1.75 (5H, m), 1.28 (9H, s), 1.80–2.01 (2H, m), 2.71 (1H, dd, *J* = 12.4, 3.2 Hz), 4.00–4.12 (1H, m), 4.26 (1H, td, *J* = 13.2, 4.0 Hz), 5.41 (1H, d, *J* = 8.4 Hz), 7.64–7.86 (4H, m). Anal. Calcd for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.17; H, 6.81; N, 8.25. $[\alpha]_D^{20}$, −27.19 (*c* 0.50, MeOH).

6.1.82. *tert*-Butyl [(1*S*,2*R*)-2-(phthalimidoyl)cyclohexyl]-carbamate ((1*S*,2*R*)-21)

Compound (**1*S*,2*R*)-21** was prepared from (**1*S*,2*S*)-20** in a manner similar to that described for (**1*R*,2*S*)-21**. $[\alpha]_D^{20}$, +27.19 (*c* 0.50, MeOH).

6.1.83. *tert*-Butyl [(1*R*,2*S*)-2-aminocyclohexyl]carbamate ((1*R*,2*S*)-22)

A solution of (**1*R*,2*S*)-21** (12.7 g, 36.8 mmol) and hydrazine hydrate (2.76 g, 55.23 mmol) in EtOH (350 mL) was heated at reflux for 2 h and the reaction mixture was concentrated in vacuo. Sodium hydroxide (10%) was added to the residue, which was then extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4 and concentrated to give (**1*R*,2*S*)-22** (7.80 g, 98.8%) as a pale yellow oil. Analytical data were taken on the maleic acid salt (colorless crystals). Mp 181–183 °C. FAB-MS *m*/*z* 216 $[MH]^+$. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.41 (9H, s), 1.46–2.05 (8H, m), 3.47–3.64 (1H, m), 3.89–4.11 (1H, m), 5.87 (1H, d, *J* = 7.0 Hz), 6.25 (2H, s), 8.10 (4H, br s). Anal. Calcd for $C_{11}H_{22}N_2O_2{\cdot}C_4H_4O_4$: C, 54.53; H, 7.93; N, 8.48. Found: C, 54.20; H, 8.01; N, 8.45. $[\alpha]_D^{20}$, −2.00 (*c* 0.50, MeOH).

6.1.84. *tert*-Butyl [(1*S*,2*R*)-2-aminocyclohexyl]carbamate ((1*S*,2*R*)-22)

Compound (**1*S*,2*R*)-22** was prepared from (**1*S*,2*R*)-21** in a manner similar to that described for (**1*R*,2*S*)-22**. Optical rotation was measured on the maleic acid salt. $[\alpha]_D^{20}$, +2.00 (*c* 0.50, MeOH).

6.2. Biological procedures

6.2.1. Receptor binding assays

Competitive binding displacement analysis of ORL1 was performed with membranes prepared from CHO-K1 cells stably expressing human ORL1 with [^{3}H]nociceptin (PerkinElmer Life Sciences) as the radioligand. Competitive binding displacement analysis of μ opioid receptors was performed with membranes prepared from CHO-K1 cells stably expressing the rat or human μ opioid receptor (Receptor Biology) with [^{3}H]diprenorphine (PerkinElmer Life Sciences) as the radioligand. Competitive binding displacement analysis of the δ and κ opioid receptors was performed with membranes prepared from CHO-K1 cells stably expressing the rat δ or κ opioid receptor with [^{3}H]diprenorphine as the radioligand. Nonspecific binding was defined as the binding observed in the presence of unlabeled nociceptin (ORL1), naloxone (μ opioid receptor), naltrindole (δ opioid receptor), or naloxone benzoylhydrazone (κ opioid receptor). Binding assays were carried out at 25 °C for 1 h in 50 mM Tris–HCl, pH 7.8, containing 5 mM $MgCl_2$, 1 mM ethylene glycol-bis(2-aminoethylether)-*N*,*N*,*N*′,*N*′-tetraacetic acid, and 0.1% bovine serum albumin. After incubation, samples were collected on GF/B glass-fiber filters presoaked in 0.3% polyethyleneimine, washed with 50 mM Tris–HCl, pH 7.5, and counted for radioactivity.

6.2.2. Inhibition of cAMP accumulation in CHO-K1 cells by (1*R*,2*S*)-17

CHO-K1 cells stably expressing human ORL1 were incubated for 5 min at 37 °C in 5% CO_2 in Krebs-Henselet Solution (10 mM NaCl, 0.59 mM KCl, 0.25 mM $CaCl_2$, 0.12 mM $MgCl_2$, 0.12 mM NaH_2PO_4,

25 mM $NaHCO_3$, and 11.5 mM glucose, pH 7.4) containing 0.5 mM 3-isobutyl-1-methylxanthine. Then a mixture containing forskolin and (**1*R*,2*S*)-17** with or without nociceptin was added to the cells to give final concentrations of 3 μM forskolin and 1–1000 nM (**1*R*,2*S*)-17**. After incubation for 10 min at 37 °C in 5% CO_2, the culture supernatant was removed and the cells were lysed with the lysis reagent supplied with the cAMP EIA System enzyme immunoassay kit (GE Healthcare). Intracellular cAMP levels were measured on the same day with the immunoassay kit according to the manufacturer's instructions.

6.3. Molecular modeling

All computation was done with MOE version 2006.08 (Chemical Computing Group, Inc.). A 3D model of ORL1 was prepared by using the X-ray crystallographic structure of bovine rhodopsin (Protein Data Bank code 1HZX) as a template. The sequences of ORL1 (Swiss-Prot Accession No. P41146) and bovine rhodopsin were aligned as described by Topham et al.[22] A set of 10 intermediate homology models was generated with the Homology module, and each intermediate was minimized to an energy gradient of 0.01 kcal mol^{-1} $Å^{-1}$. The quality of the models generated was validated by using the Protein Report module, and the model with the lowest energy was selected for further study. (**1*R*,2*S*)-17** was manually docked into the binding site of ORL1 by rotating around the single bonds of (**1*R*,2*S*)-17** and the side chains of the ligand-contacting amino acids in the binding site. Energy minimization was performed with the MMFF94x force field[23] implemented in MOE. Compound (**1*R*,2*S*)-17** and the amino acids within 7 Å of it were energy-minimized until the root-mean-square gradient of the potential energy was less than 0.1 kcal mol^{-1} $Å^{-1}$. The figures were prepared with PyMOL version 0.99 (DeLano Scientific).

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