Polycyclic *N*-Heterocyclic Compounds. Part 62[1]: Reaction of *N*-(Quinazolin-4-yl)amidine Derivatives with Hydroxylamine Hydrochloride and Anti-platelet Aggregation Activity of the Products

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The reactions of *N*-(5,6,7,8-tetrahydroquinazolin-4-yl)amidines and their amide oximes with hydroxylamine hydrochloride gave abnormal cyclization products *via* a ring cleavage of pyrimidine component accompanied with a ring closure of 1,2,4-oxadiazole to give *N*-[2-([1,2,4]oxadiazol-5-yl)cyclohexen-1-yl]formamide oximes. Similarly, *N*-(quinazolin-4-yl)amidines reacted with hydroxylamine hydrochloride gave the same results. The evaluation of inhibitory activities against platelet aggregation *in vitro* is also described to show one derivative has potent activity.

Key words rearrangement; 1,2,4-oxadiazole; anti-platelet aggregation; *N*-(quinazolin-4-yl)amidine; amide oxime; hydroxylamine hydrochloride

3,5-Disubstituted 1,2,4-oxadiazole is a well utilized scaffold for medicinal chemistry. A class of 3,5-diphenyl-1,2,4-oxadiazole based compounds have been identified as potent sphingosine-1-phosphate-1 ($S1P_1$) receptor agonists with minimal affinity for the $S1P_2$ and $S1P_3$ receptor subtypes.[2] Another derivative, 5-(3-chlorothiophen-2-yl)-3-(5-chloropyridin-2-yl)-1,2,4-oxadiazole has been identified as a novel apoptosis inducer.[3] These two examples demonstrate the potential of 3,5-disubstituted 1,2,4-oxadiazole use in the development of new pharmaceutics.

1,2,4-Oxadiazoles[4] are usually prepared by 1) Paal–Knorr type ring closure of *O*-acylamide oximes,[5] 2) reaction of imide equivalents with NH_2OH,[6] 3) ring closure of *N*-acyl *N*′-substituted amidines,[7] or 4) 1,3-dipolar cycloaddition of nitriles and nitrile oxides.[8] Additionally, we have reported the pyrimidine ring opening reaction accompanying the formation of the 1,2,4-oxadiazole ring to give *N*-[2-([1,2,4]oxadiazol-5-yl)cycloalken-1-yl]formamide oximes (**1**) by the reaction of tricyclic *N*-(aliphatic ring-fused pyrimidin-4-yl)amidine (**2**) or its amide oxime with hydroxylamine hydrochloride (Fig. 1).[9—12] In this paper, we applied this reaction to one of the bicyclic *N*-(aliphatic (or aromatic) ring-fused pyrimidin-4-yl)amidines, *i.e.* *N*-(5,6,7,8-tetrahydroquinazolin-4-yl)amidines (**3**) and *N*-(quinazolin-4-yl)-amidines (**4**). Since current antiplatelet drugs are known to have certain detrimental side effects and reduced efficacy, we tested these new analogues for anti-platelet aggregation activity.

Results and Discussion

Chemistry First, we dealt with the aliphatic ring-fused amidines (**3**). As shown in Chart 1, the requisite amidine **3** starting materials were synthesized by previously reported methods.[10—12] Amidines **3a**, **b** were prepared by the reaction of 4-amino-5,6,7,8-tetrahydroquinazoline (**5**) with commercially available *N*,*N*-dimethylformamide (or acetamide) dimethyl acetal in refluxing toluene. Other amidines **3c**—**g** were produced by the reaction of compound **5** with the Vilsmeier reagent prepared from the corresponding *N*,*N*-dimethylamide and phosphoryl chloride.

When a hydrogen is attached to the amidine moiety (R=H) the reaction of **3a** with 1.2 eq of hydroxylamine hydrochloride in methanol at room temperature gave the amide oxime (**6a**, 80% yield). **6a** was converted to the desired 1,2,4-oxadiazole derivative **7a** (22% yield) by reaction with 6 eq of hydroxylamine hydrochloride in a refluxing methanol (Chart 1).

In the ^{1}H-NMR spectrum of **7a**, a characteristic formamide oxime one-proton doublet (J=10.0 Hz) appeared at 7.47 ppm coupled with an adjacent NH proton (J=10.0 Hz) which was D_2O exchangeable. The formamide oxime signal changed to a singlet in the presence of D_2O. While the **6a**

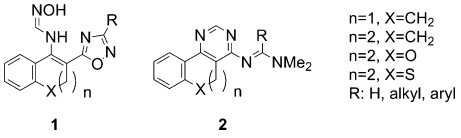

Fig. 1. Substrates (**2**) and Their Rearranged Products (**1**)

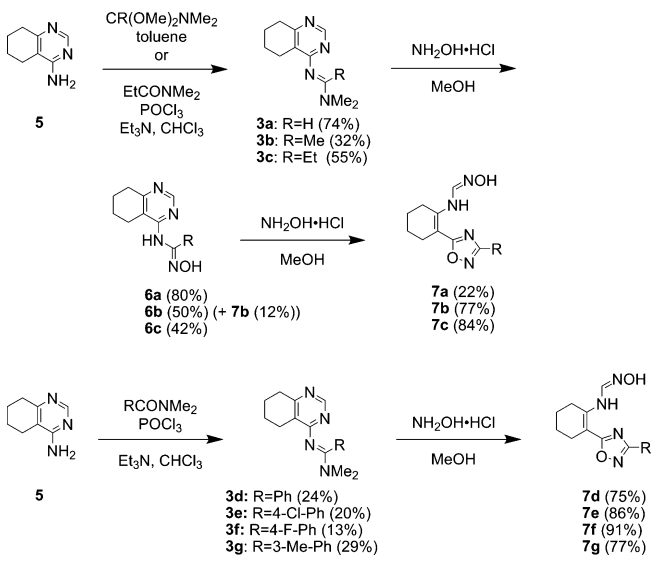

Chart 1. Synthesis of **7**

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one-proton singlet at H-2 (pyrimidine ring) disappeared. One 1,2,4-oxadiazole ring proton was observed at 8.99 ppm as a singlet. These results suggest that pyrimidine ring cleavage and 1,2,4-oxadiazole ring closure occurred when **6a** reacted with hydroxylamine hydrochloride.

Reacting alkyl group substituted amidine moieties (R=Me and Et) **3b** and **3c** with 1.1—1.2 eq of hydroxylamine hydrochloride in methanol at room temperature gave alkyl amide oximes **6b** (50%) and **6c** (42%), respectively. In the case of **3b**, we also obtained the minor product **7b** (12%). **6b** and **6c** were also converted to the desired 1,2,4-oxadiazole derivative **7b** (77%) and **7c** (84%) by reaction with 1.5—2 eq of hydroxylamine hydrochloride in methanol at room temperature.

Aryl group substituted amidine moieties **3d**—**g** needed an excess amount of hydroxylamine hydrochloride to consume starting materials completely. When 4.6—6 eq of hydroxylamine hydrochloride were used the reaction did not produce amide oximes (**6d**—**g**), but gave the desired oxadiazole **7d**—**g**.

A tentative explanation for this reactivity difference is as follows. All amide oximes (**6**) are expected to dominantly consist of the less sterically hindered (*E*)-oximes (Fig. 2).[13] Isomerization of (*E*)-oximes to (*Z*)-oximes must occur to allow ipso attack of the oxime hydroxy group on the pyrimidine ring to start this rearrangement reaction.[10—12] In the case of hydrogen or alkyl substituted **6a**—**c**, this (*E*)-oxime is rather stable. On the other hand, aryl substituents of **6d**—**g** caused (*Z*)-oxime isomerization due to their steric repulsion creating the **7d**—**g**.

After our work with aliphatic ring-fused amidines, we focused our attention on the aromatic ring-fused amidines (**4**). As shown in Chart 2, the requisite amidines **4** starting materials were synthesized by the same method as described above for amidines **3**.

When a hydrogen is attached to the amidine moiety (R=H) the reaction of **4a** with 1.2 eq of hydroxylamine hydrochloride at room temperature gave the 1,2,4-oxadiazole derivative **10a** (36%) instead of the amide oxime **9a**. This result was quite different compared to the case of *N*-(aliphatic ring-fused pyrimidin-4-yl)formamidines (**2**, **3**).[10—12] In those cases, the amide oximes were obtained when a hydrogen or alkyl group is attached to the amidine moiety. Therefore, in the present study the fused benzene moiety of quinazoline affected the reactivity by facilitating the nucleophilic attack of amide oxime (**9**) to quinazoline ring. This increased nucleophilic attack lead to a ring-cleavage and ring-closure reaction to give the 1,2,4-oxadiazole derivatives (**10a**). This assumption is supported by lowest unoccupied molecular orbital (LUMO) energy level comparison of **6a** and **9a**. Calculated LUMO energy of **6a** is −0.6795 eV, whilst that of **9a** is −1.5788 eV.[13] Therefore, it is reasonable that **9a** is more susceptible for nucleophilic attack of amide oxime, because **9a** is too unstable to isolate.

Amidines with alkyl groups substituted in the amidine moiety **4b**, **c** also gave the desired oxadiazole **10b**, **c** in 65% and 76%, respectively, when reacted with 1.5—2 eq of hydroxylamine hydrochloride. Finally, aryl group substituted amidines **4d**—**g** also gave the desired oxadiazole **10d**—**g** when reacted with the 5—10 eq of hydroxylamine hydrochloride.

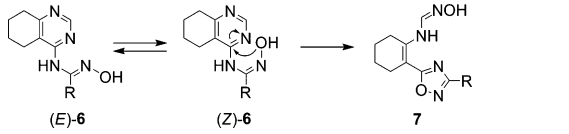

Fig. 2. (*E*,*Z*)-Isomerization of **6**

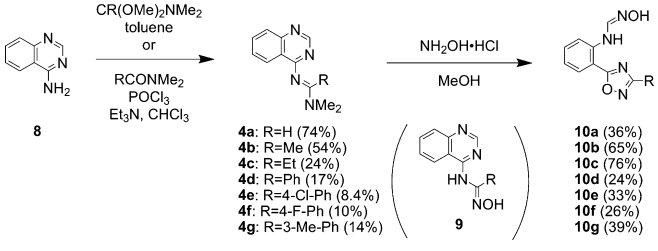

Chart 2. Synthesis of **10**

Biology Atherothrombosis is characterized by a quick and unexpected burst of an atherosclerotic plaque and following occlusive thrombus formation. It is the main cause of acute ischemic syndromes such as acute coronary syndrome or ischemic stroke, which are the major cause of death in the developed world. The most critical step of these diseases is platelet activation and aggregation, therefore antiplatelet drugs are used to protect and treat acute ischemic syndromes. Because current antiplatelet drugs can have detrimental side effects and have low efficacy, we have been exploring antiplatelet aggregation agents as possible new drugs.[14—21] The inhibitory activities of compounds **7a**—**g** and **10a**—**g** against platelet aggregation induced by arachidonic acid was assayed to demonstrate the possible therapeutic nature of these compounds.

The inhibitory assay was executed by a turbidimetric method developed by Born and Cross[22] using an aggregometer. As shown in Table 1, comparison of the inhibition rate of **7a**—**g** at a final concentration of 30 μM with that of Cilostazol[23] revealed that the 4-chlorophenyl derivative **7e** (75.2%) had potency comparable to Cilostazol (96.5%). Interestingly, neither phenyl derivative **7d** nor 4-fluorophenyl derivative **7f** showed any significant inhibitory activity against platelet aggregation. In addition, none of compounds **10a**—**g** at a final concentration of 30 μM showed any significant inhibition of platelet aggregation.

In summary, we have developed a method for synthetically

Table 1. Effects of **7a**—**g** and **10a**—**g** on Rabbit Platelet Aggregation *in Vitro*

Compound	% inhibition	Compound	% inhibition
7a	−0.9±18.3	**10a**	13.9±3.3
7b	42.6±14.8	**10b**	−2.5±1.8
7c	13.7±27.8	**10c**	8.8±8.3
7d	16.5±13.3	**10d**	−20.5±25.1
7e	75.2±10.8*	**10e**	13.0±9.6
7f	3.6±2.6	**10f**	−6.0±9.7
7g	10.7±9.6	**10g**	14.2±3.2
Cilostazol	96.5±1.3*		

Data represent % inhibition of the vehicle control group (mean±S.E. of 3 experiments). * Means significantly different from the vehicle control group at $p<0.01$ (Dunnett's multiple range test).

producing various *N*-[2-(3-alkyl(or aryl)[1,2,4]oxadiazol-5-yl)cyclohexen-1-yl (or phenyl)]formamide oximes (**7**, **10**) through the reaction of *N*-(5,6,7,8-tetrahydroquinazolin-4-yl)amidines (**3**) or *N*-(quinazolin-4-yl)amidines (**4**) with hydroxylamine hydrochloride *via* a ring cleavage of a pyrimidine component accompanied with a ring closure of 1,2,4-oxadiazole. Compound **7e** showed considerable inhibitory activity against platelet aggregation comparable to clinically used Cilostazol. We are currently exploring their structure–activity relationships for further elucidation of anti-platelet aggregation compounds.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The FAB-mass and EI-mass spectra were obtained on a VG 70 mass spectrometer and *m*-nitrobenzyl alcohol or glycerol was used as the matrix. The IR spectra were recorded on a Japan Spectroscopic FT/IR-200 spectrophotometer with KBr and frequencies are expressed in cm^{-1}. The ^{1}H-NMR spectra were recorded on a Varian VXR-200 instrument operating at 200 MHz with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ) and J values in Hz, and the signals are designated as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; br, broad; m, multiplet. Column chromatography was performed on silica gel (IR-60-63-210-W, Daiso) or aluminium oxide active neutral (Merck). TLC was carried out on Kieselgel 60F254 (Merck).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(5,6,7,8-tetrahydroquinazolin-4-yl)formamidine (3a)** 4-Amino-5,6,7,8-tetrahydroquinazoline (**5**, 400 mg, 2.68 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (383 mg, 3.21 mmol) in dry toluene (40 ml) was refluxed for 9 h. After evaporation of reaction mixture, the residue was recrystallized from *n*-hexane to give **3a** (408 mg, 74%) as colorless needles, mp 67—69 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.86 (4H, m, H-6, 7), 2.74 (4H, m, H-5, 8), 3.13 (6H, s, NMe_2), 8.52, 8.54 (each 1H, each s, H-2, C<u>H</u>NMe_2). FAB-MS *m*/*z*: 205 (MH^+). *Anal.* Calcd for $C_{11}H_{16}N_4$: C, 64.68; H, 7.89; N, 27.43. Found: C, 64.54; H, 7.74; N, 27.36.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(5,6,7,8-tetrahydroquinazolin-4-yl)acetamidine (3b)** **5** (400 mg, 2.68 mmol) and *N*,*N*-dimethylacetamide dimethyl acetal (535 mg, 4.02 mmol) in dry toluene (40 ml) was refluxed for 33 h. After evaporation of reaction mixture, the residue was purified by neutral alumina column chromatography (ethyl acetate/*n*-hexane, 1 : 2) to give **3b** (189.6 mg, 32%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.82 (4H, m, H-6, 7), 2.04 (3H, s, Me), 2.50 (2H, t, J=5.7 Hz, H-5), 2.78 (2H, t, J=5.7 Hz, H-8), 3.09 (6H, s, NMe_2), 8.57 (1H, s, H-2). FAB-MS *m*/*z*: 219 (MH^+). *Anal.* Calcd for $C_{12}H_{18}N_4 \cdot 0.5H_2O$: C, 63.41; H, 8.43; N, 24.65. Found: C, 63.57; H, 8.10; N, 24.56.

General Procedure for the Preparation of 3c—g To a solution of **5** in dry $CHCl_3$ (*ca.* 20 ml) were added *N*,*N*-dimethylalkyl (or aryl) amide, $POCl_3$, and triethylamine sequentially, and the reaction mixture was refluxed. Water was added, and then it was made basic with sat. $NaHCO_3$ aq., then extracted with $CHCl_3$. The organic phase was washed with sat. brine, dried over Na_2SO_4, then evaporated *in vacuo*. The residue was purified by column chromatography and/or recrystallization to give **3**.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(5,6,7,8-tetrahydroquinazolin-4-yl)propionamidine (3c)** To a dry $CHCl_3$ solution of **5** (2.00 g, 13.4 mmol) were added *N*,*N*-dimethylpropionamide (1.49 g, 14.7 mmol), $POCl_3$ (1.90 ml, 20.4 mmol), and triethylamine (4.15 ml, 29.8 mmol) sequentially, and the reaction mixture was refluxed for 35 h. After the workup procedure described above, the residue was purified by neutral alumina column chromatography (ethyl acetate/*n*-hexane, 1 : 3) to give **3c** (1.72 g, 55%) as colorless fine crystals, mp 48—50 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, t, J=7.7 Hz, Me), 1.83 (4H, m, H-6, 7), 2.48 (4H, m, H-5, –C<u>H</u>$_2$Me), 2.78 (2H, t, J=5.8 Hz, H-8), 3.08 (6H, s, NMe_2), 8.57 (1H, s, H-2). FAB-MS *m*/*z*: 233 (MH^+). *Anal.* Calcd for $C_{13}H_{20}N_4 \cdot 0.25H_2O$: C, 65.93; H, 8.72; N, 23.66. Found: C, 66.17; H, 8.50; N, 23.73.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(5,6,7,8-tetrahydroquinazolin-4-yl)benzamidine (3d)** To a dry $CHCl_3$ solution of **5** (180 mg, 1.21 mmol) were added *N*,*N*-dimethylbenzamide (180 mg, 1.21 mmol), $POCl_3$ (0.12 ml, 1.29 mmol), and triethylamine (0.55 ml, 3.94 mmol) sequentially, and the reaction mixture was refluxed for 24 h. After the workup procedure described above, the residue was purified by silica gel column chromatography (acetone/*n*-hexane, 1 : 3), then recrystallized from ethyl acetate–*n*-hexane to give **3d** (82.8 mg, 24%) as colorless fine crystals, mp 119—120 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.79 (4H, m, H-6, 7), 2.55 (2H, m, H-5), 2.78 (2H, m, H-8), 3.10 (6H, br s, NMe_2), 7.15—7.35 (5H, m, Ph), 8.26 (1H, s, H-2). FAB-MS *m*/*z*: 281 (MH^+). *Anal.* Calcd for $C_{17}H_{20}N_4$: C, 72.83; H, 7.19; N, 19.98. Found: C, 72.48; H, 7.01; N, 19.91.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(5,6,7,8-tetrahydroquinazolin-4-yl)-4-chlorobenzamidine (3e)** To a dry $CHCl_3$ solution of **5** (300 mg, 2.01 mmol) were added *N*,*N*-dimethyl-4-chlorobenzamide (442 mg, 2.41 mmol), $POCl_3$ (0.28 ml, 3.00 mmol), and triethylamine (1.00 ml, 7.17 mmol) sequentially, and the reaction mixture was refluxed for 24 h. After the workup procedure described above, the residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane, 1 : 1) to give **3e** (123.7 mg, 20%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.80 (4H, m, H-6, 7), 2.55 (2H, m, H-5), 2.80 (2H, m, H-8), 3.10 (6H, br s, NMe_2), 7.15 (2H, d, J=8.5 Hz, 3′,5′-Ph), 7.30 (2H, m, 2′,6′-Ph), 8.27 (1H, s, H-2). FAB-MS *m*/*z*: 315 (MH^+), 317 (MH^++2). *Anal.* Calcd for $C_{17}H_{19}ClN_4 \cdot 0.3AcOEt$: C, 64.06; H, 6.32; N, 16.42. Found: C, 63.74; H, 6.36; N, 16.76.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(5,6,7,8-tetrahydroquinazolin-4-yl)-4-fluorobenzamidine (3f)** To a dry $CHCl_3$ solution of **5** (350 mg, 2.35 mmol) were added *N*,*N*-dimethyl-4-fluorobenzamide (471 mg, 2.82 mmol), $POCl_3$ (0.28 ml, 3.00 mmol), and triethylamine (1.00 ml, 7.17 mmol) sequentially, and the reaction mixture was refluxed for 24 h. After the workup procedure described above, the residue was purified by silica gel column chromatography (acetone/*n*-hexane, 1 : 2) to give **3f** (88.9 mg, 13%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.77 (4H, m, H-6, 7), 2.50 (2H, m, H-5), 2.70 (2H, m, H-8), 3.04 (6H, br s, NMe_2), 6.96 (2H, m, 3′,5′-Ph), 7.18 (2H, m, 2′,6′-Ph), 8.32 (1H, s, H-2). FAB-MS *m*/*z*: 299 (MH^+). *Anal.* Calcd for $C_{17}H_{19}FN_4 \cdot 1/3H_2O$: C, 67.09; H, 6.51; N, 18.41. Found: C, 67.13; H, 6.53; N, 18.03.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(5,6,7,8-tetrahydroquinazolin-4-yl)-3-methylbenzamidine (3g)** To a dry $CHCl_3$ solution of **5** (250 mg, 1.68 mmol) were added *N*,*N*-dimethyl-3-methylbenzamide (328 mg, 2.01 mmol), $POCl_3$ (0.20 ml, 2.15 mmol), and triethylamine (0.45 ml, 3.23 mmol) sequentially, and the reaction mixture was refluxed for 24 h. After the workup procedure described above, the residue was purified by silica gel column chromatography (acetone/*n*-hexane, 1 : 4), then recrystallized from petroleum ether to give **3g** (142.4 mg, 29%) as colorless fine crystals, mp 91—92 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.76 (4H, m, H-6, 7), 2.27 (3H, s, Me), 2.51 (2H, m, H-5), 2.67 (2H, m, H-8), 3.02 (6H, br s, NMe_2), 6.91—7.18 (4H, m, Ph), 8.33 (1H, s, H-2). FAB-MS *m*/*z*: 295 (MH^+). *Anal.* Calcd for $C_{18}H_{22}N_4$: C, 73.44; H, 7.53; N, 19.03. Found: C, 73.67; H, 7.64; N, 19.17.

***N*-(5,6,7,8-Tetrahydroquinazolin-4-yl)formamide Oxime (6a)** To a solution of **3a** (142 mg, 0.70 mmol) in dry methanol (6.0 ml) was added $NH_2OH \cdot HCl$ (58.0 mg, 0.84 mmol), and the reaction mixture was stirred at room temperature for 4 h. Water was added, and then it was made basic with sat. $NaHCO_3$ aq. The precipitate was filtered, washed with water then recrystallized from methanol to give **6a** (106.3 mg, 80%) as colorless needles, mp 199—201 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.77 (4H, m, H-6, 7), 2.51 (2H, m, H-5), 2.68 (2H, m, H-8), 7.99 (2H, s, changed to 1H after addition of D_2O, NHC<u>H</u>=NO), 8.45 (1H, s, H-2), 10.72 (1H, s, D_2O exchangeable, OH). IR (KBr) cm^{-1}: 3420, 3130 (NH or OH). FAB-MS *m*/*z*: 193 (MH^+). *Anal.* Calcd for $C_9H_{12}N_4O$: C, 56.24; H, 6.29; N, 29.15. Found: C, 55.97; H, 6.35; N, 29.12.

***N*-(5,6,7,8-Tetrahydroquinazolin-4-yl)acetamide Oxime (6b) and *N*-[2-(3-Methyl[1,2,4]oxadiazol-5-yl)cyclohexen-1-yl]formamide Oxime (7b)** To a solution of **3b** (160 mg, 0.733 mmol) in dry methanol (6.0 ml) was added $NH_2OH \cdot HCl$ (56.0 mg, 0.806 mmol), and the reaction mixture was stirred at room temperature for 14 h. Water was added, and then it was made basic with sat. $NaHCO_3$ aq. The precipitate was filtered, washed with water then recrystallized from methanol to give **6b** (75.8 mg, 50%) as colorless needles, mp 117—118 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.78 (4H, m, H-6, 7), 2.32 (3H, s, Me), 2.45 (2H, m, H-5), 2.67 (2H, m, H-8), 7.95 (1H, s, D_2O exchangable, NH), 8.43 (1H, s, H-2), 10.52 (1H, s, D_2O exchangeable, OH). IR (KBr) cm^{-1}: 3380, 3130 (NH or OH). FAB-MS *m*/*z*: 207 (MH^+). *Anal.* Calcd for $C_{10}H_{14}N_4O$: C, 58.24; H, 6.84; N, 27.17. Found: C, 57.98; H, 6.77; N, 27.20. The mother liquid was evaporated and the residue was recrystallized from methanol to give **7b** (12%) as colorless needles, mp 188—191 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.68 (4H, m, H-4, 5), 2.33 (3H, s, Me), 2.45, 2.58 (each 2H, each m, H-3, 6), 7.45 (1H, d, J=10.0 Hz, changed to singlet after addition of D_2O, NHC<u>H</u>=NO), 10.36 (1H, s, D_2O exchangeable, OH), 11.06 (1H, d, J=10.0 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3280, 3150 (br, NH or OH). FAB-MS *m*/*z*: 223 (MH^+). *Anal.* Calcd for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.73; H, 6.24; N, 24.91.

***N*-(5,6,7,8-Tetrahydroquinazolin-4-yl)propionamide Oxime (6c)** To a solution of **3c** (279 mg, 1.20 mmol) in dry methanol (10 ml) was added $NH_2OH \cdot HCl$ (100 mg, 1.44 mmol), and the reaction mixture was stirred at room temperature for 20 h. Water was added, and then it was made basic with sat. $NaHCO_3$ aq. The precipitate was filtered, washed with water then recrystallized from methanol to give **6c** (110.3 mg, 42%) as colorless fine crystals, mp 200—203 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.06 (3H, t, J=7.4 Hz, Me), 1.78 (4H, m, H-6, 7), 2.50 (2H, m, H-5), 2.67 (2H, m, H-8), 2.87 (2H, q, J=7.4 Hz, C$\underline{H}_2$Me), 7.89 (1H, s, D_2O exchangable, NH), 8.43 (1H, s, H-2), 10.60 (1H, s, D_2O exchangeable, OH). IR (KBr) cm^{-1}: 3380, 3130 (NH or OH). FAB-MS *m/z*: 221 (MH^+). *Anal.* Calcd for $C_{11}H_{16}N_4O$: C, 59.98; H, 7.32; N, 25.44. Found: C, 59.59; H, 7.17; N, 25.18.

***N*-[2-([1,2,4]Oxadiazol-5-yl)cyclohexen-1-yl]formamide Oxime (7a)** To a solution of **6a** (360 mg, 1.87 mmol) in dry methanol (50 ml) was added $NH_2OH \cdot HCl$ (782 mg, 11.3 mmol), and the reaction mixture was refluxed for 24 h. Water was added, and then it was made basic with sat. $NaHCO_3$ aq., then extracted with $CHCl_3$. Organic phase was washed with sat. brine, dried over Na_2SO_4, then evaporated *in vacuo*. The residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane, 1 : 2), then recrystallized from methanol to give **7a** (87.1 mg, 22%) as colorless needles, mp 168—170 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.69 (4H, m, H-4, 5), 2.49, 2.60 (each 2H, each m, H-3, 6), 7.47 (1H, d, J=10.0 Hz, changed to singlet after addition of D_2O, NHC$\underline{H}$=NO), 8.99 (1H, s, H-3′), 10.43 (1H, s, D_2O exchangeable, OH), 11.09 (1H, d, J=10.0 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3240, 3150 (br, NH or OH). FAB-MS *m/z*: 209 (MH^+). *Anal.* Calcd for $C_9H_{12}N_4O_2 \cdot 0.2H_2O$: C, 51.03; H, 5.90; N, 26.45. Found: C, 51.34; H, 5.90; N, 26.78.

***N*-[2-(3-Methyl[1,2,4]oxadiazol-5-yl)cyclohexen-1-yl]formamide Oxime (7b)** To a solution of **6b** (63.0 mg, 0.31 mmol) in dry methanol (20 ml) was added $NH_2OH \cdot HCl$ (32.0 mg, 0.46 mmol), and the reaction mixture was stirred at room temperature for 3 h. Water was added, and then it was made basic with sat. $NaHCO_3$ aq. The precipitate was filtered, washed with water and then recrystallized from methanol to give **7b** (52.0 mg, 77%) as colorless needles. The spectroscopic properties were identical to those for **7b** from **3b** described above.

***N*-[2-(3-Ethyl[1,2,4]oxadiazol-5-yl)cyclohexen-1-yl]formamide Oxime (7c)** To a solution of **6c** (25.0 mg, 0.11 mmol) in dry methanol (5.0 ml) was added $NH_2OH \cdot HCl$ (15.0 mg, 0.22 mmol), and the reaction mixture was stirred at room temperature for 6 h. Water was added, and then it was made basic with sat. $NaHCO_3$ aq. The precipitate was filtered, washed with water and then recrystallized from methanol to give **7c** (22.4 mg, 84%) as colorless needles, mp 181—182 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.26 (3H, t, J=7.5 Hz, Me), 1.69 (4H, m, H-4, 5), 2.45, 2.58 (each 2H, each m, H-3, 6), 2.73 (2H, q, J=7.5 Hz, C$\underline{H}_2$Me), 7.45 (1H, d, J=10.0 Hz, changed to singlet after addition of D_2O, NHC$\underline{H}$=NO), 10.37 (1H, s, D_2O exchangeable, OH), 11.60 (1H, d, J=10.0 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3220 (br, NH or OH). FAB-MS *m/z*: 237 (MH^+). *Anal.* Calcd for $C_{11}H_{16}N_4O_2$: C, 55.92; H, 6.83; N, 23.71. Found: C, 55.73; H, 6.72; N, 23.55.

General Procedure for the Reaction of 3d—g with $NH_2OH \cdot HCl$ to Give 7d—g To a solution of amidine (**3**) in dry methanol was added $NH_2OH \cdot HCl$, and the reaction mixture was stirred at room temperature. Water was added, and then it was made basic with sat. $NaHCO_3$ aq. The precipitate was filtered, washed with water and then recrystallized from methanol to give **7**.

***N*-[2-(3-Phenyl[1,2,4]oxadiazol-5-yl)cyclohexen-1-yl]formamide Oxime (7d) 3d** (63.7 mg, 0.227 mmol) was allowed to react with $NH_2OH \cdot HCl$ (72.0 mg, 1.04 mmol) in dry methanol (5.0 ml) for 9 h. **7d** (48.3 mg, 75%) was obtained as colorless needles, mp 201—203 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.70 (4H, m, H-4, 5), 2.49, 2.62 (each 2H, each m, H-3, 6), 7.55 (1H, d, J=10.0 Hz, changed to singlet after addition of D_2O, NHC$\underline{H}$=NO), 7.44—7.63 (3H, m, Ph-3′,4′, 5′), 8.12 (2H, dd, J=7.6, 1.6 Hz, Ph-2′, 6′), 10.69 (1H, br s, D_2O exchangeable, OH), 11.62 (1H, d, J=10.0 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3200, 3100 (br, NH or OH). FAB-MS *m/z*: 285 (MH^+). *Anal.* Calcd for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.43; H, 5.83; N, 19.83.

***N*-{2-[3-(4-Chlorophenyl)[1,2,4]oxadiazol-5-yl]cyclohexen-1-yl}formamide Oxime (7e) 3e** (342 mg, 1.09 mmol) was allowed to react with $NH_2OH \cdot HCl$ (453 mg, 6.52 mmol) in dry methanol (5.0 ml) for 20 h. **7e** (297.6 mg, 86%) was obtained as colorless needles, mp 213—214 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.73 (4H, m, H-4, 5), 2.52, 2.64 (each 2H, each m, H-3, 6), 7.57 (1H, d, J=10.0 Hz, changed to singlet after addition of D_2O, NHC$\underline{H}$=NO), 7.60 (2H, d, J=8.5 Hz, Ph-3′, 5′), 8.11 (2H, d, J=8.5 Hz, Ph-2′, 6′), 10.69 (1H, s, D_2O exchangeable, OH), 11.61 (1H, d, J=10.0 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3300, 3170 (br, NH or OH). FAB-MS *m/z*: 319 (MH^+), 321 (MH^++2). *Anal.* Calcd for $C_{15}H_{15}ClN_4O_2$: C, 56.52; H, 4.74; N, 17.58. Found: C, 56.33; H, 4.80; N, 17.44.

***N*-{2-[3-(4-Fluorophenyl)[1,2,4]oxadiazol-5-yl]cyclohexen-1-yl}formamide Oxime (7f) 3f** (107.9 mg, 0.36 mmol) was allowed to react with $NH_2OH \cdot HCl$ (151 mg, 2.17 mmol) in dry methanol (5.0 ml) for 16 h. **7f** (99.4 mg, 91%) was obtained as colorless needles, mp 197—199 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.73 (4H, m, H-4, 5), 2.51, 2.64 (each 2H, each m, H-3, 6), 7.37 (2H, d, J=8.9 Hz, Ph-3′, 5′), 7.57 (1H, d, J=9.9 Hz, changed to singlet after addition of D_2O, NHC$\underline{H}$=NO), 8.17 (2H, m, Ph-2′, 6′), 10.68 (1H, s, D_2O exchangeable, OH), 11.60 (1H, d, J=9.9 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3200 (br, NH or OH). FAB-MS *m/z*: 303 (MH^+). *Anal.* Calcd for $C_{15}H_{15}FN_4O_2$: C, 59.60; H, 5.00; N, 18.53. Found: C, 59.45; H, 5.07; N, 18.51.

***N*-{2-[3-(3-Methylphenyl)[1,2,4]oxadiazol-5-yl]cyclohexen-1-yl}formamide Oxime (7g) 3g** (117 mg, 0.397 mmol) was allowed to react with $NH_2OH \cdot HCl$ (166 mg, 2.39 mmol) in dry methanol (5.0 ml) for 4 h. **7g** (101.4 mg, 77%) was obtained as colorless needles, mp 205—206 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.73 (4H, m, H-4, 5), 2.40 (3H, s, Me), 2.52, 2.64 (each 2H, each m, H-3, 6), 7.40 (2H, m, Ph-4′, 5′), 7.56 (1H, d, J=10.0 Hz, changed to singlet after addition of D_2O, NHC$\underline{H}$=NO), 7.88 (1H, m, Ph-6′), 7.97 (1H, br s, Ph-2′), 10.74 (1H, s, D_2O exchangeable, OH), 11.66 (1H, d, J=10.0 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3340 (br, NH or OH). FAB-MS *m/z*: 299 (MH^+). *Anal.* Calcd for $C_{16}H_{18}N_4O_2 \cdot CH_3OH$: C, 61.80; H, 6.71; N, 16.96. Found: C, 62.04; H, 6.75; N, 17.16.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(quinazolin-4-yl)formamidine (4a)** 4-Aminoquinazoline (**8**, 400 mg, 2.76 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (390 mg, 3.27 mmol) in dry toluene (30 ml) was refluxed for 8 h. After evaporation of reaction mixture, the residue was recrystallized from *n*-hexane to give **4a** (410 mg, 74%) as colorless fine crystals, mp 75—76 °C (lit.[24] 69 °C). ^{1}H-NMR ($CDCl_3$) δ: 3.27 (3H, s, NMe), 3.31 (3H, s, NMe), 7.48—7.59 (1H, m, H-6), 7.75—7.87 (1H, m, H-7), 7.92 (1H, br d, J=7.8 Hz, H-5), 8.52 (1H, dd, J=8.4, 1.4 Hz, H-8), 8.80 (1H, s, H-2), 8.90 (1H, s, C$\underline{H}$NMe$_2$). FAB-MS *m/z*: 201 (MH^+). *Anal.* Calcd for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 65.76; H, 6.07; N, 27.98.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(quinazolin-4-yl)acetamidine (4b) 8** (400 mg, 2.76 mmol) and *N*,*N*-dimethylacetamide dimethyl acetal (550 mg, 4.13 mmol) in dry toluene (30 ml) was refluxed for 12 h. After evaporation of reaction mixture, the residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane, 5 : 2) to give **4b** (320 mg, 54%) as colorless crystals, mp 76—78 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s, Me), 3.25 (6H, br s, NMe$_2$), 7.44—7.54 (1H, m, H-6), 7.72—7.83 (1H, m, H-7), 7.90 (1H, d, J=8.2 Hz, H-5), 8.21 (1H, dd, J=8.2, 1.4 Hz, H-8), 8.80 (1H, s, H-2). FAB-MS *m/z*: 215 (MH^+). *Anal.* Calcd for $C_{12}H_{14}N_4$: C, 67.27; H, 6.59; N, 26.15. Found: C, 67.21; H, 6.52; N, 26.08.

General Procedure for the Preparation of 4c—g To a solution of **8** in dry $CHCl_3$ were added *N*,*N*-dimethyamide, $POCl_3$, and triethylamine sequentially, and the reaction mixture was refluxed. Water was added, and then it was made basic with sat. $NaHCO_3$ aq., and then extracted with $CHCl_3$. Organic phase was washed with sat. brine, dried over Na_2SO_4, then evaporated *in vacuo*. The residue was purified by column chromatography and/or recrystallization to give **4**.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(quinazolin-4-yl)propionamidine (4c)** To a solution of **8** (2.20 g, 15.2 mmol) in dry $CHCl_3$ (50 ml) were added *N*,*N*-dimethylpropionamide (1.69 g, 16.7 mmol), $POCl_3$ (2.15 ml, 23.1 mmol), and triethylamine (6.40 ml, 45.9 mmol) sequentially, and the reaction mixture was refluxed for 30 h. After the workup procedure described above, the residue was purified by silica gel column chromatography (acetone/*n*-hexane, 1 : 4) to give **4c** (830 mg, 24%) as a colorless oil.[25] ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, t, J=7.6 Hz, Me), 2.68 (2H, q, J=7.6 Hz, C$\underline{H}_2$Me), 3.21 (6H, s, NMe$_2$), 7.42—7.52 (1H, m, H-6), 7.71—7.81 (1H, m, H-7), 7.84 (1H, d, J=8.3 Hz, H-5), 8.17 (1H, dd, J=8.3, 1.4 Hz, H-8), 8.83 (1H, s, H-2). FAB-MS *m/z*: 229 (MH^+).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(quinazolin-4-yl)benzamidine (4d)** To a solution of **8** (200 mg, 1.38 mmol) in dry $CHCl_3$ (20 ml) were added *N*,*N*-dimethylbenzamide (245 mg, 1.64 mmol), $POCl_3$ (0.20 ml, 2.1 mmol), and triethylamine (0.65 ml, 4.7 mmol) sequentially, and the reaction mixture was refluxed for 26 h. After the workup procedure described above, the residue was purified by silica gel column chromatography (acetone/*n*-hexane, 1 : 2), then recrystallized from ethyl acetate–*n*-hexane to give **4d** (65.7 mg, 17%) as colorless fine crystals, mp 78—79 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.37 (3H, s, NMe), 3.54 (3H, s, NMe), 7.32—7.57 (3H, m, H-3′, 4′, 5′), 7.62—7.74 (3H, m, H-2′, 6′, 6), 7.92 (1H, br t, J=7.7 Hz, H-7), 8.17 (1H, d, J=8.4 Hz, H-5), 8.30 (1H, s, H-2), 8.37 (1H, d, J=7.7 Hz, H-8). FAB-MS *m/z*: 277 (MH^+). *Anal.* Calcd for $C_{17}H_{16}N_4$: C, 73.89; H, 5.84; N, 20.28. Found: C, 73.93; H, 6.15;

N, 20.25.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(quinazolin-4-yl)-4-chlorobenzamidine (4e)** To a solution of **8** (2.00 g, 13.8 mmol) in dry $CHCl_3$ (60 ml) were added *N*,*N*-dimethyl-4-chlorobenzamide (2.78 g, 15.1 mmol), $POCl_3$ (1.95 ml, 20.9 mmol), and triethylamine (7.25 ml, 52.0 mmol) sequentially, and the reaction mixture was refluxed for 39 h. After the workup procedure described above, the residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane, 1 : 1) to give **4e** (360 mg, 8.4%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.03 (3H, s, NMe), 3.36 (3H, s, NMe), 7.21 (4H, s, H-2′, 3′, 5′, 6′), 7.48—7.58 (1H, m, H-6), 7.72—7.82 (1H, m, H-7), 7.85 (1H, dd, J=8.2, 1.3 Hz, H-5), 8.25 (1H, dd, J=8.4, 1.4 Hz, H-8), 8.52 (1H, s, H-2). FAB-MS *m*/*z*: 311 (MH^+), 313 (MH^++2). *Anal.* Calcd for $C_{17}H_{15}ClN_4 \cdot 0.25AcOEt$: C, 64.96; H, 5.15; N, 16.83. Found: C, 65.19; H, 5.39; N, 16.86.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(quinazolin-4-yl)-4-fluorobenzamidine (4f)** To a solution of **8** (2.20 g, 15.2 mmol) in dry $CHCl_3$ (60 ml) were added *N*,*N*-dimethyl-4-fluorobenzamide (2.79 g, 16.7 mmol), $POCl_3$ (2.15 ml, 23.1 mmol), and triethylamine (6.40 ml, 45.9 mmol) sequentially, and the reaction mixture was refluxed for 36 h. After the workup procedure described above, the residue was purified by silica gel column chromatography (ethyl acetate/*n*-hexane, 1 : 1) to give **4f** (450 mg, 10%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 3.06 (3H, br s, NMe), 3.37 (3H, br s, NMe), 6.88—7.00 (2H, m, H-3′, 5′), 7.23—7.34 (2H, m, H-2′, 6′), 7.48—7.58 (1H, m, H-6), 7.72—7.82 (1H, m, H-7), 7.86 (1H, dd, J=8.3, 1.3 Hz, H-5), 8.25 (1H, dd, J=8.4, 1.3 Hz, H-8), 8.51 (1H, s, H-2). FAB-MS *m*/*z*: 295 (MH^+). *Anal.* Calcd for $C_{17}H_{15}FN_4 \cdot 0.25AcOEt$: C, 68.34; H, 5.42; N, 17.71. Found: C, 68.29; H, 5.63; N, 18.06.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(quinazolin-4-yl)-3-methylbenzamidine (4g)** To a solution of **8** (2.15 g, 14.8 mmol) in dry $CHCl_3$ (60 ml) were added *N*,*N*-dimethyl-3-methylbenzamide (2.66 g, 16.3 mmol), $POCl_3$ (1.70 ml, 18.2 mmol), and triethylamine (6.25 ml, 44.8 mmol) sequentially, and the reaction mixture was refluxed for 24 h. After the workup procedure described above, the residue was purified by silica gel column chromatography (acetone/ethyl acetate/cyclohexane, 1 : 3 : 1), then recrystallized from ethyl acetate–*n*-hexane to give **4g** (590 mg, 14%) as colorless needles. ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s, Me), 2.99 (3H, br s, NMe), 3.32 (3H, br s, NMe), 6.91—7.12 (4H, m, H-2′, 4′, 5′, 6′), 7.43—7.56 (1H, m, H-6), 7.68—7.81 (2H, m, H-5, 7), 8.24 (1H, d, J=8.4 Hz, H-8), 8.56 (1H, s, H-2). FAB-MS *m*/*z*: 291 (MH^+). *Anal.* Calcd for $C_{18}H_{18}N_4 \cdot 0.5H_2O$: C, 72.22; H, 6.40; N, 18.71. Found: C, 72.06; H, 6.44; N, 18.64.

General Procedure for the Reaction of 4 with $NH_2OH \cdot HCl$ to give 10 To a solution of amidine (**4**) in dry methanol was added $NH_2OH \cdot HCl$, and the reaction mixture was stirred at room temperature. Water was added, and then it was made basic with sat. $NaHCO_3$ aq. The precipitate was filtered, washed with water then recrystallized from methanol to give **10**.

***N*-[2-([1,2,4]Oxadiazol-5-yl)phenyl]formamide Oxime (10a) 4a** (145 mg, 0.724 mmol) was allowed to react with $NH_2OH \cdot HCl$ (61.0 mg, 0.878 mmol) in dry methanol (10 ml) for 5 h. **10a** (53.4 mg, 36%) was obtained as colorless needles, mp 165—167 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.09 (1H, m, H-4), 7.55—7.69 (2H, m, H-5, 6), 7.92 (1H, d, J=10.1 Hz, changed to singlet after addition of D_2O, NHC<u>H</u>=NO), 8.08 (1H, d, J=7.6 Hz, H-3), 9.29 (1H, s, H-3′), 10.46 (1H, s, D_2O exchangeable, OH), 10.55 (1H, d, J=10.1 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3260, 3130 (NH or OH). FAB-MS *m*/*z*: 205 (MH^+). *Anal.* Calcd for $C_9H_8N_4O_2$: C, 52.94; H, 3.95; N, 27.44. Found: C, 52.69; H, 4.19; N, 27.35.

***N*-[2-(3-Methyl[1,2,4]oxadiazol-5-yl)phenyl]formamide Oxime (10b) 4b** (250 mg, 1.17 mmol) was allowed to react with $NH_2OH \cdot HCl$ (122 mg, 1.76 mmol) in dry methanol (8.0 ml) for 19 h. **10b** (166.3 mg, 65%) was obtained as colorless needles, mp 189—191 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.45 (3H, s, Me), 7.07 (1H, m, H-4), 7.53—7.68 (2H, m, H-5, 6), 7.90 (1H, d, J=10.0 Hz, changed to singlet after addition of D_2O, NHC<u>H</u>=NO), 8.02 (1H, d, J=7.7 Hz, H-3), 10.41 (1H, s, D_2O exchangeable, OH), 10.54 (1H, d, J=10.0 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3220 (br) (NH or OH). FAB-MS *m*/*z*: 219 (MH^+). *Anal.* Calcd for $C_{10}H_{10}N_4O_2 \cdot 0.1H_2O$: C, 54.59; H, 4.67; N, 25.47. Found: C, 54.61; H, 4.80; N, 25.49.

***N*-[2-(3-Ethyl[1,2,4]oxadiazol-5-yl)phenyl]formamide Oxime (10c) 4c** (360 mg, 1.58 mmol) was allowed to react with $NH_2OH \cdot HCl$ (220 mg, 3.17 mmol) in dry methanol (8.0 ml) for 19 h. **10c** (277 mg, 76%) was obtained as colorless needles, mp 189—190 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.32 (3H, t, J=7.5 Hz, Me), 2.82 (2H, q, J=7.5 Hz, C<u>H</u>$_2$Me), 7.05 (1H, m, H-4), 7.52—7.68 (2H, m, H-5, 6), 7.90 (1H, d, J=10.1 Hz, changed to singlet after addition of D_2O, NHC<u>H</u>=NO), 8.02 (1H, d, J=8.2 Hz, H-3), 10.41 (1H, s, D_2O exchangeable, OH), 10.71 (1H, d, J=10.1 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3240, 3170, 3130 (NH or OH). FAB-MS *m*/*z*: 233 (MH^+). *Anal.* Calcd for $C_{11}H_{12}N_4O_2$: C, 56.89; H, 5.21; N, 24.12. Found: C, 56.65; H, 5.30; N, 23.97.

***N*-[2-(3-Phenyl[1,2,4]oxadiazol-5-yl)phenyl]formamide Oxime (10d) 4d** (41.0 mg, 0.148 mmol) was allowed to react with $NH_2OH \cdot HCl$ (63.0 mg, 0.907 mmol) in dry methanol (5.0 ml) for 48 h. **10d** (9.9 mg, 24%) was obtained as a white powder, mp 250—253 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.11 (1H, br t, J=6.8 Hz, H-4), 7.55–7.72 (5H, m, H-5, 6, 3′, 4′, 5′), 8.01 (1H, d, J=10.0 Hz, changed to singlet after addition of D_2O, NHC<u>H</u>=NO), 8.11 (1H, br d, J=6.8 Hz, H-3), 8.20 (2H, m, H-2′, 6′), 10.67 (1H, s, D_2O exchangeable, OH), 11.08 (1H, d, J=10.0 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3220 (br) (NH or OH). EI-MS *m*/*z*: 280 (M^+). *Anal.* Calcd for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19.99. Found: C, 64.03; H, 4.59; N, 19.68.

***N*-{2-[3-(4-Chlorophenyl)[1,2,4]oxadiazol-5-yl]phenyl}formamide Oxime (10e) 4e** (257 mg, 0.827 mmol) was allowed to react with $NH_2OH \cdot HCl$ (345 mg, 4.96 mmol) in dry methanol (10 ml) for 19 h. **10e** (85.2 mg, 33%) was obtained as colorless needles, mp 245—247 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.11 (1H, m, H-4), 7.58—7.73 (4H, m, H-5, 6, 3′, 5′), 8.01 (1H, d, J=9.9 Hz, changed to singlet after addition of D_2O, NHC<u>H</u>=NO), 8.10 (1H, dd, J=7.8, 1.4 Hz, H-3), 8.16 (2H, m, H-2′, 6′), 10.64 (1H, s, D_2O exchangeable, OH), 11.04 (1H, d, J=9.9 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3220, 3140 (br) (NH or OH). FAB-MS *m*/*z*: 315 (MH^+), 317(MH^++2). *Anal.* Calcd for $C_{15}H_{11}ClN_4O_2$: C, 57.24; H, 3.52; N, 17.80. Found: C, 57.03; H, 3.84; N, 17.65.

***N*-{2-[3-(4-Fluorophenyl)[1,2,4]oxadiazol-5-yl]phenyl}formamide Oxime (10f) 4f** (468 mg, 1.59 mmol) was allowed to react with $NH_2OH \cdot HCl$ (664 mg, 9.56 mmol) in dry methanol (10 ml) for 6 h. **10f** (124.8 mg, 26%) was obtained as colorless needles, mp 165—168 °C. ^{1}H-NMR (DMSO-d_6) δ: 7.09 (1H, m, H-4), 7.42 (2H, m, H-3′, 5′), 7.56—7.73 (2H, m, H-5, 6), 8.00 (1H, d, J=10.0 Hz, changed to singlet after addition of D_2O, NHC<u>H</u>=NO), 8.10 (1H, br d, J=7.7, Hz, H-3), 8.24 (2H, m, H-2′, 6′), 10.63 (1H, s, D_2O exchangeable, OH), 11.04 (1H, d, J=10.0 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3220, 3130 (br) (NH or OH). FAB-MS *m*/*z*: 299 (MH^+). *Anal.* Calcd for $C_{15}H_{11}FN_4O_2$: C, 60.40; H, 3.72; N, 18.78. Found: C, 60.23; H, 4.07; N, 18.78.

***N*-{2-[3-(3-Methylphenyl)[1,2,4]oxadiazol-5-yl]phenyl}formamide Oxime (10g) 4g** (186.7 mg, 0.643 mmol) was allowed to react with $NH_2OH \cdot HCl$ (447 mg, 6.43 mmol) in dry methanol (15 ml) for 9 h. **10g** (74.4 mg, 39%) was obtained as colorless needles, mp 255—257 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.43 (3H, s, Me), 7.10 (1H, m, H-4), 7.46 (2H, m, H-4′, 5′), 7.68 (2H, m, H-5, 6), 8.02 (1H, d, J=10.0 Hz, changed to singlet after addition of D_2O, NHC<u>H</u>=NO), 8.06 (3H, m, H-3, 2′, 6′), 10.74 (1H, s, D_2O exchangeable, OH), 11.12 (1H, d, J=10.0 Hz, D_2O exchangeable, NH). IR (KBr) cm^{-1}: 3210 (br) (NH or OH). FAB-MS *m*/*z*: 295 (MH^+). *Anal.* Calcd for $C_{16}H_{14}N_4O_2$: C, 65.30; H, 4.79; N, 19.04. Found: C, 65.02; H, 4.94; N, 18.89.

Preparation of Platelet Blood was collected from a male Albino rabbit (3—3.5 kg weight) with 0.1 volume of 3.8% sodium citrate as the anticoagulant. After mixing, platelet rich plasma (PRP) was obtained by removing erythrocytes and leukocytes by centrifugation (4 °C, 1000 rpm, 10 min). Platelet poor plasma (PPP) was prepared by further centrifugation (4 °C, 3000 rpm, 15 min). The PRP was diluted by PPP to be 3.0×10^5 cells/ml, and then used for the aggregation.

Measurement of Platelet Aggregation The plasma described above (223 μl) was preincubated at 37 °C for 2 min. Synthetic compounds **7a**—**g** and **10a**—**g** (2 μl) (DMSO solution) was added, followed by an addition of aggregating agent 25 μl (arachidonic acid 25 μg/ml) 1 min later. Platelet aggregation was measured by continuous recording of light transmission through plasma for 10 min using an aggregometer (Sysmex, AA-100) at 37 °C. Cilostazol[23] was used as a positive control. All compounds were used at a 30 μM final concentration. The inhibition rate was calculated according to the method already described.[14]

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