Polycyclic *N*-Heterocyclic Compounds. Part 66: Synthesis of *N*-[2-([1,2,4]Oxadiazol-5-yl)cyclopenten-1-yl]formamide Oximes and Their Evaluation as Inhibitors of Platelet Aggregation [1]

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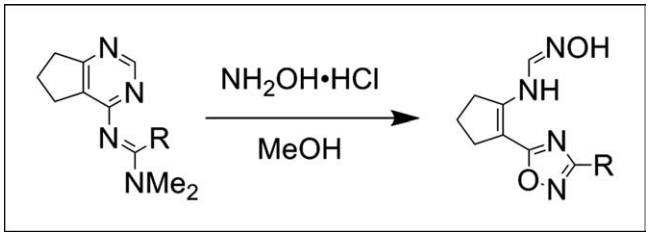

N-[2-([1,2,4]Oxadiazol-5-yl)cyclopenten-1-yl]formamide oximes were synthesized by fusion of (6,7-dihydro-5*H*-cyclopenta[1,2-*d*]pyrimidin-4-yl)amidines and/or their amide oximes with hydroxylamine hydrochloride through a subsequent rearrangement reaction. Assay of the products for anti-platelet aggregation activity revealed that certain of them showed promising inhibitory effect on arachidonic acid-induced platelet aggregation.

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INTRODUCTION

Platelet activation and aggregation are the most critical steps in the development of acute ischemic syndromes such as acute coronary syndrome or ischemic stroke, major causes of death in the developed world. Drugs designed to interfere with platelet activation and aggregation are thus important for the prevention and treatment of these syndromes. Unfortunately, current antiplatelet drugs often have drawbacks that include side effects and less than ideal efficacy. Accordingly, there continues to be much research directed to the development of new drugs for this purpose [2–7].

We have previously reported that *N*-[2-(3-substituted [1,2,4]oxadiazol-5-yl)cyclohexen-1-yl]formamide oximes (**2**) are accessible by reaction of N^1,N^1-dimethyl-N^2-(5,6,7,8-tetrahydroquinazolin-4-yl)amidines (**1**) and/or their amide oximes with hydroxylamine hydrochloride followed by pyrimidine ring cleavage and 1,2,4-oxadiazole ring closure (Fig. 1). A study of biological properties of these compounds revealed that one member of the group (R = 4-Cl-Ph) had considerable activity as an inhibitor of arachidonic acid-induced platelet aggregation [8]. To develop more active compounds in this series, we decided to explore the structure–activity relationships of the related compounds, *N*-[2-(3-substituted [1,2,4]oxadiazol-5-yl)cyclopenten-1-yl]formamide oximes (**3**). In this report, we describe the synthesis and evaluation of these compounds in detail.

RESULTS AND DISCUSSION

We initiated the synthetic efforts with the aliphatic 5-membered ring-fused amidine **5**. As shown in Scheme 1, amidines **5**, required as starting materials, were synthesized by the previously reported method [8]. Thus, amidines **5a** and **5b** were prepared by reaction of 4-amino-6,7-dihydro-5*H*-cyclopenta[1,2-*d*]pyrimidine (**4**) with commercially available *N*,*N*-dimethylformamide (or acetamide) dimethyl acetal in refluxing toluene. Other amidines **5c–g** were prepared by the reaction of compound **4** with the Vilsmeier reagent prepared from the corresponding *N*,*N*-dimethylamide and phosphoryl chloride [9].

When a hydrogen is attached to the amidine moiety (R = H), the reaction of **5a** with 1.2 equiv of hydroxylamine hydrochloride in methanol at room temperature gave the amide oxime (**6a**) in 87% yield. Compound **6a** was converted to the desired 1,2,4-oxadiazole derivative **3a** in 86% yield by reaction with 6 equiv of hydroxylamine hydrochloride in a refluxing methanol (Scheme 1).

When an alkyl group was attached to the amidine moiety (R = Me and Et), the reaction of **5b** and **5c** with 1.5 equiv of hydroxylamine hydrochloride in methanol at room temperature did not produce amide oximes (**6b** and **6c**), but gave exclusively oxadiazole **3b** (53%) and **3c** (45%), respectively. Other amidines **5d–g** having an aryl group substituted in the amidine moiety required an excess amount of hydroxylamine hydrochloride to

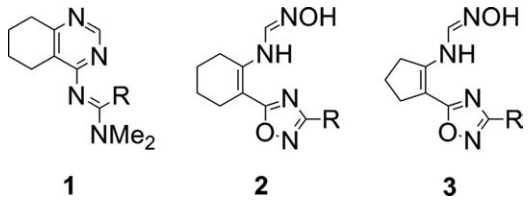

Figure 1. Substrate (**1**) and rearranged products (**2** and **3**).

consume starting materials completely. In such cases, the reaction did not produce amide oximes (**6d–g**), but gave the desired oxadiazoles **3d–g** by the reaction with 6–8 equiv of hydroxylamine hydrochloride. These phenomena are in full accord with previous examples [8].

The activities of **3a–g** as inhibitors of arachidonic acid-induced platelet aggregation were assayed. This was carried out by a turbidimetric method developed by Born and Cross [10] using an aggregometer. As shown in Table 1, a comparison of the inhibition rate at the final concentration of 30 mmol/L with that of Cilostazol [11] showed that **3b** and **3e** had potency comparable with Cilostazol. Considering that **2e** (R = 4-Cl-Ph, % inhibition: 75.2 ± 10.8) is the most potent and **2b** (R = Me, % inhibition:42.6 ± 14.8) is the second potent among **2**, which were synthesized previously [8], it seems that methyl and 4-chlorophenyl groups are key substituents for the activity.

In summary, we have synthesized various *N*-[2-(3-alkyl(or aryl)[1,2,4]oxadiazol-5-yl)cyclopenten-1-yl]formamide oximes (**3**) through the reaction of *N*-(6,7-dihydro-5*H*-cyclopenta[1,2-*d*]pyrimidin-4-yl)amidines (**5**) with hydroxylamine hydrochloride. The reaction involves a ring cleavage of a pyrimidine component accompanied by a ring closure to the 1,2,4-oxadiazole. Among the series, compound **3e** showed the best inhibitory activity against platelet aggregation and had activity comparable with that of the clinically used Cilostazol.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus, and were uncorrected. Elemental analyses were performed on a Yanagimoto MT-5 CHN Corder elemental analyzer. The fast atom bombardment (FAB) mass spectra were obtained on a VG 70 mass spectrometer and *m*-nitrobenzyl alcohol was used as the matrix. Their spectra were recorded on a Japan Spectroscopic FT/IR-200 spectrophotometer with potassium bromide 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. The signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. Column chromatography was performed on aluminium oxide active neutral (Merck). Thin layer chromotography (TLC) was carried out on Kieselgel 60F254 (Merck).

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(6,7-dihydro-5*H*-cyclopenta[1,2-*d*]pyrimidin-4-yl)formamidine (5a).** A mixture of 4-amino-6,7-dihydro-5*H*-cyclopenta[1,2-*d*]pyrimidine (**4**, 300 mg, 2.22 mmol) and

Scheme 1. Synthesis of **3**.

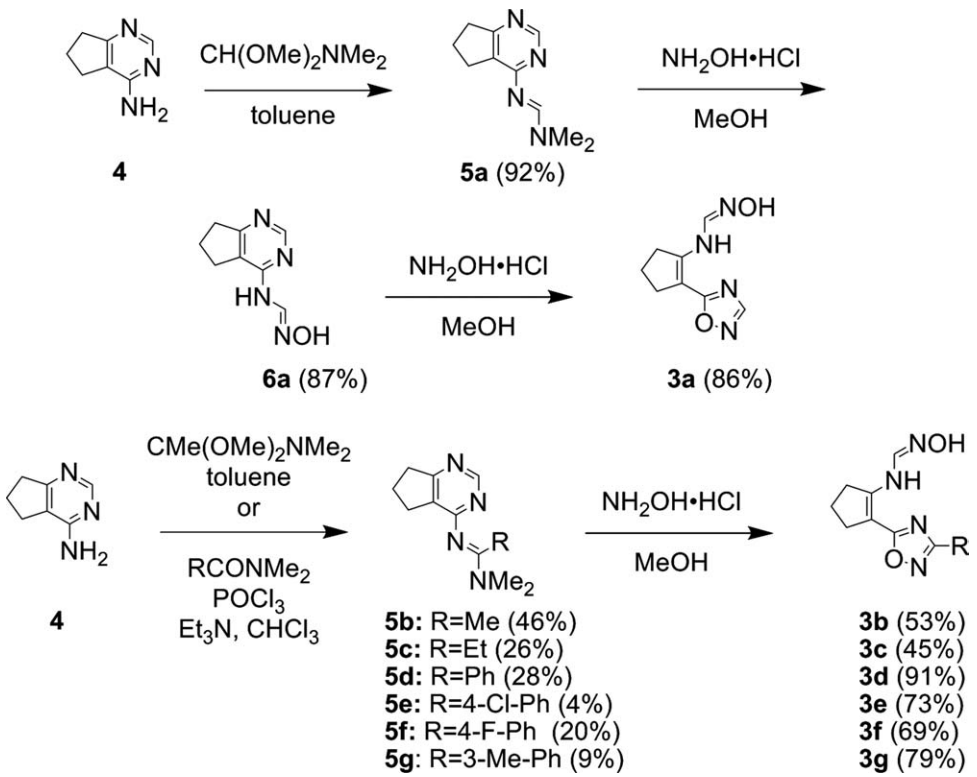

Table 1

Effects of **3a–g** on rabbit platelet aggregation *in vitro*.

Compound	% Inhibition	Compound	% Inhibition
3a	31.9 ± 1.8	**3e**	83.6 ± 5.4[a]
3b	70.4 ± 11.2[a]	**3f**	1.9 ± 0.9
3c	13.8 ± 6.9	**3g**	27.0± 7.5
3d	5.0 ± 14.8	Cilostazol	96.5 ± 1.3[a]

Data represent % inhibition of the vehicle control group (Mean ± S.E. of three experiments).

[a] Means significantly different from the vehicle control group at $P < 0.01$ (Dunnett's multiple range test).

N,*N*-dimethylformamide dimethyl acetal (319 mg, 2.68 mmol) in dry toluene (40 mL) was refluxed for 10 h. After removal of solvent *in vacuo*, the residue was recrystallized from *n*-hexane to give **5a** (389 mg, 92%) as yellow needles, m.p. 73–74°C; ^{1}H-NMR (deuterochloroform): δ 2.11 (m, 2H, H6), 2.95 (m, 4H, H5 and H7), 3.14 (s, 6H, $N(CH_3)_2$), 8.57 (s, 1H, C*H*$N(CH_3)_2$), 8.63 (s, 1H, H2); FAB-ms: *m*/*z* 191 (MH^+). Anal. Calcd. for $C_{10}H_{14}N_4 \cdot 0.2H_2O$: C, 61.96; H, 7.49; N, 28.90. Found: C, 62.28; H, 7.25; N, 29.08.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(6,7-dihydro-5*H*-cyclopenta[1,2-*d*]pyrimidin-4-yl)acetamidine (5b).** A mixture of compound **4** (350 mg, 2.59 mmol) and *N*,*N*-dimethylacetamide dimethyl acetal (776 mg, 5.83 mmol) in dry toluene (40 mL) was refluxed for 54 h. After removal of solvent *in vacuo*, the residue was purified by column chromatography (ethyl acetate/*n*-hexane, 1:7) to give **5b** (244 mg, 46%) as a colorless oil; ^{1}H-NMR (deuterochloroform): δ 2.08 (m, 2H, H6), 2.11 (s, 3H, CH_3), 2.78 (t, 2H, J = 7.5 Hz, H5), 3.00 (t, 2H, J = 7.4 Hz, H7), 3.12 (s, 6H, $N(CH_3)_2$), 8.62 (s, 1H, H2); FAB-ms: *m*/*z* 205 (MH^+). Anal. Calcd. for $C_{11}H_{16}N_4 \cdot 0.2H_2O$: C, 63.56; H, 7.95; N, 26.95. Found: C, 63.94; H, 7.84; N, 26.63.

General procedure for the reaction of 4 with *N*,*N*-dimethylamide to give 5c–g. To a solution of **4** in dry chloroform (ca. 20 mL), *N*,*N*-dimethylamide, phosphoryl chloride, and triethylamine were added sequentially, and then the mixture was refluxed for the appropriate time. Water was added to quench the reaction, and the mixture was basified with saturated aqueous sodium bicarbonate solution, then extracted with chloroform. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, and then evaporated *in vacuo*. The residue was purified by column chromatography and/or recrystallization to give **5**.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(6,7-dihydro-5H-cyclopenta[1,2-d]pyrimidin-4-yl)propionamidine (5c).** To a dry chloroform solution of **4** (2.50 g, 18.5 mmol), *N*,*N*-dimethylpropionamide (2.06 g, 20.4 mmol), phosphoryl chloride (2.60 mL, 27.9 mmol), and triethylamine (7.50 mL, 53.8 mmol) were added sequentially, and then the reaction mixture was refluxed for 30 h. The residue was purified by column chromatography (*n*-hexane), recrystallized from petroleum ether to give **5c** (1.03 g, 26%) as colorless fine crystals, m.p. 58–59°C; ^{1}H-NMR (deuterochloroform): δ 1.11 (t, 3H, J = 7.6 Hz, CH_3), 2.08 (m, 2H, H6), 2.54 (q, 2H, J = 7.6 Hz, C$H_2$$CH_3$), 2.77 (t, 2H, J = 7.4 Hz, H5), 3.01 (t, 2H, J = 7.4 Hz, H7), 3.12 (s, 6H, $N(CH_3)_2$), 8.60 (s, 1H, H2); FAB-ms: *m*/*z* 219 (MH^+). Anal. Calcd. for $C_{12}H_{18}N_4$: C, 66.02; H, 8.31; N, 25.67. Found: C, 65.83; H, 8.10; N, 25.71.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(6,7-dihydro-5H-cyclopenta[1,2-d]pyrimidin-4-yl)benzamidine (5d).** To a dry chloroform solution of **4** (500 mg, 3.70 mmol), *N*,*N*-dimethylbenzamide (610 mg, 4.09 mmol), phosphoryl chloride (0.42 mL, 4.51 mmol), and triethylamine (1.80 mL, 12.9 mmol) were added sequentially, and then the reaction mixture was refluxed for 37 h. The residue was purified by column chromatography (ethyl acetate/*n*-hexane, 1:2), recrystallized from ethyl acetate/*n*-hexane to give **5d** (280 mg, 28%) as colorless fine crystals, m.p. 113–115°C; ^{1}H-NMR (deuterochloroform): δ 1.93 (m, 2H, H6), 2.61 (t, 2H, J = 7.4 Hz, H5), 2.84 (t, 2H, J = 7.4 Hz, H7), 3.07 (s, 6H, $N(CH_3)_2$), 7.22 (m, 5H, Ph), 8.43 (s, 1H, H2); FAB-ms: *m*/*z* 267 (MH^+). Anal. Calcd. for $C_{16}H_{18}N_4$: C, 72.15; H, 6.81; N, 21.04. Found: C, 71.90; H, 6.87; N, 20.81.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(6,7-dihydro-5H-cyclopenta[1,2-d]pyrimidin-4-yl)-4-chlorobenzamidine (5e).** To a dry chloroform solution of **4** (3.00 g, 22.2 mmol), *N*,*N*-dimethyl-4-chlorobenzamide (4.49 g, 24.5 mmol), phosphoryl chloride (3.15 mL, 33.8 mmol), and triethylamine (10.9 mL, 8.1 mmol) were added sequentially, and then the reaction mixture was refluxed for 50 h. The residue was purified by column chromatography (ethyl acetate/*n*-hexane, 1:6) to give **5e** (270 mg, 4%) as a colorless oil; ^{1}H-NMR (deuterochloroform): δ 2.05 (m, 2H, H6), 2.72 (t, 2H, J = 7.5 Hz, H5), 2.90 (t, 2H, J = 7.5 Hz, H7), 3.06 (br s, 6H, $N(CH_3)_2$), 7.18 (d, 2H, J = 8.7 Hz, Ph-3′ and 5′), 7.28 (d, 2H, J = 8.7 Hz, Ph-2′ and 6′), 8.39 (s, 1H, H2); FAB-ms: *m*/*z* 301 (MH^+), 303 ($MH^+ + 2$). Anal. Calcd. for $C_{16}H_{17}ClN_4 \cdot 0.1$AcOEt: C, 63.42; H, 6.10; N, 18.04. Found: C, 63.57; H, 6.07; N, 18.08.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(6,7-dihydro-5H-cyclopenta[1,2-d]pyrimidin-4-yl)-4-fluorobenzamidine (5f).** To a dry chloroform solution of **4** (3.20 g, 23.7 mmol), *N*,*N*-dimethyl-4-fluorobenzamide (4.35 g, 26.0 mmol), phosphoryl chloride (3.35 mL, 35.9 mmol), and triethylamine (9.95 mL, 71.1 mmol) were added sequentially, and then the reaction mixture was refluxed for 20 h. The residue was purified by column chromatography (ethyl acetate/*n*-hexane, 1:6), recrystallized from petroleum ether to give **5f** (1.35 g, 20%) as colorless fine crystals, m.p. 79–80°C; ^{1}H-NMR (deuterochloroform): δ 1.99 (m, 2H, H6), 2.65 (t, 2H, J = 7.5 Hz, H5), 2.88 (t, 2H, J = 7.5 Hz, H7), 3.06 (br s, 6H, $N(CH_3)_2$), 6.97 (m, 2H, Ph-3′ and 5′), 7.22 (m, 2H, Ph-2′ and 6′), 8.40 (s, 1H, H2); FAB-ms: *m*/*z* 285 (MH^+). Anal. Calcd. for $C_{16}H_{17}FN_4$: C, 67.59; H, 6.03; N, 19.70. Found: C, 67.55; H, 6.14; N, 19.63.

***N*^{1},*N*^{1}-Dimethyl-*N*^{2}-(6,7-dihydro-5H-cyclopenta[1,2-d]pyrimidin-4-yl)-3-methylbenzamidine (5g).** To a dry chloroform solution of **4** (500 mg, 3.70 mmol), *N*,*N*-dimethyl-3-methylbenzamide (663 mg, 4.06 mmol), phosphoryl chloride (0.40 mL, 4.29 mmol), and triethylamine (0.90 mL, 6.43 mmol) were added sequentially, and then the reaction mixture was refluxed for 43 h. The residue was purified by column chromatography (ethyl acetate/*n*-hexane, 1:3) to give **5g** (91.0 mg, 9%) as a colorless oil; ^{1}H-NMR (deuterochloroform): δ 1.93 (m, 2H, H6), 2.26 (s, 3H, CH_3), 2.61 (t, 2H, J = 7.7 Hz, H5), 2.81 (t, 2H, J = 7.7 Hz, H7), 3.00 (br s, 6H, $N(CH_3)_2$), 6.95–7.17 (m, 4H, Ph), 8.44 (s, 1H, H2); FAB-ms: *m*/*z* 281 (MH^+). Anal. Calcd. for $C_{17}H_{20}N_4 \cdot 1/3H_2O$: C, 71.30; H, 7.27; N, 19.56. Found: C, 71.42; H, 7.17; N, 19.25.

***N*-(6,7-Dihydro-5*H*-cyclopenta[1,2-*d*]pyrimidin-4-yl)formamide oxime (6a).** To a solution of **5a** (220 mg, 1.16 mmol) in dry methanol (10 mL) was added hydroxylamine hydrochloride (96.7 mg, 1.39 mmol), and the reaction was then stirred at

room temperature for 4 h. Water was added, and the mixture was then basified with saturated aqueous sodium bicarbonate solution. The resulting precipitate was filtered, washed with water, and the solid was recrystallized from dioxane/methanol to give **6a** (178.5 mg, 87%) as a white powder, m.p. 124–126°C; ir (potassium bromide): 3410, 3190 (NH or OH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.01 (m, 2H, H6), 2.84 (m, 4H, H5, and H7), 7.94 (d, 1H, J = 9.7 Hz, changed to singlet after addition of deuterium oxide, NCH=NO), 8.49 (s, 1H, H2), 8.62 (d, 1H, J = 9.7 Hz, deuterium oxide exchangeable, NH), 10.59 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: m/z 179 (MH^+). Anal. Calcd. for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found: C, 53.72; H, 5.79; N, 31.14.

***N*-[2-([1,2,4]Oxadiazol-5-yl)cyclopenten-1-yl]formamide oxime (3a).** To a solution of **6a** (58.0 mg, 0.325 mmol) in dry methanol (15 mL) was added hydroxylamine hydrochloride (136 mg, 1.96 mmol), and the reaction was then refluxed for 3 h. Water was added, and the mixture was then basified with saturated aqueous sodium bicarbonate solution. The precipitate was filtered, washed with water, and the solid was recrystallized from methanol to give **3a** (54.2 mg, 86%) as colorless needles, m.p. 193–195°C; ir (potassium bromide): 3260 (br, NH or OH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.01 (m, 2H, H4), 2.74 (t, 2H, J = 7.4 Hz, H5), 2.88 (t, 2H, J = 7.4 Hz, H3), 7.35 (d, 1H, J = 10.4 Hz, changed to singlet after addition of deuterium oxide, NCH=NO), 8.59 (s, 1H, H3′), 9.98 (d, 1H, J = 10.4 Hz, deuterium oxide exchangeable, NH), 10.57 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: m/z 195 (MH^+). Anal. Calcd. for $C_8H_{10}N_4O_2{\cdot}0.1H_2O$: C, 49.03; H, 5.25; N, 28.59. Found: C, 49.07; H, 5.38; N, 28.64.

General procedure for the reaction of 5b–g with hydroxylamine hydrochloride to give 3b–g. To a solution of amidine (**5**) in dry methanol, hydroxylamine hydrochloride was added, and then the mixture was stirred at room temperature for the appropriate time. Water was added, and the mixture was then basified with saturated aqueous sodium bicarbonate solution. The precipitate was filtered, washed with water, and the solid was recrystallized from methanol to give **3**.

***N*-[2-(3-Methyl[1,2,4]oxadiazol-5-yl)cyclopenten-1-yl]formamide oxime (3b).** Compound **5b** (188 mg, 0.90 mmol) was allowed to react with hydroxylamine hydrochloride (96.0 mg, 1.38 mmol) in dry methanol (6.0 mL) for 9 h. Compound **3b** (98.7 mg, 53%) was obtained as pale yellow needles, m.p. 185–187°C; ir (potassium bromide): 3240 (br, NH or OH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.00 (m, 2H, H4), 2.33 (s, 3H, CH_3), 2.70 (t, 2H, J = 7.3 Hz, H5), 2.86 (t, 2H, J = 7.3 Hz, H3), 7.33 (d, 1H, J = 10.4 Hz, changed to singlet after addition of deuterium oxide, NCH=NO), 9.89 (d, 1H, J = 10.4 Hz, deuterium oxide exchangeable, NH), 10.50 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: m/z 209 (MH^+). Anal. Calcd. for $C_9H_{12}N_4O_2{\cdot}0.1H_2O$: C, 51.47; H, 5.86; N, 26.68. Found: C, 51.50; H, 5.88; N, 26.85.

***N*-[2-(3-Ethyl[1,2,4]oxadiazol-5-yl)cyclopenten-1-yl]formamide oxime (3c).** Compound **5c** (420.0 mg, 1.92 mmol) was allowed to react with hydroxylamine hydrochloride (200 mg, 2.88 mmol) in dry methanol (10 mL) for 28 h. Compound **3c** (193.3 mg, 45%) was obtained as colorless needles, m.p. 155–158°C; ir (potassium bromide): 3290 (br, NH or OH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.24 (t, 3H, J = 7.5 Hz, CH_2CH_3), 2.00 (m, 2H, H4), 2.70 (m, 4H, H5, and CH_2CH_3), 2.86 (t, 2H, J = 7.4 Hz, H3), 7.34 (d, 1H, J = 10.3 Hz, changed to singlet after addition of deuterium oxide, NCH=NO), 10.04 (d, 1H, J = 10.3 Hz, deuterium oxide exchangeable, NH), 10.48 (s, 1H, deuterium oxide exchangeable, 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, 6.35; N, 24.96.

***N*-[2-(3-Phenyl[1,2,4]oxadiazol-5-yl)cyclopenten-1-yl]formamide oxime (3d).** Compound **5d** (67.4 mg, 0.25 mmol) was allowed to react with hydroxylamine hydrochloride (106 mg, 1.53 mmol) in dry methanol (4.0 mL) for 5 h. Compound **3d** (62.0 mg, 91%) was obtained as colorless needles, m.p. 190–192°C; ir (potassium bromide): 3260, 3200 (br, NH or OH), 3120 (br, NH or OH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.04 (m, 2H, H4), 2.77 (t, 2H, J = 7.5 Hz, H5), 2.91 (t, 2H, J = 7.5 Hz, H3), 7.42 (d, 1H, J = 10.4 Hz, changed to singlet after addition of deuterium oxide, NCH=NO), 7.59 (m, 3H, Ph-3′, 4′, and 5′), 8.07 (m, 2H, Ph-2′, and 6′), 10.36 (d, 1H, J = 10.4 Hz, deuterium oxide exchangeable, NH), 10.69 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: m/z 271 (MH^+). Anal. Calcd. for $C_{14}H_{14}N_4O_2{\cdot}0.2H_2O$: C, 61.39; H, 5.30; N, 20.46. Found: C, 61.36; H, 5.37; N, 20.45.

***N*-[2-[3-(4-Chlorophenyl)[1,2,4]oxadiazol-5-yl]cyclopenten-1-yl]formamide oxime (3e).** Compound **5e** (190.0 mg, 0.63 mmol) was allowed to react with hydroxylamine hydrochloride (264 mg, 3.80 mmol) in dry methanol (6.0 mL) for 19 h. Compound **3e** (140.8 mg, 73%) was obtained as yellow needles, m.p. 200–203°C; ir (potassium bromide): 3220, 3140 (br, NH or OH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.04 (m, 2H, H4), 2.77 (t, 2H, J = 7.5 Hz, H5), 2.91 (t, 2H, J = 7.5 Hz, H3), 7.43 (d, 1H, J = 10.4 Hz, changed to singlet after addition of deuterium oxide, NCH=NO), 7.65 (m, 2H, Ph-3′ and 5′), 8.05 (m, 2H, Ph-2′ and 6′), 10.27 (d, 1H, J = 10.4 Hz, deuterium oxide exchangeable, NH), 10.69 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: m/z 305 (MH^+), 307 (MH^+ + 2). Anal. Calcd. for $C_{14}H_{13}ClN_4O_2$: C, 55.18; H, 4.30; N, 18.39. Found: C, 55.23; H, 4.49; N, 18.39.

***N*-[2-[3-(4-Fluorophenyl)[1,2,4]oxadiazol-5-yl]cyclopenten-1-yl]formamide oxime (3f).** Compound **5f** (291.7 mg, 1.03 mmol) was allowed to react with hydroxylamine hydrochloride (430 mg, 6.19 mmol) in dry methanol (10 mL) for 6 h. Compound **3f** (202.9 mg, 69%) was obtained as yellow crystals, m.p. 206–209°C; ir (potassium bromide): 3280, 3180 (br, NH or OH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.04 (m, 2H, H4), 2.77 (t, 2H, J = 7.4 Hz, H5), 2.91 (t, 2H, J = 7.4 Hz, H3), 7.40 (m, 2H, Ph-3′, and 5′), 7.41 (d, 1H, J = 10.0 Hz, changed to singlet after addition of deuterium oxide, NCH=NO), 8.09 (m, 2H, Ph-2′, and 6′), 10.29 (d, 1H, J = 10.0 Hz, deuterium oxide exchangeable, NH), 10.69 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: m/z 289 (MH^+). Anal. Calcd. for $C_{14}H_{13}FN_4O_2$: C, 58.33; H, 4.55; N, 19.44. Found: C, 58.04; H, 4.71; N, 19.25.

***N*-[2-[3-(3-Methylphenyl)[1,2,4]oxadiazol-5-yl]cyclopenten-1-yl]formamide oxime (3g).** Compound **5g** (182.0 mg, 0.649 mmol) was allowed to react with hydroxylamine hydrochloride (361 mg, 5.19 mmol) in dry methanol (8.0 mL) for 22 h. Compound **3g** (146 mg, 79%) was obtained as colorless needles, m.p. 193–194°C; ir (potassium bromide): 3240, 3120 (br, NH or OH) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.05 (m, 2H, H4), 2.40 (s, 3H, CH_3), 2.77 (t, 2H, J = 7.4 Hz, H5), 2.91 (t, 2H, J = 7.4 Hz, H3), 7.42 (d, 1H, J = 10.3 Hz, changed to singlet after addition of deuterium oxide, NCH=NO), 7.45 (m, 2H, Ph-4′ and 5′), 7.85 (m, 1H, Ph-6′), 7.91 (br s, 1H, Ph-2′), 10.46 (d, 1H, J = 10.3 Hz, deuterium oxide exchangeable, NH), 10.72 (s, 1H, deuterium oxide exchangeable, OH); FAB-ms: m/z 285

(MH^+). Anal. Calcd. for $C_{15}H_{16}N_4O_2 \cdot 0.2H_2O$: C, 62.57; H, 5.74; N, 19.46. Found: C, 62.80; H, 5.87; N, 19.45.

Measurement of platelet aggregation. Preparation of platelet and measurement of platelet aggregation were done according to the method described previously [8].

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REFERENCES AND NOTES

[1] Part 65: Okuda, K.; Deguchi, H.; Hirota, T.; Sasaki, K. Chem Pharm Bull 2010, 58, 755.

[2] Hsieh, P. W.; Hwang, T. L.; Wu, C. C.; Chang, F. R.; Wang, T. W.; Wu, Y. C. Bioorg Med Chem Lett 2005, 15, 2786.

[3] Hung, C. C.; Tsai, W. J.; Kuo, L. M. Y.; Kuo, Y. H. Bioorg Med Chem 2005, 13, 1791.

[4] Wang, T. C.; Chen, I. L.; Lu, P. J.; Wong, C. H.; Liao, C. H.; Tsiao, K. C.; Chang, K. M.; Chen, Y. L.; Tzeng, C. C. Bioorg Med Chem 2005, 13, 6045.

[5] Hsieh, P. W.; Hwang, T. L.; Wu, C. C.; Chiang, S. Z.; Wu, C. I.; Wu, Y. C. Bioorg Med Chem Lett 2007, 17, 1812.

[6] Chen, I. L.; Chang, K. M.; Miaw, C. L.; Liao, C. H.; Chen, J. J.; Wang, T. C. Bioorg Med Chem 2007, 15, 6527.

[7] Hsieh, P. W.; Chiang, S. Z.; Wu, C. C.; Lo, Y. C.; Shih, Y. T.; Wu, Y. C. Bioorg Med Chem 2008, 16, 5803.

[8] Okuda, K.; Zhang, Y.-X.; Ohtomo, H.; Hirota, T.; Sasaki, K. Chem Pharm Bull 2010, 58, 369.

[9] It seemed that amidines **5** decomposed slightly during reaction as well as purification by column chromatography. In the case of **5e** and **5g**, severe decomposition occurred to cause quite law yield (5 and 9%, respectively).

[10] Born, G. V. R.; Cross, M. J. J Physiol 1963, 168, 178.

[11] Ikeda, Y. Thromb Haemostasis 1999, 82, 435.