# Potent Platelet-Derived Growth Factor-$\beta$ Receptor (PDGF-$\beta$R) Inhibitors: Synthesis and Structure–Activity Relationships of 7-[3-(Cyclohexylmethyl)ureido]-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one Derivatives

Katsuyuki AOKI,*[,a,c] Tatsuhiro OBATA,[a] Yosuke YAMAZAKI,[a] Yoshikazu MORI,[a,c] Hiroko HIROKAWA,[a] Jun-ichi KOSEKI,[a] Tomohisa HATTORI,[a] Kazuaki NIITSU,[a] Shuichi TAKEDA,[a] Masaki ABURADA,[b] and Ken-ichi MIYAMOTO[c]

[a] *R & D Division, Tsumura & Co.; 3586 Yoshiwara, Ami-machi, Inashiki-gun, Ibaraki 300–1192, Japan:* [b] *Research Institute of Pharmaceutical Sciences, Musashino University; 1–1–20 Shinmachi, Nishitokyo, Tokyo 202–8585, Japan: and* [c] *Department of Clinical Pharmacy, Graduate School of Natural Science and Technology, Kanazawa University; 13–1 Takaramachi, Kanazawa, Ishikawa 920–8641, Japan.*

Received August 10, 2006; accepted November 14, 2006; published online December 8, 2006

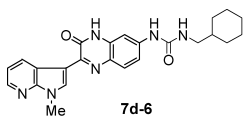
**We found previously that 7-[3-(cyclohexylmethyl)ureido]-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one (7d-6) has considerable potency as a PDGF inhibitor. This compound showed potent inhibitory activity in a PDGF-induced CPA (Cell Proliferation Assay) and APA (Auto-Phosphorylation Assay) ($IC_{50}$= 0.05 $\mu$mol/l in CPA, 0.03 $\mu$mol/l in APA). Therefore, we tried to develop a novel and effective PDGF-$\beta$R inhibitor by optimizing a series of its derivatives. We found that trifluoroacetic acid (TFA)-catalyzed coupling of pyrrolo[2,3-b]pyridines with quinoxalin-2-ones proceeded efficiently under mild oxidation condition with manganese(IV) oxide ($MnO_2$) *in situ*, so this method was applied to prepare a series of derivatives. Results of *in vitro* screening of newly synthesized derivatives identified compound 7d-9 as having potent ($IC_{50}$=0.014 $\mu$mol/l in CPA, 0.007 $\mu$mol/l in APA) and selective [$IC_{50}$ values against vascular endothelial growth factor receptor 2 (VEGFR2, kinase domain region, KDR), epidermal growth factor receptor (EGFR), c-Met (hepatocyte growth factor receptor) and insulin growth factor I receptor (IGF-IR)/$IC_{50}$ against PDGFR were each >1000] inhibitory activity. Moreover, in this series of derivatives, 7b-2 showed potent inhibitory activity toward both PDGF- and VEGF-induced signaling (PDGFR: $IC_{50}$=0.004 $\mu$mol/l in CPA, 0.0008 $\mu$mol/l in APA, KDR: $IC_{50}$=0.008 $\mu$mol/l in APA). Herein we report a new and convenient synthetic method for this series of derivatives and its SAR study.**

**Key words** platelet-derived growth factor (PDGF); tyrosine kinase inhibitor; pyrrolo[2,3-b]pyridine; quinoxalin-2-one; Friedel–Crafts reaction

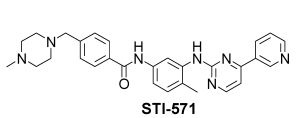
PDGF[1—3] is a glycoprotein that is produced by a large number of normal as well as transformed cell types, and it acts not only on connective tissue cells but also on other types of cells. It is also well known that PDGF participates in the onset of illness, *e.g.*, arteriosclerosis and restenosis,[4—8] fibrosis,[9,10] nephritis,[11] along with its role in physiological phenomena such as generating processes in living organisms and aiding the wound healing process. An attractive target to treat proliferative disorders is to block abnormal PDGF-induced cell proliferation. PDGF-induced cell proliferation is caused by the ligand binding to its cell surface receptor, followed by dimerization of the receptor and auto-phosphorylation of tyrosine kinase domain.[12—16]

Various recent approaches to blocking the pathways mediated by PDGFR tyrosine kinase have led to the discovery of a wide range of small-molecule inhibitors, *e.g.*, the indole-2-ones,[17—20] the quinoxalines,[21—23] the tyrophostines,[24,25] the pyridylpyrimidines,[26,27] the quinolines and quinazolines,[28—34] the indoles,[35,36] the imidazoles,[37,38] the pyrazoles.[39] We also found previously that the in-house compound 7-[3-(cyclohexylmethyl)ureido]-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one (**7d-6**) showed potent inhibitory activity toward PDGF-induced CPA and APA. Table 1 shows the inhibitory activity of **7d-6** ($IC_{50}$=0.05 $\mu$mol/l in CPA, 0.03 $\mu$mol/l in APA) against PDGF compared to the inhibitory activity of STI-571,[26,27] CT52923[28] and SU6668,[17] which have been evaluated in a clinical trial. As the data show, **7d-6** had a more potent inhibitory activity in CPA and APA against PDGF than did the other compounds. Encouraged by these promising results, we carried out a more extensive Structure–Activity Relationships (SAR) study of 3-

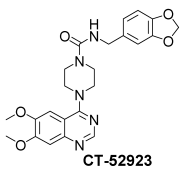
Table 1. Inhibitory Activities of the Inhibitors against PDGF



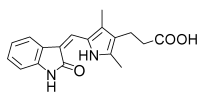

**7d-6**



**STI-571**



**CT-52923**




**SU-6668**

| Compd. | CPA PDGF-BB $IC_{50}$ ($\mu$mol) | APA PDGFR-$\beta$ $IC_{50}$ ($\mu$mol) |
|---|---|---|
| **7d-6** | 0.05 | 0.03 |
| STI-571 | 0.4 | 0.34 |
| CT-52923 | 0.1 | 0.08 |
| SU-6668 | 0.6 | 0.10 |

**7d-6**, (lead compound in this series), CPA: PDGF-induced proliferation of human MC *in vitro*. APA: PDGF receptor auto-phosphorylation of human AoSMC *in vitro*. PDGF-BB: platelet-derived growth factor-BB, PDGFR-$\beta$: platelet-derived growth factor receptor-$\beta$.

* To whom correspondence should be addressed. e-mail: aoki_katsuyuki@mail.tsumura.co.jp

{pyrrolo[2,3b]pyridin-3-yl}quinoxalin-2-ones by modifying the position and substituent of the urea, modifying the 1 and 7-position on the pyrrolo[2,3-b]pyridine ring, and changing the substituent on the quinoxalin-2-one ring. We also developed a convenient synthetic method for the basic framework, *i.e.* the 3-{pyrrolo[2,3b]pyridin-3-yl}quinoxalin-2-ones, as a synthetic protocol has never been reported for this compound. This then allowed us to carry out a more extensive SAR study. Herein we report a new and convenient synthetic method for this series of derivatives and we describe an *in vitro* SAR study.

## Chemistry

Typical approaches to synthesizing 3-(indol-3-yl)quinoxalin-2-ones[40—45] rely on condensation of 2-(indol-3-yl)-2-oxoacetate with 1,2-phenylenediamine (see Chart 1, A). Condensation of 2-(indol-3-yl)-2-oxoacetate, which was prepared by oxalyl chloride treatment of indoles, with 1,2-phenylenediamines easily afforded the desired product. However, using this condition with a substituted quinoxalin-2-one might generate an inseparable mixture of isomers. Moreover, our results indicated that the reaction of 7-azaindole with oxalyl chloride failed to yield the corresponding 3-{pyrrolo[2,3-b]pyridine-3-yl}-3-oxoacetate under conventional conditions for this reaction. Chupakhin *et al.*,[46] previously reported a synthetic method for 3-(indol-3-yl)quinoxalin-2-one that included acetic acid-catalyzed Friedel–Crafts type coupling (see Chart 1, B). The condition for this reaction was mild and convenient compared with the condition[40—45] described previously. However, the yield was not sufficient because products with different oxidizing states were generated, *i.e.*, an unsaturated coupling-product and a saturated one. It occurred to us that addition of a mild oxidant such as $MnO_2$ *in situ* after the acid-catalyzed coupling of indoles with quinoxalin-2-one might accelerate the oxidation from the saturated coupling-product to the unsaturated one. Thus we attempted a novel synthetic route to generate 3-{pyrrolo[2,3-b]pyridin-3-yl}quonoxalin-2-one derivatives utilizing this strategy (see Chart 1, C).

A concise description of the preparation of starting materials, *i.e.*, compounds **1a**—**i** and **4a**—**d**, is outlined in Charts 2 and 3. Almost all of the compounds **1a**—**h** were directly pre-

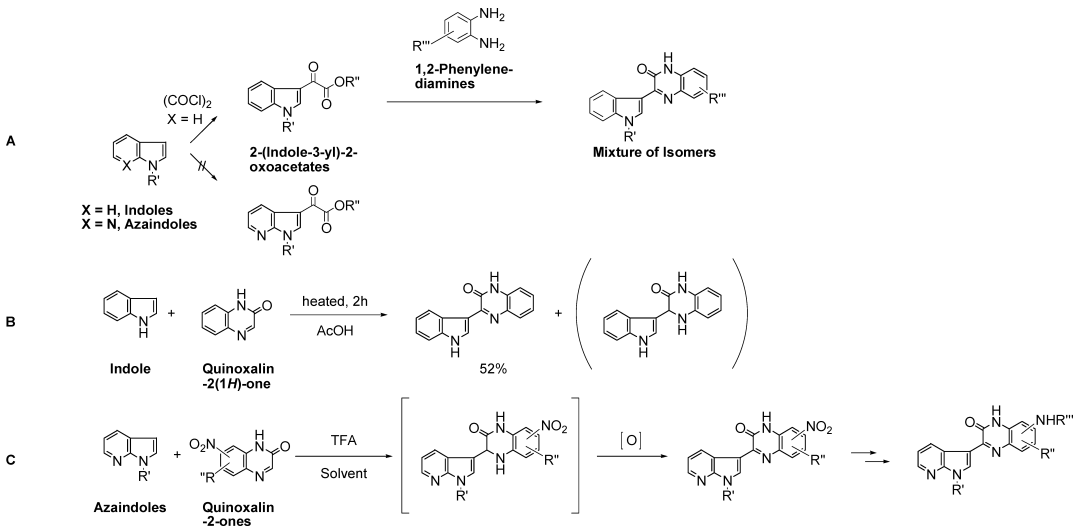
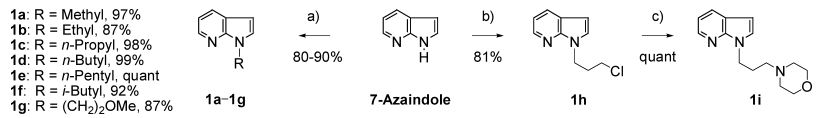
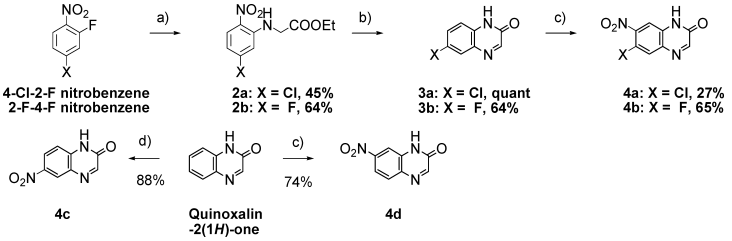



Chart 1. (A) Typical Synthetic Procedure for 3-(Indol-3-yl)quinoxalin-2-ones and Our Result in Preparing 2-{Pyrrolo[2,3-b]pyridin-3-yl}-2-oxoacetate, (B) Synthetic Method of Ref. 18, (C) Our Strategy for Synthesis of 3-{Pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2-ones




a) NaH, alkyl halide, DMF, b) 1-bromo-3-chloropropane, NaH, DMF, c) morpholine, 110 °C

Chart 2



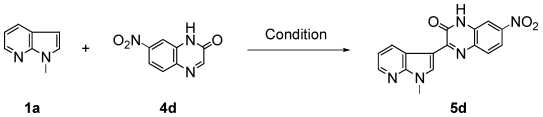

a) Ethyl 2-aminoacetate, $K_2CO_3$, 80 °C, b) 1) 10% Pd–C, EtOH, 2) 2 mol/l NaOH aq., 3% $H_2O_2$ aq., 80 °C, c) fuming $HNO_3$, AcOH, d) $NaNO_3$, $cH_2SO_4$.

Chart 3

pared by coupling of 7-azaindole treated with sodium hydride (NaH) in dimethylformamide (DMF) with the corresponding alkylhalides. Compound **1i** was prepared by substituting the corresponding **1h** with morpholine in DMF. Nitration of quinoxalin-2-one as described in the literature[47,48] provided **4c** and **4d**. **4a** and **4b** were prepared from 4-chloro-2-fluoronitrobenzene or 2,4-difluoronitrobenzene by following the substitution with ethyl 2-aminoacetate with potassium carbonate ($K_2CO_3$) in DMF, reduction by 10% Pd–C in EtOH, and mild oxidation with 3% $H_2O_2$ aq.

Next, we examined the optimal reaction conditions for Friedel-Crafts type coupling (see Table 2). However, our studies using the previous condition[46] led to an unsatisfactory result (Entry 3, 4) because the insoluble saturated coupling-product was deposited and the reaction did not progress following oxidation. In our work-up of this reaction, after filtration of manganese residue with celite, the organic solvent is removed *in vacuo*. Then the deposited precipitate is filtered to give the desired compound. Further purification of the product of this reaction was not necessary. In general, the reaction condition for oxidation with $MnO_2$ should provide the nitro compounds in higher yield than the condition with $H_2O_2$ aq. (Entry 1, 2). It is desirable to use a solvent such as DMF for the solvent of this reaction, as it can dissolve the saturated product obtained by coupling, in order to proceed to the following reaction with $MnO_2$. The other compounds **5a**—**m** (see Table 3, Entry 1—13) were also prepared by the same procedure as that used for **5d**, from corresponding indoles (**1a**—**i**, 7-azaindole, and 1-methylindole) and quinoxalin-2-ones (**4a**—**d**).

Table 2. Synthesis of 7-Nitro-3-(1*H*-pylloro[2,3-b]pyridin-3yl)quinoxalin-2(1*H*)-one (**5d**)



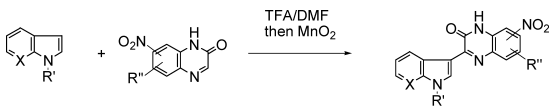

| Entry | Condition | **5d** Yield (%)[a] |
|---|---|---|
| 1 | TFA/DMF (1/10), 80 °C, 1 h, then $MnO_2$,[b] 80 °C, 0.5 h | 87 |
| 2 | TFA/DMF (1/11), 80 °C, 1 h, then 2 mol/l NaO $H_{aq}$, 3% $H_2O_2$ aq., 80 °C, 0.5 h | 51 |
| 3 | AcOH, 80 °C, 6 h | Trace[c] |
| 4 | AcOH, refl, 24 h | 46 |

*a*) Isolated yield, *b*) 3-fold amount compared to starting material. *c*) The saturated product was obtained as a major product.

Almost all of the amino compounds (**6b**—**d**, **6f**—**m**) were prepared (Table 4) from the corresponding nitro compounds by a reduction with 10% Pd–C, HCOOH, triethylamine (TEA) in solvent (typically DMF) without over-reduction (Method A, Entry 2—4 and 6—13). *tert*-Boc (*tert*-butoxycarbonyl) protection at the 1-position on pyrrolo[2,3-b]pyridine ring, followed by the same reduction, provided **6e** (Method B, Entry 5). **6a** could not be obtained by Method A due to accompanying hydrogenolysis of the chlorine atom at the 6-position on the quinoxalin-2-one ring, so it was prepared by reduction with iron powder in conc. hydrochloric acid and MeOH (Method C, Entry 1).

The preparation methods for **7d-1**—**d-5** are outlined in Chart 4. Condensation of triphosgene-treated **6d** with *N*-(2-chloroethyl)-*N*′-cyclohexylmethylamine hydrochloride (see Experimental section), followed by addition of 1,8-diazabicyclo[5.4.0]undec-7ene (DBU) provided **7d-1** in modest yield. **7d-2** was prepared by a reaction of **6d** with cyclohexylmethyl thioisocyanate in THF. **7d-3** was prepared by a reaction of phenyl chloroformate-treated **6d** with cyclohexanemethanol. **7d-4** and **7d-5** were prepared by a reaction of **6d** with the corresponding acid chloride. Preparation of the other derivatives is outlined in Chart 5. Almost all of the derivatives **7d-6**—**d-20** with various functional groups at the terminal position of the urea were prepared by condensation of **6d** with various corresponding amines, after treatment with either triphosgene or phenyl chlorocarbonate of **6d**. **7c-1**, which has

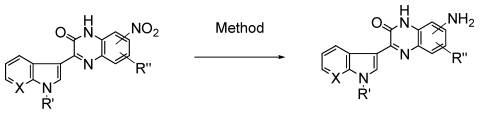
Table 3. Synthesis of Nitro Products (**5a**—**5m**)




| Entry | Indoles | Quinoxalines | Nitro products | | | | |
|---|---|---|---|---|---|---|---|
| | | | No. | X | R′ | R″, $NO_2$ | Yield (%)[a] |
| 1 | **1a** | **4a** | **5a** | N | Me | 6-Cl, 7-$NO_2$ | 66 |
| 2 | **1a** | **4b** | **5b** | N | Me | 6-F, 7-$NO_2$ | 87 |
| 3 | **1a** | **4c** | **5c** | N | Me | 6-$NO_2$ | 66 |
| 4 | **1a** | **4d** | **5d** | N | Me | 7-$NO_2$ | 87 |
| 5 | 7-Azaindole | **4d** | **5e** | N | H | 7-$NO_2$ | Quant |
| 6 | 1-Methylindole | **4d** | **5f** | CH | Me | 7-$NO_2$ | 84 |
| 7 | **1b** | **4b** | **5g** | N | Et | 6-F, 7-$NO_2$ | 84 |
| 8 | **1c** | **4b** | **5h** | N | *n*-Pr | 6-F, 7-$NO_2$ | 72 |
| 9 | **1d** | **4b** | **5i** | N | *n*-Bu | 6-F, 7-$NO_2$ | Quant |
| 10 | **1e** | **4b** | **5j** | N | *n*-Pent | 6-F, 7-$NO_2$ | 75 |
| 11 | **1f** | **4b** | **5k** | N | *i*-Bu | 6-F, 7-$NO_2$ | 71 |
| 12 | **1g** | **4b** | **5l** | N | $(CH_2)_2OMe$ | 6-F, 7-$NO_2$ | 72 |
| 13 | **1i** | **4b** | **5m** | N | $(CH_2)_3$Mor[b] | 6-F, 7-$NO_2$ | 77 |

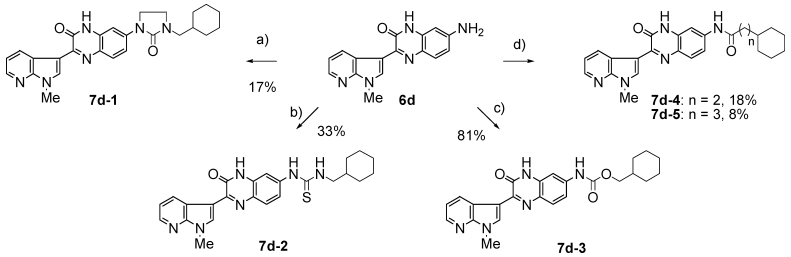
*a*) Isolated yield, *b*) morpholin-1-yl.

Table 4. Synthesis of Amino Products (**6a**—**6m**)




| Entry | Nitro compounds | Method | Amino products | | | | |
|---|---|---|---|---|---|---|---|
| | | | No. | X | R′ | R″, $NH_2$ | Yield (%)[a] |
| 1 | **5a** | C | **6a** | N | Me | 6-Cl, 7-$NH_2$ | 81 |
| 2 | **5b** | A | **6b** | N | Me | 6-F, 7-$NH_2$ | Quant |
| 3 | **5c** | A | **6c** | N | Me | 6-$NH_2$ | 98 |
| 4 | **5d** | A | **6d** | N | Me | 7-$NH_2$ | 71 |
| 5 | **5e** | B | **6e** | N | *t*-Boc | 7-$NH_2$ | 89[b] |
| 6 | **5f** | A | **6f** | CH | Me | 7-$NH_2$ | 89 |
| 7 | **5g** | A | **6g** | N | Et | 6-F, 7-$NH_2$ | 62 |
| 8 | **5h** | A | **6h** | N | *n*-Pr | 6-F, 7-$NH_2$ | 69 |
| 9 | **5i** | A | **6i** | N | *n*-Bu | 6-F, 7-$NH_2$ | 79 |
| 10 | **5j** | A | **6j** | N | *n*-Pent | 6-F, 7-$NH_2$ | 93 |
| 11 | **5k** | A | **6k** | N | *i*-Bu | 6-F, 7-$NH_2$ | 69 |
| 12 | **5l** | A | **6l** | N | $(CH_2)_2OMe$ | 6-F, 7-$NH_2$ | 72 |
| 13 | **5m** | A | **6m** | N | $(CH_2)_3$Mor[c] | 6-F, 7-$NH_2$ | 77 |

Method A: 10% Pd–C, HCOOH, TEA, DMF, 80 °C, 1—2 h, Method B: 1) *t*-$Boc_2O$, TEA, DMAP, DMF, 2) 10% Pd–C, HCOOH, TEA, DMF, 80 °C, 1—2 h, Method C: Fe, conc. HCl, MeOH–DMF, 100 °C, 2 h. *a*) Isolated yield, *b*) 2 steps yield, *c*) morpholin-1-yl.




a) 1) Triphosgene, DIEA, then amine, THF or NMP (*N*-methyl pyrrolidone), 2) DBU, b) cyclohexylmethylisothiocyanate, TEA, THF, c) phenyl chloroformate, DIEA, then cyclohexanemethanol, NMP, d) carboxylic acid chloride, TEA, THF.

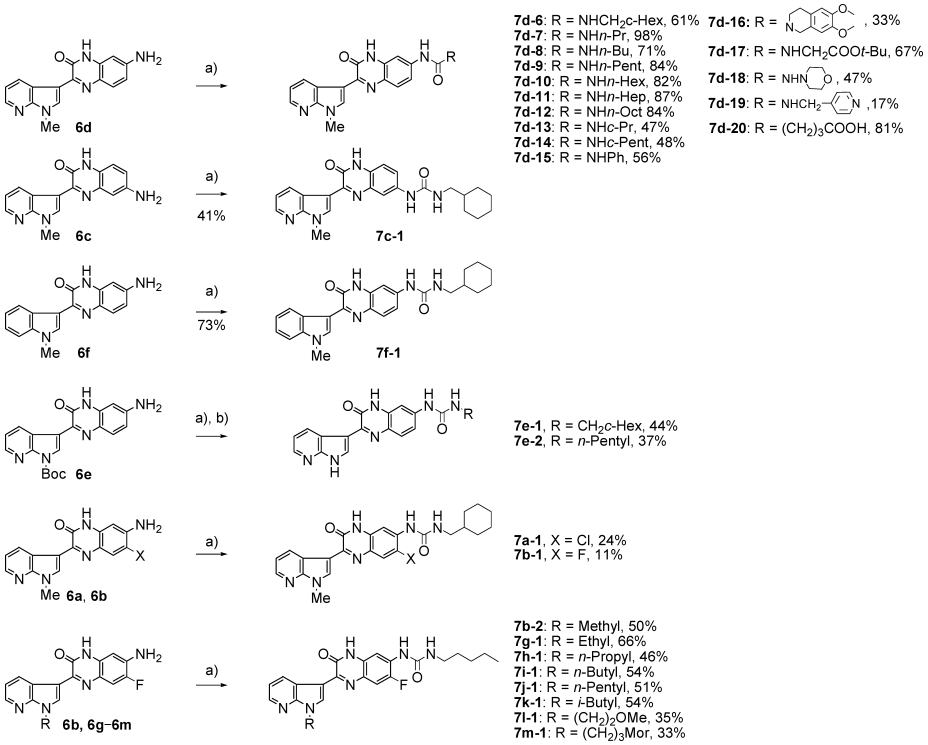
Chart 4

a urea group at the 6-position, and **7f-1**, which bears an indole ring, were prepared from **6c** and **6f** following the same procedure as that used in the preparation of **7d-6**. The halogenated compounds (**7a-1**, **7b-1**) at the 6-position on the quinoxalin-2-one ring and 1-substituted derivatives (**7b-2**—**7m-1**) were also prepared from the corresponding amines (**6a**, **6b**, **6g**—**m**) in the same manner. The same procedure was used for the corresponding **6e** as in the preparation of **7d-6**, and this was followed by de-protection of each *tert*-boc derivative with TFA, provided the corresponding **7e-1** and **7e-2**.

We have demonstrated that the synthetic method described here can be used to prepare various analogues and derivatives through a short process involving direct coupling of various indols with quinoxalin-2-ones, without carrying out special activation reactions. Moreover, since it is not necessary to carry out this reaction under strict anhydrous conditions or to perform special purification in the work-up process, the conditions of this reaction make it a very useful method to synthesize the basic framework of interest.

## Result and Discussion

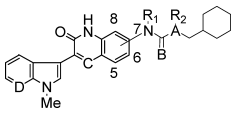
**Structure Activity Relation Study. Effect of Hetero Atom on the Basic Framework and the Position of the Terminal Urea (Table 5)** Although **7d-6**, which has a urea unit, has already demonstrated a potent inhibitory effect, **7d-1**, which was modified to a cyclic urea, and the amides **7d-4** and **7d-5** were less active than **7d-6**. On the other hand, the carbamate **7d-3** retained PDGF inhibitory potency. **7c-1**, with a cyclohexylmethylurea that was substituted at the 6-position on quinoxalin-2-ones showed a significant loss of activity. Modification to thiourea in **7d-2** decreased not only the inhibitory activity ($IC_{50}$=0.81 $\mu$mol/l in CPA, 2.64 $\mu$mol/l in APA), but also the selectivity (VEGF 37.0% inhibition, b-FGF 44.5% inhibition 2 $\mu$mol/l). Moreover, although no remarkable difference was seen in comparing the inhibitory effect of the quinolin-2-one ring of **7n-1** (see Experimental section) with the quinoxalin-2-one ring of **7d-6**, the pyrrolo[2,3-b]pyridine ring of **7d-6** increased the inhibitory activity more than did the indole ring of **7f-1**. These data showed that nitrogen at the 7-position on indole was necessary for the inhibitory activity; on the other hand, nitrogen at the 4-position on quinoxalin-2-one was not sufficient for effective inhibition. Although conversion of quinoxalin-2-one to quinolin-2-one did not make any difference in the inhibitory activity described above, it is still necessary to retain the synthetic availability of nitrogen at the 4-position on quinoxalin-2-one in order to utilize the basic framework in




a) 1) Triphosgen or phenyl chloroformate, 2) amines, b) TFA, 1,2-dichloroethane.

Chart 5

Table 5. Effect of Hetero Atom on the Basic Framework and the Position of the Terminal Urea



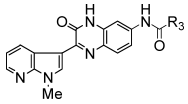
| Compd. | Position | $R_1$ | $R_2$ | A | B | C | D | CPA Inhibition (%)[a] | | | CPA $IC_{50}$ ($\mu$mol/l) | APA $IC_{50}$ ($\mu$mol/l) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | PDGF-BB | VEGF | b-FGF | PDGF-BB | PDGFR-$\beta$ |
| **7d-6** | 7 | H | H | N | O | N | N | 129.7[b] | 18.3[b] | 7.8[b] | 0.050 | 0.030 |
| **7d-1** | 7 | $CH_2CH_2$ | | N | O | N | N | 26.4 | −1.2 | −4.0 | — | 1.895 |
| **7d-2** | 7 | H | H | N | S | N | N | 130.6 | 37.0 | 44.5 | 0.813 | 2.640 |
| **7c-1** | 6 | H | H | N | O | N | N | 7.8 | −10.1 | −3.0 | — | — |
| **7n-1** | 7 | H | H | N | O | CH | N | 119.5 | −14.1 | −2.5 | 0.070 | 0.020 |
| **7f-1** | 7 | H | H | N | O | N | CH | 61.1 | 26.1 | 26.8 | 0.116 | 0.744 |
| **7d-3** | 7 | H | O | | O | N | N | 105.7 | −8.8 | 10.7 | 0.167 | 0.027 |
| **7d-4** | 7 | H | $CH_2$ | | O | N | N | 46.3 | 23.9 | 39.5 | 2.575 | — |
| **7d-5** | 7 | H | $CH_2CH_2$ | | O | N | N | 75.2 | −7.8 | 1.5 | 0.621 | — |

*a*) Inhibition % 1 $\mu$mol/l, *b*) 2 $\mu$mol/l, —: not tested, CPA: PDGF-induced proliferation of human MC *in vitro*. APA: PDGF receptor auto-phosphorylation of human AoSMC *in vitro*. PDGF-BB: platelet-derived growth factor-BB, PDGFR-$\beta$: platelet-derived growth factor receptor-$\beta$, VEGF: vascular endothelial growth factor, b-FGF: basic-fibroblast growth factor.

this series.

**Substituent Effect at the Terminal Urea (Table 6)** In order to examine substituent effects at the terminal urea in detail, we decided to obtain the SAR for insertion effects of methylenes with lengths from C3 to C8 in a straight alkyl chain on urea, as seen in **7d-7**—**d-12**. Results showed that the maximal inhibitory activity ($IC_{50}$=0.007 $\mu$mol/l) in the APA assay was observed for **7d-9**, with a five-carbon on the alkyl chain, and the maximal inhibitory activity ($IC_{50}$=0.009 $\mu$mol/l) in the CPA assay was observed for **7d-10**, which had a six-carbon. Moreover, when we plotted the length of alkyl chain against the common logarithms of $1/IC_{50}$, clear parabolic curves were obtained for both CPA and APA (Fig. 1). In the case of the cyclopropylmethyl derivative **7d-13**, which has a smaller-sized aliphatic ring compared with **7d-6**, the inhibitory activity has disappeared. Also, the cyclopentyl compound **7d-14**, with a shorter alkyl chain than that of **7d-6**, gave a similar result as **7d-13**. Although **7d-15**, with an aromatic ring on the urea, showed loss of potency toward PDGF, the 6,7-dimethoxy1-1,2,3,4-tetrahydroisoquinoline derivative

Table 6. Substituent Effect at the Terminal Urea



| Compd. | $R_3$ | CPA Inhibition (%)[a] | | | CPA $IC_{50}$ ($\mu$mol/l) | APA $IC_{50}$ ($\mu$mol/l) |
|---|---|---|---|---|---|---|
| | | PDGF-BB | VEGF | b-FGF | PDGF-BB | PDGFR-$\beta$ |
| **7d-6** | $NHCH_2c$-Hex | 129.7[b] | 18.3[b] | 7.8[b] | 0.050 | 0.030 |
| **7d-7** | NH *n*-Pr | 24.6[b] | 19.9[b] | 4.7[b] | — | 0.905 |
| **7d-8** | NH *n*-Bu | 83.7 | −1.4 | 0 | 0.140 | 0.017 |
| **7d-9** | NH *n*-Pent | 118.2 | −1.4 | −5.3 | 0.014 | 0.007 |
| **7d-10** | NH *n*-Hex | 121.9 | 2.4 | 1.8 | 0.009 | 0.010 |
| **7d-11** | NH *n*-Hep | 112.6 | −25.9 | −0.6 | 0.025 | 0.052 |
| **7d-12** | NH *n*-Oct | 97.1 | 3.2 | −29.2 | 0.075 | 0.230 |
| **7d-13** | NH*c*-Pr | 16.6 | −9.3 | −10.4 | — | — |
| **7d-14** | NH*c*-Pent | 24.4[b] | 30.0[b] | 14.3[b] | — | — |
| **7d-15** | NHPh | 32.9[b] | 20.7[b] | 2.4[b] | — | — |
| **7d-16** | Dmiq[c] | 115.3 | 5.1 | −3.3 | 0.013 | 0.050 |
| **7d-17** | $NHCH_2COOt$-Bu | 110.7 | −36.3 | 17.4 | 0.020 | 0.010 |
| **7d-18** | NHMor[d] | 121.4[b] | 14[b] | −1.1[b] | 0.200 | 0.070 |
| **7d-19** | $NHCH_2$(4-Pyr)[e] | 30.9 | 16.4[b] | 5.6[b] | — | 1.450 |
| **7d-20** | $NH(CH_2)_3COOH$ | 43.7 | 5.7 | 15.6 | 2.904 | — |

*a*) Inhibition % 1 $\mu$mol/l, *b*) 2 $\mu$mol/l, —: not tested, CPA: PDGF-induced proliferation of human MC *in vitro*. APA: PDGF receptor auto-phosphorylation of human AoSMC *in vitro.* PDGF-BB: platelet-derived growth factor-BB, PDGFR-$\beta$: platelet-derived growth factor receptor-$\beta$, VEGF: vascular endothelial growth factor, b-FGF: basic-fibroblast growth factor, *c*) 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, *d*) morpholin-1-yl, *e*) 4-pyridyl.

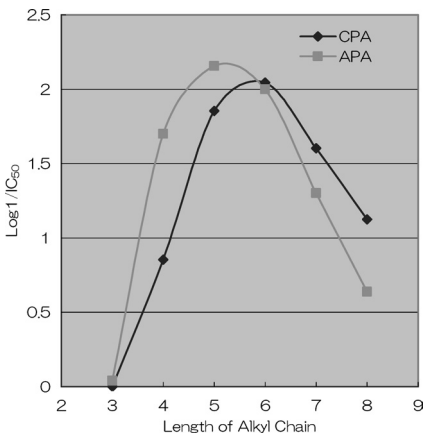


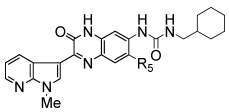

Fig. 1. Correlation of log $1/IC_{50}$ and Length of Alkyl Chain (C3—C8) at the Terminal Urea (**7d-7**—**d-12**)

CPA: PDGF-induced proliferation of human MC *in vitro*. APA: PDGF receptor auto-phosphorylation of human AoSMC *in vitro*. Although the exact value of $IC_{50}$ for a C3-alkyl compound **7d-7** in CPA was not calculated, we expect from the data regarding inhibition % (42.3% 10 $\mu$mol/l) that the $IC_{50}$ is over 10 $\mu$mol/l.

**7d-16** ($IC_{50}$=0.013 $\mu$mol/l in CPA, 0.05 $\mu$mol/l in APA), which has a similar aromatic ring to that of **7d-15**, showed potent inhibitory activity. Introduction of *tert*-butyl hydantoate on urea led to increased inhibitory activity (**7d-17**: $IC_{50}$=0.02 $\mu$mol/l in CPA, 0.01 $\mu$mol/l in APA). In the case of polar groups such as carboxyl and pyridyl (**7d-18**—**d-20**), the inhibitory activity tend to be somewhat decreased. These data show that it is desirable for the functional group on urea to be a substituent that can make a lipophilic interaction at a certain distance from the urea position.

**Introduction Effect of a Fluorine Atom on Quinoxalin-2-one Ring (Table 7)** Promising improvements in PDGF potency were observed for halogenated derivatives. Compared with **7d-6**, the introduction of a fluorine atom at the 6-position on the quoinoxalin-2-one ring showed more PDGF potency (3-fold) in the cellular assay (**7b-1**: $IC_{50}$=0.02 $\mu$mol/l in CPA, 0.009 $\mu$mol/l in APA), but conversion to a chlorine atom at the same position completely blocked the inhibitory activity (**7a-1**). Remarkable difference were observed in these halogenated derivatives because the chlorine atom was electrically neutral but sterically bulkier, compared with the fluorine atom. Thus, it appeared that the fluorine atom was a more favorable substituent at this position.

Table 7. Effect of Introducing a Fluorine Atom on the Quinoxalin-2-one Ring

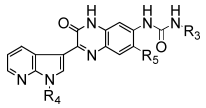


| Compd. | $R_5$ | CPA Inhibition (%)[a] | | | CPA $IC_{50}$ ($\mu$mol/l) | APA $IC_{50}$ ($\mu$mol/l) |
|---|---|---|---|---|---|---|
| | | PDGF-BB | VEGF | b-FGF | PDGF-BB | PDGFR-$\beta$ |
| **7d-6** | H | 129.7[b] | 18.3[b] | 7.8[b] | 0.050 | 0.030 |
| **7b-1** | F | 89.6 | −11.5 | −8.6 | 0.020 | 0.009 |
| **7a-1** | Cl | 13.9 | −3.1 | −0.6 | — | — |

*a*) Inhibition % 1 $\mu$mol/l, *b*) 2 $\mu$mol/l, —: not tested, CPA: PDGF-induced proliferation of human MC *in vitro*. APA: PDGF receptor auto-phosphorylation of human AoSMC *in vitro*. PDGF-BB: platelet-derived growth factor-BB, PDGFR-$\beta$: platelet-derived growth factor receptor-$\beta$, VEGF: vascular endothelial growth factor, b-FGF: basic-fibroblast growth factor.

**Effect of Introducing Substituents at the 1-Position on the Pyrrolo[2,3-b]-pyridine Ring (Table 8)** Removal of the methyl group at the 1-position on the pyrrolo[2,3-b]pyridine led to loss of inhibitory activity for the cyclohexyl compound **7e-1** and the *n*-pentyl compound **7e-2**. The *n*-Pentyl group of urea (**7d-9**) and the 6-fluoro atom on the quinoxalin-2-one ring (**7b-1**) have previously been shown to be ef-

Table 8. Effect of Introducing Substituents at the 1-Position on the Pyrrolo[2,3-b]pyridine Ring



| Compd. | $R_3$ | $R_4$ | $R_5$ | CPA Inhibition (%)[a] | | | CPA $IC_{50}$ ($\mu$mol/l) | APA $IC_{50}$ ($\mu$mol/l) |
|---|---|---|---|---|---|---|---|---|
| | | | | PDGF-BB | VEGF | b-FGF | PDGF-BB | PDGFR-$\beta$ |
| **7d-6** | $CH_2c$-Hex | Me | H | 129.7[b] | 18.3[b] | 7.8[b] | 0.050 | 0.030 |
| **7e-1** | $CH_2c$-Hex | H | H | 50 | 11.6 | 3.4 | — | — |
| **7d-9** | *n*-Pent | Me | H | 118.2 | −1.4 | −5.25 | 0.014 | 0.007 |
| **7e-2** | *n*-Pent | H | H | 99.4 | −7.7 | 0.5 | 0.171 | 0.120 |
| **7b-2** | *n*-Pent | Me | F | 122.3 | 55.1 | 0.5 | 0.004 | 0.0008 |
| **7g-1** | *n*-Pent | Et | F | 139.3 | −6.1 | −19.9 | 0.016 | 0.0060 |
| **7h-1** | *n*-Pent | *n*-Pr | F | 117.2 | 14.1 | 11.8 | 0.023 | 0.0080 |
| **7i-1** | *n*-Pent | *n*-Bu | F | 117.9 | 7.2 | −27.3 | 0.040 | 0.0220 |
| **7j-1** | *n*-Pent | *n*-Pent | F | 69 | 3.8 | −6.2 | — | 0.2740 |
| **7k-1** | *n*-Pent | *i*-Bu | F | 117.3 | 6.0 | −16.5 | 0.054 | 0.0210 |
| **7l-1** | *n*-Pent | $(CH_2)_2OMe$ | F | 127.2 | 11.9 | −24.4 | 0.045 | 0.0050 |
| **7m-1** | *n*-Pent | $(CH_2)_3$Mor[c,d] | F | 145.2 | −14.0 | −4.8 | 0.111 | 0.0180 |

*a*) Inhibition % 1 $\mu$mol/l, CPA: PDGF-induced proliferation of human MC *in vitro*. APA: PDGF receptor auto-phosphorylation of human AoSMC *in vitro*, PDGF-BB: platelet-derived growth factor-BB, PDGFR-$\beta$: platelet-derived growth factor receptor-$\beta$, VEGF: vascular endothelial growth factor, b-FGF: basic-fibroblast growth factor, *c*) morpholin-1-yl, *d*) HCl salt.

fective substituents increasing the potency against PDGF, and still more potent inhibitory activity against PDGF is obtained by combining these substituents ($IC_{50}$=0.004 $\mu$mol/l in CPA, 0.0008 $\mu$mol/l in APA) (**7b-2**). Although simple alkyl chains at the 1-position on the pyrrolo[2,3-b]pyridine ring have not affected the inhibitory activity in the CPA (**7b-2**—**j-1**), the SAR study indicated that the inhibitory activity of these compounds in APA might be decreased along with the length of the alkyl chain. Introduction of an alkyl chain with a 3-morpholinopropyl group (**7m-1**: $IC_{50}$=0.111 $\mu$mol/l in CPA, 0.018 $\mu$mol/l in APA) at the 1-position on the pyrrolo[2,3-b]pyridine ring led to less inhibitory activity in CPA and APA than was seen for the simple alkyl group. Introduction of a methoxyethyl group, compared with a simple alkyl group, retained the potency in both the CPA and APA (**7l-1**: $IC_{50}$=0.045 $\mu$mol/l in CPA, 0.005 $\mu$mol/l in APA).

**Summary of $IC_{50}$ Values for a Series of Compounds Tested against PDGF and Their Selectivity to the Other Growth Factors (Table 9)** Finally, a summary of the $IC_{50}$ values for a series of compounds tested against PDGF and other growth factors is given in Table 7. **7d-6**, **7d-9** and **7m-1** not only potently inhibited PDGF-induced cell proliferation and auto-phosphorylation, but also showed selectivity for PDGF when tested against other growth factors. In particular, **7d-9** showed very good PDGF potency ($IC_{50}$=0.014 $\mu$mol/l in CPA, 0.007 $\mu$mol/l in APA) with strong selectivity for PDGF over the other growth factors (the $IC_{50}$ values against KDR, EGFR, c-Met and IGF-IR/$IC_{50}$ against PDGFR were each >1000). Taking into consideration the improved water solubility in the successful optimization of derivatives in this series, **7l-1** and **7m-1**, which have the water-soluble groups 3-morpholinopropyl and methoxyethyl, might be especially promising candidates as PDGF inhibitors. Although it appeared that fluorinated derivatives (**7b-1**, **7b-2**) were promising candidates as PDGF inhibitors deserving further optimization, it was revealed that they had not only strong PDGF potency, but they also inhibited VEGF. Nonetheless,

Table 9. Summary of $IC_{50}$ Values ($\mu$mol/l) for a Series of Compounds Acting against PDGF and the Selectivity with Respect to Other Growth Factors

| Compd. | CPA | APA | | | | |
|---|---|---|---|---|---|---|
| | PDGF-BB | PDGFR-$\beta$ | KDR | EGFR | c-Met | IGF-IR |
| | | PDGF | VEGF | EGF | HGF | IGF-I |
| **7d-6** | 0.050 | 0.0300 | >10 | >10 | >10 | >10 |
| **7d-9** | 0.014 | 0.0070 | >10 | >10 | >10 | >10 |
| **7b-1** | 0.020 | 0.0090 | 0.100 | >10 | >10 | >10 |
| **7b-2** | 0.004 | 0.0008 | 0.008 | >10 | >10 | >10 |
| **7l-1** | 0.045 | 0.0050 | 0.070 | >10 | >10 | >10 |
| **7m-1** | 0.111 | 0.0180 | >10 | >10 | >10 | >10 |

CPA: PDGF-induced proliferation of human MC *in vitro*. APA: PDGF receptor auto-phosphorylation of human AoSMC *in vitro*. PDGF-BB: platelet-derived growth factor-BB, PDGF: platelet-derived growth factor, VEGF: vascular endothelial growth factor, EGF: epidermal growth factor, HGF: hepatocyte growth factor, IGF-I: Type 1 insulin-like growth factor, PDGFR-$\beta$: platelet-derived growth factor receptor-$\beta$, KDR: VEGF receptor 2, EGFR: epidermal growth factor receptor, c-Met: hepatocyte growth factor receptor, IGF-IR: Type 1 insulin-like growth factor receptor.

**7b-2** in particular might be a lead compound for a dual PDGF/VEGF inhibitor[20] that could be further improved by optimizing the features affecting potency against both PDGF and VEGF. In addition to the studies described herein, homology modeling of PDGF-$\beta$ plus docking studies of the kinase domain have been completed and the results of these studies will be reported soon.

## Conclusions

During our efforts to improve the synthesis of derivatives, we discovered that TFA-catalyzed coupling of 7-azaindoles with quinoxalin-2-ones proceeded efficiently under mild oxidation conditions with $MnO_2$ *in situ* (Tables 2, 3), and we therefore applied these conditions and prepared a series of derivatives (Charts 4, 5). Moreover, as a result of evaluating the substituent effect on the pyrrolo[2,3-b]pyridine ring in an SAR study, we found that the nitrogen at the 7-position on

the pyrrolo[2,3-b]pyridine ring markedly influenced the PDGF receptor tyrosine kinase inhibition (Table 5, **7d-6** *vs.* **7f-1**). Next, we showed that the 7-position on the quinoxalin-2-one ring would be the optimal substitution position (Table 5, **7c-1** *vs.* **7d-6**). Furthermore, as a result of scrutinizing the substituent effect on urea, it was found that inhibitory activity was correlated with the length of a straight alkyl chain substituent (Table 6, **7d-7**—**d-12**), and we found that the PDGF potency was reinforced by nonpolar substituents (Table 6, **7d-18**—**d-20**). Furthermore, using the insight gained by evaluating the substituent effect on the quinoxalin-2-one ring, we showed clearly that potent inhibitory activity against the PDGF and VEGF receptors resulted from introduction of a fluorine atom at the 6-position (Table 9, **7b-1**, **7b-2**, **7l-1**). Finally, we demonstrated that compound **7d-9**, which has a potent ($IC_{50}$=0.014 $\mu$mol/l in CPA, 0.007 $\mu$mol/l in APA) and selective ($IC_{50}$ against KDR, EGFR, c-Met and IGF-IR/$IC_{50}$ against PDGFR were each >1000) inhibitory activity (Table 9), as well as compound **7b-2**, showed potent inhibitory activity not only toward PDGF-induced signaling but also toward VEGF (PDGFR: $IC_{50}$=0.004 $\mu$mol/l in CPA, 0.0008 $\mu$mol/l in APA, KDR: $IC_{50}$=0.008 $\mu$mol/l in APA).

**Experimental**

The $^1$H-NMR spectra were measured with a JEOL EX-200 (200 MHz) spectrometer with TMS as the internal reference, and chemical shifts are expressed in $\delta$ (ppm). The IR spectrum was measured with a JASCO FT/IR-430 spectrometer. The HR-ESI-MS was taken on a MICROMASS Q-Tof micro.

**General Procedure for the Synthesis of 1a, 1b, 1c, 1d, 1e, 1f, 1g. 1-Methyl-1*H*-pyrrolo[2,3-b]pyridine, 1a** To a solution of 7-azaindole (500 mg, 4.23 mmol) in DMF (5.0 ml) was added NaH (2.2 g, 55.0 mmol) at 0 °C under argon, and the reaction mixture was stirred at room temperature for 0.5 h. Methyl iodide (0.8 ml, 12.7 mmol) was added to the stirring reaction mixture, and the mixture was allowed to stir at room temperature for 15 h. Water was added to the resulting reaction mixture, and the water phase was extracted with $Et_2O$. The combined organic phase was dried over $Na_2SO_4$. Then the organic solvent was removed *in vacuo*. The evaporated residue was purified by flash column chromatography on silica-gel (hexane/AcOEt 3/1) to give the title compound as a yellow oil (544 mg): 97% Yield; $^1$H-NMR ($CDCl_3$) $\delta$: 1.48 (3H, s), 6.45 (1H, d, $J$=3.5 Hz), 7.05 (1H, dd, $J$=4.7, 7.8 Hz), 7.24 (1H, d, $J$=3.5 Hz), 7.90 (1H, dd, $J$=1.6, 7.8 Hz), 8.32 (1H, dd, $J$=1.6, 4.7 Hz).

**1-(3-Chloropropyl)-1*H*-pyrrolo[2,3-b]pyridine, 1h** Replacing methyl iodide with 1-bromo-2-chloroethane and following the same procedure as in the preparation of **1a** gave the title compound as a colorless oil: 81.4% Yield; $^1$H-NMR ($CDCl_3$) $\delta$: 3.92 (2H, t, $J$=6.1 Hz), 4.62 (2H, t, $J$=6.1 Hz), 6.47 (1H, d, $J$=3.5 Hz), 7.08 (1H, dd, $J$=4.7, 7.8 Hz), 7.29 (1H, d, $J$=3.5 Hz), 7.92 (1H, dd, $J$=1.5, 7.8 Hz), 8.30 (1H, dd, $J$=1.5, 4.7 Hz).

**1-(3-Morpholinopropyl)-1*H*-pyrrolo[2,3-b]pyridine, 1i** To a solution of **1h** (633 mg, 3.52 mmol) in DMF (6.0 ml) was added morpholine (1.23 ml), and the reaction mixture was stirred at 110 °C for 4.5 h. Water was added to the resulting reaction mixture, and the water phase was extracted with AcOEt. The combined organic phase was dried over $Na_2SO_4$. Then the organic solvent was removed *in vacuo*. The evaporated residue was purified by flash column chromatography on silica-gel (AcOEt→AcOEt/MeOH 10/1) to give the title compound as a yellow oil: Quantitative Yield; $^1$H-NMR ($CDCl_3$) $\delta$: 2.06 (2H, m), 2.33 (2H, t, $J$=7.2 Hz), 2.38—2.42 (4H, m), 3.67—3.72 (4H, m), 4.37 (2H, t, $J$=6.8 Hz), 6.43 (1H, d, $J$=3.5 Hz), 7.04 (1H, dd, $J$=4.7, 7.9 Hz), 7.23 (1H, d, $J$=3.5 Hz), 7.89 (1H, dd, $J$=1.6, 7.9 Hz), 8.31 (1H, dd, $J$=1.6, 4.7 Hz).

**Ethyl 2-(4-Chloro-2-nitrophenylamino)acetate, 2a** To a mixture of $K_2CO_3$ (4.1 g, 30.0 mmol) and ethyl 2-aminoacetate hydrochloride (7.06 g, 51.0 mmol) in DMF (15 ml) and water (1.0 ml) was added 4-chloro-2-fluoronitrobenzene (8.05 g, 46.0 mmol) at 80 °C, and the reaction mixture was stirred at 80 °C for 1 h. Water was added to the resulting reaction mixture, and the water phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over $MgSO_4$. The organic solvent was removed *in vacuo*. The evaporated residue was purified by flash column chromatography on silica-gel (hexane/EtOAc 4/1) to give the title compound as a yellow solid (5.31 g): 45% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.33 (3H, t, $J$=7.1 Hz), 4.06 (2H, d, $J$=5.3 Hz), 4.31 (2H, q, $J$=7.2 Hz), 6.66—6.72 (2H, m), 8.16 (1H, d, $J$=9.8 Hz), 8.46 (1H, br s).

**Ethyl 2-(4-Fluoro-2-nitrophenylamino)acetate, 2b** Replacing 4-chloro-2-fluoronitrobenzene with 2,4-difluoronitrobenzene and following the same procedure as in the preparation of **2a** gave **2b** as a yellow solid: 44%. Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.33 (3H, t, $J$=7.2 Hz), 4.04 (2H, d, $J$=5.3 Hz), 4.30 (2H, q, $J$=7.2 Hz), 6.34 (1H, dd, $J$=2.5, 11.1 Hz), 6.44 (1H, ddd, $J$=2.5, 7.2, 9.4 Hz), 8.26 (1H, dd, $J$=6.0, 9.4 Hz), 8.55 (1H, br s).

**6-Chloroquinoxalin-2(1*H*)-one, 3a** A mixture of 10% Pd–C wet (0.9 g) and **2a** (5.31 g, 21.0 mmol) in EtOH (68 ml) was stirred overnight at room temperature under $H_2$. After the filtration to remove the catalyst with celite, the filtrate was concentrated *in vacuo*. To a solution of this yellow solid in 2 mol/l NaOH aq. (68 ml) in MeOH (34 ml) was added 3% $H_2O_2$ aq. (68 ml), and the reaction mixture was stirred at 100 °C for 1.5 h. The resulting reaction mixture was acidified with acetic acid (AcOH), and water was added to the mixture. Then the precipitated product was filtered to give the title compound as a yellow solid (3.94 g): Quantitative. Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.30 (1H, d, $J$=8.7 Hz), 7.51 (1H, dd, $J$=2.4, 8.7 Hz), 7.75 (1H, d, $J$=2.4 Hz), 8.09 (1H, s).

**6-Fluoroquinoxalin-2(1*H*)-one, 3b** Replacing **2a** with **2b** and following the same procedure as in the preparation of **3a** gave the title compound as a charcoal solid: 76%. Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.33 (1H, dd, $J$=5.2, 9.0 Hz), 7.48 (1H, ddd, $J$=2.9, 9.0, 9.2 Hz), 7.63 (1H, dd, $J$=3.8, 9.2 Hz), 12.46 (1H, br s).

**6-Chloro-7-nitroquinoxalin-2(1*H*)-one, 4a** Replacing quinoxalin-2(1*H*)-one with **3a** and following the same procedure as in the preparation of **4d** gave the title compound as a yellow solid: 27% Yield (4 step); $^1$H-NMR (DMSO-$d_6$) $\delta$: 7.89 (1H, s), 8.19 (1H, s), 8.36 (1H, s), 12.66 (1H, br s).

**6-Fluoro-7-nitroquinoxalin-2(1*H*)-one, 4b** Replacing quinoxalin-2(*1H*)-one with **3b** and following the same procedure as in the preparation of **4d** gave the title compound as a white solid: 65% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 6.83 (1H, d, $J$=13 Hz), 7.64 (1H, d, $J$=7.6 Hz), 8.87 (1H, d, $J$=3.2 Hz), 11.01 (1H, br s).

**6-Nitroquinoxalin-2(1*H*)-one, 4c** To a solution of quinoxalin-2(1*H*)-one (2.2 g, 15.0 mmol) in conc. $H_2SO_4$ (25 ml) was added potassium nitrate (1.5 g, 15.0 mmol) quickly at 0 °C, and the reaction mixture was stirred at room temperature for 0.5 h. The reaction mixture was poured into crushed ice (500 ml), and then the precipitated product was filtered and washed with water to give the title compound as a white solid (2.53 g): 88%.Yield; $^1$H-NMR ($CDCl_3$) $\delta$: 7.45 (1H, d, $J$=9.1 Hz), 8.33 (1H, s), 8.39 (1H, dd, $J$=2.5, 9.1 Hz,), 8.55 (1H, d, $J$=2.5 Hz), 12.92 (1H, br s). ESI-MS *m/z*: +ESI 192 (M+1), −ESI 190 (M−1).

**7-Nitroquinoxalin-2(1*H*)-one, 4d** To a suspension of quinoxalin-2(1*H*)-one (25 g, 17.1 mmol) in AcOH (500 ml) was added a solution of fuming nitric acid (8.6 ml) in AcOH (50 ml) dropwise at room temperature, and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was poured into crushed ice (50 ml), and then the precipitated product was filtered and washed with water and small amount of AcOEt to give the title compound as a pale yellow solid (24.4 g): 74%. Yield; $^1$H-NMR ($CDCl_3$) $\delta$: 2.52 (3H, s), 7.98—8.11 (3H, m), 8.36 (1H, s), 12.72 (1H, br s).

**General Procedure for the Synthesis of 5a, 5b, 5c, 5d, 5e, 5f, 5g, 5h, 5i, 5j, 5k, 5l, 5m, 3-{1-Methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-7-nitroquinoxalin-2(1*H*)-one, 5d** To a mixture of **1a** (132 mg, 1.0 mmol) and **4d** (191 mg, 1.0 mmol) in DMF (10 ml) was added TFA (1.0 ml) at room temperature, and the reaction mixture was stirred at 80 °C for 1 h. Then $MnO_2$ (300 mg) was added to the stirring reaction mixture, and the mixture was stirred at 80 °C for 1 h. After filtration of the precipitate with celite, the filtrate was concentrated *in vacuo*. The evaporated residue was triturated in MeOH/$Et_2O$, and the precipitated product was filtrated to give the title compound as a yellow solid (280.3 mg): 87.3% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.95 (3H, s), 7.36 (1H, dd, $J$=4.7, 7.8 Hz), 7.99—8.15 (3H, m), 8.42 (1H, dd, $J$=1.7, 4.7 Hz), 9.10 (1H, dd, $J$=1.7, 7.8 Hz), 9.14 (1H, s), 12.80 (1H, s). ESI-MS *m/z*: +ESI 322 (M+1), −ESI 320 (M+1).

**Alternative Procedure for the Synthesis of 5d (Table 2, Entry 2)** To a mixture of **1a** (350 mg, 2.64 mmol) and **4d** (506 mg, 2.64 mmol) in DMF (5.0 ml) was added TFA (0.45 ml), and the reaction mixture was stirred at 80 °C for 15 min. Then 3% $H_2O_2$ aq. (10 ml) and 2 mol/l NaOH aq. (10 ml) were added to the stirring reaction mixture, and the mixture was stirred at 80 °C for 1 h. The resulting reaction mixture was acidified with AcOH, and water was added to the mixture. Then the precipitated product was filtered to

give the title compound as a charcoal solid (436 mg): 51% Yield.

**7-Amino-6-chloro-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one, 6a (Table 4, Method C)** To a mixture of **5a** (50 mg, 0.14 mmol) conc. HCl (0.5 ml) and MeOH (0.5 ml) in DMF was added powder of iron (124 mg) at room temperature, and the reaction mixture was stirred at 100 °C for 2 h. The resulting reaction mixture was filtered with celite, and the filtrate was concentrated *in vacuo*. The precipitate was washed with MeOH to give title compound as a yellow solid (37 mg): 81% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.91 (3H, s), 6.64 (1H, s), 7.27 (1H, dd, $J$=4.7, 7.8 Hz), 7.78 (1H, s), 8.37 (1H, dd, $J$=1.5, 4.7 Hz), 8.86 (1H, s), 9.08 (1H, dd, $J$=1.5, 7.8 Hz), 12.27 (1H, br s). ESI-MS *m/z*: +ESI 327 (M+1), −ESI 325 (M−1).

**General Procedure for the Synthesis of 6b, 6c, 6d, 6f, 6g, 6h, 6i, 6i, 6j, 6k, 6l, 6m, 7-Amino-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one, 6d (Method A)** To a mixture of **5d** (436 mg, 1.35 mmol) and 10% Pd–C wet (85 mg) in MeOH (50 ml) were added TEA (19 ml) and HCOOH (2.4 ml) at room temperature, and then the reaction mixture was refluxed for 1.5 h. The catalyst was removed by filtration with celite, and the filtrate was concentrated *in vacuo*. Water was added to the residue, and the precipitated product was filtered and washed with a small amount of AcOEt to give the title compound as a yellow solid (281 mg): 71% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.80 (3H, s), 5.86 (2H, s), 6.39 (1H, d, $J$=2.3 Hz), 6.59 (1H, dd, $J$=2.3, 8.7 Hz), 7.25 (1H, dd, $J$=4.7, 7.9 Hz), 7.53 (1H, d, $J$=8.7 Hz), 8.35 (1H, dd, $J$=1.6, 4.7 Hz), 8.82 (1H, s), 9.04 (1H, dd, $J$=1.6, 7.9 Hz), 12.14 (1H, br s). ESI-MS *m/z*: +ESI 292 (M+1), −ESI 290 (M−1).

***tert*-Butyl 3-(6-Amino-3,4-dihydro-3-oxoquinoxalin-2-yl)-1*H*-pyrrolo-[2,3-b]pyridine-1-carboxylate, 6e (Method B)** To a mixture of **5e** (600 mg, 1.95 mmol) and TEA (0.82 ml, 5.85 mmol) and dimethylaminopyridine (DMAP) (120 mg) in DMF (20 ml) was added *tert*-$Boc_2O$ (1.27 g, 5.85 mmol) at room temperature, and then the reaction mixture was stirred at 60 °C for 1 h. Water was added to the resulting reaction mixture, and the water phase was extracted with $CHCl_3$. The combined organic phase was washed with Brine and dried over $Na_2SO_4$. The organic solvent was removed *in vacuo*, and the residue was triturated in $Et_2O$. The precipitate was filtered to give *tert*-butyl 3-(1,2-dihydro-7-nitro-2-oxoquinoxalin-3-yl)-1*H*-pyrrolo-[2,3-b]pyridin-1-carboxylate as a yellow solid (588 mg): 74% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.67 (9H, s), 7.48 (1H, dd, $J$=4.7, 8.0 Hz), 8.14—8.16 (3H, m), 8.53 (1H, dd, $J$=1.8, 4.7 Hz), 9.20 (1H, dd, $J$=1.8, 8.0 Hz), 9.35 (1H, s). ESI-MS *m/z*: +ESI 408 (M+1), −ESI 406 (M−1). Replacing **5d** with *tert*-butyl 3-(1,2-dihydro-7-nitro-2-oxoquinoxalin-3-yl)-1*H*-pyrrolo-[2,3-b]pyridine-1-carboxylate and following the same procedure in DMF as in the preparation of **6d** gave the title compound as a yellow solid: 65% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.65 (9H, s), 6.08 (2H, s), 6.41 (1H, d, $J$=2.4 Hz), 6.64 (1H, dd, $J$=2.2, 8.7 Hz), 7.41 (1H, dd, $J$=4.7, 8.0 Hz), 7.59 (1H, d, $J$=8.7 Hz), 8.46 (1H, dd, $J$=1.7, 4.7 Hz), 9.07 (1H, s), 9.16 (1H, dd, $J$=1.7, 8.0 Hz), 12.23 (1H, s). ESI-MS *m/z*: +ESI 378 (M+1), −ESI 376 (M−1).

**7-[3-(Cyclohexylmethyl)-2-oxoimidazolidin-1-yl]-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one, 7d-1** To a mixture of cyclohexane carboxyaldehyde (3.6 ml, 30 mmol) and 2-chloroethylamine (1.16 g, 10 mmol) in EtOH (12 ml) was added 10% Pd–C (100 mg), and then the mixture was stirred at room temperature for 2 h under $H_2$. After removing the catalyst by filtration with celite, the filtrate was crystallized from $Et_2O$ to give a *N*-(2-chloroethyl)-*N*′-(cyclohexylmethyl)amine hydrochloride as a white solid (357 mg): 17% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.85—1.24 (5H, m), 1.65—1.80 (6H, m), 2.79 (2H, d), 3.27 (2H, t, $J$=6.5 Hz), 3.94 (2H, t, $J$=6.5 Hz), 9.02 (2H, br s). To a suspension of **6d** (100 mg, 0.346 mmol) and DIEA (0.2 ml, 1.04 mmol) in THF (5.0 ml) was added triphosgene (102 mg, 0.346 mmol) at room temperature, and the mixture was stirred at 60 °C for 3 h. *N*-(2-chloroethyl)-*N*′-(cyclohexylmethyl)amine hydrochloride (220 mg, 1.04 mmol) and diisopropylethylamine (DIEA) (0.3 ml, 1.72 mmol) were added to the mixture, and the reaction mixture was stirred at room temperature for 1 h. Water was added to the resulting reaction mixture, and the water phase was extracted with $CHCl_3$. The combined organic phase was dried over $Na_2SO_4$. The organic solvent was removed *in vacuo*. Then to a mixture of the residue in THF (5.0 ml) was added DBU (0.5 ml) at room temperature, and the reaction mixture was refluxed for 1.5 h. Water was added to the resulting reaction mixture, and the water phase was extracted with AcOEt. The combined organic phase was dried over $Na_2SO_4$. The organic solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica-gel ($CH_2Cl_2$/Acetone 4/1→$CH_2Cl_2$/MeOH 14/1) to give title compound as a yellow solid (28 mg): 17% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.90—1.70 (11H, m), 3.06 (2H, d), 3.42—3.54 (2H, m), 3.84—3.89 (2H, m), 3.93 (3H, s), 7.30 (1H, dd), 7.54—7.59 (2H, m), 7.81 (1H, m), 8.38 (1H, dd), 8.95 (1H, s), 9.10 (1H, dd), 12.38 (1H, s). IR (KBr) cm$^{-1}$: 2920, 2849, 1694, 1661. ESI-MS *m/z*: +ESI 457 (M+1), −ESI 455 (M−1). HR-ESI-MS *m/z*: 457.2331 (Calcd for $C_{26}H_{29}N_6O_2$: 457.2352).

**7-[3-(Cyclohexylmethyl)thioureido]-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one, 7d-2** To a suspension of **6d** (289 mg, 1.0 mmol) and DIEA (1 drop) in 1-methyl pyrrolidone (5.0 ml) was added cyclohexylmethylisocyanate (168 mg, 1.08 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h. Cyclohexylmethylisocyanate (620 mg, 4.0 mmol) and DIEA (903 mg, 7.0 mmol) were added to the reaction mixture at room temperature. The reaction mixture was stirred at 100 °C for 24 h. To the resulting reaction mixture was added MeOH, and the precipitate was filtered to give the title compound as a charcoal solid (147 mg): 33% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.78—1.40 (5H, m), 1.50—1.85 (6H, m), 3.93 (3H, s), 7.31 (1H, dd, $J$=4.7, 7.9 Hz), 7.38—7.50 (1H, m), 7.61 (1H, d, $J$=2.3 Hz), 7.80 (1H, d, $J$=8.8 Hz), 7.86—8.06 (1H, m), 8.39 (1H, dd, $J$=1.7, 4.7 Hz), 8.99 (1H, s), 9.10 (1H, dd, $J$=1.7, 7.9 Hz), 9.78 (1H, br s), 12.50 (1H, s). IR (KBr) cm$^{-1}$: 3242, 2921, 1662, 1538. ESI-MS *m/z*: +ESI 447 (M+1), −ESI 445 (M−1). HR-ESI-MS *m/z*: 447.1943 (Calcd for $C_{24}H_{27}N_6OS$: 447.1967).

**Cyclohexylmethyl {3,4-Dihydro-2-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-3-oxoquinoxalin-6-yl}carbamate, 7d-3** Replacing aminomethylcyclohexane with cyclohexanemethanol and following the same procedure as in the preparation of **7d-6** gave the title compound as a pale yellow solid: 81% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.98—1.91 (11H, m), 3.93 (3H, s), 3.97 (2H, d), 7.28—7.35 (2H, m), 7.70 (1H, d, $J$=2.1 Hz), 7.78 (1H, d, $J$=8.7 Hz), 8.39 (1H, dd, $J$=1.6, 4.7 Hz), 8.96 (1H, s), 9.10 (1H, dd, $J$=1.6, 7.8 Hz), 10.25 (1H, s), 12.47 (1H, s). IR (KBr) cm$^{-1}$: 3422, 2925, 1720, 1667, 1546, 1233. ESI-MS *m/z*: +ESI 432 (M+1), −ESI 430 (M−1). HR-ESI-MS m/z: 432.2018 (Calcd for $C_{24}H_{26}N_5O_3$: 432.2036).

**2-Cyclohexyl-*N*-{3,4-dihydro-2-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-3-oxoquinoxalin-6-yl}acetamide, 7d-4.** To a solution of cyclohexylacetic acid (31 mg, 0.22 mmol) and DMF (1 drop) in $CH_2Cl_2$ (5.0 ml) was added thionyl chloride (125 mg, 1 mmol), and the mixture was refluxed for 0.5 h. After evaporation of the organic solvent, a solution of **6d** (58 mg, 0.2 mmol) and TEA (20 mg, 0.2 mmol) in DMF (4.0 ml) was added to the stirring residue. The reaction mixture was sonicated for 10 min at room temperature. Diluted sodium bicarbonate aq was added to the resulting reaction mixture, and the precipitated crude product was collected by filtration. The crude product was purified by flash column chromatography on silica-gel (hexane/AcOEt 1/1→1/3) to give the title compound as a pale yellow solid (15 mg): 18% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.82—1.40 (5H, m), 1.55—1.99 (6H, m), 2.24 (2H, d, $J$=7.1 Hz), 3.93 (3H, s), 7.31 (1H, dd, $J$=4.8, 8.1 Hz), 7.43 (1H, dd, $J$=2.1, 8.7 Hz), 7.79 (1H, d, $J$=8.7 Hz), 7.86 (1H, d, $J$=2.1 Hz), 8.39 (1H, dd, $J$=1.5, 4.8 Hz), 8.97 (1H, s), 9.10 (1H, dd, $J$=1.5, 8.1 Hz), 10.19 (1H, s), 12.46 (1H, s). IR (KBr) cm$^{-1}$: 3264, 2918, 2850, 1666, 1536. ESI-MS *m/z*: +ESI 416 (M+1), −ESI 414 (M−1). HR-ESI-MS *m/z*: 416.2074 (Calcd for $C_{24}H_{26}N_5O_2$: 416.2087).

**3-Cyclohexyl-*N*-{3,4-dihydro-2-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-3-oxoquinoxalin-6-yl}propanamide, 7d-5** Replacing cyclohexylacetic acid with 3-cyclohexylpropanoic acid and following the same procedure as in the preparation of **7d-4** gave the title compound as a pale yellow solid: 8% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.78—1.03 (2H, m, 2H), 1.05—1.35 (4H, m), 1.44—1.83 (7H, m), 2.37 (2H, d, $J$=7.6 Hz), 3.93 (3H, s), 7.31 (1H, dd, $J$=4.7, 7.9 Hz), 7.43 (1H, dd, $J$=2.3, 8.8 Hz), 7.80 (1H, d, $J$=8.8 Hz), 7.86 (1H, d, $J$=2.3 Hz), 8.39 (1H, dd, $J$=1.6, 4.7 Hz), 8.97 (1H, s), 9.10 (1H, dd, $J$=1.6, 7.9 Hz), 10.21 (1H, s), 12.48 (1H, s). ESI-MS *m/z*: +ESI 430 (M+1), −ESI 428 (M−1).

**7-[3-(Cyclohexylmethyl)ureido]-3-{1-methyl-1*H*-pyrrolo[2,3-b]-pyridin-3-yl}quinoxalin-2(1*H*)-one, 7d-6** To a suspension of **6d** (145 mg, 0.5 mmol) and TEA (0.1 ml) in THF (5.0 ml) was added triphosgene (163 mg, 0.55 mmol) at room temperature, and the mixture was stirred at 60 °C for 6 h. Aminomethylcyclohexane (0.3 ml) was added to the mixture, and the reaction mixture was stirred at 60 °C for 18 h. Aminomethylcyclohexane (0.3 ml) was added to the mixture again, and the reaction mixture was stirred at 80 °C for 1 h. Water was added to the resulting reaction mixture, and the precipitate was filtered to give the title compound as a pale yellow solid (133 mg); 61% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.84—1.86 (11H, m), 2.97 (2H, t, $J$=6.1 Hz), 3.92 (3H, s), 6.27 (1H, t), 7.21—7.33 (2H, m), 7.59 (1H, d, $J$=2.2 Hz), 7.72 (1H, d, $J$=8.8 Hz), 8.38 (1H, dd, $J$=1.6, 4.7 Hz), 8.82 (1H, s), 8.93 (1H, s), 9.08 (1H, dd, $J$=1.6, 7.9 Hz), 11.98 (1H, br s). IR (KBr) cm$^{-1}$: 3306, 2920, 1662, 1538. ESI-MS *m/z*: +ESI 431 (M+1), −ESI 429 (M−1). HR-ESI-MS *m/z*: 431.2178 (Calcd for $C_{24}H_{27}N_6O_2$: 431.2195).

**3-{1-Methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-7-(3-propylureido)-**

**quinoxalin-2(1*H*)-one, 7d-7** Replacing aminomethylcyclohexane with *n*-propylamine and following the same procedure as in the preparation of **7d-6** gave the title compound as a charcoal solid: 98% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.89 (3H, t, $J$=6.6 Hz), 1.46 (2H, qui, $J$=6.6 Hz), 3.09 (2H, td, $J$=6.6, 5.6 Hz), 3.93 (3H, s), 6.77 (1H, d, $J$=5.6 Hz), 7.25—7.31 (2H, m), 7.61—7.72 (2H, m), 8.36 (1H, dd), 8.98 (1H, s), 9.12 (1H, dd), 9.25 (1H, s). IR (KBr) cm$^{-1}$: 3309, 2960, 1663, 1538. ESI-MS *m/z*: +ESI 377 (M+1), −ESI 375 (M−1). HR-ESI-MS *m/z*: 377.1725 (Calcd for $C_{20}H_{21}N_6O_2$: 377.1726).

**7-(3-Butylureido)-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one, 7d-8** To a suspension of **6d** (5.77 g, 20 mmol) and DIEA (5.6 ml, 32 mmol) in 1-methyl pyrrolidone (50 ml) was added phenyl chloroformate (3.9 g, 25 mmol) at room temperature, and the mixture was stirred at room temperature for 21 h. To the resulting reaction mixture was added MeOH (200 ml), and the deposited precipitate was filtered to give phenyl {3,4-dihydro-2-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-3-oxoquinoxalin-6-yl}carbamate as a brown solid (6.11 g); 74% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.93 (3H, s), 7.16—7.55 (7H, m), 7.73 (1H, d, $J$=2.4 Hz), 7.84 (1H, d, $J$=8.8 Hz), 8.39 (1H, dd, $J$=1.7, 4.6 Hz), 8.97 (1H, s), 9.10 (1H, dd, $J$=1.7, 7.9 Hz), 10.59 (1H, s), 12.51 (1H, br s).

To a solution of phenyl {3,4-dihydro-2-{1-methyl-1*H*-pyrrolo[2,3-b]-pyridin-3-yl}-3-oxoquinoxalin-6-yl}carbamate (88 mg, 0.24 mmol) in DMF (2.0 ml) was added *n*-butylamine (78 mg, 1.2 mmol) at room temperature, and the mixture was stirred at 100 °C for 1 h. To the resulting reaction mixture was added MeOH (8.0 ml), and the deposited precipitate was filtered to give the title compound as a brown solid (67 mg); 71% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.91 (3H, t, $J$=7.1 Hz), 1.18—1.58 (4H, m), 3.02—3.22 (2H, m), 3.92 (3H, s), 6.20 (1H, t, $J$=5.6 Hz), 7.32—7.21 (2H, m), 7.60 (1H, d, $J$=2.3 Hz), 7.72 (1H, d, $J$=8.7 Hz), 8.38 (1H, dd, $J$=1.5, 4.8 Hz), 8.81 (1H, s), 8.93 (1H, s), 9.08 (1H, dd, $J$=1.5, 7.9 Hz), 12.36 (1H, s). IR (KBr) cm$^{-1}$: 3316, 2932, 1663, 1539. ESI-MS *m/z*: +ESI 391 (M+1), −ESI 389 (M−1). HR-ESI-MS *m/z*: 391.1882 (Calcd for $C_{21}H_{23}N_6O_2$: 391.1882).

**3-{1-Methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-7-(3-pentylureido)quinoxalin-2(1*H*)-one, 7d-9** Replacing *n*-butylamine with *n*-pentylamine and following the same procedure from phenyl {3,4-dihydro-2-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-3-oxoquinoxalin-6-yl}carbamate as in the preparation of **7d-8** gave the title compound as a charcohol charcoal solid: 84% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.89 (3H, t, $J$=6.5 Hz, 3H), 1.16—1.55 (6H, m), 3.00—3.19 (2H, m), 3.92 (3H, s), 6.22 (1H, t, $J$=5.0 Hz), 7.24 (1H, dd, $J$=2.2, 8.6 Hz), 7.30 (1H, dd, $J$=4.6, 7.8 Hz), 7.60 (1H, d, $J$=2.2 Hz), 7.72 (1H, d, $J$=8.6 Hz), 8.38 (1H, dd, $J$=1.5, 4.6 Hz), 8.83 (1H, s), 8.93 (1H, s), 9.08 (1H, dd, $J$=1.5, 7.8 Hz), 12.36 (1H, br s). IR (KBr) cm$^{-1}$: 3315, 2931, 1663, 1539. ESI-MS *m/z*: +ESI 405 (M+1), −ESI 403 (M−1). HR-ESI-MS *m/z*: 405.2016 (Calcd for $C_{22}H_{25}N_6O_2$: 405.2039).

**7-(3-Hexylureido)-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one, 7d-10** Replacing *n*-butylamine with *n*-hexylamine and following the same procedure from phenyl {3,4-dihydro-2-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-3-oxoquinoxalin-6-yl}carbamate as in the preparation of **7d-8** gave the title compound as a charcoal solid: 82% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.77—1.00 (3H, m), 1.11—1.59 (8H, m), 3.00—3.20 (2H, m), 3.92 (3H, s), 6.20 (1H, t, $J$=5.5 Hz), 7.32—7.21 (2H, m), 7.60 (1H, d, $J$=2.3 Hz), 7.72 (1H, d, $J$=8.5 Hz), 8.38 (1H, dd, $J$=1.6, 4.6 Hz), 8.81 (1H, s), 8.93 (1H, s), 9.08 (1H, dd, $J$=1.6, 7.9 Hz), 12.37 (1H, s). IR (KBr) cm$^{-1}$: 3313, 2929, 1663, 1539. ESI-MS *m/z*: +ESI 419 (M+1), −ESI 417 (M−1). HR-ESI-MS *m/z*: 419.2173 (Calcd for $C_{23}H_{27}N_6O_2$: 419.2195).

**7-(3-Heptylureido)-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-quinoxalin-2(1*H*)-one, 7d-11** Replacing *n*-butylamine with *n*-heptylamine and following the same procedure from phenyl {3,4-dihydro-2-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-3-oxoquinoxalin-6-yl}carbamate as in the preparation of **7d-8** gave the title compound as a charcoal solid: 87% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.87 (3H, t, $J$=6.5 Hz), 1.10—1.58 (10H, m), 2.99—3.17 (2H, m), 3.92 (3H, s), 6.21 (1H, t, $J$=5.5 Hz), 7.32—7.21 (2H, m), 7.60 (1H, d, $J$=2.2 Hz), 7.72 (1H, d, $J$=8.8 Hz), 8.38 (1H, dd, $J$=1.5, 4.8 Hz), 8.82 (1H, s), 8.93 (1H, s), 9.08 (1H, dd, $J$=1.5, 8.1 Hz), 12.37 (1H, s). IR (KBr) cm$^{-1}$: 3314, 2926, 1663, 1599. ESI-MS *m/z*: +ESI 433 (M+1), −ESI 431 (M−1). HR-ESI-MS *m/z*: 433.2333 (Calcd for $C_{24}H_{29}N_6O_2$: 433.2352).

**3-{1-Methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-7-(3-octylureido)quinoxalin-2(1*H*)-one, 7d-12** Replacing *n*-butylamine with *n*-octylamine and following the same procedure from phenyl {3,4-dihydro-2-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-3-oxoquinoxalin-6-yl}carbamate as in the preparation of **7d-8** gave the title compound as a charcoal solid: 84% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.73—1.00 (3H, m), 1.10—1.60 (12H, m), 3.00—3.20 (2H, m), 3.92 (3H, s), 6.20 (1H, t, $J$=5.5 Hz), 7.24 (3H, dd, $J$=2.2, 9.0 Hz), 7.30 (1H, dd, $J$=4.6, 7.9 Hz), 7.59 (1H, d, $J$=2.2 Hz), 7.72 (1H, d, $J$=9.0 Hz), 8.38 (1H, dd, $J$=1.5, 4.6 Hz), 8.81 (1H, s), 8.93 (1H, s), 9.08 (1H, dd, $J$=1.5, 7.9 Hz), 12.37 (1H, s). IR (KBr) cm$^{-1}$: 3315, 2926, 1663, 1539. ESI-MS *m/z*: +ESI 447 (M+1), −ESI 445 (M−1). HR-ESI-MS *m/z*: 447.2489 (Calcd for $C_{25}H_{31}N_6O_2$: 447.2508).

**7-[3-(Cyclopropylmetyl)ureido]-3-{1-methyl-1*H*-pyrrolo[2,3-b]-pyridin-3-yl}quinoxalin-2(1*H*)-one, 7d-13** Replacing aminomethylcyclohexane with cyclopropylmethylamine and following the same procedure as in the preparation of **7d-6** gave the title compound as a charcoal solid: 84% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.13—0.27 (2H, m), 0.36—0.52 (2H, m), 0.85—1.11 (1H, m), 2.92—3.10 (2H, m), 3.92 (3H, s), 6.29 (1H, t, $J$=5.9 Hz), 7.24 (1H, dd, $J$=2.1, 8.6 Hz), 7.30 (1H, dd, $J$=4.7, 7.9 Hz), 7.61 (1H, d, $J$=2.1 Hz), 7.73 (1H, d, $J$=8.6 Hz), 8.38 (1H, dd, $J$=1.6, 4.7 Hz), 8.86 (1H, s), 8.93 (1H, s), 9.08 (1H, dd, $J$=1.6, 7.9 Hz), 12.36 (1H, s). IR (KBr) cm$^{-1}$: 3314, 1662, 1539. ESI-MS *m/z*: +ESI 389 (M+1), −ESI 387 (M−1). HR-ESI-MS *m/z*: 389.1718 (Calcd for $C_{21}H_{21}N_6O_2$: 389.1726).

**7-(3-Cyclopenylureido)-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-quinoxalin-2(1*H*)-one, 7d-14** Replacing aminomethylcyclohexane with cyclopentylamine and following the same procedure as in the preparation of **7d-6** gave the title compound as a yellow solid: 48% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.35—1.91 (8H, m), 3.31 (3H, s), 3.32 (1H, m), 6.27 (1H, d), 7.22 (1H, dd, $J$=2.1, 8.7 Hz), 7.29 (1H, dd, $J$=4.6, 7.9 Hz), 7.59 (1H, d, $J$=2.1 Hz), 7.72 (1H, d, $J$=8.7 Hz), 8.37 (1H, dd, $J$=1.6, 4.6 Hz), 8.71 (1H, s), 8.93 (1H, s), 9.07 (1H, dd, $J$=1.6, 7.9 Hz), 12.35 (1H, br s). IR (KBr) cm$^{-1}$: 3302, 2954, 1662, 1539. ESI-MS *m/z*: +ESI 403 (M+1), −ESI 401 (M−1). HR-ESI-MS *m/z*: 403.1873 (Calcd for $C_{22}H_{23}N_6O_2$: 403.1882).

**3-{1-Methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-7-(3-phenylureido)-quinoxalin-2(1*H*)-one, 7d-15** Replacing aminomethylcyclohexane with cyclopentylamine and following the same procedure as in the preparation of **7d-6** gave the title compound as a charcoal solid: 56% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.93 (3H, s), 6.99 (1H, t), 7.31 (4H, m), 7.49 (2H, m), 7.68 (1H, d), 7.78 (1H, d), 8.38 (1H, dd), 8.82 (1H, s), 8.95 (1H, s), 9.10 (1H, dd), 9.18 (1H, s), 12.42 (1H, br s). IR (KBr) cm$^{-1}$: 3301, 3137, 3056, 2948, 1659, 1539. ESI-MS *m/z*: +ESI 411 (M+1), −ESI 409 (M−1). HR-ESI-MS *m/z*: 411.1576 (Calcd for $C_{23}H_{19}N_6O_2$: 411.1569).

**3,4-Dihydro-*N*-{3,4-dihydro-2-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-3-oxoquinoxalin-6-yl}-6,7-dimethoxyisoquinoline-2(1*H*)-carboxamide, 7d-16** Replacing aminomethylcyclohexane with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride and following the same procedure as in the preparation of **7d-6** gave the title compound as a pale yellow solid: 33% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.78 (2H, t, $J$=5.5 Hz), 3.72 (2H, t, $J$=5.5 Hz), 3.74 (6H, s), 3.93 (3H, s), 4.59 (2H, s), 6.77 (2H, s), 7.29 (1H, dd, $J$=4.7, 7.9 Hz), 7.43 (1H, dd, $J$=2.1, 8.8 Hz), 7.67 (1H, d, $J$=2.1 Hz), 7.76 (1H, d, $J$=8.8 Hz), 8.38 (1H, dd, $J$=1.5, 4.7 Hz), 8.95 (1H, br s), 8.95 (1H, s), 9.09 (1H, dd, $J$=1.5, 7.9 Hz), 12.44 (1H, br s). IR (KBr) cm$^{-1}$: 3415, 2837, 1656, 1536, 1516. ESI-MS *m/z*: +ESI 511 (M+1), −ESI 509 (M−1). HR-ESI-MS *m/z*: 511.2086 (Calcd for $C_{28}H_{27}N_6O_4$: 511.2094).

***tert*-Butyl {3-{2-{1-Methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-3,4-dihydro-3-oxoquinoxalin-6-yl}ureido}acetate, 7d-17** Replacing *n*-butylamine with *tert*-butyl 2-aminoacetate and following the same procedure from phenyl {3,4-dihydro-2-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-3-oxoquinoxalin-6-yl}carbamate as in the preparation of **7d-8** gave the title compound as a charcoal solid: 67% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.44 (9H, s), 3.79 (2H, d, $J$=5.8 Hz), 3.93 (3H, s), 6.46 (1H, t, $J$=5.8 Hz), 7.26 (1H, dd, $J$=2.2, 8.7 Hz), 7.30 (1H, dd, $J$=4.8, 7.8 Hz), 7.62 (1H, d, $J$=2.2 Hz), 7.74 (1H, d, $J$=8.7 Hz), 8.38 (1H, dd, $J$=1.5, 4.8 Hz), 8.94 (1H, s), 9.09 (1H, dd, $J$=1.5, 7.8 Hz), 9.20 (1H, s), 12.39 (1H, s). IR (KBr) cm$^{-1}$: 3389, 2978, 1741, 1654, 1540. ESI-MS *m/z*: +ESI 449 (M+1), −ESI 447 (M−1). HR-ESI-MS *m/z*: 449.1911 (Calcd for $C_{23}H_{25}N_6O_2$: 449.1937).

**3-{1-Methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-7-(3-morpholinoureido)-quinoxalin-2(1*H*)-one, 7d-18** Replacing aminomethylcyclohexane with 1-aminomorpholine and following the same procedure as in the preparation of **7d-6** gave the title compound as a pale yellow solid: 47% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 2.77 (4H, m), 3.73 (3H, s), 3.93 (3H, s), 7.29 (1H, dd, $J$=4.6, 7.9 Hz), 7.41 (1H, dd, $J$=2.0, 8.8 Hz), 7.77 (1H, d, $J$=8.8 Hz), 7.85 (1H, d, $J$=2.0 Hz), 7.94 (1H, s), 8.38 (1H, dd, $J$=1.6, 4.6 Hz), 8.87 (1H, s), 8.94 (1H, s), 9.11 (1H, dd, $J$=1.6, 7.9 Hz), 12.37 (1H, br s). IR (KBr) cm$^{-1}$: 3399, 3216, 2958, 1689, 1536. ESI-MS *m/z*: +ESI 420 (M+1), −ESI 418 (M−1). HR-ESI-MS *m/z*: 420.1766 (Calcd for $C_{21}H_{22}N_7O_3$: 420.1784).

**3-{1-Methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-7-{3-[(4-pyridyl)methyl]-ureido}quinoxalin-2(1*H*)-one, 7d-19** Replacing aminomethylcyclohexane with 4-pycolylamine and following the same procedure as in the preparation of **7d-6** gave the title compound as a charcoal solid: 17% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.92 (3H, s), 4.38 (2H, d), 7.25—7.38 (6H, m), 7.64—7.74 (2H, m), 8.37 (1H, dd), 8.50 (2H, m), 8.97 (1H, s), 9.11 (1H, dd), 9.52 (1H,

br s). IR (KBr) $cm^{-1}$: 3306, 1663, 1537, 1443. ESI-MS *m/z*: +ESI 426 (M+1), −ESI 424 (M−1). HR-ESI-MS *m/z*: 426.1674 (Calcd for $C_{23}H_{20}N_7O_2$: 426.1678).

**4-{3-{2-{1-Methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-3,4-dihydro-3-oxoquinoxalin-6-yl}-ureido}butyric Acid, 7d-20** Replacing *n*-butylamine with ethyl 4-aminobutylate and following the same procedure from phenyl {3,4-dihydro-2-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-3-oxoquinoxalin-6-yl}carbamate as in the preparation of **7d-8** gave the title compound as a charcoal solid: 81% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.58—1.80 (2H, m), 2.27 (2H, t, *J*=7.4 Hz), 3.15—2.97 (2H, m), 3.93 (3H, s), 6.16—6.40 (1H, m), 7.25 (1H, dd, *J*=2.1, 8.8 Hz), 7.30 (1H, dd, *J*=4.7, 7.9 Hz), 7.61 (1H, d, *J*=2.1 Hz), 7.73 (1H, d, *J*=8.8 Hz), 8.38 (1H, dd, *J*=1.6, 4.7 Hz), 8.89 (1H, s), 8.93 (1H, s), 9.09 (1H, dd, *J*=1.6, 7.9 Hz), 12.38 (1H, s). IR (KBr) $cm^{-1}$: 3300—2500, 2941, 1663, 1539. ESI-MS *m/z*: +ESI 421 (M+1), −ESI 419 (M−1). HR-ESI-MS *m/z*: 421.1599 (Calcd for $C_{21}H_{21}N_6O_4$: 421.1599).

**6-[3-(Cyclohexylmethyl)ureido]-3-{1-methyl-1*H*-pyrrolo[2,3-b]-pyridin-3-yl}quinoxalin-2(1*H*)-one, 7c-1** To a suspension of **6c** (70 mg, 0.24 mmol) and DIEA (0.25 ml, 1.44 mmol) and DMAP (10 mg) in $CH_2Cl_2$ (3.0 ml) was added phenyl chloroformate (0.18 ml, 1.44 mmol) at room temperature, and the mixture was stirred at room temperature for 1.5 h. Aminomethylcyclohexane (0.6 ml) and DMF (4.0 ml) were added to the mixture, and the reaction mixture was stirred at 80 °C for 15 h. Water was added to the resulting reaction mixture, and the water phase was extracted with $CHCl_3$. The combined organic phase was dried over $Na_2SO_4$. The organic solvent was removed *in vacuo*. The residue was triturated in $Et_2O$, and the precipitate was filtered to give the title compound as pale yellow solid (41 mg); 40% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.89—1.91 (11H, m), 2.97 (2H, t), 3.94 (3H, s), 6.21 (1H, t), 7.19 (1H, d, *J*=8.7 Hz), 7.29 (1H, d, *J*=2.2 Hz), 7.35 (1H, dd, *J*=4.6, 7.9 Hz), 8.11 (1H, d, *J*=2.2 Hz), 8.40 (1H, dd, *J*=1.6, 4.6 Hz), 8.51 (1H, s), 9.04 (1H, s), 9.09 (1H, dd, *J*=1.6, 7.9 Hz), 12.39 (1H, s). IR (KBr) $cm^{-1}$: 3318, 2919, 1665, 1538. ESI-MS *m/z*: +ESI 431 (M+1), −ESI 429 (M−1). HR-ESI-MS *m/z*: 431.2185 (Calcd for $C_{24}H_{27}N_6O_2$: 431.2195).

**7-[3-(Cyclohexylmethyl)ureido]-3-(1-methyl-indolyl-3-yl)quinoxalin-2(1*H*)-one, 7f-1** Replacing **6d** with **6f** and following the same procedure in DMF as in the preparation of **7d-6** gave the title compound as a charcoal solid: 73% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.77—1.55 (6H, m), 1.55—1.81 (5H, m), 2.90—3.05 (2H, m), 3.90 (3H, s), 6.17—6.32 (1H, m), 7.16—7.37 (3H, m), 7.49—7.65 (2H, m), 7.70 (1H, d, *J*=8.5 Hz), 8.71—8.93 (3H, m), 12.28 (1H, br s). IR (KBr) $cm^{-1}$: 3302, 2918, 1661, 1537. ESI-MS *m/z*: +ESI 430 (M+1), −ESI 428 (M−1). HR-ESI-MS *m/z*: 430.2225 (Calcd for $C_{25}H_{28}N_5O_2$: 430.2243).

**7-[3-(Cyclohexylmethyl)ureido]-3-{1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one, 7e-1** Replacing **6d** with **6e** and following the same procedure as in the preparation of **6d** gave a crude product. Then to a mixture of TFA (1.0 ml) the above crude product in 1,2-dichloroethane (5.0 ml) was stirred at 60 °C for 1 h. The precipitate was filtered and washed with a small amount of AcOEt to give the title compound as a yellow solid (49 mg): 44% Yield (2 steps); $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.87—1.72 (11H, m), 2.96 (2H, t), 6.25 (1H, t), 7.19—7.29 (2H, m), 7.61 (1H, d, *J*=2.1 Hz), 7.73 (1H, d, *J*=9.0 Hz), 8.33 (1H, d, *J*=4.9 Hz), 8.79 (1H, s), 8.85 (1H, d, *J*=2.7 Hz), 9.08 (1H, d, *J*=8.0 Hz), 12.13 (1H, s), 12.31 (1H, s). IR (KBr) $cm^{-1}$: 3316, 3221, 2923, 2852, 1676, 1558. ESI-MS *m/z*: +ESI 417 (M+1), −ESI 415 (M−1). HR-ESI-MS *m/z*: 417.2026 (Calcd for $C_{22}H_{27}N_6O_2$: 417.2039).

**7-(3-Pentylureido)-3-{1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one, 7e-2** Replacing aminomethylcyclohexane with *n*-pentylamine and following the same procedure as in the preparation of **7e-1** gave the title compound as a yellow solid: 37% Yield (2 steps); $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.89 (3H, t, *J*=6.7 Hz), 1.27—1.49 (6H, m), 3.11 (2H, td), 6.22 (1H, t), 7.23 (1H, dd, *J*=2.4, 8.7 Hz), 7.27 (1H, dd, *J*=4.6, 7.8 Hz), 7.62 (1H, d, *J*=2.4 Hz), 7.73 (1H, d, *J*=8.7 Hz), 8.33 (1H, dd, *J*=1.6, 4.6 Hz), 8.82 (1H, s), 8.85 (1H, d, *J*=2.8 Hz), 9.09 (1H, dd, *J*=1.6, 7.8 Hz), 12.15 (1H, s), 12.32 (1H, s). IR (KBr) $cm^{-1}$: 3309, 3223, 2932, 1676, 1558. ESI-MS *m/z*: +ESI 391 (M+1), −ESI 389 (M−1). HR-ESI-MS *m/z*: 391.1881 (Calcd for $C_{21}H_{23}N_6O_2$: 417.391.1882).

**6-Chloro-7-[3-(cyclohexylmethyl)ureido]-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one, 7a-1** Replacing **6d** with **6a** and following the same procedure as in the preparation of **7d-6** gave the title compound as a yellow solid: 11% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.93 (3H, s), 7.26 (1H, t, *J*=4.7 Hz), 7.30 (1H, dd, *J*=4.7, 8.0 Hz), 7.97 (1H, s), 7.17 (1H, d, *J*=12 Hz), 8.32 (1H, s), 8.39 (1H, dd, *J*=1.7, 4.7 Hz), 8.96 (1H, s), 9.11 (1H, dd, *J*=1.7, 8.0 Hz), 12.44 (1H, br s). IR (KBr) $cm^{-1}$: 3317, 2921, 1662, 1536. ESI-MS *m/z*: +ESI 465 (M+1), −ESI 462 (M−1). HR-ESI-MS *m/z*: 465.1786 (Calcd for $C_{24}H_{26}N_6O_235Cl$: 465.1806), 467.1792 (Calcd for $C_{24}H_{26}N_6O_237Cl$: 467.1776).

**7-[3-(Cyclohexylmethyl)ureido]-6-fluoro-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one, 7b-1** Replacing **6d** with **6b** and following the same procedure as in the preparation of **7d-6** gave the title compound as a yellow solid: 11% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 3.93 (3H, s), 6.83 (1H, t), 7.29 (1H, dd, *J*=4.6, 7.9 Hz), 7.17 (1H, d, *J*=12 Hz), 8.27 (1H, d, *J*=8.0 Hz), 8.59 (1H, d, *J*=2.8 Hz), 8.97 (1H, s), 9.06 (1H, dd, *J*=1.6, 7.9 Hz), 12.44 (1H, br s). IR (KBr) $cm^{-1}$: 3343, 2923, 1672, 1538. ESI-MS *m/z*: +ESI 450 (M+1), −ESI 448 (M−1). HR-ESI-MS *m/z*: 449.2080 (Calcd for $C_{24}H_{26}N_6O_2F$: 449.2101).

**6-Fluoro-3-{1-methyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-7-(3-pentylureido)quinoxalin-2(1*H*)-one, 7b-2** Replacing **6c** with **6b** and following the same procedure as in the preparation of **7c-1** gave the title compound as a yellow solid: 50% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.89 (3H, t), 1.26—1.49 (6H, m), 3.13 (2H, m), 3.93 (3H, s), 7.29 (1H, dd, *J*=4.7, 7.9 Hz), 7.72 (1H, d, *J*=12.2 Hz), 8.27 (1H, d, *J*=7.9 Hz), 8.38 (1H, dd, *J*=1.6, 4.7 Hz), 8.57 (1H, br s), 8.96 (1H, s), 9.09 (1H, dd, *J*=1.6, 7.9 Hz), 12.18 (1H, s). IR (KBr) $cm^{-1}$: 3338, 2928, 2857, 1671, 1537. ESI-MS *m/z*: +ESI 423 (M+1), −ESI 421(M−1). HR-ESI-MS *m/z*: 423.1928 (Calcd for $C_{22}H_{24}N_6O_2F$: 423.1945).

**3-{1-Ethyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-6-fluoro-7-(3-pentylureido)-quinoxalin-2(1*H*)-one, 7g-1** Replacing **6c** with **6g** and following the same procedure as in the preparation of **7c-1** gave the title compound as a yellow solid: 66% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.89 (3H, t), 1.28—1.48 (9H, m), 3.13 (2H, dd), 4.41 (1H, q), 6.79 (1H, t), 7.29 (1H, dd, *J*=4.7, 7.9 Hz), 7.72 (1H, d, *J*=12.2 Hz), 8.27 (1H, d, *J*=7.9 Hz), 8.37 (1H, dd, *J*=1.6, 4.7 Hz), 8.58 (1H, br s), 9.00 (1H, s), 9.10 (1H, dd, *J*=1.6, 7.9 Hz), 12.44 (1H, s). IR (KBr) $cm^{-1}$: 3343, 2933, 1664, 1534. ESI-MS *m/z*: +ESI 437 (M+1), −ESI 435 (M−1). HR-ESI-MS *m/z*: 437.2117 (Calcd for $C_{23}H_{26}N_6O_2F$: 437.2101).

**6-Fluoro-7-(3-pentylureido)-3-{1-propyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}quinoxalin-2(1*H*)-one, 7h-1** Replacing **6c** with **6h** and following the same procedure as in the preparation of **7c-1** gave the title compound as a yellow solid: 46% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.88 (3H, t, *J*=7.4 Hz), 0.89 (3H, t, *J*=6.8 Hz), 1.26—1.87 (8H, m), 3.13 (1H, td), 4.34 (2H, t, *J*=7.0 Hz), 6.79 (1H, t), 7.29 (1H, dd, *J*=4.7, 7.9 Hz), 7.72 (1H, d, *J*=12.1 Hz), 8.27 (1H, d, *J*=7.9 Hz), 8.37 (1H, dd, *J*=1.6, 4.7 Hz), 8.57 (1H, br s), 8.98 (1H, s), 9.09 (1H, d, *J*=1.6, 7.9 Hz), 12.45 (1H, br s). IR (KBr) $cm^{-1}$: 3343, 2961, 2931, 1665, 1533. ESI-MS *m/z*: +ESI 451 (M+1), −ESI 449 (M−1). HR-ESI-MS *m/z*: 451.2234 (Calcd for $C_{24}H_{28}N_6O_2F$: 451.2258).

**3-{1-Butyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-6-fluoro-7-(3-pentylureido)quinoxalin-2(1*H*)-one, 7i-1** Replacing **6c** with **6i** and following the same procedure as in the preparation of **7c-1** gave the title compound as a yellow solid: 54% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.87—0.94 (6H, m), 1.25—1.49 (8H, m), 1.76—1.97 (2H, m), 3.13 (2H, td), 4.37 (2H, t), 6.79 (1H, t), 7.29 (1H, dd, *J*=4.7, 8.0 Hz), 7.72 (1H, d, *J*=12.1 Hz), 8.27 (1H, d, *J*=7.9 Hz), 8.37 (1H, dd, *J*=1.4, 4.7 Hz), 8.57 (1H, br s), 8.98 (1H, s), 9.10 (1H, dd, *J*=1.4, 7.9 Hz), 12.43 (1H, br s). IR (KBr) $cm^{-1}$: 3343, 2956, 2931, 1665, 1534. ESI-MS *m/z*: +ESI 465 (M+1), −ESI 463 (M−1). HR-ESI-MS *m/z*: 465.2417 (Calcd for $C_{25}H_{30}N_6O_2F$: 465.2414).

**6-Fluoro-3-{1-pentyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-7-(3-pentylureido)quinoxalin-2(1*H*)-one, 7j-1** Replacing **6c** with **6j** and following the same procedure as in the preparation of **7c-1** gave the title compound as a yellow solid: 51% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.81—1.97 (18H, m), 3.13 (2H, td), 4.37 (2H, d, *J*=7.2 Hz), 6.79 (1H, t), 7.28 (1H, dd, *J*=4.7, 8.0 Hz), 7.74 (1H, d, *J*=12.1 Hz), 8.27 (1H, d, *J*=7.9 Hz), 8.37 (1H, dd, *J*=1.6, 4.7 Hz), 8.57 (1H, br s), 8.98 (1H, s), 9.09 (1H, d, *J*=1.6, 8.0 Hz), 12.44 (1H, br s). IR (KBr) $cm^{-1}$: 3343, 2930, 1665, 1534. ESI-MS *m/z*: +ESI 479 (M+1), −ESI 477 (M−1). HR-ESI-MS *m/z*: 479.2567 (Calcd for $C_{26}H_{32}N_6O_2F$: 479.2571).

**6-Fluoro-3-{1-isobutyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-7-(3-pentylureido)quinoxalin-2(1*H*)-one, 7k-1** Replacing **6c** with **6k** and following the same procedure as in the preparation of **7c-1** gave the title compound as a yellow solid: 54% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.87—0.91 (9H, m), 1.27—1.34 (6H, m), 2.22 (1H, m), 3.14 (2H, td), 4.19 (2H, d, *J*=7.2 Hz), 6.79 (1H, t), 7.29 (1H, dd, *J*=4.7, 7.9 Hz), 7.72 (1H, d, *J*=12.2 Hz), 8.28 (1H, d, *J*=7.9 Hz), 8.36 (1H, dd, *J*=1.5, 4.7 Hz), 8.57 (1H, br s), 8.96 (1H, s), 9.10 (1H, d, *J*=1.5, 7.9 Hz), 12.39 (1H, br s). IR (KBr) $cm^{-1}$: 3346, 2958, 2930, 1665, 1534. ESI-MS *m/z*: +ESI 465 (M+1), −ESI 463 (M−1). HR-ESI-MS *m/z*: 465.2416 (Calcd for $C_{25}H_{30}N_6O_2F$: 465.2414).

**6-Fluoro-3-{1-(2-methoxyethyl)-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-7-(3-pentylureido)quinoxalin-2(1*H*)-one, 7l-1** Replacing **6c** with **6l** and fol-

lowing the same procedure as in the preparation of **7c-1** gave the title compound as a yellow solid: 35% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.89 (3H, t, $J$=6.8 Hz), 1.27—1.49 (6H, m), 3.13 (2H, td), 3.26 (3H, s), 3.76 (2H, t, $J$=5.1 Hz), 4.54 (2H, d, $J$=5.1 Hz), 6.79 (1H, t), 7.30 (1H, dd, $J$=4.7, 7.9 Hz), 7.72 (1H, d, $J$=12.2 Hz), 8.28 (1H, d, $J$=7.9 Hz), 8.37 (1H, dd, $J$=1.7, 4.7 Hz), 8.57 (1H, br s), 8.98 (1H, s), 9.10 (1H, d, $J$=1.7, 7.9 Hz), 12.43 (1H, br s). IR (KBr) cm$^{-1}$: 3340, 2930, 1660, 1536. ESI-MS *m/z*: +ESI 467 (M+1), −ESI 465 (M−1). HR-ESI-MS *m/z*: 467.2209 (Calcd for $C_{24}H_{28}N_6O_3F$: 467.2207).

**6-Fluoro-3-{1-(3-morpholinopropyl)-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-7-(3-pentylureido)quinoxalin-2(1*H*)-one Hydrochloride, 7m-1** Replacing **6c** with **6m** and following the same procedure as in the preparation of **7c-1** gave the title compound as a yellow solid: 33% Yield; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.89 (3H, t, $J$=6.7 Hz), 1.24—1.49 (6H, m), 1.97—3.81 (10H, m), 4.41 (2H, t, $J$=5.6 Hz), 6.83 (1H, t), 7.30 (1H, dd, $J$=4.6, 8.0 Hz), 7.72 (1H, d, $J$=12.1 Hz), 8.27 (1H, d, $J$=7.9 Hz), 8.37 (1H, dd, $J$=1.4, 4.6 Hz), 8.60 (1H, br s), 9.03 (1H, s), 9.10 (1H, d, $J$=1.4, 8.0 Hz), 12.47 (1H, s). IR (KBr) cm$^{-1}$: 3340, 2931, 1663, 1536. ESI-MS *m/z*: +ESI 536 (M+1-HCl), −ESI 534 (M−1-HCl). HR-ESI-MS *m/z*: 536.2780 (Calcd for $C_{28}H_{35}N_7O_3F$: 536.2785).

**7-[3-(Cyclohexylmethyl)ureido]-3-{1-methyl-1*H*-pyrrolo[2,3-b]-pyridin-3-yl}-2-quinolone, 7n-1** This compound was synthesized by a method similar to that described in reference 36) for the purpose of comparison with **7d-6**; $^1$H-NMR (DMSO-$d_6$) $\delta$: 0.89—1.73 (1H, m), 2.96 (2H, t), 3.88 (3H, s), 6.31 (1H, t), 7.14—7.24 (2H, m), 7.54 (1H, d), 7.65 (1H, d), 8.22—8.48 (4H, m), 8.78 (1H, br s), 11.79 (1H, br s). IR (KBr) cm$^{-1}$: 3314, 2922, 2851, 1642, 1546. ESI-MS *m/z*: +ESI 430 (M+1), −ESI 428 (M−1) HR-ESI-MS *m/z*: 430.2226 (Calcd for $C_{25}H_{28}N_5O_2$: 430.2243).

**Cell Proliferation Assay (CPA)** Normal human mesangial cells (NHMC) were cultured in RPMI1640 (NISSUI) with 20% fetal bovine serum (FBS) at 37 °C. NHMC were plated on 96-well plates in RPMI1640 with 20% FBS and allowed to adhere overnight. The cells were starved for 24 h in RPMI1640 without FBS. Then a 48-h proliferation assay was performed. The test compounds were added to cells in RPMI1640 with 0.5% FBS, and after 1 h this was followed by the addition of recombinant human (rh) PDGF-BB (DIACLONE) at 50 ng/ml. During the final 24 h, the cells were supplemented with 5-bromo-2′-deoxyuridine (BrdU, Amersham). The cell proliferation was determined by measuring incorporation of BrdU by ELISA. Normal human glomerular endothelial cells (GEC) were used for the cell proliferation assays, with proliferation induced by VEGF and bFGF. GEC were plated on 96-well plates in DMEM/F-12 with 10%FBS, 20 ng/ml acidic-FGF and 50 U/ml heparin at 37 °C, and incubated for 24 h. Next the test compounds were added to cells followed after 1 h by the addition of rh VEGF (R&D) at 10 ng/ml or rh FGF-basic (PEPRO TECH) at 1 ng/ml. GEC were incubated for 48 h. Cell number was measured by a soluble tetrazolium/formazan assay using the live cell counting reagent tetraColorONE (Seikagaku kogyo). Inhibition % was calculated with the following equation, using the value of each absorbance. Inhibition %=$\{1-(A-C)/(B-C)\}\times 100$ ($A$: absorbance well with sample addition, $B$: absorbance of growth factor containing well, $C$: absorbance of well containing no growth factor). The $IC_{50}$ values were was calculated with SOFT max PRO.

**Receptor Auto-Phosphorylation Assay (APA)** Human aortic smooth muscle cells (hAOSMC) were used for the assay of PDGF $\beta$ receptor as follows. hAOSMC were cultured in DMEM/F-12 (GIBCO) with 10% FBS at 37 °C. Cells were plated in 12-well plates in DMEM/F-12 with 10% FBS and allowed to adhere overnight. The cells were cultured for 24 h in DMEM/F-12 with 0.1% FBS. Then the test compounds were added to cells in DMEM/F-12 with 0.1% FBS. After incubation at 37 °C for 2 h, cells were stimulated by rhPDGF-BB 50 ng/ml for 5 min. After removal of the medium, cells were washed with ice-cold PBS with 100 $\mu$mol/l $Na_3VO_4$. Then the cells were lysed in 50 mmol/l Tris–HCl (pH 7.5), 150 mmol/l NaCl, 1% Igepal CA-630, 0.5% deoxycholate, 0.1% sodium dodecyl sulfate, 50 mmol/l NaF, 1 mmol/l $Na_3VO_4$ and a protease inhibitor cocktail (SIGMA) at 4 °C for 30 min. The lysates were cleared by centrifugation at 12000×$g$ for 15 min. The supernatants were transferred into a 96 well plate in which the wells were previously coated with 5 $\mu$g/ml anti-$\beta$ PDGFR Ab (R&D) and incubated at 4 °C overnight. Subsequently, each well was washed with 0.05% Tween 20-PBS and incubated with horseradish peroxidase-conjugated anti-phosphotyrosine Ab (PY-20-HRP, Santa Cruz) for 1 h. After washing, 3,3′,5,5′-tetra-methylbenzidine (TMBZ) was added to each well, and the rate of substrate formation was monitored at 450 nm. Autophosphorylation assays of KDR, EGFR, Met and IGF-IR were carried out by the same method as that used for the PDGF$\beta$ receptor. For KDR, human umbilical vascular endothelial cells (HUVEC) were used. The cells were stimulated by 10 ng/ml rhVEGF (R&D) for 5 min and the anti-KDR Ab (SIGMA) was used for receptor capture. Auto-phosphorylation of EGFR was assayed using human epithelial carcinoma cells (A431) treated with 50 ng/ml rhEGF (R&D) for 3 min and anti-EGFR Ab (R&D) was used for receptor capture. Similarly, auto-phosphorylation of Met using A431 was induced by 100 ng/ml rhHGF (R&D) for 5 min, and Met was captured with anti-Met Ab (SIGMA). For auto-phosphorylation of IGF-IR, human breast cancer cells (MCF-7) were treated with 100 ng/ml rhIGF-I (PEPRO TECH) for 3 min and IGF-IR was bound by anti-IGF-IR Ab (R&D). Inhibition % was calculated using the following equation and inserting the value of each absorbance. Inhibition %=$\{1-(A-C)/(B-C)\}\times 100$ ($A$: absorbance of sample addition well, $B$: absorbance of control well, $C$: absorbance of non-stimulated well). The $IC_{50}$ values were calculated with SOFT max PRO.

## References


1) Heldin C. H., Westermark B., Wasteson A., *Proc. Natl. Acad. Sci. U.S.A.*, **76**, 3722—3726 (1979).
2) Heldin C. H., Westermark B., *Cell Regul.*, **1**, 555—566 (1990).
3) Heldin C. H., *EMBO J.*, **11**, 4251—4259 (1992).
4) Grotendrost G. R., Seppa H. E. J., Kleinman H. K., Martin G. R., *Proc. Nat. Acad. Sci. U.S.A.*, **78**, 3669—3672 (1981).
5) Wilcox J. N., Smith K. M., Williams L. T., Schwartz S. M., Gordon D., *J. Clin. Invest.*, **82**, 1134—1143 (1988).
6) Ross R., Masuda J., Raines E. W., Gown A. M., Katsuda S., Sasahara M., Malden L. T., Masuko H., Sato H., *Science*, **248**, 1009—1012 (1990).
7) Ferns G. A. A., Raines E. W., Sprugel K. H., Motani A. S., Reidy M. A., Ross R., *Science*, **253**, 1129—1132 (1991).
8) Jawien A., Bowen-Pope D. F., Lindner V., Schwartz S. M., Clowes A. W., *J. Clin. Invest.*, **89**, 507—511 (1992).
9) Bonner J. C., Lindroos P. M., Rice A. B., Moomaw C. R., Morgan D. L., *Am. J. Physiol.*, **274**, L72—80 (1998).
10) Friedman S. L., *J. Biol. Chem.*, **275**, 2247—2250 (2000).
11) Yasuhisa K., *Medicinal Research Reviews*, **23**, 15—31 (2003).
12) Hart C. E., Forstrom J. W., Kelly J. D., Seifert R. A., Smith R. A., Ross R., Murray M. J., Bowen-Pope D. F., *Science*, **240**, 1529—1531 (1988).
13) Ullrich A., Schlessinger J., *Cell*, **61**, 203—212 (1990).
14) Heidaran M. A., Pierce J. H., Yu J.-C., Lombardi D., Artrip, J. E., Fleming T. P., Thomason A., Aaronson S. A., *J. Biol. Chem.*, **266**, 20232—20237 (1991).
15) Kanakaraj P., Raj S., Khan S. A., Bishayee S., *Biochemistry*, **30**, 1761—1767 (1991).
16) Claesson-Welsh L., *J. Biol. Chem.*, **269**, 32023—32026 (1994).
17) Laird A. D., Vajkoczy P., Shawver L. K., Thurnher A., Liang C., Mohammadi M., Schlessinger J., Ulrich A., Hubbard S. R., Blake R. A., Fong A. T., Strawn L. M., Sun L., Tang C., Hawtin R., Tang F., Shemoy N., Hirth K. P., McMahon G., Cherrington J. M., *Cancer Res.*, **60**, 4152—4160 (2000).
18) Sun L., Tran N., Liang C., Hubbard S., Tang F., Lipson K., Schreck R., Zhou Y., McMahon G., Tang C., *J. Med. Chem.*, **43**, 2655—2663 (2000).
19) Sun L., Liang C., Shirazian S., Zhou Y., Miller T., Cui J., Fukuda J. Y., Chu J. Y., Nematalla A., Wang X., Chen H., Sistla A., Luu T. C., Tang F., Wei J., Tang C., *J. Med. Chem.*, **46**, 1116—1119 (2003).
20) Motzer R. J., Michaelson D., Redman B. G., Hudes G. R., Wilding G., Figlin R. A., Ginsberg M. S., Kim S. T., Baum C. M., DePrimo S. E., Li J. Z., Bello C. L., Theuer C. P., George D. J., Rini B. I., *J. Clin. Oncol.*, **24**, 1—3 (2006).
21) Myers M. R., He W., Hanney B., Setzer N., Maguire M. P., Zulli A., Bilder G., Galzcinski H., Amin D., Needle S., Spada A. P., *Bioorg. Med. Chem. Lett.*, **13**, 3091—3095 (2003).
22) He W., Myers M. R., Hanney B., Spada A. P., Bilder G., Galzcinski H., Amin D., Needle S., Page K., Jayyosi Z., Perrone M. H., *Bioorg. Med. Chem. Lett.*, **13**, 3097—3100 (2003).
23) Gazit A., Yee K., Uecker A., Bohmer F. D., Sjoblom T., Ostman A., Waltenberger J., Golomb G., Banai S., Heinrich M. C., Levitzki A., *Bioorg. Med. Chem.*, **11**, 2007—2018 (2003).
24) Dolle R. E., Dunn J. A., Bobko M., Singh B., Kuster J. E., Baizman E., Harris A. L., Sawutz D. G., Miller D., Wang S., Faltynek C. R., Xie W., Sarup J., Bode D. C., Pagani E. D., Silver P. J., *J. Med. Chem.*, **37**, 2627—2629 (1994).
25) Gazit A., App H., McMahon G., Chen J., Levitzki A., Bohmer F. D., *J. Med. Chem.*, **39**, 2170—2177 (1996).

26) Buchdunger E., Zimmermann J., Mett H., Meyer T., Muller M., Regenass U., Lydon N. B., *Proc. Natl. Acad. Sci. U.S.A.*, **92**, 2558—2562 (1995).
27) Manley P. W., Breitenstein W., Brueggen J., Cowan-Jacob S. W., Furet P., Mestan J., Meyer T., *Bioorg. Med. Chem. Lett.*, **14**, 5793—5797 (2004).
28) Matsuno K., Ichimura M., Nakajima T., Tahara K., Fujiwara S., Kase H., Ushiki J., Giese N. A., Pandey A., Scarborough R. M., Lokker N. A., Yu J.-C., Irie J., Tsukuda E., Ide S., Oda S., Nomoto Y., *J. Med. Chem.*, **45**, 3057—3066 (2002).
29) Pandey A., Volkots D. L., Seroogy J. M., Rose J. W., Yu J.-C., Lambing J. L., Hutchaleelaha A., Hollenbach S. J., Abe K., Giese N. A., Scarborough R. M., *J. Med. Chem.*, **45**, 3772—3793 (2002).
30) Matsuno K., Nakajima T., Ichimura M., Giese N. A., Yu J.-C., Lokker N. A., Ushiki J., Ide S., Oda S., Nomoto Y., *J. Med. Chem.*, **45**, 4513—4523 (2002).
31) Matsuno K., Seishi T., Nakajima T., Ichimura M., Giese N. A., Yu J.-C., Oda S., Nomoto Y., *Bioorg. Med. Chem. Lett.*, **13**, 3001—3004 (2003).
32) Matsuno K., Ushiki J., Seishi T., Ichimura M., Giese N. A., Yu J.-C., Takahashi S., Oda S., Nomoto Y., *J. Med. Chem.*, **46**, 4910—4925 (2003).
33) Heath J. A., Mehrotra M. M., Chi S., Yu J.-C., Hutchaleelaha A., Hollenbach S. J., Giese N. A., Scarborough R. M., Pandey A., *Bioorg. Med. Chem. Lett.*, **14**, 4867—4872 (2004).
34) Furuta T., Sakai T., Senga T., Osawa T., Kubo K., Shimizu T., Suzuki R., Yoshino T., Endo M., Miwa A., *J. Med. Chem.*, **49**, 2186—2192 (2006).
35) Mahboobi S., Teller S., Pongratz H., Hufsky H., Sellmer A., Botzki A., Uecker A., Beckers T., Baasner S., Schaechtele C., Ueberall F., Kassack M. U., Dove S., Boehmer F.-D., *J. Med. Chem.*, **45**, 1002—1018 (2002).
36) Kato S., Fujisawa A., Nanayama T., Jpn. Patent, JP2001089471 (2001).
37) Palmer B. D., Smaill J. B., Boyd M., Boschelli D. H., Doherty A. M., Hamby J. M., Khatana S. S., Kramer J. B., Kraker A. J., Panek R. L., Lu G. H., Dahring T. K., Winters R. T., Showalter H. D. H., Denny W. A., *J. Med. Chem.*, **41**, 5457—5465 (1998).
38) Palmer B. D., Kraker A. J., Hartl B. G., Panopoulos A. D., Panek R. L., Batley B. L., Lu G. H., Trumpp-Kallmeyer S., Showalter H. D. H., Denny W. A., *J. Med. Chem.*, **42**, 2373—2382 (1999).
39) Ho C. Y., Ludovici D. W., Maharoof U. S. M., Mei J., Sechler J. L., Tuman R. W., Strobel E. D., Andraka L., Yen H.-K., Leo G., Li J., Almond H., Lu H., DeVine A., Tominovich R. M., Baker J., Emanuel S., Gruninger R. H., Middleton S. A., Johnson D. L., Galemmo R. A., Jr., *J. Med. Chem.*, **48**, 8163—8173 (2005).
40) Dormidontov Y. P., Lapkin I. I., Lapteva V. V., *Tr. Estestvenno-nauch. In-ta pri Perm. Un-te*, **13**, 170—173 (1975).
41) Bergstrand H., Karabelas K., Sjo P., PCT Int., WO9813368 A1 19980402 (1998).
42) Karabelas K., Lonn H., Sjo P., PCT Int. Appl., WO9946260 A1 19990916 (1999).
43) Karabelas K., Sjo P., PCT Int., WO9946264 A1 19990916 (1999).
44) Nixey Thomas, Tempest Paul, Hulme, Christopher., *Tetrahedron Lett.*, **43**, 1637—1639 (2002).
45) Bolotov V. V., Kovalenko S. N., Kovaleva S. V., Stepanenko V. I., *Khimiya Geterotsiklicheskikh Soedinenii*, **40**, 211—213 (2004).
46) Chupakhin O. N., Sidorov E. O., Postovskii I. Y., *Khimiya Geterotsiklicheskikh Soedinenii.*, **10**, 1433—1434 (1975).
47) Cheeseman G. H. W., *J. Chem. Soc.*, **1961**, 1246—1251.
48) Cheeseman G. H. W., *J. Chem. Soc.*, **1962**, 1170—1176.