Design, Synthesis, and Structure–Activity Relationships of 3,4-Dihydropyridopyrimidin-2(1*H*)-one Derivatives as a Novel Class of Sodium/Calcium Exchanger Inhibitor

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Design, synthesis, and structure–activity relationships for 3,4-dihydropyridopyrimidin-2(1*H*)-one derivatives, which are aza-3,4-dihydro-2(1*H*)-quinazolinone derivatives, as the sodium/calcium (Na^+/Ca^{2+}) exchanger inhibitors are discussed. These studies based on 3,4-dihydro-2(1*H*)-quinazolinone derivatives led to the discovery of a structurally novel and potent Na^+/Ca^{2+} exchanger inhibitor, 3,4-dihydropyridopyrimidin-2(1*H*)-one derivative (26), with an IC_{30} value of 0.02 μM. Compound 26 directly inhibited the Na^+-dependent Ca^{2+} influx *via* the Na^+/Ca^{2+} exchanger after Na^+-free treatment in cardiomyocytes.

Key words sodium/calcium exchanger; Na^+/Ca^{2+} exchanger; 3,4-dihydropyridopyimidin-2(1*H*)-one

The sodium/calcium (Na^+/Ca^{2+}) exchanger is involved in myocardial Ca^{2+} regulation.[1)] Clinically, coronary reperfusion by thrombolytic therapy or percutaneous transluminal angioplasty has emerged as a fundamental strategy in the management of ischemic heart disease. Nonetheless, it has been suggested that sometimes early restitution of blood flow after a period of hypoxia results in the deteriorous effects called reperfusion injury.[2,3)]

Intracellular Ca^{2+} overload *via* activation of the Na^+/Ca^{2+} exchanger after ischemic reperfusion has been indicated as a potential cause of this, which induces post-ischemic cardiac injury.[1,3—9)] Thus, inhibition of the Na^+/Ca^{2+} exchanger, which would lead to prevention of Ca^{2+} overload, could become a new approach for the treatment of ischemic reperfusion injury. Our research therefore focused upon the discovery of an inhibitor of the Na^+/Ca^{2+} exchanger with high potency and selectivity. A number of compounds, including peptidic and non-peptidic compounds have been reported as Na^+/Ca^{2+} exchanger inhibitors (Fig. 1). As a peptidic inhibitor, Val-Met-Arg-Phe-NH_2 (**1**) with IC_{50} value of 1.5 μM has been reported, which is a non-selective inhibitor.[10)] As a non-peptidic inhibitor, aroylguanidine derivative (**2**)[11)] with IC_{50} value of 3.4 μM has been reported which is a modified amiloride derivative as is dimethylamiloride (**3**).[12)] Furthermore, KB-R7943 (**4**),[13,14)] SEA0400 (**5**),[15,16)] benzyloxyphenyl derivative (**6**)[17)] and SN-6 (**7**)[18)] have been reported.

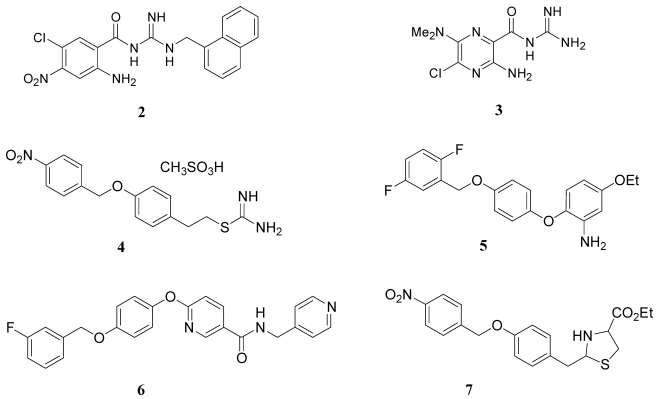

Fig. 1. Chemical Structures of Non-Peptidic Inhibitor of the Na^+/Ca^{2+} Exchanger: (**2**) Aroylguanidine Derivative; (**3**) Dimethylamiloride; (**4**) KB-R7943; (**5**) SEA0400; (**6**) Benzyloxyphenyl Derivative; (**7**) SN-6

We have already reported design, synthesis and structure–activity relationships for 3,4-dihydro-2(1*H*)-quinazolinone derivatives with the inhibitory activities of the Na^+/Ca^{2+} exchanger.[19,20)] In the previous article, we disclosed that these studies based on lead compound **8** with a moderate potent inhibitory activity led to the identification of a structurally novel and highly potent inhibitor against the Na^+/Ca^{2+} exchanger **9** (SM-15811), which directly inhibited the Na^+-dependent Ca^{2+} influx *via* the Na^+/Ca^{2+} exchanger in cardiomyocytes with high potency and exerted the protective effect against myocardial ischemic reperfusion injury (Fig. 2). In order to explore a novel class of inhibitors with new skeleton, we designed, synthesized and evaluated 3,4-dihydropyridopyrimidin-2(1*H*)-one derivatives, which is an aza-3,4-dihydro-2(1*H*)-quinazolinone derivatives (Fig. 3). Herein, we wish to report the results.

Chemistry

Synthesis of 4-phenyl-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-one (**19**), 4-phenyl-3,4-dihydropyrido[3,4-*d*]pyrimidin-2(1*H*)-one (**20**), and 4-phenyl-3,4-dihydropyrido[4,3-*d*]pyrimidin-2(1*H*)-one (**21**) having a *N*,*N*-diethylaminoethyl as a chain aminoalkyl group at the 3-position is illustrated in Chart 1. Trichloroacetylation of aminobenzoylpyridine **10**,[21)] **11**,[21)] and **12**[21)] with trichloroacetyl chloride, followed by

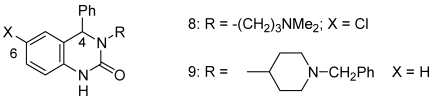

Fig. 2. Chemical Structure of 3,4-Dihydro-2(1*H*)-quinazolinone Derivative **8** and **9** (SM-15811)

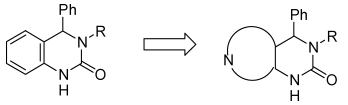

Fig. 3. Conversion of 3,4-Dihydro-2(1*H*)-quinazolinone Skeleton into 3,4-Dihydropyridopyrimidin-2(1*H*)-one Skeleton

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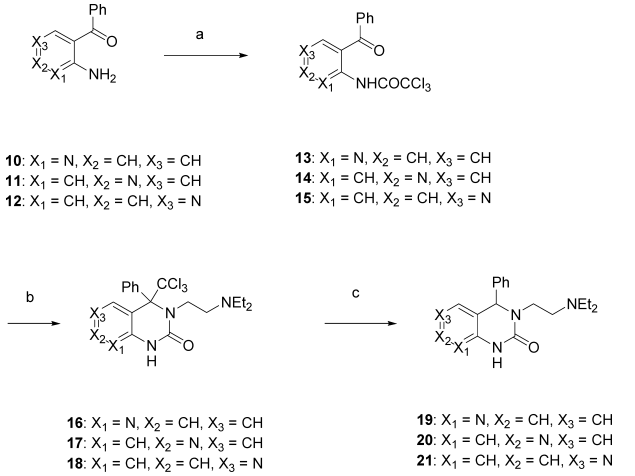
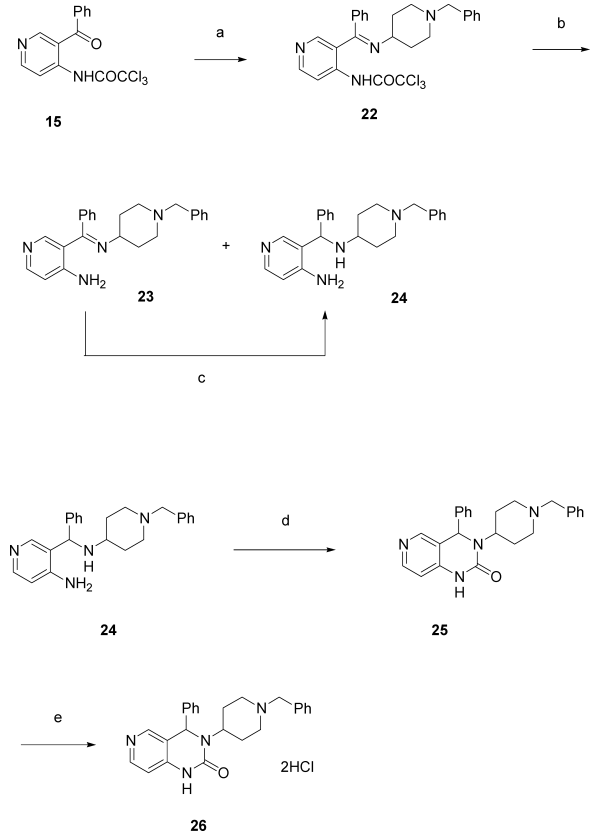


Reagents: (a) CCl_3COCl, Et_3N, THF; (b) $Et_2N(CH_2)_2NH_2$, DMSO; (c) (i) $NaBH_4$, DMF; (ii) EtOH, reflux.

Chart 1

treatment with *N*,*N*-diethylethylenediamine in dimethylsulfoxide (DMSO) gave directly cyclized products **16**—**18**, with accompanying rearrangement of trichloromethyl group. Removal of the trichloromethyl group leading to the 3,4-dihydropyridopyrimidin-2(1*H*)-one **19**—**21** was effected by $NaBH_4$. A new signal at 5.75 ppm for **19**, 5.76 ppm for **20**, and 5.80 ppm for **21** indicated that trichloromethyl group at the 4-position of 3,4-dihydropyridopyrimidin-2(1*H*)-one (**16**—**18**) was replaced with hydrogen atom. These data supported the formation of 3,4-dihydropyridopyrimidin-2(1*H*)-one (**16**—**18**) by the treatment of tricloroamide (**13**—**15**) with *N*,*N*-diethylethylenediamine, respectively.

Synthesis of 4-phenyl-3,4-dihydropyrido[4,3-*d*]pyrimidin-2(1*H*)-one **26** having 1-benzylpiperidin-4-yl at the 3-position is illustrated in Chart 2. Treatment of trichloroacetylamide **15** with 4-amino-1-benzylpiperidine in DMSO gave imine **22**. Removal of the trichloroacetyl moiety with $NaBH_4$ gave a mixture of imine **23** and diamine **24**. After separation of imine **23** and diamine **24**, imine **23** was converted into diamine **24** by treating with $LiAlH_4$ in tetrahydrofuran (THF). Treatment of diamine **24** with 1,1′-carbonyldiimidazole led to cyclization to afford **25**, which was then converted into HCl salt of **26** by treating **25** with HCl/diethyl ether.



Reagents: (a) 4-aminobenzylpiperidine, DMSO; (b) $NaBH_4$, EtOH; (c) $LiAlH_4$, THF; (d) 1,1′-caronyldiimidazole, THF; (e) HCl/diethyl ether.

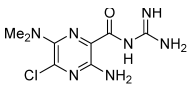
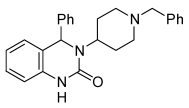
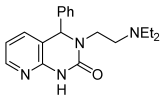
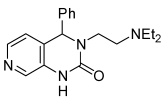
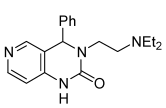
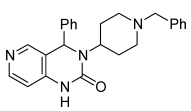
Chart 2

Pharmacological Results and Discussion

The inhibitory activity of test compounds on Na^+/Ca^{2+} exchange was measured by the inhibition of Na^+- and K^+-free contracture in isolated guinea pig left atria, performed as described previously.[22] The inhibitory activities were calculated as IC_{30} values. In this system, Val-Met-Arg-Phe-NH_2 (**1**) and dimethylamiloride (**3**), which are known inhibitors of the Na^+/Ca^{2+} exchanger, showed inhibitory activities with IC_{30} values of 10 μM and 30 μM, respectively.

At first, in order to investigate the possibility of replacing the 2,3-dihydro-2(1*H*)-quinazolinone skeleton with aza-2,3-dihydro-2(1*H*)-quinazolinone, we designed and synthesized 4-phenyl-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-one (**19**), 4-phenyl-3,4-dihydropyrido[3,4-*d*]pyrimidin-2(1*H*)-one (**20**) and 4-phenyl-3,4-dihydropyrido[4,3-*d*]pyrimidin-2(1*H*)-one (**21**) having a *N*,*N*-diethylaminoethyl as a chain aminoalkyl group at the 3-position. Their inhibitory activities were

Table 1. Inhibitory Activities against the Na^+/Ca^{2+} Exchanger

Compound[a]	Structure	IC_{30} (μM)
1	Val-Met-Arg-Phe-NH_2	10
3		30
9[b]		0.017
19		4.4
20		6.2
21		2.7
26[c]		0.02

a) All the compounds tested were racemic. *b*) Compound tested as citrate. *c*) Compound tested as HCl salt.

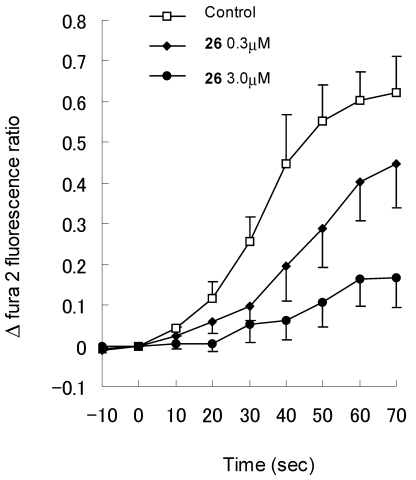


Fig. 4. Effect of **26** on the Na^+/Ca^{2+} Exchange Activity in Rat Cardiomyocytes

The Na^+/Ca^{2+} exchange activity was estimated as the increase in fura 2 fluorescence ratio induced by exposing to the Na^+-free HEPES-based buffer using a Ca^{2+} sensitive fluorescent indicator fura 2. Each point represents the mean±S.E.M. of 5 experiments.

4.4, 6.2 and 2.7 μM, respectively. Among them, 4-phenyl-3,4-dihydropyrido[4,3-*d*]pyrimidin-2(1*H*)-one skeleton (**21**) showed strongest activity. Since we have investigated the effects of substituents at the 3-position of the 3,4-dihydro-2(1*H*)-quinazolinone on the activities,[19,20] we introduced a 1-benzylpiperidin-4-yl at the 3-position of 4-phenyl-3,4-dihydropyrido[4,3-*d*]pyrimidin-2(1*H*)-one. As we anticipated, compound **26** increased the activity dramatically, showing the strong activity with an IC_{30} value of 0.02 μM. Its activity was almost same as previously reported compound **9**[11] having the 3,4-dihydro-2(1*H*)-quinazolinone skeleton.

We found that **26** having 3,4-dihydropyrido[4,3-*d*]pyrimidin-2(1*H*)-one skeleton had strong inhibitory activity against Na^+- and K^+-free contracture after 30 min of K^+ free incubation in isolated left atria from guinea pigs. Moreover, we evaluated **26** by fura 2 fluorescence ratio (an index of $[Ca^{2+}]_i$) increased by Na^+-dependent Ca^{2+} influx *via* the Na^+/Ca^{2+} exchanger after Na^+-free treatment in cardiomyocytes.[23] Figure 4 shows the results. **26** concentration-dependently attenuated the increase in Na^+-free induced fura 2 fluorescence ratio, indicating **26** directly inhibited the Na^+-dependent Ca^{2+} influx *via* Na^+/Ca^{2+} exchanger after Na^+-free treatment in cardiomyocytes.

Conclusion

We designed, synthesized and evaluated 3,4-dihydropyridopyrimidin-2(1*H*)-one derivatives, in which 2,3-dihydro-2(1*H*)-quinazolinone skeleton is replaced with aza-2,3-dihydro-2(1*H*)-quinazolinone skeleton, in order to investigate a novel class of Na^+/Ca^{2+} exchanger inhibitors. At first, we investigated the possibility of replacing the 3,4-dihydro-2(1*H*)-quinazolinone skeleton with 3,4-dihydropyridopyrimidin-2(1*H*)-one. Although their inhibitory activities were not so strong, they showed activity. Then, based on the results we have already reported, we introduced the 4-benzylaminopiperidin-4-yl at the 3-position to enhance the activity. These simple and effective studies led to the identification of 3,4-dihydropyridopyrimidin-2(1*H*)-one derivative **26** having a new type of skeleton with an IC_{30} value of 0.02 μM, which concentration-dependently attenuated the increase in Na^+-free induced fura 2 fluorescence ratio, indicating **26** directly inhibited the Na^+-dependent Ca^{2+} influx *via* the Na^+/Ca^{2+} exchanger after Na^+-free treatment in cardiomyocytes. Compound **26** would be a useful tool as a novel class of the Na^+/Ca^{2+} exchanger inhibitor as well as indicate a potential for generating a novel class of highly potent Na^+/Ca^{2+} exchanger inhibitors.

Experimental

Melting points were measured on a Thomas-Hoover melting point apparatus and uncorrected. ^{1}H-NMR spectra were recorded on a JEOL GX270 or JEOL JNM-LA300 spectrometers in the stated solvents using tetramethylsilane as an internal standard. Elemental analyses were obtained from Sumitomo Analytical Center Inc. and results obtained were within±0.4% of theoretical values. Thin layer chromatography and flash column chromatography were performed on silica gel glass-backed plates (5719, Merck & Co.) and silica gel 60 (230—400 or 70—230 mesh, Merck & Co.), respectively. Unless otherwise noted, all the materials were obtained from commercial suppliers and used without further purification. All solvents were commercially available grade. All reactions were carried out under a nitrogen atmosphere unless otherwise mentioned.

The Representative Example of Synthesis of 13—15. *N*-(3-Benzoylpyridin-2-yl)-2,2,2-trichloroacetamide (13) To a stirred THF solution (20 ml) of 2-amino-3-benzoylpyridine (**10**) (1.10 g, 5.54 mmol) and triethylamine (610 mg, 6.03 mmol) was added trichloroacetyl chloride (1.00 g, 5.50 mmol) dropwise at 5—15 °C. The mixture was stirred at ambient temperature for 3 h. The mixture was poured into ice/water and the resultant mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was crystallized from EtOH to give **13** (1.40 g, yield 74%) as a white powder. ^{1}H-NMR ($CDCl_3$) δ: 8.73—8.75 (1H, m), 7.99—8.02 (1H, m), 7.71—7.77 (2H, m), 7.62—7.68 (1H, m), 7.42—7.56 (2H, m), 7.23—7.28 (1H, m).

The following compounds (**14**, **15**) were prepared by a similar method described above for the synthesis of **13** using the appropriate starting material(s).

***N*-(4-Benzoylpyridin-3-yl)-2,2,2-trichloroacetamide (14)** The title compound was prepared from 3-amino-4-benzoylpyridine (**11**) to give **14** in 96% yield. ^{1}H-NMR ($CDCl_3$) δ: 11.52 (1H, br s), 9.88 (1H, s), 8.62 (1H, d, J=5.0 Hz), 7.77—7.81 (2H, m), 7.67—7.73 (1H, m), 7.53—7.59 (2H, m), 7.49 (1H, dd, J=5.0, 0.7 Hz).

***N*-(3-Benzoylpyridin-4-yl)-2,2,2-trichloroacetamide (15)** The title compound was prepared from 4-amino-5-benzoylpyridine (**12**) to give **15** in 92% yield. ^{1}H-NMR ($CDCl_3$) δ: 12.59 (1H, br s), 8.90 (1H, s), 8.79 (1H, d, J=6.3 Hz), 8.60 (1H, d, J=5.6 Hz), 7.65—7.79 (3H, m), 7.52—7.59 (2H, m).

The Representative Example of Synthesis of 16—18. 3-[2-(Diethylamino)ethyl]-4-phenyl-4-(trichloromethyl)-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-one (16) To a stirred DMSO solution (50 ml) of **13** (1.40 g, 4.07 mmol) at room temperature was added *N*,*N*-diethylethylenediamine (520 mg, 4.48 mmol), and the mixture was stirred at room temperature for 24 h. The reaction mixture was poured into ice/water, then the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ 1 : 9) to give **16** (240 mg, yield 23%). mp 252—254 °C; ^{1}H-NMR ($CDCl_3$) δ: 9.42 (1H, br s), 8.33—8.38 (2H, m), 7.31—7.46 (3H, m), 7.13—7.19 (2H, m), 6.83 (1H, dd, J=7.9, 4.9 Hz), 3.89—4.00 (1H, m), 3.15—3.26 (1H, m), 2.75—2.85 (1H, m), 2.20—2.34 (4H, m), 1.92—2.02 (1H, m), 0.79 (6H, m).

The following compounds (**17**, **18**) were prepared by a similar method described above for the synthesis of **16** using the appropriate starting material(s).

3-[2-(Diethylamino)ethyl]-4-phenyl-4-(trichloromethyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-2(1*H*)-one (17) The title compound was prepared from **14** to give **17** in 64% yield. ^{1}H-NMR ($CDCl_3$) δ: 9.97 (1H, s), 8.33 (1H, d, J=5.3 Hz), 7.50—7.54 (3H, m), 7.17—7.20 (2H, m), 6.81 (1H, dd, J=5.3, 0.7 Hz), 3.52—3.57 (2H, m), 2.77—2.80 (2H, m), 2.44 (4H, q, J=7.3 Hz), 0.94 (6H, t, J=7.3 Hz).

3-[2-(Diethylamino)ethyl]-4-phenyl-4-(trichloromethyl)-3,4-dihydropyrido[4,3-*d*]pyrimidin-2(1*H*)-one (18) The title compound was prepared from **15** to give **18** in 32% yield. ^{1}H-NMR ($CDCl_3$) δ: 10.45 (1H, br s), 8.30 (1H, d, J=5.6 Hz), 7.95 (1H, s), 7.52 (2H, m), 7.31—7.40 (3H, m), 6.79 (1H, d, J=5.6 Hz), 3.30—3.46 (2H, m), 2.70—2.81 (1H, m), 2.44

(4H, d, J=7.3 Hz), 1.97—2.08 (1H, m), 0.93 (6H, t, J=7.3 Hz).

The Representative Example of Synthesis of 19—21. 3-[2-(Diethylamino)ethyl]-4-phenyl-3,4-dihydropyrido[2,3-*d*]pyrimidin-2(1*H*)-one (19) To a stirred *N*,*N*-dimethylfomamide (DMF) solution (10 ml) of **16** (240 mg, 0.543 mmol) at 0 °C was added sodium borohydride (82 mg, 2.17 mmol), and the mixture was stirred at ambient temperature for 3 h. The reaction mixture was poured into ice/water, then the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was dissolved in EtOH, then the mixture was heated under reflux for 5 h. The mixture was evaporated to dryness. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ 1 : 9) to give **19** (110 mg, yield 63%). mp 160—163 °C (from EtOAc); ^{1}H-NMR ($CDCl_3$) δ: 8.14 (1H, dd, J=5.0, 1.7 Hz), 7.78 (1H, br s), 7.31—7.39 (5H, m), 7.25—7.28 (1H, m), 6.82 (1H, dd, J=7.4, 5.0 Hz), 5.75 (1H, s), 3.77—3.87 (1H, m), 2.99—3.03 (1H, m), 2.69—2.79 (1H, m), 2.42—2.60 (5H, m), 0.99 (6H, t, J=7.4 Hz); *Anal.* Calcd for $C_{19}H_{24}N_4O \cdot 1/3H_2O$: C, 69.06; H, 7.52; N, 16.96. Found: C, 68.87; H, 7.40; N, 16.83.

The following compounds (**20**, **21**) were prepared by a similar method described above for the synthesis of **19** using the appropriate starting material(s).

3-[2-(Diethylamino)ethyl]-4-phenyl-3,4-dihydropyrido[3,4-*d*]pyrimidin-2(1*H*)-one (20) The title compound was prepared from **17** to give **20** in 54% yield. mp 138—141 °C (from EtOAc); ^{1}H-NMR ($CDCl_3$) δ: 8.11 (1H, s), 8.11 (1H, d, J=5.0 Hz), 7.68 (1H, br s), 7.30—7.36 (5H, m), 6.86 (1H, d, J=5.0 Hz), 5.76 (1H, s), 3.77—3.87 (1H, m), 2.97—3.08 (1H, m), 2.66—2.78 (1H, m), 2.41—2.59 (5H, m), 0.99 (6H, t, J=7.3 Hz); *Anal.* Calcd for $C_{19}H_{24}N_4O$: C, 70.34; H, 7.46; N, 17.27. Found: C, 69.95; H, 7.35; N, 16.98.

3-[2-(Diethylamino)ethyl]-4-phenyl-3,4-dihydropyrido[4,3-*d*]pyrimidin-2(1*H*)-one (21) The title compound was prepared from **18** to give **21** in 66% yield. mp 133—134 °C (from EtOH/diethyl ether); ^{1}H-NMR ($CDCl_3$) δ: 8.26 (1H, d, J=5.3 Hz), 8.16 (1H, s), 7.30—7.36 (5H, m), 6.63 (1H, d, J=5.3 Hz), 5.80 (1H, s), 3.81—3.89 (1H, m), 2.97—3.09 (1H, m), 2.73—2.76 (1H, m), 2.44—2.60 (5H, m), 0.99 (6H, t, J=7.3 Hz); *Anal.* Calcd for $C_{19}H_{24}N_4O \cdot 0.28H_2O$: C, 69.26; H, 7.51; N, 17.01. Found: C, 68.93; H, 7.11; N, 16.84.

***N*-{3-[(*E*)-[(1-Benzylpiperidin-4-yl)imino](phenyl)methyl]pyridin-4-yl}-2,2,2-trichloroacetamide (22)** To a stirred DMSO solution (100 ml) of **15** (19.6 g, 57.0 mmol) at room temperature was added 4-amino-1-benzylpiperidine (13.0 g, 68.3 mmol), and the mixture was stirred at ambient temperature for 48 h. The mixture was poured into ice/water, then the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by silica gel column chromatography (hexane/EtOAc 1 : 1) to give the crude product. This crude product was crystallized from EtOAc to give **22** (18.5 g, yield 63%). mp 151—152 °C; ^{1}H-NMR ($CDCl_3$) δ: 8.60 (1H, d, J=5.9 Hz), 8.52 (1H, d, J=5.9 Hz), 8.07 (1H, s), 7.51—7.53 (3H, m), 7.27—7.32 (5H, m), 7.14—7.18 (2H, m), 3.44 (2H, s), 3.14—3.22 (1H, m), 2.87 (2H, m), 1.96—2.08 (2H, m), 1.52—1.83 (4H, m).

3-[(*E*)-[(1-Benzylpiperidin-4-yl)imino](phenyl)methyl]pyridin-4-amine (23) and 3-[[(1-Benzylpiperidin-4-yl)amino](phenyl)methyl]-pyridin-4-amine (24) To a stirred EtOH solution (150 ml) of **22** (18.0 g, 34.9 mmol) at 0 °C was added $NaBH_4$ (2.65 g, 70.1 mmol), and the mixture was stirred at ambient temperature for 5 h. The reaction mixture was poured into ice/water, then EtOH was evaporated. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ 1 : 9) to give **23** (4.82 g, yield 37%) and **24** (6.65 g, yield 51%).

To a stirred suspension of $LiAlH_4$ (680 mg, 17.9 mmol) in THF (100 ml) at room temperature was added a THF solution (30 ml) of **23** (6.65 g, 17.9 mmol), and the mixture was heated under reflux for 1 h. After the mixture was cooled to room temperature, a mixture of THF and H_2O (1 : 1) was added dropwisely. Then, the resultant mixture was filtered through celite. The filtrate was concentrated and the residue was extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ 1 : 9) to give **24** (4.20 g, yield 63%).

Compound **23**: ^{1}H-NMR ($CDCl_3$) δ: 7.80 (1H, d, J=5.6 Hz), 7.74 (1H, s), 7.43—7.46 (3H, m), 7.22—7.33 (5H, m), 7.11—7.14 (2H, m), 6.49 (1H, d, J=5.6 Hz), 3.47 (2H, s), 3.15—3.22 (1H, m), 2.77—2.81 (2H, m), 1.95—2.02 (2H, m), 1.73—1.87 (2H, m), 1.63—1.67 (2H, m).

Compound **24**: ^{1}H-NMR ($CDCl_3$) δ: 8.06 (1H, d, J=5.6 Hz), 7.98 (1H, s), 7.24—7.35 (10H, m), 6.42 (1H, d, J=5.6 Hz), 5.59 (2H, br s), 5.08 (1H, s), 3.48 (2H, s), 2.82 (1H, m), 2.45 (1H, m), 1.86—2.00 (4H, m), 1.36—1.54 (2H, m).

3-(1-Benzylpiperidin-4-yl)-4-phenyl-3,4-dihydropyrido[4,3-*d*]pyrimidin-2(1*H*)-one (25) To a stirred THF solution (100 ml) of **24** (8.00 g, 21.5 mmol) at room temperature was added 1,1′-carbonyldiimidazole (5.00 g, 30.8 mmol), and the mixture was heated under reflux for 8 h. After the mixture was cooled to room temperature, the mixture was evaporated to dryness. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ 1 : 9) to give the crude crystal. This crude crystal was crystallized from EtOH/diethyl ether to give **25** (4.20 g, yield 49%). mp 209—210 °C (from EtOH/diethyl ether); ^{1}H-NMR ($CDCl_3$) δ: 8.35 (1H, s), 8.26 (1H, d, J=5.6 Hz), 8.09 (1H, br s), 7.23—7.38 (10H, m), 6.65 (1H, d, J=5.6 Hz), 5.64 (1H, s), 4.36 (1H, m), 3.46 (2H, s), 2.96 (1H, m), 2.80 (1H, m), 2.00—2.10 (3H, m), 1.50—1.65 (3H, m); *Anal.* Calcd for $C_{25}H_{26}N_4O$: C, 75.35; H, 6.58; N, 14.05. Found: C, 74.97; H, 6.41; N, 14.02.

HCl Salt of 3-(1-Benzylpiperidin-4-yl)-4-phenyl-3,4-dihydropyrido-[4,3-*d*]pyrimidin-2(1H)-one (26) To a stirred EtOH solution of **25** at room temperature was added 1 M HCl/diethyl ether, and the mixture was stirred at ambient temperature for 30 min. The mixture was evaporated to dryness. The residue was recrystallized from EtOH/diethyl ether to give **26**. mp >230 °C; ^{1}H-NMR ($CDCl_3$) δ: 11.27 (1H, s), 10.66 (1H, br s), 8.81 (1H, s), 8.45 (1H, d, J=6.8 Hz), 7.56 (2H, m), 7.43—7.48 (5H, m), 7.39 (2H, m), 7.31 (1H, m), 7.24 (1H, d, J=6.8 Hz), 6.04 (1H, s), 4.27 (1H, m), 4.21 (2H, s), 3.21—3.42 (3H, m), 2.95—3.04 (2H, m), 1.88 (1H, m), 1.65 (2H, m); *Anal.* Calcd for $C_{25}H_{26}N_4O \cdot 2HCl \cdot 3/2H_2O$: C, 60.24; H, 6.27; N, 11.24. Found: C, 60.04; H, 6.22; N, 11.04.

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