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Synthesis and structure–activity relationships of phenoxypyridine derivatives as novel inhibitors of the sodium–calcium exchanger

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Abstract—The sodium–calcium exchanger (NCX) is known as the transporter that controls the concentration of Ca^{2+} in cardiac myocytes. In the setting of heart failure and myocardial ischemia-reperfusion, NCX underlies an arrhythmogenic transient inward current responsible for delayed after—depolarizations and nonreentrant initiation of ventricular tachycardia. NCX is an attractive target for treatment in heart failure and myocardial ischemia-reperfusion. We have designed and synthesized a series of phenoxypyridine derivatives, based on compound **3**. These derivatives have been evaluated for their inhibitory activity against both the reverse and forward mode of NCX in CCL39 cells. We have discovered several novel potent NCX inhibitors (**39q**, **48k**), which have a high selectivity for reverse NCX inhibitory activity.

1. Introduction

Ca^{2+} is an important second messenger in most cell types, and controls contraction in myocytes. The sodium–calcium exchanger (NCX) plays an important role in maintaining the calcium balance in cardiac myocytes,[1] but in the setting of heart failure and myocardial ischemia-reperfusion, an increase in Na^+ levels leads to a calcium overload via the NCX.[2–7] This is also responsible for contractile dysfunction. Approaches that inhibited the NCX could have potential anti-arrhythmic effects in pathophysiological states, such as heart failure or myocardial ischemia-reperfusion. NCX typically functions in the forward mode but can also function in the reverse mode. The reverse mode of NCX has a more important role with regards to calcium overload. Consequently, selective inhibition of the reverse NCX mode could provide a novel therapeutic approach to the prevention and treatment of reperfusion arrhythmias, aberrant myocardial contracture, and necrosis. Indeed, reverse mode NCX inhibitors are currently considered beneficial in treating the above diseases.[8]

Recently, several NCX inhibitors have been identified (Fig. 1).[9–12] The arylguanidine compound **1** has been reported, which is based on a known sodium–proton exchanger (NHE) inhibitor.[9] A series of phenoxybenzyl derivatives **2**–**3**[10,11] and a qunazoline derivative **4**[12] have also been reported. KB-R7943 (**2**) has been shown to have an IC_{50} value of 0.32 μM and exhibits a greater effect on the reverse NCX than on the forward NCX in single cardiac ventricular cells of the guinea pig with the whole-cell voltage-clamp technique.[13] Compound **3** has been reported as a potent NCX inhibitor.[11] The NCX inhibitory structure–activity relationships of these compounds have not been reported in detail to date. We focused on compound **3** and planned to create novel and more selective reverse NCX inhibitors. In order to improve inhibitory activity and selectivity for the reverse NCX, modifications to the 3-fluorobenzylphenyl, amide, and pyrrolidine functions were undertaken.

In this paper, we describe the results of our work on the synthesis and structure–activity relationships of these potent and selective reverse NCX inhibitors.

Keywords: Sodium–calcium exchanger; NCX; transporter; Anti-arrhythmias.
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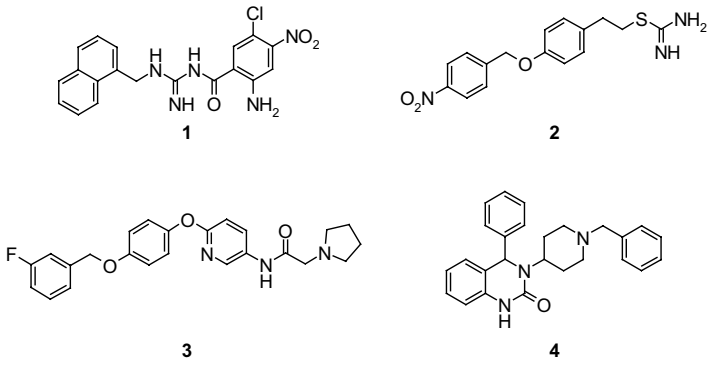
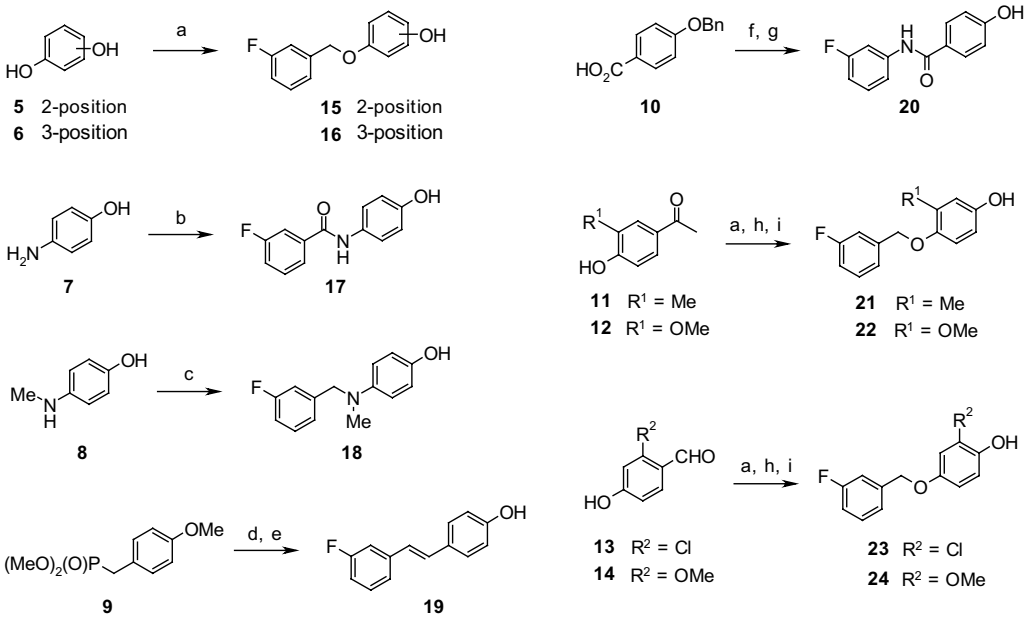


Figure 1. Several inhibitors of sodium–calcium exchanger: (**1**) aroylguanidine analogue; (**2**) KB-R7943; (**3**) patented compound of JP11092454; (**4**) SM-15811.

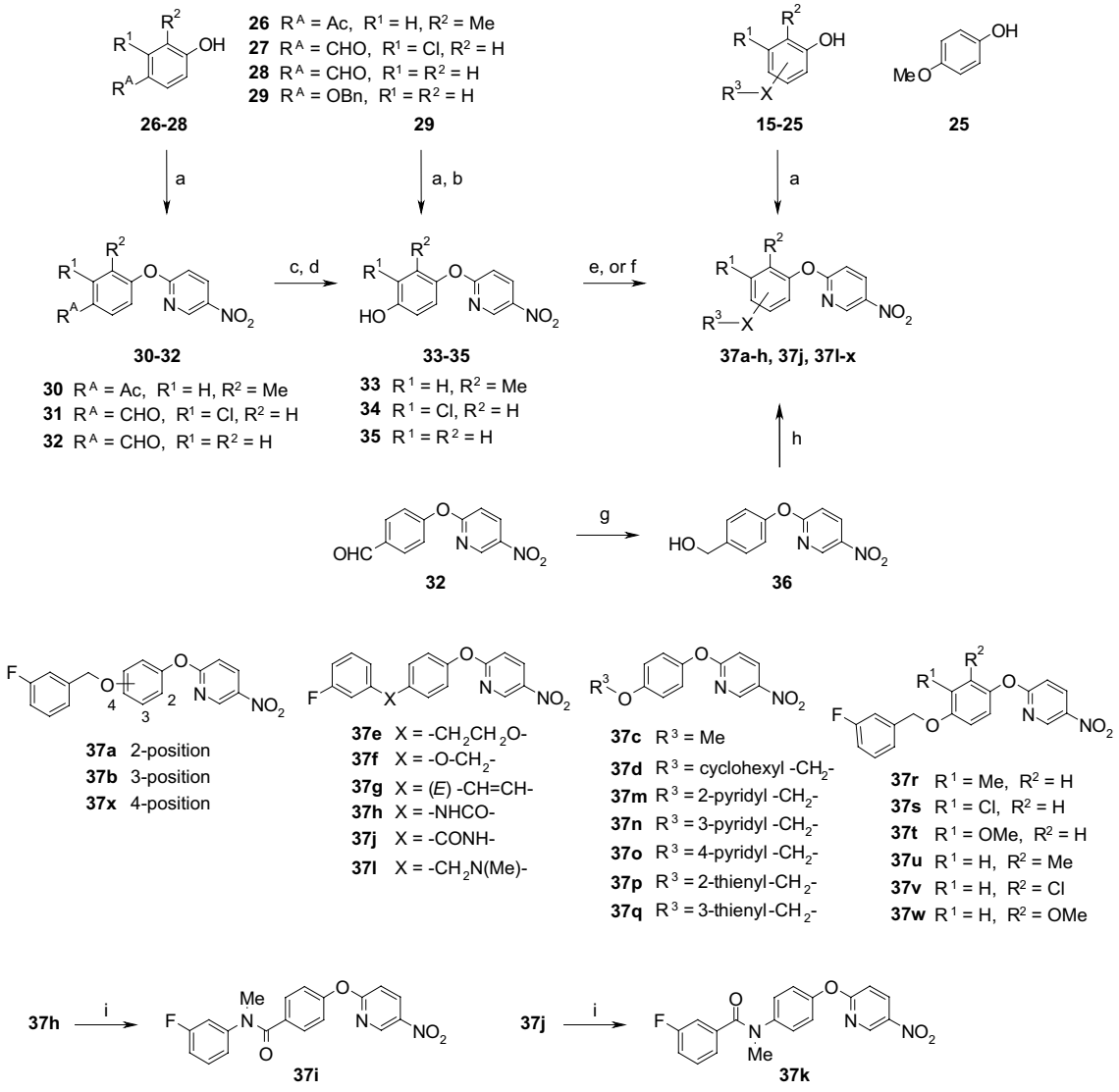
2. Chemistry

The synthesis schemes of the novel *N*-(6-phenoxypyridin-3-yl)acylamide derivatives **39a**–**w**, compounds **40**–**43**, 6-{4-[(3-fluorobenzyl)oxy]phenoxy}nicotinamide derivatives **48a**–**m** and compound **47** are summarized in Schemes 1–4. In Scheme 1, intermediates **15**–**24** were prepared from starting materials **5**–**14**. Intermediates **15** and **16** were prepared from **5** and **6**, respectively, via *O*-alkylation with 3-fluorobenzylbromide. Intermediate **17** was obtained from compound **7** via condensation with 3-fluorobenzoic acid. Reductive alkylation of **8** with 3-fluorobenzaldehyde afforded intermediate **18**. Reaction of **9** with 3-fluorobenzaldehyde followed by the removal of the methyl group with BBr_3 afforded the intermediate **19**. Compound **10** was converted into **20** via condensation with 3-fluoroaniline and removal of the associated benzyl group. *O*-alkylation of compounds **11**–**14** with 3-fluorobenzylbromide followed by a Baeyer–Villiger reaction and subsequent hydrolysis gave intermediates **21**–**24**, respectively.

We described the synthesis of intermediates **37a**–**x** as shown in Scheme 2. Compounds **26** and **27** were converted to intermediates **33** and **34** via condensation with 2-chloro-5-nitropyridine, followed by a Baeyer–Villiger reaction, and subsequent hydrolysis. Condensation of **29** with 2-chloro-5-nitropyridine followed by benzyl removal afforded compound **35**. Condensation of **28** with 2-chloro-5-nitropyridine and subsequent reduction with sodium borohydride of the aldehyde afforded alcohol derivative **36**. Condensation of compounds **15**–**25** with 2-chloro-5-nitropyridine afforded intermediates **37a**–**c**,**g**,**h**,**j**,**l**,**r**,**t**,**v**,**w**, respectively. Alkylation of **33** and **34** with 3-fluorobenzylbromide afforded intermediates **37u** and **37s**. Under Mitsunobu conditions, the reaction of **35** with 2-(3-fluorophenyl)ethanol and **36** with 3-fluorophenol gave **37e** and **37f**, respectively. Alkylation of **35**



Scheme 1. Synthesis of intermediates **15**–**24**. Reagents and conditions: (a) 3-fluorobenzylbromide, K_2CO_3, DMF; (b) 3-fluorobenzoic acid, $(COCl)_2$, DMF, dichloroethane, then Et_3N, **7**; (c) 3-fluorobenzaldehyde, $NaBH(OAc)_3$, AcOH, THF; (d) NaH, 15-crown-5, 3-fluorobenzaldehyde, THF; (e) BBr_3, CH_2Cl_2, −78 °C, then MeOH; (f) $(COCl)_2$, DMF, dichloroethane, then Et_3N, 3-fluoroaniline; (g) pentamethylbenzene, TFA; (h) *m*-chloroperbenzoic acid, CH_2Cl_2; (i) K_2CO_3, MeOH.



Scheme 2. Synthesis of intermediates **37a**–**x**. Reagents and conditions: (a) 2-chloro-5-nitropyridine, K_2CO_3, DMF, 100 °C; (b) pentamethylbenzene, TFA; (c) *m*-chloroperbenzoic acid, CH_2Cl_2; (d) K_2CO_3, MeOH; (e) R^3–Br, K_2CO_3, DMF; (f) R^3–OH, DEAD, PPh_3, THF; (g) $NaBH_4$, MeOH, THF; (h) 3-fluorophenol, DEAD, PPh_3, THF; (i) NaH, MeI, THF.

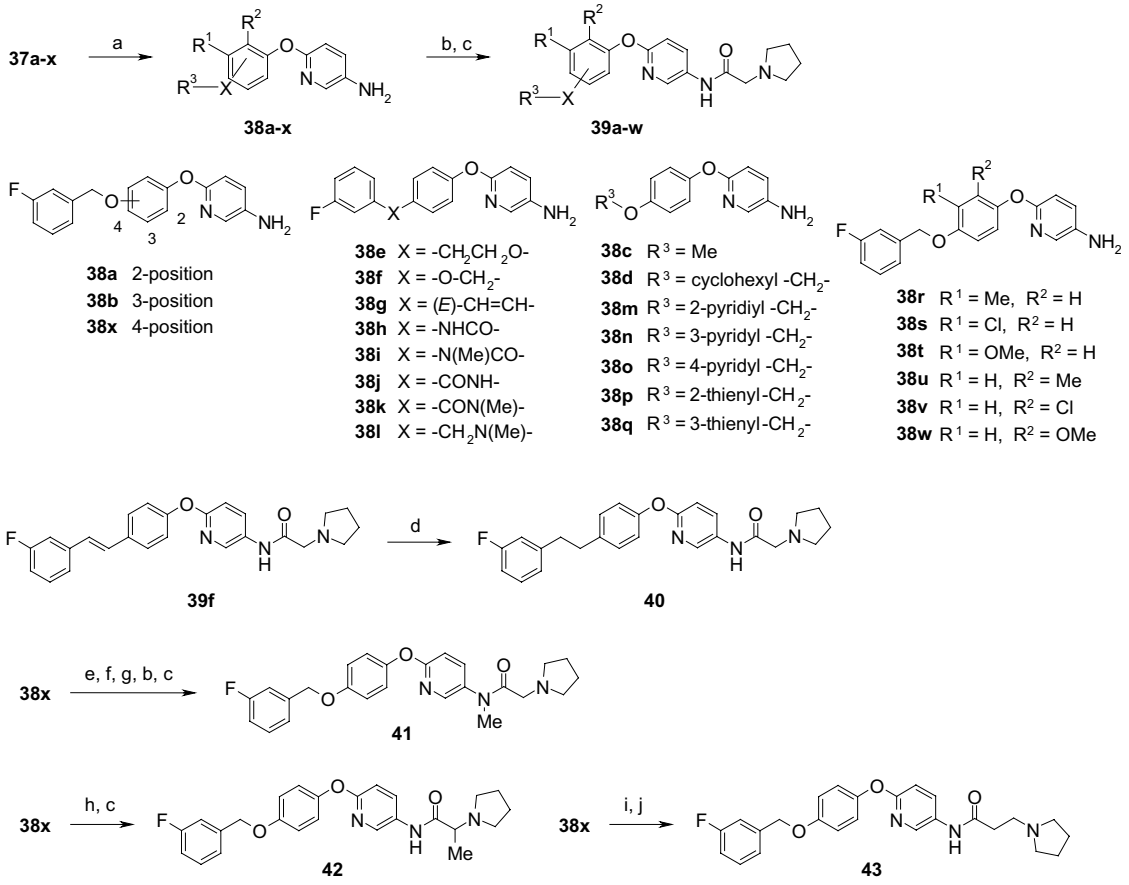
with several halides afforded **37d**, **37m**–**q**, and **37x**. Compounds **37h** and **37j** were converted to **37i** and **37k** via alkylation with methyl iodide.

Reduction of compounds **37a**–**x** gave amino derivatives **38a**–**x**. Condensation of compounds **38a**–**w** with chloroacetic anhydride followed by alkylation with pyrrolidine afforded the *N*-(6-phenoxypyridin-3-yl)acylamide derivatives **39a**–**w** (Scheme 3). 3-Fluorophenylethyl derivative **40** was obtained via hydrogenation of compound **39f**. Compound **41** was prepared from **38x** in five steps, as follows: trifluoroacetylation of amino group: methylation of the trifluoroacetylamino group using iodo-methane: hydrolysis of the trifluoroacetyl group; amidation with chloroacetic anhydride and alkylation with pyrrolidine. Compound **42** was prepared by the acylation of compound **38x** with 2-bromopropionyl bromide followed by alkylation with pyrrolidine. Acylation of compound **38x** with acryloyl chloride followed by alkylation gave compound **43**.

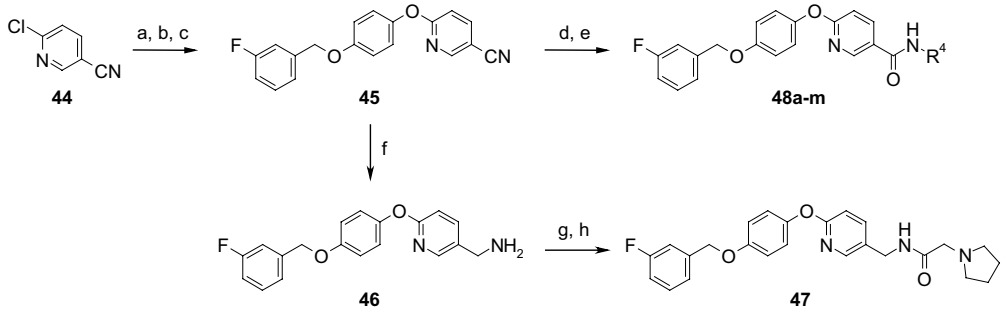
6-{4-[(3-Fluorobenzyl)oxy]phenoxy}nicotinamide derivatives **48a**–**m**, and compound **47** were synthesized from 2-chloro-5-cyanopyridine as illustrated in Scheme 4. Condensation of compound **44** with 4-benzyloxyphenol followed by debenzylation and *O*-alkylation with 3-fluorobenzylbromide gave compound **45**. Subsequent reduction of **45** followed by condensation with chloroacetic anhydride and alkylation with pyrrolidine afforded compound **47**. Hydrolysis of the cyano function of compound **45** followed by condensation with a selection of amines afforded compounds **48a**–**m**.

3. Results and discussion

In order to measure the inhibitory effect of the synthesized compounds on the reverse mode of NCX activity, a Na^+-dependent Ca^{2+} influx assay was performed according to reported protocols, using ^{45}Ca and CCL39 cells



Scheme 3. Synthesis of compounds **39a**–**w**, **40**–**43**. Reagents and conditions: (a) $SnCl{\cdot}H_2O$, THF, 70 °C or Fe, NH_4Cl, H_2O, EtOH, 90 °C or Pd–C, H_2, THF; (b) $(ClCH_2CO)_2O$, $CHCl_3$; (c) K_2CO_3, pyrrolidine, MeCN, 90 °C; (d) Pd–C, H_2, MeOH; (e) TFAA, CH_2Cl_2; (f) MeI, K_2CO_3, 2-butanone, reflux; (g) NaOH, MeOH; (h) 2-bromopropionyl bromide, $NaHCO_3$, AcOEt–H_2O; (i) Et_3N, THF, acryloyl chloride; (j) pyrrolidine, K_2CO_3, MeCN, 80 °C.



Scheme 4. Synthesis of compounds **47**, **48a**–**m**. Reagents and conditions: (a) 4-benzyloxyphenol, K_2CO_3, DMF, 100 °C; (b) pentamethylbenzene, TFA; (c) 3-fluorobenzylbromide, K_2CO_3, MeCN, 80 °C; (d) 5 M NaOH, EtOH, reflux; (e) WSC·HCl, HOBt, THF, R^4NH_2; (f) $BH_3{\cdot}THF$, THF; (g) $(ClCH_2CO)_2O$, $CHCl_3$; (h) K_2CO_3, pyrrolidine, MeCN, 90 °C.

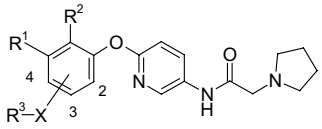
stably expressing NCX1.1.[10] A concentration-response curve was drawn to determine the concentration required to prevent 50% of the influx of ^{45}Ca (reverse mode NCX) induced by a Na^+ overload. The inhibitory effect of the synthesized compounds on forward mode NCX activity was assayed by a cell necrosis assay, which also used NCX1.1-expressing CCL39 cells. Again a concentration-response curve was drawn to determine the concentration required to induce 50% of the cell necrosis by a Ca^{2+} overload.[14]

The inhibitory potencies of our novel compounds were thus evaluated in reverse mode and forward mode NCX assays. These compounds were then compared to KB-R7943 (**2**) and compound **3** (Fig. 1).

The structure–activity relationships of our novel series of NCX inhibitors are summarized in Tables 1–3.

Both KB-R7943 (**2**) and patented compound **3** were examined as reference compounds. KB-R7943 (**2**) is

Table 1. Inhibitory activity of phenoxypyridine derivatives against the sodium–calcium exchanger

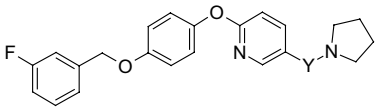


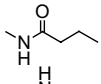
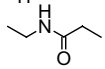
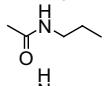
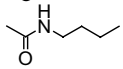
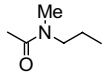
Compd	Position	R^3–X–	R^1	R^2	^{45}Ca influx[a] IC_{50} (μM)[c]	Cell necrosis[b] EC_{50} (μM)[c]	Selectivity[d]
39a	2	3-F–C_6H_4–CH_2O–	H	H	>100	NT[e]	—
39b	3	3-F–C_6H_4–CH_2O–	H	H	31	NT[e]	—
39c	4	MeO–	H	H	>100	NT[e]	—
39d	4	Cyclohexyl–CH_2O–	H	H	44	NT[e]	—
39e	4	3-F–C_6H_4–$(CH_2)_2O$–	H	H	11	52	4.7
39f	4	3-F–C_6H_4–OCH_2–	H	H	6.3	17	2.7
39g	4	3-F–C_6H_4–(*E*)–CH=CH–	H	H	60	NT[e]	—
40	4	3-F–C_6H_4–$(CH_2)_2$–	H	H	3.6	70	19
39h	4	3-F–C_6H_4–NHCO–	H	H	39	NT[e]	—
39i	4	3-F–C_6H_4–N(Me)CO–	H	H	25	NT[e]	—
39j	4	3-F–C_6H_4–CONH–	H	H	10	NT[e]	—
39k	4	3-F–C_6H_4–CON(Me)–	H	H	>100	NT[e]	—
39l	4	3-F–C_6H_4–CH_2N(Me)–	H	H	9.6	NT[e]	—
39m	4	2–Pyridyl–CH_2O–	H	H	9.5	>100	>10
39n	4	3–Pyridyl–CH_2O–	H	H	3.9	>100	>25
39o	4	4–Pyridyl–CH_2O–	H	H	1.7	>100	>58
39p	4	2-Thienyl–CH_2O–	H	H	1.3	80	62
39q	4	3-Thienyl–CH_2O–	H	H	0.60	58	97
39r	4	3-F–C_6H_4–CH_2O–	Me	H	2.0	>100	>50
39s	4	3-F–C_6H_4–CH_2O–	Cl	H	3.6	NT[e]	—
39t	4	3-F–C_6H_4–CH_2O–	OMe	H	5.8	51	8.8
39u	4	3-F–C_6H_4–CH_2O–	H	Me	5.7	57	10
39v	4	3-F–C_6H_4–CH_2O–	H	Cl	4.8	72	15
39w	4	3-F–C_6H_4–CH_2O–	H	OMe	2.8	83	29
2					5.1	24	4.7
3	4	3-F–C_6H_4–CH_2O–	H	H	0.94	34	36

[a] Activity at the NCX1.1 expressed in CCL39 cells. ^{45}Ca influx mean NCX inhibitory activity for reverse mode.
[b] Activity at the NCX1.1 expressed in CCL39 cells. Cell necrosis mean NCX inhibitory activity for forward mode.
[c] IC_{50} values and EC_{50} values were determined in a single experimental run in triplicate.
[d] Ratio of EC_{50} value of Cell necrosis and IC_{50} value of ^{45}Ca influx.
[e] Not tested.

one of the most well known reverse NCX inhibitors, which is used as a model for testing the effects of heart failure disease.[15] In our ^{45}Ca influx assay KB-R7943 (**2**) exhibited an IC_{50} value of 5.1 μM against reverse NCX, whereas compound **3** exhibited an IC_{50} value of 0.94 μM for reverse NCX. Compound **3**, which showed an EC_{50} value of 34 μM for cell necrosis induced by inhibition of NCX forward mode, also showed a higher selectivity than KB-R7943 (**2**). Consequently, compound **3** was selected as a lead compound.[16] We studied these compounds' structure–activity relationships as they were not known. This study led us to introduce several linkages connecting the 3-fluorophenyl moiety with the phenoxy part of compound **3**, and to transform the 3-fluorophenyl group to various hetero-aryl groups. We also converted the amide linkage and pyrrolidine moiety into inverse amides and several other functional groups. Initially, a number of phenoxypyridine derivatives with various structural motifs were prepared, in order to identify the optimum 3-fluorophenylmethyloxyphenyl moiety. The results of this optimization exercise are shown in Table 1. Substitution at both the 2-position and 3-position with a 3-fluorophenylmethyloxy unit led to a substantial decrease in reverse NCX inhibitory activity (compounds **39a**,**b**). Changing the 3-fluorophenylmethyl group into another group such as a methoxy group (**39c**) or cyclohexylmethoxy group (**39d**) also caused a strong reduction in the observed potency. These results suggested that the 3-fluorophenyl ring and its position play an important and significant role with regards to activity. We then examined modifications to the linker (–CH_2O–) connecting the 3-fluorophenyl moiety with the phenoxy unit. The length of linker was increased in compound **39e** and a 12-fold decrease in activity was observed. Consequently, other linker systems such as —OCH_2— (**39f**), —CH=CH— (**39g**), amide (**39h**–**k**) and —CH_2N(Me)— (**40**) were examined. Compounds **39g**–**l** gave a reduction in reverse NCX activity. These results indicate that both a straight conformation of the linker unit (such as in **39g**) and the polarity of the linking unit (such as in **39h**–**k**) are detrimental to NCX activity, whereas the –CH_2O– linker unit is beneficial with respect to activity. The 2-pyridyl derivative (**39m**) showed a 10-fold decrease in the reverse NCX inhibitory activity compared to compound **3**. However, the 4-pyridyl derivative (**39o**) showed only a

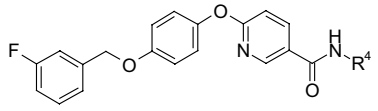
Table 2. Inhibitory activity of phenoxypyridine derivatives against the sodium–calcium exchanger

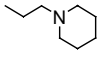
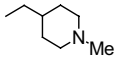
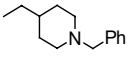
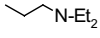
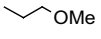
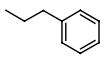
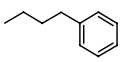
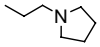


Compd	Y	^{45}Ca influx[a] IC_{50} (μM)[c]	Cell necrosis[b] EC_{50} (μM)[c]	Selectivity[d]
41		11	>100	>9.0
42		2.1	26	40
43		1.6	44	27
47		2.4	58	24
48a		0.78	45	57
48b		1.8	47	26
48c		6.3	NT[e]	—
3		0.94	34	36

For footnotes a–e refer to Table 1.

Table 3. Inhibitory activity of phenoxypyridine derivatives against the sodium–calcium exchanger



Compd	R^4	^{45}Ca influx[a] IC_{50} (μM)[c]	Cell necrosis[b] EC_{50} (μM)[c]	Selectivity[d]
48d		0.90	37	41
48e		2.0	32	16
48f		2.6	>60	23
48g		1.3	36	28
48h		1.4	>100	>71
48i		1.5	NT[e]	—
48j		6.1	55	9.0
48k		0.79	>100	>120
48l		2.8	>100	>36
48m		7.1	NT[e]	—
48a		0.78	45	57
3		0.94	34	36

For footnotes a–e refer to Table 1.

2-fold decrease in the reverse NCX inhibitory activity when compared to compound **3**. This indicates that hydrophilicity is disfavored at the nearest part of the linker. Compound **39q**, containing a 3-thienyl group, showed an IC_{50} value of 0.6 μM for reverse NCX. This compound also had a higher selectivity (ratio of forward to reverse = 97) for reverse NCX when compared to compound **3**. Introduction of some substituents into the phenoxy moiety did not improve reverse NCX inhibitory activity (compounds **39r**–**w**).

We converted the amide function of compound **3** into another amide linker (Table 2). The *N*-methyl amide derivative (**41**) showed a 12-fold decrease in the inhibition of reverse NCX. Replacement of the amide function with several other amide linkers and inverse amide linkers as in compounds **42**, **43**, **47**, **48a**, and **48b** showed equivalent or slightly less potent inhibitory activity for reverse NCX. These indicated that changes in the amide part are well tolerated as regards activity. Among them, the inversion of the amide bond (compound **48a**) showed equivalent activity and similar selectivity compared to compound **3**. The α-methyl amide derivative **42** showed a 2-fold decrease in inhibitory activity; this indicates that introduction of substituents at this position might be unfavorable to inhibitory action. Introduction of the *N*-methyl amide template (compound **48c**) showed a 8-fold decrease in inhibitory activity when compared to compound **48a**. The introduction of the *N*-methyl amide template (**41**, **48c**) appears not to be tolerated with regards to reverse NCX inhibitory activity.

Finally, we attempted to convert the pyrrolidine unit into another functional group based on compound **48a** (Table 3). The replacement of the pyrrolidine unit with several other groups such as amino, methoxy, and alkyl that is piperidino and cyclohexyl groups (compounds **48d**–**i**) led to slightly reduced activity compared to **48a**. Cyclohexyl derivative **48i** and methoxy derivative **48h** showed similar activity compared to piperidino derivative **48e**. This indicated that the basic functional groups might not be important for reverse NCX inhibitory activity. These results prompted us to exchange the pyrrolidino unit with various phenyl ring systems (compounds **48j**–**m**). Benzyl amide derivative **48k** showed equivalent activity and higher selectivity compared to **48a**; whereas neutral substituents (compounds **48h**, **48k**) showed a tendency to reduce the forward NCX inhibitory activity.

4. Conclusion

A series of 2-phenoxypyridine derivatives have been prepared and evaluated for their inhibitory activities and selectivities for the reverse mode of NCX versus the forward mode. Compound **3** was selected as a lead compound. By modifying the phenoxybenzyl moiety, we found the thienylmethoxyphenyl structure (compound **39q**) to enhance reverse NCX inhibitory activity and to increase selectivity. By modifying the amide moiety, compound **48a,** possessing the novel 6-phenoxynicotinamide structure, was identified as a novel reverse NCX inhibitor. As a result of structural modifications based upon compound **48a**, we found a novel reverse NCX inhibitor in compound **48k**, which has both a potent inhibitory activity and a high selectivity for the reverse mode. Compounds **39q** and **48k** have IC_{50} values of 0.60 and 0.79 μM for reverse NCX, respectively, and higher selectivity when compared to compound **3**. Compounds **39q** and **48k** when compared to KB-R7943 (**2**), showed a 6-fold and 8-fold increase in potency respectively. Further research of this series to discover potent and selective NCX inhibitors for the reverse mode is in progress and will be reported in the near future.

5. Experimental

5.1. Chemistry

Melting points were determined with a Yanaco MP-500D melting point apparatus or a Büchi B-545 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL JNM-LA300 or a JNM-EX400 spectrometer and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard (in NMR description, s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad peak). Mass spectra were recorded on a Hitachi M-80 or a JEOL JMS-LX2000 spectrometer. The elemental analyses were performed with a Yanaco MT-5 microanalyzer (C, H, N) and were within ±0.4% of theoretical values. Drying of organic solutions during workup was done over anhydrous Na_2SO_4.

5.1.1. 2-(3-Fluorobenzyloxy)phenol (15). To the mixture of 2-hydroxyphenol (**5**) (5.39 g, 49 mmol) and K_2CO_3 (6.76 g, 49 mmol), DMF (150 mL) was added 3-fluorobenzylbromide (2.0 mL, 16.3 mmol) at room temperature. The mixture was stirred at room temperature for 5 h. Water was added to the reaction mixture. The mixture was partitioned between AcOEt and water. The organic layer was washed with brine, dried, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 10:1–8:1) to give **15** (2.62 g, 74%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.12 (2H, s), 6.68–6.74 (1H, m), 6.75–6.84 (2H, m), 6.97 (1H, dd, J = 8.3, 1.5 Hz), 7.10–7.17 (1H, m), 7.28–7.37 (2H, m), 7.38–7.45 (1H, m), 9.00 (1H, s); MS (FAB) *m*/*z* 218 $(M-H)^-$.

5.1.2. 3-(3-Fluorobenzyloxy)phenol (16). Compound **16** was prepared from 3-hydroxyphenol (**6**) by a procedure similar to that described for **15**. Compound **16** was obtained as a brown oil (65%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.06 (2H, s), 6.35–6.46 (3H, m), 7.06 (1H, t, J = 8.3 Hz), 7.11–7.18 (1H, m), 7.23–7.29 (2H, m), 7.40–7.47 (1H, m), 9.41 (1H, s); MS (FAB) *m*/*z* 218 $(M-H)^-$.

5.1.3. 3-Fluoro-*N*-(4-hydroxyphenyl)benzamide (17). To the mixture of 3-fluorobenzoic acid (2.83 g, 20 mmol) and dichloroethane (50 mL), dimethylformamide (0.2 mL) was added $(COCl)_2$ (1.84 mL, 21 mmol) at room

temperature. After stirring for 2 h, the mixture was added to the mixture of **7** (2.0 g, 18.3 mmol) and dichloroethane (30 mL), Et_3N (5.1 mL, 37 mmol) at 0 °C. The mixture was stirred at room temperature for overnight. H_2O was added, the precipitate was filtered, and dried in vacuo to give (**17**) (3.40 g) as a violet solid (80%). ^1H NMR (400 MHz, DMSO-d_6): δ 7.31 (2H, d, J = 8.8 Hz), 7.43–7.50 (1H, m), 7.57–7.72 (1H, m), 7.75–7.92 (3H, m), 8.00 (1H, d, J = 8.0 Hz), 10.43 (1H, s); MS (FAB) m/z 229 $(M-2H)^-$.

5.1.4. 4-[(3-Fluorobenzyl)(methyl)amino]phenol (18). To the mixture of 4-methylaminophenol (**8**) (0.5 equiv of H_2SO_4 salt, 1.72 g, 10 mmol) and THF (20 mL), Et_3N (1.39 mL, 10 mmol) was added 3-fluorobenzaldehyde (1.24 g, 10 mmol) at 0 °C. Acetic acid (0.57 mL, 10 mmol) and $NaBH(OAc)_3$ (2.33 g, 10 mmol) were added to the mixture at 0 °C. The mixture was stirred at room temperature for overnight. The mixture was partitioned between AcOEt and H_2O. The organic layer was washed with saturated $NaHCO_3$, brine, dried, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:0–2:1) to give **18** (1.93 g, 83%) as a light pink syrup. ^1H NMR (300 MHz, $CDCl_3$): δ 2.91 (3H, br s), 4.33 (1H, s), 4.39 (2H, br s), 6.62–6.80 (4H, m), 6.88–7.04 (3H, m), 7.22–7.31 (1H, m); MS (FAB) m/z 231 $(M+H)^+$.

5.1.5. 4-[(*E*)-2-(3-Fluorophenyl)vinyl]phenol (19). To the mixture of **9** (4.02 g, 15.6 mmol) and THF (30 mL) was added 60% NaH (650 mg, 16.3 mmol) at 0 °C. 3-Fluorobenzaldehyde (1.5 mL, 14.1 mmol) and 15-crown-5 (0.08 mL) were added to the mixture at 0 °C. The reaction mixture was stirred at room temperature for 2 h. H_2O was added to the mixture. The organic layer was extracted with AcOEt, dried, and evaporated in vacuo. The residue was recrystallized with hexane (13 mL). The precipitate was collected to give 1-fluoro-3-[(*E*)-2-(4-methoxyphenyl)vinyl]benzene (68%). The product (790 mg, 3.46 mmol) was dissolved in CH_2Cl_2 (10 mL). To the mixture was added BBr_3 of CH_2Cl_2 solution (1 M, 10 mL) at −78 °C. The mixture was stirred at −78 °C to room temperature for 5 h. MeOH (3.46 mmol) was added to the mixture at −78 °C. The mixture was stirred at room temperature for 1 h. The organic layer was washed with saturated $NaHCO_3$ and brine, dried, evaporated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1) to give **19** (234 mg, 32%) as a colorless oil; ^1H NMR (400 MHz, DMSO-d_6): δ 6.78 (2H, d, J = 8.7 Hz), 6.99–7.07 (2H, m), 7.23 (1H, d, J = 8.7 Hz), 7.34–7.45 (5H, m), 9.63 (1H, br s); MS (FAB) m/z 214 $(M)^+$.

5.1.6. *N*-(3-Fluorophenyl)-4-hydroxybenzamide (20). 4-(Benzyloxy)-*N*-(3-fluorophenyl)benzamide (3.64 g, 55% yield as a colorless solid) was prepared from **10** (5.22 g, 23 mmol) and 3-fluoroaniline (2.31 g, 23 mmol) according to the procedure similar to that described for **17**. 4-(Benzyloxy)-*N*-(3-fluorophenyl)benzamide (1.18 g, 3.7 mmol) was added to the mixture of pentamethylbenzene (1.63 g, 11 mmol) and trifluoroacetic acid (8 mL) at room temperature. The mixture was stirred for 6 h. The solvent was removed under reduced pressure. To the residue were added H_2O (8 mL) and $CHCl_3$ (8 mL). The mixture was stirred, the precipitate was filtered, and dried in vacuo to afford **20** as a colorless solid (82%). ^1H NMR (400 MHz, DMSO-d_6): δ 6.84–6.92 (3H, m), 7.32–7.40 (1H, m), 7.51–7.57 (1H, m), 7.71–7.77 (1H, m), 7.85 (2H, d, J = 8.3 Hz), 10.15 (2H, d, J = 7.9 Hz); MS (FAB) m/z 232 $(M+H)^+$.

5.1.7. 4-[(3-Fluorobenzyl)oxy]-3-methylphenol (21). To the mixture of **11** (0.75 g, 5.0 mmol) and MeCN (8 mL), K_2CO_3 (0.83 g, 6.9 mmol) was added 3-fluorobenzylbromide (0.67 mL, 5.5 mmol) at room temperature. The mixture was stirred at 80 °C for 1 h. The mixture was partitioned between Et_2O and aqueous NaOH. The organic layer was washed with brine and dried, evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 4:1) to give 1-{4-[(3-fluorobenzyl)oxy]-3-methylphenyl}ethanone (1.26 g, 98%) as a colorless solid. The intermediate (1.26 g, 4.9 mmol) was dissolved in dichloroethane (15 mL). To the mixture was added *m*-chloroperbenzoic acid (1.37 g, 6.37 mmol) at 0 °C. The mixture was stirred at room temperature for overnight. *m*-Chloroperbenzoic acid (0.42 g, 2.45 mmol) was added to the mixture at 0 °C. The mixture was stirred at room temperature for 7 h. The mixture was filtered, washed with dichloroethane. To the filtrate was added saturated Na_2SO_3, the mixture was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with saturated $NaHCO_3$ and brine, dried, and evaporated. To the mixture of residue and MeOH (13 mL) was added K_2CO_3 (1.02 g, 7.35 mmol). The mixture was stirred at room temperature for 5 h. The solvent was removed under reduced pressure. the residue was partitioned between AcOEt and aqueous HCl. The organic layer was washed with brine, dried, evaporated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 2:1) to give **21** (1.01 g, 89% for two steps) as a colorless solid. ^1H NMR (300 MHz, $CDCl_3$): δ 2.24 (3H, s), 4.99 (2H, s), 5.04 (1H, br s), 6.59 (1H, dd, J = 8.6, 2.9 Hz), 6.67–6.74 (2H, m), 6.83–7.04 (1H, m), 7.12–7.21 (2H, m), 7.29–7.37 (1H, m); MS (FAB) m/z 232 $(M)^+$.

The following compounds (**22**–**24**) were prepared by a procedure similar to that described for **21**.

5.1.8. 4-[(3-Fluorobenzyl)oxy]-3-methoxyphenol (22). Brown oil (74% for three steps). ^1H NMR (300 MHz, $CDCl_3$): δ 3.84 (3H, s), 5.04 (2H, s), 6.26 (1H, dd, J = 8.6, 2.9 Hz), 6.47 (1H, d, J = 2.8 Hz), 6.72 (1H, d, J = 8.6 Hz), 6.93–7.01 (1H, m), 7.06–7.19 (2H, m), 7.26–7.35 (1H, m); MS (FAB) m/z 248 $(M)^+$.

5.1.9. 2-Chloro-4-[(3-fluorobenzyl)oxy]phenol (23). White solid (73% for three steps). ^1H NMR (300 MHz, $CDCl_3$): δ 4.99 (2H, s), 5.19 (1H, s), 6.81 (1H, dd, J = 8.9, 2.9 Hz), 6.91–7.05 (3H, m), 7.10–7.19 (2H, m), 7.30–7.38 (1H, m); MS (FAB) m/z 252 $(M+H)^+$.

5.1.10. 4-[(3-Fluorobenzyl)oxy]-2-methoxyphenol (24). Pale yellow oil (50% for three steps). ^1H NMR (300 MHz, $CDCl_3$): δ 3.86 (3H, s), 4.99 (2H, s), 5.24

(1H, s), 6.43 (1H, dd, $J = 8.6$, 2.8 Hz), 6.56 (1H, d, $J = 2.7$ Hz), 6.82 (1H, d, $J = 8.6$ Hz), 6.96–7.05 (1H, m), 7.10–7.21 (2H, m), 7.29–7.38 (1H, m); MS (FAB) m/z 248 $(M)^+$.

5.1.11. 4-[(5-Nitropyridin-2-yl)oxy]benzaldehyde (32). To the mixture of 4-hydroxybenzaldehyde **28** (1.21 g, 9.90 mmol), K_2CO_3 (1.96 g, 14.2 mmol) and DMF (15 mL) was added 5-chloro-2-nitropyridine (1.50 g, 9.46 mmol) at 0 °C. The mixture was stirred at room temperature. To the mixture was added H_2O. The precipitate was filtered and dried in vacuo to afford **32** as a pale brown solid (2.09 g, 90%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39 (1H, d, $J = 8.8$ Hz), 7.48 (2H, d, $J = 8.8$ Hz), 8.03 (2H, d, $J = 8.8$ Hz), 8.68 (1H, dd, $J = 8.8$, 3.0 Hz), 9.05 (1H, d, $J = 2.9$ Hz), 10.03 (1H, s); MS (FAB) m/z 245 $(M+H)^+$.

5.1.12. 4-[(5-Aminopyridin-2-yl)oxy]-3-methylphenol (33). Intermediate **30** was prepared from **26** (1.5 g, 10 mmol) by a procedure similar to that described for **32**. 1-{3-Methyl-4-[(5-nitropyridin-2-yl)oxy]phenyl}ethanone (**30**) was obtained as a yellow oil (2.44 g, 89%). The intermediate **30** (2.44 g, 8.94 mmol) was dissolved in dichloroethane (25 mL). To the mixture was added *m*-chloroperbenzoic acid (2.89 g, 13.4 mmol) at 0 °C. The mixture was stirred at room temperature for 3 days. *m*-Chloroperbenzoic acid (1.93 g, 8.94 mmol) was added to the mixture at 0 °C. The mixture was stirred at room temperature for 3 days. The mixture was filtered, washed with dichloroethane. To the filtrate was added saturated Na_2SO_3, the mixture was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with saturated $NaHCO_3$ and brine, dried, and evaporated. To the mixture of residue and MeOH (26 mL) was added K_2CO_3 (1.85 g, 13.4 mmol). The mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residue was partitioned between AcOEt and aqueous HCl. The organic layer was washed with brine, dried, evaporated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 4:1–3:1) to give **33** (1.31 g, 59% for two steps) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.09 (3H, s), 5.23 (1H, br s), 6.67–6.76 (2H, m), 6.93 (1H, d, $J = 8.4$ Hz), 7.01 (1H, d, $J = 9.1$ Hz), 8.47 (1H, dd, $J = 9.1$, 2.7 Hz), 9.04 (1H, d, $J = 2.7$ Hz); MS (FAB) m/z 247 $(M)^+$.

5.1.13. 2-Chloro-4-[(5-nitropyridin-2-yl)oxy]phenol (34). Compound **34** was prepared from **27** by a procedure similar to that described for **33**. Compound **34** was obtained as a yellow solid (50% for two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.57 (1H, br s), 6.98–7.11 (3H, m), 7.19 (1H, d, $J = 2.8$ Hz), 8.48 (1H, dd, $J = 9.0$, 2.9 Hz), 9.04 (1H, d, $J = 2.9$ Hz); MS (FAB) m/z 266 $(M)^+$.

5.1.14. 4-[(5-Nitropyridin-2-yl)oxy]phenol (35). To the mixture of 4-(benzyloxy)phenol **29** (25 g, 125 mmol), *t*-BuOK (16.8 g, 150 mmol), and DMF (250 mL) was added 5-chloro-2-nitropyridine (19.8 g, 125 mmol) at 0 °C. The mixture was stirred at room temperature. To the mixture was added H_2O. The precipitate was filtered and dried in vacuo to afford 5-[4-(benzyloxy)phenoxy]-2-nitropyridine as a brown powder (35 g, 87%). The compound (31 g, 96 mmol) was dissolved in trifluoroacetic acid (200 mL). To the mixture was added pentamethylbenzene (17 g, 115 mmol) at 0 °C. The mixture was partitioned between AcOEt and aqueous $NaHCO_3$. The organic layer was dried and concentrated in vacuo. The residue was crystallized from AcOEt/hexane to give **35** as a yellow solid (76%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.82 (2H, d, $J = 9.2$ Hz), 7.02 (2H, d, $J = 9.2$ Hz), 7.15 (1H, d, $J = 9.0$ Hz), 8.58 (1H, dd, $J = 9.0$, 2.8 Hz), 9.02 (1H, d, $J = 2.8$ Hz), 9.50 (1H, s); MS (FAB) m/z 233 $(M+H)^+$.

5.1.15. {4-[(5-Nitropyridin-2-yl)oxy]phenyl}methanol (36). Compound **32** (2.09 g, 8.56 mmol) was dissolved in MeOH (17 mL) and THF (17 mL). $NaBH_4$ (324 mg, 8.56 mmol) was added to the mixture at 0 °C. The mixture was stirred for 1 h at room temperature, and was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried, evaporated to afford **36** as a yellow oil (71%): ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.53 (2H, d, $J = 5.8$ Hz), 5.24 (1H, t, $J = 5.6$ Hz), 7.18 (2H, d, $J = 8.3$ Hz), 7.24 (1H, d, $J = 9.3$ Hz), 7.41 (2H, d, $J = 8.3$ Hz), 8.62 (1H, dd, $J = 9.3$, 2.9 Hz), 9.02 (1H, d, $J = 2.4$ Hz); MS (FAB) m/z 247 $(M+H)^+$.

5.1.16. 2-{4-[2-(3-Fluorophenyl)ethoxy]phenoxy}-5-nitropyridine (37a). The mixture of **15** (1.01 g, 4.6 mmol) and 5-nitro-2-chloropyridine (700 mg, 4.42 mmol), K_2CO_3 (915 mg, 6.6 mmol), and DMF (7 mL) was stirred at 100 °C for 4 h. To the reaction mixture was added water at room temperature. The precipitate was collected and washed with water, dried in vacuo to afford **37a** as a pale yellow solid (1.63 g, 100%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.09 (2H, s), 6.73–6.77 (1H, m), 6.97 (1H, d, $J = 7.3$ Hz), 7.02–7.09 (2H, m), 7.23–7.33 (5H, m), 8.59 (1H, dd, $J = 9.2$, 3.0 Hz), 8.99 (1H, d, $J = 2.9$ Hz); MS (FAB) m/z 341 $(M+H)^+$.

5.1.17. *N*-(3-Fluorophenyl)-*N*-methyl-4-[(5-nitropyridin-2-yl)oxy]benzamide (37i). Compound **37h** was prepared from **20** by a procedure similar to that described for **32**. To the mixture of **37h** (350 mg, 0.99 mmol) and THF (15 mL), 60% of NaH (48 mg, 1.20 mmol) was added MeI (0.093 mL, 5 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h. The mixture was partitioned between AcOEt and H_2O. The organic layer was washed with brine, dried, evaporated. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 3:1–2:1) to give **37i** (350 mg, 96%) as a pale yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.39 (3H, s), 7.00–7.08 (2H, m), 7.13 (2H, d, $J = 8.3$ Hz), 7.18–7.26 (2H, m), 7.28–7.41 (3H, m), 8.52 (1H, dd, $J = 8.8$, 3.0 Hz), 9.01 (1H, d, $J = 3.0$ Hz); MS (FAB) m/z 368 $(M+H)^+$.

5.1.18. 3-Fluoro-*N*-{4-[(5-nitropyridin-2-yl)oxy]phenyl}-benzamide (37j). Compound **37j** was prepared from **17** by a procedure similar to that described for **32**. Compound **37j** was obtained as a pale yellow solid (13%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.22–7.28 (2H, m), 7.32 (1H, d, $J = 9.3$ Hz), 7.43–7.50 (1H, m), 7.57–7.72 (1H, m), 7.77–7.88 (4H, m), 8.63 (1H, dd, $J = 9.3$,

2.9 Hz), 9.04 (1H, d, J = 2.9 Hz), 10.42 (1H, br s); MS (FAB) m/z 354 $(M+H)^+$.

5.1.19. 3-Fluoro-*N*-methyl-*N*-{4-[(5-nitropyridin-2-yl)-oxy]phenyl}benzamide (37k). Compound **37k** was prepared from **37j** by a procedure similar to that described for **37i**. Compound **37k** was obtained as a pale yellow solid (49%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.40 (3H, s), 7.07–7.18 (5H, m), 7.22 (1H, d, J = 8.8 Hz), 7.27–7.35 (3H, m), 8.64 (1H, dd, J = 8.8, 2.9 Hz), 9.02 (1H, d, J = 3.0 Hz); MS (FAB) m/z 368 $(M+H)^+$.

5.1.20. 6-{2-[(3-Fluorobenzyl)oxy]phenoxy}pyridin-3-amine (38a). The mixture of **15** (1.01 g, 4.6 mmol) and 5-nitro-2-chloropyridine (700 mg, 4.42 mmol), K_2CO_3 (915 mg, 6.6 mmol), and DMF (7 mL) was stirred at 100 °C for 4 h. To the reaction mixture was added water at room temperature. The precipitate was collected and washed with water, dried in vacuo to afford 2-{4-[2-(3-fluorophenyl)ethoxy]phenoxy}-5-nitropyridine (**37a**) as a pale yellow solid (1.63 g). Compound **37a** was dissolved in THF (40 mL), $SnCl_2{\cdot}2H_2O$ (4.99 g, 22 mmol) was added to the mixture. The mixture was stirred at 70 °C for 2 h and recooled to room temperature. To the reaction mixture were added 1 M NaOH and celite (10 g). The mixture was filtrated through a celite pad, washed with THF. The filtrate was partitioned between AcOEt and H_2O. The organic layer was washed and dried, evaporated under pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 2:1–3:2) to give **38a** (922 mg, 67% for two steps) as a brown oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.92 (2H, s), 5.07 (2H, s), 6.72 (1H, d, J = 8.3 Hz), 6.91–6.99 (2H, m), 7.00–7.14 (6H, m), 7.30–7.37 (1H, m), 7.45 (1H, d, J = 2.9 Hz); MS (FAB) m/z 311 $(M+H)^+$.

5.1.21. 6-{3-[(3-Fluorobenzyl)oxy]phenoxy}pyridin-3-amine (38b). Compound **38b** was prepared from **16** by a procedure similar to that described for **38a**. Compound **38b** was obtained as a brown oil (100% for two steps). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.09 (2H, s), 5.13 (2H, s), 6.51 (1H, dd, J = 8.3, 2.5 Hz), 6.61 (1H, t, J = 2.4 Hz), 6.72–6.77 (2H, m), 7.08 (1H, dd, J = 8.7, 3.0 Hz), 7.12–7.29 (4H, m), 7.39–7.47 (1H, d, J = 2.9 Hz) 7.57 (1H, d, J = 2.9 Hz); MS (FAB) m/z 311 $(M+H)^+$.

5.1.22. 6-(4-Methoxyphenoxy)pyridin-3-amine (38c). Compound **37c** was prepared from 4-methoxyphenol (**25**) (822 mg, 6.63 mmol) by a procedure similar to that described for **37a**. 2-(4-Methoxyphenoxy)-5-nitropyridine (**37c**) was obtained as a pale yellow solid (1.50 g, 97% yield). To the EtOH (30 mL) solution of **37c** were added powder of Fe (1.70 g, 30 mmol) and water (3 mL) solution of NH_4Cl (261 mg, 4.9 mmol) at room temperature. The mixture was stirred at 90 °C for 6 h, it was cooled at room temperature and filtered and washed with $CHCl_3$. The filtrate was partitioned between $CHCl_3$ and water, the organic layer was washed with 1 M NaOH and brine, dried, and evaporated under pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 2:1–3:2) to give **38c** (744 mg, 56%) as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.73 (3H, s), 5.00 (2H, s), 6.69 (1H, d, J = 8.3 Hz), 6.87–6.94 (4H, m), 7.05 (1H, dd, J = 8.3, 3.0 Hz), 7.50 (1H, d, J = 3.0 Hz); MS (FAB) m/z 217 $(M+H)^+$.

The following compounds (**38g**,**l**,**r**,**t**,**v**,**w**) were prepared by a procedure similar to that described for **38c**.

5.1.23. 6-{4-[(*E*)-2-(3-Fluorophenyl)vinyl]phenoxy}pyridin-3-amine (38g). From compound **19** (57% for two steps) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.14 (2H, s), 6.80 (1H, d, J = 8.3 Hz), 6.88 (2H, d, J = 8.8 Hz), 7.04–7.19 (3H, m), 7.32 (1H, d, J = 16.6 Hz), 7.38–7.47 (3H, m), 7.54–7.60 (3H, m); MS (FAB) m/z 307 $(M+H)^+$.

5.1.24. 6-{4-[(3-Fluorobenzyl)(methyl)amino]phenoxy}pyridin-3-amine (38l). From compound **18** (99% for two steps) as a yellow syrup: ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.99 (3H, s), 3.44 (2H, br s), 4.47 (2H, s), 6.67–6.74 (3H, m), 6.89–7.07 (6H, m), 7.24–7.32 (1H, m), 7.69 (1H, d, J = 3.1 Hz); MS (FAB) m/z 324 $(M+H)^+$.

5.1.25. 6-{4-[(3-Fluorobenzyl)oxy]-3-methylphenoxy}pyridin-3-amine (38r). From compound **21** (100% for two steps) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (3H, s), 3.48 (2H, br s), 5.04 (2H, s), 6.72 (1H, d, J = 8.6 Hz), 6.78–6.93 (3H, m), 6.97–7.08 (2H, m), 7.13–7.22 (2H, m), 7.30–7.38 (1H, m), 7.69 (1H, d, J = 2.9 Hz); MS (FAB) m/z 325 $(M+H)^+$.

5.1.26. 6-{4-[(3-Fluorobenzyl)oxy]-3-methoxyphenoxy}-pyridin-3-amine (38t). From compound **22** (81% for two steps) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.50 (2H, br s), 3.85 (3H, s), 5.10 (2H, s), 6.53 (1H, dd, J = 8.8, 2.8 Hz), 6.67–6.75 (2H, m), 6.82 (1H, d, J = 8.6 Hz), 6.94–7.03 (1H, m), 7.07 (1H, dd, J = 8.6, 3.1 Hz), 7.15–7.22 (2H, m), 7.27–7.37 (1H, m), 7.71 (1H, d, J = 3.1 Hz); MS (FAB) m/z 350 $(M+H)^+$.

5.1.27. 6-{2-Chloro-4-[(3-fluorobenzyl)oxy]phenoxy}pyridin-3-amine (38v). From compound **23** (74% for two steps) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.47 (2H, br), 5.03 (2H, s), 6.78 (1H, dd, J = 8.6, 0.6 Hz), 6.87 (1H, dd, J = 8.8, 2.9 Hz), 6.98–7.21 (6H, m), 7.31–7.40 (1H, m), 7.63 (1H, dd, J = 2.9, 0.6 Hz); MS (FAB) m/z 345 $(M+H)^+$.

5.1.28. 6-{4-[(3-Fluorobenzyl)oxy]-2-methoxyphenoxy}-pyridin-3-amine (38w). From compound **24** (73% for two steps) as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.42 (2H, br s), 3.75 (3H, s), 5.03 (2H, s), 6.51 (1H, dd, J = 8.8, 2.7 Hz), 6.65 (1H, d, J = 2.7 Hz), 6.74 (1H, d, J = 8.6 Hz), 6.98–7.08 (3H, m), 7.14–7.23 (2H, m), 7.31–7.39 (1H, m), 7.64 (1H, d, J = 2.9 Hz); MS (FAB) m/z 341 $(M+H)^+$.

5.1.29. 6-[4-(Cyclohexylmethoxy)phenoxy]pyridin-3-amine (38d). Compound **37d** was prepared from **35** by a procedure similar to that described for **15**. The mixture of **37d** (348 mg, 1.06 mmol), THF (10 mL), and 10% of palladium-activated carbon (35 mg) was stirred at room

temperature under H_2 (normal atmosphere) for overnight. The mixture was filtered, the filtrate was concentrated under reduced pressure to give **38d** as a beige solid (49% for two steps): ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.97–1.10 (2H, m), 1.10–1.32 (3H, m), 1.60–1.84 (6H, m), 3.73 (2H, d, J = 6.4 Hz), 5.00 (2H, s), 6.68 (1H, d, J = 8.8 Hz), 6.88 (4H, s), 7.04 (1H, dd, J = 8.8, 2.9 Hz), 7.49 (1H, d, J = 2.9 Hz); MS (FAB) m/z 299 $(M+H)^+$.

5.1.30. 6-{4-[2-(3-Fluorophenyl)ethoxy]phenoxy}pyridin-3-amine (38e). To the mixture of **35** (581 mg, 2.50 mmol) and THF (10 mL), Ph_3P (852 mg, 3.25 mmol) were added a solution of DEAD (0.512 mL, 3.25 mmol) and 2-(3-fluorophenyl)ethanol (420 mg, 3.00 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at room temperature for 6 h. The mixture was partitioned between AcOEt and aqueous NaOH, the organic layer was washed with brine, dried, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/AcOEt = 1:0–4:1) to give **37e** (904 mg,) as a yellow syrup. Compound **38e** was prepared from **37e** by a procedure similar to that described for **38c**. Compound **38e** was obtained as a yellow syrup (93% for two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.08 (2H, t, J = 6.8 Hz), 3.47 (2H, br s), 4.15 (2H, t, J = 6.8 Hz), 6.71 (1H, d, J = 8.6 Hz), 6.84–7.08 (7H, m), 7.23–7.31 (2H, m), 7.68 (1H, d, J = 2.9 Hz); MS (FAB) m/z 325 $(M+H)^+$.

5.1.31. 6-{4-[(3-Fluorophenoxy)methyl]phenoxy}pyridin-3-amine (38f). Compound **37f** was prepared from **36** by a procedure similar to that described for **37e**. Compound **37f** was obtained as a colorless solid (42%). Compound **38f** was prepared from **37f** by a procedure similar to that described for **38c**. Compound **38f** was obtained as a beige solid (93%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.06 (2H, s), 5.11 (2H, s), 6.73–6.80 (2H, m), 6.83–6.92 (2H, m), 6.96 (2H, d, J = 8.3 Hz), 7.08 (1H, dd, J = 8.8, 3.0 Hz), 7.28–7.35 (1H, m), 7.41 (2H, d, J = 8.3 Hz), 7.55 (1H, d, J = 2.9 Hz); MS (FAB) m/z 311 $(M+H)^+$.

5.1.32. 4-[(5-Aminopyridin-2-yl)oxy]-*N*-(3-fluorophenyl)benzamide (38h). Compound **37h** was prepared from compound **20** by a procedure similar to that described for **37a**. Compound **38h** was prepared from **37h** by a procedure similar to that described for **38d**. Compound **38h** was obtained as a colorless solid (92% for two steps). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.21 (2H, s), 6.86 (1H, d, J = 8.7 Hz), 6.88–6.95 (1H, m), 7.03–7.08 (2H, m), 7.12 (1H, dd, J = 8.3, 2.9 Hz), 7.34–7.42 (1H, m), 7.53–7.57 (1H, m), 7.60 (1H, d, J = 2.9 Hz), 7.72–7.78 (1H, m), 7.92–7.97 (2H, m), 10.34 (1H, s); MS (FAB) m/z 324 $(M+H)^+$.

5.1.33. 4-[(5-Aminopyridin-2-yl)oxy]-*N*-(3-fluorophenyl)-*N*-methylbenzamide (38i). Compound **38i** was prepared from compound **37i** by a procedure similar to that described for **38d**. Compound **38i** was obtained as a colorless oil (98%): ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.38 (3H, m), 5.17 (2H, s), 6.73–6.80 (3H, m), 6.95–7.08 (3H, m), 7.13–7.18 (1H, m), 7.23–7.33 (3H, m), 7.56 (1H, d, J = 2.9 Hz); MS (FAB) m/z 338 $(M+H)^+$.

5.1.34. *N*-{4-[(5-Aminopyridin-2-yl)oxy]phenyl}-3-fluorobenzamide (38j). Compound **38j** was prepared from compound **37j** by a procedure similar to that described for **38c**. Compound **38j** was obtained as a beige solid (41%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.08 (2H, s), 6.76 (1H, d, J = 8.8 Hz), 6.94–6.99 (2H, m), 7.08 (1H, dd, J = 8.3, 2.9 Hz), 7.41–7.48 (1H, m), 7.53–7.63 (2H, m), 7.68–7.73 (2H, m), 7.73–7.84 (2H, m), 10.28 (1H, s); MS (FAB) m/z 323 $(M+H)^+$.

5.1.35. 6-[4-(Pyridin-2-ylmethoxy)phenoxy]pyridin-3-amine (38m). Compound **37m** was prepared from compound **35** by a procedure similar to that described for **15**. Compound **38m** was prepared from **37m** by a procedure similar to that described for **38c**. Compound **38m** was obtained as a colorless oil (79% for two steps). ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.02 (2H, s), 5.15 (2H, s), 6.70 (1H, d, J = 8.3 Hz), 6.92 (2H, d, J = 9.0 Hz), 6.99 (2H, d, J = 9.0 Hz), 7.05 (1H, dd, J = 8.8, 2.9 Hz), 7.32–7.37 (1H, m), 7.49–7.54 (2H, m), 7.82–7.87 (1H, m), 8.58 (1H, d, J = 4.9 Hz); MS (FAB) m/z 294 $(M+H)^+$.

The following compounds (**38n**,**o**–**q**,**s**,**u**,**x**) were prepared by a procedure similar to that described for **38m**.

5.1.36. 6-[4-(Pyridin-3-ylmethoxy)phenoxy]pyridin-3-amine (38n). From compound **35** (73% for two steps) as a pale yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.01 (2H, s), 5.12 (2H, s), 6.70 (1H, d, J = 8.3 Hz), 6.92 (2H, d, J = 9.3 Hz), 7.00 (2H, d, J = 9.3 Hz), 7.05 (1H, dd, J = 8.8, 2.9 Hz), 7.40–7.45 (1H, m), 7.50 (1H, d, J = 2.9 Hz), 7.85–7.89 (1H, m), 8.55 (1H, dd, J = 4.9, 1.5 Hz), 8.67 (1H, d, J = 2.0 Hz); MS (FAB) m/z 294 $(M+H)^+$.

5.1.37. 6-[4-(Pyridin-4-ylmethoxy)phenoxy]pyridin-3-amine (38o). From compound **35** (51% for two steps) as a pale yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.01 (2H, s), 5.16 (2H, s), 6.70 (1H, d, J = 8.8 Hz), 6.92 (2H, d, J = 9.3 Hz), 6.98 (2H, d, J = 9.3 Hz), 7.05 (1H, dd, J = 9.0, 3.0 Hz), 7.44 (2H, d, J = 5.9 Hz), 7.49 (1H, d, J = 2.9 Hz), 8.54–8.59 (2H, m); MS (FAB) m/z 294 $(M+H)^+$.

5.1.38. 6-[4-(2-Thienylmethoxy)phenoxy]pyridin-3-amine (38p). From compound **35** (38% for two steps) as a pale yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.00 (2H, s), 5.25 (2H, s), 6.69 (1H, d, J = 8.8 Hz), 6.87–7.08 (6H, m), 7.20 (1H, d, J = 3.6 Hz), 7.50 (1H, d, J = 3.2 Hz), 7.55 (1H, d, J = 4.8 Hz); MS (FAB) m/z 299 $(M+H)^+$.

5.1.39. 6-[4-(3-Thienylmethoxy)phenoxy]pyridin-3-amine (38q). From compound **35** (100% for two steps) as a pale yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.01 (2H, s), 5.51 (2H, s), 6.69 (1H, d, J = 8.3 Hz), 6.89–6.99 (4H, m), 7.05–7.08 (1H, m), 7.17–7.19 (1H, m), 7.50 (1H, d, J = 2.9 Hz), 7.54–7.57 (2H, m); MS (FAB) m/z 299 $(M+H)^+$.

5.1.40. 6-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenoxy}pyridin-3-amine (38s). From compound **34** (79% for two steps) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ

3.52 (2H, br s), 5.11 (2H, s), 6.75 (1H, d, $J = 8.6$ Hz), 6.91–6.93 (2H, m), 6.97–7.11 (2H, m), 7.14–7.25 (2H, m), 7.31–7.39 (2H, m), 7.68 (1H, d, $J = 2.9$ Hz); MS (FAB) m/z 345 $(M+H)^+$.

5.1.41. 6-{4-[(3-Fluorobenzyl)oxy]-2-methylphenoxy}pyridin-3-amine (38u). From compound **33** (87% for two steps) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (3H, s), 3.44 (2H, br s), 5.02 (2H, s), 6.66 (1H, d, $J = 8.6$ Hz), 6.78 (1H, dd, $J = 8.6$, 2.9 Hz), 6.86 (1H, d, $J = 2.7$ Hz), 6.93 (1H, d, $J = 8.8$ Hz), 6.97–7.02 (1H, m), 7.05 (1H, dd, $J = 8.6$, 2.9 Hz), 7.13–7.22 (2H, m), 7.30–7.38 (1H, m), 7.66 (1H, d, $J = 2.9$ Hz); MS (FAB) m/z 325 $(M+H)^+$.

5.1.42. 6-{4-[(3-Fluorobenzyl)oxy]phenoxy}pyridin-3-amine (38x). From compound **35** (86% for two steps) as an orange syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.48 (2H, br s), 5.03 (2H, s), 6.72 (1H, dd, $J = 8.6$, 0.5 Hz), 6.91–7.08 (6H, m), 7.14–7.20 (2H, m), 7.29–7.38 (1H, m), 7.69 (1H, dd, $J = 3.0$, 0.6 Hz); MS (FAB) m/z 311 $(M+H)^+$.

5.1.43. *N*-(6-{2-[(3-Fluorobenzyl)oxy]phenoxy}pyridin-3-yl)-2-pyrrolidin-1-ylacetamide dihydrochloride (39a). To the mixture of **38a** (922 mg, 2.97 mmol) and $CHCl_3$ (10 mL) was added $(ClCH_2CO)O$ (533 mg, 3.12 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. It was concentrated under reduced pressure, the residue was dissolved in EtOAc. The organic layer was washed with 1 M NaOH, water, and brine, dried, and evaporated under reduced pressure to afford 2-chloro-*N*-(6-{2-[(3-fluorobenzyl)oxy]phenoxy}pyridin-3-yl)acetamide (1.12 g, 98%) as a brown oil. The crude compound was dissolved in MeCN (14 mL). To the mixture was added K_2CO_3 (440 mg, 3.19 mmol) and pyrrolidine (1.21 mL, 14.5 mmol) at room temperature. The reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was cooled to room temperature and partitioned between AcOEt and water. The organic layer was washed with brine and dried, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH/NH_4OH = 100:1:0.1–70:1:0.1) to give the free base of **39a** (444 mg). This material was converted to its hydrochloride salt by treating it with 4 M HCl(g)/dioxane (0.32 mL). The crude salt was crystallized from EtOH/AcOEt to give **39a** as a colorless solid (311 mg, 23% yield for two steps from **38a**): mp 186–187 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84–2.08 (4H, m), 3.06–3.20 (2H, m), 3.54–3.68 (2H, m), 4.26 (2H, d, $J = 5.4$ Hz), 5.08 (2H, s), 6.85 (1H, d, $J = 9.8$ Hz), 6.95 (1H, d, $J = 7.3$ Hz), 6.98–7.10 (3H, m), 7.14–7.23 (3H, m), 7.27–7.34 (1H, m), 8.05 (1H, dd, $J = 8.8$, 2.9 Hz), 8.34 (1H, d, $J = 2.4$ Hz), 10.39 (1H, br s), 11.06 (1H, s); MS (FAB) m/z 422 $(M+H)^+$. Anal. Calcd for $C_{24}H_{24}FN_3O_3 \cdot 2HCl \cdot 0.2H_2O$: C, 57.88; H, 5.34; N, 8.44; Cl, 14.24. Found: C, 57.99; H, 5.22; N, 8.41; Cl, 13.99.

The following compounds (**39b–j**, **39l–w**) were prepared by a procedure similar to that described for **39a**.

5.1.44. *N*-(6-{3-[(3-Fluorobenzyl)oxy]phenoxy}pyridin-3-yl)-2-pyrrolidin-1-ylacetamide dihydrochloride (39b). White powder (25% for two steps): mp 141–146 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84–2.08 (4H, m), 3.08–3.20 (2H, m), 3.56–3.67 (2H, m), 4.28 (2H, d, $J = 5.4$ Hz), 5.13 (2H, s), 6.68 (1H, dd, $J = 8.0$, 2.2 Hz), 6.67 (1H, t, $J = 2.2$ Hz), 6.86 (1H, dd, $J = 8.0$, 2.2 Hz), 7.05 (1H, d, $J = 8.8$ Hz), 7.13–7.19 (1H, m), 7.25–7.34 (3H, m), 7.41–7.47 (1H, m), 8.09 (1H, dd, $J = 8.8$, 2.9 Hz), 8.42 (1H, d, $J = 2.4$ Hz), 10.41 (1H, br s), 11.15 (1H, s); MS (FAB) m/z 422 $(M+H)^+$. Anal. Calcd for $C_{24}H_{24}FN_3O_3 \cdot 1.4HCl \cdot 0.5H_2O$: C, 59.86; H, 5.53; N, 8.73; Cl, 10.31. Found: C, 59.71; H, 5.46; N, 8.76; Cl, 10.54.

5.1.45. *N*-[6-(4-Methoxyphenoxy)pyridin-3-yl]-2-pyrrolidin-1-ylacetamide hydrochloride (39c). White powder (90% for two steps): mp 182–184 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84–2.07 (4H, m), 3.05–3.25 (2H, br), 3.53–3.70 (2H, br), 3.76 (3H, s), 4.26 (2H, s), 6.93–7.08 (5H, m), 8.04 (1H, dd, $J = 8.8$, 2.9 Hz), 8.36 (1H, d, $J = 3.0$ Hz), 10.35 (1H, br s), 11.04 (1H, s); MS (FAB) m/z 328 $(M+H)^+$. Anal. Calcd for $C_{18}H_{21}N_3O_3 \cdot HCl$: C, 59.42; H, 6.09; N, 11.55; Cl, 9.74. Found: C, 59.14; H, 6.07; N, 11.53; Cl, 9.61.

5.1.46. *N*-{6-[4-(Cyclohexylmethoxy)phenoxy]pyridin-3-yl}-2-pyrrolidin-1-ylacetamide hydrochloride (39d). White powder (76% for two steps): mp 221–223 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.98–1.11 (2H, m), 1.14–1.32 (3H, m), 1.62–2.07 (10H, m), 3.06–3.21 (2H, m), 3.56–3.67 (2H, m), 3.77 (2H, d, $J = 5.8$ Hz), 4.26 (2H, s), 6.92–7.04 (5H, m), 8.03 (1H, dd, $J = 8.8$, 2.9 Hz), 8.35 (1H, d, $J = 2.9$ Hz), 10.31 (1H, br s), 11.00 (1H, s); MS (FAB) m/z 410 $(M+H)^+$. Anal. Calcd for $C_{24}H_{31}N_3O_3HCl$: C, 64.63; H, 7.23; N, 9.42; Cl, 7.95. Found: C, 64.41; H, 7.33; N, 9.41; Cl, 7.92.

5.1.47. *N*-(6-{4-[2-(3-Fluorophenyl)ethoxy]phenoxy}pyridin-3-yl)-2-pyrrolidin-1-ylacetamide oxalate (39e). Beige powder (70% for two steps): mp 140–141 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86–1.93 (4H, m), 3.07 (2H, t, $J = 6.8$ Hz), 3.99 (2H, s), 4.21 (2H, t, $J = 6.8$ Hz), 6.94–7.09 (6H, m), 7.16–7.22 (2H, m), 7.33–7.39 (1H, m), 8.03 (1H, dd, $J = 8.8$, 2.5 Hz), 8.33 (1H, d, $J = 2.4$ Hz), 10.61 (1H, br s); MS (FAB) m/z 436 $(M+H)^+$. Anal. Calcd for $C_{25}H_{26}N_3O_3F \cdot C_2H_2O_4$: C, 62.32; H, 5.42; N, 8.14; F, 3.68. Found: C, 62.15; H, 5.14; N, 8.15; F, 3.69.

5.1.48. *N*-(6-{4-[(3-Fluorophenoxy)methyl]phenoxy}pyridin-3-yl)-2-pyrrolidin-1-ylacetamide hydrochloride (39f). White powder (86% for two steps): mp 202–203 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.85–2.07 (4H, br s), 3.04–3.30 (2H, br), 3.46–3.70 (2H, br), 4.27 (2H, s), 5.12 (2H, s), 6.75–6.80 (1H, m), 6.85–6.95 (2H, m), 7.09 (1H, d, $J = 8.7$ Hz), 7.13 (2H, d, $J = 8.3$ Hz), 7.29–7.37 (1H, m), 7.49 (2H, d, $J = 8.8$ Hz), 8.09 (1H, dd, $J = 8.8$, 2.5 Hz), 8.40 (1H, d, $J = 2.9$ Hz), 10.35 (1H, br s), 11.08 (1H, s); MS (FAB) m/z 422 $(M+H)^+$. Anal. Calcd for $C_{24}H_{24}N_3O_3F \cdot HCl$: C, 62.95; H, 5.50; N, 9.18; Cl, 7.74; F, 4.15. Found: C, 62.84; H, 5.43; N, 9.19; Cl, 7.80; F, 4.25.

5.1.49. *N*-(6-{4-[(*E*)-2-(3-Fluorophenyl)vinyl]phenoxy}-pyridin-3-yl)-2-pyrrolidin-1-ylacetamide hydrochloride (39g). White powder (93% for two steps): mp 260–261 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86–2.06 (4H, m), 3.08–3.20 (2H, m), 3.57–3.66 (2H, m), 4.28 (2H, d, J = 5.4 Hz), 7.06–7.15 (4H, m), 7.22 (1H, d, J = 16.6 Hz), 7.37 (1H, d, J = 16.6 Hz), 7.40–7.50 (3H, m), 7.65 (2H, d, J = 8.8 Hz), 8.10 (1H, dd, J = 8.8, 3.0 Hz), 8.42 (1H, d, J = 3.0 Hz), 10.35 (1H, br s), 11.10 (1H, s); MS (FAB) m/z 418 $(M+H)^+$. Anal. Calcd for $C_{25}H_{24}N_3O_2F\cdot1.25HCl\cdot0.5H_2O$: C, 63.61; H, 5.60; N, 8.90; Cl, 9.39; F, 4.02. Found: C, 63.69; H, 5.48; N, 8.93; Cl, 9.39; F, 4.01.

5.1.50. *N*-(3-Fluorophenyl)-4-({5-[(pyrrolidin-1-ylacetyl)-amino]pyridin-2-yl}oxy)benzamide hydrochloride (39h). White powder (88% for two steps): mp 259–261 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.85–2.07 (4H, m), 3.11–3.18 (2H, m), 3.53–3.70 (2H, m), 4.28 (2H, s), 6.90–6.97 (1H, m), 7.19 (1H, d, J = 8.8 Hz), 7.25 (2H, d, J = 8.8 Hz), 7.35–7.43 (1H, m), 7.56–7.60 (1H, m), 7.74–7.80 (1H, m), 8.02 (2H, d, J = 8.7 Hz), 8.10–8.15 (1H, m), 8.42–8.45 (1H, m), 10.20–10.30 (1H, br), 10.44 (1H, s), 10.96–11.04 (1H, m); MS (FAB) m/z 435 $(M+H)^+$. Anal. Calcd for $C_{24}H_{23}N_4O_3F\cdot HCl\cdot0.7H_2O$: C, 59.61; H, 5.29; N, 11.59; Cl, 7.33; F, 3.93. Found: C, 59.56; H, 5.21; N, 11.60; Cl, 7.24; F, 3.72.

5.1.51. *N*-(3-Fluorophenyl)-*N*-methyl-4-({5-[(pyrrolidin-1-ylacetyl)amino]pyridin-2-yl}oxy)benzamide hydrochloride (39i). White powder (78% for two steps): mp 160–162 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.85–2.06 (4H, m), 3.07–3.22 (2H, m), 3.38 (3H, s), 3.50–3.70 (2H, m), 4.27 (2H, s), 6.94–7.09 (5H, m), 7.16–7.21 (1H, m), 7.28–7.35 (3H, m), 8.09 (1H, dd, J = 8.8, 2.9 Hz), 8.41 (1H, d, J = 3.0 Hz), 10.37 (1H, s), 11.14 (1H, s); MS (FAB) m/z 449 $(M+H)^+$. Anal. Calcd for $C_{25}H_{25}N_4O_3F\cdot HCl\cdot0.1H_2O$: C, 61.65; H, 5.43; N, 11.51; Cl, 7.28; F, 3.90. Found: C, 61.45; H, 5.38; N, 11.60; Cl, 7.08; F, 3.74.

5.1.52. 3-Fluoro-*N*-[4-({5-[(pyrrolidin-1-ylacetyl)amino]-pyridin-2-yl}oxy)phenyl]benzamide hydrochloride (39j). White powder (91% for two steps): mp 240–245 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.85–2.08 (4H, m), 3.07–3.19 (2H, m), 3.57–3.72 (2H, m), 4.27 (2H, d, J = 5.4 Hz), 7.07 (1H, d, J = 8.8 Hz), 7.12 (2H, d, J = 9.3 Hz), 7.43–7.49 (1H, m), 7.57–7.64 (1H, m), 7.70–7.86 (4H, m), 8.07 (1H, dd, J = 8.8, 2.5 Hz), 8.39 (1H, d, J = 2.5 Hz), 10.30 (1H, br s), 10.41 (1H, s), 11.01 (1H, s); MS (FAB) m/z 435 $(M+H)^+$. Anal. Calcd for $C_{24}H_{23}N_4O_3F\cdot1.3HCl\cdot1.2H_2O$: C, 57.25; H, 5.35; N, 11.31; Cl, 9.15; F, 3.77. Found: C, 57.19; H, 5.11; N, 11.34; Cl, 9.02; F, 3.87.

5.1.53. *N*-(6-{4-[(3-Fluorobenzyl)(methyl)amino]phenoxy}-pyridin-3-yl)-2-pyrrolidin-1-ylacetamide oxalate (39l). White powder (48% for two steps): mp 195–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88–1.94 (4H, m), 3.02 (3H, s), 3.15–3.23 (4H, m), 4.02 (2H, s), 4.57 (2H, s), 6.72 (2H, d, J = 9.3 Hz), 6.90–6.95 (3H, m), 7.01–7.11 (3H, m), 7.34–7.41 (1H, m), 8.00 (1H, dd, J = 8.8, 3.0 Hz), 8.31 (1H, d, J = 2.9 Hz), 10.63 (1H, s); MS (FAB) m/z 435 $(M+H)^+$. Anal. Calcd for $C_{25}H_{27}N_4O_2F\cdot C_2H_2O_4$: C, 61.82; H, 5.57; N, 10.68; F, 3.62. Found: C, 61.80; H, 5.57; N, 10.81; F, 3.65.

5.1.54. *N*-{6-[4-(Pyridin-2-ylmethoxy)phenoxy]pyridin-3-yl}-2-pyrrolidin-1-ylacetamide dihydrochloride (39m). White powder (50% for two steps): mp 216–218 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84–2.07 (4H, m), 3.07–3.18 (2H, m), 3.56–3.65 (2H, m), 4.26 (2H, d, J = 5.9 Hz), 5.26 (2H, s), 7.02 (1H, d, J = 8.8 Hz), 7.07 (4H, s), 7.49–7.54 (1H, m), 7.69 (1H, d, J = 7.8 Hz), 8.00–8.06 (2H, m), 8.34 (1H, d, J = 2.4 Hz), 8.67 (1H, d, J = 4.9 Hz), 10.25 (1H, br s), 10.93 (1H, s); MS (FAB) m/z 405 $(M+H)^+$. Anal. Calcd for $C_{23}H_{24}N_4O_3F\cdot2HCl\cdot3.2H_2O$: C, 53.81; H, 5.89; N, 10.91. Found: C, 54.00; H, 5.93; N, 10.95.

5.1.55. *N*-{6-[4-(Pyridin-3-ylmethoxy)phenoxy]pyridin-3-yl}-2-pyrrolidin-1-ylacetamide dihydrochloride (39n). White powder (11% for two steps): mp 175–176 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82–2.08 (4H, m), 3.06–3.20 (2H, m), 3.56–3.66 (2H, m), 4.26 (2H, d, J = 4.9 Hz), 5.30 (2H, s), 7.03 (1H, d, J = 8.7 Hz), 7.09 (4H, s), 7.91–7.96 (1H, m), 8.05 (1H, dd, J = 8.8, 3.0 Hz), 8.36 (1H, d, J = 2.4 Hz), 8.46 (1H, d, J = 7.8 Hz), 8.82 (1H, d, J = 4.9 Hz), 8.89 (1H, s), 10.31 (1H, br s), 11.02 (1H, s); MS (FAB) m/z 405 $(M+H)^+$. Anal. Calcd for $C_{23}H_{24}N_4O_3F\cdot2HCl\cdot3.3H_2O$: C, 51.98; H, 6.07; N, 10.45. Found: C, 52.29; H, 5.91; N, 10.67.

5.1.56. *N*-{6-[4-(Pyridin-4-ylmethoxy)phenoxy]pyridin-3-yl}-2-pyrrolidin-1-ylacetamide dihydrochloride (39o). White powder (44% for two steps): mp 210–215 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84–2.08 (4H, m), 3.07–3.19 (2H, m), 3.57–3.67 (2H, m), 4.27 (2H, s), 5.44 (2H, s), 7.03 (1H, d, J = 8.8 Hz), 7.09 (4H, s), 7.96 (2H, d, J = 6.4 Hz), 8.06 (1H, dd, J = 8.8, 3.0 Hz), 8.36 (1H, d, J = 2.4 Hz), 8.87 (2H, d, J = 6.3 Hz), 10.37 (1H, br s), 11.09 (1H, s); MS (FAB) m/z 405 $(M+H)^+$. Anal. Calcd for $C_{23}H_{24}N_4O_3\cdot2HCl\cdot1.7H_2O$: C, 54.38; H, 5.83; N, 11.03; Cl, 13.96. Found: C, 54.64; H, 5.82; N, 11.01; Cl, 13.61.

5.1.57. 2-Pyrrolidin-1-yl-*N*-{6-[4-(2-thienylmethoxy)phenoxy]pyridin-3-yl}acetamide hydrochloride (39p). White powder (72% for two steps): mp 162–164 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83–2.07 (4H, m), 3.05–3.20 (2H, m) 3.54–3.67 (2H, m), 4.25 (2H, s) 5.29 (2H, s), 7.01 (1H, d J = 8.8 Hz), 7.03–7.06 (5H, m), 7.21–7.23 (1H, m), 7.55–7.58 (1H, m), 8.04 (1H, dd, J = 8.8, 2.5 Hz), 8.35 (1H, d, J = 2.9 Hz), 10.26 (1H, br s), 10.94 (1H, s); MS (FAB) m/z 410 $(M+H)^+$. Anal. Calcd for $C_{22}H_{23}N_3O_3S\cdot HCl\cdot0.3H_2O$: C, 58.54; H, 5.49; N, 9.31; Cl, 7.85; S, 7.10. Found: C, 58.17; H, 5.52; N, 9.09; Cl, 7.74; S, 7.49.

5.1.58. 2-Pyrrolidin-1-yl-*N*-{6-[4-(3-thienylmethoxy)-phenoxy]pyridin-3-yl}acetamide hydrochloride (39q). White powder (81% for two steps): mp 184–186 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.85–2.07 (4H, m), 3.06–3.20 (2H, m), 3.56–3.66 (2H, m), 4.26 (2H, s), 5.09 (2H, s), 7.01 (1H, d, J = 9.3 Hz), 7.02–7.07 (4H,

m), 7.29 (1H, dd, $J = 4.8$, 1.4 Hz), 7.55–7.60 (2H, m), 8.04 (1H, dd, $J = 8.7$, 2.4 Hz), 8.36 (1H, d, $J = 2.9$ Hz), 10.30 (1H, br s), 10.97 (1H, s); MS (FAB) *m/z* 410 $(M+H)^+$. Anal. Calcd for $C_{22}H_{23}N_3O_3S{\cdot}HCl{\cdot}H_2O$: C, 56.95; H, 5.65; N, 9.06; Cl, 7.64; S, 6.91. Found: C, 56.92; H, 5.67; N, 8.90; Cl, 7.67; S, 7.30.

5.1.59. *N*-(6-{4-[(3-Fluorobenzyl)oxy]-3-methylphenoxy}-pyridin-3-yl)-2-pyrrolidin-1-ylacetamide oxalate (39r). White powder (44% for two steps): mp 174–176 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83–1.87 (4H, m), 2.22 (3H, s), 3.08–3.23 (4H, br), 3.97 (2H, s), 5.15 (2H, s), 6.87–6.92 (1H, m), 6.93–7.03 (3H, m), 7.13–7.20 (1H, m), 7.28–7.35 (2H, m), 7.43–7.50 (1H, m), 8.03 (1H, dd, $J = 8.7$, 2.1 Hz), 8.33 (1H, d, $J = 2.2$ Hz), 10.61 (1H, s); MS (FAB) *m/z* 436 $(M+H)^+$. Anal. Calcd for $C_{25}H_{26}N_3O_3F{\cdot}0.9C_2H_2O_4$: C, 62.34; H, 5.42; N, 8.14; F, 3.68. Found: C, 62.64; H, 5.39; N, 8.18; F, 3.67.

5.1.60. *N*-(6-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenoxy}-pyridin-3-yl)-2-pyrrolidin-1-ylacetamide oxalate (39s). White powder (50% for two steps): mp 178–180 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83–1.93 (4H, m), 3.01–3.13 (4H, m), 3.88 (2H, s), 5.24 (2H, s), 7.02–7.11 (2H, m), 7.15–7.22 (1H, m), 7.23–7.35 (4H, m), 7.44–7.45 (1H, m), 8.08 (1H, dd, $J = 8.8$, 2.9 Hz), 8.35 (1H, d, $J = 2.9$ Hz), 10.56 (1H, s); MS (FAB) *m/z* 456 $(M+H)^+$. Anal. Calcd for $C_{24}H_{23}N_3O_3FCl{\cdot}0.7C_2H_2O_4$: C, 58.79; H, 4.74; N, 8.10; Cl, 6.83; F, 3.66. Found: C, 58.96; H, 4.72; N, 8.17; Cl, 6.85; F, 3.69.

5.1.61. *N*-(6-{4-[(3-Fluorobenzyl)oxy]-3-methoxyphenoxy}-pyridin-3-yl)-2-pyrrolidin-1-ylacetamide oxalate (39t). White powder (83% for two steps): mp 159–161 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84–1.94 (4H, m), 3.12 (4H, br s), 3.75 (3H, s), 3.93 (2H, s), 5.10 (2H, s), 6.60 (1H, dd, $J = 8.8$, 2.2 Hz), 6.80 (1H, d, $J = 2.9$ Hz), 6.97 (1H, d, $J = 8.8$ Hz), 7.02 (1H, d, $J = 8.8$ Hz), 7.13–7.20 (1H, m), 7.25–7.32 (2H, m), 7.42–7.48 (1H, m), 8.04 (1H, d, $J = 8.8$, 2.9 Hz), 8.35 (1H, d, $J = 2.2$ Hz), 10.57 (1H, s); MS (FAB) *m/z* 452 $(M+H)^+$. Anal. Calcd for $C_{25}H_{26}N_3O_4F{\cdot}0.9C_2H_2O_4$: C, 60.45; H, 5.26; N, 7.89; F, 3.57. Found: C, 60.72; H, 5.48; N, 7.84; F, 3.59.

5.1.62. *N*-(6-{4-[(3-Fluorobenzyl)oxy]-2-methylphenoxy}-pyridin-3-yl)-2-pyrrolidin-1-ylacetamide oxalate (39u). White powder (56% for two steps): mp 189–190 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86–1.95 (4H, m), 2.04 (3H, s), 3.13–3.27 (4H, m), 4.03 (2H, s), 5.12 (2H, s), 6.87 (1H, dd, $J = 8.8$, 2.9 Hz), 6.94–7.00 (3H, m), 7.14–7.20 (1H, m), 7.27–7.33 (2H, m), 7.42–7.49 (1H, m), 8.02 (1H, dd, $J = 8.8$, 3.0 Hz), 8.28 (1H, d, $J = 2.9$ Hz), 10.65 (1H, s); MS (FAB) *m/z* 436 $(M+H)^+$. Anal. Calcd for $C_{25}H_{26}N_3O_3F{\cdot}C_2H_2O_4$: C, 61.71; H, 5.37; N, 8.00; F, 3.62. Found: C, 61.75; H, 5.42; N, 8.06; F, 3.59.

5.1.63. *N*-(6-{2-Chloro-4-[(3-fluorobenzyl)oxy]phenoxy}-pyridin-3-yl)-2-pyrrolidin-1-ylacetamide oxalate (39v). White powder (70% for two steps): mp 183–186 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86–1.97 (4H, m), 3.13–3.27 (4H, m), 4.03 (2H, s), 5.18 (2H, s), 7.03–7.10 (2H, m), 7.16–7.28 (3H, m), 7.28–7.34 (2H, m), 7.43–7.50 (1H, m), 8.07 (1H, dd, $J = 8.8$, 2.8 Hz), 8.28 (1H, d, $J = 3.0$ Hz), 10.68 (1H, s); MS (FAB) *m/z* 456 $(M+H)^+$. Anal. Calcd for $C_{24}H_{23}N_3O_3ClF{\cdot}C_2H_2O_4$: C, 57.20; H, 4.62; N, 7.70; Cl, 6.49; F, 3.48. Found: C, 57.03; H, 4.61; N, 7.73; Cl, 6.28; F, 3.51.

5.1.64. *N*-(6-{4-[(3-Fluorobenzyl)oxy]-2-methoxyphenoxy}-pyridin-3-yl)-2-pyrrolidin-1-ylacetamide oxalate (39w). White powder (72% for two steps): mp 172–174 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87–1.97 (4H, m), 3.15–3.28 (4H, m), 3.67 (3H, s), 4.04 (2H, s), 5.15 (2H, s), 6.60 (1H, dd, $J = 8.8$, 2.9 Hz), 6.81 (1H, d, $J = 2.9$ Hz), 6.93 (1H, d, $J = 8.8$ Hz), 7.03 (1H, d, $J = 8.8$ Hz), 7.15–7.21 (1H, m), 7.29–7.36 (2H, m), 7.43–7.50 (1H, m), 7.98 (1H, dd, $J = 8.8$, 2.9 Hz), 8.24 (1H, d, $J = 2.2$ Hz), 10.65 (1H, s); MS (FAB) *m/z* 452 $(M+H)^+$. Anal. Calcd for $C_{25}H_{26}N_3O_3F{\cdot}C_2H_2O_4$: C, 59.88; H, 5.21; N, 7.76; F, 3.51. Found: C, 59.94; H, 5.13; N, 7.79; F, 3.80.

5.1.65. 3-Fluoro-*N*-methyl-*N*-[4-({5-[(pyrrolidin-1-ylacetyl)amino]pyridin-2-yl}oxy)phenyl]benzamide hydrochloride (39k). Compound **38k** was prepared from **37k** by a procedure similar to that described for **38d**. Compound **39k** was prepared from **38k** by a procedure similar to that described for **39a**. Compound **39k** was obtained as a colorless solid (87% for three steps): mp 189–190 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82–2.04 (4H, m), 3.05–3.15 (2H, m), 3.38 (3H, m), 3.53–3.67 (2H, m), 4.26 (2H, s), 6.99–7.06 (3H, m), 7.07–7.18 (3H, m), 7.21–7.38 (3H, m), 8.06 (1H, dd, $J = 8.8$, 2.5 Hz), 8.37 (1H, d, $J = 2.5$ Hz), 10.20 (1H, br s), 10.88–10.95 (1H, m); MS (FAB) *m/z* 449 $(M+H)^+$. Anal. Calcd for $C_{25}H_{25}N_4O_3F{\cdot}HCl{\cdot}0.5H_2O$: C, 60.79; H, 5.51; N, 11.34; Cl, 7.18; F, 3.85. Found: C, 60.90; H, 5.41; N, 11.32; Cl, 7.03; F, 3.58.

5.1.66. *N*-(6-{4-[2-(3-Fluorophenyl)ethyl]phenoxy}pyridin-3-yl)-2-pyrrolidin-1-ylacetamide dihydrochloride (40). Compound **40** was prepared from **39g** by a procedure similar to that described for **38d**. Compound **40** was obtained as a colorless solid (86%): mp 193–195°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84–2.08 (4H, m), 2.86–2.95 (4H, m), 2.96–3.20 (2H, m), 3.52–3.67 (2H, m), 4.26 (2H, d, $J = 5.3$ Hz), 6.97–7.05 (4H, m), 7.07–7.13 (2H, m), 7.26 (2H, d, $J = 8.3$ Hz), 7.28–7.45 (1H, m), 8.05 (1H, dd, $J = 8.8$, 2.9 Hz), 8.37 (1H, d $J = 2.9$ Hz), 10.24 (1H, s), 10.94 (1H, s); MS (FAB) *m/z* 420 $(M+H)^+$. Anal. Calcd for $C_{25}H_{26}N_3O_2F{\cdot}1.3HCl{\cdot}0.8H_2O$: C, 62.39; H, 6.05; N, 8.73; Cl, 9.58; F, 3.95. Found: C, 62.38; H, 6.11; N, 8.71; Cl, 9.62; F, 4.12.

5.1.67. *N*-(6-{4-[(3-Fluorobenzyl)oxy]phenoxy}pyridin-3-yl)-*N*-methyl-2-pyrrolidin-1-ylacetamide oxalate (41). To the mixture of **38x** (480 mg, 1.55 mmol) and $CHCl_3$ (5 mL) was added trifluoroacetic acid anhydrate (0.44 mL, 3.09 mmol) at 0 °C. The mixture was stirred for 30 min, concentrated in vacuo. To the residue were added 2-butanone (5 mL) and K_2CO_3 (1.07 g, 7.75 mmol), MeI (0.48 mL, 7.75 mmol) at room temperature. The mixture was stirred at 40 °C for 2 h. After cooled at room temperature, the suspension was filtered,

the filtrate was concentrated in vacuo to give yellow solid. The intermediate was dissolved in MeOH (5 mL). NaOH (1 M, 2.3 mL, 2.3 mmol) was added to the mixture. The mixture was stirred for 1 h, concentrated in vacuo. The residue was partitioned between $CHCl_3$ and H_2O. The organic layer was dried, evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 99:1) to give 6-{4-[(3-fluorobenzyl)oxy]phenoxy}-*N*-methylpyridin-3-amine (495 mg, 99% for three steps). Compound **41** was prepared from 6-{4-[(3-fluorobenzyl)oxy]phenoxy}-*N*-methylpyridin-3-amine by a procedure similar to that described for **39a**. Compound **41** was obtained as a colorless solid (48% for two steps): mp 155–156 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81–1.95 (4H, m), 3.10–3.30 (7H, m), 3.88 (1.6H, s), 4.39 (0.4H, s), 5.15 (2H, s), 7.05–7.21 (6H, m), 7.27–7.33 (2H, m), 7.43–7.49 (1H, m), 7.75–7.81 (0.2H, m), 7.91 (0.8H, dd, J = 8.8, 2.4 Hz), 8.06–8.09 (0.2H, m), 8.17 (0.8H, d, J = 2.4 Hz); MS (FAB) m/z 436 $(M+H)^+$. Anal. Calcd for $C_{25}H_{26}N_3O_3F\cdot C_2H_2O_4$: C, 61.71; H, 5.37; N, 8.00; F, 3.62. Found: C, 61.66; H, 5.33; N, 8.10; F, 3.70.

5.1.68. *N*-(6-{4-[(3-Fluorobenzyl)oxy]phenoxy}pyridin-3-yl)-2-pyrrolidin-1-ylpropanamide oxalate (42). To the mixture of **38x** (510 mg, 1.64 mmol), AcOEt (3 mL) and H_2O (3 mL), $NaHCO_3$ (166 mg, 1.97 mmol) was added 2-bromopropionyl bromide (0.19 mL, 1.81 mmol) at 0 °C. The mixture was stirred at room temperature for 10 min. The mixture was partitioned between $CHCl_3$ and 1 M NaOH. The organic layer was dried and concentrated in vacuo. The residue was crystallized from AcOEt/hexane to give 2-bromo-*N*-(6-{4-[(3-fluorobenzyl)oxy]phenoxy}pyridin-3-yl)propanamide as a white solid (554 mg, 76%). The compound (544 mg, 1.22 mmol) was dissolved in CH_3CN (6 mL). K_2CO_3 (220 mg, 1.59 mmol) and pyrrolidine (0.52 mL, 6.11 mmol) were added to the mixture at room temperature. The mixture was stirred at 80 °C for 80 min. The mixture was partitioned between $CHCl_3$ and 1 M NaOH. The organic layer was dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 98:2) to give the free base of **42**. This material was converted to its oxalate by treating it with oxalic acid (110 mg, 1.22 mmol) in MeOH. The mixture was concentrated in vacuo. The crude salt was crystallized from AcOEt/hexane to give **42** as a colorless solid (448 mg, 70%): mp 133–135 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.48 (3H, br s), 1.80–1.95 (4H, m), 3.02–3.20 (4H, m), 3.86 (1H, br s), 5.14 (2H, s), 6.99 (1H, d, J = 8.8 Hz), 7.04 (4H, s), 7.13–7.20 (1H, m), 7.27–7.33 (2H, m), 7.42–7.48 (1H, m), 8.07 (1H, d, J = 8.0 Hz), 8.36 (1H, s), 10.77 (1H, br s); MS (FAB) m/z 436 $(M+H)^+$. Anal. Calcd for $C_{25}H_{26}N_3O_3F\cdot C_2H_2O_4$: C, 61.71; H, 5.37; N, 8.00; F, 3.62. Found: C, 61.95; H, 5.36; N, 8.06; F, 3.81.

5.1.69. *N*-(6-{4-[(3-Fluorobenzyl)oxy]phenoxy}pyridin-3-yl)-3-pyrrolidin-1-ylpropanamide hydrochloride (43). To the mixture of **38x** (330 mg, 1.00 mmol) and THF (5 mL), Et_3N (0.17 mL, 1.20 mmol) was added acryloyl chloride (0.09 mL, 1.1 mmol) at 0 °C. After stirring at room temperature for 30 min, the mixture was partitioned between $CHCl_3$ and aqueous HCl. The organic layer was washed with aqueous NaOH, dried, evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 99:1) to give intermediate (314 mg, 86%). The mixture of intermediate and toluene (2 mL) pyrrolidine (0.69 mL, 8.23 mmol) was stirred at 80 °C. After cooling at room temperature, the mixture was partitioned between $CHCl_3$ and aqueous NaOH. The organic layer was washed, dried, evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 98:2–92:8) to give the free base of **43** (415 mg). This material was converted to its hydrochloride salt by treating it with 4 M HCl(g)/AcOEt (0.25 mL). The crude salt was crystallized from EtOH/AcOEt to give **43** as a colorless solid (196 mg, 50% for two steps): mp 190–191 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79–2.08 (4H, m), 2.78 (2H, t, J = 7.7 Hz), 2.79–3.02 (2H, m), 3.37–3.55 (4H, m), 5.13 (2H, s), 6.96 (1H, d, J = 8.8 Hz), 7.04 (4H, s), 7.13–7.20 (1H, m), 7.26–7.34 (1H, m), 7.40–7.49 (2H, m), 8.03 (1H, dd, J = 8.8, 2.9 Hz), 8.32 (1H, d, J = 2.9 Hz), 10.51 (1H, s), 10.67 (1H, br s); MS (FAB) m/z 436 $(M+H)^+$. Anal. Calcd for $C_{25}H_{26}N_3O_3F\cdot HCl$: C, 63.62; H, 5.77; N, 8.90; Cl, 7.51; F, 4.03. Found: C, 63.53; H, 5.60; N, 8.88; Cl, 7.46; F, 4.41.

5.1.70. 6-{4-[(3-Fluorobenzyl)oxy]phenoxy}nicotinonitrile (45). 6-[4-Benzyloxy)phenoxy]nicotinonitrile was prepared from 2-chloro-5-nitropyridine (**44**) by a procedure similar to that described for **37a**. 6-[4-(benzyloxy)phenoxy]nicotinonitrile was converted to 6-(4-hydroxyphenoxy)nicotinonitrile by a procedure of de-benzylation using pentamethylbenzene similar to that described for **20**. Compound **45** was prepared from 6-(4-hydroxyphenoxy)nicotinonitrile by a procedure similar to that described for **15**. Compound **45** was obtained as a beige powder (73% for three steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.07 (2H, s), 6.98–7.09 (6H, m), 7.15–7.21 (2H, m), 7.33–7.40 (1H, m), 7.90 (1H, dd, J = 8.6, 2.4 Hz), 8.46–8.47 (1H, m); MS (FAB) m/z 321 $(M+H)^+$.

5.1.71. [(6-{4-[(3-Fluorobenzyl)oxy]phenoxy}pyridin-3-yl)methyl]amine (46). To the mixture of **45** (801 mg, 2.50 mmol) and THF (10 mL) was added 1.0 M THF solution of BH_3–THF complex (5.5 mL, 5.5 mmol) at 0 °C. The mixture was stirred at room temperature for 8 h. To the mixture were added MeOH (5 mL) and 1 M HCl (5 mL) at 0 °C. The mixture was stirred at 70 °C for 1 h. NaOH (1 M) was added to the mixture at 0 °C. The mixture was partitioned between $CHCl_3$ and brine. The organic layer was dried, evaporated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 98:2–92:8) to give **46** as a light yellow oil (402 mg, 50%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (2H, s), 5.06 (2H, s), 6.85 (1H, d, J = 8.4 Hz), 6.94–7.09 (5H, m), 7.14–7.22 (2H, m), 7.31–7.39 (1H, m), 7.67 (1H, dd, J = 8.4, 2.4 Hz), 8.10 (1H, d, J = 2.5 Hz); MS (FAB) m/z 325 $(M+H)^+$.

5.1.72. *N*-[(6-{4-[(3-Fluorobenzyl)oxy]phenoxy}pyridin-3-yl)methyl]-2-pyrrolidin-1-ylacetamide hydrochloride (47). Compound **47** was prepared from **46** and 2-bromopropionyl bromide by a procedure similar to that described

for **39a**. Compound **47** was obtained as a colorless solid (53% for two steps): mp 154–155 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82–2.02 (4H, br), 2.95–3.18 (2H, br), 3.43–3.62 (2H, br), 4.06 (2H, s), 4.31 (2H, d, J = 5.9 Hz), 5.14 (2H, s), 6.95 (1H, d, J = 8.3 Hz), 7.04 (4H, s), 7.14–7.20 (1H, m), 7.27–7.33 (2H, m), 7.42–7.49 (1H, m), 7.75 (1H, dd, J = 8.3, 2.4 Hz), 8.05 (1H, d, J = 2.4 Hz), 9.08–9.14 (1H, m), 10.19 (1H, br s); MS (FAB) m/z 436 (M+H)$^+$. Anal. Calcd for $C_{25}H_{26}N_3O_3F$·HCl: C, 63.62; H, 5.77; N, 8.90; Cl, 7.51; F, 4.03. Found: C, 63.53; H, 5.76; N, 9.08; Cl, 7.52; F, 4.08.

5.1.73. 6-{4-[(3-Fluorobenzyl)oxy]phenoxy}-*N*-(2-pyrrolidin-1-ylethyl)nicotinamide oxalate (48a). To the mixture of **45** (1.4 g, 4.4 mmol) and EtOH (15 mL) was added 5 M NaOH (8.7 mL). The mixture was stirred at 100 °C for 3.5 h. The solvent was removed under reduced pressure. HCl (2 M) was added at 0 °C. The precipitate was filtered and dried in vacuo to afford beige powder as 6-{4-[(3-fluorobenzyl)oxy]phenoxy}nicotinic acid (1.5 g, 100%). To the mixture of 6-{4-[(3-fluorobenzyl)oxy]phenoxy}nicotinic acid (373 mg, 1.10 mmol) and (2-pyrrolidin-1-ylethyl)amine (114 mg, 1.00 mmol), THF (10 mL) and 1*H*-1,2,3-benzotriazol-1-ol (68 mg, 0.50 mmol) was added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (211 mg, 1.10 mmol). The mixture was stirred at room temperature for 11 h. The mixture was partitioned between $CHCl_3$ and aqueous NaOH. The organic layer was dried and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 98:2–92:8) to give the free base of **48a** (462 mg). This material was converted to its oxalate salt by treating it with oxalic acid (90 mg, 1.00 mmol) in MeOH (10 mL). The mixture was concentrated in vacuo. The crude salt was crystallized from CH_3 CN/AcOEt to give **48a** as a colorless solid (316 mg, 60% for two steps from **45**): mp 115–118 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83–1.95 (4H, m), 3.23–3.31 (6H, m), 3.55–3.62 (2H, m), 5.15 (2H, s), 7.02–7.12 (5H, m), 7.14–7.20 (1H, m), 7.28–7.34 (2H, m), 7.42–7.49 (1H, m), 8.25 (1H, dd, J = 8.8, 2.4 Hz), 8.59 (1H, d, J = 2.4 Hz), 8.87 (1H, t, J = 5.6 Hz); MS (FAB) m/z 436 (M+H)$^+$. Anal. Calcd for $C_{25}H_{26}N_3O_3F·C_2H_2O_4$: C, 61.71; H, 5.37; N, 8.00; F, 3.62. Found: C, 61.99; H, 5.38; N, 8.00; F, 3.70.

The following compounds (**48b**–**m**) were prepared by a procedure similar to that described for **48a**.

5.1.74. 6-{4-[(3-Fluorobenzyl)oxy]phenoxy}-*N*-(3-pyrrolidin-1-ylpropyl)nicotinamide oxalate (48b). Beige powder (57% for two steps): mp 139–140 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82–1.98 (6H, m), 3.05–3.15 (2H, m), 3.27–3.38 (2H, m), 3.50–3.95 (4H, br), 5.15 (2H, s), 7.05–7.13 (5H, m), 7.14–7.21 (1H, m), 7.27–7.34 (2H, m), 7.43–7.50 (1H, m), 8.21 (1H, d, J = 8.8 Hz), 8.58 (1H, s), 8.64 (1H, br s); MS (FAB) m/z 450 (M+H)$^+$. Anal. Calcd for $C_{26}H_{28}N_3O_3F·C_2H_2O_4$: C, 62.33; H, 5.60; N, 7.79; F, 3.52. Found: C, 62.16; H, 5.58; N, 7.87; F, 3.52.

5.1.75. 6-{4-[(3-Fluorobenzyl)oxy]phenoxy}-*N*-methyl-*N*-(2-pyrrolidin-1-ylethyl)nicotinamide oxalate (48c). White powder (23% for two steps): mp 139–140 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.92 (4H, br s), 2.98 (3H, s), 3.21–3.40 (6H, m), 3.76 (2H, br s), 5.15 (2H, s), 7.02 (1H, d, J = 8.3 Hz), 7.04–7.14 (4H, m), 7.14–7.21 (1H, m), 7.28–7.34 (2H, m), 7.43–7.49 (1H, m), 7.90–8.01 (1H, m), 8.24 (1H, s); MS (FAB) m/z 450 (M+H)$^+$. Anal. Calcd for $C_{26}H_{28}N_3O_3F·C_2H_2O_4$: C, 62.33; H, 5.60; N, 7.79; F, 3.52. Found: C, 62.39; H, 5.73; N, 7.87; F, 3.61.

5.1.76. 6-{4-[(3-Fluorobenzyl)oxy]phenoxy}-*N*-(2-piperidin-1-ylethyl)nicotinamide oxalate (48d). White powder (59% for two steps): mp 143–144 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.51 (2H, br s), 1.68–1.75 (4H, m), 3.09–3.17 (6H, m), 3.57–3.64 (2H, m), 5.15 (2H, s), 7.03–7.12 (5H, m), 7.14–7.21 (1H, m), 7.28–7.34 (2H, m), 7.43–7.49 (1H, m), 8.24 (1H, dd, J = 8.8, 2.5 Hz), 8.59 (1H, d, J = 2.5 Hz), 8.87 (1H, t, J = 5.3 Hz),; MS (FAB) m/z 450 (M+H)$^+$. Anal. Calcd for $C_{26}H_{28}N_3O_3F·C_2H_2O_4·0.1H_2O$: C, 62.12; H, 5.62; N, 7.76; F, 3.51. Found: C, 62.00; H, 5.58; N, 7.81; F, 3.61.

5.1.77. 6-{4-[(3-Fluorobenzyl)oxy]phenoxy}-*N*-[(1-methylpiperidin-4-yl)methyl]nicotinamide (48e). White powder (23% for two steps): mp 142–149 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10–1.22 (2H, m), 1.41–1.54 (1H, m), 1.58–1.66 (2H, m), 1.75–1.84 (2H, m), 2.13 (3H, s), 2.70–2.77 (2H, m), 3.11–3.16 (2H, m), 5.15 (2H, s), 7.00–7.12 (5H, m), 7.14–7.20 (1H, m), 7.28–7.33 (2H, m), 7.42–7.49 (1H, m), 8.22 (1H, dd, J = 8.3, 2.4 Hz), 8.49–8.53 (1H, m), 8.57 (1H, d, J = 2.5 Hz); MS (FAB) m/z 450 (M+H)$^+$; HRMS: (M+H)$^+$ Calcd for $C_{26}H_{28}N_3O_3F$, 450.2193. Found: 450.2191.

5.1.78. *N*-[(1-Benzylpiperidin-4-yl)methyl]-6-{4-[(3-fluorobenzyl)oxy]phenoxy}nicotinamide (48f). White powder (54% for two steps): mp 136–137 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.11–1.24 (2H, m), 1.47–1.58 (1H, m), 1.59–1.67 (2H, m), 1.83–1.92 (2H, m), 2.75–2.82 (2H, m), 3.11–3.17 (2H, m), 3.43 (2H, br s), 5.15 (2H, s), 7.02 (1H, d, J = 8.8 Hz), 7.04–7.12 (4H, m), 7.14–7.34 (8H, m), 7.42–7.49 (1H, m), 8.21 (1H, dd, J = 8.8, 2.4 Hz), 8.47–8.51 (1H, m), 8.56 (1H, d, J = 2.5 Hz); MS (FAB) m/z 526 (M+H)$^+$. Anal. Calcd for $C_{32}H_{32}N_3O_3F$: C, 73.12; H, 6.14; N, 7.99; F, 3.61. Found: C, 72.93; H, 6.15; N, 8.00; F, 3.84.

5.1.79. *N*-[2-(Diethylamino)ethyl]-6-{4-[(3-fluorobenzyl)oxy]phenoxy}nicotinamide oxalate (48g). White powder (65% for two steps): mp 128–129 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (6H, t, J = 7.4 Hz), 3.09–3.20 (6H, m), 3.55–3.62 (2H, m), 5.15 (2H, s), 7.03–7.13 (5H, m), 7.14–7.21 (1H, m), 7.28–7.34 (2H, m), 7.43–7.49 (1H, m), 8.24 (1H, dd, J = 8.3, 2.4 Hz), 8.59 (1H, d, J = 2.5 Hz), 8.90–8.95 (1H, m); MS (FAB) m/z 438 (M+H)$^+$. Anal. Calcd for $C_{25}H_{28}N_3O_3F·C_2H_2O_4$: C, 61.47; H, 5.73; N, 7.93; F, 3.60. Found: C, 61.46; H, 5.70; N, 7.98; F, 3.81.

5.1.80. 6-{4-[(3-Fluorobenzyl)oxy]phenoxy}-*N*-(2-methoxyethyl)nicotinamide hydrobromide (48h). Colorless solid (52% for two steps): mp 110–115 °C; ^{1}H NMR

(400 MHz, DMSO-d_6): δ 3.26 (3H, s), 3.39–3.48 (4H, m), 5.15 (2H, s), 7.01–7.13 (6H, m), 7.14–7.21 (1H, m), 7.28–7.34 (2H, m), 7.43–7.49 (1H, m), 8.23 (1H, dd, J = 8.8, 2.5 Hz), 8.58 (1H, d, J = 2.4 Hz), 8.60 (1H, br s); MS (FAB) m/z 397 $(M+H)^+$. Anal. Calcd for $C_{22}H_{21}N_2O_4F{\cdot}HBr{\cdot}0.7H_2O$: C, 56.09; H, 5.07; N, 5.95. Found: C, 56.12; H, 4.70; N, 5.98.

5.1.81. *N*-(Cyclohexylmethyl)-6-{4-[(3-fluorobenzyl)-oxy]-phenoxy}nicotinamide (48i). White powder (72% for two steps): mp 149–151 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.84–0.97 (2H, m), 1.07–1.25 (3H, m), 1.46–1.79 (6H, m), 3.10 (2H, t, J = 6.8 Hz), 5.15 (2H, s), 7.02 (1H, d, J = 8.3 Hz), 7.04–7.12 (4H, m), 7.28–7.34 (2H, m), 7.43–7.49 (1H, m), 8.22 (1H, dd, J = 8.3, 2.5 Hz), 8.46 (1H, t, J = 5.8 Hz), 8.56 (1H, d, J = 1.9 Hz); MS (FAB) m/z 435 $(M+H)^+$. Anal. Calcd for $C_{26}H_{27}N_2O_3F$: C, 71.87; H, 6.26; N, 6.45; F, 4.37. Found: C, 71.93; H, 6.41; N, 6.35; F, 4.15.

5.1.82. 6-{4-[(3-Fluorobenzyl)oxy]phenoxy}-*N*-phenyl-nicotinamide (48j). White powder (72% for two steps): mp 163–164 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.16 (2H, s), 7.08–7.21 (7H, m), 7.29–7.38 (4H, m), 7.43–7.49 (1H, m), 7.72–7.77 (2H, m), 8.34 (1H, dd, J = 8.8, 2.4 Hz), 8.69 (1H, d, J = 2.5 Hz), 10.28 (1H, s); MS (FAB) m/z 415 $(M+H)^+$. Anal. Calcd for $C_{25}H_{19}N_2O_3F$: C, 72.45; H, 4.62; N, 6.76; F, 4.58. Found: C, 72.50; H, 4.52; N, 6.72; F, 4.54.

5.1.83. *N*-Benzyl-6-{4-[(3-fluorobenzyl)oxy]phenoxy}-nicotinamide (48k). White powder (71% for two steps): mp 105–106 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.48 (2H, d, J = 5.9 Hz), 5.15 (2H, s), 7.03–7.13 (5H, m), 7.14–7.20 (2H, m), 7.23–7.36 (6H, m), 7.42–7.49 (1H, m), 8.27 (1H, dd, J = 8.8, 2.5 Hz), 8.63 (1H, d, J = 2.5 Hz), 9.03 (1H, t, J = 5.9 Hz); MS (FAB) m/z 429 $(M+H)^+$. Anal. Calcd for $C_{26}H_{21}N_2O_3F$: C, 72.88; H, 4.94; N, 6.54; F, 4.53. Found: C, 73.06; H, 5.00; N, 6.52; F, 4.43.

5.1.84. 6-{4-[(3-Fluorobenzyl)oxy]phenoxy}-*N*-(2-phenyl-ethyl)nicotinamide (48l). White powder (82% for two steps): mp 138–139 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.84 (2H, t, J = 7.6 Hz), 3.44–3.57 (2H, m), 5.15 (2H, s), 7.02–7.13 (5H, m), 7.14–7.34 (8H, m), 7.43–7.48 (1H, m), 8.19 (1H, dd, J = 8.8, 2.4 Hz), 8.54 (1H, d, J = 2.5 Hz), 8.62 (1H, t, J = 5.6 Hz); MS (FAB) m/z 443 $(M+H)^+$. Anal. Calcd for $C_{27}H_{23}N_2O_3F$: C, 73.29; H, 5.24; N, 6.33; F, 4.29. Found: C, 73.36; H, 5.27; N, 6.37; F, 4.13.

5.1.85. 6-{4-[(3-Fluorobenzyl)oxy]phenoxy}-*N*-(3-phenyl-propyl)nicotinamide (48m). White powder (78% for two steps): mp 109–110 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.77–1.87 (2H, m), 2.63 (2H, t, J = 7.8 Hz), 3.24–3.31 (2H, m), 5.15 (2H, s), 7.02–7.13 (5H, m), 7.16–7.33 (8H, m), 7.42–7.48 (1H, m), 8.21 (1H, dd, J = 8.3, 2.4 Hz), 8.52 (1H, t, J = 5.3 Hz), 8.57 (1H, d, J = 2.4 Hz); MS (FAB) m/z 457 $(M+H)^+$. Anal. Calcd for $C_{28}H_{25}N_2O_3F$: C, 73.69; H, 5.52; N, 6.14; F, 4.16. Found: C, 73.87; H, 5.55; N, 6.24; F, 4.00.

5.2. Pharmacology

5.2.1. ^{45}Ca influx assay. We examined the inhibitory effects of several compounds on Na^+/Ca^{2+} exchange for reverse mode in NCX1.1-expressed CCL39 cells according to the reported protocols.[10] The cells were loaded with Na^+ by incubation with monensin-BSS (10 μM monensin, 1 mM ouabain, 10 mM Hepes/Tris (pH 7.4), 146 mM NaCl, 4 mM KCl, 2 mM $MgCl_2$, 10 mM of glucose, and 0.1% BSA) at 37 °C for 30 min. $^{45}Ca^{2+}$ uptake was initiated by switching the medium to Na^+-free BSS (10 μM verapamil, 1 mM ouabain, 10 mM Hepes/Tris (pH 7.4), 146 mM choline chloride, 4 mM KCl, 2 mM $MgCl_2$, 10 mM of glucose, 0.1% BSA, and 0.1 mM $CaCl_2$) containing 55.5 kBq/mL $^{45}CaCl_2$ and test compounds. After 15 min incubation at room temperature, the cells were washed three times with ice-cold wash-buffer (10 mM $LaCl_3$, 120 mM choline chloride, and 10 mM Hepes/Tris (pH 7.4)) and solubilized with 0.1 M NaOH. The radioactivity was measured by using a TopCount Microplate Scintillation Counter (Packard Instrument Company). Concentration-response curve was drawn to determine the concentration inducing 50% influx of ^{45}Ca induced by Na^+ overload. IC_{50} values were determined in a single experimental run in triplicate.

5.2.2. Cell necrosis assay.[14] NCX1.1-expressed CCL39 cells were incubated with ionomycin-BSS (10 μM ionomycin, 1 mM ouabain, 10 mM Hepes/Tris (pH 7.4), 146 mM NaCl, 4 mM KCl, 2 mM $MgCl_2$, 10 mM of glucose, and 0.1% BSA) containing test compounds at 37 °C for 30 min. The cells were washed three times with PBS and dyed with Crystal Violet for 15 min. The cells were washed three times with PBS and the intracellular dye of necrosis cells was solubilized with EtOH and absorbance at 595 nm was measured. Concentration-response curve was drawn to determine the concentration inducing 50% cell necrosis induced by Ca^{2+} overload. EC_{50} values were determined in a single experimental run in triplicate.

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16. We referred to patents of NCX inhibitors such as JP10218844[17] and JP11049752,[18] besides JP11092454.[11] Several patented compounds were synthesized and evaluated. Among them, compound **3** was the most potent NCX inhibitor in our assay. The structure was also interesting.
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