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Cyclooxygenase-1-Selective Inhibitors Are Attractive Candidates for Analgesics That Do Not Cause Gastric Damage. Design and in Vitro/in Vivo Evaluation of a Benzamide-Type Cyclooxygenase-1 Selective Inhibitor

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Although cyclooxygenase-1 (COX-1) inhibition is thought to be a major mechanism of gastric damage by nonsteroidal anti-inflammatory drugs (NSAIDs), some COX-1-selective inhibitors exhibit strong analgesic effects without causing gastric damage. However, it is not clear whether their analgesic effects are attributable to COX-1-inhibitory activity or other bioactivities. Here, we report that *N*-(5-amino-2-pyridinyl)-4-(trifluoromethyl)benzamide (**18f**, TFAP), which has a structure clearly different from those of currently available COX-1-selective inhibitors, is a potent COX-1-selective inhibitor (COX-1 $IC_{50} = 0.80 \pm 0.05$ μM, COX-2 $IC_{50} = 210 \pm 10$ μM). This compound causes little gastric damage in rats even at an oral dose of 300 mg/kg, though it has an analgesic effect at as low a dose as 10 mg/kg. Our results show that COX-1-selective inhibitors can be analgesic agents without causing gastric damage.

Introduction

Stomach irritation is a major side effect of nonsteroidal anti-inflammatory drugs (NSAIDs)[1,2] and is thought to be caused by inhibition of cyclooxygenase-1 (COX-1), an enzyme involved in prostaglandin (PG) synthesis. Vane et al. proposed that COX-1 inhibition is the ringleader in the mechanism of gastric ulcer formation induced by NSAIDs[3,4] because PGs are thought to be important for the protection of gastric mucosa and the expression level of COX-1 in the gastrointestinal tract is much higher than that of another representative cyclooxygenase, cyclooxygenase-2 (COX-2).[4–6] Therefore, in the development of NSAIDs, it has been considered desirable to minimize COX-1 inhibition. Nevertheless, it should be emphasized that there is no evidence of COX-1-selective inhibition being the cause of gastric damage.

Langenbach et al. reported that COX-1 knockout mice do not spontaneously develop gastric lesions, as further evidence that inhibition of COX-1 alone is not sufficient to induce gastric damage.[7] Moreover, Wallace et al. reported that gastric ulcers are not formed by COX-1-selective inhibition.[8] According to their report, a COX-1-selective inhibitor, **2** (SC-560),[9] and a COX-2-selective inhibitor, **3** (celecoxib)[10] (Figure 1), did not cause gastric damage when independently administered to rats, whereas simultaneous administration of both inhibitors resulted in the formation of gastric ulcers. These findings are supported by the results of a study by Tanaka et al.[11] showing that COX-1 inhibition up-regulates COX-2 expression, resulting in production of PGE_2 to a level necessary for mucosal integrity. These results suggest that formation of gastric ulcers is not caused solely by COX-1 inhibition.

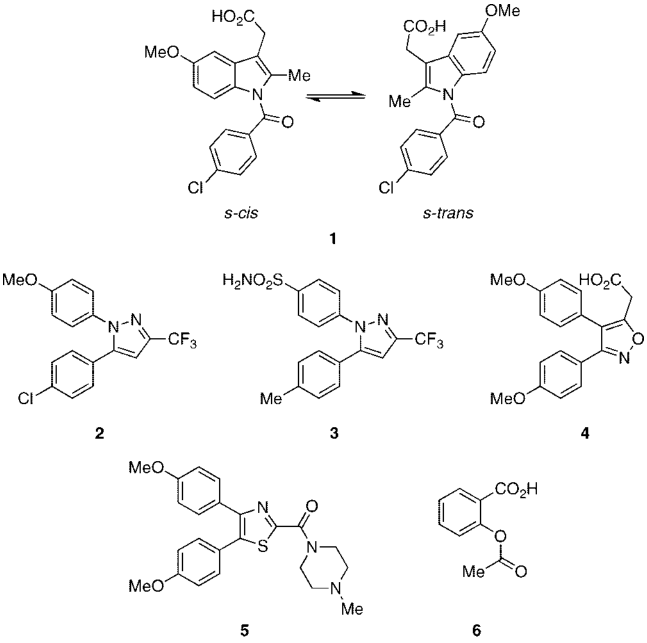

Figure 1. Chemical structures of known COX inhibitors.

Only a few COX-1-selective inhibitors are currently available; these include **2**, **4** (mofezolac),[12,13] which is used as a painkiller in Japan, and **5** (FR122047),[14–16] developed as an antiplatelet aggregation agent (Figure 1). Although showing more potent analgesic effects than those of COX-2-selective inhibitors,[12,14] **4** and **5** also possess COX-2-inhibitory activity (**4**,[12] COX-1 $IC_{50} = 0.0014$ μM, COX-2 $IC_{50} = 0.44$ μM; **5**,[14] COX-1 $IC_{50} = 0.028$ μM, COX-2 $IC_{50} = 65$ μM), and COX-2 inhibition may occur in vivo, depending on the dosage. These two drugs were not originally developed as COX-1-selective inhibitors. The fact that COX-1-deficient mice are more desensitized to pain than COX-2-deficient mice supports the idea that COX-1 inhibition may be more effective than COX-2 inhibition for analgesic action.[17] Furthermore, the reported rate of gastrointestinal dysfunction caused by **4** is very low,[18] indicating that COX-1-selective inhibitors may be useful as analgesics without causing gastric damage.

This background prompted us to search for a new, highly COX-1-selective inhibitor without COX-2-inhibitory activity in vivo. We have reported the development of benzenesulfonanilide-type COX-1-selective inhibitors[19] by mimicry of the

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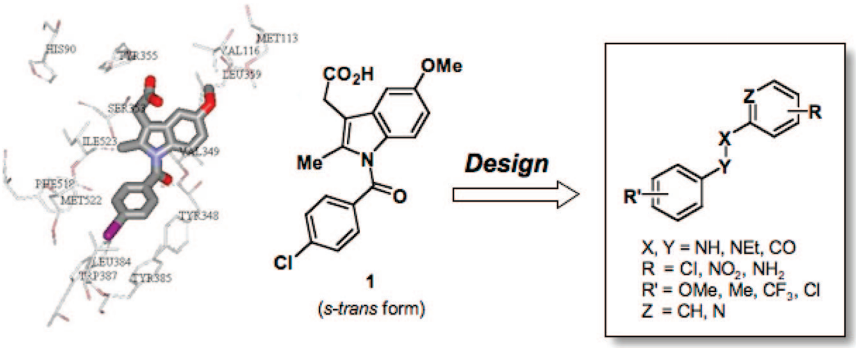


Figure 2. X-ray structure of **1** in COX-1 (left), quoted from ref 24, and strategy for molecular design of structurally simple COX-1-selective inhibitors bearing a benzamide skeleton (right).

structures of **2**, **4**, and **5**. These benzenesulfonanilide-type compounds exhibit potent COX-1 inhibitory activities in vitro, though their analgesic effect is weak because of their low oral absorption in mice. It was reported that the inhibition of prostaglandin E_2 synthesis by **2** is independent of COX-1 inhibition.[20] Therefore, since both representative COX-1-selective inhibitors described above and our benzenesulfonanilide-type COX-1 inhibitor have similar molecular structures, it is not clear whether their analgesic effects are attributed to their COX-1-inhibitory activity or to other bioactivities based on the similar chemical structure. Thus, in order to clarify the situation, we aimed to develop new COX-1-selective inhibitors with structures that are clearly different from those of currently available COX-1-selective inhibitors in order to confirm that COX-1-selective inhibitors can show analgesic activity without causing gastric damage.

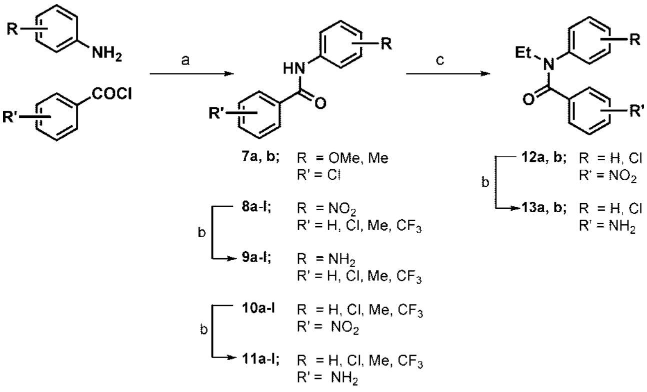
Design Strategy

For the design of new COX-1-selective inhibitors, we focused on **1** (indomethacin).[21] Compound **1**, which possesses more potent inhibitory activity against COX-1 than against COX-2, not only exhibits potent anti-inflammatory and analgesic effects but also causes the formation of severe gastric ulcers.[22] This is considered to be due to its potent inhibitory activities against both COX-1 and COX-2. It is also known that there is a difference in the conformations of **1** relevant to the interactions with COX-1 and COX-2[23,24] (Figure 1). Compound **1** interacts with COX-1 in *s-trans* or *s-cis* conformation, with the aromatic rings being located in the same or opposite direction at the amide bond, respectively. On the other hand, the interaction with COX-2 involves only the *s-cis* form. Therefore, we designed and synthesized compounds possessing a benzanilide skeleton, which has been reported to exist in *s-trans* conformation both in various solutions and in the crystal,[25,26] that would mimic the *s-trans* structure of **1** involved in the interaction with COX-1 (Figure 2).

Chemistry

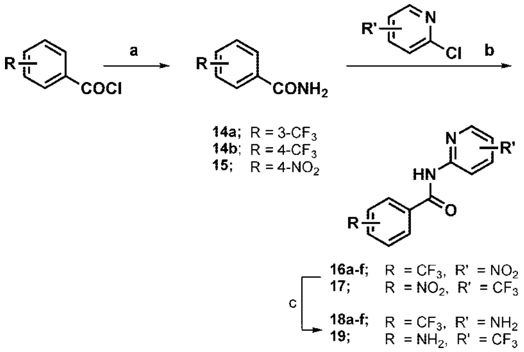
Benzanilide derivatives **7a** and **7b** were synthesized from aniline derivatives and benzoyl chloride derivatives in dichloromethane with triethylamine, as shown in Scheme 1. N-Ethylation of **10a** and **10b** was performed by treatment with NaH and ethyl iodide in anhydrous DMF. Reduction of nitro derivatives **8a−l**, **10a−l**, **12a**, and **12b** gave amino derivatives **9a−l**, **11a−l**, **13a**, and **13b**. Aminopyridine derivatives **18a−f** and **19** were prepared according to Scheme 2. Amides **14a**, **14b**, and **15** were prepared as shown and reacted with 2-chloropyridine derivatives in the presence of tris(dibenzylideneacetone)dipalladium as a catalyst. Reduction of compounds **16a−f** and **17** afforded aminopyridine derivatives **18a−f** and **19**. The amide-bond-reversed compound corresponding to **18f** was synthesized according to Scheme 3. Substitution of a cyano group for the bromo atom of 2-bromo-5-nitropyridine was performed by reaction with copper cyanide and sodium cyanide in DMF. After hydrolysis of the cyano group of compound **20** in hydrochloric acid, coupling reaction with compound **21** and 4-aminobenzotrifluoride followed by reduction of the amino group gave compound **22**.

Scheme 1[a]



[a] Reagents and conditions: (a) triethylamine, dichloromethane; (b) H_2, Pd/C, EtOAc or Sn, HCl, THF; (c) ethyl iodide, NaH, DMF.

Scheme 2[a]

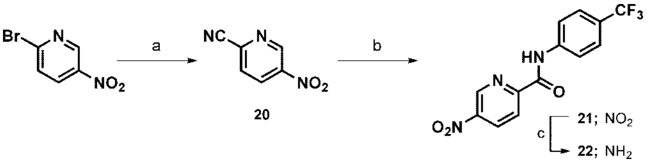


[a] Reagents and conditions: (a) NH_3; (b) cesium carbonate, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, tris(dibenzylideneacetone)dipalladium, dioxane; (c) H_2, Pd/C, EtOAc.

Results and Discussion

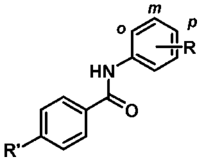
Table 1 shows the COX-inhibitory activities of the benzanilide derivatives at a concentration of 100 μM. Although the

Scheme 3[a]



[a] Reagents and conditions: (a) CuCN, NaCN, DMF; (b) (i) 10 N HCl; (ii) 4-aminobenzotrifluoride, EDC, HOBt, DMF; (c) H$_2$, Pd/C, EtOAc.

Table 1. COX-Inhibitory Activity of Compounds **1**, **6**, **7**, and **9**[a]



compd	R	R′	% inhibition at 100 μM COX-1	COX-2
1			89 ± 1	85 ± 1
6			53 ± 1	25 ± 2
7a	*p*-OMe	Cl	35 ± 1	11 ± 1
7b	*p*-Me	Cl	23 ± 3	32 ± 2
9a	*p*-NH$_2$	H	54 ± 6	0 ± 0
9b	*p*-NH$_2$	Cl	49 ± 0	16 ± 0
9c	*p*-NH$_2$	Me	53 ± 3	1 ± 0
9j	*o*-NH$_2$	CF$_3$	53 ± 2	10 ± 2
9k	*m*-NH$_2$	CF$_3$	76 ± 2	31 ± 1
9l	*p*-NH$_2$	CF$_3$	63 ± 3	30 ± 2

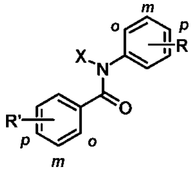
[a] Data shown are the mean ± SEM ($n = 4$).

lead compound **1**, which possesses chloro, methyl, and methoxy groups, shows potent COX-inhibitory activity, the compounds possessing the same substituent groups, **7a**, **7b, 9a**, **9b**, and **9c**, showed weak inhibitory activity. On the other hand, compounds bearing trifluoromethyl and amino groups **9j**, **9k**, and **9l** showed moderate COX-inhibitory activity. Thus, compounds with the benzanilide group reversed in the structure were evaluated (Table 2). We found that the amide-bond-reversed compounds bearing trifluoromethyl and amino substituents, **11j**, **11k**, **11n**, and **11q**, also showed potent COX-1-selective inhibitory activity. On the other hand, the N-ethylated compounds (**13a** and **13b**) and the nitro derivatives, the precursors of the amino compounds (**10k**, **10n**, and **10q**), exhibited no COX-inhibitory activity.

Next, in order to evaluate further the benzanilide-type COX inhibitors, the regioisomers bearing trifluoromethyl and amino groups were prepared. As shown in Table 3, compounds **9h** and **11j** showed potent COX-1-selective inhibitory activity. However, these compounds have low water solubility. In order to overcome this problem, aminopyridine derivatives were prepared (Table 4). Although compound **18b**, a pyridine derivative of compound **9h**, showed no COX-1-selective inhibitory activity, surprisingly, *N*-(5-amino-2-pyridinyl)-4-(trifluoromethyl)benzamide (**18f**, TFAP) showed very potent COX-1-selective inhibitory activity. The IC_{50} value of **1** (COX-1 IC_{50} = 0.80 ± 0.05 μM) was better than that of **6** (aspirin)[27] and equivalent to that of **1**. The water solubility was increased. The COX-1-selectivity of **18f** was 275 times versus COX-2, while those of **6** and **1** were 7.1 and 110 times, respectively. On the other hand, compounds **19** and **22** possessing the reversed structure of **18f** showed low COX-inhibitory activity.

In order to understand the binding mode to COX-1, a docking study[28] was performed. As shown in Figure 3, **1** and **18f** bind to the catalytic site of COX-1. The stabilized structure of **18f** could be placed in almost the same position as that of **1**. In addition, the amino group of **18f** exhibited hydrogen bonding with Leu 384, supporting the importance of this amino group.

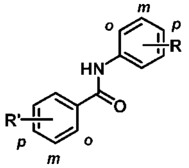
Table 2. COX-Inhibitory Activity of Compounds **1**, **6**, **10**, **11**, and **13**[a]



compd	R	R′	X	% inhibition at 100 μM COX-1	COX-2
1				89 ± 1	85 ± 1
6				53 ± 1	25 ± 2
11a	*p*-H	*p*-NH$_2$	H	40 ± 3	14 ± 2
11b	*p*-Cl	*p*-NH$_2$	H	53 ± 4	18 ± 1
11c	*p*-Me	*p*-NH$_2$	H	56 ± 3	13 ± 2
11d	*o*-Me	*o*-NH$_2$	H	53 ± 4	23 ± 2
11e	*m*-Me	*o*-NH$_2$	H	67 ± 2	0 ± 0
11f	*p*-Me	*o*-NH$_2$	H	57 ± 1	0 ± 0
11g	*p*-H	*o*-NH$_2$	H	64 ± 2	0 ± 0
11h	*p*-Cl	*o*-NH$_2$	H	52 ± 1	6 ± 1
13a	*p*-H	*o*-NH$_2$	Et	5 ± 0	0 ± 0
13b	*p*-Cl	*o*-NH$_2$	Et	23 ± 2	9 ± 0
11i	*o*-CF$_3$	*o*-NH$_2$	H	32 ± 1	0 ± 0
11j	*m*-CF$_3$	*o*-NH$_2$	H	90 ± 1	46 ± 2
11k	*p*-CF$_3$	*o*-NH$_2$	H	68 ± 2	3 ± 0
11n	*p*-CF$_3$	*m*-NH$_2$	H	70 ± 2	41 ± 2
11q	*p*-CF$_3$	*p*-NH$_2$	H	71 ± 2	14 ± 0
10k	*p*-CF$_3$	*o*-NO$_2$	H	31 ± 2	17 ± 0
10n	*p*-CF$_3$	*m*-NO$_2$	H	13 ± 2	11 ± 0
10q	*p*-CF$_3$	*p*-NO$_2$	H	0 ± 0	4 ± 2

[a] Data shown are the mean ± SEM ($n = 4$).

Table 3. COX-Inhibitory Activity of Compounds **1**, **6**, **9**, and **11**[a]

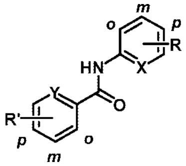


compd	R	R′	IC_{50} (μM) COX-1	COX-2
1			0.10 ± 0.03	11 ± 2
6			100 ± 10	710 ± 40
9d	*o*-NH$_2$	*o*-CF$_3$	>100	>100
9e	*m*-NH$_2$	*o*-CF$_3$	94 ± 7	>100
9f	*p*-NH$_2$	*o*-CF$_3$	>100	>100
9g	*o*-NH$_2$	*m*-CF$_3$	72 ± 5	>100
9h	*m*-NH$_2$	*m*-CF$_3$	7.2 ± 0.7	>100
9i	*p*-NH$_2$	*m*-CF$_3$	62 ± 11	>100
9j	*o*-NH$_2$	*p*-CF$_3$	88 ± 19	>100
9k	*m*-NH$_2$	*p*-CF$_3$	14 ± 0	>100
9l	*p*-NH$_2$	*p*-CF$_3$	29 ± 5	>100
11i	*o*-CF$_3$	*o*-NH$_2$	>100	>100
11j	*m*-CF$_3$	*o*-NH$_2$	10 ± 1	>100
11k	*p*-CF$_3$	*o*-NH$_2$	16 ± 1	>100
11l	*o*-CF$_3$	*m*-NH$_2$	>100	>100
11m	*m*-CF$_3$	*m*-NH$_2$	>100	>100
11n	*p*-CF$_3$	*m*-NH$_2$	19 ± 3	>100
11o	*o*-CF$_3$	*p*-NH$_2$	>100	>100
11p	*m*-CF$_3$	*p*-NH$_2$	>100	>100
11q	*p*-CF$_3$	*p*-NH$_2$	30 ± 3	>100

[a] Data shown are the mean ± SEM ($n = 4$).

Although the IC_{50} value of this compound for COX-1 is larger than that of **1** (COX-1 IC_{50} = 0.10 ± 0.03 μM, COX-2 IC_{50} = 11 ± 2 μM), **18f** is thought to be a good candidate for in vivo COX-1-selective inhibitory activity because of its high COX-1 selectivity and low potency of COX-2 inhibition. It was confirmed that **18f** given orally to rats at 30 mg/kg showed a C_{max} value of 12 μM, indicating that **18f** has the potential to selectively inhibit COX-1 in vivo. In an acute toxicity study,

Table 4. COX-Inhibitory Activity of Compounds **1**, **6**, **18**, **19**, and **22**[a]



compd	R	R′	X	Y	IC$_{50}$ (μM) COX-1	IC$_{50}$ (μM) COX-2
1					0.10 ± 0.03	11 ± 2
6					100 ± 10	710 ± 40
18a	*o*-NH$_2$	*m*-CF$_3$	N	CH	>100	>100
18b	*m*-NH$_2$	*m*-CF$_3$	N	CH	>100	>100
18c	*p*-NH$_2$	*m*-CF$_3$	N	CH	12 ± 1	>100
18d	*o*-NH$_2$	*p*-CF$_3$	N	CH	>100	>100
18e	*m*-NH$_2$	*p*-CF$_3$	N	CH	>100	>100
18f	*p*-NH$_2$	*p*-CF$_3$	N	CH	0.80 ± 0.05	210 ± 10
19	*p*-CF$_3$	*p*-NH$_2$	N	CH	10 ± 2	>100
22	*p*-CF$_3$	*p*-NH$_2$	CH	N	>100	>100

[a] Data shown are the mean ± SEM ($n = 4$).

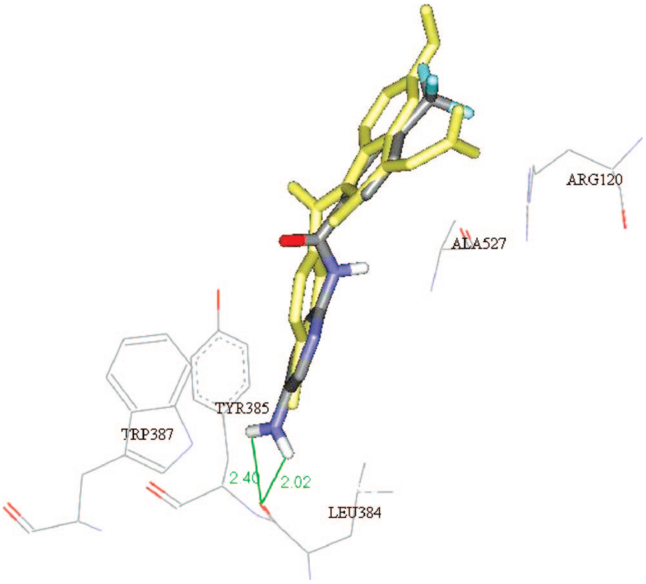


Figure 3. Potential binding modes of **1** (yellow stick) and **18f** (colored by element, stick) in the COX-1 active site. The 2H-bonds are indicated with green lines.

18f was administered orally at doses of up to 300 mg/kg to mice, and no toxic symptoms were observed up to 14 days (data not shown).

Figure 4a–d shows photographs of excised stomachs and Figure 4e gastric damage scores, which are averages of the length of the gastric damage per stomach at 5 h after administration of each compound. Even at a dose of 300 mg/kg, **18f** caused little gastric damage (Figure 4b,e), but **1** caused significant gastric damage at a dose of as little as 10 mg/kg (Figure 4c,d,e), while **6** induced obvious gastric ulcer formation (Figure 4e, photographs not shown). Moreover, **18f** did not induce gastric ulcer formation even after consecutive doses of 30 mg/kg everyday for 1 week. These results are similar to the results of a study by Wallace et al.,[8] showing that COX-1-selective inhibitors alone do not cause gastric damage. Since NSAIDs possessing potent COX-1 inhibitory activity tend to have potent analgesic effects as mentioned above, the effect of **18f** in mice was examined by means of the acetic acid-induced writhing test.[14] Administration of **18f** at a dose of 10 or 30 mg/kg resulted in a significant reduction in the number of writhes, as was the case for **1** at a dose of 10 mg/kg (Figure 5a). In addition, **18f** reduced formalin-induced pain at a dose of 30 mg/kg in rats (Figure 5b). These results indicate that **18f** has an analgesic effect without causing gastric damage.

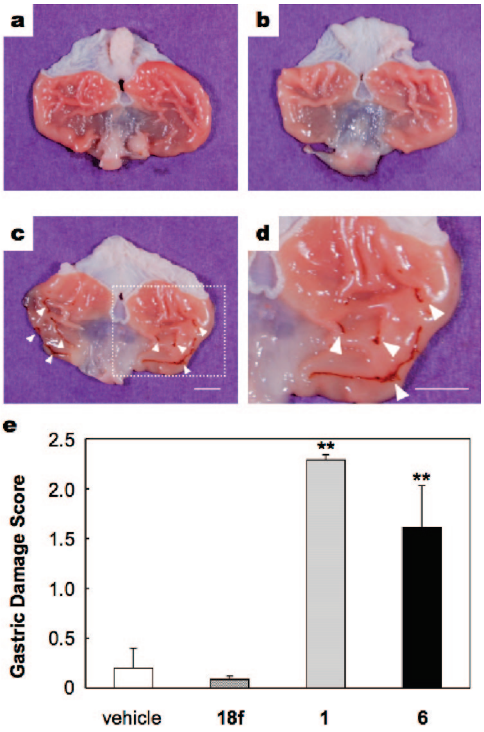


Figure 4. Photographs and gastric damage scores of **18f**, **1**, and **6**: (a) vehicle; (b) treated with **18f** (300 mg/kg); (c) treated with **1**(10 mg/kg); (d) enlarged illustration of part c. Scale bars indicate 5 mm. White triangles indicate ulcers. (e) Gastric damage score was calculated by measuring the lengths, in millimeters, and summing the values for each rat. Compounds **18f**, **1**, and **6** were administered at 300, 10, and 30 mg/kg, respectively. Data shown are the mean ± SEM ($n = 4$/group). The following indicates significantly different from the vehicle: (**) $p < 0.01$.

Conclusion

We designed and synthesized benzamide-type COX-1-selective inhibitors based on the structure of **1**. Among them, **18f** exhibits a potent analgesic effect without causing gastric ulcers, in contrast to **1**, which inhibits both COX-1 and COX-2 and causes gastric ulceration.[22] These findings indicate that our strategy of mimicking the conformations of well-known NSAIDs that bind specifically to COX-1 should be useful for the development of new analgesic agents that do not cause gastric damage.

Pain relief for terminal cancer patients is recommended by the World Health Organization (WHO),[29] and one widely used painkiller for cancer patients is acetaminophen (paracetamol),[30] the target molecule of which has been reported to be COX-3, an isoform of COX-1.[31] In addition, NSAIDs possessing potent COX-1 inhibitory activity tend to show potent COX-3 inhibitory activity.[31] Therefore, new COX-1-selective inhibitors are likely to be candidate analgesics for treatment of cancer patients. They are also candidate anticancer drugs with both analgesic activity and antitumor activity[18,32] because of their expected antiangiogenesis effect.[33] The results presented in this article require a reconsideration of the widely held view that COX-1 inhibition is the main culprit in causing gastric ulceration.

Experimental Section

General Methods. Melting points were determined with a Yanagimoto hot-stage melting point apparatus and are uncorrected.

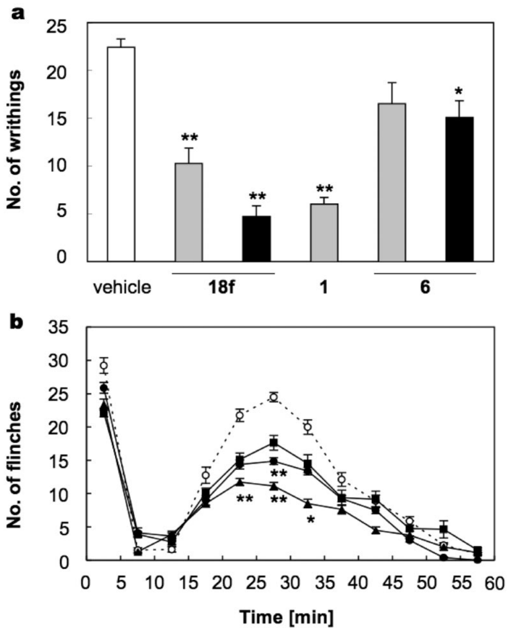


Figure 5. Analgesic effect tests: (a) acetic acid-induced writhing test in mice. Gray and black bars indicate number of writhes at 10 and 30 mg/kg, respectively. Each value is the average of the total number of writhes ± SEM ($n = 10$–11/group). (b) Formalin test in rats. Open circles, circles, triangles, and squares indicate vehicle, **18f**, **1**, and **6**, respectively. Each compound was orally administered at 30 mg/kg. Data shown are the average of the total number of pain-related behaviors ± SEM ($n = 8$/group). The following indicates significantly different from the vehicle: (∗) $p < 0.05$; (∗∗) $p < 0.01$.

IR spectra were recorded on a JASCO FT/IR350 (KBr). NMR spectra were recorded on a VarianVXR-300 (^{1}H 300 MHz) spectrometer. Proton chemical shifts were referenced to the TMS internal standard. Elemental analysis was carried out with a Yanagimoto MT-5 CHN recorder elemental analyzer and results were within ±0.4% of the theoretical values. FAB-MS was carried out with a VG70-SE.

General Procedure for Synthesis of Substituted Benzanilides from Anilines (GP-A). To a solution of aniline (2.0 mmol) in dichloromethane (10.0 mL) were added triethylamine (0.3 mmol) and benzoyl chloride (2.0 mmol). The mixture was stirred at room temperature overnight, then extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography or recrystallized from an appropriate solvent to give a substituted benzanilide.

General Procedure for Reduction of Nitro-Substituted Benzanilides. GP-B-1. Nitro-substituted benzanilide (2.0 mmol) was dissolved in EtOAc (10.0 mL) and hydrogenated (1 bar H_2) over 10% palladium on charcoal. The mixture was filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography or recrystallized using an appropriate solvent to give an amino-substituted benzanilide.

GP-B-2. To a solution of halogen-substituted nitrobenzanilide (1.0 mmol) in THF (4.0 mL) were added tin powder (3.5 mmol) and concentrated HCl. Then the mixture was refluxed for 30 min. After the reaction was finished, the mixture was basified with 2 N NaOH solution. The mixture was filtered through Celite, and the filtrate was extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography or recrystallized using an appropriate solvent to give the corresponding halogen-substituted aminobenzanilide.

General Procedure for Synthesis of N-Alkylated Benzanilides (GP-C). To a solution of sodium hydride (3.6 mmol) (60% in mineral oil, washed with *n*-hexane) in DMF (2.0 mL) was added a solution of substituted nitrobenzanilide (2.0 mmol) in DMF (2.0 mL). Then the mixture was stirred at room temperature for 15 min. To the resulting mixture was added alkyl iodide (2.4 mmol), and then stirring was continued at room temperature for another 1 h. To the reaction mixture was added water, and the organics were extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by recrystallization gave N-alkylated benzanilide.

General Procedure for Synthesis of Trifluoromethylbenzamides from Trifluoromethylbenzoyl Chloride (GP-D). Trifluoromethylbenzoyl chloride (2.0 mmol) was added to aqueous NH_3 (6.0 mL). The mixture was stirred at room temperature for 30 min, then extracted with EtOAc. The organic layer was washed with H_2O and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was purified by recrystallization using an appropriate solvent to give a substituted trifluoromethylbenzamide.

General Procedure for Synthesis of *N*-Pyridinylbenzamides from Trifluoromethylbenzamide (GP-E). To a solution of trifluoromethylbenzamide (1.0 mmol) in dioxane (10.0 mL) were added chloronitropyridine (1.0 mmol), cesium carbonate (1.1 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.2 mmol), and tris(dibenzylideneacetone)dipalladium (0.05 mmol). The mixture was stirred at reflux overnight, then filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure. The residue was purified by silica gel column chromatography or recrystallized using an appropriate solvent to give a substituted *N*-pyridinylbenzamide.

4-Chloro-*N*-(4-methoxyphenyl)benzamide (7a). According to the general procedure (GP-A), **7a** was obtained in 91% yield as a white powder after recrystallization from EtOAc/*n*-hexane. Mp 214.0–215.0 °C. IR (KBr) cm^{-1}: 3344 (NH), 1650 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.18 (s, 1H), 7.97 (d, 2H, $J = 8.0$ Hz), 7.65 (d, 2H, $J = 9.0$ Hz), 7.59 (d, 2H, $J = 8.0$ Hz), 6.92 (d, 2H, $J = 9.0$ Hz), 3.75 (s, 3H). FAB-MS *m*/*z*: 261 [M]$^+$, 262 [M + H]$^+$, 263 [M + 2]$^+$, 264 [M + 2 + H]$^+$. Anal. ($C_{14}H_{12}ClNO_2$) C, H, N.

4-Chloro-*N*-(4-tolyl)benzamide (7b). According to the general procedure (GP-A), **7b** was obtained in 92% yield as white needles after recrystallization from CH_2Cl_2/*n*-hexane. Mp 219.0–221.0 °C. IR (KBr) cm^{-1}: 3348 (NH), 1654 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.20 (s, 1H), 7.97 (dd, 2H, $J = 7.0$, 2.0 Hz), 7.63 (d, 2H, $J = 8.5$ Hz), 7.60 (dd, 2H, $J = 7.0$, 2.0 Hz), 7.16 (d, 2H, $J = 8.5$ Hz), 2.28 (s, 3H). FAB-MS *m*/*z*: 245 [M]$^+$, 246 [M + H]$^+$, 247 [M + 2]$^+$, 248 [M + 2 + H]$^+$. Anal. ($C_{14}H_{12}ClNO$) C, H, N.

***N*-(4-Nitrophenyl)benzamide (8a).** According to the general procedure (GP-A), **8a** was obtained in 85% yield as yellow needles after column chromatography (eluent: EtOAc/*n*-hexane = 1/4). Mp 202.0–204.0 °C. IR (KBr) cm^{-1}: 3336 (NH), 1657 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.80 (s, 1H), 8.27 (dd, 2H, $J = 9.2$, 2.0 Hz), 8.07 (dd, 2H, $J = 9.2$, 2.0 Hz), 7.99 (dt, 2H, $J = 7.0$, 1.6 Hz), 7.67–7.54 (m, 3H). FAB-MS *m*/*z*: 243 [M + H]$^+$.

4-Chloro-*N*-(4-nitrophenyl)benzamide (8b). According to the general procedure (GP-A), **8b** was obtained in 86% yield as a yellow powder after column chromatography (eluent: EtOAc/*n*-hexane = 1/4). Mp 223.0–225.0 °C. IR (KBr) cm^{-1}: 3290 (NH), 1666 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.90 (s, 1H), 8.27 (dd, 2H, $J = 9.4$, 2.2 Hz), 8.05 (dd, 2H, $J = 9.4$, 2.2 Hz), 8.01 (dd, 2H, $J = 9.1$, 2.0 Hz), 7.65 (dd, 2H, $J = 9.1$, 2.0 Hz). FAB-MS *m*/*z*: 277 [M + H]$^+$, 279 [M + 2 + H]$^+$.

4-Methyl-*N*-(4-nitrophenyl)benzamide (8c). According to the general procedure (GP-A), **8c** was obtained in 40% yield as white needles after column chromatography (eluent: EtOAc/*n*-hexane = 1/5). Mp 210.0–211.0 °C. IR (KBr) cm^{-1}: 3369 (NH), 1674 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.70 (s, 1H), 8.26 (dd, 2H, *J*

= 9.0, 2.0 Hz), 8.07 (dd, 2H, J = 9.0, 2.0 Hz), 7.91 (d, 2H, J = 8.2 Hz), 7.37 (d, 2H, J = 8.2 Hz), 2.40 (s, 3H). FAB-MS *m/z*: 257 [M + H]$^+$.

***N*-(2-Nitrophenyl)-2-trifluoromethylbenzamide (8d).** According to the general procedure (GP-A), **8d** was obtained in 77% yield as yellow feathers after column chromatography (eluent: EtOAc/*n*-hexane = 1/10). Mp 133.0–135.0 °C. IR (KBr) cm^{-1}: 3234 (NH), 1660 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.96 (s, 1H), 8.01 (d, 1H, J = 8.0 Hz), 7.87 (t, 2H, J = 8.5 Hz), 7.79–7.71 (m, 3H), 7.63 (d, 1H, J = 8.0 Hz), 7.47 (td, 1H, J = 8.0, 1.3 Hz). FAB-MS *m/z*: 311 [M + H]$^+$.

***N*-(3-Nitrophenyl)-2-trifluoromethylbenzamide (8e).** According to the general procedure (GP-A), **8e** was obtained in 99% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 160.0–161.0 °C. IR (KBr) cm^{-1}: 3236 (NH), 1657 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.08 (s, 1H), 8.73 (t, 1H, J = 2.1 Hz), 8.02–7.99 (m, 2H), 7.90–7.73 (m, 4H), 7.67 (t, 1H, J = 8.2 Hz). FAB-MS *m/z*: 311 [M + H]$^+$.

***N*-(4-Nitrophenyl)-2-trifluoromethylbenzamide (8f).** According to the general procedure (GP-A), **8f** was obtained in 99% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 207.0–208.0 °C. IR (KBr) cm^{-1}: 3266 (NH), 1671 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.18 (s, 1H), 8.26 (dd, 2H, J = 9.4, 2.2 Hz), 7.93 (dd, 2H, J = 9.4, 2.2 Hz), 7.88–7.71 (m, 4H). FAB-MS *m/z*: 311 [M + H]$^+$.

***N*-(2-Nitrophenyl)-3-trifluoromethylbenzamide (8g).** According to the general procedure (GP-A), **8g** was obtained in 55% yield as white needles after column chromatography (eluent: EtOAc/*n*-hexane = 1/10). Mp 100.0–102.0 °C. IR (KBr) cm^{-1}: 3356 (NH), 1686 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.97 (s, 1H), 8.29–8.25 (m, 2H), 8.03 (dd, 2H, J = 8.3, 1.5 Hz), 7.86–7.70 (m, 3H), 7.48 (td, 1H, J = 8.3, 1.7 Hz). FAB-MS *m/z*: 311 [M + H]$^+$.

***N*-(3-Nitrophenyl)-3-trifluoromethylbenzamide (8h).** According to the general procedure (GP-A), **8h** was obtained in 98% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 135.0–136.0 °C. IR (KBr) cm^{-1}: 3339 (NH), 1661 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.90 (s, 1H), 8.78 (t, 1H, J = 2.0 Hz), 8.34 (s, 1H), 8.30 (d, 1H, J = 8.0 Hz), 8.21 (dt, 1H, J = 8.0, 1.0 Hz), 8.02–7.99 (m, 2H), 7.83 (t, 1H, J = 7.7 Hz), 7.69 (t, 1H, J = 8.2 Hz). FAB-MS *m/z*: 311 [M + H]$^+$.

***N*-(4-Nitrophenyl)-3-trifluoromethylbenzamide (8i).** According to the general procedure (GP-A), **8i** was obtained in 81% yield as yellow needles after recrystallization from EtOAc/*n*-hexane. Mp 160.0–162.0 °C. IR (KBr) cm^{-1}: 3389 (NH), 1689 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.99 (s, 1H), 8.28 (dd, 4H, J = 9.5, 2.2 Hz), 8.09 (dd, 2H, J = 9.5, 2.2 Hz), 8.02 (d, 1H, J = 7.9 Hz), 7.82 (1H, t, J = 7.9 Hz). FAB-MS *m/z*: 311 [M]$^+$.

***N*-(2-Nitrophenyl)-4-trifluoromethylbenzamide (8j).** According to the general procedure (GP-A), **8j** was obtained in 40% yield as yellow needles after column chromatography (eluent: EtOAc/*n*-hexane = 1/10). Mp 112.0–113.0 °C. IR (KBr) cm^{-1}: 3361 (NH), 1692 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.96 (s, 1H), 8.15 (d, 2H, J = 8.1 Hz), 8.03 (dd, 1H, J = 8.4, 1.1 Hz), 7.97 (d, 2H, J = 8.1 Hz), 7.79 (dd, 1H, J = 8.4, 1.1 Hz), 7.75 (td, 1H, J = 7.6, 1.4 Hz), 7.47 (td, 1H, J = 7.6, 1.4 Hz). FAB-MS *m/z*: 311 [M + H]$^+$.

***N*-(3-Nitrophenyl)-4-trifluoromethylbenzamide (8k).** According to the general procedure (GP-A), **8k** was obtained in 98% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 192.0–195.0 °C. IR (KBr) cm^{-1}: 3343 (NH), 1665 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.92 (s, 1H), 8.81 (dd, 1H, J = 2.3, 2.0 Hz), 8.21 (d, 1H, J = 8.2 Hz), 8.20 (d, 2H, J = 8.8 Hz), 8.00 (ddd, 1H, J = 8.2, 2.3, 2.0 Hz), 7.96 (d, 2H, J = 8.8 Hz), 7.96 (t, 1H, J = 8.2 Hz). FAB-MS *m/z*: 311 [M + H]$^+$.

***N*-(4-Nitrophenyl)-4-trifluoromethylbenzamide (8l).** According to the general procedure (GP-A), **8l** was obtained in 65% yield as white needles after column chromatography (eluent: EtOAc/*n*-hexane = 1/6). Mp 196.0–198.0 °C. IR (KBr) cm^{-1}: 3393 (NH), 1686 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.10 (s, 1H), 8.29 (d, 2H, J = 9.5 Hz), 8.18 (d, 2H, J = 8.0 Hz), 8.07 (d, 2H, J = 9.5 Hz), 7.95 (d, J = 8.0 Hz, 2H). FAB-MS *m/z*: 311 [M + H]$^+$.

***N*-(4-Aminophenyl)benzamide (9a).** According to the general procedure (GP-B-1), **9a** was obtained in 82% yield as a gray solid after recrystallization from EtOAc/*n*-hexane. Mp 125.0–127.0 °C. IR (KBr) cm^{-1}: 3379, 3330 (NH$_2$), 3053 (NH), 1645 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.85 (s, 1H), 7.91 (dt, 2H, J = 7.9, 1.7 Hz), 7.50 (m, 3H), 7.36 (dd, 2H, J = 8.7, 2.1 Hz), 6.54 (dd, 2H, J = 8.7, 2.1 Hz), 4.90 (s, 2H). FAB-MS *m/z*: 212 [M]$^+$, 213 [M + H]$^+$. Anal. ($C_{13}H_{12}N_2O$) C, H, N.

***N*-(4-Aminophenyl)-4-chlorobenzamide (9b).** According to the general procedure (GP-B-2), **9b** was obtained in 88% yield as white granules after recrystallization from EtOAc/*n*-hexane. Mp 217.0–218.0 °C. IR (KBr) cm^{-1}: 3400, 3330 (NH$_2$), 3220 (NH), 1644 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.95 (s, 1H), 7.95 (dd, 2H, J = 8.6, 2.0 Hz), 7.57 (dd, 2H, J = 8.6, 2.0 Hz), 7.35 (dd, 2H, J = 8.6, 2.0 Hz), 6.54 (dd, 2H, J = 8.6, 2.0 Hz), 4.95 (s, 2H). FAB-MS *m/z*: 246 [M]$^+$, 247 [M + H]$^+$. Anal. ($C_{13}H_{11}ClN_2O \cdot {}^1/_5H_2O$) C, H, N.

***N*-(4-Aminophenyl)-4-methylbenzamide (9c).** According to the general procedure (GP-B-1), **9c** was obtained in 79% yield as a purple powder after recrystallization from EtOAc/*n*-hexane. Mp 179.0–180.0 °C. IR (KBr) cm^{-1}: 3477, 3383 (NH$_2$), 3358 (NH), 1649 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.80 (s, 1H), 7.83 (d, 2H, J = 8.3 Hz), 7.35 (dd, 2H, J = 8.7, 2.0 Hz), 7.30 (d, 2H, J = 8.3 Hz), 6.53 (dd, 2H, J = 8.7, 2.0 Hz), 4.90 (s, 2H), 2.37 (s, 3H). FAB-MS *m/z*: 226 [M]$^+$, 227 [M + H]$^+$. Anal. ($C_{14}H_{14}N_2O \cdot {}^1/_5H_2O$) C, H, N.

***N*-(2-Aminophenyl)-2-trifluoromethylbenzamide (9d).** According to the general procedure (GP-B-1), **9d** was obtained in 80% yield as brown needles after recrystallization from EtOAc/*n*-hexane. Mp 167.0–168.0 °C. IR (KBr) cm^{-1}: 3384, 3317 (NH$_2$), 3171 (NH), 1661 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.78 (s, 1H), 7.85–7.80 (m, 2H), 7.24 (dd, 1H, J = 8.0, 1.5 Hz), 6.97 (td, 1H, J = 8.0, 1.5 Hz), 6.77 (dd, 1H, J = 8.0, 1.5 Hz), 6.59 (td, 1H, J = 8.0, 1.5 Hz), 6.47–6.36 (m, 2H), 4.90 (s, 2H). FAB-MS *m/z*: 280 [M]$^+$, 281 [M + H]$^+$. Anal. ($C_{14}H_{11}F_3N_2O \cdot {}^1/_{15}H_2O$) C, H, N.

***N*-(3-Aminophenyl)-2-trifluoromethylbenzamide (9e).** According to the general procedure (GP-B-1), **9e** was obtained in 99% yield as brown needles after recrystallization from EtOAc/*n*-hexane. Mp 110.0–111.0 °C. IR (KBr) cm^{-1}: 3434, 3247 (NH$_2$), 3075 (NH), 1661 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.22 (s, 1H), 7.82 (d, 1H, J = 7.8 Hz), 7.76 (d, 1H, J = 7.4 Hz), 7.66 (d, 1H, J = 7.8 Hz), 7.63 (d, 1H, J = 7.4 Hz), 7.06 (t, 1H, J = 2.0 Hz), 6.94 (t, 1H, J = 7.9 Hz), 6.72 (dt, 2H, J = 7.9, 1.0 Hz), 6.31 (dt, 1H, J = 7.9, 1.0 Hz), 5.11 (s, 2H). FAB-MS *m/z*: 280 [M]$^+$, 281 [M + H]$^+$. Anal. ($C_{14}H_{11}F_3N_2O \cdot {}^2/_{13}H_2O$) C, H, N.

***N*-(4-Aminophenyl)-2-trifluoromethylbenzamide (9f).** According to the general procedure (GP-B-1), **9f** was obtained in 96% yield as a brown powder after recrystallization from EtOAc/*n*-hexane. Mp 171.0–173.0 °C. IR (KBr) cm^{-1}: 3449, 3367 (NH$_2$), 3237 (NH), 1631 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.08 (s, 1H), 8.13–7.61 (m, 4H), 7.30 (dd, 2H, J = 8.7, 2.0 Hz), 6.53 (dd, 2H, J = 8.7, 2.0 Hz), 4.94 (s, 2H). FAB-MS *m/z*: 280 [M]$^+$, 281 [M + H]$^+$. Anal. ($C_{14}H_{11}F_3N_2O$) C, H, N.

***N*-(2-Aminophenyl)-3-trifluoromethylbenzamide (9g).** According to the general procedure (GP-B-1), **9g** was obtained in 65% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 175.0–177.0 °C. IR (KBr) cm^{-1}: 3394, 3219 (NH$_2$), 3043 (NH), 1633 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.85 (s, 1H), 7.78 (d, 1H, J = 8.0 Hz), 7.71 (d, 1H, J = 7.5 Hz), 7.54–7.50 (m, 2H), 7.17–7.06 (m, 3H), 6.75 (dt, 1H, J = 7.8, 1.0 Hz), 5.33 (s, 2H). FAB-MS *m/z*: 280 [M]$^+$, 281 [M + H]$^+$. Anal. ($C_{14}H_{11}F_3N_2O$) C, H, N.

***N*-(3-Aminophenyl)-3-trifluoromethylbenzamide (9h).** According to the general procedure (GP-B-1), **9h** was obtained in 97% yield as white needles after recrystallization from CH_2Cl_2/*n*-hexane. Mp 105.0–106.0 °C. IR (KBr) cm^{-1}: 3402, 3329 (NH$_2$), 3248 (NH), 1654 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.18 (s, 1H), 8.25 (s, 1H), 8.24 (d, 1H, J = 8.7 Hz), 7.95 (d, 1H, J = 7.8 Hz), 7.76 (d, 1H, J = 7.8 Hz), 7.08 (t, 1H, J = 2.0 Hz), 6.98 (t, 1H, J = 8.0 Hz), 6.86 (dt, 1H, J = 8.0, 2.0 Hz), 6.33 (dt, 1H, J = 8.0, 2.0 Hz), 5.12 (s, 2H). FAB-MS *m/z*: 280 [M]$^+$, 281 [M + H]$^+$. Anal. ($C_{14}H_{11}F_3N_2O \cdot {}^{1}/_{9}H_2O$) C, H, N.

***N*-(4-Aminophenyl)-3-trifluoromethylbenzamide (9i).** According to the general procedure (GP-B-1), **9i** was obtained in 81% yield as brown plates after recrystallization from EtOAc/*n*-hexane. Mp 125.0–126.0 °C. IR (KBr) cm^{-1}: 3458, 3225 (NH_2), 3054 (NH), 1635 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.12 (s, 1H), 8.26 (s, 1H), 8.15 (d, 1H, J = 8.2 Hz), 7.92 (d, 1H, J = 8.0 Hz), 7.52 (t, 1H, J = 8.0 Hz), 7.38 (dd, 2H, J = 8.7, 2.0 Hz), 6.52 (dd, 2H, J = 8.7, 2.0 Hz), 4.98 (s, 2H). FAB-MS *m/z*: 280 [M]$^+$, 281 [M + H]$^+$. Anal. ($C_{14}H_{11}F_3N_2O$) C, H, N.

***N*-(2-Aminophenyl)-4-trifluoromethylbenzamide (9j).** According to the general procedure (GP-B-1), **9j** was obtained in 99% yield as white granules after recrystallization from EtOAc/*n*-hexane. Mp 216.0–218.5 °C. IR (KBr) cm^{-1}: 3419, 3343 (NH_2), 3288 (NH), 1648 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.86 (s, 1H), 8.18 (d, 2H, J = 8.1 Hz), 7.89 (d, 2H, J = 8.1 Hz), 7.17 (d, 1H, J = 7.6 Hz), 6.99 (td, 1H, J = 7.6, 1.3 Hz), 6.87 (dd, 1H, J = 7.6, 1.3 Hz), 6.60 (td, 1H, J = 7.6, 1.3 Hz), 4.96 (s, 2H). FAB-MS *m/z*: 280 [M]$^+$, 281 [M + H]$^+$. Anal. ($C_{14}H_{11}F_3N_2O$) C, H, N.

***N*-(3-Aminophenyl)-4-trifluoromethylbenzamide (9k).** According to the general procedure (GP-B-1), **9k** was obtained in 74% yield as white feathers after column chromatography (eluent: EtOAc/*n*-hexane = 1/3). Mp 159.0–162.0 °C. IR (KBr) cm^{-1}: 3454, 3368 (NH_2), 3291 (NH), 1646 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.16 (s, 1H), 8.10 (d, 2H, J = 8.4 Hz), 7.89 (d, 2H, J = 8.4 Hz), 7.09 (dd, 1H, J = 2.2, 1.0 Hz), 6.97 (td, 1H, J = 8.0, 1.0 Hz), 6.86 (dd, 1H, J = 8.0, 1.0 Hz), 6.33 (ddd, 1H, J = 8.0, 2.2, 1.0 Hz), 5.12 (s 2H). FAB-MS *m/z*: 280 [M]$^+$, 281 [M + H]$^+$. Anal. ($C_{14}H_{11}F_3N_2O \cdot {}^{1}/_{6}H_2O$) C, H, N.

***N*-(4-Aminophenyl)-4-trifluoromethylbenzamide (9l).** According to the general procedure (GP-B-1), **9l** was obtained in 89% yield as a white powder after recrystallization from EtOAc/*n*-hexane. Mp 223.0–224.0 °C. IR (KBr) cm^{-1}: 3425, 3318 (NH_2), 3250 (NH), 1639 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.09 (s, 1H), 8.11 (d, 2H, J = 8.0 Hz), 7.87 (dd, 2H, J = 8.0 Hz), 7.38 (dd, 2H, J = 8.7, 2.0 Hz), 6.55 (d, 2H, J = 8.7, 2.0 Hz), 4.96 (s, 2H). FAB-MS *m/z*: 280 [M]$^+$, 281 [M + H]$^+$. Anal. ($C_{14}H_{11}F_3N_2O$) C, H, N.

4-Nitro-*N*-(phenyl)benzamide (10a). According to the general procedure (GP-A), **10a** was obtained in 74% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 144.0–146.0 °C. IR (KBr) cm^{-1}: 3321 (NH), 1651 (CO).^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.60 (s, 1H), 8.38 (dd, 2H, J = 9.0, 2.1 Hz), 8.18 (dd, 2H, J = 9.0, 2.1 Hz), 7.78 (dt, 2H, J = 8.7, 1.2 Hz), 7.38 (tt, 2H, J = 7.4, 2.0 Hz), 7.14 (tt, 1H, J = 7.4, 2.0 Hz). FAB-MS *m/z*: 243 [M + H]$^+$.

***N*-(4-Chlorophenyl)-4-nitrobenzamide (10b).** According to the general procedure (GP-A), **10b** was obtained in 95% yield as yellow granules after recrystallization from CH_2Cl_2/*n*-hexane. Mp 231.0–232.5 °C. IR (KBr) cm^{-1}: 3419 (NH), 1681 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.70 (s, 1H), 8.38 (dd, 2H, J = 8.9, 2.0 Hz), 8.18 (dd, 2H, J = 8.9, 2.0 Hz), 7.82 (dd, 2H, J = 9.1, 2.1 Hz), 7.44 (dd, 2H, J = 9.1, 2.1 Hz). FAB-MS *m/z*: 276 [M]$^+$, 277 [M + H]$^+$ 278 [M + 2]$^+$, 279 [M + 2 + H]$^+$.

4-Nitro-*N*-(4-tolyl)benzamide (10c). According to the general procedure (GP-A), **10c** was obtained in 96% yield as yellow needles after recrystallization from EtOAc/*n*-hexane. Mp 200.0–202.0 °C. IR (KBr) cm^{-1}: 3320 (NH), 1648 (CO).^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.50 (s, 1H), 8.36 (dd, 2H, J = 8.9, 2.0 Hz), 8.17 (dd, 2H, J = 8.9, 2.0 Hz), 7.65 (d, 2H, J = 8.4 Hz), 7.18 (d, 2H, J = 8.4 Hz), 2.29 (s, 3H). FAB-MS *m/z*: 257 [M + H]$^+$.

2-Nitro-*N*-(2-tolyl)benzamide (10d). According to the general procedure (GP-A), **10d** was obtained in 68% yield as yellow needles after recrystallization from CH_2Cl_2/*n*-hexane. Mp 175.0–177.0 °C. IR (KBr) cm^{-1}: 3237 (NH), 1658 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.10 (s, 1H), 8.13 (d, 1H, J = 8.0 Hz), 7.90–7.71 (m, 3H), 7.44 (dd, 1H, J = 8.0, 1.3 Hz), 7.27–7.12 (m, 3H), 2.26 (s, 3H). FAB-MS *m/z*: 257 [M + H]$^+$.

2-Nitro-*N*-(3-tolyl)benzamide (10e). According to the general procedure (GP-A), **10e** was obtained in 83% yield as white needles after recrystallization from CH_2Cl_2/*n*-hexane. Mp 134.0–136.5 °C. IR (KBr) cm^{-1}: 3466 (NH), 1650 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.60 (s, 1H), 8.16–7.73 (m, 4H), 7.50 (s, 1H), 7.46 (d, 1H, J = 8.0 Hz), 7.24 (t, 1H, J = 8.0 Hz), 6.94 (d, 1H, J = 8.0 Hz), 2.31 (s, 3H). FAB-MS *m/z*: 256 [M]$^+$, 257 [M + H]$^+$.

2-Nitro-*N*-(4-tolyl)benzamide (10f). According to the general procedure (GP-A), **10f** was obtained in 79% yield as white needles after recrystallization from CH_2Cl_2/*n*-hexane. Mp 219.0–221.0 °C. IR (KBr) cm^{-1}: 3292 (NH), 1647 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.60 (s, 1H), 8.14 (dd, 1H, J = 8.0, 1.5 Hz), 7.87 (td, 1H, J = 7.3, 1.5 Hz), 7.76 (td, 2H, J = 7.3, 1.5 Hz), 7.54 (dd, 2H, J = 8.5, 1.8 Hz), 7.16 (dd, 2H, J = 8.5, 1.8 Hz), 2.28 (s, 3H). FAB-MS *m/z*: 257 [M + H]$^+$.

2-Nitro-*N*-(phenyl)benzamide (10g). According to the general procedure (GP-A), **10g** was obtained in 84% yield as white granules after column chromatography (eluent: EtOAc/*n*-hexane = 1/2). Mp 155.0–156.0 °C. IR (KBr) cm^{-1}: 3254 (NH), 1658 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.65 (s, 1H), 8.17 (dd, 1H, J = 7.0, 2.0 Hz), 7.88 (td, 1H, J = 7.0, 2.0 Hz), 7.77 (d, 2H, J = 7.0 Hz), 7.66 (dd, 2H, J = 7.0, 2.0 Hz), 7.36 (t, 2H, J = 8.0 Hz), 7.12 (t, 1H, J = 7.0 Hz). FAB-MS *m/z*: 243 [M + H]$^+$.

***N*-(4-Chlorophenyl)-2-nitrobenzamide (10h).** According to the general procedure (GP-A), **10h** was obtained in 86% yield as yellow needles after recrystallization from EtOAc/*n*-hexane. Mp 235.0–238.0 °C. IR (KBr) cm^{-1}: 3421 (NH), 1678 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.70 (s, 1H), 8.38 (dd, 2H, J = 8.9, 2.0 Hz), 8.18 (dd, 2H, J = 9.0, 2.1 Hz), 7.82 (dd, 2H, J = 8.9, 2.0 Hz), 7.44 (dd, 2H, J = 9.0, 2.1 Hz). FAB-MS *m/z*: 276 [M]$^+$, 277 [M + H]$^+$, 278 [M + 2]$^+$, 279 [M + 2 + H]$^+$.

2-Nitro-*N*-(2-trifluoromethylphenyl)benzamide (10i). According to the general procedure (GP-A), **10i** was obtained in 35% yield as a white powder after column chromatography (eluent: EtOAc/*n*-hexane = 1/3). Mp 178.0–181.0 °C. IR (KBr) cm^{-1}: 3222 (NH), 1655 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.50 (s, 1H), 8.19 (dd, 1H, J = 8.1, 1.2 Hz), 7.90 (t, 1H, J = 7.5 Hz), 7.82–7.75 (m, 3H), 7.68–7.52 (m, 3H). FAB-MS *m/z*: 311 [M + H]$^+$.

2-Nitro-*N*-(3-trifluoromethylphenyl)benzamide (10j). According to the general procedure (GP-A), **10j** was obtained in 98% yield as white plates after recrystallization from CH_2Cl_2/*n*-hexane. Mp 130.0–132.0 °C. IR (KBr) cm^{-1}: 3243 (NH), 1652 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.00 (s, 1H), 8.18 (dd, 1H, J = 8.1, 1.1 Hz), 8.16 (s, 1H), 7.93–7.76 (m, 4H), 7.62 (t, 1H, J = 8.0 Hz), 7.50 (d, 1H, J = 8.0 Hz). FAB-MS *m/z*: 311 [M + H]$^+$.

2-Nitro-*N*-(4-trifluoromethylphenyl)benzamide (10k). According to the general procedure (GP-A), **10k** was obtained in 76% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 183.0–185.0 °C. IR (KBr) cm^{-1}: 3281 (NH), 1658 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.00 (s, 1H), 8.19 (dt, 1H, J = 8.0, 1.0 Hz), 7.90–7.79 (m, 5H), 7.74 (d, J = 8.5 Hz, 2H). FAB-MS *m/z*: 311 [M + H]$^+$. Anal. ($C_{14}H_9F_3N_2O_3 \cdot {}^{1}/_{10}H_2O$) C, H, N.

3-Nitro-*N*-(2-trifluoromethylphenyl)benzamide (10l). According to the general procedure (GP-A), **10l** was obtained in 39% yield as white feathers after column chromatography (eluent: EtOAc/*n*-hexane = 1/3). Mp 140.0–141.5 °C. IR (KBr) cm^{-1}: 3268 (NH), 1651 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.59 (s, 1H), 8.78 (t, 1H, J = 2.0 Hz), 8.47 (dd, 1H, J = 8.0, 2.0 Hz), 8.38 (dd, 1H, J = 7.0, 2.0 Hz), 7.90–7.75 (m, 3H), 7.59 (t, 2H, J = 8.0 Hz). FAB-MS *m/z*: 311 [M + H]$^+$.

3-Nitro-*N*-(3-trifluoromethylphenyl)benzamide (10m). According to the general procedure (GP-A), **10m** was obtained in 92% yield as white feathers after recrystallization from EtOAc/*n*-hexane. Mp 135.0–135.5 °C. IR (KBr) cm^{-1}: 3283 (NH), 1656 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.87 (s, 1H), 8.83 (dd, 1H, J = 1.8, 0.7 Hz), 8.49–8.41 (m, 2H), 8.24 (s, 1H), 8.08 (d, 1H, J = 9.0 Hz), 7.87 (t, 1H, J = 8.0 Hz), 7.64 (t, 1H, J = 8.0 Hz). FAB-MS *m/z*: 311 [M + H]$^+$.

3-Nitro-*N*-(4-trifluoromethylphenyl)benzamide (10n). According to the general procedure (GP-A), **10n** was obtained in 90% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 210.0–212.0 °C. IR (KBr) cm^{-1}: 3314 (NH), 1658 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.90 (s, 1H), 8.80 (t, 1H, J = 2.0

Hz), 8.49–8.40 (m, 2H), 8.02 (d, 2H, *J* = 8.7 Hz), 7.87 (t, 1H, *J* = 8.0 Hz), 7.76 (d, 2H, *J* = 8.7 Hz). FAB-MS *m*/*z*: 311 $[M + H]^+$. Anal. ($C_{14}H_9F_3N_2O_3$) C, H, N.

4-Nitro-*N*-(2-trifluoromethylphenyl)benzamide (10o). According to the general procedure (GP-A), **10o** was obtained in 58% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 225.0–227.0 °C. IR (KBr) cm^{-1}: 3114 (NH), 1683 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.54 (s, 1H), 8.38 (d, 2H, *J* = 9.0 Hz), 8.24–8.15 (m, 4H), 8.17 (d, 2H, *J* = 9.0 Hz). FAB-MS *m*/*z*: 311 $[M + H]^+$.

4-Nitro-*N*-(3-trifluoromethylphenyl)benzamide (10p). According to the general procedure (GP-A), **10p** was obtained in 98% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 209.0–211.0 °C. IR (KBr) cm^{-1}: 3301 (NH), 1660 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.86 (s, 1H), 8.40 (dd, 2H, *J* = 7.0, 2.0 Hz), 8.25 (s, 1H), 8.21 (dd, 2H, *J* = 7.0, 2.0 Hz), 8.06 (d, 1H, *J* = 8.0 Hz), 7.64 (t, 1H, *J* = 8.0 Hz), 7.50 (d, 1H, *J* = 8.0 Hz). FAB-MS *m*/*z*: 311 $[M + H]^+$.

4-Nitro-*N*-(4-trifluoromethylphenyl)benzamide (10q). According to the general procedure (GP-A), **10q** was obtained in 71% yield as white needles after column chromatography (eluent: EtOAc/*n*-hexane = 1/4). Mp 216.0–217.0 °C. IR (KBr) cm^{-1}: 3416 (NH), 1669 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.90 (s, 1H), 8.40 (dd, 2H, *J* = 8.9, 2.0 Hz), 8.20 (dd, 2H, *J* = 8.9, 2.0 Hz), 8.02 (d, 2H, *J* = 8.6 Hz), 7.75 (d, 2H, *J* = 8.6 Hz). FAB-MS *m*/*z*: 311 $[M + H]^+$. Anal. ($C_{14}H_9F_3N_2O_3$) C, H, N.

4-Amino-*N*-(phenyl)benzamide (11a). According to the general procedure (GP-B-1), **11a** was obtained in 93% yield as white granules after recrystallization from EtOAc/*n*-hexane. Mp 136.0–138.0 °C. IR (KBr) cm^{-1}: 3488, 3394 (NH_2), 3350 (NH), 1647 (CO).^1H NMR (300 MHz, DMSO-d_6) δ: 9.80 (s, 1H), 7.74 (dd, 2H, *J* = 7.8, 1.9 Hz), 7.71 (dd, 2H, *J* = 8.7, 2.0 Hz), 7.30 (tt, 2H, *J* = 7.8, 2.0 Hz), 7.03 (tt, 1H, *J* = 7.8, 2.0 Hz), 6.59 (dd, 2H, *J* = 7.4, 2.0 Hz), 5.70 (s, 2H). FAB-MS *m*/*z*: 213 $[M + H]^+$. Anal. ($C_{13}H_{12}N_2O \cdot {}^1/_5H_2O$) C, H, N.

4-Amino-*N*-(4-chlorophenyl)benzamide (11b). According to the general procedure (GP-B-2), **11b** was obtained in 86% yield as white granules after recrystallization from EtOAc/*n*-hexane. Mp 197.0–198.0 °C. IR (KBr) cm^{-1}: 3412, 3330 (NH_2), 3223 (NH), 1651 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 9.87 (s, 1H), 7.79 (dd, 2H, *J* = 9.0, 2.1 Hz), 7.70 (dd, 2H, *J* = 8.7, 1.8 Hz), 7.35 (dd, 2H, *J* = 9.0, 2.1 Hz), 6.59 (dd, 2H, *J* = 8.7, 1.8 Hz), 5.78 (s, 2H). FAB-MS *m*/*z*: 246 $[M]^+$, 247 $[M + H]^+$, 248 $[M + 2]^+$, 249 $[M + 2 + H]^+$. Anal. ($C_{13}H_{11}ClN_2O \cdot {}^1/_9H_2O$) C, H, N.

4-Amino-*N*-(4-tolyl)benzamide (11c). According to the general procedure (GP-B-1), **11c** was obtained in 91% yield as a white powder after recrystallization from EtOAc/*n*-hexane. Mp 165.0–167.0 °C. IR (KBr) cm^{-1}: 3468, 3359 (NH_2), 3214 (NH), 1650 (CO).^1H NMR (300 MHz, DMSO-d_6) δ: 9.70 (s, 1H), 7.96 (d, 2H, *J* = 8.7 Hz), 7.61 (d, 2H, *J* = 8.0 Hz), 7.10 (d, 2H, *J* = 8.0 Hz), 6.58 (d, 2H, *J* = 8.7 Hz), 5.72 (s, 2H), 2.26 (s, 3H). FAB-MS *m*/*z*: 227 $[M + H]^+$. Anal. ($C_{14}H_{14}N_2O \cdot {}^1/_{10}H_2O$) C, H, N.

2-Amino-*N*-(2-tolyl)benzamide (11d). According to the general procedure (GP-B-1), **11d** was obtained in 87% yield as white plates after recrystallization from EtOAc/*n*-hexane. Mp 101.0–102.0 °C. IR (KBr) cm^{-1}: 3485, 3378 (NH_2), 3265 (NH), 1605 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 9.60 (s, 1H), 7.68 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.30–7.13 (m, 5H), 6.72 (dd, 1H, *J* = 8.0, 1.2 Hz), 6.56 (td, 1H, *J* = 8.0, 1.0 Hz), 6.37 (s, 2H), 2.20 (s, 3H). FAB-MS *m*/*z*: 226 $[M]^+$, 227 $[M + H]^+$. Anal. ($C_{14}H_{14}N_2O$) C, H, N.

2-Amino-*N*-(3-tolyl)benzamide (11e). According to the general procedure (GP-B-1), **11e** was obtained in 78% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 115.0–117.0 °C. IR (KBr) cm^{-1}: 3470, 3365 (NH_2), 3277 (NH), 1635 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 9.90 (s, 1H), 7.60 (td, 2H, *J* = 8.2, 1.5 Hz), 7.50 (d, 1H, *J* = 8.0 Hz), 7.22–7.16 (m, 2H), 6.90 (d, 1H, *J* = 8.0 Hz), 6.74 (dd, 1H, *J* = 8.0, 1.0 Hz), 6.57 (td, 1H, *J* = 8.0, 1.0 Hz), 6.30 (s, 2H), 2.30 (s, 3H). FAB-MS *m*/*z*: 226 $[M]^+$, 227 $[M + H]^+$. Anal. ($C_{14}H_{14}N_2O$) C, H, N.

2-Amino-*N*-(4-tolyl)benzamide (11f). According to the general procedure (GP-B-1), **11f** was obtained in 87% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 149.0–150.0 °C. IR (KBr) cm^{-1}: 3466, 3363 (NH_2), 3276 (NH), 1635 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 9.90 (s, 1H), 7.62–7.57 (m, 3H), 7.21–7.11 (m, 3H), 6.74 (dd, 1H, *J* = 8.2, 1.2 Hz), 6.58 (td, 1H, *J* = 8.2, 1.2 Hz), 6.30 (s, 2H), 2.27 (s, 3H). FAB-MS *m*/*z*: 226 $[M]^+$, 227 $[M + H]^+$. Anal. ($C_{14}H_{14}N_2O$) C, H, N.

2-Amino-*N*-(phenyl)benzamide (11g). According to the general procedure (GP-B-1), **11g** was obtained in 83% yield as white granules after recrystallization from EtOAc/*n*-hexane. Mp 128.0–129.5 °C. IR (KBr) cm^{-1}: 3470, 3420 (NH_2), 3364 (NH), 1600 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.00 (s, 1H), 7.70 (d, 2H, *J* = 8.0 Hz), 7.66 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.26 (t, 2H, *J* = 8.0 Hz), 7.24 (t, 1H, *J* = 8.0 Hz), 7.21 (t, 1H, *J* = 8.0 Hz), 6.75 (dd, 1H, *J* = 8.0, 1.2 Hz), 6.60 (t, 1H, *J* = 8.0 Hz), 6.37 (br s, 2H). FAB-MS *m*/*z*: 212 $[M]^+$, 213 $[M + H]^+$. Anal. ($C_{13}H_{12}N_2O$) C, H, N.

2-Amino-*N*-(4-chlorophenyl)benzamide (11h). According to the general procedure (GP-B-1), **11h** was obtained in 88% yield as a white powder after recrystallization from EtOAc/*n*-hexane. Mp 198.0–199.5 °C. IR (KBr) cm^{-1}: 3412, 3329 (NH_2), 3223 (NH), 1651 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 9.85 (s, 1H), 7.77 (dd, 2H, *J* = 8.9, 2.0 Hz), 7.72 (dd, 2H, *J* = 8.7, 2.0 Hz), 7.36 (dd, 2H, *J* = 8.9, 2.0 Hz), 6.59 (dd, 2H, *J* = 8.7, 2.0 Hz), 5.80 (s, 2H). FAB-MS *m*/*z*: 246 $[M]^+$, 247 $[M + H]^+$, 248 $[M + 2]^+$, 249 $[M + 2 + H]^+$. Anal. ($C_{13}H_{11}ClN_2O \cdot {}^1/_{12}H_2O$) C, H, N.

2-Amino-*N*-(2-trifluoromethylphenyl)benzamide (11i). According to the general procedure (GP-B-1), **11i** was obtained in 99% yield as a white solid after recrystallization from EtOAc/*n*-hexane. Mp 123.0–125.0 °C. IR (KBr) cm^{-1}: 3420, 3288 (NH_2), 3250 (NH), 1648 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 9.90 (s, 1H), 7.79–7.52 (m, 5H), 7.21 (td, 1H, *J* = 8.5, 1.0 Hz), 6.75 (dd, 1H, *J* = 8.5, 1.0 Hz), 6.58 (td, 1H, *J* = 8.5, 1.0 Hz), 6.40 (s, 2H). FAB-MS *m*/*z*: 280 $[M]^+$, 281 $[M + H]^+$. Anal. ($C_{14}H_{11}F_3N_2O$) C, H, N.

2-Amino-*N*-(3-trifluoromethylphenyl)benzamide (11j). According to the general procedure (GP-B-1), **11j** was obtained in 94% yield as brown plates after recrystallization from EtOAc/*n*-hexane. Mp 132.0–134.0 °C. IR (KBr) cm^{-1}: 3476, 3371 (NH_2), 3296 (NH), 1581 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.27 (s, 1H), 8.21 (s, 1H), 7.99 (d, 1H, *J* = 8.0 Hz), 7.63–7.22 (m, 4H), 6.77 (dd, 1H, *J* = 8.0, 1.0 Hz), 6.60 (m, 1H), 6.40 (s, 2H). FAB-MS *m*/*z*: 280 $[M]^+$, 281 $[M + H]^+$. Anal. ($C_{14}H_{11}F_3N_2O$) C, H, N.

2-Amino-*N*-(4-trifluoromethylphenyl)benzamide (11k). According to the general procedure (GP-B-1), **11k** was obtained in 90% yield as brown granules after recrystallization from EtOAc/*n*-hexane. Mp 160.0–162.0 °C. IR (KBr) cm^{-1}: 3464, 3360 (NH_2), 3297 (NH), 1641 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.30 (s, 1H), 7.95 (d, 2H, *J* = 8.5 Hz), 7.69 (d, 2H, *J* = 8.5 Hz), 7.64 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.22 (td, 1H, *J* = 8.0, 1.3 Hz), 6.76 (dd, 1H, *J* = 8.0, 1.3 Hz), 6.60 (td, 1H, *J* = 8.0, 1.3 Hz), 6.37 (s, 2H). FAB-MS *m*/*z*: 280 $[M]^+$, 281 $[M + H]^+$. Anal. ($C_{14}H_{11}F_3N_2O \cdot {}^1/_{10}H_2O$) C, H, N.

3-Amino-*N*-(2-trifluoromethylphenyl)benzamide (11l). According to the general procedure (GP-B-1), **11l** was obtained in 60% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 83.0–85.0 °C. IR (KBr) cm^{-1}: 3449, 3358 (NH_2), 3225 (NH), 1648 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 9.90 (s, 1H), 8.33 (s, 1H), 8.30 (d, 1H, *J* = 8.0 Hz), 7.95 (d, 1H, *J* = 7.5 Hz), 7.76 (t, 1H, *J* = 8.0 Hz), 7.14 (d, 1H, *J* = 7.5 Hz), 6.99 (td, 1H, *J* = 7.5, 1.4 Hz), 6.79 (dd, 1H, *J* = 7.5, 1.3 Hz), 6.60 (t, 1H, *J* = 7.5 Hz), 4.97 (s, 2H). FAB-MS *m*/*z*: 289 $[M + H]^+$. Anal. ($C_{14}H_{11}F_3N_2O \cdot {}^1/_{20}H_2O$) C, H, N.

3-Amino-*N*-(3-trifluoromethylphenyl)benzamide (11m). According to the general procedure (GP-B-1), **11m** was obtained in 98% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 83.0–84.0 °C. IR (KBr) cm^{-1}: 3384, 3277 (NH_2), 3083 (NH), 1653 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.38 (s, 1H), 8.24 (s, 1H), 8.03 (d, 1H, *J* = 8.5 Hz), 7.57 (t, 1H, *J* = 8.0 Hz), 7.42 (d, 1H, *J* = 8.0 Hz), 7.17 (t, 1H, *J* = 8.0 Hz), 7.10–7.06 (m, 2H), 6.77 (dd, 1H, *J* = 8.0, 1.5 Hz), 5.36 (s, 2H). FAB-MS *m*/*z*: 280 $[M]^+$, 281 $[M + H]^+$. Anal. ($C_{14}H_{11}F_3N_2O \cdot {}^1/_{10}H_2O$) C, H, N.

3-Amino-*N*-(4-trifluoromethylphenyl)benzamide (11n). According to the general procedure (GP-B-1), **11n** was obtained in 89% yield as white plates after recrystallization from EtOAc/*n*-hexane. Mp 213.0–216.0 °C. IR (KBr) cm^{-1}: 3475, 3334 (NH$_2$), 3222 (NH), 1659 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.20 (s, 1H), 8.00 (d, 2H, J = 8.5 Hz), 7.70 (d, 2H, J = 8.5 Hz), 7.17 (t, 1H, J = 8.0 Hz), 7.10–7.05 (m, 2H), 6.77 (dd, 1H, J = 8.0, 1.5 Hz), 5.40 (s, 2H). FAB-MS *m*/*z*: 280 [M]$^+$, 281 [M + H]$^+$. Anal. ($C_{14}H_{11}F_3N_2O \cdot {}^1/_7H_2O$) C, H, N.

4-Amino-*N*-(2-trifluoromethylphenyl)benzamide (11o). According to the general procedure (GP-B-1), **11o** was obtained in 95% yield as white powder after recrystallization from EtOAc/*n*-hexane. Mp 185.0–187.0 °C. IR (KBr) cm^{-1}: 3484, 3377 (NH$_2$), 3228 (NH), 1624 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 9.50 (s, 1H), 7.82 (d, 1H, J = 7.5 Hz), 7.67 (t, 1H, J = 7.5 Hz), 7.54 (t, 1H, J = 7.5 Hz), 7.33 (dd, 2H, J = 8.5, 1.8 Hz), 7.29 (d, 1H, J = 7.5 Hz), 6.39 (d, 2H, J = 8.5, 1.8 Hz), 5.94 (s, 2H). FAB-MS *m*/*z*: 280 [M]$^+$, 281 [M + H]$^+$. Anal. ($C_{14}H_{11}F_3N_2O$) C, H, N.

4-Amino-*N*-(3-trifluoromethylphenyl)benzamide (11p). According to the general procedure (GP-B-1), **11p** was obtained in 79% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 123.0–124.0 °C. IR (KBr) cm^{-1}: 3350, 3317 (NH$_2$), 3216 (NH), 1654 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.05 (s, 1H), 8.24 (s, 1H), 8.02 (d, 1H, J = 9.0 Hz), 7.73 (dd, 2H, J = 8.5, 1.8 Hz), 7.54 (t, 1H, J = 8.0 Hz), 7.37 (d, 1H, J = 9.0 Hz), 6.61 (dd, 2H, J = 8.5, 1.8 Hz), 5.82 (s, 2H). FAB-MS *m*/*z*: 280 [M]$^+$, 281 [M + H]$^+$. Anal. ($C_{14}H_{11}F_3N_2O$) C, H, N.

4-Amino-*N*-(4-trifluoromethylphenyl)benzamide (11q). According to the general procedure (GP-B-1), **11q** was obtained in 99% yield as white granules after recrystallization from EtOAc/*n*-hexane. Mp 232.0–233.0 °C. IR (KBr) cm^{-1}: 3509, 3418 (NH$_2$), 3343 (NH), 1657 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.10 (s, 1H), 7.98 (d, 2H, J = 8.5 Hz), 7.73 (dd, 2H, J = 8.7, 2.0 Hz), 7.66 (d, 2H, J = 8.5 Hz), 6.63 (dd, 2H, J = 8.7, 2.0 Hz), 5.80 (s, 2H). FAB-MS *m*/*z*: 281 [M + H]$^+$. Anal. ($C_{14}H_{11}F_3N_2O \cdot {}^1/_5H_2O$) C, H, N.

***N*-Ethyl-2-nitro-*N*-(phenyl)benzamide (12a).** According to the general procedure (GP-C), **12a** was obtained in 92% yield as white plates after column chromatography (eluent: EtOAc/*n*-hexane = 1/2). Mp 85.5–88.5 °C. IR (KBr) cm^{-1}: 1635 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.95 (dd, 1H, J = 8.0, 1.0 Hz), 7.57 (td, 1H, J = 8.0, 1.0 Hz), 7.70 (td, 1H, J = 8.0, 1.0 Hz), 7.39 (dd, 1H, J = 8.0, 1.0 Hz), 7.32–7.20 (m, 5H), 4.03 (q, 2H, J = 7.0 Hz), 3.90 (t, 3H, J = 7.0 Hz). FAB-MS *m*/*z*: 271 [M + H]$^+$.

***N*-(4-Chlorophenyl)-*N*-ethyl-2-nitrobenzamide (12b).** According to the general procedure (GP-C), **12b** was obtained in 80% yield as white needles after column chromatography (eluent: EtOAc/*n*-hexane = 1/3). Mp 90.0–91.5 °C. IR (KBr) cm^{-1}: 1650 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.09 (d, 2H, J = 8.5 Hz), 7.53 (d, 2H, J = 8.5 Hz), 7.36 (d, 2H, J = 8.5 Hz), 7.27 (d, 2H, J = 8.5 Hz), 3.87 (q, 2H, J = 7.0 Hz), 1.10 (t, 3H, J = 7.0 Hz). FAB-MS *m*/*z*: 305 [M + H]$^+$.

2-Amino-*N*-ethyl-*N*-phenylbenzamide (13a). According to the general procedure (GP-B-1), **13a** was obtained in 84% yield as white needles after column chromatography (eluent: EtOAc/*n*-hexane = 1/3). Mp 101.0–102.5 °C. IR (KBr) cm^{-1}: 3443, 3394 (NH$_2$), 3316 (NH), 1620 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.26–7.10 (m, 5H), 6.80 (td, 1H, J = 8.0, 1.5 Hz), 6.70 (dd, 1H, J = 8.0, 1.5 Hz), 6.59 (dd, 1H, J = 8.0, 1.5 Hz), 6.20 (td, 1H, J = 7.4, 1.5 Hz), 5.30 (s, 2H), 3.93 (q, 2H, J = 7.0 Hz), 1.15 (t, 3H, J = 7.0 Hz). FAB-MS *m*/*z*: 240 [M]$^+$, 241 [M + H]$^+$. Anal. ($C_{15}H_{16}N_2O$) C, H, N.

2-Amino-*N*-(4-chlorophenyl)-*N*-ethylbenzamide (13b). According to the general procedure (GP-B-1), **13b** was obtained in 95% yield as white feathers after recrystallization from EtOAc/*n*-hexane. Mp 165.0–166.5 °C. IR (KBr) cm^{-1}: 3455, 3348 (NH$_2$), 1631 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.33 (dd, 2H, J = 8.7, 2.0 Hz), 7.09 (dd, 2H, J = 8.7, 2.0 Hz), 6.94 (dd, 2H, J = 8.4, 1.8 Hz), 6.33 (dd, 2H, J = 8.4, 1.8 Hz), 5.48 (s, 2H), 3.80 (q, 2H, J = 7.0 Hz), 1.05 (t, 3H, J = 7.0 Hz). FAB-MS *m*/*z*: 274 [M]$^+$, 275 [M + H]$^+$, 276 [M + 2]$^+$, 277 [M + 2 + H]$^+$. Anal. ($C_{15}H_{15}ClN_2O$) C, H, N.

3-Trifluoromethylbenzamide (14a). According to the general procedure (GP-D), **14a** was obtained in 85% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 120.0–121.5 °C. IR (KBr) cm^{-1}: 3190, 3185 (NH$_2$), 1678 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.19 (s, 2H), 8.16 (d, 1H, J = 8.0 Hz), 7.88 (d, 1H, J = 8.0 Hz), 7.70 (t, 1H, J = 8.0 Hz), 7.58 (s, 1H). FAB-MS *m*/*z*: 190 [M + H]$^+$.

4-Trifluoromethylbenzamide (14b). According to the general procedure (GP-D), **14b** was obtained in 92% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 185.0–187.0 °C. IR (KBr) cm^{-1}: 3369, 3171 (NH$_2$), 1658 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.19 (s, 1H), 8.06 (d, 2H, J = 8.3 Hz), 7.84 (d, 2H, J = 8.3 Hz), 7.67 (s, 1H). FAB-MS *m*/*z*: 190 [M + H]$^+$.

4-Nitrobenzamide (15). Nitrobenzoyl chloride (3.0 mmol) was added to aqueous NH$_3$ (4.5 mL). The mixture was stirred at room temperature for 30 min, then extracted with EtOAc. The organic layer was washed with H$_2$O and brine and dried over MgSO$_4$. The solvent was removed under reduced pressure. The residue was purified by recrystallization (EtOAc/*n*-hexane) to yield **15** (81%) as white needles. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.30 (dd, 2H, J = 9.1, 2.1 Hz), 8.2 (s, 1H), 8.09 (dd, 2H, J = 9.1, 2.1 Hz), 7.75 (s, 1H).

***N*-(3-Nitro-2-pyridinyl)-3-trifluoromethylbenzamide (16a).** According to the general procedure (GP-E), **16a** was obtained in 48% yield as a yellow oil after column chromatography (eluent: EtOAc/*n*-hexane = 1/2). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.86 (s, 1H), 8.78 (dd, 1H, J = 4.8, 1.5 Hz), 8.47 (dd, 1H, J = 8.0, 1.5 Hz), 8.37 (s, 1H,), 8.29 (d, 1H, J = 8.0 Hz), 8.03 (d, 1H, J = 8.0 Hz), 7.81 (t, 1H, J = 8.0 Hz), 7.53 (dd, 1H, J = 8.0, 4.8 Hz). FAB-MS *m*/*z*: 312 [M + H]$^+$.

***N*-(4-Nitro-2-pyridinyl)-3-trifluoromethylbenzamide (16b).** According to the general procedure (GP-E), **16b** was obtained in 55% yield as a white powder after column chromatography (eluent: EtOAc/*n*-hexane = 1/8). Mp 140.0–142.0 °C. IR (KBr) cm^{-1}: 3301 (NH), 1662 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.78 (s, 1H), 8.94 (d, 1H, J = 2.1 Hz), 8.77 (d, 1H, J = 5.0 Hz), 8.42 (s, 1H), 8.33 (d, 1H, J = 8.0 Hz), 8.01 (d, 1H, J = 8.0 Hz), 7.90 (dd, 1H, J = 8.0, 2.1 Hz), 7.79 (t, 1H, J = 8.0 Hz). FAB-MS *m*/*z*: 312 [M + H]$^+$.

***N*-(5-Nitro-2-pyridinyl)-3-trifluoromethylbenzamide (16c).** According to the general procedure (GP-E), **16c** was obtained in 84% yield as a yellow powder after column chromatography (eluent: EtOAc/*n*-hexane = 1/5). Mp 145.0–147.0 °C. IR (KBr) cm^{-1}: 3373 (NH), 1693 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.86 (s, 1H), 9.26 (dd, 1H, J = 2.7, 0.7 Hz), 8.67 (dd, 1H, J = 9.0, 2.7 Hz), 8.43 (d, 1H, J = 9.0, 0.7 Hz), 8.40 (s, 1H), 8.32 (d, 1H, J = 8.0 Hz), 8.00 (d, 1H, J = 8.0 Hz), 7.79 (t, 1H, J = 8.0 Hz). FAB-MS *m*/*z*: 312 [M + H]$^+$.

***N*-(3-Nitro-2-pyridinyl)-4-trifluoromethylbenzamide (16d).** According to the general procedure (GP-E), **16d** was obtained in 59% yield as white feathers after column chromatography (eluent: EtOAc/*n*-hexane = 1/2). Mp 184.0–185.0 °C. IR (KBr) cm^{-1}: 3282 (NH), 1671 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.81 (s, 1H), 8.77 (dd, 1H, J = 4.8, 1.7 Hz), 8.46 (dd, 1H, J = 8.0, 1.7 Hz), 8.20 (d, 2H, J = 8.0 Hz), 7.93 (d, 2H, J = 8.0 Hz), 7.56 (dd, 1H, J = 8.0, 4.8 Hz). FAB-MS *m*/*z*: 312 [M + H]$^+$.

***N*-(4-Nitro-2-pyridinyl)-4-trifluoromethylbenzamide (16e).** According to the general procedure (GP-E), **16e** was obtained in 48% yield as colorless granules after column chromatography (eluent: EtOAc/*n*-hexane = 1/3). Mp 207.0–208.0 °C. IR (KBr) cm^{-1}: 3281 (NH), 1671 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.71 (s, 1H), 8.94 (dd, 1H, J = 2.1, 0.7 Hz), 8.77 (dd, 1H, J = 5.5, 0.7 Hz), 8.23 (d, 2H, J = 8.0 Hz), 7.93–7.90 (m, 3H). FAB-MS *m*/*z*: 312 [M + H]$^+$.

***N*-(5-Nitro-2-pyridinyl)-4-trifluoromethylbenzamide (16f).** According to the general procedure (GP-E), **16f** was obtained in 92% yield as yellow needles after column chromatography (eluent: EtOAc/*n*-hexane = 1/2). Mp 115.0–116.0 °C. IR (KBr) cm^{-1}: 3327 (NH), 1646 (CO). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.82 (s, 1H), 9.25 (dd, 1H, J = 2.8, 0.7 Hz), 8.69 (dd, 1H, J = 9.3, 2.8 Hz), 8.45 (dd, 1H, J = 9.3, 0.7 Hz), 8.22 (d, 2H, J = 8.0 Hz), 7.91 (d, 2H, J = 8.0 Hz). FAB-MS m/z: 312 $[M + H]^+$.

4-Nitro-*N*-(5-trifluoromethyl-2-pyridinyl)benzamide (17). To a solution of **15** (2.8 mmol) in dioxane (20.0 mL) were added 2-chloro-5-triflyoromethylpyridine (2.8 mmol), cesium carbonate (3.1 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (0.1 mmol), and tris(dibenzylideneacetone)dipalladium (0.03 mmol). The mixture was stirred at reflux overnight, then filtered through a pad of Celite, and the filtrate was extracted with EtOAc (50 mL × 3). The organic layer was collected, washed with H_2O (50 mL × 2) and brine (50 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/*n*-hexane = 1/8) to yield **17** (69%) as a white powder. ^1H NMR (300 MHz, DMSO-d_6) δ: 11.66 (s, 1H), 8.81 (dd, 1H, J = 1.7, 0.8 Hz), 8.42 (d, 1H, J = 8.7 Hz), 8.35 (dd, 2H, J = 9.0, 2.1 Hz), 8.28 (dd, 1H, J = 8.7, 1.7 Hz), 8.24 (dd, 2H, J = 9.0, 2.1 Hz).

***N*-(3-Amino-2-pyridinyl)-3-trifluoromethylbenzamide (18a).** According to the general procedure (GP-B-1), **18a** was obtained in 86% yield as a white powder after recrystallization from EtOAc/*n*-hexane. Mp 187.0–189.5 °C. IR (KBr) cm^{-1}: 3320, 3298 (NH_2), 3200 (NH), 1643 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.59 (s, 1H), 8.36 (s, 1H), 8.30 (d, 1H, J = 7.0 Hz), 7.94 (d, 1H, J = 8.0 Hz), 7.76 (t, 1H, J = 8.0 Hz), 7.72 (s, 1H), 7.17–7.09 (m, 2H), 5.07 (s, 2H). FAB-MS m/z: 281 $[M]^+$, 282 $[M + H]^+$. Anal. ($C_{13}H_{10}F_3N_3O$) C, H, N.

***N*-(4-Amino-2-pyridinyl)-3-trifluoromethylbenzamide (18b).** According to the general procedure (GP-B-1), **18b** was obtained in 85% yield as white needles after recrystallization from EtOAc/*n*-hexane. Mp 179.0–182.0 °C. IR (KBr) cm^{-1}: 3498, 3337 (NH_2), 3220 (NH), 1660 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.63 (s, 1H), 8.32 (s, 1H), 8.27 (d, 1H, J = 8.0 Hz), 7.93 (d, 1H, J = 8.0 Hz), 7.80 (d, 1H, J = 5.5 Hz), 7.73 (t, 1H, J = 8.0 Hz), 7.41 (s, 1H), 6.30 (dd, 1H, J = 8.0, 2.0 Hz), 6.16 (s, 1H). FAB-MS m/z: 282 $[M + H]^+$. Anal. ($C_{13}H_{10}F_3N_3O \cdot {}^2/_3H_2O$) C, H, N.

***N*-(5-Amino-2-pyridinyl)-3-trifluoromethylbenzamide (18c).** According to the general procedure (GP-B-1), **18c** was obtained in 92% yield as a yellow powder after recrystallization from EtOAc/*n*-hexane. Mp 115.0–117.0 °C. IR (KBr) cm^{-1}: 3383, 3314(NH_2), 3197 (NH), 1671 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.77 (s, 1H), 8.35 (s, 1H), 8.29 (d, 1H, J = 7.8 Hz), 7.90 (d, 1H, J = 7.8 Hz), 7.83 (d, 1H, J = 8.8 Hz), 7.73 (d, 1H, J = 2.5 Hz), 7.73 (t, 1H, J = 8.0 Hz), 7.18 (dd, 1H, J = 8.0, 2.5 Hz), 5.30 (s, 2H). FAB-MS m/z: 281 $[M]^+$, 282 $[M + H]^+$. Anal. ($C_{13}H_{10}F_3N_3O$) C, H, N.

***N*-(3-Amino-2-pyridinyl)-4-trifluoromethylbenzamide (18d).** According to the general procedure (GP-B-1), **18d** was obtained in 91% yield as white granules after recrystallization from EtOAc/*n*-hexane. Mp 207.0–208.0 °C. IR (KBr) cm^{-1}: 3350, 3296 (NH_2), 3200 (NH), 1653 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.57 (s, 1H), 8.20 (d, 2H, J = 8.0 Hz), 7.89 (d, 2H, J = 8.0 Hz), 7.72 (br s, 1H), 7.16–7.08 (m, 2H), 5.10 (s, 2H). FAB-MS m/z: 282 $[M + H]^+$. Anal. ($C_{13}H_{10}F_3N_3O \cdot {}^1/_5H_2O$) C, H, N.

***N*-(4-Amino-2-pyridinyl)-4-trifluoromethylbenzamide (18e).** According to the general procedure (GP-B-1), **18e** was obtained in 91% yield as white granules after recrystallization from EtOAc/*n*-hexane. Mp 221.0–223.0 °C. IR (KBr) cm^{-1}: 3499, 3336 (NH_2), 3222 (NH), 1658 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.53 (s, 1H), 8.15 (d, 2H, J = 8.0 Hz), 7.85 (d, 2H, J = 8.0 Hz), 7.80 (d, 1H, J = 6.0 Hz), 7.43 (d, 1H, J = 2.0 Hz), 6.30 (dd, 1H, J = 6.0, 2.0 Hz), 6.17 (s, 2H). FAB-MS m/z: 282 $[M + H]^+$. Anal. ($C_{13}H_{10}F_3N_3O$) C, H, N.

***N*-(5-Amino-2-pyridinyl)-4-trifluoromethylbenzamide (18f, TFAP).** According to the general procedure (GP-B-1), **18f** was obtained in 91% yield as light-brown plates after recrystallization from EtOAc/*n*-hexane. Mp 140.5–141.5 °C. IR (KBr) cm^{-1}: 3353, 3194 (NH_2), 3060 (NH), 1658 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.62 (s, 1H), 8.16 (d, 2H, J = 8.5 Hz), 7.84 (d, 2H, J = 8.5 Hz), 7.81 (s, 1H), 7.75 (dd, 1H, J = 2.9, 0.7 Hz), 7.03 (dd, 1H, J = 9.0, 0.7 Hz), 5.22 (s, 2H). FAB-MS m/z: 282 $[M + H]^+$. Anal. ($C_{13}H_{10}F_3N_3O$) C, H, N.

4-Amino-*N*-(5-trifluoromethyl-2-pyridinyl)benzamide (19). According to the general procedure (GP-B-1), **19** was obtained in 94% yield as light-brown plates after recrystallization from CH_2Cl_2/*n*-hexane. Mp 167.5–169.0 °C. IR (KBr) cm^{-1}: 3491, 3377 (NH_2), 3301 (NH), 1669 (CO). ^1H NMR (300 MHz, DMSO-d_6) δ: 10.68 (s, 1H), 8.71 (d, 1H, J = 1.0 Hz), 8.38 (d, 1H, J = 8.8 Hz), 8.17 (dd, 1H, J = 8.8, 1.9 Hz), 7.81 (d, 2H, J = 8.7 Hz), 6.58 (d, 1H, J = 8.7 Hz), 5.91 (s, 2H). FAB-MS m/z: 282 $[M + H]^+$. Anal. ($C_{13}H_{10}F_3N_3O$) C, H, N.

2-Cyano-5-nitropyridine (20). To a mixture of sodium cyanide (4.9 mmol) and copper cyanide (7.3 mmol) was added DMF (7.5 mL) at room temperature with stirring. The mixture was heated to 150 °C. 2-Bromo-5-nitropyridine (0.7 mmol) was dissolved in DMF (2.5 mmol) with warming to 150 °C, and this temperature of the solution was maintained throughout the addition. The reaction mixture was heated under reflux for 1.5 h. The reaction mixture was poured into aqueous 1 M potassium phosphate (monobasic) solution (10 mL) and extracted with EtOAc (50 mL × 3). The organic layer was collected, washed with H_2O (50 mL × 2) and brine (50 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/*n*-hexene = 1/7) to yield **20** (85%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ: 9.54 (dd, 1H, J = 2.5, 0.7 Hz), 8.68 (dd, 1H, J = 8.4, 2.5 Hz), 7.98 (dd, 1H, J = 8.4, 0.7 Hz).

5-Nitro-*N*-(4-trifluoromethylphenyl)-2-pyridinecarboxamide (21). A solution of **20** (1.7 mmol) and 10 N HCl (3 mL) was heated under reflux for 20 h. The solvent was evaporated under reduced pressure. To a mixture of the residue, 4-aminobenzotrifluororide (0.7 mmol), EDC (0.7 mmol), and HOBt (0.7 mmol) was added DMF (3 mL). The mixture was stirred at room temperature for 24 h. The reaction mixture was poured into H_2O (30 mL) and extracted with EtOAc (10 mL × 3). The organic layer was collected, washed with H_2O (10 mL × 2) and brine (20 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/*n*-hexene = 1/5) to yield **21** (21%) as a white powder. ^1H NMR (300 MHz, $CDCl_3$) δ: 10.04 (s, 1H), 9.46 (dd, 1H, J = 2.5, 0.7 Hz), 8.74 (dd, 1H, J = 8.6, 2.5 Hz), 8.54 (dd, 1H, J = 8.6, 0.7 Hz), 7.92 (d, 2H, J = 8.4 Hz), 7.68 (d, 2H, J = 8.4 Hz).

5-Amino-*N*-(4-trifluoromethylphenyl)-2-pyridinecarboxamide (22). According to the general procedure (GP-B-1), **22** was obtained in 64% yield as a white powder after recrystallization from CH_2Cl_2/*n*-hexane. Mp 155.0–156.0 °C. IR (KBr) cm^{-1}: 3473, 3340(NH_2), 3236 (NH), 1676 (CO). ^1H NMR (300 MHz, $CDCl_3$) δ: 8.01 (dd, 1H, J = 2.8, 0.7 Hz), 7.88 (d, 2H, J = 8.5 Hz), 7.62 (d, 2H, J = 8.5 Hz), 7.09 (dd, 1H, J = 8.5, 2.8 Hz), 4.13 (s, 2H). FAB-MS m/z: 282 $[M + H]^+$. Anal. ($C_{13}H_{10}F_3N_3O \cdot {}^1/_5H_2O$) C, H, N.

In Vitro COX Assay. The in vitro biological activity of the compounds was assessed with a colorimetric COX (ovine) inhibitory screening assay kit (Cayman Chemical, catalog no. 760111) according to the supplier's protocol. Each experiment was performed at least four times, and the mean value was calculated. The results are shown as the mean ± SEM.

Molecular Docking Study.[26] The docking program used was AutoDock 3.05 developed by Morris et al.[26] The 3D coordinate structure of COX-1 (1PGF) was retrieved from the Brookhaven Protein Data Bank, URL http://www.rcsb.org/pdb/Welcome.do, and water molecules and ions were removed before the docking.

Animals. Male ICR mice and male SD rats, weighing 15–30 and 170–200 g, respectively, were obtained from Charles River Laboratories Japan, Inc. Only water was provided ad libitum during the 12 h before experimentation. The study was conducted according to internationally accepted principles of laboratory animal use.

Gastric Damage Scoring.[8] A 0.5% CMC (carboxymethyl cellulose) vehicle (1% ethanol in distilled water), **1** (10 mg/kg), **18f** (300 mg/kg), and **6** (30 mg/kg) were orally administered to the rats ($n = 4$) at a volume of 5 mL/kg, respectively. Five hours later, the rats were anesthetized with diethyl ether. The stomach of each rat was taken out and viewed using a stereoscopic microscope. The stomach damage images were captured by using a CCD camera (Monicam2000, Motic China Group), and hemorrhagic damage was analyzed using Motic Images Plus 2.0S software. The damage scoring was performed by measuring the lengths of the ulcers in millimeters, and the sum of the damage values gave an overall gastric damage score for each rat.

Writhing Test.[14] Groups of mice ($n = 9$–11) were treated po with a solution of **1**, **18f**, or **6** at a dose of 10 or 30 mg/kg or with solvent (1% ethanol and 0.5% CMC in distilled water) at a volume of 30 mL/kg of animal. Muscular contraction was induced by ip administration of 0.7% acetic acid at a volume of 10 mL/kg for 30 min after the treatment. The number of muscular contractions (writhes) was counted starting at 10 min after injection for a period of 10 min. Data represent the average of the total numbers of writhes observed.

Formalin-Induced Pain Test.[14] Groups of rats ($n = 8$) were treated powith a solution of **1** at 10 mg/kg, **18f** or **6** at 30 mg/kg, or solvent (1% ethanol and 0.5% CMC in distilled water) at a volume of 5 mL/kg 2 h before formalin injection. For formalin injection, the animals were gently restricted, and 0.1 mL of 5% formalin was injected subcutaneously into the plantar surface of the right hind paw. Time zero of the study was defined as the time of formalin injection. Immediately after injection, each animal was placed in an open Plexiglass box, which permitted observation. Reaction to pain was quantified by counting the number of bites, licks, flinches, and shakes of the injected paw. Animals were observed for 60 min.

Statistical Analysis. Comparisons among groups of data were performed using a one-way analysis of variance followed by Dunnett's multiple comparison test. An associated probability (p value) of <0.05 was considered to be significant.

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Supporting Information Available: Combustion analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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