Synthesis and Biological Activity of *N*-(Aminoiminomethyl)-1*H*-indole Carboxamide Derivatives as Na^+/H^+ Exchanger Inhibitors

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A series of *N*-(aminoiminomethyl)-1*H*-indole carboxamide derivatives were synthesized and their inhibitory potencies against the Na^+/H^+ exchanger were measured. Variation of the carbonylguanidine group at the 2- to 7-position of the indole ring system showed that a substitution at the 2-position improved the Na^+/H^+ exchanger inhibitory activity the most *in vitro*. This led to the synthesis and evaluation of an extensive series of *N*-(aminoiminomethyl)-1*H*-indole-2-carboxamide derivatives. Derivatives having an alkyl or substituted alkyl group at the 1-position of the indole ring system showed higher levels of *in vitro* activities. *N*-(aminoiminomethyl)-1-(2-phenylethyl)-1*H*-indole-2-carboxamide (49) had the strongest activity.

Key words Na^+/H^+ exchanger inhibitor; synthesis; biological activity; *N*-(aminoiminomethyl)-1*H*-indole carboxamide derivative

The Na^+/H^+ exchanger, one of the plasma membrane ion transporters, regulates the intracellular pH by extrusion of H^+ and concomitant influx of Na^+ into the cell.[1] It has been suggested that stimulation of the Na^+/H^+ exchanger in cardiac ischemia followed by reperfusion induces postischemic cardiac injury, because activation of this exchanger may result in increased Na^+ influx followed by Ca^{2+} overload *via* the Na^+/Ca^{2+} exchanger.[1] In addition, it has been noted that the stimulation of the Na^+/H^+ exchanger plays an important role in several diseases such as hypertension,[2] neointimal formation[3] and nephropathy.[4] In fact, since a report that inhibition of the Na^+/H^+ exchanger was effective in cardiac ischemic-reperfusion injury,[5—10] Na^+/H^+ exchanger inhibitors have attracted much attention. An example of a Na^+/H^+ exchanger inhibitor is amiloride (Fig. 1), a potent diuretic. Extensive studies on amiloride derivatives by the Merck group[11] led to the discovery of potent inhibitors such as ethyl isopropyl amiloride (EIPA; Fig. 1). Recently, it has been reported that a benzoylguanidine derivative (Hoe642; Fig. 1) is capable of inhibiting the Na^+/H^+ exchanger and affects cardiac ischemia-reperfusion.[12] These derivatives have a characteristic monocyclic aroylguanidine structure. First, we studied various aroylguanidine derivatives, such as monocyclic, bicyclic and tricyclic aroylguanidine derivatives, with the aim of finding new lead compounds as potent and selective Na^+/H^+ exchanger inhibitors, and have identified some bicyclic aroylguanidine derivatives as such inhibitors. Notably, we have discovered indole ring-fused aroylguanidine derivatives (*e.g.*, *N*-(aminoiminomethyl)-1-methyl-1*H*-indole carboxamide (**24**), to be potent Na^+/H^+ exchanger inhibitors.[13] There are known bicyclic aroylguanidine compounds such as naphthyl, benzofuryl and quinolyl carbonylguanidine. However, the indolyl carbonylguanidine types were new compounds. Thus we focused on the indolyl carbonylguanidine derivatives to investigate the relationship between structure and Na^+/H^+ exchanger inhibitory activity using these indole derivatives. In the present report, we describe the synthesis of *N*-(aminoiminomethyl)-1*H*-indole carboxamide derivatives and their Na^+/H^+ exchanger inhibitory activities in an *in vitro* system.

Chemistry

The general synthetic pathways for the preparation of 1*H*-indole carboxylic acid derivatives, which are key intermediates, are shown in Charts 1—5. Methyl 1*H*-indole carboxylates **2a**—**2d** were synthesized by esterification of the corresponding 1*H*-indole carboxylic acid **1a**—**1d** with the $SOCl_2$/MeOH or HCl/MeOH systems (Chart 1). Methyl 1*H*-indole-6-carboxylate (**2e**) was prepared by the method of Tischler and Lanza.[14] N-Alkylation and esterification by one-pot reaction of the carboxylic acid **1a**—**1d** with alkyl halides was carried out using NaH as a base in *N*,*N*-dimethylformamide (DMF) to give the *N*-alkylated ester **3a**—**3d**. Isopropyl derivative **7a** and benzyl derivative **7b** could be prepared from 1*H*-indole-5-carboxylic acid (**1d**) employing the same protocol. N-Alkylation of the methyl 1*H*-indole carboxylate **2** with alkyl halides was also carried out using NaH as a base in DMF to give the *N*-alkylated compounds (**3e**, **4**—**6**). Methyl 1-methyl-1*H*-indole-7-carboxylate (**12**) was synthesized as shown in Chart 2. N-Methylation and esterification of 1*H*-indole-7-carboxylic acid[15] by the same synthetic method used for **3a**—**3d** gave a mixture of desired ester **12** and methyl 1, 3-dimethyl 1*H*-indole-7-carboxylate (1 : 1 mixture), which were not easily separated by chromatography. Then the desired compound **12** was synthesized as follows. Ethyl 7-carbomethoxy 1*H*-indole-2-carboxylate (**9**) was prepared from methyl anthranylate as a starting material using the modified Fischer indole synthetic method.[16] N-Methylation of **9** gave

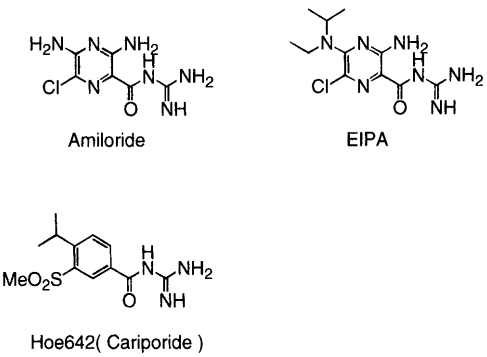

Fig. 1

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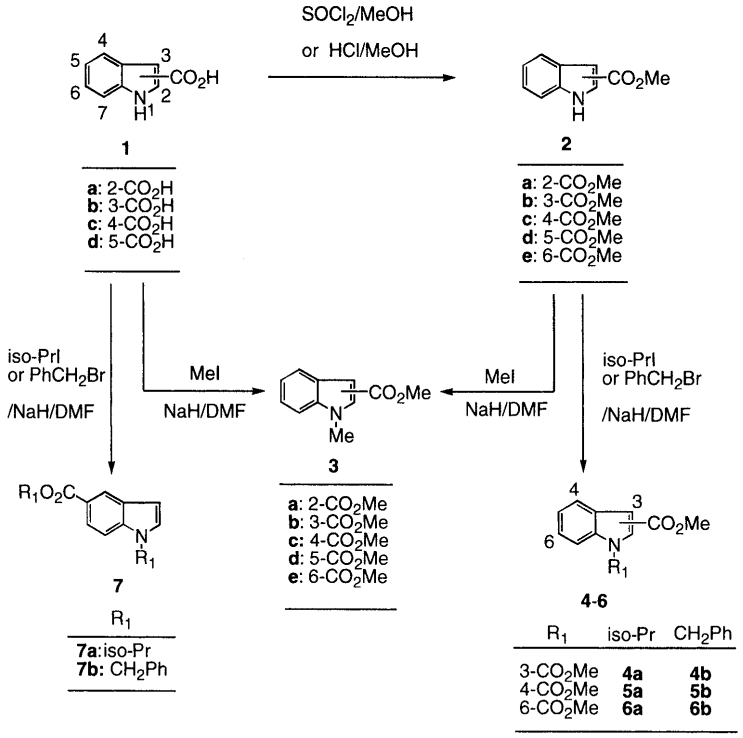
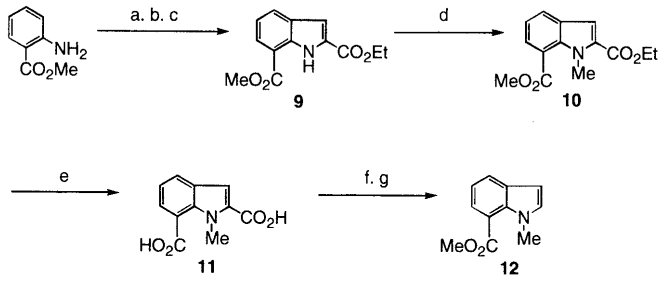
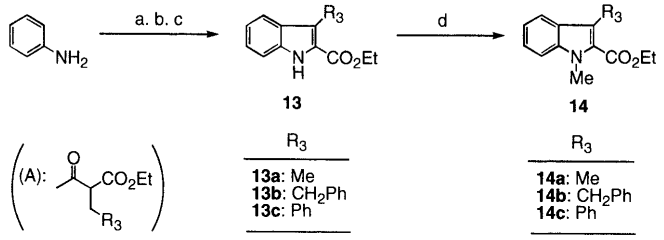


Chart 1



(a) $NaNO_2$/c.HCl; (b) Ethyl 2-methylacetoacetate/KOH/EtOH–H_2O; (c) PPA; (d) MeI/NaH/DMF; (e) KOH/EtOH–H_2O; (f) CuO/quinoline; (g) $SOCl_2$/MeOH.

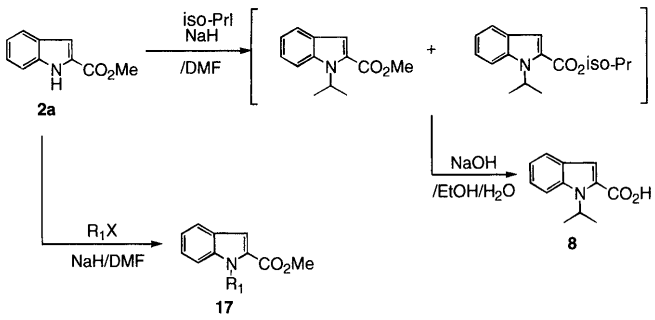
Chart 2



(a) $NaNO_2$/c.HCl; (b) (A)/KOH/EtOH–H_2O; (c) HCl/EtOH; (d) MeI/NaH/DMF.

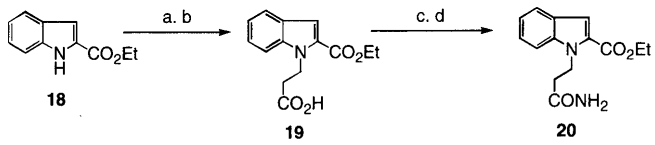
Chart 3

the 1-methylated ester **10**, which was converted to dicarboxylic acid **11** by alkaline hydrolysis of the two ester groups. Selective decarboxylation of the 2-position of **11** could be achieved by heating at 180 °C for 30 min in the presence of a catalytic amount of CuO in quinoline to give 1-methyl-1*H*-indole-7-carboxylic acid, which was converted to the methyl ester **12** by esterification with the $SOCl_2$/MeOH system. Ethyl 1,3-disubstituted-1*H*-indole-2-carboxylate derivatives (**13a**—**13c**, **14a**, **14b**) were synthesized as shown in Chart 3. Ethyl 3-substituted-1*H*-indole-2-carboxylates (**13a**—**13c**), prepared from aniline as a starting material by a sequence of reactions similar to the synthesis of **9**, were converted to the 1,3-disubstituted compounds (**14a**—**14c**) by N-methylation using NaH as a base in DMF. Methyl 1-substituted-1*H*-indole-2-carboxylates (**17a**—**17k**) were prepared by N-alkylation of **2a** with the corresponding R_1X (**17a**—**17f**, **17h** and **17i**; X=Br. **17g** and **17j**; X=Cl. **17k**; X=OMs) using NaH as a base in DMF as shown in Chart 4. On the other hand, the reaction of **2a** with iso-PrI under the condition of heating at 80 °C using NaH as a base in DMF gave the mixture of methyl 1-isopropyl-1*H*-indole-2-carboxylate and isopropyl 1-isopropyl-1*H*-indole-2-carboxylate, which were not easily separated by chromatography. Then the carboxylic acid **8**, which was prepared by alkaline hydrolysis of the mixture, was used in the last synthetic step. Ethyl 1-(2-carboxyethyl)-1*H*-indole-2-carboxylate (**19**) and ethyl 1-(2-carbamoylethyl)-1*H*-indole-2-carboxylate (**20**) were synthesized as shown in Chart 5. The acid **19** was prepared by the Michael addition of ethyl 1*H*-indole-2-carboxylate (**18**) with ethyl acrylate in the presence of benzyltrimethylammonium hydroxide (Triton B) in 1,4-dioxane followed by selective hydrolysis of the aliphatic ester group by treating with a mixture of acetic acid and 30% aqueous sulfuric acid. The acid **19** was treated with 1,1′-carbonyldiimidazole in tetrahydrofuran (THF) followed by conversion to a carbamoyl group with ammonia to give the amide **20**. Methyl 1-hydroxy-1*H*-indole-2-carboxylate (**21**) and methyl 1-methoxy-1*H*-indole-2-carboxylate (**22**) were prepared by the method of Baxter and Swan.[17] Ethyl 3-methoxymethoxy-1-methyl-1*H*-indole-2-carboxylate (**16**) was prepared from ethyl 3-hydroxy-1-methyl-1*H*-indole-2-carboxylate[18] by treating with methoxymethylchloride using K_2CO_3 as a base in DMF. In the last



	R1	X
17a	$(CH_2)_2CH_3$	Br
17b	$(CH_2)_2OCH_3$	Br
17c	CH_2Ph	Br
17d	$(CH_2)_2Ph$	Br
17e	$(CH_2)_3Ph$	Br
17f	H_2C-(p-Br-Ph)	Br
17g	H_2C-(p-OCH_3-Ph)	Cl
17h	H_2C-(2-naphthyl)	Br
17i	$(CH_2)_3OTHP$	Br
17j	$(CH_2)_4OTHP$	Cl
17k	$(CH_2)_3NHBoc$	OMs

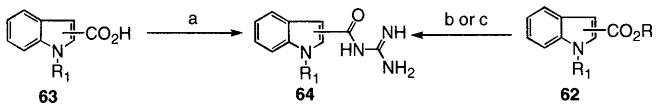
Chart 4



(a) Ethyl acrylate/Triton B/1,4-dioxane; (b) $CH_3CO_2H/H_2SO_4/H_2O$; (c) 1,1′-carbonyldiimidazole/THF; (d) NH_3.

Chart 5

synthetic step the 1*H*-indole carboxylic acid derivatives of the general formula (**62**, **63**) were converted to carbonylguanidine derivatives of the general formula (**64**) as shown in Chart 6. The carboxylic acids **63** were treated with 1,1′-carbonyldiimidazole in THF, then reacted with a mixture of guanidine hydrochloride and triethylamine at room temperature in DMF to give **64**. The compounds **64** were also synthesized by heating of the ester **62** with excessive guanidine, which was prepared from the hydrochloride using NaOMe in MeOH, in MeOH or by the reaction of the ester **62** with excessive guanidine at room temperature in DMF. *N*-(aminoiminomethyl)-3-hydroxy-1-methyl-1*H*-indole-2-carboxamide (**47**) was prepared from the corresponding methoxymethyl (MOM) substance (**16**) by carbonylguanidine synthesis, deprotection with HCl in aqueous THF followed by treatment with methanesulfonate. The 1-(3-hydroxypropyl) compound **51**, 1-(4-hydroxybutyl) compound **52** and 1-(3-aminopropyl) compound **56** were prepared from the corresponding tetrahydro-2*H*-pyranyl (THP) substances (**17i**, **17j**) and *tert*-butoxycarbonyl (Boc) substance (**17k**) by carbonylguanidine synthesis followed by deprotection and salt formation with HCl in MeOH.



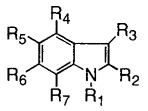
(a) (1) 1,1′-carbonyldiimidazole/THF
(2) guanidine hydrochloride/Et_3N/DMF [Method B]
(b) guanidine hydrochloride/NaOMe/MeOH [Method A]
(c) guanidine hydrochloride/NaOMe/DMF [Method C]

Chart 6

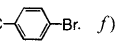
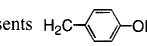
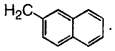
Biological Results and Discussion

The Na^+/H^+ exchanger inhibitory activity was assessed by observing the effects on the acidosis-induced change in intracellular pH[19] in rat myocardium cells. All compounds were tested as hydrochloride or methanesulfonate salts. The results are listed in Table 4. First, the effect of the position of the carbonylguanidine group on the indole ring was examined using a series of *N*-(aminoiminomethyl)-1-methyl-1*H*-indole carboxamide derivatives (**24**, **28**, **31**, **35**, **38**, **41**). The 2-, 5- and 6-carbonylguanidine derivatives (**24**, **35**, **38**) showed potent inhibiting activity for the Na^+/H^+ exchanger, while the 3-, 4- and 7-carbonylguanidine derivatives (**28**, **31**, **41**) showed poor activity. The effect of a substituent (hydrogen, isopropyl , benzyl) at the 1-position of indole carbonylguanidine derivatives was also examined. Unsubstituted compounds at the 1-position (**23**, **27**, **34**) reduced the inhibitory activity for the Na^+/H^+ exchanger, and the introduction of an isopropyl group resulted in potent activity in the 2- and 3-carbonylguanidine derivatives (**25**, **29**) but poor activity in the 4-, 5- and 6-carbonylguanidine derivatives (**32**, **36**, **39**), while the introduction of a benzyl group afforded potent activity to the 2-carbonylguanidine derivative (**26**) but poor activity to the 3-, 4-, 5- and 6-carbonylguanidine derivatives (**30**, **33**, **37**, **40**). These results suggest that the indole-2-carbonylguanidine derivatives show potent inhibitory activity for the Na^+/H^+ exchanger. Next, the effect of a substituent at the 3-position of 1*H*-indole-2-carbonylguanidine derivatives was examined. The introduction of a methyl group at the 3-position of 1-unsubstituted-1*H*-indole-2-carbonylguanidine led to an improvement of activity (**42** *vs.* **23**) but the introduction of a benzyl group led to a slight worsening of it (**43** *vs.* **23**). The introduction of various substituents (methyl, benzyl, phenyl , hydroxy) at the 3-position of 1-methyl-1*H*-indole-2-carbonylguanidine led to a worsening of the activity (**41** *vs.* **24**), especially, a benzyl, phenyl or hydroxy group (**45**, **46**, **47** *vs.* **24**). These results suggest that the introduction of sterically larger substituents at the 3-position of 1*H*-indole-2-carbonylguanidine gives rise to a loss of potency. Finally, the effect of various substituents at the 1-position of 1*H*-indole-2-carbonylguanidine was examined. Substitution of an *n*-propyl group at the 1-position increased the inhibitory activity (**48**; IC_{50}=30 nM) compared with that of methyl (**24**; IC_{50}=50 nM). The 1-(2-methoxyethyl) compound (**53**) showed almost the same activity as **24**. The 1-benzyl derivatives (**26**, **57**, **58**) showed a reduced inhibitory effect on the Na^+/H^+ exchanger in comparison with **24**. The 1-(2-naphthyl) compound (**59**) also had a reduced inhibitory effect. On the other hand, substitution of a phenethyl group at the 1-position led to an improvement of activity (**49**; IC_{50}=15 nM). However, substitution of the 1-(3-phenylpropyl) group, a larger arylalkyl group, again led to a reduc-

Table 1. *N*-(Aminoiminomethyl)-1*H*-indole Carboxamide Derivatives



Compd.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	sm[a]	Method[b]	Yield %[c]
23	H	AG	H	H	H	H	H	**2a**	A	61.9
24	Me	AG	H	H	H	H	H	**3a**	A	30.8
25	iso-Pr	AG	H	H	H	H	H	**8**	B	47.4
26	CH_2Ph	AG	H	H	H	H	H	**17c**	A	54.9
27	H	H	AG	H	H	H	H	**2b**	A	42.2
28	Me	H	AG	H	H	H	H	**3b**	A	35.9
29	iso-Pr	H	AG	H	H	H	H	**4a**	A	49.7
30	CH_2Ph	H	AG	H	H	H	H	**4b**	A	66.2
31	Me	H	H	AG	H	H	H	**3c**	A	66.1
32	iso-Pr	H	H	AG	H	H	H	**5a**	A	49.0
33	CH_2Ph	H	H	AG	H	H	H	**5b**	A	42.6
34	H	H	H	H	AG	H	H	**2d**	A	55.9
35	Me	H	H	H	AG	H	H	**3d**	A	68.9
36	iso-Pr	H	H	H	AG	H	H	**7a**	C	67.9
37	CH_2Ph	H	H	H	AG	H	H	**7b**	C	65.4
38	Me	H	H	H	H	AG	H	**3e**	A	62.1
39	iso-Pr	H	H	H	H	AG	H	**6a**	A	37.7
40	CH_2Ph	H	H	H	H	AG	H	**6b**	A	44.5
41	Me	H	H	H	H	H	AG	**12**	A	37.4
42	H	AG	Me	H	H	H	H	**13a**	A	86.3
43	H	AG	CH_2Ph	H	H	H	H	**13b**	C	28.8[d]
44	Me	AG	Me	H	H	H	H	**14a**	A	55.5
45	Me	AG	CH_2Ph	H	H	H	H	**14b**	A	26.7
46	Me	AG	Ph	H	H	H	H	**14c**	A	59.5
47	Me	AG	OH	H	H	H	H	**16**	D	50.0[d]
48	$(CH_2)_2CH_3$	AG	H	H	H	H	H	**17a**	A	53.2
49	$(CH_2)_2Ph$	AG	H	H	H	H	H	**17d**	A	55.1
50	$(CH_2)_3Ph$	AG	H	H	H	H	H	**17e**	A	39.0
51	$(CH_2)_3OH$	AG	H	H	H	H	H	**17i**	E	48.6
52	$(CH_2)_4OH$	AG	H	H	H	H	H	**17j**	E	84.0
53	$(CH_2)_2OCH_3$	AG	H	H	H	H	H	**17b**	C	86.4
54	$(CH_2)_2CO_2H$	AG	H	H	H	H	H	**19**	C	29.0
55	$(CH_2)_2CONH_2$	AG	H	H	H	H	H	**20**	C	42.5
56	$(CH_2)_3NH_2$	AG	H	H	H	H	H	**17k**	E	46.0
57	P-1[e]	AG	H	H	H	H	H	**17f**	A	53.3
58	P-2[f]	AG	H	H	H	H	H	**17g**	A	54.8
59	P-3[g]	AG	H	H	H	H	H	**17h**	A	56.4
60	OH	AG	H	H	H	H	H	**21**	A	42.0
61	OCH_3	AG	H	H	H	H	H	**22**	A	24.9

AG=  *a*), *b*) See Experimental. *c*) Yield of HCl salt. *d*) Yield of $MeSO_3H$ salt. *e*) P-1 represents  . *f*) P-2 represents  .
g) P-3 represents  .

tion in activity. Substitution of various substituted alkyl groups at the 1-position (**51**, **52**, **55**, **56**) resulted in about 3-fold less potent inhibitory activity than that of 1-*n*-propyl (**48**). The 1-(2-carboxyethyl) compound (**54**) also showed a reduction in potency (IC_{50}=540 nM). The introduction of a hydroxy group at the 1-position (**60**), as well as at the 3-position (**47**), led to a marked worsening of the inhibitory activity (IC_{50}>10000 nM). However, the introduction of a methoxy group at the 1-position (**61**) had an inhibitory effect on the Na^+/H^+ exchanger (IC_{50}=300 nM).

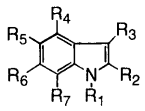
Conclusion

A series of *N*-(aminoiminomethyl)-1*H*-indole carboxamide derivatives was synthesized and evaluated as novel potent Na^+/H^+ exchanger inhibitors. First, variation of the carbonylguanidine group at the 2- to 7-position of the indole ring system showed that a substitution at the 2-, 3-, 5- and 6-position, especially the 2-position, strengthened the Na^+/H^+ exchanger inhibitory activities the most *in vitro*. The introduction of larger substituents at the 3-position of the 1*H*-indole-2-carbonylguanidine molecule led to a reduction of activity, while introduction of substituents at the 1-position of 1*H*-indole-2-carbonylguanidine led to an improvement of activity. Among the compounds with a variety of substituents at the 1-position of the 1*H*-indole-2-carbonylguanidine molecule, *N*-(aminoiminomethyl)-1-(2-phenylethyl)-1*H*-indole-2-carboxamide (**49**) showed the most potent Na^+/H^+ exchanger inhibitory activity.

Experimental

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. Spectra were recorded for all compounds and were consistent with the assigned structures. NMR spectra were recorded on JEOL GX-270

Table 2. Physical Data for *N*-(Aminoiminomethyl)-1*H*-indole Carboxamide Derivatives



Compd.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	mp (°C) (recryst. solvent)[a]	Formula	Analysis (%)[b] Calcd (Found) C	H	N
23	H	AG	H	H	H	H	H	291 (dec.) (IPA–H_2O)[c]	$C_{10}H_{10}N_4O \cdot HCl$	50.32 (50.34)	4.65 (4.74)	23.47 (23.34)
24	Me	AG	H	H	H	H	H	285—287 (dec.) (H_2O)	$C_{11}H_{12}N_4O \cdot HCl$	52.28 (52.10)	5.19 (5.30)	22.17 (21.80)
25	iso-Pr	AG	H	H	H	H	H	160—162 (H_2O)	$C_{13}H_{16}N_4O \cdot HCl \cdot 0.20H_2O$	54.91 (54.93)	6.17 (6.17)	19.70 (19.65)
26	CH_2Ph	AG	H	H	H	H	H	215—216 (IPA–H_2O)	$C_{17}H_{16}N_4O \cdot HCl \cdot 0.25H_2O$	61.26 (61.16)	5.29 (5.37)	16.81 (16.72)
27	H	H	AG	H	H	H	H	272 (dec.) (IPA–H_2O)	$C_{10}H_{10}N_4O \cdot HCl$	50.32 (50.05)	4.65 (4.69)	23.47 (23.28)
28	Me	H	AG	H	H	H	H	260—261 (dec.) (H_2O)	$C_{11}H_{12}N_4O \cdot HCl \cdot 0.20H_2O$	51.55 (51.55)	5.27 (5.38)	21.86 (21.82)
29	iso-Pr	H	AG	H	H	H	H	246—247 (IPA–H_2O)	$C_{13}H_{16}N_4O \cdot HCl$	55.62 (55.46)	6.10 (5.98)	19.96 (19.89)
30	CH_2Ph	H	AG	H	H	H	H	250—251 (EtOH–H_2O)	$C_{17}H_{16}N_4O \cdot HCl$	62.10 (61.89)	5.21 (5.18)	17.04 (16.95)
31	Me	H	H	AG	H	H	H	136—137 (H_2O)	$C_{11}H_{12}N_4O \cdot HCl \cdot H_2O$	48.80 (48.63)	5.58 (5.71)	20.70 (20.61)
32	iso-Pr	H	H	AG	H	H	H	196—197 (EtOH)	$C_{13}H_{16}N_4O \cdot HCl$	55.62 (55.46)	6.10 (6.08)	19.96 (19.98)
33	CH_2Ph	H	H	AG	H	H	H	208—209 (IPA–H_2O)	$C_{17}H_{16}N_4O \cdot HCl \cdot H_2O$	58.87 (58.91)	5.52 (5.45)	16.15 (16.09)
34	H	H	H	H	AG	H	H	217—218 (IPA–H_2O)	$C_{10}H_{10}N_4O \cdot HCl \cdot H_2O$	46.79 (46.55)	5.10 (5.05)	21.83 (21.67)
35	Me	H	H	H	AG	H	H	291—292 (dec.) (IPA–H_2O)	$C_{11}H_{12}N_4O \cdot HCl$	52.28 (52.16)	5.19 (5.31)	22.17 (22.04)
36	iso-Pr	H	H	H	AG	H	H	219—220 (IPA–H_2O)	$C_{13}H_{16}N_4O \cdot HCl$	55.62 (55.45)	6.10 (6.05)	19.96 (19.81)
37	CH_2Ph	H	H	H	AG	H	H	229—230 (IPA–H_2O)	$C_{17}H_{16}N_4O \cdot HCl \cdot H_2O$	58.87 (58.71)	5.52 (5.57)	16.15 (16.00)
38	Me	H	H	H	H	AG	H	296—297 (dec.) (IPA–H_2O)	$C_{11}H_{12}N_4O \cdot HCl$	52.28 (52.23)	5.19 (5.41)	22.17 (22.10)
39	iso-Pr	H	H	H	H	AG	H	214—215 (IPA–H_2O)	$C_{13}H_{16}N_4O \cdot HCl \cdot H_2O$	52.26 (52.00)	6.41 (6.29)	18.75 (18.55)
40	CH_2Ph	H	H	H	H	AG	H	224—225 (IPA–H_2O)	$C_{17}H_{16}N_4O \cdot HCl \cdot H_2O$	58.87 (58.85)	5.52 (5.46)	16.15 (16.03)
41	Me	H	H	H	H	H	AG	183—184 (H_2O)	$C_{11}H_{12}N_4O \cdot HCl$	52.28 (52.11)	5.19 (5.25)	22.17 (22.03)
42	H	AG	Me	H	H	H	H	287 (dec.) (IPA–H_2O)	$C_{11}H_{12}N_4O \cdot HCl$	52.28 (52.30)	5.19 (5.25)	22.17 (22.03)
43	H	AG	CH_2Ph	H	H	H	H	233—234 (IPA–H_2O)	$C_{17}H_{16}N_4O \cdot CH_4SO_3$	55.66 (55.53)	5.19 (5.27)	14.42 (14.37)
44	Me	AG	Me	H	H	H	H	229—230 (dec.) (MeOH)	$C_{12}H_{14}N_4O \cdot HCl \cdot 0.60CH_4O$	52.92 (52.67)	6.13 (6.38)	19.59 (19.90)
45	Me	AG	CH_2Ph	H	H	H	H	181—182 (IPA–H_2O)	$C_{18}H_{18}N_4O \cdot HCl \cdot 0.34H_2O \cdot 0.30C_3H_8O$	61.86 (61.86)	6.06 (6.06)	15.10 (15.27)
46	Me	AG	Ph	H	H	H	H	257—258 (dec.) (MeOH)	$C_{17}H_{16}N_4O \cdot HCl \cdot 0.20CH_4O$	61.63 (61.90)	5.35 (5.66)	16.71 (16.72)
47	Me	AG	OH	H	H	H	H	206 (dec.) (EtOH–H_2O)	$C_{11}H_{12}N_4O_2 \cdot CH_4SO_3$	41.61 (41.85)	5.24 (5.28)	16.18 (15.82)
48	$(CH_2)_2CH_3$	AG	H	H	H	H	H	230—231 (IPA–H_2O)	$C_{13}H_{16}N_4O \cdot HCl \cdot H_2O$	52.26 (52.28)	6.41 (6.39)	18.75 (18.73)
49	$(CH_2)_2Ph$	AG	H	H	H	H	H	266—268 (IPA–H_2O)	$C_{18}H_{18}N_4O \cdot HCl$	63.06 (62.93)	5.59 (5.65)	16.34 (16.26)
50	$(CH_2)_3Ph$	AG	H	H	H	H	H	110—111 (IPA–H_2O)	$C_{19}H_{20}N_4O \cdot HCl \cdot H_2O$	60.88 (60.88)	6.18 (6.22)	14.95 (14.89)
51	$(CH_2)_3OH$	AG	H	H	H	H	H	204—205 (IPA–H_2O)	$C_{13}H_{16}N_4O_2 \cdot HCl \cdot 0.40H_2O$	51.37 (51.42)	5.90 (5.97)	18.43 (18.49)
52	$(CH_2)_4OH$	AG	H	H	H	H	H	227—228 (H_2O)	$C_{14}H_{18}N_4O_2 \cdot HCl$	54.11 (53.96)	6.16 (6.07)	18.03 (17.93)

Table 2. (Continued)

Compd.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	mp (°C) (recryst. solvent)[a]	Formula	Analysis (%)[b] Calcd (Found) C	H	N
53	$(CH_2)_2OCH_3$	AG	H	H	H	H	H	178—179 (IPA–H_2O)	$C_{13}H_{16}N_4O_{22}\cdot HCl$	52.62 (52.50	5.77 5.71	18.88 18.73)
54	$(CH_2)_2CO_2H$	AG	H	H	H	H	H	254 (H_2O)	$C_{13}H_{14}N_4O_3\cdot HCl\cdot H_2O$	47.49 (47.29	5.21 5.21	17.04 16.94)
55	$(CH_2)_2CONH_2$	AG	H	H	H	H	H	283 (dec.) (IPA–H_2O)	$C_{13}H_{15}N_5O_2\cdot HCl$	50.41 (50.19	5.21 5.20	22.61 22.31)
56	$(CH_2)_3NH_2$	AG	H	H	H	H	H	296—297 (dec.) (H_2O)	$C_{13}H_{17}N_5O\cdot 2HCl$	47.00 (47.03	5.76 5.67	21.08 20.85)
57	P-1	AG	H	H	H	H	H	264—265 (IPA–H_2O)	$C_{17}H_{15}BrN_4O\cdot HCl$	50.08 (49.92	3.96 4.02	13.74 13.65)
58	P-2	AG	H	H	H	H	H	242—243 (IPA–H_2O)	$C_{18}H_{18}N_4O_2\cdot HCl$	60.25 (59.97	5.34 5.38	15.61 15.35)
59	P-3	AG	H	H	H	H	H	257—258 (IPA–H_2O)	$C_{21}H_{18}N_4O\cdot HCl\cdot H_2O$	63.55 (63.76	5.33 5.35	14.12 13.98)
60	OH	AG	H	H	H	H	H	226 (dec.) (IPA–H_2O)	$C_{10}H_{10}N_4O_2\cdot HCl$	47.16 (46.80	4.35 4.71	22.00 21.65)
61	OMe	AG	H	H	H	H	H	214 (dec.) (IPA–H_2O)	$C_{11}H_{12}N_4O_2\cdot HCl\cdot 0.30H_2O$	48.29 (48.34	5.01 5.39	20.48 20.27)

a) IPA represents 2-propanol. *b*) Analytical results are within ±0.4% of the theoretical values in C, H, N analysis. AG, P-1, P-2, P-3 are the same as those in Table 1.

Table 3. Spectral Data for *N*-(Aminoiminomethyl)-1*H*-indole Carboxamide Derivatives

Compd.	IR spectra cm^{-1} (KBr)	^{1}H-NMR spectra δ (ppm) (DMSO-d_6)
23	1686, 1626, 1556, 1540, 1517, 1313, 1238, 1206, 1146	7.09—7.14 (1H, m), 7.28—7.34 (1H, m), 7.49 (1H, d, *J*=8.3 Hz), 7.71 (1H, br s), 8.47 (2H, br s), 8.70 (2H, br s), 12.06 (1H, br s), 12.13 (1H, br s)
24	1691, 1625, 1566, 1514, 1469, 1437, 1328, 1247, 1220	4.04 (3H, m), 7.12—7.21 (1H, m), 7.31—7.44 (1H, m), 7.61 (1h, d, *J*=8.6 Hz), 7.73 (1H, d, *J*=7.9 Hz), 7.89 (1H, s), 8.49 (2H, br s), 8.71 (2H, br s), 11.94 (1H, br s)
25	1702, 1615, 1566, 1512, 1478, 1446, 1381, 1321, 1204	1.61 (6H, d, *J*=7.3 Hz), 5.46—5.57 (1H, m), 7.15 (1H, t, *J*=7.9 Hz), 7.32—7.38 (1H, m), 7.68—7.78 (3H, m), 8.51 (2H, br s), 8.67 (2H, br s), 11.8—11.9 (1H, m)
26	1690, 1615, 1567, 1512, 1475, 1452, 1325, 1245, 1208	5.86 (2H, s), 7.03 (2H, d, *J*=6.6 Hz), 7.17—7.39 (4H, m), 7.57 (1H, d, *J*=8.3 Hz), 7.78 (1H, d, *J*=7.9 Hz), 7.98 (1H, s), 8.42 (2H, br s), 8.62 (2H, br s), 11.91 (1H, br s)
27	1684, 1618, 1570, 1540, 1518, 1438, 1322, 1245, 1174	7.20—7.29 (2H, m), 7.53 (1H, dd, *J*=1.7, 6.6 Hz), 8.12—8.16 (1H, m), 8.29 (2H, m), 8.66 (2H, br s), 8.83 (1H, d, *J*=3.3 Hz), 11.80 (1H, br s), 12.23 (1H, br s)
28	1674, 1577, 1539, 1463, 1372, 1263, 1246, 1190, 1107	3.91 (3H, s), 7.25—7.37 (2H, m), 7.58—7.61 (1H, m), 8.15 (1H, dd, *J*=1.3, 6.6 Hz), 8.29 (2H, br s), 8.61 (2H, br s), 8.78 (1H, s), 11.79 (1H, br s)
29	1685, 1636, 1577, 1540, 1459, 1377, 1308, 1228, 1170	1.53 (6H, d, *J*=6.6 Hz), 4.85—4.90 (1H, m), 7.24—7.34 (2H, m), 7.67 (1H, d, *J*=7.6 Hz), 8.14—8.17 (1H, m), 8.30 (2H, br s), 8,62 (2H, br s), 9.12 (1H, s), 11.87 (1H, br s)
30	1699, 1628, 1573, 1527, 1465, 1377, 1232, 1205, 1181	5.53 (2H, s), 7.23—7.37 (7H, m), 7.62—7.66 (1H, m), 8.15—8.18 (1H, m), 8.30 (2H, br s), 8.56 (2H, br s), 8.95 (1H, s), 11.82 (1H, br s)
31	1693, 1625, 1561, 1504, 1448, 1301, 1275, 1192, 1125	3.88 (3H, s), 6.97 (1H, d, *J*=3.0 Hz), 7.29—7.35 (1H, m), 7.56 (1H, d, *J*=3.0 Hz), 7.84 (1H, d, *J*=7.9 Hz), 7.98 (1H, d, *J*=7.6 Hz), 8.47 (2H, br s), 8.73 (2H, br s), 11.70 (1H, br s)
32	1694, 1623, 1567, 1500, 1439 1320, 1275, 1184, 1155	1.48 (6H, d, *J*=6.6 Hz), 4.87 (1H, m), 7.01 (1H, d, *J*=3.0 Hz), 7.26—7.31 (1H, m), 7.72 (1H, d, *J*=3.3 Hz), 7.91 (1H, d, *J*=8.3 Hz), 8.02 (1H, d, *J*=7.6 Hz), 8.54 (2H, br s), 8.83 (2H, br s), 11.85 (1H, br s)
33	1693, 1630, 1570, 1505, 1438, 1360, 1276, 1231, 1179	5.52 (2H, s), 7.03 (1H, d, *J*=3.0 Hz), 7.17—7.32 (6H, m), 7.74 (1H, t, *J*=1.7 Hz), 7.84 (1H, d, *J*=7.9 Hz), 7,98 (1H, d, *J*=7.6 Hz) 8.48 (2H, br s), 8.77 (2H, br s), 11.79 (1H, br s)
34	1685, 1654, 1611, 1560, 1458, 1363, 1290, 1237, 1182	6.61—6.63 (1H, m), 7.50—7.56 (2H, m), 7.85—7.89 (1H, m), 8.45 (2h, br s), 8.49 (1H, d, *J*=1.7 Hz), 8.75 (2H, br s), 11.64 (1H, br s), 11.71 (1H, br s)
35	1684, 1609, 1560, 1458, 1347, 1303, 1257, 1240, 1183	3.86 (3H, s), 6.62—6.64 (1H, m), 7.50 (1H, d, *J*=3.3 Hz), 7.61 (1H, d, *J*=8.9 Hz), 7.91—7.95 (1H, m), 8.44 (2H, br s), 8.47 (1H, d, *J*=1.3 Hz), 8.72 (2H, br s), 11.70 (1H, br s)
36	1679, 1622, 1608, 1558, 1433, 1297, 1271, 1186, 1140	1.48 (6H, d, *J*=6.6 Hz), 4.81—4.88 (1H, m), 6.67 (1H, d, *J*=3.3 Hz), 7.68—7.71 (2H, m), 7.89—7.93 (1H, m), 8.3—8.6 (3H, m), 8.73 (2H, br s), 11.70 (1H, br s)
37	1688, 1605, 1562, 1454, 1346, 1301, 1278, 1245, 1183	5.51 (2H, s), 6.69 (1H, d, *J*=2.6 Hz), 7.20—7.34 (5H, m), 7.62—7.68 (2H, m), 7.88 (1H, dd, *J*=1.7, 8.9 Hz), 8.43—8.48 (3H, m), 8.72 (2H, br s), 11.70 (1H, br s)
38	1704, 1617, 1560, 1502, 1423, 1360, 1328, 1262, 1225	3.94 (3H, s), 6.55 (1H, dd, *J*=0.7, 3.0 Hz), 7.61 (1H, d, *J*=3.0 Hz), 7.67—7.78 (2H, m), 8.44 (2H, br s), 8.60 (1H, s), 8.85 (2H, br s), 12.00 (1H, br s)
39	1698, 1611, 1575, 1482, 1465, 1325, 1263, 1226, 1122	1.51 (6H, d, *J*=6.6 Hz), 4.92—5.02 (1H, m), 6.59 (1H, d, *J*=3.0 Hz), 7.66—7.81 (3H, m), 8.41 (2H, br s), 8.66 (1H, s), 8.86 (2H, br s), 12.04 (1H, br s)
40	1696, 1613, 1566, 1500, 1454, 1359, 1320, 1257, 1113	5.57 (2H, s), 6.62 (1H, d, *J*=3.0 Hz), 7.24—7.32 (5H, m), 7.69—7.79 (2H, m), 7.81 (1H, d, *J*=3.0 Hz), 8.43 (2H, br s), 8.71 (1H, s), 8.86 (2H, s), 12.06 (1H, br s)
41	1707, 1642, 1586, 1524, 1440, 1322, 1272, 1221, 1148	3.78 (3H, s), 6.60 (1H, d, *J*=3.3 Hz), 7.16 (1H, t, *J*=7.6 Hz), 7.44 (1H, d, *J*=3.0 Hz), 7.53 (1H, d, *J*=7.6 Hz), 7.85 (1H, d, *J*=7.9 Hz), 8.44 (2H, br s), 8.52 (2H, br s), 11.90 (1H, br s)
42	1692, 1623, 1576, 1552, 1528, 1316, 1282, 1195, 1099	2.60 (3H, s), 7.12 (1H, t, *J*=7.9 Hz), 7.31—7.44 (2H, m), 7.70 (1H, d, *J*=7.9 Hz), 8.46 (4H, br s), 11.78 (1H, br s), 11.94 (1H, br s)

Table 3. (Continued)

Compd.	IR spectra cm^{-1} (KBr)	^{1}H-NMR spectra δ (ppm) (DMSO-d_6)
43	1694, 1589, 1541, 1456, 1318, 1266, 1199, 1160, 1044	2.46 (3H, s), 4.45 (2H, s), 7.06—7.22 (2H, m), 7.22—7.35 (5H, m), 7.50 (1H, d, J=8.4 Hz), 7.66 (1H, d, J=8.1 Hz), 8.2—8.6 (4H, m), 11.16 (1H, br s), 11.61 (1H, br s)
44	1695, 1614, 1573, 1520, 1470, 1443, 1400, 1240, 1136	2.56 (3H, s), 3.84 (3H, s), 7.12—7.18 (1H, m), 7.34—7.40 (1H, m), 7.53 (1H, d, J=8.3 Hz), 7.69 (1H, d, J=7.9 Hz), 8.6—8.7 (4H, m), 11.67 (1H, br s)
45	1688, 1614, 1568, 1514, 1441, 1402, 1369, 1240, 1133	3.86 (3H, s), 4.40 (2H, s), 7.08—7.24 (6H, m), 7.35 (1H, t, J=7.3 Hz), 7.55 (1H, d, J=8.2 Hz), 7.68 (1H, d, J=7.9 Hz), 8.54 (4H, br s), 11.95 (1H, br s)
46	1677, 1625, 1574, 1528, 1439, 1372, 1258, 1240, 1189	3.94 (3H, s), 7.18—7.24 (1H, m), 7.39—7.49 (6H, m), 7.64—7.69 (2H, m), 8.32 (2H, br s), 8.63 (2H, br s), 11.50(1H, br s)
47	3408, 3196, 1700, 1662, 1595, 1578	2.33 (3H, s), 3.90 (3H, s), 7.05—7.11 (1H, m), 7.37—7.43 (1H, m), 7.47—7.54 (1H, m), 7.90—7.93 (1H, m), 8.1—8.5 (2H, br s), 8.6—8.9 (2H, br s), 10.38 (1H, br s)
48	1710, 1629, 1616, 1570, 1511 1475, 1443, 1243, 1214	0.85 (3H, t, J=7.6 Hz), 1.66—1.77 (2H, m), 4.51 (2H, dd, J=6.9, 7.6 Hz), 7.10—7.23 (1H, m), 7.32—7.45 (1H, m),7.65 (1H, d, J=8.6 Hz), 7.73 (1H, d, J=7.9 Hz), 7.97 (1H, s), 8.52 (2H, br s), 8.77 (2H, br s), 12.01 (1H, br s)
49	1688, 1625, 1614, 1565, 1512, 1476, 1354, 1324, 1220	2.97—3.03 (2H, m), 4.73—4.79 (2H, m), 7.13—7.24 (6H, m), 7.32—7.38 (1H, m), 7.59 (1H, d, J=7.9 Hz), 7.73 (1H, d, J=7.9 Hz), 7.84 (1H, s), 8.43 (2H, br s), 8.62 (2H, br s), 11.78 (1H, br s)
50	1696, 1679, 1615, 1565, 1512 1475, 1322, 1239, 1214	1.97—2.13 (2H, m), 4.59 (2H, t, J=7.0 Hz), 5.62 (2H, t, J=8.0 Hz), 7.11—7.34 (6H, m), 7.40 (1H, dt, J=1.0, 8.0 Hz),7.57 (1H, d, J=8.0 Hz), 7.76 (1H, d, J=8.0 Hz), 7.81 (1H, s), 8.3—8.7 (4H, m), 11.75 (1H, br s)
51	1692, 1620, 1580, 1476, 1366, 1326, 1246, 1223, 1127	1.90 (2H, dt, J=7.3, 6.9 Hz), 3.39 (2H, t, J=6.3 Hz), 4.60 (2H, t, J=6.9 Hz), 7.18 (1H, dd, J=7.0, 7.8 Hz), 7.41 (1H, dd, J=7.1, 8.5 Hz), 7.65 (1H, d, J=8.2 Hz), 7.74 (1H, d, J=7.8 Hz), 7.88 (1H, s), 8.3—8.9 (4H, m), 11.87 (1H, br s)
52	1677, 1636, 1587, 1511, 1475, 1449, 1325, 1218, 1125	1.30—1.50 (2H, m), 1.62—1.86 (2H, m), 3.38 (2H, t, J=6.5 Hz), 4.43 (1H, br s), 4.56 (2H, t, J=7.3 Hz), 7.17 (1H, t, J=7.4 Hz), 7.40 (1H, ddd, J=1.0, 6.9, 7.4 Hz), 7.65 (1H, d, J=8.3 Hz), 7.73 (1H, d, J=7.9 Hz), 7.96 (1H, s), 8.52 (2H, br s), 8.76 (2H, br s), 12.00 (1H, s)
53	1686, 1641, 1587, 1515, 1474, 1245, 1214, 1126, 1103	3.16 (3H, s), 3.63 (2H, t, J=5.3 Hz), 4.72 (2H, t, J=5.3 Hz), 7.11—7.22 (1H, m), 7.31—7.44 (1H, m), 7.66 (1H, d, J=8.6 Hz), 7.72 (1H, d, J=7.9 Hz), 7.89 (1H, s), 8.49 (2H, br s), 8.70 (2H, br s), 11.96 (1H, br s)
54	3419, 1684, 1616, 1570, 1474, 1448, 1300, 1227, 1211	2.72 (2H, t, J=7.3 Hz), 4.76 (2H, t, J=7.4 Hz), 7.17 (1H, t, J=7.9 Hz), 7.40 (1H, ddd, J=1.0, 6.9, 7.4 Hz), 7.68 (1H, d, J=8.6 Hz), 7.73 (1H, d, J=7.9 Hz), 7.91 (1H, s), 8.50 (2H, br s), 8.72 (2H, br s), 12.22 (1.5H, br s)
55	1697, 1675, 1615, 1563, 1475, 1325, 1250, 1224, 1170	2.55 (2H, t, J=7.3 Hz), 4.74 (2H, t, J=7.3 Hz), 6.85 (1H, br s), 7.17 (1H, t, J=6.9 Hz), 7.33 (H, br s), 7.39 (1H, ddd, J=1.0, 7.3, 7.8 Hz), 7.70 (2H, dd, J=8.4, 17.7 Hz), 7.82 (1H, s), 8.46 (2H, br s), 8.64 (2H, br s), 11.85 (1H, br s)
56	1694, 1575, 1511, 1475, 1449, 1373, 1326, 1248, 1214	2.05 (2H, ddd, J=7.6, 11.4, 14.5 Hz), 2.63—2.86 (2H, m), 4.65 (2H, t, J=7.3 Hz), 7.19 (1H, t, J=7.9 Hz), 7.42 (1H, t, J=7.6 Hz), 7.74 (2H, d, J=8.6 Hz), 7.83—8.16 (4H, m), 8.27—9.03 (4H, m), 12.00—12.30 (1H, br s)
57	1674, 1614, 1568, 1484, 1476, 1446, 1324, 1242, 1209	5.82 (2H, s), 6.99 (2H, d, J=8.3 Hz), 7.17—7.23 (1H, m), 7.35—7.40 (1H, m), 7.47 (2H, d, J=8.3 Hz), 7.57 (1H, d, J=8.3 Hz), 7.79 (1H, d, J=7.9 Hz), 8.06 (1H, s), 8.47 (2H, br s), 8.69 (2H, br s), 12.07 (1H, br s)
58	1692, 1625, 1572, 1514, 1475, 1446, 1352, 1324, 1246	3.68 (3H, s), 5.78 (2H, s), 6.82 (2H, d, J=8.6 Hz), 7.03 (2H, d, J=8.6 Hz), 7.18 (1H, t, J=7.3 Hz), 7.34—7.40 (1H, m), 7.61 (1H, d, J=8.6 Hz), 7.77 (1H, d, J=7.9 Hz), 7.92 (1H, s), 8.43 (2H, br s), 8.60 (2H, br s), 11.89 (1H, br s)
59	1696, 1615, 1569, 1511, 1475, 1456, 1320, 1242, 1202	6.02 (2H, s), 7.17—7.27 (2H, m), 7.32—7.38 (1H, m), 7.43—7.48 (3H, m), 7.60 (1H, d, J=7.9 Hz), 7.73—7.86 (4H, m), 8.07 (1H, s), 8.43 (2H, br s), 8.67 (2H, br s), 12.04 (1H, br s)
60	1717, 1693, 1620, 1560, 1512, 1475, 1440, 1235, 1212	7.13—7.19 (1H, m), 7.37—7.43 (1H, m), 7.48—7.52 (2H, m), 7.69—7.73 (1H, m), 8.45 (2H, m), 8.70 (2H, m), 11.4—11.8 (2H, m)
61	1691, 1625, 1566, 1518, 1478, 1440, 1385, 1320, 1216	4.16 (3H, d, J=0.7 Hz), 7.21—7.26 (1H, m), 7.44—7.50 (1H, m), 7.62 (1H, d, J=8.6 Hz), 7.74—7.79 (2H, m), 8.48 (2H, br s), 8.66 (2H, br s), 11.93 (1H, br s)

and JEOL JNM-LA300 instruments with tetramethylsilane as an internal standard; chemical shifts are given on the δ scale (ppm), coupling constants (J values) are expressed in hertz (Hz), and the following abbreviations are used. s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=double doublet, dt=double triplet, ddd=double double doublet and br=broad. Mass spectra (MS) were recorded with a Finnigan ITS40 and JEOL JMS-SX-102 mass spectrometer. Infrared (IR) spectra were recorded with a Hitachi 260-10 IR spectrophotometer. Element analysis was done with a Heraeus elemental analyzer. For column chromatography, Merck Kieselgel 60 (70—230 mesh) was used. Yields were not maximized. 1*H*-indole-2-carboxylic acid (**1a**), 1*H*-indole-3-carboxylic acid (**1b**), 1*H*-indole-4-carboxylic acid (**1c**), 1*H*-indole-5-carboxylic acid (**1d**), methyl 1*H*-indole-2-carboxylate (**2a**), methyl 1*H*-indole-3-carboxylate (**2b**) and methyl 1*H*-indole-4-carboxylate (**2c**) were commercial products.

Methyl 1*H*-Indole-5-carboxylate (2d) A mixture of 1*H*-indole-5-carboxylic acid **1d** (1.00 g, 6.21 mmol) and 10% hydrogen chloride/methanol (50 ml) was refluxed for 2 h. The reaction mixture was then poured into ice water and neutralized with sodium bicarbonate. The mixture was extracted three times with ethyl acetate (AcOEt). The combined extracts were washed with aqueous sodium bicarbonate solution. After drying over anhydrous magnesium sulfate ($MgSO_4$), the solvent was distilled off under reduced pressure (0.42 g, 38.6% yield). A portion of the residue was recrystallized from 2-propanol/hexane to give **2d**: mp 118—119 °C (lit.,[20] mp 124—125 °C); ^{1}H-NMR ($CDCl_3$) δ 3.93 (3H, s), 6.64—6.66 (1H, m), 7.26—7.29 (1H, m), 7.40 (1H, dd, J=0.7, 8.6 Hz), 7.91 (1H, dd, J=1.7, 8.6 Hz), 8.3—8.6 (2H, m).

General Procedure for Esterification and *N*-alkylation of 1*H*-Indole Carboxylic Acid. Methyl 1-Methyl-1*H*-indole-2-carboxylate (3a) To a suspension of 60% sodium hydride (0.99 g, 24.8 mmol) in DMF (40 ml) was added 1*H*-indole-2-carboxylic acid **1a** and the mixture was stirred at room temperature for 1 h. A solution of methyl iodide (7.05 g, 49.6 mmol) in DMF (10 ml) was then added dropwise to the mixture at room temperature and the whole stirred at the same temperature for 5 h. The reaction mixture was poured into ice water. The resulting mixture was then extracted three times with AcOEt, and the combined extracts were washed with water. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure and the residue was recrystallized from hexane to give **3a** (1.70 g, 72.4% yield): mp 79—80 °C (lit.,[21] mp 97.5—98.5 °C); ^{1}H-NMR ($CDCl_3$) δ 3.91 (3H, s), 4.08

Table 4. Na^+/H^+ Exchange Inhibitory Activity for *N*-(Aminoiminomethyl)-1*H*-indole Carboxamide Derivatives (**23**—**61**)

Compd.	Activity IC_{50} (nM)	Compd.	Activity IC_{50} (nM)
23	900	**44**	100
24	50	**45**	>10000
25	100	**46**	>10000
26	80	**47**	>10000
27	>10000	**48**	30
28	1000	**49**	15
29	170	**50**	150
30	>3000	**51**	75
31	5500	**52**	90
32	5000	**53**	43
33	>10000	**54**	540
34	700	**55**	100
35	300	**56**	80
36	1000	**57**	880
37	3000	**58**	180
38	150	**59**	750
39	640	**60**	>10000
40	6000	**61**	300
41	1000		
42	100	EIPA	100
43	1300		

(3H, s), 7.12—7.18 (1H, m), 7.30 (1H, s), 7.32—7.41 (2H, m), 7.66—7.70 (1H, m).

In a similar manner to that described above, compounds **3b**—**3d**, **7a** and **7b** were prepared. Starting materials, alkyl halides, yields, melting points (except for **7a**) and spectral data are given below.

Methyl 1-Methyl-1*H*-indole-3-carboxylate (**3b**)[22]: 1*H*-indole-3-carboxylic acid **1b**, methyl iodide, 80.9%, mp 85—86 °C (from methanol), ^{1}H-NMR ($CDCl_3$) δ 3.82 (3H, s), 3.91 (3H, s), 7.24—7.37 (3H, m), 7.77 (1H, s), 8.14—8.20 (1H, m).

Methyl 1-Methyl-1*H*-indole-4-carboxylate (**3c**): 1*H*-indole-4-carboxylic acid **1c**, methyl iodide, 72.4%, mp 48—49 °C (lit.,[23] mp 40—60 °C) (from hexane), ^{1}H-NMR ($CDCl_3$) δ 3.84 (3H, s), 3.98 (3H, s), 7.10—7.11 (1H, m), 7.20 (1H, d, J=3.0 Hz), 7.24—7.29 (1H, m), 7.53 (1H, d, J=8.2 Hz), 7.91 (1H, dd, J=1.0, 7.6 Hz).

Methyl 1-Methyl-1*H*-indole-5-carboxylate (**3d**): 1*H*-indole-5-carboxylic acid **1d**, methyl iodide, 89.4%, mp 105—106 °C (from methanol), ^{1}H-NMR ($CDCl_3$) δ 3.82 (3H, s), 3.93 (3H, s), 6.58 (1H, dd, J=1.0, 3.3 Hz), 7.11 (1H, d, J=3.3 Hz), 7.32 (1H, d, J=8.6 Hz), 7.91—7.95 (1H, m), 8.39—8.40 (1H, m).

Isopropyl 1-Isopropyl-1*H*-indole-5-carboxylate (**7a**): 1*H*-indole-5-carboxylic acid **1d**, isopropyl iodide, 72.3%, oil, ^{1}H-NMR ($CDCl_3$) δ 1.38 (6H, d, J=6.3 Hz), 1.53 (6H, d, J=6.6 Hz), 4.62—4.75 (1H, m), 5.21—5.35 (1H, m), 6.60 (1H, d, J=3.3 Hz), 7.27 (1H, d, J=3.3 Hz), 7.36 (1H, d, J=8.6 Hz), 7.90 (1H, dd, J=1.7, 8.6 Hz), 8.38 (1H, d, J=1.7 Hz); MS *m/z* 245 (M^+).

Benzyl 1-Benzyl-1*H*-indole-5-carboxylate (**7b**): 1*H*-indole-5-carboxylic acid **1d**, benzyl bromide, 66.1%, mp 87—88 °C (from 2-propanol), ^{1}H-NMR ($CDCl_3$) δ 5.33 (2H, s), 5.38 (2H, s), 6.64 (1H, d, J=3.3 Hz), 7.06—7.49 (12H, m), 7.92 (1H, dd, J=1.7, 8.9 Hz), 8.45—8.46 (1H, m).

Methyl 1-Methyl-1*H*-indole-6-carboxylate (3e) To a suspension of 60% sodium hydride (0.68 g, 17.1 mmol) in DMF (50 ml) was added methyl 1*H*-indole-6-carboxylate **2e** (3.00 g, 17.1 mmol) and the mixture was stirred at room temperature for 1 h. A solution of methyl iodide (4.86 g, 34.4 mmol) in DMF (10 ml) was then added dropwise to the mixture at room temperature and the whole stirred at the same temperature for 5 h. The reaction mixture was poured into ice water. The resulting mixture was then extracted three times with AcOEt. The combined extracts were washed with water. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure and the residue was recrystallized from methanol to give **3e** (2.75 g, 86.9%): mp 88—89 °C (lit.,[23] mp 89 °C); ^{1}H-NMR ($CDCl_3$) δ 3.86 (3H, s), 3.95 (3H, s), 6.51—6.53 (1H, m), 7.21 (1H, d, J=3.3 Hz), 7.63 (1H, d, J=8.6 Hz), 7.78—7.82 (1H, m), 8.10 (1H, s).

In a similar manner to that described above, compounds **14a**—**14c** were prepared. Starting materials, yields, melting points (**14a**, **14c**) and spectral data are given below.

Ethyl 1,3-Dimethyl-1*H*-indole-2-carboxylate (**14a**): Ethyl 3-methyl-1*H*-indole-2-carboxylate **13a**, 90.4%, mp 75—76 °C (from methanol) (lit.,[24] 69—70 °C), ^{1}H-NMR ($CDCl_3$) δ 1.42—1.47 (3H, m), 2.59 (3H, s), 4.01 (3H, s), 4.37—4.45 (2H, m), 7.10—7.18 (1H, m), 7.31—7.38 (2H, m), 7.64—7.67 (1H, m).

Ethyl 3-Benzyl-1-methyl-1*H*-indole-2-carboxylate (**14b**): Ethyl 3-benzyl-1*H*-indole-2-carboxylate **13b**, 77.6%, oil, ^{1}H-NMR ($CDCl_3$) δ 1.30—1.33 (3H, m), 4.03 (3H, d, J=0.7 Hz), 4.30—4.38 (2H, m), 4.49 (2H, s), 7.07—7.25 (6H, m), 7.31—7.38 (2H, m), 7.61—7.64 (1H, m); MS *m/z* 293 (M^+).

Ethyl 1-Methyl-3-phenyl-1*H*-indole-2-carboxylate (**14c**)[25]: Ethyl 3-phenyl-1*H*-indole-2-carboxylate **13c**, 99.0%, mp 44—46 °C (from 2-propanol), ^{1}H-NMR ($CDCl_3$) δ 1.01—1.07 (3H, m), 4.08 (3H, s), 4.13—4.21 (2H, m), 7.10—7.16 (1H, m), 7.34—7.42 (7H, m), 7.54 (1H, d, J=8.2 Hz).

In a similar manner to that described above, compounds **17a**—**17k** were prepared by using methyl 1*H*-indole-2-carboxylate **2a** and an appropriate alkyl halide or substituted alkyl halide (see Chart 4). Yields, melting points (**17c**, **17d**, **17f**, **17h**, **17k**) and spectral data are given below.

Methyl 1-Propyl-1*H*-indole-2-carboxylate (**17a**): 60.0%, oil, ^{1}H-NMR ($CDCl_3$) δ 0.94 (3H, t, J=7.3 Hz), 1.76—1.90 (2H, m), 3.91 (3H, s), 4.54 (2H, t, J=7.9 Hz), 7.14 (1H, ddd, J=1.3, 6.6, 7.3 Hz), 7.27—7.45 (3H, m), 7.68 (1H, dt, J=7.9, 1.0 Hz); MS *m/z* 217 (M^+).

Methyl 1-(2-Methoxyethyl)-1*H*-indole-2-carboxylate (**17b**): 85.0%, oil, ^{1}H-NMR ($CDCl_3$) δ 3.28 (3H, s), 3.73 (2H, t, J=5.9 Hz), 3.91 (3H, s), 4.74 (2H, t, J=5.9 Hz), 7.14 (1H, ddd, J=1.0, 6.9, 7.4 Hz), 7.31 (1H, d, J=0.7 Hz), 7.36 (1H, dd, J=1.3, 6.9 Hz), 7.48 (1H, dd, J=0.7, 8.6 Hz), 7.66 (1H, dd, J=1.1, 8.3 Hz); MS *m/z* 233 (M^+).

Methyl 1-Benzyl-1*H*-indole-2-carboxylate (**17c**): 99.3%, mp 81—82 °C (from methanol) (lit.,[26] 84—86 °C), ^{1}H-NMR ($CDCl_3$) δ 3.86 (3H, s), 5.84 (2H, s), 7.02—7.06 (2H, m), 7.13—7.44 (7H, m), 7.70—7.73 (1H, m).

Methyl 1-(2-Phenylethyl)-1*H*-indole-2-carboxylate (**17d**): 33.2%, mp 99—100 °C (from 2-propanol), ^{1}H-NMR ($CDCl_3$) δ 3.06 (2H, t, J=7.9 Hz), 3.90 (3H, s), 4.74—4.80 (2H, m), 7.11—7.33 (9H, m), 7.66—7.69 (1H, m).

Methyl 1-(3-Phenylpropyl)-1*H*-indole-2-carboxylate (**17e**): 83.0%, oil, ^{1}H-NMR ($CDCl_3$) δ 2.06—2.22 (2H, m), 2.69 (2H, d, J=8.0 Hz), 3.90 (3H, s), 4.60 (2H, t, J=8.0 Hz), 7.05—7.40 (9H, m), 7.66 (1H, d, J=8.0 Hz); MS *m/z* 293 (M^+).

Methyl 1-(4-Bromobenzyl)-1*H*-indole-2-carboxylate (**17f**): 81.4%, mp 92—93 °C (from 2-propanol), ^{1}H-NMR ($CDCl_3$) δ 3.87 (3H, s), 5.79 (2H, s), 6.92 (2H, dd, J=2.0, 6.6 Hz), 7.15—7.23 (1H, m), 7.31—7.38 (5H, m), 7.70—7.74 (1H, m).

Methyl 1-(4-Methoxybenzyl)-1*H*-indole-2-carboxylate (**17g**): 84.2%, oil, ^{1}H-NMR ($CDCl_3$) δ 3.74 (3H, s), 3.88 (3H, s), 5.77 (2H, s), 6.77 (2H, dd, J=2.3, 6.6 Hz), 7.02 (2H, d, J=8.0 Hz), 7.12—7.18 (1H, m), 7.26—7.40 (3H, m), 7.68—7.71 (1H, m); MS *m/z* 295 (M^+).

Methyl 1-(2-Naphthylmethyl)-1*H*-indole-2-carboxylate (**17h**): 75.1%, mp 112—113 °C (from 2-propanol), ^{1}H-NMR ($CDCl_3$) δ 3.86 (3H, s), 6.00 (2H, s), 7.14—7.32 (3H, m), 7.37—7.43 (5H, m), 7.66—7.78 (4H, m).

Methyl 1-[3-(2-Tetrahydropyranyl)oxypropyl]-1*H*-indole-2-carboxylate (**17i**): 97.8%, oil, ^{1}H-NMR ($CDCl_3$) δ 1.42—1.97 (6H, m), 2.11 (2H, dt, J=11.2, 5.9 Hz), 3.33 (1H, dt, J=8.3, 7.9 Hz), 3.40—3.55 (1H, m), 3.72—3.88 (2H, m), 3.94 (3H, s), 4.52 (1H, dd, J= 3.0, 4.3 Hz), 4.69 (2H, dt, J=1.7, 0.9 Hz), 7.14 (1H, ddd, J=1.0, 7.0, 7.9 Hz), 7.27—7.37 (2H, m), 7.48 (1H, dd, J=0.9, 8.5 Hz), 7.66 (1H, dt, J=7.9, 1.0 Hz); MS *m/z* 317 (M+).

Methyl 1-[4-(2-Tetrahydropyranyl)oxybutyl]-1*H*-indole-2-carboxylate (**17j**): 75.0%, oil, ^{1}H-NMR ($CDCl_3$) δ 1.30—2.00 (10H, m), 3.31—3.55 (2H, m), 3.70—3.90 (2H, m), 3.91 (3H, s), 4.56 (1H, t, J=3.5 Hz), 4.61 (2H, t, J=7.3 Hz), 7.14 (1H, ddd, J=1.3, 6.9, 7.6 Hz), 7.27—7.38 (2H, m), 7.42 (1H, dd, J=0.7, 8.3 Hz), 7.67 (1H, dt, J=7.9 Hz, 1.0 Hz); MS *m/z* 331 (M^+).

Methyl 1-(3-*tert*-Butoxycarbonylaminopropyl)-1*H*-indole-2-carboxylate (**17k**): 53.0%, mp 80—81 °C (from 2-propanol), ^{1}H-NMR ($CDCl_3$) δ 1.45 (9H, s), 1.90—2.10 (2H, m), 3.00—3.20 (2H, m), 3.91 (3H, s), 4.62 (2H, t, J=6.9 Hz), 4.98 (1H, br s), 7.06—7.20 (1H, m), 7.28—7.44 (3H, m), 7.68 (1H, d, J=7.3 Hz).

Ethyl 7-Carbomethoxy-1*H*-indole-2-carboxylate (9) To a solution of ethyl 2-methylacetacetate (14.4 g, 0.10 mol) in ethanol (100 ml) was added dropwise 50% aqueous potassium hydroxide (50 g) at 0 °C. Ice (70 g) was added to the solution, then a diazonium salt solution prepared by mixing methyl anthranilate (15.1 g, 0.10 mol), sodium nitrite (13.6 g, 0.20 mol) and 35% aqueous hydrochloric acid (60 g) was added to the mixture at once. The reaction mixture was stirred at 0 °C for 30 min and then extracted three times with Et_2O. The combined extracts were washed with water. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure and the residue was added to polyphosphoric acid (PPA) (60 g). The mixture was gradually heated to 190 °C and kept at this temperature for 5 min. The reac-

tion mixture was cooled to 60 °C and water was then added thereto. The mixture was extracted three times with AcOEt. The combined extracts were washed with water. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt/hexane=5/95) followed by recrystallization from hexane to give **9** (7.00 g, 32.5% yield): mp 53—54 °C; ^{1}H-NMR ($CDCl_3$) δ 1.43 (3H, t, J=7.3 Hz), 4.01 (3H, s), 4.39—4.47 (2H, m), 7.17—7.23 (1H, m), 7.28 (1H, d, J=2.3 Hz), 7.89—7.92 (1H, m), 8.02 (1H, dd, J=1.0, 7.6 Hz), 10.24 (1H, br s).

Ethyl 7-Carbomethoxy-1-methyl-1*H*-indole-2-carboxylate (10) In a similar manner to that described for the preparation of **3e**, compound **9** (5.00 g, 20.2 mmol) was methylated to give **10** (5.20 g, 98.5% yield): mp 55—56 °C (from 2-propanol); ^{1}H-NMR ($CDCl_3$) δ 1.39—1.44 (3H, m), 3.99 (3H, s), 4.04 (3H, s), 4.34—4.42 (2H, m), 7.15—7.18 (1H, m), 7.37 (1H, s), 7.71—7.75 (1H, m), 7.81 (1H, dd, J=1.0, 7.9 Hz).

1-Methyl-1*H*-indole-2, 7-dicarboxylic Acid (11) A mixture of ethyl 7-carbomethoxy-1-methyl-1*H*-indole-2-carboxylate **10** (5.20 g, 19.9 mmol), 2 N aqueous sodium hydroxide (90 ml) and ethanol (150 ml) was refluxed for 3 h. The reaction mixture was concentrated under reduced pressure. 2 N aqueous hydrochloric acid was added to acidify the reaction mixture. The precipitated solid was filtered and dried under reduced pressure and the solid was recrystallized from 2-propanol to give **11** (4.30 g, 98.6% yield): mp 292 °C ; ^{1}H-NMR (dimethyl sulfoxide-d_6 (DMSO-d_6)) δ 4.00 (3H, s), 7.14—7.20 (1H, m), 7.34 (1H, s), 7.65 (1H, dd, J=1.0, 7.3 Hz), 7.85 (1H, dd, J=1.0, 7.9 Hz), 13.10 (1.7H, br s).

Methyl 1-Methyl-1*H*-indole-7-carboxylate (12) A mixture of 1-methyl-1*H*-indole-2,7-dicarboxylic acid (4.60 g, 21.0 mmol), CuO (0.50 g) and quinoline (50 ml) was stirred for 1 h with heating at 180 °C. After cooling, the reaction mixture was poured into 2 N aqueous hydrochloric acid (200 ml). The mixture was extracted three times with AcOEt and the combined extracts were washed with brine. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (methanol/chloroform=3/97) to give 1-methyl-1*H*-indole-7-carboxylic acid (1.82 g, 49.0% yield). To a solution of this acid (1.82 g, 10.4 mmol) in methanol (70 ml) was added dropwise thionyl chloride (3.09 g, 26.0 mmol) at 0 °C. The reaction mixture was refluxed for 2 h and the solvent was then distilled off under reduced pressure. Ice water was poured onto the resulting residue and 28% aqueous ammonium hydroxide was added to render the mixture alkaline. The mixture was extracted three times with AcOEt. The combined extracts were washed with water and dried over $MgSO_4$. The solvent was then distilled off under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane=5/95) to give **12** (1.16 g, 59.0% yield) as an oil.: ^{1}H-NMR ($CDCl_3$) δ 3.88 (3H, s), 3.96 (3H, s), 6.54 (1H, d, J=3.3 Hz), 7.05 (1H, d, J=3.3 Hz), 7.10 (1H, t, J= 7.6 Hz), 7.67 (1H, d, J=7.3 Hz), 7.75—7.78 (1H, m); MS *m/z*: 189 (M^+).

General Procedure for N-Alkylation of Methyl 1*H*-Indole Carboxylate. Methyl 1-Isopropyl-1*H*-indole-3-carboxylate (4a)[27] To a suspension of 60% sodium hydride (0.46 g, 11.4 mmol) in DMF (25 ml) was added methyl 1*H*-indole-3-carboxylate **2b** (2.00 g, 11.4 mmol) and the mixture was stirred at room temperature for 1 h. A solution of isopropyl iodide (2.13 g, 12.6 mmol) in DMF (10 ml) was then added to the mixture at room temperature and the whole heated at 80 °C for 5 h. The reaction mixture was poured into ice water. The resulting mixture was then extracted three times with AcOEt. The combined extracts were washed with water. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt/hexane=5/95) to give **4a** (1.91 g, 77.0% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ 1.56 (6H, d, J=6.9 Hz), 3.92 (3H, s), 4.64—4.74 (1H, m), 7.24—7.31 (2H, m), 7.39—7.42 (1H, m), 7.96 (1H, s), 8.15—8.20 (1H, m); MS *m/z*: 217 (M^+).

In a similar manner to that described above, compounds **5a**, **6a**, **4b**, **5b** and **6b** were prepared. Starting materials, alkyl halides, yields, melting points (**4b**, **6a**, **6b**) and spectral data are given below.

Methyl 1-Isopropyl-1*H*-indole-4-carboxylate (**5a**): Methyl 1*H*-indole-4-carboxylate **2c**, isopropyl iodide, 65.9%, oil, ^{1}H-NMR ($CDCl_3$) δ 1.54 (6H, d, J=6.6 Hz), 3.98 (3H, s), 4.67—4.77 (1H, m), 7.14 (1H, d, J=3.3 Hz), 7.24 (1H, t, J=7.9 Hz), 7.37 (1H, d, J=3.3 Hz), 7.58 (1H, d, J=8.3 Hz), 7.88—7.91 (1H, m); MS *m/z*: 217 (M^+).

Methyl 1-Isopropyl-1*H*-indole-6-carboxylate (**6a**): Methyl 1*H*-indole-6-carboxylate **2e**, isopropyl iodide, 64.5%, mp 86—87 °C (from hexane), ^{1}H-NMR ($CDCl_3$) δ 1.55 (6H, d, J=6.9 Hz), 3.94 (3H, s), 4.73—4.83 (1H, m), 6.54—6.55 (1H, m), 7.38 (1H, d, J=3.3 Hz), 7.62 (1H, dd, J=0.7, 8.3 Hz), 7.76—7.80 (1H, m), 8.15 (1H, s).

Methyl 1-Benzyl-1*H*-indole-3-carboxylate (**4b**): Methyl 1*H*-indole-3-carboxylate **2b**, benzyl bromide, 94.4%, mp 64—65 °C (from 2-propanol) (lit.,[28] mp 67.0—67.5 °C), ^{1}H-NMR ($CDCl_3$) δ 3.91 (3H, s), 5.34 (2H, s), 7.13—7.17 (2H, m), 7.20—7.36 (6H, m), 7.85 (1H, s), 8.17—8.21 (1H, m).

Methyl 1-Benzyl-1*H*-indole-4-carboxylate (**5b**): Methyl 1*H*-indole-4-carboxylate **2c**, benzyl bromide, 99.0%, oil, ^{1}H-NMR ($CDCl_3$) δ 3.99 (3H, s), 5.36 (2H, s), 7.05—7.09 (2H, m), 7.17—7.33 (6H, m), 7.45—7.48 (1H, m), 7.90 (1H, dd, J=1.0, 7.6 Hz); MS *m/z*: 265 (M^+).

Methyl 1-Benzyl-1*H*-indole-6-carboxylate (**6b**): Methyl 1*H*-indole-6-carboxylate **2e**, benzyl bromide, 99.0%, mp 78—79 °C (from 2-propanol-hexane), ^{1}H-NMR ($CDCl_3$) δ 3.90 (3H, s), 5.37 (2H, s), 6.57—6.58 (1H, m), 7.08—7.11 (2H, m), 7.24—7.37 (4H, m), 7.65 (1H, d, J=8.3 Hz), 7.78—7.82 (1H, m), 8.08 (1H, s).

General Procedure for Preparation of Ethyl 3-Substituted-1*H*-indole-2-carboxylate. Ethyl 3-Methyl-1*H*-indole-2-carboxylate (13a) To a solution of ethyl 2-ethylacetacetate (15.8 g, 0.10 mmol) in ethanol (100 ml) was added dropwise 50% aqueous potassium hydroxide (50 g) at 0 °C. Ice (167 g) was added to the solution, then a diazonium salt solution prepared by mixing aniline (9.30 g, 0.10 mol), sodium nitrite (7.50 g, 0.11 mol) and 35% aqueous hydrochloric acid (42 ml) was added to the mixture at once. The reaction mixture was stirred at 0 °C for 30 min and then extracted three times with Et_2O. The combined extracts were washed with water. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure and the residue was added to 10% hydrochloric acid/ethanol (80 ml). The mixture was refluxed for 15 min and then poured into ice water. The mixture was extracted three times with Et_2O. The combined extracts were washed successively with water and aqueous sodium bicarbonate solution. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt/hexane=3/97) followed by recrystallization from methanol to give **13a** (14.0 g, 69.0% yield): mp 133—134 °C (lit.,[29] mp 132—133 °C); ^{1}H-NMR ($CDCl_3$) δ 1.41—1.46 (3H, m), 2.61 (3H, s), 4.42 (2H, dd, J=7.3, 14.2 Hz), 7.11—7.17 (1H, m), 7.29—7.38 (2H, m), 7.66 (1H, d, J=7.9 Hz), 8.71 (1H, br s).

In a similar manner to that described above, compounds **13b** and **13c** were prepared using aniline and an appropriate ethyl 2-substituted acetoacetate (Chart 3 A). Yields, melting points and spectral data are given below.

Ethyl 3-Benzyl-1*H*-indole-2-carboxylate (**13b**): 63.9%, mp 144—145 °C (from 2-propanol) (lit.,[30] mp 144—146 °C), ^{1}H-NMR ($CDCl_3$) δ 1.35—1.40 (3H, m), 4.36—4.44 (2H, m), 4.51 (2H, s), 7.06—7.40 (8H, m), 7.61 (1H, d, J= 7.9 Hz), 8.79 (1H, br s).

Ethyl 3-Phenyl-1*H*-indole-2-carboxylate (**13c**): 52.2%, mp 136—137 °C (from 2-propanol) (lit.,[31] mp 137—138 °C), ^{1}H-NMR ($CDCl_3$) δ 1.23 (3H, t, J=7.3 Hz), 4.29 (2H, dd, J=7.3, 14.2 Hz), 7.11—7.17 (1H, m), 7.32—7.48 (5H, m), 7.54—7.57 (2H, m), 7.63 (1H, d, J=7.9 Hz), 9.09 (1H, br s).

Ethyl 3-Methoxymethyloxy-1-methyl-1*H*-indole-2-carboxylate (16) A mixture of ethyl-3-hydroxy-1-methyl-1*H*-indole-2-carboxylate **15** (1.93 g, 8.80 mmol), chloromethylmethylether (1.06 g, 13.2 mmol), potassium carbonate (3.65 g, 26.4 mmol) and DMF (70 ml) was stirred at room temperature for 2 h. The reaction mixture was filtered, and the filtrate was poured into cooled brine. The mixture was extracted with AcOEt. The extract was washed with brine and dried over anhydrous sodium sulfate. The solvent was then distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (AcOEt/hexane=1/25) to give **16** (1.96 g, 85.0% yield) as an oil: ^{1}H-NMR ($CDCl_3$) δ 1.43 (3H, t, J=7.1 Hz), 3.67 (3H, s), 3.98 (3H, s), 4.42 (2H, q, J=7.1 Hz), 5.24 (2H, s), 7.12 (1H, m), 7.33—7.35 (2H, m), 7.75 (1H, m); MS *m/z*: 263 (M^+).

1-Isopropyl-1*H*-indole-2-carboxylic Acid (8) To a suspension of 60% sodium hydride (1.36 g, 34.2 mmol) in DMF (80 ml) was added methyl 1*H*-indole-2-carboxylate **2a** (6.00 g, 34.2 mmol) and the mixture was stirred at room temperature for 1 h. A solution of isopropyl iodide (6.40 g, 37.7 mmol) in DMF (20 ml) was then added at room temperature and the mixture heated at 80 °C for 5 h. The reaction mixture was poured into ice water. The resulting mixture was then extracted three times with AcOEt, and the combined extracts were washed with water. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure. The residue was then added to a mixture of 2 N aqueous sodium hydroxide (150 ml) and ethanol (150 ml). The reaction mixture was refluxed for 1 h and the solvent was distilled off under reduced pressure. Thereafter ice water was added to the residue and the resulting mixture was acidified with 35% aqueous hydrochloric acid and extracted three times with AcOEt. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure. The residue was recrystallized from aqueous methanol to give **8** (3.71 g, 53.3% yield): mp 112—113 °C; ^{1}H-NMR (DMSO-d_6) δ 1.58 (6H, d, J=6.9 Hz), 5.74—5.85 (1H, m), 7.05—7.11 (1H, m), 7.19—7.28 (2H, m), 7.64—7.72 (2H, m), 12.9 (1H, br s).

Ethyl 1-(2-Carboxyethyl)-1*H*-indole-2-carboxylate (19) A mixture of ethyl 1*H*-indole-2-carboxylate **18**[32] (9.50 g, 50.2 mmol), ethyl acrylate (6.03 g, 60.2 mmol), 40% methanol solution of *N*-benzyltrimethylammonium hydroxide (4.20 g, 10.0 mmol) and 1,4-dioxane (120 ml) was stirred at 65 °C for 6 h. The reaction mixture was concentrated under reduced pressure and the resulting residue was added to AcOEt (500 ml). The organic layer was washed with brine. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure. The residue was then added to a mixture of acetic acid (250 ml) and 30% aqueous sulfuric acid (250 ml). The mixture was stirred at 75 °C for 2.5 h. The reaction mixture was then cooled to room temperature. Water (600 ml) was added dropwise to the mixture and the precipitated solid was filtered and dried under reduced pressure. The solid was recrystallized from acetonitrile to give **19** (8.72 g, 71.5% yield): mp 122—123 °C; ^{1}H-NMR ($CDCl_3$) δ 1.39—1.44 (3H, m), 2.88—2.94 (2H, m), 4.38 (2H, dd, J=7.3, 14.2 Hz), 4.83—4.89 (2H, m), 7.13—7.19 (1H, m), 7.33—7.39 (2H, m), 7.45—7.48 (1H, m), 7.67 (1H, dd, J=1.0, 7.25 Hz).

Ethyl 1-(2-Carbamoylethyl)-1*H*-indole-2-carboxylate (20) A mixture of ethyl 1-(2-carboxyethyl)-1*H*-indole-2-carboxylate **19** (2.00 g, 7.65 mmol), 1,1′-carbonyldiimidazole (1.49 g, 9.19 mmol) and THF (60 ml) was stirred at room temperature for 2.5 h. The reaction mixture was then cooled to 0 °C and ammonia gas was introduced to the mixture at 0 °C for 1 h. After being stirred at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure and the resulting residue was added to AcOEt. The organic layer was washed successively with saturated aqeuous ammonium chloride and brine. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (methanol/chloroform=5/95) followed by recrystallization from 2-propanol: hexane to give **20** (1.69 g, 84.5% yield): mp 125—126 °C; ^{1}H-NMR ($CDCl_3$) δ 1.42 (3H, t, J=7.2 Hz), 2.71—2.76 (2H, m), 4.34—4.41 (2H, m), 4.81—4.86 (2H, m), 5.61 (1H, br s), 5.76 (1H, br s), 7.12—7.17 (1H, m), 7.32—7.37 (2H, m), 7.51 (1H, d, J=8.6 Hz), 7.65 (1H, d, J=7.9 Hz).

General Procedure for the Preparation of *N*-(Aminoiminomethyl)-1*H*-indole Carboxamide Derivatives (23—61). *N*-(Aminoiminomethyl)-1-methyl-1*H*-indole-2-carboxamide Hydrochloride (24) [Method A] A mixture of guanidine hydrochloride (8.58 g, 89.8 mmol), sodium methoxide (4.85 g, 89.8 mmol) and methanol (70 ml) was stirred at room temperature. The precipitated sodium chloride was filtered off to obtain the solution. Then methyl 1-methyl-1*H*-indole-2-carboxylate **3a** (1.70 g, 8.97 mmol) was added to the thus obtained solution. Subsequently methanol was distilled off under reduced pressure. The resulting residue was heated at 130 °C for 5 min and then allowed to stand at room temperature for 1 h. Thereafter water was poured onto the reaction mixture and the mixture was extracted three times with AcOEt. The combined extracts were washed with water. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure. The resulting residue was purified by silica gel column chromatography (methanol/chloroform=3/97) to give the *N*-(aminoiminomethyl)-1-methyl-1*H*-indole-2-carboxamide. The compound was dissolved in chloroform and treated with hydrogen chloride/diethyl ether to give *N*-(aminoiminomethyl)-1-methyl-1*H*-indole-2-carboxamide hydrochloride **24** (0.70 g, 30.8% yield).

In a similar manner to that described above (method A), compounds **23**, **26—35**, **38—42**, **44—46**, **48—50** and **57—61** were prepared. Starting materials and yields are listed in Table 1. Physical data are listed in Table 2. Spectral data are listed in Table 3.

***N*-(Aminoiminomethyl)-1-isopropyl-1*H*-indole-2-carboxamide Hydrochloride (25) [Method B]** A mixture of 1-isopropyl-1*H*-indole-2-carboxylic acid **8** (2.00 g, 9.84 mmol), 1,1′-carbonyldiimidazole (2.39 g, 14.8 mmol) and THF (60 ml) was stirred at room temperature for 2 h and then at 45 to 50 °C for 1 h. After cooling to room temperature, a mixture of guanidine hydrochloride (5.64 g, 59.0 mmol), triethylamine (5.97 g, 59.0 mmol) and DMF (30 ml) was added to the reaction mixture and the whole stirred at room temperature for 12 h. The mixture was then distilled off under reduced pressure and water was added to the resulting residue. The pH was adjusted to between 5 and 6 with 2 N aqueous hydrochloric acid, and the mixture was extracted three times with AcOEt. After drying over $MgSO_4$, the extract was treated with hydrogen chloride/diethyl ether. The precipitated solid was filtered and dried under reduced pressure to give *N*-(aminoiminomethyl)-1-isopropyl-1*H*-indole-2-carboxamide hydrochloride **25** (1.31 g, 47.4% yield). Physical data are listed in Table 2. Spectral data are listed in Table 3.

***N*-(Aminoiminomethyl)-1-isopropyl-1*H*-indole-5-carboxamide Hydrochloride (36) [Method C]** A mixture of guanidine hydrochloride (5.61 g, 58.7 mmol), sodium methoxide (3.17 g, 58.7 mmol) and DMF (20 ml) was stirred at room temperature for 1 h. A solution of isopropyl 1-isopropyl-1*H*-indole-5-carboxylate **7a** (0.72 g, 2.93 mmol) in DMF (10 ml) was then added dropwise to the mixture at room temperature and the whole stirred at the same temperature for 1 d. The reaction mixture was poured into brine. The resulting mixture was then extracted two times with AcOEt. The combined extracts were washed two times with brine. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure. The residue was dissolved in ethanol and treated with hydrogen chloride/ethanol to give *N*-(aminoiminomethyl)-1-isopropyl-1*H*-indole-5-carboxamide hydrochloride **36** (0.56 g, 67.9% yield).

In a similar manner to that described above (method C), compounds **37** and **53—55** were prepared. Compound **43** was obtained by treating with methanesulfonic acid/ aqueous 2-propanol instead of with hydrogen chloride/ethanol. Starting materials and yields are listed in Table 1. Physical data are listed in Table 2. Spectral data are listed in Table 3.

***N*-(Aminoiminomethyl)-3-hydroxy-1-methyl-1*H*-indole-2-carboxamide Methanesulfonate (47) [Method D]** A mixture of guanidine hydrochloride (7.12 g, 74.5 mmol), sodium methoxide (4.02 g, 74.5 mmol) and DMF (50 ml) was stirred at room temperature for 1 h. A solution of ethyl 3-methoxymethyloxy-1-methyl-1*H*-indole-2-carboxylate **16** (1.95 g, 7.45 mmol) in DMF (30 ml) was then added dropwise to the mixture at 0 °C and the whole stirred at room temperature for 1 d. The reaction mixture was poured into ice water. The resulting mixture was then extracted with AcOEt. The extract was washed with brine. After drying over $MgSO_4$, the solvent was distilled off under reduced pressure. The residue was dissolved in THF and treated with methanesulfonic acid to give crude *N*-(aminoiminomethyl)-3-methoxymethyloxy-1-methyl-1*H*-indole-2-carboxamide methanesulfonate. This crude product was then added to a mixture of 35% aqueous hydrochloric acid (5 ml) and THF (80 ml) and stirred at room temperature for 2 h. The reaction mixture was poured into aqueous ammonium hydroxide. The resulting mixture was extracted with AcOEt, and the extract was washed with brine. After drying over anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The residue was dissolved in THF and treated with methanesulfonic acid to give crude *N*-(aminoiminomethyl)-3-hydroxy-1-methyl-1*H*-indole-2-carboxamide methanesulfonate **47** (1.47 g). This crude product was washed with methanol to give pure **47** (1.20 g, 50.0% yield). Physical data are listed in Table 2. Spectral data are listed in Table 3.

***N*-(Aminoiminomethyl)-1-(3-hydroxypropyl)-1*H*-indole-2-carboxamide Hydrochloride (51) [Method E]** The reaction was carried out in a manner similar to that for the preparation of compound **22** (method A) except for using methyl 1-[3-(2-tetrahydropyranyl)oxypropyl]-1*H*-indole-2-carboxylate **17i** (1.59 g, 5.01 mmol), guanidine hydrochloride (4.79 g, 50.1 mmol), sodium methoxide (2.71 g, 50.1 mmol) and methanol (30 ml). *N*-(aminoiminomethyl)-1-[3-(2-tetrahydropyranyl)oxypropyl]-1*H*-indole-2-carboxamide was obtained in an amount of 1.04 g, and dissolved in hydrochloric acid/methanol. The solution was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure and then a solvent mixture of methanol and Et_2O was added to the resulting residue. The precipitates that formed were filtered and dried under reduced pressure to give *N*-(aminoimnomethyl)-1-(3-hydroxypropyl)-1*H*-indole-2-carboxamide hydrochloride **51** (0.69 g, 48.6% yield).

In a similar manner to that described above (method E), compounds **52** and **55** were prepared. Starting materials and yields are listed in Table 2. Spectral data are listed in Table 3.

Na^+/H^+ Exchange Inhibitory Activity Assay Cardiac myocytes were isolated by the enzymatic digestion method reported by Isenberg and Klockner[33] and Yamamoto.[34] Briefly, rats [male Sprague-Dawley (SD) rats, 6—7 weeks] were anesthetized with diethyl ether, and hearts were removed and mounted on a modified Langendorff perfusion system for the retrograde perfusion of the coronary circulation. Hearts were perfused first with normal Krebs solution for 5 min; second, with calcium-free Krebs solution for 10 min; third , with calcium-free Krebs solution containing 0.015% collagenase for 5—20 min; and, finally, with Kraftbruhe solution (composition in mM: KCl 70, KH_2PO_4 2, glutamic acidmonopotassium 70, taurine 20, glucose 11, EGTA 0.5, Hepes 10, pH adjusted to 7.4 with Tris) for 5 min. The right ventricle wall was suspended in Kraftbruhe solution and myocytes were dispersed by gentle stirring. After the cells had sedimented, the suspension buffer was displaced by calcium-free Hepes solution, then normal Hepes solution was added stepwise to make the final Ca^{2+} concentration 2.2 mM.

For the measurement of pHi, myocytes were loaded with the membrane permeable acetoxymethyl(AM)ester from the pH sensitive fluorescent indicator 2′,7′-bis(carboxyethyl)-5,6-carboxyfluorescein(BCECF)/AM for 30 min at room temperature. Myocytes loaded with BCECF/AM were then allowed to settle on a laminin coated glass coverslip at the bottom of a small chamber, which was mounted on the stage of an inverted microscope. After adhering to the coverslip, myocytes were superfused with normal Hepes so-

lution. Intracellular BCECF was illuminated at 450 and 490 nm and the BCECF-ratio (490 nm/450 nm) of emitted light signal at 530 nm was measured with a fluorescence image analyzer. The emission intensity ratio (BCECF-ratio) was used an index of pHi.[12] According to the methods of Scholz *et al.*,[12] Nakanishi *et al.*[35] or Loh *et al.*,[36] the Na^+/H^+ exchanger inhibition activity was determined by the inhibition of pHi recovery from acidosis. Intracellular acidification was produced by the NH_4Cl prepulse technique; the cells were perfused first with normal Hepes buffer containing 20 mM NH_4Cl and then with normal Hepes buffer. This measurement was performed under HCO_3^--free conditions, in which the pHi recovery from acidosis is restricted to the Na^+/H^+ exchanger. After the BCECF-ratio had recovered to a normal value, the acidification procedure was repeated again with the test compound or vehicle. The percent recovery of the BCECF-ratio from the negative peak at the second NH_4Cl prepulse against the first NH_4Cl prepulse was determined at each time point and plotted (BCECF-ratio recovery). As the BCECF-ratio recovery rate was linear until 2 min from the peak of acidosis (negative peak of BCECF-ratio), the percent BCECF-ratio recovery at 2 min from the peak of acidosis with the test compound against that with vehicle was determined as the Na^+/H^+ exchanger inhibitory action of the test compound. The concentration of the test compound to inhibit pHi recovery from acidosis by 50% was determined (IC_{50} values) and used as the Na^+/H^+ exchanger inhibitory activity.

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