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Novel 5-HT$_3$ Antagonists. Isoquinolinones and 3-Aryl-2-pyridones

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Synthesis and pharmacological evaluation of a series of 1,2-dihydro-1-[(5-methyl-1-imidazol-4-yl)methyl]-2-oxopyridine 5-HT$_3$ antagonists are described. The key pharmacophoric elements were defined as a basic nitrogen, a linking group capable of hydrogen bonding interactions, and an aromatic moiety. 1,2-Dihydro-2-oxopyridine moiety could be a good linking group because of its nicely planar structure. The steric limitations of the aromatic moiety were investigated by X-ray analysis and computer analysis and shown to be optimal when the aromatic moiety was constrained within an arched planar system, which could be successfully replaced by 3-(2-thienyl)-2-oxopyridine function or 6-amino-7-chloro-1-isoquinolinone function without any loss of the activity. Among the synthesized compounds, **42** showed the most potent activity in the inhibition of Bezold–Jarisch reflex in rats. Compounds **44a** and **64** were orally active in the protection against cisplatin-induced emesis in dogs or ferrets. Structure–activity relationships are discussed.

Recently a great deal of attention has been paid on 5-HT$_3$ receptor antagonists, which have demonstrated high efficacy in the control of cancer chemotherapy-induced emesis as well as in animal models of anxiety and schizophrenia. Since the pilot work in this field was carried out by two research groups[1a,b] which synthesized two series of selective 5-HT$_3$ antagonists (Chart I) typified by MDL 72,222 (**1**) and ICS 205-930 (**2**), new types of selective antagonists have been developed by Glaxo (Ondansetron, **3a**), Beecham (BRL 43694, **4**), Delalande (Zacopride, **5a**), and Pfizer (CP-93,318, **6**).

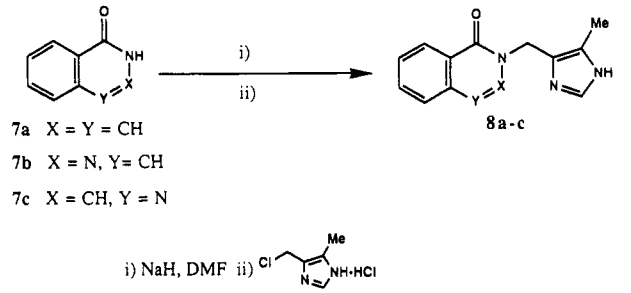
Chemically we paid attention to the carbonyl side chains of the known antagonists because most of the previously reported 5-HT$_3$ antagonists contain the characteristic carbonyl side chain or carbonyl bioisostere such as thiazole in CP-93,318 (**6**).

According to the literature,[2,3] both **3b** (GR 65630) and **5c** were reported to show more potent 5-HT$_3$ antagonistic activity than their corresponding parent compounds **3a** and **5b** (BRL 24682).

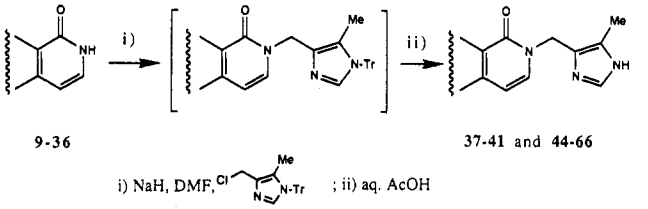
Hybridization of these two information (Chart II) was viewed as an attractive entity for synthetic modification with an expected increased potency compared with the known antagonists. Thus, an expanded synthetic program was undertaken with the aim of developing new potent antagonists.

In this report, we describe the successful modification of **8a** to obtain highly potent antagonists. Compounds **38**, **39**, **42**, **43**, **44a**, **54a**, and **64** were the most potent ones (Table II) among the synthesized compounds. Especially, **44a** and **64** were orally active in the protection against cisplatin-induced emesis (Table IV). Full details of the synthesis, structure–activity relationships, and some pharmacological evaluations are discussed.

Scheme I. Preparation of **8a–c**



Scheme II. Preparation of **37–41** and **44–66**



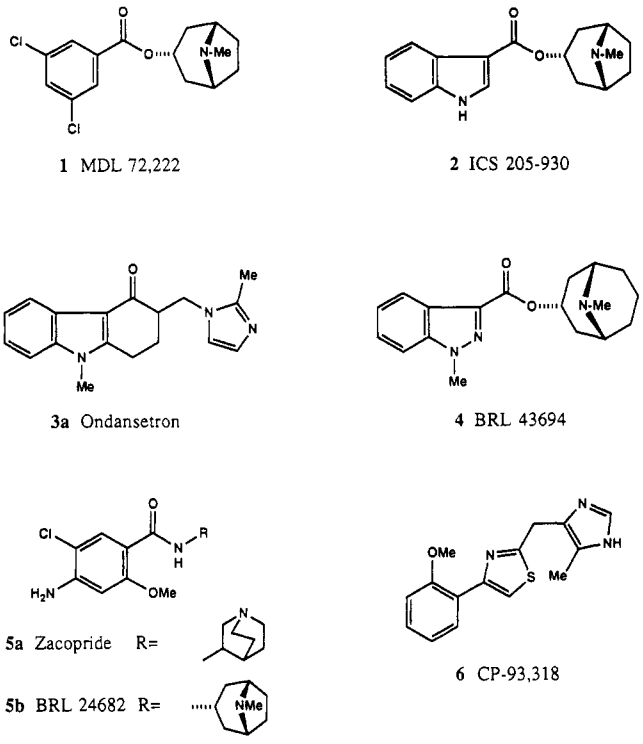
(1) (a) Kilpatrick, G. J.; Bunce, K. T.; Tyers, M. B. 5-HT$_3$ Receptors. *Med. Res. Rev.* **1990**, *10*, 441. (b) Rosen, T.; Nagel, A. A.; Rizzi, J. P. Novel Serotonin-3 Receptor Antagonists. *SYNLETT* **1991**, 213 and references therein.

(2) Frank, D. K.; Steven, D. J. B.; Gareth, J. S. Benzotriazinones as "Virtual Ring" Mimics of *o*-Methoxybenzamides: Novel and Potent 5-HT$_3$ Receptor Antagonists. *J. Med. Chem.* **1990**, *33*, 2942.

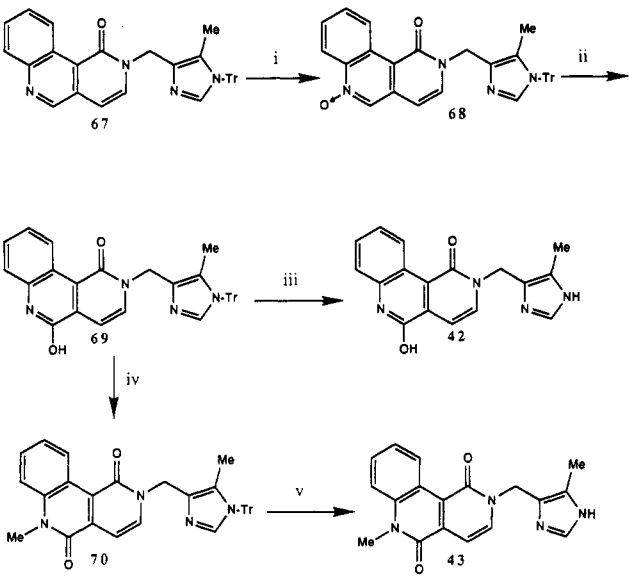
(3) Kilpatrick, G. J.; Jones, B. J.; Tyers, M. B. Identification and distribution of 5-HT$_3$ receptors in rat brain using radioligand binding. *Nature* **1987**, *330*, 746.

0022-2623/92/1835-3307$03.00/0

Chart I



Scheme III. Preparation of **42** and **43**[a]



[a] (i) *m*-CPBA, $CHCl_3$; (ii) *p*-TsCl, K_2CO_3, $CHCl_3$; (iii) Aqueous AcOH; (iv) NaH, DMF, MeI; (v) Aqueous AcOH.

Chemistry

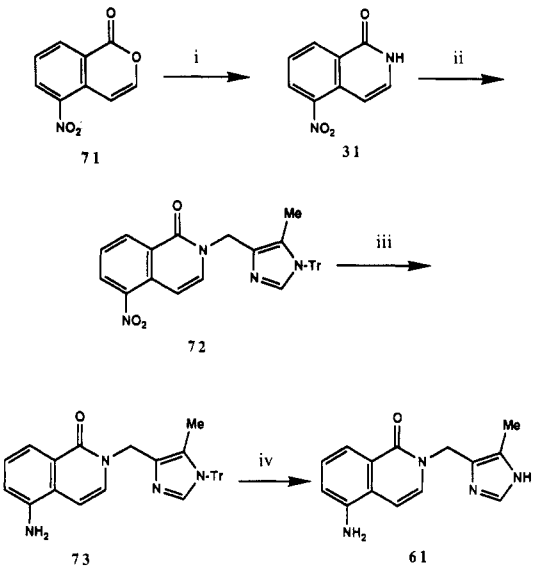
Preparations of **8a–c** (Scheme I) were carried out by simple N-alkylation of commercially available **7a–c** with 4-(chloromethyl)-5-methylimidazole in the presence of sodium hydride in DMF at room temperature.

Most of the key intermediates **10–20, 29–30,** and **32–36** or **21–28** (Chart III) were prepared by Curtius rearrangement of the corresponding α,β-unsaturated cinnamoyl azide or $\alpha,\beta,\gamma,\delta$-dienoyl azide followed by a thermal cyclization of the formed isocyanate,[4] respectively.

As shown in Scheme II, N-alkylation of these 2-pyridone derivatives was carried out with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)imidazole in the presence of sodium hydride in DMF at room temperature. Deprotection under acidic condition gave the desired products **37–41, 44–60,** and **62–66** (Charts IV and V).

Preparations of **42** and **43** are shown in Scheme III. Compound **69** was prepared from **67**, which was prepared by N-alkylation (Scheme II) of **11** and by oxidation with *m*-CPBA followed by rearrangement of the formed *N*-oxide **68**. Deprotection of **69** afforded **42**. N-Methylated **43** was prepared from **69** by methylation with methyl iodide in the presence of sodium hydride in DMF followed by acidic deprotection.

Scheme IV. Preparation of **61**[a]



[a] (i) NH_3, EtOH; (ii) NaH, DMF, 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)imidazole; (iii) HCO_2NH_4, PdC, DMF (iv) Aqueous AcOH.

Table I. Activity of **8a–c**

compd	antagonism of B–J reflex: ID_{50}, μg/kg iv (n = 3)[a]
8a	38.7 (14.3–105)[b]
8b	>100
8c	>100
Ondansetron (**3a**)	0.86 (0.68–1.10)[b]

[a] Number of rats. [b] 95% confidence limits.

Scheme IV displays the preparation of **61**. Compound **72** was prepared from **71** by the treatment with ethanolic ammonia followed by N-alkylation with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)imidazole in a similar manner as described in Scheme II. Transfer hydrogenation by ammonium formate over palladium on carbon in DMF and subsequent deprotection gave **61**.

Pharmacological Results and Discussion

Our initial efforts were started with finding a planar linking group capable of hydrogen bonding.[5,6] Among the compounds synthesized, **8a** containing 2-pyridone as a linking group, was the only one that was discovered to possess the moderate inhibitory activity against B-J

(4) Eloy, F.; Deryckere, A. Sur une Synthese Nouvelle des Dérivés de la Pyridine. *J. Heterocycl. Chem.* **1970**, *7*, 1191.

(5) Turconi, M.; Nicola, M.; Quintero, M. G.; Maiocchi, L.; Micheletti, R.; Giraldo, E.; Donetti, A. Synthesis of a New Class of 2,3-Dihydro-2-oxo-1*H*-benzimidazole-1-carboxylic Acid Derivatives as Highly Potent 5-HT_3 Receptor Antagonists. *J. Med. Chem.* **1990**, *33*, 2101.

(6) Hibert, M. F.; Hoffmann, R.; Miller, R. C.; Carr, A. A. Conformation-Activity Relationship Study of 5-HT_3 Receptor Antagonists and a Definition of a Model for This Receptor Site. *J. Med. Chem.* **1990**, *33*, 1594.

Chart II. Hybridization of **3b** and **5c**

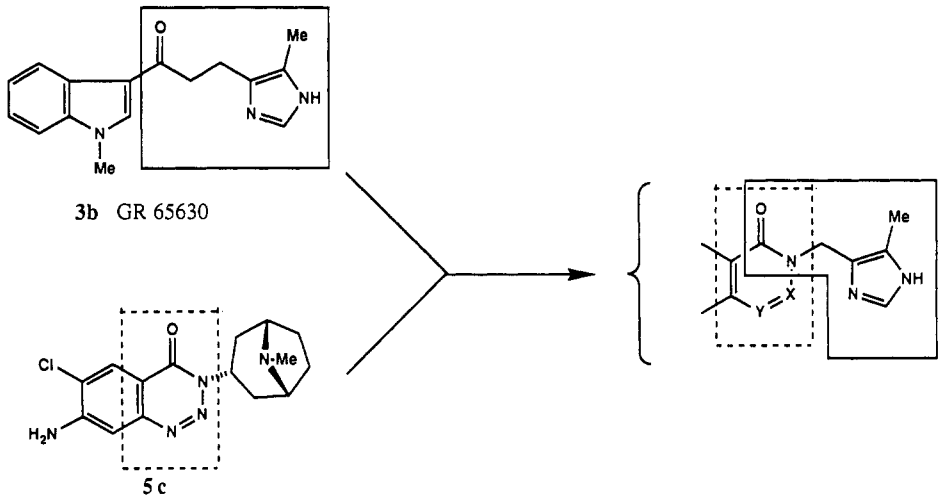
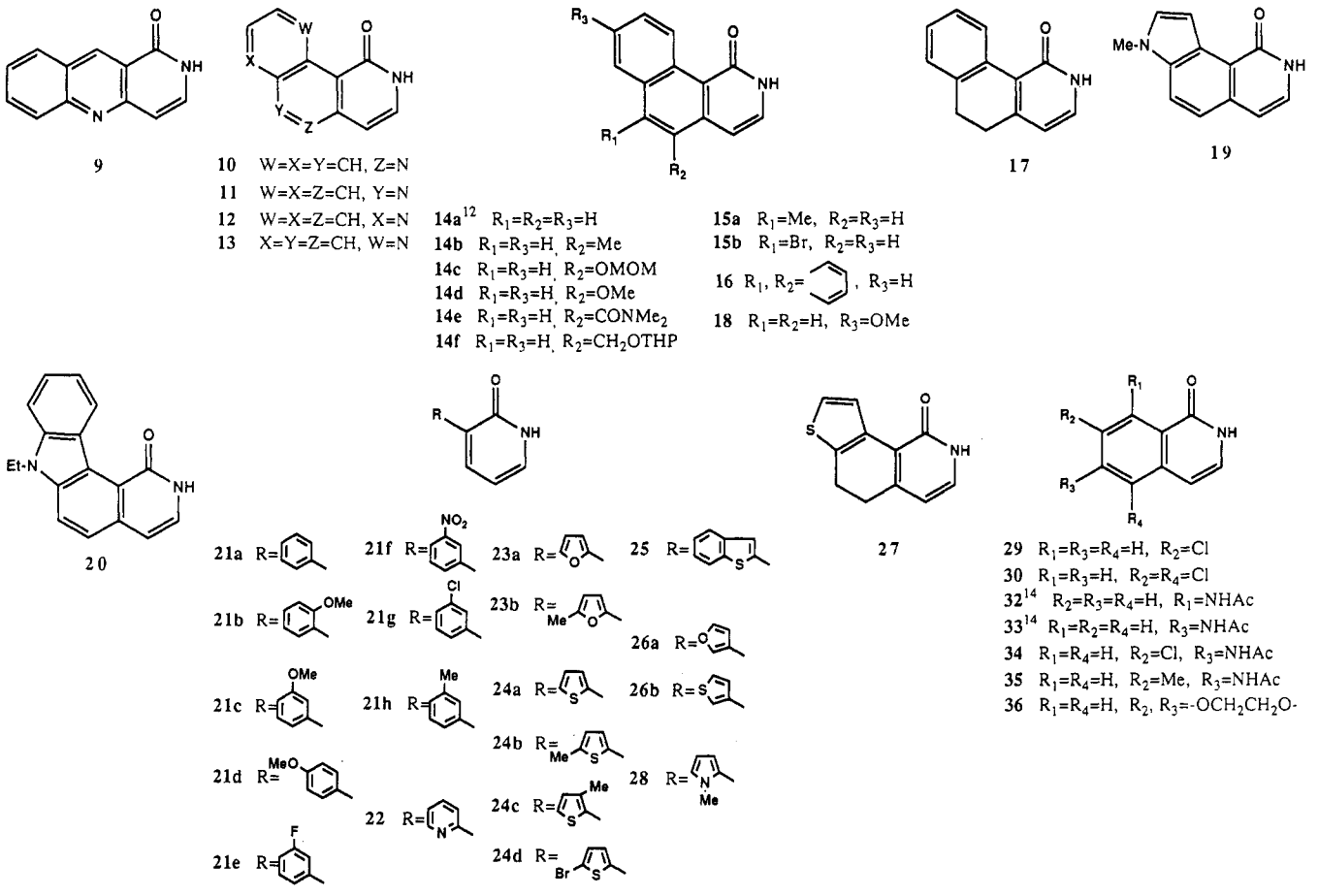


Chart III



functional assay, inducing a transient bradicardia upon intravenous administration of 5-hydroxytryptamine to rats (Table I).

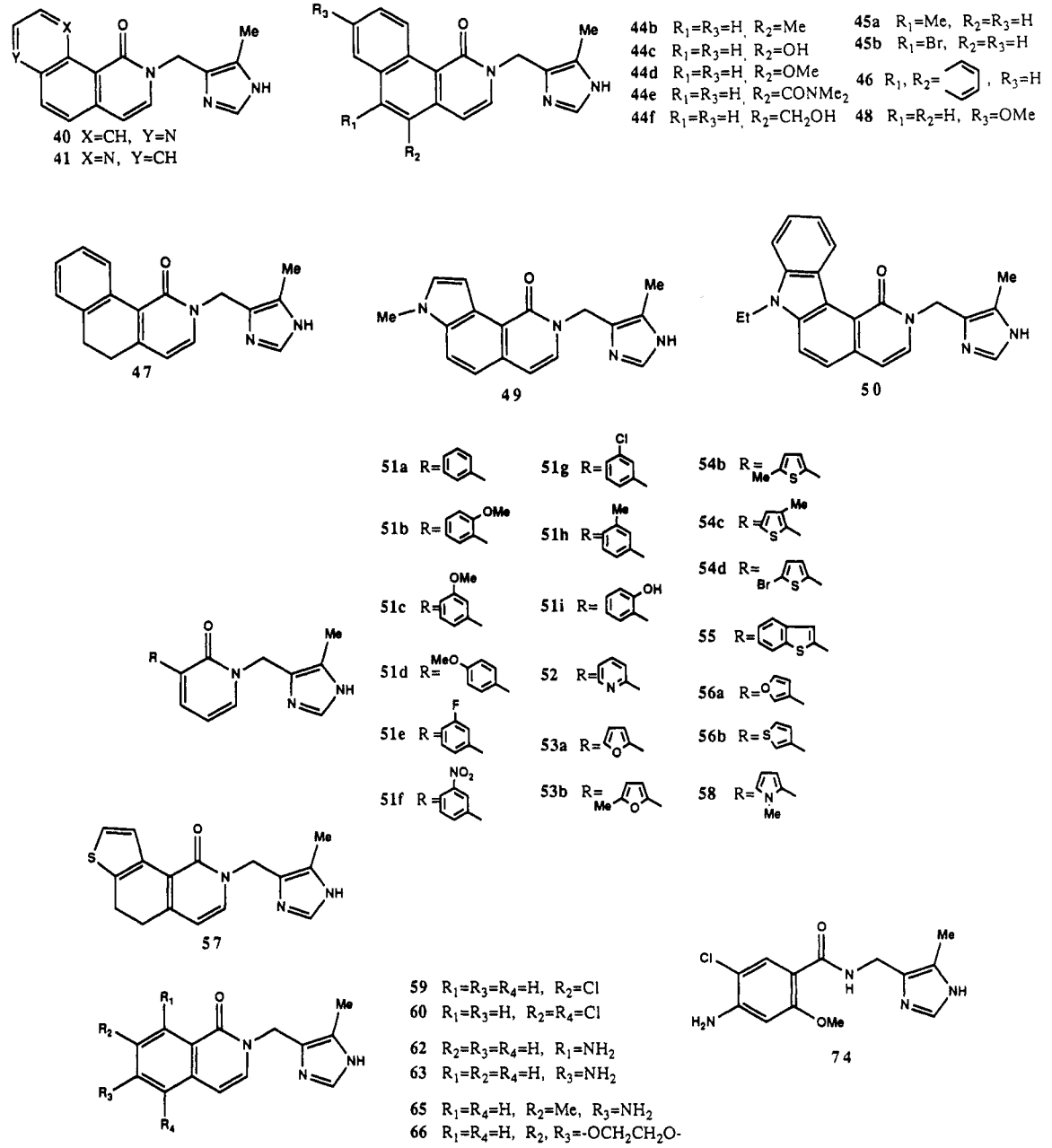
Our next efforts were focused on the modification of the fused benzene ring of **8a**. In order to find the favorable orientation (a or b) for the extension of additional aromatic ring (Chart V), compounds **37**[7] and **38** were synthesized which were easily prepared from **9**[7,8] and **10**, respectively. Compound **38**, which contained an arched tricyclic aromatic moiety, showed approximately 100 times greater potency than **8a** in B-J functional assay upon intravenous administration in rats (Tables I and II). On the other hand, compound **37** showed much less potency than **38**. Based on these results, more favorable orientation of an additional benzene ring was discovered to be a.

This discussion was confirmed to be reasonable because **44a** and **39** also showed potent activity (Table II). But

(7) For the sake of exact comparison, the corresponding carbon analog was needed. But according to Curtius rearrangement method used in the preparation of **14a**, it was impossilbe to obtain another isomer corresponding to **9** even as a minor product. Fortunately the ring B in tricyclic system of **44a** was discovered to be replaceable by pyridine ring.

(8) Eloy, F.; Deryckere, A. Sur un nouveau procédé de synthèse des benzo[*h*]isoquinoléines (aza-3 phénanthrènes). *Chim. Thér.* **1970**, no. 2, 121.

Chart IV



replacement of the additional fused benzene (ring A) by more hydrophilic pyridine ring remarkably reduced the potency as shown in the lesser potency of **40** and **41**. Especially competed formation of hydrogen bonding (N···H-receptor and C=O···H-receptor) between the two hetero atoms, nitrogen (in ring A) and the carbonyl oxygen in **41**, is suggested to give a serious negative effect on the capability of hydrogen bonding formation of the carbonyl oxygen with the receptor because the carbonyl oxygen in **41** is considered to have less chances of hydrogen bonding formation than that in **44a** for the contribution of two different kinds of hydrogen bonding with the receptor. And less lipophilic ring A of **40** was also proved to reduce the potency. More potent antagonistic activity than **38**, **39**, and **44a** was obtained in **42**,[9] while N-methylated **43** showed almost the same potency as **38**, **39**, and **44a**. Potent activity of these two compounds **42** and **43** suggested the possibility of further modification of ring B of the tricyclic aromatic system of **44a**. Compounds **44b–f**, **45a–b**, **46**, and **47** (Chart IV) were synthesized, and their antagonistic activity was investigated (Table II). Remarkable reduction or increase of potency was not observed in these derivatives. The reduction of potency in **48** and **50** and the less reduction in **49** indicate that there is a limitation to the size of the ligand aromatic moiety of the 5-HT_3 antagonists which can fit into the 5-HT_3 receptor.[10]

Quite potent activity of **47** prompted the removal of ring B from the tricyclic aromatic system of **44a**. Some of the 3-phenyl-2-pyridone derivatives **51a–i** still retained the moderate potency. Introduction of relatively hydrophilic bulky groups such as *p*-OCH_3 in **51d** and *m*-NO_2 in **51f** remarkably reduced antagonistic activity. In addition to

(9) For its most potent activity in B-J reflex assay among the synthesized antagonists, **42** showed less potency in antiemetic activity than **44a** after oral administration. Intravenous administration was not tried.

(10) Swain, C. J.; Baker, R.; Kneen, C.; Moseley, J.; Saunders, J.; Seward, E. M.; Stevenson, G.; Beer, M.; Stanton, J.; Watling, K. Novel 5-HT_3 Antagonists. Indole Oxadiazoles. *J. Med. Chem.* **1991**, *34*, 140.

Chart V

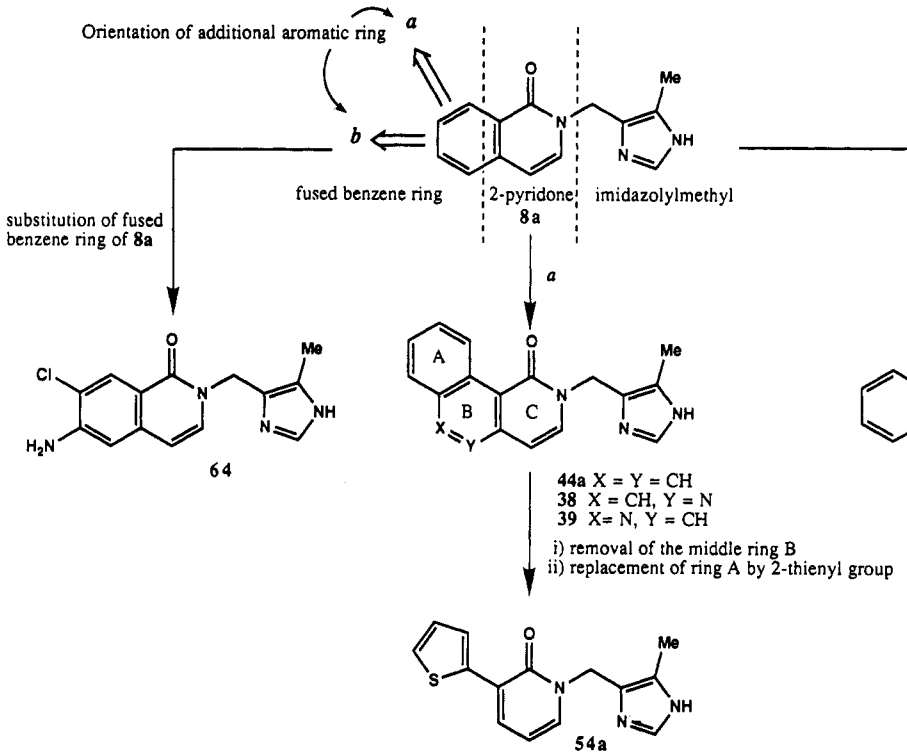


Table II. Inhibition of B–J Reflex by New 5-HT$_3$ Antagonists

compd	antagonism of B–J reflex: ID_{50}, μg/kg iv (n = 3)[a] (95% confidence limits)	compd	antagonism of B–J reflex: ID_{50}, μg/kg iv (n = 3)[a] (95% confidence limits)
37	19.5 (14.1–26.8)	**51e**	29.9 (15.5–57.4)
38	0.16 (0.10–0.24)	**51f**	>100
39	0.28 (0.21–0.36)	**51g**	10.0 (5.11–19.7)
40	2.86 (1.79–4.59)	**51h**	9.03 (5.52–14.8)
41	24.3 (14.7–40.1)	**51i**	40.0 (22.4–71.5)
42	0.05 (0.02–0.12)	**52**	10.4 (6.80–15.9)
43	0.23 (0.18–0.29)	**53a**	0.90 (0.52–1.53)
44a	0.30 (0.20–0.44)	**53b**	9.18 (5.32–15.8)
44b	1.09 (0.64–1.87)	**54a**	0.27 (0.21–0.34)
44c	0.62 (0.46–0.84)	**54b**	3.62 (2.22–5.90)
44d	2.53 (1.66–3.85)	**54c**	0.44 (0.30–0.66)
44e	7.46 (4.95–11.2)	**54d**	7.49 (4.51–12.4)
44f	0.68 (0.41–1.11)	**55**	>100
45a	0.82 (0.64–1.05)	**56a**	8.65 (5.86–12.8)
45b	6.21 (4.54–8.49)	**56b**	3.10 (1.70–5.65)
46	6.95 (4.97–9.70)	**57**	2.78 (1.95–3.95)
47	0.46 (0.28–0.75)	**58**	43.3 (27.8–67.2)
48	56.6 (38.1–84.3)	**59**	25.5 (17.8–36.5)
49	1.64 (0.84–3.23)	**60**	34.6 (20.6–58.2)
50	43.9 (27.1–71.1)	**61**	>100
51a	12.0 (8.21–17.5)	**62**	53.1 (34.2–82.4)
51b	18.2 (12.4–26.9)	**63**	37.9 (24.6–58.3)
51c	26.7 (14.1–50.6)	**64**	0.36 (0.23–0.57)
51d	>100	**65**	4.10 (2.04–8.26)
		66	>100
		74	3.53 (2.38–5.24)

[a] Number of rats.

their hydrophilic ring A, another main cause of the marked reduction of potency in **51b** and **51i** was speculated to be an increased torsion angle between phenyl ring and 2-pyridone ring comparable to that of **44a** or **47**. Introduction of lipophilic groups such as *m*-F, *m*-Cl, and *m*-Me into the phenyl group in **51a** did not give a deleterious effect on antagonistic activity of **51a**.

In order to find a new structure by making their torsion angle less, five-membered aromatic rings which could cause the less steric repulsion were investigated as a smaller aromatic equivalent (Chart VI).

Among the synthesized compounds, 2-furanyl and 2-thienyl derivatives **53a** and **54a** were the optimized ones

Chart VI. Steric Repulsion between Two Rings

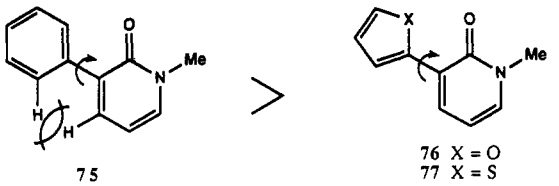
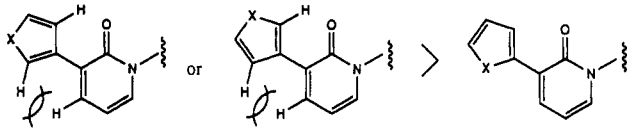


Chart VII. Steric Repulsion between Two Rings

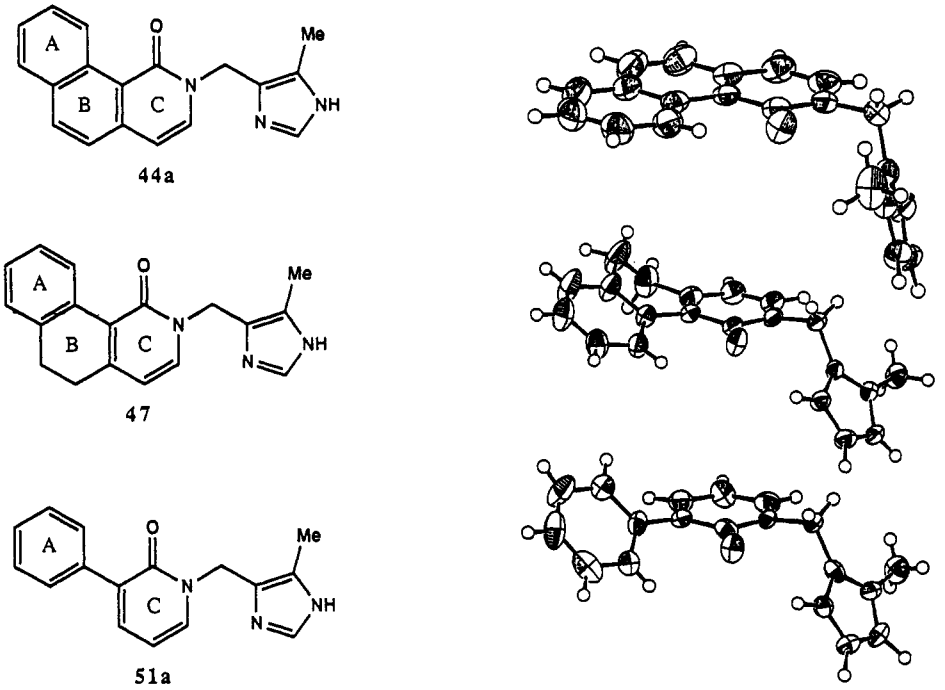


in size in each series (Table II). Furthermore, **54a** was optimized both in size and lipophilicity. Substitution of thiophene resulted in the reduced activity as illustrated in **54b–d** and **55** (Table II). Because of their predictable larger hindrance than that of **53a** and **54a** to approach to the presumed optimized planar structure (Chart VII), 3-furanyl and 3-thienyl derivatives **56a** and **56b** also gave the reduced potency comparing to their corresponding isomers **53a** and **54a**.

Additionally, pyrrole (less lipophilic than furane and thiophene) could be another candidate of a five-membered aromatic ring as far as the size was concerned. The marked reduction in potency of **58** comparing to the other analogous derivatives such as **53a–b**, **54a–d**, and **56a–b** indicates that there is a limitation of aromatic group to both size and lipophilicity. X-ray analysis of **44a**, **47**, and **51a** strongly suggested that an arrangement of rings A and C approaching planarity (Chart VIII) might be optimal for potent activity.

Subsequently, we tried to prove that the furane or thiophene ring of **53a** or **54a** and 2-pyridone could easily approach to the same plane. Unfortunately, we could not obtain good crystal of **54a** for X-ray analysis. For such a reason, conformational analysis of bicyclic aromatic sys-

Chart VIII. The ORTEP[21] Drawings of **44a**, **47**, and **51a**

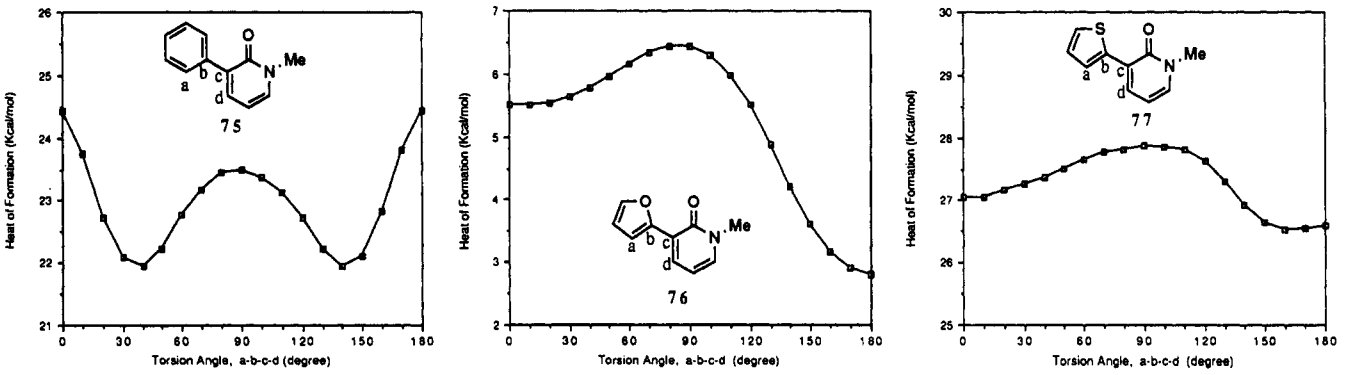


44a: Arrangement of the atoms of 1-oxobenz[*h*]isoquinoline moiety was planar within 0.04 Å;

47: The dihedral angle between 2-pyridone ring and benzene ring was 27°;

51a: The dihedral angle between 2-pyridone ring and benzene ring was 46°.

Chart IX. Heat of Formation Curves by the AM1 Method for the Rotation about the Central Bond (a–b–c–d) in Model Compounds



tems of **51a**, **53a**, and **54a** was tried as an alternative method. To simplify the calculation, corresponding *N*-methyl derivatives **75–77** were used as model compounds (Chart IX).

Based on heat of formation curves by the AM1[11] method for **76**, conformer b (torsion angle, a–b–c–d = 180°) is considered to be the most stable conformer of the furan derivative **76**. Although the most stable conformer is not always optimal structure for binding, the result of this analysis means that this system can easily approach to the presumed optimal structure energetically. The same analysis as described above can be applicable to the case of thiophene derivatives **77**.

For comparison, conformational analysis of phenyl derivative **75** was also conducted. In this case the most stable conformer showed about 40° and 140° of torsion angle which were close to the result of X-ray analysis (46°).

As a result, 1,2-dihydro-3-(2-thieno)-2-pyridone was discovered to be a perfect bioisostere of the arched planar aromatic tricyclic system of 1,2-dihydro-1-benz[*h*]iso-

(11) Dewar, M. J. S.; Zeobisch, E. G.; Healy, E. F.; Stewart, J. J. P. AM1: A New General Purpose Quantum Mechanical Molecular Model. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

Table III. Acute Lethal Toxicity

compd	acute lethal toxicity (mouse)	compd	acute lethal toxicity (mouse)
44a	5/10 (0.4 mg/kg, iv)	**64**	0/10 (50 mg/kg, iv)
54a	6/10 (100 mg/kg, iv)	Ondansetron (**3a**)	5/10 (8.4 mg/kg, iv)

quinolinone moiety of **44a** to serotonin 3 receptor. These analyses, using X-ray or computer, gave a reasonable explanation to the potency of **54a**.

Another attempt to increase the potency of **8a** simply by introducing one or two functional groups into the fused benzene ring of **8a** was also performed. Introduction of chlorine (**59** and **60**) or amino group (**61–63**) could not increase the potency. However, 6-amino-7-chloro-1,2-dihydro-1-isoquinolinone derivative **64**, which is the most rigid form of **74**, showed marked increase in potency which was not accomplished in the other analogously substituted systems such as **65** and **66**. The fused benzene ring (R_1, R_2) in **46** (Chart IV) seems to be too bulky in size to be tolerated by the receptor although the amino substituent in **64** occupies a region of space similar to the fused benzene ring in **46**. Much less potency of **37** should be attributed to the unfavorable orientation of extended π-electron which should be corresponded to the chloro substitutent in **64**.

Tables III and IV summarize the acute lethal toxicity in mice, and the inhibitory effects of the three antagonists **44a**, **54a**, and **64** in ferrets or dogs by oral administration or intravenous administration on cisplatin-induced emesis. These antagonists were the most effective in antiemetic assay.

Thus, a new series of 5-HT$_3$ antagonists has been developed. In particular, **44a** and **64** were shown to be orally active and more potent than Ondansetron (**3a**). Further pharmacological evaluations of these antagonists will be discussed in due course.

Summary and Conclusions

New structures of 5-HT$_3$ antagonists have been developed. In particular, compound **42** showed extremely potent inhibitory activity in B-J reflex assay after intravenous administration. This compound suggested further modification of B ring in **44a** and finally led to another new structure **54a** whose aromatic part was proved to be a perfect bioisostere of the arched planar aromatic system in **44a**. Among all of the compounds synthesized, **44a** and **64** were shown to be orally effective and more potent than Ondansetron (**3a**) both in inhibition of B-J reflex and protection from emesis caused by cisplatin.

In the process of searching for these new 5-HT$_3$ antagonists, we found at least six important criteria to obtain potent antagonistic activity:

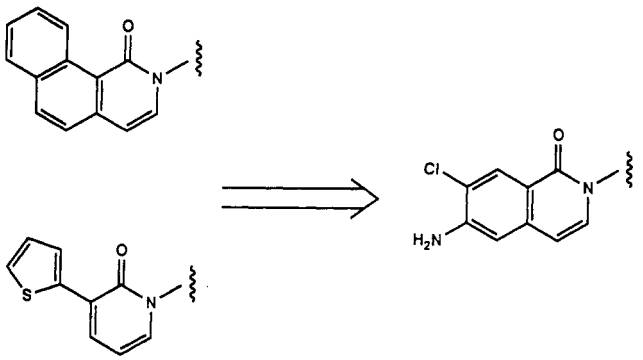
(1) The 2-pyridone function could be one of the optimized linking groups when imidazolyl methyl moiety was used as a basic nitrogen.

Table IV. Protection against Cisplatin-Induced Emesis

		iv (in ferrets)			iv (in dogs)		
compd	dose,[a] mg/kg	n[c]	no. of emetic episodes	no. of retches	n[c]	no. of emetic episodes	no. of retches
control		21	11.3 ± 0.8	137.4 ± 11.5	(9)	13.4 ± 1.7	147.9 ± 18.3
44a	0.01[b]	4	10.8 ± 1.9	144.5 ± 42.2			
	0.03[b]	4	5.0 ± 1.5**	79.0 ± 14.1*	(5)	10.2 ± 3.2	143.8 ± 55.7
	0.1[b]	4	2.0 ± 0.7***	65.0 ± 17.1*	(5)	4.4 ± 3.3*	53.8 ± 46.4*
	0.3[b]	4	0***	11.8 ± 7.3***	(5)	3.4 ± 1.4**	42.4 ± 16.4**
54a	0.03[b]	6	6.0 ± 0.6**	90.8 ± 7.5*			
	0.1[b]	3	1.3 ± 0.7***	22.0 ● 3.6**			
ondansetron	0.03[b]				(4)	10.5 ± 3.4	118.8 ± 35.4
(**3a**)	0.1[b]				(5)	2.2 ± 0.6***	9.0 ± 3.0***
	0.3[b]				(8)	4.1 ± 1.0***	35.4 ± 11.1***
control		9	9.8 ± 0.6	133.0 ± 15.4			
64	0.01	4	10.0 ± 1.5	116.8 ± 13.1			
	0.03	4	4.8 ± 0.9***	71.0 ± 10.5*			
	0.1	4	1.3 ± 0.9***	26.5 ± 15.3**			
	0.3	4	0.8 ± 0.8***	18.8 ± 13.7***			
ondansetron	0.1	4	6.3 ± 1.4	114.0 ± 19.8			
(**3a**)	0.3	4	3.5 ± 0.9***	42.5 ± 7.5**			
	1.0	4	0***	2.5 ± 1.5***			
		po (in ferrets)			po (in dogs)		
compd	dose,[a] mg/kg	n[c]	no. of emetic episodes	no. of retches	n[c]	no. of emetic episodes	no. of retches
control		8	6.3 ± 0.7	90.9 ± 11.7	(15)	9.3 ± 1.0	115.3 ± 17.7
44a	0.1	4	4.8 ± 0.3	89.3 ± 10.9	(5)	10.8 ± 4.4	133.2 ± 71.1
	0.3	4	1.3 ± 0.8**	31.5 ± 8.8**	(5)	4.0 ± 2.1*	27.8 ± 13.5*
	1.0	3	0***	1.0 ± 1.0**	(4)	1.8 ± 0.8**	26.3 ± 10.1*
ondansetron	0.3				(4)	9.0 ± 2.1	112.8 ● 39.7
(**3a**)	1.0				(4)	2.8 ± 1.6**	29.8 ± 20.1*
	3.0				(4)	2.0 ± 0.6**	22.8 ± 11.4*
control		12	11.3 ± 0.8	137.8 ± 14.3			
64	0.03	3	8.8 ± 1.2	142.2 ± 14.7			
	0.1	3	1.2 ± 0.8***	18.6 ± 9.5***			
	0.3	3	0.2 ± 0.2***	3.5 ± 3.5***			
ondansetron	0.1	3	8.5 ± 1.4	125.3 ± 17.3			
(**3a**)	0.3	3	6.3 ± 1.3**	84.8 ± 20.3			
	1.0	3	2.3 ± 1.3***	39.5 ± 17.3**			

[a] See the Experimental Section. [b] Animals were pretreated with two doses of the compound. Otherwise stated, animals were pretreated with one dose of the compound. [c] Number of animals. *$P < 0.05$. **$P < 0.01$. ***$P < 0.001$ vs control (Student's t test).

Chart X. Bioisostere of an Arched Planar System



(2) A compact lipophilic aromatic moiety is needed as the component of ring A. A presumed ring A in **64** is speculated to be the chloro substituent.

(3) An arched planar arrangement of aromatic moiety containing linking carbonyl group is definitely necessary as an aromatic moiety.

(4) An arrangement of the aryl (ring A) and the linking group (ring C) approaching planarity may be optimal for the potent antagonistic activity, which was clearly supported by the relationship between the result of X-ray analysis of **44a**, **47**, and **51a** and their potency in B-J reflex inhibition assay. Ring B is not always necessary if the planarity between ring A and C is retained as illustrated in **53a** and **54a**.

(5) The aromatic part of **44a** or **54a** was successfully replaced by 6-amino-7-chloro-1-isoquinolinone moiety of **64** with any loss of the potency (Chart X).

As far as the positional requirements for the aromatic rings are concerned, there is no perfect overlap between the aromatic rings of **64** and **44a**, **54a**. The same consideration as described in the literature[2] that 6-amino and 7-chloro groups in the 1-isoquinolinone of **64** complement the structural requirements found in the fused naphthalene ring of **44a** or 2-thienyl group attached to the 2-pyridone ring of **54a** could be plausible explanation also in our case.

(6) Additionally the high potency of **38**, **39**, **42**, **43**, and **64** in B-J reflex inhibition strongly suggests the existence of a specific interaction between the ligand nitrogen atom (nitrogen of ring B in **38**, **39**, **42**, **43** and amino substituent in **64**) and a binding pocket in the 5-HT_3 receptor recognition site.

Experimental Section

Chemistry. General Directions. All ^1H NMR spectra were taken on JEOL FX-90Q or Varian VXR-200 spectrometer. MS spectra were obtained on JEOL JMS-DX-303HF. IR spectra were measured on Perkin-Elmer FT-IR 176X. Melting points were uncorrected. Column chromatography was carried out on silica gel (E. Merck, particle size 0.063–0.02 mm). Thin-layer chromatography and preparative chromatography were performed on silica gel (Merck Art no. 5715). All solvents were distilled before use. High-resolution mass spectra of all compounds were within ±3 mmu of the theoretical values.

General Method A. 1,2-Dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxoisoquinoline Hydrochloride (8a). This procedure illustrates the general method for preparation of **8b** and **8c**. To a stirred suspension of NaH (8.28 mmol) in DMF (7 mL) was added a suspension of commercially available isocarbostyril **7a** (300 mg, 2.07 mmol) in DMF (2 mL) under an atmosphere of argon. After the mixture was stirred for 20 min at room temperature, a suspension of 4-(chloromethyl)-5-methylimidazole hydrochloride (690 mg, 4.13 mmol) in DMF (2 mL) was added. The resulting mixture was stirred at room temperature for 40 min. Additional NaH (4.14 mmol) and imidazolyl chloride (345 mg, 2.07 mmol) were added successively, and the mixture was stirred for additional 30 min. The reaction mixture was poured into ice/water and the product was extracted with $CHCl_3$ three times. The combined organic layers were dried ($MgSO_4$) and concentrated to give a brown oil (800 mg), which was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 20:1) to give **8a** (366 mg, 74%) as a pale yellow solid. The solid was converted into the HCl salt by the treatment with methanolic hydrogen chloride. The HCl salt of **8a**: R_f 0.43 ($CHCl_3$/MeOH = 10:1); mp 234–237 °C; ^1H NMR (CD_3OD) δ 8.80 (s, 1 H), 8.35 (brd, 1 H), 6.75 (d, 1 H, J = 7 Hz), 5.28 (s, 2 H), 2.48 (s, 3 H); IR (KBr) 3083, 2992, 2813, 2740, 2653, 2359, 1653, 1623, 1599 cm^{-1}; MS m/e 239 (M^+). Anal. ($C_{14}H_{13}N_3O$·HCl) C, H, N.

1,2-Dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxophthalazine dihydrochloride (8b): yield 30%; R_f 0.71 ($CHCl_3$/MeOH = 5:1); mp 233–236 °C; ^1H NMR ($CDCl_3$ + CD_3OD) δ 8.53 (brs, 1 H), 8.35 (br, 2 H), 5.43 (s, 2 H), 2.45 (s, 3 H); IR (KBr) 3436, 2715, 1648 cm^{-1}; MS m/e 240 (M^+). Anal. ($C_{13}H_{12}N_4O$·HCl) C, H, N.

3,4-Dihydro-3-[[5(4)-methyl-4(5)-imidazolyl]methyl]-4-oxoquinazoline dihydrochloride (8c): yield 60%; R_f 0.34 ($CHCl_3$/MeOH = 5:1); mp 215–218 °C; ^1H NMR ($CDCl_3$ + CD_3OD) δ 9.45 (s, 1 H), 8.83 (s, 1 H), 8.37 (d, 1 H, J = 7 Hz), 8.02 (t like, 1 H, J = 7 Hz), 7.78 (q like, 2 H, J = 7 Hz), 5.42 (s, 2 H), 2.55 (s, 3 H); IR (KBr) 3424, 3107, 2985, 2711, 2618, 1714, 1658, 1558 cm^{-1}; MS m/e 240 (M^+). Anal. ($C_{13}H_{12}N_4O$·HCl) C, H, N.

Compounds 10–15 and 18–20. General Method B. Compounds **10–15** and **18–20** were prepared according to the method described for the preparation of **14a** in the literature.[8]

Compound 10: yield 12%; ^1H NMR ($CDCl_3$) δ 9.92 (d, 1 H, J = 8 Hz), 7.47 (d, 1 H, J = 7 Hz), 6.98 (d, 1 H, J = 7 Hz).

Compound 11: yield 74%; ^1H NMR (DMSO-d_6) δ 12.08 (br, 1 H), 7.63 (t, 1 H, J = 7 Hz), 6.93 (d, 1 H, J = 7 Hz); MS m/e 196 (M^+).

Compound 12: yield 69%; ^1H NMR (DMSO-d_6) δ 11.96 (br, 1 H), 7.53 (t, 1 H, J = 6.8 Hz), 6.83 (d, 1 H, J = 6.8 Hz).

Compound 13: yield 93% (crude). This compound was used for the next reaction without further purification.

Compound 14a[12] (R = H): yield 72%; ^1H NMR ($CDCl_3$) δ 11.7 (br, 1 H), 7.38 (d, 1 H, J = 7 Hz), 6.72 (d, 1 H, J = 7 Hz); MS m/e 195 (M^+).

Compound 14b (R = Me): yield 68%; MS m/e 209 (M^+).

Compound 14c (R = OMOM): yield 65%; MS m/e 225 (M^+).

Compound 14d (R = OMe): yield 71%; ^1H NMR (DMSO-d_6) δ 11.77 (br, 1 H), 4.04 (s, 3 H); MS m/e 225 (M^+).

Compound 14e [R = CON(Me)$_2$]: yield 63%; ^1H NMR (CD_3OD) δ 10.12 (d, 1 H, J = 7.5 Hz), 3.26 (s, 3 H), 2.92 (s, 3 H); MS m/e 266 (M^+).

Compound 14f (R = CH_2OTHP): yield 56%; ^1H NMR ($CDCl_3$) δ 10.61 (br, 1 H), 5.18 (d, 1 H, J = 12 Hz), 4.87 (d, 1 H, J = 12 Hz), 4.80 (t, 1 H, J = 3 Hz), 4.05–3.90 (m, 1 H), 3.65–3.55 (m, 1 H), 2.00–1.50 (m); MS m/e 309 (M^+).

Compound 15a (R = Me): yield 30%; ^1H NMR (DMSO-d_6) δ 10.49 (br, 1 H), 2.75 (s, 3 H); MS m/e 209 (M^+).

Compound 15b (R = Br): yield 53%; ^1H NMR (DMSO-d_6) δ 11.81 (brs, 1 H), 7.47 (t, 1 H, J = 6.3 Hz), 6.75 (d, 1 H, J = 6.3 Hz); MS m/e 275 (M^+ + 1).

Compound 18: yield 62%; ^1H NMR ($CDCl_3$) δ 9.98 (d, 1 H, J = 10 Hz), 3.98 (s, 3 H).

Compound 19: yield 53%; ^1H NMR (DMSO-d_6) δ 11.15 (br, 1 H), 3.92 (s, 3 H); MS m/e 198 (M^+).

Compound 20: yield 50%; ^1H NMR (CD_3OD) δ 9.73 (d, 1 H, J = 10 Hz), 7.98 (d, 1 H, J = 8 Hz), 7.73 (d, 1 H, J = 8 Hz), 7.15 (d, 1 H, J = 5 Hz), 6.80 (d, 1 H, J = 5 Hz), 4.55 (q, 2 H, J = 8 Hz), 1.45 (t, 3 H, J = 8 Hz); MS m/e 262 (M^+).

2-Hydroxy-3-phenylpyridine (21a). Compounds **17** and **21–28** were also prepared according to the general method B[4,8] with α,β,γ,δ-dienoic acid used as a starting material instead of the cinnamic acid derivative.

Compound 21a: yield 63%; ^1H NMR (DMSO-d_6) δ 6.30 (t, 1 H, J = 7 Hz), 7.63 (dd, 1 H, J = 2, 7 Hz), 7.71 (d, 2 H, J = 6

(12) Rivalle, C.; Bisagni, E. Nouvelle synthèse des pyrido[4,3-*b*]-quinoléines substituées sur leur sommet 1. *J. Heterocycl. Chem.* **1980**, *17*, 245.

Hz), 11.78 (br, 1 H); MS m/e 171 (M^+).

Compound 21b (X = *o*-OMe): yield 69%; MS m/e 201 (M^+).

Compound 21c (X = *m*-OMe):[4] yield 74%.

Compound 21d (X = *p*-OMe): yield 68%; MS m/e 201 (M^+).

Compound 21e (X = *m*-F): yield 27%; MS m/e 189 (M^+).

Compound 21f (X = *m*-NO_2): yield 73%; MS m/e 216 (M^+).

Compound 21g (X = *m*-Cl): yield 84%; MS m/e 205 (M^+).

Compound 21h (X = *m*-Me): yield 67%; MS m/e 185 (M^+).

Preparation of Compounds 29,[13] 30, and 32–36. The same procedure as described in the general method B[4,8] was applied to the corresponding cinnamic acid derivatives.

Compound 29: yield 35%; ^{1}H NMR (DMSO-d_6) δ 11.77 (d, 1 H, J = 10 Hz), 6.91 (d, 1 H, J = 7 Hz); MS m/e 181, 179 (M^+).

Compound 30: yield 8%; ^{1}H NMR ($CDCl_3$) δ 8.23 (s, 1 H), 7.88 (1 H, s), 7.65 (d, 1 H, J = 8 Hz), 6.95 (d, 1 H, J = 8 Hz); MS m/e 213 (M^+).

Compound 32: yield 42%,[14] R_f 0.61 ($CDCl_3$/MeOH = 10:1); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ 12.83 (brs, 1 H), 10.90 (brs, 1 H), 8.43 (d, 1 H, J = 8 Hz), 7.38 (t, 1 H, J = 8 Hz), 6.98 (d, 1 H, J = 8 Hz), 6.80 (d, 1 H, J = 7 Hz), 6.23 (d, 1 H, J = 7 Hz), 2.00 (s, 3 H); MS (FAB) m/e 203 (M^+ + 1).

Compound 33: yield 24%;[14] R_f 0.27 ($CDCl_3$/MeOH = 10:1); MS m/e 202 (M^+).

Compound 34: yield 64%; ^{1}H NMR (CD_3OD) δ 8.35 (s, 1 H), 8.33 (1 H, s), 7.14 (d, 1 H, J = 7.5 Hz), 6.59 (d, 1 H, J = 7.5 Hz), 2.28 (s, 3 H); MS m/e 236 (M^+).

Compound 35: yield 36%; ^{1}H NMR (DMSO-d_6) δ 10.45 (brs, 1 H), 8.35 (s, 1 H), 8.15 (s, 1 H), 7.95 (s, 1 H), 6.90 (t, 1 H, J = 7 Hz), 6.35 (d, 1 H, J = 7 Hz), 2.33 (s, 3 H), 2.10 (s, 3 H); MS (FAB) m/e 217 (M^+ + 1).

Compound 36: yield 75%; ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1 H), 7.01 (1 H, s), 6.96 (d, 1 H, J = 8 Hz), 6.50 (d, 1 H, J = 8 Hz), 4.50–4.25 (m, 4 H); MS m/e 203 (M^+).

1,2-Dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxobenz[*h*]isoquinoline Hydrochloride (44a). General Method C. This procedure illustrates the general method for preparation of **37–41, 44–50, 51a–h,** and **52–58**. To a stirred suspension of NaH (1.47 mol) in DMF (3.3 L) was added a solution of 3,4-dihydro-3-azaphenanthrene-4-one (**14a**) (240 g, 1.23 mol) dropwise in an ice/water bath under an atmosphere of argon. The solution was stirred for 20 min at room temperature until evolution of H_2 ceased. A suspension of 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)imidazole (350 g, 0.938 mol) in DMF (1 L) was added. The mixture was stirred at room temperature for 12 h and was poured into ice/water with stirring, and a resulting precipitate was collected by filtration and dried on air at room temperature to give white powder (663 g) which was submitted to the next deprotection reaction without further purification. A heterogeneous mixture of the white powder, AcOH (3 L), and water (3 L) was refluxed for 2 h with stirring. After cooling, a resulting precipitate of triphenylmethyl alcohol was removed by filtration, and the solid was washed with water. The filtrate was concentrated under reduced pressure, and the residue was treated with ethanolic hydrogen chloride under reflux for 2 h. After cooling, a resulting precipitate was collected by filtration to give **44a** (320 g, 80%) as the HCl salt: R_f 0.44 ($CHCl_3$/MeOH = 5:1); mp 220–230 °C dec; ^{1}H NMR (CD_3OD) δ 10.09 (d like, 1 H, J = 8 Hz), 8.72 (s, 1 H), 8.12 (d, 1 H, J = 8.4 Hz), 7.97 (dd, 1 H, J = 2, 8 Hz), 7.79 (d, 1 H, J = 7 Hz), 6.87 (d, 1 H, J = 7 Hz), 5.37 (s, 2 H), 2.50 (s, 3 H); IR (KBr) 3087, 2991, 2820, 2750, 1653, 1611, 1547 cm^{-1}; MS m/e 289 (M^+ – HCl). Anal. ($C_{18}H_{15}N_3O$·HCl) C, H, N.

1,2-Dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxopyrido[4,3-*b*]quinoline dihydrochloride (37): yield 74%; R_f 0.33 ($CHCl_3$/MeOH = 5:1); mp 258 °C dec; ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 9.88 (s, 1 H), 8.80 (s, 1 H), [8.48 (d) and 8.42 (d), 2 H, J = 8 Hz], 7.05 (d, 1 H, J = 10 Hz), 5.40 (s, 2 H), 2.57 (s, 3 H); IR (KBr) 3435, 1678, 1622 cm^{-1}; MS m/e 290 (M^+ – HCl). Anal. ($C_{17}H_{14}N_4O$·2HCl) C, H, N.

1,2-Dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxopyrido[4,3-*c*]isoquinoline dihydrochloride (38): yield 43%; R_f 0.42 ($CHCl_3$/MeOH = 5:1); mp 192–195 °C dec; ^{1}H NMR (DMSO-d_6) δ 14.85–14.50 (br, 1 H), 9.87 (d like, 1 H, J = 8 Hz), 9.70 (s, 1 H), 8.98 (s, 1 H), 8.40–8.30 (m, 2 H), 8.08 (ddd, 1 H, J = 2, 7, 8 Hz), 7.85 (ddd, 1 H, J = 1, 7, 8 Hz), 7.05 (d, 1 H, J = 7 Hz), 5.37 (s, 2 H), 2.42 (s, 3 H); IR (KBr) 3600–3300, 2996, 2641, 1669, 1605, 1566 cm^{-1}; MS m/e 290 (M^+ – 2 HCl). Anal. ($C_{17}H_{14}N_4O$·2HCl) C, H, N.

1,2-Dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxopyrido[4,3-*c*]quinoline dihydrochloride (39): yield 23%; R_f 0.46 ($CHCl_3$/MeOH = 5:1); mp 224 °C dec; ^{1}H NMR (CD_3OD + $CDCl_3$) δ 10.20–10.10 (m, 1 H), 9.80 (s, 1 H), 8.80 (s, 1 H), 8.40–8.30 (m, 2 H), 8.20–8.00 (m, 2 H), 7.28 (d, 1 H, J = 7 Hz), 5.48 (s, 2 H), 2.59 (s, 3 H); IR (KBr) 3412, 2981, 2735, 2638, 2086, 1965, 1662, 1621, 1553 cm^{-1}; MS m/e 290 (M^+ – 2 HCl). Anal. ($C_{17}H_{14}N_4O$·$^3/_2$HCl) C, H, N.

1,2-Dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxopyrido[3,4-*f*]quinoline dihydrochloride (40): yield 15%; R_f 0.42 ($CHCl_3$/MeOH = 5:1); mp 231 °C dec; ^{1}H NMR (CD_3OD + $CDCl_3$) δ 11.23 (ddd, 1 H, J = 0.8, 1.4, 8.8 Hz), 9.20 (dd, 1 H, J = 1.4, 5.4 Hz), 8.78 (s, 1 H), 8.46 (dd, 1 H, J = 0.8, 9 Hz), 8.37 (d, 1 H, J = 9 Hz), 8.29 (dd, 1 H, J = 5.4, 8.8 Hz), 8.18 (d, 1 H, J = 7 Hz), 7.10 (d, 1 H, J = 7 Hz), 5.45 (s, 2 H), 2.57 (s, 3 H); IR (KBr) 3365, 3028, 2591, 1641, 1620, 1596, 1572 cm^{-1}; MS m/e 290 (M^+ – 2HCl). Anal. ($C_{17}H_{14}N_4O$·2HCl) C, H, N.

9,10-Dihydro-9-[[5(4)-methyl-4(5)-imidazolyl]methyl]-10-oxopyrido[4,3-*h*]quinoline dihydrochloride (41): yield 22%; R_f 0.13 ($CHCl_3$/MeOH = 5:1); mp 208 °C dec; ^{1}H NMR (CD_3OD + $CDCl_3$) δ 9.39 (dd, 1 H, J = 1.4, 6 Hz), 9.32 (dd, 1 H, J = 1.4, 8.4 Hz), 8.85 (s, 1 H), 8.56 (d, 1 H, J = 8.8 Hz), 8.35 (d, 1 H, J = 7.2 Hz), 8.30 (dd, 1 H, J = 6, 8.4 Hz), 8.20 (d, 1 H, J = 8.8 Hz), 7.27 (d, 1 H, J = 7.2 Hz), 5.58 (s, 2 H), 2.58 (s, 3 H); IR (KBr) 3356, 3030, 1631, 1608, 1592, 1566, 1517 cm^{-1}; MS m/e 290 (M^+ – 2HCl). Anal. ($C_{17}H_{14}N_4O$·2HCl) C, H, N.

1,2-Dihydro-6-methyl-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxobenz[*h*]isoquinoline hydrochloride (44b): yield 22%; R_f 0.33 ($CHCl_3$/MeOH = 10:1); mp 209–211 °C; ^{1}H NMR (CD_3OD) δ 10.04 (d, 1 H, J = 8 Hz), 2.50 (s, 3 H); MS m/e 303 (M^+ – HCl). Anal. ($C_{19}H_{17}N_3O$·HCl) C, H, N.

1,2-Dihydro-5-hydroxy-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxobenz[*h*]isoquinoline hydrochloride (44c): yield 31%; R_f 0.30 ($CHCl_3$/MeOH = 5:1); mp 120–125 °C; ^{1}H NMR (CD_3OD + $CDCl_3$) δ 9.94 (s, 1 H), 2.51 (s, 3 H); IR (KBr) 3156, 1650, 1616, 1518 cm^{-1}; MS m/e 305 (M^+ – HCl). Anal. ($C_{18}H_{15}N_3O_2$·HCl) C, H, N.

1,2-Dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-5-methoxy-1-oxobenz[*h*]isoquinoline hydrochloride (44d): yield 31%; R_f 0.52 ($CHCl_3$/MeOH = 5:1); mp 256–259 °C; ^{1}H NMR (CD_3OD + $CDCl_3$) δ 10.00–9.95 (m, 1 H), 8.72 (s, 1 H), 4.08 (s, 3 H), 2.52 (s, 3 H); IR (KBr) 3008, 1654, 1613, 1553, 1503 cm^{-1}; MS m/e 319 (M^+ – HCl). Anal. ($C_{19}H_{17}N_3O_2$·HCl) C, H, N.

***N*,*N*-Dimethyl-1,2-dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxobenz[*h*]isoquinoline-5-carboxamide hydrochloride (44e)**: yield 32%; R_f 0.18 ($CHCl_3$/MeOH = 10:1); mp 203–205 °C; ^{1}H NMR (CD_3OD) δ 10.15 (d, 1 H, J = 8 Hz), 3.25 (s, 3 H), 2.93 (s, 3 H), 2.51 (s, 3 H); IR (KBr) 3423, 3029, 2646, 1653, 1603, 1553 cm^{-1}; MS m/e 360 (M^+ – HCl). Anal. ($C_{21}H_{20}N_4O_2$·HCl) C, H, N.

1,2-Dihydro-5-(hydroxymethyl)-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxobenz[*h*]isoquinoline hydrochloride (44f): yield 19%; R_f 0.27 ($CHCl_3$/MeOH = 5:1); mp 214–217 °C; ^{1}H NMR (CD_3OD + $CDCl_3$) δ 10.05 (d, 1 H, J = 8 Hz), 5.35 (s, 2 H), 4.99 (s, 3 H), 2.52 (s, 3 H); IR (KBr) 3355, 2994, 2883, 2743, 2652, 1657, 1606, 1522 cm^{-1}; MS m/e 319 (M^+ – HCl). Anal. ($C_{19}H_{17}N_3O_2$·HCl) C, H, N.

1,2-Dihydro-6-methyl-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxobenz[*h*]isoquinoline hydrochloride (45a): yield 22%; R_f 0.30 ($CHCl_3$/MeOH = 10:1); mp 231–133 °C; ^{1}H NMR (CD_3OD) δ 10.17 (dd, 1 H, J = 2, 8 Hz), 2.79 (s, 3 H), 2.52 (s, 3 H); IR (KBr) 2993, 2839, 2755, 2653, 1655, 1610, 1549 cm^{-1}; MS m/e 303 (M^+ – HCl). Anal. ($C_{19}H_{17}N_3O$·HCl) C, H, N.

6-Bromo-1,2-dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxobenz[*h*]isoquinoline hydrochloride (45b): yield

(13) Fischer, U.; Möhler, H.; Schneider, F.; Widmer, U. 78. Tricyclic Pyridine Derivatives with High Affinity to the Central Benzodiazepine Receptor. *Helv. Chim. Acta* **1990**, *73*, 763.

(14) Curtius rearrangement of 3-acetylaminocinnamic acid azide followed by the usual thermal cyclization of the formed isocyanate gave a mixture of two regioisomers **32** (42%) and **33** (24%) which were transformed to each product **62** and **63**, respectively.

45%; R_f 0.45 ($CHCl_3$/MeOH = 10:1); mp 205–207 °C; ^1H NMR (DMSO-d_6) δ 10.18 (m, 1 H), 2.40 (s, 3 H); IR (KBr) 2992, 2838, 2753, 2654, 1655, 1609, 1586, 1545 cm^{-1}; MS m/e 369 ($M^+ + 1$ – HCl). Anal. ($C_{18}H_{14}BrN_3O$·HCl) C, H, N.

1,2-Dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxodibenz[*f*,*h*]isoquinoline hydrochloride (46): yield 59%; R_f 0.35 ($CHCl_3$/MeOH = 5:1); mp 257–259 °C; ^1H NMR (DMSO-d_6) δ 10.23–10.18 (m, 1 H), 2.52 (s, 3 H); IR (KBr) 3400, 3087, 2997, 2839, 2764, 2656, 1651, 1607, 1558 cm^{-1}; MS m/e 339 (M^+ – HCl). Anal. ($C_{22}H_{17}N_3O$·HCl) C, H, N.

1,2,5,6-Tetrahydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-oxobenz[*h*]isoquinoline hydrochloride (47): yield 35%; R_f 0.26 ($CHCl_3$/MeOH = 10:1); mp 198 °C; ^1H NMR (CD_3OD + $CDCl_3$) δ 8.72 (s, 1 H), 2.90–2.70 (m, 4 H), 2.48 (s, 3 H); IR (KBr) 2973, 1650, 1594, 1528 cm^{-1}; MS m/e 291 (M^+ – HCl). Anal. ($C_{18}H_{17}N_3O$·HCl) C, H, N.

1,2-Dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-8-methoxy-1-oxobenz[*h*]isoquinoline hydrochloride (48): yield 41%; R_f 0.57 ($CHCl_3$/MeOH = 5:1); mp 234–237 °C; ^1H NMR (CD_3OD + $CDCl_3$) δ 10.00 (d, 1 H, J = 10 Hz), 3.98 (s, 3 H), 2.50 (s, 3 H); IR (KBr) 2991, 2750, 1654, 1605, 1552 cm^{-1}; MS m/e 319 (M^+ – HCl). Anal. ($C_{19}H_{16}N_3O_2$·HCl) C, H, N.

1,2-Dihydro-7-methyl-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxopyrrolo[2,3-*h*]isoquinoline hydrochloride (49): yield 11%; R_f 0.21 ($CHCl_3$/MeOH = 10:1); mp 218–219 °C; ^1H NMR (CD_3OD + $CDCl_3$) δ 8.69 (s, 1 H), 5.32 (s, 2 H), 3.96 (s, 3 H), 2.48 (s, 3 H); IR (KBr) 3391, 2887, 1643, 1595, 1500 cm^{-1}; MS m/e 292 (M^+ – HCl). Anal. ($C_{17}H_{16}N_4O$·HCl) C, H, N.

1,2-Dihydro-7-ethyl-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-5-oxopyrido[2,3-*h*]carbazole hydrochloride (50): yield 36%; R_f 0.38 ($CHCl_3$/MeOH = 10:1); mp 120–125 °C; ^1H NMR (CD_3OD + $CDCl_3$) δ 9.78 (d, 1 H, J = 10 Hz), 5.35 (s, 2 H), 4.58 (q, 2 H, J = 8 Hz), 2.53 (s, 3 H), 2.45 (t, 3 H, J = 8 Hz); IR (KBr) 3402, 1649, 1612 cm^{-1}; MS m/e 356 (M^+ – HCl). Anal. ($C_{22}H_{20}N_4O$·HCl) C, H, N.

1,2-Dihydro-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxo-3-phenylpyridine hydrochloride (51a): yield 36%; R_f 0.46 ($CHCl_3$/MeOH = 5:1); mp 221–223 °C; ^1H NMR (CD_3OD + $CDCl_3$) δ 8.73 (s, 1 H), 7.82 (d, 1 H, J = 7 Hz), 6.50 (t like, 3 H, J = 7 Hz), 5.26 (s, 2 H), 2.46 (s, 3 H); IR (KBr) 3163, 2984, 1641, 1585, 1552 cm^{-1}; MS m/e 265 (M^+ – HCl). Anal. ($C_{16}H_{15}N_3O$·HCl) C, H, N.

1,2-Dihydro-3-(*o*-methoxyphenyl)-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxopyridine hydrochloride (51b): yield 58%; R_f 0.32 ($CHCl_3$/MeOH = 10:1); mp 117–120 °C; ^1H NMR (CD_3OD) δ 5.20 (s, 2 H), 3.78 (s, 3 H), 2.38 (s, 3 H); IR (KBr) 3431, 1641, 1555 cm^{-1}; MS m/e 295 (M^+ – HCl). Anal. ($C_{17}H_{17}N_3O_2$·HCl·$^1/_2H_2O$) C, H, N.

1,2-Dihydro-3-(*m*-methoxyphenyl)-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxopyridine hydrochloride (51c): yield 54%; R_f 0.49 ($CHCl_3$/MeOH = 5:1); mp 166–169 °C dec; ^1H NMR (DMSO-d_6) δ 5.21 (s, 2 H), 3.77 (s, 3 H), 2.37 (s, 3 H); IR (KBr) 3419, 3014, 2883, 1646, 1585, 1552 cm^{-1}; MS m/e 295 (M^+ – HCl). Anal. ($C_{17}H_{17}N_3O_2$·HCl) C, H, N.

1,2-Dihydro-3-(*p*-methoxyphenyl)-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxopyridine hydrochloride (51d): yield 68%; R_f 0.32 ($CHCl_3$/MeOH = 10:1); mp 185–188 °C; ^1H NMR (CD_3OD) δ 5.25 (s, 2 H), 3.81 (s, 3 H), 2.45 (s, 3 H); MS m/e 295 (M^+ – HCl). Anal. ($C_{17}H_{17}N_3O_2$·HCl) C, H, N.

1,2-Dihydro-3-(*m*-fluorophenyl)-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxopyridine hydrochloride (51e): yield 60%; R_f 0.67 ($CHCl_3$/MeOH = 5:1); mp 220–223 °C dec; ^1H NMR (DMSO-d_6) δ 8.95 (s, 1 H), 8.08 (dd, 1 H, J = 2, 8 Hz), 7.75 (dd, 1 H, J = 2, 8 Hz), 7.60 (dd, 1 H, J = 2, 8 Hz), 7.15 (dt like, 1 H), 6.45 (t, 1 H, J = 8 Hz), 5.23 (s, 2 H), 2.38 (s, 3 H); IR (KBr) 2972, 1651, 1596, 1551 cm^{-1}; MS m/e 283 (M^+ – HCl). Anal. ($C_{16}H_{14}FN_3O$·HCl) C, H, N.

1,2-Dihydro-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-3-(*m*-nitrophenyl)-2-oxopyridine hydrochloride (51f): yield 60%; R_f 0.28 ($CHCl_3$/MeOH = 10:1); mp 209–211 °C; ^1H NMR (CD_3OD) δ 8.74 (s, 1 H), 8.63 (t, 1 H, J = 2 Hz), 8.21 (dd, 1 H, J = 2, 8 Hz), 8.03 (dt, 1 H, J = 1, 8 Hz), 7.91 (dd, 1 H, J = 2, 7 Hz), 7.82 (dd, 1 H, J = 2, 7 Hz), 7.65 (t, 1 H, J = 8 Hz), 6.56 (t, 1 H, J = 7 Hz), 5.29 (s, 2 H), 2.46 (s, 3 H); IR (KBr) 3436, 2991, 2839, 1651, 1593, 1556, 1520 cm^{-1}; MS m/e 310 (M^+ – HCl). Anal. ($C_{16}H_{14}N_4O_3$·HCl) C, H, N.

3-(*m*-Chlorophenyl)-1,2-dihydro-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxopyridine hydrochloride (51g): yield 37%; R_f 0.32 ($CHCl_3$/MeOH = 10:1); mp 193–196 °C; ^1H NMR (CD_3OD) δ 8.74 (s, 1 H), 7.85 (dd, 1 H, J = 2, 7 Hz), 7.52 (dt, 1 H, J = 2, 7 Hz), 6.52 (t, 1 H, J = 7 Hz), 5.26 (s, 2 H), 2.45 (s, 3 H); IR (KBr) 3544, 3153, 1645, 1588 cm^{-1}; MS m/e 299 (M^+ – HCl). Anal. ($C_{16}H_{14}ClN_3O$·HCl) C, H, N.

1,2-Dihydro-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxo-3-(*m*-tolyl)pyridine hydrochloride (51h): yield 64%; R_f 0.35 ($CHCl_3$/MeOH = 10:1); mp 195–197 °C; ^1H NMR (CD_3OD) δ 5.26 (s, 2 H), 2.45 (s, 3 H), 2.36 (s, 3 H); IR (KBr) 3436, 2853, 1642, 1587 cm^{-1}; MS m/e 279 (M^+ – HCl). Anal. ($C_{17}H_{17}N_3O$·HCl) C, H, N.

1′,2′-Dihydro-1′-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2′-oxo-2,3′-bipyridine dihydrochloride (52): yield 36%; R_f 0.37 ($CHCl_3$/MeOH = 5:1); mp 207–209 °C dec; ^1H NMR (CD_3OD) δ 8.90–8.80 (m, 2 H), 8.77 (dd, 1 H, J = 1.6, 7.6 Hz), 8.41 (dd, 1 H, J = 1.6, 6.6 Hz), 7.99 (dd, 1 H, J = 2.6, 6.6 Hz), 6.86 (t, 1 H, J = 6.8 Hz), 5.47 (s, 2 H), 2.53 (s, 3 H); IR (KBr) 3339, 3095, 1651, 1580, 1553, 1517 cm^{-1}. Anal. ($C_{15}H_{14}N_4O$·2HCl) C, H, N.

1,2-Dihydro-3-(2-furyl)-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxopyridine hydrochloride (53a): yield 41%; R_f 0.26 ($CHCl_3$/MeOH = 10:1); mp 195 °C dec; ^1H NMR (CD_3OD + $CDCl_3$) δ 8.73 (s, 1 H), 7.97 (dd, 1 H, J = 2, 8 Hz), 7.73 (dd, 1 H, J = 2, 8 Hz), 7.54 (d, 1 H, J = 2 Hz), 7.28 (d, 1 H, J = 2 Hz), 5.27 (s, 2 H), 2.47 (s, 3 H); IR (KBr) 2992, 2823, 2746, 1657, 1598 cm^{-1}; MS m/e 255 (M^+ – HCl). Anal. ($C_{14}H_{13}N_3O_2$·HCl) C, H, N.

1,2-Dihydro-3-(5-methyl-2-furyl)-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxopyridine hydrochloride (53b): yield 41%; R_f 0.11 ($CHCl_3$/MeOh = 10:1); mp 188–191 °C; ^1H NMR (CD_3OD) δ 5.26 (s, 2 H), 2.45 (s, 3 H), 2.34 (s, 3 H); IR (KBr) 3085, 2996, 2856, 2819, 1651, 1604, 1586 cm^{-1}; MS m/e 270 (M^+ – HCl). Anal. ($C_{15}H_{15}N_3O_2$·HCl) C, H, N.

1,2-Dihydro-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxo-3-(2-thienyl)pyridine hydrochloride (54a): yield 50%; R_f 0.58 ($CHCl_3$/MeOH = 10:1); mp 203 °C; ^1H NMR (CD_3OD + $CDCl_3$) δ 8.75 (s, 1 H), 7.95 (d, 1 H, J = 8 Hz), 7.75 (d, 1 H, J = 8 Hz), 7.65 (m, 1 H), 7.40 (d, 1 H, J = 5 Hz), 7.10 (t, 1 H, J = 5 Hz), 6.50 (t, 1 H, J = 8 Hz), 5.27 (s, 2 H), 2.47 (s, 3 H); IR (KBr) 3435, 2991, 2855, 2752, 1645, 1586, 1544 cm^{-1}; MS m/e 271 (M^+ – HCl). Anal. ($C_{14}H_{13}N_3OS$·HCl) C, H, N, S.

1,2-Dihydro-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-3-(5-methyl-2-thienyl)-2-oxopyridine hydrochloride (54b): yield 58%; R_f 0.16 ($CHCl_3$/MeOH = 19:1); mp 178–180 °C; ^1H NMR (CD_3OD) δ 5.27 (s, 2 H), 2.48 (s, 3 H), 2.45 (s, 3 H); IR (KBr) 3042, 1641, 1586, 1562, 1548 cm^{-1}; MS m/e 285 (M^+ – HCl). Anal. ($C_{15}H_{15}N_3OS$·HCl) C, H, N.

1,2-Dihydro-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-3-(3-methyl-2-thienyl)-2-oxopyridine hydrochloride (54c): yield 36%; R_f 0.65 ($CHCl_3$/MeOH = 10:1); mp 209–211 °C; ^1H NMR (CD_3OD) δ 5.25 (s, 2 H), 2.44 (s, 3 H), 2.17 (s, 3 H); IR (KBr) 3436, 2968, 1650, 1639, 1589, 1563, 1535 cm^{-1}; MS m/e 285 (M^+ – HCl). Anal. ($C_{15}H_{15}N_3OS$·HCl) C, H, N.

3-(5-Bromo-2-thienyl)-1,2-dihydro-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxopyridine hydrochloride (54d): yield 83%; R_f 0.32 ($CHCl_3$/MeOH = 10:1); mp 145–147 °C; ^1H NMR (CD_3OD) δ 8.73 (s, 1 H), 8.05 (d, 1 H, J = 7 Hz), 7.79 (d, 1 H, J = 7 Hz), 7.44 (d, 1 H, J = 4 Hz), 7.08 (d, 1 H, J = 4 Hz), 6.53 (t, 1 H, J = 7 Hz), 5.29 (s, 2 H), 2.46 (s, 3 H); IR (KBr) 3436, 3014, 1640, 1580, 1546 cm^{-1}; MS m/e 351 (M^+ – HCl). Anal. ($C_{14}H_{12}BrN_3OS$·HCl) C, H, N.

3-Benzo[*b*]thienyl-1,2-dihydro-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxopyridine hydrochloride (55): yield 47%; R_f 0.25 ($CHCl_3$/MeOH = 20:1); mp 229–231 °C dec; ^1H NMR (DMSO-d_6) δ 8.95 (s, 1 H), 8.18 (d, 1 H, J = 8 Hz), 8.15 (s, 1 H), 8.05 (d, 1 H, J = 8 Hz), 7.95 (d, 1 H, J = 10 Hz), 7.83 (d, 1 H, J = 10 Hz), 7.35 (quint, 2 H, J = 5 Hz), 6.53 (t, 1 H, J = 8 Hz), 5.28 (s, 2 H), 2.40 (s, 3 H); IR (KBr) 3414, 2990, 2858, 2749, 1647, 1593, 1543 cm^{-1}; MS m/e 321 (M^+ – HCl). Anal. ($C_{18}H_{15}N_3OS$·HCl) C, H, N.

1,2-Dihydro-3-(3-furyl)-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxopyridine hydrochloride (56a): yield 38%; R_f 0.46 ($CHCl_3$/MeOH = 5:1); mp 187–189 °C; ^1H NMR (CD_3OD + $CDCl_3$) δ 8.73 (s, 1 H), 6.48 (t, 1 H, J = 6.8 Hz), 5.28 (s, 2 H), 2.47 (s, 3 H); IR (KBr) 2982, 2727, 1656, 1599, 1571, 1544 cm^{-1}; MS m/e 255 (M^+ – HCl). Anal. ($C_{14}H_{13}N_3O_2$·HCl) C, H, N.

1,2-Dihydro-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxo-3-(3-thienyl)pyridine hydrochloride (56b): yield 31%; R_f 0.46 ($CHCl_3$/MeOH = 5:1); mp 187–189 °C; ^{1}H NMR (CD_3OD + $CDCl_3$) δ 8.73 (s, 1 H), 8.15 (dd, 1 H, J = 1.2, 3.2 Hz), 7.86 (dd, 1 H, J = 1.8, 7 Hz), 7.79 (dd, 1 H, J = 1.8, 7 Hz), 7.52 (dd, 1 H, J = 1.2, 5 Hz), 7.40 (dd, 1 H, J = 3.2, 7 Hz), 6.49 (t, 1 H, J = 7 Hz), 5.28 (s, 2 H), 2.47 (s, 3 H); IR (KBr) 3396, 3029, 2887, 1646, 1558 cm^{-1}; MS m/e 271 (M^+ – HCl). Anal. ($C_{14}H_{13}N_3OS$·HCl) C, H, N.

1,2,5,6-Tetrahydro-2-[[5(4)-methyl-4(5)-imidazolyl]-methyl]-1-oxothiopheno[2,3-*h*]isoquinoline hydrochloride (57): yield 38%; R_f 0.40 ($CHCl_3$/MeOH = 10:1); mp 222–225 °C dec; ^{1}H NMR (CD_3OD + $CDCl_3$) δ 8.70 (s, 1 H), 8.03 (d, 1 H, J = 5 Hz), 7.63 (d, 1 H, J = 8 Hz), 7.15 (d, 1 H, J = 5 Hz), 6.40 (d, 1 H, J = 8 Hz), 5.23 (s, 2 H), 2.46 (s, 3 H); IR (KBr) 3400, 3087, 2992, 2815, 2749, 2655, 1645, 1576 cm^{-1}; MS m/e 297 (M^+ – HCl). Anal. ($C_{16}H_{15}N_3OS$·HCl) C, H, N.

1,2-Dihydro-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-2-oxo-3-(1-methyl-2-pyrrolyl)pyridine hydrochloride (58): yield 28%; R_f 0.48 ($CHCl_3$/MeOH = 5:1); mp 218 °C; ^{1}H NMR (CD_3OD + $CDCl_3$) δ 8.61 (s, 1 H), 7.85 (dd, 1 H, J = 2, 6.8 Hz), 7.50 (dd, 1 H, J = 2, 6.8 Hz), 6.48 (t, 1 H, J = 6.8 Hz), 5.27 (s, 2 H), 3.51 (s, 3 H), 2.45 (s, 3 H); IR (KBr) 2988, 2878, 1641, 1589, 1569 cm^{-1}; MS m/e 268 (M^+ – HCl). Anal. ($C_{15}H_{16}N_4O$·HCl) C, H, N.

6-Amino-7-chloro-1,2-dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxoisoquinoline dihydrochloride (64). Compounds **59**, **60**, and **62–66** were prepared according to the general method C from the corresponding substituted dihydro-1-isoquinolinones **29**, **30**, and **32–36**. The preparation of **64** is representative. To a stirred suspension of NaH (80.0 mmol) in DMF (200 mL) was added a suspension of **34** (16.0 g, 67.6 mmol) in DMF (200 mL) slowly in an ice bath under an atmosphere of argon. After the mixture was stirred for 20 min, powdered 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)imidazole (30.2 g, 82.0 mmol) was added. The reaction mixture was stirred at room temperature for 3 h and was poured into ice/water (1 L). A resulting precipitate was collected by filtration. The wet solid was directly treated with 6 N HCl (225 mL) in MeOH (200 mL) under refluxing for 30 min. After cooling, the mixture was concentrated to remove MeOH, and the resulting precipitate was removed by filtration. The filtrate was evaporated to give a solid material. After washing with Et_2O/EtOH (1:1), the solid was suspended in EtOH and the mixture was refluxed under stirring. The resulting precipitate was collected by filtration and dried under reduced pressure to give **64** as the HCl salt (12.2 g, 49.5% based on **34**): R_f 0.32 ($CHCl_3$/MeOH/AcOH = 10:2:1); mp 249.5–251.5 °C; ^{1}H NMR (CD_3OD) δ 8.75 (s, 1 H), 8.02 (s, 1 H), 7.45 (d, 1 H, J = 8 Hz), 7.08 (s, 1 H), 6.55 (d, 1 H, J = 8 Hz), 5.20 (s, 2 H), 2.45 (s, 3 H); IR (KBr) 2990, 2765, 2494, 1672, 1626, 1612, 1509 cm^{-1}; MS m/e 288 (M^+ – 2HCl). Anal. ($C_{14}H_{13}ClN_4O$·2HCl) C, H, N, Cl.

7-Chloro-1,2-dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]-methyl]-1-oxoisoquinoline hydrochloride (59): yield 8%; R_f 0.23 ($CHCl_3$/MeOH = 10:1); mp 228–231 °C; ^{1}H NMR (CD_3OD + $CDCl_3$) δ 8.75 (s, 1 H), 7.54 (d, 1 H, J = 7 Hz), 6.74 (d, 1 H, J = 7 Hz), 5.26 (s, 2 H), 2.48 (s, 3 H); IR (KBr) 3082, 2993, 2819, 1651, 1626, 1597 cm^{-1}; MS m/e 273 (M^+ – HCl). Anal. ($C_{14}H_{12}ClN_3O$·HCl) C, H, N.

5,7-Dichloro-1,2-dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxoisoquinoline hydrochloride (60): yield 28%; R_f 0.35 ($CHCl_3$/MeOH = 10:1); mp 255–258 °C; ^{1}H NMR (CD_3OD) δ 8.70 (s, 1 H), 8.23 (s, 1 H), 7.88 (s, 1 H), 7.65 (d, 1 H, J = 10 Hz), 6.95 (d, 1 H, J = 10 Hz), 5.25 (s, 2 H), 2.45 (s, 3 H); IR (KBr) 3449, 3105, 3016, 2799, 1656, 1625, 1589 cm^{-1}; MS m/e 307 (M^+ – HCl). Anal. ($C_{14}H_{11}Cl_2N_3O$·HCl) C, H, N.

8-Amino-1,2-dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]-methyl]-1-oxoisoquinoline dihydrochloride (62): yield 58%; R_f 0.71 ($CHCl_3$/MeOH/AcOH = 5:5:1); mp 182–184 °C dec; ^{1}H NMR (DMSO-d_6) δ 14.55 (br, 1 H), 8.97 (s, 1 H), 7.58 (d, 1 H, J = 8 Hz), 7.30 (t, 1 H, J = 8 Hz), 6.63 (d, 1 H, J = 9 Hz), 6.42 (d, 1 H, J = 9 Hz), 5.10 (s, 2 H), 2.38 (s, 3 H); IR (KBr) 3411, 3099, 3013, 1651, 1616, 1553 cm^{-1}; MS m/e 254 (M^+ – 2HCl). Anal. ($C_{14}H_{14}N_4O$·2HCl) C, H, N.

6-Amino-1,2-dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]-methyl]-1-oxoisoquinoline dihydrochloride (63): yield 63%; R_f 0.57 ($CHCl_3$/MeOH/AcOH = 5:5:1); mp 178–181 °C dec; ^{1}H NMR (DMSO-d_6) δ 14.50 (br, 1 H), 8.96 (s, 1 H), 8.05 (d, 1 H, J = 8 Hz), 7.68 (d, 1 H, J = 8 Hz), 6.49 (d, 1 H, J = 8 Hz), 5.16 (s, 2 H), 2.38 (s, 3 H); IR (KBr) 3108, 3014, 1672, 1633, 1538 cm^{-1}; MS m/e 254 (M^+ – 2HCl). Anal. ($C_{14}H_{14}N_4O$·2HCl) C, H, N.

6-Amino-1,2-dihydro-7-methyl-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxoisoquinoline dihydrochloride (65): yield 20%; R_f 0.50 ($CHCl_3$/MeOH = 3:1); mp 194–197 °C; ^{1}H NMR (DMSO-d_6 + $CDCl_3$) δ 14.3 (br), 8.79 (s, 1 H), 8.00 (s, 1 H), 7.54 (d, 1 H, J = 7 Hz), 7.10 (m, 1 H), 6.41 (d, 1 H, J = 7 Hz), 5.16 (s, 2 H), 2.43 (s, 3 H), 2.32 (s, 3 H); IR (KBr) 2856, 1669, 1625, 1517 cm^{-1}; MS m/e 269 (M^+ – 2HCl). Anal. ($C_{15}H_{16}N_4O$·2HCl) C, H, N.

6,7-Dihydro-7-[[5(4)-methyl-4(5)-imidazolyl]methyl]-6-oxodioxino[2,3-*g*]isoquinoline hydrochloride (66): yield 27%; R_f 0.40 ($CHCl_3$/MeOH = 10:1); ^{1}H NMR (CD_3OD + $CDCl_3$) δ 9.63 (s, 1 H), 7.75 (d, 1 H, J = 8 Hz), 7.30 (d, 1 H, J = 8 Hz), 7.04 (s, 1 H), 6.55 (d, 1 H, J = 8 Hz), 5.18 (s, 2 H), 2.45 (s, 3 H); IR (KBr) 2991, 1736, 1651, 1605, 1504 cm^{-1}; MS m/e 297 (M^+ – HCl). Anal. ($C_{16}H_{15}N_3O_3$·HCl) C, H, N.

4-[[(4-Amino-5-chloro-2-methoxybenzoyl)amino]-methyl]-5-methylimidazole Dihydrochloride (74). To a stirred solution of 4-amino-5-chloro-2-methoxybenzoic acid (375 mg, 1.86 mmol) and Et_3N (0.34 mL) in CH_2Cl_2 (10 mL) was added ethyl chloroformate (0.2 mL) dropwise at 0 °C under an atmosphere of argon. After stirring for 1 h, a suspension of 4-(aminomethyl)-5-methyl-1-(triphenylmethyl)imidazole (660 mg, 1.86 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was stirred at room temperature for 12 h. After concentration, the desired product was purified by column chromatography on silica gel ($CHCl_3$:MeOH = 50:1) to give white powder (340 mg). A mixture of the white powder, AcOH, and water was refluxed with stirring. After cooling, the resulting precipitate was removed by filtration. The residue which was obtained after concentration of the filtrate was subjected to column chromatography on silica gel ($CHCl_3$/MeOH = 20:1) to give **74**. Treatment with HCl in dioxane gave the hydrochloride salt (143 mg, 21%): R_f 0.54 ($CHCl_3$/MeOH = 5:1); mp 207–210 °C; ^{1}H NMR (CD_3OD) δ 8.68 (s, 1 H), 7.83 (s, 1 H), 6.53 (s, 1 H), 5.55 (s, 2 H), 3.95 (s, 3 H), 2.40 (s, 3 H); IR (KBr) 3365, 3132, 3030, 2908, 1665, 1529 cm^{-1}; MS m/e 294 (M^+ – 2HCl). Anal. ($C_{13}H_{15}ClN_4O_2$·2HCl) C, H, N.

Preparation of Compound 69. To a stirred solution of **67** (12.4 g, 23.2 mmol) in $CHCl_3$ (230 mL) was added *m*-CPBA (4.02 g, 23.2 mmol) at room temperature. After stirring for 12 h, the reaction mixture was washed with aqueous $NaHCO_3$, water, and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was subjected to column chromatography on silica gel ($CHCl_3$/MeOH = 50:1) to give **68** as a yellow solid (3.37 g, 26%): R_f 0.53 ($CHCl_3$/MeOH = 10:1); ^{1}H NMR ($CDCl_3$) δ 10.1 (m, 1 H), 8.85 (m, 1 H), 8.63 (s, 1 H), 7.90–7.75 (m, 3 H), 7.35–7.25 (m), 7.20–7.10 (m), 6.49 (d, 1 H, J = 7.5 Hz), 5.19 (s, 2 H), 1.62 (s, 3 H); MS m/e 548 (M^+). To a stirred solution of the above product (3.37 g, 6.14 mmol) in $CHCl_3$ (60 mL) was added *p*-toluenesulfonyl chloride (1.53 g, 8.00 mmol) and 10% aqueous K_2CO_3 (60 mL), successively, at room temperature. After the reaction mixture was stirred for 12 h, the organic layer was separated and washed with water and then brine, dried ($MgSO_4$), and concentrated. The residue was subjected to column chromatography on silica gel ($CHCl_3$/MeOH = 50:1 then 20:1) to give **69** as a yellow solid (1.14 g, 34%): ^{1}H NMR ($CDCl_3$) δ 9.98 (s, 1 H), 9.72 (d, 1 H, J = 8 Hz), 7.77 (d, 1 H, J = 7 Hz), 7.50 (t, 1 H, J = 8 Hz), 5.20 (s, 1 H); MS (FAB) m/e 549 (M^+ + 1).

2-[[5(4)-Methyl-4(5)-imidazolyl]methyl]-1,5-dioxo-1,2,5,6-tetrahydropyrido[4,3-*c*]quinoline Hydrochloride (42). The mixture of **69** (548 mg, 1.00 mmol), AcOH (3 mL), and water (3 mL) were refluxed for 1 h. After cooling, the reaction mixture was concentrated to give a residue. The residue was subjected to column chromatography on silica gel ($CHCl_3$/MeOH/AcOH/H_2O = 90:10:1:1) followed by the usual treatment with ethanolic hydrogen chloride to give **42** (206 mg, 60%) as the hydrochloride salt: R_f 0.32 ($CHCl_3$/MeOH = 5:1); ^{1}H NMR (DMSO-d_6) δ 14.60–14.30 (br, 1 H), 12.21 (s, 1 H), 9.50 (dd, 1 H, J = 2, 8 Hz), 8.94 (s, 1 H), 8.14 (d, 1 H, J = 7 Hz), 7.50 (ddd, 1 H, J = 2, 7, 8 Hz), 7.38 (dd, 1 H, J = 2, 8 Hz), 7.26 (ddd, 1 H, J = 2, 7, 8 Hz), 7.05 (d, 1 H, J = 7 Hz), 5.31 (s, 2 H), 2.40 (s, 3 H); IR (KBr) 3015, 2844, 1651, 1582, 1533 cm^{-1}; MS m/e 306 (M^+ – HCl).

6-Methyl-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1,5-dioxo-1,2,5,6-tetrahydropyrido[4,3-c]quinoline Hydrochloride (43). To a stirred suspension of **69** (85 mg, 0.155 mmol) in DMF (1.5 mL) was added NaH (0.185 mmol). After the mixture was stirred at room temperature for 10 min, 1 M solution of MeI in DMF (0.185 mL, 0.185 mmol) was added. The mixture was stirred at room temperature for 30 min and was poured into water. The product was extracted with AcOEt. The organic layer was washed with water, brine, dried (Na_2SO_4), and concentrated to give **70** as a solid, which was suspended in AcOH/water (1:1, 2 mL) and refluxed for 1 h. After removal of the solvent by evaporation, a residue was subjected to column chromatography on silica gel ($CHCl_3$/MeOH = 20:1) to give **43**, which was converted into the HCl salt by the usual treatment with methanolic hydrogen chloride (30 mg, 54%): R_f 0.47 ($CHCl_3$/MeOH = 5:1); ^1H NMR (DMSO-d_6) δ 14.70–14.30 (br, 1 H), 9.68 (dd, 1 H, J = 1, 8 Hz), 8.96 (s, 1 H), 8.17 (d, 1 H, J = 7 Hz), 7.70–7.50 (m, 2 H), 7.40–7.30 (m, 1 H), 7.11 (d, 1 H, J = 7 Hz), 5.31 (s, 2 H), 3.73 (s, 3 H), 2.40 (s, 3 H); IR (KBr) 3470, 3001, 1636, 1604, 1577, 1543 cm^{-1}; MS m/e 320 (M^+ – HCl).

1,2-Dihydro-1-[[5(4)-methyl-4(5)-imidazolyl]methyl]-3-(o-hydroxyphenyl)-2-oxopyridine Hydrochloride (51i). A mixture of **51b** (100 mg, 0.3 mmol) and pyridinium hydrochloride (1.5 g) was heated at 190 °C for 1 h with stirring. After cooling, the reaction mixture was treated with aqueous $NaHCO_3$ and the product was extracted with $CHCl_3$/MeOH (9:1) (30 mL × 3). The combined organic layers were dried ($MgSO_4$) and concentrated to give a residue. The residue was subjected to preparative TLC using $CHCl_3$/MeOH (10:1) as developing solvent system to give **51i**, which was converted into the hydrochloride salt by the treatment with ethanolic hydrogen chloride (39 mg, 46%): R_f 0.37 ($CHCl_3$/MeOH = 5:1); mp 230–233 °C dec; ^1H NMR (D_2O) δ 8.50 (s, 1 H), 7.85 (d, 1 H, J = 8 Hz), 7.70 (d, 1 H, J = 8 Hz), 7.38 (t, 1 H, J = 8 Hz), 7.25 (d, 1 H, J = 8 Hz), 7.05 (t, 1 H, J = 8 Hz), 7.00 (d, 1 H, J = 8 Hz), 6.69 (t, 1 H, J = 7 Hz), 5.33 (s, 2 H), 2.38 (s, 3 H); IR (KBr) 3436, 2972, 1634, 1562 cm^{-1}; MS m/e 281 (M^+ – HCl). Anal. ($C_{16}H_{15}N_3O_2$·HCl) C, H, N.

Preparation of Compound 71. A solution of methyl 2-methyl-3-nitrobenzoate (5.9 g, 30 mmol) and DMF dimethyl acetal (12 mL, 90 mmol) in DMF (30 mL) was heated at 110–120 °C for 7 h. After cooling, the reaction mixture was concentrated. The residue was subjected to column chromatography on silica gel (hexane/AcOEt = 10:1) to give **71** (3.83 g, 67%) as a dark brown solid: ^1H NMR ($CDCl_3$) δ 8.65 (m, 1 H), 8.49 (m, 1 H), 7.67 (dd, 1 H, J = 7.5 Hz), 7.43 (d, 1 H, J = 6 Hz), 7.38 (d, 1 H, J = 6 Hz); MS m/e 191 (M^+).

Preparation of Compound 31. A solution of **71** (382 mg, 2 mmol) in ethanolic NH_3 was stirred at room temperature for 20 h in an autoclave and concentrated to give a residue. The residue was subjected to column chromatography on silica gel ($CHCl_3$/MeOH = 20:1) to give **31** (226 mg, 59%) as a solid: ^1H NMR ($CDCl_3$) δ 8.70, (m, 1 H), 8.45 (m, 1 H), 7.65 (t, 1 H, J = 8 Hz), 7.73 (d, 1 H, J = 6 Hz), 7.27 (d, 1 H, J = 6 Hz); MS m/e 196 (M^+).

Preparation of Compound 72. N-Alkylation of **31** (223 mg, 1.17 mmol) with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)imidazole by the usual manner gave **72** (660 mg, quant) as a solid: ^1H NMR ($CDCl_3$) δ 8.66 (dd, 1 H, J = 1.5, 7 Hz), 8.30 (dd, 1 H, J = 1.5, 6 Hz), 7.61 (d, J = 7 Hz), 7.54 (s), 7.40 (d, J = 6 Hz), 7.30–7.00 (m), 5.50 (s, 2 H), 1.90 (s, 3 H); MS (FAB) m/e 527 (M^+ + 1).

Preparation of Compound 73. To a stirred suspension of **72** (330 mg, 0.627 mmol) and 10% Pd/C (330 mg) in DMF/MeOH (1:1, 12 mL) was added ammonium formate (395 mg, 6.27 mmol) under an atmosphere of argon. After 30 min, Pd/C was removed by filtration and the filtrate was concentrated to give a residue. The residue was dissolved in dioxane/water and then freeze dried to give **73** (345 mg, quant.) as a pale orange powder: MS (FAB) m/e 497 (M^+ + 1).

5-Amino-1,2-dihydro-2-[[5(4)-methyl-4(5)-imidazolyl]methyl]-1-oxoisoquinoline Dihydrochloride (61). A mixture of **73** (345 mg, 0.627 mmol) and AcOH (6 mL) and water (6 mL) was heated at 100 °C for 1 h. The resulting precipitate was removed by filtration and the filtrate was concentrated. The residue was subjected to column chromatography on silica gel ($CHCl_3$/MeOH = 10:1) to give **61** (131 mg) as a brown amorphous, which was converted into the dihydrochloride salt by the treatment with ethanolic hydrogen chloride (148 mg, 72%): R_f 0.15 ($CHCl_3$/MeOH = 5:1); mp 166–169 °C dec; ^1H NMR (DMSO-d_6) δ 14.50 (br, 1 H), 8.95 (s, 1 H), 7.85–7.75 (m, 2 H), 7.38–7.35 (m, 2 H), 6.80 (d, 1 H, J = 8 Hz), 5.18 (s, 2 H), 2.36 (s, 3 H); IR (KBr) 3300–3500, 3014, 2839, 1667, 1633, 1558, 1533 cm^{-1}; MS m/e 245 (M^+ – 2HCl). Anal. ($C_{14}H_{14}N_4O$·2HCl) C, H, N.

X-ray Crystallographic Determination of 44a, 47, and 51a. General Procedures. Diffraction data for three compounds were collected with graphite-monochromated Cu Kα radiation on a Rigaku AFC-5R automatic four-cycle diffractometer and $2\theta/\omega$ scan mode up to 126° in 2θ at room temperature. TEXSAN,[15] structure analysis software package, with micro VAX 3500, was used for all computations. The structure was solved by direct methods using MITHRIL[16] in combination with difference Fourier recycling. The full-matrix least-squares refinement was carried out using ORFLS[17] with non-H atoms treated anisotropically. The ideal positions for hydrogen atoms were calculated and were verified on a difference Fourier map. Then they included further refinement. [$R_w = (\sum s^2(|F_o| - |F_c|)^2/\sum s^2|F_o|^2)^{1/2}$.]

44a: $C_{18}H_{16}N_3O$·HCl (mol wt 325.80); a colorless crystal recrystallized from methanol, dimensions 0.1 × 0.05 × 0.2 mm, used for data collection; monoclinic; space group $P2_1/c$; a = 23.395 (3) Å, b = 4.4848 (5) Å, c = 15.863 (2) Å, β = 109.189 (8)°; Z = 4; D_c = 1.38 g/cm^3. A total of 2662 independent reflections were collected. The scan width was 1.3° and scan speed 8.0 deg/s. The final refinement converged to R = 0.038 and R_w = 0.029 for 272 variables and 1412 [$I > 3\sigma(I)$] refractions. The highest residual peak in a difference Fourier map is 0.18 $Å^{-3}$.

47: $C_{18}H_{17}N_3O$·HCl (mol wt 327.81); a colorless crystal recrystallized from methanol, dimensions 0.3 × 0.08 × 0.4 mm, used for data collection; monoclinic; space group $P2_1/c$; a = 12.979 (2) Å, b = 8.159 (3) Å, c = 15.741 (3) Å, β = 100.00 (1)°; Z = 4; D_c = 1.33 g/cm^3. A total of 2246 independent reflections were collected. The scan width was 1.3° and scan speed 8.0 deg/s. The final refinement converged to R = 0.040 and R_w = 0.035 for 280 variables and 1875 [$I > 3\sigma(I)$] refractions. The highest residual peak in a difference Fourier map is 0.42 $Å^{-3}$.

51a: $C_{16}H_{15}N_3O$·HCl (mol. wt 301.77); a colorless crystal recrystallized from methanol, of dimensions 0.3 × 0.08 × 0.4 mm, used for data collection; monoclinic; space group $P2_1/c$; a = 14.777 (3) Å, b = 8.189 (2) Å, c = 13.116 (3) Å, β = 109.47 (2)°; Z = 4; D_c = 1.34 g/cm^3. A total of 2621 independent reflections were collected. The scan width was 1.3° and scan speed 8.0 deg/s. The final refinement converged to R = 0.091 and R_w = 0.108 for 254 variables and 1984 [$I > 3\sigma(I)$] refractions. The highest residual peak in a difference Fourier map is 0.50 $Å^{-3}$.

Calculation Method. Molecular orbital calculation was performed on VAX 3800 computer by the AM1[11] method with MOPAC Version 6.01.[18] Fixing torsion angles every 10°, all other internal coordinates were optimized.

Pharmacological Methods. Bezold-Jarisch Reflex in Anesthetized Rats. A modified procedure reported by Fozard et al.[19] was followed. The inhibitory activity of the test compounds toward transient bradicardia induced by rapid, bolus iv injection of 5-HT (10 μg/kg) in rats was studied. Male rats (301–570 g) were anesthetized with urethane 1.25 mg/kg, ip. The carotid artery was cannulated for monitoring continuous heart rate and blood pressure. The femoral artery was cannulated for iv injection of the test compounds. The Bezold-Jarisch reflex was evoked by rapid, bolus iv injection of 5-HT and the fall in heart rate was measured. The test compounds were injected 2 min prior to challenge with 5-HT. Probit analysis was used to obtain ID_{50}

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values and 95% confidence limits.

Cisplatin-Induced Emesis in Ferrets and Dogs. A modified procedure reported by Gylys et al.[20] was followed. The inhibitory activity of the test compounds toward emesis induced by iv administration of cisplatin in ferrets (14 mg/kg) or in dogs (5 mg/kg) was studied. For iv evaluation, animals were pretreated with two doses of the compound intravenously 30 min prior to and 60 min after challenge with cisplatin and then the number of emetic episodes and retches was monitored for 5 h (**44a** and **54a**), or animals were pretreated with one dose of the compound intravenously right before challenge with cisplatin, and then the number of emetic episodes and retches was monitored for 5 h (**64**). For po evaluation, animals were pretreated with the compound orally 60 min prior to challenge with cisplatin, and then the number of emetic episodes and retches was monitored for 5 h (**44a** and **64**). Drugs were prepared daily in saline for iv administration or distilled water for po administration before use. The results were expressed as mean ± SE. Statistical analysis was performed using Student's *t* test.

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Synthesis and Excitatory Amino Acid Pharmacology of a Series of Heterocyclic-Fused Quinoxalinones and Quinazolinones

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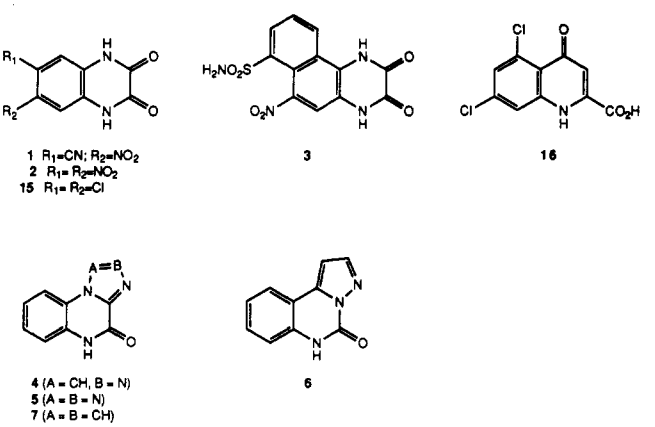
As part of our program aimed at the development of potent excitatory amino acid antagonists, we synthesized and evaluated a series of substituted 1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-ones, **4**, tetrazolo[1,5-*a*]quinoxalin-4(5*H*)-ones, **5**, and pyrazolo[1,5-*c*]quinazolin-5(6*H*)-ones, **6**, and an imidazo[1,2-*a*]quinoxalin-4(5*H*)-one, **7**. In general, the same heterocycles which demonstrated the best affinity for the AMPA receptor also demonstrated the best affinity for the glycine site on the NMDA receptor complex. 1-Propyl-7,8-dichloro-1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-one, **4d**, was found to bind with the greatest affinity to the AMPA receptor with an IC_{50} of 0.83 μM and antagonized 40 μM AMPA-induced depolarization in the cortical slice preparation with an IC_{50} of 44 μM. 7,8-Dichloro-1,2,4-triazolo[4,3-*a*]quinoxalin-4(5*H*)-one, **4a**, and 7,8-dichloroimidazo[1,2-*a*]quinoxalin-4(5*H*)-one, **7**, possessed the best affinity for the glycine site with IC_{50} values of 0.63 and 1.26 μM, respectively. It is noteworthy that the SAR for the heterocyclic compounds did not directly parallel that of known quinoxalinediones (e.g. DNQX, **2**, and DCQX, **15**) at the AMPA receptor nor that of the kynurenic acids at the glycine site on the NMDA receptor complex.

Glutamate neurotoxicity is thought to play a role in a number of pathophysiological conditions including ischemia,[1] brain[2] and spinal cord trauma,[3] and a variety of neurodegenerative disorders.[4] Excitatory amino acid antagonists may have important therapeutic potential in the treatment of these disease states. Although molecular biologist's cloning efforts are in the process of further defining glutamate receptors, at least three ionotropic glutamate receptors have been identified by classical methodology. These ionotropic receptors are named for the agonists which activate them: *N*-methyl-D-aspartic acid (NMDA), 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propanoic acid (AMPA), and kainic acid (KA). Several modulatory sites have been identified for the NMDA receptor-ion channel complex including a glutamate recognition site, a glycine recognition site, and an ion channel site to which compounds such as phencyclidine (PCP) and MK-801 (dizocilpine) bind.[5]

A number of quinoxalinediones, including 6-cyano-7-nitroquinoxaline-2,3-dione (**1**, CNQX), 6,7-dinitroquinoxaline-2,3-dione (**2**, DNQX), and 6-nitro-7-sulfamoylbenzo[*f*]quinoxaline-2,3-dione (**3**, NBQX) are potent antagonists of the AMPA receptor (Chart I).[6]

Chart I



CNQX and DNQX were found to also have affinity for the glycine binding site on the NMDA receptor.[7] As part of

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