Synthesis and Structure−Activity Relationships of Fused Imidazopyridines: A New Series of Benzodiazepine Receptor Ligands

Susumu Takada,* Takashi Sasatani, Nobuo Chomei, Makoto Adachi, Toshio Fujishita, Masami Eigyo, Shunji Murata, Kazuo Kawasaki, and Akira Matsushita

Shionogi Research Laboratories, Shionogi & Company, Ltd., Sagisu, Fukushima-ku, Osaka 553, Japan

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2-Arylimidazo[4,5-*c*]quinolines and analogous fused imidazopyridines were synthesized and evaluated as benzodiazepine receptor ligands. Affinity to the receptors was greatly affected by the bulkiness of the aryl group at the 2-position, compared to the pyrazoloquinolines such as CGS-9896. Derivatives with an isoxazole moiety at the 2-position showed high binding affinity and *in vivo* activity. In the imidazo[4,5-*c*]quinoline series, substitution at the 6-position decreased or abolished activity. Most derivatives with an unsubstituted isoxazolyl group showed antagonist or inverse agonist activity except for the 7-halo analogues, which exhibited agonist activity. On the other hand, 5-methylisoxazol-3-yl or 3-methylisoxazol-5-yl derivatives generally exhibited agonist activity. A similar substitution effect on the isoxazole moiety was observed in the imidazopyridines fused with a nonaromatic ring. From the detailed pharmacological evaluation, S-8510, 2-(3-isoxazolyl)-3,6,7,9-tetrahydroimidazo[4,5-*d*]pyrano[4,3-*b*]pyridine monophosphate, possessing weak inverse agonist activity was selected as a therapeutic candidate for the treatment of some symptoms of senile dementia.

Introduction

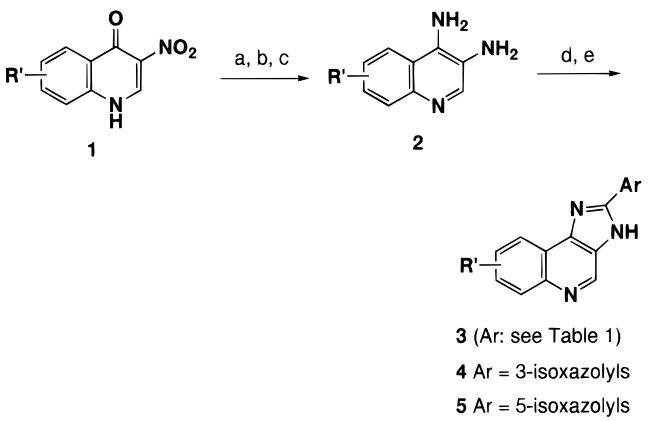
Benzodiazepines and related ligands are generally believed to interact with a specific site ("benzodiazepine receptor") that is allosterically coupled with a neuroinhibitory, postsynaptic $GABA_A$ receptor and a chloride ionophore channel.[1−3] These ligands exert a continuum of intrinsic efficacy, from positive efficacy (agonists; anxiolytic/anticonvulsant/sedative) through nil efficacy (receptor antagonists) to negative efficacy (inverse agonists; anxiogenic/proconvulsant/convulsant). Partial agonists and partial inverse agonists exist between these three categories. Although numerous agonists and one antagonist (Flumazenil) have been used therapeutically,[4] the inverse agonists have not. It is believed that partial inverse agonists may be useful as cognition enhancers.[5−7]

Previously we reported that variation of the size of the alkyl substituent on a series of thienylpyrazoloquinolines results in a shift from their being inverse agonists to antagonists to agonists.[8] In order to refine the structure-related shifts in functional activity and to develop more efficacious ligands, chemical manipulation of the ring system was investigated. In this report, we describe the synthesis and structure−activity relationships of imidazo[4,5-*c*]quinolines and the analogous fused imidazopyridines, which comprise a new series of benzodiazepine (BZ) receptor ligands with positive and negative functional effects.

Chemistry

Scheme 1 outlines our synthetic routes to arylimidazo[4,5-*c*]quinolines **3**−**5** *via* the diaminoquinolines **2**. The 3-nitroquinolin-4-ones series **1** were prepared from corresponding anthranilic acids in a manner similar to that described by Bacheman *et al.*[9] Successive treatment of **1** with phosphorus oxychloride and ammonia gave 4-amino-3-nitroquinolines, which were converted into the 3,4-diaminoquinolines **2** in good yield. These

Scheme 1[a]



[a] (a) $POCl_3$; (b) NH_3; (c) H_2/Pd−C; (d) ArCOOH, HMPA/CH_3CN, $SOCl_2$; (e) HMPA/AcOH, reflux.

in turn were treated with various aromatic carboxylic acids (ArCOOH) and thionyl chloride in a mixture of hexamethylphosphoramide (HMPA) and acetonitrile to afford the corresponding amides, which were cyclized by heating in a mixture of HMPA and acetic acid to provide the desired imidazoquinolines **3**−**5**.

The preparation of [*e*]-fused 2-arylimidazo[4,5-*c*]pyridines **14** and **15** is illustrated in Scheme 2. A fused 3-nitropyridine (**8**) was prepared by heating a cyclic ketone (**7**) and 3,5-dinitro-1-methyl-2-pyridone in methanolic ammonia in the manner reported by Tohda and co-workers.[10] Hydrogenation of **8** and protection of the resulting amino group with trichloroacetyl chloride afforded the amide **10**. Oxidation of **10** with 3-chloroperoxybenzoic acid gave the *N*-oxide **11**, which was treated with fuming nitric acid followed by concentrated ammonium hydroxide to provide 3-amino-4-nitropyridine 1-oxide **12**. Reduction of 1-oxo and 4-nitro groups in **12** was accomplished in a single step by hydrogenation with Raney nickel to give the fused 3,4-diaminopyridine **13**. Finally, monoacylation of **13** with an appropriate aroyl chloride and subsequent thermal cyclization

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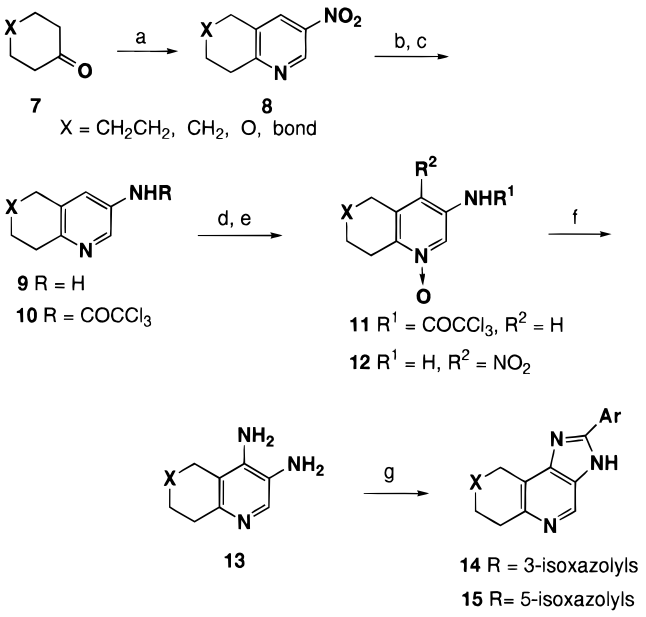
Scheme 2[a]



[a] (a) 1-Methyl-3,5-dinitro-2-pyridone/NH_3/MeOH; (b) H_2/5% Pd−C/MeOH; (c) Et_3N/CH_2Cl_2, Cl_3CCOCl; (d) MCPBA/CH_2Cl_2; (e) fuming HNO_3, aq NH_4OH; (f) H_2/Raney Ni/MeOH; (g) DMF, $ArCOCl/CH_2Cl_2$, $AcONa/HOCH_2CH_2OH$, 150 °C.

provided the desired fused 2-arylimidazo[4,5-*c*]pyridines **14** and **15** in good yield.

Pharmacological Methods

Affinity to the BZ Receptor. This was measured by displacement of [^{3}H]diazepam to receptor preparation obtained from the cerebral cortex of Wistar rats. The procedure is given in our previous paper.[11]

Agonist Activity. This was evaluated by inhibition of pentylenetetrazole (PTZ)-induced convulsions. Groups of 8−16 male mice were challenged with a convulsive dose (125 mg/kg, sc) of PTZ 1 h after oral administration of the test compounds. The dose required to prevent tonic convulsions and death in 50% of the animals during a 2-h observation period was calculated by the probit method.

Inverse Agonist Activity. This was evaluated by potentiation of PTZ-induced convulsions. Groups of 8−16 male mice were challenged with a subconvulsive dose (75 or 90 mg/kg, sc) of PTZ 1 h after oral administration of the test compounds. The dose required to produce tonic convulsions and death in 50% of the animals during a 2-h observation period was calculated by the probit method. Both the agonist and inverse agonist activities seemed to be mediated *via* BZ receptors because these effects were completely antagonized by the BZ antagonist Ro-15-1788.[12]

Antagonist Activity. This was assessed by disruption of the anticonvulsant actions of diazepam against PTZ. Groups of 8−16 male mice were challenged with an effective dose (1 mg/kg, sc) of diazepam, which offers 100% protection against the convulsions induced by PTZ (125 mg/kg, sc). Thirty minutes later, the animals were administered a convulsive dose (125 mg/kg) of PTZ immediately after intravenous injection of the test compounds. The dose required to produce tonic convulsions and death in 50% of the animals during a 2-h observation period was calculated by the probit method.

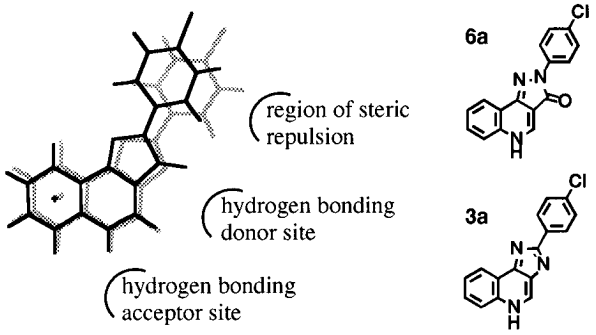


Figure 1. Superimposition of pyrazoloquinoline **6a** (black lines) and imidazoquinoline **3a** (5H-tautomer; gray lines).

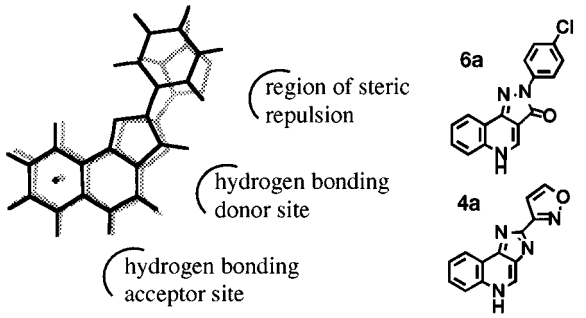


Figure 2. Superimposition of **6a** (black lines) and **4a** (5H-tautomer; gray lines).

Results and Discussion

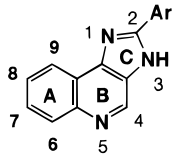
The role of the hydrogen atom at the 5-position of the pyrazolo[4,3-*c*]quinolines as the hydrogen bond donor is well-defined for high affinity to BZ receptors.[11,13,14] We thought that an imidazo[4,5-*c*]quinoline might be a bioisostere of an pyrazolo[4,3-*c*]quinoline because a tautomer with a hydrogen atom at the 5-position of the former may exist when it interacts with the receptor protein. Compounds initially synthesized in this series exhibited a broad range of affinities (K_i = 1.7−270 nM) in comparison to their corresponding pyrazoloquinolines (K_i = 0.22−0.83 nM) as shown in Table 1.

Furthermore, the steric requirements for the 2-substituent in the former appear to be much greater than that in the latter series. This may be rationalized by the binding site model proposed by Cook *et al.*[14] Thus, in a bioactive form (5H-tautomer) of the imidazoquinolines, the imidazole N3 nitrogen atom may interact at the hydrogen-bond-donor site on the binding protein. Therefore, the aryl substituent at the 2-position may be closer to the surface of the lipophilic pocket than that of pyrazoloquinolines in which the carbonyl oxygen has been suggested to interact with the hydrogen-bond-donor site as shown in Figure 1.[15]

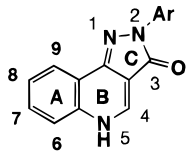
Although thienyl compounds **3c**,**d** showed relatively high *in vitro* affinities for the receptor, neither exhibited activity *in vivo*. Therefore, a number of analogues with a variety of 5-membered heteroaromatic substituents at the 2-position were synthesized and tested. Among them, isoxazolyl compounds were found to exhibit both high *in vitro* affinity and *in vivo* activity. The isoxazole moiety is considered to be small enough to be accommodated by BZ receptor in its lipophilic area (Figure 2).

Table 2 shows the pharmacological activities of compounds having an isoxazol-3-yl moiety at the 2-position when the inverse agonist activities were assessed by

Table 1. Affinities of 2-Arylimidazo[4,5-*c*]quinolines and 2-Arylpyrazolo[4,3-*c*]quinolin-3-ones



3a-d

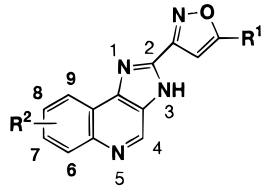


6a-d

compd	K_i (nM)[a] (mean ± SD)	compd	K_i (nM)[a] (mean ± SD)	Ar
3a	270 ± 67	**6a** (CGS-9896)[b,c]	0.83 ± 0.15	*p*-chlorophenyl
3b	22.0 ± 9.9	**6b** (CGS-8216)[b,c]	0.22 ± 0.01	phenyl
3c	4.5 ± 1.5	**6c** (S-135)[c]	0.32 ± 0.02	5-methylthien-3-yl
3d	1.7 ± 0.5	**6d**[c]	0.41 ± 0.18	thien-2-yl

[a] Displacing potential to [^{3}H]diazepam binding in rat cerebral cortex. [b] See ref 13. [c] See ref 8.

Table 2. Pharmacological Activities of 2-(Isoxazol-3-yl)imidazo[4,5-*c*]quinolines



4a-m

					inverse agonist act[c]	
compd	R^1	R^2	K_i[a] (nM) (mean ± SD)	agonist act[b] ED_{50}[d] (mg/kg po)	PTZ = 90 mg/kg sc, ED_{50}[d] (mg/kg po)	PTZ = 75 mg/kg sc, ED_{50}[d] (mg/kg po)
4a	H	H	0.6 ± 0.2		10.11 (6.70−16.70)	inactive to 10 iv
4b	Me	H	0.9 ± 0.4	16.42 (10.50−29.44)		
4c	Et	H	1.1 ± 0.4	19.23 (13.53−26.49)		
4d	H	6-F	40.0 ± 18.6		37.5% (10 iv)[e]	
4e	H	6-Cl	524 ± 138	inactive to 10 iv	inactive to 10 iv	
4f	H	7-F	0.9 ± 0.4	39.93 (23.35−)		
4g	H	7-Cl	3.5 ± 1.5	27.22 (17.54−46.06)		
4h	H	7-MeO	7.2 ± 2.0		8.77 (3.64−18.22)	16.17 (11.71−22.28)
4i	H	8-F	0.8 ± 0.2		16.46 (7.70−119.81)	64.12 (28.18−)
4j	H	8-Cl	0.8 ± 0.3		14.21 (9.76−20.68)	25% (50 po)[e]
4k	H	8-MeO	0.5 ± 0.2		31.53 (22.39−75.90)	25% (50 po)[e]
4l	H	9-F	3.4 ± 0.9		21.19 (14.60−34.51)	35.73 (25.87−58.54)
4m	H	9-Cl	7.8 ± 4.1		5.95 (3.53−11.93)	7.21 (4.54−12.28)

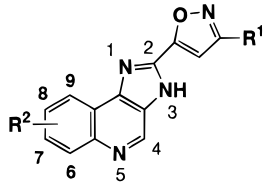
[a] Displacing potential to [^{3}H]diazepam binding in rat cerebral cortex. [b] Mouse pentylenetetrazole anticonvulsant test. See text for schedule details. [c] Mouse pentylenetetrazole proconvulsant activity. See text for schedule details. [d] ED_{50} values and their 95% confidence limits were calculated by the probit method. [e] Percentage of the animals affected at that dose.

potentiation of the convulsions induced by two subconvulsive doses (75 and 90 mg/kg, sc) of PTZ. Since a higher intrinsic activity of inverse agonists is defined as the ability to potentiate the convulsant action of the lower dose of PTZ, the assay using 75 mg/kg PTZ indicates higher negative efficacy than the one using 90 mg/kg PTZ. Compound **4a** having no substituent on both the isoxazole and benzene ring showed high affinity and moderate inverse agonist activity, as judged by its potentiation of the proconvulsions caused only by 90 mg/kg PTZ.

Substitution at the 5′-position with an alkyl group (**4b**,**c**) led to a shift from inverse agonist to agonist profile of activity. The similar substitution effect has been observed for the series of 2-(thien-2-yl)pyrazolo-[4,3-*c*]quinolines.[8] In order to examine the structure−activity relationships in detail, compounds with a halogen or a methoxy on the benzene ring were synthesized in which the isoxazole ring was kept unsubstituted. Substitution at the 6-position resulted in marked loss of affinity and *in vivo* activity (**4d**,**e**). The affinities and inverse activities were retained in the 8-substituted compounds **4i**−**k**. Halogenation at the 9-position moderately decreased affinity but increased inverse activity showing potentiation of proconvulsions caused by 75 mg/kg PTZ (**4l**,**m**). Interestingly, substitution with a halogen at the 7-position altered the intrinsic activity from an inverse agonist to an agonist type (**4f**,**g**), while substitution with a methoxy group at the same position enhanced the inverse agonist activity (**4h**).

Table 3 summarizes the biological data of compounds having an isoxazol-5-yl moiety at the 2-position. Compound **5a** with no substituent on the ring exhibited high affinity comparable to **4a**. Although **5a** did not possess either agonist or inverse agonist activity, it exhibited antagonist activity (zero efficacy). The 3′-methyl analogue **5b** displayed more potent agonist activity than the corresponding isoxazol-3-yl analogue **4b**. With 3′-methylisoxazole fixed at the 2-position, the effects of the substituent on the benzene ring were investigated. Halogenation at the 6-position led to low affinity and a loss of *in vivo* activity (**5d**,**c**). Analogues substituted at

Table 3. Pharmacological Activities of 2-(Isoxazol-5-yl)imidazo[4,5-*c*]quinolines

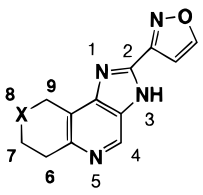


5a-m

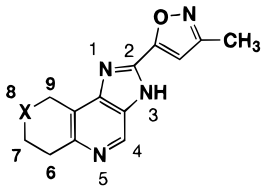
compd	R^1	R^2	K_i,[a] (nM) (mean ± SD)	agonist act[b] ED_{50}[e] (mg/kg po)	inverse agonist act[c] PTZ = 90 mg/kg sc, ED_{50}[e] (mg/kg iv)	antagonist act[d] ED_{50}[e] (mg/kg iv)
5a	H	H	1.0 ± 0.3	inactive to 10 iv	inactive to 10 iv	1.94 (1.35−2.77)
5b	Me	H	0.9 ± 0.3	5.89 (3.79−8.57)		
5c	Et	H	1.2 ± 0.3	13.53 (9.99−19.58)		
5d	Me	6-F	302 ± 104	inactive to 50 po[f]		
5e	Me	6-Cl	3354 ± 535	inactive to 10 iv	inactive to 10 iv	
5f	Me	7-F	1.4 ± 0.4	5.15 (3.54−7.18)		
5g	Me	7-Cl	18.8 ± 6.0	29.83 (22.06−42.65)		
5h	Me	7-MeO	9.5 ± 1.9	inactive to 10 iv	inactive to 10 iv	46.2% (10 iv)[g]
5i	Me	8-F	1.1 ± 0.3	5.41 (2.96−12.99)		
5j	Me	8-Cl	0.5 ± 0.2	10.56 (4.78−17.08)		
5k	Me	8-MeO	0.9 ± 0.2	21.55 (11.44−77.99)		
5l	Me	9-F	4.9 ± 1.7	4.86 (3.24−7.03)		
5m	Me	9-Cl	13.7 ± 4.2	8.53 (5.08−16.82)		

[a−c] See the corresponding footnotes in Table 2. [d] Antagonist activity. See text for schedule details. [e] ED_{50} values and their 95% confidence limits were calculated by the probit method. [f] ED_{50} = 8.42 mg/kg iv. [g] Percentage of the animals affected at that dose.

Table 4. Pharmacological activities of Fused Imidazopyridines



14a-d



15a-d

compd	X	K_i,[a] (nM) (mean ± SD)	agonist act[b] ED_{50}[d] (mg/kg po)	inverse agonist act[c] PTZ = 90 mg/kg sc, ED_{50}[d] (mg/kg po)	inverse agonist act[c] PTZ = 75 mg/kg sc, ED_{50}[d] (mg/kg po)
14a	CH_2CH_2	5.2 ± 2.9	inactive to 10 iv	inactive to 10 iv	antagonist[e]
14b	CH_2	1.2 ± 0.4	inactive to 10 iv	inactive to 10 iv	antagonist[f]
14c	O	2.7 ± 0.9		19.63 (11.92−34.02)	25% (50 po)[g]
14d	bond	5.3 ± 1.8		4.72 (2.69−7.22)	9.22 (6.76−12.51)
15a	CH_2CH_2	15.6 ± 5.3	12.37 (6.01−25.87)		
15b	CH_2	2.2 ± 0.3	8.12 (5.85−10.65)		
15c	O	3.3 ± 1.4	11.21 (7.81−16.06)		
15d	bond	14.6 ± 6.9	5.97 (4.41−8.53)		
diazepam		5.0 ± 0.4	0.67 (0.47−0.94)		
CGS-9896		0.83 ± 0.15	1.17 (1.06−2.93)		
CGS-8216		0.22 ± 0.01		12.77 (5.43−33.74)	25% (50 po)[g]

[a−d] See the corresponding footnotes in Table 2. [e] Antagonist activity: ED_{50} = 4.61 (3.78−6.29) mg/kg iv. See text for schedule details. [f] Antagonist activity: ED_{50} = 0.55 (0.26−2.04) mg/kg iv. [g] Percentage of the animals affected at that dose.

the 8-position retained affinity and agonist activity (**5i**−**k**). The 9-halo derivatives **5l**,**m** exhibited moderately low affinities and retained agonist activities. Substitution at the 7-position resulted in diverse effects. Fluoro compound **5f** maintained its affinity and agonist activity, while chloro compound **5g** displayed reduced affinity but retained moderate agonist activity. Introduction of a methoxy group at the 7-position (**5h**) lowered the affinity by 10-fold and abolished agonist activity resulting in a very weak antagonist activity.As mentioned above, substitution on ring A has a pronounced effect on affinity and a lesser effect on efficacy. This observation led us to try further structural modification in which the benzene ring was replaced by a nonaromatic ring. For comparison with imidazoquinolines **4a** and **5b**, [*e*]-fused imidazo[4,5-*c*]pyridines **14a**−**d** and **15a**−**d** were prepared, respectively. Compounds **14a**−**d** showed lower binding affinities by 2−10-fold than **4a**, but all of them exhibited *in vivo* activities. **14a**,**b** with a 7- or 6-membered carbocyclic ring showed antagonist activity (zero efficacy), while **14d** with a 5-membered carbocyclic ring exhibited strong inverse activity. Pyrano derivative **14c** displayed moderate inverse agonist activity with efficacy lying in between those of **14b**,**d**. These findings

suggest that decreasing the size of ring A enhances inverse agonist activity in the compounds with an isoxazol-3-yl group at the 2-position. On the other hand, compounds **15a**−**d** with a 3-methylisoxazol-5-yl group exhibited agonist activity regardless of the difference of ring A. It is worth noting that all the 3-methylisoxazol-5-yl derivatives possessed considerably high agonist activity although their affinities were lower than that of **5b**.

Finally, several members of these series were selected for further pharmacological and toxicological evaluations as drug candidates. For example, the partial agonists **5b** and **15b** are potential anxiolytics which could be free of muscle relaxation or other sedative effects.[16] Antagonists such as **5a** and **14b** are expected to be useful as antidotes to sedative overdose. Partial inverse agonists **4b** and **14c** were evaluated as cognition enhancers. Presently, compound **14c** (S-8510) is under clinical investigation for the treatment of senile dementia. The detailed pharmacological results will be reported in due course.

Experimental Section

Melting points were determined on a Yanagimoto hot plate micromelting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi 260-10 infrared spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian VXR-200 spectrometer. Chemical shifts are given in parts per million relative to tetramethylsilane as the internal standard.

3,4-Diaminoquinolines (2). 3-Nitro-4-hydroxyquinolines **1** (prepared by condensation[9] of anthranilic acids with methazonic acid or by nitration[17] of quinolin-4-ones) were heated with phosphorus oxychloride to give 4-chloroquinolines which were treated with ammonia followed by hydrogenation of the resulting 4-amino-3-nitroquinolines, affording the title compounds: **2a** (R = H), mp 168−170 °C dec; **2b** (R = 5-F), mp 168−169.5 °C dec; **2c** (R = 5-Cl), mp 157−159 °C (lit.[17] mp 158−159 °C); **2d** (R = 6-F), mp 196−198 °C dec; **2e** (R = 6-Cl), mp 206−209 °C; **2f** (R = 6-MeO), mp 181−182 °C dec; **2g** (R = 7-F), mp 185−188 °C dec; **2h** (R = 7-Cl), mp 193−195 °C dec (lit.[17] mp 191−192 °C); **2i** (R = 7-MeO), mp 136−139 °C dec; **2j** (R = 8-F), mp 167−169 °C dec; **2k** (R = 8-Cl), mp 159−161 °C dec.

2-Aryl-3*H*-imidazo[4,5-*c*]quinolines 3−5. 2-(Isoxazol-3-yl)-3*H*-imidazo[4,5-*c*]quinoline (4a). General Procedure. To a stirred solution of isoxazole-3-carboxylic acid (249 mg, 2.2 mmol) in a mixture of hexamethylphosphoramide (HMPA) (4 mL) and acetonitrile (0.4 mL) was added, dropwise, thionyl chloride (250 mg, 2.1 mmol) at −5−0 °C under nitrogen. After stirring at the same temperature for 30 min, 3,4-diaminoquinoline **2a** (318 mg, 2 mmol) was added and the mixture was stirred at 0−5 °C for 4 h. The mixture was diluted with ice−water and neutralized with saturated aqueous sodium bicarbonate. The resulting precipitate was filtered, washed with water, and dried to give 4-amino-3-[(isoxazol-3-ylcarbonyl)amino]quinoline as a crude product. This was suspended in a mixture of HMPA (6 mL) and acetic acid (1.5 mL) and heated at 180 °C for 20 min under nitrogen. The cooled mixture was diluted with water and neutralized with saturated aqueous sodium bicarbonate. The resulting solid was chromatographed on silica gel with chloroform/methanol (10:1, v/v) as eluent followed by crystallization from ethyl acetate to give **4a** as white crystals (382 mg, 82%): mp 271−274 °C dec (AcOEt); ^{1}H-NMR (DMSO-d_6) 7.28 (1H, d, J = 2 Hz), 7.60−7.85 (2H, m), 8.10−8.27 (1H, m), 8.52−8.70 (1H, m), 9.19 (1H, d, J = 2 Hz), 9.29 (1H, s). Anal. ($C_{13}H_8N_4O\cdot{}^1/_8H_2O$) C, H, N.

Compounds **3a**−**d**, **4b**−**m**, and **5a**−**m** in Tables 1−3 were prepared in the same way as **4a** using the corresponding 3,4-diaminoquinolines **2** and the appropriate carboxylic acids.

2-(4-Chlorophenyl)-3*H*-imidazo[4,5-*c*]quinoline (3a): mp 335−337 °C dec (EtOH); ^{1}H-NMR (DMSO-d_6) 7.6−7.9 (4H, m), 8.0−8.6 (4H, m) 9.26 (1H, br s), 13.85 (1H, br s). Anal. ($C_{16}H_{10}N_3Cl$) C, H, N, Cl.

2-Phenyl-3*H*-imidazo[4,5-*c*]quinoline (3b): mp 298−300 °C (EtOH); ^{1}H-NMR (DMSO-d_6) 7.50−7.80 (5H, m), 8.05−8.65 (4H, m), 9.25 (1H, s). Anal. ($C_{16}H_{11}N_3\cdot{}^1/_3H_2O$) C, H, N.

2-(5-Methylthien-2-yl)-3*H*-imidazo[4,5-*c*]quinoline (3c): mp 293−295 °C (EtOH); ^{1}H-NMR (DMSO-d_6) 2.55 (3H, s), 7.57−7.80 (3H, m), 8.05−8.25 (2H, m), 8.39−8.59 (1H, m), 9.21 (1H, s). Anal. ($C_{15}H_{11}N_3S$) C, H, N, S.

2-(Thien-2-yl)-3*H*-imidazo[4,5-*c*]quinoline (3d): mp 304−305 °C (EtOH); ^{1}H-NMR (DMSO-d_6) 7.25−7.40 (1H, m), 7.55−7.90 (3H, m), 7.95−8.30 (2H, m), 8.40−8.55 (1H, m), 9.20 (1H, s). Anal. ($C_{14}H_9N_3S$) C, H, N, S.

2-(5-Methylisoxazol-3-yl)-3*H*-imidazo[4,5-*c*]quinoline (4b): mp 273−274 °C (AcOEt); ^{1}H-NMR (DMSO-d_6) 2.57 (3H, s), 6.92 (1H, s), 7.61−7.82 (2H, m), 8.10−8.17 (1H, m), 8.53−8.68 (1H, m), 9.26 (1H, s). Anal. ($C_{14}H_{10}N_4O$) C, H, N.

2-(5-Ethylisoxazol-3-yl)-3*H*-imidazo[4,5-*c*]quinoline (4c): mp 268−269 °C (AcOEt); ^{1}H-NMR (DMSO-d_6) 1.33 (3H, t, J = 7 Hz), 2.91 (2H, q, J = 7 Hz), 6.92 (1H, s), 7.58−7.83 (2H, m), 8.09−8.20 (1H, m), 8.53−8.65 (1H, m), 9.24 (1H, s). Anal. ($C_{15}H_{12}N_4O$) C, H, N.

6-Fluoro-2-(isoxazol-3-yl)-3*H*-imidazo[4,5-*c*]quinoline (4d): mp 329−332 °C dec (MeOH−CH_2Cl_2); ^{1}H-NMR (DMSO-d_6) 7.29 (1H, d, J = 2 Hz), 7.43−7.81 (2H, m), 8.32−8.43 (1H, m), 9.25 (1H, d, J = 2 Hz), 9.31 (1H, s). Anal. ($C_{13}H_7N_4FO$) C, H, N.

6-Chloro-2-(isoxazol-3-yl)-3*H*-imidazo[4,5-*c*]quinoline (4e): mp 284−287 °C dec (AcOEt−CH_2Cl_2); ^{1}H-NMR (DMSO-d_6) 7.30 (1H, d, J = 2 Hz), 7.60−7.98 (2H, m), 8.53−8.63 (1H, m), 9.22 (1H, d, J = 2 Hz), 9.39 (1H, s). Anal. ($C_{13}H_7N_4ClO\cdot{}^7/_8H_2O$) C, H, N.

7-Fluoro-2-(isoxazol-3-yl)-3*H*-imidazo[4,5-*c*]quinoline (4f): mp 297−299 °C (AcOEt−MeOH); ^{1}H-NMR (DMSO-d_6) 7.26 (1H, d, J = 2 Hz), 7.50−7.93 (2H, m), 8.57−8.73 (1H, m), 9.19 (1H, d, J = 2 Hz), 9.29 (1H, s). Anal. ($C_{13}H_7N_4FO\cdot{}^1/_6H_2O$) C, H, N.

7-Chloro-2-(isoxazol-3-yl)-3*H*-imidazo[4,5-*c*]quinoline (4g): mp 302−306 °C dec (MeOH−$CHCl_3$); ^{1}H-NMR (DMSO-d_6) 7.25 (1H, d, J = 2 Hz), 7.65−7.79 (1H, dd, J = 8, 2 Hz), 8.17 (1H, d, J = 2 Hz), 8.60 (1H, d, J = 8 Hz), 9.17 (1H, d, J = 2 Hz), 9.29 (1H, s). Anal. ($C_{13}H_7N_4ClO\cdot{}^1/_8H_2O$) C, H, N.

2-(Isoxazol-3-yl)-7-methoxy-3*H*-imidazo[4,5-*c*]quinoline (4h): mp 293−296 °C dec (MeOH−AcOEt); ^{1}H-NMR (DMSO-d_6) 3.94 (3H, s), 7.28 (1H, d, J = 2 Hz), 7.37 (1H, dd, J = 9, 2 Hz), 7.57 (1H, d, J = 2 Hz), 8.48 (1H, d, J = 9 Hz), 9.21 (1H, s), 9.23 (1H, d, J = 2 Hz). Anal. ($C_{14}H_{10}N_4O_2$) C, H, N.

8-Fluoro-2-(isoxazol-3-yl)-3*H*-imidazo[4,5-*c*]quinoline (4i): mp 308−310 °C dec (MeOH−AcOEt); ^{1}H-NMR (DMSO-d_6) 7.30 (1H, d, J = 2 Hz), 7.50−7.73 (1H, m), 8.14−8.37 (2H, m), 9.25 (1H, d, J = 2 Hz), 9.27 (1H, s). Anal. ($C_{13}H_7N_4FO$) C, H, N.

8-Chloro-2-(isoxazol-3-yl)-3*H*-imidazo[4,5-*c*]quinoline (4j): mp 299−302 °C dec (AcOEt−MeOH); ^{1}H-NMR (DMSO-d_6) 7.30 (1H, d, J = 2 Hz), 7.74 (1H, dd, J = 8, 2 Hz), 8.17 (1H, d, J = 8 Hz), 8.66 (1H, d, J = 2 Hz), 9.20 (1H, d, J = 2 Hz), 9.30 (1H, s). Anal. ($C_{13}H_7N_4ClO$) C, H, N.

2-(Isoxazol-3-yl)-8-methoxy-3*H*-imidazo[4,5-*c*]quinoline (4k): mp 279−281 °C dec (MeOH−AcOEt); ^{1}H-NMR (DMSO-d_6) 3.96 (3H, s), 7.26 (1H, d, J = 2 Hz), 7.38 (1H, d, J = 2 Hz), 7.99−8.09 (2H, m), 9.10 (1H, s), 9.22 (1H, d, J = 2 Hz). Anal. ($C_{14}H_{10}N_4O_2\cdot{}^1/_4H_2O$) C, H, N.

9-Fluoro-2-(isoxazol-3-yl)-3*H*-imidazo[4,5-*c*]quinoline (4l): mp 277−279 °C (MeOH−AcOEt); ^{1}H-NMR (DMSO-d_6) 7.33 (1H, d, J = 2 Hz), 7.43−7.85 (2H, m), 7.96−8.06 (1H, m), 9.22 (1H, d, J = 2 Hz), 9.32 (1H, s). Anal. ($C_{13}H_7N_4FO$) C, H, N.

9-Chloro-2-(isoxazol-3-yl)-3*H*-imidazo[4,5-*c*]quinoline (4m): mp 210−212 °C (MeOH); ^{1}H-NMR (DMSO-d_6) 7.31 (1H, d, J = 2 Hz), 7.57−7.90 (2H, m), 8.13−8.19 (1H, m), 9.24 (1H, d, J = 2 Hz), 9.33 (1H, s). Anal. ($C_{13}H_7N_4OCl\cdot{}^1/_2CH_3OH$) C, H, N, Cl.

2-(Isoxazol-5-yl)-3*H*-imidazo[4,5-*c*]quinoline (5a): mp 280−285 °C dec (AcOEt−MeOH); ^{1}H-NMR (DMSO-d_6) 7.26

(1H, d, J = 2 Hz), 7.73 (2H, m), 8.15 (1H, m), 8.55 (1H, m), 8.81 (1H, d, J = 2 Hz), 9.28 (1H, s). Anal. ($C_{13}H_8N_4O$) C, H, N.

2-(3-Methylisoxazol-5-yl)-3*H*-imidazo[4,5-*c*]quinoline (5b): mp 303−305 °C (EtOH−AcOEt); ^{1}H-NMR (DMSO-d_6) 2.40 (3H, s), 7.10 (1H, s), 7.73 (2H, m), 8.16 (1H, m), 8.54 (1H, m), 9.26 (1H, s). Anal. ($C_{14}H_{10}N_4O$) C, H, N.

2-(3-Ethylisoxazol-5-yl)-3*H*-imidazo[4,5-*c*]quinoline (5c): mp 254−256 °C (AcOEt−MeOH); ^{1}H-NMR (DMSO-d_6) 1.32 (3H, t, J = 7 Hz), 2.81 (2H, q, J = 7 Hz), 7.19 (1H, s), 7.75 (2H, m), 8.18 (1H, m), 8.56 (1H, m), 9.29 (1H, s). Anal. ($C_{15}H_{12}N_4O\cdot{}^1/_8H_2O$) C, H, N.

6-Fluoro-2-(3-methylisoxazol-5-yl)-3*H*-imidazo[4,5-*c*]-quinoline (5d): mp 275−277 °C dec (AcOEt−EtOH); ^{1}H-NMR (DMSO-d_6) 2.38 (3H, s), 7.14 (1H, s), 7.38−7.80 (3H, m), 8.23−8.36 (1H, m), 9.28 (1H, s). Anal. ($C_{14}H_9N_4OF$) C, H, N.

6-Chloro-2-(3-methylisoxazol-5-yl)-3*H*-imidazo[4,5-*c*]-quinoline (5e): mp 303−305 °C dec (AcOEt−CH_2Cl_2); ^{1}H-NMR (DMSO-d_6) 2.40 (3H, s), 7.12 (1H, s), 7.59−7.95 (2H, m), 8.45−8.55 (1H, m), 9.36 (1H, s). Anal. ($C_{14}H_9N_4ClO$) C, H, N.

7-Fluoro-2-(3-methylisoxazol-5-yl)-3*H*-imidazo[4,5-*c*]-quinoline (5f): mp 308−310 °C dec (AcOEt−MeOH); ^{1}H-NMR (DMSO-d_6) 2.40 (3H, s), 7.11 (1H, s), 7.52−7.92 (2H, m), 8.44−8.63 (1H, m), 9.27 (1H, s). Anal. ($C_{14}H_9N_4OF$) C, H, N.

7-Chloro-2-(3-methylisoxazol-5-yl)-3*H*-imidazo[4,5-*c*]-quinoline (5g): mp 319−321 °C dec (AcOEt−MeOH); ^{1}H-NMR (DMSO-d_6) 2.38 (3H, s), 7.12 (1H, s), 7.70 (1H, dd, J = 8, 2 Hz), 8.15 (1H, d, J = 2 Hz), 8.52 (1H, d, J = 8 Hz), 9.27 (1H, s). Anal. ($C_{14}H_9N_4OCl\cdot CH_3OH$) C, H, N, Cl.

7-Methoxy-2-(3-methylisoxazol-5-yl)-3*H*-imidazo[4,5-*c*]-quinoline (5h): mp 280−282 °C dec (AcOEt−MeOH); ^{1}H-NMR (DMSO-d_6) 2.38 (3H, s), 3.95 (3H, s), 7.08 (1H, s), 7.35 (1H, dd, J = 8, 2 Hz), 7.55 (1H, d, J = 2 Hz), 8.43 (1H, d, J = 8 Hz), 9.18 (1H, s). Anal. ($C_{14}H_{12}N_4O_2\cdot{}^1/_8CH_3COOC_2H_5$) C, H, N.

8-Fluoro-2-(3-methylisoxazol-5-yl)-3*H*-imidazo[4,5-*c*]-quinoline (5i): mp 293−295 °C (AcOEt); ^{1}H-NMR (DMSO-d_6) 2.38 (3H, s), 7.11 (1H, s), 7.44−7.68 (12H, m), 8.10−8.27 (2H, m), 9.22 (1H, s). Anal. ($C_{14}H_9N_4OF\cdot{}^1/_4H_2O$) C, H, N.

8-Chloro-2-(3-methylisoxazol-5-yl)-3*H*-imidazo[4,5-*c*]-quinoline (5j): mp 310−311 °C dec (AcOEt−MeOH); ^{1}H-NMR (DMSO-d_6) 2.41 (3H, s), 7.12 (1H, s), 7.69 (1H, dd, J = 9, 2 Hz), 8.15 (1H, d, J = 9 Hz), 8.52 (1H, d, J = 2 Hz), 9.26 (1H, s). Anal. ($C_{14}H_9N_4OCl\cdot{}^5/_6H_2O$) C, H, N.

8-Methoxy-2-(3-methylisoxazol-5-yl)-3*H*-imidazo[4,5-*c*]-quinoline (5k): mp 283−284 °C (AcOEt−MeOH); ^{1}H-NMR (DMSO-d_6) 2.38 (3H, s), 3.93 (3H, s), 7.11 (1H, s), 7.33 (1H, dd, J = 9, 2 Hz), 7.89 (1H, d, J = 2 Hz), 8.04 (1H, d, J = 9 Hz), 9.09 (1H, s). Anal. ($C_{15}H_{12}N_4O_2\cdot{}^1/_8H_2O$) C, H, N.

9-Fluoro-2-(3-methylisoxazol-5-yl)-3*H*-imidazo[4,5-*c*]-quinoline (5l): mp 292−294 °C (AcOEt−MeOH); ^{1}H-NMR (DMSO-d_6) 2.40 (3H, s), 7.31 (1H, s), 7.45−7.86 (2H, m), 7.97−8.07 (1H, m), 9.35 (1H, s). Anal. ($C_{14}H_9N_4OF$) C, H, N.

9-Chloro-2-(3-methylisoxazol-5-yl)-3*H*-imidazo[4,5-*c*]-quinoline (5m): mp 243−245 °C (MeOH); ^{1}H-NMR (DMSO-d_6) 2.40 (3H, s), 7.28 (1H, s), 7.73−7.90 (2H, m), 8.14−8.20 (1H, m), 9.35 (1H, s). Anal. ($C_{14}H_9N_4ClO$) C, H, N, Cl.

Fused 3-Nitropyridines (8). Following the method reported by Y. Tohda *et al.*,[10] compounds **8** were prepared by ring transformation of 1-methyl-3,5-dinitro-2-pyridone with cyclic ketones in the presence of ammonia.

3-Nitro-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine (8c). General Procedure. A suspension of 1-methyl-3,5-dinitro-2-pyridone (3.98 g, 20 mmol) and tetrahydro-4*H*-pyran-4-one (2.40 g, 24 mmol) in methanolic ammonia (1.1 M, 200 mL) was heated at 55 °C for 5 h. The reaction mixture was concentrated *in vacuo*, and the residue was taken up in benzene. The insoluble materials were removed by filtration, and the filtrate was concentrated. The residue was subjected to chromatography on silica gel with chloroform/toluene (1:1) as eluent. The resulting product was recrystallized from methanol to yield **8c** as crystals (2.22 g, 62%): mp 131−132°C; ^{1}H-NMR (DMSO-d_6) 3.02 (2H, t, J = 6 Hz), 4.02 (2H, t, J = 6 Hz), 4.83 (2H, s), 8.39 (1H, d, J = 2 Hz), 9.19 (1H, d, J = 2 Hz). Anal. ($C_8H_8N_2O_3$) C, H, N.

3-Nitro-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (8a): X = CH_2CH_2; mp 86−87 °C (CH_2Cl_2−*i*-PrOH); ^{1}H-NMR (DMSO-d_6) 1.67−1.93 (6H, m), 2.91 (2H, m), 3.16 (2H, m), 8.17 (1H, d, J = 3 Hz), 9.12 (1H, d, J = 3 Hz). Anal. ($C_{10}H_{12}N_2O_2$) C, H, N.

Data for compounds **8b** (X = CH_2) and **8d** (X = bond) are described in the literature.[10]

Fused 3-Aminopyridines 9. 3-Amino-5,6,7,8-tetrahydroquinoline (9b). General Procedure. A suspension of 3-nitro-5,6,7,8-tetrahydroquinoline (**8b**) (15.8 g, 88.7 mmol) and 5% palladium on carbon (1.6 g) in methanol (300 mL) was hydrogenated at room temperature under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated to afford a crude product which was recrystallized from methylene chloride/isopropyl ether giving **9b** (12.76 g, 97%): mp 97−98 °C; ^{1}H-NMR ($CDCl_3$) 1.80 (4H, m), 2.68 (2H, t, J = 6 Hz), 2.80 (2H, t, J = 6 Hz), 3.30 (2H, br s), 6.70 (1H, m), 7.88 (1H, d, J = 3 Hz). Anal. ($C_9H_{12}N_2$) C, H, N.

3-Amino-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (9a): mp 79−80 °C (CH_2Cl_2−*i*-Pr_2O); ^{1}H-NMR ($CDCl_3$) 1.61−1.83 (6H, m), 2.87 (2H, m), 2.93 (2H, m), 3.34 (2H, br s), 6.76 (1H, d, J = 3 Hz), 7.79 (1H, d, J = 3 Hz). Anal. ($C_{10}H_{14}N_2$) C, H, N.

3-Amino-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine (9c): mp 138−139 °C (CH_2Cl_2−*i*-Pr_2O); ^{1}H-NMR (DMSO-d_6) 2.67 (2H, t, J = 6 Hz), 3.89 (2H, t, J = 6 Hz), 4.55 (2H, s), 5.10 (2H, br s), 6.56 (1H, d, J =3 Hz), 7.76 (1H, d, J = 3 Hz). Anal. ($C_8H_{10}N_2O$) C, H, N.

3-Amino-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (9d): mp 114−115 °C (CH_2Cl_2−*i*-Pr_2O); ^{1}H-NMR ($CDCl_3$) 2.08 (2H, m), 2.84 (2H, t, J = 8 Hz), 2.88 (2H, t, J = 8 Hz), 3.30 (2H, br s), 6.86 (1H, m), 7.85 (1H, m). Anal. ($C_8H_{10}N_2$) C, H, N.

Fused 3-[(Trichloroacetyl)amino]pyridines (10). 3-[(Trichloroacetyl)amino]-5,6,7,8-tetrahydroquinoline (10b). General Procedure. To a stirred solution of **9b** (12.68 g, 85.6 mmol) and triethylamine (2.4 mL) in methylene chloride (130 mL) was added, dropwise, a solution of trichloroacetyl chloride (10.5 mL, 94.2 mmol) in methylene chloride (30 mL) with ice cooling over a period of 7 min. The reaction mixture was stirred at room temperature for 20 min, mixed with saturated saline, and made weakly alkaline with aqueous ammonia. The organic layer was separated, and the aqueous layer was extracted with methylene chloride. The combined organic extracts were washed (brine), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel with methanol/methylene chloride (1:9) as eluent. The product was recrystallized from ethyl acetate to give **10b** (24.21 g, 95%): mp 157−159 °C; IR (Nujol) 1724 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.79−1.95 (4H, m), 2.84 (2H, t, J = 6 Hz), 2.92 (2H, t, J = 6 Hz), 7.86 (1H, m), 8.40 (1H, d, J = 2 Hz). Anal. ($C_{11}H_{11}N_2Cl_3O$) C, H, N, Cl.

3-[(Trichloroacetyl)amino]-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (10a): mp 171−173 °C (MeOH−$CHCl_3$−AcOEt); IR (Nujol) 1712 cm^{-1}; ^{1}H-NMR (DMSO-d_6) 1.58−1.83 (6H, m), 2.77 (2H, m), 2.96 (2H, m), 7.78 (1H, d, J = 2 Hz), 8.47 (1H, d, J = 2 Hz), 10.93 (1H, s). Anal. ($C_{12}H_{13}N_2Cl_3O$) C, H, N, Cl.

3-[(Trichloroacetyl)amino]-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine (10c): mp 137−138 °C (CH_2Cl_2−*i*-Pr_2O); ^{1}H-NMR ($CDCl_3$) 3.02 (2H, t, J = 6 Hz), 4.08 (2H, t, J = 6 Hz), 4.80 (2H, s), 7.89 (1H, d, J = 3 Hz), 8.44 (1H, br s), 8.45 (1H, d, J = 3 Hz). Anal. ($C_{10}H_9N_2Cl_3O_2$) C, H, N.

3-[(Trichloroacetyl)amino]-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (10d): mp 166−167 °C (CH_2Cl_2−*i*-Pr_2O); IR (Nujol) 1707 cm^{-1}; ^{1}H-NMR (DMSO-d_6) 2.08 (2H, m), 2.88 (2H, t, J = 8 Hz), 2.92 (2H, t, J = 8 Hz), 7.85 (1H, m), 8.48 (1H, m), 10.94 (1H, s). Anal. ($C_{10}H_9N_2Cl_3O$) C, H, N, Cl.

Fused 3-[(Trichloroacetyl)amino]pyridine 1-Oxides 11. 3-[(Trichloroacetyl)amino]-5,6,7,8-tetrahydroquinoline 1-Oxide (11b). General Procedure. To a solution of **10b** (24.03 g, 81.9 mmol) in methylene chloride (40 mL) was added 3-(chloroperoxy)benzoic acid (80% purity; 21.2 g, 98.3 mmol) at room temperature, and the mixture was stirred for 45 min. The mixture was mixed with isopropyl ether, and the resulting crystals were filtered to give **11b** (25.06 g, 99%): mp 244−246 °C dec; IR (Nujol) 1721 cm^{-1}; ^{1}H-NMR (DMSO-d_6)

1.62−1.86 (4H, m), 2.69 (2H, d, J = 6 Hz), 2.75 (2H, t, J = 6 Hz), 7.43 (1H, d, J = 2 Hz), 8.51 (1H, d, J = 2 Hz), 11.06 (1H, s). Anal. ($C_{11}H_{11}N_2Cl_3O_2$) C, H, N, Cl.

3-[(Trichloroacetyl)amino]-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine 1-oxide (11a): mp 241−242 °C dec (MeOH−AcOEt); IR (Nujol) 1723 cm^{-1}; ^{1}H-NMR (DMSO-d_6) 1.53−1.81 (6H, m), 2.81 (2H, m), 3.23 (2H, m), 7.44 (1H, d, J = 2 Hz), 8.51 (1H, d, J = 2 Hz), 11.06 (1H, s). Anal. ($C_{12}H_{13}N_2Cl_3O_2$) C, H, N, Cl.

3-[(Trichloroacetyl)amino]-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine 1-oxide (11c): mp 237−250 °C (MeOH−acetone); IR (Nujol) 1728 cm^{-1}; ^{1}H-NMR (DMSO-d_6) 2.76 (2H, t, J = 6 Hz), 3.96 (2H, t, J = 6 Hz), 4.68 (2H, s), 7.45 (1H, d, J = 2 Hz), 8.56 (1H, d, J = 2 Hz), 11,14 (1H, s). Anal. ($C_{10}H_9N_2Cl_3O_3$) C, H, N, Cl.

3-[(Trichloroacetyl)amino]-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine 1-oxide (11d): mp 228−233 °C dec (MeOH−*i*-PrOH); IR (Nujol) 1716 cm^{-1}; ^{1}H-NMR (DMSO-d_6) 2.08 (2H, m), 2.93 (2H, t, J = 8 Hz), 2.99 (2H, t, J = 8 Hz), 7.54 (1H, d, J = 1 Hz), 8.43 (1H, d, J = 1 Hz), 11.10 (1H, s). Anal. ($C_{10}H_9N_2Cl_3O_2$) C, H, N, Cl.

Fused 3-Amino-4-nitropyridine 1-Oxides 12. 3-Amino-4-nitro-5,6,7,8-tetrahydroquinoline 1-Oxide (12b). General Procedure. A suspension of **11b** (1.00 g, 3.2 mmol) in fuming nitric acid (d = 1.52; 5 mL) was stirred at 55 °C for 5 h. The nitric acid was evaporated *in vacuo*, and the residue was neutralized with aqueous ammonia and heated at 60 °C for 2 h. The reaction mixture containing the resulting solid was mixed with isopropyl ether/2-propanol (1:1, 10 mL), and the precipitate was filtered. The filtrate was concentrated *in vacuo* and extracted with methanol/chloroform (1:10). The extract was concentrated and combined with the precipitate obtained above and then chromatographed on silica gel with methanol/chloroform (1:50) as eluent. The product was recrystallized from methylene chloride/2-propanol to give **12b** (525 mg, 78%): mp 199−201 °C dec; ^{1}H-NMR (DMSO-d_6): 1.55−1.97 (4H, m), 2.61 (2H, t, J = 6 Hz), 2.74 (2H, t, J = 6 Hz), 6.53 (2H, s), 7.96 (1H, s). Anal. ($C_9H_{11}N_3O_3$) C, H, N.

3-Amino-4-nitro-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]-pyridine 1-oxide (12a): mp 188−194 °C dec (MeOH−*i*-PrOH); ^{1}H-NMR (DMSO-d_6) 1.46−1.76 (6H, m), 2.66 (2H, m), 3.16 (2H, m), 6.22 (2H, s), 7.84 (1H, s). Anal. ($C_{10}H_{13}N_3O_3$) C, H, N.

3-Amino-4-nitro-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine 1-oxide (12c): mp 200−201 °C (THF−*i*-PrOH); ^{1}H-NMR (DMSO-d_6) 2.66 (2H, t, J = 6 Hz), 3.88 (2H, t, J = 6 Hz), 4.85 (2H, s), 7.23 (2H, s), 8.07 (1H, s). Anal. ($C_8H_9N_3O_4$) C, H, N.

3-Amino-4-nitro-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine 1-oxide (12d): mp 225−226 °C dec (MeOH−*i*-PrOH); ^{1}H-NMR (DMSO-d_6) 2.04 (2H, m), 2.84 (2H, t, J = 7 Hz), 3.33 (2H, t, J = 7 Hz), 7.23 (2H, s), 7.90 (1H, s). Anal. ($C_8H_9N_3O_3$) C, H, N.

Fused 3,4-Diaminopyridines 13. 3,4-Diamino-5,6,7,8-tetrahydroquinoline (13b). General Procedure. A mixture of **12b** (5.00 g, 23.9 mmol) and Raney nickel (12.9 g) in methanol was hydrogenated at room temperature under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on alumina with methanol/chloroform (1:20) as eluent. The product was recrystallized from methylene chloride/ethyl acetate to give **13b** (3.37g, 86%): mp 169−170 °C dec; ^{1}H-NMR (DMSO-d_6) 1.68 (4H, m), 2.38 (2H, t, J = 6 Hz), 2.54 (2H, t, J = 6 Hz), 4.26 (2H, s), 4.97 (2H, s), 7.47 (1H, s). Anal. ($C_9H_{13}N_2$) C, H, N.

3,4-Diamino-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (13a): mp 167−168 °C ($CHCl_3$−*i*-Pr_2O); ^{1}H-NMR (DMSO-d_6) 1.48−1.74 (6H, m), 2.58 (2H, m), 2.70 (2H, m), 4,26 (2H, s), 5,02 (2H, s), 7.36 (1H, s). Anal. ($C_{10}H_{15}N_3$) C, H, N.

3,4-Diamino-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine (13c): mp 196−200 °C dec (aqueous MeOH); ^{1}H-NMR ($CDCl_3$) 2.88 (2H, t), 3.05 (2H, br s), 3.84 (2H, s), 4.00 (2H, t), 4.63 (2H, s), 7.87 (1H, s). Anal. ($C_8H_{11}N_3O\cdot H_2O$) C, H, N.

3,4-Diamino-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine (13d): mp 190−193 °C (AcOEt); ^{1}H-NMR (DMSO-d_6) 1.94 (2H, m), 2.61 (2H, t, J = 7 Hz), 2.63 (2H, t, J = 7 Hz), 4.26 (2H, s), 5.08 (2H, s), 7.43 (1H, s). Anal. ($C_8H_{11}N_3$) C, H, N.

Fused 2-(Isoxazol-3-yl)-3*H*-imdazo[4,5-*c*]pyridines 14. 2-(Isoxazol-3-yl)-3,6,7,9-tetrahydroimidazo[4,5-*d*]pyrano-[4,3-*b*]pyridine Monophosphate Monohydrate (14c). General Procedure. To a stirred solution of 3,4-diamino-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridine monohydrate (**13c**) (5.88 g, 32 mmol) in *N*,*N*-dimethylformamide (50 mL) was added a solution of isoxazole-3-carbonyl chloride (4.43 g, 33.6 mmol) in methylene chloride (4.7 mL) at ice-bath temperature. The mixture was stirred at room temperature for 45 min, mixed with triethylamine (4.7 mL), and stirred for 1 h. The resulting crystals were collected by filtration, mixed with sodium acetate (500 mg) and ethylene glycol (79 mL), and heated at 150 °C for 5 h. The solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel with methanol/chloroform (1:9) as eluent. The product was treated with phosphoric acid in aqueous 2-propanol to give **14c** (8.60 g, 75%): mp 239−241 °C dec (aqueous *i*-PrOH); ^{1}H-NMR (DMSO-d_6) 2.98 (2H, t, J = 6 Hz), 4.05 (2H, t, J = 6 Hz), 5.01 (2H, s), 7.24 (1H, d, J = 2 Hz), 8.84 (1H, s), 9.21 (1H, d, J = 2 Hz). Anal. ($C_{12}H_{10}N_4O_2\cdot H_3PO_4\cdot H_2O$) C, H, N, P.

2-(Isoxazol-3-yl)-3,6,7,8,9,10-hexahydrocyclohept[*b*]imidazo[4,5-*d*]pyridine hydrochloride (14a): mp 191−193 °C (MeOH−*i*-PrOH); ^{1}H-NMR (D_2O) 1.78−2.02 (6H, m), 3.24 (4H, m), 7.15 (1H, m), 8.86 (1H, s), 8.96 (1H, m). Anal. ($C_{14}H_{14}N_4O\cdot$HCl) C, H, N, Cl.

2-(Isoxazol-3-yl)-6,7,8,9-tetrahydro-3*H*-imidazo[4,5-*c*]-quinoline hydrochloride (14b): mp 263−267 °C dec (MeOH−*i*-PrOH); ^{1}H-NMR (DMSO-d_6) 1.87−1.93 (4H, m), 3.08−3.14 (4H, m), 7.44 (1H, d, J = 2 Hz), 9.32 (1H, s), 9.34 (1H, d, J = 2 Hz). Anal. ($C_{13}H_{12}N_4O\cdot HCl\cdot{}^1/_2H_2O$) C, H, N, Cl.

2-(Isoxazol-3-yl)-3,6,7,8-tetrahydrocyclopent[*b*]imidazo-[4,5-*c*]pyridine hydrochloride (14d): mp 252−256 °C dec (MeOH−*i*-PrOH); ^{1}H-NMR (D_2O) 2.46 (2H, m), 3.27 (2H, t), 3.31 (2H, t), 7.09 (1H, m), 8.94 (1H, m), 8.95 (1H, s). Anal. ($C_{12}H_{10}N_4O\cdot$HCl) C, H, N, Cl.

Fused 2-(3-Methylisoxazol-5-yl)-3*H*-imidazo[4,5-*c*]pyridines 15. These compounds were prepared from 3-methylisoxazole-5-carbonyl chloride and the appropriate fused diaminopyridine in a method analogous to that used for the preparation of **14c**.

2-(3-Methylisoxazol-5-yl)-3,6,7,8,9,10-hexahydrocyclohept[*b*]imidazo[4,5-*d*]pyridine (15a): mp 243−260 °C dec (MeOH−*i*-PrOH); ^{1}H-NMR (D_2O) 1.77−2.03 (6H, m), 2.43 (3H, s), 3.23 (4H, m), 7.14 (1H, s), 8.84 (1H, s). Anal. ($C_{15}H_{16}N_4O\cdot$HCl) C, H, N, Cl.

2-(3-Methylisoxazol-5-yl)-6,7,8,9-tetrahydro-3*H*-imidazo-[4,5-*c*]quinoline hydrochloride (15b): mp 272−280 °C dec (MeOH−*i*-PrOH); ^{1}H-NMR (DMSO-d_6) 1.91 (4H, br s), 2.41 (3H, s), 3.11 (4H, br s), 7.57 (1H, s), 9.29 (1H, s). Anal. ($C_{14}H_{14}N_4O\cdot$HCl) C, H, N, Cl.

2-(3-Methylisoxazol-5-yl)-3,6,7,9-tetrahydroimidazo-[4,5-*d*]pyrano[4,3-*b*]pyridine hydrochloride (15c): mp 266−272 °C dec (MeOH); ^{1}H-NMR (D_2O) 2.42 (3H, s), 3.24 (2H, t, J = 5 Hz), 4.24 (2H, t, J = 5 Hz), 5.10 (2H, s), 7.11 (1H, s), 9.05 (1H, s). Anal. ($C_{13}H_{12}N_4O_2\cdot$HCl) C, H, N, Cl.

2-(3-Methylisoxazol-5-yl)-3,6,7,8-cyclopent[*b*]imidazo-[4,5-*c*]pyridine hydrochloride (15d): mp 290−293 °C dec (MeOH−*i*-PrOH); ^{1}H-NMR (D_2O) 2.42 (3H, s), 2.45 (2H, m), 3.25 and 3.33 (2H each, m), 7.05 (1H, s), 8.91 (1H, m). Anal. ($C_{13}H_{12}N_4O\cdot$HCl) C, H, N, Cl.

Molecular Modeling. These studies were carried out using the Sybyl Molecular Modeling Software Package (version 6.10).[18] Each structure was energy minimized within MOPAC version 6.0 (PM3).[19] In Figures 1 and 2, four atom pairs were used to produce the least-squares superposition: (1) the N1 nitrogen atoms, (2) the carbonyl oxygen or N3 nitrogen atoms, (3) the N5 nitrogen atoms, and (4) the centroids of the benzene rings of the quinoline moieties.

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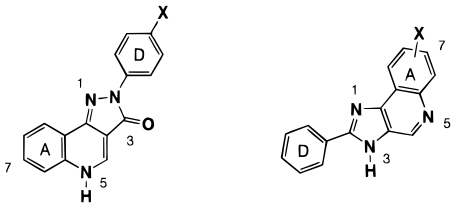
(15) Because the N3H imidazoquinolines are more stable than the N5H tautomers, the reviewer proposed an alternative alignment of the pyrazoloquinolines with the N3H tautomers of the imidazoquinolines as shown in the following figure (see below). As the reviewer suggested, this alignment is consistent with Fryer's observation that substituents on ring A of pyrazoloquinolines can mimic the pharmacological effects of substituents on ring D. Fryer had proposed that pyrazoloquinolines possessing substituents on ring A bind in an inverted orientation to BZR so that substituents on ring A occupy volumes comparable to ring D substituents. (For Fryer's work, see: Fryer, R. I.; Zhang, P.; Rios, R.; Gu, Z. Q.; Basile, A. S.; Skolnick, P. Structure-activity relationship studies at benzodiazepine receptors (BzR): a comparison of the substituent effects of pyrazoloquinolinone analogues. *J. Med. Chem.* **1993**, *36*, 1669−1673.) Nonetheless, the inverted orientation to the BZR seems to be at variance with the effects of the alkyl group on the isoxazole rings which led to the shifts from inverse agonist to agonist (*e.g.*, **4a** vs **4b**, **14c** vs **15c**, **14d** vs **15d**) in analogy with data reported for the 2-thienylpyrazoloquinolines. Thus, compounds **4b** and **15c**,**d** do not possess any substituent at the 7- or 8-position which is needed to exhibit effects toward agonist in the inverted model. Although some of our data (*e.g.*, effects of the 7-halo substituents of **4f**,**g**) may be attributed to this model, the entire structure−activity relationships can be well accounted for by the alignment using the N5H imidazoquinolines shown in Figures 1 and 2.



(16) While the muscle relaxation effects of **5b** and **15b** are 40- and 10-fold less potent than that of diazepam, respectively (traction test using mice), both possessed potent anxiolytic effects comparable to diazepam (anticonflict test using rats). The detailed data will be reported elsewhere.
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(19) *QCPE Program #455* (Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, Bloomington, IN 47405); J. J. P. Stewart, Frank J. Seiler Research Laboratory, U.S. Air Force Academy, CO 80840.

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