Articles

Cyclic Guanidines. 17.[1] Novel (N-Substituted amino)imidazo[2,1-*b*]quinazolin-2-ones: Water-Soluble Platelet Aggregation Inhibitors

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A series of novel 1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one derivatives substituted with a secondary amino group has been prepared and tested for the activities of inhibiting platelet aggregation in rats in vitro and ex vivo. Most of the compounds were found to be the potent inhibitors of platelet aggregation. Some of the active compounds were soluble in water and effective via iv infusion in rats. Structure–activity relationships have indicated that a lipophilic secondary amino group located at position 6 or 7 contributed to retention of potent activity. Among the compounds studied, 7-piperidino-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one (**13g**, DN-9693) was the most favorable compound.

In view of the importance of prophylactic agents for thrombosis and atherosclerosis, inhibitors of platelet aggregation are of considerable interest. Some potent compounds have already been reported (Chart I): 1,2,3,5,6,7,8,9-octahydro[1]benzothieno[2,3-*d*]imidazo-[1,2-*a*]pyrimidin-2-one[2] (I, DH-6471), 6,7-dichloro-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one[3] (II, BL-4162A), 7-bromo-3,6-dimethyl-1,2,3,5-tetrahydroimidazo-[2,1-*b*]quinazolin-2-one[4] (III, Ro 14-2523), 6-[4-(1-cyclohexyltetrazol-2-yl)butyroxy]carbostyryl[5] (IV, OPC-13013), etc. However, these compounds were insoluble in water and were not able to be administered parenterally.

We have also pointed out the essential contribution of the lactam structure and lipophilic substitution in platelet aggregation inhibitory activity on the studies of imidazothienopyrimidinones.[2] However, the compounds of this series were chemically unstable. So, introduction of a lipophilic dialkylamino or alicyclic amino group, which might form a water-soluble acid salt, into the more chemically stable imidazoquinazoline ring described by Beverung et al.[3] was tried. This paper describes the synthesis and biological activities of a series of (N-substituted amino)-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-ones.

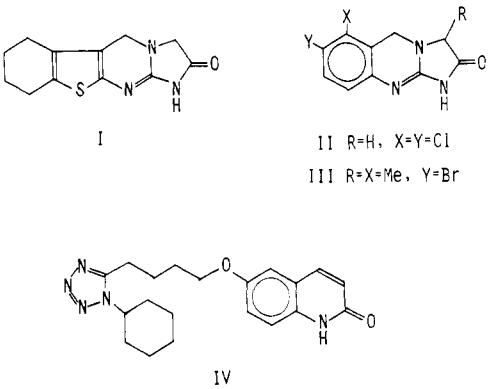
Chemistry. Synthesis of the (N-substituted amino)-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-ones (**13**) was carried out by two sequences shown in Scheme I.

Most of the compounds (**13**) were prepared by a novel synthetic route reported in our previous paper.[6] Starting materials, 2-chloronitrobenzenes (**1**) and 2-nitroanilines (**2**), were converted to the corresponding 2-nitrobenzonitriles (**3**) by usual cyanations. The active halogens of **3** were reacted with the corresponding secondary amines to give the key intermediates (**4**). Reduction of the nitro group of **4** followed by heating with urea gave crude quinazoline-2,4-diones (**6**). The crude diones **6** were chlorinated with phosphoryl chloride in the presence of diisopropylethylamine to yield 2,4-dichloroquinazoline derivatives (**7**).

The dichloro compounds (**7**) were treated with an excess of sodium borohydride to give crude 2-chloro-3,4-dihydroquinazolines (**8**) in an almost quantitative yield. Condensation of **8** with ethyl bromoacetate in the presence of concentrated sodium hydroxide solution and phase-transfer catalyst in methylene chloride gave oily 3-substituted intermediates (**9**), which were heated with ethanolic ammonia in a sealed tube to afford most of the desired compounds (**13a,b,d,g,h,k,l,p–r,t–y**).

On the reaction of **5** with urea under heating, the 5-pyrrolidino derivative (**5f**) decomposed. Chlorination of 5-chloro 6-(N-substituted amino) derivatives (**6o,s**) was not good as a preparative method because of the formation of many byproducts. In the case of **6s**, in particular, the desired dichloroquinazoline (**7s**) was not found in the reaction mixture. Preparation of these compounds was

Chart I



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(5) (a) Hidaka, H.; Naka, M.; Endo, M.; Kanamori, M.; Kimura, Y. Presentation—VIIIth International Congress on Pharmacology, Tokyo, 1981. (b) Nishi, T.; Nakagawa, K. Ger. Offen. 2934747, 1979; *Chem. Abstr.* **1980**, *93*, 26293.
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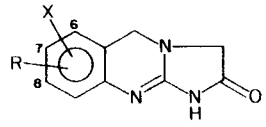
Table I. (N-Substituted amino)-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one Derivatives (**13a–z**) and Their Inhibition of Platelet Aggregation



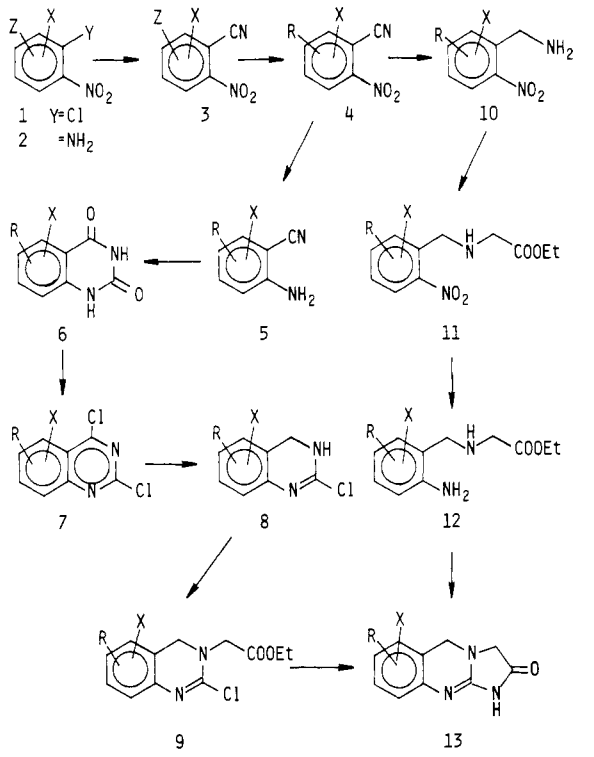
13a–z

compd	R	X	method (SM)[a]/yield, %	mp,[b] °C	formula[c]	inhibn of blood platelet aggregation: in vitro: EC_{50}[d] [collagen], μM	in vitro: EC_{50}[d] [ADP], μM	ex vivo[e] collagen: ΔA/min × 10^3 control	ex vivo[e] collagen: ΔA/min × 10^3 test	ex vivo[e] ADP: ΔA × 10^3 control	ex vivo[e] ADP: ΔA × 10^3 test
13a	6-NMe_2	H	A/44	232–233	$C_{12}H_{14}N_4O$·2HCl·0.5H_2O	1.5	2.7				
13b	6-N⟨ ⟩	H	A/35	242–245	$C_{15}H_{18}N_4O$·2HCl·2H_2O	20	22.5				
13c	7-NMe_2	H	C (**13n**)/64	250–252	$C_{12}H_{14}N_4O$·2HCl·0.5H_2O	1.4	5.4	137 ± 16	71 ± 55 (48)	270 ± 31	193 ± 23* (29)
13d	7-NMe, $CH_2C_6H_5$	H	A/66	178–180	$C_{18}H_{18}N_4O$·2HCl·H_2O		26				
13e	7-NHMe	H	C (**13d**)/80	175–178	$C_{11}H_{12}N_4O$·2HCl·H_2O		24				
13f	7-N⟨ ⟩	H	C (**13o**)/62	>280	$C_{14}H_{16}N_4O$·2HCl·H_2O	1.9	2.6				
13g	7-N⟨ ⟩	H	A/57; C (**13p**)/84	>280	$C_{15}H_{18}N_4O$·2HCl·H_2O	0.33	3.8	168 ± 18	68 ± 94* (60)	183 ± 23	121 ± 55* (34)
13h	7-N⟨ ⟩, Me	H	A/30	unclear	$C_{16}H_{20}N_4O$·2HCl·H_2O	1.7	2.0	160 ± 15	145 ± 17 (9)	208 ± 13	190 ± 32 (9)
13i	7-N⟨ ⟩, Me	H	C (**13r**)/42	170–180	$C_{16}H_{20}N_4O$·2HCl·1.5H_2O	18	2.8	170 ± 12	122 ± 62 (28)	230 ± 31	188 ± 26 (18)
13j	7-N⟨ ⟩O	H	C (**13v**)/82	>280	$C_{14}H_{16}N_4O_2$·2HCl·2H_2O	2.0	5.0	170 ± 12	154 ± 19 (9)	230 ± 31	201 ± 19 (13)
13k	8-N⟨ ⟩	H	A/57	272–275	$C_{15}H_{18}N_4O$·2HCl·H_2O	8.0	46				
13l	8-N⟨ ⟩O	H	A/56	>280	$C_{14}H_{16}N_4O_2$·2HCl·0.5H_2O		96				
13m	7-NMe_2	6-Cl	B/61	186–188	$C_{12}H_{13}ClN_4O$·2HCl·H_2O	1.2	7.0	137 ± 16	19 ± 33* (86)	270 ± 31	98 ± 41** (64)
13n	7-NEt_2	6-Cl	B/37	223–225	$C_{14}H_{17}ClN_4O$·2HCl·0.5H_2O	1.3	5.6	137 ± 16	41 ± 47 (70)	270 ± 31	201 ± 26* (26)
13o	7-N⟨ ⟩	6-Cl	B/91	unclear	$C_{14}H_{15}ClN_4O$·2HCl·H_2O	2.7	3.0				
13p	7-N⟨ ⟩	6-Cl	A/56	235–237	$C_{15}H_{17}ClN_4O$·2HCl·2H_2O	1.2	7.9				
13q	7-N⟨ ⟩, Me	6-Cl	A/58	>280	$C_{16}H_{19}ClN_4O$·2HCl·1.5H_2O	1.4	4.0				
13r	7-N⟨ ⟩, Me	6-Cl	A/57	240–245	$C_{16}H_{19}ClN_4O$·2HCl·H_2O	2.3	4.0				
13s	7-N⟨ ⟩N-Me	6-Cl	B/63	229–232	$C_{15}H_{18}ClN_5O$·2HCl	3.0	8.0	190 ± 12	149 ± 21 (12)	230 ± 31	189 ± 30 (18)
13t	7-NMe_2	8-Cl	A/65	>280	$C_{12}H_{13}ClN_4O$·2HCl·2H_2O	0.44	1.1	160 ± 15	82 ± 43* (49)	208 ± 13	150 ± 25* (28)

13u		8-Cl	A/60	185–187	$C_{15}H_{17}ClN_4 \cdot 2HCl \cdot H_2O$	0.46	0.4	160 ± 15	39 ± 49* (76)	208 ± 13	137 ± 45* (34)
13v		8-Cl	A/86	269–270	$C_{14}H_{15}ClN_4O_2 \cdot HCl \cdot 0.5H_2O$	0.1	0.36	170 ± 12	55 ± 67* (68)	230 ± 31	122 ± 31* (47)
13w		8-Me	A/60	200–202	$C_{16}H_{20}N_4O \cdot 2HCl \cdot H_2O$	0.58	5.4	*f*			
13x	8-NMe_2	6-Cl	A/68	>280	$C_{12}H_{13}ClN_4O \cdot 2HCl \cdot MeOH$		290				
13y		6-Cl	A/59	>280	$C_{15}H_{17}ClN_4O \cdot 2HCl \cdot H_2O \cdot MeOH$		350				
13z		7-Me	B/64	unclear	$C_{16}H_{20}N_4O \cdot 2HCl \cdot 0.5H_2O$		220				
V[g]	7-NH_2	H				16	170				
I	DH-6471					0.1	2.0	183 ± 15	73 ± 52* (60)	159 ± 11	112 ± 42* (30)
II[g]	BL-4162A					0.02	0.8	142 ± 27	67 ± 75 (53)	269 ± 11	248 ± 52 (8)

[a] SM = starting material. [b] Compounds were recrystallized from MeOH/EtOH. [c] All compounds were analyzed for C, H, and N. Analytical results obtained for these elements were within 0.4% of the calculated value. [d] Effective concentration required for 50% inhibition of platelet aggregation. [e] Data represent mean ±SD of five animals given vehicle or compound at an oral dose of 10 mg/kg 1 h before the test. Figures in parentheses are the percent inhibition of platelet aggregation (vs. control): *, $p < 0.05$; **, $p < 0.01$. [f] Platlet aggregation could not be measured optically because this compound caused hemolysis. [g] V (dihydrochloride hydrate) and II (hydrochloride hemihydrate) were synthesized in our institute for experimental use.

Scheme I[a]



[a] R = (N-substituted amino) group; X = H, Cl, Me; Z = Cl, I, NO_2.

carried out by a method similar to that described by Beverung et al.[3b]

The cyano group of the key intermediates (**4o,s**) was reduced with sodium borohydride in the presence of trifluoroacetic acid in tetrahydrofuran to give 2-nitrobenzylamines (**10o,s**) in good yield. Reaction of **10o,s** with ethyl bromoacetate followed by catalytic reduction and then treatment with cyanogen bromide afforded the target products (**13o,s**). By a similar way, compounds **13m**, **13n**, and **13z** were also obtained.

Some of the compounds (**13c,f,g,i,j**) were prepared by catalytic hydrogenation of the corresponding chloro derivatives (**13o,p,r,v**), respectively. For the comparison of the platelet aggregation inhibitory effect, monomethylamino derivative (**13e**) was synthesized by catalytic reduction of benzylmethylamino derivative (**13d**).

These compounds obtained here formed the dihydrochloride salts. Among the salts, dialkyl- and monoalkylamino derivatives (**13a,c,e,m,n,t**) and 7-alicyclic amino derivatives (**13g,h,i,j,w**) except for 7-pyrrolidino ketone (**13f**) were soluble in water. However, other compounds such as the 6-piperidino derivative (**13b**) and especially the compounds (**13o–r,u,v,y**) having an additional chlorine atom were insoluble in water. It was suggested that the substitution caused a decrease of the basicity.

Structure–Activity Relationships. The inhibitory effects on platelet aggregation in vitro and ex vivo are shown in Table I. Some of the compounds obtained here were equally active to BL-4162A, the most preferable compound having the imidazo[2,1-*b*]quinazolin-2-one ring system. It was found that the activity was considerably influenced by the kind of N-substituted amino group and its replacing position on the benzene ring. The compounds with a moderately lipophilic or bulky amino group such as a dimethylamino, piperidino, or morpholino group at position 7 had most potent activity [for example, **13g,t,-u,v,...**]. However, a very bulky substitution at position 6 gave less active compounds, suggesting some steric effects

Table II. Duration of Inhibition of Platelet Aggregation in Rats after a Single Oral Dose of (N-Substituted amino)-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one Derivative (**13c,g,t,u**) at 10 mg/kg

	1 h after dose[b]				3 h after dose[b]			
	collagen: ΔA/min × 10^3		ADP: ΔA × 10^3		collagen: ΔA/min × 10^3		ADP: ΔA × 10^3	
compd	control[a]	test	control[a]	test	control[a]	test	control[a]	test
13c	137 ± 10	71 ± 55 (48)	270 ± 31	193 ± 23* (29)	177 ± 20	154 ± 24 (13)	174 ± 30	160 ± 18 (14)
13g	168 ± 18	68 ± 94* (60)	183 ± 23	121 ± 55* (34)	177 ± 20	118 ± 16 (34)	174 ± 30	158 ± 9 (15)
13t	160 ± 15	82 ± 43 (49)	208 ± 13	150 ± 25** (28)	177 ± 20	136 ± 13 (23)	174 ± 30	171 ± 38 (8)
13u	160 ± 15	39 ± 49** (76)	208 ± 13	137 ± 45* (34)	191 ± 5	180 ± 34 (6)	201 ± 13	189 ± 12 (6)

[a] Vehicle alone was administration 1 or 3 h before blood collection. [b] Data represent mean ±SD of five animals. Figures in parentheses are percent inhibition of platelet aggregation (vs. control): *, $p < 0.05$; **, $p < 0.01$.

Table III. Inhibition of Blood Platelet Aggregation in Rats after Intravenous Infusion of (N-Substituted amino)-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one Derivatives (**13c,g,j,m**)

	dose,	collagen:[a] ΔA/min × 10^3		ADP:[a] ΔA × 10^3	
compd	mg/kg	control	test	control	test
13c	1 (15 min)	199 ± 11	58 ± 71* (71)	184 ± 10	142 ± 16* (23)
13g	1 (15 min)	199 ± 11	0** (100)	184 ± 10	116 ± 11 (37)
13j	10 (10 min)	175 ± 15	90 ± 38* (49)	242 ± 46	202 ± 36 (17)
13m	10 (10 min)	188 ± 20	0*** (100)	272 ± 18	208 ± 49* (24)

[a] Data represent mean ±SD of five animals. Figure in parentheses are percent inhibition of platelet aggregation (vs. control): *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

around this poistion [**13a >> 13b**]. Replacement by a N-substituted amino group at position 8 resulted in considerable decrease of the activity [**13k,l**]. The monoalkylamino group also caused a decrease of the activity [**13e**], and the 7-(N-unsubstituted amino) derivtive (**V**) reported by Beverung et al.[3b] considerably diminished the effect. Additional 8-chloro substitution on 7-(N-substituted amino) compounds enhanced the activity, but 6-chloro or 8-methyl substitution gave relatively less active compounds [**13u > 13g; 13t > 13c > 13m; 13g > 13w**]. Introduction of chlorine into 8-(N-substituted amino) compounds also decreased the activity [**13k > 13y**]. Among these compounds, 8-chloro-7-(N-substituted amino) derivatives (**13t–v**) were the most effective compounds in vitro and ex vivo after oral administration in rats.

Some of the potent active compounds were tested for the duration of their action ex vivo after single oral administration of 10 mg/kg of body weight to rats. As shown in Table II, these compounds (**13c,g,t,u**) were very short acting.

Some of the water-soluble compounds were also tested for their ability to inhibit platelet aggregation ex vivo after iv infusion, and results are shown in Table III. These compounds (**13c,g,m,j**) significantly inhibited platelet aggregation during the infusion of 1 mg/kg (for 15 min) or 10 mg/kg (for 10 min) of body weight to rats. Such a compound giving significant inhibition of platelet aggregation after parenteral administration has not been reported, and it will contribute to development of the clinical usefulness of inhibiting platelet aggregation.

Some of the compounds that showed a potent antiplatelet activity ex vivo after administration were also tested for their effects on blood pressure and heart rate in normal rats. As shown in Table IV, compound **13g** even at high dose produced a relatively minor decrease in blood pressure and a slight increase in heart rate, both changes being much less than those by other compounds **13m,t**. These results suggest that **13g** is the most preferable antithrombotic drug with little effect on the cardiovascular system.

Among the compounds obtained here, 7-piperidino-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one dihydrochloride (**13g**, DN-9693) is the best compound in view of chemical and biological evaluation: solubility in water, potency of the platelet aggregation inhibition, weak cardiovascular action, low toxicity. Clinical evaluation of **13g** under parenteral administration is in progress, and the results will be reported elsewhere.

Table IV. Systolic Blood Pressure and Heart Rate in Rats after an Oral Dose of (N-Substituted amino)-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one Derivatives (**13g,m,t**) at 50 mg/kg

	initial value:[a] BP, mmHg;	time after, h				
compd	heart rate, beats/min	1	2	3	5	7
13g	132 ± 2.5;	18**[b]	12**	12**	12**	9
	382 ± 10	27**[c]	32**	27**	25**	17**
13m	135 ± 2.2;	45**	43**	35**	36**	34**
	358 ± 7.9	46**	46**	43**	41**	38**
13t	131 ± 2.7;	30**	27**	26**	28**	23**
	365 ± 8.5	42**	50**	47**	46**	41**

[a] Six animals were used in each group. Data represent mean ±SD. [b] Decrease in blood pressure (ΔmmHg). [c] Percent change in heart rate (%): **, $p < 0.01$ (vs. initial value).

Experimental Section

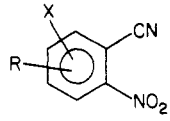
Melting points are uncorrected. IR spectra were taken on a Hitachi 285 spectrometer. ^{1}H NMR spectra were recorded with Hitachi R-40 (90 MHz) and JNM-FX 90Q (90 MHz) spectrometers (Me_4Si as an internal standard). For column chromatography, silica gel (Merck, 0.05-0.2 mm) was used. Where analyses are indicted only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.

5-Iodo-4-methyl-2-nitrobenzonitrile (3F). Fuming HNO_3 (0.9 mL, d = 1.52 g/cm^3) was added to a suspension of 3-iodo-4-methylacetanilide (3.4 g, 12.4 mmol) in Ac_2O (20 mL) at 5–7 °C with stirring. When the addition ended, the insoluble material dissolved to give a clear solution. The reaction solution was stirred at room temperature for 1 h. The precipitate formed again was collected by filtration and washed with petroleum ether to give 5-iodo-4-methyl-2-nitroacetanilide; mp 149–151 °C; ^{1}H NMR ($CDCl_3$) δ 7.96 (1 H, s, 6-H), 9.29 (1 H, s, 3-H).

This acetanilide (2.2 g, 7 mmol) was mixed with concentrated HCl (13 mL) and EtOH (13 mL), and the mixture was refluxed with stirring for 1.5 h. The reaction mixture was concentrated to dryness under reduced pressure. The residue was treated with a small volume of EtOH, and a yellow insoluble material was collected by filtration to give 5-iodo-4-methyl-2-nitroaniline (1.85 g, 95%); mp 157–158 °C; ^{1}H NMR ($CDCl_3$) δ 7.36 (1 H, s, 6-H), 7.90 (1 H, s, 3-H).

This aniline (11.0 g, 40 mmol) was dissolved in acetone (150 mL), and to the solution were added concentrated HCl (8 mL) and water (40 mL). A solution of $NaNO_2$ (3.05 g, 44 mmol) in water (10 mL) was added to the mixture at 5–7 °C with stirring for 30 min. The reaction mixture was added to a solution of CuCN, freshly prepared from $CuSO_4 \cdot 5H_2O$ (10 g, 40 mmol) and

Table V. (N-Substituted amino)-2-nitrobenzonitriles (4)



4[a]

compd	yield, %	mp, °C	recryst solvent	formula[b]
4d	94	133–135	benzene	$C_{15}H_{13}N_3O_2$
4h	70	82–83	benzene	$C_{13}H_{15}N_3O_2$
4l	55	194–195	acetone	$C_{11}H_{11}N_3O_2$
4m	90	162–164	benzene	$C_9H_8ClN_3O_2$
4n	88	102–104	benzene	$C_{11}H_{12}ClN_3O_2$
4o	88	170–173	benzene	$C_{11}H_{10}ClN_3O_2$
4p	94	208–210	benzene	$C_{12}H_{12}ClN_3O_2$
4q	70	113–115	benzene	$C_{13}H_{14}ClN_3O_2$
4r	95	173–175	benzene	$C_{13}H_{14}ClN_3O_2$
4s	91	210–212	benzene	$C_{12}H_{13}ClN_4O_2$
4t	80	166–167	benzene/hexane	$C_9H_8ClN_3O_2$
4u	85	200–202	benzene	$C_{12}H_{12}ClN_3O_2$
4v	93	163–164	benzene	$C_{11}H_{10}ClN_3O_2$
4w	73	100–102	benzene/hexane	$C_{13}H_{15}N_3O_2$
4x	50	177–178	benzene	$C_9H_8ClN_3O_2$
4y	45	161–162	benzene/hexane	$C_{12}H_{12}ClN_3O_2$
4z	31	106–108	benzene/hexane	$C_{13}H_{15}N_3O_2$

[a] Substituents R and X are alphabetized in Table I. [b] See footnote *c*, Table I.

KCN (10.4 g, 160 mmol), under heating at 60–70 °C with stirring. The heating at 70–80 °C was continued to remove acetone. After cooling, the mixture was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to dryness under reduced pressure to give **3F** (4.1 g, 34%); mp 182–183 °C; ^1H NMR ($CDCl_3$) δ 8.12 (1 H, s, 3-H), 8.30 (1 H, s, 6-H). Anal. ($C_8H_5IN_2O_2$) C, H, N.

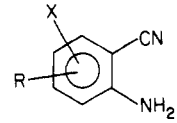
By a similar way, 4-iodo-5-methyl-2-nitrobenzonitrile (**3H**) [mp 158–161 °C; ^1H NMR ($CDCl_3$) δ 7.66 (1 H, s, 6-H), 8.69 (1 H, s, 3-H). Anal. ($C_8H_5IN_2O_2$) C, H, N] was obtained from 4-iodo-3-methylacetanilide.

6-Chloro-2,4-dinitrobenzonitrile (3G). A mixture of 1,6-dichloro-2,4-dinitrobenzene (35.6 g, 0.15 mol) and CuCN (14.8 g, 0.165 mol) in *N,N*-dimethylacetamide (180 mL) was heated at 130–150 °C for 4 h with stirring. The reaction mixture was poured into ice water (1 L). The precipitate formed was collected by filtration and extracted with AcOEt. The extract was washed with water, dried, and concentrated to dryness under reduced pressure. The residue was purified through a silica gel column with an eluent of $CHCl_3$ to give **3G** (13.2 g, 40%); mp 121–122 °C. Anal. ($C_7H_2ClN_3O_4$) C, H, N.

2-Nitro-5-piperidinobenzonitrile[7] (4g). A mixture of 5-chloro-2-nitrobenzonitrile[8] (**3B**) (63.9 g, 0.35 mol) and piperidine (95 mL, 1 mol) in DMF (200 mL) was stirred at 50 °C for 30 min. The reaction mixture was poured into water, and the precipitate formed was collected by filtration, washed with water and MeOH, and dried to give **4g** (80 g, 95%); mp 125–126 °C (benzene) [lit.[7] mp 127–128 °C].

By a similar method, other (N-substituted amino)-2-nitrobenzonitriles (**4a,b,d,h,k–z**) were obtained from the corresponding 2,6-dinitrobenzonitriles[9] (**3A**), 5-chloro-2-nitrobenzonitrile (**3B**), 2,4-dinitrobenzonitrile (**3C**), 5,6-dichloro-2-nitrobenzonitrile[10] (**3D**), 4,5-dichloro-2-nitrobenzonitrile[11] (**3E**), or **3F–G**. These new compounds, except for known compounds **4a,b**,[12] **4g**,[7] and **4k**,[13] are listed in Table V.

Table VI. (N-Substituted amino)-2-aminobenzonitriles (5)



5[a]

compd	yield, %	mp, °C	recryst solvent	^1H NMR[b] (δ) or formula[c]
5d	98	97–98	Et_2O	$C_{15}H_{15}N_3$
5h	80	oil		0.9 (3 H, d), 1.65 (6 H, m), 2.9 (2 H, m), 3.3 (1 H, m)
5k	92	97–98	benzene/hexane	$C_{12}H_{15}N_3$
5l	85	143–144	EtOH	$C_{11}H_{13}N_3O$
5o	73	102–103	Et_2O	$C_{11}H_{12}ClN_3$
5p	56	137–138	Et_2O	$C_{12}H_{14}ClN_3$
5q	65	140–142	Et_2O	$C_{13}H_{16}ClN_3$
5r	64	146–148	benzene/hexane	$C_{13}H_{16}ClN_3$
5s	66	159–161	benzene	$C_{12}H_{14}ClN_4$
5t	92	133–136	Et_2O	$C_9H_{10}ClN_3 \cdot 0.5H_2O$
5u	75	129–130	Et_2O	$C_{12}H_{14}ClN_3$
5v	76	169–171	MeOH	$C_{11}H_{12}ClN_3O$
5w	91	84–85	Et_2O	$C_{13}H_{17}N_3$
5x	82	141–142	benzene	$C_9H_{10}ClN_3$
5y	58	oil		1.6 (6 H, m), 3.2 (4 H, m)

[a] Substituents R and X are alphabetized in Table I. [b] Chemical shifts of substituted amino moiety (in $CDCl_3$). [c] See footnote *c*, Table I.

2-Amino-5-piperidinobenzonitrile (5g). Compound **4g** (80 g, 0.35 mol) was added to a mixture of concentrated HCl (700 mL) and $SnCl_2 \cdot 2H_2O$ (226 g, 1 mol) with stirring while externally cooling, followed by stirring at room temperature for an additional 2 h. The reaction mixture was poured into water having dissolved therein NaOH (700 g), and the precipitate was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to dryness under reduced pressure. The residue was purified through silica gel column with an eluent of $CHCl_3$ to give **5g** (52.2 g, 74%); mp 87–88 °C (Et_2O) [lit.[7] mp 92–94 °C].

By a similar method, other (N-substituted amino)-2-aminobenzonitriles (**5a,b,d,h,k,l,o–y**) were obtained, and the new compounds, except for known compounds **5a,b**[12] and **5g**,[7] are listed in Table VI.

6-Piperidinoquinazoline-2,4(1*H*,3*H*)-dione (6g). A mixture of **5g** (50 g, 0.25 mol) and urea (100 g) was heated at 180–210 °C for 2.5 h. After cooling, the reaction residue was pulverized and washed successively with water, acetone, and Et_2O. The powder was added to concentrated HCl (300 mL) and refluxed for 3 h. After cooling, an insoluble matter was removed by filtration, and the filtrate was neutralized with aqueous ammonia to pH 7. The precipitate formed was collected by filtration, washed with water, and dried to give the crude free base of **6g**. The free base was treated with 10% HCl–MeOH solution and the resulting mixture was concentrated to dryness under reduced pressure to obtain the crude hydrocloride salt of **6g**: 50 g, (79%); mp >280 °C. The crude product was used for next reaction without further purification.

By a similar method, other (N-substituted amino)-quinazoline-2,4(1*H*,3*H*)-diones (**6a,b,d,k,l,p–y**) listed in Table VII were obtained.

2,4-Dichloro-6-piperidinoquinazoline (7g). A mixture of **6g** (50 g, 0.18 mol) and *N,N*-diisopropylethylamine (70 mL) in phosphoryl chloride (500 mL) was refluxed for 18 h with stirring and concentrated to dryness under reduced pressure. The residue was poured into ice water. A precipitate was extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to dryness under reduced pressure. The residue was purified through silica gel column with eluent of $CHCl_3$ to give **7g**: 35.4 g (66%); mp 100–101 °C (Et_2O). Anal. ($C_{13}H_{13}Cl_2N_3$) C, H, N.

By a similar method, other (N-substituted amino)-2,4-dichloroquinazolines (**7a,b,d,h,k,l,p–r,t–y**) listed in Table VIII were obtained.

(7) Elslager, E. F.; Clarke, J.; Werbel, L. M.; Worth, D. F. *J. Med. Chem.* **1972**, *15*, 827.
(8) Cullen, E.; L'Ecuyer, Ph. *Can. J. Chem.* **1961**, *39*, 862.
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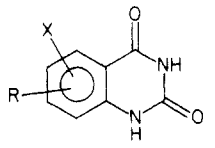
(11) Rosowsky, A.; Marini, J. L.; Nadel, M. E.; Modest, R. J. *J. Med. Chem.* **1970**, *13*, 882.
(12) Klaubert, D. H.; Sellstedt, J. H.; Guinosso, C. J.; Capetola, R. J.; Bell, S. C. *J. Med. Chem.* **1981**, *24*, 742.
(13) Holmes, C. W. N.; Loudon, J. D. *J. Chem. Soc.* **1940**, 1521.

Table VII. (N-Substituted amino)quinazoline-2,4(1*H*,3*H*)-diones (6)

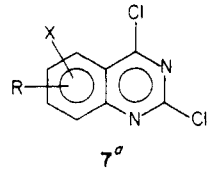


6[a]

compd	yield, %	mp, °C	^{1}H NMR[b] (δ)
6a	49	>280	3.42 (6 H, s)
6b	55	>280	1.55 (6 H, m), 2.9 (4 H, m)
6d	88	>280	3.15 (3 H, s), 4.60 (2 H, s)
6k	55	>280	1.7 (6 H, m)
6l	75	>280	2.2 (4 H, m), 2.7 (4 H, m)
6p	89	>280	1.62 (6 H, m), 2.9 (4 H, m)
6q	53	>280	0.95 (3 H, d), 1.8 (6 H, m), 3.25 (2 H, m), 3.75 (1 H, m)
6r	68	>280	0.97 (3 H, d), 1.5 (5 H, m), 2.70 (2 H, t), 3.13 (2 H, d)
6s	94	>280	2.76 (3 H, s), 3.0 (8 H, m)
6t	95	>280	2.75 (6 H, s)
6u	95	>280	1.65 (6 H, m), 2.9 (4 H, m)
6v	95	>280	3.1 (4 H, m), 3.7 (4 H, m)
6w	96	>280	1.7 (6 H, m), 3.15 (4 H, m)
6x	82	>280	2.98 (6 H, s)
6y	53	>280	2.56 (6 H, m), 3.34 (4 H, m)

[a] Substituents R and X are alphabetized in Table I. [b] Chemical shifts of substituted amino moiety (in Me_2SO-d_6).

Table VIII. (N-Substituted amino)-2,4-dichloroquinazolines (7)



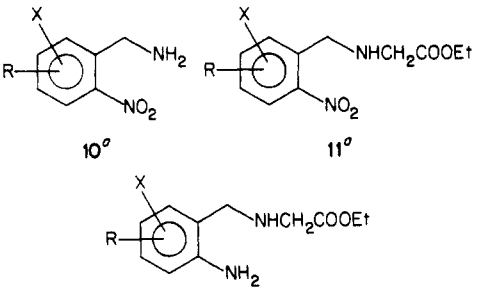
7[a]

compd	yield, %	mp, °C	recryst solvent	^{1}H NMR[b] (δ) or formula[c]
7a	48	139–141	Et_2O	$C_{10}H_9Cl_2N_3$
7b	84	oil		1.6 (6 H, m), 2.7 (2 H, m), 3.35 (2 H, m)
7d	58	104–105	Et_2O	$C_{16}H_{13}Cl_2N_3$
7h	75	91–92	Et_2O/hexane	$C_{14}H_{15}Cl_2N_3$
7k	77	113–115	Et_2O	$C_{13}H_{13}Cl_2N_3$
7l	62	220–221	acetone	$C_{12}H_{11}Cl_2N_3O$
7p	51	114–116	Et_2O/hexane	$C_{13}H_{12}Cl_2N_3$
7q	22	82–84	Et_2O/hexane	$C_{14}H_{14}Cl_2N_3$[d]
7r	27	150–154	Et_2O	$C_{14}H_{14}Cl_2N_3$[e]
7t	58	113–114	Et_2O/hexane	$C_{10}H_8Cl_2N_3$
7u	68	136–138	Et_2O	$C_{13}H_{12}Cl_2N_3$
7v	60	146–148	Et_2O	$C_{12}H_{10}Cl_2N_3O$
7w	55	113–114	Et_2O	$C_{14}H_{15}Cl_2N_3$
7x	94	194–195	acetone	$C_{10}H_8Cl_2N_3$
7y	88	82–86	Et_2O/hexane	$C_{13}H_{12}Cl_2N_3$

[a] Substituents R and X are alphabetized in Table I. [b] Chemical shifts of substituted amino moiety (in $CDCl_3$). [c] See footnote *c*, Table I. [d] C: calcd, 50.86; found, 50.40. [e] C: calcd, 50.86; found, 50.42.

6-Chloro-2-nitro-5-pyrrolidinobenzylamine (10o). A solution of trifluoroacetic acid (12 mL, 0.16 mol) in THF (20 mL) was added to a mixture of $NaBH_4$ (6 g, 0.16 mol) and THF (40 mL) at 10–15 °C. Compound **4o** (8.3 g, 33 mmol) was added to the mixture with stirring. After cooling the heat generated, the stirring was continued at room temperature overnight. The mixture was concentrated to a half-volume under reduced pressure and poured into 10% HCl (60 mL), followed by refluxing for 1.5 h. The THF was evaporated under reduced pressure. The aqueous layer was washed with benzene, rendered alkaline with NaOH solution, and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to dryness under reduced pressure. The residue was purified through a silica gel column with eluent of $CHCl_3$/MeOH (100:1) to give **10o**: 44 g (52%); mp 97–98 °C. Anal. ($C_9H_{13}N_3O_2$) C, H, N.

Table IX. (N-Substituted amino)-2-nitrobenzylamines (10), Ethyl [(N-Substituted amino)-2-nitrobenzylamino]acetates (11), and Ethyl [(N-substituted amino)-2-aminobenzylamino]acetates (12)



10[a] 11[a]

12[a]

compd	yield, %	mp, °C	recryst solvent	^{1}H NMR[b] (δ) or formula[c]
10m	52	oil		4.09 (2 H, s)
10n	47	85–86	hexane	$C_{11}H_{16}ClN_3O_2$
10s	57	115–116	Et_2O	$C_{12}H_{17}ClN_4O_2 \cdot 0.5H_2O$
10z	85	oil		3.96 (2 H, s)
11m	70	oil		3.50 (2 H, s), 4.21 (2 H, s)
11n	70	oil		3.52 (2 H, s), 4.16 (2 H, s)
11s	46	oil		3.47 (2 H, s), 4.20 (2 H, s)
11z	46	oil		3.41 (2 H, s), 3.97 (2 H, s)
12m	82	56–58	Et_2O/hexane	$C_{13}H_{20}ClN_3O_2$
12n	75	oil		3.41 (2 H, s), 4.01 (2 H, s)
12s	71	88–90	Et_2O/hexane	$C_{16}H_{25}ClN_4O_2 \cdot H_2O$
12z	90	oil		3.39 (2 H, s), 3.72 (2 H, s)

[a] Substituents R and X are alphabetized in Table I. [b] Chemical shifts of benzyl methylene and acetate methylene moiety (in $CDCl_3$). [c] See footnote *c*, Table I. [d] N: calcd, 19.07; found, 18.50. [e] H: calcd, 7.58; found, 7.10.

By a similar method, other (N-substituted amino)-2-nitrobenzylamines (**10m,n,s,z**) listed in Table IX were obtained.

Ethyl (6-Chloro-2-nitro-5-pyrrolidinobenzylamino)acetate (11o). A mixture of **10o** (6.5 g, 24 mmol) and Na_2CO_3 (1.4 g, 13 mmol) in DMF (80 mL) was heated to 80 °C, and a solution of ethyl bromoacetate (4.2 g, 26 mmol) in DMF (60 mL) was added thereto dropwise over a period of 2.5 h. DMF was removed under reduced pressure. The residue was dissolved in 5% HCl and washed with benzene. The aqueous layer was made alkaline with aqueous ammonia and extracted with $CHCl_3$. The extract was washed with water, dried, and concentrated to dryness under reduced pressure. The residue was purified through a silica gel column with eluent of $CHCl_3$ to give **11o** (6.65 g, 76.5%) as an oil: ^{1}H NMR ($CDCl_3$) δ 4.18 (2 H, s), 3.47 (6 H, br s, CH_2, CH_2NCH_2).

By a similar method, other ethyl [(N-substituted amino)-2-nitrobenzylamino]acetates (**11m,n,s,z**) listed in Table IX were obtained.

Ethyl (2-Amino-6-chloro-5-pyrrolidinobenzylamino)-acetate (12o). Compound **11o** (4.0 g, 11.7 mmol) was dissolved in EtOH (70 mL) and catalytically reduced in the presence of PtO_2 (0.15 g) at room temperature under atmospheric pressure. The catalyst was filtered off, and the filtrate was concentrated to dryness under reduced pressure to give **12o**: 2.65 g (72%); mp 69–70 °C (Et_2O/hexane). Anal. ($C_{15}H_{22}ClN_3O_2 \cdot 0.5H_2O$) C, H, N.

By a similar method, other ethyl[(N-substituted amino)-2-aminobenzylamino]acetates (**12m,n,s,z**) listed in Table IX were obtained.

(N-Substituted amino)-1,2,3,5-tetrahydroimidazo[2,1-*b*]-quinazolin-2-ones (13). Method A. 7-Piperidino-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one Dihydrochloride (13g). To a solution of **7g** (34 g, 0.12 mol) in $CHCl_3$ (100 mL) and EtOH (150 mL) was added portionwise $NaBH_4$ (22.8 g, 0.6 mol) with stirring. The reaction mixture was continued to stir for 30 min. The solvent was evaporated under reduced pressure,

and the residue was treated with water. An insoluble solid was collected by filtration, washed with water, and dried under reduced pressure to give crude **8g** (27 g, 91%) as an amorphous powder.

A mixture of the crude **8g** (27 g, 0.108 mol), ethyl bromoacetate (19.8 g, 0.12 mol), 10 M NaOH (50 mL), and tetrabutylammonium iodide (1 g) in CH_2Cl_2 (200 mL) was stirred for 1 h. The reaction mixture was washed with water, dried, and concentrated to dryness under reduced pressure to give crude oily **9g** (32 g, 90%).

The resulting crude **9g** (32 g, 97 mmol) was added to 10% NH_3–EtOH solution (100 mL), and the mixture was heated in sealed tube at 120–130 °C for 4 h. After cooling, the solid separated was collected, washed with water and EtOH, and dried to give the free base of **13g** (24.6 g, 57% from **7g**), which was converted to the hydrochloride by treatment with 5% HCl–MeOH solution: mp >280 °C (MeOH/EtOH); IR (KBr) 1780, 1770, 1675, 1610, 1590 cm^{-1}; ^1H NMR (D_2O) δ 1.7–2.3 (6 H, m), 3.60 (4 H, t), 4.36 (2 H, s), 4.86 (2 H, s), 7.27 (1 H, d), 7.45–7.7 (2 H, m). Anal. ($C_{15}H_{18}N_4O\cdot 2HCl\cdot H_2O$) C, H, N.

Other compounds (**13a,b,d,g,h,k,l,p–r,t–y**) listed in Table I were similarly prepared.

Method B. 6-Chloro-7-pyrrolidino-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one Dihydrochloride (13o). To a solution of **12o** (2.6 g, 8.3 mmol) in EtOH (30 mL) was added a solution of BrCN (0.88 g, 8.3 mmol) in EtOH (10 mL), followed by stirring at room temperature overnight. The reaction mixture was adjusted to pH 8–9 with a saturated $NaHCO_3$ solution, and the stirring was continued for an additional 1 h. Readjustment of pH 10 with 2 M NaOH solution precipitated a solid, which was then collected filtration, washed with water, and dried to give **13o** (2.2 g, 91%) as the free base. This product was converted to the dihydrochloride in a usual manner: mp unclear dec (EtOH); IR (KBr) 1790, 1680, 1590 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.92 (4 H, br s), 3.33 (4 H, br s), 4.30 (2 H, s), 4.66 (2 H, s), 7.12 (1 H, d), 7.29 (1 H, d). Anal. ($C_{14}H_{15}ClN_4O\cdot 2HCl\cdot H_2O$) C, H, N.

Other compounds (**13m,n,s,z**) listed in Table I were similarly prepared.

Method C. 6-Pyrrolidino-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-2-one Dihydrochloride (13f). Compound **13o** (1.5 g, 4.12 mmol) was dissolved in MeOH (50 mL) and catalytically reduced in the presence of 10% Pd/charcoal (0.25 g) at room temperature under atmospheric pressure. After completion of the reduction, the catalyst was removed by filtration, and the filtrate was concentrated to dryness under reduced pressure to give **13f**: 0.84 g (61%); mp >280 °C (MeOH/EtOH); IR (KBr) 1800, 1670, 1600, 1510 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.37 (4 H, br s), 3.88 (4 H, br s), 4.45 (2 H, s), 4.93 (2 H, s), 7.35 (1 H, d), 7.54 (2 H, m). Anal. ($C_{14}H_{16}N_4O\cdot 2HCl\cdot H_2O$) C, H, N.

Other compounds (**13c,e,i,j**) listed in Table I were similarly prepared.

Biological Method. Test animals, the preparation of platelet-rich plasma, the platelet aggregation test in vitro and ex vivo after po administration, and measurement of blood pressure and heart rate were reported in the previous paper.[2]

Platelet Aggregation Test ex Vivo at Intravenous Infusion. The compounds to be tested were dissolved in a physiological saline solution and continuously infused to fed rats under pentobarbital anesthesia through the femoral vein at dose of 1 mg/kg (15 min) or 10 mg/kg (10 min) of body weight. Either 15 or 10 min later, citrated blood was taken from the heart, and platelet aggregation was measured as in the in vitro test.

Registry No. **3A**, 35213-00-4; **3B**, 34662-31-2; **3C**, 4110-33-2; **3D**, 2112-22-3; **3E**, 28523-93-5; **3F**, 97112-59-9; **3G**, 2112-21-2; **3H**, 97112-60-2; **4a**, 63140-76-1; **4b**, 63365-13-9; **4d**, 17511-27-2; **4g**, 13514-94-8; **4h**, 97112-61-3; **4k**, 97112-62-4; **4l**, 28340-71-8; **4m**, 97112-63-5; **4n**, 97112-64-6; **4o**, 96336-87-7; **4p**, 97112-65-7; **4q**, 97112-66-8; **4r**, 97112-67-9; **4s**, 97112-68-0; **4t**, 28340-66-1; **4u**, 97112-69-1; **4v**, 97112-70-4; **4w**, 97112-71-5; **4x**, 97112-72-6; **4y**, 97112-73-7; **4z**, 97112-74-8; **5a**, 63365-11-7; **5b**, 63365-14-0; **5d**, 17511-28-3; **5g**, 13514-93-7; **5h**, 97112-75-9; **5k**, 97112-76-0; **5l**, 28340-72-9; **5o**, 97112-77-1; **5p**, 97112-78-2; **5q**, 97112-79-3; **5r**, 97112-80-6; **5s**, 97112-81-7; **5t**, 28340-67-2; **5u**, 97112-82-8; **5v**, 97112-83-9; **5w**, 97112-84-0; **5x**, 97112-85-1; **5y**, 97112-86-2; **6a**, 97112-87-3; **6b**, 96336-84-4; **6d**, 97112-88-4; **6g**, 96086-60-1; **6g**·HCl, 97112-89-5; **6k**, 97112-90-8; **6l**, 97112-91-9; **6p**, 97112-92-0; **6q**, 97112-93-1; **6r**, 97112-94-2; **6s**, 97112-95-3; **6t**, 97112-96-4; **6u**, 97112-97-5; **6v**, 97112-98-6; **6w**, 97112-99-7; **6x**, 97113-00-3; **6y**, 97113-01-4; **7a**, 97113-02-5; **7b**, 96336-85-5; **7d**, 97113-03-6; **7g**, 96086-61-2; **7h**, 97113-04-7; **7k**, 97113-05-8; **7l**, 97113-06-9; **7p**, 97113-07-0; **7q**, 97113-08-1; **7r**, 97113-09-2; **7t**, 97113-10-5; **7u**, 97113-11-6; **7v**, 97113-12-7; **7w**, 97113-13-8; **7x**, 97113-14-9; **7y**, 97113-15-0; **8g**, 96086-62-3; **9g**, 96086-66-7; **10m**, 97113-16-1; **10n**, 97113-17-2; **10o**, 96336-88-8; **10s**, 97113-18-3; **10z**, 97113-19-4; **11m**, 97113-20-7; **11n**, 97113-21-8; **11o**, 96336-89-9; **11s**, 97113-22-9; **11z**, 97113-23-0; **12m**, 96336-67-3; **12n**, 96336-68-4; **12o**, 96336-90-2; **12s**, 96336-69-5; **12z**, 96336-70-8; **13a**, 96336-94-6; **13a**·2HCl, 96336-95-7; **13b**, 96336-92-4; **13b**·2HCl, 96336-93-5; **13c**, 96337-22-3; **13c**·2HCl, 96337-23-4; **13d**, 97113-24-1; **13d**·2HCl, 96336-97-9; **13e**, 97113-25-2; **13e**·2HCl, 97113-26-3; **13f**, 96336-80-0; **13f**·2HCl, 96336-79-7; **13g**, 96086-67-8; **13g**·2HCl, 96086-68-9; **13h**, 96336-99-1; **13h**·2HCl, 96336-98-0; **13i**, 97113-27-4; **13i**·2HCl, 96336-81-1; **13j**, 96336-83-3; **13j**·2HCl, 96336-82-2; **13k**, 97113-28-5; **13k**·2HCl, 96337-00-7; **13l**, 96337-03-0; **13l**·2HCl, 96337-02-9; **13m**, 96336-74-2; **13m**·2HCl, 96336-73-1; **13n**, 96336-76-4; **13n**·2HCl, 96336-75-3; **13o**, 96337-20-1; **13o**·2HCl, 96337-21-2; **13p**, 96337-05-2; **13p**·2HCl, 96337-04-1; **13q**, 97113-29-6; **13q**·2HCl, 96337-06-3; **13r**, 97113-30-9; **13r**·2HCl, 96337-07-4; **13s**, 97113-31-0; **13s**·2HCl, 96336-77-5; **13t**, 96337-12-1; **13t**·2HCl, 96337-11-0; **13u**, 96337-14-3; **13u**·2HCl, 96337-13-2; **13v**, 96337-16-5; **13v**·2HCl, 97113-32-1; **13w**, 96337-18-7; **13w**·2HCl, 96337-17-6; **13x**, 97113-33-2; **13x**·2HCl, 96337-09-6; **13y**, 97113-34-3; **13y**·2HCl, 96337-10-9; **13z**, 97113-35-4; **13z**·2HCl, 96336-78-6; Ne_2NH, 124-40-3; $PhCH_2NHMe$, 103-67-3; Et_2NH, 109-89-7; NH_3, 7664-41-7; BrCN, 506-68-3; 3-iodo-4-methylacetanilide, 97113-36-5; 5-iodo-4-methyl-2-nitroacetanilide, 97113-37-6; 5-iodo-4-methyl-2-nitroaniline, 97113-38-7; 4-iodo-3-methylacetanilide, 97113-39-8; 1,6-dichloro-2,4-dinitrobenzene, 2213-80-1; piperidine, 110-89-4; pyrrolidine, 123-75-1; 2-methylpiperidine, 109-05-7; 4-methylpiperidine, 626-58-4; morpholine, 110-91-8; 1-methylpiperazine, 109-01-3; urea, 57-13-6; ethyl bromoacetate, 105-36-2; 5-chloro-4-methyl-2-nitrobenzonitrile, 97113-40-1; 4,6-dichloro-2-nitrobenzonitrile, 58580-01-1; 4-chloro-5-methyl-2-nitrobenzonitrile, 97113-41-2.