acid was stirred and cooled as 3.8 g (0.1 mol) of sodium borohydride pellets was added over 0.5 h. The mixture was stirred at room temperature for several hours, during which time additional pellets of sodium borohydride were added. Stirring was continued until no more starting material was present by TLC.

The mixture was cooled, diluted with water, made alkaline with NH_4OH, and extracted several times with methylene chloride. The extracts were dried ($MgSO_4$) and filtered, and the filtrate was evaporated to give the product as a glass. The glass was dissolved in alcohol and treated with an alcoholic solution of fumaric acid. The fumarate precipitated and was recrystallized from alcohol: ^1H NMR (Me_2SO-d_6) δ 7.11 (m, 4 H, aromatic H), 6.56 (m, 4 H, thiophene H and fumarate H), 3.28 (m, 4 H, CH_2N), 3.08 (s, 3 H, aromatic NCH_3), 2.58 (m, 4 H, CH_2N), 2.28 (s, 3 H, NCH_3).

Pharmacological Testing Methods. Antagonism of *d*-amphetamine lethality in grouped mice was determined using a previously reported procedure.[9] Groups of 10 mice were treated with the test compound at graded doses and placed in wire mesh cages (20 × 13 × 13.5 cm) in a controlled temperature room at 22 ± 2 °C. After 30 min, *d*-amphetamine sulfate in saline was administered at a dose of 15 mg/kg, which caused 90–100% deaths in untreated grouped mice. Deaths were measured after 24 h. ED_{50} values were determined and defined as the dose of compound that prevented death in 50% of the test animals.

Effects of the compounds on locomotor activity in rats were determined as previously described[9] by oral treatment of groups of five rats with graded doses of the test compounds. Locomotor activity was determined for each individual rat as measured over a 5-min interval at the time of peak effect (previously measured using a selected dose of the compound) utilizing an Animex activity counter. The MDD_{50} was measured from a linear-regression analysis and is defined as the dose that produces 50% reduction in motor activity as compared to the control animals.

Inhibition of tetrabenazine-induced depression of exploratory behavior in mice was determined in the reported manner.[9] Groups of five mice were treated with a dose of the test compound orally and after 1 h were treated with tetrabenazine hexamate (aqueous) at a dose of 30 mg/kg ip. Treated mice were placed on a horizontal disk (18-in. diameter) after 30 min and exploratory behavior was measured within 10 s according to an observational response rating scale. The MED (minimum effective dose) was established by dosing initially at 25 mg/kg orally and halving the dose until the test compound is found inactive in the above procedure.

Synthesis and Antiarrhythmic Activity of New Benzofuran Derivatives

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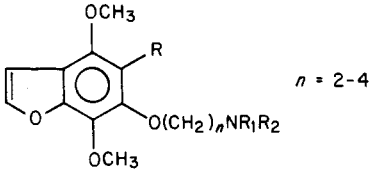
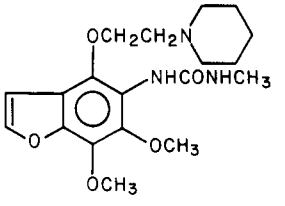
Various 5-aminobenzofuran derivatives were prepared from khellin and screened intravenously in the dog for their potential antiarrhythmic activity against ouabain-induced ventricular arrhythmia and in the Harris test. From systematic structural variations it was found that two methoxy groups in positions 4 and 7 on the benzofuran ring, a tertiary aminoethoxy side chain in position 6, and a *N*-methylurea group in position 5 led to the most active compounds. These were then tested orally in the Harris test in the dog. The two long-acting derivatives *N*-[4,7-dimethoxy-6-(2-pyrrolidinoethoxy)-5-benzofuranyl]-*N'*-methylurea (**8j**) and *N*-[4,7-dimethoxy-6-(2-piperidinoethoxy)-5-benzofuranyl]-*N'*-methylurea (**8m**) showed advantages when compared to quinidine and disopyramide and have been selected for further studies.

The benzofuran ring system is the basic skeleton of numerous compounds possessing cardiovascular activities.[1] In a sustained effort to find cardiovascular active agents derived from khellin,[2-4] a series of *N*-[[6-[alkyl(and dialkyl)amino]alkoxy]-4,7-dimethoxy-5-benzofuranyl] derivatives was prepared and screened for its potential activity.

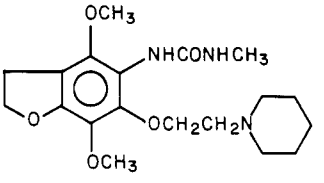
Several of the compounds typified by 1 exhibited a marked antiarrhythmic activity, as shown by their antagonism to ouabain-induced ventricular arrhythmia in the dog.[5] Since these compounds were not active enough against ventricular arrhythmia induced by Harris coronary ligation,[6] synthesis was extended to compounds **2–13**. Derivatives **8** were the most potent in both tests previously quoted. The results of this study suggested further modifications, which led to the synthesis of compounds **14–16d** (see Table I) and **17–19**. Synthesis and structure–activity relationships are described herein.



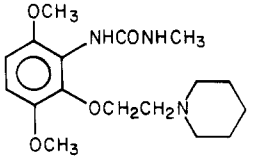
1, R = $NHCOCH_3$
2, R = NH_2
3, R = $NHCH_3$
4, R = NHCHO
5, R = NHCO-alkyl
6, R = NHCOO-alkyl
7, R = $NHCONH_2$
8, R = $NHCONHCH_3$
9, R = NHCONH-alkyl
10, R = $NHSO_2NHCH_3$
11, R = $NHCSNHCH_3$
12, R = $NHCON(CH_3)_2$
13, R = $N(CH_3CONHCH_3$



17



18



19

(1) F. Binon, *Chim. Ther.*, **7**, 156 (1972).
(2) C. Fauran and J. Eberle, *Chim. Ther.*, 8, 475 (1973); G. Raynaud, B. Pourrias, J. Thomas, and M. Thomas, *ibid.*, 8, 479 (1973) and **9**, 85 (1974).
(3) B. Pourrias and F. Friedrich, *Eur. J. Pharmacol.*, **49**, 203 (1978).
(4) G. Bourgery, A. Lacour, B. Pourrias, G. C. Bregeon (Delalande S.A.) French Patent 2358143 (July 12, 1976) and 2396008 (June 27, 1977).
(5) B. R. Lucchesi, *J. Pharmacol. Exp. Ther.*, **137**, 291 (1962).
(6) A. S. Harris, *Circulation*, 1, 1318 (1950).

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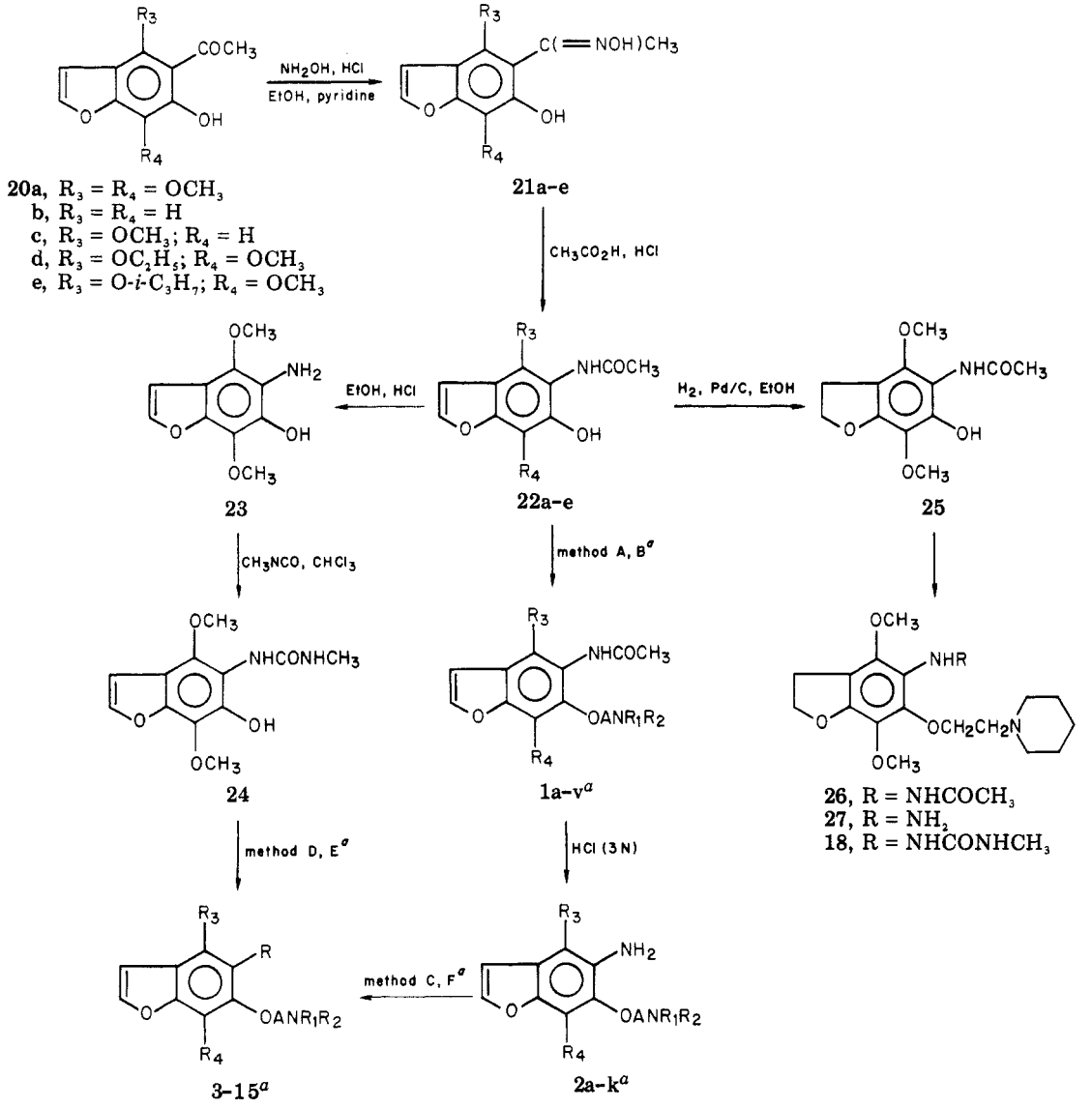
Scheme I



[a] See Table I and Experimental Section.

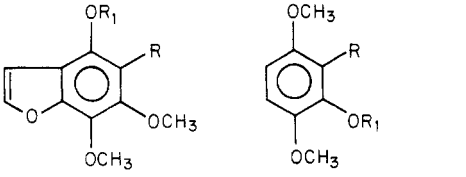
Chemistry. Synthesis of derivatives **1–15** was carried out according to the classical synthetic methods presented in Scheme I. Two main pathways were followed due to the instability of the ureido side chain in some amination steps.

The benzofuranic derivatives were prepared from the commercially available khellinone (**20a**) and visnaginone (**20c**), from the already known 1-[6-hydroxy-5-benzofuranyl]ethanone[7] (**20b**) and 1-[4-ethoxy-6-hydroxy-7-methoxy-5-benzofuranyl]ethanone[8] (**20d**) or from the new 1-[6-hydroxy-4-isopropoxy-7-methoxy-5-benzofuranyl]-ethanone (**20e**) obtained by basic hydrolysis of 4-isopropoxy-9-methoxy-7-methyl-5*H*-furo[3,2-*g*][1]benzopyran described elsewhere.[9]

The dihydrobenzofuran compound **18** could not be obtained by direct catalytic reduction of the benzofuran **8m** but could be obtained from the acetamido derivative **22a**, which was easily hydrogenated and converted to **18**.

Compounds **17** and **19** were synthesized as shown in Scheme II following the sequence used in Scheme I to prepare the derivative **8m** but starting with 1-[6,7-dimethoxy-4-hydroxy-5-benzofuranyl]ethanone[10] (**28a**) and 3,6-dimethoxy-2-hydroxyacetophenone[11] (**29a**).

Scheme II



28a-e
28a → 28e → 17

29a-e
29a → 29e → 19

	R	R_1
a	$COCH_3$	H
b	$C(=NOH)CH_3$	H
c	$NHCOCH_3$	H
d	$NHCOCH_3$	
e	NH_2	

(7) W. Gruber and K. Horvath, *Monatsh. Chem.*, 81, 819 (1950).
(8) C. Musante and A. Stener, *Gazz. Chim. Ital.*, 86, 297 (1956).
(9) H. Abu-Shady and T. O. Soine, *J. Am. Pharm. Assoc.*, 41, 325 (1952).
(10) H. Abu-Shady and T. O. Soine, *J. Am. Pharm. Assoc.*, 41, 403 (1952).

Pharmacological Methods. The antiarrhythmic activity was first evaluated as the ability to immediately restore a normal sinus rhythm in dogs with ventricular arrhythmias induced by ouabain infusion. The antiarrhythmic effect was measured as the percentage of total recovery (sinus rhythm recovery = SRR). Results are presented in Table II. Mongrel dogs weighing 7 to 15 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg). Lead II of the electrocardiogram was monitored continuously and recorded on a Hewlett Packard electrocardiograph (HP 1500 B). Ventricular tachycardia was induced by the intravenous administration of 50 μg/kg ouabain, followed by an additional 5 μg/kg every 15 min until tachycardia developed.

Compounds were injected iv until sinus rhythm was restored. Increasing doses of 1, 2, and 4 mg were injected at intervals of 1 min up to one-tenth of the LD_{50} (iv) in mice. It was found that the iv LD_{50} values estimated in the mouse for compounds **8j** and **8m** are in good agreement with the intravenous LD_{50} in the dog. Compounds failing to cause a return to normal rhythm for at least 30 min were discarded.

Active compounds were then studied in the dog affected by dysrhythmia induced by the method of Harris.[6] Mongrel dogs 12 to 20 kg in weight were anesthetized intravenously with pentobarbital sodium, 30 mg/kg. Mechanical ventilation with room air was instituted through a cuffed endotracheal tube by means of a Bird respirator. Under aseptic conditions, the heart was exposed through the left fifth intercostal space. The anterior descending branch of the left coronary artery was dissected free about 5 to 8 mm distal to the edge of the left atrial appendage. A double ligature was passed under the artery and the vessel was occluded in two stages. The animals were studied 18 to 24 h later in the unesthetized state in a quiet environment. Lead II of the electrocardiogram was monitored continuously and recorded on a HP 1500 B electrocardiograph. Products were given iv, and antiarrhythmic activities were observed as increases in the percentage of normal beats before (initial sinus complexes = ISC) and after (final sinus complexes = FSC) administration of the compound assayed (Table III).

The products rated as active (giving a return to normal sinus rhythm for at least 30 min) were finally given po in the same assay (Table III). Those displaying a long-lasting activity were selected for further pharmacological investigations.

When the recovery of sinus rhythm was less than 100% (ouabain dogs and Harris dogs), the duration of the antiarrhytyhmic activity was defined as the period after which the initial arrhythmia appeared again.

The limited number of animals ($n \leq 5$) used in both screening tests was insufficient for statistical analysis of the results. Quinidine and disopyramide were used as standards in all tests to compare with our compounds.

Discussion

In the first set of compounds (**1a–m**) carrying an acetamido group, only **1h** and **1k** showed a long-lasting activity in the ouabain test (Table II). Compounds **1n–v** were used only as intermediates for the corresponding 8 derivatives once it was ascertained that the derivatives 1 were inactive intravenously in the Harris test (Table III).

In a second set of products (**2a–7, 8m, 9a–g**) with a 6-(2-piperidinoethoxy) side chain and different substituents in position 5 of the benzofuran ring, activity was observed only for derivatives **4** (NHCHO), **6c** ($NHCO_2$-i-C_3H_7), **8m** ($NHCONHCH_3$), and **9a** ($NHCONHC_2H_5$) in the ouabain test. Others were inactive or too toxic to be tested.

The favorable effect of the ureido group in **8m** and **9a** was evaluated in a third set of compounds (**8, 10–19**). Most of the compounds 8 had antiarrhythmic activity. However, no clear relationship between activity and structure of the compounds in this set could be established, although a tertiary amino group with a two to four carbon atom link between oxygen and nitrogen seemed to be the common characteristic of the active products. Secondary amines were not favorable, namely, **8a** was inactive, **8b** with a low ratio toxicity/activity had a short duration of action, and **8c** was highly toxic. On the other hand, it is interesting to underline the increasing toxicity in the tertiary amino groups with the size of the ring (**8j, 8m, 8p, 8q**). The active compounds were evaluated in the Harris test; only the products with tertiary amino functions in a five-, six-, or seven-membered ring and a two carbon atom link (**8j, 8m, 8p, 8s**) showed activity.

To emphasize the influence of the variations on the urea group it should also be stated that (1) substitution of the *N*-methyl of **8m** with other alkyl groups led to a loss of activity, except for **9a**, and to a dramatic increase in toxicity (**9a–g**); (2) introduction of an additional methyl on one of the two nitrogens in **8m** gave **12** and **13** which were less interesting than the parent compound, particularly in the Harris test; (3) substitution of the carbonyl group with SO_2 or C=S gave inactive compounds **10** and **11**. Other fundamental variations have shown (a) the importance of the two methoxy groups on the benzofuran ring (**16a–d**); (b) that reduction or absence of the furan ring led to less active or inactive compounds **18** and **19**; (c) the importance of the right place of the substituents in **8m** to get activity (**17**).

On the basis of these results, **8j, 8m,** and **8p** were tested orally in the Harris test. **8j** and **8m** abolished severe ventricular arrhythmia and gave complete recovery with return to normal sinus rhythm for several hours with a good correlation between dose and effect.

Conclusion

This study has disclosed new antiarrhythmic compounds orally active in a model considered as predictive of clinical activity. Comparison with quinidine and disopyramide for toxicity and activity was in favor of **8j** and **8m**. Further toxicological and pharmacological studies have confirmed a favorable therapeutic margin and will be reported elsewhere. **8j** and **8m** have been selected for clinical investigation.

Experimental Section

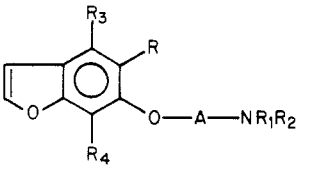
Chemical Methods. Melting points were determined with a Köfler heating bank (uncorrected). Analytical thin-layer chromatographies were performed on glass plates coated with a 0.2-mm layer of silica gel 60 F_{254} (Merck), and column chromatographies were performed on silica gel 60 (Merck, 70–230 mesh, activity II–III). IR absorption spectra were taken with a Perkin-Elmer 197 spectrophotometer. NMR spectra were recorded on a Varian TA60 spectrometer using Me_4Si as internal standard; chemical shifts are given in δ values and coupling constants (J) in hertz. Where analyses are indicated by symbols of the elements, results agree within ±0.4% of the calculated values.

4,7-Dimethoxy-6-(2-piperidinoethoxy)-5-benzofuranamine Dihydrochloride (2a). **1h** (39.8 g, 0.1 mol) was heated under reflux for 5 h in 100 mL of HCl (2 N). The solution was cooled

(11) W. Baker, N. C. Brown, and A. Scott, *J. Chem. Soc.*, 1939 (1922).

(12) L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.*, **57**, 261 (1944).

Table I. Characteristics of the Compounds Synthesized during the Course of the Study



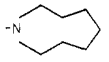
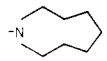
no.	R	$-NR_1R_2$	A	R_3	R_4	yield, % (synth method)	mp, °C	crystn solvent	formula[a]
1a	$NHCOCH_3$	$-NHCH_3$	$(CH_2)_2$	OCH_3	OCH_3	30 (A)	170	EtOH	$C_{15}H_{20}N_2O_5 \cdot HI$
1b	$NHCOCH_3$	$-NHC_2H_5$	$(CH_2)_2$	OCH_3	OCH_3	30 (A)	154	EtOH	$C_{16}H_{22}N_2O_5 \cdot (COOH)_2 \cdot 0.375H_2O$
1c	$NHCOCH_3$	$-NH_iC_3H_7$	$(CH_2)_2$	OCH_3	OCH_3	52 (A)	218	EtOH	$C_{17}H_{24}N_2O_5 \cdot HI$
1d	$NHCOCH_3$	$-NH_cC_6H_{11}$	$(CH_2)_2$	OCH_3	OCH_3	40 (A)	178	EtOH	$C_{20}H_{28}N_2O_5 \cdot HCl \cdot 0.875H_2O$
1e	$NHCOCH_3$	$-N(CH_3)_2$	$(CH_2)_2$	OCH_3	OCH_3	40 (B)	110	EtOH	$C_{16}H_{22}N_2O_5 \cdot HCl \cdot H_2O$
1f	$NHCOCH_3$	$-N(C_2H_5)_2$	$(CH_2)_2$	OCH_3	OCH_3	42 (B)	85	acetone	$C_{18}H_{25}N_2O_5 \cdot CH_3SO_3H \cdot H_2O$
1g	$NHCOCH_3$	-c-$N(CH_2CH_2)_2$	$(CH_2)_2$	OCH_3	OCH_3	60 (B)	148	acetone	$C_{18}H_{24}N_2O_5 \cdot CH_3SO_3H$
1h	$NHCOCH_3$	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	OCH_3	33 (B)	260	PrOH	$C_{19}H_{26}N_2O_5 \cdot HCl$
1i	$NHCOCH_3$	-c-NC_5H_{10}	$(CH_2)_3$	OCH_3	OCH_3	87 (B)	188	EtOH	$C_{20}H_{28}N_2O_5 \cdot CH_3SO_3H$
1j	$NHCOCH_3$		$(CH_2)_2$	OCH_3	OCH_3	80 (A)	218	EtOH	$C_{20}H_{28}N_2O_5 \cdot HCl$
1k	$NHCOCH_3$		$(CH_2)_2$	OCH_3	OCH_3	67 (A)	189	EtOH	$C_{21}H_{30}N_2O_5 \cdot HCl$
1l	$NHCOCH_3$	-c-$N(CH_2CH_2)_2O$	$(CH_2)_2$	OCH_3	OCH_3	50 (B)	200	EtOH	$C_{18}H_{24}N_2O_6 \cdot HCl$
1m	$NHCOCH_3$	-c-$N(CH_2CH_2)_2$-N-CH_3	$(CH_2)_2$	OCH_3	OCH_3	55 (A)	160	EtOH	$C_{19}H_{27}N_3O_5 \cdot 2HCl \cdot 2.5H_2O$
1n	$NHCOCH_3$	$-N(CH_3)_2$	$(CH_2)_3$	OCH_3	OCH_3	80 (B)	oil	EtOH	base[b]
1o	$NHCOCH_3$	-c-NC_3H_6	$(CH_2)_2$	OCH_3	OCH_3	56 (A)	oil	EtOH	base[b]
1p	$NHCOCH_3$	-c-$N(CH_2CH_2)_2$	$(CH_2)_3$	OCH_3	OCH_3	72 (A)	103	Et_2O	base[b]
1q	$NHCOCH_3$	-c-$N(CH_2CH_2)_2$	$(CH_2)_4$	OCH_3	OCH_3	52 (A)	oil	*c*	base[b]
1r	$NHCOCH_3$	-c-NC_5H_{10}	$(CH_2)_4$	OCH_3	OCH_3	40 (A)	oil	*c*	base[b]
1s	$NHCOCH_3$	-c-NC_5H_{10}	$(CH_2)_2$	H	H	43 (B)	oil	*d*	base[b]
1t	$NHCOCH_3$	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	H	40 (B)	235	MeOH	$C_{18}H_{24}N_2O_4 \cdot HCl$
1u	$NHCOCH_3$	-c-NC_5H_{10}	$(CH_2)_2$	OC_2H_5	OCH_3	94 (B)	156	acetone	oxalate
1v	$NHCOCH_3$	-c-NC_5H_{10}	$(CH_2)_2$	O-*i*-C_3H_7	OCH_3	65 (B)	>250	$(i\text{-Pr})_2O$	base[b]
2a	NH_2	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	OCH_3	76	203	EtOH	$C_{17}H_{24}N_2O_4 \cdot 2HCl$
2b	NH_2	-c-NC_5H_{10}	$(CH_2)_2$	H	H	72	oil	EtOH	base[b]
2c	NH_2	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	H	45	oil	EtOH	base[b]
2d	NH_2	-c-NC_5H_{10}	$(CH_2)_2$	OC_2H_5	OCH_3	48	oil	EtOH	base[b]
2e	NH_2	-c-NC_5H_{10}	$(CH_2)_2$	O-*i*-C_3H_7	OCH_3	90	oil	EtOH	base[b]
2f	NH_2	$-N(CH_3)_2$	$(CH_2)_3$	OCH_3	OCH_3	94	oil	EtOH	base[b]
2g	NH_2	-c-NC_3H_6	$(CH_2)_2$	OCH_3	OCH_3	78	oil	EtOH	base[b]
2h	NH_2	-c-$N(CH_2CH_2)_2$	$(CH_2)_3$	OCH_3	OCH_3	82	oil	EtOH	base[b]
2i	NH_2	-c-$N(CH_2CH_2)_2$	$(CH_2)_4$	OCH_3	OCH_3	60	oil	EtOH	base[b]
2j	NH_2	-c-NC_5H_{10}	$(CH_2)_3$	OCH_3	OCH_3	83	oil	EtOH	base[b]
2k	NH_2	-c-NC_5H_{10}	$(CH_2)_4$	OCH_3	OCH_3	70	oil	EtOH	base[b]
3	$NHCH_3$	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	OCH_3	69	168	acetone	$C_{18}H_{26}N_2O_4 \cdot 1.1(COOH)_2$
4	NHCHO	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	OCH_3	60	222	acetone + EtOH	$C_{18}H_{24}N_2O_5 \cdot HCl$
5a	$NHCOCF_3$	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	OCH_3	26	181	Et_2O + EtOH	$C_{19}H_{23}F_3N_2O_5 \cdot HCl$
5b	NHCO-*i*-C_3H_7	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	OCH_3	66 (C)	184	$(i\text{-Pr})_2O$	$C_{21}H_{30}N_2O_5 \cdot HCl \cdot H_2O$
5c	NHCO-c-C_6H_{11}	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	OCH_3	86 (C)	207	*i*-PrOH	$C_{24}H_{33}N_2O_5 \cdot HCl \cdot 0.5H_2O$
5d	$NHCOC_6H_5$	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	OCH_3	39 (C)	195	EtOH	$C_{24}H_{28}N_2O_5 \cdot HCl$
6a	$NHCOOCH_3$	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	OCH_3	57 (C)	171	*i*-PrOH	$C_{19}H_{26}N_2O_6 \cdot HCl$
6b	$NHCOOC_2H_5$	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	OCH_3	66 (C)	119	acetone	$C_{20}H_{28}N_2O_6 \cdot HCl \cdot H_2O$
6c	NHCOO-*i*-C_3H_7	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	OCH_3	70 (C)	117	$(i\text{-Pr})_2O$	$C_{31}H_{30}N_2O_6$
6d	NHCOO-c-C_6H_{11}	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	OCH_3	84	160	Et_2O	$C_{24}H_{34}N_2O_6 \cdot (COOH)_2$
7	$NHCONH_2$	-c-NC_5H_{10}	$(CH_2)_2$	OCH_3	OCH_3	53	102	AcOEt + $(i\text{-Pr})_2O$	$C_{18}H_{25}N_3O_5$
8a	$NHCONHCH_3$	$-NHCH_3$	$(CH_2)_2$	OCH_3	OCH_3	22 (D)	147	AcOEt	$C_{15}H_{21}N_3O_5$
8b	$NHCONHCH_3$	$-NH_iC_3H_7$	$(CH_2)_2$	OCH_3	OCH_3	18 (D)	140	AcOEt	$C_{17}H_{25}N_3O_5$
8c	$NHCONHCH_3$	$-NH_cC_6H_{11}$	$(CH_2)_2$	OCH_3	OCH_3	20 (D)	135	AcOEt + petr ether	$C_{20}H_{29}N_3O_5$
8d	$NHCONHCH_3$	$-N(CH_3)_2$	$(CH_2)_2$	OCH_3	OCH_3	53 (E)	143	AcOEt	$C_{16}H_{23}N_3O_5$

Table I (*Continued*)

no.	R	$-NR_1R_2$	A	R_3	R_4	yield, % (synth method)	mp, °C	crystn solvent	formula[a]
8e	$NHCONHCH_3$	$-N(CH_3)_2$	$(CH_2)_3$	OCH_3	OCH_3	66 (F)	132	AcOEt	$C_{17}H_{25}N_3O_5 \cdot 0.125H_2O$
8f	$NHCONHCH_3$	$-N(C_2H_5)_2$	$(CH_2)_2$	OCH_3	OCH_3	58 (E)	134	AcOEt	$C_{18}H_{27}N_3O_5$
8g	$NHCONHCH_3$	$-N(C_2H_5)_2$	$(CH_2)_3$	OCH_3	OCH_3	52 (E)	135	cyclohexane	$C_{19}H_{29}N_3O_5$
8h	$NHCONHCH_3$	$-N(C_3H_7)_2$	$(CH_2)_2$	OCH_3	OCH_3	77 (E)	142	AcOEt + $(i\text{-Pr})_2O$	$C_{20}H_{31}N_3O_5$
8i	$NHCONHCH_3$	$-c\text{-}NC_3H_6$	$(CH_2)_2$	OCH_3	OCH_3	18 (F)	155	acetone	$C_{17}H_{23}N_3O_5 \cdot (COOH)_2 \cdot {}^4/_3H_2O$
8j	$NHCONHCH_3$	$-c\text{-}N(CH_2CH_2)_2$	$(CH_2)_2$	OCH_3	OCH_3	37 (E)	116	AcOEt + $(i\text{-Pr})_2O$	$C_{18}H_{25}N_3O_5$
8k	$NHCONHCH_3$	$-c\text{-}N(CH_2CH_2)_2$	$(CH_2)_3$	OCH_3	OCH_3	35 (F)	132	AcOEt	$C_{19}H_{27}N_3O_5$
8l	$NHCONHCH_3$	$-c\text{-}N(CH_2CH_2)_2$	$(CH_2)_4$	OCH_3	OCH_3	42 (F)	126	$(i\text{-Pr})_2O$	$C_{20}H_{29}N_3O_5 \cdot {}^1/_3H_2O$
8m	$NHCONHCH_3$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OCH_3	OCH_3	60 (E)	120	$(i\text{-Pr})_2O$	$C_{19}H_{27}N_3O_5$
8n	$NHCONHCH_3$	$-c\text{-}NC_5H_{10}$	$(CH_2)_3$	OCH_3	OCH_3	59 (F)	137	AcOEt	$C_{20}H_{29}N_3O_5$
8o	$NHCONHCH_3$	$-c\text{-}NC_5H_{10}$	$(CH_2)_4$	OCH_3	OCH_3	79 (F)	132	AcOEt	$C_{21}H_{31}N_3O_5$
8p	$NHCONHCH_3$		$(CH_2)_2$	OCH_3	OCH_3	61 (D)	130	AcOEt	$C_{20}H_{29}N_3O_5$
8q	$NHCONHCH_3$		$(CH_2)_2$	OCH_3	OCH_3	64 (D)	122	AcOEt	$C_{21}H_{31}N_3O_5$
8r	$NHCONHCH_3$	$-c\text{-}N(CH_2CH_2)_2O$	$(CH_2)_2$	OCH_3	OCH_3	63 (E)	128	AcOEt	$C_{18}H_{25}N_3O_6$
8s	$NHCONHCH_3$	$-c\text{-}N(CH_2CH_2)_2\text{-}N\text{-}CH_3$	$(CH_2)_2$	OCH_3	OCH_3	80 (D)	118	C_6H_6 + *n*-heptane	$C_{19}H_{28}N_4O_5 \cdot H_2O$
9a	$NHCONHC_2H_5$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OCH_3	OCH_3	83 (F)	112	C_6H_6	$C_{20}H_{29}N_3O_5$
9b	$NHCONHC_3H_7$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OCH_3	OCH_3	78 (F)	126	$(i\text{-Pr})_2O$	$C_{21}H_{31}N_3O_5$
9c	$NHCONH\text{-}i\text{-}C_3H_7$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OCH_3	OCH_3	70 (F)	124	toluene	$C_{21}H_{31}N_3O_5$
9d	$NHCONHC_4H_9$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OCH_3	OCH_3	59 (F)	116	AcOEt	$C_{22}H_{33}N_3O_5$
9e	$NHCONH\text{-}t\text{-}C(CH_3)_3$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OCH_3	OCH_3	23 (F)	129	AcOEt	$C_{22}H_{33}N_3O_5$
9f	$NHCONH\text{-}c\text{-}C_6H_{11}$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OCH_3	OCH_3	42 (F)	186	EtOH	$C_{24}H_{35}N_3O_5 \cdot (COOH)_2$
9g	$NHCONHC_6H_5$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OCH_3	OCH_3	72 (F)	137	AcOEt	$C_{24}H_{29}N_3O_5$
10	$NHSO_2NHCH_3$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OCH_3	OCH_3	40	190	EtOH	$C_{18}H_{27}N_3O_6S \cdot HCl$
11	$NHC(=S)NHCH_3$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OCH_3	OCH_3	80 (F)	101	$(i\text{-Pr})_2O$	$C_{19}H_{27}N_3O_4S$
12	$NHCON(CH_3)_2$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OCH_3	OCH_3	50 (C)	114	petr ether	$C_{20}H_{29}N_3O_5$
13	$N(CH_3)CONHCH_3$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OCH_3	OCH_3	64 (F)	213	AcOEt + acetone	$C_{20}H_{29}N_3O_5 \cdot HCl$
14	$NHCONHCH_3$	$-c\text{-}NC_5H_{10}$	$CH_2CH(CH_3)$	OCH_3	OCH_3	43	129	petr ether	$C_{20}H_{29}N_3O_5$
15	$NHCONHCH_3$	$-c\text{-}NC_5H_{10}$	$CH(CH_3)CH_2$	OCH_3	OCH_3	50	147	AcOEt + $(i\text{-Pr})_2O$	$C_{20}H_{29}N_3O_5$
16a	$NHCONHCH_3$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	H	H	52 (F)	228	acetone	$C_{17}H_{22}N_3O_3 \cdot HCl$
16b	$NHCONHCH_3$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OCH_3	H	59 (F)	168	$(i\text{-Pr})_2O$	$C_{18}H_{25}N_3O_4$
16c	$NHCONHCH_3$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	OC_2H_5	OCH_3	48 (F)	120	$(i\text{-Pr})_2O$	$C_{20}H_{29}N_3O_5$
16d	$NHCONHCH_3$	$-c\text{-}NC_5H_{10}$	$(CH_2)_2$	O-*i*-C_3H_7	OCH_3	64 (F)	156	$(i\text{-Pr})_2O$	$C_{21}H_{31}N_3O_5$
17						55 (F)	120	$(i\text{-Pr})_2O$	$C_{19}H_{27}N_3O_5$
18						77 (F)	150	Et_2O	$C_{19}H_{29}N_3O_5$
19						21 (F)	96	$(i\text{-Pr})_2O$	$C_{17}H_{27}N_3O_4 \cdot 0.25H_2O$

[a] When molecular formulas are given, elemental analyses for C, H, and N are within ±0.4% of theoretical values. [b] Not analyzed. [c] Purification by column chromatography: SiO_2; CH_2Cl_2/MeOH, 90:10. [d] See footnote *c*; solvent, toluene.

(ice) and made basic with concentrated NaOH, extracted 3 times with $(i\text{-Pr})_2O$. The organic layers were dried over Na_2SO_4 and distilled off under vacuum. The oily residue was dissolved in acetone, gazeous HCl was introduced with cooling (ice), and the precipitated dihydrochloride was filtered and recrystallized from absolute ethanol to give 29.8 g (76%) of **2a**: mp 203 °C; IR (KBr) 3450 (NH) cm^{-1}. Anal. ($C_{17}H_{26}ClN_2O_4$) C, H, N.

***N*-[4,7-Dimethoxy-6-(2-piperidinoethoxy)-5-benzofuranyl]methylamine Oxalate (3).** A solution of **4** (3 g, 8 mmol) in 20 mL of THF was added at room temperature to a suspension of $LiAlH_4$ (0.66 g, 17 mmol) in 60 mL of THF. After 2 h at this temperature, $LiAlH_4$ was hydrolyzed by the usual way. Solvents were distilled off under vacuum after drying (Na_2SO_4). The oily residue was converted into oxalate and the precipitate was filtered from acetone to give 3.3 g (69%) of **3**: mp 168 °C; IR (neat) 3200 (NH) cm^{-1}; NMR ($CDCl_3$) δ 1.5 [m, 6 H, $(CH_2)_3$], 2.6 (m, 6 H, NCH_2), 3 (s, 3 H, NCH_3), 3.9 (s, 3 H, OCH_3), 4.1 (s, 3 H, OCH_3), 4.15 (t, 2 H, OCH_2), 4.4 (s, 1 H, NH), 6.8 (d, 1 H, ArCH=, J = 2 Hz), 7.5 (d, 1 H, OCH=, J = 2 Hz). Anal. ($C_{18}H_{28}N_2O_4 \cdot 1.1$oxalate) C, H, N.

***N*-[4,7-Dimethoxy-6-(2-piperidinoethoxy)-5-benzofuranyl]formamide Hydrochloride (4).** Amino derivative **2a** (3.2 g, 10 mmol) was dissolved in 16 mL of formic acid, and 2 g of molecular sieve (Merck, 4 Å, perlform ca 2 mm) was added.

Table II. Results of the Ouabain Test

compd	toxicity: LD_{50}, mg/kg iv[a]	act. against ouabain-induced ventricular arrhythmia: dose, mg/kg iv	SRR,[b] %	duration, min
1a	96	(2)[d]	inact	
1b	68	(3)	inact	
1c	88	6 (3)	33	<30
1d	11.5	1 (1)	50	<30
1e	137.5	(2)	inact	
1f	85	(2)	inact	
1g	80	4 (1)	33	<30
1h	52	2.5 (3)	100	>50
1i	40.5	(2)	inact	
1j	33	(1)	inact	
1k	21	1 (3)	100	>50
1l	200	(2)	inact	
1m	200 (30%)	10 (3)	66	<30
2a	21	(3)	inact	
4	46	4 (1)	100	10
5a	22	(1)	inact	
5b	78	(4)	inact	
5c	7	NT[c]		
5d	2.5	NT[c]		
6a	15	(1)	inact	
6b	13	(1)	inact	
6c	10	1 (1)	100	>100
6d	15	(1)	inact	
7	40	(2)	inact	
8a	67	(1)	inact	
8b	49	4 (3)	100	<30
8c	9.5	1 (1)	100	120
8d	100	1 (1)	100	30
8e	44	(2)	inact	
8f	74	2 (1)	100	>120
8g	76	2 (1)	100	15
8h	52	2 (2)[d]	100	45-120
8i	1000 (40%)[e]	2 (1)	100	10
8j	88	2 (2)	100	69-120
8k	32	4 (2)	100	>60
8l	36	(3)	inact	
8m	50	2 (5)	100	>60
8n	42.5	2 (1)	100	>100
8o	68	4 (3)	100	<30
8p	31	2 (1)	100	95
8q	14	2 (3)	100	30
8r	100 (0%)	(2)	inact	
8s	145	5 (1)	100	120
9a	28	2 (3)	100	120
9b	18.5	(3)	inact	
9c	25	(3)	inact	
9d	22	(1)	inact	
9e	11.5	(2)	inact	
9f	42	(2)	inact	
9g	9	(2)	inact	
10	39	(1)	inact	
11	17	(2)	inact	
12	25	4 (1)	50	60
13	66	2 (3)	100	<10
14	36	2 (2)	100	60
15	23	1 (2)	100	15
16a	67	(2)	inact	
16b	100	2 (2)	100	
16c	10 (100%)		NT[c]	
16d	11	(1)	inact	
17	200 (10%)	(5)	inact	
18	180	8 (1)	100	<30
19	135	(4)	inact	
quinidine	89	10 (1)	50	60
disopyramide	60	5 (4)	100	25

[a] Estimated in the mouse.[12] [b] Percent of normal sinus rythm recovery. [c] Estimated as too toxic to be tested. [d] Number of animals. [e] Administered iv.

The suspension was refluxed for 5 h and then poured into AcOEt and saturated aqueous $NaHCO_3$. The organic layer was decanted and dried (Na_2SO_4), and the solvent was distilled under vacuum. The oily residue was dissolved in acetone and EtOH–HCl (saturated) was added; the hydrochloride was then filtered and dried to give 2.4 g (69%) of **4**: mp 222 °C; IR (KBr) 1740 (CO), 3160 (NH) cm^{-1}; NMR ($CDCl_3$) δ 1.6 [m, 6 H, $(CH_2)_3$], 2.5 [t, 6 H, $N(CH_2)_3$, J = 6 Hz], 3.9 (s, 3 H, OCH_3), 4.1 (s, 3 H, OCH_3), 4.3 (t, 2 H, OCH_2), 6.9 (d, 1 H, ArCH=, J = 2 Hz), 7.6 (d, 1 H, OCH=, J = 2 Hz), 8.6 (d, 1 H, CHO, J = 11 Hz), 10.4 (m, 1 H, NH). Anal. ($C_{18}H_{25}ClN_2O_5$) C, H, N.

***N*-[4,7-Dimethoxy-6-(2-piperidinoethoxy)-5-benzofuranyl]trifluoroacetamide Hydrochloride (5a).** The amino compound **2a** (32 g, 0.1 mol) was dissolved in 200 mL of Et_2O and 7.9 g (0.1 mol) of pyridine. Trifluoroacetic anhydride (42 g, 0.2 mol) was added and the mixture was heated under reflux for 3 h. The white precipitate was filtered, dissolved in aqueous ethanol (50 °C), neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The organic layer was decanted, dried, and evaporated. The solid residue was recrystallized from petroleum ether, giving 21 g of base. It was dissolved in EtOH, and EtOH–HCl was added to yield 12 g (26%) of **5a**: mp 181 °C; IR (KBr) 1720 (CO) cm^{-1}. Anal. ($C_{19}H_{23}F_3N_2O_5$) C, H, N.

***N*-[4,7-Dimethoxy-6-(2-piperidinoethoxy)-5-benzofuranyl]carbamic Acid Cyclohexyl Ester Oxalate (6d).** The amino compound **2a** (3.2 g, 10 mmol) in 10 mL of dry toluene was added in 50 mL of dry toluene saturated with $COCl_2$. **Caution**: The whole apparatus was placed under a stream of N_2 which was bubbled through two flasks filled with methanolic NaOH. The solution was refluxed 1.5 h and then cooled (ice). Phosgene was swept off with N_2, and the precipitate was filtered and dried to give 3 g (84%) of 4,7-dimethoxy-6-(2-piperidinoethoxy)-5-benzofuranisocyanide hydrochloride, mp 149 °C.

The above isocyanide (2.6 g, 6.8 mmol), cyclohexanol (1.4 g, 13.6 mmol), and Et_3N (1.4 g, 13.6 mmol) were refluxed for 2 h in dry acetonitrile (50 mL). The precipitate of Et_3N·HCl was filtered off, the acetonitrile was distilled under vacuum, and the residue was purified by chromatography (SiO_2, 50 g; eluent $CHCl_3$). The oxalate was recrystallized from CH_3CN to give 1.3 g (46%) of **6d**: mp 160 °C; IR (KBr) 1720 (NCOO), 3150 (NH) cm^{-1}; NMR ($CDCl_3$) δ 1.6 [m, 16 H, $(CH_2)_5$ + $(CH_2)_3$], 2.45 [t, 6 H, $N(CH_2)_3$], 4.05 (s, 3 H, OCH_3), 4.1 (s, 3 H, OCH_3), 4.3 (t, 2 H, OCH_2, J = 6 Hz), 4.8 [m, 1 H, $OCH(CH_2)_2$], 6.9 (d, 1 H, ArCH=, J = 2 Hz), 7.6 (d, 1 H, OCH=, J = 2 Hz), 9.5 (s, 1 H, NH). Anal. ($C_{26}H_{36}N_2O_{10}$) C, H, N.

***N*-[4,7-Dimethoxy-6-(2-piperidinoethoxy)-5-benzofuranyl]urea (7).** Amino derivative **2a** (10 g, 31 mmol) was dissolved in acetic acid (10 mL) and H_2O (150 mL). KOCN (2.7 g, 31 mmol) in 8 mL of H_2O was added slowly to the solution, keeping it at +30 °C. Then the solution was stirred overnight at room temperature, K_2CO_3 was added, and the mixture was extracted with AcOEt and dried (Na_2SO_4). The solvents were vacuum distilled, and the solid residue was crystallized from AcOEt–$(i\text{-Pr})_2O$ (1:1), giving 6 g (53%) of **7**: mp 102 °C; IR (KBr) 1660 (CO), 3200 and 3300 (NH) cm^{-1}; NMR ($CDCl_3$) δ 1.5 [m, 6 H, $(CH_2)_3$], 2.4 [m, 6 H, $N(CH_2)_3$], 3.95 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.25 (t, 2 H, OCH_2, J = 5 Hz), 5.5 (s, NH_2), 6.85 (d, 1 H, ArCH=, J = 2 Hz), 7.55 (d, 1 H, OCH=, J = 2 Hz), 8.4 (s, NH). Anal. ($C_{18}H_{25}N_3O_5$) C, H, N.

***N*-Methyl[[4,7-dimethoxy-6-(2-piperidinoethoxy)-5-benzofuranyl]amino]sulfonamide Hydrochloride (10).** Freshly prepared $ClSO_2NHCH_3$[13] dissolved in 10 mL of dry toluene was added dropwise to a solution of **2a** (8 g, 25 mmol) in 100 mL of dry toluene at room temperature, with a vigorous stirring. The hydrochloride **10** was formed immediately. After the solution stirred for 0.5 h, the precipitate was filtered and recrystallized from EtOH to give 4.5 g (40%) of **10**: mp 190 °C; IR (KBr) 1600 (NSO_2N), 3340 (NH) cm^{-1}. Anal. ($C_{18}H_{28}ClN_3O_6S$) C, H, N.

***N*-[4,7-Dimethoxy-6-(2-piperidinopropoxy)-5-benzofuranyl]-*N'*-methylurea (14).** **22a** (40 g, 0.16 mol) and chloroacetone (20.6 g, 0.22 mol) were heated under reflux for 2.5 h in

(13) G. Schulze and G. Weiss (BASF) Belgium Patent 667 311 (Jan 24, 1966); *Chem. Abstr.*, **65**, 5368*d* (1966).

Table III. Activity against Harris Coronary Ligation Induced Ventricular Arrhythmia

compd	dose, mg/kg iv	% ISC[a]	% FSC[b]	duration, min	dose, mg/kg po	% ISC[a]	% FSC[b]	duration, min
1h	6 (1)[c]	inact						
1k	2 (1)	5	17	<30				
6c	1 (1)	30	50	10				
8c	1 (1)	inact						
8d	2 (2)	5	20	10-60				
8f	4 (1)	inact						
8h	2 (1)	30	37	5				
8j	2 (1)	15	75	60	2 (1)[c]	33	100	60
	5 (6)	18	100	60	12.5 (1)	19	95	180
					12.5 (1)	12	81	180
					20 (3)	0	100	180
					20 (1)	26	100	240
8k	5 (2)	0	9	20				
8m	2.5 (5)	3	45	40	6.25 (3)	1	14	60
	5 (5)	14	85	90	12.5 (5)	5	90	240
					25 (3)	13	98	300
8n	2 (3)	inact						
8p	2 (3)	3	78	40	12.5 (1)	5	90	5
8q	2 (2)	inact						
8s	5 (1)	1	50	30				
	10 (1)	18	98	<30				
9a	2 (1)	25	90	<30				
12	2 (1)	22	52	40				
quinidine	10 (3)	5	67	>90	25 (2)	9	25	120
					12.5 (3)	9	56	240
disopyramide	5 (3)	19	100	60	25 (1)	1	100	180

[a] Percent of initial sinus complexes. [b] Percent of final sinus complexes. [c] Number of animals.

a suspension of K_2CO_3 (62 g, 0.45 mol) in CH_3CN (500 mL). The solution was filtered and vacuum distilled, and the residue was crystallized from Et_2O to yield 34 g (69%) of *N*-[4,7-dimethoxy-6-(2-oxopropoxy)-5-benzofuranyl]acetamide (**30**), mp 100 °C. Anal. ($C_{15}H_{17}NO_6$) C, H, N.

Derivative **30** (3.17 g, 0.103 mol) was dissolved in EtOH (400 mL) and $NaBH_4$ (12 g, 0.3 mol) was added. The reaction mixture was heated for 1 h under reflux. The solvent was vacuum distilled, and the oily residue was extracted with H_2O and CH_2Cl_2. Evaporation of the organic layer and crystallization of the residue from Et_2O gave 24.5 g (76%) of *N*-[4,7-dimethoxy-6-(2-hydroxypropoxy)-5-benzofuranyl]acetamide (**31**), mp 122 °C. Anal. ($C_{15}H_{19}NO_6$) C, H, N.

Compound **31** (2.8 g, 9 mmol) and thionyl chloride (1.2 g, 10 mmol) were heated 1 h under reflux in benzene (40 mL). After the mixture cooled, the organic layer was washed with H_2O and $NaHCO_3$, dried (Na_2SO_4), and vacuum evaporated. The residue was purified by column chromatography (SiO_2, 30 g; eluent CH_2Cl_2) and crystallized from petroleum ether to give 1.4 g (50%) of *N*-[4,7-dimethoxy-6-(2-chloropropoxy)-5-benzofuranyl]acetamide (**32**), mp 140 °C. Anal. ($C_{15}H_{18}ClNO_5$) C, H, N.

Derivative **32** (3 g, 9 mmol) and NaI (1.4 g, 9 mmol) were heated at 100 °C for 24 h in piperidine (50 mL), poured into H_2O, extracted with CH_2Cl_2, and washed with H_2O. The organic layer was dried and vacuum distilled to give 1.5 g (44%) of *N*-[4,7-dimethoxy-6-(2-piperidinopropoxy)-5-benzofuranyl]acetamide (**33**) (oil). It was hydrolyzed by the same procedure for **2a** to give 4,7-dimethoxy-6-(2-piperidinopropoxy)-5-benzofuranamine (**34**): yield 59% (oil).

Derivative **34** was converted into **14** by the general procedure of method F: mp 129 °C; yield 43%; IR (KBr) 1670 (CO), 3200 (NH) cm^{-1}. Anal. ($C_{20}H_{29}N_3O_5$) C, H, N.

***N*-[4,7-Dimethoxy-6-(1-methyl-2-piperidinoethoxy)-5-benzofuranyl]-*N'*-methylurea (15).** Compound **24** (13.3 g, 0.05 mol), *N*-(2-chloropropionyl)piperidine (12 g, 68 mmol), and K_2CO_3 (13.8 g, 0.1 mol) were heated under reflux for 6 h in acetonitrile (120 mL). Mineral salts were filtered off, solvent was vacuum evaporated, and the residue was purified by chromatography (SiO_2, 50 g; eluent $CHCl_3$) to give 8.5 g (41%) of *N*-[4,7-dimethoxy-6-[(1-methyl-2-piperidinocarbonyl)ethoxy]-5-benzofuranyl]-*N'*-methylurea (oil).

It (8.5 g, 21 mmol) was reduced by $LiAlH_4$ (2.3 g, 60 mmol) in THF (150 mL). After heating for 4 h under reflux and the usual workup, the product was purified by column chromatography (SiO_2, 10 g; eluent $CHCl_3$) and crystallized from AcOEt–(i-Pr)$_2$O (2:8) to give 4 g (50%) of **15**: mp 147 °C; IR (KBr) 1640 (CO), 3280 and 3320 (NH) cm^{-1}. Anal. ($C_{20}H_{29}N_3O_5$) C, H, N.

1-(6-Hydroxy-4-isopropoxy-7-methoxy-5-benzofuranyl)-ethanone (20e). A mixture of 136 g (0.47 mol) of 4-isopropoxy-9-methoxy-7-methyl-5*H*-furo[3,2-*g*][1]benzopyran and 132 g (2.35 mol) of KOH were heated under reflux in 1300 mL of H_2O for 1 h, then cooled, and 180 mL of HCl (12 N) was added. The precipitate was collected, washed with H_2O until neutral pH, and dried under vacuum to yield 91 g (71%) of **20e**: mp 47 °C; IR (KBr) 1610 (CO), 3400 (OH) cm^{-1}; NMR ($CDCl_3$) δ 1.4 [d, 6 H, $(CH_3)_2C$, J = 6 Hz], 2.7 (s, 3 H, CH_3CO), 4 (s, 3 H, OCH_3), 4.8 [q, 1 H, $CH(CH_3)_2$, J = 6 Hz], 6.8 (d, 1 H, ArCH=, J = 2 Hz), 7.5 (d, 1 H, OCH=, J = 2 Hz), 12.8 (s, OH).

1-(4,7-Dimethoxy-6-hydroxy-5-benzofuranyl)ethanone Oxime (21a). Hydroxylamine hydrochloride (33.6 g, 0.48 mol) was suspended in 200 mL of EtOH (96 °C) and heated under reflux. A solution of Khellinone (**20a**) (94.4 g, 0.4 mol) in 25 mL of H_2O and 48 mL of concentrated NaOH was added dropwise for 1 h. Heating was continued for 6 h. Solvents were distilled off, and the solid residue was recrystallized in 600 mL of H_2O and 100 mL of EtOH (96 °C) to give 82 g (82%) of **21a**: mp 145 °C; NMR (Me_2SO-d_6) δ 2.1 (s, 3 H, CH_3C=NOH), 3.9 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 7 (d, 1 H, ArCH=, J = 2 Hz), 7.8 (d, 1 H, OCH=, J = 2 Hz).

The following oximes were prepared in the same manner as **21a**.

1-(6-Hydroxy-5-benzofuranyl)ethanone oxime (21b): from **20b**;[7] yield 95%; mp 168 °C (dioxane).

1-(6-Hydroxy-4-methoxy-5-benzofuranyl)ethanone oxime (21c): from Visnaginone (**20c**); yield 35%; mp 153 °C (EtOH, 80 °C). Anal. ($C_{11}H_{11}NO_4$) C, H, N.

1-(4-Ethoxy-6-hydroxy-7-methoxy-5-benzofuranyl)-ethanone oxime (21d): from **20d**;[8] yield 94%; mp 136 °C (toluene).

1-(6-Hydroxy-4-isopropoxy-7-methoxy-5-benzofuranyl)-ethanone oxime (21e): from **20e**; yield 95%; mp 140 °C (2-propanol).

***N*-(4,7-Dimethoxy-6-hydroxy-5-benzofuranyl)acetamide (22a).** Oxime **21a** (50.2 g, 0.1 mol) was heated at 90 °C in a solution of AcOH saturated with gazeous HCl for 30 min; 800 mL of H_2O was then added and the temperature was maintained at 50 °C. The solution was cooled (ice), and the precipitate was filtered and washed with cold water to give 37.8 g (75%) of **22a**: mp 160 °C (MeOH); IR (KBr) 1630 (CO), 3290 (NH and OH) cm^{-1}. Anal. ($C_{12}H_{13}NO_5$) C, H, N.

The following acetamides were prepared in the same manner as **22a**.

***N*-(6-Hydroxy-5-benzofuranyl)acetamide (22b)**: from **21b**; yield 50%; mp 219 °C (dioxane).

***N*-(6-Hydroxy-4-methoxy-5-benzofuranyl)acetamide (22c)**: from **21c**; yield 41%; mp 155 °C. Anal. ($C_{11}H_{11}NO_4$) C, H, N.

***N*-(4-Ethoxy-6-hydroxy-7-methoxy-5-benzofuranyl)acetamide (22d)**: from **21d**; yield 45%; mp of the sodium salt >260 °C (EtOH).

***N*-(6-Hydroxy-4-isopropoxy-7-methoxy-5-benzofuranyl)-acetamide (22e)**: from **21e**; yield 50%; mp 126 °C.

5-Amino-4,7-dimethoxy-6-benzofuranol (23): The acetamide **22a** (110 g, 0.44 mol) was dissolved in 700 mL of EtOH saturated with HCl and then heated under reflux for 20 h. The solvent was distilled off under vacuum, and the oily residue was dissolved in 360 mL of H_2O. The pH of the solution (ice cooled) was adjusted to pH 4 by NaOH. The light brown precipitate was filtered, washed with H_2O, and dried to yield 82.5 g (90%): mp 131 °C; IR (KBr) 3320 and 3400 (NH and OH) cm^{-1}; NMR ($CDCl_3$) δ 3.9 (s, 3 H, OCH_3), 4.1 (s, 3 H, OCH_3), 6.75 (d, 1 H, ArCH=, J = 2 Hz), 7.4 (d, 1 H, OCH=, J = 2 Hz). Anal. ($C_{10}H_{11}NO_4$) C, H, N.

***N*-(4,7-Dimethoxy-6-hydroxy-5-benzofuranyl)-*N'*-methylurea (24).** Amino derivative **23** (20.9 g, 0.1 mol) was dissolved in 200 mL of $CHCl_3$, methyl isocyanate (5.7 g, 0.1 mol) was added, and the solution was kept for 2 h at room temperature with stirring. $CHCl_3$ was vacuum distilled, and the oily residue was crystallized from Et_2O to give 23 g (89%) of **24**: mp 110 °C; IR (KBr) 1655 (NCON), 3350 (NH) cm^{-1}; NMR δ 2.8 (d, 3 H, NCH_3, J = 4 Hz), 3.9 (s, 3 H, OCH_3), 4.1 (s, 3 H, OCH_3), 6.3 (q, 1 H, $NHCH_3$, J = 4 Hz), 6.75 (d, 1 H, ArCH=, J = 2 Hz), 7.4 (d, 2 H, OCH= and ArNH). Anal. ($C_{12}H_{14}N_2O_5$) C, H, N.

***N*-(2,3-Dihydro-4,7-dimethoxy-6-hydroxy-5-benzofuranyl)acetamide (25).** Acetamide **22a** (63 g, 0.25 mol) was dissolved in 1400 mL of EtOH, 6.3 g of 10% Pd on carbon was cautiously added, and the mixture was stirred at 80 °C for 7 h in a stainless-steel hydrogenator under 10 atm of hydrogen. After the mixture cooled, the catalyst was filtered, the solvent was distilled off, and the residue was crystallized from Et_2O to yield 35 g (56%) of **25**, mp 120 °C.

***N*-[2,3-Dihydro-4,7-dimethoxy-6-(2-piperidinoethoxy)-5-benzofuranyl]acetamide oxalate hydrate (26)** was prepared from **25** following the general procedure of method B: yield 77%; mp 143 °C; IR (neat) 1670 (CO), 3200 (br, NH) cm^{-1}. Anal. ($C_{19}H_{28}N_2O_5 \cdot 1.5(COOH)_2 \cdot 0.25H_2O$) C, H, N.

2,3-Dihydro-4,7-dimethoxy-6-(2-piperidinoethoxy)-5-benzofuranamine (27) was prepared from **26** by the same procedure used to prepare **2a**: yield 84% (oil).

1-(6,7-Dimethoxy-4-hydroxy-5-benzofuranyl)ethanone oxime (28b) was prepared from **28a**[10] by the same procedure used to prepare **21a**: yield 97% (oil).

***N*-(6,7-Dimethoxy-4-hydroxy-5-benzofuranyl)acetamide (28c)** was prepared from **28b** by the same procedure used to prepare **22a**: yield 65%; mp 124 °C (Et_2O/petroleum ether, 10:90). Anal. ($C_{12}H_{13}NO_5$) C, H, N.

***N*-[6,7-Dimethoxy-4-(2-piperidinoethoxy)-5-benzofuranyl]acetamide (28d)** was prepared from **28c** as described in method B: yield 50% (oil).

6,7-Dimethoxy-4-(2-piperidinoethoxy)-5-benzofuranamine (28e) was prepared from **28d** following the procedure for **2a**: yield 92% (oil).

3,6-Dimethoxy-5-hydroxyacetophenone oxime (29b) was prepared from 3,6-dimethoxy-5-hydroxyacetophenone (**29a**)[11] as described above for **21a**: yield 100% (oil).

***N*-(3,6-Dimethoxy-5-hydroxyphenyl)acetamide (29c)** was prepared from **29b** by the same procedure used to prepare **22a**: yield 26%; mp 127 °C (EtOH, 96 °C); IR (KBr) 1630 (CO), 3300 (OH and NH) cm^{-1}; NMR ($CDCl_3$) δ 2.2 (s, 3 H, CH_3CO), 3.75 (s, 3 H, OCH_3), 3.8 (s, 3 H, OCH_3), 6.3 and 6.65 (d, 2 H, aromatic, J = 9 Hz), 8.1 and 10 (2 s, 2 H, NH and OH).

***N*-[3,6-Dimethoxy-5-(2-piperidinoethoxy)phenyl]acetamide (29d)** was prepared from **29c** following the procedure of method B: yield 35% (oil).

3,6-Dimethoxy-5-(2-piperidinoethoxy)aniline (29e) was prepared from **29d** as described earlier for **2a**: yield 82% (oil); NMR ($CDCl_3$) δ 1.6 [6 H, $(CH_2)_3$], 2.1 (s, 3 H, CH_3CO), 2.4 [t, 6 H, $N(CH_2)_3$], 3.8 (s, 6 H, $2OCH_3$), 4.2 (t, 2 H, OCH_2, J = 5 Hz), 6.6 and 6.7 (d, 2 H, aromatic, J = 8 Hz), 9.2 (s, 1 H, NH).

General Procedures. One example is given for each method, and common intermediates are described.

Method A. *N*-[6-(2-Chloroethoxy)-4,7-dimethoxy-5-benzofuranyl]acetamide (35): Intermediate for the Preparation of Compounds 1a–d,j,k,m,o. Compound **22a** (25.1 g, 0.1 mol) and *p*-toluenesulfonic acid β-chloroethyl ester (21 g, 0.1 mol) were heated at 90 °C in a solution of NaOH (4.6 g in 20 mL of H_2O) for 2 h. The solution was poured into H_2O and ice and the precipitate was filtered and recrystallized from EtOH to give 13 g (37%), mp 180 °C. Anal. ($C_{14}H_{16}ClNO_5$) C, H, N.

***N*-[4,7-Dimethoxy-6-[2-(isopropylamino)ethoxy]-5-benzofuranyl]acetamide Hydriodide (1c).** The intermediate **3c** (31.3 g, 0.1 mol), isopropylamine (5.2 mL, 0.12 mol), and KI (16.6 g, 0.1 mol) were heated under reflux for 24 h in acetonitrile (300 mL). Mineral salts were filtered off, solvent was distilled off, and the solid residue was crystallized in EtOH to give 24 g (52%) of **1c**: mp 218 °C; IR (KBr) 1640 (CO), 3200 (NH) cm^{-1}. Anal. ($C_{17}H_{25}IN_2O_5$) C, H, N.

***N*-[6-(3-Chloropropoxy)-4,7-dimethoxy-5-benzofuranyl]-acetamide: for the Preparation of 1p.** This compound was prepared from **22a** (12.6 g, 50 mmol) and 1-bromo-3-chloropropane in the presence of K_2CO_3 (13.8 g, 0.1 mol) by heating under reflux for 6 h in acetonitrile (200 mL). Filtration of minerals, evaporation of the solvent, and crystallization from $(i\text{-Pr})_2O$ afforded 11 g (67%) of product, mp 100 °C.

***N*-[6-(4-Chlorobutoxy)-4,7-dimethoxy-5-benzofuranyl]-acetamide (36): for the Preparation of 1q and 1r: 36** was prepared as described above from **22a**, giving 71% of compound: mp 70 °C. Anal. ($C_{16}H_{20}ClNO_5$) C, H, N.

Method B. *N*-[4,7-Dimethoxy-6-[2-(dimethylamino)ethoxy]-5-benzofuranyl]acetamide Hydrochloride Hydrate (1e). **22a** (15 g, 60 mmol), K_2CO_3 (25 g, 0.18 mol), and 2-(dimethylamino)-1-chloroethane hydrochloride (13 g, 0.11 mol) were refluxed in acetonitrile (150 mL) for 8 h. After filtration, the solvent was evaporated. The residual oil was converted into the hydrochloride and the salt was recrystallized from EtOH to give 9 g (40%) of **1e**: mp 110 °C. Anal. ($C_{16}H_{22}N_2O_5 \cdot HCl \cdot H_2O$) C, H, N.

Method C. *N*-[4,7-Dimethoxy-6-(2-piperidinoethoxy)-5-benzofuranyl]isobutyramide Hydrochloride Hydrate (5b). To a solution of **2a** (16 g, 50 mmol) in dry toluene (600 mL) was added 5.8 g (55 mmol) of isobutyryl chloride. After the solution stirred for 12 h at room temperature, the precipitate of **5b** was filtered and recrystallized from EtOH to yield 14 g (66%) of **5b**: mp 184 °C; IR (KBr) 1670 (CO), 3450 (NH) cm^{-1}. Anal. ($C_{21}H_{30}N_2O_5 \cdot HCl \cdot H_2O$) C, H, N.

Method D. *N*-[6-(2-Chloroethoxy)-4,7-dimethoxy-5-benzofuranyl]-*N'*-methylurea. This intermediate was prepared from **24** (150 g, 0.58 mol), 1-bromo-2-chloroethane (172 g, 1.2 mol), and K_2CO_3 (207 g, 1.5 mol) in refluxing acetonitrile (1.4 L) for 4.30 h. Mineral salts were hot filtered off, and the solution was cooled (ice) to precipitate the desired product, which was washed with $(i\text{-Pr})_2O$ to give 186 g (62%): mp 205 °C; IR (KBr) 1630 (CO), 3300 (NH) cm^{-1}; NMR (Me_2SO-d_6) δ 2.6 (d, 3 H, CH_3N, J = 5 Hz), 3.85 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 3.7 and 4.4 (m, 4 H, OCH_2CH_2Cl), 6 (q, 1 H, $NHCH_3$, J = 5 Hz), 7.1 (d, 1 H, ArCH=, J = 2 Hz), 7.2 (s, 1 H, ArNH), 7.9 (d, 1 H, OCH=, J = 2 Hz).

***N*-[4,7-Dimethoxy-6-[2-(isopropylamino)ethoxy]-5-benzofuranyl]-*N'*-methylurea (8b).** The above intermediate (11.5 g, 35 mmol), isopropylamine (8.2 g, 0.14 mol), NaI (7.5 g, 50 mmol), and K_2CO_3 (4.8 g, 35 mmol) were refluxed for 15 h in acetonitrile (100 mL). Mineral salts were filtered off, the solvent was distilled off, and the solid residue was recrystallized from AcOEt to give 2.2 g (18%) of **8b**: mp 140 °C; IR (KBr) 1630 (CO), 3320 (NH) cm^{-1}. Anal. ($C_{17}H_{25}N_3O_5$) C, H, N.

Method E. *N*-[6-[3-(Diethylamino)propoxy]-4,7-dimethoxy-5-benzofuranyl]-*N'*-methylurea (8q). Compound **24** (12 g, 4.5 mmol), K_2CO_3 (21 g, 0.15 mol), and 1-chloro-3-(diethylamino)propane (11.2 g, 60 mmol) were heated under reflux in acetonitrile (100 mL) for 4 h. Minerals were filtered off. After evaporation of the solvent, the solid residue was recrystallized

from cyclohexane to give 10 g (52%) of **8g**: mp 135 °C; IR (KBr) 1630 (CO), 3280 and 3340 (NH) cm^{-1}. Anal. ($C_{19}H_{23}N_3O_5$) C, H, N.

Method F. *N*-[4,7-Dimethoxy-6-[2-(dimethylamino)ethoxy]-5-benzofuranyl]-*N'*-methylurea Hydrate (8e). Compound **2f** (10 g, 34 mmol) was dissolved in dry toluene and treated dropwise with methyl isocyanate (**caution**: lachrymatory) (2.4 mL, 40 mmol) at room temperature. The solution was stirred for 5 h, the solvent was distilled off under vacuum at 50 °C, and the residue was recrystallized from AcOEt to give 8 g (66%) of **8e**: mp 132 °C; IR 1620 (CO), 3320 (NH) cm^{-1}. Anal. ($C_{17}H_{25}N_3O_5 \cdot 0.5H_2O$) C, H, N.

Synthesis of Seleno- and Thioguanine–Platinum(II) Complexes and Their Antitumor Activity in Mice

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Selenoguanine–, selenoguanosine–, thioguanine–, and thioxanthine–platinum(II) complexes were synthesized, and their antitumor activities were studied against L1210 cells in mice and in an in vitro system. These compounds exhibited antitumor activity of medium strength and showed very low toxicity. The effect of the selenoguanine–platinum(II) complex in mice was retained longer than that of the parent compound, selenoguanine, because the selenoguanine–platinum(II) complex very slowly released selenoguanine into the blood.

Mautner et al.[1] have shown that selenoguanine (SeG) is as effective an inhibitor as thioguanine (TG) to the growth of several experimental tumors, is less toxic to the host, and shows a somewhat superior therapeutic index than thioguanine.

Many platinum complexes, such as *cis*-dichlorodiammine–platinum(II), have been tested as antitumor agents.[2-8] Several nucleosides and nucleoside bases complexed with *cis*-diaminoplatinum(II) have been shown to be good antitumor agents in experimental animals.[9]

In this article, we describe the antitumor activity of some selenoguanine–platinum(II) [SeG–Pt(II)] and thioguanine–platinum(II) [TG–Pt(II)] complexes and their structural assignments.

Structure Assignment. The UV spectrum of SeG–Pt(II) shows absorption maxima at 297, 340, and 368 nm in aqueous base. These maxima are not observed in the parent compound under the same conditions. These values are closed to those of the protonated form of selenoguanine and indicate the formation of a SeG–Pt(II) complex. This implies that the N^7 position of selenoguanine, which is a protonation site in the molecule, chelates to platinum. The similarity of the UV spectrum of the selenoguanosine–platinum(II) complex with that of SeG–Pt(II) [237, 273 (sh), 303, and 370 nm] also supports N^7 as the chelation site in the complexes.

^{13}C nuclear magnetic resonance spectra of the complexes were obtained with rather poor resolution due to their limited solubility, even in aqueous base. When compared with the parent SeG, the spectra of SeG–Pt(II) shows a marked downfield shift (3.03–3.07 ppm) for two carbons, positions 2 and 8, and an upfield shift (0.54–4.19 ppm) for three carbons, positions 4, 5, and 6. Other platinum complexes, such as TG–Pt(II), TGR–Pt(II), TX–Pt(II), and SeGR–Pt(II), show similar shifts.

Selenoguanine, similarly to thioguanine, is predominantly in the selenocarboxamide, (thiocarboxamide) rather than in iminoselenol (iminothiol) form in aqueous solution or in the solid state at room temperature.[10-16] ^{13}C NMR has shown that carbon 6 shifts upfield when the thiocarboxamide converts to the iminothiol (selenocarboxamide to iminoselenol).[17,18] The fact that the carbon 6 signals of the SeG–Pt(II) and TG–Pt(II) complexes were shifted upfield by 2.41–4.19 ppm indicates that selenium is bound to platinum as a seleno ether type compound.

Studies on the interaction of nucleosides or nucleotides with *cis*-dichlorodiammineplatinum(II) have indicated that the N^7 and O^6 atoms of guanosine and inosine are the sites of bond formation with platinum.[19-21]

The selenium atom, the strongest nucleophilic center in selenoguanine, could be the site of binding to the tetrachloroplatinate ion to produce *cis*- or *trans*-dichlorobis(selenoguanin-6-yl)platinum(II). The results of the following kinetic study support this view. Subsequent intramolecular displacement will afford the SeG–Pt(II) complex. Owing to the strong trans influences of sulfur or selenium in the molecule,[22] the intermediates are con-

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