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Isoquinolinol derivatives: potent, short-acting inotropic and vasodilating agents with potential utility for cardiac emergencies

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Summary — The synthesis and cardiovascular evaluation of a series of 4-nitroisoquinolin-3-ol derivatives are reported. These compounds are potent, short-acting cardiovascular agents with both positive inotropic and peripheral vasodilating effects when administered intravenously. Compounds with this profile could be of particular therapeutic benefit in cardiac emergencies such as severe late stage heart failure and myocardial infarction. Of particular interest is 7-ethoxy-6-methoxy-1-methyl-4-nitroisoquinolin-3-ol (**6**) which has potent, non β-adrenergic parenteral inotropic properties similar to those of dopamine, and also has peripheral vasodilator activity, up to 10-fold greater than amrinone.

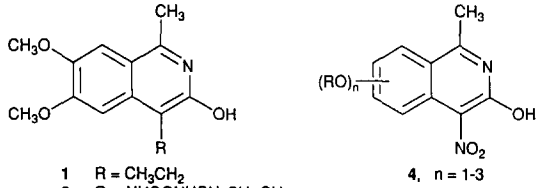
Résumé — Dérivés de l'isoquinolinol: agents d'activités forte et brève, à la fois inotrope et vasodilatatrice intéressants pour les urgences cardiaques. *La synthèse et l'évaluation cardiovasculaire d'une série de dérivés du 4-nitroisoquinolin-3-ol est rapportée. Administrés par injection intraveineuse, ces composés ont une action énergique et brève, ayant des effets à la fois inotrope positif et vasodilatateur périphérique. Ces composés pourraient avoir un intérêt thérapeutique dans les cas d'urgence cardiaque comme les sévères arrêts du cœur en dernière instance et les infarctus du myocarde. D'intérêt particulier est le 7-éthoxy-6-méthoxy-1-méthyl-4-nitroisoquinolin-3-ol (**6**) qui a de puissantes activités inotropes parentérales non béta-adrénergique, similaires à celles de la dopamine. Il a aussi une activité vasodilatatrice périphérique dix fois plus énergique que l'amrinone.*

cardiotonic / vasodilation / renal vasodilation / isoquinolinol / amrinone / dopamine

Introduction

Intravenous cardiac stimulants are used in the hospital setting for cardiovascular emergencies characterized by acute reductions in myocardial contractile force. Life-threatening reductions in contractility can occur during myocardial infarction, cardiogenic shock, or end-stage congestive heart failure. Intravenous cardiac stimulants currently approved for use in the United States include dopamine [1] (a β-adrenoreceptor stimulant and dopaminergic renal vasodilator), dobutamine [2] (an α- and β-adrenoreceptor stimulant), amrinone [3] and milrinone [4] (selective phosphodiesterase inhibitors and peripheral vasodilators). Inotropic vasodilators such as amrinone and milrinone assist the failing heart by both improving contractility and decreasing cardiac afterload *via* reduction in peripheral vascular resistance [5].

We have recently reported that 4-substituted isoquinolin-3-ol derivatives represent a new class of cardiovascular agents whose overall cardiovascular profile is strongly influenced by the nature of the 4-substituent [6, 7]. For example, our studies have shown that the 4-ethyl compound **1** is a potent cardiotonic agent with modest general peripheral vasodilating properties[6], the 4-ureido compound **2** is a potent and selective renal vasodilator [7], and the 4-acylamino compound **3** has a mixed inotropic/renal vasodilating profile of moderate potency [7]. Additional work reported herein has provided further evidence of the significance of the 4-substituent. We now describe a series of alkoxy substituted 4-nitroisoquinolin-3-ol derivatives (*cf* **4**) with an intravenous cardiovascular profile encompassing both positive inotropic and systemic peripheral vasodilating activity.



1 R = CH_3CH_2
2 R = $NHCONHCH_2CH{=}CH_2$
3 R = $NHCOCH_3$

4, n = 1-3

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Chemistry and pharmacology

The alkoxy substituted 4-nitro compounds **5-15** (table I) were prepared by nitration of the corresponding 4-unsubstituted isoquinolin-3-ols using methods we have previously described [7]. Cardiotonic and renal vasodilatory activities are summarized in table I and compared to the standards amrinone and dopamine. Compounds were administered by intravenous infusion in anesthetized instrumented dogs and contractile force (CF), left ventricular dP/dt, renal blood flow (RBF), mean arterial blood pressure (MAP) and heart rate (HR) were measured directly, while renal vascular resistance (RVR) was calculated as the ratio of mean arterial blood pressure to renal blood flow. These measurements were compared to pretreatment control values and are reported as percent changes for the specified parameter. Prior to drug administration, an intravenous dose of dopamine was administered to each animal to assess myocardial inotropic and renal vasodilator responsiveness.

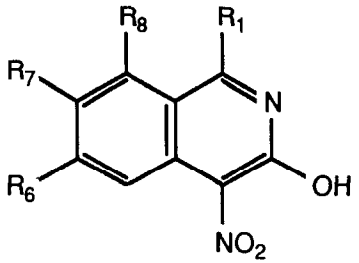
The lead for this report was discovered upon testing **5** (with the 6,7-dimethoxy substitution pattern preferred in our previous 6-alkyl (cardiotonic [6]) and 4-ureido (renal vasodilating [7]) series) which was found to have interesting cardiotonic and renal vasodilating properties. We examined the effect of changes in the alkoxy substitution pattern, particularly in the 6- and 7-positions. In terms of cardiotonic activity, increasing the 7-substituent size to ethoxy (**6**) significantly enhanced potency. Further increase of substituent size to 7-butoxy (**7**) returned potency to that of the lead **5**. The activity of 6,7-methylenedioxy analogue **8** was also similar to **5**. The increased potency caused by 7-ethoxy substitution was not general in scope since 6-ethoxy congener **9** had activity similar to **5**. 6,7-Diethoxy **10** or 7-methoxy **11** compounds were highly potent cardiotonic agents. The fact that the 6,7,8-trimethoxy substituted compound **12** had good cardiotonic activity suggests that the 8-position has little bearing on this effect. Cardiotonic activity is diminished only when the 6-methoxy substituent is absent while maintaining 8-methoxy substitution (**13**) or when the 1-methyl group is absent (**14**) or replaced by a more sterically demanding group such as phenyl (**15**).

Compared to the above structure activity analysis wherein almost all the compounds in the series are potent positive inotropes, good renal vasodilator activity is much less common and very sensitive to substituent alteration. Thus, while 6,7-dimethoxy (**5**), 6-methoxy-7-butoxy (**7**), 6,7-diethoxy (**10**) and 6,7,8-trimethoxy (**12**) compounds all had moderate potency, only 6-methoxy-7-ethoxy derivative **6** had noteworthy renal vasodilatory potency similar to the best derivatives from our previous report [7]. Derivatives with other alkoxy substitution (**8**, **9**, **11**, **13**) or 1-substitution (**14**, **15**) patterns were not of interest. Of this group of compounds, **6** stands alone as worthy of further study as a renal vasodilator.

Examination of the RBF, MAP and CF data in table I suggests that, within this series of 4-nitro analogues, the ability to increase contractility generally parallels their vasodilator potency and a moderate chronotropic effect is also apparent for the better inotropic vasodilators (*cf* **5**, **6**) in the series. The data also show that the 4-nitro compounds most effective at elevating renal blood flow (**5–7**, **10**, **12**) also reduce MAP and RVR concomitantly, suggesting that these compounds are general peripheral vasodilators and that the renal bed acts as one of the regional circulations contributing to the overall vasodilator activity of the compounds. Several of the less active compounds (*cf* **9**, **14**) display a trend toward more renal vasodilator activity, but are significantly less potent and less selective than the most interesting analogues in our earlier 4-ureido series.

Based on these observations, the 7-ethoxy-6-methoxy analogue **6** was selected for further study. As shown in figure 1, the hemodynamic activity of **6** was unaltered by combined treatment with propranolol and atropine, indicating that the inotropic and vasodilator activities of **6** were direct hemodynamic effects and not secondary β-adrenergic or muscarinic cholinergic reflex responses. A quantitative comparison of cardiovascular activities of **6** with those of dopamine and amrinone is shown in table II. The inotropic potencies, expressed as the iv dose that increases CF by 35% (ED_{35}), clearly show that isoquinoline **6** is a more potent cardiotonic agent than either dopamine or amrinone, while dopamine is the superior renal vasodilator as indicated by its potency for increasing RBF by 10% (ED_{10}). Amrinone is the least potent of the 3 compounds for either parameter. The CF/RBF selectivity ratio, the ratio of the ED_{35} values for increasing CF to the ED_{10} values for increasing RBF, is an index of the overall inotropic or renal vasodilator selectivity of a compound in this model. This ratio is lowest for **6**, the most potent inotrope, and 100-fold higher for dopamine, the most potent renal dilator. On this scale, the ratio for amrinone falls between the ratios for **6** and dopamine and lies closest to that of **6**. Compound **6** is also a potent inhibitor of isolated phosphodiesterase (PDE) fraction III isoenzyme, which may account for its cardiotonic activity. Isoquinolinol **6** is ≈ 3-fold more potent than amrinone as a PDE fraction III inhibitor, somewhat inconsistent with the relative *in vivo* cardiotonic potencies observed for these 2 compounds. Since **6** is more than ≈ 30-fold more potent *in vivo* than amrinone, it is likely that additional mechanisms producing positive inotropic activity are at work. While **6** is very potent when administered intravenously, oral administration to conscious instrumented dogs ($n = 4$) of a dose of 10 mg/kg resulted in

Table I. Cardiovascular data and physical properties of the 4-nitroisoquinolin-3-ols.



					Renal Vasodilation[a]					Cardiotonic Activity[b]							
Cmpd	R_1	R_6	R_7	R_8	dose	N	RBF	RVR	MAP	N	dose	CF	dP/dt	HR	MAP	mp, °C	Formula[c]
5	Me	OMe	OMe	H	1.20	3	29	-38	-23	2	1.875	98	20	9	-61	>310	$C_{12}H_{12}N_2O_5$
6	Me	OMe	OEt	H	0.14	2	60	-40	-23	2	0.875	162	98	32	-37	257-260d	$C_{13}H_{14}N_2O_5$
										3	0.07	114	52	15	-16		
7	Me	OMe	O-*n*-Bu	H	1.20	2	34	-47	-29	2	1.875	100	13	11	-41	210d	$C_{15}H_{18}N_2O_5$
8	Me	methylenedioxy		H	6.20	2	3	-8	-8	2	1.875	94	30	14	-7	300d	$C_{11}H_8N_2O_5$
9	Me	OEt	OMe	H	1.20	2	-8	-20	6	2	1.875	110	32	22	-45	>300d	$C_{13}H_{14}N_2O_5$
10	Me	OEt	OEt	H	1.34	3	33	-43	-26	2	1.875	156	52	22	-23	240-243d	$C_{14}H_{16}N_2O_5$[d]
11	Me	H	OMe	H	1.24	2	8	-30	-25	2	0.875	114	64	25	-10	>250	$C_{11}H_{10}N_2O_4$[d]
12	Me	OMe	OMe	OMe	1.20	2	60	-52	-26	2	1.875	102	42	16	-34	250-252	$C_{13}H_{14}N_2O_6$
13	Me	H	OMe	OMe	6.20	1	20	-20	-8	2	1.875	31	13	6	-6	214-216	$C_{12}H_{12}N_2O_5$
14	H	OMe	OMe	H	6.20	4	38	-30	-5	2	1.875	16	22	0	-8	>300d	$C_{11}H_{10}N_2O_5$
15	Ph	OMe	OMe	H	1.34	1	28	-26	-5	2	1.875	5	8	-14	-5	248-250	$C_{17}H_{14}N_2O_5$
amrinone					1.00	3	15	-17	-5	6	1.875	134±16	74±10	12±4	-10±3		
dopamine					0.03	25	32±3	-27±2	-6±1	17	0.030	95±7	29±3	0±1	-7±3		

[a]Renal artery blood flow (RBF) was measured in closed-chest, pentobarbital anesthetized dogs using an electromagnetic flow probe. Mean arterial pressure (MAP) was recorded from a cannulated femoral artery. Renal vascular resistance was calculated as MAP/RBF. Data are reported as the percent change from baseline. N indicates the number of animals tested. [b]Cardiotonic activity was monitored in open-chest anesthetized dogs. Contractile force (CF) was determined using a Walton Brodie strain gauge while left ventricular dP/dt, a confirming index of contractility, was measured with a pressure tip catheter in the left ventricle. Mean arterial pressure (MAP) and heart rate were obtained from a cannulated artery. Data are reported as the percent change from baseline. N indicates the number of animals tested. [c]All compounds were analyzed for carbon, hydrogen and nitrogen (C, H, N) within ± 0.4%. [d]Isolated as a hemihydrate.

a peak increase in contractility (d*P*/d*t*) of only 47% within 30 min which declined rapidly to control.

The duration of inotropic action of **6** was determined after a single sustained infusion (1.25 μg/kg per min for 60 min) in the open chest canine model. In this manner, a selective increase in contractility (> 40% increase in CF at 60 min) was achieved with minimal vasodilation or chronotropic effects (HR and MAP within ± 10% of control at 60 min). Upon termination of infusion, the increased contractility dropped to less than half of its peak effect within 15 min, indicating a very short duration of action. Similarly, in anesthetized closed chest dogs, infusion of **6** at a higher dose (0.14 mg/kg; table I) provided increased renal blood flow (60%) and concommitant reductions in renal vascular resistance and mean arterial pressure. Within 15 min of cessation of infusion of **6**, renal blood flow responses and mean arterial pressure returned to within 10% of control values.

Conclusion

We have found that, when administered intravenously, a series of 4-nitroisoquinolin-3-ol derivatives produce very short-acting cardiotonic and vasodilating cardiovascular effects. In particular, the 1-methyl-7-ethoxy-6-methoxy-4-nitroisoquinolin-3-ol (**6**) is notable for its potent intravenous positive inotropic and vasodilatory properties. These actions are distinguishable from those of amrinone and dopamine and are not mediated *via* β-adrenergic receptors. Compounds with this profile may have a therapeutic benefit in cardiac emergency situations such as severe late-stage heart failure and myocardial infarction. Furthermore, the short duration of action of **6** enhances its potential for intravenous use in cardiac emergencies.

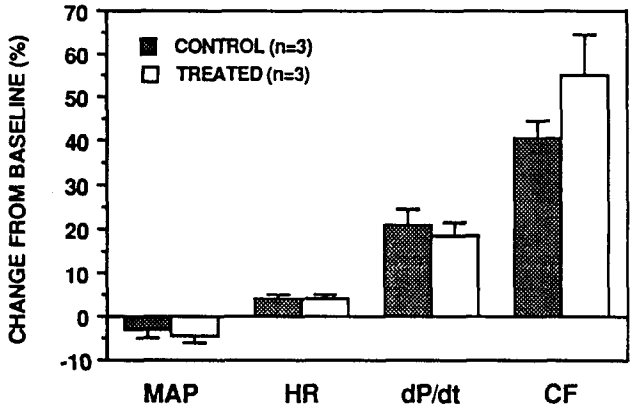
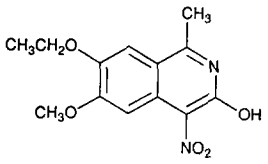


Fig 1. Hemodynamic response to compound **6** in dogs before and after treatment with autonomic antagonists. MAP: mean arterial pressure. HR: heart rate. dP/dt: rate of pressure development in the left ventricle. CF: myocardial contractile force. Compound **6** was administered by iv infusion (10 μg/kg, total dose) to open-chest instrumented dogs (n = 3) before and after treatment with propranolol (0.5 mg/kg) and atropine (1.0 mg/kg) to block β-adrenergic and muscarinic cholinergic receptors. Hemodynamic indices are reported as % change from baseline. None of the values were statistically different after autonomic blockade.

Table II. Cardiotonic, renal vasodilatory and phosphodiesterase inhibitory potencies of **6**, dopamine and amrinone.



Compound	*CF*[a] ED_{35} (μg/kg iv)	*RBF*[b] ED_{10} (μg/kg iv)	*CF/RBF ratio*[c] ED_{35}/ED_{10}	*PDE FrIII*[d] IC_{50} (μM)
6	13.0	141.4	0.09	22 ± 14
Dopamine	34.2	3.8	9	–
Amrinone	481.7	1232	0.39	60 ± 16

[a]Dose of compound (μg/kg, iv) calculated to increase myocardial contractile force by 35%, as measured with the Walton Brodie strain gauge and obtained by linear regression analysis. [b]Dose of compound (μg/kg, iv) calculated to increase renal blood flow by 10% in open chest dogs, obtained by linear regression analysis. [c]An index of the relative inotropic or renal vasodilator selectivity of a given agent. [d]Potency to inhibit canine cardiac, cyclic AMP-specific, phosphodiesterase isozyme fraction III *in vitro*.

Experimental protocols

Melting point determinations were carried out on either a Mel-Temperature or Thomas–Hoover capillary melting point apparatus and are uncorrected. All compounds had spectra (IR, UV, ^{1}H NMR and MS) consistent with their assigned structures and were found to be homogeneous by thin–layer chromatography (TLC). Combustion analyses for C, H and N were within ± 0.4% of theory unless noted otherwise. Compounds in table I were prepared according to the general procedures given below. Physical properties of the compounds are summarized in table I.

7-Ethoxy-3-hydroxy-6-methoxy-1-methylisoquinoline•0.25 hydrate

To an ice-cooled, mechanically stirred solution of 4-ethoxy-3-methoxybenzylcyanide (25 g, 0.13 mol) in acetic anhydride (74 ml, 0.785 mol) 70% perchloric acid (15.5 ml, 0.182 mol) was added over a period of 15 min and the mixture stirred at rt

for 42 h. Ether (200 ml) was added and the solid perchlorate salt was collected by filtration and dried *in vacuo* (47.3 g, 100%), mp = 188–190°C. A sample of this solid (36.37 g, 0.1 mol) was slurried in ice-cold water (400 ml) with mechanical stirring and concentrated ammonium hydroxide (80 ml) was added over a period of 10 min. After an additional 30 min stirring, the solid was collected by filtration and then suspended in chloroform/methanol (2 l/0.7 l). The mixture was heated to reflux, a small amount of undissolved material was removed by filtration and the filtrate was concentrated to *ca* 200 ml. The analytical product was collected by filtration and dried *in vacuo*, 18.7 g (81.3%), mp = 235-240°C (d). ^{1}H NMR (trifluoroacetic acid) δ 7.43, 7.30, 7.23 (3 s, 3H, aromatic *H*), 4.42 (q, 2H, OCH_2), 4.20 (s, 3H, OCH_3), 3.10 (s, 3H, CH_3) and 1.62 (t, 3H, CH_3); MS m/z 233 (M^+). Anal $C_{13}H_{15}NO_3 \cdot 0.25H_2O$ (C, H, N).

7-Ethoxy-3-hydroxy-6-methoxy-1-methyl-4-nitroisoquinoline **6**

7-Ethoxy-3-hydroxy-6-methoxy-1-methylisoquinoline•0.25 hydrate (4.67 g, 0.02 mol) was partially dissolved in acetic acid (150 ml) with warming. This mixture was cooled to *ca* 15°C with an ice-water bath under mechanical stirring and 90% nitric acid (4 ml, 0.08 mol) was added over 3 min. After stirring for an additional 20 min, the brick red-orange mixture was poured onto 600 ml ice to give an orange flocculent solid. The product was collected by filtration, washed with water (2 x 200 ml) and dried to give a red-orange solid, 3.37 g (60%), mp = 195–230°C. The product was dissolved in boiling chloroform (1 l) and methanol (0.5 l), filtered and the filtrate evaporated. The residue was triturated in chloroform (100 ml)–methanol (50 ml) and the solid collected by filtration to give the analytical material, 1.38 g (24%), mp = 257–260°C (d). ^{1}H NMR (trifluoroacetic acid) δ 8.65, 7.65 (2 s, 2H, aromatic *H*), 4.43 (q, 2H, OCH_2), 4.33 (s, 3H, OCH_3), 3.22 (s, 3H, CH_3) and 1.63 (t, 3H, CH_2CH_3); MS m/z 278 (M^+). Anal $C_{13}H_{14}N_2O_5$ (C, H, N).

Cardiotonic and renal vasodilator activity in anesthetized dogs

Cardiotonic activity was determined using essentially the method of Alousi [3] as follows: mongrel dogs were anesthetized with sodium pentobarbital (45 mg/kg, ip) and artificially respired. When administered in this manner, the effect of the pentobarbital is prolonged relative to intravenous administration and is comparable to giving a continuous iv infusion after an initial intravenous loading dose. Resting values for hemodynamic parameters are presented in table III.

Table III. Control values for hemodynamic parameters in anesthetized dogs (n = 31).

Parameter	*Absolute value*
Mean arterial pressure	102 ± 3 mmHg
Heart rate	140 ± 4 beats/min
dP/dt_{max}	2636 ± 121 mmHg/s
Contractile force	96.0 ± 2.4 g

Catheters were placed in a femoral artery and vein for the recording of mean arterial blood pressure (MAP) and administration of drugs, respectively. A Millar catheter-tip pressure transducer (PC-370) was inserted into the left ventricle and dP/dt_{max} was derived as an index of myocardial contractility. Heart rate (HR) was determined with a cardiotachometer. A right thoracotomy was performed at the 4th intercostal space and a Walton Brodie strain gauge was sutured to the right ventricular free wall to measure changes in myocardial contractile force (CF). After stabilization from surgery, an infusion of dopamine (10–15 μg/kg per min) was administered to assess responsiveness to inotropic stimulation. Compounds were administered as 5 min iv infusions in stepwise increasing doses.

For the study employing autonomic blockade, atropine sulfate (1 mg/kg) and propranolol (0.5 mg/kg) were administered intravenously (n = 3) before the test compound to block muscarinic and β-adrenergic receptor-mediated responses. This dose of atropine completely abolished the effects of right vagal stimulation, while the dose of propranolol reduced the agonist effects of isoproterenol (0.1 μg/kg, iv) on contractile force from 153 ± 37% to 15 ± 3.0% and on heart rate from 27 ± 6% to 4 ± 1% (both $P < 0.05$).

Renal vasodilatory activity was determined essentially using the method of Goldberg [8] as follows: animals were anesthetized and respired as above. A renal artery was approached by retroperitoneal flank incision and renal blood flow (RBF) was measured using an electromagnetic probe on the renal artery and a Carolina Medical Electronics flowmeter. Mean arterial blood pressure (MAP) was recorded from a cannulated femoral artery. Renal vascular resistance (RVR) was calculated as the ratio of MAP/RBF.

Cardiotonic activity in conscious, instrumented canines

Mongrel dogs (n = 4) were anesthetized through a cephalic vein with 5% Surital and under sterile surgical technique, heparin-filed Tygon catheters were inserted into a femoral or carotid artery and femoral or jugular vein to record arterial blood pressure and deliver drugs, respectively. Catheters were exteriorized at the nape of the neck. A left thoracotomy was performed and a Konigsberg pressure transducer was inserted into the left ventricle (to record left ventricular pressure and derive dP/dt_{max}) through a stab wound in the apex of the heart and secured with a purse string suture. This transducer was calibrated *in vitro* against a mercury manometer before implantation. The chest was closed and negative pressure reestablished. Animals were allowed at least 1 week to recover. Dogs were trained to lie quietly in an isolation cage while mean arterial pressure, heart rate, and dP/dt_{max} were continuously monitored. Drugs were administered orally *via* a gastric tube in 10 ml of 0.25% Methocel vehicle.

Phosphodiesterase (PDE) inhibition

Canine heart tissue was homogenized for 90 s in 10 ml of distilled water (4 °C). After sonication for 5 min at 4°C, the crude material was centrifuged at 40 000 *g* for 20 min. The supernatant was filtered through nylon mesh and applied to a DEAE cellulose column (2.5 x 25 cm) equilibrated with 70 mM sodium acetate buffer (pH 6.5) containing 5 mM mercaptoethanol and 30% ethylene glycol. After applying the clear supernatant, 2 bed volumes of equilibration buffer were used to wash the column. Fractions I, II, and III were eluted with 200, 350 and 800 mM sodium acetate respectively. Fraction III was pooled, dialyzed at 4 °C and stored at – 20 °C.

The cyclic AMP PDE assay of Thompson and Appleman was employed [9]. Enzyme buffer (0.05 M Tris–HCl, pH 7.4 containing 5 mM $MgCl_2$) and compound were placed in plastic tubes (0.4 ml final vol). Substrate (0.05–0.25 μM) with 2 x 10^5 cpm of tracer ^{3}H-cAMP was added and the reaction allowed to proceed for 20 min at rt. After terminating the reaction in boiling water, snake venom was added for 25 min to convert 5'-AMP to adenosine. Ion exchange resin was then added to remove any remaining cAMP and an aliquot of the supernatant was placed in a scintillation vial with 5 ml of cocktail to count radioactivity.

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