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Spasmolytic Constituents of *Cedrus deodara* (Roxb.) Loud: Pharmacological Evaluation of Himachalol

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Abstract □ Himachalol has been identified as the major antispasmodic constituent in the wood of *Cedrus deodara*. The pharmacological studies of himachalol on various isolated smooth muscles (guinea pig ileum, rabbit jejunum, rat uterus, and guinea pig seminal vesicle) and against different agonists (acetylcholine, histamine, serotonin, nicotine, and barium chloride) indicated spasmolytic activity similar to that of papaverine. It was a more potent antagonist of barium chloride-induced spasm of guinea pig ileum than papaverine but less effective in reverting a similar spasm of rabbit jejunum and had no relaxing effect alone. In the conscious immobilized cat, intragastric administration of himachalol or papaverine (100 mg/kg) produced equal inhibition of carbachol-induced spasm of the intestine, lasting about 2 hr, but himachalol had a faster onset of action. Himachalol was devoid of spasmolytic effect on the bronchial musculature of guinea pig but was 3.3 times more potent than papaverine in antagonizing epinephrine-induced contraction of the guinea pig seminal vesicle. Intravenous injection of himachalol (3–10 mg/kg) in the cat produced a dose-dependent fall in blood pressure and an increased femoral blood flow.

Keyphrases □ *Cedrus deodara*—spasmolytic constituents, pharmacological evaluation of himachalol □ Himachalol—spasmolytic constituent of *C. deodara*, pharmacological evaluation □ Spasmogens—pharmacological evaluation of himachalol □ Medicinal plants—pharmacological evaluation of himachalol from *C. deodara*

During the biological screening of Indian plants for the presence of active substances, it was observed that a 50% ethanol extract from the wood of *Cedrus deodara* (Roxb.) Loud (N.O. Pinaceae)[1] possessed significant antispasmodic activity (1). Detailed studies were undertaken, and the present article describes the identification of the major spasmolytic constituent as the known sesquiterpene himachalol (I) (2, 3) and its pharmacological evaluation.

EXPERIMENTAL

Extraction and Identification of Himachalol—The alcoholic extract of the plant wood (10 kg) was separated into petroleum ether-soluble, chloroform-soluble, water-soluble, and water-insoluble fractions. The petroleum ether-soluble fraction (510 g) showed an enhancement of antispasmodic activity, and it was subjected to chromatography over alumina (10 kg) in hexane solution.

The progressive elution of the column by solvents with increasing polarity and the biological evaluation of the resultant eluates led to the isolation of a fraction (65.3 g), which was eluted with hexane–benzene (1:1). This fraction was dissolved in acetonitrile (80 ml) and allowed to stand in a deep freeze when a crystalline deposit was obtained. It was filtered and recrystallized as colorless rhombuses (23 g), mp 67°. It was found to be homogeneous by TLC and GLC and exhibited antispasmodic activity.

This crystalline substance, $C_{15}H_{26}O$ (M^+ 222), was an unsaturated sesquiterpene alcohol; IR (KBr): 3320, 1130, 1025, 1650, and 862 cm^{-1}; NMR ($CDCl_3$): 0.86, 1.0 (3H, each s, two quaternary CH_3), 1.23 (3H, s, one CH_3 attached to a carbon linked to an oxygen), 1.65 (3H, one vinylic CH_3), and 5.55 (1H, d, J = 5 Hz, one olefinic proton) ppm. On the basis of physical and spectral data, it was identified as himachalol (2, 3).

Acute Toxicity—Mice of either sex, 15–25 g, were divided into groups of 10 each. They were deprived of food for 16 hr and administered graded doses of himachalol and papaverine orally or intraperitoneally. Himachalol was used as a suspension in gum acacia, and papaverine hydrochloride was used as an aqueous solution.

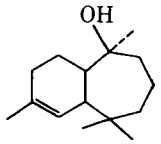
The volume of the oral and intraperitoneal injections never exceeded 0.2 and 0.1 ml/10 g of body weight, respectively. The mortality over the next 72 hr was recorded, and the LD_{50} value was calculated by the probit analysis method (4).

***In Vitro* Spasmolytic Activity**—*Guinea Pig Ileum*—Sections of ileum (4–5 cm long) were suspended in an organ bath of 16-ml capacity, containing aerated Tyrode solution at 35–36°. Acetylcholine chloride (1×10^{-8} g/ml), histamine acid phosphate (2.5×10^{-8} g/ml), serotonin (5×10^{-7} g/ml), nicotine sulfate (5×10^{-7} g/ml), and barium chloride (2×10^{-5} g/ml) were used as spasmogens and left in contact with the tissue for 15–20 sec. Contractions (1:6 magnification; 1 g tension) in response to spasmogen alone and in the presence of various concentrations of himachalol or papaverine were recorded using a frontal writing lever on a smoked drum.

An alcoholic solution of himachalol was added to the bath 1 min before the addition of the spasmogen and was washed out 15–20 sec later with two changes of bath solution at a 1-min interval. The concentration causing 50% reduction of contraction was calculated by plotting the log molar concentration and percent inhibition curve. Papaverine in an aqueous solution was used as the reference standard. The effect of different concentrations of himachalol and papaverine on the cumulative dose–response curve of the ileum to histamine was also studied using the Van Rossum and Van Den Brink (5) technique.

Rabbit Jejunum—Jejunum pieces (5–6 cm long) were set up as described for the guinea pig ileum. The effect of himachalol and papaverine was studied on the tone, motility, and barium chloride (2×10^{-5} g/ml)-induced spasm of the intestine.

Rat Uterus—Virgin rats, 100–230 g, were given stilbestrol (1



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[1] The plant sample was identified by Dr. B. Gupta and Mr. B. N. Mehrotra of the Botany Unit, Central Drug Research Institute, Lucknow, India. A voucher specimen (No. 27) has been preserved in the institute herbarium.

mg/kg sc) on 2 successive days and sacrificed 18 hr after the second injection. One uterine horn was mounted in an organ bath containing 16 ml of aerated de Jalon solution at 31°. The contractions were recorded with a frontal writing lever as in the case of gut preparations. The spasmogen oxytocin[2] (0.06 mU/ml) or serotonin (2.5×10^{-7} g/ml) was added every 5 min, and himachalol was added 1 min before the spasmogen.

Guinea Pig Seminal Vesicle—The preparation was set up in oxygenated Locke solution at 37° as described by Stone and Loew (6). Epinephrine (5×10^{-6} g/ml) was used as the agonist. Himachalol or papaverine was added to the bath 3 min before the addition of epinephrine and washed out 3 min later with two changes of bath solution. The relative potency of himachalol with respect to papaverine was calculated from log dose–response curves for the two agents.

Guinea Pig Tracheal Chain—The tracheal chain, containing 10–14 rings, was set up as described by Castillo and De Beer (7). The effect of himachalol or papaverine on the responses of the tissue to histamine (2.5×10^{-6} g/ml) and acetylcholine (7.5×10^{-6} g/ml) was tested after contact for 1 min with the tissue.

***In Vivo* Spasmolytic Activity**—*GI Propulsion of Charcoal Suspension in Rats*—Experiments were performed in rats, 100–225 g, fasted for 18–24 hr. A standardized charcoal meal (10% charcoal in 2% gum acacia in water) was administered orally to groups of five to six rats each. Himachalol or papaverine (20–100 mg/kg) was administered orally or intraperitoneally before, after, or along with the charcoal meal in a volume maintained at 1 ml/100 g of body weight. Control animals were given normal saline.

The time for which himachalol or papaverine was allowed to act varied from 15 to 60 min, depending on the time of administration in relation to the charcoal meal. Animals were sacrificed by decapitation 30 min after the test meal. The small intestine from the pylorus to the cecum was quickly removed, and the total intestinal length as well as the length through which the charcoal suspension progressed was measured. These measurements were used for calculating the percentage of the total intestinal length through which the charcoal meal traveled.

Effect on Intestinal Movements in Cats—In the first series of experiments, the effect of himachalol on normal intestinal motility was studied in anesthetized (pentobarbital sodium, 35 mg/kg iv) cats. The right femoral vein, left common carotid artery, and trachea were routinely cannulated. The abdomen was opened by a midline incision. One end of an actively motile loop of the small intestine was attached to Jackson's enterograph, and the other end was connected by a thread to an isotonic frontal writing lever. The intestinal movements as well as the carotid blood pressure were recorded on a smoked kymograph. Himachalol or papaverine was administered intravenously in doses ranging from 1 to 10 mg/kg.

The second series of experiments was performed with 12 cats, 3–4 kg. The surgery was performed under ether anesthesia, and the animal was then immobilized with hayatin methiodide (0.3 mg/kg iv) (8). All cut surfaces were infiltrated with 2% procaine to avoid pain. Positive pressure artificial ventilation was given through a tracheal cannula. A small rubber catheter was introduced through the esophagus into the stomach for administration of himachalol or papaverine.

The intestinal movements were recorded as already described. The intestine was brought into a state of contraction by injecting carbachol (1×10^{-5} g/kg) through the cannulated femoral vein. The inhibitory effect of himachalol or papaverine on the carbachol-induced spasm was measured after intragastric administration of 10, 30, and 100 mg/kg of himachalol or papaverine.

Guinea Pig Bronchial Muscle—The method used was based on that of Konzett and Rossler (9). Guinea pigs, 400–650 g, were anesthetized with urethan (1.2 g/kg). The trachea and the jugular vein were cannulated, and artificial ventilation was given at the rate of 72 strokes/min by means of a constant-volume pump delivering 10–15 ml of air/stroke. The air escaping through the side arm of the tracheal cannula operated the float in a manometer (Condon) to record its volume on the kymograph.

Histamine administration (5 μg/kg iv) was spaced at intervals of 15 min before and after himachalol or papaverine administration (1–10 mg/kg). The percent increase or decrease in the height of the excursion of the float indicated the intensity of bronchoconstriction or bronchodilatation, respectively.

[2] Syntocinon.

Table I—Comparison of Spasmolytic Activity of Himachalol with Papaverine on Various Isolated Smooth Muscle Preparations

Tissue	Species	Spasmogen	ED_{50} of Himachalol, μM	Relative Potency (Papaverine = 1)
Ileum	Guinea pig	Acetylcholine	8.1	1.47
		Histamine	3.8	1.74
		Serotonin	3.1	2.30
		Nicotine	2.3	3.60
		Barium	1.1	4.12
Jejunum	Rabbit	Barium	11.7	0.38
Uterus	Rat	Serotonin	52.6	0.12
		Oxytocin	14.8	0.32
Seminal vesicle	Guinea pig	Epinephrine	12.6	3.3

Effect on Cardiovascular System—*Isolated Guinea Pig Auricle*—The preparation was set up according to the method described earlier (10). Himachalol was dissolved in 0.05 ml of alcohol and added to the bath solution to study its effect on the rate, amplitude, and maximal frequency response to electrical stimulation.

Blood Pressure and Blood Flow Studies in Cats—Animals of both sexes, 3–4.5 kg, were anesthetized with chloralose (80 mg/kg iv) or pentobarbital sodium (35 mg/kg iv) and tracheotomized. The right femoral vein was cannulated for injecting drugs. Carotid blood pressure was monitored with a pressure transducer[3]. The left femoral artery was exposed, and a flow transducer with a lumen of 2-mm diameter attached to electromagnetic blood flowmeter[4] was placed around the artery. Both arterial blood flow and blood pressure were recorded[5].

In some cats, blood pressure and contraction of the nictitating membrane elicited by electrical stimulation of the preganglionic cervical sympathetic nerve were also recorded on a kymograph. Responses to epinephrine, acetylcholine, and histamine were recorded before and after himachalol.

RESULTS

Acute Toxicity—The LD_{50} value of himachalol (with 95% confidence limits) in mice by the oral route was 265 mg/kg (182–394), and it was 247 mg/kg (191–323) by the intraperitoneal route. The LD_{50} values for papaverine (with 95% confidence limits) were 129 mg/kg (111–149) and 116 mg/kg (107–126) by the oral and intraperitoneal routes, respectively.

***In Vitro* Spasmolytic Activity**—Himachalol was dissolved in alcohol and added to the bath in a volume of 0.04 ml to make a final solvent concentration of 0.25% in the bath. This amount of alcohol alone had no effect on isolated smooth muscle preparations. Himachalol, like papaverine, in increasing concentrations (4.5×10^{-7}–2.25×10^{-5} *M*) produced a graded antagonism to acetylcholine, histamine, serotonin, nicotine, and barium in the guinea pig ileum preparation. Himachalol was 4.1 times more potent than papaverine in antagonizing the action of barium and 1.47 times more potent than papaverine against acetylcholine. The relative potencies against other spasmogens were between these extremes (Table I).

In one experiment the ED_{50} concentration of himachalol and 2.5×10^{-7} g/ml histamine were added to 20 ml of Tyrode solution and allowed to stand for 10 min. When the organ bath containing the ileum was filled with this mixture, the contraction was only 50% of that obtained with the same concentration of histamine alone. Since a prolonged contact failed to increase antagonism by himachalol, chemical antagonism was considered unlikely.

In rabbit jejunum preparations, however, himachalol (4.5×10^{-6}–1.35×10^{-4} *M*) was only one-third as active as papaverine in antagonizing the spasm induced by barium chloride. Unlike pa-

[3] Statham P23 DC.
[4] Biotronex Laboratory model 610.
[5] On a Grass model P-7 polygraph.

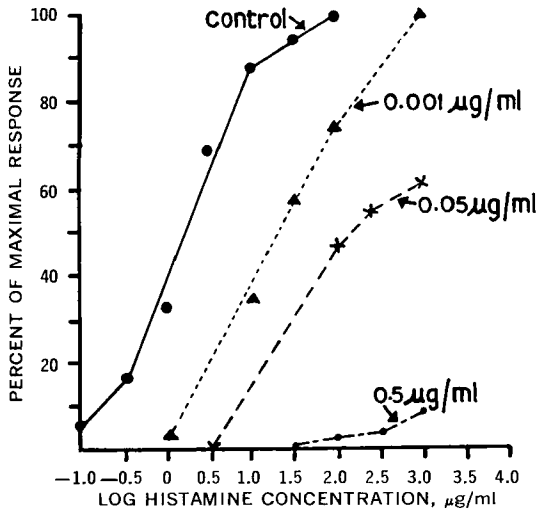

Figure 1—*Cumulative dose–response curve of ileum to histamine in the absence and presence of three concentrations of himachalol.*

paverine, it did not have any direct effect on tone and motility of the jejunum. Similarly, himachalol had a weaker spasmolytic activity against oxytocin and serotonin in the rat uterus. Himachalol (4.5×10^{-6}–4.5×10^{-5} *M*), however, strongly inhibited epinephrine-induced spasm of the guinea pig seminal vesicle, and the antagonism lasted for 6–9 min.

The relative potencies of himachalol and papaverine, assessed by calculating the ED_{50} values in various isolated smooth muscle preparations, are shown in Table I. Himachalol (4.5×10^{-6}–1.35×10^{-4} *M*) tended to cause contraction of the tracheal chain, whereas papaverine in similar concentrations relaxed the tissue. Himachalol at the same time caused a 30–50% reduction in contractions produced by acetylcholine and histamine, whereas papaverine completely abolished the effect of these spasmogens.

Cumulative dose–response studies in the guinea pig ileum showed that, in lower concentrations, both himachalol and papaverine could shift the curve for histamine to the right and that the maximal response to histamine could be obtained by increasing its concentration. In the presence of higher concentrations of either, however, histamine failed to achieve its maximum height of contraction (Figs. 1 and 2).

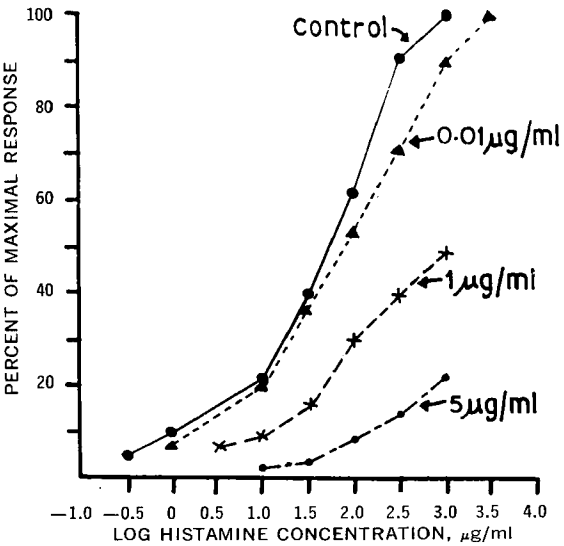

Figure 2—*Cumulative dose–response curve of ileum to histamine and the curves obtained in the presence of three concentrations of papaverine.*

Table II—Effects of Himachalol and Papaverine on Blood Pressure and Intestinal Movements in Cats under Pentobarbital Anesthesia

Compound	Dose, mg/kg iv	Fall in Blood Pressure, mm Hg ± *SE*	Duration of Fall, min ± *SE*	Average Intestinal Relaxation, mm
Himachalol	1	0 (4)[a]	—	9.5 (2)
	3	48 ± 7 (10)	5 ± 0.5	11.7 (4)
	10	65 ± 8 (5)	16 ± 6	27.0 (2)
Papaverine	1	33 ± 4 (4)	5 ± 2	7.0 (2)
	3	50 ± 4 (8)	17 ± 5	11.5 (4)
	10	81 ± 5 (4)	40 ± 5	19.15 (2)

[a] Figures in parentheses indicate number of experiments.

***In Vivo* Spasmolytic Activity**—Oral administration of up to 100 mg/kg himachalol or papaverine had no significant effect on the peristaltic movements in rats. Papaverine, however, significantly inhibited the propulsion of a charcoal meal in rats when given intraperitoneally 30 min before the test meal; himachalol had no such effect.

In anesthetized cats the effect of intravenously administered himachalol and papaverine was compared at doses ranging from 1 to 10 mg/kg on the normal tone and movements of the intestine. Both himachalol and papaverine decreased the tone of the GI musculature and, to a smaller extent, the amplitude of rhythmic contractions. The relaxation lasted for 1–5 min and was generally more marked with himachalol (Table II).

In conscious immobilized cats, intragastric administration of 10 mg/kg himachalol or papaverine had no effect. Higher doses (30–100 mg/kg) reduced the spontaneous motility as well as the spasm induced by carbachol (10 µg/kg). The reduction in both cases was proportional to the dose. Himachalol and papaverine were almost equiactive in inhibiting spontaneous activity, but papaverine caused greater reduction of carbachol-induced spasm (Fig. 3).

Both himachalol and papaverine seemed to have poor absorption from the intestine, since the fall in blood pressure was not evident even at a dose of 100 mg/kg by the intragastric route. There was an appreciable fall in blood pressure in the same preparation when himachalol or papaverine was given intravenously at a dose of 3 mg/kg.

The duration of the spasmolytic action of himachalol and papaverine was also compared. In these animals, carbachol injections were spaced at intervals of 15 min to produce spasm of the intestine. The reduction in the height of contraction was observed for 2 hr following a single intragastric administration of himachalol or papaverine. The results obtained with 100 mg/kg of both agents were plotted in Fig. 4. Himachalol had a faster but somewhat less sustained action than papaverine.

In the Konzett–Rossler preparation, himachalol caused bronchoconstriction in guinea pigs in doses of 1–10 mg/kg iv in 0.05 ml of ethanol. This amount of ethanol alone had no effect on the bronchial musculature. The spasm produced by histamine was not blocked by himachalol in a dose of 3 mg/kg. Similar doses of papaverine caused pronounced relaxation and partially inhibited the effect of histamine.

Both himachalol and papaverine occasionally potentiated the response to histamine. Figure 5 illustrates an experiment in which himachalol-induced bronchoconstriction remained unaffected by prior administration of a dose of pyrilamine maleate (5 mg/kg iv) that completely abolished the histamine effect.

Cardiovascular Effects of Himachalol—In anesthetized cats, himachalol (1–10 mg/kg iv) caused a dose-dependent fall in blood pressure, which slowly returned to its original level in 5–15 min. The hypotensive effect was less than that of an equal dose of papaverine (Table II).

There was a partial antagonism to the pressor effect of epinephrine and to the depressor response to histamine and acetylcholine. The depressor action of himachalol was not modified by pretreatment with pyrilamine maleate (5 mg/kg iv) or atropine sulfate (2 mg/kg iv).

The respiration and contraction of the nictitating membrane elicited by electrical stimulation of the preganglionic sympathetic

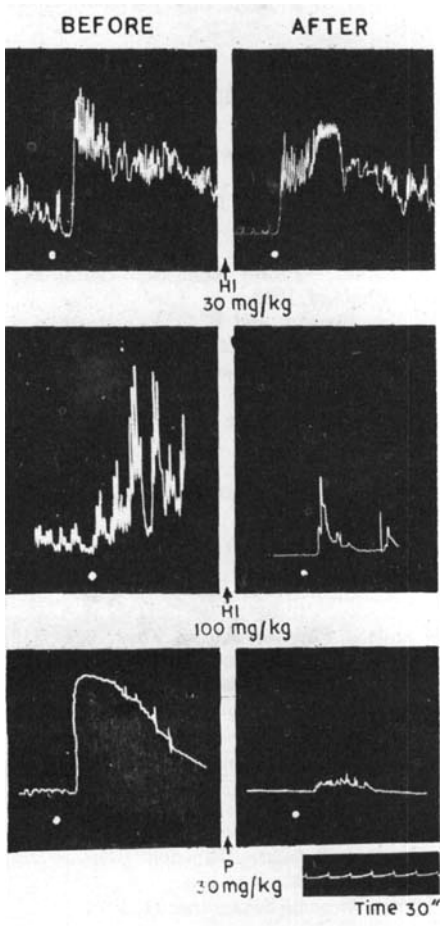

Figure 3—*Kymograph tracing showing the effect of carbachol (10 μg/kg iv) on intestinal movements of an immobilized cat before and after intragastric administration of himachalol (30 mg/kg, upper panel; 100 mg/kg, middle panel) and papaverine (30 mg/kg, lower panel).*

nerve were not affected up to a dose of 10 mg/kg iv. At a dose of 5 mg/kg, himachalol increased the femoral blood flow by 7.7% while lowering the blood pressure by 12%. Papaverine in a similar dose produced hypotension (28.5%) and enhanced the flow by 8.7%. The records from a typical experiment are shown in Fig. 6.

Cardiac rate was not affected by himachalol in these animals. The rate and amplitude of a spontaneously beating auricle were depressed by himachalol at concentrations of 4.5×10^{-6}–4.5×10^{-5} *M*. The maximal frequency response was also inhibited by 9–21%, depending on concentration. Papaverine in equal concentrations depressed the contractility and maximal frequency response to the same extent.

DISCUSSION

In gut preparations, there are abundant distinct receptors with which different agonists like acetylcholine, histamine, serotonin, nicotine, and barium chloride react to elicit a contractile response. While histamine seems to act directly on the muscle cells, others are known to act both directly through specific receptors and indirectly through nerve terminals (11–15).

Since himachalol has been found to inhibit the effect of all of the spasmogens, it appears to exert its action in the sequence of events following an interaction between the spasmogen and the receptor on the muscle cell. Papaverine also shows the same phenomenon. These observations establish the fact that, like papaverine, himachalol has nonspecific spasmolytic activity not only on the smooth muscle preparations of the gut but also in the guinea pig seminal vesicle and rat uterus.

Cumulative dose–response studies (Figs. 1 and 2) seem to indicate that himachalol, like papaverine, is a noncompetitive antagonist at high concentrations and a competitive antagonist at low concentrations. Himachalol is more potent than papaverine in guinea pig ileal and seminal vesicle preparations, whereas it is less effective than papaverine in the rat uterus, rabbit jejunum, and guinea pig tracheal chain. The species and organ variations seem to account for the decrease in potency in the latter preparations.

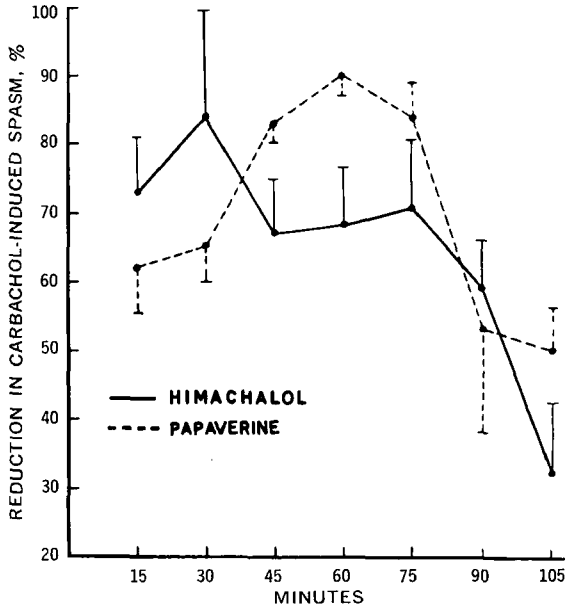

Figure 4—*Effect of himachalol and papaverine (100 mg/kg) on carbachol-induced spasm of the intestine in immobilized conscious cats. Mean values with standard errors obtained from five experiments each have been plotted. Himachalol has a faster but less sustained action.*

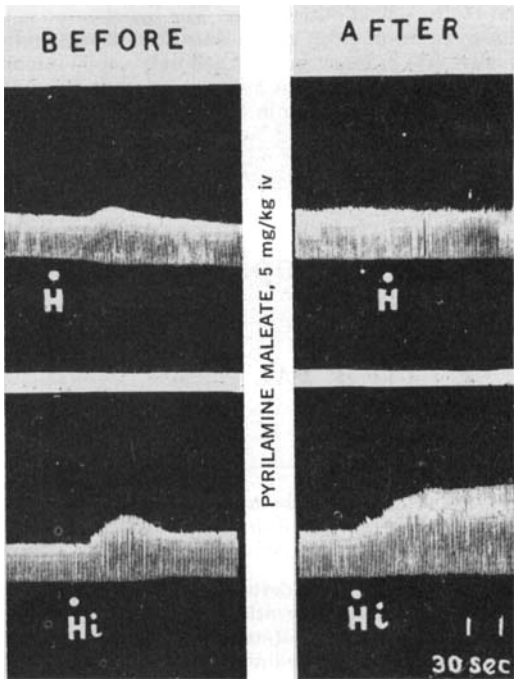

Figure 5—*Kymograph record of the effect of histamine and himachalol on the bronchial resistance in anesthetized guinea pigs. The left-hand panel shows bronchoconstriction caused by histamine (H, 5 μg/kg) and himachalol (Hi, 3 mg/kg). The right-hand panel shows antagonism of histamine (H) by pretreatment with pyrilamine maleate (5 mg/kg iv) and no effect on himachalol (Hi)-induced constriction.*

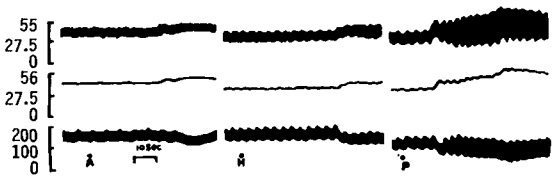

Figure 6—*Polygraph records showing, from below upward, the effects of himachalol and papaverine on blood pressure, mean femoral blood flow, and pulsatile femoral blood flow in an anesthetized cat. Key: A, control response to 0.25 ml of alcohol alone 30 sec after intravenous injection; H, hypotension and increase in the mean and pulsatile femoral blood flow 30 sec after intravenous injection of 5 mg/kg of himachalol dissolved in 0.25 ml of alcohol; and P, marked hypotension and increase in the mean and pulsatile femoral blood flow following injection of papaverine (2 mg/kg iv).*

There is a qualitative difference in the effect of the two compounds on guinea pig bronchial muscle. Himachalol causes constriction of bronchial muscle and papaverine causes relaxation. The constriction caused by himachalol cannot be blocked by pyrilamine, an antihistaminic agent, and, therefore, it seems unlikely that the constriction is due to release of histamine (Fig. 5). It is also unlikely that pulmonary congestion caused by himachalol would bring about bronchoconstriction by diminishing air inflow through bronchial tubes since papaverine causes greater vasodilation but does not cause any increase in bronchial resistance. Bronchoconstriction probably is the result of a directly stimulating action of himachalol in some unknown way.

Himachalol, like papaverine, produces systemic hypotension and peripheral vasodilation. The hypotensive effect is not mediated by cholinergic or histaminic receptor sites since the hypotension remains unaffected following pretreatment with atropine and pyrilamine. A stimulation of β-adrenergic receptors by himachalol can also be ruled out due to the absence of any tachycardia or relaxant effect on the bronchial musculature. The hypotension is unlikely to be due to a cardiac effect either, since there is no significant effect on heart rate in intact animals and only a mild inhibitory effect on the isolated auricle. The hypotension, therefore, appears to result mainly from a decrease in the peripheral resistance due to vasodilation caused by a direct relaxant action on the vascular smooth muscle.

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Possible Antineoplastic Agents I

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Abstract □ A few thalidomide and glutarimide derivatives were synthesized. Several compounds possessed significant antineoplastic activity against Ehrlich ascites carcinoma in Swiss albino mice.

Keyphrases □ Thalidomide derivatives—6-alkyl-2-[3′- or 4′-nitrophthalimido]glutarimides synthesized and screened as possible antineoplastic agents □ Glutarimide derivatives—6-alkyl-3-phenylglutarimides synthesized and screened as possible antineoplastic agents □ Antineoplastic agents, potential—synthesis and screening of thalidomide and glutarimide derivatives

The teratogenic effect of thalidomide (2-phthalimidoglutarimide, I) has been well established in humans and animals (1). To account for this manifestation, Faigle *et al.* (2) isolated a number of suspected metabolites of thalidomide and showed them to be derived from D-glutamic acid, an unnatural amino acid, in place of L-glutamic acid, the natural amino acid. They also pointed out the similarity between *N*-(*O*-carbobenzoxyl)glutamic acid, a metabolite of thalidomide, and folic acid. All of these observations led them to conclude that the metabolites of thalidomide might act as vitamin antagonists or antimetabolites. Since then, a number of claims and counterclaims on the antiglutamine, antifolic, and antivitamin activities of thalidomide have been made, the objective being to utilize thalidomide as a possible antineoplastic agent.