ISSN: 0975-08232

IJPSR (2010), Vol. 1, Issue 2 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received 06 January, 2010; received in revised form 25 January, 2010; accepted 28 January, 2010

SYNTHESIS OF SOME N-HETROCYCLIC ANALOGS OF VASICINE

N. MAHAJAN[*1], K. L. DHAR[2], O. P SURI.[2], K. NEPALI[2], N. KAMRA.[3], A. GARG[4], A. SHARMA [5]

Department of Pharmaceutical Sciences, Lovely School of Pharmaceutical Sciences, Lovely Professional University*[1], Phagwara, Punjab., India

Department of Pharmaceutical Chemistry, ISF college of Pharmacy[2], Moga, 142001, Punjab., India

Department of Pharmaceutical Chemistry, B. N. College of Pharmacy[3], Udaipur, Rajasthan

Bharti Institute of Pharmaceutical Sciences[4], Sri Ganganagar, Rajasthan, India

Department of Chemistry, Lovely School of Chemistry, Lovely Professional University[5], Phagwara, Punjab., India

Keywords:

Vasicine,

RLX,

Antihistamanics

***Correspondence for Author**

Nipun Mahajan

Department of Pharmaceutical Sciences,

Lovely School of Pharmaceutical sciences,

Lovely Professional University, Phagwara, Punjab., India

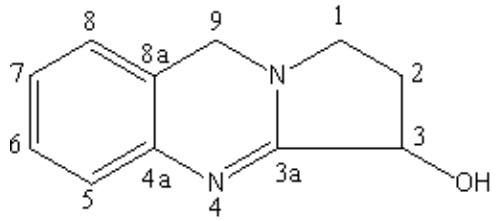
e-mail: npn.mahajan@gmail.com

ABSTRACT

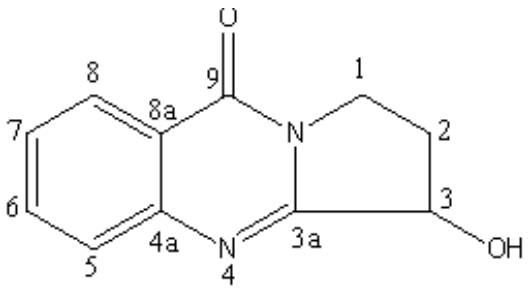
Vasicine is a pyrralazoquinazoline monobasic alkaloid obtained from the Plant *Adhatoda vasica.* In the present paper, the experiment were carried out to synthesis the various analogs of *Vasicine*, where the five membered ring C, was converted to seven membered ring, thus producing 7,8,9,10-Tetrahydroazepino[2,1-b] quinazolin-12(6H)one (RLX), was reported to be 6-10 times more potent than aminophylline as a bronchodilatory agent. A series of new compounds were synthesized, as modification in ring A and in ring B. The resulted compounds were evaluated for the antihistaminic activity to synthesis even more potent compounds.

INTRODUCTION:

Adhatoda vasica Nees. (Acantheace) leaves have been used in Indian system of medicines for many centuries.[1] *Adhatoda vasica* contains two major alkaloids, *vasicine* and *vasicinone.*[2, 3] *Vasicine* is reported to have antihistaminic effects, uterine stimulant activity, moderate hypotensive activity[4], thrombopoeitic activity[5], it relieves from cough and breathlessness[6], its local use gives relief in pyorrhoea and in bleeding gums [7]. Autooxidised product of *vasicine*, *vasicinone* was also reported to cause bronchodilatory effect both in vivo and in vitro, but it was later proved in IIIM Jammu that *vasicinone* is of little activity.



Vasicine

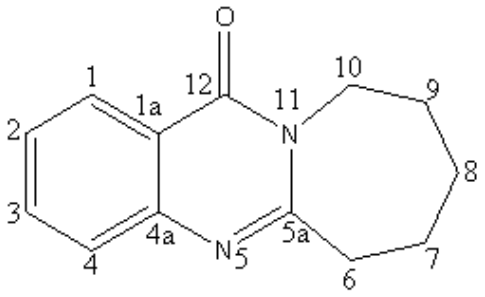


Vasicinone

First, it was reported that configuration at C-3 is *R* but now it has been established that C-3 has S configuration. Therefore, a number of compounds were synthesized to find a relation between the structure and bronchodilatory activity. In first instances, ring A substituted *vasicine* were synthesized which on pharmacological screening revealed no enhancement of activity. Next attention was concentrated on ring B and *deoxyvasicine* was prepared which have little or no bronchodilatory activity.

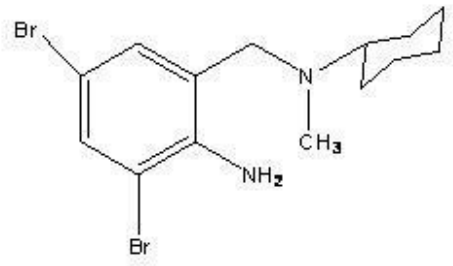
It was interesting to note that with increase in size of ring C activity got enhanced and deoxydihomo "C" *vasicinone* was found to be 6 -10 times more potent than aminophylline.

The seven membered ring C analogue 7, 8, 9, 10-Tetrahydroazepino [2, 1-b] quinazolin-12-(6H)-one, has been synthesized in IIIM Jammu. It showed marked increase in bronchodilatory activity.



7, 8, 9, 10- Tetrahydroazepino[2, 1- b] quinazolin-12-(6H)-one

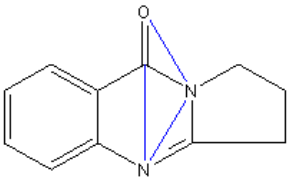
A series of analogues of vasicine were prepared for the bronchodilatory activity. For example Vasicine like compound – Bromhexine:



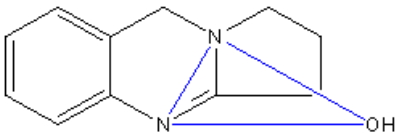
Bromhexine (2- amino- 3, 5- dibromo- N- cyclohexyl- N- methylbenzenemethanamine)

It was concluded that only one of two oxygen function is required i.e. either at C-9 or C-3. So deoxyvasicinone is active and

vasicinone has little or no bronchodilatory activity as compared to vasicine.



DEOXYVASICINONE



VASICINE

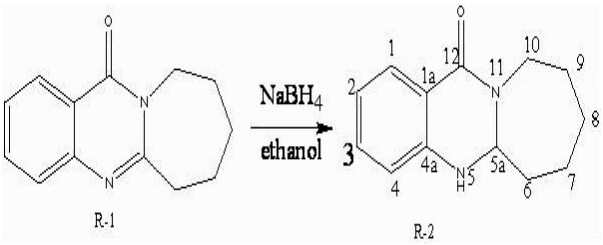
With increase in size of ring C upto 7 carbons bronchodilatory activity get enhanced but thereafter increase in ring size decreases the activity. Structure activity relationship studies lead to synthesis of 7, 8, 9, 10-Tetrahydroazepino [2, 1-b] quinazolin-12(6H) one which was found to be potent bronchodilator.

Pharmacological studies have shown that it does not have any untoward effect.

The objective of the present studies was to carry out the various substitutions at ring A & B to synthesis even more potent bronchodilator with less untoward effects.

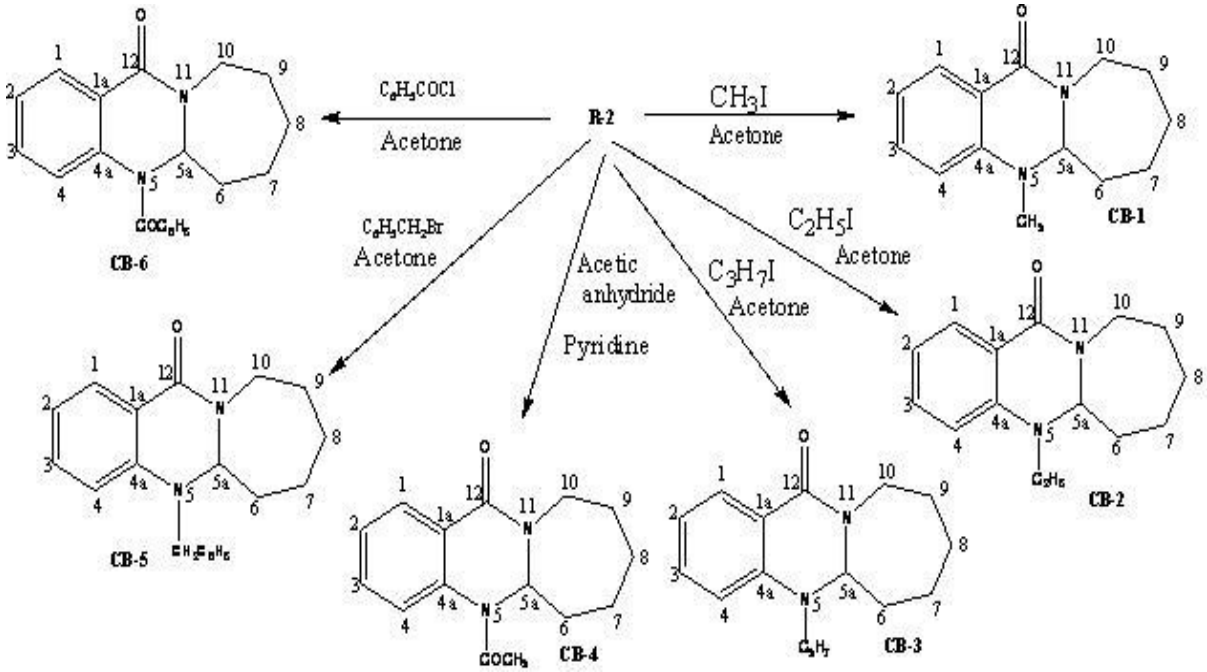
PROPOSED SCHEME:

PART –A



REDUCTION OF C=N

PART –B



N-ALKYL/ALKANOYL/BENZYL SUBSTITUTION

Modification of Ring A

Compound code	R_1	R_2	R_3	R_4
RLX	H	H	H	H
CA-1	H	Br	H	H
CA-2	H	Br	H	Br
CA-3	H	OCH_3	H	OCH_3
CA-4	H	OH	H	OH
CA-5	H	NO_2	H	H
CA-6	H	SO_3H	H	H

Modification of Ring B

COMPOUND CODE	SUSTITUTUION AT N (POSITION 5)
CB-1	CH_3
CB-2	$C2H_5$
CB-3	$C3H_7$
CB-4	$COCH_3$
CB-5	COC_6H_5
CB-6	$CH_2C_6H_5$

EXPERIMENTAL:

Melting points were determined on Buchi 535 M.pt. apparatus. Mass spectra were recorded on JEOL JMS D-300 mass spectrometer at 70 eV and IR spectra on Hitachi 270-30 spectrophotometer. NMR spectra were recorded on Bruker DPX-200 spectrometer. Elemental analytical data have been determined on Carlo Erba, Model 1106, and elemental analyzer. Microwave irradiation was carried out in BPL BMC 900T commercial microwave oven operating at a frequency of 2450 *MHz.*

SPECTRAL DATA OF PRODUCTS:

RLX: 7, 8, 9, 10-Tetrahydroazepino [2, 1-b] quinazolin-12 (6H) one

^{1}H NMR (200 MHz, $CDCl_3$,) δ 08.25 (1H, *d*, J= 8.12 Hz, H- 1), 7.10-7.90 (3H, *m*, H-2, 3, 4), 4.20 (2H, *t*, H-10), 3.15 (2H, *t*, H-6), 1.7- 2.20 (6H, *bs*, H-7, 8, 9).

^{13}C NMR (50 MHz, $CDCl_3$) δ 136.3 (C-1), 127.8 (C-1a), 120.5 (C-2), 129 (C-3), 118(C-4), 137(C-4a), 158.3 (C-5a), 32.8 (C-6), 24.1(C-7),26.4(C-8),28.9(C-9),44.468(C-10),164(C-12).

RLX-H: 5a, 6, 7, 8, 9, 10-Hexahydroazepino [2, 1-b] - quinazoline -12 (5H) one

^{1}H NMR (200 MHz, CDCl3, δ, TMS=0) 7.88 (1H, d, J= 7.79Hz, H-1) 7.26 (1H, dd, J=1.39 and 7.79Hz, H-3), 6.82 (1H, dd, J=1.35 and 7.79Hz, H-2), 6.64 (1H, d, J=7.79Hz, H-4), 4.94 (1H, t H-5a), 4.46 (2H, t H-10), 2.93 (2H, m, H-6), 1.25-2.14 (6H, m, H-7, 8, 9).

^{13}C NMR (50 MHz, CDCl3) δ 135.47 (C-1), 117.82 (C-2), 130.38 (C-3), 116.531 (C-4), 149.31 (C-4a), 72.27 (C-5a), 36.87 (C-6), 25.49 (C-7), 29.89 (C-8), 31.05 (C-9), 44.830 (C-10), 166.36 (C-12), 120.80 (C-1a).

CA-1: 2-Bromo-5a, 6, 7, 8, 9, 10-Hexahydroazepino [2, 1-b]- quinazoline -12 (5H) one

^{1}H NMR (200MHz, CD3OD, δ, TMS=0) 8.4 (1H, d, J=2.20 Hz, H-1), 8.07 (2H, dd, J=2.25 and 7.85 Hz,H-3), 7.6 (1H, d, J=8.64 Hz,H-4), 4.20 (2H, t, H-10), 3.15 (2H, m, H-6), 1.7-2.20 (6H, bs, H-7, 8, 9).

CA-2: 2, 4-Dibromo-5a, 6, 7, 8, 9, 10-Hexahydroazepino [2, 1-b] - quinazoline -12 (5H) one

^{1}H NMR (200MHz, CDCl3, δ, TMS=0) 8.35 (1H, d, J=2.21 Hz, H-1), 8.09 (2H, d, J=2.21 Hz, H-3), 4.30 (2H, t, H-10), 3.01 (2H, t, H-6), 1.7-2.20 (6H, bs, H-7, 8, 9).

CA-3: 2, 4-Dimethoxy-5a, 6, 7, 8, 9, 10-Hexahydroazepino [2, 1-b] - quinazoline -12 (5H) one

^{1}H NMR (200MHz, CDCl3, δ, TMS=0) 7.9 (1H, d, J=2.04, H-1), 7.03 (1H, d, J=2.04, H-3), 4.0 (6H, s, OCH3 -2,4) 4.30 (2H, t, H-10), 3.01 (2H, t, H-6), 1.7-2.20 (6H, bs, H-7, 8, 9).

CA-4: -2, 4-Dihydroxy-5a, 6, 7, 8, 9, 10-Hexahydroazepino [2, 1-b] - quinazoline -12 (5H) one

^{1}H NMR (200MHz, CD3OD, δ, TMS=0) 7.6 (1H, d, J=2.04, H-1), 7.02 (1H, d, J=2.04, H-3), 4.0 (4H, s, OH-2, 4), 4.30 (2H, t, J=3.56 and 4.19 Hz, H-10), 3.01 (2H, t, H-6), 1.7-2.20 (6H, bs, H-7, 8 ,9).

CA-5: 2-Nitro-5a, 6, 7, 8, 9, 10-Hexahydroazepino [2, 1-b] - quinazoline -12 (5H) one

^{1}H NMR (200MHz, CDCl3, δ, TMS=0) 9.01 (1H, d, J=2.58Hz,H-1), 8.45 (2H, dd, J=2.58 and 7.83Hz, H-3), 7.7 (1H, d, J=8.97Hz, H-4), 4.20 (2H, t, H-10), 3.15 (2H, t, H-6) ,1.7-2.20 (6H, bs, H-7, 8, 9).

CA-6: -5a, 6, 7, 8, 9, 10-Hexahydroazepino [2, 1-b] - quinazoline -12 (5H) one -2- sulfonic acid

^{1}H NMR (200MHz, CDCl3, δ, TMS=0) 8.9 (1H, d, J=2.58Hz, H-1), 8.35 (2H, dd, J=2.58 and 7.83Hz, H-3), 7.6 (1H, d, J=8.97, H-4), 4.20 (2H, t, H-10), 3.15 (2H, t, H-6), 1.7-2.20 (6H, bs, H-7, 8, 9).

CB-1: 5-Methyl-5a, 6, 7, 8, 9, 10-Hexahydroazepino [2, 1-b] - quinazoline -12(5H) one

^{1}H NMR (200 MHz, CDCl3) δ 7.98 (1H, d, J= 7.83Hz, H-1), 7.36 (1H, dd, J= 1.49 and 7.83 Hz, H-3), 6.92 (1H, dd, J= 1.35 and 7.85, H-2), 6.63 (1H, d, J= 7.79 Hz, H-4), 4.98 (1H, t, H-5a), 4.46 (2H, t, H-10), 2.94 (3H, s, H-5), 1.25-2.14 (8H, m, H-6, 7, 8, 9).

CB-2: 5- Ethyl-5a, 6, 7, 8, 9, 10-Hexahydroazepino [2, 1-b] - quinazoline -12(5H) one

^{1}H NMR (200 MHz, CDCl3) δ 7.81 (1H, dd, J=7.86 Hz, H-1), 7.34 (1H, dd, J=1.41 and 7.83Hz, H-3), 6.78 (1H, dd, J=1.41 and 7.73 Hz, H-2), 6.63 (1H, d, J=7.79, H-4), 3.40 (2H, q, H-1′), 4.98 (1H, t, H-5a), 4.46 (2H, t, H-10), 1.25-2.14 (11H, m, H-6, 7, 8, 9, 2′).

CB-3: 5-Propyl-5a, 6, 7, 8, 9, 10-Hexahydroazepino [2, 1-b] - quinazoline-12 (5H) one

^{1}H NMR (200MHz, CDCl3, δ, TMS=0) δ 7.78 (1H,d, J= 7.83 Hz, H-1), 7.32 (1H, dd, J=1.42 and 7.87 Hz, H-3), 6.78 (1H, dd, J=1.35 and 7.86 Hz, H-2), 6.61 (1H, d, J=7.79 Hz, H-4) 3.35 (2H, t, J=3.66 and 4.21 Hz, H-1′), 4.85 (1H, t H-5a), 4.46 (2H, t, J=4.58 Hz, H-10), 1.25-2.14 (13H, m, H-6, 7, 8, 9, 2′, 3′).

CB-4: 5-Acetyl-5a, 6, 7, 8, 9, 10-Hexahydroazepino [2, 1-b] - quinazoline -12 (5H) one

^{1}H NMR (200 MHz, CDCl3) δ 8.06 (1H, d, J= 7.86 Hz ,H-1), 7.26-7.63 (1H, m, H-2,3,4), 2.95(H, m,J =6.31 Hz, H-5a, 10b), 4.45 (2H, t, H-10a), 2.21 (3H, s, H-5) 1.25-2.04 (8H, m, H-6, 7, 8, 9).

CB-5: 5-Benzyl-5a, 6, 7, 8, 9, 10-Hexahydroazepino [2, 1-b] - quinazoline -12(5H) one

^{1}H NMR (CDCl3, 200MHz,) δ 7.98 (1H, d, J=7.61Hz, H-1), 7.26-7.34
(6H, m, H-3, 2′, 3′, 4′, 5′, 6′), 6.71 (1H, t, H-2), 6.66 (H-4, d, J=7.60 Hz, H-4), 5.59 (1H, t, H-5a), 1.25-2.14 (8H, m, H-6, 7, 8, 9), 3.01 (1H, m, H-10a), 4.56 (1H, m, H-10b).

CB-6: 5-Benzoyl-5a, 6, 7, 8, 9, 10-Hexahydroazepino [2, 1-b] - quinazoline -12 (5H) one

^{1}H NMR (CDCl3, 200MHz) δ 7.98 (1H, d, J=7.61 Hz, H-1), 7.26-7.34 (6H, m, H-3, 2′, 3′, 4′, 5′, 6′), 6.71 (1H, t, H-2), 6.66 (H-4, d, J=7.60 Hz, H-4), 5.59 (1H, t, H-5a), 1.25-2.14 (8H, m, H-6, 7, 8, 9), 3.01 (1H, m, H-10a), 4.56(1H, m, H-10b).

PHARMACOLOGICAL ACTIVITY:

MATERIAL & METHODS:

Animals - Guinea pig of either sex 300-500g; Drugs- Etofylline, Test compounds; Physiological solution: Krebs-Heneseleit solution (KHS). The prepared compounds were tested for in vivo Bronchodilator activity. The isolated guinea pig tracheal chain preparation was used following the method described by Castillo and de beer[33] except the tracheal ring were opened by severing the cartilage[34]. Inhibition of histamine and acetylcholine induced isotonic contraction in isolated guinea pig tracheal chain preparations were observed. Etofylline was used as standard bronchodilator.

Guinea pigs of either sex, weighing 300-500g, were sacrificed by head below and carotid bleeding. The trachea was dissected out and transferred to a dish containing Krebs-Heneseleit solution (KHS) and cut transversely between the segments of cartilage, so as to give number of rings of trachea. About 7-8 of these were tied to form the chain of approximately 4-5 cm in length. The chain was suspended in 20ml of organ bath containing KHS continuously aerated with 95% oxygen and 5% carbon

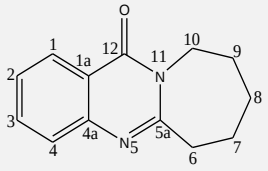
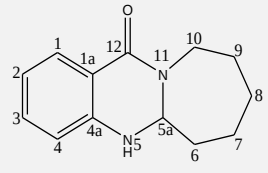
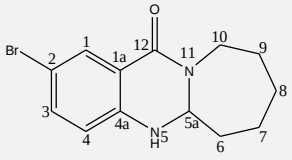
dioxide and maintained at 37 ºC. The composition (m moles) of KHS was NaCl 118, KCl 4.7, $MgSO_4.7H_2O$ 1.2, $CaCl_2$ 2.2 KH_2PO_4 1.2, $NaHCO_3$ 24.9 and (+) – glucose 11.1 .The response was recorded isotonically on a kymograph. The tissue was adjusted to an initial tension of 1.5g and allowed to equilibrate (60-90min) The relaxation effect of the compounds was studied on the tracheal chain precontracted with histamine diphosphate ($1^{X}10$-6 g/ml). The test compounds were tested as percent of relaxing of pre-contracted muscle back to baseline tension (100%) if there was relaxation to slightly below the base line it was also taken as 100% relaxation[10].

RESULTS AND DISCUSSIONS:

7, 8, 9, 10-Tetrahydroazepino [2, 1-b] quinazolin-12-(6H)-one (RLX) was synthesized and various substitutions were made on the Rings A and B. The compounds were purified by repeated crystallization from appropriate solvent. The structures of the compounds were ascertained by spectral data.

The synthesised compounds were evaluated for their *in vitro* bronchodilatory activity using isolated guinea pig tracheal chain. The results are summarized in table 3 and a comparative study has been illustrated with the help of fig. 1. The RLX showed 65% relaxation activity against histamine-induced tracheal contraction as compared to 43% relaxation shown by etofylline. The substitution of one H-atom to N-5 in ring B of RLX leads to RLX-H, which completely blocked the relaxation effect of RLX. Further, the substitution of bromine at R_2 in ring A (CA-1) & methyl substitution at N-5 of ring B (CB-2) showed only slight relaxation activity with 31% & 32% respectively. However, none of the modified compounds showed significant bronchodilatory effect on isolated guinea pig tracheal chain as compared to etofylline, as shown in fig. 1.

Table1: List of products synthesised after modification of Ring A

CODE OF COMPOUND	STRUCTURE OF PRODUCT FORMED	MELTING POINT °C	% YIELD	TIME (HRS)
RLX		97	65	10
RLX-H		168	85	2
CA-1		102	67.1	2

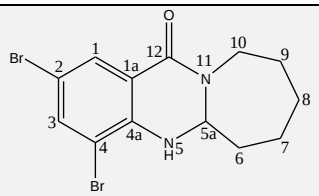
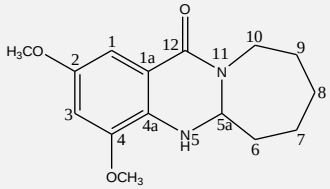
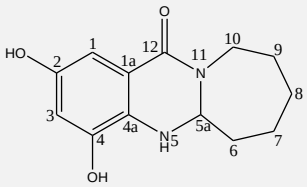
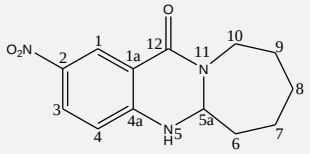
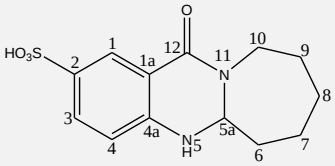
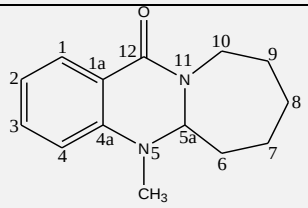
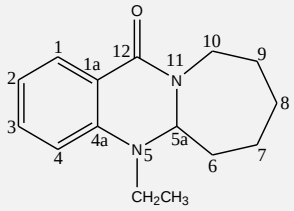
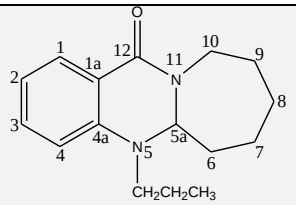
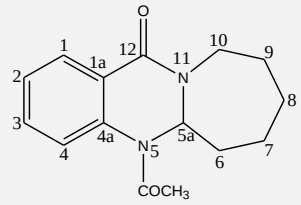
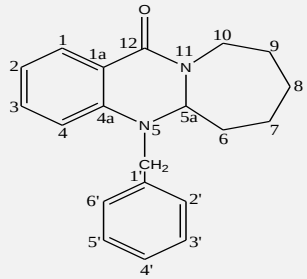
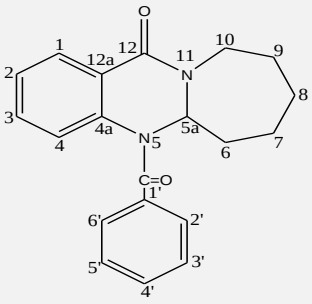
CA-2		163	55.6	3
CA-3		121	95	12
CA-4		260	85.2	12
CA-5		146	49.8	20 min
CA-6		152	51.7	1

Table 2: List of products synthesised after modification of Ring B

CODE OF COMPOUND	STRUCTURE OF PRODUCT FORMED	MELTING POINT °C	% YIELD	TIME (HRS)
CB-1		154	75.1	2
CB-2		168	60	2

CB-3		174	51.9	2
CB-4		170	56	6
CB-5		170	63.5	4
CB-6		180	50.3	2

The synthesized compounds were evaluated for the bronchodilatory activity.

Table 3: Bronchodilator Activity Evaluation of Vasicine Analogues

SAMPLE CODE	BRONCHODILATORY ACTIVITY *
RLX	65%
RLX-H	-
CA-1	31%
CA-2	25%
CA-3	19%

CA-4	1.7%
CA-5	21%
CA-6	13%
CB-1	32%
CB-2	29%
CB-3	21%
CB-4	27%
CB-5	15%
CB-6	19%
Etofylline	43%

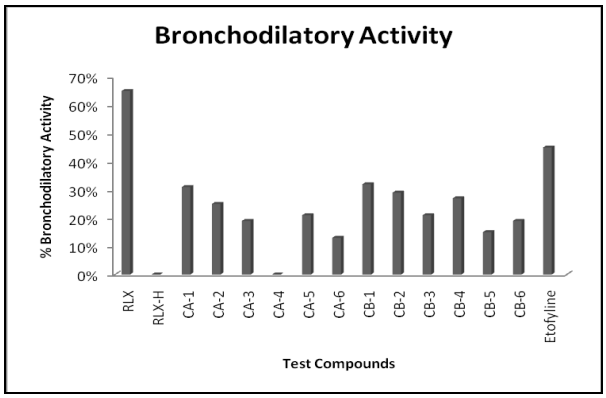


Figure 1: Comparative Bronchodilatory Activity of Test Compounds with Etofylline

CONCLUSION:

It may be concluded that the loss of activity in CA-1 to CA-6 & CB-1 to 6, as well as in the parent compound, may be due to antagonistic effect of the stereoisomers.

ACKNOWLEDGEMENT:

The authors are grateful to S. Kaul, Scientist at IIIM, Jammu for his guidance & support in this research. We are also thankful to Dr. Rao, University Institute of pharmaceutical Sciences, Panjab University, Chandigarh for his support in this project.

REFERENCES:

1. Pandita K: Seasonal variation of alkaloids of *Adhatoda vasica* and detection of glycosides and N-Oxides of vasicine and vasicinone. Planta Med. 1983; 48: 81-82.
2. Atal CK: Chemistry and Pharmacology of vasicine - A new oxytocic and abortifacient. P.58, New Delhi 1980.
3. Chopra RN: Some observations on the pharmacological action and therapeutic properties of *Adhatoda vasica*. Ind. J. Med. Res. 1925; 13: 205.
4. Amin, AH and Mehta DR: A bronchodilator alkaloid (vasicinone) from *Adhatoda vasica* nees. Nature 1959; 184:1317.
5. Atal CK *et al*.: Thrombopoeitic activity of vasicine hydrochloride. Ind. J. Exp. Biol. 1982; 20:704-709.
6. Gogate VM: Dravyagunavignyana, Continental Prakashan, Pune. Ind. J. Physiol. Pharmacol. 1982; 32(2): 120-125.
7. Doshi JJ *et.al*: Effect of Adhatoda *vasica* Massage in Pyorrhoea. Pharmaceutical Biology 1983; 21(4):173-176.

8. Castillo JC and de Beer ED: The tracheal chain. I.A preparation for the study of antispasmodics with particular reference to bronchodilator drugs. J. Pharmacol. Exp. Ther. 1974; 90: 104-112.
9. Akcasu A: The physiologic and pharmacologic characteristics of the tracheal muscle. Arch. Int. Pharmacodyn.Ther. 1959; 122: 201-207.
10. Mahindroo N *et al*: Synthesis and Structure-Activity Relationships of Vasicine Analogues as Bronchodilatory Agents. Medicinal Chemistry Research 2005; 14(6): 347-368.
11. Dhar KL *et al*: Studies on Some Biologically Active Azepinoquinazolines: Part I- An Approach to Potent Bronchodilatory Compounds. Indian J. Chem. 1988; 27B, 937-940.