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MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Vasicine and structurally related quinazolines

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Abstract Natural products are diverse sources of important chemical constituents. Most of the metabolites isolated from them are heterocycles possessing diverse pharmacological actions. Vasicine, a heterocyclic alkaloid possessing a privileged quinazoline nucleus is primarily present in the leaves o the plant *Adhatoda vasica nees*, family Acanthaceae. Vasicine and structurally related quinazolines have been an area of interest for the researchers all around the world. The present review provides an up to date compilation of the alkaloid vasicine, its biosynthesis, synthesis, biological attributes, design of its synthetic analogues along with structurally related quinazolines.

Keywords Quinazoline · Antitussive · Synthesis · Bronchodilator · Alkaloid

Introduction

Natural products are diverse sources of important chemical constituents. Most of the metabolites isolated from them are heterocycles possessing diverse pharmacological actions. Vasicine, a heterocyclic alkaloid possessing a privileged quinazoline nucleus is primarily present in the leaves o the plant *Adhatoda vasica nees*, family Acanthaceae (Atal, 1980). *Adhatoda vasica* is a small, evergreen shrub with a multitude of uses in traditional Ayurveda (Chopra, 1982). The plant is distributed through out India up to an altitude of 1,300 m and mainly found in sub-Himalayan regions; also found in Nepal, Pakistan, Myanmar and Germany (Ali, 1998). Leaves are simple, petiolate, ex-stipulate, 10–20 cm long and 3–10 cm broad, lanceolate having crenate margin, tapering base and an acuminate apex with characteristic odour and bitter taste (Satakopan and Thomas, 1970). The plant, particularly the leaves are used for the treatment of respiratory ailments (Hooper, 1888). Chopra (1982) explored the potential of the plant as antitubercular agent. *Adhatoda vasica* is also believed to have abortifacient properties. It is used in some parts of India to stimulate uterine contractions, thus speeding childbirth (Satakopan and Thomas, 1970). Vasicine was first isolated as a pure alkaloid by Hooper (1888) from the leaves of *Adhatoda vasica*. The chemical investigation of this alkaloid was carried out in detail after it was again isolated by Sen and Ghose (1924). After a lot of contradictions (Ghose *et al.*, 1932; Spath and Nikawitz, 1934; Reynolds and Robinson, 1934; Mooris *et al.*, 1935; Spath and Platzer, 1935; Spath *et al.*, 1935) the structure of vasicine was finally established to be a tricyclic heterocycle (Fig. 1). The pharmacological profile of the plant is mainly attributed to the presence of number of alkaloids among which vasicine is the major one (Shrivastava *et al.*, 2006; Maikhuri and Gangwar, 1965; Dhar *et al.*, 1981). In addition to vasicine, the leaves and roots of *Adhatoda* contain the alkaloids L-vasicinone, deoxyvasicine, maiontone, vasicinolone and vasicinol (Jain and Sharma, 1982).

Detailed pharmacological investigation on bronchodilatory potential of vasicine was carried out by Chopra and Ghosh (1925). It was reported to cause relaxation of

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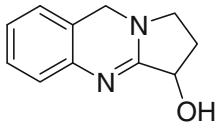
Fig. 1 Structure of vasicine



tracheal muscle at low concentrations and contraction at high concentrations. It also exhibited protection against histamine-induced bronchospasm (Cambridge *et al.*, 1962; Lahiri and Pradhan, 1964).

Another alkaloid vasicinone, an auto-oxidation product of vasicine, was also reported to cause bronchodilatory effect both in vitro and in vivo (Amin *et al.*, 1963). Bhide *et al.* (1974, 1976) reported that vasicinone (Fig. 2) was more potent than vasicine and possessed antiasthmatic activity comparable to that of sodium cromoglycate.

Atal (1980), after an in depth study on pharmacological, toxicological and pharmacokinetic studies, reported that vasicine is highly active as bronchodilatory agent both in vitro and in vivo, and its activity is comparable to theophylline. Vasicine was also highlighted as potential oxytocic, abortifacient agent and uterotonic (Wakhloo *et al.*, 1979; Gupta *et al.*, 1977; Tothill, 1967; Chan *et al.*, 1963; Chandhok *et al.*, 1978).

Biosynthesis of vasicine

Number of theories and supporting evidences has been proposed for the biosynthesis of the quinazoline alkaloids. However, the below-mentioned pathway seems to be the most probable (Groger and Mornas, 1960; Johne and Groger, 1968; Johne *et al.*, 1968; Liljegren, 1968; Leete, 1967; Liljegren, 1971) (Fig. 3).

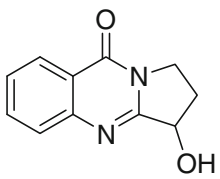
Synthesis

Schopf and Oechler (1936) scheme involved the synthesis of vasicine from 2-aminobenzaldehyde and y-amino-a-hydroxybutyraldehyde (Leonard and Martell, 1960) (Fig. 4).

DL-Vasicine was prepared by Southwick and Casanova (1958) in a six-step sequence starting from *O*-nitrobenzylamine (Mohrle and Gundlach, 1970) (Fig. 5).

Another reaction scheme for improving the yield was proposed (Wasserman and Kuo, 1991) where 2-aminobenzylamine employed acted as a trinucleophile, forming the tricyclic carbon skeleton of vasicine (threefold donor–acceptor process) (Fig. 6).

Fig. 2 Structure of vasicinone



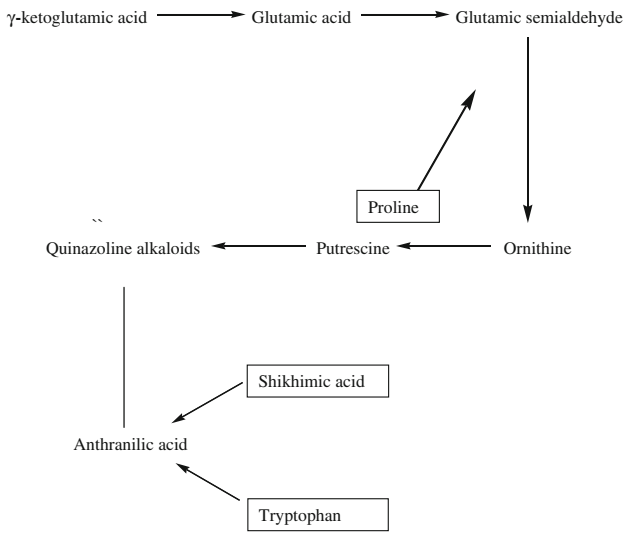


Fig. 3 Biosynthesis of quinazoline alkaloids

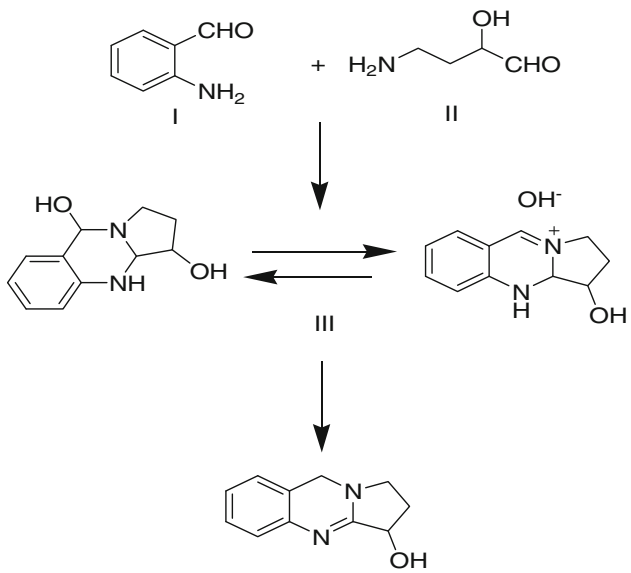


Fig. 4 Schopf and Oechler scheme

Synthesis of vasicinone

Eguchi *et al.* (1996) reported the synthesis of racemic vasicinone from 3-hydroxy-γ-lactam and anthranilic acid (Fig. 7) and the synthesis of (*S*)-vasicinone from L-aspartic acid and anthranilic acid utilizing intramolecular aza-Wittig reaction (Fig. 8).

A convenient route to both (*S*)- and (*R*)-vasicinone was also reported for the asymmetric oxidation of deoxyvasicinone by employing (*R*)- and (*S*)-Davis reagents. The results showed that L-vasicinone has the (*S*)-configuration (Fig. 9).

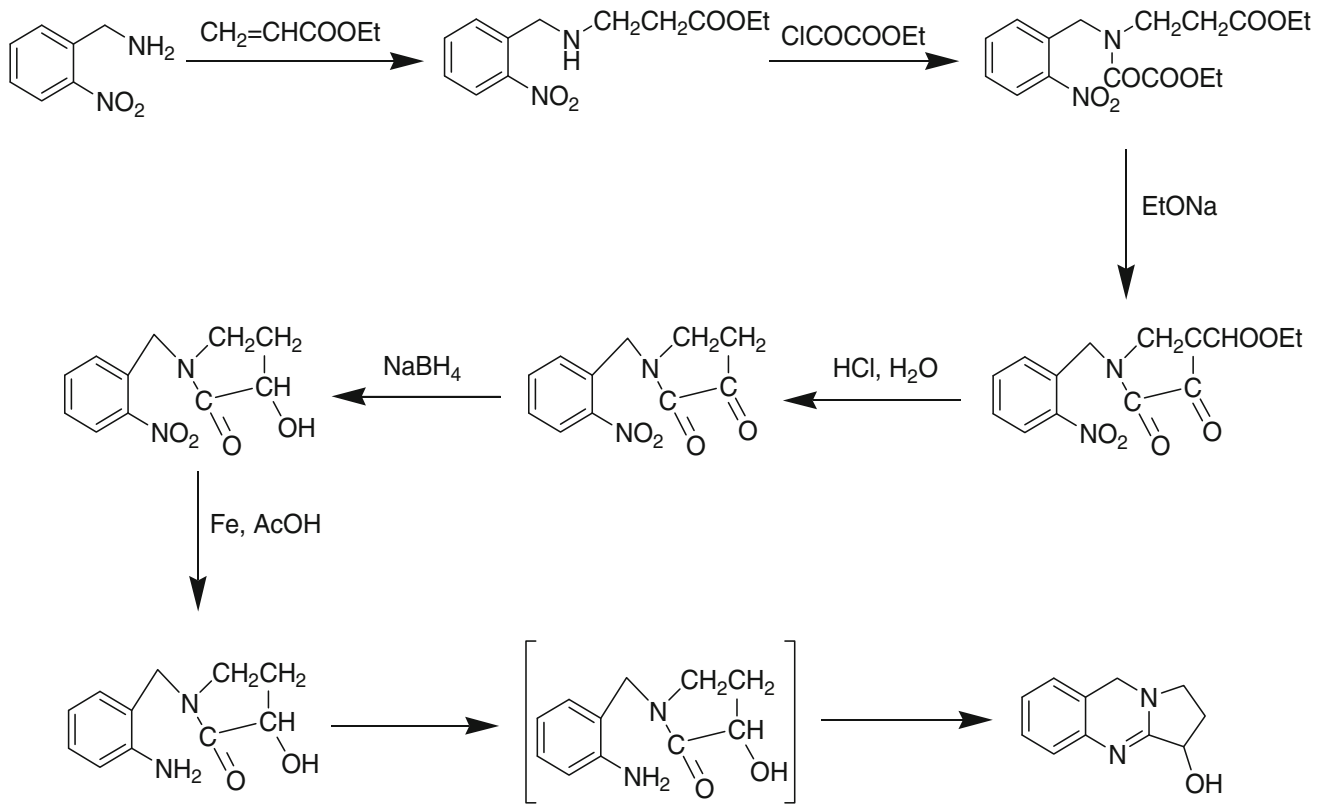


Fig. 5 Synthesis of DL-vasicine

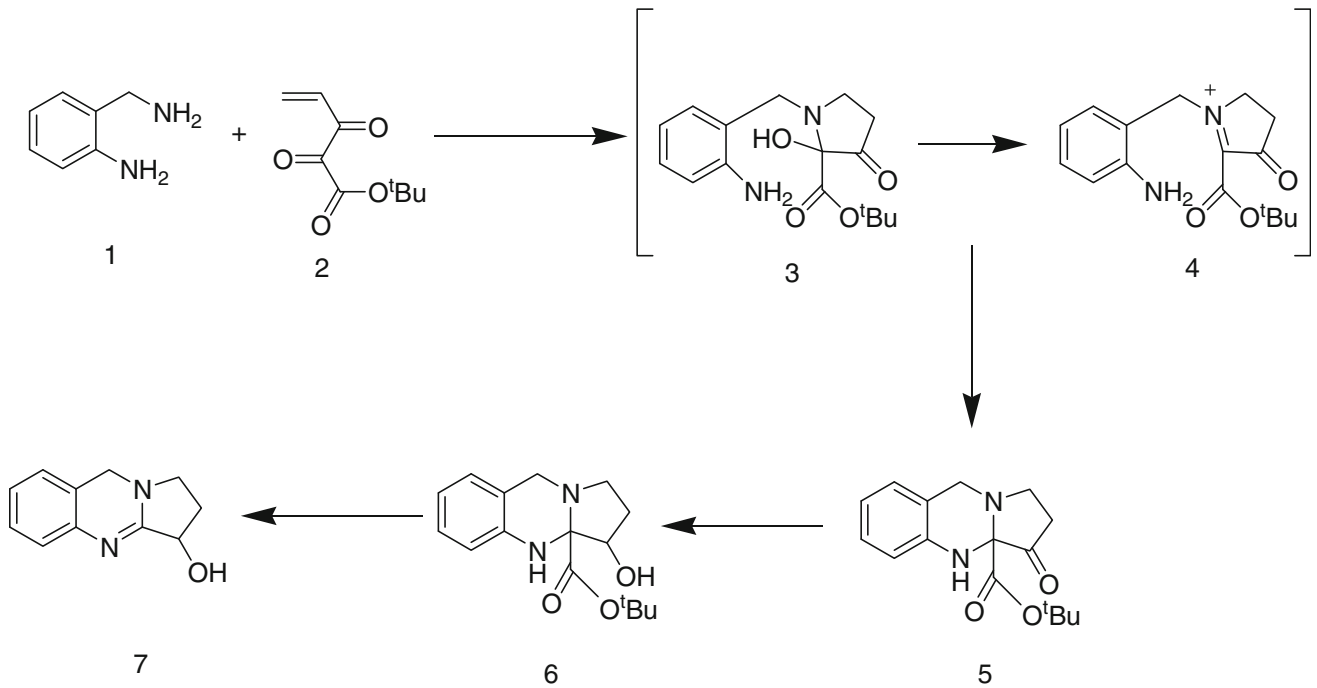


Fig. 6 Synthesis of vasicine

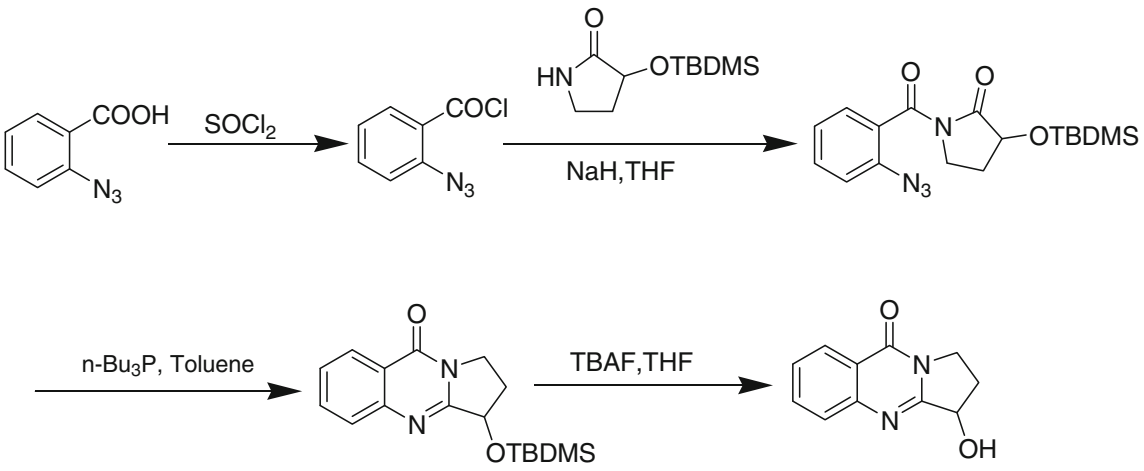


Fig. 7 Synthesis of DL-vasicinone via intramolecular aza-Wittig reactions

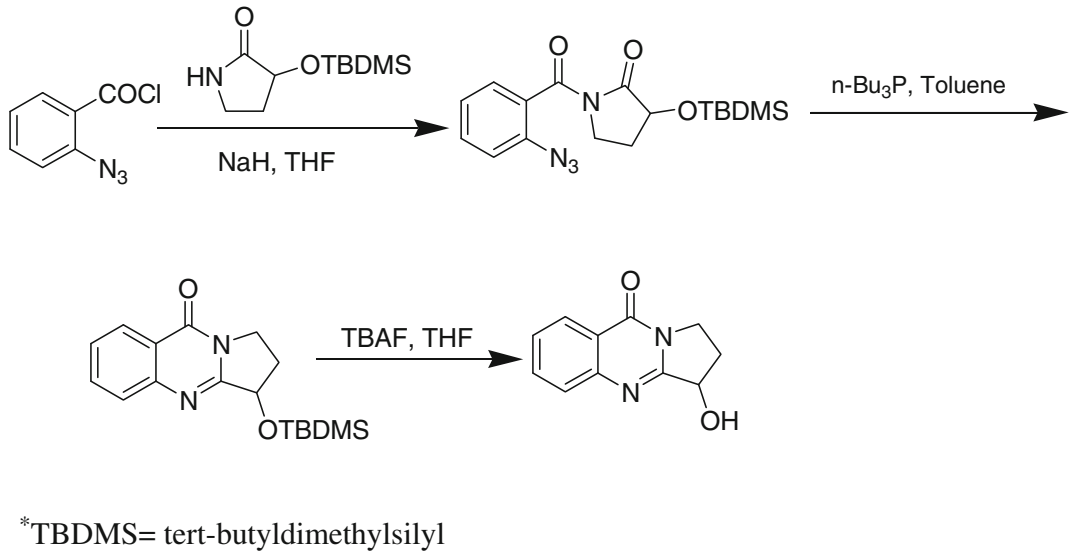
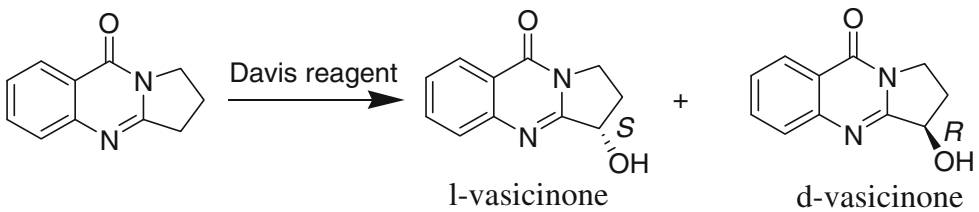


Fig. 8 Synthesis of L-vasicinone via intramolecular aza-Wittig reaction

Fig. 9 Synthesis of vasicinone by Davis reagent



Chemical as well as enzymatic methods for the synthesis of bronchodilatory pyrrolo [2,1-*b*]quinazoline alkaloids (azidoreductive cyclization strategy) utilizing TMSCl-NaI and bakers' yeast in good yields was reported by Kamal *et al.* (2001) (Fig. 10). Vasicinone was synthesized as well as resolved by using different lipases (Fig. 11).

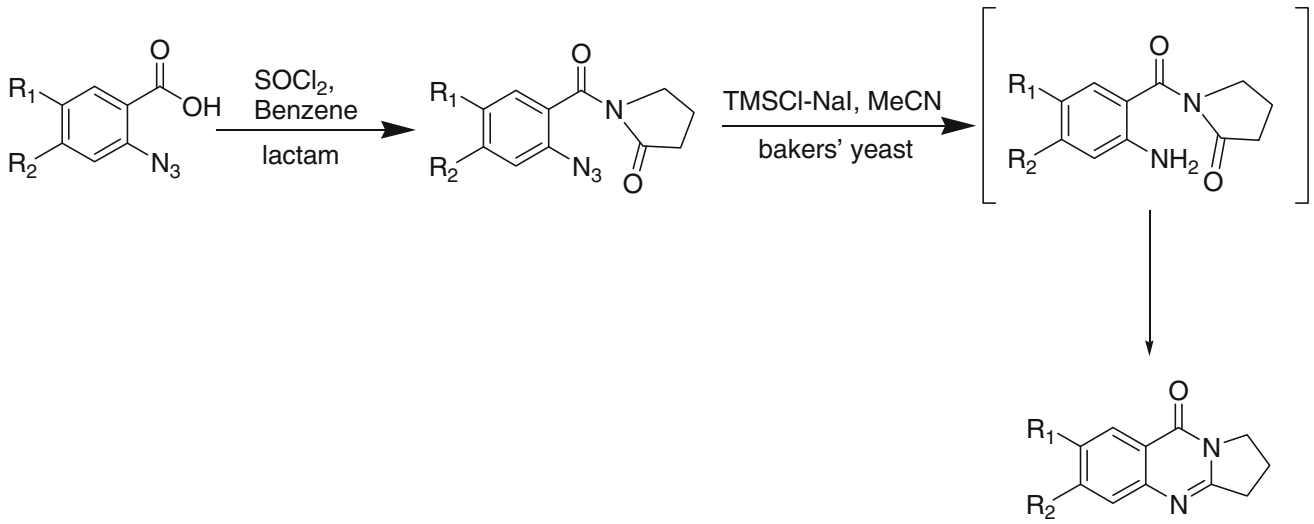


Fig. 10 Synthesis of vasicinone

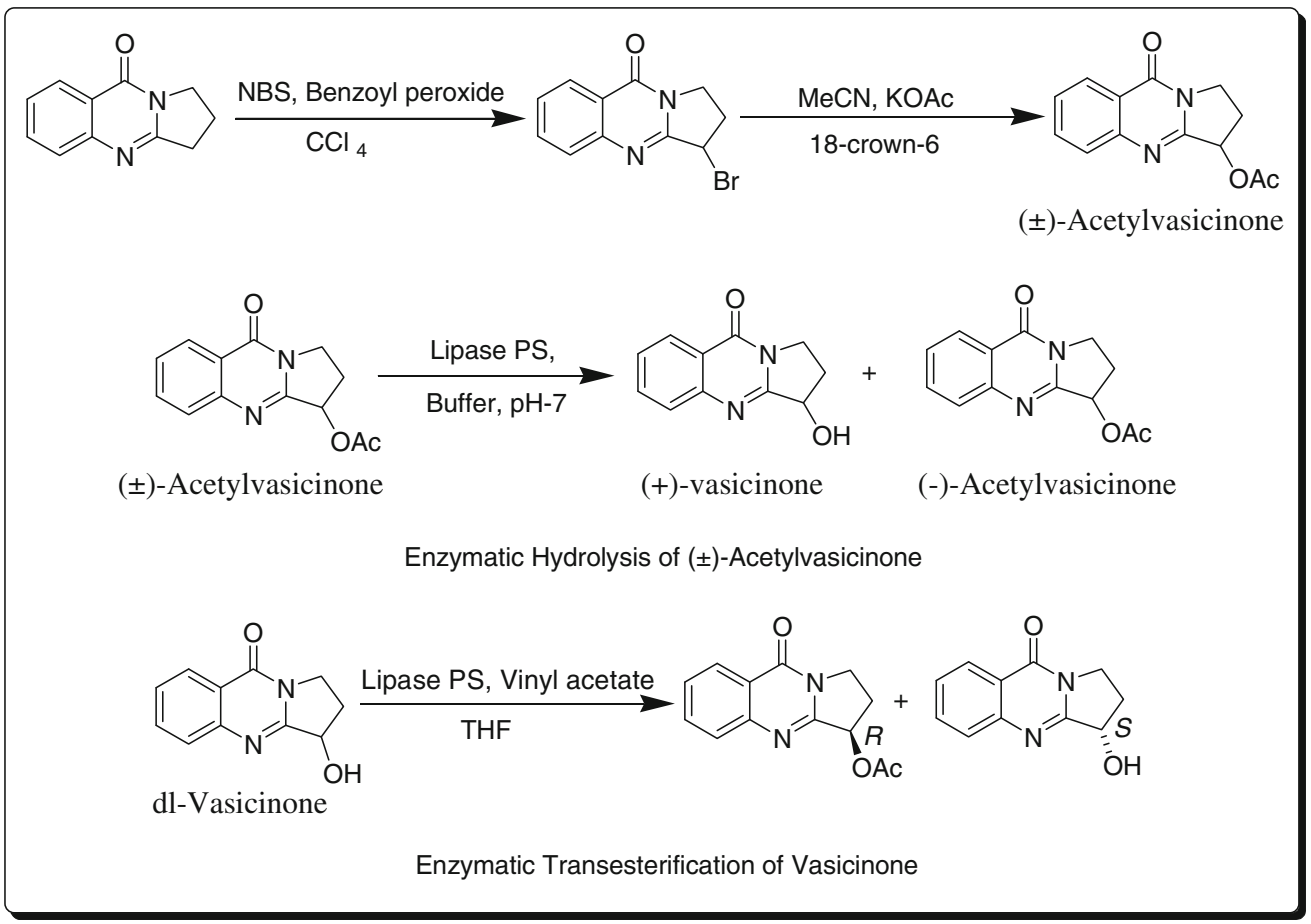
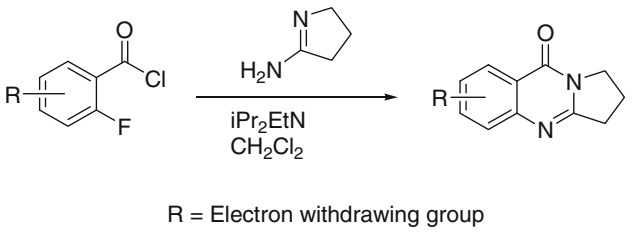


Fig. 11 Chemical and enzymatic method for the synthesis of vasicinone



R = Electron withdrawing group

Fig. 12 Synthesis of deoxyvasicinone

Synthesis of deoxyvasicinone

Deetz *et al.* (2001) presented a one-step method for the preparation of highly functionalized 4(3*H*)-quinazolinone derivatives (Fig. 12).

An efficient procedure for preparation of 4(3*H*)-quinazolinone (deoxyvasicinone) has been established by the reaction of lactam-HCl salts with $POCl_3$ followed by cyclization with methyl anthranilate by Lee *et al.* (2003) (Fig. 13).

Liu *et al.* (2005) reported the syntheses of deoxyvasicinone and 8-hydroxyvasicinone via novel microwave-assisted domino reactions (Fig. 14).

Bowman *et al.* (2007) proposed a method for the synthesis of deoxyvasicinone which involved cyclisation of alkyl radicals (Fig. 15).

Kamal *et al.* (2004) have demonstrated an efficient, cost-effective and ecofriendly protocol for the synthesis fused [2,1-*b*]quinazolinone systems (Fig. 16).

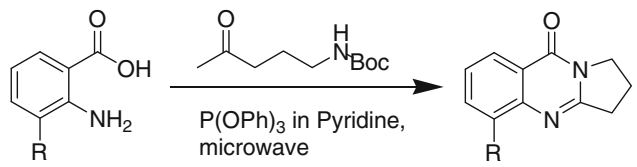
Stereochemistry and nomenclature of vasicine

After lot of contradictions, the configuration at C-3 has been found to 3*S* (Joshi *et al.*, 1994; 1996) (Fig. 17).

Earlier vasicine was numbered according to fused pyrrolo quinazoline system (Manske and Holmes, 1972–1976; 1953) (Fig. 18). This numbering system was later changed (Fig. 19). At present, the IUPAC name which is being used is shown below (Fig. 20).

Semisynthetic derivatives of vasicine

Bromhexine, a semisynthetic derivative of the alkaloid vasicine and its metabolite are widely used mucolytic



Deoxyvasicinone (n=1, R=H)

8-Hydroxydeoxyvasicinone (n=1, R=OH)

Fig. 14 Synthesis of deoxyvasicinone

agents (Grange and Snell, 1996). Ambroxol is the principal metabolite of Bromhexine (Fig. 21).

Vasicine when investigated was not found to inhibit the growth of *Mycobacterium tuberculosis* (Chopra and Ghosh, 1925). However, distillate from the plant exhibit in vitro antimycobacterial effects (Gupta and Chopra, 1954) which indicated that vasicine might not be the active constituent.

Inhibitory effects of benzylamines on mycobacteria were reported by Meindl *et al.* (1984). Piacenza (1966) reported the antitubercular effect of Bromhexine given to patients as an expectorant.

Bromhexine exhibited pH-dependent growth inhibition of strains of *M. tuberculosis* in a study conducted by Medical Research Council of Ireland.

Grange and Snell (1996) reported the inhibitory effects of Ambroxol, which is a principal metabolite of the Bromhexine for the first time.

Extraction of vasicine

An improved process for the isolation of vasicine from the *Adhatoda vasica*, comprises of the below-mentioned steps (Chattopadhyay *et al.*, 2003):

a. Preparation of alcoholic extract of dried and pulverized leaves at an ambient temperature.
b. Concentrating the alcoholic extract to obtain a concentrated extract.
c. Treating and stirring the extract with an aqueous organic acid (preferably citric acid) for 2–24 h.
d. Extracting the acid solution with an organic solvent (preferably dichloromethane).

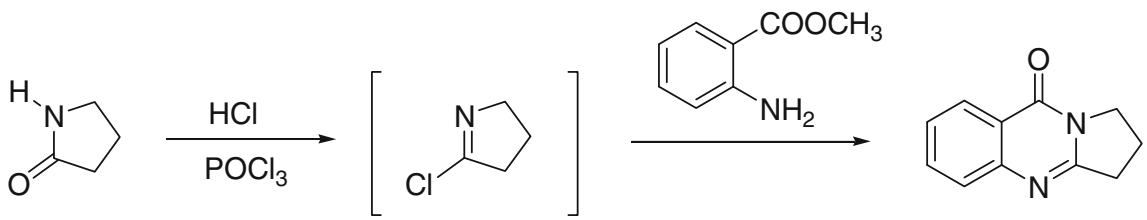
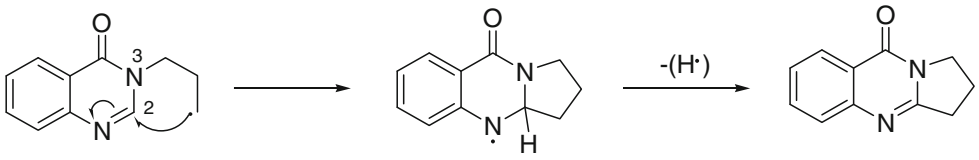


Fig. 13 Synthesis of deoxyvasicinone

Fig. 15 Synthesis of deoxyvasicinone



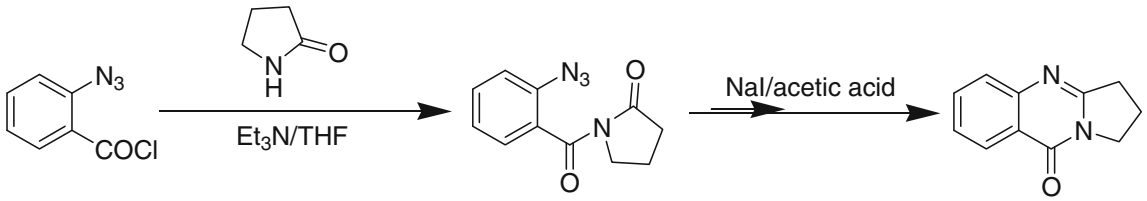
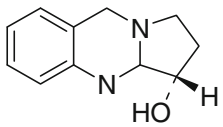


Fig. 16 Synthesis of deoxyvasicinone

Fig. 17 Structure of vasicine with S configuration at C-3



(-)-Vasicine

Fig. 18 Structure of vasicine

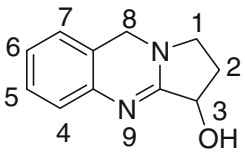


Fig. 19 Structure of vasicine

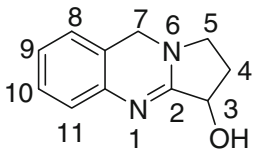
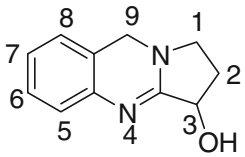


Fig. 20 1,2,3, 9-tetrahydropyrrolo [2,1-*b*]quinazolin-3-ol



e. Separating the organic layer and aqueous acidic layer.
f. Basifying the aqueous acidic solution with a base (preferably aqueous ammonia).
g. Extracting the basified solution with an organic solvent (preferably chloroform).
h. Separating the organic layer, drying and filtering.
i. Evaporating the organic layer to obtain an amorphous residue.
j. Treating the amorphous residue with an organic solvent or mixture of organic solvents to obtain vasicine (preferred solvent used is a mixture of petroleum ether–acetone in the ratio 1:1 to 2:1).

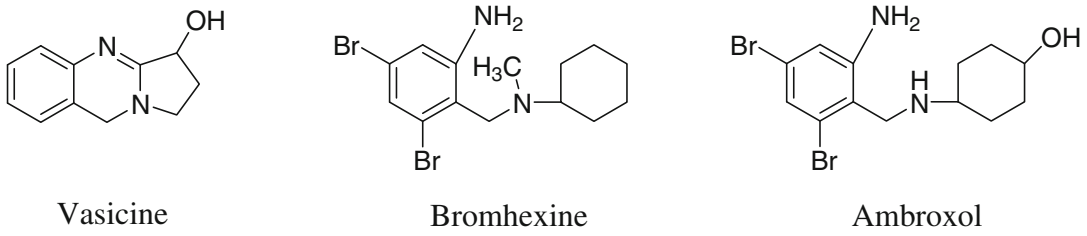
The vasicine obtained by this method has a minimum purity of 80%. The earlier reported procedures had following disadvantages: The procedure reported by Atal (1980) involved following steps:

a. Extracting the leaves of the plant with 95% alcohol. Preparation of alcoholic extract of leaves of the plant.
b. Treating the concentrated alcoholic extract with aqueous 2% H_2SO_4.
c. Basifying the aqueous acidic solution with ammonia and extracting with chloroform.
d. Concentrating the chloroform layer and the residue again dissolved in aqueous 2% H_2SO_4.
e. Repeating the process of basification with ammonia, followed by extraction with chloroform.

The drawback of this procedure is that it involves use of strong mineral acid like H_2SO_4 for extraction which result in considerable degradation of vasicine, which is further aggravated by repeating the process of same mineral acid treatment twice.

Mehta *et al.* (1963) also reported a procedure which involved following steps:

a. The leaves were refluxed with 90% alcohol.
b. The solvent was evaporated and the alcoholic extract obtained was dissolved with hot distilled water.
c. The aqueous extract was filtered.
d. Filtrate was extracted with chloroform to remove the colouring matters and then made alkaline with 5% caustic soda, and again extracted with chloroform.
e. The combined chloroform extracts were extracted with 5% hydrochloric acid, and then acidic solution was made alkaline with ammonia and again extracted with chloroform.



Vasicine Bromhexine Ambroxol

Fig. 21 Vasicine and its semisynthetic derivatives

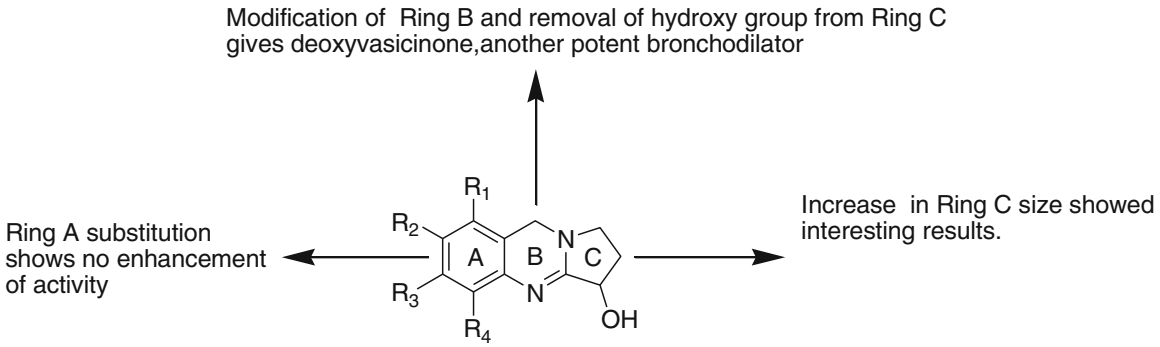
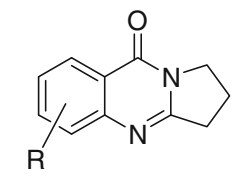


Fig. 22 SAR of vasicine

Fig. 23 Ring A of deoxyvasicinone substituted with alkoxy group



R= alkoxy

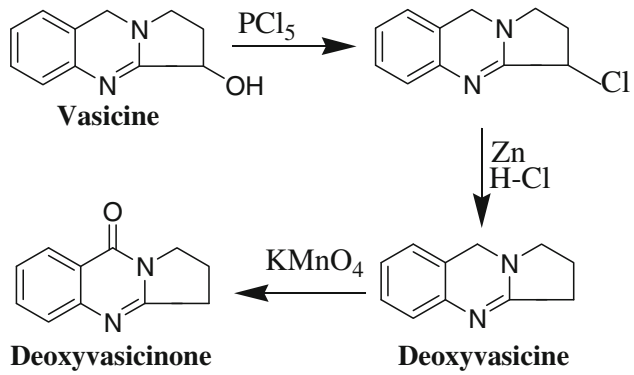


Fig. 24 Synthesis of deoxyvasicinone

f. After repeating the process twice the final chloroform extract was concentrated to give a crude total alkaloid from which vasicine was isolated as vasicine hydrochloride with 2 g yield.

The first drawback of the above process includes the extraction of the alcohol extract with hot water, which further has two drawbacks:

(a) Vasicine could not be quantitatively extracted from its aqueous solution.
(b) Hot water extraction will convert vasicine into its auto-oxidation product vasicinone.

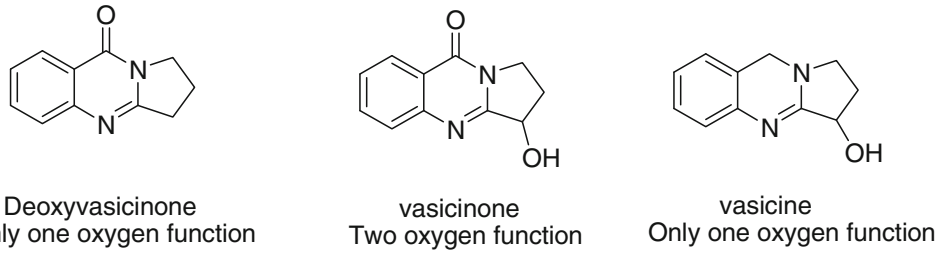
Medicinal attributes

Vasicine has been reported to produce bronchodilation (Chopra and Ghosh, 1925), bronchoconstriction (Amin *et al.*, 1963), relaxation of tracheal muscle at low concentration, contraction at high concentration and protection against histamine-induced bronchospasm (Cambridge *et al.*, 1962), slight relaxation of tracheal chain and protection against histamine-induced brochospasm in guinea pigs (Lahiri and Pradhan, 1964). Vasicine possesses uterotonic stimulating and oxytocic activity and causes abortifacient effects by the release of prostaglandins under the influence of oestrogens (Gupta *et al.*, 1978).

Bronchodilatory action of vasicine

Vasicine was found to have bronchodilatory activity both in vitro and in vivo, its activity was comparable to

Fig. 25 Structures of deoxyvasicinone, vasicinone, vasicine



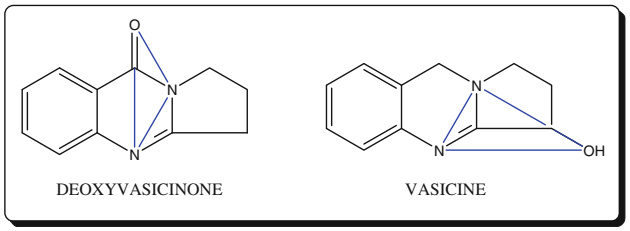


Fig. 26 The N–N–O triangle

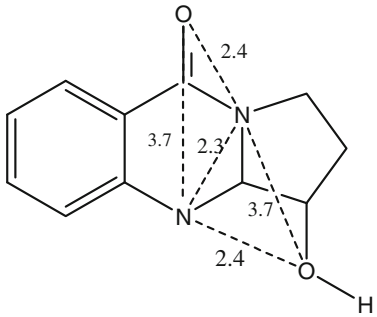


Fig. 27 Bond distance (Å) in N–N–O triangles

Fig. 28 Deoxyvasicinone with $n = 1$–4

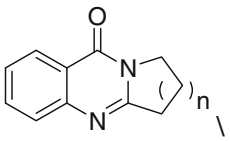
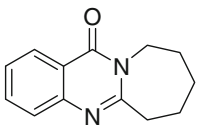


Fig. 29 Structure of dihomo analogue



theophylline while vasicinone showed bronchodilatory activity in vitro and in vivo. The two alkaloids in combination showed more bronchodilatory activity both in vivo and in vitro. Relaxant effect of vasicine, vasicinone and theophylline was seen only when the tracheal chain was in contracted state. Vasicine showed inhibition of histamine-induced bronchoconstriction in anaesthetized guinea pigs (Collier *et al.*, 1960).

Antioxidant and anti-inflammatory activity of vasicine

In a study to investigate antioxidant and anti-inflammatory activity of alkaloid (Srinivasarao *et al.*, 2006), significant decrease in lipid peroxidation and significant increase in antioxidants superoxide dismutase, catalase, glutathione peroxidase and reduced glutathione was observed with vasicine.

Abortifacient and oxytocic activity

Vasicine possesses uterotonic activity, oxytocic and abortifacient activity (Gupta *et al.*, 1977). The uterotonic activity of vasicine was investigated on the uteri of different species of animals and in different hormonal states and was found to be similar to oxytocin and methyl ergometerine. The uterotonic effect was influenced by the degree of priming of the uterus by oestrogens which are known to enhance the synthesis of prostaglandins in the uterus (Atal, 1980).

Vasicine in oestradiol primed guinea pigs showed abortifacient effect. The effect was enhanced in oestradiol pretreatment and reduced after pretreatment with indomethacin and aspirine. Thus it was clear that the abortifacient effect of vasicine was mediated through the release of prostaglandins.

Seasonal variation of vasicine

Pandita *et al.* (1983) reported that the plant *Adhatoda vasica* was rich in its alkaloidal content in the months of August–October. The total alkaloid content was about 2% out of which vasicine was about 95%.

Seasonal variation of vasicine in *Adhatoda vasica* and *A. beddomie* has been reported by Bagchi *et al.* (2003). And the study revealed that vasicine content in both the species peaked during of March and September coinciding with flowering time with higher concentration in March.

SAR studies on vasicine

The detailed SAR has been represented diagrammatically (Fig. 22).

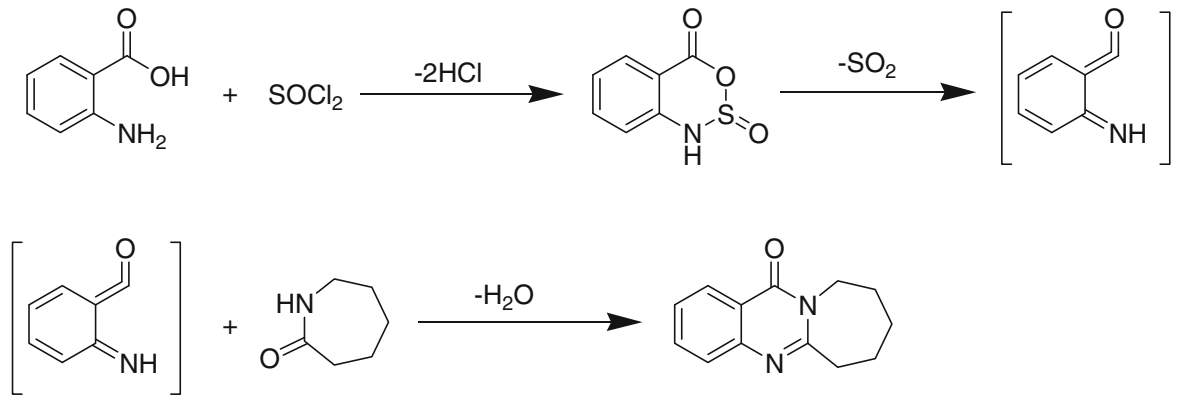


Fig. 30 Synthesis of the seven-membered analogue

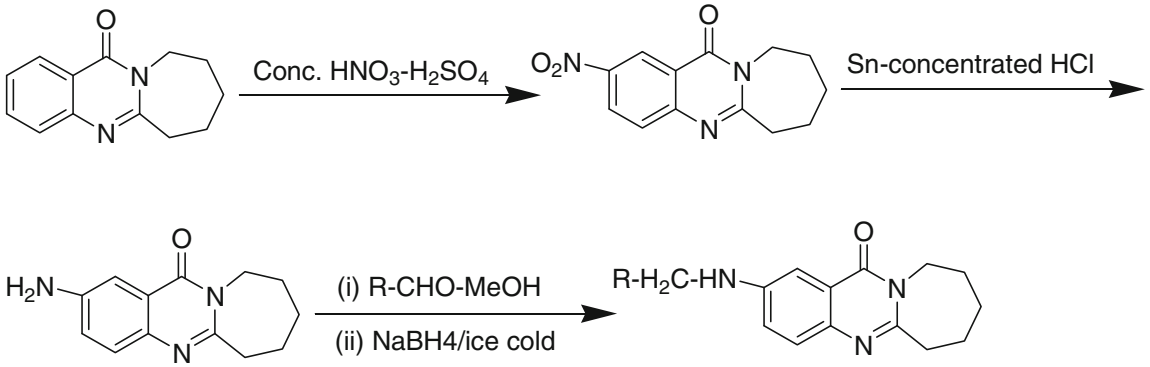
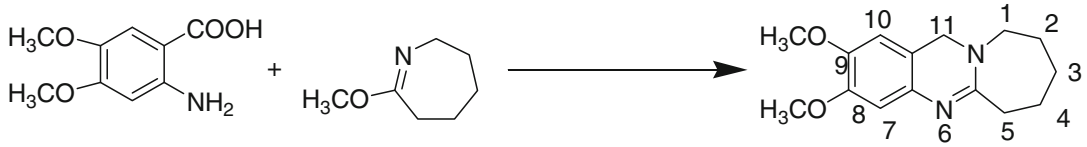


Fig. 31 Synthesis of benzylamine derivatives of the seven membered analogue



*The numbering given by the authors does not correspond to the one reported earlier.

Fig. 32 Synthesis of 8,9-dimethoxy derivative

Ring A modification

SAR studies on vasicine revealed no enhancement of activity on different substitutions on Ring A (Atal *et al.*, 1979) (Fig. 23).

Ring B modification

Deoxyvasicinone having a carbonyl function at C-9 was synthesized (Fig. 24). The molecule showed significant bronchodilatory potential.

Detailed investigation on the deoxyvasicinone and comparison with vasicinone (oxidative product of vasicine having two oxygen functions at C-3 and C-9) lead to the conclusion that only one oxygen function is required for bronchodilatory activity as vasicinone was found to be devoid of any bronchodilatory effects (Fig. 25). This was proved by scientists of IIIM (CSIR), Jammu. Though there are contradictory reports about the potential of vasicinone as Bronchodilator.

Thus only one oxygen function and the N–N–O triangle (Fig. 26) was proposed to be the necessary condition which is present in both deoxyvasicinone and vasicine. Both deoxyvasicnone and vasicine are having identical triangles with same bond length are formed (Fig. 27).

Ring C modification

Ring C plays a significant role in the enhancement of the bronchodilator potential of the molecule (Fig. 28).

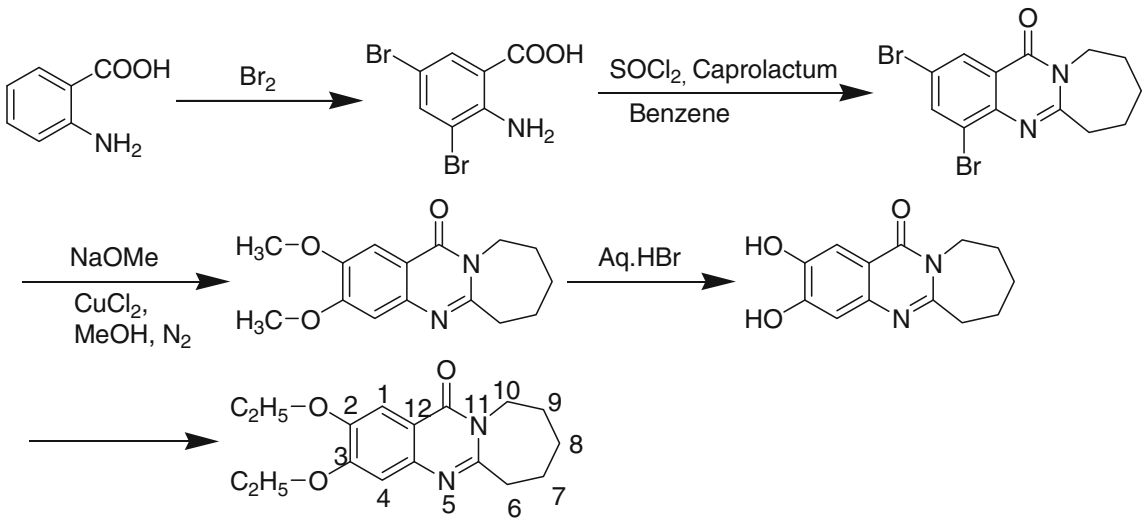


Fig. 33 Synthesis of 2,3-diethoxy derivative

Fig. 34 Synthesis of 2,3-diethoxy-6,7,8,9,10,12-hexahydroazepino [2,1-*b*]quinazolin-12-one

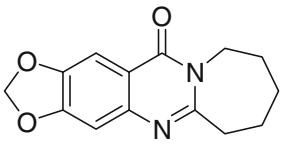


Fig. 35 Dibromo derivative of deoxyvasicinone

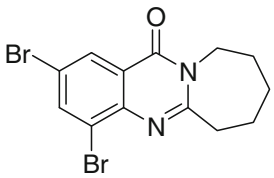
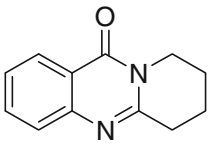


Fig. 36 Mackinazolinone



Molecules with $n = 1$–4 were synthesized. A remarkable increase in the bronchodilatory potential activity was observed when the size of the ring was increased till $n = 3$, i.e. the dihomo analogue. In fact the dihomo analogue was found to be the most potent bronchodilator of the series. The molecule with $n = 4$ showed decrease in activity which led to the conclusion that n should not be greater than 3. The seven-membered analogue was found to be 6–10 times more potent than aminophyline on dose basis.

Dihomo analogue of deoxyvasicinone

The seven-membered ring derivative (Fig. 29) was synthesized by Sharma *et al.* (1993) of IIIM, Jammu (Fig. 30).

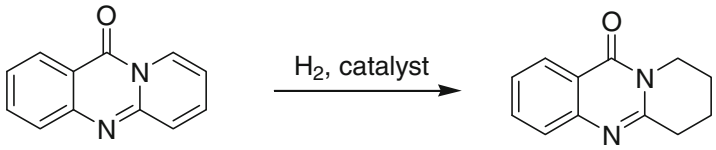
Pharmacological evaluation deoxydihomo "C" vasicinone

Pharmacological investigations showed that the deoxydihomo "C" vasicinone possessed potent bronchodilatory activity which was proved by number of in vivo and in vitro experiments. Isolated guinea pig tracheal chain was employed for the invitro experiments. Its bronchodilatory activity was recorded against both spasmogens and antigen-induced bronchoconstriction in the sensitized tissues. Mediation of the effect by direct action on the smooth muscles like aminophylline and not through the adrenoreceptor stimulation was the mechanism which was revealed after lot of study. Toxicological studies were also satisfactory (Nepali *et al.*, 2010).

Further research carried on this dihomo analogue

Jindal *et al.* (2002) synthesized various derivatives of deoxydihomo vasicinone with decreased activity than the lead) (Fig. 31) and also reported 8,9-dimethoxy derivative to have significant bronchodilatory potential (Fig. 32). A group of scientists from R.R.L., Jammu led by Zabir (2005) again synthesized (Fig. 33) and evaluated some novel quinazoline derivative for bronchodilatory activity and reported that 2,4-diethoxy-6,7,8,9,10,12-hexahydroazepino[2,1-*b*]quinazolin-12-one possesses marked bronchodilator activity evaluated on contracted trachea or constricted tracheo-bronchial tree. On intestinal smooth muscle too it showed relaxant effect. Tracheal relaxant effect was not found to be mediated through β-adrenoceptors. Cumulative dose–response study with acetylcholine and histamine indicated for its non-specific direct effect on smooth muscles. It was found to be more potent than theophylline

Fig. 37 Synthesis of mackinazolinone



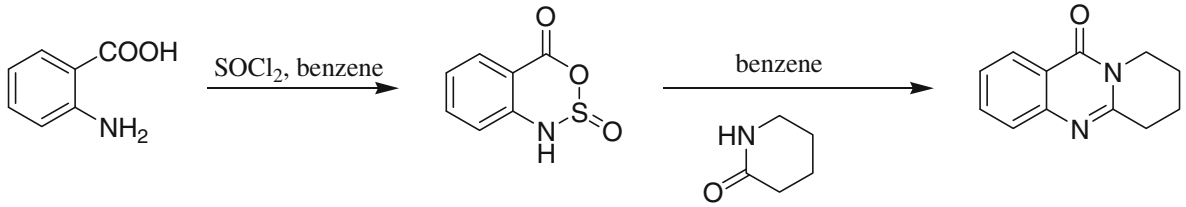
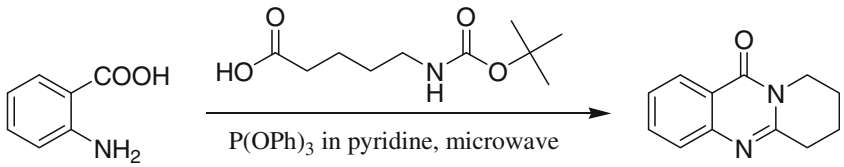


Fig. 38 Synthesis of mackinazolinone

Fig. 39 Synthesis of mackinazolinone



and less to that of salbutamol on dose basis. It was found devoid of anti-allergic activity. It was also found to be free from any adverse effect. Mahindroo *et al.* (2005) reported a derivative of deoxydihomo analogue having significant bronchodilatory potential (Fig. 34) Nepali *et al.* (2010) while exploring the antitussive effect of dihomo deoxyvasicinone synthesized various derivatives and reported 2, 4-dibromo-7,8,9,10-tetrahydroazepino[2,1-*b*]quinazolin-12 (6H) one to be a potent antitussive (Fig. 35). The compound caused notable decrease in cough frequency and increase in cough latency in citric acid-induced cough model in guinea pigs. Compound showed notable antitussive effect as compared with codeine (10 mg/kg).

Structurally related alkaloid: mackinazolinone and isaindigotone

Mackinazoline

Mackinazolinone (Fig. 36), an quinazolinone alkaloid fused with a piperidine ring system, was isolated (Johns and Lamberton, 1965; Fitzgerald *et al.*, 1966) from *Mackinalaya* species.

Synthesis

Spath and Ruffner (1938) synthesized mackinazolinone by the reduction of pyridoquinazoline (Fig. 37).

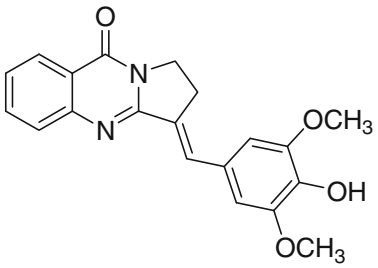


Fig. 40 Isaindigotone

Kametani *et al.* (1977) synthesized mackinazolinone in good yields from the reaction of the unstable sulfonamide anhydride with 2-pyrrolidone (Fig. 38).

Liu *et al.* (2005) carried out the synthesis of mackinazolinone via novel microwave-assisted domino reaction (Fig. 39).

Mackinazolinone possesses a broad spectrum of pharmacological activities (Johns and Lamberton, 1965; Fitzgerald *et al.*, 1966).

Isaindigotone An alkaloid having deoxyvasicinone as a core structural unit (Fig. 40). Isaindigotone was isolated from the root of *Isatis indigotica* Fort, which is a biennial herbaceous plant widely present in China (Wu *et al.*, 1997). Its chemical structure comprises of the deoxyvasicinone moiety conjugated with a substituted benzylidene.

Pan *et al.* (2008) prepared deoxyvasicinone by the condensation of 2-pyrrolidone and methyl anthranilate in the presence of phosphorous oxychloride and then the

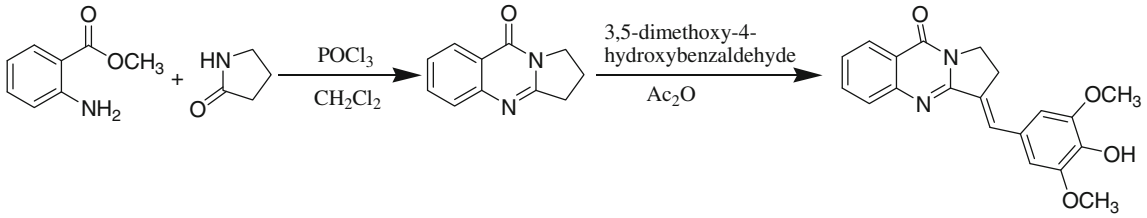
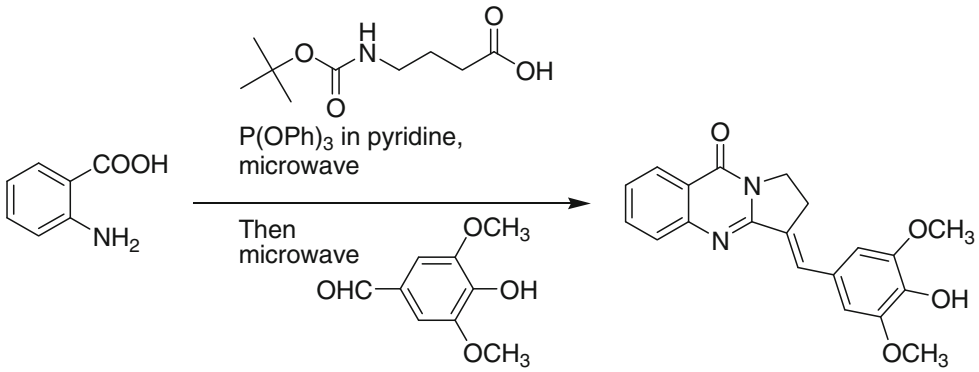


Fig. 41 Synthesis of isaindigotone

Fig. 42 Synthesis of isaindigotone



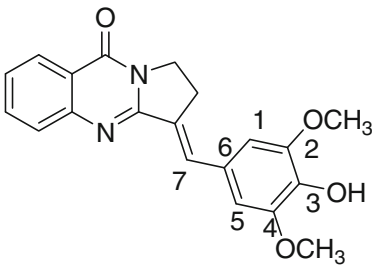


Fig. 43 Isaindigotone

treatment of deoxyvasicinone with 3,5-dimethoxy-4-hydroxybenzaldehyde gave isaindigatone by the Claisen–Schmidt condensation (Molina *et al.*, 2001) (Fig. 41).

Liu *et al.* (2005) reported a novel three-component one-pot total synthesis of isaindigotone promoted by microwave irradiation (Fig. 42).

Isaindigotone was assigned as E configuration on the basis of the Nuclear Overhauser Enhancement Spectroscopy (NOESY). On irradiation of the proton H-7, only enhancement of the equivalent protons H-6 and H-2 was observed. Moreover, on irradiation of the equivalent protons H-6 and H-2, signal of protons H-7 and H-2 was enhanced, respectively (Liu *et al.*, 2005) (Fig. 43). Isaindigotone (Wu *et al.*, 1997; Molina *et al.*, 2001; Liu *et al.*, 2005) exhibit anti-inflammatory, antimicrobial and antidepressant activities.

Alkaloid isaindigotone is reported to have antinociceptive, anti-inflammatory, and antipyretic effects in animal study (Ho and Chang, 2002). Alkaloid isaindigotone and its derivatives are also reported to have inhibitive function on leukocytes and act as a scavenger of superoxide either through the hypoxanthine/xanthine oxidase system or through stimulated human neutrophils (Molina *et al.*, 2001).

Conclusion

The overall conclusion of the review is that vasicine is an privileged phytoconstituent with number of medicinal attributes. Moreover, the up to date compilation of the literature on the molecule will make it convenient for the researchers to further explore the potential of the molecule by synthesizing various analogues taking vasicine as a lead.

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