RESULTS AND DISCUSSION

1. Synthetic Modifications of Vasicine

*Adhatoda vasicina* Nees. is a highly reputed Ayurvedic medicinal plant used in treatment of respiratory ailments particularly treatment of cough, bronchitis, asthma and tuberculosis. One of the components, vasicine, a dihydroquinazoline alkaloid, was found to be active bronchodilator. The respiratory stimulant effect is mediated mainly by its action on respiratory centre and partly through chemosensory fibers. When given orally, vasicine gets metabolized to vasicinone during its first passage through the liver after absorption from the gastrointestinal tract. Vasicinone is inactive, although an earlier report claimed it to be active bronchodilator. Vasicinone is further metabolized to other products.

A number of analogues have been synthesized at Regional Research Laboratory, Jammu to increase the stability and activity of vasicine. One of the analogues, RLX (19) has been found to be 6-10 times as active as aminophyline. On the basis of these analogues a structure activity relationship has been drawn. Oxygen function at C-3 and C-9 as in vasicinone makes the compound devoid of activity. The NNO triangle is essential for activity as deoxyvasicinone and vasicine are active. The C-ring size affects activity, seven membered ring being the most active.
The analogues of vasicine were prepared starting from various amino acids and condensing them with the lactams. The RLX, a vasicine analogue, was taken as a lead molecule and the NNO triangle, which has been proved to be essential for the activity, was kept intact. The changes done in vasicine to study SAR were divided into three main categories, changes in the substituents in the Ring A, removal of Ring A and substitution in Ring B, and changes in Ring C.

The synthesized compounds were subjected to pharmacological evaluation for bronchodilatory activity using Guinea pig tracheal chain seeing relaxation on the histamine and acetylcholine preconstricted tracheal chain.

1.1 Changes in the Substituents in the Ring A

1.1.1 7,8,9,10-Tetrahydroazepino[2,1-b]quinazolin-12(6H)-one (RLX) (19)

Anthranilic acid was converted to sulfinamide anhydride (20) by refluxing it with thionyl chloride. The sulfinamide anhydride was condensed with caprolactum under anhydrous conditions to give 7,8,9,10-tetrahydroazepino[2,1-b]quinazolin-12(6H)-one (19) in 70% yield. The compound was Dragendorff positive and analyzed for C_{13}H_{14}N_{2}O. The infrared spectrum exhibited absorption at 1658 cm^{-1} indicating...
the presence of C=O and at 1632 cm\(^{-1}\) indicating the presence of C=N. The molecular ion peak appeared at \(m/z\) 214 in the mass spectrum. The \(^1\)H NMR exhibited signals at \(\delta\) 8.25 (1H, \(q\), \(J = 2\) and 8 Hz, H at C-1), 7.10 - 7.90 (3H, m, H at C-2, C-3, C-4), 4.20 (2H, \(t\), H at C-10), 2.90 - 3.15 (2H, \(t\), H at C-6) and 1.70 - 2.20 (6H, bs, H at C-7, C-8, C-9). The spectral data matches with the data of the desired compound 19. The proposed mechanism of the reaction given in Scheme 3.\(^{148}\) The sulphinamide anhydride (20) first breaks, liberating SO\(_2\) to give ortho iminoketene, which enters in (4+2) addition reaction with the cyclic lactams such as caprolactam (21), followed by dehydration to give the desired compound.

1.1.2 7,8,9-Trihydropyrido[2,1-b]quiazolin-11(6H)-one (22)

Anthranilic acid was condensed with \(\delta\)-valerolactam by the same procedure as described under 1.1.1 to give 7,8,9-trihydropyrido-[2,1-b]-quiazolin-11(6H)-one (22) in 64% yield. The compound was Dragendorff positive and analyzed for C\(_{12}\)H\(_{12}\)N\(_2\)O. It exhibited \(\lambda_{\text{max}}\) at 248 nm and the infrared spectrum showed bands at 1650 cm\(^{-1}\) diagnostic of C=O and at 1632 cm\(^{-1}\) indicating presence of C=N. The molecular ion peak appeared at \(m/z\) 200 in the mass spectrum. The \(^1\)H NMR exhibited signals at \(\delta\) 8.20 (1H, \(q\), \(J = 2\) and 8 Hz, H at C-1), 7.10 - 7.90 (3H, m, H at C-2, C-3, C-4), 3.90 - 4.20 (2H, \(t\), H at C-9), 2.80 - 3.15 (2H, \(t\), H at C-6), 1.70 - 2.30 (4H, \(m\), H at C-7, C-8). The spectral data confirmed the formation of compound 22.
1.1.3 7,8-Dihydropyrrolo[2,1-b]quinazolin-9(6H)-one (23)

Anthraniolic acid was condensed with γ-butyrolactum by the same procedure as described earlier to give 7,8-dihydropyrrolo[2,1-b]quinazolin-9(6H)-one (23) in 64% yield. The compound was Dragendorff positive and analyzed for C_{11}H_{10}N_{2}O. It exhibited \( \lambda_{max} \) at 246 nm and the infrared spectrum showed bands at 1662 cm\(^{-1}\) diagnostic of C=O and at 1630 cm\(^{-1}\) indicating the presence of C=N. The molecular ion peak appeared at \( m/z \) 186 in the mass spectra. The \(^1\)H NMR exhibited signals at \( \delta \) 8.23 (1H, q, \( J = 2 \) and 8 Hz, H at C-1), 7.55 (3H, m, H at C-2, C-3, C-4), 4.50 (2H, \( t \), H at C-8), 3.18 (2H, \( t \), H at C-6), 2.25 (2H, \( m \), H at C-7). The data was consistent with the structure of the desired compound 23.

1.1.4 Azepino[2,1-b]-1,3-dioxolo[4,5-g]-7,8,9,10-tetrahydroquinazolin-12(6H)-one (28)

The compound 28 was prepared in the following steps:

1.1.4a 6-Nitropiperonal (25)

The finely pulverized piperonal (3,4-methylenedioxybenzaldehyde) (24) on reaction with concentrated nitric acid at 2°C, and further processing as described in the experimental part gave 6-nitropiperonal in 70% yield. The compound analyzed for C_{8}H_{5}NO_{5} and exhibited \( \lambda_{max} \) at 283 nm. The band at 1705 cm\(^{-1}\) in the infrared spectrum was diagnostic of aromatic aldehyde while those at 1536 and 1350 cm\(^{-1}\)
indicated presence of a nitro group. The bands at 2780, 925 and 725 cm\(^{-1}\) indicated presence of methylenedioxy group.\(^3\) The mass spectrum showed molecular ion peak at \(m/z\) 195. The \(^1\)H NMR exhibited signals at \(\delta\) 10.45 (1H, s, CHO), 7.79 (1H, s, H at C-2), 7.69 (1H, s, H at C-5), 6.23 (2H, s, -O-CH\(_2\)-O-) confirming the formation of 6-nitropiperonal (25).

1.1.4b 6-Aminopiperonal (26)

The 6-nitropiperonal (25) was reduced to 6-aminopiperonal (26) with a mixture of ferrous sulphate heptahydrate and ammonium hydroxide.\(^1\) The yield, however, was quite low with this procedure (45%); the reduction was therefore carried out using iron powder and ammonium chloride solution.\(^1\) The desired compound (26) was obtained in 76% yield and analyzed for C\(_6\)H\(_7\)N0\(_3\). The compound exhibited \(\lambda_{\text{max}}\) at 298 nm. The IR spectrum showed bands at 3520, 3430, 3290 and 70
1268 cm\(^{-1}\) confirming the presence of amino group.\(^{152}\) The \(^1\)H NMR exhibited signals at \(\delta\) 9.66 (1H, s, CHO), 6.90 (1H, s, H at C-2), 6.23 (1H, s, H at C-5), 6.00 (2H, s, -O-CH\(_2\)-O-). The mass spectrum showed the molecular ion peak at \(m/z\) 165 while the base peak appeared at \(m/z\) 62. The data was supportive of the formation of 26.

1.1.4c 6-Amino-3,4-methylenedioxybenzoic acid (27)

The aldehyde group in 6-aminopiperonal (26) was oxidised to carboxylic acid group with the silver oxide\(^{153}\) to give 6-amino-3,4-methylenedioxybenzoic acid (27) in 88\% yield. The compound analyzed for C\(_8\)H\(_7\)N\(_3\)O\(_4\). It exhibited \(A_{max}\) at 277 nm. The compound was positive to bromocresol blue, confirming the presence of carboxyl group. The IR spectrum showed bands at 2800 and 1740 cm\(^{-1}\) indicating presence of carboxylic acid, while bands at 3520 and 3430 cm\(^{-1}\) confirmed the presence of amino group. The \(^1\)H NMR exhibited signals at \(\delta\) 12.10 (1H, s, COOH), 7.72 (1H, s, H at C-2), 7.28 (1H, s, H at C-5), 6.30 (2H, s, -O-CH\(_2\)-O-).

1.1.4d Azepino[2,1-b]-1,3-dioxolo[4,5-g]-7,8,9,10-tetrahydroquinazolin-12(6H)-one (28)

6-Amino-3,4-methylenedioxybenzoic acid (27) as obtained above was condensed with caprolactum to give azepino[2,1-b]-1,3-dioxolo[4,5-g]-7,8,9,10-tetrahydroquinazolin-12(6H)-one (28) in 58\% yield and analyzed for C\(_{14}\)H\(_{14}\)N\(_2\)O\(_3\). The compound was Dragendroff positive and showed molecular ion peak at \(m/z\) 258
with base peak at $\text{m/z} 229$. It exhibited $\lambda_{\text{max}}$ at 239 nm in the UV spectrum. The infrared spectrum showed band 1670 cm$^{-1}$ indicating presence of C(=O)N and the one at 1624 cm$^{-1}$ indicated presence of C=N. The $^1$H NMR exhibited signals at $\delta$ 7.58

(1H, s, H at C-13), 7.00 (1H, s, H at C-4), 6.11 (2H, s, H at C-2), 4.40 - 4.42 (2H, t, H at C-10), 3.02 -3.06 (2H, t, H at C-6), 1.86 (6H, m, H at C-7, C-8, C-9). The data supported the structure 28.

1.1.5 Pyrido[2,1-b]-1,3-dioxolo[4,5-g]-7,8,9-trihydroquinazolin-11(6H)-one (29)

6-Amino-3,4-methylenedioxybenzoic acid (27) was condensed with 2-piperidone to give pyrido[2,1-b]-1,3-dioxolo[4,5-g]-7,8,9-trihydroquinazolin-11(6H)-one (29) in 47% yield which analyzed for C$_{13}$H$_{12}$N$_{2}$O$_{3}$. The compound was Dragendroff positive and showed molecular ion peak at $\text{m/z} 244$ with base peak at $\text{m/z} 215$. It exhibited $\lambda_{\text{max}}$ at 242 nm in the UV spectrum. The infrared spectrum showed band 1662 cm$^{-1}$ indicating the presence of C(=O) N and the band at 1630 cm$^{-1}$ indicated the presence of C=N. The $^1$H NMR exhibited signals at $\delta$ 7.57 (1H, s, H at
C-12), 6.98 (1H, s, H at C-4), 6.10 (2H, s, H at C-2), 4.05 - 4.10 (2H, t, H at C-9),
2.95-3.01 (2H, t, H at C-6), 1.91-2.06 (4H, m, H at C-7, C-8). The data supported the
structure 29.

1.1.6 Pyrrolo[2,1-b]-1,3-dioxolo[4,5-g]-7,8-dihydroquinazolin-10(6H)-one (30)

6-Amino-3,4-methylenedioxybenzoic acid (27) was condensed with 2-
pyrrolidinone to give pyrrolo[2,1-b]-1,3-dioxolo[4,5-g]-7,8-dihydroquinazolin-10(6H)-
one (30) in 44% yield. It analyzed for C_{12}H_{10}N_{2}O_{3}. The compound was Dragendorff
positive and showed molecular ion peak at m/z 230 with base peak at m/z 201. It
exhibited $\lambda_{max}$ at 242 nm in the UV spectrum. The infrared spectrum showed band
1658 cm$^{-1}$ indicating presence of C(=O) N and the band at 1634 cm$^{-1}$ indicated
presence of C=N. The $^1$H NMR exhibits signals at $\delta$ 7.61 (1H, s, H at C-11), 7.04
(1H, s, H at C-4), 6.13 (2H, s, H at C-2), 4.18-4.25 (2H, t, H at C-8), 3.14-3.21 (2H,
t, H at C-6), 2.09 - 2.20 (2H, m, H at C-7) confirming the formation of the compound 30.

1.1.7 2,3,4-Trimethoxy-7,8,9,10-tetrahydroazepino[2,1-b]quinazolin-12(6H)-one (35)

The compound was prepared in the following steps:

1.1.7a 2-Nitro-3,4,5-trimethoxybenzaldehyde (32)

3,4,5-Trimethoxybenzaldehyde (31) was nitrated$^{154}$ with a mixture of
concentrated nitric acid and concentrated sulphuric acid in the presence of sodium
persulphate to give 2-nitro-3,4,5-trimethoxybenzaldehyde (32) in 24% yield. The compound analyzed for C_{10}H_{11}NO_{6}. It exhibited molecular ion peak at \textit{m/z} 241 and the base peak at \textit{m/z} 196. It exhibited \( \lambda_{\text{max}} \) at 290 nm. The infrared spectrum showed bands at 1698 (CHO), 1520 and 1350 (NO\textsubscript{2}), 850 (C-N) and 740 cm\(^{-1}\) (C-N-O). The \textsuperscript{1}H NMR exhibited signals at \( \delta \) 9.90 (1H, s, CHO), 7.30 (1H, s, Ar-H), 3.90-4.00 (9H, bs, -OCH\textsubscript{3}) confirming the formation of 32.

1.1.7b 2-Amino-3,4,5-trimethoxybenzaldehyde (33)

2-Nitro-3,4,5-trimethoxybenzaldehyde (32) was reduced to 2-amino-3,4,5-trimethoxybenzaldehyde (33) using iron powder and ammonium chloride solution.\textsuperscript{151} The desired amine was obtained in 76% yield and analyzed for C\textsubscript{10}H\textsubscript{13}NO\textsubscript{4}. The compound exhibited \( \lambda_{\text{max}} \) at 305 nm. The IR spectrum showed bands at 3400 (NH\textsubscript{2}), 3150 (NH\textsubscript{2}), 3000 (OH).
3290 (NH), 2840 (OCH₃) and 1698 cm⁻¹ (CHO). The compound showed molecular ion peak at m/z 211 in the mass spectrum. The ¹H NMR exhibited signals at δ 9.91 (1H, s, CHO), 6.90 (1H, s, Ar-H), 3.90-4.00 (9H, bs, -OCH₃). The data supported the structure 33.

1.1.7c  2-Amino-3,4,5-trimethoxybenzoic acid (34)

The aldehyde group in 2-amino-3,4,5-trimethoxybenzaldehyde (33) was oxidised to carboxylic acid group with the silver oxide to give 2-amino-3,4,5-trimethoxybenzoic acid (34) in 50% yield. The compound analyzed for C₁₀H₁₃NO₅. It exhibited λ_max at 284 nm. The compound was positive to bromocresol blue, confirming the presence of carboxyl group. The IR spectrum showed bands at 2800 and 1740 cm⁻¹ indicating presence of carboxylic acid while bands at 3430 and 3290 cm⁻¹ confirmed the presence of amino group. The molecular ion peak appeared at m/z 227 in the mass spectrum. The ¹H NMR exhibited signals at δ 12.06 (1H, s, COOH), 6.90 (1H, s, Ar-H), 3.90-4.00 (9H, bs, -OCH₃).

![Scheme 9: Synthesis of Compound 34](image)

1.1.7d  2,3,4-Trimethoxy-7,8,9,10-tetrahydroazepino[2,1-β]quinazolin-12(6H)-one (35)

2-Amino-3,4,5-trimethoxybenzoic acid (34) was condensed with caprolactum to give 2,3,4-trimethoxy-7,8,9,10-tetrahydroazepino[2,1-β]quinazolin-12(6H)-one (35).
(35) in 37% yield. The compound analyzed for C\textsubscript{16}H\textsubscript{20}N\textsubscript{2}O\textsubscript{4} and exhibited $\lambda_{\text{max}}$ at 325 nm. The IR spectrum showed bands at 1670 cm\textsuperscript{-1} (C=O) and 1633 cm\textsuperscript{-1} (C=N). The mass spectrum exhibited molecular ion peak at $m/z$ 304 while base peak appeared at $m/z$ 227. The $^1$H NMR showed signals at δ 7.90 (1H, s, Ar-H), 4.40 - 4.42 (2H, t, C\textsubscript{-10}), 3.02-3.06 (2H, t, H at C-6), 4.05 (3H, s, OCH\textsubscript{3} at C-4), 3.95 (6H, s, OCH\textsubscript{3} at C-2 and C-3), 1.86 (6H, m, H at C-7, C-8, C-9). The data supports the structure 35.

1.2 Removal of Ring A and Substitution in Ring B

In this series the compounds were prepared starting from 3-amino-3-phenylpropionic acid using the same method as used when starting from anthranilic acids. The yields were very low and a number of side products were formed which were separated by suitable chromatographic techniques. The 3-amino-3-phenylpropionic acid also got self-condensed under the reaction conditions.

1.2.1 2-Pheny\textsubscript{l}-2,6,7,8,9,10-hexahydro-3\textsubscript{H}-pyrimido[1,2-\textalpha]azepin-4-one (38)

3-Amino-3-phenylpropionic acid (36) was converted to sulfinamide anhydride (37) by refluxing it with thionyl chloride. The sulfinamide anhydride was condensed with condensed with caprolactum (21) to give 2-phenyl-2,6,7,8,9,10-hexahydro-3\textsubscript{H}-pyrimido[1,2-\textalpha]azepin-4-one (38) in 11% yield. The compound analyzed for C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}O and exhibited $\lambda_{\text{max}}$ at 208 and 230 nm. The infrared
spectrum exhibited band at 1657 cm\(^{-1}\) indicating the presence of C=O and at 1633 cm\(^{-1}\) which was diagnostic of C=N. The mass spectrum showed molecular ion peak at \(m/z\) 242. The \(^1\)H NMR exhibited signals at \(\delta\) 7.23 (5H, bs, H in Ph ring), 5.02 - 5.21 (1H, t, H at C-2), 4.27-4.31(2H, m, H at C-6), 3.26 ( 2H, m, H at C-10), 2.26-2.69 (2H, t, H at C-3), 1.79 (6H, m, H at C-7, C-8, C-9). The data confirms the formation of 38.

**Scheme 10**: Synthesis of Compound 38

1.2.2 2-Phenyl-2,6,7,8,9-pentahydro-3//-pyrido[1,2-a]pyrimidin-4-one (39)

3-Amino-3-phenylpropionic acid (36) was condensed with 2-piperidone to give 2-phenyl-2,6,7,8,9-pentahydro-3//-pyrido[1,2-a]pyrimidin-4-one (39) in 8% yield. The compound analyzed for C\(_{14}\)H\(_{16}\)N\(_2\)O and exhibited \(\lambda_{max}\) at 215 and 237 nm. The infrared spectrum showed bands at 1657 and at 1633 cm\(^{-1}\) indicating the
presence of C=O and C=N, respectively. The mass spectrum showed molecular ion peak at \( m/z \) 228. The \(^1\)H NMR exhibited signals at \( \delta \) 7.20 (5H, bs, H in Ph ring), 5.02-5.21 (1H, t, H at C-2), 4.07-4.11 (2H, t, H at C-6), 3.06 (2H, m, H at C-9), 2.34-2.60 (2H, t, H at C-3), 1.91 (4H, m, H at C-7, C-8) confirming the formation of 39.

1.2.3 2-PhenyI-2,6,7,8-tetrahydro-3//-pyrrolo[1,2-a]pyrimidin-4-one (40)

The compound 40 was synthesized by condensing 3-amino-3-phenylpropionic acid (36) with 2-pyrrolidinone in 8% yield. It analyzed for C\(_{13}\)H\(_{14}\)N\(_2\)O and exhibited \( \lambda_{\text{max}} \) at 218 nm. The IR spectrum showed bands at 1662 and 1630 cm\(^{-1}\) indicating the presence of C=O and C=N, respectively. The mass spectrum showed molecular ion peak at \( m/z \) 214. The \(^1\)H NMR exhibited signals at \( \delta \) 7.39 (5H, bs, H in Ph ring), 4.81-4.89 (1H, t, H at C-2), 4.17-4.21 (2H, t, H at C-6), 3.26 (2H, t, H at C-8), 2.34-2.53 (2H, d, H at C-3), 2.01 (2H, m, H at C-7). The data supported the structure of 40.

1.3 Changes in Ring C

The changes were made in the ring C by replacing the ring with aliphatic and aromatic substituents. The long chain aliphatic substitutions were made in ring B. The aromatic ring was attached to the nitrogen atom. Fluoro substituted phenyl ring was also attached to the nitrogen atom in the quinazoline ring to study the effect of fluoro group on the activity. The effect of removal of keto group was also studied.
1.3.1 6-Methyl-7,8-dihydro-1,3-dioxolo[4,5-g]quinazoline (41)

6-Aminopiperonal was acetylated with acetic anhydride in presence of pyridine. The N-acetyl-6-aminopiperonal thus obtained on refluxing with formic acid and formamide, gave 6-methyl-7,8-dihydro-1,3-dioxolo[4,5-g]quinazoline (41) in 30% yield. The compound analyzed for C_{10}H_{10}N_{2}O_{2} and exhibited λ_{max} at 217 and 206 nm. The IR spectrum showed band at 1632 cm\(^{-1}\) indicating presence of C=\text{N}. The mass spectrum showed molecular ion peak at m/z 190 and the base peak at m/z 189. The \(^1\)H NMR exhibited signals at δ 7.02 (1H, s, H at C-4), 6.55 (1H, s, H at C-10), 5.88 (2H, s, -O-CH\(_2\)-O-), 4.46 (2H, s, H at C-8), 2.01 (3H, s, CH\(_3\)). The data was consistent with the structure of desired compound 41.

1.3.2 2-Methyl-3-phenyl-3H-quinazolin-4-one (43)

For the synthesis of the title compound, 2-methyl-3,1-benzoxazin-4-one (42) was synthesized by refluxing anthranilic acid with acetic anhydride.\(^{155}\) It was then reacted with aniline in presence of phosphorous oxychloride to give 2-methyl-3-phenylquinazolin-4-one (43) in 51% yield.\(^{156}\) The compound analyzed for C\(_{15}\)H\(_{12}\)N\(_2\)O and exhibited λ_{max} at 270 nm. The IR spectrum showed bands at 1660 and 1632 cm\(^{-1}\) indicating the presence of C=O and C=\text{N}, respectively. The mass spectrum exhibited
molecular ion peak at \( m/z \) 236 with base peak at \( m/z \) 77. Other prominent peaks were at \( m/z \) 235, 220, 144, 143, 118, 116, 105, 103, 89 and 76. The \(^1\)H NMR exhibited signals at \( \delta \) 8.22-8.40 (1H, \( d \), H at C-5), 7.62-7.85 (3H, \( m \), H at C-6, C-7, C-8), 7.20 - 7.54 (5H, \( m \), Ph), 2.25 (3H, s, CH\(_3\)). The data was supportive of formation of 43.

1.3.3 3-(4-Fluorophenyl)-2-methyl-3H-quinazolin-4-one (44)

2-Methyl-3,1-benzoxazin-4-one (42) was condensed with 4-fluoroaniline to give 3-(4-fluorophenyl)-2-methyl-3H-quinazolin-4-one (44) in 52% yield. The compound analyzed for C\(_{15}\)H\(_{11}\)N\(_2\)OF and exhibited \( \lambda_{\text{max}} \) at 268 nm. The IR spectrum showed bands at 1660 and 1632 cm\(^{-1}\) indicating the presence of C=O and C=N, respectively. The mass spectrum exhibited molecular ion peak at \( m/z \) 254 with base
peak at $m/z$ 94. Other prominent peaks were at $m/z$ 238, 183, 144, 135, 102, 89, 76, 69 and 51. The $^1$H NMR exhibited signals at $\delta$ 8.22-8.40 (1H, $d$, H at C-5), 7.62-7.85 (3H, $m$, H at C-6, C-7, C-8), 7.44 (2H, $d$, H at C-3' and C-5'), 7.25 (2H, $d$, H at C-2' and C-6'), 2.25 (3H, $s$, CH$_3$). The data supported the structure of 44.

1.3.4 2-Ethyl-3-phenyl-3$H$-quinazolin-4-one (45)

2-Ethyl-3,1-benzoxazin-4-one was synthesized by refluxing anthranilic acid with propionic anhydride. It was reacted with aniline in presence of phosphorous oxychloride to give 2-ethyl-3-phenyl-3$H$-quinazolin-4-one (45) in 52% yield. The compound analyzed for C$_{16}$H$_{14}$N$_2$O and exhibited $\lambda$ max at 266 nm. The IR spectrum showed bands at 1658 and 1628 cm$^{-1}$ indicating the presence of C=O and C=N, respectively. The mass spectrum exhibited molecular ion peak at $m/z$ 250 with base peak at $m/z$ 77. Other prominent peaks were at $m/z$ 249, 235, 221, 193, 146, 132, 119, 116, 103, 91 and 76. The $^1$H NMR exhibited signals at $\delta$ 8.27-8.40 (1H, $d$, H at C-5), 7.62-7.85 (3H, $m$, H at C-6, C-7, C-8), 7.20 -7.54 (5H, $m$, Ph), 2.23-2.60 (2H, $q$, $J = 7$ Hz, CH$_2$), 1.20 (3H, $t$, $J = 7$ Hz, CH$_3$). The data was supportive of the formation of 45.
1.3.5 2-Ethyl-3-(4-fluorophenyl)-3H-quinazolin-4-one (46)

2-Ethyl-3,1-benzoxazin-4-one was reacted with 4-fluoroaniline in presence of phosphorous oxychloride to give 2-ethyl-3-(4-fluorophenyl)-3H-quinazolin-4-one (46) in 42% yield. The compound analyzed for C_{16}H_{13}N_{2}OF and exhibited $\lambda_{\text{max}}$ at 272 nm. The IR spectrum showed bands at 1658 and 1630 cm$^{-1}$ indicating the presence of C=O and C=N, respectively. The mass spectrum exhibited molecular ion peak at $m/z$ 268 with base peak at $m/z$ 94. Other prominent peaks were at $m/z$ 253, 249, 239, 234, 220, 193, 146, 132, 119, 116, 103, 76, 69 and 52. The $^1$H NMR exhibited signals at $\delta$ 8.27-8.40 (1H, $d$, H at C-5), 7.62-7.85 (3H, $m$, H at C-6, C-7, C-8), 7.44 (2H, $d$, H at C-3' and C-5'), 7.25 (2H, $d$, H at C-2' and C-6'), 2.23-2.60 (2H, $q$, $J = 7$ Hz, CH$_2$), 1.20 (3H, $t$, $J = 7$ Hz, CH$_3$). The data supported the structure of 46.

1.3.6 2-Propyl-3-phenyl-3H-quinazolin-4-one (47)

2-Propyl-3,1-benzoxazin-4-one was synthesized by refluxing anthranilic acid with butyric anhydride. It was reacted with aniline in presence of phosphorous oxychloride to give 2-propyl-3-phenyl-3H-quinazolin-4-one (47) in 45% yield. The compound analyzed for C$_{17}$H$_{16}$N$_2$O and exhibited $\lambda_{\text{max}}$ at 265 nm. The IR
spectrum showed bands at 1660 and 1632 cm\(^{-1}\) indicating the presence of C=O and C=N, respectively. The mass spectrum exhibited molecular ion peak at \(m/z\) 264 with base peak at \(m/z\) 77. Other prominent peaks were at \(m/z\) 249, 235, 233, 221, 193, 146, 132, 119, 116, 103, 91 and 76. The \(^1\)H NMR exhibited signals at \(\delta\) 8.27-8.40 (1H, \(d\), H at C-5), 7.62-7.85 (3H, \(m\), H at C-6, C-7, C-8), 7.30 -7.50 (5H, \(m\), Ph), 2.23-2.60 (2H, \(q\), \(J = 7\) Hz, CH\(_2\)CH\(_2\)CH\(_3\)), 1.60-1.45 (2H, \(m\), CH\(_2\)CH\(_3\)), 1.05 (3H, \(t\), \(J = 5\) Hz, CH\(_3\)). The data supported the structure of 47.

1.3.7 2-Propyl-3-(4-fluorophenyl)-3H-quinazolin-4-one (48)

2-Propyl-3,1-benzoxazin-4-one was reacted with 4-fluoroaniline in presence of phosphorous oxychloride to give 2-propyl-3-(4-fluorophenyl)-3H-quinazolin-4-one (48) in 32% yield. The compound analyzed for C\(_{17}\)H\(_{15}\)N\(_2\)OF and exhibited \(\lambda_{\text{max}}\) at 269 nm. The IR spectrum showed bands at 1670 and 1625 cm\(^{-1}\) indicating the presence of C=O and C=N, respectively. The mass spectrum exhibited molecular
ion peak at m/z 282 with base peak at m/z 94. Other prominent peaks were at m/z 267, 263, 253, 248, 239, 234, 220, 193, 191, 173, 166, 146, 132, 130, 119, 116, 105, 103, 77, 76, 69, 65, 64, 52. The $^1$H NMR exhibited signals at δ 8.27-8.40 (1H, d, H at C-5), 7.62-7.85 (3H, m, H at C-6, C-7, C-8), 7.44 (2H, d, H at C-3’ and C-5’), 7.25 (2H, d, H at C-2’ and C-6’), 2.23-2.60 (2H, q, $J = 7$ Hz, CH$_2$CH$_2$CH$_3$), 1.60-1.45 (2H, m, CH$_2$CH$_2$CH$_3$), 1.05 (3H, t, $J = 5$Hz, CH$_3$). The data was supportive of formation of 48.

1.3.8 2-Pentyl-3-phenyl-3$H$-quinazolin-4-one (51)

Caproic acid (49) was reacted with thionyl chloride to give caproyl chloride. The caproylchloride was condensed with anthranilic acid to give 2-pentyl-3,1-benzoxazin-4-one (50) in 80% yield. The latter was condensed with aniline in presence of phosphorous oxychloride to give 2-pentyl-3-phenyl-3$H$-quinazolin-4-one (51) in 30% yield. The compound analyzed for C$_{19}$H$_{20}$N$_2$O and exhibited

$$
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH} + \text{SOCl}_2 & \rightarrow \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COCl} \\
\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COCl} + \text{O} & \rightarrow \text{N} \\
\text{NH}_2 & \rightarrow \text{N} \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 & \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3
\end{align*}
$$

Scheme 12 : Synthesis of Compound 51

The compound exhibited $\lambda_{\text{max}}$ at 270 nm. The IR spectrum showed bands at 1650 and 1624 cm$^{-1}$ indicating the presence of C=O and C=N, respectively. The mass spectrum exhibited molecular
ion peak at $m/z$ 292 with base peak at $m/z$ 235. Other prominent peaks were at $m/z$ 277, 263, 254, 249, 236, 222, 218, 146, 144, 137, 121, 119, 93, 91, 89 and 77.

The $^1$H NMR exhibited signals at $\delta$ 8.27-8.40 (1H, $d$, H at C-5), 7.62-7.85 (3H, $m$, H at C-6, C-7, C-8), 7.20 -7.54 (5H, $m$, Ph), 2.20-2.60 (2H, $q$, $J = 8$ Hz, H at C-1'), 1.30-1.83 (6H, $m$, H at C-2', C-3', C-4'), 0.92 (3H, $t$, $J = 5$ Hz, CH$_3$). The data supported the structure of 51.

1.3.9 2-Pentyl-3-(4-fluorophenyl)-3H-quinazolin-4-one (52)

2-Pentyl-3,1-benzoxazin-4-one (49) as obtained under 1.3.8 was condensed with 4-fluoroaniline in presence of phosphorous oxychloride to give 2-pentyl-3-(4-fluorophenyl)-3H-quinazolin-4-one (52) in 29% yield. The compound analyzed for C$_{19}$H$_{19}$N$_2$OF and exhibited $\lambda_{	ext{max}}$ at 269 nm. The IR spectrum showed bands at 1659 and 1630 cm$^{-1}$ indicating the presence of C=O and C=N, respectively. The mass spectrum exhibited molecular ion peak at $m/z$ 310 with base peak at $m/z$ 94. The $^1$H NMR exhibited signals at $\delta$ 8.27-8.40 (1H, $d$, H at C-5), 7.62-7.85 (3H, $m$, H at C-6, C-7, C-8), 7.44 (2H, $d$, H at C-3" and C-5"), 7.25 (2H, $d$, H at C-2" and C-6"), 2.20-2.60 (2H, $q$, $J = 8$ Hz, H at C-1'), 1.30-1.83 (6H, $m$, H at C-2', C-3', C-4'), 0.92 (3H, $t$, $J = 5$ Hz, CH$_3$). The data supported the structure of 52.
1.4 Microwave Mediated Synthesis

Though the first paper on use of microwave energy in organic chemistry appeared in mid 1980’s only, a tremendous interest has been generated in microwave mediated organic synthesis. The use of such non-conventional reaction conditions reveals several features such as:

(a) A reduction in the usual thermal degradation and/or better selectivity.

(b) There seems to be a marked rate enhancement as compared to conventional heating for some reactions especially under heterogeneous conditions.

(c) Cleaner reaction conditions.

(d) Ease of work-up after reaction.

(e) Minimum use of solvents.

The microwave dielectric heating effect uses the ability of some liquids and solids to transform electro energy into heat and thereby drive chemical reactions. The \textit{in situ} mode of energy conversion has many attractions to the chemist, because its magnitude depends on the properties of molecules. This allows some control of the material’s properties and may lead to reaction selectively.

Keeping these advantages in mind, an attempt was made to synthesize some of the analogues of vasicine which were prepared by conventional method by microwave mediated reaction. After a number of failures we were able to synthesize some dihydroquinazolines and some other heterocyclic compounds by microwave mediated reactions in good yields and with much cleaner and simpler reaction conditions. The time required for the reaction was also much less as compared to the conventional
method. The Table 4 gives the comparative account of yields and the reaction times of the compounds prepared both by conventional and microwave method.

Table 4: Comparative yields and reaction times by classical and microwaves mediated synthesis

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield(%)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Classical</td>
<td>MWI</td>
</tr>
<tr>
<td>19</td>
<td>70</td>
<td>60</td>
</tr>
<tr>
<td>22</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>23</td>
<td>64</td>
<td>60</td>
</tr>
<tr>
<td>28</td>
<td>58</td>
<td>63</td>
</tr>
<tr>
<td>29</td>
<td>47</td>
<td>55</td>
</tr>
<tr>
<td>30</td>
<td>44</td>
<td>52</td>
</tr>
</tbody>
</table>

The table shows that the yields of the compound are almost the same as obtained by conventional method and the time required for reaction is almost one-tenth the time required by conventional method. The use of thionyl chloride is also avoided. The organic solvents are required in minimal amount for adsorption and extraction only.

2. Bronchodilatory Activity Evaluation of Vasicine Analogue

The prepared compounds were tested for *in vitro* bronchodilatory activity. The isolated guinea pig tracheal chain preparation was used following the method described by Castillo and de Beer except that the tracheal rings were opened by severing the cartilage. Etofylline was used as the standard bronchodilator. Relaxation effect of the compounds was studied on the tracheal chain precontracted
with histamine diphosphate (1×10^{-6} g/ml) or acetyl choline (1×10^{-6} g/ml). The results are shown in the Table 5.

**Table 5 : In vitro Bronchodilatory Activity Evaluation of Vasicine Analogues**

<table>
<thead>
<tr>
<th>Compound</th>
<th><strong>In vitro</strong> guinea pig trachea % relaxation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Histamine</td>
</tr>
<tr>
<td>19</td>
<td>100</td>
</tr>
<tr>
<td>22</td>
<td>40</td>
</tr>
<tr>
<td>23</td>
<td>20</td>
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<tr>
<td>28</td>
<td>100</td>
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<td>29</td>
<td>50</td>
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<td>38</td>
<td>50</td>
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<td>39</td>
<td>20</td>
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<tr>
<td>40</td>
<td>-</td>
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<tr>
<td>41</td>
<td>-</td>
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<tr>
<td>43</td>
<td>100</td>
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<td>46</td>
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<td>47</td>
<td>50</td>
</tr>
<tr>
<td>48</td>
<td>10</td>
</tr>
<tr>
<td>51</td>
<td>-</td>
</tr>
<tr>
<td>52</td>
<td>-</td>
</tr>
<tr>
<td>Etofylline</td>
<td>40</td>
</tr>
</tbody>
</table>
The compounds 19 (RLX), 28, 43 and 45 showed good relaxation in the histamine precontracted guinea pig tracheal chain. The compounds 19, 28, 29 and 38 also showed relaxation in the acetylcholine precontracted guinea pig tracheal chain.

3. Structure Activity Relationship Studies on Vasicine Analogues

Compounds were prepared with changes in ring A, absence of ring A and substitution in ring B and the absence of ring C. The NNO triangle was kept intact but the ring sizes were varied. The compounds with the seven member C ring were found to be the most active and confirmed the earlier observation made by Dhar et al.\textsuperscript{107} Compound with methylenedioxy group in the ring A and seven membered C ring was as active as RLX (19) in relaxing the histamine precontracted guinea pig tracheal chain. The removal of the ring A resulted in the loss of activity, thus the quinazoline system was found essential for activity. The oxygen functionality at C-9 is another essential feature for activity as its removal results in complete loss of bronchodilatory activity.

Compounds without ring C having aromatic and aliphatic substitutions in ring B showed good \textit{in vitro} bronchodilatory activity. The increase in chain length of aliphatic substituent resulted in decrease in activity thus suggesting that increase in lipophilicity cause decrease in activity. The compounds with \textit{para} fluoro substituted phenyl ring at position 3 were less active than compounds without fluoro group.
4. Application of Microwaves for Synthesis of 1,4-Dihydropyridines as Potential Medicinal Agents

The pharmacological profile of 1,4-dihydropyridines has increased interest in an efficient and high yield synthetic process to these compounds. Microwave mediated synthesis as described earlier, seems to be a good alternative for the traditional approaches with its high yields and clean reactions. 4-Aryl-1,4-dihydropyridines are the primary line of treatment in a number of cardiovascular diseases like variant and exertional angina, certain types of cardiac arrhythmias and hypertension.

The dihydropyridines have been synthesized conventionally using Hantzsch synthesis\textsuperscript{135} or modified Hantzsch synthesis. The yields are comparatively low and the reaction time is generally 10-12 hrs. Keeping in view the fast and clean synthesis with high yields microwave mediated synthesis was designed for synthesis of three different series of 4-aryl-1,4-dihydropyridines. The aromatic aldehyde was condensed with alkyl acetoacetates to form dihydropyridine ring using ammonium acetate as source of ammonia. The reactions were carried out on basic alumina, which acted as a solid support. The solvent was used only for extraction of the product, which was obtained in high yields after processing. The reaction was in single step and reaction time consumed was less than ten minutes. The downstream processing was very simple and fast. The process can be scaled up and is industrially useful.

In total ninety-six compounds were prepared, in three series with 3,5-dimethoxycarbonyl (Table 7), 3,5-diethoxycarbonyl (Table 8) and 3-methoxycarbonyl-5-ethoxycarbonyl (Table 9) groups in the 1,4-dihydropyridine ring, respectively. The tables are given in experimental part.
4.1 4-Aryl-2,6-dimethyl-3,5-dimethoxycarbonyl-1,4-dihydropyridines (53)

The spectral data of the compounds was found to be in accordance with the assigned structures. The infrared spectra shows bands at 3350-3330 (NH), 1700-1680 (C=O) besides other bands depending on the substituents in the aryl ring. The molecular ion peak appeared at the expected \( m/z \) values. The \(^1\)H NMR spectra of 3,5-dimethoxycarbonyl derivatives (53) generally showed signals at \( \delta 2.30-2.33 \) (6H, s, \( \text{CH}_3 \) at C-2 and C-6 positions of the dihydropyridine ring), 3.16-3.68 (6H, s, \( \text{COOCH}_3 \)), 4.90-5.72 (1H, s, H at C-4), 5.90-6.30 (1H, s, NH).

4.2 4-Aryl-2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridines (54)

The \(^1\)H NMR spectra of 3,5-diethoxycarbonyl (54) derivatives generally showed signals at \( \delta 2.25 \) (6H, t, \( \text{COOCH}_2\text{CH}_3 \) at C-3 and C-5 positions of the dihydropyridine ring), 2.30-2.33 (6H, s, \( \text{CH}_3 \) at C-2 and C-6 positions of the dihydropyridine ring), 4.00-4.10 (4H, s, \( \text{COOCH}_2\text{CH}_3 \) at C-3 and C-5 positions of the dihydropyridine ring), 4.90-5.72 (1H, s, H at C-4), 5.90-6.30 (1H, s, NH).
The $^1$H NMR spectra of the 3-methoxycarbonyl-5-ethoxycarbonyl (55) derivatives generally showed signals at $\delta$ 2.25 (3H, t, COOCH$_2$CH$_3$), 2.30-2.40 (6H, s, CH$_3$ at C-2 and C-6 positions of the dihydropyridine ring), 3.16-3.80 (3H, s, COOCH$_3$), 4.00-4.10 (2H, s, COOCH$_2$CH$_3$), 4.90-5.72 (1H, s, H at C-4), 5.90-6.30 (1H, s, NH).

The spectral data of the representative compounds is given in the Table 10 in the experimental part. The high yields and the less reaction time besides minimum use of solvents makes this a attractive process for synthesis of 1,4-dihydropyridines.