Resume' and Discussion

The work carried out towards achieving the proposed plan has been discussed under the following two main headings :

4.1 Chemical studies

4.2 Biological studies

4.1 Chemical studies

The synthetic work has been divided into the following heads:

4.1.1 Synthesis of starting materials and intermediates

- Synthesis of 6-nitroveratric acid
- Synthesis of 2-amino-4,5-dimethoxybenzonitrile
- Synthesis of substituted anilines
- Synthesis of substituted benzyl bromides

4.1.2 Synthesis of 3-*n*.butyl-2-chloromethyl-6,7-dimethoxyquinazolin-4(3*H*)-one

- Synthesis of 3-*n*.butyl-6,7-dimethoxy-2-[(4-substituted piperazin-1-yl) methyl] quinazolin-4(3*H*)-ones (**Series I**)
- Synthesis of 2-[(3/4-Substituted phenylamino)methyl]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-ones (**Series II**)

4.1.3 Synthesis of 3-(3/4-substituted benzyl)-2-*n*.butyl-6,7-dimethoxyquinzolin-4(3*H*)-ones (**Series III**)

4.1.4 Synthesis of 2-chloro-6,7-dimethoxyquinazolin-4-amine

- Synthesis of 6,7-dimethoxy-2-(4-substituted piperazin-1-yl)quinazolin-4-amines (**Series IV**)

4.1.5 Synthesis of 2-chloromethyl-6,7-dimethoxyquinazolin-4-amine

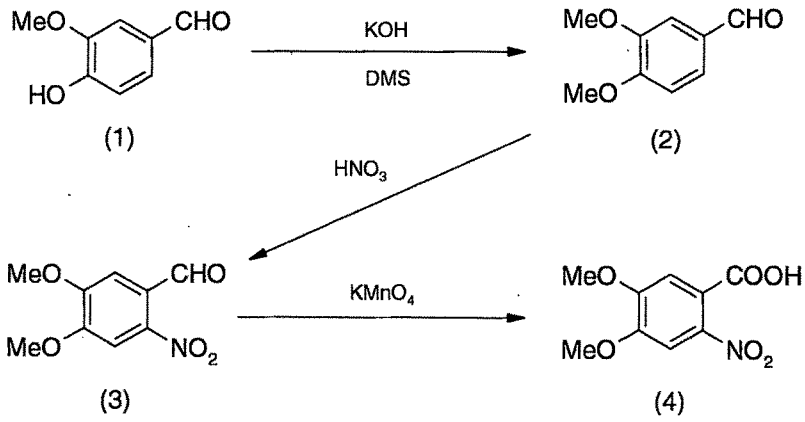
- Synthesis of 6,7-dimethoxy-2-(4-substituted piperazin-1-yl)quinazolin-4-amines (**Series V**)
- Synthesis of 2-[(aryl(alkyl)amino/heteroaryl)methyl]-6,7-dimethoxyquinazolin-4-amines (**Series VI**)

4.1.1 Synthesis of starting materials and intermediates

- **Synthesis of 6-nitroveratric acid (4)**

Vanillin (**1**) was methylated using dimethyl sulfate (DMS) under basic conditions to give verateraldehyde (**2**) as per the reported procedure.[370, 371](**Scheme 1**) Nitration of verateraldehyde (**2**) with concentrated nitric acid yielded 6-

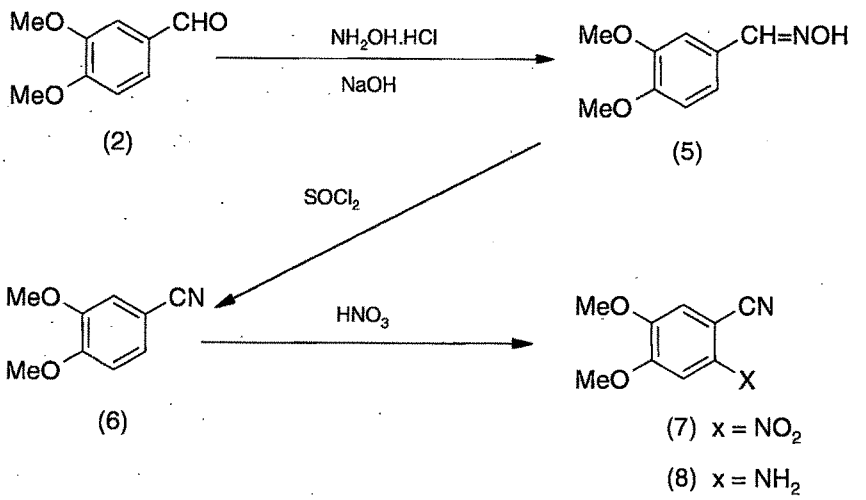
nitroverateraldehyde (**3**)[372] Its IR spectrum showed strong peaks at 1523 (N=O asym. str), 1336 (N=O sym. str) and 1686 cm^{-1} (C=O str). 6-Nitroveratraldehyde was subjected to potassium permanganate oxidation to obtain 6-nitroveratric acid (**4**).[373] 6-Nitroveratric acid (**4**) showed a broad peak of O-H around 3300 cm^{-1} and a shift in the peak of C=O stretching to 1703 cm^{-1} from 1686 cm^{-1} of 6-nitroveratraldehyde.



Scheme 1

- **Synthesis of 2-amino-4,5-dimethoxybenzonitrile**

Veratraldoxime (**5**) was prepared from veratraldehyde (**2**) by reacting it with hydroxylamine. Compound (**5**) showed characteristic broad peak at 3458 (O-H str) and absence of aldehydic (C=O) peak around 1670 cm^{-1} in its IR spectrum. Veratral-



Scheme 2

doxime (**5**) was dehydrated with thionyl chloride to get 3,4-dimethoxybenzonitrile (**6**)[374], which showed characteristic peak at 2221cm^{-1} (-C≡N) and absence of broad peak of O-H in its IR spectrum. Nitration of 3,4-dimethoxy benzonitrile (**6**) with conc.

nitric acid gave 4,5-dimethoxy-2-nitrobenzonitrile (**7**)[375]. Molecular ion peak was observed at m/z 208.06 in its mass spectrum. Its IR spectrum showed characteristic peaks at 2226 (-C≡N str), 1570 (N=O asym str) and 1397 cm^{-1} (N=O sym str). 4,5-Dimethoxy-2-nitrobenzonitrile (**7**) was reduced with tin and concentrated hydrochloric acid to yield 2-amino-4,5-dimethoxybenzonitrile[376] (**8**). Molecular ion peak was observed at m/z 178 in its mass spectrum. Its IR spectrum displayed characterisitic peaks at 3452 (N-H str) and 2210 cm^{-1} (-C≡N str).

- **Synthesis of substituted anilines**

Substituted anilines required for the synthesis of titled compounds were either procured from commercial sources or prepared in the laboratory. 3/4-Aminobenzoic acids were refluxed in methanol with continuously passing hudrogen chloride gas through them in order to get methyl 3/4-aminobenzoates. IR spectra showed peaks of C=O group at (1723 and 1714 cm^{-1}) respectively. The 3/4-Nitroanilines were acetylated to get 3/4-nitroacetanilides. Upon reduction with iron powder and ammonium chloride in aq methanol they yielded 3/4-acetamidoanilines respectively. IR spectra of these compounds showed peaks of N-H and C=O group for 3-acetamidoaniline (3413 and 1674 cm^{-1}) and 4-acetamidoaniline (3370 and 1664 cm^{-1}).

Methylsulfonation of 3/4-nitroanilines afforded 3/4-methanesulfonamido nitrobenzenes respectively, which upon reduction with iron powder and ammonium chloride in aq methanol afforded the corresponding amines. IR spectra of these compounds showed peaks of N-H and SO_2 group for 3-methanesulfonamidoaniline (3406, 1317 and 1147 cm^{-1}) and 4-methanesulfonamidoaniline (3414, 1397 and 1146 cm^{-1}).

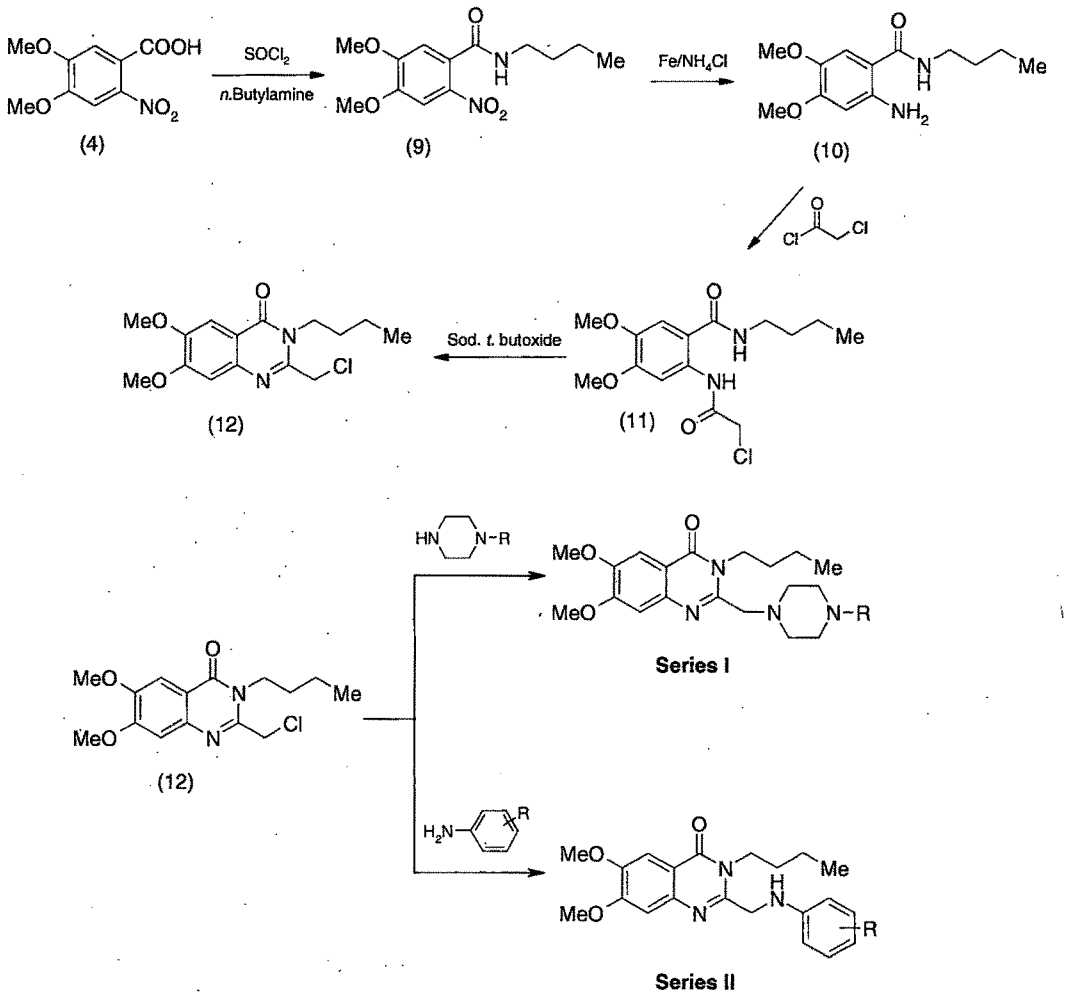
5-(3/4-Aminophenyl)-1*H*-tetrazoles were prepared in four steps from *m* and *p*-nitrobenzaldehydes. Aldoximes of 3/4-nitrobenzaldehydes were prepared by using hydroxylamine hydrochloride. The aldoximes were further dehydrated with thionyl chloride to afford the 3/4-nitrocyanobenzenes. IR spectra of these compounds confirmed the presence of the CN group (2236 and 2232 cm^{-1}). The cyano function was then converted to tetrazole moiety by using sodium azide. The corrsponding 5-(3/4-nitrophenyl)-1*H*-tetrazoles were further reduced to the 5-(3/4-aminophenyl)-1*H*-tetrazoles by iron powder and ammonium chloride in aq methanol.

- **Synthesis of substituted benzyl bromides**

Substituted benzyl bromides were prepared from substituted toluenes. 3-Tolunitrile, 3/4-methyl benzoates and 3-nitrotoluene were brominated by following a common preocedure. Substituted toluenes *were* brominated by using *N*-bromosuccinimide and benzoyl peroxide in DCM. The reaction mixture was refluxed until the reaction completed. This way 3-cyanobenzyl bromide, methyl 3/4-bromomethylbenzoate and 3-nitrobenzyl bromide were prepared.

4.1.2 Synthesis of 3-*n*.Butyl-2-(chloromethyl)-6,7-dimethoxyquinazolin-4(3*H*)-one (12)

The acid chloride of 6-nitroveratric acid (**4**) prepared by its treatment with thionyl chloride was treated with *n*.butylamine in tetrahydrofuarn (THF) in presence



Seheme 3

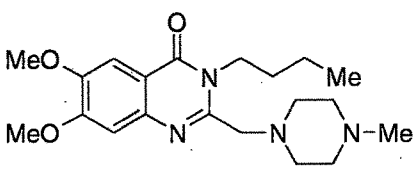
of triethylamine (TEA) to obtain *N*-*n*.butyl-4,5-dimethoxy-2-nitrobenzamide (**9**)

(**Scheme-3**). Compound (**9**) showed characteristic IR peaks at 3270 (N-H str), 1640 (C=O str), 1519 (N=O asym) and 1349 cm^{-1} (N=O sym). Reduction of *N*-*n*.butyl-4,5-dimethoxy-2-nitrobenzamide (**9**) with iron powder and ammonium chloride in aq. ethanol gave 2-amino-*N*-*n*.butyl-4,5-dimethoxybenzamide (**10**). Peaks were observed at 3409 (N-H str) and 1637 cm^{-1} (C=O str) in its IR spectrum. 2-Amino-*N*-*n*.butyl-4,5-dimethoxybenzamide (**10**) was then reacted with chloroacetyl chloride to form 2-(2-chloroacetamido)-*N*-*n*.butyl-4,5-dimethoxybenzamide (**11**). Its IR spectrum showed peaks at 3404 (N-H str), 1666 (C=O str), 1262 (C-N str) and 1212 cm^{-1} (Ar-O str). Molecular ion peak was obtained at m/z 329 in its mass spectrum. 2-(2-Chloroacetamido)-*N*-*n*.butyl-4,5-dimethoxybenzamide (**11**) was cyclised in presence of sodium *t*.butoxide and ethylene glycol to form 3-*n*.butyl-2-(chloromethyl)-6,7-dimethoxyquinazolin-4(3*H*)-one (**12**). The IR peaks were observed are 1669 (C=O str), 1260 (Ar-O str) and 1039 cm^{-1} (O-CH_3 str). Its mass spectrum showed molecular ion peak at m/z 311.

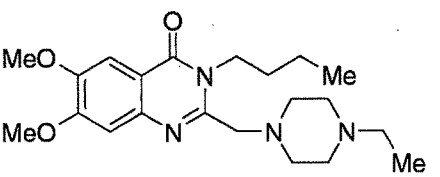
- **Synthesis of 3-*n*.butyl-6,7-dimethoxy-2-[(4-substituted piperazin-1-yl)methyl] quinazolin-4(3*H*)-ones (Series I)**

Synthesis of 3-*n*.butyl-6,7-dimethoxy-2-[(4-substitutedpiperazin-1-yl)methyl]quinazolin-4(3*H*)-ones were accomplished by following **Scheme 3**. Compound (**12**) and substituted amines in DMF were stirred at 60°C until the reaction was complete.

3-*n*.Butyl-6,7-dimethoxy-2-[(4-methylpiperazin-1-yl)methyl]quinazoline-4(3*H*)-one (**I-1**) displayed characteristic peaks at 1662 (C=O str), 1242 (Ar-O str) and 1012 cm^{-1} (O-CH_3 str) in its IR spectrum.



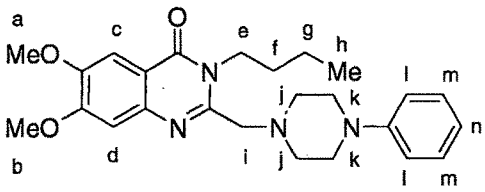
(**I-1**)

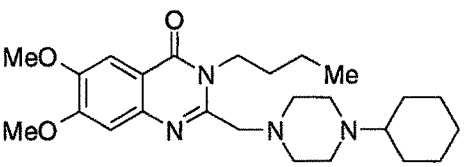


(**I-2**)

3-*n*.Butyl-2-[(4-ethylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4(3*H*)-one (**I-2**) showed characteristic peaks at 1663 (C=O str), 1266 (Ar-O str) and 1019 cm^{-1} (O-CH_3 str) in its IR spectrum.

3-*n*.Butyl-6,7-dimethoxy-2-[(4-phenylpiperazin-1-yl)methyl]quinazolin-4(3*H*)-one (**I-3**) displayed characteristic peaks at 1667 (C=O str), 1266 (Ar-O str) and 1053 cm^{-1} (O-CH_3 str) in its IR spectrum. Signals appeared at δ 7.43 (s, 1H, Ar-H_c), 7.22-7.15 (m, 3H, Ar-H_l and Ar-H_d), 6.93-6.91 (m, 2H, Ar-H_m), 6.79-6.75 (m, 1H, Ar-H_n), 4.15-4.11 (t, 2H, CH_{2e}), 3.90 (s, 3H, $OCH_{3a/3b}$), 3.87 (s, 3H, $OCH_{3a/3b}$), 3.69 (s, 2H, CH_{2i}), 3.12 (b, 4H, 2 × CH_{2k}), 2.63 (m, 4H, 2 × CH_{2j}), 1.72-1.69 (m, 2H, CH_{2f}), 1.41-1.35 (m, 2H, CH_{2g}) and 0.94-0.92 (t, 3H, CH_{3h}) in its NMR spectrum.

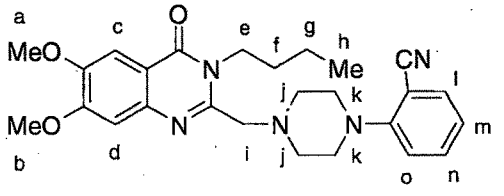




(I-3) **(I-4)**

3-*n*.Butyl-2-[(4-cyclohexylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4(3*H*)-one (**I-4**) displayed characteristic peaks at 1660 (C=O str), 1271 (Ar-O str) and 1051 cm^{-1} (O-CH_3 str) in its IR spectrum.

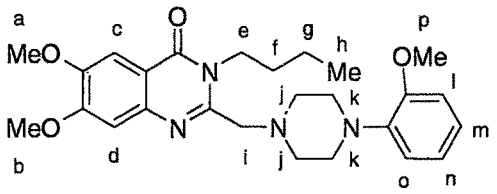
IR spectrum of 2-[4-((3-*n*.butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2-yl)methyl)piperazin-1-yl]benzonitrile (**I-5**) displayed characteristic IR peaks at 2220 (C≡N str), 1669 (C=O str), 1265 (Ar-O str) and 1016 cm^{-1} (O-CH_3 str). Its NMR spectrum showed signals at δ 7.72-7.69 (m, 1H, Ar-H_l), 7.62-7.57 (m, 1H, Ar-H_n), 7.44 (s, 1H, Ar-H_c), 7.17 (s, 1H, Ar-H_d), 7.14-7.08 (m, 2H, Ar-$H_{n,o}$), 4.16-4.12 (t, 3H, N-CH_{2e}), 3.90 (s, 3H, O-$CH_{3a/b}$), 3.87 (s, 3H, O-$CH_{3a/b}$), 3.71 (s, 2H, CH_{2i}), 3.14 (b, 4H, CH_{2k}), 2.68 (b, 4H, CH_{2j}), 1.73-1.69 (m, 2H, CH_{2f}), 1.42-1.37 (m, 2H, CH_{2g}) and 0.96-0.93 (t, 3H, CH_{3h})



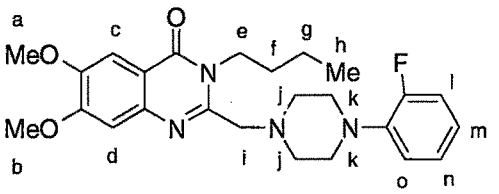
(I-5)

3-*n*.Butyl-6,7-dimethoxy-2-[(4-(2-methoxyphenyl)piperazin-1-yl)methyl]quinazolin-4-(3*H*)-one (**I-6**) displayed characteristic peaks at 1669 (C=O str), 1238 (Ar-O str) and 1053 cm^{-1} (O-CH_3 str) in its IR spectrum. Its gave signals at δ 7.42 (s, 1H, Ar-

H_c), 7.14 (s, 1H, Ar-H_d), 6.92-6.85 (m, 4H, Ar-$H_{o\text{-}l}$), 4.13 (m, 2H, N-CH_{2e}), 3.90 (s, 3H, O-$CH_{3a/b}$), 3.86 (s, 3H, O-$CH_{3a/b}$), 3.76 (s, 3H, O-CH_{3p}), 3.68 (s, 2H, -CH_{2i}), 2.95 (b, 4H, CH_{2k}), 2.61 (b, 4H, CH_{2j}), 1.73 (m, 2H, CH_{2f}), 1.39-1.37 (m, 2H, CH_{2g}) and 0.95-0.92 (t, 3H, CH_{3h}) in its NMR spectrum.



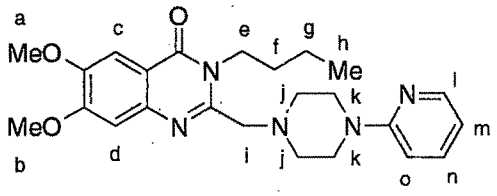
(I-6)



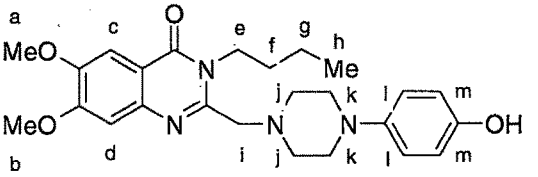
(I-7)

3-*n*.Butyl-2-[(4-(2-fluorophenyl)piperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-(3*H*)-one (**I-7**) displayed characteristic peaks at 1666 (C=O str), 1237 (Ar-O str) and 1052 cm^{-1} (O-CH_3 str) in its IR spectrum. Its NMR peaks were obtained at δ 7.42 (s, 1H, Ar-H_c), 7.15 (s, 1H, Ar-H_d), 7.13-7.07 (m, 2H, Ar-H_n and H_l), 7.03-6.95 (m, 2H, Ar-H_o and H_m), 4.15-4.11 (m, 2H, N-CH_{2e}), 3.90 (s, 3H, O-$CH_{3a/b}$), 3.87 (s, 3H, O-$CH_{3a/b}$), 3.69 (s, 2H, CH_{2i}), 3.00 (s, 4H, CH_{2k}), 2.65 (s, 4H, CH_{2j}), 1.73-1.69 (m, 2H, CH_{2f}), 1.44-1.34 (m, 2H, CH_{2g}) and 0.96-0.92 (t, 3H, CH_{3h}). Molecular ion peak was observed at m/ z 467.45 in its mass spectrum.

IR spectrum of 3-*n*.butyl-6,7-dimethoxy-2-[(4-(pyridin-2-yl)piperazin-1-yl)methyl]quinazolin-4(3*H*)-one (**I-8**) showed characteristic peaks at 1668 (C=O str), 1244 (Ar-O str) and 1052 cm^{-1} (O-CH_3 str). Its NMR showed signals at δ 8.1 (m, 1H, Ar-H_l), 7.55-7.50 (m, 1H, Ar-H_m), 7.43 (s, 1H, Ar-H_c), 7.15 (s, 1H, Ar-H_d), 6.82-6.80



(I-8)

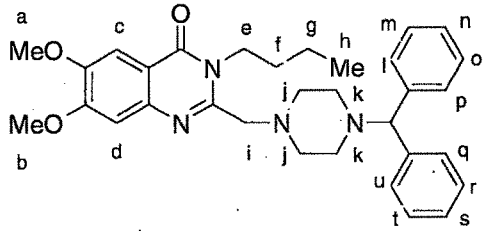


(I-9)

(m, 1H, Ar-H_o), 6.66-6.63 (m, 1H, Ar-H_n), 4.17-4.13 (t, 2H, N-CH_{2e}), 3.90 (s, 3H, O$CH_{3a/b}$), 3.87 (s, 3H, O$CH_{3a/b}$), 3.68 (s, 2H, CH_{2i}), 3.46 (b, 4H, 2 × CH_{2k}), 2.57 (b, 4H, 2 × CH_{2j}), 1.73-1.69 (m, 2H, CH_{2f}), 1.42- 1.35 (m, 2H, CH_{2g}) and 0.97-0.93 (t, 3H, CH_{3h}).

3-*n*.Butyl-2-[(4-(4-hydroxyphenyl)piperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-(3*H*)-one (**I-9**) gave characteristic peaks at 1660 (C=O str), 1272 (Ar-O str) and 1020 cm^{-1} (O-CH_3 str) in its IR spectrum. Its NMR showed signals at δ 8.85 (s, 1H, O*H*), 7.43 (s, 1H, Ar-H_c), 7.15 (s, 1H, Ar-H_d), 6.77-6.75 (d, 2H, Ar-H_m), 6.64-6.62 (d, 2H, Ar-H_l), 4.14-4.10 (t, 2H, N-CH_{2e}), 3.90 (s, 3H, $OCH_{3a/b}$), 3.86 (s, 3H, $OCH_{3a/b}$), 3.67 (s, 2H, CH_{2i}), 2.95 (bs, 4H, 2 × CH_{2k}), 2.60 (bs, 4H, 2 × CH_{2j}), 1.72-1.68 (m, 2H, CH_{2f}), 1.40- 1.33 (m, 2H, CH_{2g}) and 0.94-0.90 (t, 3H, CH_{3h}).

2-[(4-Benzhydrylpiperazin-1-yl)methy]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (**I-10**) displayed characteristic peaks at 1668 (C=O str), 1268 (Ar-O str) and 1005 cm^{-1} (O-CH_3 str) in its IR spectrum. Its NMR signals appeared at δ 7.40-7.10 (m, 12H, Ar-$H_{c,\ d}$ and $_{l-u}$), 4.07-4.04 (t, 2H, N-CH_{2e}), 3.88 (s, 3H, $OCH_{3a/b}$), 3.85 (s, 3H, $OCH_{3a/b}$), 3.68 (s, 2H, CH_{2i}), 2.69 (b, 4H, 2 × CH_{2k}), 2.08 (b, 4H, 2 × CH_{2j}), 1.67 (b, 2H, CH_{2f}), 1.36-1.33 (m, 2H, CH_{2g}) and 0.92-0.88 (t, 3H, CH_{3h}).



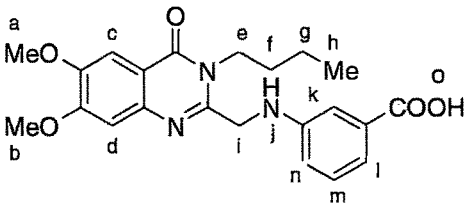
(I-10)

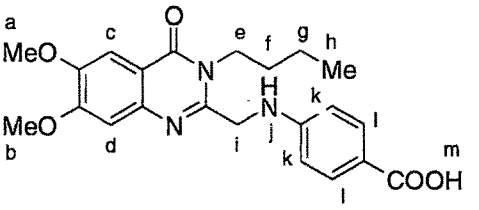
- **Synthesis of 2-[(3/4-substituted phenylamino)methyl]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (Series II)**

Synthesis of 2-[(3/4-substituted phenylamino)methyl]-3-*n*.butyl-6,7-dimethoxy quinazolin-4(3*H*)-ones were accomplished by **Scheme 3** as discussed above. 3-*n*.Butyl-2-(chloromethyl)-6,7-dimethoxyquinazolin-4(3*H*)-one (**12**) was reacted with different 3/4-substituted anilines in presence of flame dried cesium carbonate in dry DMF to obtain corresponding 2-[(3/4-substituted phenylamino)methyl]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one.

3-[(3-*n*.Butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2-yl)methylamino] benzoic acid (**II-1**) displayed characterstic peaks at 3360 (broad O-H str), 1717 and 1662 (C=O str), 1226 (Ar-O str) and 1098 cm^{-1} (O-CH_3 str) in its IR spectrum. Signals appeared at δ 7.61 (s, 1H, Ar-H_c), 7.49-7.47 (m, 1H, Ar-H_l), 7.39-7.38 (m, 1H, Ar-

H_k), 7.28-7.21 (m, 1H, Ar-H_m), 7.08 (s, 1H, Ar-H_d), 6.91-6.88 (m, 1H, Ar-H_n), 5.39 (s, 2H, CH_{2i}), 4.12-4.08 (t, 2H, N-CH_2), 4.01 (s, 3H, $OCH_{3a/3b}$), 4.00 (s, 3H, $OCH_{3a/3b}$), 1.78-1.72 (m, 2H, CH_{2f}); 1.43-1.37 (m, 2H, CH_{2g}) and 0.93-0.89 (t, 3H, CH_{3h}) in its NMR spectrum. Molecular ion peak was observed at m/z 410.9 in its mass spectrum.

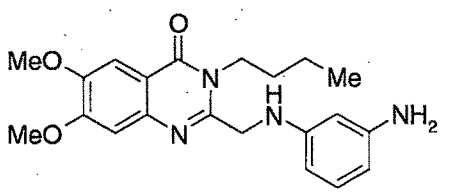


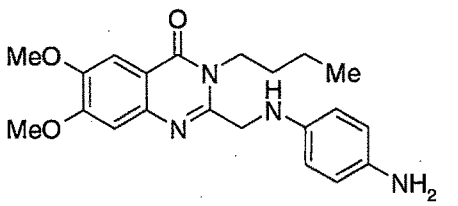


(II-1) **(II-2)**

4-[(3-*n*.Butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2yl)methylamino] benzoic acid (**II-2**) showed characteristic peaks at 1700, 1657 (C=O str), 1272 (Ar-O str) and 1028 cm^{-1} (O-CH_3 str) in IR spectrum. Its NMR spectrum gave signals at δ 7.91-7.89 (d, 2H, Ar-H_l), 7.61 (s, 1H, Ar-H_c), 7.09 (s, 1H, Ar-H_d), 6.66-6.64 (d, 2H, Ar-H_k), 5.37 (s, 2H, NH-CH_2), 4.14-4.04 (t, 2H, N-CH_{2e}), 4.00 (s, 3H, $OCH_{3a/3b}$), 3.98 (s, 3H, $OCH_{3a/3b}$), 1.77-1.74 (m, 2H, CH_{2f}), 1.42-1.36 (m, 2H, CH_{2g}) and 0.91-0.88 (t, 3H, CH_{3h}). Molecular ion peak was observed at 410.9 (m/z) in its mass spectrum.

2-[(3-Aminophenylamino)methyl]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (**II-3**) showed characteristic IR peaks at 3131 (N-H str), 1663 (C=O str), 1210 (Ar-O str) and 1167 cm^{-1} (O-CH_3 str). Mass spectrum of the compound (**II-3**) showed molecular ion peak at m/z 382.13.

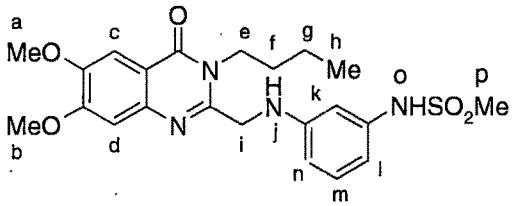




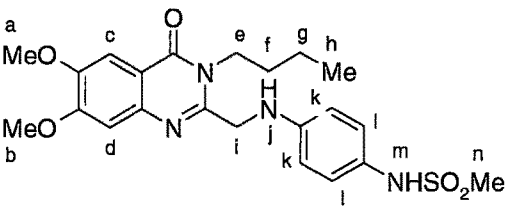
(II-3) **(II-4)**

2-[(4-Aminophenylamino)methyl]-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (**II-4**) showed characteristic peaks at 3127 (N-H str), 1678 (C=O str), 1261 (Ar-O str) and 1095 cm^{-1} (O-CH_3 str) in its IR spectrum. Molecular ion peak was observed at m/z 381.20 in its mass spectrum.

IR apectrum of *N*-[3-[(3-*n*.butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2yl)methylamino]phenyl]methanesulfonamide (**II-5**) showed characteristic peaks at 3444 and 3361 (N-H str), 1678 (C=O str), 1331 and 1147 (SO_2 str) and 1082 cm^{-1} (O-CH_3 str). Peaks were observed at δ 7.57 (s, 1H, Ar-H_c), 7.13-7.09 (m, 1H, Ar-H_m), 6.93 (s, 1H, Ar-H_d), 6.92-6.88 (m, 2H, Ar-H_n and H_l), 6.60-6.58 (m, 1H, Ar-H_k), 4.99 (s, 2H, CH_{2i}), 4.14-4.11 (t, 2H, N-CH_{2e}), 3.98 (s, 6H, $OCH_{3a/b}$), 3.73 (b, 1H, NH_o), 3.23 (s, 3H, CH_{3p}), 1.71-1.67 (m, 2H, CH_{2f}), 1.47-1.41 (m, 2H, CH_{2g}) and 0.99-0.95 (t, 3H, CH_{3h}) in its NMR spectrum. Molecular ion peak was observed at 460.10 (m/z) in its mass spectrum.



(II-5)

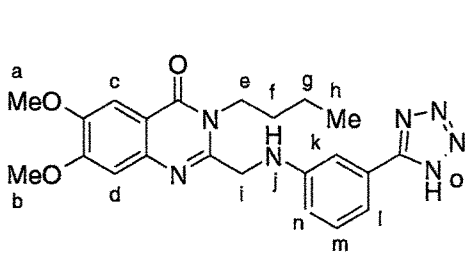


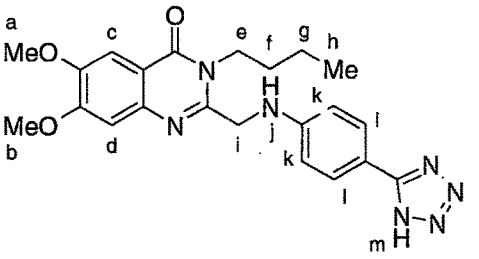
(II-6)

N-[4-[(3-*n*.Butyl-3,4-dihydro-6,7-dimethoxy-4-oxoquinazolin-2yl)methylamino]phenyl]methanesulfonamide (**II-6**) displayed characteristic peaks at 3462 and 3366 (N-H str), 1655 (C=O str), 1338 and 1145 (SO_2 str), 1272 (Ar-O str) and 1078 cm^{-1} (O-CH_3 str) in its IR spectrum. Its NMR spectrum gave signals at δ 7.56 (s, 1H, Ar-H_c) 7.31-7.28 (d, 2H, Ar-H_k), 6.94 (s, 1H, Ar-H_d), 6.60-6.58 (d, 2H, Ar-H_l), 4.96 (s, 2H, CH_{2i}), 4.16-4.12 (t, 2H, N-CH_{2e}), 3.99 (s, 3H, $OCH_{3a/3b}$), 3.98 (s, 3H, $OCH_{3a/3b}$), 3.16 (s, 3H, CH_{3n}), 1.68-1.61 (m, 2H, CH_{2f}), 1.46-1.41 (m, 2H, CH_{2g}) and 0.99-0.95 (t, 3H, CH_{3h}). Molecular ion peak was observed at 460.09 (m/z) in mass spectrum.

Characteristic peaks at 3416 (N-H str), 1665 (C=O str), 1262 (Ar-O str) and 1038 cm^{-1} (O-CH_3 str) were obsereved in IR spectrum for 2-[(3-(1*H*-tetrazol-5-yl)phenylaminomethyl)-3-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (**II-7**). Its NMR spectrum showed signals at δ 7.52 (s, 1H, Ar-H_c), 7.45 (s, 1H, Ar-H_k), 7.40-7.38 (m, 1H, Ar-H_n), 7.22-7.18 (m, 1H, Ar-H_m), 6.91 (s, 1H, Ar-H_d) 6.78-6.77 (d, 1H, Ar-H_l), 6.14 (s, 2H, N*H*), 4.21-4.13 (t, 2H, N-CH_{2e}), 3.95 (s, 3H, $OCH_{3a/b}$), 3.90 (s, 3H, $OCH_{3a/b}$), 1.66-1.59 (m, 2H, CH_{2f}), 1.51-1.43 (h, 2H, CH_{2g}) and 0.88-0.85 (t, 3H, CH_{3h}). Molecular ion peak was obsereved at m/z 434.98 in mass spectrum.

2-[(4-(1*H*-Tetrazol-5-yl)phenylaminomethyl]-3-*n*.butyl-6,7-dimethoxyquinazo -lin-4(3*H*)-one (**II-8**) showed characteristic peaks at 3359 (N-H str), 1664 (C=O str), 1270 (Ar-O str) and 1037 cm^{-1} (O-CH_3 str) in its IR spectrum. Signals appeared in its NMR spectrum at δ 7.80-7.78 (d, 2H, Ar-H_l), 7.49 (s, 1H, Ar-H_c), 6.89 (s, 1H, Ar-H_d),



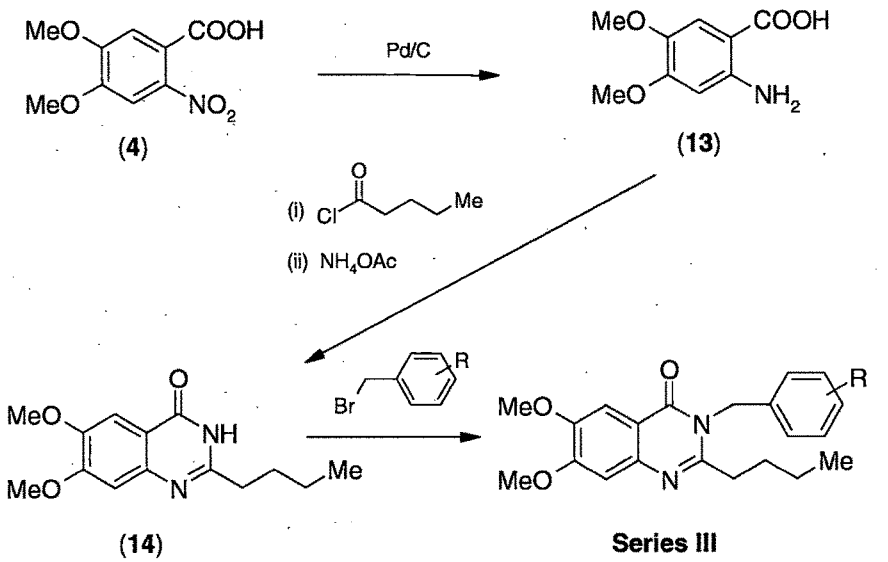


(II-7) **(II-8)**

6.72-6.69 (d, 2H, Ar-H_k), 6.14 (s, 2H, N*H*), 4.19-4.15 (t, 2H, NCH_{2i}), 3.98 (s, 3H, O$CH_{3a/b}$), 3.92 (s, 3H, O$CH_{3a/b}$), 1.62-1.55 (m, 2H, CH_{2f}), 1.48-1.42 (m, 2H, CH_{2g}) and 0.99-0.84(t, 3H, CH_{3h}). Molecular ion peak was observed at m/z 435.17 in mass spectrum.

4.1.3 Synthesis of 3-(3/4-substituted benzyl)-2-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-ones (Series III)

Reduction of 6-nitroveratric acid (**4**) with palladium charcoal afforded 4,5-dimethoxyanthranilic acid (**13**) which showed characteristic peak at 3374cm^{-1}. A solu-

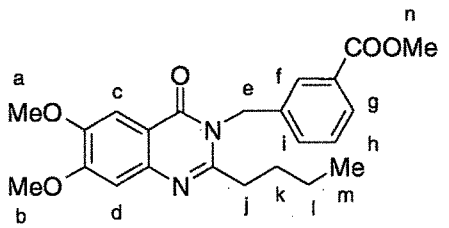


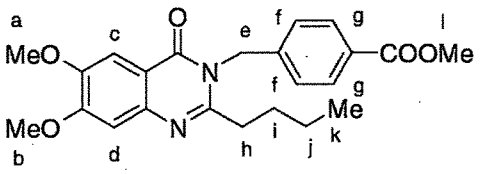
Scheme 4

tion of 4, 5-dimethoxyanthranilic acid (**13**) and valeroyl chloride in DMF was heated

to afford the cyclised compound 2-*n*.butyl-6,7-dimethoxy-benz[1,3-*d*]-4*H*-oxazin-4-one. It was isolated and characterized through IR. Its IR spectrum showed peak at 1746 (C=O str.) cm^{-1}. However, this compound was sensitive to moisture and therefore it was treated *in situ* with ammoniun acetate to afford the desired compound 2-*n*.Butyl-6,7-dimethoxyquinazolin-4(3*H*)-one (**14**) as solid. Its IR spectrum showed peaks at 3157 (N-H str.) and 1670 (C=O str.) cm^{-1}. The molecular ion peak was observed at m/z 262.06 in its mass spectrum. Compound (**14**) was thenreacted with different substituted benzyl bromides in acetone at RT in order to get 3-(3/4-substituted benzyl)-2-*n*.butyl-6,7-dimethoxyquinazolin- 4(3*H*)-ones (**Scheme 4**).

Methyl 3-[(2-*n*.butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl) benzoate (**III-1**) displayed characteristic peaks at 1669 (C=O str.), 1273 (Ar-O str.) and 1032 cm^{-1} (O-CH_3 str.) in its IR spectrum.

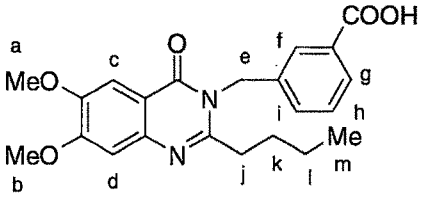




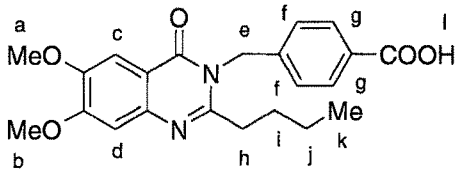
(III-1) **(III-2)**

Methyl 4-[(2-*n*.butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzoate (**III-2**) showed characteristic peaks at 1720, 1654 (C=O str.), 1283, (Ar-O str.) and 1012 cm^{-1} (O-CH_3 str.) in its IR spectrum. NMR signals were appeared at δ 7.94- 7.92 (d, 2H, Ar-H_g), 7.46 (s, 1H, Ar-H_c), 7.29-7.27 (d, 2H, Ar-H_f), 7.11 (s, 1H, Ar-H_d), 5.46 (s, 2H, CH_{2e}), 3.92 (s, 3H, $OCH_{3a/b}$), 3.87 (s, 3H, $OCH_{3a/b}$), 3.83 (s, 3H, OCH_{3l}), 2.68-2.65 (t, 2H, CH_{2h}), 1.67-1.59 (m, 2H, CH_{2i}), 1.33-1.24 (m, 2H, CH_{2j}) and 0.82-0.79 (t, 3H, CH_{3k}).

3-[(2-*n*.Butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzoic acid (**III-3**) displayed characteristic peaks at 3130 (O-H str.), 1703, 1660 (C=O str.) and 1288 cm^{-1} (Ar-O str.) in its IR spectrum. Its NMR spectrum exhibited signals at δ 7.86-7.84 (d, 1H, Ar-H_g), 7.68 (s, 1H, Ar-H_f), 7.51-7.43 (m, 3H, Ar-$H_{c, h, i}$), 7.11 (s, 1H, Ar-H_d), 5.77 (s, 2H, N-CH_{2e}), 3.92 (s, 3H, $OCH_{3a/b}$), 3.88 (s, 3H, $OCH_{3a/b}$), 2.71-2.67 (m, 2H, CH_{2j}), 1.64-1.60 (m, 2H, CH_{2k}), 1.31-1.27 (m, 2H, CH_{2l}) and 0.84-0.77 (t, 3H, CH_{3m}).



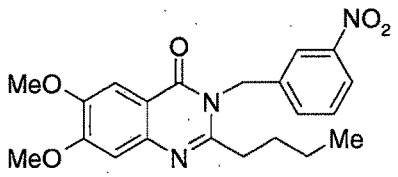
(III-3)



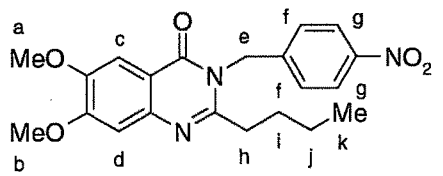
(III-4)

4-[(2-*n*.Butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzoic acid (**III-4**) displayed characteristic peaks at 3413 (O-H str.), 1670, 1638 (C=O str.), 1254 (Ar-O str.) and 1058 cm^{-1} (O-CH_3 str.) in its IR spectrum. Signals were obtained at δ 8.23-8.21 (d, 2H, Ar-H_g), 7.46 (s, 1H, Ar-H_c), 7.43-7.41 (d, 2H, Ar-H_f), 7.12 (s, 1H, Ar-H_d), 5.51 (s, 2H, N-CH_{2e}), 3.93 (s, 3H, O$CH_{3a/b}$), 3.88 (s, 3H, O$CH_{3a/b}$), 2.70-2.66 (m, 2H, CH_{2h}), 1.69-1.62 (m, 2H, CH_{2i}), 1.35-1.23 (m, 2H, CH_{2j}) and 0.87-0.83 (t, 3H, CH_{3k}) in its NMR spectrum.

2-*n*.Butyl-6,7-dimethoxy-3-(3-nitrobenzyl)quinazolin-4(3*H*)-one (**III-5**) displayed characteristic peaks at 1664 (C=O str.), 1530 (N=O asym.), 1351 (N=O sym.) and 1228 cm^{-1} (Ar-O str.) in its IR spectrum.



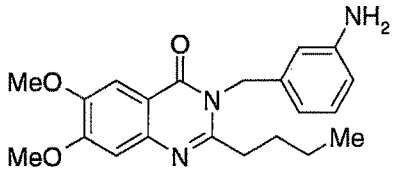
(III-5)



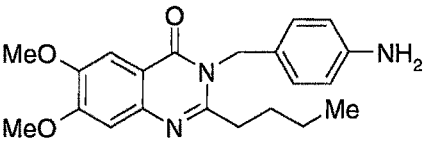
(III-6)

2-*n*.Butyl-6,7-dimethoxy-3-(4-nitrobenzyl)quinazolin-4(3*H*)-one (**III-6**) showed characteristic peaks at 1657 (C=O str.), 1520 (N=O asym.), 1345 (N=O sym.) and 1230 cm^{-1} (Ar-O str.) in its IR spectrum. Its ^{1}NMR spectrum showed signals at 8.20-8.18 (d, 2H, Ar-H_g), 7.50 (s, 1H, Ar-H_c), 7.44-7.41 (d, 2H, Ar-H_f) 7.10 (s, 1H, Ar-H_d), 5.29 (s, 2H, NCH_2), 3.97 (s, 3H, O$CH_{3a/b}$), 3.92 (s, 3H, O$CH_{3a/b}$), 2.71-2.67 (t, 2H, CH_{2h}), 1.73-1.67 (m, 2H, CH_{2i}), 1.39-1.33 (m, 2H, CH_{2j}) and 0.90-0.86 (t, 3H, CH_{3k}).

3-(3-Aminobenzyl)-2-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one(**III-7**) displayed characteristic peaks at 3413, 3115 (N-H str.), 1664 (C=O str.) and 1271 (Ar-O str.) in its IR spectrum.



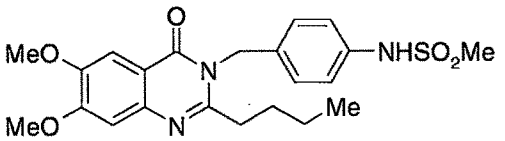
(III-7)



(III-8)

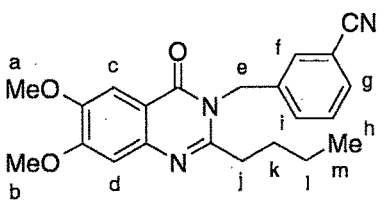
3-(4-Aminobenzyl)-2-*n*.butyl-6,7-dimethoxyquinazolin-4(3*H*)-one **(III-8)** displayed characteristic peaks at 3413, 3159 (N-H str.), 1658 (C=O str.), 1266 cm^{-1} (Ar-O str.) in its IR spectrum.

IR spectrum of *N*-[4-((2-*n*.butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl)phenyl]methanesulfonamide **(III-9)** displayed characteristic peaks at 3414 and 3143 (N-H str.), 1659 (C=O str.), 1335 (S=O str.), 1247 (Ar-O str.), 1152 (S=O str.) and 1013 cm^{-1} (O-CH_3 str.) in its IR spectrum.

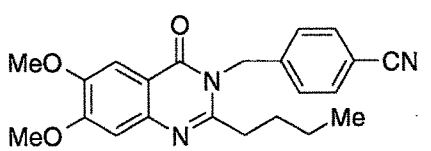


(III-9)

3-[(2-*n*.Butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzonitrile **(III-10)** displayed characteristic peaks at 2230 (C≡N str.), 1660 (C=O str.), 1245 (Ar-O str.) and 1012 cm^{-1} (O-CH_3 str) in its IR spectrum. Peaks were observed at δ 7.63-7.62 (m, 1H, Ar-H_g), 7.56-7.51 (m, 4H, Ar-$H_{c, f, h, i}$), 7.20 (s, 1H, Ar-H_d), 5.46 (s, 2H, NCH_{2e}), 4.00 (s, 3H. O-$CH_{3a/b}$), 3.97 (s, 3H, O-$CH_{3a/b}$), 2.81-2.77 (t, 2H, CH_{2j}), 1.74-1.68 (m, 2H, CH_{2k}), 1.43-1.38 (m, 2H, CH_{2l}) and 0.92-0.88 (t, 3H, CH_{3m}). Molecular ion peak was observed at m/z 377.90 in its mass spectrum.



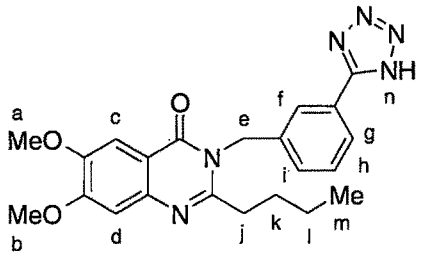
(III-10)



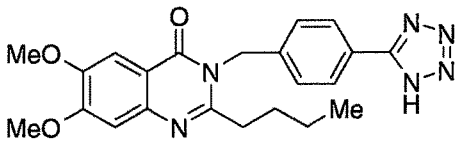
(III-11)

4-[(2-*n*.Butyl-6,7-dimethoxy-4-oxoquinazolin-3(4*H*)-yl)methyl]benzonitrile **(III-11)** displayed characteristic peaks at 2228 (C≡N str.), 1658 (C=O str.), 1245 (Ar-O str.) and 1013 cm^{-1} (O-CH_3 str.) in its IR spectrum.

2-*n*.Butyl-6,7-dimethoxy-3-[3-(1*H*-tetrazol-5-yl)benzyl]quinazolin-4(3*H*)-one (**III-12**) displayed characteristic peaks at 3132 (N-H str.), 1638 (C=O str.), 1245 (Ar-O str.) and 1024 cm^{-1} (O-CH_3 str.) in its IR spectrum. NMR signals appeared at 7.96-7.94 (d, 1H, Ar-H_g), 7.82 (s, 1H, Ar-H_c), 7.61-7.57 (t, 1H, Ar- H_h), 7.48 (s, 1H, Ar-H_f), 7.42-7.40 (d, 1H, Ar-H_i), 7.12 (s, 1H, Ar-H_d), 5.48 (s, 2H, CH_{2e}), 3.92 (s, 3H, O-$CH_{3a/b}$), 3.88 (s, 3H, O-$CH_{3a/b}$), 2.74-2.71 (t, 2H, CH_{2j}), 1.69-1.61 (m, 2H, CH_{2k}), 1.32-1.26 (m, 2H, CH_{2l}), 0.84-0.80 (t, 3H, CH_{3m}).



(**III-12**)

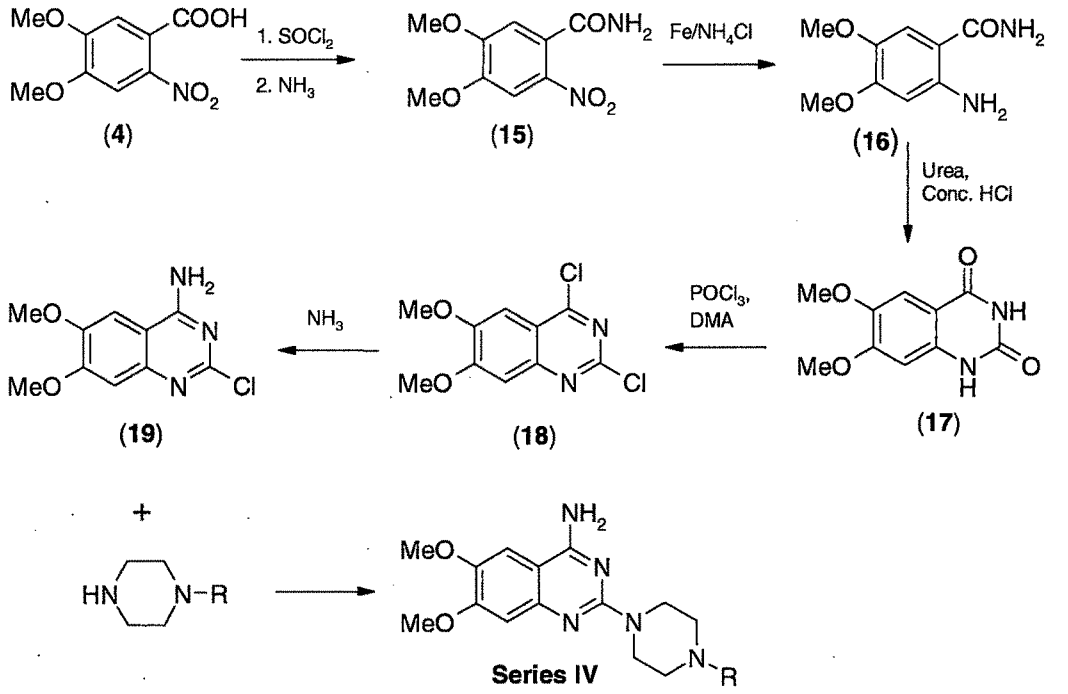


(**III-13**)

2-*n*.Butyl-6,7-dimethoxy-3-[4-(1*H*-tetrazol-5-yl)benzyl]quinazolin-4(3*H*)-one (**III-13**) displayed characteristic peaks at 3418, 3013 (N-H str.), 1649 (C=O str.), 1252 (Ar-O str.) and 1067 cm^{-1} (O-CH_3 str.) in its IR spectrum.

4.1.4 Synthesis of 2-chloro-6,7-dimethoxyquinazolin-4-amine (19)

The acid (**4**) was converted into amide (**15**) by treatment of its acid chloride with ammonia. Nitro group of the amide (**15**) was reduced to amino using iron-ammonium chloride to obtain 2-amino-4,5-dimethoxybenzamide (**16**). The amide (**16**) was condensed with urea in presence of catalytic amount of hydrochloric acid to afford 6,7-dimethoxy-1,2,3,4-tetrahydroquinazoline-2,4-dione (**17**).[377] Compound (**17**) was treated with phosphorus oxychloride in presence of catalytic amount of *N,N*-dimethylaniline (DMA) to yield 2,4-dichloro-6,7-dimethoxyquinazoline (**18**)[378]. In light of the reported[379] susceptibility of 4-chloroquinazoline towards moisture, compound (**18**) was used immediately after its preparation. Compound (**18**) was treated with dry ammonia gas in THF for 36 hours to obtain 4-amino-2-chloro-6,7-dimethoxyquoinazoline (**19**). IR spectrum for compound (**19**) showed characteristic peaks at 3409 & 3326 (N-H str.), 1279 (C-N str.), 1250 (Ar-O str.) and 1026 cm^{-1} (O-CH_3 str.). Its mass apectrum showed M+H peak at m/z 240.

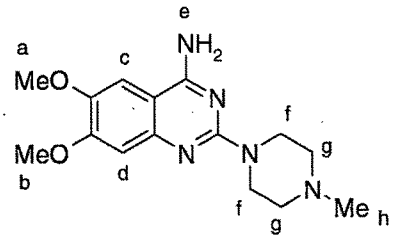


Scheme 5

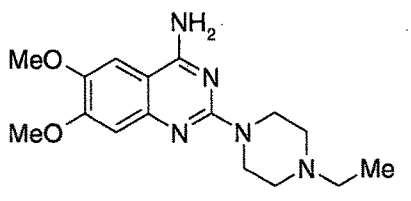
- **Synthesis of 6,7-dimethoxy-2-(4-substituted piperazin-1-yl)quinazolin-4-amines (Series IV)**

6,7-Dimethoxy-2-(4-substituted piperazin-1-yl)quinazolin-4-amines were prepared by reacting substituted piperazines with compound (**19**). Compound (**19**) and substituted piperazines in DMF were stirred at 100° C in sealed tube until the reaction was complete (**Scheme 5**).

6,7-Dimethoxy-2-(4-methylpiperazin-1-yl)quinazolin-4-amine (**IV-1**) showed characteristic peaks at 3555 and 3334 (N-H str.), 1280 (C-N str.), 1244 (Ar-O str.) and



(**IV-1**)

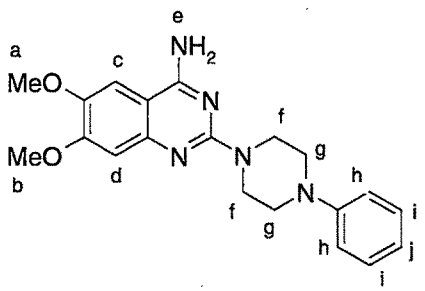


(**IV-2**)

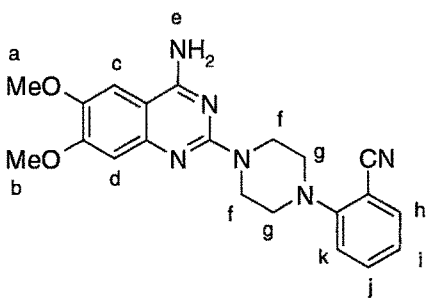
1002 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.40 (s, 1H, Ar-H_d), 7.09 (b, 2H, NH_{2e}), 6.70 (s, 1H, Ar-H_c), 3.82 (s, 3H, $OCH_{3a/b}$), 3.77 (s, 3H, $OCH_{3a/b}$), 3.68 (b, 4H, 2 × CH_{2f}), 2.33 (b, 4H, 2 × CH_{2g}) and 2.19 (s, 3H, CH_{3h}).

2-(4-Ethylpiperazin-1-yl)-6,7-dimethoxyquinazolin-4-amine (**IV-2**) displayed characteristic peaks at 3291 and 3086 (N-H str.), 1294 (C-N str.) and 1248 (Ar-O str.) in its IR spectrum.

IR spectrum of 6,7-dimethoxy-2-(4-phenylpiperazin-1-yl)quinazolin-4-amine (**IV-3**) displayed characteristic peaks at 3456 and 3262 (N-H str.), 1288 (C-N str.), 1235 (Ar-O str.) and 1033 cm^{-1} (O-CH_3 str.). Its NMR showed signals at δ 7.42 (s, 1H, Ar-H_d), 7.25-7.21 (m, 2H, Ar-H_i), 7.15 (b, 2H, NH_{2e}), 7.01-6.99 (d, 2H, Ar-H_h), 6.82-6.78 (m, 1H, Ar-H_j), 6.74 (s, 1H, Ar-H_c), 3.83 (s, 6H, OCH_{3a} and OCH_{3b}), 3.17-3.15 (m, 8H, 4 × CH_{2f} and CH_{2g}) in its NMR spectrum.



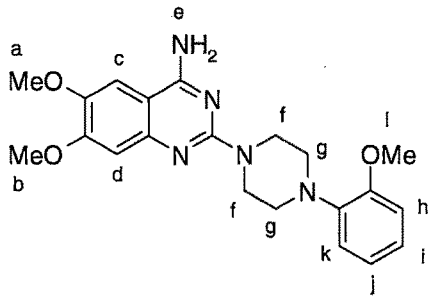
(**IV-3**)



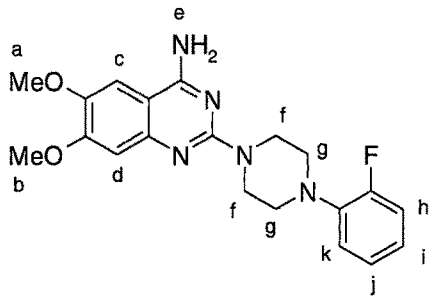
(**IV-4**)

2-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]benzonitrile (**IV-4**) showed characteristic peaks at 3491 and 3321 (N-H str.), 2218 (C≡N str.), 1284 (C-N str.), 1217 (Ar-O str.) and 1034 cm^{-1} (O-CH_3 str.) in its IR spectrum. Peaks were observed at δ 7.75-7.73 (dd, 1H, Ar-H_h), 7.73-7.60 (m, 1H, Ar-H_j), 7.43 (s, 1H, Ar-H_d), 7.23-7.06 (m, 4H, Ar-H_k, Ar-H_i and NH_{2e}), 6.75 (s, 1H, Ar-H_c), 3.90-3.88 (m, 4H, 2 × CH_{2g}), 3.84 (s, 3H, $OCH_{3a/3b}$), 3.79 (s, 3H, $OCH_{3a/3b}$) and 3.19-3.17 (m, 4H, 2 × CH_{2f}) in its NMR spectrum. Molecular ion peak was observed at m/z 390.21 in its mass spectrum.

IR spectrum of 6,7-dimethoxy-2-[4-(2-methoxyphenyl)piperazin-1-yl]quinazolin-4-amine (**IV-5**) displayed characteristic peaks at 3412 and 3211 (N-H str.), 1291 (C-N str.), 1247 (Ar-O str.) and 1028 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.42 (s, 1H, Ar-H_d), 7.13 (b, 2H, NH_{2e}), 6.97-6.85 (m, 4H, Ar H_h-H_k), 6.73 (s, 1H, Ar-H_c), 3.85-3.83 (b, 7H, 2 × CH_{2g} and OCH_{3l}), 3.80 (s, 3H, $OCH_{3a/b}$), 3.78 (s, 3H, $OCH_{3a/b}$) and 2.98-2.96 (t, 4H, 2 × CH_{2f}).



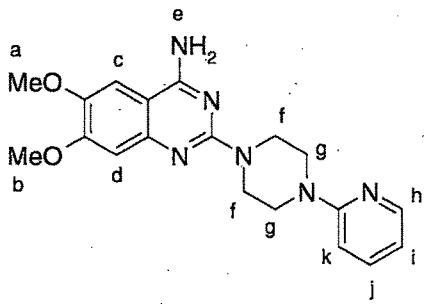
(IV-5)



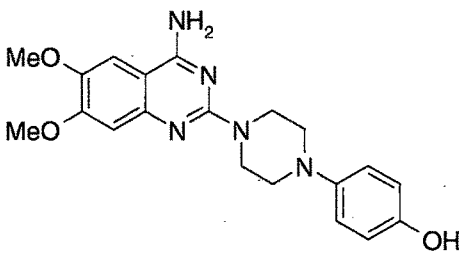
(IV-6)

2-[4-(2-Fluorophenyl)piperazin-1-yl]-6,7-dimethoxyquinazolin-4-amine (**IV-6**) displayed characteristic peaks at 3484 and 3371 (N-H str.), 1281 (C-N str.), 1235 (Ar-O str.) and 1033 cm^{-1} (O-CH_3 str.) in its IR spectrum. Signals appeared at δ 7.42 (s, 1H, Ar-H_d), 7.18-6.98 (m, 6H, Ar H_h-H_k and NH_{2e}), 6.74 (s, 1H, Ar-H_c), 3.88-3.86 (t, 4H, 2 × CH_{2g}), 3.83 (s, 3H, $OCH_{3a/b}$), 3.78 (s, 3H, $OCH_{3a/b}$) and 3.04-3.02 (t, 4H, 2 × CH_{2f}) in its NMR spectrum.

6,7-Dimethoxy-2-(4-(pyridin-2-yl)piperazin-1-yl)quinazolin-4-amine (**IV-7**) showed characterristic peaks at 3433 and 3189 (N-H str.), 1277 (C-N str.), 1235 (Ar-O str.) and 1033 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 8.13-8.12 (dd, 1H, Ar-H_h), 7.57-7.53 (m, 1H, Ar-H_i), 7.42 (s, 1H, Ar-H_d), 7.18 (b, 2H, NH_{2e}), 6.89-6.87 (d, 1H, Ar-H_k), 6.76 (s, 1H, Ar-H_c), 6.67-6.64 (m, 1H, Ar-H_j), 3.83-3.78 (m, 10H, 2 × CH_{2g} and 2 × OCH_3) and 3.55-3.52 (t, 4H, 2 × CH_{2f}).



(IV-7)

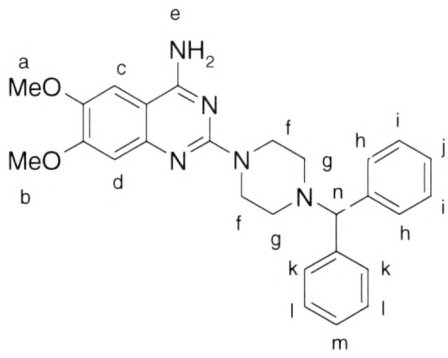


(IV-8)

IR spectrum of 4-[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)piperazin-1-yl]phenol (**IV-8**) displayed characterristic peaks at and 3357 (N-H str.), 3145 (broad O-H str.), 1279 (C-N str.) and 1230 cm^{-1} (Ar-O str.).

2-(4-Benzhydrylpiperazin-1-yl)-6,7-dimethoxyquinazolin-4-amine (**IV-9**) showed characterristic peaks at 3438 and 3330 (N-H str.), 1277 (C-N str.), 1239 (Ar-

O str.) and 1030 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.46-7.09 (m, 13H, 11 Ar-H_d, H_{h-m} and NH_{2e}), 6.68 (s, 1H, Ar-H_c), 4.30 (s, 1H, CH_n), 3.80 (s, 3H, O$CH_{3a/b}$), 3.76 (s, 3H, O$CH_{3a/b}$), 3.70 (s, 4H, 2 × CH_{2f}) and 2.36-2.33 (b, 4H, 2 × CH_{2g}).



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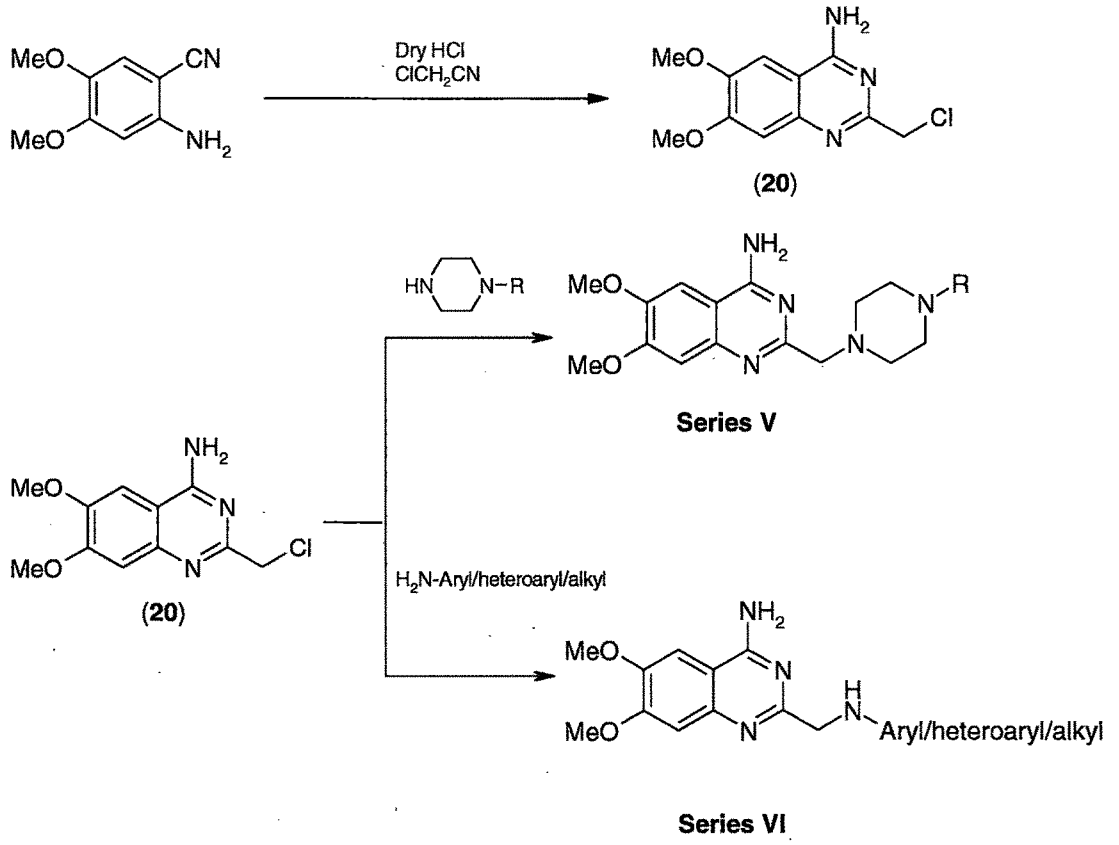
(IV-9)

4.1.5 Synthesis of 2-(chloromethyl)-6,7-dimethoxyquinazolin-4-amine (20)

2-(Chloromethyl)-6,7-dimethoxyquinazolin-4-amine (**20**) was required to prepare the desired 4-aminoquinazoline derivatives. It was prepared by reacting compound (**8**) with chloroacetonitrile in presence of dry hydrogen chloride in dioxane. Reaction was controlled and monitored regularly to prevent the formation of unwanted 2-(chloromethyl)-4-chloro-6,7-dimethoxyquinazolin. IR spectrum of compound (**20**) showed absence of peak of nitrile group around 2210 cm^{-1}. Peaks were observed at m/z 252.98 (M^+) and 254.99 (M+2) in its mass spectrum (**Scheme 6**).

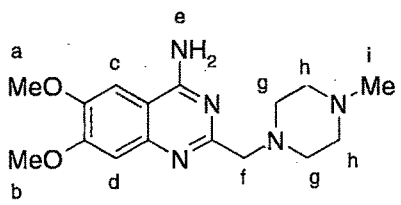
Synthesis of compounds belonging to Series V and Series VI were accomplished by following **Scheme 6**. Compound (**20**) and substituted amines were stirred at 60°C until the reaction was complete.



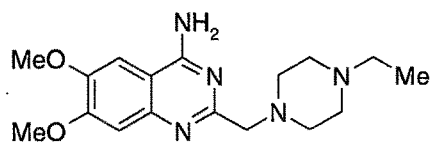
Scheme-6

- **Synthesis of 6,7-dimethoxy-2-(4-substituted piperazin-1-yl)quinazolin-4-amines (Series V)**

6,7-Dimethoxy-2-[(4-methylpiperazin-1-yl)methyl]quinazolin-4-amine (**V-1**) displayed characteristic peaks at 3131 (N-H str.), 1261 (C-N str.) and 1225 (Ar-O str.) in its IR spectrum. Its NMR spectrum gave signals δ 7.53 (s, 1H, Ar-H_d), 7.41 (b, 2H, NH_{2e}), 7.07 (s, 1H, Ar-H_c), 3.87 (s, 3H, $OCH_{3a/b}$), 3.85 (s, 3H, $OCH_{3s/3b}$), 3.40 (s, 2H, CH_{2f}), 2.50 (b, 4H, 2 × CH_{2g}), 2.28 (b, 4H, 2 × CH_{2h}) and 2.12 (s, 3H, CH_{2i}).



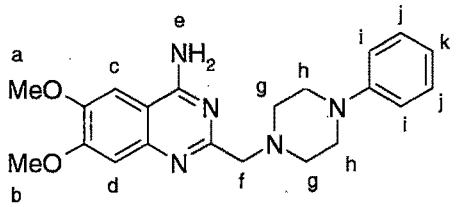
(**V-1**)



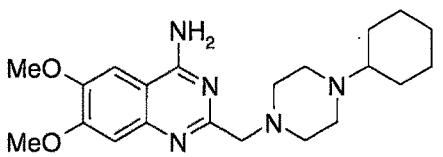
(**V-2**)

2-[(4-Ethylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (**V-2**) showed characteristic peaks at 3306 and 3146 (N-H str.), 1279 (C-N str.), 1248 (Ar-O str.) and 1016 cm^{-1} (O-CH_3 str.) in its IR spectrum.

6,7-Dimethoxy-2-[(4-phenylpiperazin-1-yl)methyl]quinazolin-4-amine (**V-3**) displayed characteristic peaks at 3313 and 3151 (N-H str.), 1281 (C-N str.), 1222 (Ar-O str.) and 1015 cm^{-1} (O-CH_3 str.) in its IR spectrum. Signals appeared at δ 7.55 (s, 1H, Ar-H_d), 7.44 (b, 2H, NH_{2e}), 7.21-7.17 (t, 2H, Ar-H_j), 7.09 (s, 1H, Ar-H_c), 6.92-6.90 (d, 2H, Ar-H_i), 6.77-6.73 (t, 1H, Ar-H_k), 3.89 (s, 3H, OC$H_{3a/b}$), 3.85 (s, 3H, OC$H_{3a/3b}$), 3.49 (s, 2H, CH_{2f}), 3.10-3.09 (t, 4H, CH_{2h}) and 2.64- 2.62 (t, 4H, CH_{2g}) in its NMR spectrum.



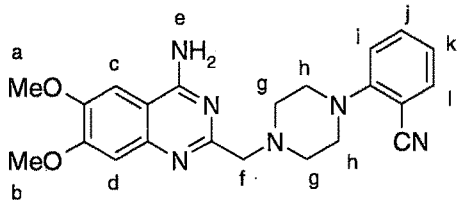
(**V-3**)



(**V-4**)

2-[(4-Cyclohexylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (**V-4**) displayed characteristic peaks at 3387 and 3171 (N-H str.), 1223 (Ar-O str.) and 1017 cm^{-1} (O-CH_3 str.) in its IR spectrum.

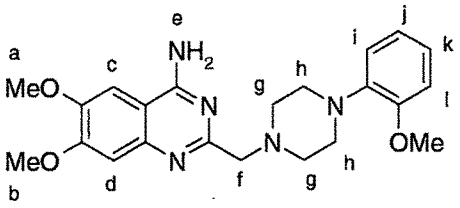
IR spectrum of 2-[4-((4-amino-6,7-dimethoxyquinazolin-2-yl)methyl) piperazin-1-yl]benzonitrile (**V-5**) displayed characteristic peaks at 3382 and 3132 (N-H str.), 2223 (C≡N str), 1265 (C-N str.) and 1221 cm^{-1} (Ar-O str.) in its IR spectrum. Peaks were observed at δ 7.57-7.50 (m, 3H, Ar- H_d , H_j and H_l), 7.19 (b, 2H, NH_{2e}), 7.13 (s, 1H, Ar-H_c), 7.07-7.00 (m, 2H, Ar-H_i and H_k), 3.93 (s, 6H, OCH_{3a} and OCH_{3b}), 3.63 (s, 2H, CH_{2f}), 3.24 (b, 4H, CH_{2h}) and 2.77 (b, 4H, CH_{2g}) in its NMR spectrum.



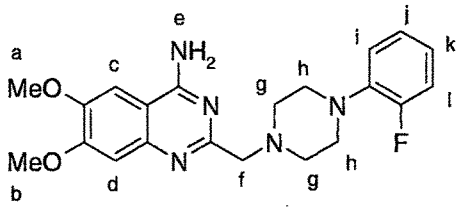
(**V-5**)

6,7-Dimethoxy-2-[(4-(2-methoxyphenyl)piperazin-1-yl)methyl]quinazolin-4-amine (**V-6**) displayed characteristic peaks at 3299 and 3145 (N-H str.), 1275 (C-N str.), 1241 (Ar-O str.) and 1017 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum displayed signals at δ 7.58 (s, 1H, Ar-H_d), 7.17 (s, 1H, Ar-H_c), 6.95-6.84 (m,

4H, Ar- $H_{i\text{-}l}$), 3.96 (s, 6H, $OCH_{3a,\ 3b}$), 3.83 (s, 3H, OCH_3), 3.67 (s, 2H, CH_{2m}), 3.10 (b, 4H, CH_{2h}) and 2.79 (b, 4H, CH_{2g}). Molecular ion peak was observed at m/z 404.8 in its mass spectrum.



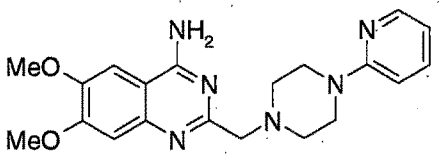
(V-6)



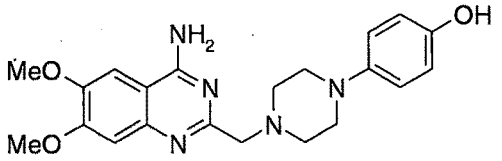
(V-7)

2-[(4-(2-Fluorophenyl)piperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (**V-7**) showed characteristic peaks at 3324 and 3161 (N-H str.), 1279 (C-N str.), 1233 (Ar-O str.) and 1014 cm^{-1} (O-CH_3 str.) in its IR spectrum. Signals appeared at δ 7.59 (s, 3H, Ar-H_d and NH_{2e}), 7.27 (s, 1H, Ar-H_c), 7.07-6.89 (m, 4H, Ar-$H_{i\text{-}l}$), 4.00 (s, 6H, OCH_{3a} and OCH_{3b}), 3.74 (s, 2H, CH_{2f}), 3.17 (b, 4H, CH_{2h}) and 2.81 (b, 4H, CH_{2g}) in its NMR spectrum.

IR spectrum of 6,7-dimethoxy-2-[(4-(pyridin-2-yl)piperazin-1-yl)methyl] quinazolin-4-amine (**V-8**) displayed characteristic IR peaks at 1272 (C-N str.) and 1240 cm^{-1} (Ar-O str.).



(V-8)

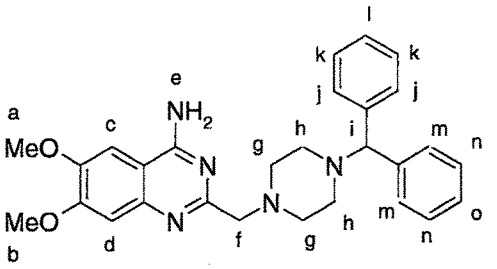


(V-9)

4-[4-((4-Amino-6,7-dimethoxyquinazolin-2-yl)methyl)piperazin-1-yl]phenol (**V-9**) displayed characteristic peaks at 3419 (N-H str.), broad 3190 (O-H str.), 1255 (C-N str.) and 1226 cm^{-1} (Ar-O str.) in its IR spectrum.

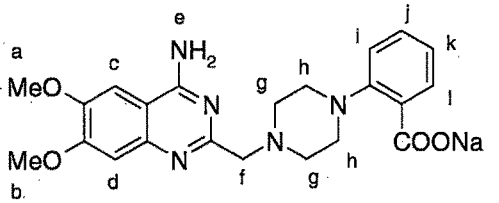
2-[(4-Benzhydrylpiperazin-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (**V-10**) displayed characteristic peaks at 3490 and 3297 (N-H str.), 1279 (C-N str.), 1252 (Ar-O str.) and 1078 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum exhibited signals at δ 7.55 (s, 1H, Ar-H_d), 7.41-7.22 (m, 9H, Ar-*H*), 7.16-7.11 (m, 4H,

Ar-*H* and NH_{2e}), 4.22 (s, 1H, CH_i), 3.93 (s, 6H, OCH_{3a} and OCH_{3b}), 3.59 (s, 2H, CH_{2f}), 2.64 (b, 4H, CH_{2h}) and 2.42 (b, 4H, CH_{2g}).



(V-10)

Sodium 2-[4-((4-amino-6,7-dimethoxyquinazolin-2-yl)methyl)piperazin-1-yl] benzoate (**V-11**) displayed molecular ion peak at 423.9 (M/Z) in mass spectrum. Its NMR spectrum showed signals at δ 7.44 (s, 1H, Ar-H_d), 7.24-7.21 (m, 2H, Ar-*H*), 7.13 (s, 1H, Ar-H_c), 7.05-6.90 (m, 4H, Ar-*H* and NH_{2e}), 3.95 (s, 3H, $OCH_{3a/b}$), 3.91 (s, 3H, $OCH_{3a/b}$), 3.55 (s, 2H, CH_{2f}), 3.02 (b, 4H, CH_{2h}) and 2.61 (b, 4H, CH_{2g}).



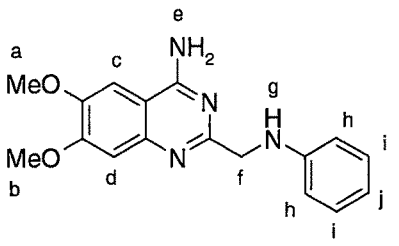
(V-11)

- **Synthesis of 2-[(aryl(alkyl)amino/heteroaryl)methyl]-6,7-dimethoxyquinazolin-4-amines (Series VI)**

Syntheses of 2-[(aryl(alky)amino/heteroaryl)methyl]-6,7-dimethoxy quinazoline-4-amines were accomplished by following the above described general **Scheme 6** in which 2-(chloromethyl)-6,7-dimethoxyquinazolin-4-amine (**20**) was reacted with different amines in presence of flame dried potassium carbonate in dry DMF at 60°C to obtain corresponding 2-[(aryl(alky)amino/heteroaryl)methyl]-6,7-dimethoxyquinazolin-4-amines.

N-[(4-Amino-6,7-dimethoxyquinzaolin-2-yl)methyl]aniline (**VI-1**) displayed characteristic peaks at 3384 and 3126 (N-H str.), 1254 (C-N str.) and 1216 (Ar-O str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.57 (s, 1H, Ar-H_d), 7.37 (b,

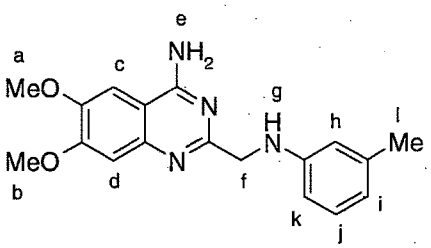
2H, NH_{2e}), 7.10-7.07 (m, 3H, Ar-H_h and H_c), 6.67- 6.65 (m, 2H, Ar-H_i), 6.58-6.54 (m,



(VI-1)

1H, Ar-H_j), 5.69 (b, 1H, NH_g), 4.21-4.20 (d, 2H, CH_{2f}) and 3.93 (s, 3H, OC$H_{3a/b}$) and 3.91 (s, 3H, OC$H_{3a/b}$). M+H peak was observed at m/z 310.5 in its mass spectrum.

2-[(3-Toluidino)-*N*-methyl]-6,7-dimethoxyquinazolin-4-amine **(VI-2)** displayed characteristic peaks at 3396 and 3119 (N-H str.), 1270 (C-N str.) and 1242 (Ar-O str.) in its IR spectrum. Peaks were observed at δ 7.52 (s, 1H, Ar-H_d), 7.28 (b, 2H, NH_{2e}), 7.03 (s, 1H, Ar-H_c), 6.93-6.89 (m, 1H, Ar-H_j), 6.43-6.39 (m, 2H, Ar-H_h and H_k), 6.34-6.32 (m, 1H, Ar-H_i), 5.52 (b, 1H, NH_g), 4.13-4.12 (d, 2H, CH_{2f}), 3.87 (s, 3H, OC$H_{3a/b}$), 3.85 (s, 3H, OC$H_{3a/b}$) and 2.16 (s, 3H, CH_{3l}) in its NMR spectrum.



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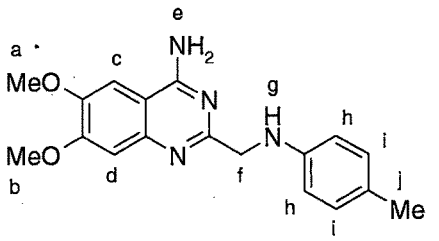


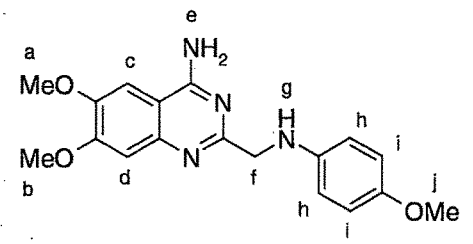
(VI-3)

2-[(4-Toluidino)-*N*-methyl]-6,7-dimethoxyquinazolin-4-amine **(VI-3)** displayed characteristic peaks at 3414 and 3126 (N-H str.), 1254 (C-N str.), 1222 (Ar-O str.) and 1014 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.58 (s, 1H, Ar-H_d), 7.47 (b, 2H, NH_{2e}), 7.11 (s, 1H, Ar-H_c), 6.91-6.88 (d, 2H, Ar-H_i), 6.59-6.57 (d, 2H, Ar-H_h), 5.57 (b, 1H, NH_g), 4.18 (s, 2H, CH_{2f}), 3.93 (s, 3H, OC$H_{3a/b}$), 3.90 (s, 3H, OC$H_{3a/b}$) and 2.17 (s, 3H, CH_{3j}). M+H peak was obsereved at m/z 324.9 in its mass spectrum.

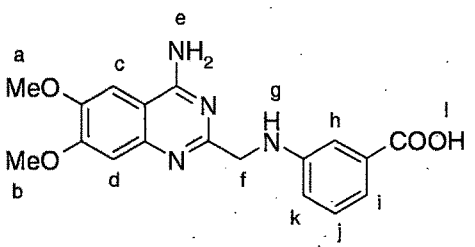
6,7-Dimethoxy-2-[(4-methoxyphenylamino)methyl]quinazolin-4-amine **(VI-4)** displayed characteristic peaks at 3444 and 3124 (N-H str), 1250 (Ar-O str) and 1030

cm^{-1} (O-CH_3 str) in its IR spectrum. Signals were observed at δ 7.97-7.97 (b, 2H, NH_{2e}), 7.69-7.67 (d, 2H, Ar-H_i), 7.53 (s, 1H, Ar-H_d), 7.05 (s, 1H, Ar-H_c), 6.63-6.60 (d, 2H, Ar-H_h), 6.50 (b, 1H, NH_g), 4.25-4.24 (d, 2H, CH_{2f}), 3.89 (s, 3H, OC$H_{3a/b}$), 3.86 (s, 3H, OC$H_{3a/b}$) and 3.71 (s, 3H, OCH_{3j}) in its NMR spectrum.

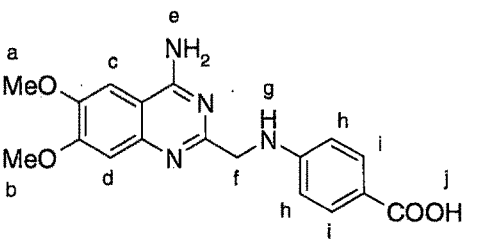
IR spectrum of 3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino] benzoic acid (**VI-5**) displayed characteristic peaks at 3444 and 3322 (N-H str.), 3122 (broad O-H str.), 1705 (C=O str.), 1279 (C-N str.) and 1235 cm^{-1} (Ar-O str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.56 (s, 1H, Ar-H_d), 7.35-7.27 (m, 4H, Ar-H_h, Ar-H_i and NH_{2e}), 7.15-7.11 (m, 1H, Ar-H_j), 7.01 (s, 1H, Ar-H_c), 6.85-6.83 (m, 1H, Ar-H_k), 5.23 (s, 2H, CH_{2f}), 4.92 (b, 1H, NH_g) and 3.93 (s, 6H, 2 × OCH_{3a} and OCH_{3b}).



(VI-4)



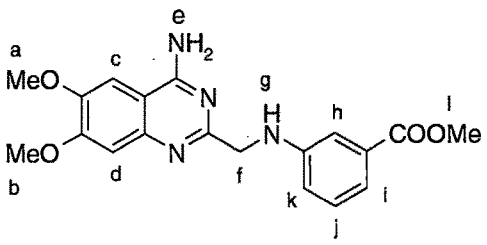
(VI-5)



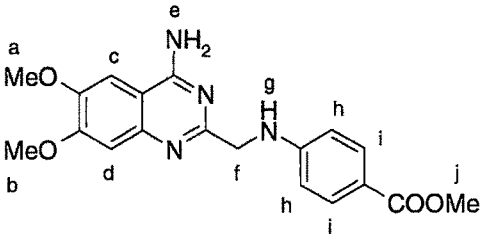
(VI-6)

Characteristic peaks were observed for 4-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino]benzoic acid (**VI-6**) displayed peaks at 3425 and 3369 (N-H str.), 3120 (broad O-H str.), 1673 (C=O str.), 1279 (C-N str.), 1218 (Ar-O str.) and 1018 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.75-7.73 (d, 2H, Ar-H_i), 7.57 (s, 1H, Ar-H_d), 7.39 (b, 2H, NH_{2e}), 7.04 (s, 1H, Ar-H_c), 6.61-6.58 (d, 2H, Ar-H_h), 5.69 (b, 2H, NH_g and OH_j), 5.16 (s, 2H, CH_{2f}) and 3.93 (s, 6H, 2 × OCH_{3a} and OCH_{3b}). M+H peak was observed at m/z 354.9 in its mass spectrum.

Methyl 3-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino]benzoate (**VI-7**) displayed characteristic peaks at 3343 and 3202 (N-H str.), 1715 (C=O str.), 1293 (C-N str.), 1228 (Ar-O str.) and 1031 cm^{-1} (O-CH_3 str) in its IR spectrum. Peaks were observed at δ 7.52 (s, 1H, Ar-H_d), 7.35 (b, 2H, NH_{2e}), 7.03 (s, 1H, Ar-H_c), 6.99-6.95 (m, 1H, Ar-H_j), 6.60 (s, 1H, Ar-H_h), 6.54-6.52 (m, 1H, Ar- H_i), 6.46-6.44 (m, 1H, Ar-H_k), 6.08 (b, 1H, NH_g) 4.14 (b, 2H, CH_{2f}) and 3.86 (s, 3H, OC$H_{3a/b}$) 3.84 (s, 3H, OC$H_{3a/b}$) in its NMR spectrum.



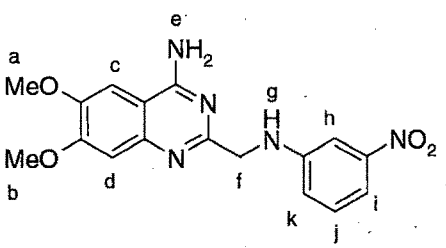
(**VI-7**)



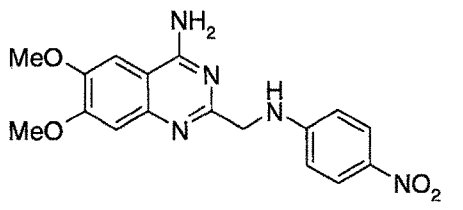
(**VI-8**)

Methyl 4-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino]benzoate (**VI-8**) displayed characteristic peaks at 3419 and 3133 (N-H str.), 1684 (C=O str.), 1276 (C-N str.) and 1227 cm^{-1} (Ar-O str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.51 (s, 1H, Ar-H_d), 7.28-7.18 (b, 2H, NH_{2e}), 7.03 (s, 1H, Ar-H_c), 6.68-6.65(d, 2H, Ar-H_i), 6.60-6.56 (d, 2H, Ar-H_h), 5.20 (b, 1H, NH_g), 4.11 (s, 2H, CH_{2f}), 3.90 (s, 3H, OC$H_{3a/b}$), 3.86 (s, 3H, OC$H_{3a/b}$) and 3.61 (s, 3H, COOCH_{3j}).

Characterisitics peaks were observed for 2-[(3-nitrophenylamino)methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-9**) at 3374 and 3125 (N-H str.), 1518 (N=O asym.), 1347 (N=O sym.) and 1244 cm^{-1} (Ar-O str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.54 (s, 1H, Ar-H_d), 7.45 (s, 1H, Ar-H_h), 7.33- 7.31(m, 3H, Ar-*H* and NH_2), 7.26-7.22 (m, 1H, Ar-H_j), 7.05 (s, 1H, Ar-H_c), 7.04-7.01 (m, 1H, Ar-*H*), 6.57-



(**VI-9**)

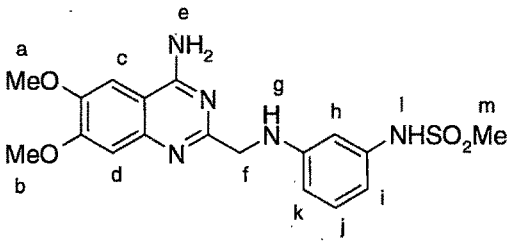


(**VI-10**)

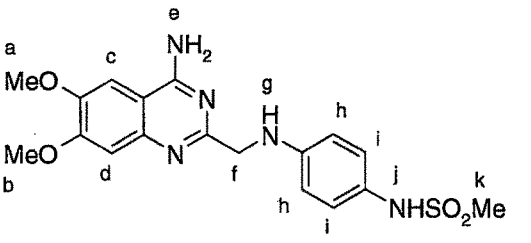
6.55 (t, 1H, N*H*), 4.26-4.25 (d, 2H, CH_{2f}), 3.90 (s, 3H, OC$H_{3a/b}$) and 3.84 (s, 3H, OC$H_{3a/b}$).

IR spectrum. of 2-[(4-nitrophenylamino)methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-10**) showed characteristic peaks at 3367 and 3128 (N-H str.), 1527 (N=O asym.), 1345 (N=O sym.) and 1247 (Ar-O str.) cm^{-1} in its IR spectrum.

N-[3-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]phenyl]methane sulfonamide (**VI-11**) displayed characteristic peaks at 3450 and 3361 (N-H str.), 1319 (S=O asym.), 1147 (S=O sym.) 1249 (Ar-O str.) and 1031 cm^{-1} (O-CH_3 str.) in its IR spectrum. Signals were seen at δ 7.57 (s, 1H, Ar-H_d), 7.39 (b, 2H, NH_{2e}), 7.01 (s, 1H, Ar-H_c), 6.93-6.89 (m, 1H, Ar-H_j), 6.75-6.74 (t, 1H, Ar-H_h), 6.58-6.56 (dd, 1H, Ar-H_k), 6.46-6.44 (dd, 1H, Ar-H_i), 4.95-4.93 (d, 2H, NH_g and NH_i), 4.76 (s, 2H, CH_{2f}), 3.92 (s, 6H, OCH_{3a} and OCH_{3b}) and 3.30 (s, 3H, CH_{3m}) in its NMR spectrum. Molecular ion peak was observed at m/z 403.8 in its mass spectrum



(VI-11)

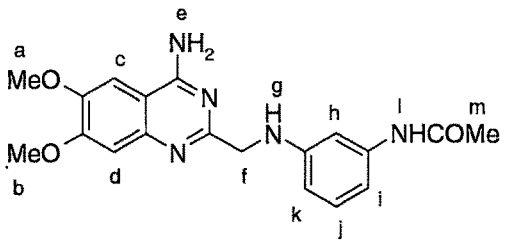


(VI-12)

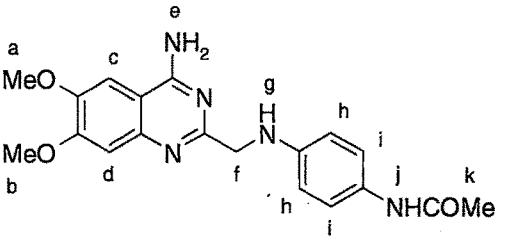
IR spectrum of *N*-[4-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino] phenyl]methane sulfonamide (**VI-12**) displayed characteristic peaks at 3417and 3144 (N-H str.), 1320 (S=O asym.) and 1153 cm^{-1} (S=O sym.). Its NMR spectrum gave signals at δ 7.57 (s, 1H, Ar-H_d),7.40 (b, 2H, NH_{2e}), 7.05 (s, 1H, Ar-H_c), 7.03-7.01 (d, 2H, Ar-H_i), 6.47-6.45 (d,2H, Ar-H_h), 4.90 (b, 2H, NH_g and NH_i), 4.69 (s, 2H, CH_{2f}), 3.92 (s, 3H, OC$H_{3a/3b}$), 3.91 (s, 3H, OC$H_{3a/3b}$) and 3.28 (s, 3H, CH_{3k}). Molecular ion peak was observed at m/z 403.4 in its mass spectrum.

N-[3-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]phenyl]acetamide (**VI-13**) displayed characteristic peaks at 3450, 3396 and 3124 (N-H str.), 1663 (C=O str.), 1248 (Ar-O str.) and 1032 cm^{-1} (O-CH_3 str.) in its IR spectrum. Peaks were obtained at δ 7.54 (s, 1H, Ar-H_d), 7.34 (b, 2H, NH_{2e}), 7.07 (s, 2H, Ar-H_c and H_h), 6.97-6.93 (t, 1H, Ar-H_j), 6.70-6.68 (m, 1H, Ar-H_i), 6.33-6.31 (m, 1H, Ar-H_k), 5.62 (b, 1H, NH_g), 4.16 (s, 2H, CH_{2f}), 3.93 (s, 3H, OC$H_{3a/b}$), 3.90 (s, 3H, OC$H_{3a/b}$) and 2.00 (s, 3H, CH_{3m}) in its NMR spectrum.

N-[4-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]phenyl]acetamide (**VI-14**) displayed characteristic peaks at 3362 and 3131 (N-H str.), 1656 (C=O str.), 1239 (Ar-O str.) and 1028 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectr-



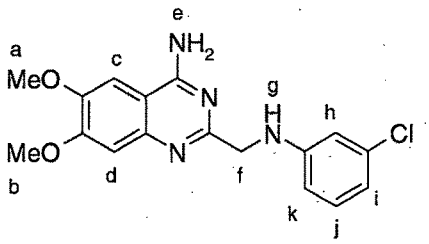
(VI-13)



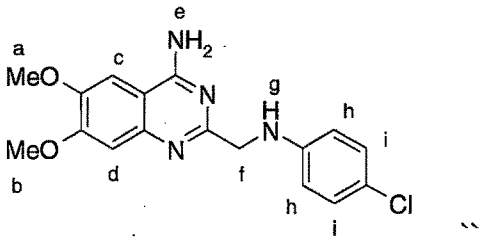
(VI-14)

um gave signals at δ 9.39 (b, 1H, NH_j), 7.54 (s, 1H, Ar-H_d), 7.32-7.20 (m, 4H, Ar-H_i and NH_{2e}), 7.06 (s, 1H, Ar-H_c), 6.58-6.56 (d, 2H, Ar-H_h), 5.49 (b, 1H, NH_g), 4.15 (s, 2H, CH_{2f}), 3.90 (s, 3H, OC$H_{3a/b}$), 3.88 (s, 3H, OC$H_{3a/b}$) and 1.96 (s, 3H, CH_{3k}).

2-[(3-Chlorophenylamino)methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-15**) displayed characteristic peaks at 3502, 3388 and 3125 (N-H str.) and 1258 cm^{-1} (Ar-O str.) in its IR spectrum. Its NMR spectrum gave signals at δ 10.61 (b, 1H, NH_g), 8.39 (s, 1H, Ar-H_d), 8.09-8.07 (m, 1H, Ar-H_i), 7.69-7.67 (m, 2H, Ar-H_k), 7.64 (s, 2H, NH_{2e}), 7.44-7.40 (t, 1H, Ar-H_j), 7.27 (s, 1H, Ar-H_c), 3.92 (s, 3H, OC$H_{3a/b}$), 3.91(s, 3H, OC$H_{3a/b}$) and 3.84 (s, 2H, CH_{2f}).



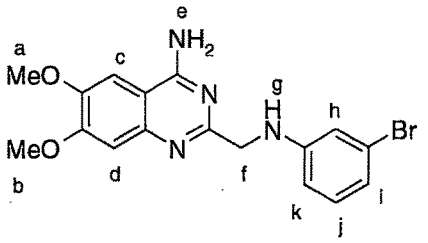
(VI-15)



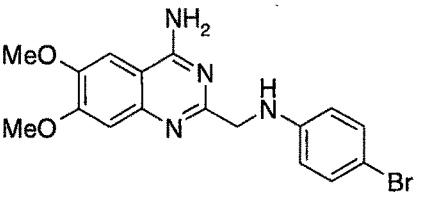
(VI-16)

2-[(4-Chlorophenylamino)methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-16**) showed characteristic peaks at 3482, 3389 and 3316 (N-H str.), 1256 (Ar-O str.) and 1013 cm^{-1} (O-CH_3 str.) in its IR spectrum. Its NMR spectrum gave signals at δ 7.51 (s, 1H, Ar-H_d), 7.29 (b, 2H, NH_{2e}), 7.03 (s, 1H, Ar-H_c), 7.02-6.99 (d, 2H, Ar-H_i), 6.60-6.58 (d, 2H, Ar-H_h), 5.84 (b, 1H, NH_g), 4.14-4.13 (d, 2H, CH_{2f}), 3.87 (s, 3H, OC$H_{3a/b}$) and 3.85 (s, 3H, OC$H_{3a/b}$).

3-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]bromobenzene (**VI-17**) displayed characteristic peaks at 3421 and 3122 (N-H str.) and 1229 cm^{-1} (Ar-O str.) in its IR spectrum. Its NMR showed sigmals at 7.57 (s, 1H, Ar-H_d), 7.47 (s, 2H, NH_{2e}), 7.07 (s, 1H, Ar-H_c), 7.69-7.67 (t, 1H, Ar-H_j), 6.80-6.79 (t, 1H, Ar-H_i), 6.65-6.61 (m, 2H, Ar-H_h and H_k), 3.88 (s, 3H, $OCH_{3a/b}$), 3.85 (s, 3H, $OCH_{3a/b}$) and 3.17 (s, 2H, CH_{2f}).



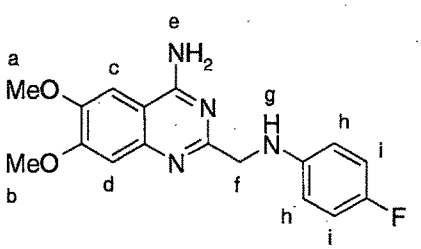
(VI-17)



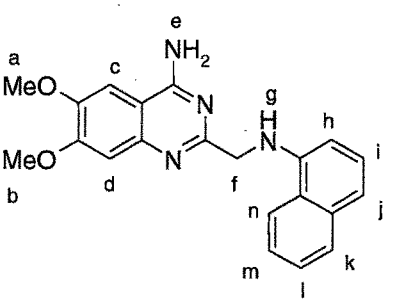
(V1-18)

IR spectrum of 4-[(4-amino-6,7-dimethoxyquinazolin-2-yl)methylamino] bromobenzene (**VI-18**) displayed characteristic peaks at 3380 and 3127 (N-H str.), and 1239 cm^{-1} (Ar-O str.).

4-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]fluorobenzene (**VI-19**) displayed characteristic peaks at 3383 and 3123 (N-H str.) and 1247 cm^{-1} (Ar-O str.) in its IR spectrum. Signals appeared at δ 7.53 (s, 1H, Ar-H_d), 7.27 (b, 2H, NH_{2e}), 7.05 (s, 1H, Ar-H_c), 6.84-6.79 (m, 2H, Ar-H_i), 6.63-6.58 (m, 2H, Ar-H_h), 5.54 (b, 1H, NH_g), 4.14 (s, 2H, CH_{2f}) and 3.90 (s, 3H, $OCH_{3a/b}$), 3.88 (s, 3H, $OCH_{3a/b}$) in its NMR spectrum.



(VI-19)

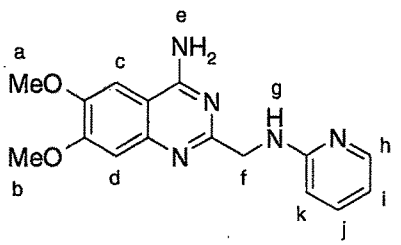


(VI-20)

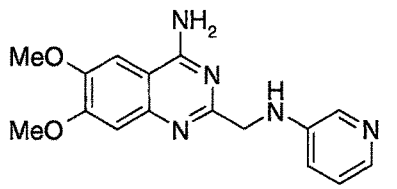
1-[(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylamino]naphthalene (**VI-20**) displayed characteristic peaks at 3390 and 3129 (N-H str.) and 1245 cm^{-1} (Ar-O str.)

in its IR spectrum. Its NMR spectrum gave signals at δ 8.16-8.14 (d, 1H, Ar-H_n), 7.76-7.75 (d, 1H, Ar-H_k), 7.60 (s, 1H, Ar-H_d), 7.49-7.41 (m, 2H, Ar-H_m, H_h), 7.30-7.26 (t, 1H, Ar-H_i), 7.15-7.11 (m, 2H, Ar-H_c and H_j), 6.56-6.54 (d, 2H, NH_2), 4.40-4.39 (d, 2H, CH_{2f}), 3.98 (s, 3H, $OCH_{3a/b}$) and 3.93 (s, 3H, $OCH_{3a/b}$). Molecular ion peak was observed at m/z 360.6 in its mass spectrum.

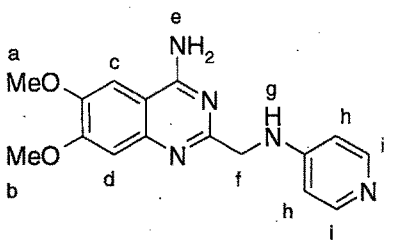
6,7-Dimethoxy-2-[(pyridin-2-ylamino)methyl]quinazolin-4-amine **(VI-21)** showed characteristic peaks at 3343 and 3134 (N-H str) and 1249 cm^{-1} (Ar-O str) in its IR spectrum. Its NMR spectrum showed signals at δ 7.97 (b, 1H), 7.74 (b, 2H), 7.59 (s, H, Ar-H_d), 6.99-6.96 (d, 1H, Ar-H), 6.85 (s, 1H, Ar-H_c), 6.72 (s, 1H), 5.31 (s, 2H, CH_{2f}) and 3.85 (s, 6H, $OCH_{3a, 3b}$).



(VI-21)



(VI-22)

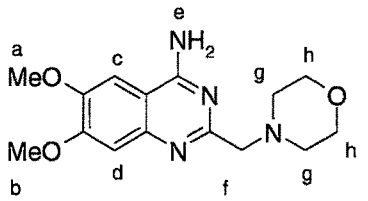


(VI-23)

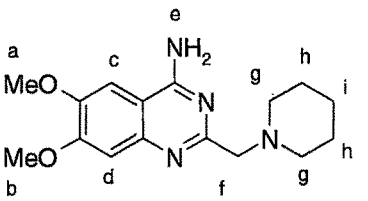
6,7-Dimethoxy-2-[(pyridin-3-ylamino)methyl]quinazolin-4-amine **(VI-22)** displayed characteristic peaks at 3339 and 3190 (N-H str) and 1250 cm^{-1} (Ar-O str) in its IR spectrum.

IR apectrum of 6,7-dimethoxy-2-[(pyridin-4-ylamino)methyl]quinazolin-4-amine (**VI-23**) displayed characteristic IR peaks at 3221, 3110 (N-H str) and 1256 cm^{-1} (Ar-O str). Its ^{1}H-NMR spectrum gave signals at δ 8.16-8.14 (m, 2H, Ar-H_i), 7.59 (s, 1H, Ar-H_d), 6.93 (m, 3H, Ar-H_c and H_h), 5.32 (s, 2H, CH_{2f}), 3.90 (s, 6H, OCH_{3a} and OCH_{3b}) and 3.33 (b, 3H, NH_{2e} and NH_g).

6,7-Dimethoxy-2-(4-morpholinomethyl)quinazolin-4-amine (**VI-24**) displayed characteristic peaks at 3310, 3132 (N-H str) and 1249 cm^{-1} (Ar-O str) in its IR spectrum. Peaks were observed at δ 7.86 (s, 1H, Ar-H_d), 7.14 (s, 1H, Ar-H_c), 7.05 (b, 2H, NH_{2e}), 3.95 (s, 6H, OCH_{3a} and OCH_{3b}), 3.71-3.69 (t, 4H, CH_{2h}), 3.57 (s, 2H, CH_{2f}) and 2.58-2.57 (b, 4H, 2 × CH_2) in ^{1}H-NMR spectrum.



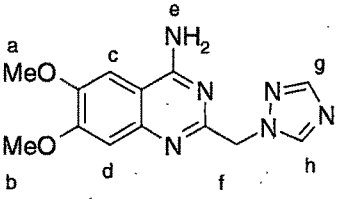
(VI-24)



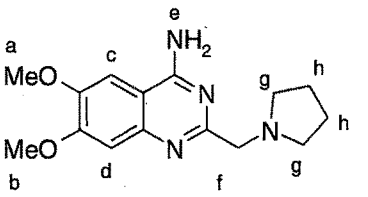
(VI-25)

6,7-Dimethoxy-2-[(piperidin-1-yl)methyl]quinazolin-4-amine (**VI-25**) displayed characteristic peaks at 3316 (N-H str) and 1245 cm^{-1} (Ar-O str) in its IR spectrum.

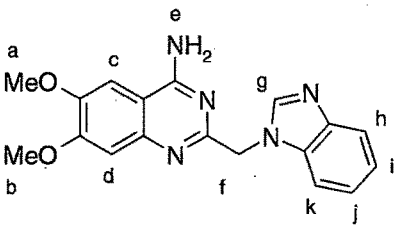
6,7-Dimethoxy-2-[(1*H*-1,2,4-triazol-1-yl)methyl]quinazolin-4-amine (**VI-26**) displayed characteristic peaks at 3401 and 3338 (N-H str) and 1233 cm^{-1} (Ar-O str) in its IR spectrum. Its NMR spectrum gave signals δ 8.52 (s, 1H, Ar-H_g), 7.89 (s, 1H, Ar-H_h), 7.62 (s, 1H, Ar-H_d), 7.10 (s, 1H, Ar-H_c), 5.45 (s, 2H, CH_{2f}) and 3.97 (s, 3H, OC$H_{3a/b}$) and 3.95 (s, 3H, OC$H_{3a/b}$).



(VI-26)



(VI-27)



(VI-28)

6,7-Dimethoxy-2-[(pyrrolidin-1-yl)methyl]quinazolin-4-amine (**VI-27**) displayed characteristic peaks 1245 cm^{-1} (Ar-O str) in its IR spectrum. Signals were

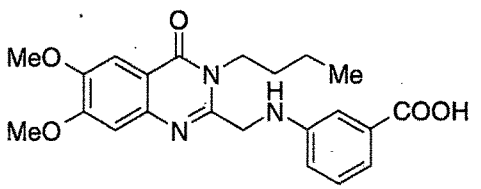
observed at 7.53 (s, 1H, Ar-H_d), 7.37 (b, 2H, NH_{2e}), 7.06 (s, 1H, Ar-H_c), 3.87 (s, 3H, OC$H_{3a/b}$), 3.84 (s, 3H, OC$H_{3a/b}$), 3.54 (s, 2H, CH_{2f}) 2.51-2.50 (m, 4H, 2 × CH_2) and 1.67-1.64 (m, 4H, CH_{2h}) in its NMR spectrum.

2-[(1*H*-Benzimidazol-1-yl)methyl]-6,7-dimethoxyquinazolin-4-amine (**VI-28**) displayed characteristic peaks at 3295 and 3122 (N-H str), and 1256 cm^{-1} (Ar-O str) in its IR spectrum. Its NMR spectrum gave signals at δ 8.33 (s, 1H, Ar-H_g), 7.68-7.66 (m, 3H, Ar-*H*, and NH_{2e}), 7.59 (s, 1H Ar-H_d), 7.49-7.46 (m, 1H, Ar-*H*), 7.21-7.19 (m, 2H, Ar-*H*), 7.05 (s, 1H, Ar-H_c), 5.46 (s, 2H, CH_{2f}), 3.93 (s, 3H, OC$H_{3a/b}$) and 3.90 (s, 3H, OC$H_{3a/b}$).

4.2 Biological activity

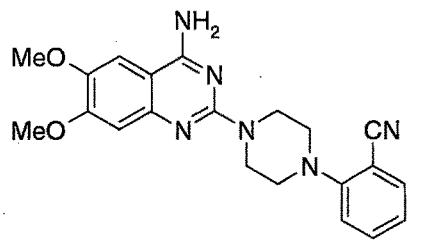
As determination of pA_2 values is a time consuming job, preliminary screening of the synthesized compounds was performed by observing the effects of the compounds on the modulation of responses of nonadrenaline and ang II on the rat blood pressure. Compounds showing significant changes in the responses of the two agonists were chosen for *in vitro* studies. Compounds of **Series I** and **III** did not show noticeable changes, hence were not selected for determination of pA_2 values.

Table 7 shows the pA_2 values for the compounds for both of the receptor types. Compound (**II-1**) showed the highest potency on both the receptors in **Series-II**. Both of the tetrazoles (**II-7** & **II-8**) showed low potency in blocking both the receptor types (α_1 and AT_1). The *p*-amino group bearing compound (**II-4**) was almost inactive.



$\alpha_1 = 7.45$ $AT_1 = 6.14$

(II-1)



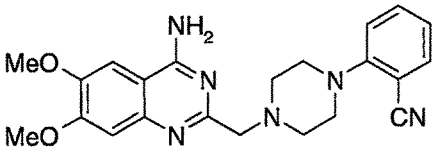
$\alpha_1 = 8.59$ $AT_1 = 9.04$

(IV-4)

Only one compound (**IV-4**) was used for determination of pA_2 values in the **Series-IV**. This compound (**IV-4**) showed very high antagonistic potency on both the

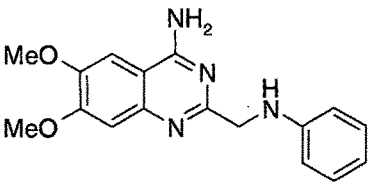
types of receptors. The activity is comparable to prazosin (**AP1**) and losartan (**AT1**).

Series V proved to be the most friutful one. Compound (**V-5**) in the series surpassed tha activity of the standerd drugs. None of the compounds could match compound (**V-5**) in potency against both of these receptors.



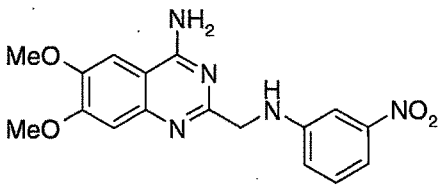
$\alpha_1 = 10.1$ $AT_1 = 8.83$

(V-5)



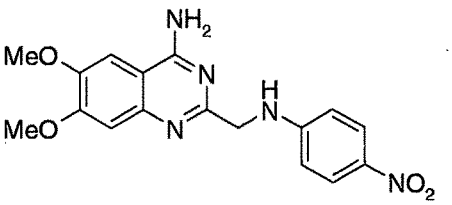
$\alpha_1 = 9.87$ $AT_1 = 8.37$

(VI-1)



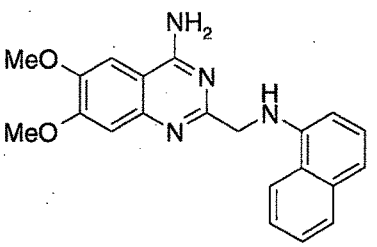
$\alpha_1 = 9.38$ $AT_1 = 7.64$

(VI-9)



$\alpha_1 = 8.09$ $AT_1 = 9.04$

(VI-10)



$\alpha_1 = 8.37$ $AT_1 = 7.07$

(VI-20)

Series VI offered four potent compounds, two of them have non-substituted aryl rings (**VI-1** and **VI-20**) while the remaining two have electron withdrawing nitro groups at *m*- and *p*-positions (**VI-9** and **VI-10**). Remaining compounds did not show promising activity.

As is evident from the structures of compounds, various groups like acidic, basic, neutral, bulky, non-bulky, aromatic, aliphatic and heteroaromatic have been attached to the quinazoline motif. Activity has been shown by compounds having aromatic rings in the side chain. Certain interesting observations were made as given below:

- 6,7-Dimethoxyquinazoline has proved to be a very good motif for development of dual acting α_1 and AT_1 receptor antagonists.
- 4-Amino group provides much more potent dual antagonists than compounds of 4-oxo group.
- Attachment of a basic nitrogen to the quinazoline ring through one carbon linker gives more potent compounds.
- Attachment of an aromatic ring to the basic nitrogen provides better dual acting compounds.
- Small-sized electron withdrawing groups like CN, NO_2 provide more potent derivatives.
- Presence of an acidic group in the side chain is not a must to exhibit AT_1 antagonistic activity unlike losartan.
- Unsubstituted aromatic rings (**VI-1**, **VI-20**) or neutral groups (**IV-4**, **V-5**, **VI-9**, **VI-10**) are ideal for dual α_1-and AT_1-antagonist activities.

This work has proved beyond doubt that dual α_1 and AT_1 antagonists are a reality and not a figment of imagination. Further optimization of the lead structures is in progress in the laboratory.

Table 7: The pA_2 values of synthesized compounds

Compound	pA_2 values		Compound	pA_2 values	
	α_1	AT_1		α_1	AT_1
II-1	**7.45**	**6.14**	**VI-2**	6.16	5.38
II-2	5.27	5.75	**VI-3**	5.28	3.45
II-4	5.48	5.28	**VI-5**	5.52	4.87
II-5	6.06	5.13	**VI-6**	4.49	6.43
II-6	5.69	5.62	**VI-9**	**9.38**	**7.64**
II-7	5.63	4.9	**VI-10**	**8.09**	**9.04**
II-8	4.53	5.19	**VI-11**	4.48	3.41
IV-4	**8.59**	**9.04**	**VI-12**	NA	4.38
V-1	6.79	5.1	**VI-15**	7.02	6.27
V-2	4.19	3.22	**VI-16**	4.89	4.65
V-3	6.49	6.78	**VI-20**	**8.37**	**7.07**
V-4	4.90	3.01	**VI-23**	5.86	4.68
V-5	**10.1**	**8.83**	**VI-24**	5.26	6.15
V-6	7.45	6.34	**VI-25**	3.01	3.70
V-7	6.76	6.09	**VI-27**	3.49	3.63
V-8	5.47	3.65	**VI-28**	4.05	4.15
V-10	5.32	6.36	**Prazosin**	8.91	8.26
V-11	3.64	6.28	**Losartan**	5.46	8.08
VI-1	**9.87**	**8.37**			