4. Results 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 performed has been described under the following heads:

4.1.1 Synthesis of starting materials and intermediates

- Synthesis of 2-amino-4,5-dimethoxybenzonitrile
- Synthesis of 2-amino-4,5-methylenedioxybezonitrile
- Synthesis of 2-amino-3,4-dimethoxybenzonitrile
- Synthesis of substituted piperazines
- Synthesis of 2'/4'-substituted *N*-benzylpiperidines
- Synthesis of substituted 4-amino-1,1'-biphenyls

4.1.2 Synthesis of 4-amino-2-choloromethyl-6,7-dimethoxyquinazoline and 4-amino-2-choloroethyl-6,7-dimethoxyquinazoline

4.1.3 Synthesis of 4-amino-2-(4-substituted piperazin-1-yl)methyl-6,7-dimethoxyquinazolines (**Series I**)

4.1.4 Synthesis of 4-amino-2-(1-substituted piperidin-4-ylamino)methyl-6,7-dimethoxyquinazolines (**Series II**)

4.1.5 Synthesis of 4-amino-2-(2'/4'-substituted 1,1'-biphenyl-4-ylamino)methyl-6,7-dimethoxyquinazolines (**Series III**)

4.1.6 Synthesis of 4-amino-2-(4-substituted phenyl/arylpiperazin-1-yl)ethyl-6,7-dimethoxyquinazolines (**Series IV**)

4.1.7 Synthesis of 4-amino-2-(4-substituted phenyl/arylpiperazin-1-yl)methyl-6,7-methylenedioxy-quinazolines (**Series V**)

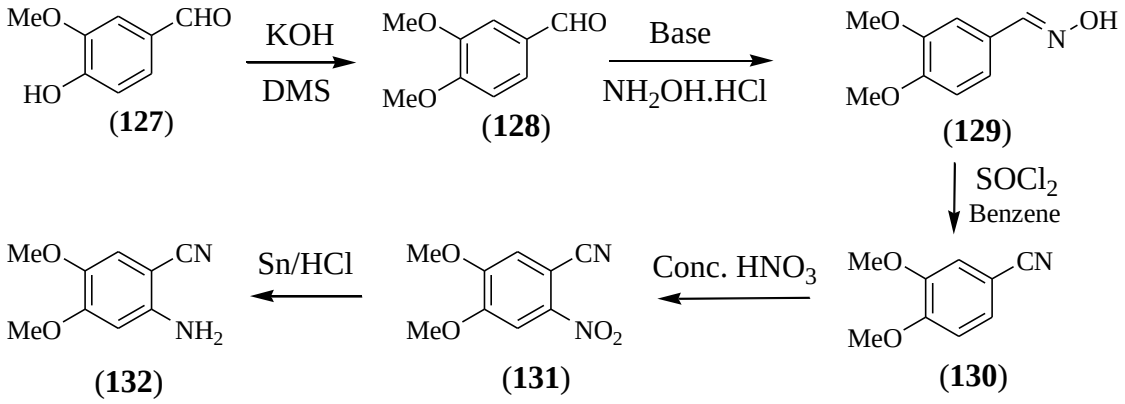
4.1.8 Synthesis of 4-amino-2-(4-substituted phenyl/arylpiperazin-1-yl)methyl-7,8-dimethoxyquinazolines (**Series VI**)

4.1.9 Synthesis of 2-(4-substituted phenyl/arylpiperazin-1-yl)methyl-7,8-dimethoxyquinazolin-4(3*H*)-ones (**Series VII**)

4.1.1 Synthesis of starting materials and intermediates

- **Synthesis of 2-amino-4,5-dimethoxybenzonitrile** (**132**)

Vanillin (**127**) was methylated using dimethyl sulphate (DMS) under basic conditions to yield veratraldehyde (**128**)[129,130] which when refluxed with hydroxylamine hydrochloride in moderately basic conditions afforded 3,4-dimethoxybenzaldoxime (**129**). The oxime (**129**) was dehydrated using thionyl chloride into 3,4-dimethoxybenzonitrile (**130**)[131]. Nitration of **130** with concentrated nitric acid afforded 2-nitro-4,5-dimethoxy benzonitrile (**131**)[132] which was selectively reduced to 2-amino-4,5-dimethoxy benzonitrile (**132**)[133] by the use of granulated tin and concentrated hydrochloric acid (**Scheme 1**). All these compounds were characterized on the basis of their physical and spectral data as reported in literature.

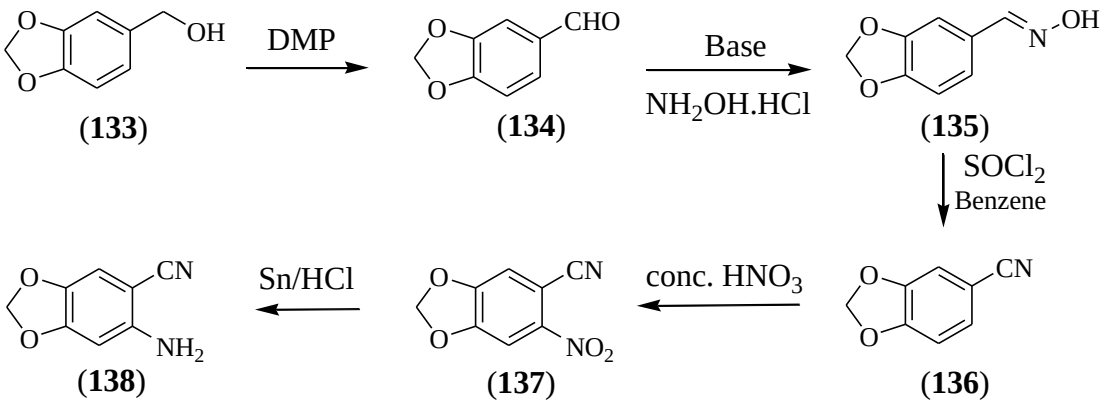


Scheme: 1

- **Synthesis of 2-amino-4,5-methylenedioxybenzonitrile (138)**

Piperonol (**133**) was oxidized to piperonal (**134**) on controlled oxidation with Dess-Martin periodinane (DMP).[134] Its IR spectrum showed peaks at 2852 (C-H str) and 1675 cm^{-1} (C=O str). Piperonal (**134**) was converted to the oxime (**135**) which showed a broad peak at 3225 cm^{-1} (O-H str) in its IR spectrum. Upon dehydration, **135** produced 3,4-methylenedioxybezonitrile (**136**) which displayed a sharp peak at 2222 cm^{-1} (C≡N str) in its IR spectrum. Nitration of **136** offered 4,5-methylenedioxy-2-nitrobezonitrile (**137**). Its IR spectrum showed two peaks at 1530 and 1338 cm^{-1} (N=O str). Tin and concentrated

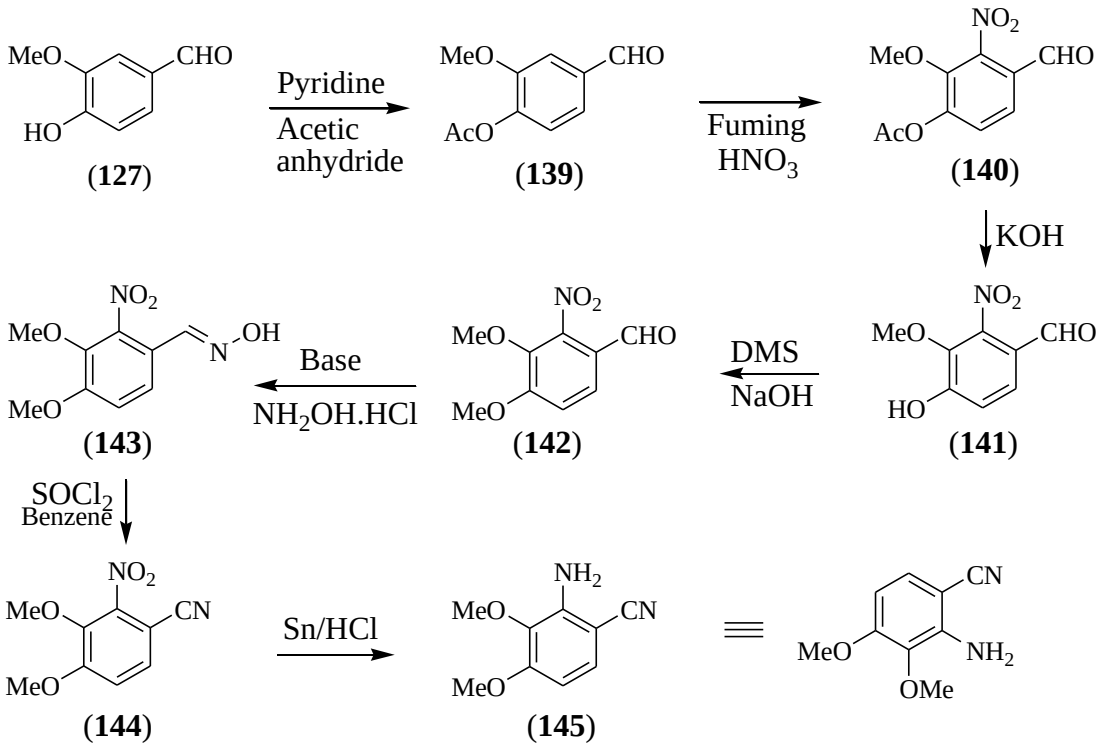
hydrochloric acid reduced **137** into 2-amino-4,5-methylenedioxybezonitrile (**138**) (**Scheme 2**), which was characterized by strong peaks at 3457 and 3363 cm^{-1} (N-H str) in its IR spectrum.



Scheme: 2

- **Synthesis of 2-amino-3,4-dimethoxybenzonitrile (145)**

Vanillin (**127**) was acetylated into acetyl vanillin (**139**) using acetic anhydride and pyridine which was characterized by the presence of a strong peak at 1756 cm^{-1} (C=O str of acetyl) in its IR spectrum.[135] Selective nitration of acetyl vanillin (**139**) with fuming nitric acid gave 4-formyl-2-methoxy-3-nitrophenyl acetate (**140**) **(Scheme 3)**. Hydrolysis of **140** under strong basic conditions yielded 4-hydroxy-3-methoxy-2-nitrobenzaldehyde (**141**) which was characterized by the disappearance of peak due to the C=O str. of acetyl group in its IR spectrum. Compound (**141**) was methylated to 3,4-dimethoxy-2-nitrobenzaldehyde (**142**) using DMS in the presence of a base.[136] IR spectrum of **142** did not show O-H str. vibrations. Compound (**142**) was converted into its oxime (**143**) in presence of hydroxylamine hydrochloride and a base as mentioned in earlier schemes (1 and 2). Upon dehydration, compound (**143**) resulted into formation of 3,4-dimethoxy-2-nitrobenzonitrile (**144**)[137] which was characterized by the appearance of a strong peak at 2234 cm^{-1} (C≡N str.) in its IR spectrum. Compound (**144**) afforded 2-amino-3,4-dimethoxybenzonitrile (**145**) on its selective reduction with tin and concentrated hydrochloric acid which showed characteristic peaks at 3476 and 3377 cm^{-1} (NH str).



Scheme: 3

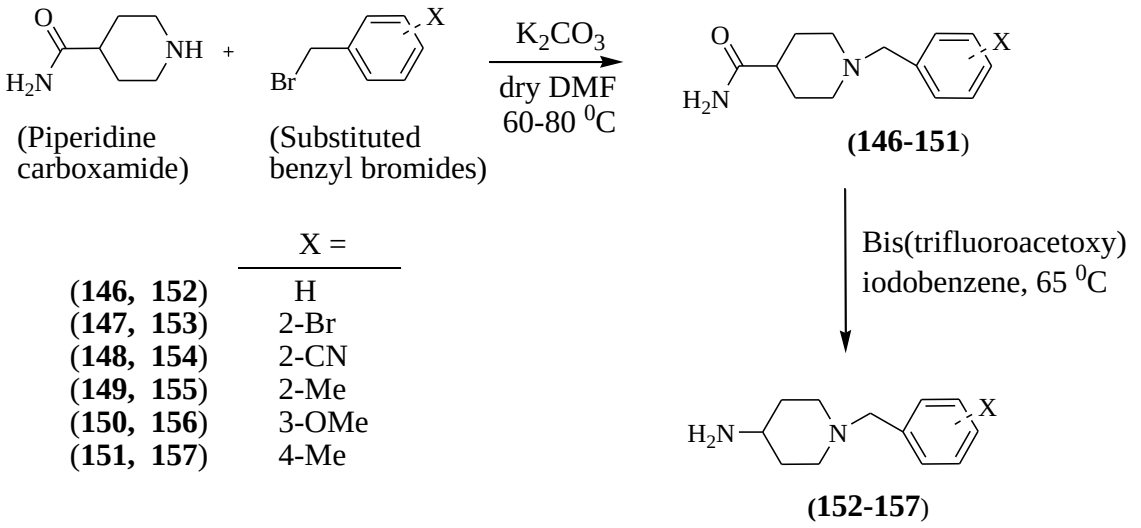
- **Synthesis of substituted piperazines**

Substituted piperazines required for the synthesis of the designed compounds were either procured from commercial sources or prepared in the laboratory.[138-145] 2/3/4-Substituted benzoyl chlorides or phenylacetyl chlorides were reacted with anhydrous piperazine in dry dioxane at room temperature. IR spectra of these compounds showed one peak around 1671 cm^{-1} for C=O stretching of amide and another one in the range of 3500-3300 cm^{-1} (N-H str). 2/4-Substituted benzyl piperazines were also synthesized in the same manner. 2/4-Substituted phenylpiperazines were synthesized by reacting 2/4-substituted anilines with bis(2-chloroethyl)amine hydrochloride in diethylene glycol monomethyl ether under microwave irradiations. IR spectra of these compounds showed peaks in the range of 3500-3300 cm^{-1} (N-H str).

- **Synthesis of 2'/4'-substituted *N*-benzylpiperidines (152-157)**

Piperidine-4-carboxamide was reacted with 2/4-substituted benzyl bromides in dry DMF using potassium carbonate yielding 2'/4'-substituted benzylpiperidine-4-carboxamides (**146-151**). Some of these compounds were characterized by mass

spectrometry. A sharp strong peak was observed in the range of 1630-1690 cm^{-1} for C=O stretching of the amide group in IR spectra of these compounds. Among them, 2'-cyano-



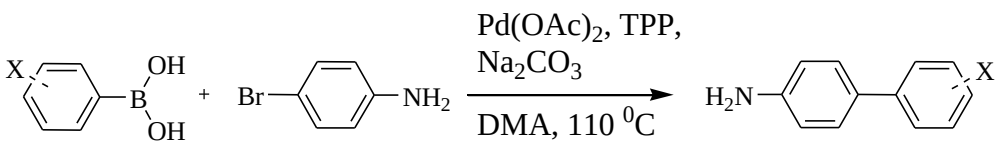
	X =
(**146, 152**)	H
(**147, 153**)	2-Br
(**148, 154**)	2-CN
(**149, 155**)	2-Me
(**150, 156**)	3-OMe
(**151, 157**)	4-Me

Scheme: 4

benzylpiperidine-4-carboxamide (**148**) showed a characteristic peak at 2222 cm^{-1} for C≡N stretching in its IR spectrum. Hoffmann's rearrangement of these compounds using bis(trifluroacetoxy)iodobenzene yielded 2'/4'-substituted benzylpiperidin-4-amines (**152-157**) (**Scheme 4**).[146] IR spectra of the substituted aminopiperidines (**152-157**) showed characteristic peaks in the range of 3500-3300 cm^{-1} (N-H str).

- **Synthesis of substituted 4-amino-1,1'-biphenyls (158-163)**

Substituted 4-aminobiphenyls (**158-163**) required for the synthesis of the respecti-



(**Substituted phenylboronic acids**) (**4-Bromo-aniline**) (**158-163**)

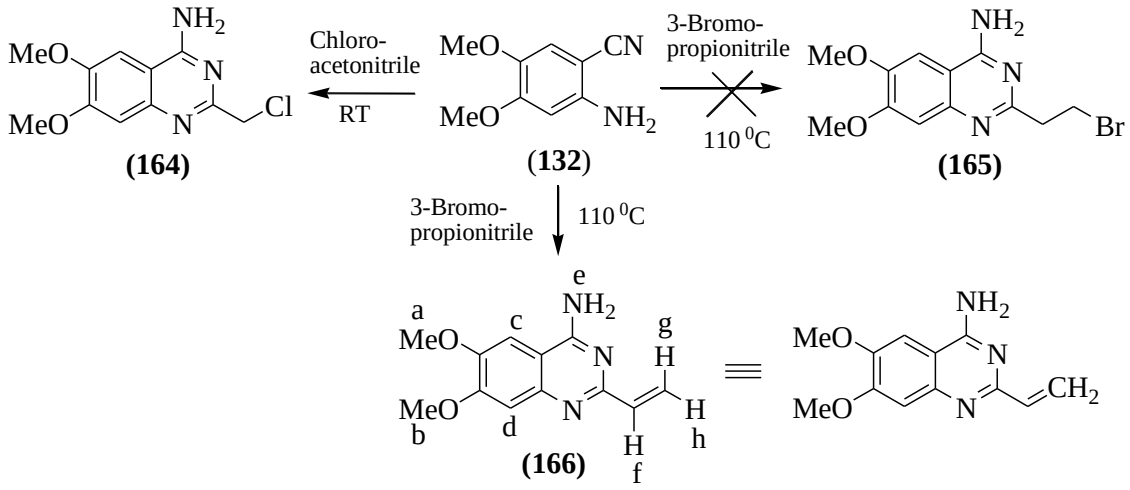
	X =
(**158**)	H
(**159**)	2-Cl
(**160**)	2-Me
(**161**)	4-CN
(**162**)	4-SMe
(**163**)	4-*t*.Bu

Scheme: 5

ve target compounds (**199-204**) were prepared through Suzuki coupling of 2/4-substituted boronic acids with 4-bromoaniline in DMA using palladium acetate, TPP and a base (**Scheme 5**).[147] Some of them were characterized through mass spectroscopy.

4.1.2 Synthesis of 4-amino-2-choloromethyl-6,7-dimethoxyquinazoline (164) and 4-amino-6,7-dimethoxy-2-vinylquinazoline (166)

4-Amino-2-chloromethyl-6,7-dimethoxyquinazoline **(164)** required for the synthesis of the titled compounds (**167-204**) was prepared by the controlled cyclization of 2-amino-4,5-dimethoxybenzonitrile **(132)** with chloroacetonitrile at room temperature in presence of dry hydrogen chloride gas[89] (**Scheme 6**). Its IR spectrum showed absence of peak around 2200 cm^{-1} for the nitrile group. Its mass spectrum displayed peaks at m/z 253.0 (M^+) and 255.0 $(M+2)^+$. On the other hand maintaining the same conditions as discussed above, when 2-amino-4,5-dimethoxybenzonitrile (**132**) was reacted with 3-bromopropionitrile to obtain 4-amino-2-bromoethyl-6,7-dimethoxyquinazoline (**165**),



Scheme: 6

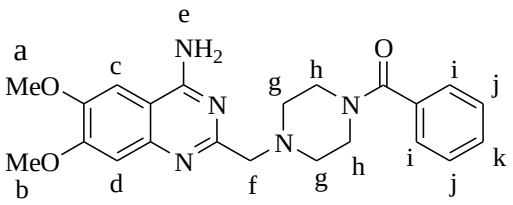
the reaction did not occur at room temperature. At increased temperatures (upto 120 ^0C), the reaction got completed but the product (**166**) was different from the desired one which was confirmed by its ^1H-NMR spectrum and mass spectrometry (**Scheme 6**). Its IR spectrum did not show a peak at 2213 cm^{-1} for nitrile group. ^1H-NMR spectrum showed two singlets at δ 7.57 (s, $1H_d$) and 7.07 (s, $1H_c$) for aromatic protons. A broad peak at δ 7.33 (s, $2H_e$) was observed for two protons of amino group. Signals were observed at δ

6.66-6.59 (m, 1H$_f$), 6.43-6.39 (d, 1H$_g$, J = 17.3), and 5.54-5.51 (d, 1H$_h$, J = 10.4) which could confirm the presence of vinylic protons. Its mass spectrum showed a molecular ion peak at m/z 231.1 (M^+). All this data indicated the formation of 4-amino-6,7-dimethoxy-2-vinylquinazoline (**166**) instead of 4-amino-2-bromoethyl-6,7-dimethoxyquinazoline **(165)**.

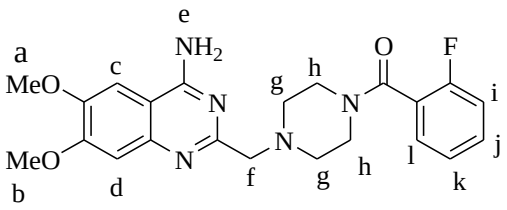
4.1.3 Synthesis of 4-amino-2-(4-substituted piperazin-1-yl)methyl-6,7-dimethoxy-quinazolines (167-192) (Series I)

The chloromethyl derivative (**164**) was reacted[89] with various substituted piperazines using a base to obtain the targeted compounds (**167-192**) (**Scheme 7**).

4-Amino-2-[4-(benzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (**167**) displayed characteristic peaks at 3309, 3146 (N-H str), and 1666 cm^{-1} (C=O str) in its IR spectrum. Its PMR spectrum showed signals at δ 7.41-7.39 (m, 2H$_{i,i}$, 2H$_{j,j}$, 1H$_k$), 7.23 (s, 1H$_d$) and 6.97 (s, 1H$_c$) for aromatic protons. A broad signal at δ 5.60 (bs, 2H$_e$) was obtained for two protons of amino group while singlets at δ 4.00 (s, 3H$_b$) and 3.97 (s, 3H$_a$) were observed for six protons of the methoxy groups. Other aliphatic protons were observed at δ 3.87 (bs, 2H$_h$), 3.71 (s, 2H$_f$), 3.50 (bs, 2H$_h$), 2.69 (bs, 2H$_g$) and 2.54 (bs, 2H$_g$). Its mass spectrum displayed a molecular ion peak at m/z 408.6 $(M + 1)^+$.

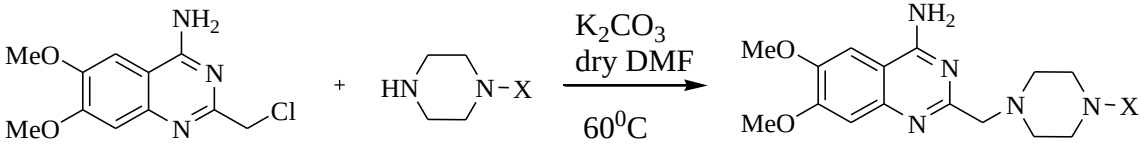


(**167**)



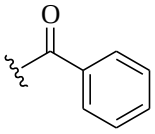
(**168**)

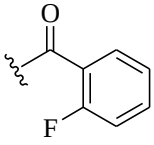
IR spectrum of 4-amino-2-[4-(2-fluorobenzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (**168**) showed characteristic peaks at 3341, 3197 (N-H str) and 1665 cm^{-1} (C=O str). Its PMR spectrum showed the signals for aromatic protons at δ 7.39-7.34 (m, 1H$_i$, 1H$_j$), 7.22 (s, 1H$_d$), 7.20-7.16 (m, 1H$_k$), 7.09 (s, 1H$_c$), and 7.07-7.05 (d, 1H$_l$, J = 8.7 Hz). A broad singlet was observed at δ 5.92 (bs, 2H$_e$) due to two protons of amino group. Among the aliphatic protons, signals appeared at δ 3.99 (s, 3H$_b$), 3.94 (s, 3H$_a$) and 3.88-3.87 (t, 2H$_h$) as a triplet which coupled with protons (CH$_g$) observed at 2.70-2.68 (t, 2H$_g$)

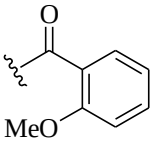


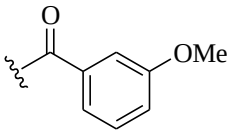
(**164**) (**167-192**)

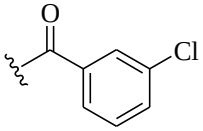
X =

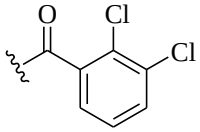
(**167**) 

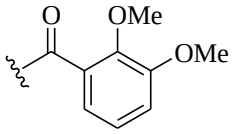
(**168**) 

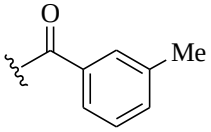
(**169**) 

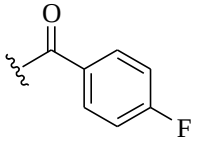
(**170**) 

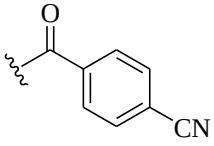
(**171**) 

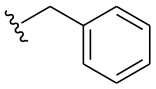
(**172**) 

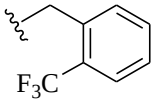
(**173**) 

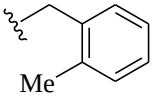
(**174**) 

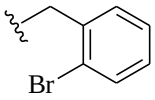
(**175**) 

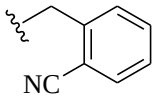
(**176**) 

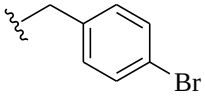
(**177**) 

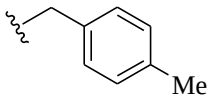
(**178**) 

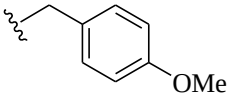
(**179**) 

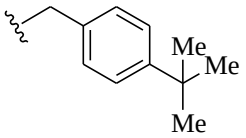
(**180**) 

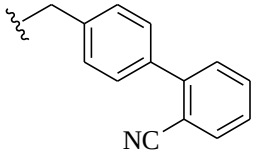
(**181**) 

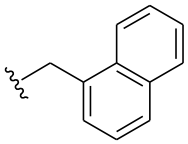
(**182**) 

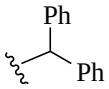
(**183**) 

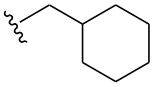
(**184**) 

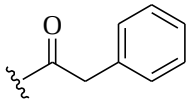
(**185**) 

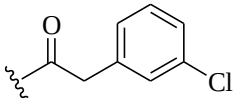
(**186**) 

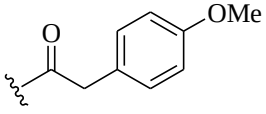
(**187**) 

(**188**) 

(**189**) 

(**190**) 

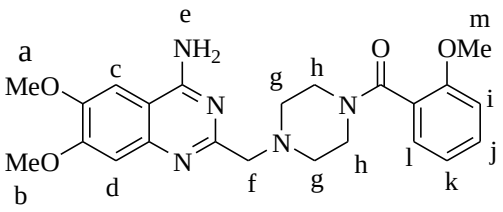
(**191**) 

(**192**) 

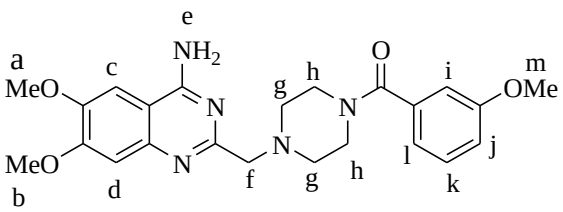
Scheme: 7

as a triplet with a coupling constant of 4.5 Hz. Other signals were observed at δ 3.70 (s, $2H_f$), 3.41 (bs, $2H_h$) and 2.50-2.48 (bs, $2H_g$). Its mass spectrum showed molecular ion peak at m/z 426.7 $(M + 1)^+$.

Compound (**169**) gave characteristic peaks at 3335, 3130 (N-H str) and 1664 cm^{-1} (C=O str) in its IR spectrum. Its PMR spectrum offered signals at δ 7.34-7.22 (m, $2H_{i,j}$), 7.21 (s, $1H_d$), 7.10 (s, $1H_c$), 6.97-6.94 (m, $1H_k$) and 6.88-6.86 (d, $1H_l$, J = 7.8 Hz) for aromatic protons. A broad peak was observed at δ 5.99 (bs, $2H_e$) for two protons of amino group. Among the aliphatic protons, signals appeared at δ 3.99 (s, $3H_m$), 3.95 (s, $3H_{a/b}$), 3.89 (bs, $2H_h$), 3.79 (s, $3H_{a/b}$), 3.70 (s, $2H_f$), 3.34 (bs, $2H_h$), 2.65 (bs, $2H_g$) and 2.48 (bs, $2H_g$). Its mass spectrum showed molecular ion peak at m/z 438.7 $(M + 1)^+$.



(**169**)

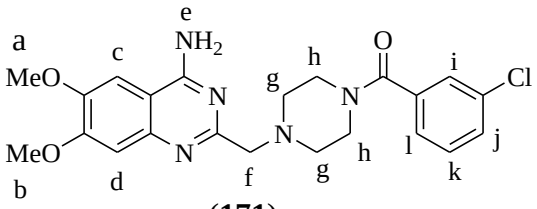


(**170**)

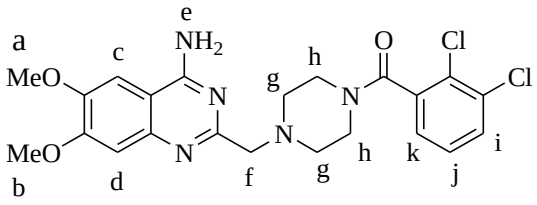
IR spectrum of compound (**170**) showed characteristic peaks at 3323, 3154 (N-H str) and 1663 cm^{-1} (C=O str) in its IR spectrum. Its PMR spectrum displayed signals at δ 7.22-7.19 (m, $1H_j$), 7.14 (s, $1H_i$), 7.00 (s, $1H_d$), 6.87-6.84 (m, $2H_{k,l}$) and 6.83 (s, $1H_c$) for aromatic protons. Aliphatic protons gave signals at δ 3.91 (s, $3H_m$) and 3.84 (s, $3H_{a/b}$) as singlet, δ 3.78 (bs, $2H_h$) as a broad singlet for two protons (CH_{2h}) of piperazine ring and 3.72 (s, $3H_{b/a}$) as singlet. A sharp peak was observed at δ 3.63 (s, $2H_f$) for two protons of methylene (CH_{2f}) spacer. Other signals appeared at δ 3.42 (bs, $2H_h$), 2.61 (bs, $2H_g$) and 2.46 (bs, $2H_g$) as broad singlets for the remaining protons of piperazine ring. Its mass spectrum displayed a molecular ion peak at m/z 437.8 $(M + 1)^+$.

Compound (**171**) gave peaks at 3320, 3150 (N-H str) and 1663 cm^{-1} (C=O str) in its IR spectrum. In its PMR spectrum, signals were observed at δ 7.31 (s, $1H_i$), 7.30-7.24 (m, $3H_{j,k,l}$), 7.20 (s, $1H_d$) and 7.17 (s, $1H_c$) for aromatic protons. Aliphatic protons gave signals at δ 3.93 (s, $3H_{a/b}$), 3.90 (s, $3H_{b/a}$), 3.79 (bs, $2H_h$), 3.65 (s, $2H_f$), 3.42 (bs, $2H_h$),

2.62 (bs, $2H_g$) and 2.49 (bs, $2H_g$). Its mass spectrum showed molecular ion peaks at m/z 442.8 $(M + 1)^+$ and 444.9 $(M + 3)^+$.



(**171**)

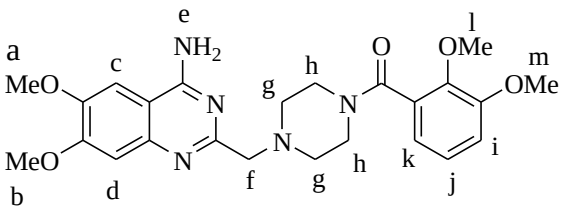


(**172**)

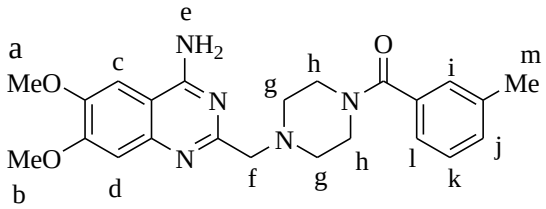
In the IR spectrum of 4-amino-2-[4-(2,3-dichlorobenzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (**172**), characteristic peaks at 3347, 3140 (N-H str) and 1675 cm^{-1} (C=O str) were observed. Its PMR spectrum offered signals at δ 7.48-7.46 (d, $1H_i$, J = 7.5 Hz), 7.25-7.23 (m, $2H_{d,j}$), 7.20-7.18 (d, $1H_k$, J = 7.5 Hz) and 6.96 (s, $1H_c$) for aromatic protons. A broad peak was observed at δ 5.70 (bs, $2H_e$) for two protons of amino group. Aliphatic region showed signals at 4.00 (s, $3H_{a/b}$), 3.98 (s, $3H_{b/a}$), 3.93 (bs, $2H_h$), 3.72 (s, $2H_f$), 3.32 (bs, $2H_h$), 2. 68 (bs, $2H_g$) and 2.51 (bs, $2H_g$). Its ^{13}C-NMR spectrum showed peaks at δ 164.73 for carbon of C=O group while aromatic signals were observed at 160.83, 160.69, 153.84, 147.96, 137.78, 134.26, 132.35, 130.49, 127.59, 125.93, 115.32, 106.54 and 102.65 whereas aliphatic carbons appeared at 55.85, 55.47, 52.85, 52.37 and 46.15. Molecular ion peaks were observed at m/z 477.7 $(M + 1)^+$ and 479.7 $(M + 3)^+$ in its mass spectrum.

4-Amino-2-[4-(2,3-dimethoxybenzoyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (**173**) displayed characteristic peaks at 3344, 3212 (N-H str) and 1621 cm^{-1} (C=O str) in its IR spectrum. Its PMR spectrum showed signals at δ 7.21 (s, $1H_d$), 7.09-7.05 (m, $1H_j$), 7.02 (s, $1H_c$), 6.92-6.90 (d, $1H_i$, J = 7.7 Hz) and 6.83-6.81 (d, $1H_k$, J = 7.7 Hz) for aromatic protons. Amino protons gave signal at δ 5.75 (bs, $2H_e$) as a broad peak whereas the aliphatic proton signals were observed at δ 3.99 (s, $3H_l$), 3.95 (s, $3H_m$) 3.89 (s, $3H_{a/b}$), 3.87 (s, $3H_{b/a}$), 3.84 (s, $2H_f$), 3.37 (bs, $2H_h$), 3.28 (bs, $2H_h$), 2.60 (bs, $2H_g$) and 2.48 (bs, $2H_g$). Its ^{13}C-NMR spectrum offered signals at δ 167.46 for carbon of C=O group, 161.17, 160.22, 154.95, 152.56, 149.03, 147.47, 144.96, 131.06, 124.73, 119.18, 116.47, 112.88, 107.44, 106.79 and 100.41 for aromatic carbons whereas signals were obtained at 65.50,

61.51, 56.26, 56.20, 55.80, 53.81, 53.08, 46.82 and 41.50 for aliphatic carbons. Its mass spectrum showed molecular ion peak at m/z 468.8 $(M + 1)^+$.



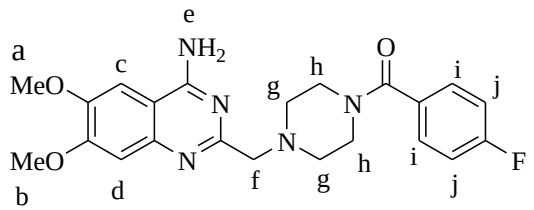
(**173**)



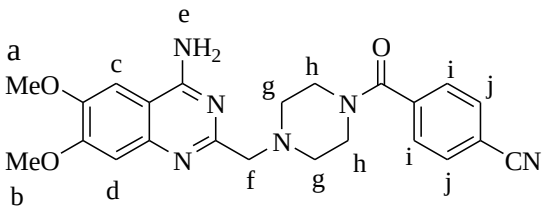
(**174**)

IR spectrum of compound (**174**) showed characteristic peaks at 3316, 3147 (N-H str) and 1667 cm^{-1} (C=O str). Its PMR spectrum showed signals at δ 7.24 (s, $1H_i$), 7.21 (s, $1H_d$), 7.19-7.06 (m, $3H_{j,k,l}$) and 6.91 (s, $1H_c$) for aromatic protons. A broad singlet at δ 5.62 (bs, $2H_e$) was observed for two protons of amino group. Signals were observed at δ 4.00 (s, $3H_{a/b}$), 3.97 (s, $3H_{a/b}$), 3.87 (bs, $2H_h$), 3.71 (s, $2H_f$), 3.50 (bs, $2H_h$), 2.69 (bs, $2H_g$), 2.62 (bs, $2H_g$) and 2.36 (s, $3H_m$) for aliphatic protons. Molecular ion peak was observed at m/z 422.9 $(M + 1)^+$ in its mass spectrum.

IR spectrum of 4-amino-2-[4-(4-fluorobenzoyl)piperazin-1-yl]methyl-6,7-dimetho-xyquinazoline (**175**) showed characteristic peaks at 3324, 3154 (N-H str) and 1662 cm^{-1} (C=O str). Its PMR spectrum displayed signals at δ 7.43-7.40 (d, $2H_{j,j}$ J = 8.5 Hz) as a doublet which coupled with protons ($CH_{i,i}$) observed at δ 7.13-7.08 (d, $2H_{i,i}$, J = 8.5 Hz) as doublet. Other signals appeared at δ 7.25 (s, $1H_d$) and 7.06 (s, $1H_c$) for aromatic protons. A broad singlet was observed at δ 6.30 (bs, $2H_e$) for amino protons. Aliphatic protons showed signals at δ 4.01 (s, $6H_{a,b}$), 3.89 (bs, $2H_h$), 3.74 (s, $2H_f$), 3.55 (bs, $2H_h$), 2.69 (bs, $2H_g$) and 2.59 (bs, $2H_g$). Its mass spectrum showed molecular ion peak at m/z 426.7 $(M + 1)^+$.



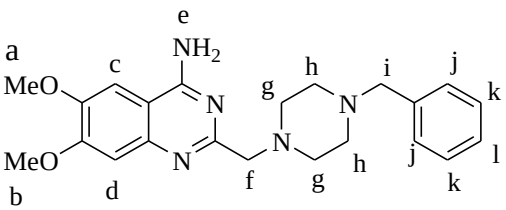
(**175**)



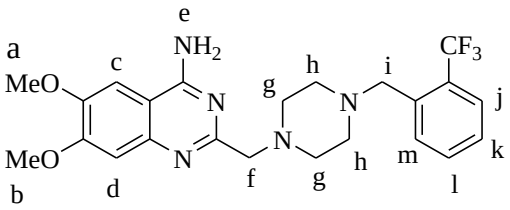
(**176**)

IR spectrum of compound (**176**) showed characteristic peaks at 3225, 3164 (N-H str), 2230 (C≡N str) and 1661 cm^{-1} (C=O str). Its PMR spectrum offered signals at δ 7.71-7.69 (d, $2H_j$, J = 7.5 Hz), 7.51-7.49 (d, $2H_i$, J = 7.5 Hz), 7.22 (s, $1H_d$) and 6.99 (s, $1H_c$) for aromatic protons. Signals were observed at δ 4.00 (s, $3H_{a/b}$), 3.95 (s, $3H_{b/a}$), 3.87 (bs, $2H_h$), 3.72 (s, $2H_f$), 3.43 (bs, $2H_h$), 2.71 (bs, $2H_g$) and 2.56 (bs, $2H_g$) for aliphatic protons. Its mass spectrum displayed molecular ion peak at m/z 433.8 $(M + 1)^+$.

IR spectrum of 4-amino-2-[(4-benzylpiperazin-1-yl)methyl]-6,7-dimethoxy-quinazoline (**177**) displayed characteristic peaks at 3429 and 3133 cm^{-1} (N-H str). Its PMR spectrum gave a broad peak at δ 7.76 (bs, $2H_e$) for two protons of the amino group. Signals were observed at δ 7.66 (s, $1H_d$), 7.32-7.23 (m, $2H_{j,j}$, $2H_{k,k}$, $1H_l$) and 7.15 (s, $1H_c$) for aromatic protons. Aliphatic protons showed signals at δ 3.96 (s, $3H_{a/b}$), 3.95 (s, $3H_{b/a}$), 3.81 (bs, $4H_{g,g}$), 3.73 (s, $2H_f$), 3.58 (s, $2H_i$), 2.81 (bs, $2H_h$) and 2.54 (bs, $2H_h$). Molecular ion peak was observed at m/z 394.9 $(M + 1)^+$ in its mass spectrum.



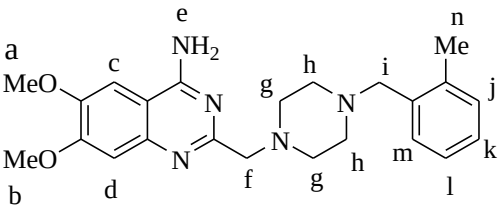
(**177**)



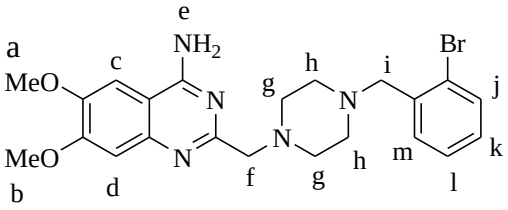
(**178**)

Compound (**178**) gave characteristic peaks at 3430 and 3290 cm^{-1} (N-H str) in its IR spectrum. Signals were seen at δ 7.79-7.77 (d, $1H_j$) and δ 7.42-7.38 (d, $1H_m$) as doublets in its PMR spectrum. Other aromatic protons were observed at δ 7.64-7.59 (m, $2H_{k,l}$), 7.57 (s, $1H_d$) and 7.09 (s, $1H_c$). A broad peak was observed at δ 7.37 (bs, $2H_e$) for two protons of amino group. Among the aliphatic protons, signals were observed at δ 3.91 (s, $3H_{a/b}$), 3.89 (s, $3H_{b/a}$), 3.61 (s, $2H_f$), 3.51 (s, $2H_i$), 2.58 (bs, $4H_{g,g}$) and 2.46 (bs, $4H_{h,h}$). Its ^{13}C-NMR spectrum offered signals at δ 161.29, 160.67, 153.82, 147.85, 146.72, 137.39, 131.96, 130.14, 127.46, 126.83, 125.64, 125.29, 122.91, 106.58 and 102.53 for aromatic carbons whereas aliphatic signals were observed at δ 65.17, 57.65, 55.82, 55.45, 52.96 and 52.72. Its mass spectrum showed molecular ion peak at m/z 462.8 $(M + 1)^+$.

Characteristic peaks at 3491 and 3071 cm^{-1} (N-H str) were observed in IR spectrum of 4-amino-2-[4-(2-methylbenzyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (**179**). It showed PMR signals at δ 7.26-7.24 (m, $4H_{j,k,l,m}$), 7.14 (s, $1H_d$) and 6.88 (s, $1H_c$) for aromatic protons. A broad peak at δ 5.44 (bs, $2H_e$) was observed for two protons of amino group. In the aliphatic region signals were observed at 4.00 (s, $3H_{a/b}$), 3.99 (s, $3H_{a/b}$), 3.68 (s, $2H_f$), 3.47 (s, $2H_i$), 2.62 (bs, $4H_{g,g}$), 2.56 (bs, $4H_{h,h}$) and 2.35 (s, $3H_n$). Signals were observed at δ 161.94, 160.13, 154.88, 148.94, 147.66, 137.48, 136.56, 130.18, 129.75, 126.90, 125.43, 107.66, 106.75 and 100.04 for aromatic carbons while aliphatic carbons gave signals at δ 65.80, 60.76, 56.28, 56.18, 53.67, 52.99 and 19.29 in its ^{13}C-NMR spectrum.



(**179**)

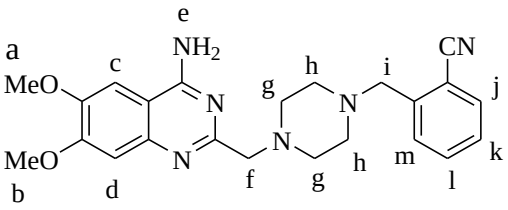


(**180**)

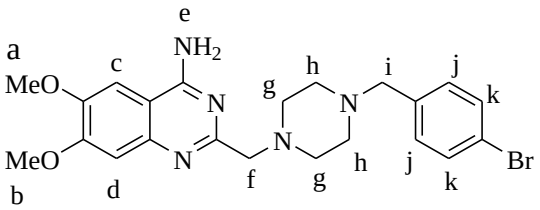
IR spectrum of compound (**180**) gave characteristic peaks at 3493 and 3277 cm^{-1} (N-H str). Its PMR spectrum showed signals at δ 7.53-7.51 (d, $1H_j$), 7.49-7.46 (d, $1H_m$) as doublets, 7.28-7.26 (m, $1H_k$) as multiplet, 7.24 (s, $1H_d$) as singlet, 7.11-7.06 (m, $1H_l$) as multiplet and 6.91 (s, $1H_c$) as singlet. Amino protons gave signal at δ 5.69 (bs, $2H_e$) as a broad peak whereas aliphatic protons showed signals at δ 4.00 (s, $3H_{a/b}$), 3.98 (s, $3H_{a/b}$), 3.70 (s, $2H_f$), 3.62 (s, $2H_i$) and 2.64 (bs, $8H_{g,g,h,h}$). Its mass spectrum showed molecular ion peaks at m/z 472.8 $(M + 1)^+$ and 474.8 $(M + 3)^+$.

Compound (**181**) displayed characteristic peaks at 3443, 3281 (N-H str) and 2225 cm^{-1} (C≡N str) in its IR spectrum. Its PMR spectrum displayed signals at δ 7.64-7.62 (d, $1H_j$, J = 7.6 Hz), 7.56-7.53 (m, $2H_{m,k}$), 7.35-7.31 (m, $1H_l$), 7.27 (s, $1H_d$) and 7.24 (s, $1H_c$) for aromatic protons. A broad peak was observed at δ 5.58 (bs, $2H_e$) for two protons of amino group. Aliphatic protons were observed at δ 4.00 (s, $3H_{a/b}$), 3.99 (s, $3H_{b/a}$), 3.73 (s, $2H_f$), 3.70 (s, $2H_i$) and 2.64 (bs, $8H_{g,g,h,h}$). In its ^{13}C-NMR spectrum, signals were observed at δ 161.74, 160.12, 154.91, 148.98, 147.62, 142.40, 132.88, 130.05, 127.47, 117.89,

112.92, 107.62, 106.75 and 100.09 for aromatic carbons. A signal was obtained at δ 132.52 for carbon of C≡N group while other signals were observed at δ 65.64, 60.37, 56.28, 56.22, 53.42 and 52.68 for aliphatic carbons. Molecular ion peak was observed at m/z 418.9 $(M + 1)^+$ in its mass spectrum.



(**181**)

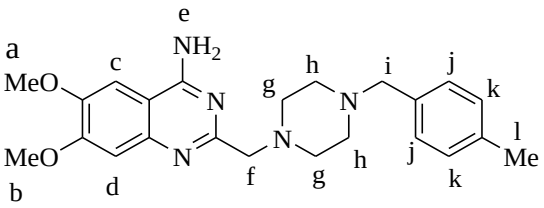


(**182**)

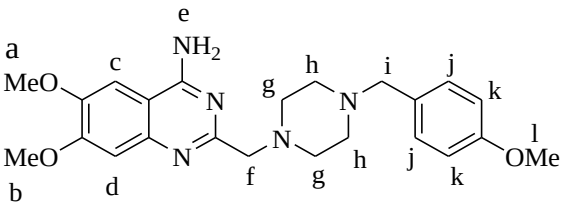
Characteristic peaks at 3324 and 3158 cm^{-1} (N-H str) were observed in IR spectrum of 4-amino-2-[4-(4-bromolbenzyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (**182**). Its PMR spectrum displayed peaks for aromatic protons ($CH_{k,k}$) at δ 7.42-7.40 (d, $2H_{k,k}$, J = 8.3 Hz) as a doublet which coupled with protons ($CH_{j,j}$) observed at δ 7.19-7.17 (d, $2H_{j,j}$, J = 8.3 Hz) as a doublet with a coupling constant of 8.3 Hz. Other aromatic protons (CH_d) and (CH_c) were observed at δ 7.23 (s, $1H_d$) and 6.95 (s, $1H_c$) as singlets, respectively. A broad peak was observed at 5.85 (bs, $2H_e$) for the two protons of amino group. Signals were observed at δ 3.98 (s, $3H_{a/b}$), 3.94 (s, $3H_{b/a}$), 3.68 (s, $2H_f$), 3.44 (s, $2H_i$), 2.63 (bs, $4H_{g,g}$) and 2.52 (bs, $4H_{h,h}$) for aliphatic protons. Its mass spectrum displayed molecular ion peaks at m/z 473.7 $(M + 1)^+$ and 474.7 $(M + 2)^+$.

IR spectrum of 4-amino-2-[4-(4-methylbenzyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (**183**) gave characteristic peaks at 3313 and 3148 cm^{-1} (N-H str). In its PMR spectrum, a signal was observed at δ 7.23 (s, $1H_d$) as singlet for proton (CH_d) in aromatic region. Protons ($CH_{k,k}$) were observed at δ 7.19-7.17 (d, $2H_{k,k}$) as a doublet which coupled with protons ($CH_{j,j}$) observed at δ 7.11-7.09 (d, $2H_{j,j}$) as a doublet with a coupling constant of 7.9 Hz. A signal was observed at δ 6.97 (s, $1H_c$) as a singlet for the remaining one aromatic proton. Amino protons (NH_{2e}) showed a broad signal at δ 6.07 (bs, $2H_e$). Signals were observed at δ 3.98 (s, $3H_{a/b}$), 3.93 (s, $3H_{b/a}$), 3.68 (s, $2H_f$), 3.47 (s, $2H_i$), 2.63 (bs, $4H_{g,g}$), 2.53 (bs, $4H_{h,h}$) and 2.32 (s, $3H_l$) for aliphatic protons. Signals were seen at δ 161.85, 160.32, 154.83, 148.88, 147.59, 136.59, 134.89, 129.04, 128.85, 107.58, 106.78

and 100.26 for aromatic carbons while signals at δ 65.73, 62.87, 56.24, 56.13, 53.47, 52.86 and 21.10 were present for aliphatic carbons in its ^{13}C-NMR spectrum. Its mass spectrum showed molecular ion peak at m/z 408.6 $(M + 1)^+$.



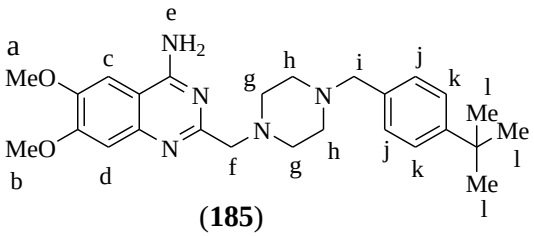
(**183**)



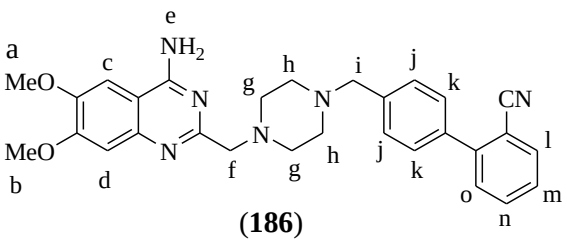
(**184**)

4-Amino-2-[4-(4-methoxybenzyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (**184**) showed characteristic peaks at 3311 and 3143 cm^{-1} (N-H str) in its IR spectrum. It showed PMR signals for aromatic protons at δ 7.24 (s, 1H$_d$), 6.90 (s, 1H$_c$) as singlets and 7.23-7.21 (d, 2H$_{k,k}$) as a doublet which coupled with protons (CH$_{j,j}$) observed at δ 6.85-6.83 (d, 2H$_{j,j}$) as doublet with a coupling constant of 9.0 Hz. A broad peak was observed at 5.63 (bs, 2H$_e$) for amino protons. Signals were observed at δ 4.00 (s, 3H$_{a/b}$), 3.98 (s, 3H$_{b/a}$), 3.79 (s, 3H$_l$), 3.69 (s, 2H$_f$), 3.46 (s, 2H$_i$), 2.63 (bs, 4H$_{g,g}$) and 2.54 (bs, 4H$_{h,h}$) for aliphatic protons. Molecular ion peak was observed at m/z 424.8 $(M + 1)^+$ in its mass spectrum.

Compound (**185**) gave characteristic peaks at 3315 and 3151 cm^{-1} (N-H str) in its IR spectrum. Its PMR spectrum displayed signals at δ 7.32-7.30 (d, 2H$_{k,k}$) as a doublet which coupled with protons (CH$_{j,j}$) observed at δ 7.23-7.21 (d, 2H$_{j,j}$) as a doublet with a coupling constant of 8.2 Hz. Other signals appeared at δ 7.23 (s, 1H$_d$) and 6.93 (s, 1H$_c$) as singlets for aromatic protons. It showed a broad peak at δ 5.85 (bs, 2H$_e$) for protons of amino group. Aliphatic protons were observed at δ 3.98 (s, 3H$_{a/b}$), 3.95 (s, 3H$_{b/a}$), 3.69 (s, 2H$_f$), 3.50 (s, 2H$_i$), 2.64 (bs, 4H$_{g,g}$), 2.55 (bs, 4H$_{h,h}$) and 1.30 (s, 9H$_{l,l,l}$). Signals were observed at δ 161.86, 160.10, 154.88, 149.90, 148.94, 147.66, 134.76, 129.09, 125.05, 107.67, 106.73 and 100.02 for aromatic carbons whereas aliphatic carbons were seen at δ 65.73, 62.71, 56.27, 56.19, 53.46, 52.74, 34.46 and 31.40 in its ^{13}C-NMR spectrum.



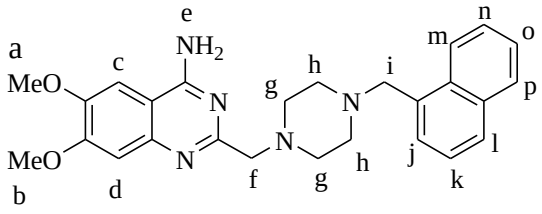
(**185**)



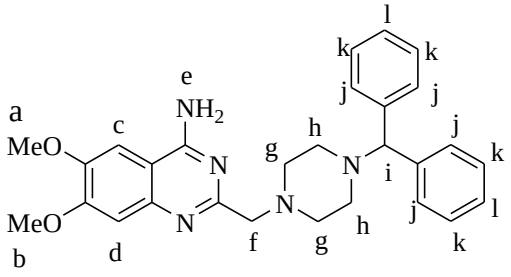
(**186**)

Characteristic peaks were observed for compound (**186**) at 3301, 3133 (N-H str) and 2224 cm^{-1} (C≡N str) in its IR spectrum. Its PMR spectrum offered signals at δ 7.84-7.82 (d, $1H_l$, J = 7.8 Hz), 7.75-7.71 (m, $1H_o$), 7.57 (s, $1H_d$), 7.55-7.54 (m, $2H_{m,n}$), 7.52-7.50 (d, $2H_{k,k}$) as a doublet which coupled with protons ($CH_{j,j}$) observed at δ 7.45-7.43 (d, $2H_{j,j}$) as a doublet with a coupling constant of 8.2 Hz and at δ 7.09 (s, $1H_c$) as a singlet for the aromatic protons. A broad singlet at δ 7.25 (bs, $2H_e$) for two protons of amino group was also observed. Signals were observed at δ 3.91 (s, $6H_{a,b}$), 3.56 (s, $2H_f$), 3.53 (s, $2H_i$), 2.59 (bs, $4H_{g,g}$) and 2.49 (bs, $4H_{h,h}$) for aliphatic protons. Its mass spectrum displayed molecular ion peak at m/z 495.9 $(M + 1)^+$.

IR spectrum of 4-amino-2-[4-(1-naphthylmethyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (**187**) displayed characteristic peaks at 3306 and 3156 cm^{-1} (N-H str). Its PMR spectrum showed aromatic protons at δ 8.26-8.24 (d, $1H_m$, J = 7.5 Hz), 7.87-7.85 (d, $1H_p$, J = 7.5 Hz), 7.80-7.78 (m, $1H_k$), 7.56 (s, $1H_d$), 7.53-7.50 (m, $2H_{n,o}$), 7.48-7.46 (d, $2H_{j,l}$) and 7.09 (s, $1H_c$). A broad signal appeared at δ 7.42 (bs, $2H_e$) for the amino protons. Among the aliphatic protons signals were observed at δ 3.90 (s, $3H_{a/b}$), 3.89 (s, $3H_{b/a}$), 3.88 (s, $2H_f$), 3.55 (s, $2H_i$), 2.60 (bs, $4H_{g,g}$) and 2.53 (bs, $4H_{h,h}$). Signals appeared at δ 160.69, 153.92, 147.94, 133.65, 133.33, 132.00, 128.00, 127.54, 127.14, 125.51, 125.39,



(**187**)

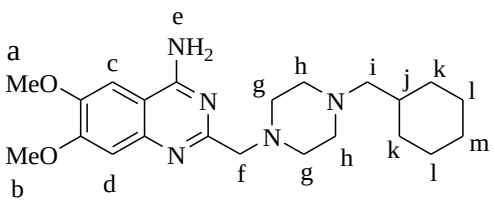


(**188**)

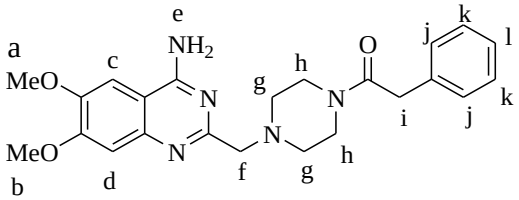
124.92, 124.58, 106.51, 106.31 and 102.60 for aromatic carbons while aliphatic carbons were observed at δ 99.49, 60.45, 55.87, 55.49, 52.91 and 52.54 in its ^{13}C-NMR spectrum. Its mass spectrum offered molecular ion peak at m/z 444.7 $(M + 1)^+$.

Compound (**188**) showed characteristic peaks at 3492 and 3270 cm^{-1} (N-H str) in its IR spectrum. Its PMR spectrum displayed signals at δ 7.41-7.39 (d, $4H_{j,j}$), 7.26 (s, $1H_d$), 7.24-7.21 (m, $4H_{k,k}$), 7.16-7.13 (m, $2H_{l,l}$) and 6.92 (s, $1H_c$) for aromatic protons. A broad peak was observed at δ 5.70 (bs, $2H_e$) for the two protons of amino group. Aliphatic protons gave signals at δ 4.23 (s, $1H_i$), 3.98 (s, $3H_{a/b}$), 3.95 (s, $3H_{b/a}$), 3.70 (s, $2H_f$), 2.65 (bs, $4H_{g,g}$) and 2.49 (bs, $4H_{h,h}$). Signals appeared at 161.71, 160.13, 154.88, 148.93, 147.58, 142.80, 128.41, 127.95, 126.85, 107.59 and 106.73 for aromatic carbons whereas the aliphatic carbons appeared at 100.14, 65.63, 56.26, 56.19, 53.79 and 51.61 in its ^{13}C-NMR spectrum.

Characteristic peaks were observed for 4-amino-2-[4-(cyclohexylmethyl)piperazin-1-yl]methyl-6,7-dimethoxyquinazoline (**189**) at 3338 and 3156 cm^{-1} (N-H str) in its IR spectrum. Its PMR spectrum offered signals at δ 7.24 (s, $1H_d$) and 6.92 (s, $1H_c$) as singlets for aromatic protons. A broad signal was observed at δ 5.72 (bs, $2H_e$) for two protons of amino group. Among the aliphatic protons, signals appeared at δ 4.00 (s, $3H_{a/b}$), 3.98 (s, $3H_{b/a}$), 3.69 (s, $2H_f$), 2.65 (bs, $4H_{g,g}$), 2.51 (bs, $4H_{h,h}$), 2.13 (d, $2H_i$), 1.77-1.64 (m, $4H_{k,k}$), 1.50-1.45 (m, $1H_j$), 1.26-1.13 (m, $4H_{l,l}$) and 0.90-0.81 (m, $2H_m$).



(**189**)

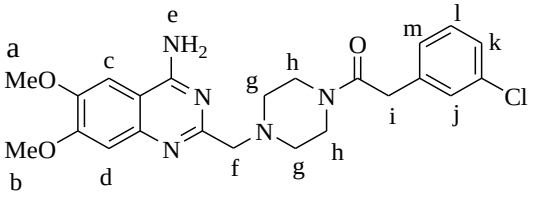


(**190**)

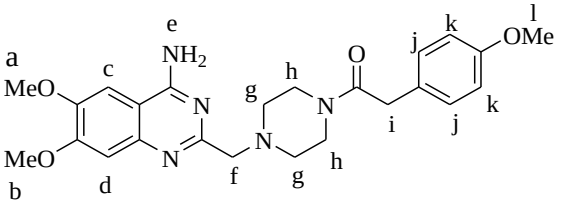
IR spectrum of 1-[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)methylpiperazin-1-yl]-2-phenylethanone (**190**) displayed characteristic peaks at 3336, 3164 (N-H str) and 1657 (C=O str) cm^{-1}. Its PMR spectrum showed a broad signal at δ 7.25 (bs, $2H_e$) for amino protons. Aromatic protons were observed at 7.23 (s, $1H_d$), 7.21-7.20 (d, $2H_{j,j}$), 7.15-7.14 (m, $2H_{k,k}$, $1H_l$) and 6.88 (s, $1H_c$). Signals were observed at 3.93 (s, $3H_{a/b}$), 3.91 (s,

$3H_{a/b}$), 3.66 (bs, $2H_h$, $2H_i$), 3.57 (s, $2H_f$), 3.47-3.45 (m, $2H_h$, J = 4.5 Hz), 2.50-2.48 (m, $2H_g$, J = 4.5 Hz) and 2.34 (m, $2H_g$) for aliphatic protons. Molecular ion peak was observed at m/z 422.9 $(M + 1)^+$ in its mass spectrum.

1-[4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)methylpiperazin-1-yl]-2-(3-chloro-phenyl)ethanone (**191**) gave characteristic peaks at 3332, 3164 (N-H str) and 1657 (C=O str) cm^{-1} in its IR spectrum. Its PMR spectrum displayed signals at δ 7.24 (s, $1H_j$), 7.23 (s, $1H_d$), 7.22-7.21 (d, $2H_{k,m}$), 7.13-7.11 (m, $1H_l$) and 6.92 (s, $1H_c$) for aromatic protons while aliphatic protons were observed at δ 4.01 (s, $3H_{a/b}$), 4.00 (s, $3H_{b/a}$), 3.75-3.73 (t, $2H_h$, J = 5.0 Hz), 3.69 (s, $2H_i$), 3.67 (s, $2H_f$), 3.54-3.51 (t, $2H_h$, J = 5.0 Hz), 2.59-2.56 (t, $2H_g$, J = 5.0 Hz) and 2.48-2.45 (t, $2H_g$, J = 5.0 Hz). Its mass spectrum offered molecular ion peaks at m/z 456.7 $(M + 1)^+$ and 457.7 $(M + 2)^+$.



(**191**)

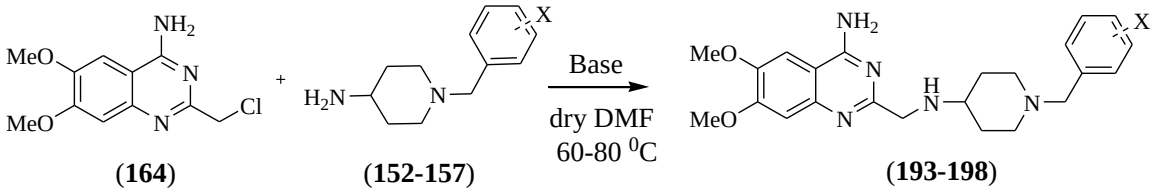


(**192**)

Characteristic peaks were observed for 1-[4-(4-amino-6,7-dimethoxyquinazolin-2-yl)methylpiperazin-1-yl]-2-(4-methoxyphenyl)ethanone (**192**) at 3333, 3161 (N-H str) and 1657 (C=O str) cm^{-1} in its IR spectrum. Its PMR spectrum offered signals at δ 7.23 (s, $1H_d$), 7.15-7.13 (d, $2H_{k,k}$, J = 8.9 Hz), 6.96 (s, $1H_c$) and 6.86-6.82 (d, $2H_{j,j}$, J = 8.9 Hz) for aromatic protons. Signals were observed at δ 4.01 (s, $3H_{a/b}$), 4.00 (s, $3H_{b/a}$), 3.79 (s, $3H_l$), 3.75-3.72 (t, $2H_h$, J = 4.9 Hz), 3.66 (s, $2H_i$), 3.65 (s, $2H_f$), 3.55-3.53 (t, $2H_h$, J = 4.9 Hz), 2.57-2.55 (t, $2H_g$, J = 4.9 Hz) and 2.44-2.41 (t, $2H_g$, J = 4.9 Hz) for aliphatic protons. Its mass spectrum displayed molecular ion peak at m/z 452.9 $(M + 1)^+$.

4.1.4 Synthesis of 4-amino-2-(1-substituted piperidin-4-ylamino)methyl-6,7-dimeth-oxyquinazolines (193-198) (Series II)

The desired compounds (**193-198**) were synthesized by the reaction of chloromethyl derivative (**164**) with substituted piperidines (**152-157**) in presence of a base **(Scheme 8)**.



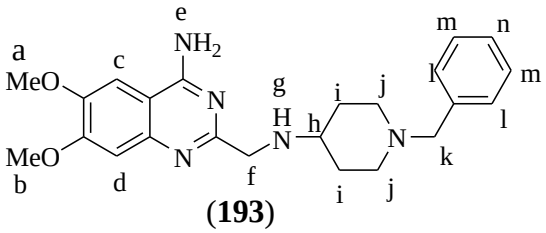
(**164**) (**152-157**) (**193-198**)

X =

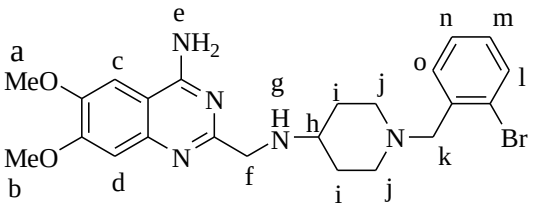
(**193**) H; (**195**) 2-CN; (**197**) 3-OMe;
(**194**) 2-Br; (**196**) 2-Me; (**198**) 4-Me

Scheme: 8

IR spectrum of 4-amino-2-[(1-benzylpiperidin-4-yl)amino]methyl-6,7-dimethoxy-quinazoline (**193**) displayed characteristic peaks at 3346 and 3196 cm^{-1} (N-H str). Its PMR spectrum showed signals at δ 7.61 (s, $1H_d$), 7.33-7.22 (m, $2H_{l,l}$, $2H_{m,m,}$,$1H_n$) and 7.05 (s, $1H_c$) for aromatic protons. Primary amino protons offered a broad peak at δ 7.50 (bs, $2H_e$) while aliphatic protons gave signals at δ 3.90 (s, $6H_{a,b}$), 3.88 (s, $2H_f$), 3.46 (s, $2H_k$), 2.84-2.76 (m, $1H_h$, $2H_j$), 2.00-1.91 (m, $2H_j$, $2H_i$) and 1.55-1.49 (m, $2H_i$). Molecular ion peak was observed at m/z 408.4 $(M + 1)^+$ in its mass spectrum.



(**193**)

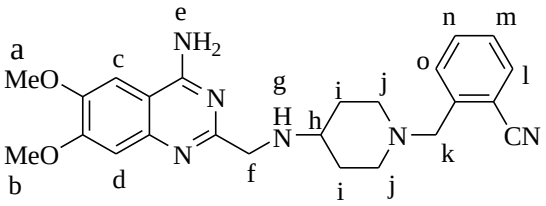


(**194**)

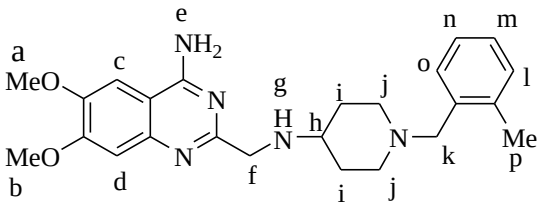
4-Amino-2-[1-(2-bromobenzyl)piperidin-4-ylamino]methyl-6,7-dimethoxyquinaz-oline (**194**) showed characteristic peaks at 3272 and 3102 cm^{-1} (N-H str). Its PMR spectrum displayed signals at δ 7.52-7.50 (d, $1H_l$, J = 7.6 Hz), 7.49-7.47 (d, $1H_o$, J = 7.6 Hz), 7.29-7.25 (m, $1H_m$), 7.15 (s, $1H_d$), 7.11-7.06 (m, $1H_n$) and 6.93 (s, $1H_c$) for aromatic protons. A broad peak was observed at δ 5.71 (bs, $2H_e$) for two protons of primary amino group. Signals were observed at δ 3.99 (s, $3H_{a/b}$), 3.96 (s, $3H_{b/a}$), 3.95 (s, $2H_f$), 3.58 (s, $2H_k$), 2.91-2.88 (m, $2H_j$), 2.64-2.59 (m, $1H_h$), 2.18-2.12 (m, $2H_j$), 1.96-1.93 (m, $2H_i$) and 1.60-1.51 (m, $2H_i$) for aliphatic and piperidine protons. Its mass spectrum displayed molecular ion peak at m/z 486.4 $(M + 1)^+$.

IR spectrum of compound (**195**) gave characteristic peaks at 3338, 3147 (N-H str) and 2225 cm^{-1} (C≡N str). Its PMR spectrum offered signals at δ 7.75-7.73 (d, $1H_l$, J = 7.5

Hz), 7.71 (s, 1H$_d$), 7.67-7.63 (m, 1H$_m$), 7.56-7.54 (d, 1H$_o$, J = 7.5 Hz), 7.46-7.42 (m, 1H$_n$) and 7.05 (s, 1H$_c$) whereas aliphatic protons were observed at 4.12 (s, 2H$_f$), 3.90 (s, 6H$_{a,b}$), 3.65 (s, 2H$_k$), 3.20-3.14 (m, 2H$_j$), 2.91-2.89 (bs, 1H$_g$, 1H$_h$), 2.15-2.08 (m, 2H$_j$, 2H$_i$) and 1.78-1.70 (m, 2H$_i$). Its mass spectrum showed molecular ion peak at m/z 433.2 $(M + 1)^+$.



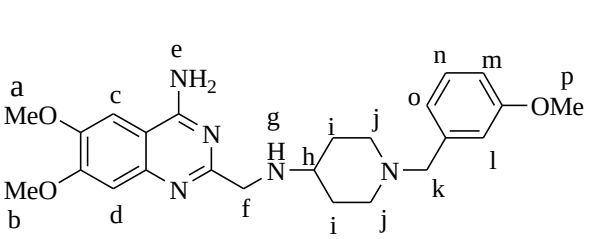
(**195**)



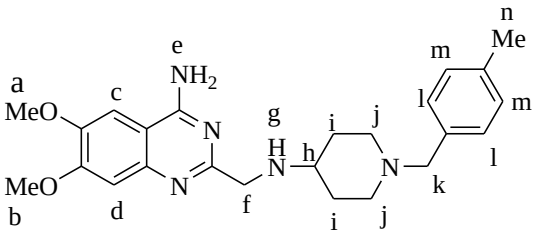
(**196**)

Characteristic IR peaks were observed for 4-amino-2-[1-(2-methylbenzyl)piperidin-4-ylamino]methyl-6,7-dimethoxyquinazoline (**196**) at 3270 and 3216 cm^{-1} (N-H str). Its PMR spectrum showed signals at δ 7.55 (s, 1H$_d$), 7.20-7.18 (m, 1H$_l$), 7.12-7.08 (m, 3H$_{m,n,o}$) and 7.04 (s, 1H$_c$) for protons of aromatic region. A broad signal was observed at δ 7.25 (bs, 2H$_e$) for primary amino protons. Among the aliphatic protons signals were observed at δ 3.91 (s, 3H$_{a/b}$), 3.90 (s, 3H$_{b/a}$), 3.73 (s, 2H$_f$), 3.39 (s, 2H$_k$), 3.30 (bs, 1H$_g$, 1H$_h$), 2.79-2.76 (m, 2H$_j$), 2.32 (s, 3H$_p$), 2.05-1.99 (m, 2H$_j$), 1.86-1.83 (m, 2H$_i$) and 1.42-1.33 (m, 2H$_i$).

IR spectrum of 4-amino-2-[1-(3-methoxybenzyl)piperidin-4-ylamino]methyl-6,7-dimethoxyquinazoline (**197**) displayed characteristic peaks at 3349 and 3209 cm^{-1} (N-H str). Its PMR spectrum displayed signals for aromatic protons at δ 7.18-7.14 (m, 1H$_n$), 7.10 (s, 1H$_d$), 7.05 (s, 1H$_c$), 6.81 (s, 1H$_l$), 6.81-6.79 (d, 1H$_m$) and 6.75-6.73 (d, 1H$_o$). A broad peak was observed at 7.10 (bs, 2H$_e$) for primary amino protons. Aliphatic protons appeared at 3.93 (s, 2H$_f$), 3.82 (s, 6H$_{a,b}$), 3.75 (s, 3H$_p$), 3.34 (s, 2H$_k$), 2.85-2.83 (m, 2H$_j$), 2.62 (bs, 1H$_h$), 1.91 (bs, 2H$_j$) and 1.82-1.67 (m, 4H$_{i,i}$). Its ^{13}C-NMR showed signals at 163.17, 160.55, 159.50, 154.56, 148.52, 146.90, 140.11, 129.05, 126.71, 121.46, 114.63, 112.27, 107.11 and 101.23 for aromatic carbons whereas signals were observed at 65.90, 62.97, 58.95, 58.25, 56.04, 55.16, 53.50 and 27.44 for aliphatic carbons.



(**197**)

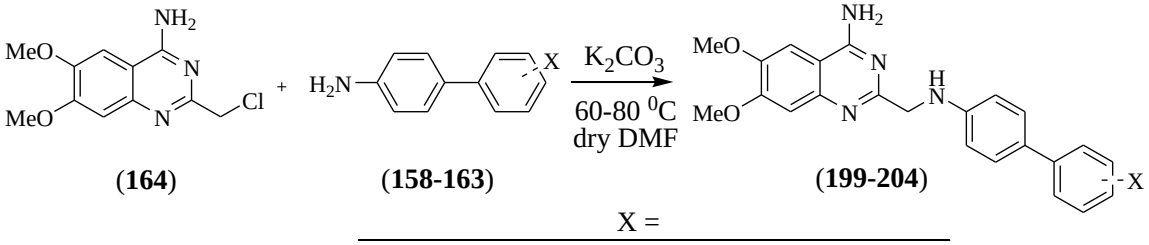


(**198**)

Compound (**198**) showed a characteristic peak at 3125 cm^{-1} (N-H str) in its IR spectrum. Its PMR spectrum offered signals for aromatic protons at δ 7.55 (s, $1H_d$), 7.16-7.14 (d, $2H_{m,m}$, J = 7.9 Hz), 7.10-7.08 (d, $2H_{l,l}$, J = 7.9 Hz) and 7.03 (s, $1H_c$). Protons of amino group were observed at δ 7.33 (bs, $2H_e$) as a broad singlet. Signals were observed at δ 3.90 (s, $3H_{a/b}$), 3.88 (s, $3H_{b/a}$), 3.70 (s, $2H_f$), 3.38 (s, $2H_k$), 3.33 (s, $1H_g$), 2.77-2.74 (m, $2H_j$), 2.49-2.48 (m, $1H_h$), 2.29 (s, $3H_n$), 1.99-1.91 (m, $2H_j$), 1.83-1.81 (m, $2H_i$) and 1.39-1.34 (m, $2H_i$) for aliphatic and piperidine protons.

4.1.5 Synthesis of 4-amino-2-(2'/4'-substituted 1,1'-biphenyl-4-ylamino)methyl-6,7-dimethoxyquinazolines (199-204) (Series III)

The 2-chloromethyl derivative (**164**) was reacted with substituted biphenyls (**158-163**) using a base in dry DMF at a temperature range of 60-80 ^{0}C to obtain the targeted compounds (**199-204**) (**Scheme 9**).[89]



(**164**) (**158-163**) (**199-204**)

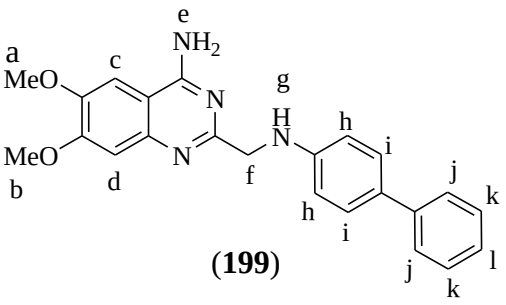
X =

(**158**, **199**) H; (**160, 201**) 2-Me; (**162, 203**) 4-SMe;
(**159, 200**) 2-Cl; (**161, 202**) 4-CN; (**163, 204**) 4-*t*.Bu

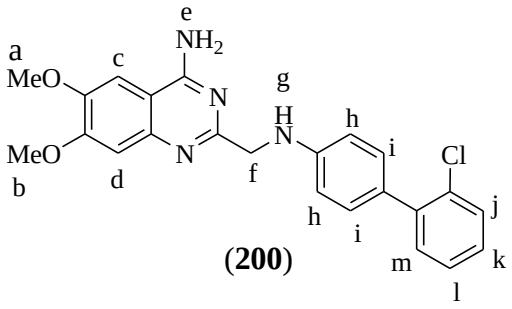
Scheme: 9

Characteristic peaks were observed for 4-amino-2-(1,1'-biphenyl-4-amino)methyl-6,7-dimethoxyquinazoline (**199**) at 3389 and 3132 cm^{-1} (N-H str) in its IR spectrum. Its PMR spectrum offered a signal for an aromatic proton (CH_d) observed at δ 7.59 (s, $1H_d$) as a singlet. Other aromatic protons ($CH_{h,h}$) were observed at δ 7.52-7.50 (d, $2H_{h,h}$) as a doublet which coupled with adjacent protons ($CH_{i,i}$) observed at δ 7.42-7.39 (d, $2H_{i,i}$) as a

doublet with a coupling constant of 8.3 Hz. Protons (CH_e) were observed at δ 7.39 (bs, $2H_e$) as a broad singlet for the amino group. Signals were obtained at δ 7.37-7.33 (m, $2H_{j,j}$), 7.21-7.18 (m, $1H_l$), 7.11 (s, $1H_c$) and 6.78-6.76 (d, $2H_{k,k}$, J = 8.3 Hz) for the remaining aromatic protons. Signal at 5.94-5.92 (t, $1H_g$, J = 4.9 Hz) coupled with the signal of (CH_f) observed at 4.27-4.26 (d, $2H_f$, J = 4.9 Hz) as a doublet with a coupling constant of 4.9 Hz. Other aliphatic protons appeared at 3.94 (s, $3H_{a/b}$) and 3.91 (s, $3H_{b/a}$) as singlets. Molecular ion peak was observed at m/z 387.1 (M^+) in its mass spectrum.



(**199**)

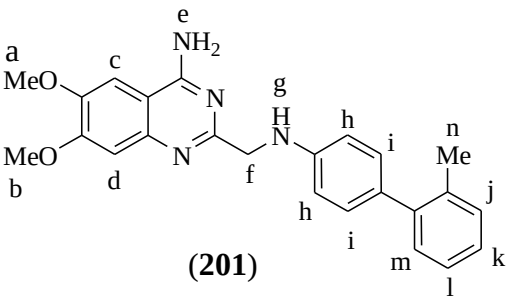


(**200**)

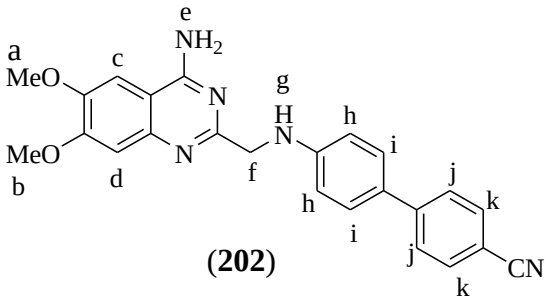
IR spectrum of 4-amino-2-(2'-chloro-1,1'-biphenyl-4-amino)methyl-6,7-dimethoxy-quinazoline (**200**) displayed characteristic peaks at 3430 and 3379 cm^{-1} (N-H str). Its PMR spectrum showed signals at δ 7.59 (s, $1H_d$), 7.44-7.42 (m, $1H_j$), 7.33-7.28 (m, $1H_m$, $1H_k$), 7.26-7.21 (m, $2H_{h,h}$, $1H_l$), 7.12 (s, $1H_c$) and 6.76-6.74 (d, $2H_{i,i}$) for aromatic protons. Amino protons showed a broad singlet at δ 7.41 (bs, $2H_e$). Proton (NH_g) of secondary amino group gave signal at δ 6.03-6.00 (t, $1H_g$, J = 4.8 Hz) as a triplet which coupled with protons of adjacent methylene (CH_{2f}) spacer observed at δ 4.27-4.26 (d, $2H_f$, J = 4.8 Hz) as a doublet with a coupling constant of 4.8 Hz. Protons of methoxy groups were observed at δ 3.94 (s, $3H_{a/b}$) and 3.91 (s, $3H_{b/a}$) as singlets. Its mass spectrum showed molecular ion peaks at m/z 421.4 (M^+) and 423.4 $(M + 2)^+$.

Compound (**201**) showed characteristic peaks at 3390 and 3132 cm^{-1} (N-H str) in its IR spectrum. Its PMR spectrum displayed signals at δ 7.25 (s, $1H_d$), 7.24-7.17 (m, $2H_{h,h}$, $4H_{j,k,l,m}$), 6.89 (s, $1H_c$) and 6.83-6.81 (d, $2H_{i,i}$, J = 8.4 Hz) for aromatic protons. Amino protons (NH_{2e} and NH_g) were observed at 5.54 (bs, $2H_e$) and 5.32 (bs, $1H_g$) as broad singlets. Since there is no coupling between amino protons (NH_g) and protons of methylene (CH_{2f}) spacer a singlet is observed at δ 4.46 (s, $2H_f$) instead of doublet for these

two protons. Other aliphatic protons showed signals at δ 4.04 (s, $3H_{a/b}$), 3.98 (s, $3H_{b/a}$) and 2.31 (s, $3H_n$). Its mass spectrum offered a molecular ion peak at m/z 400.8 (M^+).



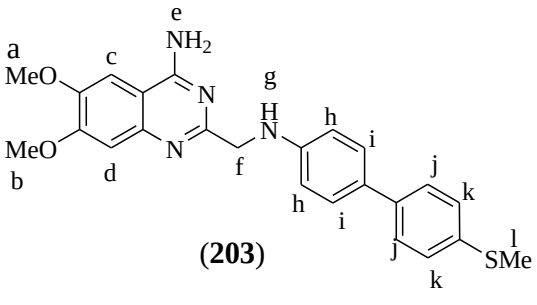
(**201**)



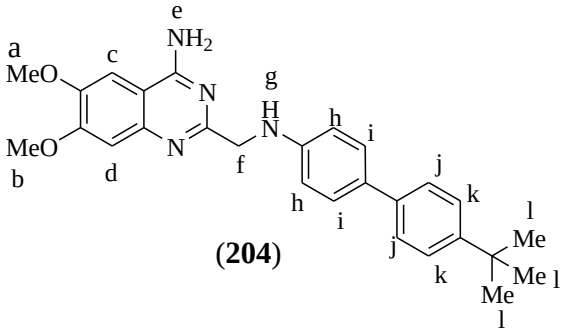
(**202**)

Characteristic peaks were observed for 4-amino-2-(4'-cyano-1,1'-biphenyl-4-amino)methyl-6,7-dimethoxyquinazoline (**202**) at 3404, 3208 (N-H str) and 2223 cm^{-1} (C≡N str) in its IR spectrum. Its PMR spectrum offered signals for aromatic protons at δ 7.71 (bs, $2H_{h,h}$, $2H_{k,k}$), 7.58 (s, $1H_d$), 7.51-7.49 (d, $2H_{j,j}$, J = 8.7 Hz), 7.09 (s, $1H_c$) and 6.80-6.78 (d, $2H_{i,i}$, J = 8.7 Hz). Amino protons were observed at δ 7.39 (bs, $2H_e$). Protons of secondary amine and aliphatic moieties were observed at δ 6.28-6.24 (t, $1H_g$), 4.28-4.27 (d, $2H_f$, J = 4.9 Hz), 3.93 (s, $3H_{a/b}$) and 3.90 (s, $3H_{b/a}$). Molecular ion peak was observed at m/z 411.6 (M^+) in its mass spectrum.

IR spectrum of 4-amino-2-(4'-methylthio-1,1'-biphenyl-4-amino)methyl-6,7-dimethoxyquinazoline (**203**) displayed characteristic peaks at 3469, 3359 and 3105 cm^{-1} (N-H str). Its PMR spectrum showed signals at δ 7.58 (s, $1H_d$), 7.48-7.46 (d, $2H_{k,k}$, J = 8.4 Hz), 7.40-7.38 (d, $2H_{h,h}$, J = 8.5 Hz), 7.26-7.23 (d, $2H_{j,j}$, J = 8.4 Hz), 7.10 (s, $1H_c$) and 6.76-6.74 (d, $2H_{ii}$, J = 8.5 Hz) for aromatic protons. Proton (CH_g) for secondary amino group was observed at δ 5.98-5.95 (t, $1H_g$) as a triplet which coupled with protons (CH_f)



(**203**)



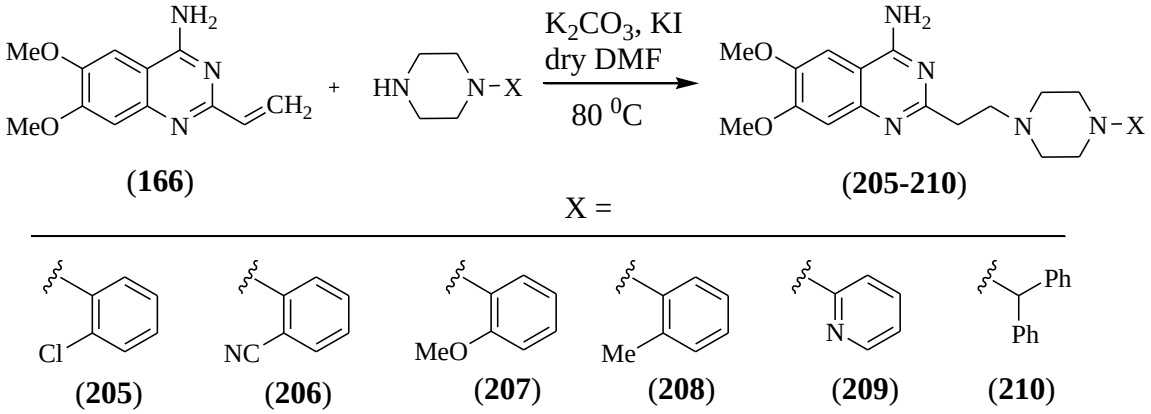
(**204**)

observed at δ 4.26-4.25 (d, $2H_f$) as a doublet with a coupling constant of 5.1 Hz. Other signals were observed at δ 3.93 (s, $3H_{a/b}$), 3.90 (s, $3H_{b/a}$) and 2.48 (s, $3H_l$) for aliphatic protons. Its mass spectrum displayed a molecular ion peak at m/z 432.6 (M^+).

Compound (**204**) showed characteristic peaks at 3384 and 3148 cm^{-1} (N-H str) in its IR spectrum. Its PMR spectrum displayed signals at δ 7.58 (s, $1H_d$), 7.45-7.43 (d, $2H_{h,h}$, J = 7.7 Hz) for aromatic protons, 7.41 (bs, $2H_e$) for amino protons, 7.41-7.39 (d, $2H_{i,i}$, J = 7.7 Hz), 7.37-7.35 (d, $2H_{k,k}$, J = 8.4 Hz), 7.10 (s, $1H_c$) and 6.76-6.74 (d, $2H_{j,j}$, J = 8.4 Hz) for the remaining aromatic protons. Signals were observed at δ 5.98-5.95 (t, $1H_g$) as a triplet for secondary amino proton (CH_g) which coupled with protons (CH_f) observed at δ 4.25-4.24 (d, $2H_f$) as a doublet with a coupling constant of 5.1 Hz. Other signals were observed at δ 3.93 (s, $3H_{a/b}$), 3.89 (s, $3H_{b/a}$) and 1.31 (s, $9H_{l,l,l}$) for aliphatic protons. Its mass spectrum offered a molecular ion peak at m/z 442.6 (M^+).

4.1.6 Synthesis of 4-amino-2-(4-substituted piperazin-1-yl)ethyl-6,7-dimethoxyquinazolines (205-210) (Series IV)

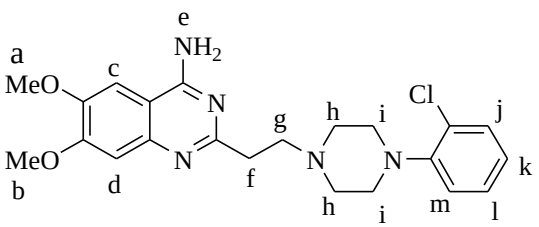
4-Amino-6,7-dimethoxy-2-vinylquinazoline (**166**) on addition of substituted aryl or heteroaryl piperazines under basic conditions offered the desired compounds (**205-210**) (**Scheme 10**).[89]



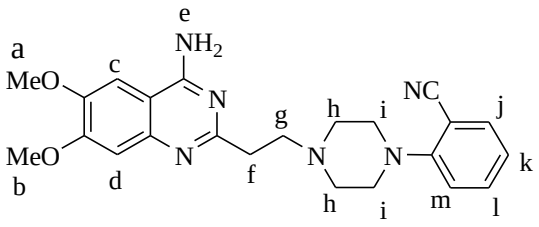
Scheme: 10

Characteristic peaks were observed for compound (**205**) at 3323 and 3095 cm^{-1} due to N-H stretching of the primary amino group. Signals were observed at δ 7.54 (s, $1H_d$), 7.36-7.33 (d, $1H_j$, J = 7.8), 7.26-7.23 (m, $1H_k$), 7.10-7.08 (d, $1H_m$, J = 7.8 Hz), 7.03 (s,

1H$_c$) and 7.01-6.97 (m, 1H$_l$) for aromatic protons in its PMR spectrum. Amino protons gave a signal at δ 7.27 (bs, 2H$_e$) as broad singlet. Signals came at δ 3.94 (s, 3H$_{a/b}$) and 3.87 (s, 3H$_{a/b}$) for six protons (CH$_{a/b}$) of methoxy groups. Aliphatic protons showed signals at δ 3.23-3.22 (t, 2H$_f$), 3.01 (bs, 4H$_{i,i}$), 2.88-2.84 (t, 2H$_g$) and 2.66 (bs, 4H$_{h,h}$). Its mass spectrum showed molecular ion peak at m/z 427.9 $(M + 1)^+$.



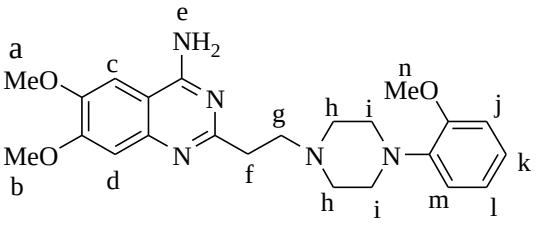
(**205**)



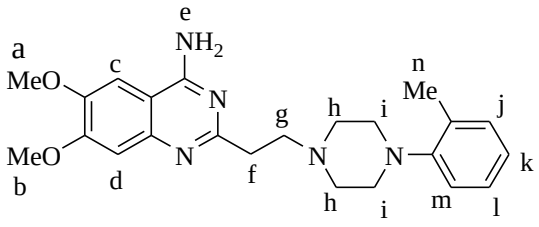
(**206**)

IR spectrum of compound (**206**) displayed characteristic peaks at 3336, 3137 (N-H str) and 2219 cm^{-1} (C≡N str). Peaks were also observed at 1641 and 1584 cm^{-1} for N-H bending. Its PMR spectrum showed signals at δ 7.57-7.54 (d, 1H$_j$, J = 7.9 Hz), 7.50-7.45 (m, 1H$_k$), 7.17 (s, 1H$_d$), 7.02 (s, 1H$_c$) and 7.01-6.99 (m, 2H$_{l,m}$) for aromatic protons. At δ 6.17 (bs, 2H$_e$) a broad signal was observed for two protons of amino group. Aliphatic protons were observed at δ 4.00 (s, 3H$_{a/b}$), 3.96 (s, 3H$_{b/a}$), 3.27-3.25 (t, 4H$_{i,i}$), 3.09-2.99 (m, 4H$_{h,h}$) and 2.81-2.79 (m, 2H$_f$, 2H$_g$). Its mass spectrum showed molecular ion peak at m/z 419.2 $(M + 1)^+$.

Characteristic peaks were observed for compound (**207**) at 3342 and 3125 cm^{-1} for N-H stretching (asym/sym) in its IR spectrum. Signals were observed at δ 7.19 (s, 1H$_d$), 7.03-6.99 (m, 1H$_k$, 1H$_c$), 6.97-6.92 (m, 1H$_m$, 1H$_l$) and 6.87-6.86 (d, 1H$_j$, J = 7.9 Hz) for aromatic protons and a broad peak was observed at δ 6.27 (bs, 2H$_e$) for two protons of amino group. Among the aliphatic protons, signals were displayed at δ 4.00 (s, 3H$_n$), 3.97 (s, 3H$_{a/b}$), 3.86 (s, 3H$_{b/a}$), 3.14 (bs, 4H$_{i,i}$), 3.10-3.05 (m, 2H$_f$), 3.02-2.98 (m, 2H$_g$) and 2.81



(**207**)

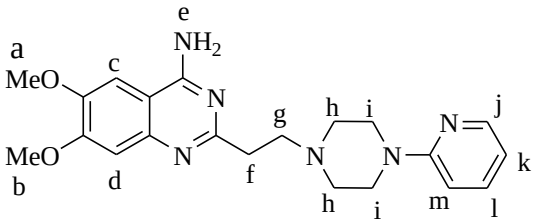


(**208**)

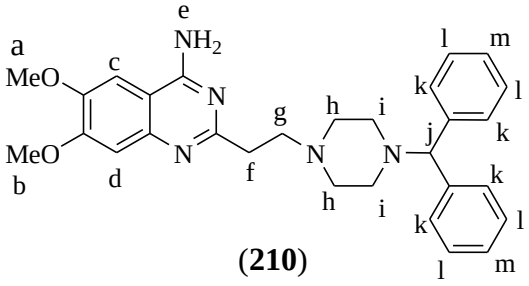
(bs, $4H_{h,h}$) in its PMR spectrum.

Compound (**208**) showed characteristic peaks at 3330 and 3161 cm^{-1} (N-H str) in its IR spectrum. Its PMR spectrum displayed signals at δ 7.19 (s, $1H_d$), 7.19-7.15 (m, $1H_j$, $1H_k$), 7.05-7.03 (d, $1H_m$, J = 7.8 Hz) and 7.00-6.96 (m, $1H_c$, $1H_l$) for aromatic protons and a broad singlet at δ 5.84 (bs, $2H_e$) for amino protons. Aliphatic protons showed signals at 4.01 (s, $3H_{a/b}$), 4.00 (s, $3H_{a/b}$), 3.13-3.07 (m, $4H_{f,g}$), 3.01-2.99 (t, $4H_{i,i}$, J = 4.5 Hz), 2.80 (bs, $4H_{h,h}$) and 2.30 (s, $3H_n$). Its mass spectrum showed molecular ion peak at m/z 408.2 $(M + 1)^+$.

IR spectrum of 4-amino-2-[4-(2-pyridyl)piperazin-1-yl]ethyl-6,7-dimethoxy-quinazoline (**209**) displayed characteristic peaks at 3374 and 3118 cm^{-1} (N-H str). In its PMR spectrum, signals were observed at δ 8.20-8.18 (d, $1H_j$, J = 6.2 Hz), 7.50-7.45 (m, $1H_k$), 7.18 (s, $1H_d$), 6.93 (s, $1H_c$), 6.66-6.63 (m, $1H_l$) and 6.63-6.60 (d, $1H_m$, J = 6.2 Hz) for the aromatic protons. Amino protons showed signals at δ 5.75 (bs, $2H_e$) as a broad singlet. Aliphatic protons were observed at 4.01 (s, $3H_{a/b}$), 3.98 (s, $3H_{b/a}$), 3.59-3.56 (t, $4H_{i,i}$, J = 5.0 Hz), 3.09-3.04 (m, $2H_f$), 3.01-2.96 (m, $2H_g$) and 2.71-2.69 (t, $4H_{h,h}$, J = 5.0 Hz). Molecular ion peak was observed at m/z 395.3 $(M + 1)^+$ in its mass spectrum.



(**209**)

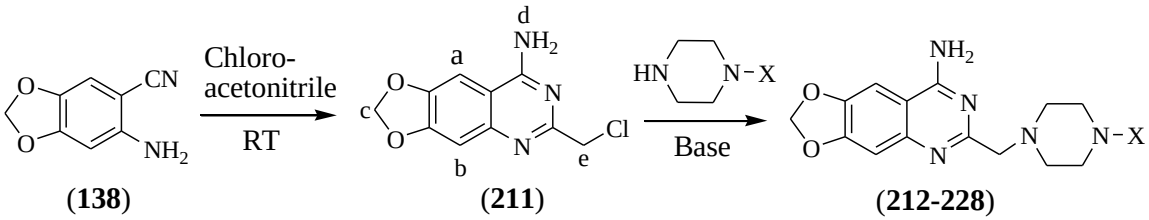


(**210**)

4-Amino-2-[4-(benzhydryl)piperazin-1-yl]ethyl-6,7-dimethoxyquinazoline (**210**) showed characteristic peaks at 3313 and 3094 cm^{-1} (N-H str) in its IR spectrum. Its PMR spectrum displayed signals for aromatic protons at δ 7.52 (s, $1H_d$), 7.42-7.40 (d, $4H_{k,k}$, J = 7.1 Hz), 7.28-7.26 (m, $4H_{l,l}$), 7.17-7.14 (m, $2H_{m,m}$) and 7.01 (s, $1H_c$). A broad signal was observed at δ 7.25 (bs, $2H_e$) for amino protons. Signals were observed at δ 4.22 (s, $1H_j$), 3.88 (s, $3H_{a/b}$), 3.86 (s, $3H_{b/a}$), 2.77 (bs, $4H_{f,g}$), 2.49 (bs, $4H_{i,i}$) and 2.33 (bs, $4H_{h,h}$) for aliphatic protons. Its mass spectrum displayed molecular ion peak at m/z 483.9 $(M + 1)^+$.

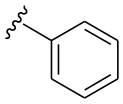
4.1.7 Synthesis of 4-amino-2-(4-substituted piperazin-1-yl)methyl-6,7-methylene-dioxyquinazolines (212-228) (Series V)

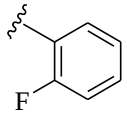
In order to see the effect of changing the 6,7-dimethoxy group to a cyclic diether on the biological activity of the resulting compounds, it was planned to synthesize some 6,7-methylenedioxy derivatives (**212-228**).

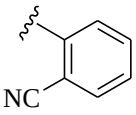


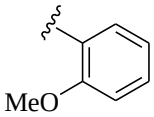
(**138**) (**211**) (**212-228**)

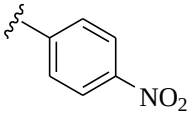
X =

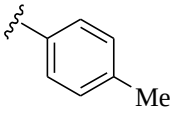
(**212**) 

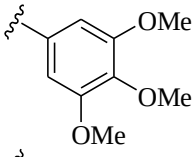
(**213**) 

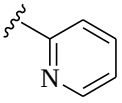
(**214**) 

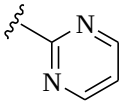
(**215**) 

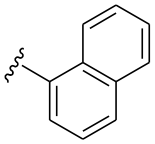
(**216**) 

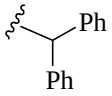
(**217**) 

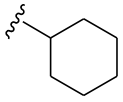
(**218**) 

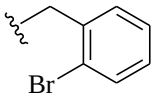
(**219**) 

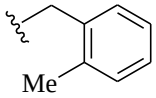
(**220**) 

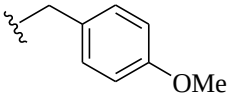
(**221**) 

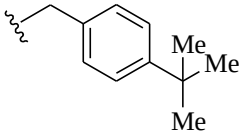
(**222**) 

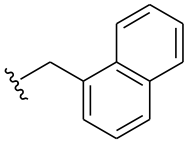
(**223**) 

(**224**) 

(**225**) 

(**226**) 

(**227**) 

(**228**) 

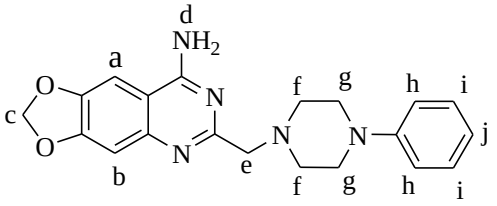
Scheme: 11

4-Amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) required for the synthesis of the projected compounds (**212-228**) was prepared by cyclization of 2-amino-4,5-methylenedioxybenzonitrile (**138**) with chloroacetonitrile at room temperature in presence of dry hydrogen chloride gas[89] (**Scheme 11**). IR spectrum of compound (**211**) did not show a peak at 2203 cm^{-1} for the nitrile (C≡N) functionality. Its PMR spectrum

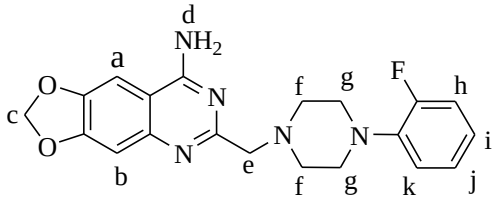
showed chemical shift values at δ 7.61 (s, 1H$_b$) and 7.02 (s, 1H$_a$) as singlets for aromatic protons. A broad signal was observed at δ 7.48 (bs, 2H$_d$) for two protons of the amino group. Protons (CH$_c$) of dioxymethylene ring showed a sharp peak at δ 6.15 (s, 2H$_c$) as singlet while the other aliphatic protons (CH$_{2e}$) were observed at δ 4.49 (s, 2H$_e$).

4-Amino-2-chloromethyl-6,7-methylenedioxyquinazoline (**211**) was reacted with substituted piperazines in dry DMF using potassium carbonate at a temperature range of 50 - 80 ^{0}C to afford the final compounds (**212-228**) of the series V (**Scheme 11**).

IR spectrum of 4-amino-6,7-methylenedioxy-2-(4-phenylpiperazin-1-yl)methyl-quinazoline (**212**) displayed characteristic peaks at 3323 and 3146 cm^{-1} (N-H str). Its PMR spectrum displayed signals at δ 7.59 (s, 1H$_b$), 7.20-7.16 (m, 2H$_{i,i}$), 7.02 (s, 1H$_a$), 6.90-6.88 (d, 2H$_{h,h}$, J = 7.7 Hz) and 6.77-6.75 (m, 1H$_j$) for the aromatic protons. Amino protons were observed at δ 7.30 (bs, 2H$_d$) as a broad singlet. Signals appeared at δ 6.14 (s, 2H$_c$) for dioxymethylene protons while other aliphatic protons gave signals at δ 3.52 (s, 2H$_e$), 3.15-3.13 (t, 4H$_{g,g}$, J = 4.9 Hz) and 2.68-2.66 (t, 4H$_{f,f}$, J = 4.9 Hz). The compound also showed high LC-MS/MS purity (> 98%) with 11.07 min retention time.



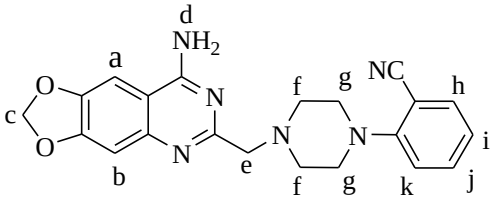
(**212**)



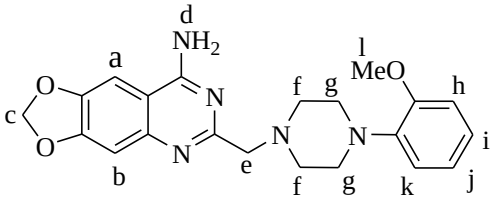
(**213**)

Compound (**213**) showed characteristic peaks at 3299 and 3134 cm^{-1} (N-H str) in its IR spectrum. Signals were observed at δ 7.58 (s, 1H$_b$), 7.07-7.02 (m, 2H$_{h,k}$), 7.01 (s, 1H$_a$), 6.98-6.90 (m, 2H$_{i,j}$) for aromatic protons in PMR spectrum. A broad signal was observed at 7.29 (bs, 2H$_d$) for two protons of amino group. Dioxymethylene protons showed signal at 6.13 (s, 2H$_c$) as singlet while other aliphatic protons were observed at 3.51 (s, 2H$_e$), 3.03-3.01 (t, 4H$_{g,g}$, J = 4.4 Hz) and 2.68-2.66 (t, 4H$_{f,f}$, J = 4.4 Hz). Molecular ion peak was observed at m/z 381.5 (M$^+$) in its mass spectrum. The compound also showed high LC-MS/MS purity (> 98%) with 11.61 min retention time.

IR spectrum of compound (**214**) showed characteristic peaks at 3341, 3136 (N-H str) and 2222 cm^{-1} (C≡N str). In its PMR spectrum, signals were obtained at δ 7.63-7.60 (d, $1H_h$, J = 7.6 Hz), 7.59 (s, $1H_b$), 7.54-7.52 (m, $1H_i$), 7.11-7.09 (d, $1H_k$, J = 7.6 Hz), 7.06-7.04 (m, $1H_j$) and 7.02 (s, $1H_a$) for aromatic protons. A broad peak was observed at δ 7.32 (bs, $2H_d$) for amino protons. Signals appeared at δ 6.13 (s, $2H_c$) for dioxymethylene protons and 3.53 (s, $2H_e$), 3.17-3.15 (t, $4H_{g,g}$, J = 4.5 Hz) and 2.72-2.69 (t, $4H_{f,f}$, J = 4.5 Hz) for other aliphatic protons. The compound also showed high LC-MS/MS purity (> 98%) with 11.44 min retention time.



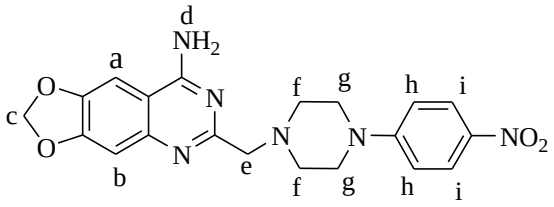
(**214**)



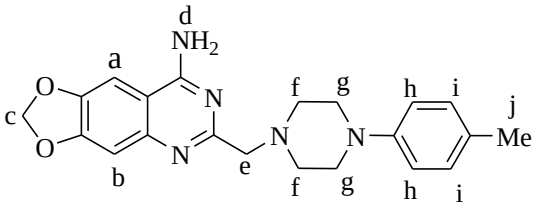
(**215**)

IR spectrum of 4-amino-2-[4-(2-methoxyphenyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (**215**) displayed characteristic peaks at 3308 and 3201 cm^{-1} (N-H str). Signals were observed at δ 7.60 (s, $1H_b$), 7.03 (s, $1H_a$), 6.94-6.90 (d, $1H_k$) and 6.87-6.85 (m, $3H_{h,i,j}$) for aromatic protons in its PMR spectrum. Signals were observed at 7.20 (bs, $2H_d$) for amino protons, 6.12 (s, $2H_c$) for dioxymethylene protons, 3.80 (s, $3H_l$), 3.57 (s, $2H_e$), 3.03 (bs, $4H_{g,g}$) and 2.71 (bs, $4H_{f,f}$) for other aliphatic protons. Molecular ion peak was observed at m/z 393.6 (M^+) in its mass spectrum. The compound also showed high LC-MS/MS purity (> 98%) with 11.33 min retention time.

4-Amino-2-[4-(4-nitrophenyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (**216**) showed characteristic peaks at 3288, 3124 (N-H str) and 1504, 1333 cm^{-1} (N=O asym/sym) in its IR spectrum. Its PMR spectrum displayed signals at δ 8.05-8.03 (d, $2H_{i,i}$, J = 9.5 Hz), 7.60 (s, $1H_b$), 7.01 (s, $1H_a$) and 6.97-6.95 (d, $2H_{h,h}$, J = 9.5 Hz) for aromatic protons. Signals were found at δ 7.30 (bs, $2H_d$) as a broad singlet for amino protons, 6.14 (s, $2H_c$) as a singlet for dioxymethylene protons, 3.54 (s, $2H_e$), 3.48-3.45 (t, $4H_{g,g}$, J = 4.9 Hz) and 2.68-2.66 (t, $4H_{f,f}$, J = 4.9 Hz) for other aliphatic protons. Its mass spectrum showed molecular ion peak at m/z 408.5 (M^+). The compound also showed high LC-MS/MS purity (> 98%) with 10.72 min retention time.



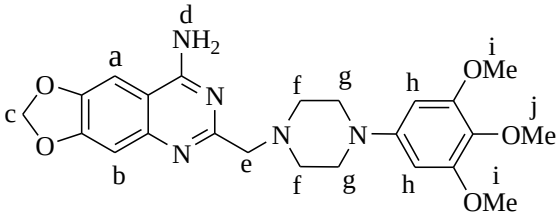
(**216**)



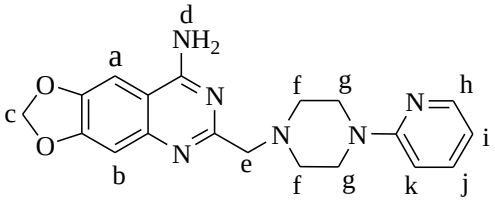
(**217**)

Characteristic peaks were observed for 4-amino-2-[4-(4-methylphenyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (**217**) at 3299 and 3133 cm^{-1} (N-H str) in its IR spectrum. Its PMR spectrum showed signals for aromatic protons at δ 7.59 (s, $1H_b$) as singlet, 7.02 (s, $1H_a$) as singlet, 7.01-6.98 (d, $2H_{i,i}$) as doublet which coupled with two protons observed at δ 6.79-6.77 (d, $2H_{h,h}$) as doublet with a coupling constant of 8.5 Hz. Signals were seen at δ 7.27 (bs, $2H_d$) as broad singlet for amino protons, 6.13 (s, $2H_c$) as singlet for dioxymethylene protons, 3.52 (s, $2H_e$), 3.09-3.07 (t, $4H_{g,g}$, J = 4.7 Hz), 2.68-2.66 (t, $4H_{f,f}$, J = 4.7 Hz) and 2.21 (s, $3H_j$) for aliphatic protons. The compound also showed high LC-MS/MS purity (> 98%) with 11.80 min retention time.

IR spectrum of 4-amino-2-[4-(3,4,5-trimethoxyphenyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (**218**) displayed characteristic peaks at 3341, 3183 (N-H str) and 1036 cm^{-1} (C-O str). Its PMR spectrum showed signals at δ 7.20 (s, $1H_b$), 7.01 (s, $1H_a$) and 6.16 (s, $2H_{h,h}$) for aromatic protons. Signals were observed at 6.10 (s, $2H_c$) as a singlet for dioxymethylene protons, 5.59 (bs, $2H_d$) as a broad singlet for amino protons, 3.84 (s, $6H_{i,i}$), 3.78 (s, $3H_j$), 3.74 (s, $2H_e$), 3.23-3.21 (t, $4H_{g,g}$) and 2.78-2.76 (t, $4H_{f,f}$) for aliphatic protons. Molecular ion peak was observed at m/z 453.3 (M^+) in its mass spectrum. The compound also showed high LC-MS/MS purity (> 98%) with 11.24 min retention time.



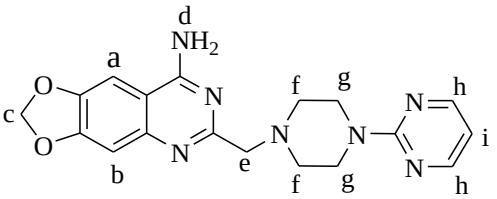
(**218**)



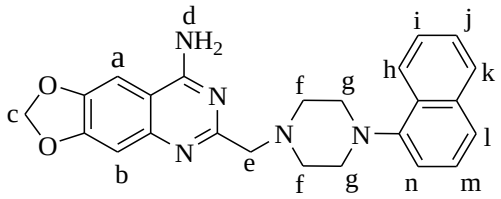
(**219**)

Compound (**219**) showed characteristic peaks at 3308, 3138 (N-H str) and 1038 cm^{-1} (C-O str) in its IR spectrum. Its PMR spectrum displayed signals at δ 8.10-8.08 (d, $1H_h$), 7.59 (s, $1H_b$), 7.49-7.45 (m, $1H_i$), 7.02 (s, $1H_a$), 6.71-6.69 (d, $1H_k$, J = 7.5 Hz) and 6.60-6.57 (m, $1H_j$) for aromatic protons. A broad singlet was observed at δ 7.19 (bs, $2H_d$) for amino protons. Among the aliphatic protons, signals were observed at δ 6.13 (s, $2H_c$) as a singlet for dioxymethylene protons, 3.55 (s, $2H_e$) as a singlet for protons of methylene spacer positioned between the quinazoline scaffold and piperazine substituent, 3.52-3.49 (t, $4H_{g,g}$, J = 4.8 Hz) as a triplet which coupled with proton ($CH_{f,f}$) observed at 2.65-2.63 (t, $4H_{f,f}$, J = 4.8 Hz) as a triplet with a coupling constant of 4.8 Hz. Its mass spectrum showed molecular ion peak at m/z 364.4 (M^+). The compound also showed high LC-MS/MS purity (> 98%) with 11.04 min retention time.

Characteristic peaks were observed for 4-amino-2-[4-(2-pyrimidinyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (**220**) at 3301, 3135 (N-H str) and 1037 cm^{-1} (C-O str) in its IR spectrum. Its PMR spectrum showed signals for aromatic protons at δ 8.29-8.27 (d, $2H_{h,h}$, J = 7.5 Hz), 7.59 (s, $1H_b$), 7.04 (s, $1H_a$) and 6.52-6.50 (m, $1H_i$). Amino protons were observed at 7.14 (bs, $2H_d$) as a broad singlet. Among the aliphatic protons, signals were observed at 6.12 (s, $2H_c$) as singlet, 3.81-3.78 (t, $4H_{g,g}$, J = 4.7 Hz) as a triplet which coupled with protons ($CH_{f,f}$) observed at 2.61-2.59 (t, $4H_{f,f}$, J = 4.7 Hz) as a triplet with a coupling constant of 4.7 Hz and 3.57 (s, $2H_e$) as a singlet. Its mass spectrum displayed molecular ion peak at m/z 365.7 (M^+). The compound also showed high LC-MS/MS purity (> 98%) with 11.14 min retention time.



(**220**)

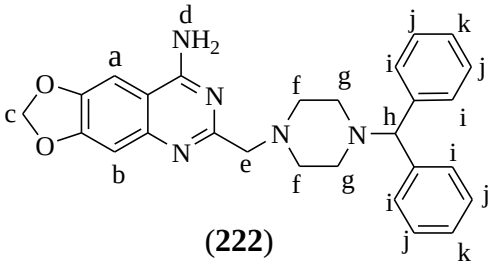


(**221**)

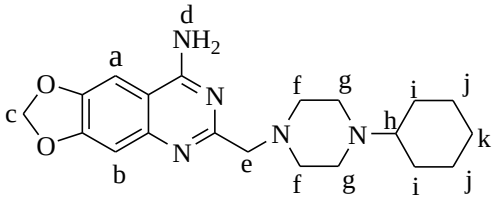
IR spectrum of compound (**221**) displayed characteristic peaks at 3277, 3105 (N-H str) and 1037 cm^{-1} (C-O str). Its PMR spectrum gave signals at δ 8.15-8.13 (d, $1H_n$, J = 7.3 Hz) as doublet, 7.82-7.79 (d, $1H_h$, J = 6.8 Hz) as doublet, 7.61 (s, $1H_b$) as singlet, 7.53-7.51 (d, $1H_l$, J = 7.3 Hz) as doublet, 7.48-7.44 (m, $2H_{i,m}$) as a multiplet, 7.40-7.36 (m, $1H_j$)

as a multiplet, 7.08-7.06 (d, 1H$_k$, J = 6.8 Hz) as doublet and 7.05 (s, 1H$_a$) as a singlet for aromatic protons. A broad peak was observed at δ 7.19 (bs, 2H$_d$) for the amino protons. Signals for aliphatic protons appeared at δ 6.13 (s, 2H$_c$), 3.65 (s, 2H$_e$), 3.12 (bs, 4H$_{g,g}$) and 2.85 (bs, 4H$_{f,f}$). Molecular ion peak was observed at m/z 413.2 (M^+) in its mass spectrum. The compound also showed high LC-MS/MS purity (> 98%) with 11.96 min retention time.

4-Amino-2-(4-benzhydrylpiperazin-1-yl)methyl-6,7-methylenedioxyquinazoline (**222**) showed characteristic peaks at 3336, 3148 (N-H str) and 1041 cm^{-1} (C-O str) in its IR spectrum. Its PMR spectrum displayed signals at δ 7.56 (s, 1H$_b$), 7.40-7.38 (d, 2H$_{i,i}$, 2H$_{i,i}$, J = 7.4 Hz), 7.25-7.22 (m, 2H$_{j,j}$, 2H$_{j,j}$), 7.15-7.11 (m, 2H$_{k,k}$) and 7.00 (s, 1H$_a$) for aromatic protons. Amino protons gave signals at δ 7.07 (bs, 2H$_d$) as a broad singlet. Signals were observed at δ 6.09 (s, 2H$_c$), 4.20 (s, 1H$_h$), 3.52 (s, 2H$_e$), 2.57 (bs, 4H$_{g,g}$) and 2.38 (bs, 4H$_{f,f}$) for the aliphatic protons. Its mass spectrum displayed molecular ion peak at m/z 454.0 (M^+).



(**222**)

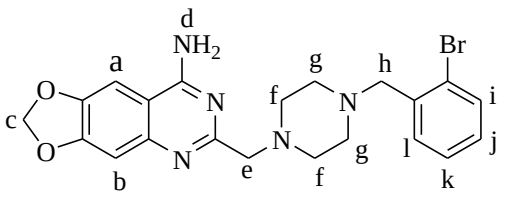


(**223**)

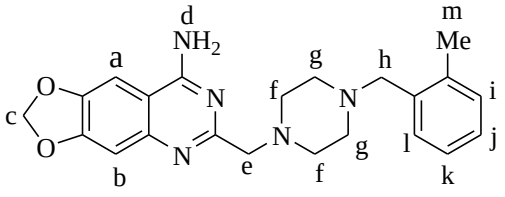
Characteristic peaks were observed for compound (**223**) at 3328, 3148 (N-H str) and 1042 cm^{-1} (C-O str) in its IR spectrum. Signals for aromatic protons were observed at δ 7.19 (s, 1H$_b$) and 6.99 (s, 1H$_a$). A broad peak was observed at δ 5.69 (bs, 2H$_d$) for amino protons. Aliphatic protons were observed at δ 6.09 (s, 2H$_c$), 3.67 (s, 2H$_e$), 2.66 (bs, 8H$_{f,f,g,g}$), 1.89-1.87 (m, 2H$_i$), 1.79-1.76 (m, 2H$_i$), 1.63-1.60 (m, 1H$_h$), 1.26-1.17 (m, 4H$_{j,j}$) and 1.10-1.09 (m, 2H$_k$). Its mass spectrum showed molecular ion peak at m/z 369.4 (M^+). The compound also showed high LC-MS/MS purity (> 98%) with 10.52 min retention time.

IR spectrum of 4-amino-2-[4-(2-bromobenzyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (**224**) displayed characteristic peaks at 3312, 3144 (N-H str)

and 1035 (C-O str). Its PMR spectrum showed signals at δ 7.58 (s, 1H$_b$), 7.54-7.51 (d, 1H$_i$, J = 7.7 Hz), 7.47-7.45 (d, 1H$_l$, J = 7.7 Hz), 7.33-7.29 (m, 1H$_j$), 7.16-7.12 (m, 1H$_k$) and 7.00 (s, 1H$_a$) for aromatic protons. Amino protons were observed at δ 7.22 (bs, 2H$_d$) as a broad singlet. Among the aliphatic protons, signals were observed at δ 6.12 (s, 2H$_c$), 3.53 (s, 2H$_e$), 3.48 (s, 2H$_h$), 2.54-2.53 (m, 4H$_{f,f}$) and 2.49 (bs, 4H$_{g,g}$). Its mass spectrum displayed molecular ion peak at m/z 455.5 (M^+).



(**224**)



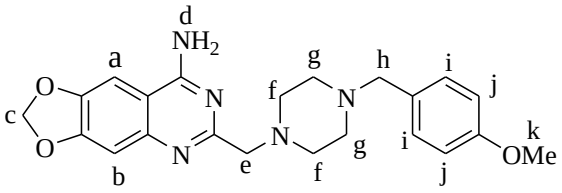
(**225**)

Compound (**225**) showed characteristic peaks at 3309, 3145 (N-H str) and 1036 cm^{-1} (C-O str) in its IR spectrum. Its PMR spectrum displayed signals at δ 7.57 (s, 1H$_b$), 7.19-7.18 (d, 1H$_i$), 7.11-7.08 (m, 3H$_{j,k,l}$) and 6.99 (s, 1H$_a$) for aromatic protons. A broad signal was observed at δ 7.19 (bs, 2H$_d$) for the amino protons. Signals were observed at δ 6.11 (s, 2H$_c$), 3.46 (s, 2H$_e$), 3.39 (s, 2H$_h$), 2.51 (bs, 4H$_{f,f}$), 2.42 (bs, 4H$_{g,g}$) and 2.32 (s, 3H$_m$) for aliphatic protons. Molecular ion peak was observed at m/z 390.7 (M^+) in its mass spectrum.

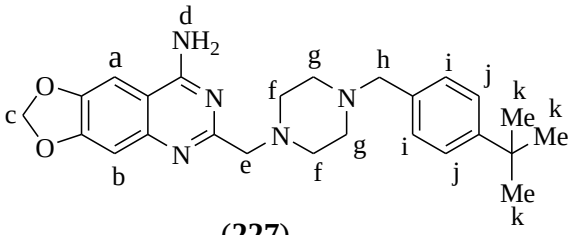
Characteristic peaks were observed for 4-amino-2-[4-(4-methoxybenzyl)piperazin-1-yl]methyl-6,7-methylenedioxyquinazoline (**226**) at 3340, 3151 (N-H str) and 1036 cm^{-1} (C-O str) in its IR spectrum. Signals were observed for aromatic protons at δ 7.57 (s, 1H$_b$), 7.18-7.16 (d, 2H$_{i,i}$, J = 8.5 Hz), 6.99 (s, 1H$_a$) and 6.83-6.80 (d, 2H$_{j,j}$, J = 8.5 Hz). Amino protons gave a broad singlet at δ 7.16 (bs, 2H$_d$). Aliphatic protons appeared at δ 6.11 (s, 2H$_c$), 3.74 (s, 3H$_k$), 3.47 (s, 2H$_e$), 3.88 (s, 2H$_h$), 2.54 (bs, 4H$_{f,f}$) and 2.39 (bs, 4H$_{g,g}$). The compound also showed high LC-MS/MS purity (> 98%) with 10.67 min retention time.

IR spectrum of 4-amino-2-[4-(4-*t*.butylbenzyl)piperazin-1-yl]methyl-6,7-methylene-dioxyquinazoline (**227**) displayed characteristic peaks at 3332, 3140 (N-H str) and 1037 cm^{-1} (C-O str). Its PMR spectrum gave signals at δ 7.57 (s, 1H$_b$), 7.29-7.27 (d, 2H$_{j,j}$, J = 8.2 Hz), 7.19-7.17 (d, 2H$_{i,i}$, J = 8.2 Hz) and 6.99 (s, 1H$_a$) for aromatic protons,

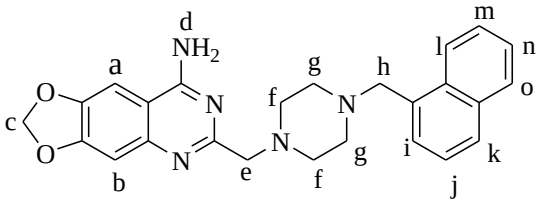
7.17 (bs, $2H_d$) as broad singlet for amino protons, 6.11 (s, $2H_c$), 3.48 (s, $2H_e$), 3.42 (s, $2H_h$), 2.55 (bs, $4H_{f,f}$), 2.41 (bs, $4H_{g,g}$) and 1.29 (s, $9H_{k,k,k}$) for aliphatic protons. The compound also showed high LC-MS/MS purity (> 98%) with 11.66 min retention time.



(**226**)



(**227**)



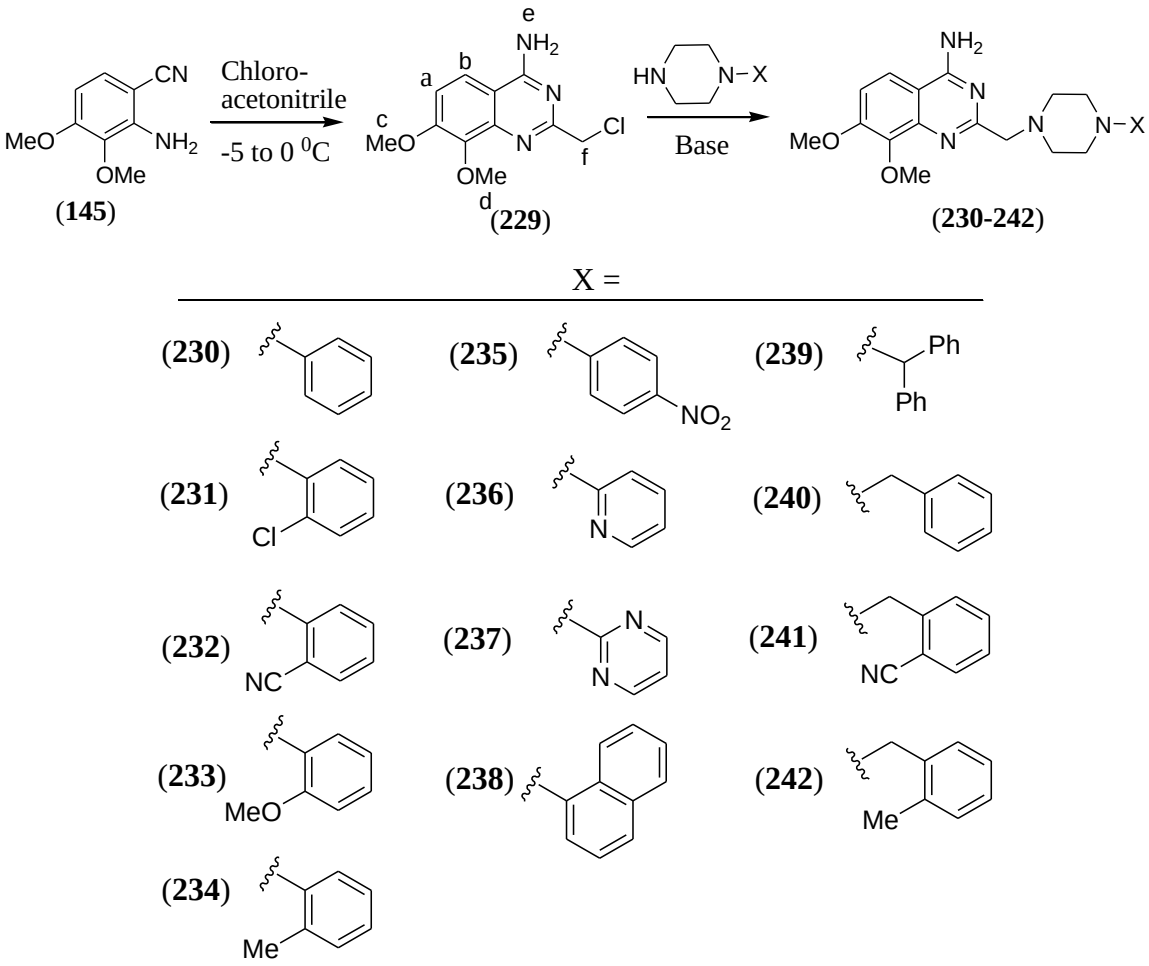
(**228**)

Compound (**228**) showed characteristic peaks at 3317, 3141 (N-H str) and 1038 cm^{-1} (C-O str) in its IR spectrum. Signals were displayed at δ 8.26-8.24 (d, $1H_i$, J = 8.0 Hz), 7.87-7.84 (d, $1H_k$, J = 8.0 Hz), 7.79-7.76 (m, $1H_n$), 7.58 (s, $1H_b$), 7.52-7.46 (m, $1H_j$, $1H_m$), 7.41-7.38 (m, $1H_o$, $1H_l$) and 6.99 (s, $1H_a$) for aromatic protons, 7.23 (bs, $2H_d$) as broad singlet for amino protons, 6.12 (s, $2H_c$), 3.85 (s, $2H_e$), 3.46 (s, $2H_h$), 2.53 (bs, $4H_{f,f}$) and 2.49 (bs, $4H_{g,g}$) for aliphatic protons in its PMR spectrum. The compound also showed high LC-MS/MS purity (> 98%) with 11.53 min retention time.

4.1.8 Synthesis of 4-amino-2-(4-substituted piperazin-1-yl)methyl-7,8-dimethoxy-quinazolines (230-242) (Series VI)

Since, conversion of 6,7-dimethoxy groups into cyclic ether moiety could not yield much effective compounds in terms of biological activity it was decided to substitute the methoxy groups at positions other than 6,7- *i.e.* 7,8-positions. 4-Amino-2-chloromethyl-7,8-dimethoxyquinazoline (**229**), required for the synthesis of the targeted compounds (**230-242**) was prepared by the reaction of 2-amino-3,4-dimethoxybenzonitrile (**145**) with chloroacetonitrile in the presence of dry hydrogen chloride gas at -5 to 0 ^0C[136] (**Scheme 12**). IR spectrum of compound (**229**) showed absence of characteristic peak at 2210 cm^{-1} for the nitrile (CN) group. Its ^{1}H-NMR spectrum gave a doublet at δ 8.00-7.97 (d, $1H_a$) for

aromatic proton (CH_a) which coupled with the other aromatic proton (CH_b) observed at 7.33-7.31 (d, $1H_b$) as a doublet with a coupling constant of 9.1 Hz. Amino protons (NH_{2e}) showed a broad signal at δ 7.78 (bs, $2H_e$). Aliphatic protons were observed at δ 4.56 (s, $2H_f$), 3.95 (s, $3H_d$) and 3.91 (s, $3H_c$). Mass spectrum also confirmed its structure which showed molecular ion peak at m/z 253.1 (M^+).

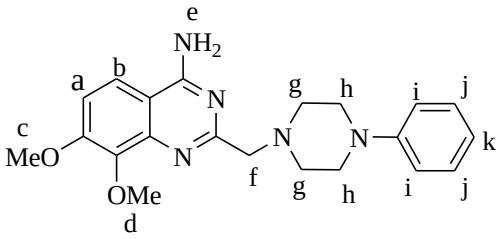


Scheme: 12

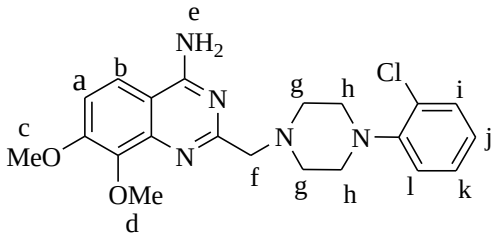
Syntheses of compounds (230-242) were accomplished by the reaction of compound (**229**) with substituted piperazines in presence of a base at a temperature range of 30 to 60 ^0C[89] (**Scheme 12**).

IR spectrum of 4-amino-7,8-dimethoxy-2-(4-phenypiperazin-1-yl)methylquinazoline (**230**) displayed characteristic peaks at 3297, 3158 (N-H str) and 1117 cm^{-1} (C-O str). Its PMR spectrum displayed signals for aromatic protons at δ 7.96-7.93 (d, $1H_a$) as a

doublet which coupled with proton (CH_b) observed at δ 7.23-7.20 (d, $1H_b$) as a doublet with a coupling constant of 9.3 Hz. Signals were observed at δ 7.18-7.16 (m, $2H_{j,j}$), 6.89-6.87 (d, $2H_{i,i}$, J = 7.7 Hz) and 6.77-6.73 (m, $1H_k$) for the remaining aromatic protons. A broad signal was observed at δ 7.50 (bs, $2H_e$) for amino protons. Among the aliphatic protons, signals were observed at δ 3.95 (s, $3H_d$), 3.94 (s, $3H_c$), 3.61 (s, $2H_f$) and 3.17-3.15 (t, $4H_{h,h}$) as triplet which coupled with protons ($CH_{g,g}$) observed at δ 2.76-2.73 (t, $4H_{g,g}$) as a triplet with a coupling constant of 4.9 Hz. Its ^{13}C-NMR spectrum showed signals at δ 162.61, 161.88, 153.90, 151.01, 145.12, 141.46, 128.67, 119.26, 118.64, 115.22, 111.83 and 108.50 for aromatic carbons whereas signals were observed at δ 65.21, 60.85, 56.09, 52.83 and 48.29 for the aliphatic carbons. Its mass spectrum displayed molecular ion peak at m/z 380.1 $(M + 1)^+$. The compound also showed high LC-MS/MS purity (> 98%) with 11.37 min retention time.



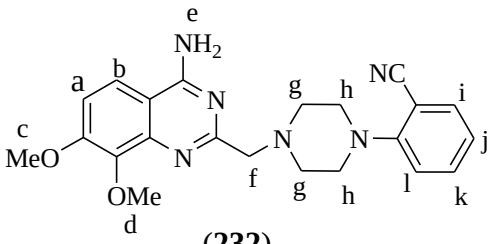
(**230**)



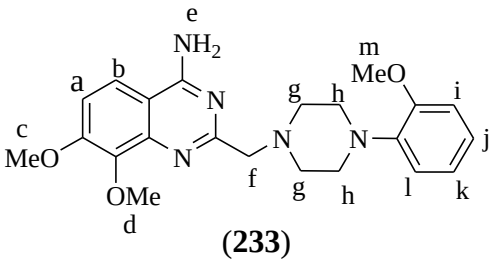
(**231**)

Characteristic peaks were observed for 4-amino-2-[4-(2-chlorophenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazoline (**231**) at 3410, 3167 (N-H str) and 1116 cm^{-1} (C-O str) in its IR spectrum. Signals were observed at δ 7.95-7.93 (d, $1H_a$) as doublet which showed coupling with proton (CH_b) observed at δ 7.22-7.19 (d, $1H_b$) as a doublet with a coupling constant of 9.1 Hz. Other signals appeared at δ 7.34-7.32 (d, $1H_i$, J = 7.5 Hz) as doublet, 7.26-7.24 (m, $1H_j$) as a multiplet, 7.10-7.08 (d, $1H_l$, J = 7.5 Hz) as doublet and 6.99-6.95 (m, $1H_k$) as a multiplet. A broad signal was observed at δ 7.44 (bs, $2H_e$) for amino protons. Aliphatic protons were observed at δ 3.97 (s, $3H_d$), 3.96 (s, $3H_c$), 3.65 (s, $2H_f$), 3.04 (bs, $4H_{h,h}$) and 2.79 (bs, $4H_{g,g}$). Its mass spectrum showed molecular ion peak at m/z 414.2 $(M + 1)^+$. The compound also showed high LC-MS/MS purity (> 98%) with 11.67 min retention time.

4-Amino-2-[4-(2-cyanophenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazoline (**232**) showed characteristic peaks at 3299, 3138 (N-H str), 2222 (C≡N str) and 1113 cm^{-1} (C-O str) in its IR spectrum. Its PMR spectrum gave signals at δ 7.96-7.94 (d, $1H_a$) as a doublet which coupled with proton (CH_b) observed at δ 7.23-7.21 (d, $1H_b$) as a doublet with a coupling constant of 9.2 Hz. Other signals were observed at δ 7.61-7.59 (d, $1H_i$, J = 7.8 Hz), 7.56-7.52 (m, $1H_j$), 7.11-7.09 (d, $1H_l$, J = 7.8 Hz) and 7.06-7.02 (m, $1H_k$). Signals were seen at δ 3.96 (s, $3H_d$), 3.95 (s, $3H_c$), 3.65 (s, $2H_f$), 3.22-3.19 (t, $4H_{h,h}$, J = 4.5 Hz) and 2.82-2.80 (t, $4H_{g,g}$, J = 4.5 Hz) for the aliphatic protons. Its ^{13}C-NMR spectrum displayed signals at δ 162.55, 161.87, 155.22, 153.92, 145.12, 141.47, 133.93, 121.46, 119.26, 118.62, 118.00, 111.86, 108.09 and 104.80 for aromatic carbons. A peak was observed at δ 133.85 for nitrile carbon (C≡N) also. Signals were observed at δ 65.03, 60.88, 56.10, 52.73 and 51.11 for aliphatic carbons. Molecular ion peak was observed at m/z 404.7 (M^+) in its mass spectrum. The compound also showed high LC-MS/MS purity (> 98%) with 11.44 min retention time.



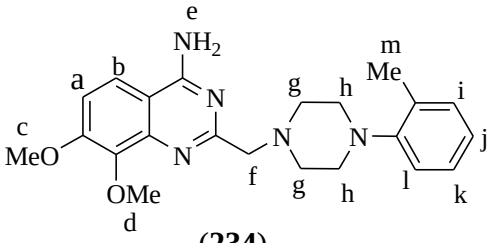
(**232**)



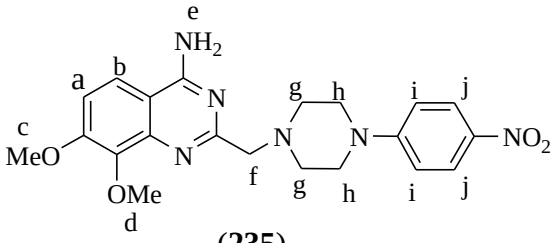
(**233**)

IR spectrum of compound (**233**) displayed characteristic peaks at 3299, 3157 (N-H str) and 1110 cm^{-1} (C-O str). Its PMR spectrum showed signals at δ 7.92-7.90 (d, $1H_a$, J = 9.1 Hz), 7.19-7.17 (d, $1H_b$, J = 9.1 Hz), 6.91-6.87 (d, $1H_i$) and 6.85-6.79 (m, $3H_{j,k,l}$) for aromatic protons, 7.43 (bs, $2H_e$) as a broad signal for amino protons, 3.93 (s, $3H_d$), 3.92 (s, $3H_c$), 3.76 (s, $3H_m$), 3.59 (s, $2H_f$), 2.99 (bs, $4H_{h,h}$) and 2.72 (bs, $4H_{g,g}$) for the aliphatic protons. Signals were observed at δ 162.67, 161.85, 153.87, 151.80, 145.12, 141.45, 141.19, 122.15, 120.65, 119.24, 117.64, 111.78, 111.41 and 108.50 for aromatic carbons while aliphatic carbons showed signals at δ 65.33, 60.86, 56.08, 55.06, 53.08 and 50.07 in its ^{13}C-NMR. The compound also showed high LC-MS/MS purity (> 98%) with 11.24 min retention time.

Characteristic peaks were observed for 4-amino-2-[4-(2-methylphenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazoline (**234**) at 3298, 3156 (N-H str) and 1112 cm^{-1} (C-O str) in its IR spectrum. Signals were observed at δ 7.96-7.94 (d, $1H_a$, J = 9.1 Hz), 7.24-7.21 (d, $1H_b$, J = 9.1 Hz), 7.14-7.12 (d, $1H_i$, J = 7.5 Hz), 7.12-7.10 (m, $1H_j$), 7.01-6.99 (d, $1H_l$, J = 7.5 Hz) and 6.94-6.90 (m, $1H_k$) for aromatic protons, 7.49 (bs, $2H_e$) as a broad singlet for amino protons whereas aliphatic protons were observed at δ 3.97 (s, $3H_d$), 3.96 (s, $3H_c$), 3.64 (s, $2H_f$), 2.90-2.88 (t, $4H_{h,h}$, J = 4.4 Hz), 2.77 (bs, $4H_{g,g}$) and 2.26 (s, $3H_m$). Its ^{13}C-NMR displayed signals at δ 162.72, 161.87, 153.88, 151.42, 145.10, 141.45, 131.66, 130.58, 126.24, 122.51, 119.25, 118.47, 111.80 and 108.50 for aromatic carbons, and δ 65.28, 60.86, 56.09, 53.31, 51.33 and 17.51 for aliphatic carbons. Its mass spectrum showed molecular ion peak at m/z 394.5 $(M + 1)^+$.



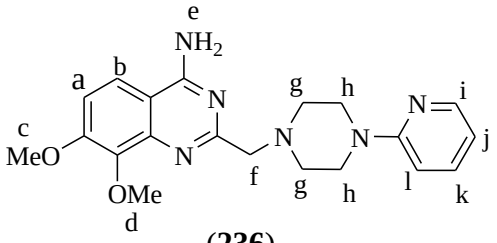
(**234**)



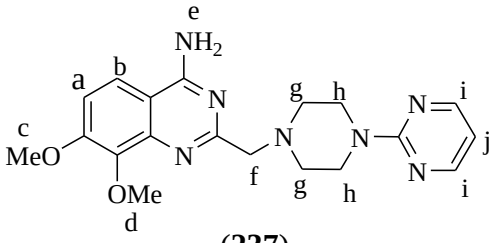
(**235**)

Compound (**235**) showed characteristic peaks at 3301, 3187 (N-H str) 1503, 1330 (N=O str) and 1110 cm^{-1} (C-O str) in its IR spectrum. Its PMR spectrum displayed signals at δ 8.05-8.03 (d, $2H_{j,j}$, J = 9.5 Hz) as doublet for $CH_{j,j}$ protons which coupled with protons ($CH_{i,i}$) observed at δ 6.96-6.94 (d, $2H_{i,i}$, J = 9.5 Hz) as a doublet with a coupling constant of 9.5 Hz. Proton (CH_a) observed at δ 7.95-7.93 (d, $1H_a$, J = 9.3 Hz) as a doublet coupled with proton (CH_b) seen at δ 7.23-7.21 (d, $1H_b$, J = 9.3 Hz) as a doublet with a coupling constant of 9.3 Hz. A broad peak observed at δ 7.49 (bs, $2H_e$) was due to protons of amino group. Among the aliphatic protons, signals were seen at δ 3.95 (s, $3H_d$), 3.93 (s, $3H_c$), 3.63 (s, $2H_f$), 3.49-3.47 (t, $4H_{h,h}$, J = 5.0 Hz) and 2.77-2.74 (t, $4H_{g,g}$, J = 5.0 Hz). In its ^{13}C-NMR spectrum, signals were observed at δ 162.40, 161.88, 154.62, 153.94, 145.07, 141.43, 136.97, 125.46, 119.28, 112.30, 111.88 and 108.48 for aromatic carbons whereas aliphatic carbons appeared at δ 64.89, 60.83, 56.10, 52.27 and 46.40. Molecular ion peak was observed at m/z 425.4 $(M + 1)^+$ in its mass spectrum. The compound also showed high LC-MS/MS purity (> 98%) with 11.48 min retention time.

IR spectrum of 4-amino-2-[4-(2-pyridinyl)piperazin-1-yl]methyl-7,8-dimethoxy-quinazoline (**236**) displayed characteristic peaks at 3297, 3158 (N-H str) and 1117 cm^{-1} (C-O str). Its PMR spectrum showed signals at δ 8.09-8.08 (d, $1H_i$), 7.96-7.93 (d, $1H_a$, J = 9.1 Hz), 7.49-7.45 (m, $1H_j$), 7.24-7.21 (d, $1H_b$, J = 9.1 Hz), 6.73-6.71 (d, $1H_l$) and 6.60-6.57 (m, $1H_k$) for the aromatic protons and 7.52 (bs, $2H_e$) as broad singlet for amino protons. Aliphatic protons appeared at δ 3.94 (s, $3H_d$, $3H_c$), 3.60 (s, $2H_f$), 3.51-3.49 (t, $4H_{h,h}$, J = 4.8 Hz) and 2.70-2.67 (t, $4H_{g,g}$, J = 4.8 Hz). In its ^{13}C-NMR, signals were obtained at δ 162.61, 161.88, 159.04, 153.93, 147.36, 145.10, 141.48, 137.12, 119.25, 112.65, 111.91, 108.50 and 106.74 whereas peaks were observed at 65.25, 60.83, 56.13, 52.63 and 44.65 for aliphatic carbons. The compound also showed high LC-MS/MS purity (> 98%) with 11.35 min retention time.



(**236**)

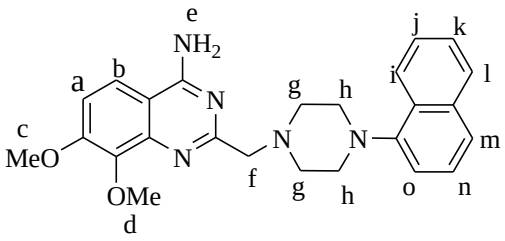


(**237**)

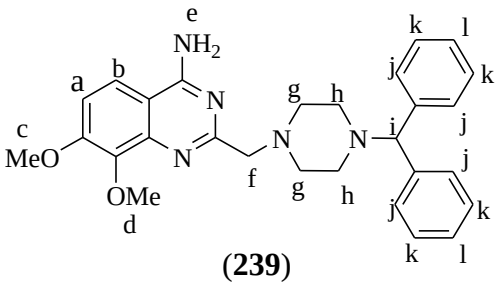
In IR spectrum of compound (**237**), characteristic peaks were observed at 3295, 3192 (N-H str) and 1111 cm^{-1} (C-O str). Its PMR spectrum showed signals at δ 8.29-8.28 (d, $2H_{i,i}$, J = 4.7 Hz), 7.93-7.91 (d, $1H_a$, J = 9.1 Hz), 7.23-7.21 (d, $1H_b$, J = 9.1 Hz) and 6.55-6.52 (m, $1H_j$) for the aromatic protons and 7.54 (bs, $2H_e$) for amino protons. Aliphatic protons were observed at δ 3.92 (s, $3H_d$), 3.90 (s, $3H_c$), 3.75-3.73 (t, $4H_{h,h}$, J = 4.9 Hz), 3.57 (s, $2H_f$) and 2.63-2.62 (t, $4H_{g,g}$, J = 4.9 Hz). Its ^{13}C-NMR displayed signals at δ 162.58, 161.88, 161.21, 157.56, 153.95, 145.07, 141.64, 119.26, 112.00, 109.71 and 103.79 for aromatic carbons whereas signal at δ 65.02, 60.80, 56.13, 52.59 and 43.80 were observed for aliphatic carbons. The compound also showed high LC-MS/MS purity (> 98%) with 11.09 min retention time.

Compound (**238**) showed characteristic peaks at 3298, 3120 (N-H str) and 1125 cm^{-1} (C-O str) in its IR spectrum. Its PMR spectrum displayed signals at δ 8.12-8.07 (m, $2H_{o,n}$), 7.92-7.91 (d, $1H_a$, J = 9.1 Hz), 7.79-7.77 (d, $1H_i$, J = 8.5 Hz), 7.50-7.48 (d, $1H_l$, J =

8.5 Hz), 7.45-7.39 (m, 1H$_j$), 7.37-7.32 (m, 1H$_k$), 7.19-7.16 (d, 1H$_b$, *J* = 9.1 Hz) and 7.06-7.04 (d, 1H$_m$, *J* = 7.4 Hz) for aromatic protons. A broad signal was observed at δ 7.39 (bs, 2H$_e$) for amino protons. Aliphatic protons appeared at δ 3.96 (s, 3H$_d$), 3.93 (s, 3H$_c$), 3.69 (s, 2H$_f$), 3.07 (bs, 4H$_{h,h}$) and 2.88 (bs, 4H$_{g,g}$). In its ^{13}C-NMR spectrum, signals were observed at δ 163.36, 162.58, 161.89, 153.89, 149.34, 145.07, 134.18, 128.17, 127.97, 125.68, 124.97, 124.03, 123.26, 122.78, 119.59, 114.19, 112.47 and 108.52 for aromatic carbons and signals at δ 65.39, 60.91, 56.07, 53.27 and 52.59 were observed for the aliphatic carbons. Molecular ion peak was observed at m/z 429.8 $(M + 1)^+$ in its mass spectrum. The compound also showed high LC-MS/MS purity (> 98%) with 11.90 min retention time.



(**238**)

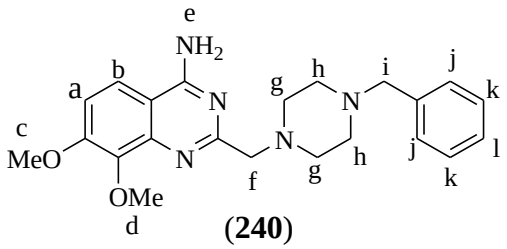


(**239**)

IR spectrum of 4-amino-2-[4-(benzhydryl)piperazin-1-yl]methyl-7,8-dimethoxy-quinazoline (**239**) displayed characteristic peaks at 3296, 3187 (N-H str) and 1118 cm^{-1} (C-O str). Its PMR spectrum showed signals at δ 7.93-7.90 (d, 1H$_a$, *J* = 9.2 Hz), 7.41-7.39 (d, 4H$_{j,j}$, *J* = 7.6 Hz), 7.27-7.23 (m, 4H$_{k,k,}$), 7.22-7.20 (d, 1H$_b$, *J* = 9.2 Hz) and 7.16-7.12 (m, 2H$_l$) for aromatic protons. Amino protons were observed at δ 7.49 (bs, 2H$_e$) as a broad singlet. Among the aliphatic protons, signals were seen at δ 4.22 (s, 1H$_i$), 3.92 (s, 3H$_d$), 3.90 (s, 3H$_c$), 3.52 (s, 2H$_f$), 2.60 (bs, 4H$_{h,h}$) and 2.34 (bs, 4H$_{g,g}$). Signals were observed at δ 162.67, 161.82, 153.88, 145.07, 142.84, 141.46, 128.25, 127.45, 126.58, 119.20, 111.90 and 108.46 for aromatic carbons and δ 75.39, 65.15, 60.82, 56.13, 52.96 and 51.49 for aliphatic carbons in its ^{13}C-NMR. Its mass spectrum displayed molecular ion peak at m/z 470.2 $(M + 1)^+$. The compound also showed high LC-MS/MS purity (> 98%) with 11.81 min retention time.

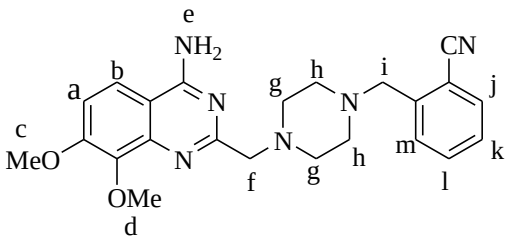
Characteristic peaks were observed for 4-amino-2-(4-benzylpiperazin-1-yl)methyl-7,8-dimethoxyquinazoline (**240**) at 3315, 3141 (N-H str) and 1121 cm^{-1} (C-O str) in its IR spectrum. Signals were observed at δ 7.93-7.91 (d, 1H$_a$, *J* = 9.1 Hz), 7.29-7.27 (d, 1H$_b$, *J* =

9.1 Hz) and 7.26-7.17 (m, $5H_{j,k,l}$) for aromatic protons, 7.54 (bs, $2H_e$) as a broad singlet for amino protons, 3.91 (s, $3H_d$), 3.89 (s, $3H_c$), 3.50 (s, $2H_f$), 3.43 (s, $2H_i$), 2.56 (bs, $4H_{g,g}$) and 2.38 (bs, $4H_{h,h}$) for the aliphatic protons in its PMR spectrum. Its ^{13}C-NMR displayed signals at δ 162.74, 161.84, 153.91, 145.08, 141.44, 138.16, 128.66, 127.92, 126.66, 119.23, 111.93 and 108.45 for aromatic carbons. Signals were seen at δ 65.24, 62.24, 60.81, 56.14, 52.83 and 52.64 for aliphatic carbons. Its mass spectrum gave molecular ion peak at m/z 394.5 $(M + 1)^+$. The compound also showed high LC-MS/MS purity (> 98%) with 11.54 min retention time.

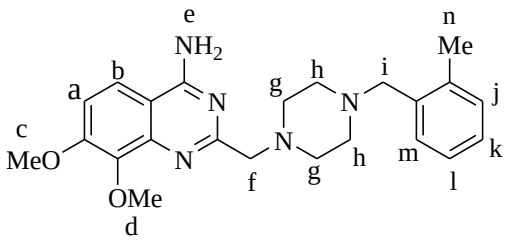


(**240**)

Compound (**241**) showed characteristic peaks at 3342, 3235 (N-H str), 2222 (C≡N str) and 1115 cm^{-1} (C-O str) in its IR spectrum. Its PMR spectrum displayed signals at δ 7.95-7.93 (d, $1H_a$, J = 9.2 Hz), 7.76-7.74 (d, $1H_j$, J = 7.6 Hz), 7.66-7.62 (m, $1H_k$), 7.56-7.54 (d, $1H_m$, J = 7.6 Hz), 7.45-7.41 (m, $1H_l$) and 7.26-7.24 (d, $1H_b$, J = 9.2 Hz) for aromatic protons. A broad signal appeared at δ 7.58 (bs, $2H_e$) for amino protons. Other protons gave signals at δ 3.93 (s, $3H_d$), 3.91 (s, $3H_c$), 3.63 (s, $2H_f$), 3.52 (s, $2H_i$), 2.58 (bs, $4H_{g,g}$) and 2.46 (bs, $4H_{h,h}$) in the aliphatic region. Signals were observed at δ 162.69, 161.85, 153.92, 145.07, 141.99, 141.41, 132.74, 129.91, 127.71, 119.24, 117.47, 112.10, 111.94 and 108.43 for aromatic carbons, 132.71 for nitrile (C≡N) carbon and 65.17, 60.81,



(**241**)



(**242**)

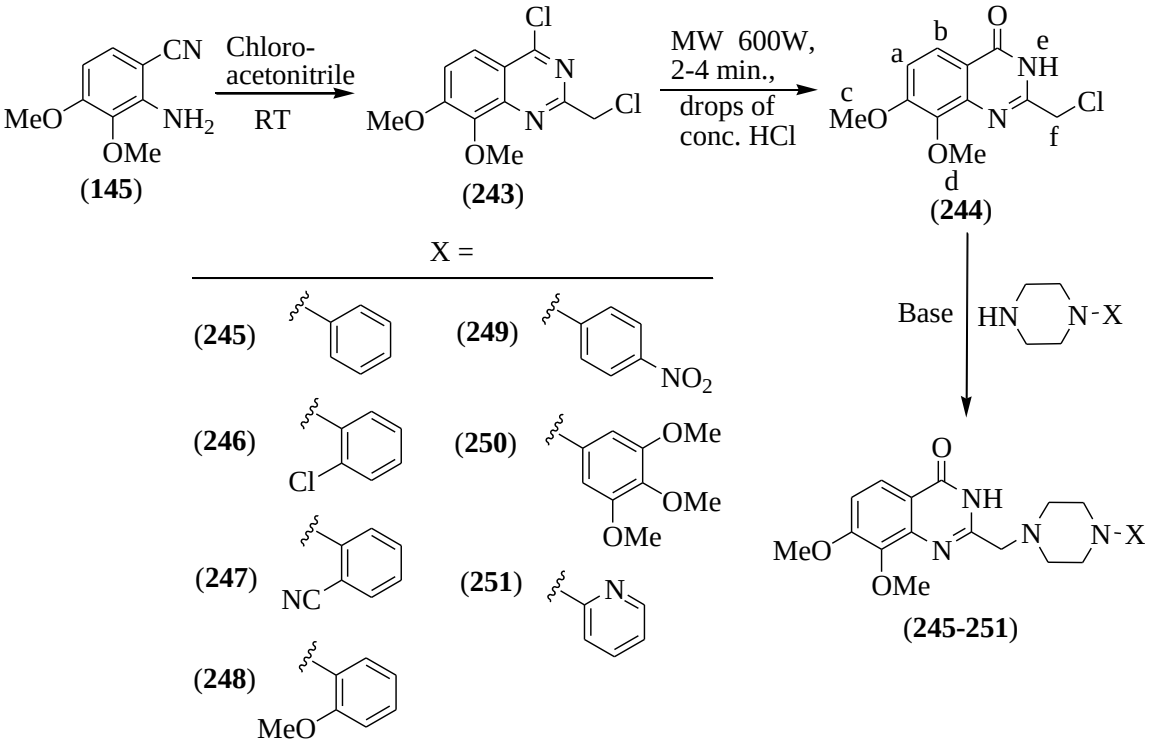
59.85, 56.13, 52.70 and 52.63 for aliphatic carbons in its ^{13}C-NMR. Molecular ion peak was observed at m/z 418.9 $(M + 1)^+$ in its mass spectrum.

IR spectrum of 4-amino-2-[4-(2-methylbenzyl)piperazin-1-yl]methyl-7,8-dimethoxy-quinazoline (**242**) displayed characteristic peaks at 3292, 3153 (N-H str) and 1118 cm^{-1} (C-O str). Its PMR spectrum showed signals at δ 7.93-7.91 (d, $1H_a$, J = 8.5 Hz), 7.20 (bs, $1H_j$, $1H_k$) and 7.10 (bs, $1H_b$, $2H_{l,m}$) for aromatic protons. A broad signal was observed at δ 7.38 (bs, $2H_e$) for amino protons. Other protons were seen at δ 3.95 (s, $6H_{c,d}$), 3.55 (s, $2H_f$), 3.41 (s, $2H_i$), 2.55 (bs, $4H_{g,g}$), 2.43 (bs, $4H_{h,h}$) and 2.32 (s, $3H_n$) for aliphatic region. Its mass spectrum displayed molecular ion peak at m/z 408.4 $(M + 1)^+$. The compound also showed high LC-MS/MS purity (> 98%) with 11.14 min retention time.

4.1.9 Synthesis of 2-(4-substituted piperazin-1-yl)methyl-7,8-dimethoxyquinazoline-4(3*H*)-ones (245-251) (Series VII)

4-Chloro-2-chloromethyl-7,8-dimethoxyquinazoline (**243**) was basically obtained as a byproduct upon the reaction of 2-amino-3,4-dimethoxybenzonitrile (**145**) with chloroacetonitrile at lower temperature (-5 to 0 ^{0}C). At room temperature it was formed as the main product (**Scheme 13**).[148] Absence of a peak at 2210 cm^{-1} for the nitrile (CN) group in its IR spectrum indicated the formation of the cyclized compound. Its mass spectrum gave peaks at m/z 274.6 $(M + 1)^+$ and 276.6 $(M + 3)^+$ which confirmed its molecular mass.

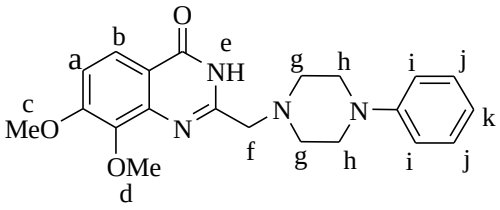
2-Chloromethyl-7,8-dimethoxyquinazolin-4(3*H*)-one (**244**) required for the synthesis of the desired compounds (**245-251**) was prepared through the hydrolysis of compound (**243**) by concentrated hydrochloric acid under microwave irradiations at 600 W for 2-4 minutes (**Scheme 13**).[148] Characteristic peaks were observed at 3138 (N-H str) and 1683 cm^{-1} (C=O str) in its IR spectrum which proved the presence of amide functionality. Its PMR spectrum displayed signals at δ 7.91-7.89 (d, $1H_b$) as doublet for aromatic proton (CH_b) which coupled with proton (CH_a) observed at δ 7.33-7.31 (d, $1H_a$) as doublet with a coupling constant of 7.9 Hz while the aliphatic protons were observed at δ 4.63 (s, $2H_f$), 3.96 (s, $3H_d$) and 3.91 (s, $3H_c$) as singlets. Molecular ion peaks were observed at m/z 255.5 $(M + 1)^+$ and 256.5 $(M + 2)^+$ in its mass spectrum which confirmed its molecular structure.



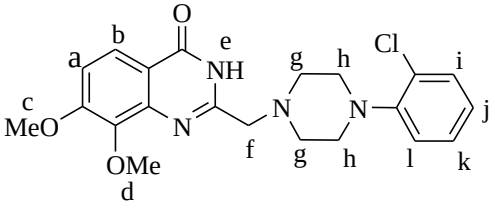
Scheme: 13

Syntheses of the designed compounds (**245-251**) were accomplished by the reaction of compound (**244**) with substituted piperazines in presence of a base at a temperature range of 30 to 60 ^{0}C (**Scheme 13**).

2-[4-(Phenylpiperazin-1-yl]methyl-7,8-dimethoxyquinazolin-4(3*H*)-one (**245**) showed characteristic peaks at 3255 (N-H str), 1678 (C=O str) and 1092 cm^{-1} (C-O str) in its IR spectrum. Its PMR spectrum displayed signals at δ 10.02 (bs, 1H$_e$) as a broad singlet for the amidic proton, 8.05-8.03 (d, 1H$_b$) as doublet which coupled with proton (CH$_a$) observed at δ 7.12-7.10 (d, 1H$_a$) as doublet with a coupling constant of 8.9 Hz. Other signals were observed at δ 7.30-7.26 (m, 2H$_{j,j}$), 6.95-6.93 (d, 2H$_{i,i}$, J = 7.8 Hz) and 6.91-6.87 (m, 1H$_k$) for aromatic protons whereas aliphatic protons gave signals at δ 4.02 (s, 3H$_d$), 3.99 (s, 3H$_c$), 3.70 (s, 2H$_f$) and 3.27-3.25 (t, 4H$_{h,h}$) as a triplet which coupled with protons (CH$_{g,g}$) observed at δ 2.78-2.76 (t, 4H$_{g,g}$) as a doublet with a coupling constant of 4.8 Hz. Molecular ion peak was observed at m/z 380.8 (M + 1)$^+$ in its mass spectrum.



(**245**)

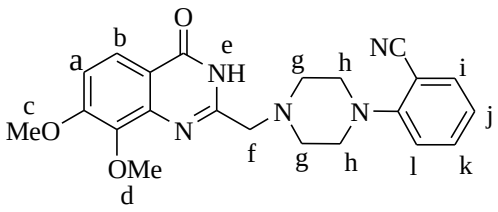


(**246**)

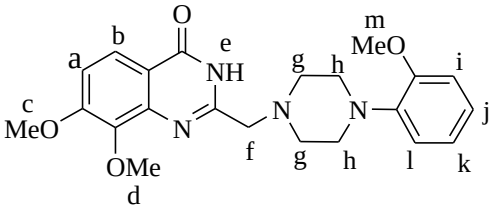
IR spectrum of compound (**246**) displayed characteristic peaks at 3159 (N-H str), 1670 (C=O str) and 1096 cm^{-1} (C-O str). Its PMR spectrum displayed signals at δ 10.05 (bs, $1H_e$) as a broad singlet for amidic proton, 8.07-8.04 (d, $1H_b$) as a doublet which coupled with a proton (CH_a) observed at 7.14-7.12 (d, $1H_a$) as doublet with a coupling constant of 8.9 Hz. Signals were observed for other aromatic protons at δ 7.38-7.35 (d, $1H_i$, J = 7.9 Hz) as a doublet which coupled with protons observed at δ 7.27-7.22 (m, $1H_j$) as multiplet, 7.06-7.04 (d, $1H_l$, J = 7.9 Hz) as doublet and 7.02-6.98 (m, $1H_k$) as multiplet. Among the aliphatic protons, signals were seen at 4.02 (s, $3H_d$), 4.00 (s, $3H_c$), 3.73 (s, $2H_f$), 3.14 (bs, $4H_{h,h}$) and 2.82-2.80 (t, $4H_{g,g}$, J = 4.5). Signals were observed at δ 161.48 for amidic C=O carbon, 157.19, 153.37, 148.85, 143.77, 142.74, 130.68, 128.83, 127.70, 124.02, 122.73, 120.47, 116.06 and 111.77 for the aromatic carbons whereas the aliphatic carbons were observed at δ 61.91, 60.62, 56.32, 53.54 and 51.12 in its ^{13}C-NMR spectrum. Mass spectrum displayed a molecular ion peak at m/z 415.1 $(M + 1)^+$.

Characteristic peaks were observed for 2-[4-(2-cyanophenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazolin-4(3*H*)-one (**247**) at 3145 (N-H str), 1676 (C=O str) and 1099 cm^{-1} (C-O str) in its IR spectrum. Signals were observed for aromatic protons at δ 11.65 (bs, $1H_e$) as a broad singlet, 7.87-7.85 (d, $1H_b$, J = 8.9 Hz) as doublet, 7.62-7.60 (d, $1H_i$, J = 8.0 Hz) as doublet, 7.56-7.52 (m, $1H_j$) as multiplet, 7.22-7.20 (d, $1H_a$, J = 8.9 Hz) as doublet, 7.12-7.10 (d, $1H_l$, J = 8.0 Hz) as doublet and 7.06-7.03 (m, $1H_k$) whereas aliphatic protons gave signals at δ 3.92 (s, $3H_d$), 3.90 (s, $3H_c$), 3.56 (s, $2H_f$), 3.21-3.19 (t, $4H_{h,h}$, J = 4.3) and 2.78-2.76 (t, $4H_{g,g}$, J = 4.3). Its ^{13}C-NMR displayed signals at δ 161.23 for amidic (C=O) carbon, 160.30, 156.35, 155.12, 153.32, 143.33, 142.28 for aromatic carbons, 133.98 for cyano (C≡N) carbon, 121.72, 121.66, 118.81, 117.97, 115.68, 111.82 and 104.94 for other aromatic carbons. Among the aliphatic carbons signals were seen at δ 61.06, 60.43, 56.02, 52.46 and 51.06. Its mass spectrum offered a molecular ion peak at

m/z 405.9 $(M + 1)^+$. The compound also showed high LC-MS/MS purity (> 98%) with 14.29 min retention time.



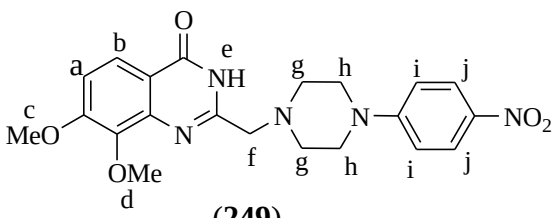
(**247**)



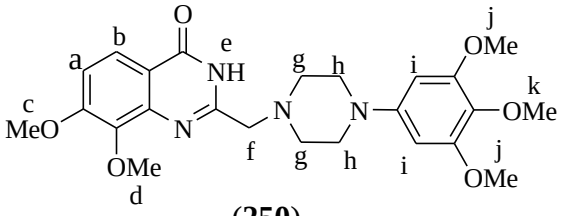
(**248**)

Compound (**248**) showed characteristic peaks at 3162 (N-H str), 1679 (C=O str) and 1091 cm^{-1} (C-O str) in its IR spectrum. Its PMR spectrum displayed signals at δ 9.97 (bs, $1H_e$) as a broad singlet for the amidic proton, 7.99-7.97 (d, $1H_b$, J = 8.9 Hz), 7.06-7.03 (d, $1H_a$, J = 8.9 Hz), 6.95-6.93 (m, $1H_j$), 6.88-6.86 (m, $2H_{i,k}$) and 6.81-6.79 (d, $1H_l$, J = 7.7 Hz) for the other aromatic protons. Signals were seen at 3.94 (s, $3H_d$), 3.92 (s, $3H_c$), 3.79 (s, $3H_m$), 3.64 (s, $2H_f$), 3.07 (bs, $4H_{h,h}$) and 2.75-2.73 (t, $4H_{g,g}$) for aliphatic protons. Signals were observed at δ 161.46 for amidic (C=O) carbon, 157.18, 153.47, 152.27, 143.79, 142.76, 140.87, 123.28, 122.74, 121.07, 118.37, 116.10, 111.77 and 111.24 for other aromatic carbons while aliphatic carbons showed signals at δ 61.89, 60.69, 56.32, 55.40, 53.62 and 50.57 in its ^{13}C-NMR spectrum. Its mass spectrum showed a molecular ion peak at m/z 411.4 $(M + 1)^+$. The compound also showed high LC-MS/MS purity (> 98%) with 14.19 min retention time.

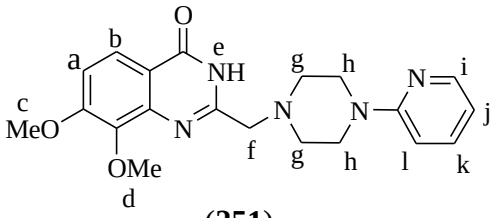
IR spectrum of 2-[4-(4-nitrophenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazolin-4(3*H*)-one (**249**) displayed characteristic peaks at 3225 (N-H str), 1666 (C=O str) and 1114 cm^{-1} (C-O str). Its PMR spectrum showed a broad signal at δ 11.51 (bs, $1H_e$) for an amidic proton while other protons gave signals at δ 8.06-8.04 (d, $2H_{j,j}$, J = 9.5 Hz) as doublet, 7.91-7.89 (d, $1H_b$) as a doublet which coupled with a proton (CH_a) observed at δ 7.19-7.17 (d, $1H_a$) as doublet with a coupling constant of 8.9 Hz and 6.94-6.91 (d, $2H_{i,i}$, J = 9.5 Hz) as doublet. Among the aliphatic protons, signals appeared at δ 3.95 (s, $3H_d$), 3.92 (s, $3H_c$), 3.59 (s, $2H_f$), 3.52-3.50 (t, $4H_{h,h}$, J = 4.9) and 2.76-2.74 (t, $4H_{g,g}$, J = 4.9). Its mass spectrum displayed a molecular ion peak at m/z 425.9 $(M + 1)^+$.



(**249**)



(**250**)



(**251**)

Characteristic peaks were observed for 2-[4-(3,4,5-trimethoxyphenyl)piperazin-1-yl]methyl-7,8-dimethoxyquinazolin-4(3*H*)-one (**250**) at 3174 (N-H str), 1679 (C=O str) and 1102 cm^{-1} (C-O str) in its IR spectrum. Signals were observed at δ 9.88 (bs, $1H_e$) as a broad peak for a proton of amide functionality, 8.07-8.05 (d, $1H_b$) as doublet which coupled with a proton (CH_a) observed at 7.15-7.13 (d, $1H_a$) as doublet with a coupling constant of 8.9 Hz, 6.19 (s, $2H_{ii}$) as a singlet for two protons (CH_i). Aliphatic protons showed signals at δ 4.02 (s, $3H_d$), 4.01 (s, $3H_c$), 3.86 (s, $6H_j$), 3.81 (s, $3H_k$), 3.72 (s, $2H_f$), 3.23-3.20 (t, $4H_{h,h}$, J = 4.8 Hz) and 2.80-2.77 (t, $4H_{g,g}$, J = 4.8 Hz). Its ^{13}C-NMR displayed a signal at δ 160.94 for amidic (C=O) carbon. Aromatic carbons were observed at δ 156.64, 153.11, 148.89, 146.43, 142.18, 142.05, 131.61, 121.95, 115.58 and 112.21 whereas the aliphatic carbons showed signals at δ 94.36, 61.32, 60.01, 56.40, 56.02, 55.71, 52.23 and 46.98. Its mass spectrum offered a molecular ion peak at m/z 471.0 $(M + 1)^+$.

Compound (**251**) showed characteristic peaks at 3298 (N-H str), 1679 (C=O str) and 1098 cm^{-1} (C-O str) in its IR spectrum. Its PMR spectrum displayed a broad signal at δ 9.96 (bs, $1H_e$) for amidic proton whereas the aromatic protons were observed at δ 8.21-8.19 (d, $1H_i$, J = 5.4 Hz), 8.06-8.04 (d, $1H_b$, J = 8.9 Hz), 7.52-7.48 (m, $1H_j$), 7.14-7.12 (d, $1H_a$, J = 8.9 Hz), 6.67-6.66 (d, $1H_l$) and 6.66-6.65 (m, $1H_k$). Signals for aliphatic protons were observed at δ 4.02 (s, $3H_b$), 4.00 (s, $3H_c$), 3.69 (s, $2H_f$), 3.64-3.61 (t, $4H_{h,h}$, J = 4.9) and 2.74-2.71 (t, $4H_{g,g}$, J = 4.9). Molecular ion peak was observed at m/z 382.4 $(M + 1)^+$ in its mass spectrum. The compound also showed high LC-MS/MS purity (> 98%) with 11.63 min retention time.

4.2 Biological activity

4.2.1 *In vitro* functional antagonism assay

The synthesized compounds were screened for antagonistic activity on both α_1- and AT_1-receptors separately by *in vitro* screening on isolated tissue preparations (**Table 6**).[149,150] Compounds (**167-176**) having a methylene spacer between the 4-amino-6,7-dimethoxyquinazoline moiety and the piperazine ring; a keto spacer (-C=O) between the piperazine ring and the phenyl ring yielded compounds with variable potencies. Compound (**176**) showed balanced but poor activity (pA_2 for α_1 = 6.93 and AT_1 = 6.87) on both the receptors. Compounds (**167-169**) were also found to be poor to moderately (pA_2 = 4-7) active on both the receptors but the activities were not balanced. Compounds (**172** & **173**) having dichloro and dimethoxy groups at 2nd and 3rd positions of phenyl ring respectively, were observed to be moderately active at AT_1-receptor but inactive at α_1-

Table 6: *In vitro* activities (pA_2 values for α_1- and AT_1-receptors) of the synthesized compounds

Comp.	(pA_2 Values)		Comp.	(pA_2 Values)		Comp.	(pA_2 Values)	
	α_1	**AT_1**		**α_1**	**AT_1**		**α_1**	**AT_1**
167	5.95	4.75	**187**	6.32	6.95	**207**	9.29	ND
168	5.66	7.75	**188**	**7.44**	**7.26**	**208**	9.27	ND
169	6.46	5.37	**189**	*	6.23	**210**	6.81	8.62
170	*	*	**190**	1.98	3.03	**213**	6.16	*
171	2.14	4.36	**191**	4.05	5.41	**214**	8.33	5.80
172	*	6.61	**192**	*	*	**215**	6.37	4.70
173	*	6.34	**193**	4.95	5.51	**217**	6.07	5.96
174	*	*	**194**	6.43	ND	**218**	6.06	5.42
175	3.28	2.15	**195**	6.55	5.78	**220**	5.68	*
176	6.93	6.87	**196**	6.79	5.66	**221**	7.57	5.25
177	4.55	5.22	**197**	6.75	5.96	**224**	6.14	6.07
178	*	6.10	**198**	6.79	6.52	**225**	6.23	6.21
179	**8.77**	**8.60**	**199**	**7.82**	**7.99**	**226**	5.06	*
180	5.08	*	**200**	6.39	7.20	**228**	6.69	5.66
181	5.89	*	**201**	6.92	6.90	**230**	6.42	4.46
182	5.91	6.49	**202**	6.37	6.92	**Terazosin**	8.51	6.24
183	5.91	6.12	**203**	6.10	7.71	**Losartan**	5.46	8.08
184	7.19	*	**204**	6.32	5.31	**20**	**10.10**	**8.83**
185	7.50	6.58	**205**	9.24	ND			
186	4.64	*	**206**	8.81	ND			

*Did not show any activity; ND = activity not done

receptor. Compounds (**170** & **174**) were found to be inactive on both the receptors. Compounds (**177-185**) in which phenyl(piperazinyl)methanone moiety was reduced to benzylpiperazine, offered better results in the preliminary screening. Compound (**179**) (pA_2 for α_1 = 8.77 and AT_1 = 8.60) among them, showed almost equal antagonistic potency to the standard drugs terazosin and losartan. Compounds (**177**, **182**, **183** & **185**) also showed dual antagonism but the potencies were ranging from poor to moderate. Compound (**178**) having strong electron withdrawing group (CF_3) at 2nd position of the phenyl ring was found to be moderately active at AT_1-receptor but inactive at α_1-receptor. Compounds (**180, 181**, **184** & **186**) were found to be moderately active at α_1-receptor but were inactive at AT_1-receptors. Compound (**188**) having benzhydryl moiety showed balanced antagonistic activity at both the receptors but showed lower potencies than terazosin for α_1- and losartan for AT_1-receptors. Compound (**187**) having 1-naphthyl moiety showed similar type of results as shown by compound (**188**).

On the other hand conversion of phenyl(piperazinyl)methanone moiety to 2-phenyl(piperazinyl)ethanone as in compounds (**190-192**), failed to produce satisfactory results on both the receptors. Though, compound (**191**) showed balanced activity but the potency was nowhere in comparison to the potencies of the standard drugs (terazosin and losartan). Compound (**192**) was found to be inactive on both the receptors.

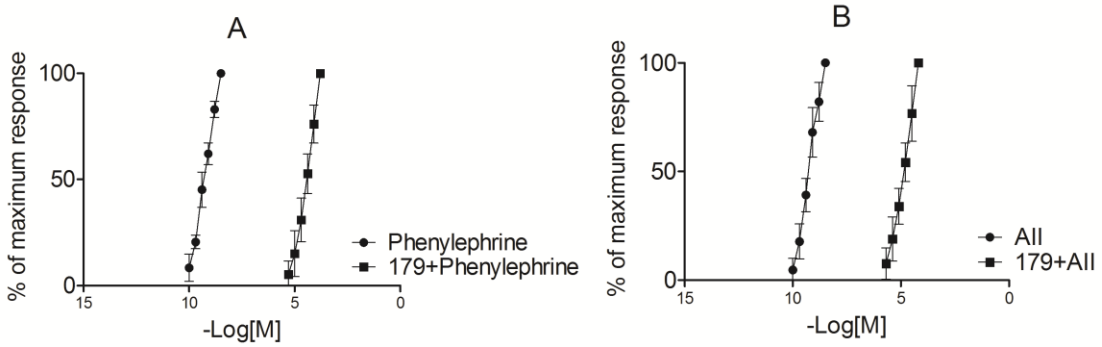


Fig. 5: Dose response plots of compound (**179**) (A) against phenylephrine on rat aortic strips (n=4). Dose response plots of compound **(179)** (B) against AII on rat aortic strips (n=4). A rightward parallel shift can be observed in presence of compound (**179**) against phenylephrine and AII mediated responses.

Compound (1**99**) showed somewhat similar (pA_2 for α_1 = 7.82 and AT_1 = 7.99) potency to compound (**179**). Compounds (**200-204**, **214-218**, **221**, **224**, **225**, **228** & **230**)

displayed activities in the pA_2 range of 4-8. Compounds (**220** & **226**) offered moderate activities only for α_1-receptor.

Thus, compound (**179**) was found to be the most potent dual antagonist amongst all of the test compounds of the series in the *in vitro* tissue experiments. As shown in **Fig. 5**, compound (**179**) showed competitive antagonism against phenylephrine and angiotensin II. A rightward parallel shift was observed in the dose response curve after addition of compound (**179**). The results demonstrated competitive dual antagonism by compound (**179**) on α_1- as well as AT_1-receptors.

4.2.2 Invasive blood pressure response

Preliminary screening results showed that compound (**179**) possessed promising antagonistic activity on both of the stated receptors (pA_2 for $\alpha_1 = 8.77$ and $AT_1 = 8.60$). So, it was planned to revalidate the *in vitro* results into *in vivo* animal model for compound (**179**). Since invasive blood pressure (IBP) measurement provides direct assessment of antihypertensive activity of an investigational compound, it has been utilized as a gold standard technique for evaluation of potential antihypertensive compounds.[151-154] Compound (**179**) was evaluated against phenylephrine (6 µg/kg) and AII (6 µg/kg) induced rise in BP in the rat model. In earlier findings, it has been proved that fall in blood pressure mediated by prazosin was not only because of α_1 antagonism (pA_2 for $\alpha_1 = 8.91$), but also due to simultaneous blockade of AT_1-receptor[155] (pA_2 for $AT_1 = 8.26$). Thus, for the present study terazosin was chosen as a standard α_1 antagonist instead of prazosin, and losartan as a standard AT_1-receptor antagonist, against phenylephrine and AII mediated pressor responses respectively.

For the purpose of comparison, the dose levels of the agonists and antagonists were maintained as per the previous study.[89] Despite having almost equal or higher potency then terazosin in the *in vitro* experiments, the selected compound (**179**) could not replicate the response of the standard α_1-blocker terazosin in the *in vivo* animal model (**Fig. 6**). This is probably due to the distribution of the test compound (**179**) on both the receptors, as it is a dual antagonist while the standard terazosin inhibits only the α_1-receptor. So the experiments were repeated by masking one receptor at a time and evaluating the test compound on the other receptor. Terazosin (0.72 µM) was used for

masking of α_1-receptor and the test compound (**179**) was evaluated for its antagonism of AII response while losartan (3.6 µM) was used for masking of AT_1-receptor and the test compound evaluated for its antagonism of phenylephrine response on α_1-receptor, as described in the previous report.[89]

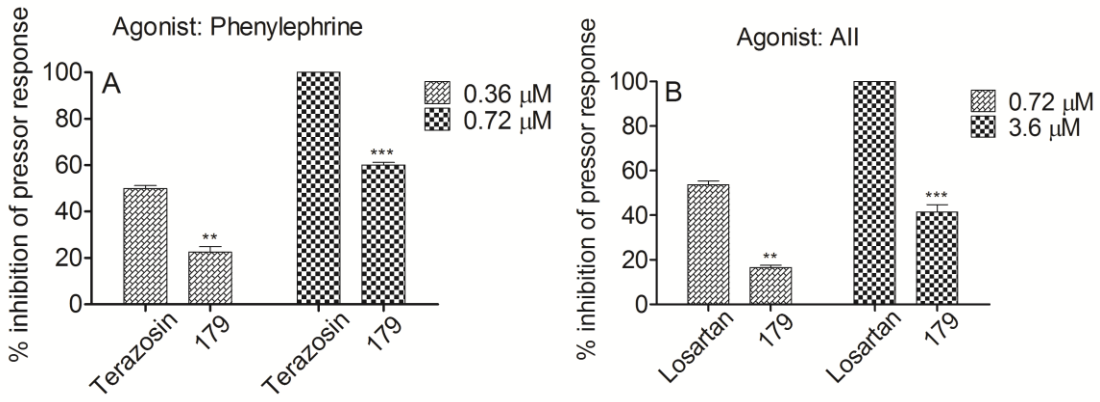


Fig. 6: (A) Inhibition of mean arterial pressor response of phenylephrine in animals (n=4) previously dosed with compound (**179**), or terazosin at equimolar levels. (B) Inhibition of mean arterial pressor response of AII in animals (n=4) previously dosed with compound (**179**), or losartan at equimolar levels. Results are expressed as Mean ± SEM values. ***p* <0.001 ****p* <0.0001.

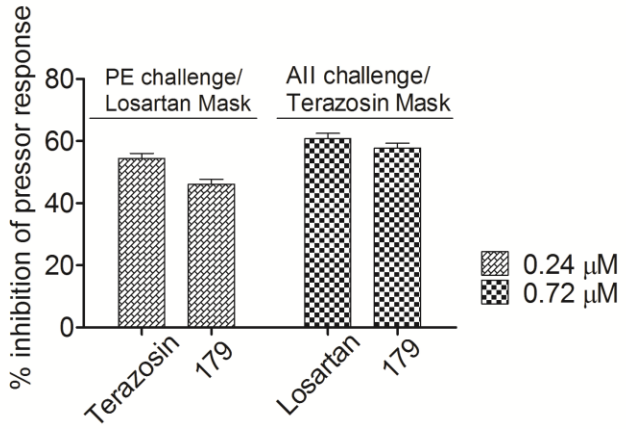


Fig. 7: (A) *In vivo* pressure response inhibition of phenylephrine and AII by compound (**179**) in normotensive rats (n=4) using losartan (3.6 µM) and terazosin (0.72 µM) respectively as masking agents. Results are expressed as Mean ± SEM values. PE=phenylephrine.

Under masking conditions, the test compound (**179**) was found to be almost equipotent to the two standard drugs, terazosin as α_1-antagonist and losartan as AT_1-antagonist (**Fig. 7**) supporting the observations of the *in vitro* experiments of dual antagonist nature of the synthesized compound.