Chapter-IV

Synthesis of 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline & 3,3’-(alkanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline.

Introduction

Literature report reveals that with the modification of substituents at different position of the quinazoline moiety there is change in the potency as inhibitors of the molecule. Some of the reports are highlighted below

4.1.1 O.I. El-Sabbagh and co-workers have reported\(^1\) the synthesis of octahydroquinazolines varying substituents at 3-position of the quinazoline moiety and studied their antihypertensive activity. All octahydroquinazoline derivatives were prepared which structurally related to the antihypertensive clinically used $\alpha_1$-blocker prazosin. Several novel 1-(4-chlorophenyl)-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydro-5-oxo-3-(substitutedphenyl) quinazoline derivatives (2–21) structurally similar to prazosin, were prepared using Mannich reaction of 3-(4-chlorophenylamino)-5,5-dimethyl-2-cyclohexenone (1) with different aromatic amines in the presence of formaline. The structures of the quinazoline derivatives were established using elemental and spectral analyses. Compounds 18, 20 and 21 were found to possess a high hypotensive effect through their expected $\alpha_1$-blocking activity like the clinically used drug prazosin but with the advantage of being not causing reflex tachycardia and having prolonged duration of action when tested in adrenaline-induced hypertension in anaesthetized rats.

Condensation of 5, 5-dimethyl-1, 3-cyclohexanedione with 4-chloroaniline was conducted by heating the reactants at reflux in toluene to afford 5, 5-dimethyl-3-(4-chlorophenylamino)-2-cyclohexenone (1). The novel 5-oxo-octahydroquinazolines (2–8) were then obtained by heating at reflux equimolar amounts of enaminone (1) and the primary aromatic amines with two equivalents of formaldehyde in ethanol containing catalytic amount of glacial acetic acid.
These quinazolines (2–8) were formed through Mannich reaction either at C-2 or arylamino group of the enaminone system. The former would be kinetically favorable being irreversible followed by ring formation using excess formaldehyde. The structures of 5-oxo-octahydroquinazolines (2–8) were established using elemental and spectral analyses. IR spectral data showed the disappearance of the NH absorption band at 3250 cm\(^{-1}\) of the starting enaminone. \(^1\)H NMR proved the disappearance of both singlet at \(\delta = 7.85\) ppm due to NH group and also the vinylic proton singlet at \(\delta = 5.65\) ppm of the starting enaminone. Moreover, the formation of the 5-oxo-octahydroquinazoline was confirmed through appearance of two characteristic singlets around \(\delta = 4.26\) and 4.87 ppm for the two methylene groups at 4- and 2-positions of the quinazoline skeleton.

The novel ester (9) was prepared by stirring equimolar amounts of 3-(4-hydroxyphenyl)-5-oxo-octahydroquinazoline (6) and ethyl bromoacetate in dimethylformamide (DMF) containing K\(_2\)CO\(_3\) at room temperature for 24 hr. The ester 9 was allowed to condense with hydrazine hydrate through refluxing the reactants in ethanol for 2 h to afford the novel hydrazide 10 in 72% yield. The chemical structures of ester 9 and hydrazide 10 were established using elemental analysis and different spectroscopic methods. Condensation of the hydrazide key intermediate 10 with aromatic aldehydes in equimolar amounts was conducted through heating the reactants in ethanol containing 10 drops of glacial acetic acid for 2 h to give the novel hydrazone derivatives 11–21. (Scheme 1)
All novel 5-oxo-octahydroquinazolines (2–21) were screened to study their effect on the arterial blood pressure whereas compounds 2, 4, 5, 9–17 and 19 which did not produce any effect were excluded. On the other hand, compounds 3, 6, 7, 8, 18, 20 and 21 which showed an effect on the arterial blood pressure were subjected to study their \( \alpha \)-blocking activity using prazosin as a reference drug. The results presented and illustrated and showed that compounds 18, 20 and 21 produced significant \( (P < 0.05) \) decrease in both SABP and DABP with rapid onset of action (after 5 min) meanwhile such compounds caused non-significant decrease in the HR. Compounds 18, 20 and 21 rapidly reversed the vasopressor effect of adrenaline into depressor response after 30 min which were sustained for 1 hour. Thus, these compounds can be considered as rapidly acting \( \alpha_1 \)-blockers like prazosin but with advantageous of being did not cause reflex tachycardia and having prolonged duration of action.

4.1.2 Tomudex (ZD1694, 22), a new quinazoline based inhibitor of thymidylate synthase (TS), has recently been introduced in a number of European territories for the treatment of advanced colorectal cancer. It is a highly potent cytotoxic agent in vitro and shows in vivo antitumor activity in a range of preclinical models without the unacceptable kidney toxicity associated with its predecessor, CB 3717 (23). In international phase III studies in patients with previously untreated advanced colorectal cancer, the efficacy and acceptable safety profile of Tomudex was confirmed. Response rates, time to progression, and survival are consistent with the published literature for 5-fluorouracil and leucovorin. In addition there were reductions in the incidence of certain potentially serious adverse events and benefits in terms of improvements in quality of life, performance status, and weight gain. All the evidence suggests that the high cytotoxicity of Tomudex (22) is due to rapid intracellular localization via the reduced folate carrier protein (RFC) and then extensive metabolism by folylpolyglutamate synthetase (FPGS) to polyglutamates which are retained within cells and are 60-70 times more potent as inhibitors of TS.6 Tumor cells however may be resistant to classical folate-based antimetabolites through reduced expression of FPGS7 or upregulation of the polyglutamate-
hydrolyzing enzyme $\gamma$-glutamyl hydrolase. This fact has prompted the search for a complementary class of agents which would not be substrates for FPGS and hence insensitive to $\gamma$-glutamyl hydrolase but would also still rely on the RFC for cellular uptake. This requirement for RFC of the Sirotnak group that in murine tumor models compounds with favorable kinetic parameters for the RFC may offer a tumor-selective advantage. Agents with this biochemical profile should therefore be active in tumors expressing (1) low levels or modified FPGS expression and (2) high levels of $\gamma$-glutamyl hydrolase and which are therefore resistant to folate-based antimitabolites that require polyglutamation for their cytotoxicity. The lack of prolonged drug retention through polyglutamation may also allow for greater control over the duration of TS inhibition. A compound not subjected to metabolic activation through polyglutamation needs to have a high intrinsic potency as a TS inhibitor. As a starting point modifications to the quinazoline antifolate ICI198583 (24) were undertaken. The combined effect of the incorporation of 7-methyl and 2$\gamma$-fluoro substituents gave the analogue ZM214888 (25), a compound showing enhanced inhibition of TS and an overall retention of growth inhibition in cell lines. Moreover, the cytotoxicity of (25) results entirely from the parent monoglutamate since 7-methyl-substituted N10-propargyl quinazoline antifolates are not substrates for FPGS. Molecular modelling studies based on an analysis of the X-ray structures of E. coli TS enzyme ternary complexes of CB 371714,15 and its tetraglutamate derivative suggested that tighter binding inhibitors may be available in this class of compounds through extension of the glutamate moiety into the dipeptide region of the ternary complex. This work describes the synthesis and biological activities of new analogues of ZM214888 that were prepared to explore the hypotheses that has resulted in compounds with improved TS and growth inhibitory properties leading to the next generation of antitumor TS inhibitors, which are not substrates for FPGS but which still require RFC-mediated uptake into cells. (Scheme 2)
Scheme 2

4.1.3 The mitogenic action of EGF is mediated by ligand-induced autophosphorylation of the EGF receptor (EGF-R), which is commonly overexpressed in numerous human cancers. Inhibitors of receptor tyrosine kinase (RTK) activity could therefore be considered as effective potential antitumor agents. For this purpose, 4-aminoquinazoline derivatives were prepared and evaluated for their ability to inhibit RTK activity and the autophosphorylation of EGF-R. In addition, these compounds were tested on A431 cell growth to estimate their antiproliferative effect. The results showed that the substituent at the 4-position of the quinazoline ring must be an aromatic amine carrying small lipophilic electron-withdrawing groups on the 3- (or 2-) position of the phenyl ring. This aromatic moiety might be far from the quinazoline provided that the linking group is conformationally restricted, such as with piperazine. Hydrophilic and non-aromatic substituents such as morpholine gave completely inactive compounds. Introduction of a bulk at the 2-position of the quinazoline ring in 2,4-diaminoquinazolines or tricyclic compounds led to inactive products. This study reports additional structure-activity relationships of a well-characterized series to develop new inhibitors of EGF-R-associated tyrosine kinase activity.
4.1.4 The synthesis of a novel series of quinazolines substituted at C-4 by five-membered ring aminoheterocycles is reported. Their in vitro structure-activity relationships versus Aurora A and B serine-threonine kinases are discussed. Frédéric H. Jung and Co-workers reported\(^4\) that quinazolines with a substituted aminothiazole at C4 possess potent Aurora A and B inhibitory activity and excellent selectivity against a panel of various serine-threonine and tyrosine kinases, as exemplified by compound 26. They also found that the position and nature of the substituent on the thiazole play key roles in cellular potency. Compounds with an acetanilide substituent at C5 have the greatest cellular activity. The importance of the C5 position for substitution has been rationalized by initio molecular orbital calculations. Results showed that the planar conformation with the sulfur of the thiazole next to the quinazoline N-3 is strongly favored over the other possible planar conformation. Compound 26 is a potent suppressor of the expression of phospho-histone H3 in tumor cells in vitro as well as in vivo, where 26, administered as its phosphate prodrug 27, suppresses the expression of phospho-histone H3 in subcutaneously implanted tumors in nude mice.
4.1.5 Regarding the structure and activity relationship of quinazolines reported in Foye's principles of medicinal chemistry\textsuperscript{5} that prazosin (28), terazosin (29) and doxazosin (30) contain a 4-amino-6,7-dimethoxy quinazoline ring system attached to a piperazine nitrogen. The only structural differences are in the groups attached to the other nitrogen of the piperazine, and the difference in these groups affords dramatic differences in some of the pharmacokinetic properties of these agents. For example when the furan ring of prazosin is reduced to form the tetrahydro furan of terazosin, the compound becomes significantly more hydrophilic. The clinical parameters shows perhaps most significant are the long half-lives and durations of action for terazosin and doxazosin, which permit once a day dosing and generally lead to increased patient compliance (Table I).
Table I

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Therapeutic dose</th>
<th>Half-life hours</th>
<th>Frequency of administration</th>
<th>Bioavailability %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prazosin (28)</td>
<td>Minipres</td>
<td>2-20</td>
<td>2-3</td>
<td>BID-TID</td>
<td>45-65</td>
</tr>
<tr>
<td>Terazosin(29)</td>
<td>Hytrin</td>
<td>1-40</td>
<td>12</td>
<td>QD-BID</td>
<td>90</td>
</tr>
<tr>
<td>Doxazosin(30)</td>
<td>Cardura</td>
<td>1-16</td>
<td>22</td>
<td>QD-BID</td>
<td>65</td>
</tr>
</tbody>
</table>

Our literature survey at this stage reveals that there is dramatic change in the behaviour as well as change in the potency of the quinazoline compounds with hydrophilic groups at different positions. Further our observations on tetrahydro pyrimidine shows that there is formation of mixture of compounds called polyols of tetrahydropyrimidines by the pyrimidine ring having hydroxyethyl group at 3, 5, 6 position of the ring.

4.1.6 Oude Alink and co-workers reported\(^6\) hydroxy ethyl substituted compounds of tetrahydropyrimidine when heated in the presence of Lewis acid such as FeCl\(_3\), AlCl\(_3\), etc polymerized to form a compound having the general structure (95) by the liberation of ammonia (Scheme 3)
The polyols of tetrahydropyrimidines and their respective polymers were found to be useful as corrosion inhibitors, and were used in fluid for drilling wells, in air drilling, used in Brine, acid Systems and as pickling inhibitors.

4.2 Synthesis of 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline & 3,3'-(alkanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline.

Prompted by the above and in view of extending programme of synthesis of octahydroquinazoline we took up the synthesis of octahydroquinazolines with hydrophilic substituents. In continuation of our studies on the synthesis octahydroquinazolines we now wish to report herein a short MW assisted synthesis of 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline and 3,3'-(alkanediyl) bis 1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline bearing 2-hydroxyethyl group in position 1 of quinazoline ring to see the impact of this hydrophilic group incorporated in position 1 on the biological properties of these molecules (Scheme 4)
4.2.1 Results and Discussion

Thus, when a solution of 3-(2-hydroxyethyl) aminocyclohexenone 35a was treated with methylamine and formaldehyde under the influence of microwaves, a product was obtained in 71% yields which was characterized as 1-(2-hydroxyethyl)-3-methyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline 36a on the basis of analytical and spectral data. The reaction of 35a with other primary amines and formaldehyde behaved in a similar manner and octahydroquinazolines 36b-d were isolated in 51-79% yields. The infrared spectra of 36a-d showed strong peaks in the region of 1530 to 1653 cm\(^{-1}\) due to extensively delocalized double bonds and carbonyl groups\(^7\). In the \(^1\)H NMR spectra of 36a-h, the methylene protons at C-7 appeared as multiplets in the range of 1.94-1.98 ppm. The methylene proton adjacent to -OH group resonated 3.60 ppm, the methylene protons at C-2 gave sharp singlet at 4.12 ppm whereas the CH\(_2\) protons in 3d appeared around 5.12 may be due to presence of two hydroxyethyl group at 1 and 3 position of quinazoline ring. The hydroxyl group gave broad singlet near 4.60 ppm which disappears with D\(_2\)O shake. The methyl protons attached to
nitr

gave singlet at 2.40 ppm. The aromatic protons appeared in their usual range. The Reactions of 35b

with formaldehyde and primary amines were subsequently examined under similar conditions and the expected 1-(2-hydroxyethyl)-3-alkyl/aryl/aralkyl/hydroxyethyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36e-h) were isolated in 61-75% yields, whose structures could be established with the help of analytical and spectral data. The infrared spectra of 36e-h showed strong peaks in the region of 1533 to 1600 cm\(^{-1}\). The \(^1\)H NMR spectra of tetrahydropyrimidine rings of 36e-h were found to have a similar pattern as those of 36a-d. However, the six methyl protons at C-7 appeared as sharp singlets around 1.06 ppm whereas in 3f it appeared at 1.01 ppm which may be due to the presence of phenyl group at N-3 position and the CH\(_2\) protons at C-6 and C-8 resonated in ranges of 2.15-2.17 and 2.30-2.40 ppm respectively.

Encouraged by the successful synthesis of octahydroquinazolines 36a-h, we then turned our attention to the synthesis of bis-octahydroquinazolines. Thus, when enaminone 35a was reacted with 1,2-diaminoethane and formaldehyde under the influence of microwaves in methanol, a product 36a was isolated in 65 % yield, the structure of which was established to be 3,3′-(ethanediyl) bis(1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline) based on analytical and spectral data. The reaction was found to be general with other diamines and with corresponding 35a-b to give the respective product 37a-d in 51-79% overall yields. We were thus able to connect two octahydroquinazoline rings through flexible aliphatic chains 37a-d. The structures of which could be established with the help of spectral and analytical data.

The infrared spectra of 37a-d showed strong peaks in the range of 1531-1653 cm\(^{-1}\) due to extensive delocalization of the enaminone moiety and carbonyl group. The \(^1\)H NMR spectra of these bis-quinazolines were found to have the same pattern as in the monomeric octahydroquinazolines except that the signals due to NCH\(_2\) protons of ethylene linkers appeared at 2.74-2.84 ppm while those in butylene appeared in the ranges of 2.54-2.86 ppm. The structure of some quinazolines and bis-quinazolines were further supported by their \(^1\)C mass spectra. The \(^1\)HNMR, Mass and \(^1\)C spectra of few compounds are given in the following pages.
Table Synthesis of 1-(2-hydroxyethyl)-3-alkyl/aryl/alkyl/aryl/3-hydroxyethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36a-h) & 3,3’-(alkanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37a-d).

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>R’/A</th>
<th>Mol.formula</th>
<th>MWI-Power/Time(Sec)</th>
<th>M.P.°C</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>36a</td>
<td>H</td>
<td>-CH₃</td>
<td>C₁₁H₁₈N₂O₂</td>
<td>180watt/180</td>
<td>Gum</td>
<td>71</td>
</tr>
<tr>
<td>36b</td>
<td>H</td>
<td>-C₆H₅</td>
<td>C₁₆H₂₀N₂O₂</td>
<td>180watt/210</td>
<td>Gum</td>
<td>68</td>
</tr>
<tr>
<td>36c</td>
<td>H</td>
<td>-CH₂-C₆H₅</td>
<td>C₁₇H₂₂N₂O₂</td>
<td>180watt/120</td>
<td>Gum</td>
<td>59</td>
</tr>
<tr>
<td>36d</td>
<td>H</td>
<td>-(CH₂)₂-OH</td>
<td>C₁₂H₂₀N₂O₃</td>
<td>180watt/120</td>
<td>90</td>
<td>51</td>
</tr>
<tr>
<td>36e</td>
<td>-CH₃</td>
<td>-CH₃</td>
<td>C₁₃H₂₂N₂O₂</td>
<td>180watt/150</td>
<td>Gum</td>
<td>61</td>
</tr>
<tr>
<td>36f</td>
<td>-CH₃</td>
<td>-C₆H₅</td>
<td>C₁₅H₂₄N₂O₂</td>
<td>180watt/180</td>
<td>68</td>
<td>65</td>
</tr>
<tr>
<td>36g</td>
<td>-CH₃</td>
<td>-CH₂-C₆H₅</td>
<td>C₁₉H₂₆N₂O₂</td>
<td>180watt/210</td>
<td>95</td>
<td>75</td>
</tr>
<tr>
<td>36h</td>
<td>-CH₃</td>
<td>-(CH₂)₂-OH</td>
<td>C₁₄H₂₄N₂O₂</td>
<td>180watt/180</td>
<td>Gum</td>
<td>72</td>
</tr>
<tr>
<td>37a</td>
<td>H</td>
<td>-CH₂-CH₂</td>
<td>C₂₂H₃₄N₄O₄</td>
<td>180watt/180</td>
<td>79</td>
<td>65</td>
</tr>
<tr>
<td>37b</td>
<td>H</td>
<td>-(CH₂)₄</td>
<td>C₂₄H₃₈N₄O₄</td>
<td>180watt/180</td>
<td>88</td>
<td>79</td>
</tr>
<tr>
<td>37c</td>
<td>-CH₃</td>
<td>-CH₂-CH₂</td>
<td>C₂₅H₄₂N₄O₄</td>
<td>180watt/150</td>
<td>Gum</td>
<td>51</td>
</tr>
<tr>
<td>37d</td>
<td>-CH₃</td>
<td>-(CH₂)₄</td>
<td>C₂₅H₄₆N₄O₄</td>
<td>180watt/150</td>
<td>Gum</td>
<td>68</td>
</tr>
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</table>

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4.2.2 Experimental
Melting points were recorded by open capillary method and are uncorrected. The IR spectra were recorded on a Perkin-Elmer-983 spectrometer. $^1$H NMR (90 MHz) spectra were recorded on Varian EM-390 spectrometer. High-resolution $^1$H NMR and $^{13}$C NMR (300MHz) spectra were recorded on Bruker ACF-300 spectrometer. The chemical shift (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to TMS as internal reference. FAB- Mass spectra (MS) were measured on JEOL 3SX 102/DA-6000 using Argon as the FAB gas and m-nitrobenzyl alcohol as the matrix. Elemental analysis was performed on a Vario-EL-III instrument. Microwave irradiation was carried out in CEM Discover Benchmate microwave digester.

4.2.3 General procedure.
Equimolar mixture of 1,3-diketone (34a,b) and ethanolamine was irradiated in microwave at 180 watt, the reaction gets completed in 2-3 minutes monitored by tlc. The reaction mixture died off under reduced pressure in hot to give the enaminone (35) which was used without isolation. A mixture of primary amine (1 mmol) and formaldehyde (2 mmol, 40% aqueous solution) in 1 mL of methanol was stirred for 5 minutes and to this was added a solution of enaminone (35) (1 mmol) in 4 ml methanol in one portion. The resulting reaction mixture was irradiated in a microwave digester for 2-4 minutes at 180 watt. At the end of the reaction (tlc), methanol was distilled off under reduced pressure to give a gum which was purified by using chromatographic column (silica gel, EtOAc) to isolate 36a-h in 51-79 % yields.
4.2.4 Individual description of the compounds

1-(2-hydroxyethyl)-3-methyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36a)

This compound was obtained as reddish brown gum with 71% yield; IR (KBr): 1530, 1653 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.95-1.97 (m, 2H), 2.30 (s, 4H), 2.40 (s, 4H), 2.60 (s, 2H), 3.35-3.42 (m, 4H), 3.65-3.70 (m, 2H), 3.90 (s, 2H), 4.60 (s, 1H); MS: m/z 211.2 (MH\(^+\)). Anal. Calc. for C\(_{11}\)H\(_{18}\)N\(_2\)O\(_2\) (210.14): C, 62.83; H, 8.63; N, 13.32 %

1-(2-hydroxyethyl)-3-phenyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36b)

This compound was obtained as reddish brown gum with 68 % yield; IR (KBr): 1541, 1599 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.96-1.98 (m, 2H), 2.10 (s, 2H), 2.21-2.25 (t, 2H), 2.34 (s, 2H), 3.18 (s, 2H), 3.60 (t, 2H), 4.08 (s, 2H), 4.60 (s, 1H), 6.79-6.94 (m, 3H), 7.18-7.21 (m, 2H); MS: m/z 273 (MH\(^+\)). Anal. Calc. for C\(_{16}\)H\(_{20}\)N\(_2\)O\(_2\) (272.15): C, 70.56; H, 7.40; N, 10.29%

1-(2-hydroxyethyl)-3-benzyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36c)
This compound was obtained as reddish brown gum with 59 % yield; IR (KBr): 1551, 1603 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.95-1.98 (m, 2H), 2.10 (s, 2H), 2.21-2.25 (t, 2H), 2.34 (s, 2H), 3.18 (s, 2H), 3.57-3.60 (m, 4H), 4.08 (s, 2H), 4.60 (s, 1H), 7.23-7.33 (m, 5H); MS: m/z 287 (MH\(^+\)). Anal. Calc. for C\(_{17}\)H\(_{22}\)N\(_2\)O\(_2\) (286.17): C, 71.30; H, 7.74; N, 9.78%  

1-(2-hydroxyethyl)-3-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36d)  

This compound was obtained as brownish solid in 51% yield, m.p 90\(^0\)C; IR (KBr): 1529, 1600 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.94-1.97 (m, 2H), 2.27 (s, 2H), 2.53 (s, 2H), 3.38 (s, 2H), 3.45 (s, 2H), 3.62-3.70 (m, 6H), 4.03 (s, 2H), 5.12 (s, 1H); MS: m/z 241 (MH\(^+\)). Anal. Calc. for C\(_{12}\)H\(_{20}\)N\(_2\)O\(_3\) (240): C, 59.98; H, 8.39; N, 11.66 Found C, 59.84; H, 8.36; N, 11.68%  

1-(2-hydroxyethyl)-3,7,7-trimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36e)
This compound was obtained as brown gum with 61 % yield; IR (KBr): 1541, 1606 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.06 (s, 6H), 2.16 (s, 2H), 2.34 (s, 2H), 2.40 (s, 3H), 3.37-3.39 (m, 4H), 3.66-3.70 (t, 2H), 3.82 (s, 2H), 4.12 (s, 1H); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 192.85, 156.60, 104.14, 70.33, 59.82, 50.70, 49.76, 46.62, 48.61, 40.48, 36.14, 31.24, 27.59; MS: m/z 239.8 (MH\(^+\)). Anal. Calc. for C\(_{13}\)H\(_{22}\)N\(_2\)O\(_2\) (238.17): C, 65.51; H, 9.30; N, 11.75%

1-(2-hydroxyethyl)-3-phenyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36f)

This compound was obtained as yellow solid in 65 % yield, m.p 68\(^0\)C; IR (KBr): 1584, 1599 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.01 (s, 6H), 2.17 (s, 2H), 2.39 (s, 2H), 3.41-3.44 (t, 2H), 3.60-3.63 (t, 2H), 4.13 (s, 1H), 4.61 (s, 1H), 4.65 (s, 2H); \(^{13}\)C NMR (CDCl\(_3\)): 192.85, 156.60, 104.14, 70.33, 59.82, 50.70, 49.76, 48.61, 46.62, 40.48, 36.14, 31.24, 27.59; MS: m/z 301.2 (MH\(^+\)). Anal. Calc. for C\(_{18}\)H\(_{24}\)N\(_2\)O\(_2\) (300.18): C, 71.97; H, 8.05; N, 9.33. Found: C, 71.85; H, 8.00; N, 9.28 %

1-(2-hydroxyethyl)-3-benzyl-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (36g)
This compound was obtained as yellow solid with 75 % yield, m.p 95\(^0\)C; IR (KBr): 1537, 1600 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.06 (s, 6H), 2.15 (s, 2H), 2.35 (s, 2H), 3.29-3.33 (t, 2H), 3.49 (s, 2H), 3.63 (t, 2H), 3.68 (s, 2H), 3.92 (s, 2H), 4.60 (1, 1H), 7.29-7.33 (m, 5H); MS: m/z 315.2 (MH\(^+\)). Anal. Calc. for C\(_{19}\)H\(_{26}\)N\(_2\)O\(_2\): C, 72.58; H, 8.33; N, 8.91. Found: C, 72.75; H, 8.27; N, 8.95 %

1-(2-hydroxyethyl)-3-(2-hydroxyethyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydro-quinazoline (36h)

This compound was obtained as brown gum with 72 % yield; IR (KBr): 1532, 1600 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.06 (s, 6H), 2.15 (s, 2H), 2.65 (t, 2H), 3.39 (s, 2H), 3.48-3.52 (m, 4H), 3.71 (s, 2H), 4.08 (1, 2H), 4.26 (s, 2H); MS: m/z 269 (MH\(^+\)). Anal. Calc. for C\(_{14}\)H\(_{24}\)N\(_2\)O\(_3\): C, 62.66; H, 9.01; N, 10.44%

4.2.5 Synthesis of 3,3'-(alkanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37a-b) and 3,3'- (alkanediyl) bis (1-(2-hydroxyethyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37c-d):

**General procedure**

Equimolar mixture of 1,3-diketone (34a,b) and ethanolamine was irradiated in microwave at 180 watt, the reaction gets completed in 2-3 minutes monitored by tlc.
The reaction mixture died off under reduced pressure in hot to give the enaminone 35. A mixture of diamine (1 mmol) and formaldehyde (4 mmol, 40% aqueous solution) in 1 mL of methanol was stirred for 5 minutes and to this was added a solution of enaminone 35 (2 mmol) in 4 mL methanol in one portion. The resulting reaction mixture was irradiated in a microwave digester for 2-3 minutes at 180 watt. At the end of the reaction (tlc), methanol was distilled off under reduced pressure to give a gum which was purified by using chromatographic column (silica gel, EtOAc) to isolate 37a-d in 51-79 % yields.

4.2.6 Individual description of the compounds

3,3’-(ethanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37a)

This compound was obtained as yellow solid in 65 % yield, m.p 75°C; IR (KBr): 1533, 1584 cm⁻¹; ¹H NMR (CDCl₃) δ 1.94-1.97 (m, 4H), 2.28-2.31 (m, 4H), 2.59-2.61 (t, 4H), 2.74 (s, 4H), 3.41-3.44 (t, 4H), 4.14 (s, 4H), 3.90 (s, 2H), 4.60 (s, 2H); MS: m/z 419.2 (MH⁺). Anal. Calc. for C₂₂H₃₄N₄O₄ (418.53): C, 63.13; H, 8.19; N, 13.39. Found: C, 63.34; H, 8.14; N, 13.33 %

3,3’-(butanediyl) bis (1-(2-hydroxyethyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37b)
This compound was obtained as yellow solid in 79 % yield, m.p 88\(^\circ\)C; IR (KBr): 1531, 1653 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.84-1.87 (m, 4H), 2.02-2.04 (m, 4H), 2.84-2.86 (m, 4H), 2.94-2.96 (t, 4H), 3.47 (s, 4H), 3.95-3.97 (t, 4H), 4.06 (s, 4H), 4.60 (s, 4H); MS: m/z 447.2 (MH\(^{+}\)). Anal. Calc. for C\(_{24}\)H\(_{38}\)N\(_4\)O\(_4\) (446.29): C, 64.55; H, 8.58; N, 12.58. Found: C, 64.39; H, 8.54; N, 12.55 %

3,3’-(ethanediyl) bis (1-(2-hydroxyethyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37c)

This compound was obtained as brown gum in 51 % yield; IR (KBr): 1558, 1600 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.03 (s, 12H), 1.90 (s, 4H), 2.65-2.67 (m, 4H), 2.84 (s, 4H), 2.94-2.96(t, 4H), 3.47(s, 4H), 4.14 (s, 4H), 3.95-3.97 (t, 4H), 4.06 (s, 4H), 4.60(s, 2H); MS: m/z 475(MH\(^{+}\)). Anal. Calc. for C\(_{26}\)H\(_{42}\)N\(_4\)O\(_4\) (418.53): C, 65.79; H, 8.92; N, 11.80%

3,3’-(butanediyl) bis (1-(2-hydroxyethyl)-7,7-dimethyl-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazoline (37d)

This compound was obtained as brown gum in 68 % yield; IR (KBr): 1536, 1606 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.03 (s, 12H), 1.63(s, 4H), 2.12 (s, 4H), 2.28 (s, 4H), 2.54(s,
4H), 3.30-3.32(t, 4H), 3.42 (s, 4H), 3.60-3.62 (t, 4H), 3.94 (s, 4H), 4.60(s, 2H); $^{13}$C NMR (CDCl$_3$): $\delta$ 193.54, 158.02, 103.73, 69.74, 53.14, 51.13, 49.40, 48.99, 39.34, 32.26, 28.62, 24.02; MS: m/z 503.5(MH$^+$). Anal. Calc. for C$_{28}$H$_{46}$N$_4$O$_4$ (418.53): C, 66.90; H, 9.22; N, 11.15%

4.2.7 Conclusion

The present chapter describes an one pot efficient, clean, simple, fast and environment friendly strategy for the synthesis of hitherto unknown octahydroquinazolines and bis- octahydroquinazolines with hydrophillic group at position 1 of the quinazoline ring from easily accessible starting materials in good yields with promising biological properties. The methodology reported herein is an example of multi-component reactions (MCRs).

4.2.8 References


5. Foye's principles of medicinal chemistry By David A. Williams, William O. Foye, Thomas L. Lemke page 306-307
6. O. Alink, A. Bernardus, B. T. Outlaw. USPAT4387074