Chapter-III

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

Introduction

Literature reports have highlighted the fact that many molecular hybrids have been synthesized and some of these compounds have been found to be biologically more active than their monomer counter parts. The following paragraphs describe some of these molecules.

3.1.1: F. Q. He and co-workers have reported the synthesis of bis-heterocyclic pyrroldiazole derivatives containing pyrazole (1 and 2). Some of these compounds exhibited certain herbicidal activities against barnyard grass and rape.

\[
\text{1: } R_1 = \text{H, NO}_2 \quad R_2 = \text{Ph, CH}_3 \quad R_3 = \text{H, 2,4-Cl}_2, 2\text{-F, 4-(Cl, Br, CH}_3, \text{OMe)} \\
\text{2: } R_1 = \text{H, NO}_2 \quad R_2 = \text{Ph, CH}_3 \quad R_3 = \text{2-F, 2,4-Cl}_2 \\
\]

3.1.2 S.C. Jain and co-workers have reported the synthesis of some unsymmetrical bis-indol-2, 3-dione (3), which was further used for the synthesis of bis-spiroindoles (4).
3.1.3a Henry and Thomson reported that condensation of 2 mmols of an alkylene polyamine having at least one primary amino group separated from another primary or secondary amino group by 3 carbon atoms with one mole of dicarboxylic preferably at 350°F to 400°F to give tetrahydropyrimidine derivative of the structure (5) given below. The water molecules formed are removed azeotropically using benzene, toluene or xylene.

\[
\text{R, R_1} = \text{CH}_3, \text{H or F}
\]

R: hydrocarbon radical containing at least 2 carbon atoms.
R': hydrogen, a hydrocarbon or a substituted hydrocarbon radical.
3.1.3b For example, the condensation of two moles of 3,3'-imino-bis-propylamine (6) with 1 mole of succinic acid (7) gave the corresponding bis-tetrahydropyrimidine (8) whose IUPAC name was 3,3'-(2,2'-(ethane-1,2-diyl)bis(5,6-dihydropyrimidine-2,1(4H)-diyl))dipropan-1-amine (Scheme 1).

![Scheme 1]

Further the compound 8 when reacted with carboxylic acid (9) (for e.g. 2mols of propionic acid) gave the product having amide linkage. (10) (Scheme 2).

![Scheme 2]

These bis tetrahydropyrimidines (8, 10) were used for stabilizing hydrocarbon distillate (for example, fuel oil, burner oil, range oil, diesel oil, marine oil, slushing oil, turbine oil) by preventing sediment formation (or dispersing them when formed), preventing discoloration, oxidation inhibitor, rust or corrosion preventative, and detergent properties. In lubricating oil the additive may function as pour point depression, viscosity index improver, antifoaming agent, oil ness additive etc. In gasoline, naphtha, aromatic solvents, kerosene, jet fuel etc it acts as corrosion inhibitor along with above mentioned properties.

3.1.4 P.S.N. Reddy and co-workers have reported the synthesis of bis-heterocycles of the type (11) and (12).
3.1.5 J.W. Lown and co-workers have reported the synthesis of bi-functional DNA alkylating C₂-linked pyrrolo [2, 1-c][1, 4] benzodiazepines (13). These were synthesized in order to probe DNA cross-linking efficiency and structural requirements for the optimum interstrand cross-linking as well as cytotoxicity.

3.1.6 1,4,5,6-tetrahydropyrimidinyl substituted compounds were also found to be useful as ash-less bases and rust inhibitors, these bis or tris THP are prepared by reacting a C₃ to C₅₀ amine containing 1,3-diaminopropane (15) group with ethylenediaminetetraacetic acid (EDTA)(14) or nitrilotriacetic acid (17) at a temperature of 150°C to 250°C for 10 to 100 hours (Scheme 3).
Scheme 3

3.2 Synthesis of enaminones

Enaminones are potential intermediates for the synthesis of a variety of heterocyclic systems like oxazoles, quinolines, dibenzodiazepines, tetrahydrobenzoxazines, tetronic acids, tetrahydrophenanthridines, pyranones, pyridine derivatives etc.

3.2.1 Unlike enamines, which have been reported to be unstable in aqueous solutions, enaminones, obtained from β-dicarbonyl compounds are quite stable and have been employed as prodrugs with variable results. For example, acetyl acetone has been used to prepare a prodrug of Cycloserine. Cycloserine (19) is known to be unstable and has a tendency to form a dimer (20) as shown Scheme 1. Preventing the formation of dimer would increase the stability both on the shelf and in physiological media.
Since the formation of the dimer (20) requires a reaction of the amino group of cycloserine, functionalization of this amino group was the easiest and most direct approach to retarding the dimer formation. Stirring a mixture of cycloserine and acetylacetone for 2 days gave (R)-4-[(1-methyl-3-oxo-1-butenyl)-amino]-3-isoxazolidinone (21), which was the condensation product of cycloserine and acetylacetone and was found to be an efficacious prodrug of increased stability under aqueous conditions.

3.2.2 There are also reports of the potential use of enaminones for biological purpose, Scheone and coworkers\textsuperscript{17} have prepared several enaminones and evaluated them for hypoglycaemic effectiveness, but their compounds gave poor activity.

3.2.3 A number of synthetic strategies for the synthesis of enaminones are known in the literature. A few recent methods are discussed in the following sections. The reaction of \(\alpha\)-metallated amines with esters under mild conditions leads to the formation of enaminoketones (also called unsymmetrical diketones)
When imine anions 23 prepared from imines (22) (Scheme 5, by standard method) is allowed to react with esters at 0°C in THF for 30 minutes, enaminoketones (24) were obtained. A twofold excess of base is required for the reaction to go to completion indicating that a second equivalent of lithium derivative preferentially metallates the imine nitrogen atom of compound 24 as soon as it forms. The anionic form of 24 prevents it from further nucleophilic attack by the imine anions.

3.2.4 β-amino-α,β unsaturated ketones (28) (β-acylenamines) were obtained in a manich reaction by heating a mixture of ketone (25), triethylorthoformate (26), and secondary amine (27) in a pressure vessel. Triethylorthoacetate can also be used with good results, but the method failed with symmetrical ketones like acetone and cyclohexanone. Coupling constant $J_{CH=CH}$ (12Hz) suggests the trans configuration (Scheme 6).

3.2.5 When N-1-(2, 2'-dichloro-1-phenylpropylidene) aniline (29) was treated with 2N sodium methoxide in MeOH and refluxed for overnight and the reaction mixture
was hydrolysed with excess of aqueous 2N HCl for overnight, the etheral extract
gave after evaporation, an oil from which a yellow solid material precipitated on
standing. The filtrate contained two compounds, namely, 2-methoxy-1-phenyl-2-
propen-1-one (30) and 1-phenyl-1, 2-propane dione (31). The solid product was
identified as 3-anilino-1-phenyl-2-propen-1-one (32) (Scheme 7).

![Scheme 7](image)

The structure elucidation of enaminoketone (32) was supported by the synthesis of
the authentic materials.

3.2.6 Reaction of ethyl formate and acetophenone with sodium ethoxide in ethereal
medium gave the sodium salt of benzoylacetaldehyde, which was condensed with
aniline hydrochloride (and p-anisidine hydrochloride) to yield β ketoenamines (32),
an additional confirmation of the formation of (32) was the conversion of (32) into
1,5-diphenylpyrazole by reacting with phenyl hydrazine (33) (Scheme 8).

![Scheme 8](image)

In order to prepare bis quinazolines of our interest we needed the starting material
bis-enaminones, which we easily prepared by following our previous strategy.
Microwave assisted organic reactions have blossomed into an important tool; with a variety of applications, particularly after the development of Microwave-induced Organic Reaction Enhancement (MORE) chemistry techniques\textsuperscript{21-22}. These techniques require open vessels with little or no solvent and are free of the risk of explosion. MORE chemistry reaction lead to extremely faster, cleaner than conventional reaction and lead to higher atom economy (less chemical waste). Because of short time requirement, ease of workability and eco-friendliness, microwaves provide an alternative to environmentally unacceptable procedures using toxic and expensive reagents\textsuperscript{23}.

3.2.7 Li Jiarong and co-workers in continuation to their previous research of cyclocondensation of aromatic \textit{o}-aminonitriles with ketones under the catalysis of ZnCl\textsubscript{2}, a new conversion to form 1,2-dihydroquinazoline-4(3\textit{H})-one derivatives was found coexisting with the normal Friedlalinder-type quinoline annulation\textsuperscript{25}. Thus, they thought similar 1,2-dihydroquinazoline-4(3\textit{H})-ones could be afforded by the reaction of \textit{o}-aminonitriles with aromatic aldehydes through this conversion. To their surprise, the reaction of 2-aminobenzonitrile with terephthalaldehyde in the sealed reactor under the catalyst of ZnCl\textsubscript{2} (0.1 mol \%) at 200 °C afforded a white product instead of the expected symmetrical bisdihydroquinazolin-4(3\textit{H})-one and this product was characterized as quinazoline-2,4(1\textit{H},3\textit{H})-dione \textsuperscript{26} on the basis of its spectra and analytical data. Moreover, its structure was further confirmed by X-ray crystallographic diffraction and compared with the authentic sample. In fact, the reactant, terephthalaldehyde, could be completely recovered from the reaction mixture. Thus, they speculated DMF was involved in the reaction. To their delight, 33 were obtained as the only product with the same reaction in the absence of terephthalaldehyde (Scheme 9). To obtain the optimal reaction conditions, a variety of catalysts were first investigated for detecting the catalytic activities of different metal ions for the product of 33. The data indicated that ZnCl\textsubscript{2} is the most effective.
3.3 Synthesis of bis-enaminones:
Bis enaminones (35a,b) prepared by the reported procedures as two equivalent of 1,3-cyclohexandione/ 3,3-dimethyl-1,3-cyclohexandione mixed with one equivalent of diamines irradiated in microwave digester at 180 watt for 2-3 minutes to give a deep brown viscous mass, immediately applied pump to remove the water formed then cooled on trituration with methanol it gives light yellowish solid mass of desired bis-enaminone (35a,b) and are filtered off and were used as synthons for the construction of bis quinazolines (Scheme 10)
3.3.1 Results and Discussion

Thus, when a mixture of 1,3-cyclohexanedione (34a) and diamine (2:1) was irradiated in a microwave digester for 2 min, work-up of the reaction mixture yielded the desired condensation product 35c-e in 75-85% yield, which was characterized on the basis of analytical and spectral data. Condensation of dimedone (34b) with diamines could be achieved under similar conditions giving 35f-h in 85-91% overall yields. The reaction of dimedone with ethylene went to completion when a mixture (2:1) of the two was subjected to microwave irradiation. In conclusion, we have demonstrated a practical application of microwave assisted, solvent-free condensation of cyclic ketones with diamines in microwave digester in very good to excellent yields.

3.3.2 General procedure.

A mixture of 1, 3-diketone (2 mmole) and diamine (1 mmole) in a 10 ml conical flask placed in a beaker was irradiated in a microwave digester. After the completion of the reaction (monitored by TLC), water formed during the reaction was distilled under reduced pressure to give a solid mass, which was triturated with methanol, filtered and then recrystallized from appropriate amount of methanol to give the bis-enaminones 35c-h. The products were identified by IR and NMR spectroscopy and also by comparing their melting points with those of the authentic products.

The description of individual bis-enaminones given below

3,3'- (ethane-1,2-diyl bise (azandiyl) bis (cyclohexan-2-enone) (35c)

This compound was obtained as pale yellow solid in 85% yield; mp 178 °C; IR (KBr): 1533, 1600, 3257, 3245 cm⁻¹; ¹H NMR (CDCl₃): δ 1.26-1.30 (m, 6H), 3.02-
3.04 (m, 4H), 3.56-3.61 (m, 8H), 5.40 (s, 2H); MS: m/z 249.4 (MH⁺). Anal. Calcd.

3,3'-((propane-1,3-diyl bis(azandiyl) bis (cyclohexan-2-enone) (35c))

This compound was obtained as pale yellow solid in 78% yield; mp 145 °C; IR
(KBr): 1537, 1560, 3257, 3244 cm⁻¹; ¹H NMR (CDCl₃): δ 1.54-1.67 (m, 6H), 2.84-
2.89 (m, 4H), 3.14-3.18 (m, 4H), 3.56-3.61 (m, 6H), 5.40 (s, 2H); MS: m/z
263.5(MH⁺). Anal. Calcd. for C₁₅H₂₂N₂O₂ (262.35): C, 68.67; H, 8.45; N, 10.68.

3,3'-((butane-1,4-diyl bis (azandiyl) bis (cyclohexan-2-enone) (35e))

This compound was obtained as pale yellow solid in 75% yield; mp 202 °C; IR
(KBr): 1531, 1566, 3247, 3243 cm⁻¹; ¹H NMR (CDCl₃): δ 1.26-1.28 (m, 4H), 1.30-
1.32 (m, 4H), 3.02-3.08 (m, 6H), 3.56-3.61 (m, 6H), 5.40 (s, 2H); MS: m/z

3,3'-((ethane-1,2-diyl bis (azandiyl) bis (-5,5-dimethylcyclohexan-2-enone) (35f))

This compound was obtained as pale yellow solid in 91% yield; mp 153 °C; IR
(KBr): 1541, 1593, 3257, 3445 cm⁻¹; ¹H NMR (CDCl₃): δ 1.01-1.08 (m, 14H), 2.24
(s, 4H), 2.50-2.55 (m, 4H) 3.56 (s, 4H), 5.46(s, 2H); MS: m/z 305.9 (MH⁺). Anal.
Calcd. for C₁₈H₂₈N₂O₂ (304.22): C, 71.02; H, 9.27; N, 9.20.
3, 3'-(propane-1,3-diyl bis(azandiyl) bis (-5,5-dimethylcyclohexan-2-enone) (35g)

This compound was obtained as pale yellow solid in 82% yield; mp 173 °C; IR (KBr): 1545, 1600, 3276, 3456, cm⁻¹; ¹H NMR (CDCl₃): δ 1.34-1.42 (m, 12H), 1.26 (s, 4H), 2.24 (s, 4H), 2.50 (s, 4H), 3.56 (s, 4H), 5.45 (s, 2H); MS: m/z 319.3(MH⁺). Anal. Calcd. for C₁₉H₃₀N₂O₂ (318.23): C, 71.66; H, 9.50; N, 8.80.

3,3'- (butane-1,4-diyl bis(azandiyl) bis (-5,5-dimethylcyclohexan-2-enone) (35h)

This compound was obtained as pale yellow solid in 85% yield; mp 168 °C; IR (KBr): 1537, 1560, 3331, 3343 cm⁻¹; ¹H NMR (CDCl₃): δ 1.01-1.04 (m, 12H), 1.26-1.28 (m, 4H), 3.02-3.04 (m, 8H), 3.52 (s, 4H), 5.40 (s, 2H); MS: m/z 333.6 (MH⁺). Anal. Calcd. for C₂₀H₃₂N₂O₂ (332.25): C, 72.25; H, 9.70; N, 8.43.

3.4: Synthesis of bis quinazolines:

Our literature survey has revealed that Bis-quinazolines compounds are a relatively new and important in the field of research for finding new biologically active molecules. Recent reports have revealed that bis-quinazolines compounds possess pesticidal properties and also antibacterial, antimalarial, antiproliferative and antitumor activities. Envisaging that the presence of two quinazoline ring in the same molecule connected by flexible aliphatic chain at 1,1' position could enhance the activity of the molecule. Bis-enaminones were reacted with formaldehyde and various diamines and the result of which are discussed herein.
3.4.1 Anjani K. Tiwari and co-workers reported the synthesis of bis quinazoline of the type (38) by condensation of 2-phenyl-4(3H)-quinazolone and 2-aryl-3-amino-4(3H)-quinazolones (37) in presence of anhydrous ZnCl₂ catalyst where they have connected the two quinazoline rings at 4 and 3 positions through secondary amine linkage. The brief procedure is given below.

**Synthesis of 3-(0-phenyl-quinazolin-4-yl-amino)-2-(phenyl/styryl/benzamidomethyl/phthalimidomethyl)-4(3H)-quinazolones (38a-d)**

The target compounds (38a-d) were synthesized by heating equimolar quantities of 2-phenyl-4(3H)-quinazolone and 2-aryl-3-amino-4(3H)-quinazolone (37) containing anhydrous zinc chloride (1.0 g) at 130 to 140 °C for 4 h. During heating, the contents were stirred occasionally. Subsequently, the hot melt was cooled to room temperature, treated with diluted hydrochloric acid (w100 ml) and then stirred vigorously. The solid was filtered off and washed with cold water. After removing water, it was dissolved in ethanol and treated by charcoal. The solvent was evaporated in vacuo and the crystalline product was washed with ethanol and dried (Scheme 11).

**Scheme 11**
The bis-quinazoline derivatives so prepared found to be active against many bacterial and fungal strains.

3.4.2 G. Grover and co-workers in the process of synthesis of biheterocycles carrying the biodynamic heterocyclic systems at position 3, a series of new nalidixic acid derivatives having quinazolones moiety were synthesised to achieve enhanced biological activity and wide spectrum of activity. Nalidixic Acid was first converted into its acid chloride using thionyl chloride as an acylating agent at laboratory temperature later it was converted to methyl ester. Nalidinoxyl chloride formed vigorously reacts with methanol to give a methyl ester of nalidixic acid. The ester on addition of hydrazine hydrate furnished nalidixic acid hydrazide. Appropriate anthranilic acid was refluxed with acetic anhydride to form Benzoxazine/Acetanthranil. 5-iodo-derivative of anthranilic acid was prepared and also utilised to obtain 6-iodo-benzoxazine/Acetanthranil. Also, 6-nitro benzoxazine/Acetanthranil was obtained by nitrations of acetanthranil using conc. H$_2$SO$_4$ and fuming HNO$_3$. Equimolar proportions of the appropriate synthesised acetanthranils and nalidixic acid hydrazide in the presence of ethanol were refluxed to synthesise quinazolones. Elemental analysis and IR spectra confirmed nalidixic acid hydrazide formation. The structures of the compounds obtained have been established on the basis of Spectral (IR, $^1$H NMR and mass) data. The current study also involves in vitro antimicrobial screening (using Agar dilution and Punchwell diffusion method) of synthesised quinazolone derivatives bearing nalidixic acid moiety on randomly collected microbial strains. The derivatives 39a, b & d showed marked inhibitory activity against enteric pathogen like Aeromonas hydrophila, a causative agent of diarrhoea in both children as well as adults. Among the respiratory pathogens included in study, derivative d was found to be active against Streptococcus pyogenes. No significant inhibitory activity was seen by any of synthesised derivatives against Coagulase negative Staphylococcus. Derivative 39a was found to show very high activity against the Candida colonies and derivative 39d was also found to exhibit inhibitory activity against Candida albicans; a normal flora of the human body which plays an important role in causing opportunistic infections in immunocompromised hosts.
Proteus vulgaris, a gram-negative bacteria included in our study was found to be inhibited by derivative 39b.

\[
\begin{align*}
\text{Scheme 12}
\end{align*}
\]
3.4.3 Synthesis of 1,1'-(alkanediyl) bis (3-alkylaryl/arylalkyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines (40a-r).

Prompted by the above observation and in continuation with our on-going programme on the development of novel synthetic strategies for bis-octahydroquinazolines, we undertook the present investigation to synthesis bis-octahydroquinazolines in which we have connected two quinazoline moiety at 1,1' position unlike previous chapter where we connected two quinazoline ring at 3,3' position and the results of our studies are reported herein (Scheme 12).

Scheme 12
3.4.4: Results and Discussion

Thus, when 3,3’-(ethane-1,2-diyl bis (azandiyl) bis (cyclohexan-2-enone) 35a was treated with methylamine and formaldehyde refluxed in methanol, a product was obtained in 61 % yields which was characterized as 1,1’-(ethane-1,2-diyl) bis-5-oxo-3-methyl-1,2,3,4,5,6,7,8-octahydroquinazoline 40a on the basis of analytical and spectral data. The reaction of 35 with other primary amines and formaldehyde behaved in a similar manner and bis-octahydroquinazolines 40b-r were isolated in 52-73% yields. The infrared spectra of 40a-r showed strong peaks in the region of 1553 to 1653 cm\(^{-1}\) due to extensively delocalized double bonds and carbonyl groups. In the \(^1\)H NMR spectra of 40a-h, the methylene protons at C-7 appeared as multiplets near 1.89-1.96 ppm except in 40e and 40f where they appeared in the vicinity of 1.01-1.18 ppm. The methyl protons at C-7 for 40i-r gave sharp singlets around 1.05 ppm. Methylene protons at C-2 for 40i-r resonated at higher \(\delta\) value than the corresponding 40a-h which may be due to presence of electronic donating methyl groups at C-7 in 40i-r. The CH\(_2\) protons at C-8 resonate close to 2.3 ppm except in 40f and 40h where they were found to resonate near 1.88 ppm and 1.95 ppm respectively. The rest methylene protons in the quinazoline ring resonated in the region of 3-4 ppm respectively, the aromatic protons appeared in the usual region. The \(^13\)C spectra of the molecules showed a sharp signal near 193 ppm due to the carbonyl carbon, the sp\(^2\) hybridised carbon of quinazoline ring along with that of benzene gave signal in the region of 102-156 ppm. The aliphatic carbons appeared in their usual range in the \(^13\)C spectrum further all the compounds were verified by their mass spectrum.
Table: Synthesis of 1,1'-(alkanediyl) bis (3-alkyl/aryl/aralkyl)-5-oxo-1,2,3,4,5,6,7,8-octahydroquinazolines (3a-r).

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<th>A</th>
<th>R'</th>
<th>Reflux (hrs)</th>
<th>M.P. °C</th>
<th>Yield %</th>
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The ¹H NMR, ¹³C and Mass Spectra of a starting material and few compounds along with the structures are given in the following pages.
Mol. mass = 304
Mol. mass = 580
3.4.5 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. Bis-enaminones 35a-f were synthesized by condensation of diketone (34a, 34b) with diamines (2:1) in microwave at 180 watt in 2-4 minutes. Due to less solubility of the bis-enaminones in methanol and other solvents at room temperature the bis-quinazolines were synthesized by refluxing in methanol at 65°C.

General procedure A mixture of primary amine (2 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 bis-enaminone 35 (1 mmol) in 4 mL methanol in one portion. The resulting reaction mixture was refluxed at 65°C for 7-15 hours. 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 40a-r in 51-73 % yields. (Scheme 12)

3.4.6 Description of the individual compounds:

1,1’-(ethane-1,2-diyl) bis-5-oxo-3-methyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40a)
This compound was obtained as light brown gum in 61% yield: IR (KBr): 1552, 1609 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.96-2.02 (m, 4H), 2.31-2.45 (m, 14H), 3.38 (s, 8H), 3.83 (s, 4H); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 21.46, 25.57, 35.63, 41.47, 41.70, 47.99, 50.28, 105.90, 157.10, 193.89; MS: m/z 359.2 (MH\(^+\)). Anal. Calc. for C\(_{20}\)H\(_{30}\)N\(_4\)O\(_2\) (358.24): C, 67.01; H, 8.44; N, 15.63%.

1,1\'-(ethane-1,2-diyl) \(3\)-phenyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40b)

This compound was obtained as yellow solid in 57% yield, m.p 106\(^\circ\)C: IR (KBr): 1557, 1603 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.86-1.89 (m, 4H), 2.29-2.32 (t, 4H, J=6.4Hz), 3.20-3.24 (m, 4H), 4.04-4.08 (m, 4H), 4.45-4.54 (m, 4H), 4.84-4.89 (m, 4H), 6.84-7.02 (m, 6H), 7.19-7.28 (m, 4H); MS: m/z 483.4 (MH\(^+\)). Anal. Calc. for C\(_{30}\)H\(_{34}\)N\(_4\)O\(_2\) (482.27): C, 74.66; H, 7.10; N, 11.61. Found: C, 74.51; H, 7.06; N, 11.63 %

1,1\'-(ethane-1,2-diyl) \(3\)-benzyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40c)
This compound was obtained as yellow solid in 52% yield, m.p 115°C: IR (KBr): 1554, 1653 cm⁻¹; ¹H NMR (CDCl₃): δ 1.89-1.92 (m, 4H), 2.24-2.32 (m, 8H), 3.11 (s, 4H), 3.50 (s, 4H), 3.60 (s, 4H), 3.70 (s, 4H), 7.26-7.34 (m, 10H); MS: m/z 511.8 (MH⁺). Anal. Calc. for C₃₂H₃₈N₄O₂ (510.30): C, 75.26; H, 7.50; N, 10.97. Found: C, 75.35; H, 7.54; N, 10.90 %

1,1'-(propane-1,3-diyl) bis-5-oxo-3-methyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40d)

![Chemical Structure](image)

This compound was obtained as pale yellow gum in 56 % yield: IR (KBr): 1553, 1600 cm⁻¹; ¹H NMR (CDCl₃): δ 1.93-1.98 (m, 6H), 2.38-2.40 (m, 4H), 2.45-2.56 (m, 4H), 3.86-3.91 (m, 4H), 4.24 (s, 4H); ¹³C NMR (CDCl₃): δ 21.17, 25.14, 35.38, 39.08, 39.29, 39.50, 39.71, 39.92, 40.13, 40.34, 41.27, 45.91, 49.87, 157.86, 193.06; MS: m/z 373.1 (MH⁺). Anal. Calc. for C₂₁H₃₂N₄O₂ (372.25): C, 75.71; H, 8.66; N, 15.04%.

1,1'-(propane-1,3-diyl) bis-5-oxo-3-phenyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40e)
This compound was obtained as brown gum in 58% yield: IR (KBr): 1573, 1653 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.03-1.09 (m, 4H), 1.14-1.25 (m, 2H), 2.12-2.20 (m, 8H), 3.15-3.18 (m, 4H), 4.11 (s, 4H), 4.47 (s, 4H), 6.89-6.93 (m, 6H), 7.23-7.26 (s, 4H); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 28.14, 29.19, 31.75, 38.82, 44.73, 45.63, 48.78, 67.53, 103.88, 117.17, 120.70, 128.70, 128.85, 147.96, 156.83, 192.64; MS: m/z 497.5 (MH\(^+\)).

Anal. Calc. for C\(_{31}\)H\(_{36}\)N\(_4\)O\(_2\) (496.28): C, 74.97; H, 7.31; N, 11.28%

1,1'-(propane-1,3-diyl) bis-5-oxo-3-benzyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40f)

This compound was obtained as yellow gum in 56% yield: IR (KBr): 1560, 1603 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.01-1.18 (m, 4H), 1.54-1.57 (m, 2H), 2.08-2.15 (m, 8H), 3.48-3.83 (m, 12H), 7.24 (s, 10H); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 21.42, 25.47, 28.93, 35.62, 46.15, 48.93, 57.90, 67.97, 104.97, 127.58, 128.49, 128.94, 129.18, 137.52, 158.08,
193.75; MS: m/z 525.6 (MH\(^+\)). Anal. Calc. for C\(_{33}\)H\(_{40}\)N\(_4\)O\(_2\) (524.32): C, 75.54; H, 7.68; N, 10.68 %

1,1′-(butane-1,4-diyl) bis-5-oxo-3-methyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40g)

This compound was obtained as yellow gum in 73 % yield: IR (KBr): 1560, 1602 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.89-1.96 (m, 8H), 2.43 (s, 6H) 2.80-2.85 (m, 4H), 2.87-2.99 (m, 4H), 3.79-3.83 (m, 4H), 4.31 (s, 4H), 4.84 (s, 4H); MS: m/z 387.1 (MH\(^+\)). Anal. Calc. for C\(_{22}\)H\(_{34}\)N\(_4\)O\(_2\) (386.53): C, 68.36; H, 8.87; N, 14.49 %

1,1′-(butane-1,4-diyl) bis-5-oxo-3-phenyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40h)

This compound was obtained as yellow gum in 65 % yield: IR (KBr): 1545, 1613 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.32-1.36 (m, 4H), 1.62-1.68(m, 4H), 2.23-2.40(m, 4H)
2.73-2.75 (m, 4H), 3.03(s, 4H), 3.79(s, 4H), 4.31 (s, 4H), 6.94-7.27(m, 10H); MS: m/z 511.6 (MH^+). Anal. Calc. for C_{32}H_{38}N_{40} (510.32): C, 75.26; H, 7.50; N, 10.97%

1,1'-((butane-1,4-diyl) bis-5-oxo-3-benzyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40i)

This compound was obtained as yellow gum in 71 % yield: IR (KBr): 1527, 1606 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.26-1.30 (m, 4H), 1.88-1.99 (m, 4H) 2.23-2.42 (m, 8H), 3.03 (s, 4H), 3.50 (s, 4H), 3.57 (s,4H), 3.74 (s,4H), 7.19-7.24 (m,10H); MS: m/z 539.1 (MH^+). Anal. Calc. for C\(_{34}\)H\(_{42}\)N\(_{42}\) (538.33): C, 75.80; H, 7.86; N, 10.40%

1,1'-((ethane-1,2-diyl) bis-5-oxo-3,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40j)

This compound was obtained as yellow gum in 53 % yield: IR (KBr): 1557, 1608 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.07(s, 12H), 2.28(s, 4H), 2.39(s, 4H), 3.36-3.42(m, 10H),
3.84(s, 4H), 5.30(s, 4H); $^{13}$C NMR (CDCl$_3$): $\delta$ 28.79, 32.23, 39.50, 41.42, 41.69, 48.04, 49.26, 53.43, 53.43, 71.46, 104.53, 155.44, 193.47; MS: m/z 415.4 (MH$^+$).

Anal. Calc. for C$_{24}$H$_{38}$N$_4$O$_2$ (414.3): C, 69.53; H, 9.24; N, 13.51%

1,1'-((ethane-1,2-diyl) bis-5-oxo-7,7-dimethyl-3-phenyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40k)

![Chemical Structure]

This compound was obtained as yellow solid in 61 % yield, m.p 245°C; IR (KBr): 1578, 1597 cm$^{-1}$; $^1$H NMR (CDCl$_3$): $\delta$ 1.05 (s, 12H), 1.87 (s, 4H), 2.12-2.24 m, 4H), 2.59 (s, 4H), 5.06 (s, 4H), 5.42 (s, 4H), 7.05 (s, 4H), 7.73 (s, 6H); MS: m/z 539.1 (MH$^+$). Anal. Calc. for C$_{34}$H$_{42}$N$_4$O$_2$ (538.33): C, 75.80; H, 7.86; N, 10.40. Found: C, 75.93; H, 7.80; N, 10.46 %

1,1'-((ethane-1,2-diyl) bis-5-oxo-3-benzyl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40l)
This compound was obtained as yellow solid in 71% yield, m.p. 205°C; IR (KBr): 1557, 1606 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.07 (s, 12H), 2.17 (s, 4H), 2.59–2.88 (m, 8H), 3.16 (s, 4H), 3.51 (s, 4H), 3.82 (s, 4H), 5.33 (s, 4H), 7.02–7.30 (m, 10H); \(^1^3\)C NMR (CDCl\(_3\)): \(\delta\) 28.27, 31.61, 38.75, 39.12, 39.33, 39.53, 39.74, 39.95, 47.49, 47.77, 47.84, 57.15, 68.14, 127.06, 127.96, 128.32, 136.91, 192.72; MS: m/z 567.5 (MH\(^+\)). Anal. Calc. for C\(_{36}\)H\(_{46}\)N\(_4\)O\(_2\) (566.36): C, 76.29; H, 8.18; N, 9.89. Found: C, 76.15; H, 8.13; N, 9.86%.

\(1,1'\)-(propane-1,3-diyl) \(1\)-bis-5-oxo-3,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40m)

This compound was obtained as yellow solid in 73% yield, m.p. 186°C; IR (KBr): 1533, 1578 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.07–1.61 (s, 18H), 1.88–1.91 (s, 4H), 2.20–2.21 (m, 4H), 3.21 (s, 6H), 3.49–3.52 (m, 4H), 5.15 (s, 4H); MS: m/z 529.9 (MH\(^+\)).
Anal. Calc. for $C_{25}H_{40}N_4O_2$ (428.32): C, 70.06; H, 9.41; N, 13.07. Found C, 70.21; H, 9.43; N, 13.02 %

1,1’-(propane-1,3-diyl) bis-5-oxo-7,7-dimethyl-3-phenyl-1,2,3,4,5,6,7,8-octahydro-quinazoline (40n)

This compound was obtained as light brown gum in 58 % yield; IR (KBr): 1560, 1599 cm$^{-1}$; $^1$H NMR (CDCl$_3$): δ 1.07 (s, 12H), 1.18 (s, 4H), 2.06-2.21 (m, 6H), 3.09-3.13 (m, 4H), 4.04 (s, 4H), 4.57 (s, 4H), 6.84-6.86 (m, 6H), 7.16-7.20 (m, 4H); $^{13}$C NMR (CDCl$_3$): δ 28.59, 29.36, 29.54, 29.70, 30.96, 31.93, 32.27, 39.33, 45.13, 46.19, 48.71, 68.18, 104.19, 117.72, 121.40, 129.40, 148.29, 158.38, 192.89; MS: m/z 553.6 (MH$^+$). Anal. Calc. for $C_{35}H_{44}N_4O_2$ (552.35): C, 76.05; H, 8.02; N, 10.14 %

1,1’-(propane-1,3-diyl) bis-5-oxo-3-benzyl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydro-quinazoline (40o)
This compound was obtained as light brown gum in 65% yield; IR (KBr): 1560, 1599 cm⁻¹; ¹H NMR (CDCl₃): δ 1.07 (s, 12H), 1.24 (s, 4H), 1.56-1.59 (t, 2H J=6.8Hz), 2.15 (s, 4H), 3.05-3.09 (m, 4H), 3.50-3.63 (m, 8H), 3.79 (s, 4H), 7.29 (s, 10H); ¹³C NMR (CDCl₃): δ 28.33, 29.19, 29.29, 31.69, 31.75, 38.66, 38.83, 45.65, 47.91, 48.83, 57.21, 67.79, 102.94, 127.10, 127.99, 128.48, 137.09, 155.70, 192.70; MS: m/z 581.6 (MH⁺). Anal. Calc. for C₃₁H₄₄N₄O₂ (580.38): C, 76.51; H, 8.33; N, 9.65%

1,1′-(butane-1,4-diyl) bis-5-oxo-7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40p)

This compound was obtained as light brown solid in 70% yield, m.p 140°C; IR (KBr): 1557, 1603 cm⁻¹; ¹H NMR (CDCl₃): δ 1.08 (s, 12H), 1.57 (s, 4H), 2.40 (s, 6H), 3.24 (s, 4H), 3.44 (s, 4H), 3.87 (s, 4H); ¹³C NMR (CDCl₃): δ 26.92, 28.79, 30.94, 32.23, 39.30, 41.50, 48.49, 49.26, 49.83, 70.83, 102.82, 155.97; MS: m/z 443.6 (MH⁺). Anal. Calc. for C₂₆H₄₂N₄O₂ (442.3): C, 70.55; H, 9.56; N, 12.66. Found: C, 70.41; H, 9.51; N, 12.70%

1,1′-(butane-1,4-diyl)bis-5-oxo-7,7-dimethyl-3-phenyl-1,2,3,4,5,6,7,8-octahydroquinazoline (40q)
This compound was obtained as light brown gum in 57 % yield; IR (KBr): 1559, 1600 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.01 (s, 12H), 1.95-2.29 (m, 8H), 3.01-3.18 (m, 8H), 4.08 (s, 4H), 4.45 (s, 4H), 6.81-6.96 (m, 6H), 7.15-7.29 (m, 4H); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 27.92, 28.35, 29.16, 30.94, 31.84, 39.21, 45.15, 48.15, 49.31, 67.80, 117.69, 120.75, 129.44, 148.60, 157.59, 192.91; MS: m/z 566.8 (M\(^+\)). Anal. Calc. for C\(_{36}\)H\(_{46}\)N\(_4\)O\(_2\) (566.78): C, 76.29; H, 8.18; N, 9.89%

1,1'-/(butane-1,4-diyl) bis-5-oxo-3-benzyl-7,7-dimethyl-1,2,3,4,5,6,7,8-octahydro-quinazoline (40r)

This compound was obtained as light yellow solid in 73 % yield, m.p 125\(^\circ\)C; IR (KBr): 1559, 1603 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 1.06 (s, 12H), 1.77 (s, 4H), 2.14-2.25
(m, 8H), 3.10 (s, 4H), 3.59-3.63 (m, 8H), 3.86 (s, 4H), 7.27-7.32 (m, 10H); $^{13}$C NMR (CDCl$_3$): δ 26.88, 28.82, 30.94, 32.24, 39.39, 48.33, 48.48, 49.30, 57.57, 68.07, 102.75, 127.51, 128.45, 128.96, 137.77, 156.50, 193.14; MS: m/z 595.6 (MH$^+$). Anal. Calc. for C$_{38}$H$_{50}$N$_4$O$_2$ (594.39): C, 76.73; H, 8.47; N, 9.42. Found: C, 76.60; H, 8.51; N, 9.39 %

3.4.6 Conclusion
The present chapter describes an efficient, simple, strategy for the synthesis of hitherto unknown bis-octahydroquinazolines in which the two quinazoline ring connected at 1,1' positon from easily accessible starting materials in good yields with promising pharmacological and biological properties. The methodology reported herein is an example of multi-component reactions (MCRs).

3.4.7 References
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