CHAPTER – III

Synthesis of spiroquinazolinones

3.1. Introduction

2,3-Dihydroquinazolin-4(1H)-ones are an important class of heterocyclic compounds that have been attracting considerable attention in recent years. The natural quinazolinones and their synthetic analogous have been reported to possess a wide range of pharmacological and biological activities including antimalarial,\(^1\) antibacterial,\(^2\) anticonvulsant,\(^3\) anticancer\(^4\) and antifungal\(^5\) activities and evaluated as antagonists of various biological receptors, such as 5-HT5A related diseases,\(^6\) calcitonin gene-related peptide\(^7\) and vasopressin V3 receptors.\(^8\) 2,3-Dihydroquinazolinones have been shown to act as potent tubulin inhibitors with impressive antiproliferative activity against several human cancer cell lines.\(^9\) Furthermore, these compounds can act analogously to the antimitotic agent colchicine.\(^10\)

Several methods for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones have been reported, which include:

(i) reductive cyclization of o-nitrobenzamide or o-azidobenzamide with aldehydes or ketones using metallic samarium in the presence of iodine or SmI\(_2\).\(^{11}\)

(ii) reductive desulfurization of 2-thioxo-3H-quinazolin-4-ones with nickel boride in dry methanol\(^{12}\)

(iii) reductive cyclization of o-nitrobenzamides and orthoformate, aldehydes, or ketones with the aid of a low-valent titanium reagent\(^{13}\)
(iv) condensation of isatoic anhydride, aldehydes, and ammonium acetate or primary amine in the presence of SnCl₂,¹⁴ p-toluenesulfonic acid,¹⁵ gallium(III) triflate,¹⁶ montmorillonite K-10,¹⁷ molecular iodine,¹⁸ silica sulfuric acid,¹⁹ Zn(PFO)₂,²⁰ ceric ammonium nitrate,²¹ MCM-41-SO₃H,²² [bmim]BF₄,²³ Al(H₂PO₄)₃,²⁴ (alum),²⁵ and Amberlyst-15/microwave.²⁶

Due to the importance of quinazolinone derivatives in organic synthesis, the development of environmentally benign, high yielding, and clean synthetic methods of 2,3-dihydroquinazolin-4(1H)-ones are in demand.

The indole core represents an interesting pharmacophore, which displays the features of biological and pharmacological properties. The heterocyclic spirooxindole ring system is a widely distributed structural framework that is present in a number of pharmaceuticals and natural products,²⁷ including cytostatic alkaloids like spirottryprostatins A and B, which have been isolated from the fermentation broth of Aspergillus fumigatus and strychnophylline.²⁸ Derivatives of spirooxindole exhibit a range of biological properties, including antimicrobial, antitumoral, antibiotic agents, and inhibitors of human NK-1 receptor.²⁹ Furthermore, the 3’-spirooxindoles formed by sharing of the 3’-carbon atom have been of interest to organic chemists because, these spirooxindole derivatives are characterized by interesting biological properties.³⁰ Spiroquinazolinone are core structures in drug discovery. These quinazolinones displayed wide range of biological activities as antitumor,³¹ antidefibrillatory,³² antidepressant,³³ analgesic,³⁴ diuretic,³⁵ antihistamine,³⁶ vasodilating agent,³⁷ antihypertensive,³⁸ CNS stimulant,³⁹ tranquilizer⁴⁰ and antianxiestic (Fig. 3.1).⁴¹ Moreover these quinazolinones also have plant growth regulatory⁴² abilities. On the other hand corresponding quinazolin-
4(3H)-ones are also important building blocks in natural products (Rutaecarpine, Fig. 3.1) and compounds of pharmacological interest.\(^{43}\)

![Chemical structures](image)

Fig. 3.1 Biologically active quinazolinone and quinazolinone based natural products

The unique structural array of oxindole core fused with cyclic ketones has highly prominent pharmacological activities have subsequently stimulated interest in the synthesis of spiroquinazolinone derivatives containing oxindole moiety. Both oxindole and quinazolinone moieties are of having valuable pharmacological properties and hence, the spiroquinazolinones are also expected to be having pharmacological properties.

Most of the synthetic protocols for spiroquinazolinones\(^{44}\) reported so far suffer from harsh reaction conditions,\(^ {45}\) prolonged time period,\(^ {46}\) use of hazardous acid catalysts,\(^ {47}\) high catalyst loading,\(^ {14}\) and expensive methods,\(^ {48}\) and therefore yields are often low due to poor selectivity in such conditions. So, the development of efficient and convenient approach to construct this type of heterocyclic compounds is necessary.
Inexpensive and readily available catalysts that bring about organic transformations in operationally simple ways are always an attractive approach for an organic as well as for a medicinal chemist and such methodology for the selective and mild synthesis of spiroquinazolinone is still not explored.

A number of literature reports are available for the condensation of 2-aminobenzamides with aldehydes/ketones yielding dihydroquinazolinone derivatives including those in the presence of p-TsOH/DDQ,\textsuperscript{49} I\textsubscript{2},\textsuperscript{50} FeCl\textsubscript{3},\textsuperscript{51} CuCl\textsubscript{2},\textsuperscript{52} TiCl\textsubscript{4}/Zn,\textsuperscript{53} chiral phosphoric acid,\textsuperscript{54} etc.,

2,3-Dihydroquinazolin-4(1H)-ones have been synthesized in high to excellent yields through direct cyclocondensation of anthranilamides and aldehydes in ionic liquids (ILs) or one-pot three-component cyclocondensation of isatoic anhydrides, ammonium acetate and aldehydes in ionic liquid-water solvent system without the use of any additional catalyst.\textsuperscript{49}

\[
\begin{array}{c}
\text{Scheme 3.1}
\end{array}
\]

Silica-supported polyphosphoric acid (PPA-SiO\textsubscript{2})\textsuperscript{47} catalyzed efficiently the reaction of anthranilamide with aryl aldehydes or ketones under solvent-free conditions to afford the corresponding 1,2,3,4-tetrahydro-4-quinazolinone derivatives.
Scheme 3.2

2,3-Dihydroquinazolin-4(1H)-ones have been synthesized in high to excellent yields via the condensation of 2-aminobenzamide with aldehydes and ketones in the presence of catalytic amount of ZrCl₄ in EtOH at room temperature.⁵⁵

Scheme 3.3

Heteropoly acids⁵⁶ efficiently catalyzed the cyclocondensation reaction of anthranilamide with aldehydes in water at ambient temperature and afforded the corresponding 2,3-dihydro-4(1H)-quinazolinones compounds in good to excellent yields.

Scheme 3.4

An efficient cyanuric chloride⁵⁷ (2,4,6-trichloro-1,3,5-triazine, TCT) catalyzed approach for the synthesis of 2,3-dihydroquinazolin-4(1H)-one and 2-
spiroquinazolinone, has been reported. The reaction allows rapid cyclization (8-20 min) with 10 mol % cyanuric chloride to give skeletal complexity in good to excellent yield.

![Scheme 3.5](image)

The heterogeneous solid acid catalyst Amberlyst-15\textsuperscript{58} displays efficient catalytic properties for the synthesis of 2,3-dihydroquinazolin-4(1H)-ones from anthranilamide and various aldehydes/ketones under mild reaction conditions and in good yields.

![Scheme 3.6](image)

An efficient synthesis of 2-monosubstituted and 2,2-disubstituted 2,3-dihydro-4(1H)-quinazolinones has been developed by using a dissolved metal reduction condensative cyclization strategy.\textsuperscript{59} Treatment of 2-nitrobenzamide and an aldehyde or ketone with iron powder in refluxing acetic acid afforded high yields of the quinazolinone compounds.
Multicomponent synthesis of dihydroquinazolinone has been reported from isatoic anhydride, aromatic aldehydes and ammonium acetate or amine catalyzed by various catalysts.

Ga(OTf)$_3$\textsuperscript{16} promoted the synthesis of a series of 2,3-dihydroquinazolin-4(1H)-ones and quinazolin-4-(3H)-ones in good to excellent yields and high selectivity by one-pot reaction of isatoic anhydride, ammonium acetate (or amines), and aldehydes in ethanol or in DMSO under mild conditions.

A wide range of mono- and disubstituted 2,3-dihydroquinazolin-4-(1H)-ones were obtained in high yields by condensation of isatoic anhydride, aldehydes with ammonium salts or primary amines in the presence of strontium chloride in aqueous ethanol under reflux\textsuperscript{60}.

Scheme 3.7

Scheme 3.8

Scheme 3.9
An efficient one-pot L-proline\textsuperscript{61} catalyzed multicomponent synthesis of 2,3-dihydro-4-(1H)-quinazolinones has been achieved with isatoic anhydride, aldehyde and ammonium acetate or amine in water under microwave irradiation.

![Scheme 3.10](image)

A wide range of mono- and disubstituted dihydroquinazolinones were synthesized via condensation of isatoic anhydride, primary amines, or ammonium salts with aromatic aldehydes in the presence of Montmorillonite K-10.\textsuperscript{17}

![Scheme 3.11](image)

A facile, efficient, and environmentally friendly procedure for the synthesis of 2,3-dihydroquinazolin-4-(1H)-ones from isatoic anhydride, aldehyde, and ammonium acetate in the presence of thiamine hydrochloride (VB\textsubscript{1})\textsuperscript{62} in EtOH has been described.

![Scheme 3.12](image)

Trifluoroethanol\textsuperscript{63} (TFE) was found to be an efficient and recyclable medium in promoting one-pot, three-component coupling reactions of isatoic
anhydride, aldehyde and ammonium acetate or primary amine to afford the corresponding 2,3-dihydroquinazolin-4-(1H)-one derivatives in high yields.

![Scheme 3.13](image)

2,3-Dihydroquinazolin-4-(1H)-one derivatives have been synthesized via an one-pot, three component reaction of isatoic anhydride and an aromatic aldehyde with ammonium acetate or primary amine catalyzed by silica-bonded N-propylsulfamic acid (SBNPSA) in refluxing ethanol.64

![Scheme 3.14](image)

2,3-Dihydroquinazolin-4-(1H)-one derivatives were synthesized via a one-pot, three component reaction of isatoic anhydride and an aromatic aldehyde with ammonium acetate or primary amine catalyzed by silica-bonded S-sulfonic acid in ethanol at 80 °C.65

![Scheme 3.15](image)
Synthesis of 2-substituted quinazolinones from 2-aminobenzamide and various aldehydes has been known for long time. But the synthesis of 2,2-disubstituted quinazolinones from 2-aminobenzamides with acyclic ketones, cyclic ketones and 1,2-dicarbonyl compounds is not yet been familiarized as unsubstituted and 2-substituted quinazolinones.

An efficient and direct procedure for the synthesis of novel spiroquinoxaline dione derivatives has been described by employing a condensation reaction of 2-aminobenzamides and isatins in the presence of a catalytic amount of KAl(SO₄)₂·12H₂O (alum) in ethanol under reflux. ⁶⁶

\[ \text{Scheme 3.16} \]

A successful strategy, for the preparation of spiroquinoxalinedione via a three-component cyclocondensation of isatoic anhydride, isatins, and amines, using the inexpensive, non-toxic, and easily available KAl(SO₄)₂·12H₂O catalyst has been described by Mohammadi et al. ⁶⁷

\[ \text{Scheme 3.17} \]
A series of 1’H-spiro[indoline-3,2’-quinazoline]-2,4’(3’H)-diones and 1’H,2H-spiro[acenaphthylene-1,2’-quinazoline]-2,4’(3’H)-diones were synthesized by the reaction of 2-nitrobenzamides with isatins and acenaphthylene-1,2-diones, respectively, mediated by SnCl$_2$·2H$_2$O system. A variety of substrates have been used in the process with moderate to good yields in shorter reaction times.

![Scheme 3.18](image)

Ethylenediamine diacetate catalyzed one-pot syntheses of biologically interesting 2,3-dihydroquinazolin-4(1H)-ones and their spirooxindole derivatives from isatoic anhydride, amines, and benzaldehydes or isatins via a three-component condensation in aqueous media have been described.

![Scheme 3.19](image)

Most of the synthetic protocols of spiroquinazolinone reported so far suffer from harsh reaction conditions, prolonged time period, use of high catalyst loading, and expensive methods, and therefore yields are often low due to poor selectivity in
such conditions. Hence, better procedures for the synthesis of spiroquinoxalinones are still awaited.

Operationally simple organic transformations with inexpensive and readily available catalysts are attractive approaches for organic, as well as for medicinal chemists. Herein, we are reporting the one-pot synthesis of some novel spiroquinoxalinones using p-toluene sulfonic acid (p-TSA) as catalyst.

3.2. Results and Discussion

Initially, we have tried the synthesis of disubstituted quinazolinone by taking anthranilamide and isatin as a model reaction, with various catalysts such as acetic acid, sulfuric acid, alum, p-TSA and also in the absence of catalyst. The yields were poor in the absence of a catalyst and also with catalysts other than the p-toluene sulfonic acid. While optimizing the mol% of the catalyst to be used, we found that 20mol% of p-TSA was better and there were no more enhancements in the rate and yield by increasing the mol% of p-TSA beyond this. Hence, we have applied 20mol% of p-TSA catalyst for further reactions.

Scheme 3.20 General reaction scheme for the synthesis of spiroquinoxalinones
Scheme 3.21 Plausible mechanism for the synthesis of spiroquinazolinones

The mechanism of the reaction may be visualized as follows; in the presence of p-toluene sulfonic acid protonation of 1,2-dicarbonyl compounds or other ketones takes place which would be followed by the addition of anthranilamide leading to the formation of an imine (A). The cyclization reaction occurs by the attack of amide -NH$_2$ group on the double bond of imine forming the spiroquinazolinone after the H$^+$ shift.

A series of spiroquinazolinone derivatives (3a-3j) were obtained from anthranilamide with different ketones such as isatin, 5-chloroisatin, 5-nitroisatin, acenaphthenequinone, norcamphor, cyclohexanone, cyclopentanone, 1,4-cyclohexadione and p-benzoquinone, by simple refluxing with p-TSA in ethanol. Because of the formation of solid product in the reaction vessel, simple washing with distilled water was enough to get the pure product.
Table - 3.1 p-TSA catalyzed synthesis of spiroquinazolinones:

<table>
<thead>
<tr>
<th>S.No</th>
<th>Ketone</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Product</th>
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<td><img src="image1" alt="Ketone Image" /></td>
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<td>82</td>
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<td>79</td>
<td><img src="image6" alt="Product Image" /> 3c</td>
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<td>6</td>
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<td>60</td>
<td>82</td>
<td><img src="image20" alt="Product Image" /> 3j</td>
</tr>
</tbody>
</table>

*Reactions were performed with 1mmol of anthranilamide and 1mmol of ketone with 20mol% of p-TSA in ethanol under reflux conditions. †Isolated Yield. ‡Anthranilamide : Ketone in 2:1 ratio.
The reaction was widely applicable to diketones such as isatin, 5-substituted isatins, acenaphthenequinone and various aliphatic cyclic ketones. Reactions have been completed within an hour for the diketones and within 10 min for the cyclic ketones as shown in the Table - 3.1. When the reaction was carried out with anthranilamide : 1,4-cyclohexadione in 1:1 ratio, we found that spiro compound has been formed on one side of the ketone (Table - 3.1, Entry-8), whereas if it is conducted with 2:1 ratio, dispiro compound has been formed (Table - 3.1, Entries 9, 10) as evidenced from the $^1$H, $^{13}$C NMR spectra and LCMS. Similarly, reaction with p-benzoquinone also resulted in the formation of dispiro compound. Unfortunately, this reaction doesn’t work well for camphor and also for the cyclic 1,3-diketones such as dimedone, 1,3-cyclohexadione and Meldrum’s acid, which may be due to the steric strain in the expected spiroquinazolinone product.

3.3. Conclusions

An efficient protocol for the synthesis of spiroquinazolinones has been developed which offered several advantages such as use of green solvent, easy separation of the product without any chromatographic techniques, mild reaction conditions, use of inexpensive and commercially available starting materials and shorter reaction time.

3.4. Experimental methods

Isatin, 5-chloroisatin, 5-nitroisatin, acenaphthenequinone, norcamphor, cyclohexanone, cyclopentanone, 1,4-cyclohexadione, p-benzoquinone and all the catalysts used were purchased from Sigma-Aldrich and used as such without further purification. The melting points of all compounds were determined with an
electrothermal apparatus using capillary tube and are uncorrected. The purities of the compounds were checked by TLC using precoated silica gel plates with hexane : ethyl acetate (6:4) as eluent. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance spectrophotometer at 400/100 MHz respectively using TMS as reference. High Resolution Mass Spectra of representative compounds were recorded on maXis 10138 Mass spectrometer at 70 eV. Elemental microanalyses were carried out on a Perkin-Elmer elemental analyzer Model 240C and a Thermo Finnigan analyser series Flash EA1112.

3.4.1. General procedure for the synthesis of spiroquinazolinones (3a-3j):

20 mol% of p-TSA was added to the 1:1 mixture of anthranilamide and ketones in 10 ml of ethanol and allowed to reflux for the appropriate time as shown in the Table - 3. 1. The solid products formed from the reaction in good to excellent yields were separated by simple filtration and washed with water to remove p-TSA for obtaining the pure compound.

Spectral data:

$^1$H-spiro[indoline-3,2’-quinazoline]-2,4’(3’H)-dione (3a): Colorless solid; mp: 260-262 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 10.29 (s, CONH); 8.35 (s, CONH); 7.61-7.59 (d, 1H); 7.48-7.46 (d, 1H); 7.32 (t, 1H); 7.27 (s, 1NH); 7.22 (t, 1H); 7.06-7.05 (t, 1H); 6.86-6.83 (d, 1H); 6.67 (t, 1H); 6.60 (d, 1H).$^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 176.48, 164.39, 147.29, 142.59, 133.77, 131.27, 129.91, 127.32, 125.83, 122.74, 117.62, 114.77, 114.32, 110.54, 71.41. LCMS (M$^+$ +1) calcd for C$_{13}$H$_{11}$N$_3$O$_2$: 266.09, found 266.
5-Chloro-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione (3b): Colorless solid; mp: 280-282 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 10.43 (s, NH); 8.39 (s, CONH); 7.61-7.59 (s, CONH); 7.49 (s, 1H); 7.38-7.33 (dd, 2H’s); 7.23 (t, 1H); 6.86-6.84 (d, 1H); 6.69 (t, 1H); 6.61-6.59 (d, 1H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 176.86, 164.06, 147.84, 142.75, 133.89, 131.09, 127.35, 126.63, 125.88, 117.87, 114.37, 112.12, 71.51. HRMS (ESI) m/z calcd for C$_{15}$H$_{10}$ClN$_3$O$_2$ (M$^+$ +1): 300.1521, found 300.0538.

5-Nitro-1'H-spiro[indoline-3,2'-quinazoline]-2,4'(3'H)-dione (3c): Colorless solid; mp: 292-294 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 11.04 (s, NH); 8.45 (s, CONH); 8.31 (d, 1H); 8.30 (s, CONH); 7.64-7.62 (d, 1H); 7.41 (s, 1H); 7.29-7.25(t, 1H); 7.08-7.05 (s, 1H); 6.75-6.73 (t, 1H); 6.63-6.61 (d, 1H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 176.86, 164.06, 149.12, 146.73, 142.98, 134.11, 130.89, 128.37, 127.44, 121.20, 118.27, 114.62, 114.56, 111.05, 71.18. HRMS (ESI) m/z calcd for C$_{15}$H$_{10}$N$_4$O$_4$ (M$^+$ +1): 311.0796, found 311.0783.

1'H,2H-spiro[acenaphthylene-1,2'-quinazoline]-2,4'(3'H)-dione (3d): Colorless solid; mp: 238-240 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 8.49 (s, -CONH); 8.38 - 8.36 (d, ArH); 8.15 - 8.13 (d, ArH); 8.01 - 7.99 (d, ArH); 7.91 - 7.81 (m, 3ArH’s); 7.68 - 7.66 (d, ArH); 7.46 (s, NH); 7.26 - 7.23 (t, ArH); 6.74 - 6.71 (t, ArH); 6.58 - 6.56 (d, ArH). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 200.87, 164.18, 147.12, 141.28, 138.41, 133.99, 132.61, 130.38, 129.73, 129.57, 128.86, 127.46, 126.85, 123.09, 122.19, 117.88, 114.86, 114.15, 74.44. HRMS (ESI) m/z calcd for C$_{19}$H$_{12}$N$_2$O$_2$ (M$^+$ +1): 301.0869, found 301.0977.
1'H-spiro[bicyclo[2.2.1]heptane-2,2'-quinazolin]-4'(3'H)-one (3e): Colorless solid; mp: 194-196 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\): 8.19 (s, -CONH); 7.57-7.53 (s, NH); 7.21-7.19 (s, 1H); 6.87-6.84 (t, 1H); 6.78-6.73 (q, 1H); 6.66-6.60 (q, 1H); 2.29-1.10 (m, 10H's). \(^13\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 163.69, 147.90, 133.51, 127.74, 116.95, 115.81, 114.57, 75.55, 46.41, 45.71, 35.17, 35.61, 28.12, 22.51. HRMS (ESI) m/z calcd for C\(_{14}\)H\(_{16}\)N\(_2\)O (M\(^+\) +1): 229.1962, found 229.1341. Anal. calcd for C\(_{14}\)H\(_{16}\)N\(_2\)O: expected: C: 73.66 H: 7.06 N: 12.27 Found: C: 73.48, H: 7.12, N: 12.15.

1'H-spiro[cyclohexane-1,2'-quinazolin]-4'(3'H)-one (3f): Colorless solid; mp: 220-222 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\): 7.93 (s, CONH); 7.58-7.56 (d, 1H); 7.23-7.19 (t, 1H); 6.82-6.80 (d, 1H); 6.62 (t, 2H's, Ar H + NH); 1.75-1.73 (d, 2H's); 1.57-1.54 (m, 6H's); 1.45-1.41 (m, 1H); 1.28-1.23 (m, 1H). \(^13\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 163.68, 147.22, 133.59, 127.56, 116.94, 115.03, 114.89, 68.26, 37.61, 25.10, 21.34. DEPT \(^1\)C NMR (135 MHz, DMSO-\(d_6\)) \(\delta\): CH\(_2\) H's: 37.61, 25.10, 21.34. HRMS (ESI) m/z calcd for C\(_{13}\)H\(_{18}\)N\(_2\)O (M\(^+\) +1): 217.1341, found: 217.1378. Anal. calcd for C\(_{13}\)H\(_{18}\)N\(_2\)O: C: 72.19 H: 7.46 N: 12.95 Found: C: 72.31, H: 7.41, N: 12.85.

1'H-spiro[cyclopentane-1,2'-quinazolin]-4'(3'H)-one (3g): Colorless solid; mp: 264-266 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\): 8.09 (s, CONH); 7.57-7.55 (t, 1H); 7.21-7.19 (t, 1H); 6.73-6.61 (m 2 ArH's + 1NH), 1.65-1.64 (d, 8H's). \(^13\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\): 163.94, 148.00, 133.49, 127.72, 117.02, 115.04, 114.81, 77.54, 22.45. LCMS (M\(^+\) +1) calcd for C\(_{12}\)H\(_{14}\)N\(_2\)O: 203.13, found: 203. Anal. calcd for C\(_{12}\)H\(_{14}\)N\(_2\)O: C: 71.26 H: 6.98 N: 13.85 Found: C: 71.32, H: 6.91, N: 13.96.
1'H-spiro[cyclohexane-1,2'-quinazoline]-4,4'(3'H)-dione (3h): Colorless solid; mp: greater than 300 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 7.68 (s, CONH); 7.59-7.56 (d, 1H); 7.26-7.23 (t, 1H); 6.78-6.76 (d, 1H); 6.67-6.64 (t, 1H); 6.53 (s, NH). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 195.35, 172.23, 147.20, 132.59, 126.46, 116.12, 113.74, 69.27, 32.48.

1''',3'''-Dihydrospiro[1',3'-dihydrospiro[cyclohexane-1,2'-quinazolin]-4''-one-4,2'''-quinazolin]-4''-one (3i): Colorless solid; mp: greater than 300 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 7.67-7.66 (s, 2CONH’s); 7.58 - 7.56 (t, 2H’’s); 7.26 -7.25 (q, 2ArH’s); 6.80 - 6.76 (t, 2ArH’s); 6.67 - 6.66 (q, 2ArH’s); 6.54 - 6.53 (s, 2NH’s); 1.87 - 1.86 (s, 8H’s). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 163.2, 146.5, 133.3, 127.3, 117.0, 114.9, 114.7, 66.7, 32.0. LCMS (M$^+$ +1) expected: 349.21, found 349. Anal. calcd for C$_{20}$H$_{20}$N$_4$O$_2$: C: 68.95 H: 5.75 N: 16.17 Found: C: 69.05, H: 5.71, N: 16.17.

(3j): Colorless solid; mp: greater than 300 °C; $^1$H NMR (400 MHz, DMSO-d$_6$) δ: 10.87 (s, 2CONH’s); 8.23 (t, 1H); 7.78-7.59 (m, 5H’’s); 7.27 (s, 2NH’s); 7.00 (m, 1H); 6.22 (t, 1H). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ: 180.92, 170.18, 145.35, 138.02, 132.40, 129.75, 125.86, 124.50, 122.13, 97.74. Anal. calcd for C$_{20}$H$_{16}$N$_4$O$_2$: C: 69.76 H: 4.68 N: 16.27 Found: C: 69.68, H: 4.61, N: 16.18.
Some representative NMR spectra

Fig. 3.2 $^1$H and $^{13}$C NMR spectra of 3a
Fig. 3.3 $^1$H and $^{13}$C NMR spectra of 3b
Fig. 3.4 $^1$H and $^{13}$C NMR spectra of 3c
Fig. 3.5 $^1$H and $^{13}$C NMR spectra of 3d
Fig. 3.6 $^1$H and $^{13}$C NMR spectra of 3e
Fig. 3.7 $^1$H and $^{13}$C NMR spectra of 3f
Fig. 3.8 $^1$H and $^{13}$C NMR spectra of 3g
Fig. 3.9 $^1$H NMR spectrum of 3h

Fig. 3.10 $^1$H NMR spectrum of 3i
Fig. 3.11 $^1$H and $^{13}$C NMR spectra of 3j
References


