Chapter IV

Pd-NHC catalysed thioetherification of 3-iodo-2-aryl substituted 4-quinolone derivatives via C-S cross coupling
IV.A. Introduction

Sulfoxidation in organic molecules has received much attention due to its importance in organic dyes, pharmaceuticals, material chemistry, agrochemicals and many bioactive products.\(^1\) Diaryl sulfides also have tremendous applications in the treatment of Parkinson’s,\(^2\) Alzheimer’s\(^3\) diseases and HIV infections,\(^4\) Breast cancer\(^5\) etc. Therefore, the development of highly efficient, novel, simple pathway for the formation C-S bond linkage in many biologically active molecules is still a great challenge for all over the world.\(^6\) Till now, many methods have been well recognized for generating the C-S bond. Migita et.al. firstly developed the carbon-sulfur bond formation between aryl halides and thiols in the presence of Pd(PPh\(_3\))\(_4\).\(^7\)

![Important biologically active diaryl sulfide scaffolds](image)

**Fig-IV.1** Important biologically active diaryl sulfide scaffolds

IV.B. Present work: Background and Objective

4-quinolones are mainly found in the pharmaceutical chemistry owing to its various biological activities, e.g., antibacterial,\(^8\) antimalarial,\(^9\) and anticancer.\(^10\) As a consequence, the synthesis of 4-quinolones and its derivatives has involved considerable interest. Therefore, many synthetic procedures are commonly available in the literature.\(^11\) 3-aryl- or 3-heteroaryl-substituted quinolones have been widely explored because of their profound biological activities. Despite 3-aryl substituted quinolones have some advantages; coupling reactions at C-3 of quinolin-4-ones remains a challenging task due to the requirement of pre-NH functionalisation and protection. In recent year, Zhang and his coworkers introduce the thioether linkage at the C-3 position of 4-quinolones via decarboxylative thioetherification.\(^12\)
But still, this method has some disadvantages such as harsh reaction condition, longer reaction time; halogen substituted starting material and prerequisite protection of –NH group.

In this arena, we have previously reported the regio-controlled nitration at C-5, C-7 position of 4-quinolones under ambient condition and regioselective bromination at C-6 position and its subsequent arylation via Suzuki cross coupling reactions. However in this chapter, we have disclosed a new, simple and efficient route of Pd-NHC catalysed thioetherification of 3-iodo-4-quinolones in promising yield under rapid and aerobic condition. To the best of our knowledge, no such study has not been well documented before.
Table IV.1. Optimization of the reaction condition for the C-S cross coupling

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol %)</th>
<th>base</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>Time (h)</th>
<th>Yield (a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$ (5 )</td>
<td>DBU</td>
<td>DMF</td>
<td>80</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$ (5 )</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>80</td>
<td>4</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>PdCl$_2$ (5 )</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>80</td>
<td>4</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>Pd(acac)$_2$ (5 )</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>80</td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>Pd-NHC (2 )</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>80</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>Pd-NHC (1)</td>
<td>DBU</td>
<td>DMF</td>
<td>80</td>
<td>2</td>
<td>83</td>
</tr>
<tr>
<td>7</td>
<td>Pd-NHC (1)</td>
<td>Et$_3$N</td>
<td>DMF</td>
<td>80</td>
<td>2</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>Pd-NHC (1)</td>
<td>Cs$_2$CO$_3$</td>
<td>DMF</td>
<td>80</td>
<td>2</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td>Pd-NHC (1)</td>
<td>DBU</td>
<td>Dioxane</td>
<td>80</td>
<td>2</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>Pd-NHC (1)</td>
<td>DBU</td>
<td>DMF</td>
<td>40</td>
<td>2</td>
<td>67</td>
</tr>
<tr>
<td>11</td>
<td>Pd-NHC (1)</td>
<td>DBU</td>
<td>DMF</td>
<td>rt</td>
<td>2</td>
<td>59</td>
</tr>
<tr>
<td>12</td>
<td>Pd-NHC (0.5)</td>
<td>K$_2$CO$_3$</td>
<td>DMF</td>
<td>80</td>
<td>2</td>
<td>72</td>
</tr>
<tr>
<td>13</td>
<td>Pd-NHC (0.5)</td>
<td>DBU</td>
<td>DMF</td>
<td>80</td>
<td>2</td>
<td>86</td>
</tr>
</tbody>
</table>

All reactions were carried out using 0.25 mmol of 3-iodo-2-aryl substituted 4-quinolones and 0.375 mmol benzene thiol in 2 mL DMF for stirring at 80 °C. Yield = Isolated yields.
Fig: IV.2. Structure of the Benzimidazole based Pd-NHC catalyst A

To optimize the reaction condition, we investigated our journey by the reaction of 3-iodo-2-aryl substituted-4-quinolone and benzene thiol in DMF, as a model reaction. Delightfully, thioetherification at C-3 position of 4-quinolone took place in the presence of Pd(OAc)$_2$ and DMF, afforded 80% yield in 4 h (Table-IV.1, entry1). Subsequently, various palladium catalysts such as PdCl$_2$, Pd(acac)$_2$, Pd-NHC were screened to proceed the reaction; (Table-IV.1, entry 3,4) among them Pd-NHC$^{15}$ served the best results (Table-IV.1, entry 13). Only 0.5 mol % of our pre-developed Pd-NHC catalyst required to catalyse the reaction. Furthermore, various solvents were also examined to achieve the fruitful result. Among them DMF proved to be the best suited solvent, affording 86% yield of 2a in 2 h (Table-IV.1, entry 13). The reaction temperature 80°C was found to be the optimal to furnish the highest yield of 2a (Table-IV.1, entry 13). The base have also a profound role in this transformation, DBU found to be superior to the other bases such as K$_2$CO$_3$, Cs$_2$CO$_3$, Et$_3$N etc (Table-IV.1, entry 5-8). After investigating the various catalysts, solvent, catalyst loading and reaction temperature, the combination of Pd-NHC (0.5 mol %), DBU (2 equiv) in DMF at 80°C for 2 h served the optimal reaction condition for this transformation.

Scheme-IV.1. Substrate scope of Pd-NHC catalysed thioetherification
All reactions were carried out using 0.25 mmol of various 3-iodo-2-aryl substituted 4-quinolones and 0.375 mmol substituted benzene thiols in 2 mL DMF for stirring at 80 °C. Yield = Isolated yields.
With the optimized reaction conditions in our hand, we explored the substrate scope of both 3-iodo substituted-4-quinolone and various substituted benzene thiols as shown in (Scheme IV.1.) A broad range of benzene thiols were allowed to react with various 3-iodo-2-phenylquinolin-4-(1H)one, affording the corresponding product 3-aryl sulfide-4-quinolone in good to excellent yields. Both electron donating and electron withdrawing groups containing benzene thiols were performed very well in this transformation. 4-fluoro substituted benzene thiol was successfully coupled with 3-iodo-2-phenylquinolin-4-(1H)one, resulting the 88% yield of the desired product (Scheme-IV.1, entry 2e). However, 2-naphthyl thiol furnished moderate to excellent yield (73%-86%) respectively (Scheme-IV.1, entry 2g, 2k 2r). Steric hindrance of naphthyl ring with the phenyl group at C-2 position of 4-quinolone might play a key role for lowering the yield in 2g and 2r. Next, we examined the influence of various groups in the C-2 substituted phenyl ring of 4-quinolone. It has been found that electron withdrawing group substituted phenyl afforded much higher yield in comparison to electron releasing group (Scheme-IV.1, entry 2h-2l, 2m, 2q, 2r). Cyclohexyl group substituted 4-quinolone also proved to be a good coupling partner with 4-chloro benzene thiol (scheme 1, entry 2n). Highest yield 92% was obtained when 2-(4-fluorophenyl)-3-iodoquinolin-4-(1H)-one was coupled with 4-fluoro benzene thiol (Scheme-IV.1, entry 2j). Surprisingly, meta substituted phenyl ring at C-2 position of 4-quinolone did not afford the corresponding product (scheme 1, entry 2t) under this optimized condition. Interestingly in various cases, the reaction completed within 1 h and afforded the promising yield of the desired C-S coupled product (Scheme-IV.1, entry 2d, 2j, 2k, 2l).

IV.C. Conclusion:

In summary, an efficient protocol of Pd-NHC catalysed rapid thioetherification of 4-quinolone is developed. This method should attract much attention to the synthetic and pharmaceutical chemistry for the synthesis of large compound production. Simultaneously, our synthesized thioether substituted 4-quinolone derivatives are under investigation for their biological activity.
IV.D. Experimental section

IV.D.1. General Informations

NMR spectra were recorded on 300 MHz spectrometer at 298 K with calibration done on the basis of solvent residual peak. Products were purified using column chromatography on silica gel (60-120 mesh). Ethyl acetate and petroleum ether (60-80°C) were used as eluents. Progress of reaction was monitored using silica gel TLC.

IV.D.2. Preparation of Various 3-iodo-2-aryl substituted 4-quinolones (1a-1f)

Initially, 2-aryl quinolin-4(1H)-one (1a, 0.25mmol), iodine (2 equiv.) and sodium carbonate (1.5 equiv.) in THF (2 ml) was stirred at room temperature for 18 hours. Then, the reaction mixture was quenched with sodium thiosulphate and the precipitate was collected by filtration and washed with ice-cold water. Afterwards, the crude product was purified through column chromatography.

IV.D.3. Preparation of various thioether substituted 4-quinolones:

Initially, various 3-iodo-2-aryl substituted 4-quinolone (0.25mmol), thiophenol (0.375mmol), DBU (0.5 mmol, 76mg) and Pd-NHC (0.5 mol%, 1.2mg) were taken in DMF (2ml) in 25 ml round bottomed flask. Afterwards, the reaction mixture was heated at 80°C for 1-2 hr. Then, it was cooled and diluted with water and the product was extracted with ethyl acetate (3 x 20 mL). Organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was then purified using column chromatography.

IV.D.4. Physical characteristics and spectral data of compounds:

1. 3-iodo-2-phenylquinolin-4(1H)-one (1a)

   ![3-iodo-2-phenylquinolin-4(1H)-one](image)

   Light Yellow solid, ¹H NMR (300 MHz, DMSO-d₆) δ 7.36-7.42 (m, 1H), 7.53-7.58 (m, 5H), 7.63-7.69 (m, 2H), 8.13 (dd, J = 8.1Hz, 0.9Hz, 1H), 12.29 (s,1H); ¹³C NMR (75 MHz, DMSO-d₆) δ 86.3, 118.8, 121.3, 124.7, 125.9, 128.8, 129.4, 130.3, 132.6, 139.7, 153.6, 174.1.
2. 2-(4-fluorophenyl)-3-iodo-quinolin-4(1H)-one (1b)\textsuperscript{15}

![Image of 2-(4-fluorophenyl)-3-iodo-quinolin-4(1H)-one (1b)]

Light Yellow solid, \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 7.38-7.45 (m, 3H), 7.62-7.71 (m, 4H), 8.15 (d, \(J = 8.0\)Hz, 1H), 12.3 (s, 1H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 86.6, 115.7, 115.9, 118.9, 121.4, 124.6, 125.9, 131.9, 132.1, 132.6, 134.8, 134.9, 139.8, 152.7, 161.5, 164.8, 174.0.

3. 2-(4-chlorophenyl)-3-iodo-quinolin-4(1H)-one (1c)\textsuperscript{15}

![Image of 2-(4-chlorophenyl)-3-iodo-quinolin-4(1H)-one (1c)]

Light Yellow solid, \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 7.37-7.42 (m, 1H), 7.59-7.73 (m, 5H), 8.15 (d, \(J = 9.9\)Hz, 1H), 12.13 (s, 1H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 86.4, 119.3, 121.6, 124.5, 125.9, 128.8, 131.5, 132.4, 134.9, 137.5, 152.9, 173.8.

4. 3-iodo-2-(4-methoxyphenyl) quinolin-4(1H)-one (1d)\textsuperscript{15}

![Image of 3-iodo-2-(4-methoxyphenyl) quinolin-4(1H)-one (1d)]

Light Yellow solid, \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 3.56 (s, 3H), 7.13 (d, \(J = 8.7\)Hz, 2H), 7.39-7.42 (m, 1H), 7.53 (d, \(J = 8.7\)Hz, 2H), 7.67-7.70 (m, 2H), 8.13 (d, \(J = 7.8\)Hz, 1H), 12.20 (s, 1H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 55.8, 86.6, 114.1, 118.8, 121.3, 124.5, 125.9, 130.7, 131.1, 132.5, 139.8, 153.4, 160.7, 174.0.

5. 2-cyclohexyl-3-iodo-quinolin-4(1H)-one (1e)

![Image of 2-cyclohexyl-3-iodo-quinolin-4(1H)-one (1e)]

Light Yellow solid, melting point: 222-224°C, \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 1.35 (s, 3H), 1.82 (dd, \(J = 18.9\)Hz, 9.6Hz, 7H), 7.34 (t, \(J = 7.2\)Hz,
1H), 7.65-7.70 (m, 1H), 7.82 (d, J = 8.3Hz, 1H), 8.07 (d, J = 8.0Hz, 1H), 11.25 (s, 1H);
\(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 25.6, 26.4, 29.9, 40.8, 49.0, 87.1, 118.7, 121.4, 124.3, 125.8, 132.3, 139.8, 157.5, 173.7.

6. 3-iodo-2-o-tolyl-quinolin-4(1H)-one (1f)

![Image of compound 1f]

Light Yellow solid, melting point: 220-222°C, \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 2.17 (s, 3H), 7.31-7.47 (m, 5H), 7.61-7.70 (m, 2H), 8.16 (d, J = 7.6Hz, 1H), 12.31 (s, 1H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 19.2, 87.1, 118.9, 121.5, 125.9, 126.5, 129.0, 130.1, 130.6, 132.5, 135.4, 138.5, 153.8, 173.8.

7. 2-phenyl-3-(phenylthio)quinolin-4(1H)-one (2a)

![Image of compound 2a]

White solid, melting point: 245-247°C, \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 6.97-7.05 (m, 3H), 7.14-7.20 (m, 2H), 7.41 (s, 1H), 7.48-7.54 (m, 5H), 7.71-7.73 (m, 2H), 8.11 (d, J = 7.8Hz, 1H), 12.29 (s, 1H). \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 108.5, 119.2, 124.5, 124.7, 124.8, 125.5, 125.9, 128.5, 129.0, 129.1, 130.2, 132.8, 135.5, 138.8, 139.9, 175.5.

8. 3-(4-methylphenylthio)-2-phenylquinolin-4(1H)-one (2b)

![Image of compound 2b]

White solid, melting point: 185-187°C, \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 2.20 (s, 3H), 6.95 (d, J = 8.4Hz, 2H), 6.99 (d, J = 8.4Hz, 2H), 7.38-7.73 (m,
8H), 8.10-8.16 (m, 1H), 12.24 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 20.8, 109.1, 119.2, 124.5, 124.6, 125.9, 128.5, 128.9, 129.1, 129.4, 129.8, 130.1, 130.3, 132.8, 134.1, 135.2, 135.6, 139.9, 156.8, 175.6.

9. 3-(4-methoxyphenylthio)-2-phenylquinolin-4(1H)-one (2c)

![Structure of 3-(4-methoxyphenylthio)-2-phenylquinolin-4(1H)-one (2c)]

White solid, melting point: 225-227°C; $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 3.67 (s, 3H), 6.78 (dd, $J = 6.9$Hz, 1.8Hz, 2H), 6.98 (dd, $J = 6.9$Hz, 1.8Hz, 2H), 7.40-7.43 (m, 1H), 7.51-7.55 (m, 5H), 7.70-7.72 (m, 2H), 8.11 (d, $J = 8.1$Hz, 1H), 12.22 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 52.1, 107.0, 111.4, 115.7, 121.1, 121.1, 122.4, 124.9, 125.0, 125.7, 125.8, 126.7, 129.3, 132.1, 136.4, 153.0, 154.2, 172.2.

10. (4-chlorophenylthio)-2-phenylquinolin-4(1H)-one (2d)

![Structure of (4-chlorophenylthio)-2-phenylquinolin-4(1H)-one (2d)]

White solid, melting point: 235-237°C; $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 6.96 (d, $J = 1.5$Hz, 2H), 6.99 (d, $J = 1.8$Hz, 2H), 7.17-7.20 (m, 1H), 7.38-7.49 (m, 5H), 7.68-7.70 (m, 2H), 8.07 (d, $J = 7.8$Hz, 1H). $^{13}$C NMR (75 MHz DMSO-d$_6$) $\delta$ 107.7, 118.7, 124.1, 124.3, 125.4, 126.8, 128.1, 128.5, 128.8, 129.7, 132.4, 134.9, 137.4, 139.4, 156.5, 174.9.
11. 3-(4-fluorophenylthio)-2-phenylquinolin-4(1H)-one (2e)

White solid, melting point: 240-242°C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 7.02-7.05 (m, 4H), 7.39-7.44 (m, 1H), 7.50-7.54 (m, 5H), 7.71-7.74 (m, 2H), 8.12 (d, $J = 7.5$Hz, 1H), 12.28 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 105.8, 105.9, 112.4, 112.7, 115.7, 121.2, 122.4, 124.4, 124.5, 124.7, 125.1, 125.6, 126.7, 129.3, 130.7, 132.0, 136.5, 153.4, 155.5, 158.7, 172.0. HRMS (ESI$^+$): [M+H]$^+$, found 348.0855. C$_{21}$H$_{15}$FNOS requires 348.0853.

12. 3-(2-bromophenylthio)-2-phenylquinolin-4(1H)-one (2f)

White solid, melting point: > 260°C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 6.86 (dd, $J = 8.1$Hz, 1.5Hz, 1H), 6.99 (dt, $J = 7.5$Hz, 1.5Hz, 1H), 7.18 (dt, $J = 7.8$Hz, 1.2Hz, 1H), 7.41-7.54 (m, 7H), 7.74-7.76 (m, 2H), 8.13 (d, $J = 7.8$Hz, 1H), 12.38 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 107.8, 119.3, 119.5, 124.6, 124.8, 125.9, 126.2, 126.3, 128.3, 128.6, 128.9, 130.3, 132.8, 132.9, 135.3, 139.5, 140.0, 157.4, 175.3. HRMS (ESI$^+$): [M+H]$^+$, found 408.0053. C$_{21}$H$_{15}$BrNOS requires 408.0052.
13. 3-(naphthalen-2-ylthio)-2-phenylquinolin-4(1H)-one (2g)

White solid, melting point: >260°C, $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 7.19-7.22 (m, 1H), 7.38-7.52 (m, 7H), 7.57-7.60 (m, 2H), 7.71-7.82 (m, 5H), 8.13 (d, $J = 8.1$Hz, 1H), 12.35 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 107.9, 118.7, 122.2, 124.1, 124.2, 124.3, 124.9, 125.4, 126.4, 126.6, 127.5, 128.0, 128.1, 128.5, 129.7, 130.7, 132.4, 133.3, 135.0, 136.1, 139.5, 156.6, 175.1.

14. 2-(4-fluorophenyl)-3-(phenythio)quinolin-4(1H)-one (2h)

White solid, melting point: 236-238°C, $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 6.99-7.07 (m, 3H), 7.15-7.20 (m, 2H), 7.30-7.44 (m, 3H), 7.57-7.62 (m, 2H), 7.69-7.77 (m, 2H), 8.12 (d, $J = 7.5$Hz, 1H), 12.30 (s, 1H).$^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 108.8, 115.4, 115.6, 119.2, 124.5, 124.7, 124.9, 125.4, 125.6, 125.9, 129.2, 131.5, 131.6, 131.8, 131.9, 132.9, 138.6, 139.9, 156.0, 161.6, 14.9, 175.5.

15. 3-(4-fluorophenylthio)-2-(4-fluorophenyl)quinolin-4(1H)-one (2i)

White solid, melting point: 230-232°C; $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 7.02-7.03 (m, 3H), 7.05-7.44 (m, 3H), 7.58-7.74 (m, 4H), 8.12 (d, $J =$
8.1Hz, 1H), 12.29 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 106.0, 111.9, 112.2, 112.5, 112.8, 115.3, 115.7, 117.9, 121.2, 121.3, 122.5, 124.5, 124.6, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 129.2, 129.4,130.5, 130.6, 131.4, 136.3, 136.4, 149.2, 152.4, 155.5, 158.2, 161.4, 170.6, 172.0. HRMS (ESI$^+$): [M+H]$^+$, found 366.0762. C$_{21}$H$_{14}$F$_2$NOS requires 366.0759.

16. 3-(4-chlorophenylthio)-2-(4-fluorophenyl)quinolin-4(1H)-one (2j)

White solid, melting point: 158-160°C, $^1$H NMR (300 MHz, DMSO-d$_6$) δ 7.01-7.04 (m, 2H), 7.22-7.25 (m, 2H), 7.32-7.45 (m, 3H), 7.57-7.62 (m, 2H), 7.69-7.75 (m, 2H), 8.12 (d, $J = 8.1$Hz, 1H), 12.22 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 107.9, 114.9, 115.2, 118.8, 124.1, 124.3, 125.4, 126.8, 128.5, 128.9, 130.9, 131.1, 131.2, 131.3, 132.4, 137.3, 139.4, 156.6, 161.1, 164.4, 174.8.

17. 2-(4-fluorophenyl)-3-(naphthalene-2-y1thio)quinolin-4(1H)-one (2k)

White solid, melting point: 170-172°C, $^1$H NMR (300 MHz, DMSO-d$_6$) δ 7.21 (dd, $J = 8.4$Hz, 2.1Hz, 1H), 7.30-7.47 (m, 6H), 7.62-7.82 (m, 7H), 8.12 (d, $J = 7.8$Hz, 1H), 12.34 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) δ 108.8, 115.4, 115.7, 119.2, 122.9, 124.7, 124.9, 125.4, 125.9, 126.9, 127.1, 127.9, 128.5, 131.2, 131.5, 131.6, 131.9, 132.8, 133.9, 136.4, 140.0, 156.1, 161.6, 164.9, 175.6.
18. 3-(2-bromophenylthio)-2-(4-fluorophenyl)quinolin-4(1H)-one (2l)

![Chemical Structure of 3-(2-bromophenylthio)-2-(4-fluorophenyl)quinolin-4(1H)-one (2l)](image)

White solid, melting point: 250-252°C.\(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 6.85 (dd, \(J = 7.8\) Hz, 1.5 Hz, 1H), 7.00 (dt, \(J = 7.5\) Hz, 1.5 Hz, 1H0, 7.15-7.20 (m, 1H), 7.31-7.37 (m, 2H), 7.41-7.61 (m, 6H), 7.73-7.76 (m, 2H), 8.13 (dd, \(J = 7.8\) Hz, 1.2 Hz, 1H), 12.30 (s, 1H).\(^13\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 108.0, 115.5, 115.7, 119.3, 119.5, 124.6, 124.9, 125.9, 126.2, 126.3, 128.4, 131.4, 131.5, 131.6, 131.7, 132.8, 133.0, 139.4, 140.0, 156.5, 161.7, 162.8, 165.0, 175.3. HRMS (ESI\(^+\)): [M+H]\(^+\) found 425.9960. \(\text{C}_{21}\text{H}_{14}\text{BrFNOS}\) requires 425.9958.

19. 3-(4-chlorophenylthio)-2-(4-methoxyphenyl)quinolin-4(1H)-one (2m)

![Chemical Structure of 3-(4-chlorophenylthio)-2-(4-methoxyphenyl)quinolin-4(1H)-one (2m)](image)

White solid, melting point: 220-222°C.\(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 3.81 (s, 3H), 7.00-7.07 (m, 4H), 7.22-7.24 (m, 2H), 7.47 (d, \(J = 8.7\) Hz, 3H), 7.71 (s, 2H), 8.10 (d, \(J = 8.1\) Hz, 1H), 12.35 (s, 1H); \(^13\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 55.8, 109.2, 114.1, 116.5, 119.2, 126.5, 127.3, 129.2, 129.8, 130.6, 130.7, 131.1, 133.1, 135.4, 141.6, 148.8, 159.8, 176.1.
20. 3-(4-chlorophenylthio)-2-cyclohexylquinolin-4(1H)-one (2n)

White solid, melting point: 238-240°C; $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 1.17-1.29 (m, 3H), 1.63-1.83 (m, 7H), 7.02-7.13 (m, 4H), 7.35 (t, $J = 7.2$Hz, 1H), 7.59 (dt, $J = 7.2$Hz, 1.5Hz, 1H), 7.80-7.83 (m, 1H), 8.05 (dd, $J = 8.1$Hz, 1.2Hz, 1H), 11.29 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 25.6, 26.3, 30.5, 42.5, 108.8, 116.1, 116.4, 118.9, 124.3, 124.4, 125.8, 128.3, 128.4, 132.6, 134.1, 134.2, 139.9, 162.5, 175.4.

21. 3-(4-fluorophenylthio)-2-(4-chlorophenyl)quinolin-4(1H)-one (2o)

White solid, melting point: 165-167°C, $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 7.00-7.03 (m, 4H), 7.37-7.43 (m, 1H), 7.52-7.58(m, 4H), 7.65-7.72 (m, 2H), 8.1 (dd, $J = 6.9$Hz, 1.5Hz, 1H), 12.30 (s, 1H). $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 115.5, 115.7, 120.8, 124.1, 124.2, 125.4, 127.6, 127.7, 128.1, 128.4, 130.6, 132.4, 133.4, 133.7, 134.5, 139.5, 147.4, 152.0, 155.2, 158.5, 161.7, 174.9.

22. 2-(4-chlorophenyl)-3-(phenythio)quinolin-4(1H)-one (2p)

White solid, melting point: 243-245°C, $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 6.99-7.07 (m, 3H), 7.16-7.21 (m, 2H), 7.40-7.45 (m, 1H), 7.57 (s, 4H), 7.68-
7.77 (m, 2H), 8.12 (d, J = 7.2Hz, 1H), 12.30 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 108.7, 119.2, 124.6, 124.7, 124.9, 125.6, 125.9, 128.6, 129.2, 131.0, 132.9, 134.2, 135.0, 138.5, 139.9, 155.8, 175.4.

23. 3-(4-fluorophenylthio)-2-(4-methoxyphenyl)quinolin-4(1H)-one (2q)

![Chemical Structure]

White solid, melting point : 190-192°C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 3.82 (s, 3H), 7.02-7.07 (m, 7H), 7.40-7.41 (m, 1H), 7.70-7.73 (m, 2H), 8.10 (d, J = 8.1Hz, 1H), 12.20 (s, 1H); $^{13}$C NMR (75MHz, DMSO-$d_6$) δ 55.8, 109.2, 113.9, 115.9, 116.2, 119.1, 124.5, 125.9, 127.7, 127.8, 127.9, 130.8, 132.7, 134.4, 139.9, 156.7, 160.9, 175.5

24. 2-(4-methoxyphenyl)-3-(naphthalene-2-ythio)quinolin-4(1H)-one (2r)

![Chemical Structure]

White solid, melting point: >260°C, $^1$H NMR (300 MHz, DMSO-$d_6$) δ 3.78 (s, 3H), 7.03 (dd, J = 6.6Hz, 2.1Hz, 2H), 7.20 (dd, J = 8.7Hz, 1.8Hz, 1H), 7.37-7.46 (m, 4H), 7.53 (dd, J = 6.9Hz, 2.1Hz, 2H), 7.70-7.82 (m, 6H), 8.11 (d, J = 7.8Hz, 1H), 12.23 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 55.8, 108.3, 113.9, 119.2, 122.5, 124.5, 124.6, 124.8, 125.4, 125.9, 126.9, 127.1, 127.7, 128.0, 128.5, 130.7, 131.2, 132.8, 133.9, 136.8, 140.0, 156.9, 160.9, 175.6.
25. 2-(4-methoxyphenyl)-3-(phenylthio)quinolin-4(1H)-one (2t)

White solid, melting point: 228-230°C, $^1$H NMR (300 MHz, DMSO-d$_6$) $\delta$ 3.76 (s, 3H), 6.78 (dd, $J = 6.9$Hz, 1.8Hz, 2H), 6.96 (dd, $J = 6.9$Hz, 1.8Hz, 2H), 7.40-7.45 (m, 1H), 7.52-7.56 (m, 5H), 7.70-7.74 (m, 2H), 8.11 (d, $J = 8.1$Hz, 1H), 12.23 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-d$_6$) $\delta$ 55.8, 109.0, 111.4, 115.7, 121.1, 122.4, 124.9, 125.0, 125.7, 125.8, 126.7, 130.7, 132.7, 134.0, 139.9, 153.0, 156.8, 160.9, 175.5.
$^1$H and $^{13}$C NMR spectra of entry 1e in DMSO-d$_6$
$^1$H and $^{13}$C NMR spectra of entry 2a (Scheme-IV.1.) in DMSO-$d_6$
$^1$H and $^{13}$C NMR spectra of entry 2i (Scheme-IV.1.) in DMSO-d$_6$
$^1$H and $^{13}$C NMR spectra of entry 2r (Scheme-IV.1.) in DMSO-d$_6$
Scan copy HRMS of entry 2b (Scheme-IV.1)

Scan copy HRMS of entry 2i (Scheme-IV.1)
IV.E. References

References are given in BIBLIOGRAPHY under Chapter IV (pp-232-233)