

**4. RESULTS AND DISCUSSION**

In order to fulfil the proposed aims and objectives, the present work is discussed under the following three main heads

**4.1 Chemical work****4.2 Biological work****4.3 Computational Study****4.1 Chemical work**

Two types of compounds have synthesized under this categories

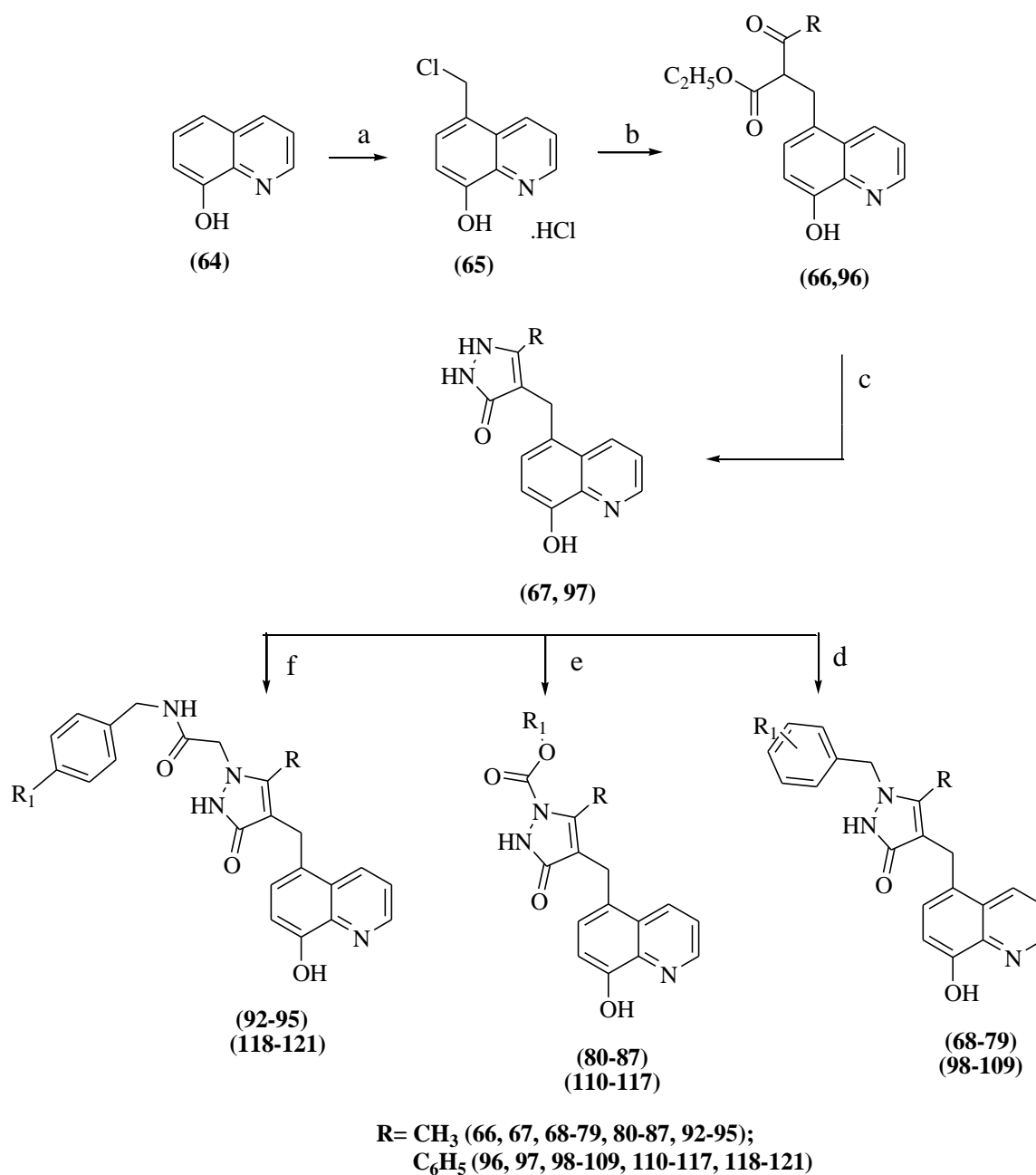
**4.1.1 Pyrazolone based multifunctional anti-AD compounds (66-121)****4.1.2 Pyrimidinone based multifunctional anti-AD compounds (122-150)****4.1.1 Pyrazolone based multifunctional anti-AD agents**

**4.1.1.1** Pyrazolone based multifunctional anti-AD compounds were synthesized by using general **Scheme 4.1.1.1 (66-121)**

Two types of compounds have synthesized under this categories

**4.1.1.2** 1,2-Dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-5-methylpyrazol-3-one derivatives (**66-95**)

**4.1.1.3** 1,2-Dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-5-phenylpyrazol-3-one derivatives (**95-121**)



**Scheme 4.1.1.1:** General synthetic scheme for compounds (66-121); reagents and conditions: (a) HCl, formaldehyde, HCl gas; (b) ethyl acetoacetate, DMF, NaH; (c) hydrazine hydrate, EtOH, reflux, 2hr; (d) substituted benzyl halide, DMF,  $\text{K}_2\text{CO}_3$ , RT; (e) substituted chloro formates, DMF,  $\text{K}_2\text{CO}_3$ , RT; (f) *N*-benzylacetamide, DMF,  $\text{K}_2\text{CO}_3$ , 80°C.

#### 4.1.1.2. 1,2-Dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-5-methylpyrazol-3-one derivatives (68-95)

The work carried out under this heading has been further divided into 3 sub headings:

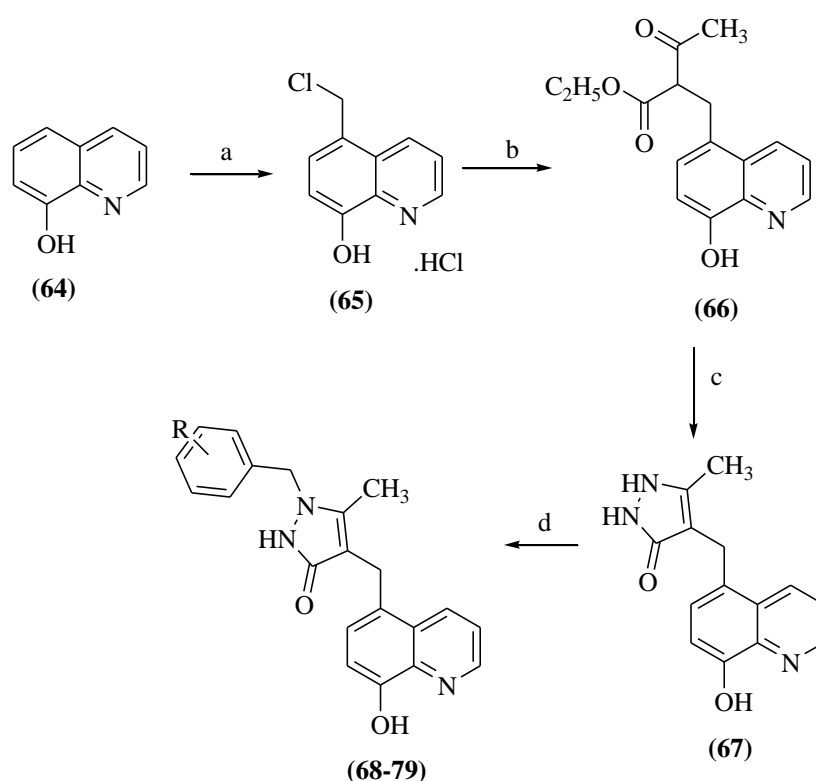
##### 4.1.1.2.1. Synthesis of *N*-substituted 1-benzyl-1,2-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-5-methylpyrazol-3-one derivatives (68-79)

4.1.1.2.2. Synthesis of *N*-substituted methyl 2,3-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-5-methyl-3-oxopyrazole-1-carboxylate derivatives (**80-87**)

4.1.1.2.3. Synthesis of *N*-substituted benzyl-2-(2,3-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-5-methyl-3-oxopyrazol-1-yl)acetamide derivatives (**92-95**)

4.1.1.2.1. Synthesis of *N*-substituted 1-benzyl-1,2-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-5-methylpyrazol-3-one derivatives (**68-79**)

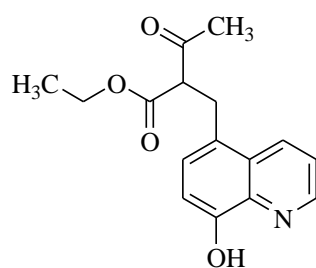
To synthesize the designed compounds the following strategies adopted as mentioned in Scheme-4.1.1.2.1



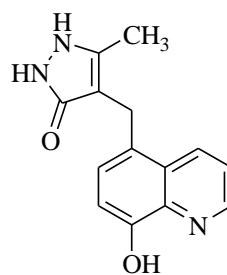
**Scheme-4.1.1.2.1.** General synthetic route for the synthesis of compounds (**68-79**); reagents and conditions: (a) HCl, formaldehyde, HCl gas; (b) ethyl acetoacetate, DMF, NaH, (c) hydrazine hydrate, EtOH, reflux, 2hr; (d) substituted benzyl amine, DMF, K<sub>2</sub>CO<sub>3</sub>, RT.

Firstly, 8-hydroxyquinoline (**64**) was treated with conc. HCl and formaldehyde in presence of HCl gas to obtain 5-(chloromethyl)-8-hydroxyquinoline hydrochloride<sup>1</sup> (**65**). Further nucleophilic substitution reaction was carried out using ethyl acetoacetate and NaH to get ethyl 2-((8-hydroxyquinolin-5-yl)methyl)-3-oxobutanoate (**66**). IR spectrum of compound (**66**) showed peaks at 3332 cm<sup>-1</sup> (for -OH), at 2970 cm<sup>-1</sup> (aromatic C-H stretching) and at 1709 cm<sup>-1</sup> for the presence of -C=O stretching. The mass spectrum showed quasi molecular ion at

$m/z$  288.46  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound offered a singlet at  $\delta$  9.69 (s, 1H) for one proton of  $-\text{OH}$ . Five aromatic protons of quinoline showed doublet at  $\delta$  8.84-8.85 (d, 1H), at  $\delta$  8.47-8.49 (d, 1H), 7.56-7.59 (q, 1H), 7.23-7.25 (d, 1H) and 6.94-6.96 (d, 1H). Three aliphatic proton showed multiplet at 3.95-4.04 (m, 3H), while two aliphatic proton obtained multiplet at  $\delta$  3.31-3.48 (m, 2H). A singlet for three proton of both methyl group was seen at  $\delta$  2.17 (s, 3H) and at  $\delta$  0.99-1.02 (s, 3H).



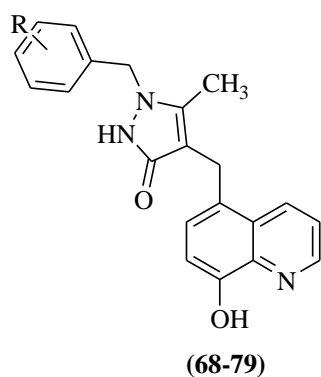
(66)



(67)

1,2-Dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-3-methylpyrazol-5-one (67) was obtained by cyclization of ethyl 2-((8-hydroxyquinolin-5-yl)methyl)-3-oxobutanoate (66) by hydrazine hydrate. IR spectrum of compound showed peaks at  $3333\text{ cm}^{-1}$  (for  $-\text{OH}$ ), at  $2970\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1713\text{ cm}^{-1}$  for the presence of  $-\text{C}=\text{O}$  stretching. The mass spectrum showed quasi molecular ion at  $m/z$  256.39  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum offered broad peaks at  $\delta$  10.43 and 9.58 for the amide and  $-\text{OH}$  proton respectively. The aromatic protons of quinoline showed doublet at  $\delta$  8.82-8.83 (d, 1H), at  $\delta$  8.62-8.60 (d, 1H), at  $\delta$  7.16-7.18 (d, 1H), at  $\delta$  6.98-6.96 (d, 1H) and  $\delta$  7.53-7.56 (dd, 1H). The signals for aliphatic protons were observed at  $\delta$  3.89 (s, 2H) and  $\delta$  1.90 (s, 3H).

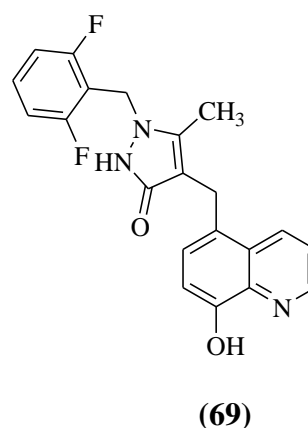
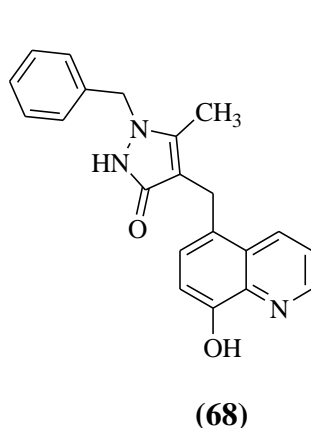
Synthesis of *N*-substituted 1-benzyl-1,2-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-5-methylpyrazol-3-one derivatives (68-79) was carried out by reacting 1,2-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-3-methylpyrazol-5-one (67) with the respective benzyl bromide as depicted in **Scheme 4.1.1.2.1**.



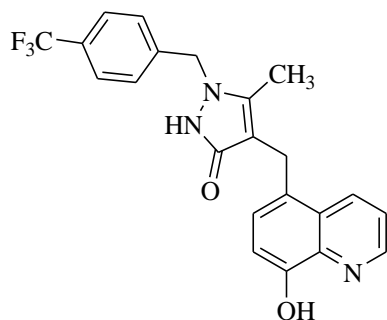
(68-79)

Comp.	R	Comp.	R
68.	H	74.	2-CF <sub>3</sub>
69.	2,6-diF	75.	2,5-diCH <sub>3</sub>
70.	4-CF <sub>3</sub>	76.	4-F
71.	3,5-diF	77.	3-Cl
72.	4-Cl	78.	3,5-diCH <sub>3</sub>
73.	2,6-diCl	79.	4-CH <sub>3</sub>

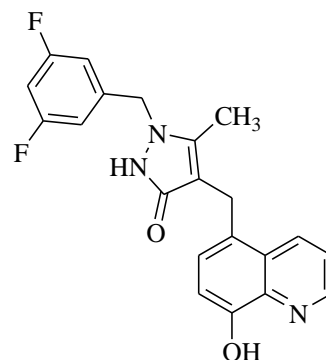
The IR spectrum of compound (**68**) showed characteristic peaks for -OH at  $3309\text{ cm}^{-1}$ , aromatic C-H stretching at  $2924\text{ cm}^{-1}$  and the presence of -C=O stretching of amide at  $1633\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z\ 346.3\ [M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**68**) offered broad peaks at  $\delta\ 9.51$  for the -OH proton. Two aromatic protons of quinoline showed doublet at  $\delta\ 8.85$  (d,  $J = 4.2\ \text{Hz}$ , 1H) and at  $\delta\ 8.62$  (d,  $J = 8.6\ \text{Hz}$ , 1H) while another 3 proton showed doublet of doublet at  $\delta\ 7.57$  (dd,  $J = 8.5, 4.2\ \text{Hz}$ , 1H) and  $6.98$  (dd,  $J = 7.8, 2.5\ \text{Hz}$ , 2H). Five aromatic proton of benzene ring obtain multiplet at  $7.36 - 7.24$  (m, 5H). Two aliphatic proton between the pyrazolone and benzene ring showed singlet at  $5.04$  (s, 2H) and another two aliphatic proton obtained singlet at  $\delta\ 3.93$  (s, 2H), while a singlet for three proton of methyl group was seen at  $\delta\ 1.97$  (s, 3H).



The IR spectrum of synthesized compounds (**69**) showed characteristic peaks for -OH at  $3314\text{ cm}^{-1}$ , aromatic C-H stretching at  $2957\text{ cm}^{-1}$  and the presence of -C=O stretching of amide at  $1698\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z\ 382.2\ [M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**69**) offered broad peaks at  $\delta\ 9.53$  for the -OH proton. Two aromatic protons of quinoline showed doublet at  $\delta\ 8.84$  (d,  $J = 5.7\ \text{Hz}$ , 1H), at  $\delta\ 8.61$  (d,  $J = 10.2\ \text{Hz}$ , 1H), at  $7.08$  (d,  $J = 8.1\ \text{Hz}$ , 1H) and at  $6.97$  and (d,  $J = 7.9\ \text{Hz}$ , 1H) while another 1 proton showed doublet of doublet at  $7.56$  (dd,  $J = 8.6, 4.2\ \text{Hz}$ , 1H). Three aromatic proton of benzene ring showed multiplet at  $7.43 - 7.39$  (m, 1H) and at  $7.18 - 7.12$  (m, 2H). Two aliphatic proton between the pyrazolone and benzene ring showed singlet at  $5.03$  (s, 2H) and another two aliphatic proton obtained singlet at  $\delta\ 3.88$  (s, 2H), while a singlet for three proton of methyl group was seen at  $\delta\ 2.14$  (s, 3H).



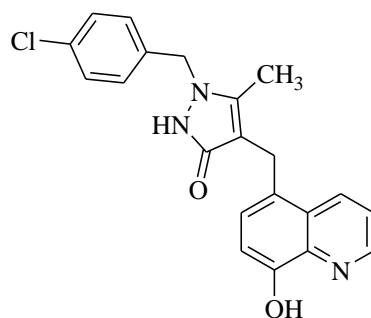
(70)



(71)

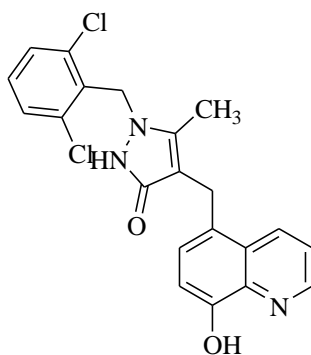
The IR spectrum of compound (70) showed characteristic peaks for -OH at 3391  $\text{cm}^{-1}$ , aromatic C-H stretching at 2958  $\text{cm}^{-1}$  and the presence of -C=O stretching of amide at 1696  $\text{cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z$  414.2  $[\text{M}+\text{H}]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (70) offered broad peaks at  $\delta$  11.53 and 9.53 for the amide and -OH proton respectively. Two aromatic protons of quinoline showed doublet at  $\delta$  8.82 (d,  $J = 5.7$  Hz, 1H), at  $\delta$  8.52 (d,  $J = 10.2$  Hz, 1H), at 7.19 (d,  $J = 7.9$  Hz, 1H) and 6.98 (d,  $J = 7.8$  Hz, 1H) while another proton showed doublet of doublet at  $\delta$  7.46 (dd,  $J = 8.6, 4.1$  Hz, 1H). Four aromatic proton of benzene ring observed at 7.74 (d,  $J = 7.6$  Hz, 1H), 7.60 (t,  $J = 6.9$  Hz, 1H) and 7.53 (d,  $J = 7.5$  Hz, 2H). Two aliphatic proton between the pyrazolone and benzene ring showed singlet at 5.33 (s, 2H) and another two aliphatic proton obtained singlet at  $\delta$  3.96 (s, 2H), while a singlet for three proton of methyl group was seen at  $\delta$  2.00 (s, 3H).

The IR spectrum of compound (71) showed characteristic peaks for -OH at 3306  $\text{cm}^{-1}$ , aromatic C-H stretching at 2920  $\text{cm}^{-1}$  and the presence of -C=O stretching of amide at 1627  $\text{cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z$  382.1  $[\text{M}+\text{H}]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (71) offered broad peaks at  $\delta$  12.35 and 9.49 for the amide and -OH proton respectively. The aromatic protons of quinoline showed signal at 8.78 (dd,  $J = 4.1, 1.6$  Hz, 1H), 8.35 (dd,  $J = 8.6, 1.6$  Hz, 1H), 7.69 – 7.64 (m, 1H), 7.58 – 7.46 (m, 3H), 7.12 (d,  $J = 7.9$  Hz, 1H) and 6.79 (d,  $J = 7.8$  Hz, 1H). The aliphatic protons the pyrazolone and benzene ring showed singlet at 5.15 (s, 2H) of showed signal at 3.97 (s, 2H), while a singlet for three proton of methyl group was seen at  $\delta$  2.14 (s, 3H).



(72)

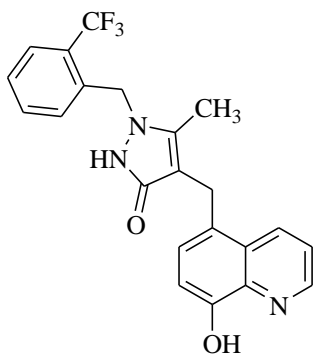
The IR spectrum of compound (72) showed characteristic peaks for -OH at  $3356\text{ cm}^{-1}$ , aromatic C-H stretching at  $2924\text{ cm}^{-1}$  and the presence of -C=O stretching of amide at  $1695\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $380.13\text{ [M+H]}^+$  and  $382.08\text{ [M+2]}^+$ . The  $^1\text{H-NMR}$  spectrum of compound (72) offered broad peaks at  $\delta\ 11.51\text{ (s, 1H)}$  and  $\delta\ 9.56\text{ (s, 1H)}$ , for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta\ 8.83\text{ (dd, } J = 4.2, 1.5\text{ Hz, 1H)}$ ,  $8.53\text{ (dd, } J = 8.6, 1.6\text{ Hz, 1H)}$ ,  $7.48\text{ (dd, } J = 8.6, 4.1\text{ Hz, 1H)}$ ,  $7.41 - 7.31\text{ (m, 4H)}$ ,  $7.17\text{ (d, } J = 7.9\text{ Hz, 1H)}$  and  $6.97\text{ (d, } J = 7.8\text{ Hz, 1H)}$ . The signals for aliphatic protons between the pyrazolone and benzene ring showed singlet at  $\delta\ 5.15\text{ (s, 2H)}$ , another two aliphatic proton showed singlet at  $\delta\ 3.93\text{ (s, 2H)}$ , while a singlet for three proton of methyl group was seen at  $1.99\text{ (s, 3H)}$ .



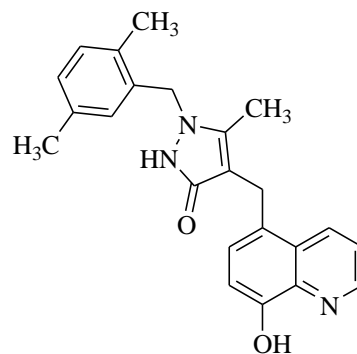
(73)

The IR spectrum of compound (73) showed characteristic peaks for -OH at  $3357\text{ cm}^{-1}$ , aromatic C-H stretching at  $2919\text{ cm}^{-1}$  and the presence of -C=O stretching of amide at  $1626\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $414.04\text{ [M+H]}^+$  and  $416.04\text{ [M+2]}^+$ . The  $^1\text{H-NMR}$  spectrum of compound (73) offered broad peaks at  $\delta\ 11.55\text{ (s, 1H)}$  and  $\delta\ 9.56\text{ (s, 1H)}$  for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta\ 8.83\text{ (dd, } J = 4.2, 1.5\text{ Hz, 1H)}$ ,  $8.52\text{ (dd, } J = 8.6, 1.6\text{ Hz, 1H)}$ ,  $7.64\text{ (d, } J = 1.5\text{ Hz, 1H)}$ ,  $7.49\text{ (dd, } J = 8.6, 4.2\text{ Hz, 1H)}$ ,  $7.36\text{ (d, } J = 1.6\text{ Hz, 2H)}$ ,  $7.19\text{ (d, } J = 7.9\text{ Hz, 1H)}$  and  $6.98\text{ (d, } J = 7.9\text{ Hz, 1H)}$ . The signals for aliphatic protons between the pyrazolone and benzene ring showed singlet

at  $\delta$  5.20 (s, 2H), another two aliphatic proton obtained singlet at  $\delta$  3.95 (s, 2H), while a singlet for three proton of methyl group was seen at 2.00 (s, 3H).



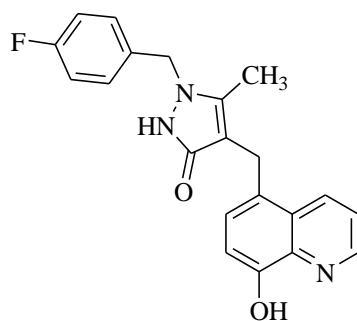
(74)



(75)

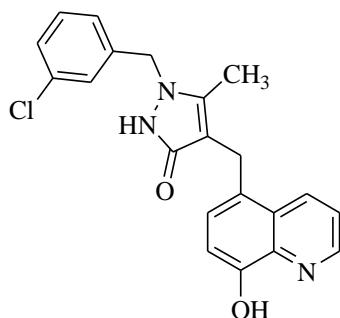
The IR spectrum of compound (74) showed characteristic peaks for -OH at 3347 cm<sup>-1</sup> and aromatic C-H stretching at 2922 cm<sup>-1</sup>. The mass spectrum showed quasi molecular ion at 414.2 [M+H]<sup>+</sup>. The <sup>1</sup>H-NMR spectrum of compound (74) offered broad peaks at 11.53 (s, 1H) and 9.56 (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated  $\delta$  8.83 (dd,  $J$  = 4.1, 1.6 Hz, 1H), 8.54 (dd,  $J$  = 8.6, 1.6 Hz, 1H), 7.68 (d,  $J$  = 8.1 Hz, 3H), 7.52 (d,  $J$  = 8.0 Hz, 3H), 7.19 (d,  $J$  = 7.8 Hz, 1H) and 6.98 (d,  $J$  = 7.8 Hz, 1H). The signals for aliphatic protons between the pyrazolone and benzene ring showed at  $\delta$  5.26 (s, 2H), another two aliphatic proton showed singlet at  $\delta$  3.96 (s, 2H), while a singlet for three proton of methyl group was seen at 2.00 (s, 3H).

The IR spectrum of compound (75) showed characteristic peaks for -OH at 3311 cm<sup>-1</sup> and aromatic C-H stretching at 2921 cm<sup>-1</sup> and the presence of -C=O stretching of amide at 1684 cm<sup>-1</sup>. The mass spectrum showed quasi molecular ion at 374.2 [M+H]<sup>+</sup>. The <sup>1</sup>H-NMR spectrum of compound (75) offered broad peaks at  $\delta$  9.51 (s, 1H) for the -OH proton. The signals for aromatic protons demonstrated  $\delta$  8.78 (d,  $J$  = 10.4 Hz, 1H), 8.61 (d,  $J$  = 10.3 Hz, 1H), 7.59 (dd,  $J$  = 9.0, 4.1 Hz, 1H), 6.96 (d,  $J$  = 7.8 Hz, 1H), 6.91 – 6.84 (m, 3H) and 6.73 (s, 1H). The signals for aliphatic protons between the pyrazolone and benzene ring appeared at  $\delta$  4.94 (s, 2H), another two aliphatic proton showed singlet at  $\delta$  3.92 (s, 2H), while a singlet for three proton of methyl group was seen at  $\delta$  2.06 (s, 3H). The six proton of methyl group observed at  $\delta$  2.18 (s, 6H).



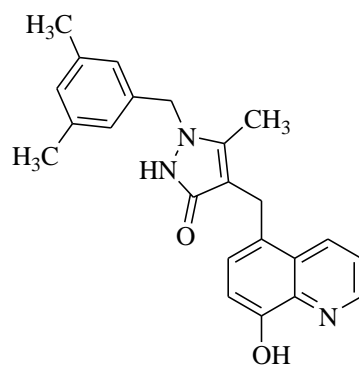
(76)

The IR spectrum of compound (76) showed characteristic peaks for -OH at 3287 cm<sup>-1</sup> and aromatic C-H stretching at 2921 cm<sup>-1</sup> and the presence of -C=O stretching of amide at 1673 cm<sup>-1</sup>. The <sup>1</sup>H-NMR spectrum of compound (76) offered broad peaks at  $\delta$  9.53 (s, 1H) for the -OH proton. The signals for aromatic protons demonstrated  $\delta$  8.84 (dd,  $J$  = 4.2, 1.6 Hz, 1H), 8.61 (dd,  $J$  = 8.6, 1.7 Hz, 1H), 7.57 (dd,  $J$  = 8.6, 4.1 Hz, 1H), 7.16 – 7.08 (m, 5H), 6.97 (d,  $J$  = 7.8 Hz, 1H). The signals for aliphatic protons between the pyrazolone and benzene ring appeared at  $\delta$  5.01 (s, 2H), another two aliphatic proton obtained singlet at  $\delta$  3.91 (s, 2H), while a singlet for three proton of methyl group was seen at  $\delta$  1.97 (s, 3H).



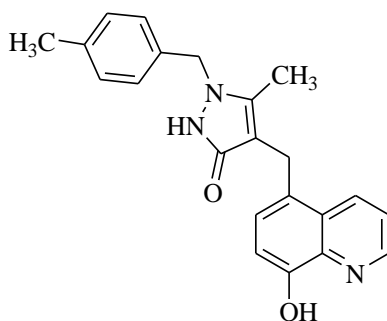
(77)

The IR spectrum of compound (77) showed characteristic peaks for -OH at 3322cm<sup>-1</sup> and aromatic C-H stretching at 2922 cm<sup>-1</sup> and the presence of -C=O stretching of amide at 1692 cm<sup>-1</sup>. The mass spectrum showed quasi molecular ion at 380.13 [M+H]<sup>+</sup> and 382.8 [M+2]<sup>+</sup>. The <sup>1</sup>H-NMR spectrum of compound (77) offered broad peaks at 11.52 (s, 1H) and 9.55 (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated  $\delta$  8.83 (dd,  $J$  = 4.1, 1.5 Hz, 1H), 8.55 (dd,  $J$  = 8.7, 1.6 Hz, 1H), 7.49 (dd,  $J$  = 8.6, 4.2 Hz, 1H), 7.41 – 7.31 (m, 4H), 7.19 (d,  $J$  = 7.9 Hz, 1H) and 6.97 (dd,  $J$  = 7.8, 2.9 Hz, 2H). The signals for aliphatic protons between the pyrazolone and benzene ring showed at  $\delta$  5.18 (s, 2H), another two aliphatic proton obtained singlet at  $\delta$  3.94 (s, 2H), while a singlet for three proton of methyl group was seen at  $\delta$  2.00 (s, 3H).



(78)

The IR spectrum of compound (78) showed characteristic peaks for -OH at 3314 cm<sup>-1</sup> and aromatic C-H stretching at 2971 cm<sup>-1</sup> and the presence of -C=O stretching of amide at 1604 cm<sup>-1</sup>. The mass spectrum showed quasi molecular ion at 374.2 [M+H]<sup>+</sup>. The <sup>1</sup>H-NMR spectrum of compound (78) offered broad peaks at 11.47 (s, 1H) and 9.54 (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated δ 8.83 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.56 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.47 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 2.9 Hz, 1H), 6.90 (s, 2H) and 6.85 (s, 1H). The signals for aliphatic protons between the pyrazolone and benzene ring showed at δ 5.07 (s, 2H), another two aliphatic proton obtained singlet at δ 3.92 (s, 2H), while a singlet for three proton of methyl group was seen at δ 2.13 (s, 3H). The two proton of methyl group observed at δ 2.22 (s, 6H).



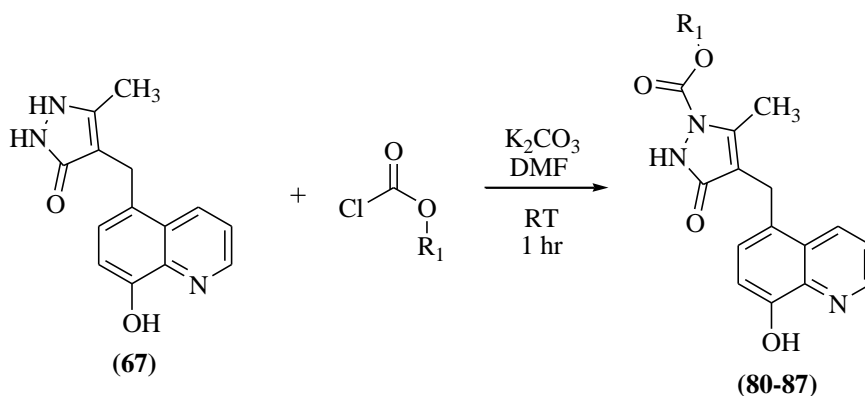
(79)

The IR spectrum of compound (79) showed characteristic peaks for -OH at 3139 cm<sup>-1</sup> and aromatic C-H stretching at 2912 cm<sup>-1</sup>. The mass spectrum showed quasi molecular ion at 360.16 [M+H]<sup>+</sup>. The <sup>1</sup>H-NMR spectrum of compound (79) offered broad peaks at δ 11.48 (s, 1H) and 9.54 (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at δ 8.82 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.54 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.46 (dd, *J* = 8.6, 4.1 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.19 – 7.12 (m, 3H) and 6.96 (d, *J* = 7.8 Hz, 1H). The signals for aliphatic protons between the pyrazolone and benzene ring showed at δ 5.11 (s, 2H),

another two aliphatic proton obtained singlet at  $\delta$  3.91 (s, 2H), while a singlet for three proton of two methyl group were seen at  $\delta$  2.29 (s, 3H) and  $\delta$  1.98 (s, 3H).

#### 4.1.1.2.2. Synthesis of *N*-substituted methyl 2,3-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-5-methyl-3-oxopyrazole-1-carboxylate derivatives (80-87)

To synthesize the designed compounds the following strategies adopted as mentioned in **Scheme-4.1.2.2**

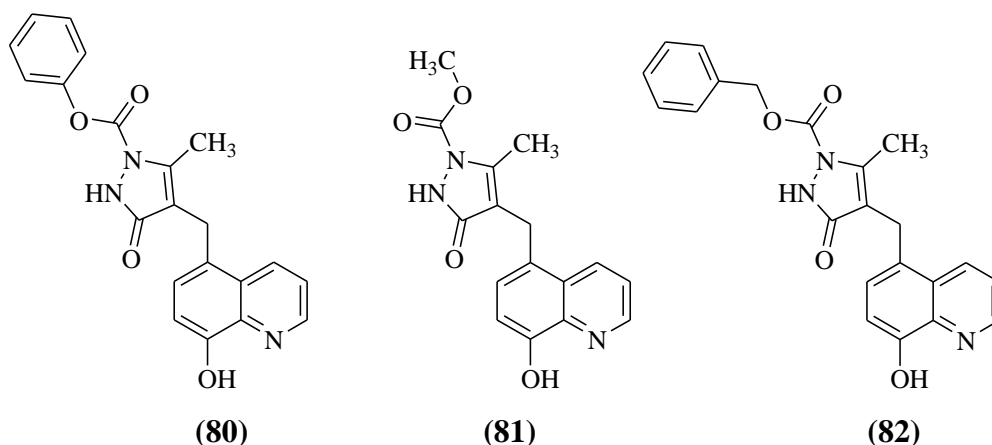


**Scheme-4.1.1.2.2.** General synthetic route for the synthesis of compounds (80-84); Reagents and conditions: substituted chloro formates, DMF,  $K_2CO_3$ , RT.

Synthesis of *N*-substituted methyl 2,3-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-5-methyl-3-oxopyrazole-1-carboxylate derivatives (80-87) was carried out by reacting 1,2-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-3-methylpyrazol-5-one (67) with various substituted chloroformates in presence base as depicted in **Scheme 4.1.1.2.2**.

Comp.	R <sub>1</sub>	Comp.	R <sub>1</sub>
80.		84.	
81.	-CH <sub>3</sub>	85.	
82.		86.	
83.		87.	

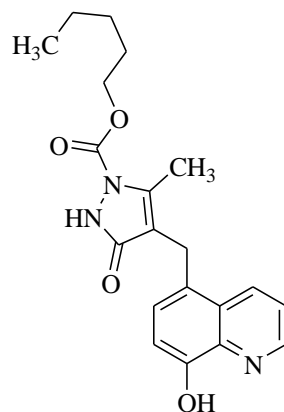
The IR spectrum of compound (**80**) showed characteristic peaks for -OH at  $3333\text{ cm}^{-1}$ , aromatic C-H stretching at  $2919\text{ cm}^{-1}$  and C=O stretching at  $1746\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $376.3\text{ [M+H]}^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**80**) offered broad peaks at  $\delta\ 11.32$  (s, 1H) and  $9.62$  (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta\ 8.87$  (dd,  $J = 4.1, 1.5\text{ Hz}$ , 1H),  $8.62$  (dd,  $J = 8.7, 1.6\text{ Hz}$ , 1H),  $7.62$  (dd,  $J = 8.6, 4.2\text{ Hz}$ , 1H),  $7.50 - 7.43$  (m, 2H),  $7.35 - 7.28$  (m, 3H),  $7.15$  (d,  $J = 8.0\text{ Hz}$ , 1H) and  $7.00$  (d,  $J = 7.9\text{ Hz}$ , 1H). The signals for aliphatic protons between the pyrazolone and quinoline ring appeared at  $\delta\ 4.02$  (s, 2H) while three proton of methyl group were seen at  $\delta\ 2.39$  (s, 3H).



The IR spectrum of compound (**81**) showed characteristic peaks for -OH at  $3399\text{ cm}^{-1}$ , aromatic C-H stretching at  $2910\text{ cm}^{-1}$  and C=O stretching at  $1750\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $314.12\text{ [M+H]}^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**81**) offered broad peaks at  $\delta\ 12.27$  (s, 1H) and  $9.61$  (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta\ 8.59$  (dd,  $J = 8.6, 1.6\text{ Hz}$ , 1H),  $8.36$  (dd,  $J = 8.6, 1.6\text{ Hz}$ , 1H),  $7.55$  (dd,  $J = 8.6, 4.1\text{ Hz}$ , 1H),  $7.15$  (d,  $J = 7.8\text{ Hz}$ , 1H) and  $6.98$  (d,  $J = 7.9\text{ Hz}$ , 1H). The signals for aliphatic protons between the pyrazolone and quinoline ring appeared at  $\delta\ 3.95$  (s, 2H) while three proton of methoxy and methyl group were seen at  $\delta\ 3.84$  (s, 3H) and  $2.07$  (s, 3H), respectively.

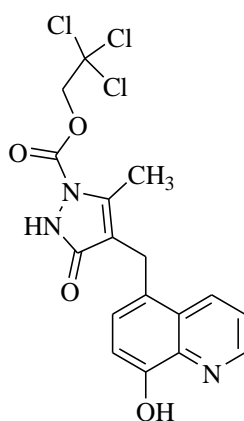
The IR spectrum of compound (**82**) showed characteristic peaks for -OH at  $3334\text{ cm}^{-1}$ , aromatic C-H stretching at  $2940\text{ cm}^{-1}$  and C=O stretching at  $1729\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $390.14\text{ [M+H]}^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**82**) offered broad peaks at  $\delta\ 11.13$  (s, 1H) and  $9.61$  (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta\ 8.86$  (dd,  $J = 4.2, 1.5\text{ Hz}$ , 1H),  $8.58$  (dd,  $J = 8.6, 1.6\text{ Hz}$ , 1H),  $7.59$  (dd,  $J = 8.6, 4.2\text{ Hz}$ , 1H),  $7.48 - 7.36$  (m, 5H),  $7.09$  (d,  $J = 7.9\text{ Hz}$ , 1H) and  $6.97$  (d,  $J = 7.9\text{ Hz}$ , 1H). The signals for aliphatic protons between the pyrazolone and benzyl

ring appeared at  $\delta$  5.31 (s, 2H) while another four proton was seen at  $\delta$  3.96 (s, 3H) and 2.35 (s, 3H).



(83)

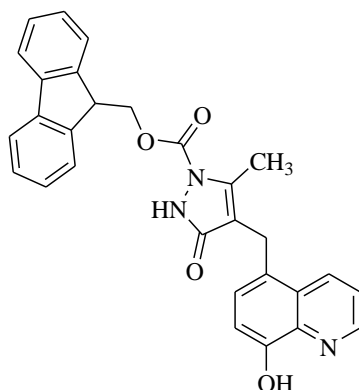
The IR spectrum of compound (83) showed characteristic peaks for -OH at  $3355\text{ cm}^{-1}$ , aromatic C-H stretching at  $2919\text{ cm}^{-1}$  and C=O stretching at  $1731\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $370.18\text{ [M+H]}^+$ . The  $^1\text{H-NMR}$  spectrum of compound (83) offered broad peaks at  $\delta$  11.10 (s, 1H) and 9.60 (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta$  8.86 (dd,  $J = 4.2, 1.5\text{ Hz}$ , 1H), 8.59 (dd,  $J = 8.6, 1.6\text{ Hz}$ , 1H), 7.60 (dd,  $J = 8.6, 4.1\text{ Hz}$ , 1H), 7.10 (d,  $J = 7.9\text{ Hz}$ , 1H) and 6.98 (d,  $J = 7.9\text{ Hz}$ , 1H). The signals for aliphatic protons observed at  $\delta$  4.24 (t,  $J = 6.6\text{ Hz}$ , 2H), 3.96 (s, 2H), 2.34 (s, 3H), 1.67 (p,  $J = 6.9\text{ Hz}$ , 2H), 1.35 – 1.30 (m, 4H) and 0.90 – 0.85 (m, 3H).



(84)

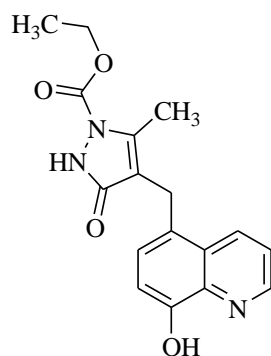
The IR spectrum of compound (84) showed characteristic peaks for -OH at  $3355\text{ cm}^{-1}$ , aromatic C-H stretching at  $2943\text{ cm}^{-1}$  and C=O stretching at  $1740\text{ cm}^{-1}$ . The  $^1\text{H-NMR}$  spectrum of compound (84) offered broad peaks at  $\delta$  11.40 (s, 1H) and 9.62 (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta$  8.86 (dd,  $J = 4.1, 1.6\text{ Hz}$ , 1H), 8.59 (dd,  $J = 8.6, 1.6\text{ Hz}$ , 1H), 7.61 (dd,  $J = 8.6, 4.2\text{ Hz}$ , 1H), 7.12 (d,  $J = 7.9\text{ Hz}$ , 1H) and

6.98 (d,  $J = 7.9$  Hz, 1H). The signals for aliphatic protons observed at  $\delta$  5.11 (s, 2H), 3.99 (s, 2H) and 2.39 (s, 3H).

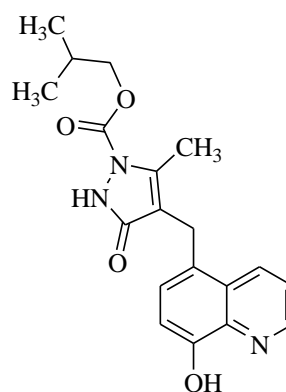


(85)

The IR spectrum of compound (85) showed characteristic peaks for -OH at  $3338\text{ cm}^{-1}$ , aromatic C-H stretching at  $2992\text{ cm}^{-1}$  and C=O stretching at  $1742\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $478.10\text{ [M+H]}^+$ . The  $^1\text{H-NMR}$  spectrum of compound (85) offered broad peaks at  $\delta$  11.10 (s, 1H) and 9.61 (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta$  8.86 (dd,  $J = 4.2, 1.5$  Hz, 1H), 8.57 (dd,  $J = 8.6, 1.6$  Hz, 1H), 7.89 (d,  $J = 4.9$  Hz, 2H), 7.76 (d,  $J = 7.3$  Hz, 2H), 7.60 (dd,  $J = 8.6, 4.1$  Hz, 1H), 7.42 (t,  $J = 7.2$  Hz, 2H), 7.35 (d,  $J = 7.5$  Hz, 2H), 7.05 (d,  $J = 7.9$  Hz, 1H) and 6.97 (d,  $J = 7.9$  Hz, 1H). The signals for aliphatic protons observed at  $\delta$  4.71 (d,  $J = 6.2$  Hz, 2H), 4.40 (t,  $J = 6.3$  Hz, 1H), 3.93 (s, 2H) and 2.04 (s, 3H).



(86)



(87)

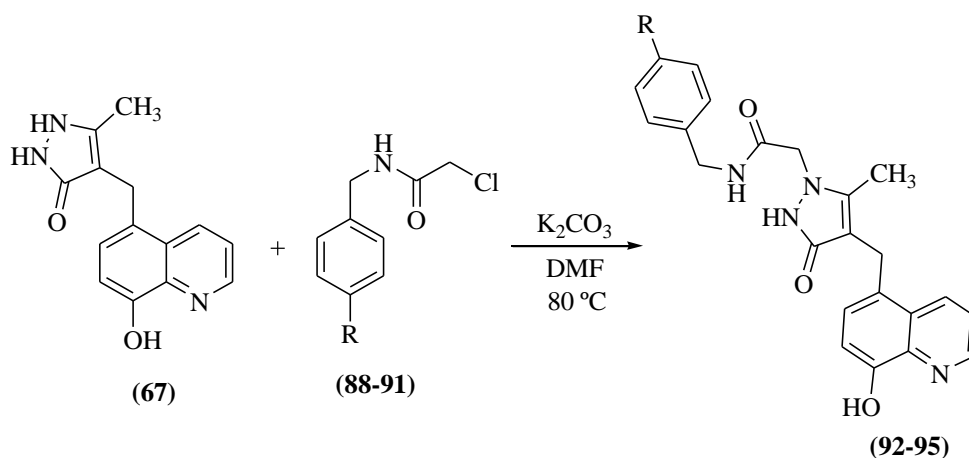
The IR spectrum of compound (86) showed characteristic peaks for -OH at  $3359\text{ cm}^{-1}$ , aromatic C-H stretching at  $2921\text{ cm}^{-1}$  and C=O stretching at  $1739\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $328.11\text{ [M+H]}^+$ . The  $^1\text{H-NMR}$  spectrum of compound (86) offered broad peaks at  $\delta$  11.11 (s, 1H) and 9.60 (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta$  8.86 (dd,  $J = 4.2, 1.5$  Hz, 1H), 8.59 (dd,  $J = 8.7,$

1.6 Hz, 1H), 7.60 (dd,  $J = 8.7, 4.2$  Hz, 1H), 7.10 (d,  $J = 7.9$  Hz, 1H) and 6.98 (d,  $J = 7.9$  Hz, 1H). The signals for aliphatic protons observed at  $\delta$  4.29 (q,  $J = 7.1$  Hz, 2H), 3.96 (s, 2H), 2.34 (s, 3H) and 1.29 (t,  $J = 7.1$  Hz, 3H).

The IR spectrum of compound (**87**) showed characteristic peaks for -OH at  $3315\text{ cm}^{-1}$ , aromatic C-H stretching at  $2918\text{ cm}^{-1}$  and C=O stretching at  $1728\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $356.16\text{ [M+H]}^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**87**) offered broad peaks at  $\delta$  11.11 (s, 1H) and 9.60 (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta$  8.86 (dd,  $J = 4.2, 1.5$  Hz, 1H), 8.59 (dd,  $J = 8.6, 1.6$  Hz, 1H), 7.60 (dd,  $J = 8.6, 4.2$  Hz, 1H), 7.10 (d,  $J = 7.9$  Hz, 1H) and 6.98 (d,  $J = 7.8$  Hz, 1H). The signals for aliphatic protons observed at  $\delta$  4.04 (d,  $J = 6.7$  Hz, 2H), 3.96 (s, 2H), 2.34 (s, 3H), 1.98 (dt,  $J = 13.4, 6.7$  Hz, 1H) and 0.94 (d,  $J = 6.7$  Hz, 6H).

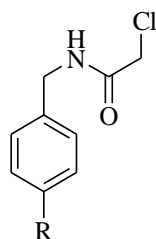
#### 4.1.1.2.3. Synthesis of *N*-substituted benzyl-2-(2,3-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-5-methyl-3-oxopyrazol-1-yl)acetamide derivatives (**92-95**)

To synthesize planned compounds the following strategies adopted as mentioned in Scheme-4.1.1.2.3



**Scheme-4.1.1.2.3.** General synthetic route for the synthesis of compounds (**92-95**); Reagents and conditions: substituted *N*-benzylacetamide, DMF,  $\text{K}_2\text{CO}_3$ ,  $80\text{ }^\circ\text{C}$ .

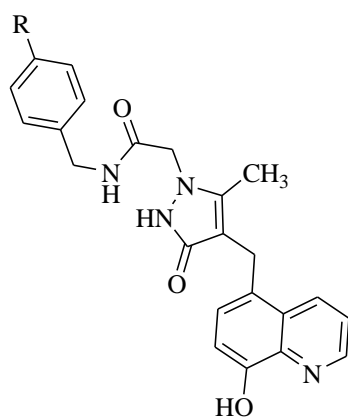
Synthesis of intermediate compounds (**88-91**) was carried out by the reaction of substituted benzyl amine with chloro acetyl chloride in presence of base to get substituted benzylacetamide (**88-91**). The characteristic data of compound (**88-91**) mentioned in table 4.1.1. Furthermore, substituted benzylacetamide (**88-91**) heated with compound (**67**) in the basic medium to get aimed compounds (**92-95**).



(88-91)

**Table 4.1.1.1.** Characterization data of substituted benzylacetamide

Comp.	R	M.P	I.R peaks ( cm <sup>-1</sup> )
<b>88.</b>	CH <sub>3</sub>	160-162°C (Reported: 164-166°C) <sup>2</sup>	3278, 2951, 2359, 1649, 1237, 806
<b>89.</b>	OCH <sub>3</sub>	118-120°C (Reported: 121-122°C) <sup>2</sup>	3278, 2915, 1649, 1513, 1108, 806
<b>90.</b>	Cl	275-276°C (Reported: 2757-278°C) <sup>3</sup>	3264, 2386, 1646, 1432, 1226, 432
<b>91.</b>	F	107-109°C (Reported: 111-112°C) <sup>4</sup>	3280, 2952, 2342, 1650, 1064, 854



(92-95)

Comp.	R
<b>92.</b>	CH <sub>3</sub>
<b>93.</b>	OCH <sub>3</sub>
<b>94.</b>	Cl
<b>95.</b>	F

The IR spectrum of compound (**92**) showed characteristic peaks for -OH at 3377cm<sup>-1</sup>, aromatic C-H stretching at 2959 cm<sup>-1</sup> and C=O stretching at 1654 cm<sup>-1</sup>. The mass spectrum showed quasi molecular ion at 417.25 [M+H]<sup>+</sup>. The <sup>1</sup>H-NMR spectrum of compound (**92**) offered broad peaks at δ 11.58 (s, 1H) and 9.56 (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at δ 8.86-8.87 (d, 1H), 8.64-8.66 (d, 1H), 8.24-8.26 (s, 1H), 7.54-7.56 (q, 1H), 7.24-7.26 (d, 1H), 7.13-7.19 (m, 3H) and 6.90-7.02 (d, 1H). The signals for aliphatic protons observed at δ 4.65 (s, 2H), 4.28-4.33 (d, 2H), 4.05 (s, 2H), 2.31-2.32 (s, 3H) and 1.19-2.03 (s, 3H).

The IR spectrum of compound (**93**) showed characteristic peaks for -OH at 3279  $\text{cm}^{-1}$ , aromatic C-H stretching at 2959  $\text{cm}^{-1}$  and C=O stretching at 1658  $\text{cm}^{-1}$ . The mass spectrum showed quasi molecular ion at 433.23  $[\text{M}+\text{H}]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**93**) offered broad peaks at  $\delta$  11.54 (s, 1H) and 9.54 (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta$  8.82-8.83 (d, 1H), 8.18-8.21 (t, 1H), 7.60-7.70 (m, 1H), 7.49-7.52 (q, 1H) and 6.84-7.22 (m, 5H). The signals for aliphatic protons observed at  $\delta$  4.59 (s, 2H), 4.25-4.26 (d, 2H), 4.10-4.15 (q, 2H), 4.00 (s, 2H), 3.73 (s, 3H) and 1.95 (s, 3H).

The IR spectrum of compound (**94**) showed characteristic peaks for -OH at 3274, aromatic C-H stretching at 2959  $\text{cm}^{-1}$  and C=O stretching at 1662  $\text{cm}^{-1}$ . Furthermore, compounds (**95**) showed characteristic peaks for -OH at 3358  $\text{cm}^{-1}$ , aromatic C-H stretching at 2924  $\text{cm}^{-1}$  and C=O stretching at 1638  $\text{cm}^{-1}$ . The mass spectrum showed quasi molecular ion at 421.22  $[\text{M}+\text{H}]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**95**) offered broad peaks at  $\delta$  11.59 (s, 1H) and 9.57 (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta$  8.86-8.89 (d, 1H), 8.64-8.67 (d, 1H), 8.32-8.34 (t, 1H), 7.75-7.77 (m, 1H), 7.70-7.72 (q, 1H), 7.54-7.56 (t, 1H), 7.19-7.24 (d, 1H), 7.13-7.18 (t, 1H) and 7.02-7.12 (d, 1H). The signals for aliphatic protons observed at  $\delta$  4.66 (d, 2H), 4.30-4.36 (d, 2H), 4.17-4.19 (t, 1H), 3.90-4.05 (s, 2H) and 1.19-2.02 (s, 3H).

#### 4.1.1.3.1,2-Dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-5-phenylpyrazol-3-one derivatives (**96-121**)

The synthetic methodologies for the preparation of the designed series of 1,2-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-3-phenylpyrazol-5-one derivatives have been discussed under three sub headings as mentioned bellows:

The work carried out under this heading has been further divided into three subheadings.

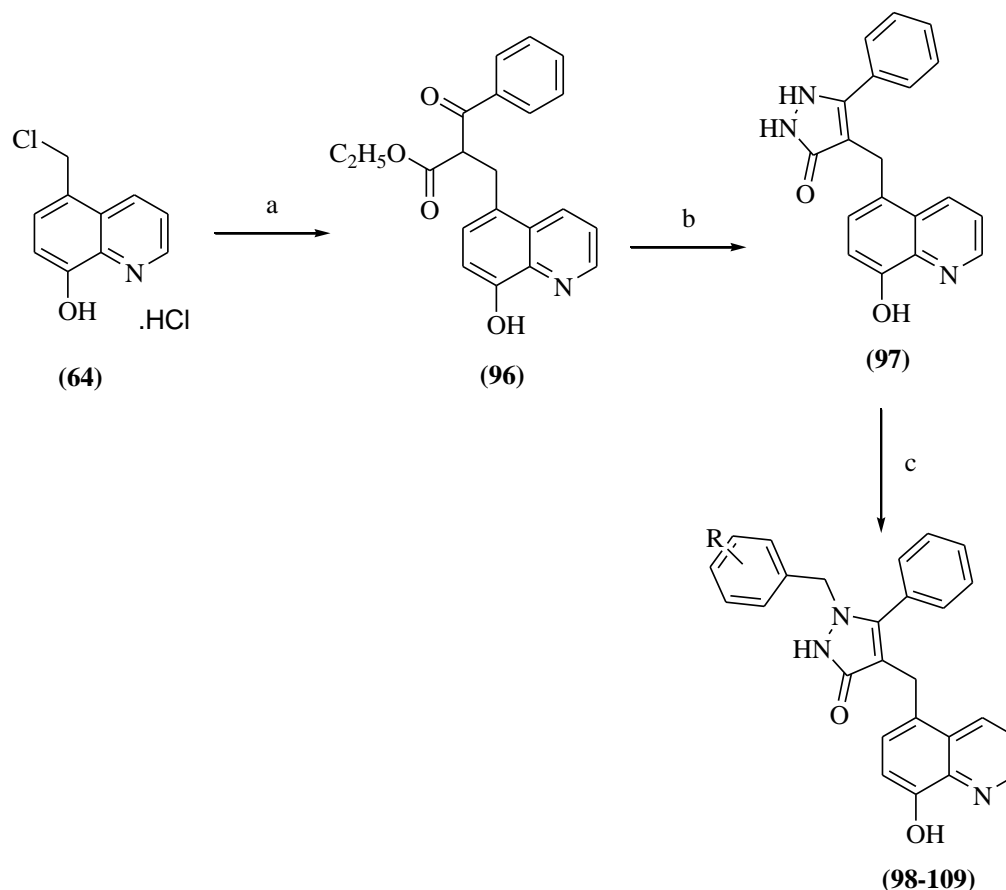
**4.1.1.3.1** Synthesis of *N*-substituted 2-benzyl-1,2-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-3-phenylpyrazol-5-one derivatives (**98-109**)

**4.1.1.3.2** Synthesis of *N*-substituted methyl 4-((8-hydroxyquinolin-5-yl)methyl)-5-oxo-3-phenyl-1*H*-pyrazole-2(5*H*)-carboxylate(**110-117**)

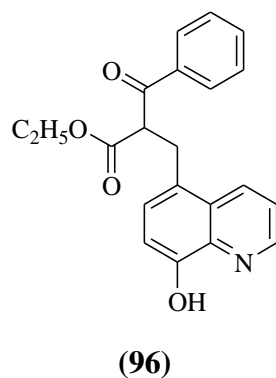
**4.1.1.3.3** Synthesis of *N*-benzyl-2-(4-((8-hydroxyquinolin-5-yl)methyl)-5-oxo-3-phenyl-1*H*-pyrazol-2(5*H*)-yl)acetamide (**118-121**)

#### 4.1.1.3.1.1. Synthesis of *N*-substituted 2-benzyl-1,2-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-3-phenylpyrazol-5-one derivatives (98-109)

To synthesize planned compounds the following strategies adopted as mentioned in Scheme-4.1.1.3.1

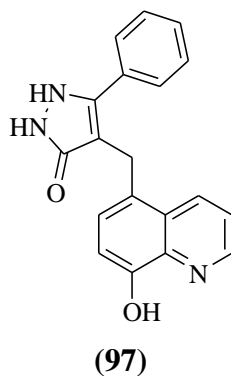


**Scheme-4.1.1.3.1.** General synthetic scheme of compounds (98-109); reagents and conditions:(a) ethyl 3-oxo-3-phenylpropanoate, DMF, NaH, (b) hydrazine hydrate, EtOH, reflux, 2h; (c) substituted benzyl amine, DMF, K<sub>2</sub>CO<sub>3</sub>, RT.



First, 5-(chloromethyl)-8-hydroxyquinoline hydrochloride (64) was treated with ethyl 3-oxo-3-phenylpropanoate in the presence of NaH to get the compound ethyl 2-(8-

hydroxyquinolin-5-yl)methyl)-3-oxo-3-phenylpropanoate (**96**). IR spectrum of compound (**96**) showed peaks at  $3334\text{ cm}^{-1}$  (for -OH), at  $2970\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1734\text{ cm}^{-1}$  for the presence of -C=O stretching. The mass spectrum showed quasi molecular ion at  $m/z$  350.59  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound offered a singlet at  $\delta$  9.63 (s, 1H) for one proton of -OH. The aromatic protons of quinoline and benzene ring appears at  $\delta$  8.84-8.85 (d, 1H), 8.55-8.58 (d, 1H), 7.86-7.88 (d, 2H), 7.57-7.63 (m, 2H), 7.45-7.49 (t, 2H), 7.27-7.29 (s, 1H) and 6.94-6.96 (d, 1H). Three aliphatic protons between the quinoline and ester moiety appears at  $\delta$  4.96-4.99 (t, 1H) and 3.88-3.96 (m, 2H), while five aliphatic proton of ester obtained triplet at  $\delta$  3.51-3.60 (t, 2H) and 0.89-0.92 (t, 3H).

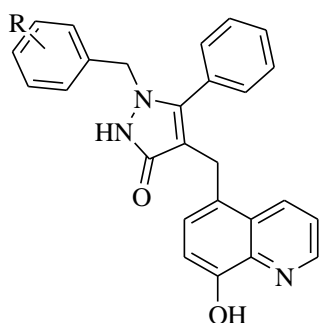


1,2-Dihydro-4-((8-hydroxyquinolin-5-yl)phenyl)-3-methylpyrazol-5-one (**97**) was obtained by cyclization of 2-(8-hydroxyquinolin-5-yl)methyl)-3-oxo-3-phenylpropanoate (**96**) by hydrazine hydrate. IR spectrum of compound (**34**) showed peaks at  $3324\text{ cm}^{-1}$  (for -OH), at  $2959\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1679\text{ cm}^{-1}$  for the presence of -C=O stretching. The mass spectrum showed quasi molecular ion at  $m/z$  318.50  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum offered broad peaks at  $\delta$  11.57 and 9.52 for the amide and -OH proton respectively. The aromatic protons of quinoline and benzene showed at  $\delta$  8.85-8.87 (s, 1H), 8.56-8.58 (d, 1H), 7.54-7.57 (q, 1H), 7.39-7.41 (t, 2H), 7.31-7.34 (t, 2H), 6.99-7.00 (d, 1H) and 6.93-6.94 (d, 2H), the signals for aliphatic protons were observed at  $\delta$  3.18 (s, 2H).

Synthesis of *N*-substituted 1-benzyl-1,2-dihydro-4-((8-hydroxyquinolin-5-yl)phenyl)-5-methylpyrazol-3-one derivatives (**35-47**) was carried out by reacting 1,2-dihydro-4-((8-hydroxyquinolin-5-yl)phenyl)-3-methylpyrazol-5-one with the respective benzyl bromide as depicted in **Scheme 4.1.3.1**.

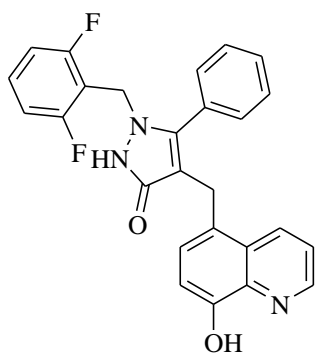
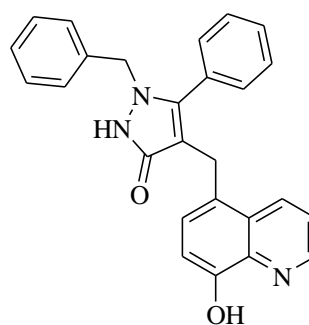
The IR spectrum of compound (**98**) showed characteristic peaks for -OH at  $3291\text{ cm}^{-1}$ , aromatic C-H stretching at  $2998\text{ cm}^{-1}$  and the presence of -C=O stretching of amide at  $1628\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z$  444.2  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum

of compound **(98)** offered broad peaks at  $\delta$  12.35 and 9.54 for the amide and -OH proton respectively. The aromatic protons of quinoline ring and two benzene ring observed at  $\delta$  8.83

**(98-109)**

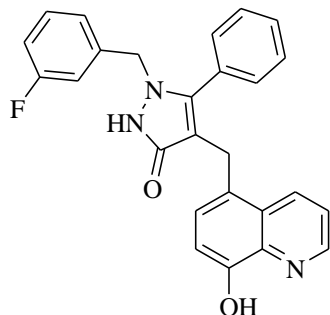
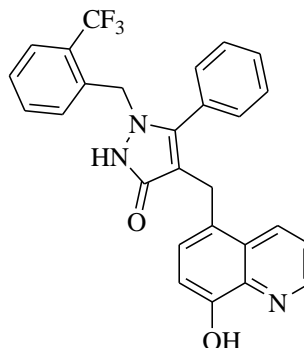
Comp.	R	Comp.	R
<b>98.</b>	2,6-diF	<b>104.</b>	4-F
<b>99.</b>	H	<b>105.</b>	4-CH <sub>3</sub>
<b>100.</b>	3-F	<b>106.</b>	3-Cl
<b>101.</b>	2-CF <sub>3</sub>	<b>107.</b>	4-Cl
<b>102.</b>	4-NO <sub>2</sub>	<b>108.</b>	2,5-diCH <sub>3</sub>
<b>103.</b>	3-OCH <sub>3</sub>	<b>109.</b>	2-F

(dd,  $J = 4.2, 1.5$  Hz, 1H), 8.47 (dd,  $J = 8.6, 1.6$  Hz, 1H), 7.49 – 7.45 (m, 2H), 7.40 – 7.31 (m, 5H), 7.11 (t,  $J = 8.1$  Hz, 2H), 6.91 (d,  $J = 8.0$  Hz, 1H) and 6.85 (d,  $J = 7.9$  Hz, 1H). Two aliphatic proton between the pyrazolone and benzene ring showed singlet at 5.28 (s, 2H) and another two aliphatic proton obtained singlet at  $\delta$  4.06 (s, 2H).

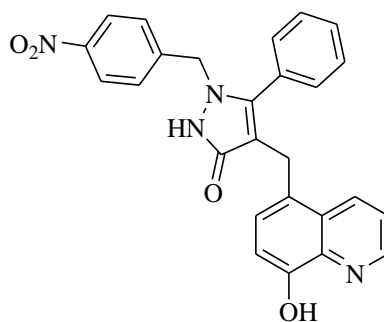
**(98)****(99)**

The IR spectrum of compound **(99)** showed characteristic peaks for -OH at 3330  $\text{cm}^{-1}$ , aromatic C-H stretching at 2912  $\text{cm}^{-1}$  and the presence of -C=O stretching of amide at 1703  $\text{cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z$  408.3  $[\text{M}+\text{H}]^+$ . The  $^1\text{H-NMR}$  spectrum of compound **(99)** offered broad peaks at  $\delta$  12.26 and 9.57 for the amide and -OH proton respectively. The aromatic protons of quinoline ring and two benzene ring observed at  $\delta$  8.85 (d,  $J = 5.7$  Hz, 1H), 8.51 (d,  $J = 10.3$  Hz, 1H), 7.51 (dd,  $J = 8.6, 4.1$  Hz, 1H), 7.43 – 7.26 (m, 10H), 6.99 (d,  $J = 8.0$  Hz, 1H) and 6.92 (s, 1H). Two aliphatic proton between the pyrazolone and benzene ring showed singlet at 5.23 (s, 2H) and another two aliphatic proton obtained singlet at  $\delta$  4.15 (s, 2H).

The IR spectrum of compound **(100)** showed characteristic peaks for -OH at  $3330\text{ cm}^{-1}$ , aromatic C-H stretching at  $2951\text{ cm}^{-1}$  and the presence of -C=O stretching of amide at  $1704\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z\ 426.72\ [M+H]^+$ .

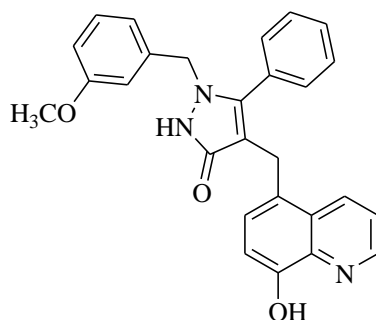
**(100)****(101)**

The IR spectrum of compound **(101)** showed characteristic peaks for -OH at  $3329\text{ cm}^{-1}$ , aromatic C-H stretching at  $2912\text{ cm}^{-1}$  and the presence of -C=O stretching at  $1725\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z\ 476.2\ [M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound **(101)** offered broad peaks at  $\delta\ 12.31$  and  $9.58$  for the amide and -OH proton respectively. The aromatic protons of quinoline ring and two benzene ring observed at  $\delta\ 8.85$  (dd,  $J = 4.2, 1.5\text{ Hz}$ , 1H),  $8.50$  (dd,  $J = 8.6, 1.6\text{ Hz}$ , 1H),  $7.72$  (d,  $J = 7.9\text{ Hz}$ , 1H),  $7.63 - 7.26$  (m, 10H),  $7.02$  (d,  $J = 7.9\text{ Hz}$ , 1H) and  $6.94$  (d,  $J = 7.9\text{ Hz}$ , 1H). Two aliphatic proton between the pyrazolone and benzene ring showed singlet at  $5.40$  (s, 2H) and another two aliphatic proton obtained singlet at  $4.18$  (s, 2H).

**(102)**

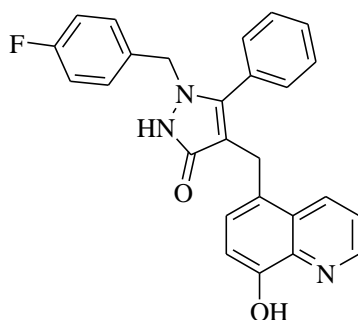
The IR spectrum of compound **(102)** showed characteristic peaks for -OH at  $3329\text{ cm}^{-1}$ , aromatic C-H stretching at  $2912\text{ cm}^{-1}$  and the presence of -C=O stretching at  $1725\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z\ 453.2\ [M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound **(102)** offered broad peaks at  $\delta\ 12.30$  and  $9.60$  for the amide and -OH proton

respectively. The aromatic protons of quinoline ring and two benzene ring observed at  $\delta$  8.86 (dd,  $J = 4.1, 1.5$  Hz, 1H), 8.50 (dd,  $J = 8.7, 1.6$  Hz, 1H), 7.57 – 7.47 (m, 5H), 7.41 (dd,  $J = 8.2, 7.1, 5.5$  Hz, 4H), 7.02 (d,  $J = 7.9$  Hz, 1H) and 6.96 (d,  $J = 7.9$  Hz, 1H). Two aliphatic proton between the pyrazolone and benzene ring showed singlet at 5.37 (s, 2H) and another two aliphatic proton obtained singlet at  $\delta$  4.19 (s, 2H).



(103)

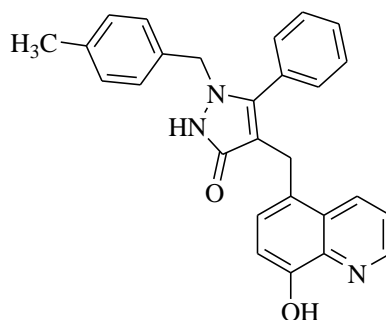
The IR spectrum of compound (103) showed characteristic peaks for -OH at  $3305\text{ cm}^{-1}$ , aromatic C-H stretching at  $2944\text{ cm}^{-1}$  and the presence of -C=O stretching at  $1708\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z$  438.3  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (103) offered broad peaks at  $\delta$  12.26 and 9.56 for the amide and -OH proton respectively. The aromatic protons of quinoline ring and two benzene ring observed at  $\delta$  8.85 (dd,  $J = 4.2, 1.5$  Hz, 1H), 8.53 (dd,  $J = 8.6, 1.6$  Hz, 1H), 7.51 (dd,  $J = 8.6, 4.1$  Hz, 1H), 7.43 – 7.32 (m, 6H), 7.24 – 7.16 (m, 2H), 7.00 – 6.97 (m, 1H), 6.91 (d,  $J = 7.9$  Hz, 1H) and 6.83 (dd,  $J = 8.2, 2.6$  Hz, 1H). Two aliphatic proton between the pyrazolone and benzene ring showed singlet at 5.20 (s, 2H) and another two aliphatic proton obtained singlet at  $\delta$  4.15 (s, 2H). Three aliphatic proton of methoxy group obtained singlet at  $\delta$  3.66 (s, 3H).



(104)

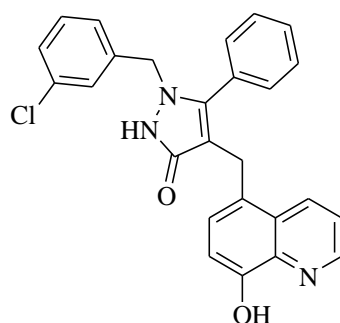
The IR spectrum of compound (104) showed characteristic peaks for -OH at  $3186\text{ cm}^{-1}$  and aromatic C-H stretching at  $2890\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z$  426.17  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (104) offered broad peaks at  $\delta$  9.50

for the -OH proton. The aromatic protons of quinoline ring and two benzene ring observed at  $\delta$  8.81 (dd,  $J = 4.2, 1.5$  Hz, 1H), 8.35 (dd,  $J = 8.6, 1.6$  Hz, 1H), 7.47 (dd,  $J = 8.6, 4.1$  Hz, 1H), 7.39 – 7.33 (m, 5H), 7.22 – 7.18 (m, 2H), 7.03 – 6.98 (m, 2H) and 6.92 – 6.86 (m, 2H). Two aliphatic proton between the pyrazolone and benzene ring showed singlet at 4.97 (s, 2H) and another two aliphatic proton obtained singlet at  $\delta$  3.91 (s, 2H).



(105)

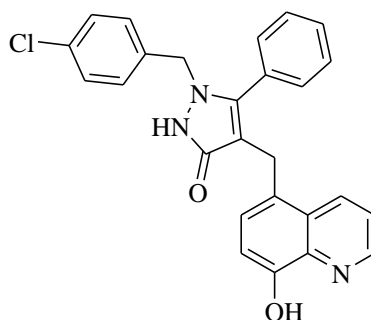
The IR spectrum of compound (105) showed characteristic peaks for -OH at  $3325\text{ cm}^{-1}$ , aromatic C-H stretching at  $2945\text{ cm}^{-1}$  and the presence of -C=O stretching at  $1642\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z$  422.99  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (105) offered broad peaks at  $\delta$  12.24 and 9.56 for the amide and -OH proton respectively. The aromatic protons of quinoline ring and two benzene ring observed at  $\delta$  8.85 (dd,  $J = 4.1, 1.6$  Hz, 1H), 8.51 (dd,  $J = 8.6, 1.6$  Hz, 1H), 7.51 (dd,  $J = 8.6, 4.2$  Hz, 1H), 7.43 – 7.29 (m, 5H), 7.20 (d,  $J = 8.1$  Hz, 2H), 7.11 (d,  $J = 7.9$  Hz, 2H), 6.97 (d,  $J = 7.9$  Hz, 1H) and 6.91 (d,  $J = 7.9$  Hz, 1H). Two aliphatic proton between the pyrazolone and benzene ring showed singlet at 5.17 (s, 2H) and another two aliphatic proton obtained singlet at  $\delta$  4.13 (s, 2H). Three aliphatic proton of methyl group obtained singlet at  $\delta$  2.27 (s, 3H).



(106)

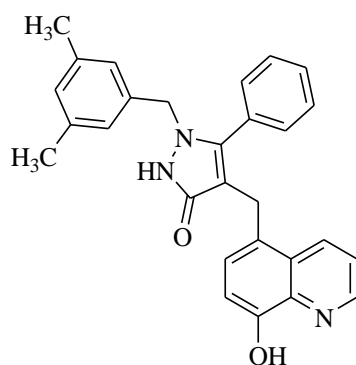
The IR spectrum of compound (106) showed characteristic peaks for -OH at  $3233\text{ cm}^{-1}$  and aromatic C-H stretching at  $2890\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z$  442.2  $[M+H]^+$  and 444.2  $[M+2]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (106) offered broad peaks at  $\delta$  12.28 (s, 1H) and 9.56 (s, 1H) for the amide and -OH proton respectively. The aromatic

protons of quinoline ring and two benzene ring observed at  $\delta$  8.85 (dd,  $J = 4.2, 1.5$  Hz, 1H), 8.51 (dd,  $J = 8.6, 1.6$  Hz, 1H), 7.51 (dd,  $J = 8.6, 4.2$  Hz, 1H), 7.44 – 7.32 (m, 8H), 7.28 – 7.23 (m, 1H), 6.99 (d,  $J = 7.9$  Hz, 1H) and 6.92 (d,  $J = 7.9$  Hz, 1H). Two aliphatic proton between the pyrazolone and benzene ring showed singlet at 5.23 (s, 2H) and another two aliphatic proton obtained singlet at  $\delta$  4.16 (s, 2H).



(107)

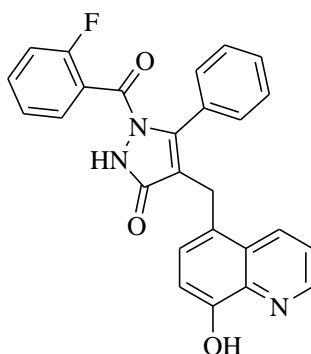
The IR spectrum of compound (107) showed characteristic peaks for -OH at  $3307\text{ cm}^{-1}$ , aromatic C-H stretching at  $2944\text{ cm}^{-1}$  and the presence of -C=O stretching at  $1675\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z$  442.2  $[M+H]^+$  and 444.2  $[M+2]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (107) offered broad peaks at  $\delta$  12.27 (s, 1H) and 9.58 (s, 1H) for the amide and -OH proton respectively. The aromatic protons of quinoline ring and two benzene ring observed at  $\delta$  8.85 (dd,  $J = 4.1, 1.6$  Hz, 1H), 8.50 (dd,  $J = 8.6, 1.6$  Hz, 1H), 7.51 (dd,  $J = 8.6, 4.2$  Hz, 1H), 7.45 – 7.27 (m, 9H), 6.98 (d,  $J = 8.0$  Hz, 1H) and 6.93 (d,  $J = 7.9$  Hz, 1H). Two aliphatic proton between the pyrazolone and benzene ring showed singlet at 5.21 (s, 2H) and another two aliphatic proton obtained singlet at  $\delta$  4.15 (s, 2H).



(108)

The IR spectrum of compound (108) showed characteristic peaks for -OH at  $3291\text{ cm}^{-1}$ , aromatic C-H stretching at  $2998\text{ cm}^{-1}$  and the presence of -C=O stretching at  $1628\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z$  436.28  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (108) offered broad peaks at  $\delta$  12.24 (s, 1H) and 9.57 (s, 1H) for the amide and -OH

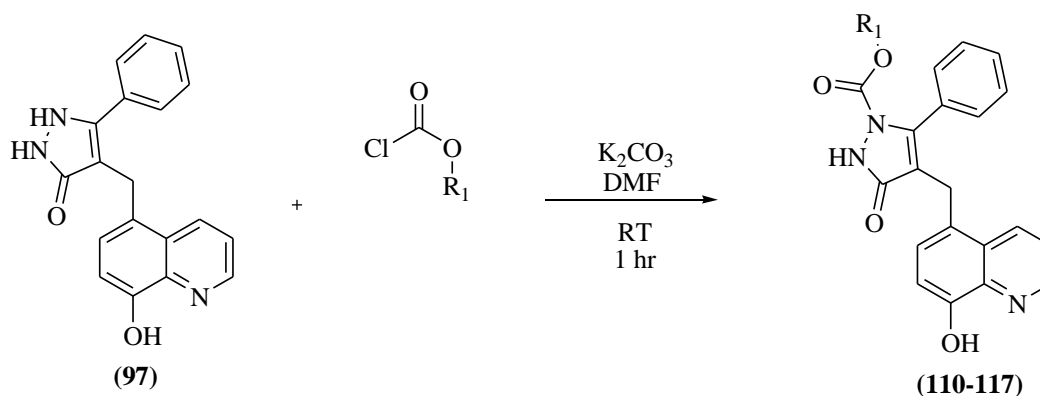
proton respectively. The aromatic protons of quinoline ring and two benzene ring observed at  $\delta$  8.85 (dd,  $J = 4.2, 1.5$  Hz, 1H), 8.51 (dd,  $J = 8.6, 1.6$  Hz, 1H), 7.51 (dd,  $J = 8.6, 4.2$  Hz, 1H), 7.44 – 7.31 (m, 6H), 6.99 (d,  $J = 8.0$  Hz, 1H), 6.92 (d,  $J = 7.9$  Hz, 1H) and 6.87 (s, 2H). Two aliphatic proton between the pyrazolone and benzene ring showed singlet at 5.13 (s, 2H) and another two aliphatic proton obtained singlet at  $\delta$  4.14 (s, 2H). Six aliphatic proton of methyl group obtained singlet at  $\delta$  2.19 (s, 6H).



(109)

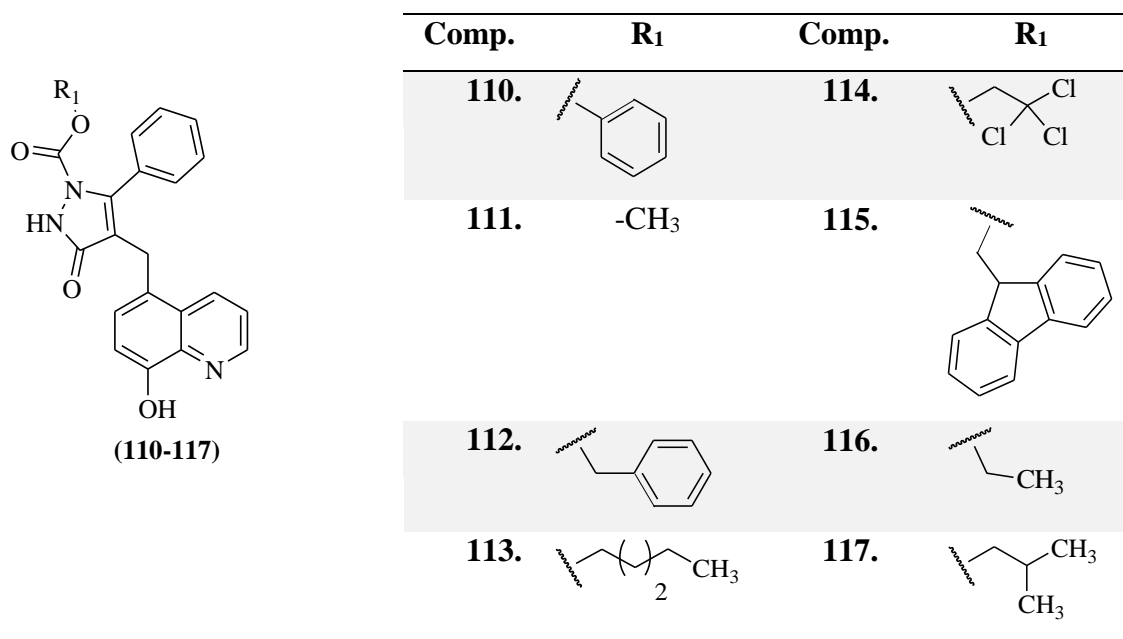
The IR spectrum of compound (109) showed characteristic peaks for -OH at  $3291\text{ cm}^{-1}$ , aromatic C-H stretching at  $2958\text{ cm}^{-1}$  and the presence of -C=O stretching at  $1728\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $m/z$  440.2  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (109) offered broad peaks at  $\delta$  9.54 (s, 1H) for -OH proton. The aromatic protons of quinoline ring and two benzene ring observed at  $\delta$  8.87 (dd,  $J = 4.2, 1.5$  Hz, 1H), 8.58 (dd,  $J = 8.6, 1.6$  Hz, 1H), 7.57 (dd,  $J = 8.6, 4.1$  Hz, 1H), 7.48 – 7.25 (m, 9H), 6.98 (d,  $J = 8.0$  Hz, 1H) and 6.92 (d,  $J = 7.9$  Hz, 1H). Two aliphatic proton between the pyrazolone and quinoline ring obtained singlet at  $\delta$  4.12 (s, 2H).

#### 4.1.1.3.1.2. Synthesis of *N*-substituted methyl 4-((8-hydroxyquinolin-5-yl)methyl)-5-oxo-3-phenyl-1*H*-pyrazole-2(5*H*)-carboxylate (110-117)

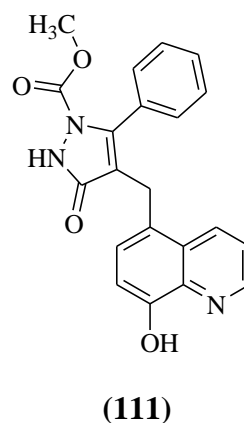
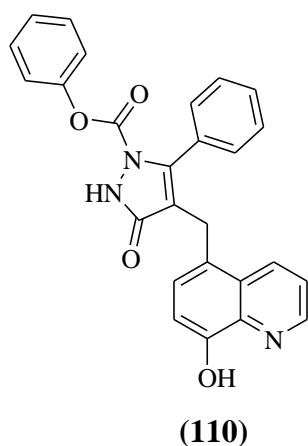


**Scheme-4.1.1.3.2.** General synthetic route for the synthesis of compounds (**110-117**); reagents and conditions: substituted chloro formates, DMF,  $K_2CO_3$ , RT.

Synthesis of *N*-substituted methyl 2,3-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-5-methyl-3-oxopyrazole-1-carboxylate derivatives (**110-117**) was carried out by reacting 1,2-dihydro-4-((8-hydroxyquinolin-5-yl)methyl)-3-methylpyrazol-5-one (**97**) with various substituted chloroformates in presence base as depicted in **Scheme-4.1.3.2**.

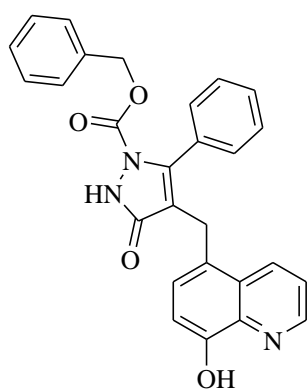
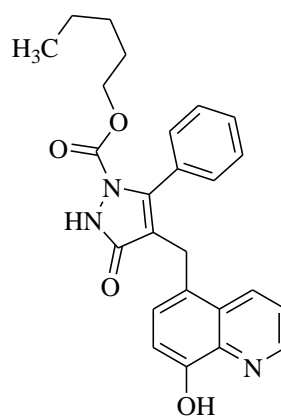


The IR spectrum of compound (**110**) showed characteristic peaks for -OH at  $3287\text{ cm}^{-1}$ , aromatic C-H stretching at  $2873\text{ cm}^{-1}$  and C=O stretching at  $1730\text{ cm}^{-1}$ . The  $^1\text{H-NMR}$  spectrum of compound (**110**) offered broad peaks at  $\delta$  9.53 (s, 1H) for the -OH proton. The signals for aromatic protons demonstrated at 8.86 (dd,  $J = 4.2, 1.6\text{ Hz}$ , 1H), 8.57 (dd,  $J = 8.6, 1.7\text{ Hz}$ , 1H), 7.57 (dd,  $J = 8.6, 4.1\text{ Hz}$ , 1H), 7.40 – 7.28 (m, 10H), 6.97 (d,  $J = 7.9\text{ Hz}$ , 1H) and 6.92 (d,  $J = 7.9\text{ Hz}$ , 1H). The signals for aliphatic protons observed at  $\delta$  4.12 (s, 2H).

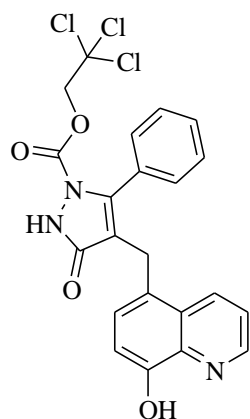


The IR spectrum of compound **(111)** showed characteristic peaks for -OH at  $3210\text{ cm}^{-1}$ , aromatic C-H stretching at  $2923\text{ cm}^{-1}$  and C=O stretching at  $1730\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at 373.76. The  $^1\text{H-NMR}$  spectrum of compound **(111)** offered broad peaks at  $\delta$  9.57 (s, 1H) for the -OH proton. The signals for aromatic protons demonstrated at  $\delta$  8.81 (dd,  $J = 4.1, 1.8\text{ Hz}$ , 1H), 8.31 (dd,  $J = 39.0, 1.7\text{ Hz}$ , 1H), 7.49 – 7.31 (m, 6H) and 6.90 (dd,  $J = 10.5, 2.5\text{ Hz}$ , 2H). The signals for two aliphatic protons between quinoline and pyrazolone ring observed at  $\delta$  3.89 (s, 2H) while three protons of methyl demonstrated singlet at  $\delta$  3.70 (s, 2H).

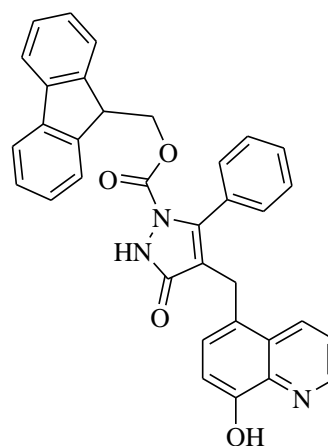
The IR spectrum of compound **(112)** showed characteristic peaks for -OH at  $3327\text{ cm}^{-1}$ , aromatic C-H stretching at  $2917\text{ cm}^{-1}$  and C=O stretching at  $1753\text{ cm}^{-1}$ . The  $^1\text{H-NMR}$  spectrum of compound **(112)** offered broad peaks at  $\delta$  11.30 (s, 1H) and 9.56 (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta$  8.84 (dd,  $J = 4.1, 1.7\text{ Hz}$ , 1H), 8.36 (dd,  $J = 8.6, 1.7\text{ Hz}$ , 1H), 7.52 (dd,  $J = 8.6, 4.2\text{ Hz}$ , 1H), 7.39 – 7.29 (m, 10H), 6.94 (d,  $J = 7.8\text{ Hz}$ , 1H) and 6.88 (d,  $J = 3.4\text{ Hz}$ , 1H). The signals for aliphatic protons observed at  $\delta$  5.17 (s, 2H) and 3.82 (s, 2H).

**(112)****(113)**

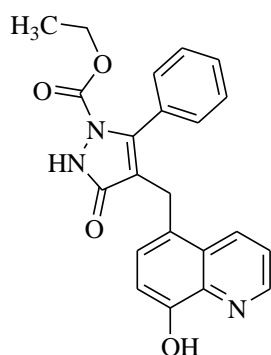
The IR spectrum of compound **(113)** showed characteristic peaks for -OH at  $3321\text{ cm}^{-1}$ , aromatic C-H stretching at  $2934\text{ cm}^{-1}$  and C=O stretching at  $1780\text{ cm}^{-1}$ . The IR spectrum of synthesized compounds **(114)** showed characteristic peaks for -OH at  $3290\text{ cm}^{-1}$ , aromatic C-H stretching at  $2943\text{ cm}^{-1}$  and C=O stretching at  $1768\text{ cm}^{-1}$ . The IR spectrum of synthesized compounds **(115)** showed characteristic peaks for -OH at  $3317\text{ cm}^{-1}$ , aromatic C-H stretching at  $2976\text{ cm}^{-1}$  and C=O stretching at  $1732\text{ cm}^{-1}$ .



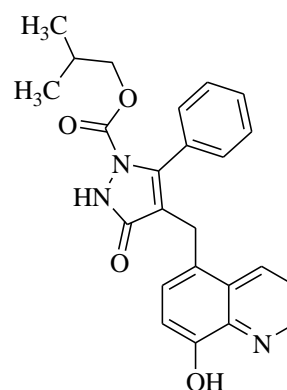
(114)



(115)



(116)

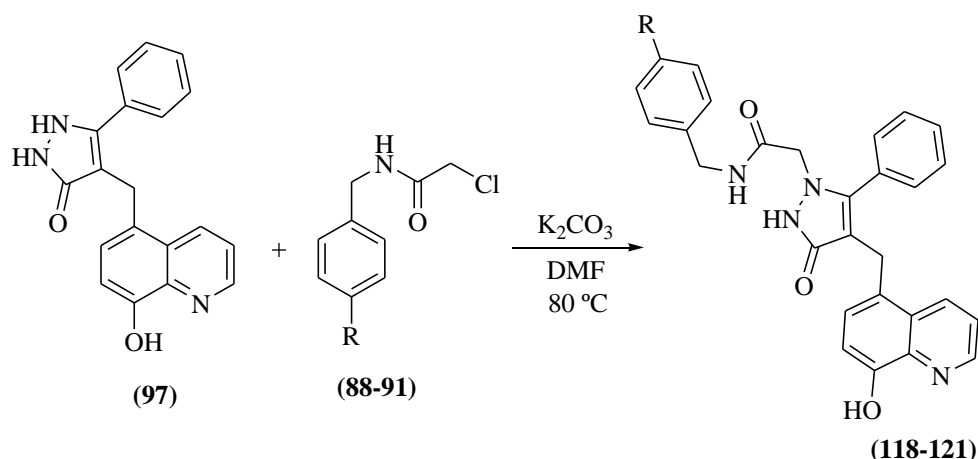


(117)

The IR spectrum of compound (116) showed characteristic peaks for -OH at  $3321\text{ cm}^{-1}$ , aromatic C-H stretching at  $2888\text{ cm}^{-1}$  and C=O stretching at  $1745\text{ cm}^{-1}$ . The IR spectrum of compound (117) showed characteristic peaks for -OH at  $3321\text{ cm}^{-1}$ , aromatic C-H stretching at  $2987\text{ cm}^{-1}$  and C=O stretching at  $1745\text{ cm}^{-1}$ .

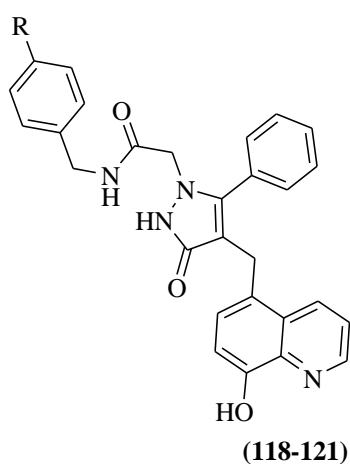
#### 4.1.1.3.1.3. Synthesis of *N*-benzyl-2-(4-((8-hydroxyquinolin-5-yl)methyl)-5-oxo-3-phenyl-1*H*-pyrazol-2(5*H*)-yl)acetamide (118-121)

To synthesize planned compounds the following strategies adopted as mentioned in **Scheme-4.1.1.3.3**



**Scheme-4.1.1.2.3.** General synthetic route for the synthesis of compounds (118-121); reagents and conditions: substituted *N*-benzylacetamide, DMF,  $K_2CO_3$ ,  $80\text{ }^\circ\text{C}$ .

The IR spectrum of compound (118) showed characteristic peaks for -OH at  $3281\text{ cm}^{-1}$ , aromatic C-H stretching at  $2949\text{ cm}^{-1}$  and C=O stretching at  $1679\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $483.22\text{ [M+H]}^+$ . The  $^1\text{H-NMR}$  spectrum of compound (118) offered broad peaks at  $\delta\ 12.30$  (s, 1H) and  $9.54$  (s, 1H) for the amide and -OH proton respectively. The signals for aromatic protons demonstrated at  $\delta\ 8.85$ - $8.86$  (d, 1H),  $8.54$ - $8.56$  (d, 1H),  $8.26$ - $8.29$  (t, 1H),  $7.52$ - $7.55$  (m, 1H),  $7.33$ - $7.42$  (m, 5H),  $7.24$ - $7.28$  (t, 1H),  $7.07$ - $7.12$  (t, 1H),  $7.01$ - $7.03$  (d, 1H) and  $6.88$ - $6.90$  (d, 2H). The signals for aliphatic protons observed at  $\delta\ 4.672$  (s, 2H),  $4.29$ - $4.30$  (d, 2H) and  $4.26$  (s, 2H).



Comp.	R
118.	F
119.	OCH <sub>3</sub>
120.	Cl
121.	CH <sub>3</sub>

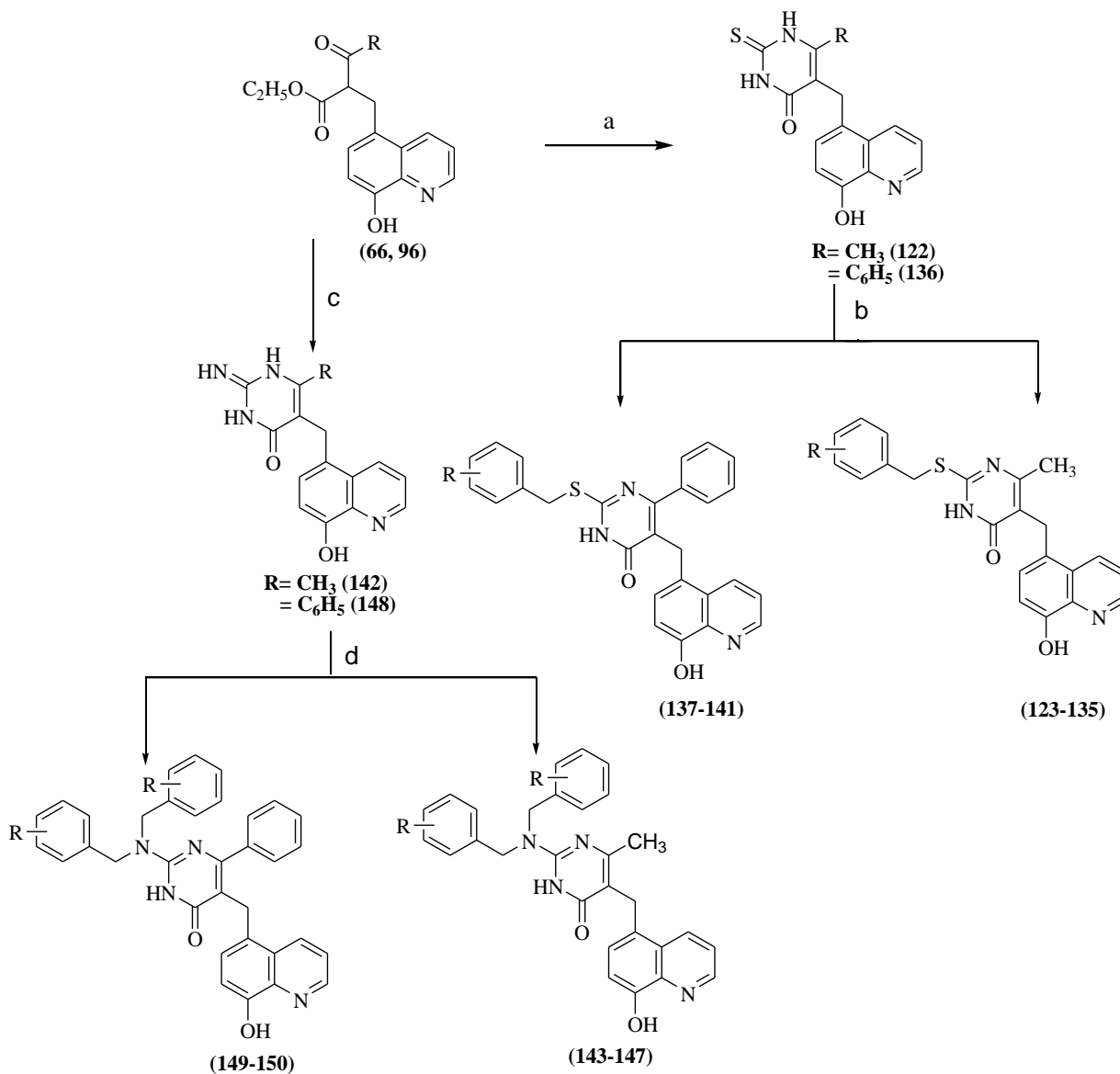
The IR spectrum of compound (119) showed characteristic peaks for -OH at  $3306\text{ cm}^{-1}$ , aromatic C-H stretching at  $2924\text{ cm}^{-1}$  and C=O stretching at  $1664\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $495.26\text{ [M+H]}^+$ . The  $^1\text{H-NMR}$  spectrum of compound (119) offered broad peaks at  $\delta\ 12.34$  (s, 1H) and  $9.57$  (s, 1H) for the amide and -OH proton respectively.

The signals for aromatic protons demonstrated at  $\delta$  8.88-8.89 (d, 1H), 8.56-8.58 (d, 1H), 8.16-8.18 (t, 1H), 7.70-7.75 (t, 1H), 7.34-7.45 (q, 1H), 7.34-7.45 (m, 5H), 7.15-7.16 (d, 1H), 7.04-7.06 (d, 1H), 6.91-6.93 (d, 1H) and 6.85-6.86 (d, 1H). The signals for aliphatic protons observed at  $\delta$  4.69 (s, 2H), 4.25-4.28 (t, 2H), 4.16-4.18 (t, 1H) and 3.74-3.59 (s, 3H)

The IR spectrum of compound (**120**) showed characteristic peaks for -OH at  $3288\text{ cm}^{-1}$ , aromatic C-H stretching at  $2926\text{ cm}^{-1}$  and C=O stretching at  $1679\text{ cm}^{-1}$ . The mass spectrum showed quasi molecular ion at  $499.19\text{ [M+H]}^+$  and  $501.12\text{ [M+2]}^+$ . While, the IR spectrum of compound (**121**) showed characteristic peaks for -OH at  $3305\text{ cm}^{-1}$ , aromatic C-H stretching at  $2926\text{ cm}^{-1}$  and C=O stretching at  $1663\text{ cm}^{-1}$ .

## 4.1.2. Pyrimidinone based multifunctional anti-AD agents

## 4.1.2.1. General scheme for synthesis of 2,3-dihydro-5-((8-hydroxyquinolin-5-yl)methyl)-6-methyl-2-thioxopyrimidin-4(1H)-one (122-150)



**Scheme-4.1.2.2.1:** General synthetic route for the synthesis of compounds; reagents and conditions: (a) DBU (diazabicyclo(5.4.0)undec-7-ene), thiourea, ethanol, reflux; (b) substituted benzyl halide, DMF, K<sub>2</sub>CO<sub>3</sub>, RT; (c) DBU(diazabicyclo(5.4.0)undec-7-ene), guanidine hydrochloride, ethanol, reflux; (d) substituted benzyl halide, DMF, K<sub>2</sub>CO<sub>3</sub>, RT.

Four types of compounds have synthesized under this categories

4.1.2.2.5-((8-Hydroxyquinolin-5-yl)methyl)-2-mercapto-6-methylpyrimidin-4(3H)one derivatives (122-135)

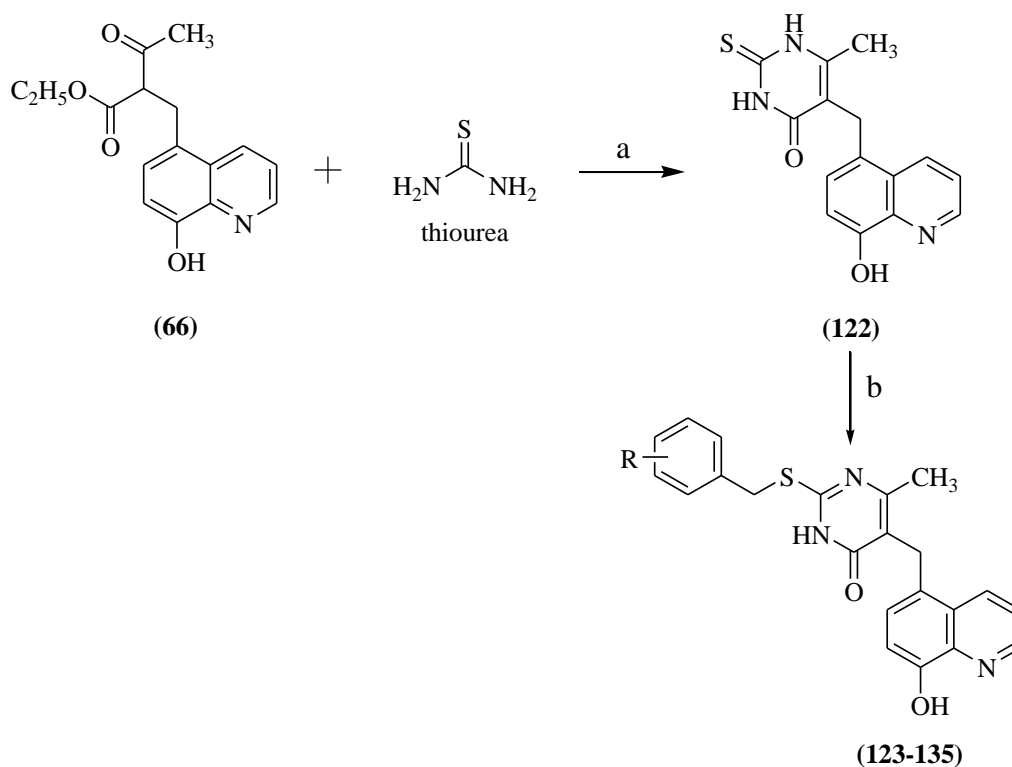
4.1.2.3.5-((8-Hydroxyquinolin-5-yl)methyl)-2-mercapto-6-phenylpyrimidin-4(3*H*)-one derivatives (**137-141**)

4.1.2.3.2-Amino-5-((8-hydroxyquinolin-5-yl)methyl)-6-methylpyrimidin-4(3*H*)-one derivatives (**142-147**)

4.1.2.4.2-(Dibenzylamino)-5-((8-hydroxyquinolin-5-yl)methyl)-6-phenylpyrimidin-4(3*H*)-one (**148-150**)

#### 4.1.2.2. Synthesis of *N*-substituted 5-((8-hydroxyquinolin-5-yl)methyl)-2-mercapto-6-methylpyrimidin-4(3*H*)one derivatives (**122-135**)

To synthesize planned compounds the following strategies adopted as mentioned in **Scheme-4.1.2.2.1**

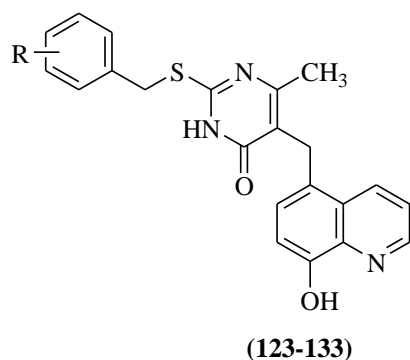


**Scheme-4.1.2.2.1.** General synthetic route for the synthesis of compounds (**123-135**); reagents and conditions: (a) DBU (diazabicyclo(5.4.0)undec-7-ene), ethanol, reflux; (b) substituted benzyl halide, DMF,  $\text{K}_2\text{CO}_3$ , RT.

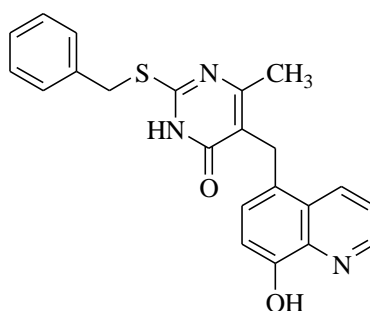
2,3-Dihydro-5-((8-hydroxyquinolin-5-yl)methyl)-6-methyl-2-thioxopyrimidin-4(1*H*)one (**122**) was obtained by cyclization of ethyl 2-((8-hydroxyquinolin-5-yl)methyl)-3-oxobutanoate (**66**) with thiourea in presence of base. IR spectrum of compound (**122**) showed peaks at  $3283\text{ cm}^{-1}$  (for -OH), at  $2837\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1641\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z$

299.4 [M+H]<sup>+</sup>. The <sup>1</sup>H-NMR spectrum of compound offered a singlet at  $\delta$  12.48 (s, 1H) and 12.28 (s, 1H) for both –NH protons and singlet at  $\delta$  9.59 (s, 1H) for one proton of –OH. The five aromatic protons of quinoline appeared at  $\delta$  8.87 (dd,  $J$  = 4.2, 1.6 Hz, 1H), 8.60 (dd,  $J$  = 8.6, 1.7 Hz, 1H), 7.61 (dd,  $J$  = 8.6, 4.1 Hz, 1H), 7.03 (d,  $J$  = 8.1 Hz, 1H) and 6.96 (d,  $J$  = 7.9 Hz, 1H). Two aliphatic proton between quinoline and pyrimidinone ring obtain singlet at  $\delta$  3.98 (s, 2H). A singlet for three proton of both methyl group was seen at  $\delta$  2.06 (s, 3H).

Furthermore, synthesis of *N*-substituted 5-((8-hydroxyquinolin-5-yl)methyl)-2-mercapto-6-methylpyrimidin-4(3*H*)one derivatives (**123-79**) was carried out by reacting ,3-dihydro-5-((8-hydroxyquinolin-5-yl)methyl)-6-methyl-2-thioxopyrimidin-4(1*H*)one (**122**) with the respective benzyl halides as depicted in **Scheme 4.2.2.1**.

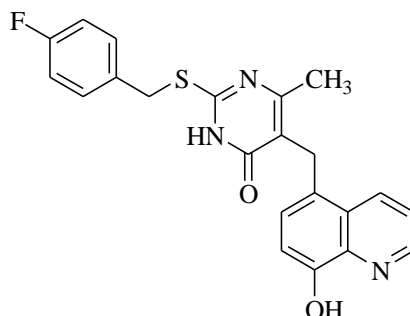


Comp.	R	Comp.	R
<b>123.</b>	H	<b>129.</b>	2-CH <sub>3</sub>
<b>124.</b>	4-F	<b>130.</b>	4-Br
<b>125.</b>	3-OCH <sub>3</sub>	<b>131.</b>	4-Cl
<b>126.</b>	3,4- <i>di</i> Cl	<b>132.</b>	3,4- <i>di</i> Cl
<b>127.</b>	3-Cl	<b>133.</b>	4-CH <sub>3</sub>
<b>128.</b>	2,5-OCH <sub>3</sub>		



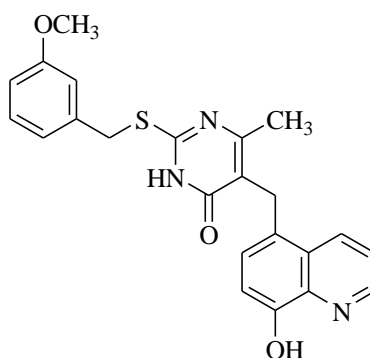
IR spectrum of compound (**123**) showed peaks at 3313 cm<sup>-1</sup> (for -OH), at 2937cm<sup>-1</sup> (aromatic C-H stretching) and at 1633 cm<sup>-1</sup> for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at m/z 390.1 [M+H]<sup>+</sup>. The <sup>1</sup>H-NMR spectrum of compound (**123**) offered a singlet at  $\delta$  9.57 (s, 1H) for one proton of –OH. The aromatic protons of quinoline and benzene ring appeared at  $\delta$  8.87 (dd,  $J$  = 4.1, 1.6 Hz, 1H), 8.65 (dd,  $J$  = 8.6, 1.6

Hz, 1H), 7.61 (dd,  $J = 8.6, 4.1$  Hz, 1H), 7.43 (d,  $J = 6.9$  Hz, 2H), 7.35 – 7.24 (m, 3H) and 6.96 (s, 2H). Two aliphatic proton between pyrimidinone and benzene ring showed singlet at  $\delta$  4.40 (s, 2H), while another two protons showed singlet at  $\delta$  4.09 (s, 2H). A singlet for three proton of both methyl group was seen at  $\delta$  2.17 (s, 3H).



(124)

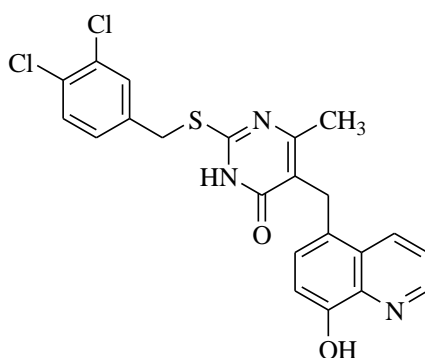
IR spectrum of compound (124) showed peaks at  $3325\text{ cm}^{-1}$  (for -OH), at  $2937\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1644\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z$  408.12  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (124) offered a singlet at  $\delta$  12.70 (s, 1H) and 9.58 (s, 1H) for amide and one proton of -OH. The aromatic protons of quinoline and benzene ring appeared at  $\delta$  8.87 (dd,  $J = 4.2, 1.6$  Hz, 1H), 8.65 (dd,  $J = 8.6, 1.7$  Hz, 1H), 7.61 (dd,  $J = 8.6, 4.1$  Hz, 1H), 7.48 (dd,  $J = 8.7, 5.5$  Hz, 2H), 7.16 (d,  $J = 8.9$  Hz, 2H) and 6.96 (s, 2H). Two aliphatic proton between pyrimidinone and benzene ring showed singlet at  $\delta$  4.39 (s, 2H), while another two protons showed singlet at  $\delta$  4.09 (s, 2H). A singlet for three proton of both methyl group was seen at  $\delta$  2.16 (s, 3H).



(125)

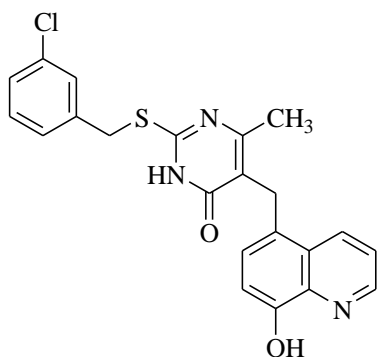
IR spectrum of compound (125) showed peaks at  $3307\text{ cm}^{-1}$  (for -OH), at  $2833\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1649\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z$  420.09  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (125) offered a singlet at  $\delta$  12.73 (s, 1H) and 9.59 (s, 1H) for amide and one proton

of -OH. The aromatic protons of quinoline and benzene ring appeared at  $\delta$  8.88 (dd,  $J = 4.2, 1.6$  Hz, 1H), 8.65 (dd,  $J = 8.6, 1.7$  Hz, 1H), 7.61 (dd,  $J = 8.6, 4.2$  Hz, 1H), 7.24 (t,  $J = 7.9$  Hz, 1H), 7.04 – 6.94 (m, 5H) and 6.83 (dd,  $J = 8.1, 3.0$  Hz, 1H). Two aliphatic proton between pyrimidinone and benzene ring showed singlet at  $\delta$  4.37 (s, 2H), while another two protons showed singlet at  $\delta$  4.09 (s, 2H). A singlet for three proton of methoxy group was seen at  $\delta$  3.73 (s, 3H) while proton of methyl group appears at  $\delta$  2.17 (s, 3H).

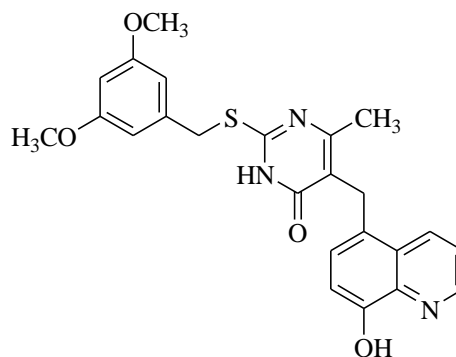


(126)

IR spectrum of compound (126) showed peaks at  $3313\text{ cm}^{-1}$  (for -OH), at  $2977\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1652\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z$  458.04  $[M]^+$  and 460  $[M+2]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (126) offered a singlet at  $\delta$  12.73 (s, 1H) and 9.59 (s, 1H) for amide and one proton of -OH. The aromatic protons of quinoline and benzene ring appeared at  $\delta$  8.88 (d,  $J = 5.4$  Hz, 1H), 8.69 – 8.61 (m, 1H), 7.75 (s, 1H), 7.65 – 7.54 (m, 2H), 7.46 (d,  $J = 10.4$  Hz, 1H) and 7.00 – 6.90 (m, 2H). Two aliphatic proton between pyrimidinone and benzene ring showed singlet at  $\delta$  4.38 (s, 2H), while another two protons showed singlet at  $\delta$  4.09 (s, 2H). A singlet for three proton of methyl group appears at  $\delta$  2.17 (s, 3H).



(127)

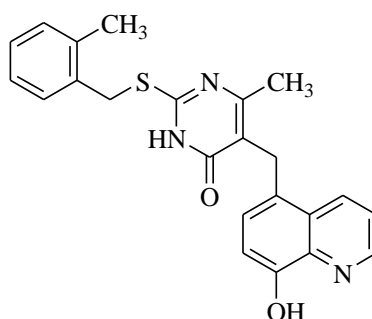


(128)

IR spectrum of compound (127) showed peaks at  $3305\text{ cm}^{-1}$  (for -OH), at  $2873\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1658\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The

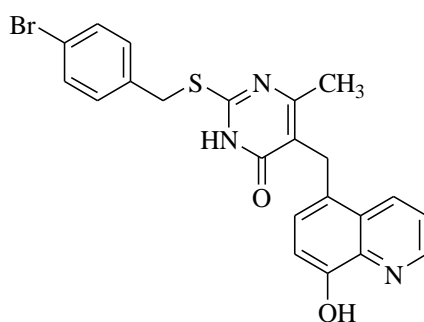
mass spectrum showed quasi molecular ion at  $m/z$  424.09  $[M+H]^+$ , 426.07  $[M+2]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**127**) offered a singlet at  $\delta$  12.77 (s, 1H) and 9.58 (s, 1H) for amide and one proton of  $-\text{OH}$ . The aromatic protons of quinoline and benzene ring appeared at  $\delta$  8.87 (dd,  $J = 4.0, 1.6$  Hz, 1H), 8.65 (dd,  $J = 8.6, 1.7$  Hz, 1H), 7.61 (dd,  $J = 8.6, 4.1$  Hz, 1H), 7.54 (s, 1H), 7.44 – 7.30 (m, 3H) and 6.96 (d,  $J = 7.5$  Hz, 2H). Two aliphatic proton between pyrimidinone and benzene ring appeared singlet at  $\delta$  4.39 (s, 2H), while another two protons showed singlet at  $\delta$  4.08 (s, 2H). A singlet for three proton of methyl group appears at  $\delta$  2.16 (s, 3H).

IR spectrum of compound (**128**) showed peaks at  $3322\text{ cm}^{-1}$  (for  $-\text{OH}$ ), at  $2835\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1650\text{ cm}^{-1}$  for the presence of  $-\text{C}=\text{O}$  stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z$  450.14  $[M+H]^+$ .



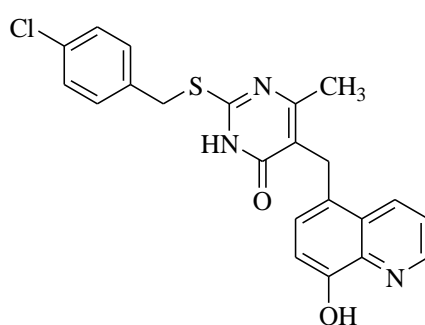
(129)

IR spectrum of compound (**129**) showed peaks at  $3320\text{ cm}^{-1}$  (for  $-\text{OH}$ ), at  $2940\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1631\text{ cm}^{-1}$  for the presence of  $-\text{C}=\text{O}$  stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z$  404.03  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**129**) offered a singlet at  $\delta$  9.58 (s, 1H) for one proton of  $-\text{OH}$ . The aromatic protons of quinoline and benzene ring appeared at  $\delta$  8.87 (dd,  $J = 4.2, 1.6$  Hz, 1H), 8.66 (dd,  $J = 8.6, 1.7$  Hz, 1H), 7.61 (dd,  $J = 8.6, 4.2$  Hz, 1H), 7.41 (d,  $J = 6.7$  Hz, 1H), 7.21 – 7.12 (m, 3H) and 6.96 (s, 2H). Two aliphatic proton between pyrimidinone and benzene ring showed singlet at  $\delta$  4.41 (s, 2H), while another two protons showed singlet at  $\delta$  4.09 (s, 2H). A singlet for three proton of both methyl group appears at  $\delta$  2.36 (s, 3H) and  $\delta$  2.17 (s, 3H).

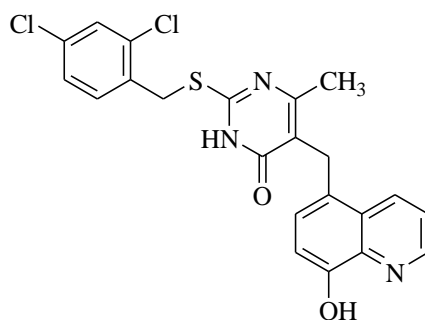


(130)

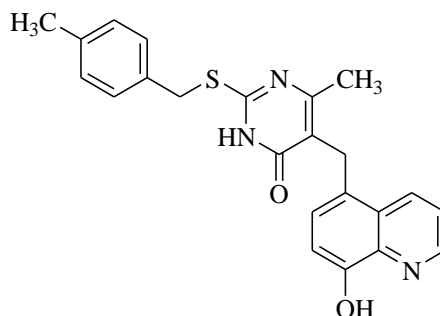
IR spectrum of compound (**130**) showed peaks at  $3331\text{ cm}^{-1}$  (for -OH), at  $2973\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1652\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z\ 470.01\ [M+H]^+$  and  $471.93\ [M+2]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**130**) offered a singlet at  $\delta\ 9.60$  (s, 1H) for one proton of -OH. The aromatic protons of quinoline and benzene ring appeared at  $\delta\ 8.87$  (dd,  $J = 4.1, 1.5\text{ Hz}$ , 1H),  $8.65$  (dd,  $J = 8.7, 1.6\text{ Hz}$ , 1H),  $7.61$  (dd,  $J = 8.6, 4.2\text{ Hz}$ , 1H),  $7.52$  (d,  $J = 6.4\text{ Hz}$ , 2H),  $7.41$  (d,  $J = 8.4\text{ Hz}$ , 2H) and  $6.95$  (s, 2H). Two aliphatic proton between pyrimidinone and benzene ring appeared singlet at  $\delta\ 4.37$  (s, 2H), while another two protons showed singlet at  $\delta\ 4.08$  (s, 2H). A singlet for three proton of methyl group appears at  $\delta\ 2.16$  (s, 3H).

**(131)**

IR spectrum of compound (**131**) showed peaks at  $3319\text{ cm}^{-1}$  (for -OH), at  $2923\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1653\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z\ 424.09\ [M+H]^+$  and  $426.07\ [M+2]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**131**) offered a singlet at  $\delta\ 12.71$  (s, 1H) and  $9.59$  (s, 1H) for amide and one proton of -OH. The aromatic protons of quinoline and benzene ring appeared at  $\delta\ 8.88$  (dd,  $J = 4.0, 1.6\text{ Hz}$ , 1H),  $8.65$  (dd,  $J = 8.7, 1.6\text{ Hz}$ , 1H),  $7.61$  (dd,  $J = 8.6, 4.1\text{ Hz}$ , 1H),  $7.44$  (d,  $J = 6.8\text{ Hz}$ , 2H),  $7.33$  (t,  $J = 7.3\text{ Hz}$ , 2H) and  $6.96$  (s, 2H). Two aliphatic proton between pyrimidinone and benzene ring showed singlet at  $\delta\ 4.41$  (s, 2H), while another two protons showed singlet at  $\delta\ 4.09$  (s, 2H). A singlet for three proton of methyl group appears at  $\delta\ 2.17$  (s, 3H).

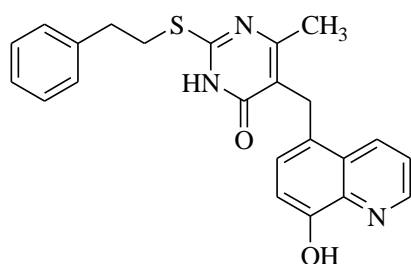
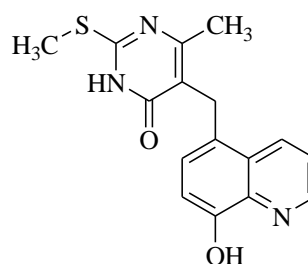
**(132)**

IR spectrum of compound **(132)** showed peaks at  $3321\text{ cm}^{-1}$  (for -OH), at  $2974\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1646\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z\ 458.04\ [M+H]^+$  and  $461.98\ [M+2]^+$ .

**(133)**

IR spectrum of compound **(133)** showed peaks at  $3324\text{ cm}^{-1}$  (for -OH), at  $2976\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1650\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z\ 404.03\ [M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound **(133)** offered a singlet at  $\delta\ 9.59$  (s, 1H) for one proton of -OH. The aromatic protons of quinoline and benzene ring appeared at  $\delta\ 8.87$  (dd,  $J = 4.2, 1.5\ \text{Hz}$ , 1H),  $8.65$  (dd,  $J = 8.6, 1.6\ \text{Hz}$ , 1H),  $7.61$  (dd,  $J = 8.6, 4.2\ \text{Hz}$ , 1H),  $7.34 - 7.28$  (m, 2H),  $7.13$  (d,  $J = 7.8\ \text{Hz}$ , 2H) and  $6.96$  (s, 2H). Two aliphatic proton between pyrimidinone and benzene ring showed singlet at  $\delta\ 4.35$  (s, 2H), while another two protons showed singlet at  $\delta\ 4.08$  (s, 2H). A singlet for three proton of methyl group appears at  $\delta\ 2.16$  (s, 3H).

Additionally, synthesis of compound **(134)** and **(135)** was carried out by reacting 3-dihydro-5-((8-hydroxyquinolin-5-yl)methyl)-6-methyl-2-thioxopyrimidin-4(1H)one (**(122)**) with 1-(2-bromoethyl)benzene and methyl iodide.

**(134)****(135)**

IR spectrum of compound **(134)** showed peaks at  $3307\text{ cm}^{-1}$  (for -OH), at  $2916\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1648\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z\ 404.12\ [M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of

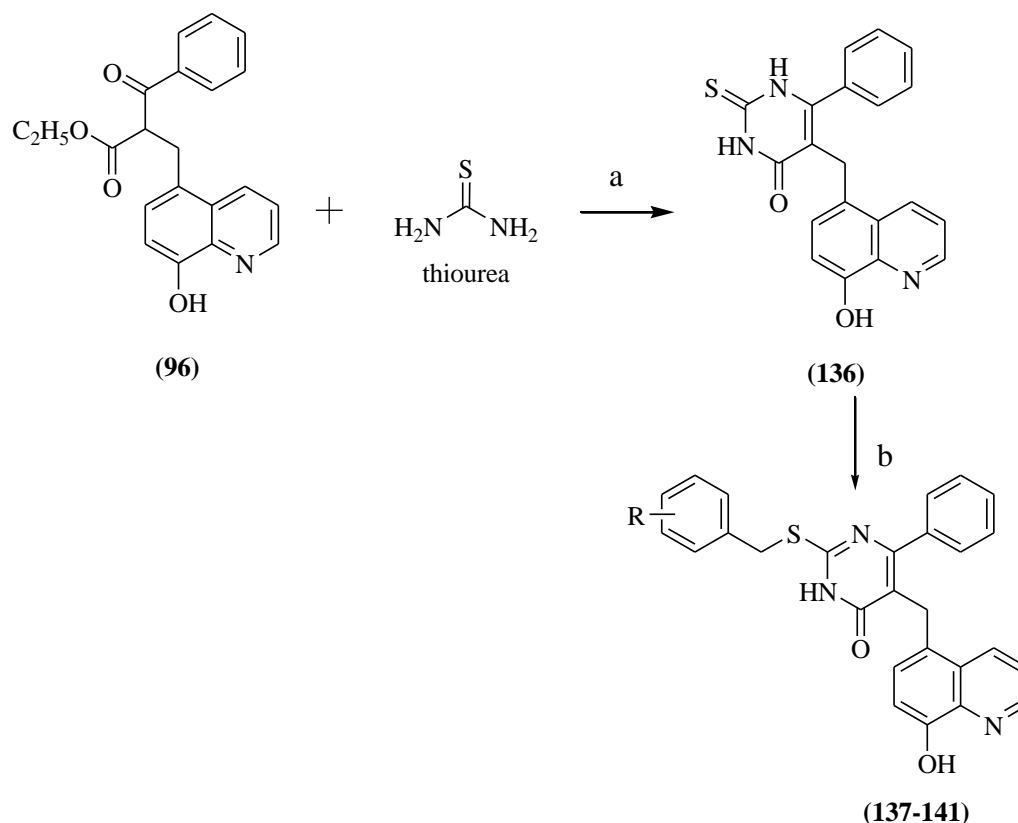
compound (**134**) offered a singlet at  $\delta$  12.65 (s, 1H) and 9.58 (s, 1H) for amide and one proton of -OH. The aromatic protons of quinoline and benzene ring appeared at  $\delta$  8.88 (dd,  $J = 4.2, 1.6$  Hz, 1H), 8.66 (dd,  $J = 8.6, 1.7$  Hz, 1H), 7.61 (dd,  $J = 8.6, 4.1$  Hz, 1H), 7.35 – 7.19 (m, 5H) and 6.96 (s, 2H). Two aliphatic proton between pyrimidinone and benzene ring showed singlet at  $\delta$  4.08 (s, 2H), while another four protons showed singlet at  $\delta$  3.40 – 3.34 (m, 2H) and 2.97 (t,  $J = 7.6$  Hz, 2H). A singlet for three proton of methyl group appears at  $\delta$  2.15 (s, 3H).

IR spectrum of compound (**135**) showed peaks at  $3331\text{ cm}^{-1}$  (for -OH), at  $2912\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1655\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z$  314  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**135**) offered a singlet at  $\delta$  9.56 (s, 1H) for one proton of -OH. The aromatic protons of quinoline and benzene ring appeared at  $\delta$  8.87 (dd,  $J = 4.2, 1.5$  Hz, 1H), 8.65 (dd,  $J = 8.6, 1.6$  Hz, 1H), 7.61 (dd,  $J = 8.6, 4.1$  Hz, 1H) and 6.95 (s, 2H). Two aliphatic proton between pyrimidinone and quinoline ring showed singlet at  $\delta$  4.09 (s, 2H), while another three protons with sulphur showed singlet at  $\delta$  2.49 (s, 3H). A singlet for three proton of methyl group appears at  $\delta$  2.13 (s, 3H).

#### 4.1.2.2. Synthesis of *N*-substituted 5-((8-hydroxyquinolin-5-yl)methyl)-2-mercapto-6 phenylpyrimidin-4(3*H*)-one derivatives (**137-141**)

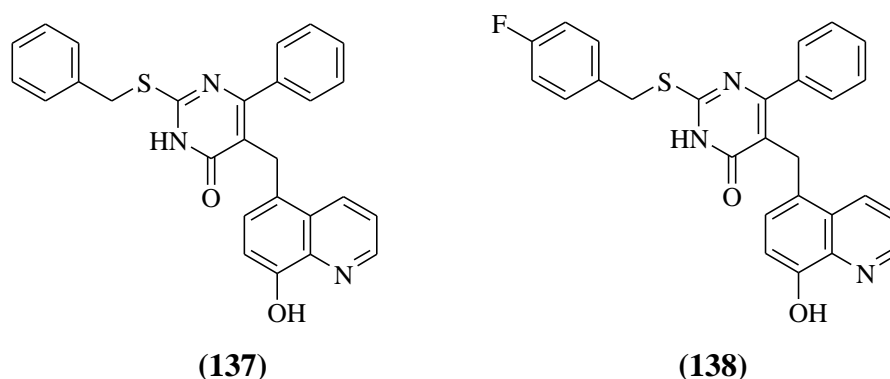
To synthesize designed compounds the following strategies adopted as mentioned in **Scheme-4.1.2.2.1**

2,3-Dihydro-5-((8-hydroxyquinolin-5-yl)methyl)-6-methyl-2-thioxopyrimidin-4(1*H*)one (**136**) was obtained by cyclization of ethyl 2-((8-hydroxyquinolin-5-yl) methyl)-3-oxobutanoate (**96**) with thiourea in presence of base. IR spectrum of compound (**136**) showed peaks at  $3389\text{ cm}^{-1}$  (for -OH), at  $2853\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1654\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The  $^1\text{H-NMR}$  spectrum of compound offered a singlet at  $\delta$  12.62 (s, 1H) and 12.50 (s, 1H) for both -NH protons and singlet at  $\delta$  9.57 (s, 1H) for one proton of -OH. The aromatic protons of quinoline and benzene ring appeared at  $\delta$  8.82 (dd,  $J = 4.2, 1.6$  Hz, 1H), 8.30 (dd,  $J = 8.6, 1.7$  Hz, 1H), 7.51 – 7.47 (m, 1H), 7.42 – 7.34 (m, 5H), 7.03 (d,  $J = 7.9$  Hz, 1H) and 6.92 (d,  $J = 7.9$  Hz, 1H). Two aliphatic proton between quinoline and pyrimidinone ring obtained singlet at 3.79 (s, 2H).



**Scheme-4.1.2.2.1.** General synthetic route for the synthesis of compounds; reagents and conditions: (a) DBU (diazabicyclo(5.4.0)undec-7-ene), ethanol, reflux; (b) substituted benzyl halide, DMF, K<sub>2</sub>CO<sub>3</sub>, RT.

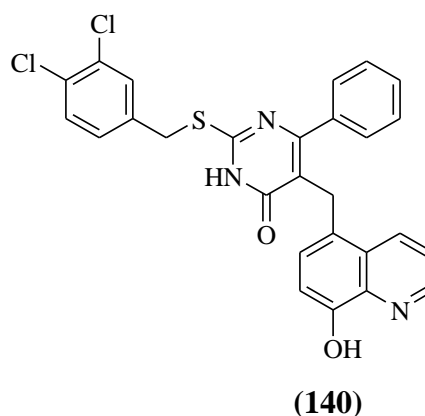
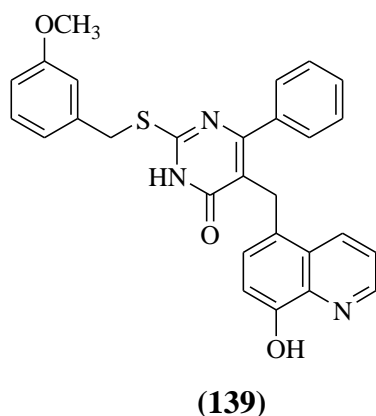
Furthermore, synthesis of *N*-substituted 5-((8-hydroxyquinolin-5-yl)methyl)-2-mercapto-6-phenylpyrimidin-4(3*H*)-one derivatives (**137** & **141**) was carried out by reacting, 2,3-dihydro-5-((8-hydroxyquinolin-5-yl)methyl)-6-methyl-2-thioxopyrimidin-4(1*H*)one (**136**) with the respective benzyl halides as depicted in **Scheme 4.2.2.2**.



IR spectrum of compound (**137**) showed peaks at 3341 cm<sup>-1</sup> (for -OH), at 2840 cm<sup>-1</sup> (aromatic C-H stretching) and at 1634 cm<sup>-1</sup> for the presence of -C=O stretching for amide. The <sup>1</sup>H-NMR spectrum of compound (**137**) offered a singlet at δ 9.59 (s, 1H) for one proton of -OH. The aromatic protons of quinoline and ten protons of both benzene rings showed at δ 8.86 (dd, *J*

= 4.1, 1.6 Hz, 1H), 8.42 (dd,  $J = 8.7, 1.6$  Hz, 1H), 7.55 – 7.51 (m, 1H), 7.39 – 7.25 (m, 11H) and 6.97 (q,  $J = 7.9$  Hz, 2H). Two aliphatic proton between pyrimidinone and benzene ring appeared singlet at  $\delta$  4.47 (s, 2H), while another two protons showed singlet at  $\delta$  4.15 (s, 2H).

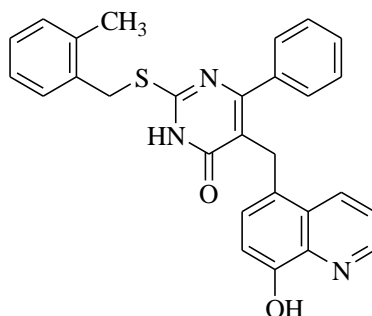
IR spectrum of compound (**138**) showed peaks at  $3328\text{ cm}^{-1}$  (for -OH), at  $2829\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1640\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z$  470.08  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**138**) offered a singlet at  $\delta$  12.95 (s, 1H) and 9.60 (s, 1H) for amide and one proton of -OH. The aromatic protons of quinoline and both benzene rings showed at  $\delta$  8.86 (dd,  $J = 4.2, 1.6$  Hz, 1H), 8.40 (dd,  $J = 8.6, 1.7$  Hz, 1H), 7.53 (dd,  $J = 8.6, 4.1$  Hz, 1H), 7.48 – 7.32 (m, 7H), 7.19 – 7.12 (m, 2H) and 6.95 (s, 2H). Two aliphatic proton between pyrimidinone and benzene ring showed singlet at  $\delta$  4.43 (s, 2H), while another two protons showed singlet at  $\delta$  4.05 (s, 2H).



IR spectrum of compound (**139**) showed peaks at  $3339\text{ cm}^{-1}$  (for -OH), at  $2833\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1643\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z$  482  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (**139**) offered a singlet at  $\delta$  12.93 (s, 1H) and 9.58 (s, 1H) for amide and one proton of -OH. The aromatic protons of quinoline and benzene rings showed at  $\delta$  8.86 (dd,  $J = 4.2, 1.6$  Hz, 1H), 8.40 (dd,  $J = 8.7, 1.6$  Hz, 1H), 7.53 (dd,  $J = 8.6, 4.1$  Hz, 1H), 7.47 (d,  $J = 9.6$  Hz, 2H), 7.36 (t,  $J = 8.1$  Hz, 3H), 7.23 (t,  $J = 8.1$  Hz, 1H), 6.97 (d,  $J = 17.8$  Hz, 4H) and 6.82 (d,  $J = 9.6$  Hz, 1H). Two aliphatic proton between pyrimidinone and benzene ring appeared singlet at  $\delta$  4.41 (s, 2H), while another two protons showed singlet at  $\delta$  4.06 (s, 2H). A singlet for three proton of methoxy group appears at  $\delta$  3.61 (s, 3H).

IR spectrum of compound (**140**) showed peaks at  $3323\text{ cm}^{-1}$  (for -OH), at  $2928\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1646\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The  $^1\text{H-NMR}$  spectrum of compound (**140**) offered a singlet at  $\delta$  9.57 (s, 1H) for one proton of -OH.

The aromatic protons of quinoline and benzene rings appeared at  $\delta$  8.86 (d,  $J = 4.3$  Hz, 1H), 8.52 (d,  $J = 8.8$  Hz, 1H), 7.98 (d,  $J = 7.7$  Hz, 1H), 7.65 – 7.33 (m, 8H) and 6.98 (dd,  $J = 15.8, 8.1$  Hz, 2H). Two aliphatic proton between pyrimidinone and benzene ring showed singlet at  $\delta$  4.47 (s, 2H), while another two protons showed singlet at  $\delta$  4.13 (s, 2H).

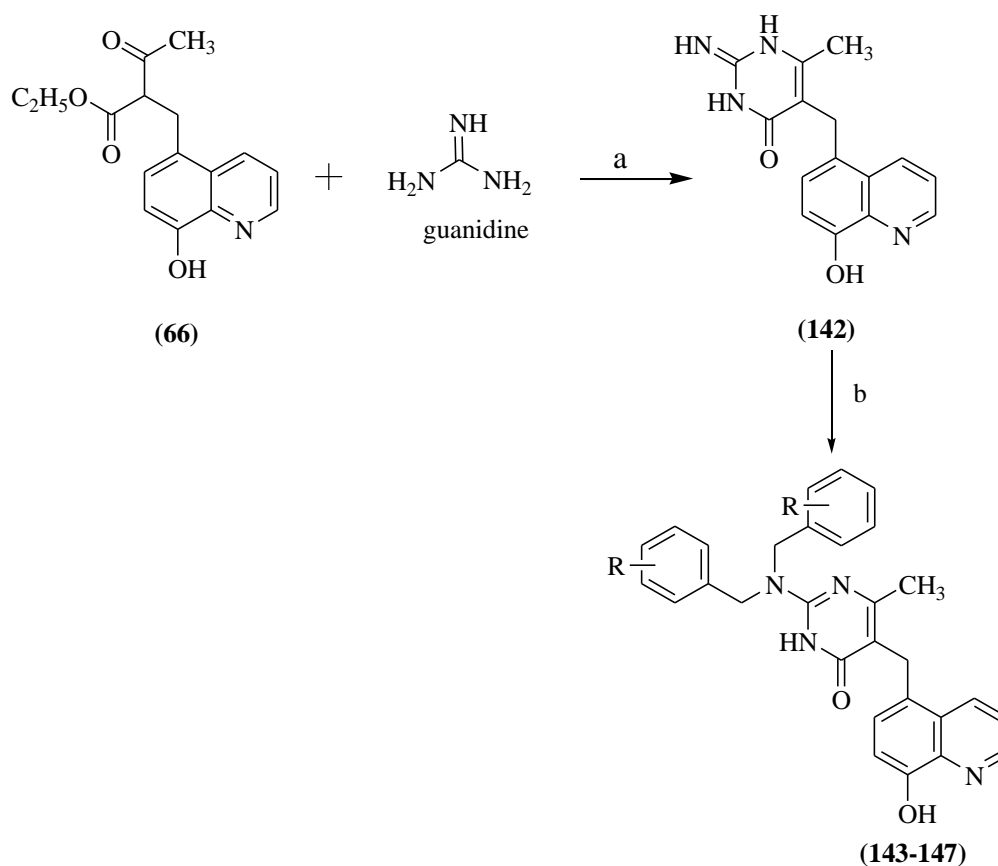


(141)

IR spectrum of compound (141) showed peaks at  $3357\text{ cm}^{-1}$  (for -OH), at  $2974\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1651\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The  $^1\text{H-NMR}$  spectrum of compound (141) offered a singlet at  $\delta$  12.92 (s, 1H) and 9.59 (s, 1H) for amide and one proton of -OH. The aromatic protons of quinoline and benzene rings appeared at  $\delta$  8.86 (dd,  $J = 4.2, 1.6$  Hz, 1H), 8.41 (dd,  $J = 8.6, 1.7$  Hz, 1H), 7.56 – 7.41 (m, 6H), 7.22 – 7.11 (m, 4H) and 6.95 (s, 2H). Two aliphatic proton between pyrimidinone and benzene ring appeared singlet at  $\delta$  4.44 (s, 2H), while another two protons showed singlet at  $\delta$  4.05 (s, 2H). A singlet for three proton of methyl group appears at  $\delta$  2.34 (s, 3H).

#### 4.1.2.3. Synthesis of 2-amino-5-((8-hydroxyquinolin-5-yl)methyl)-6-methylpyrimidin-4(3H)-one derivatives (142-147)

To synthesize planned compounds the following strategies adopted as mentioned in Scheme-4.2.3.1

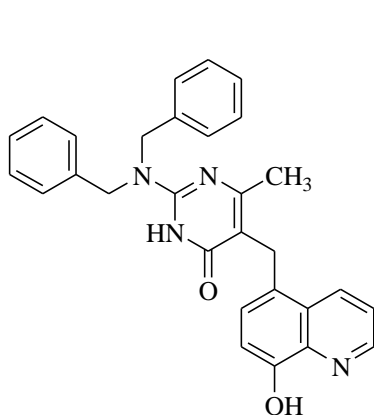


**Scheme-4.1.2.3.1.** General synthetic route for the synthesis of compounds (143-147); reagents and conditions: (a) DBU (diazabicyclo(5.4.0)undec-7-ene), ethanol, reflux; (b) substituted benzyl halide, DMF,  $K_2CO_3$ , RT.

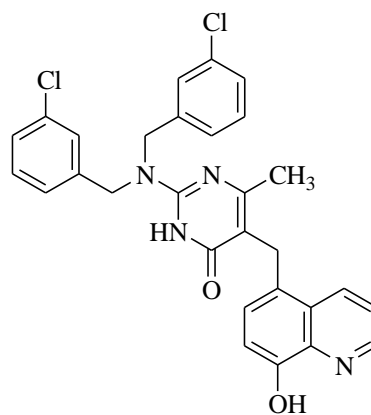
2,3-Dihydro-5-((8-hydroxyquinolin-5-yl)methyl)-2-imino-6-methylpyrimidin-4(1H)-one (142) was obtained by cyclization of ethyl 2-((8-hydroxyquinolin-5-yl)methyl)-3-oxobutanoate (96) with guanidine in presence of base. IR spectrum of compound (142) showed peaks at  $3323\text{ cm}^{-1}$  (for -OH), at  $2892\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1655\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z$  283.2  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (142) offered a singlet at  $\delta$  11.08 (s, 1H) and 9.59 (s, 1H) for amide and one proton of -OH. The five aromatic protons of quinoline appeared at  $\delta$  8.86 (dd,  $J = 4.2, 1.6$  Hz, 1H), 8.68 (dd,  $J = 8.6, 1.7$  Hz, 1H), 7.59 (dd,  $J = 8.6, 4.1$  Hz, 1H), 7.03 – 6.94 (m, 1H) and 6.57 (s, 1H). Two aliphatic proton between quinoline and pyrimidinone ring showed singlet at  $\delta$  3.99 (s, 2H). A singlet for three proton of both methyl group was seen at  $\delta$  1.96 (s, 3H).

IR spectrum of compound (143) showed peaks at  $3347\text{ cm}^{-1}$  (for -OH), at  $3033\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1666\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z$  463.69  $[M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (143) offered aromatic protons of quinoline and benzene rings appeared at  $\delta$  8.88 (dd,

$J = 4.1, 1.6$  Hz, 1H), 8.61 (dd,  $J = 8.6, 1.7$  Hz, 1H), 7.58 – 7.51 (m, 3H), 7.44 – 7.33 (m, 3H), 7.20 (q,  $J = 4.7$  Hz, 5H), 7.13 (d,  $J = 8.1$  Hz, 1H), 6.83 (d,  $J = 8.0$  Hz, 1H) and 6.41 (s, 1H). Four aliphatic protons between pyrimidinone and benzene ring demonstrated singlet at  $\delta$  5.30 (s, 2H) and 5.24 (s, 2H). Two protons between quinoline and pyrimidinone ring showed singlet at  $\delta$  4.15 (s, 2H). A singlet for three proton of methyl group was appears at  $\delta$  2.09 (s, 3H).



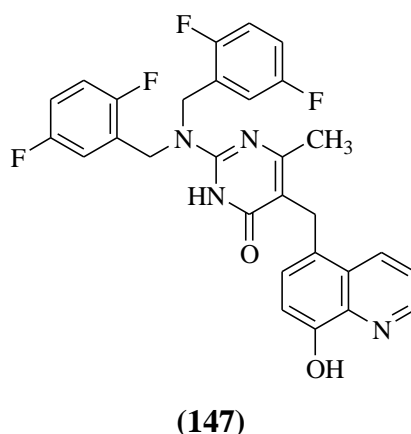
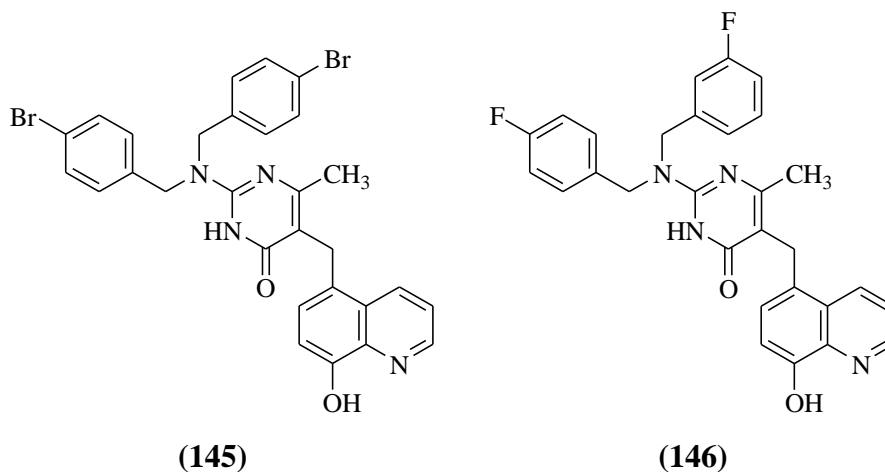
(143)



(144)

IR spectrum of compound (144) showed peaks at  $3344\text{ cm}^{-1}$  (for -OH), at  $3061\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1672\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z$  533.80  $[M+H]^+$  and 535.97  $[M+2]^+$ . The  $^1\text{H}$ -NMR spectrum of compound (144) offered aromatic protons of quinoline and benzene rings appeared at  $\delta$  8.90 (dd,  $J = 4.1, 1.6$  Hz, 1H), 8.66 (dd,  $J = 8.6, 1.7$  Hz, 1H), 7.62 – 7.34 (m, 7H), 7.26 (d,  $J = 2.0$  Hz, 1H), 7.20 – 7.12 (m, 2H) and 7.05 (d,  $J = 8.1$  Hz, 2H). Four aliphatic protons between pyrimidinone and benzene ring showed singlet at  $\delta$  5.29 (s, 2H) and 5.18 (s, 2H). Two protons between quinoline and pyrimidinone ring demonstrated singlet at  $\delta$  4.09 (s, 2H). A singlet for three proton of methyl group was appears at  $\delta$  2.00 (s, 3H).

IR spectrum of compound (145) showed peaks at  $3274\text{ cm}^{-1}$  (for -OH), at  $2875\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1619\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The  $^1\text{H}$ -NMR spectrum of compound (145) offered aromatic protons of quinoline and benzene rings demonstrated at  $\delta$  8.89 (dd,  $J = 4.1, 1.6$  Hz, 1H), 8.61 (dd,  $J = 8.6, 1.7$  Hz, 1H), 7.63 – 7.55 (m, 3H), 7.50 (d,  $J = 8.3$  Hz, 2H), 7.42 – 7.38 (m, 2H), 7.12 (dd,  $J = 11.6, 8.2$  Hz, 2H), 6.81 (d,  $J = 8.0$  Hz, 1H) and 6.40 (s, 2H). Four aliphatic protons between pyrimidinone and benzene ring showed singlet at  $\delta$  5.25 (d,  $J = 7.3$  Hz, 4H). Two protons between quinoline and pyrimidinone ring appeared singlet at  $\delta$  4.14 (s, 2H). A singlet for three proton of methyl group was showed at  $\delta$  2.10 (s, 3H).

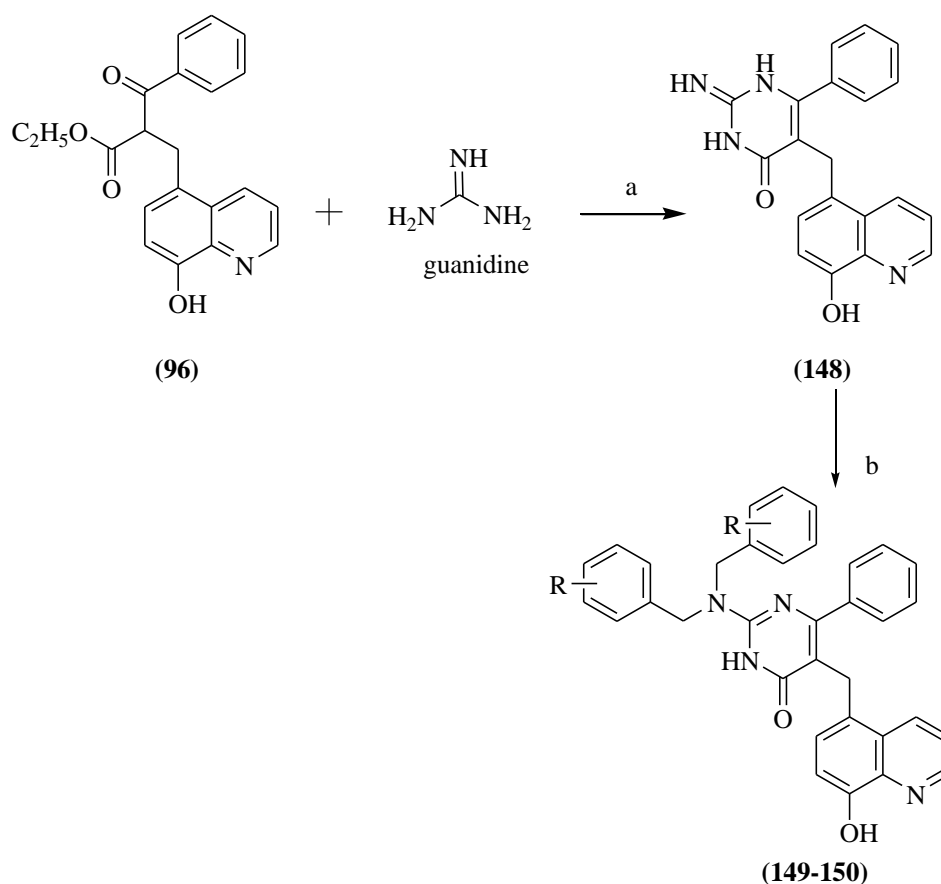


IR spectrum of compound (146) showed peaks at  $3334\text{ cm}^{-1}$  (for -OH), at  $2825\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1636\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z\ 499.74\ [M+H]^+$ .

IR spectrum of compound (147) showed peaks at  $3406\text{ cm}^{-1}$  (for -OH), at  $2910\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1656\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z\ 535.80\ [M+H]^+$ .

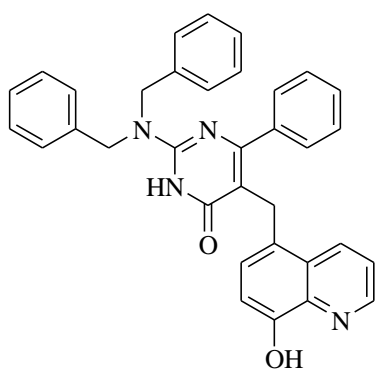
#### 4.1.2.4. Synthesis of 2-(dibenzylamino)-5-((8-hydroxyquinolin-5-yl)methyl)-6-phenylpyrimidin-4(3H)-one (148-150)

To synthesize planned compounds the following strategies adopted as mentioned in **Scheme-4.1.2.4.1**

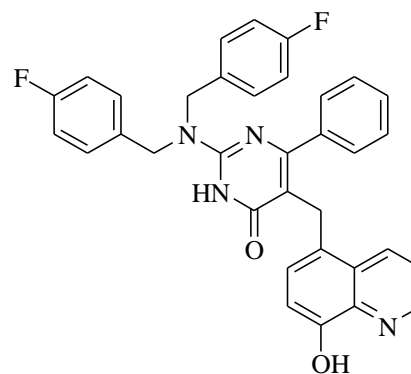


**Scheme-4.1.2.2.1.** General synthetic route for the synthesis of compounds; reagents and conditions: (a) DBU (diazabicyclo(5.4.0)undec-7-ene), ethanol, reflux; (b) substituted benzyl halide, DMF,  $K_2CO_3$ , RT.

2,3-Dihydro-5-((8-hydroxyquinolin-5-yl)methyl)-2-imino-6-phenylpyrimidin-4(1H)-one (**148**) was obtained by cyclization of ethyl 2-((8-hydroxyquinolin-5-yl)methyl)-3-oxo-3-phenylpropanoate (**96**) with guanidine in presence of base. IR spectrum of compound (**148**) showed peaks at  $3323\text{ cm}^{-1}$  (for -OH), at  $3049\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1655\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The  $^1\text{H-NMR}$  spectrum of compound (**148**) offered a singlet at  $\delta$  11.04 (s, 1H) and 9.49 (s, 1H) for -NH and one proton of -OH. The aromatic protons of quinoline and benzene appeared at  $\delta$  8.83 (dd,  $J = 4.1, 1.5\text{ Hz}$ , 1H), 8.38 (dd,  $J = 8.6, 1.6\text{ Hz}$ , 1H), 7.52 – 7.22 (m, 6H), 6.95 (s, 1H) and 6.51 (s, 1H). Two aliphatic proton between quinoline and pyrimidinone ring showed singlet at  $\delta$  3.91 (s, 2H).



(149)



(150)

IR spectrum of compound (149) showed peaks at  $3437\text{ cm}^{-1}$  (for -OH) and at  $1666\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z\ 525.75\ [M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (149) offered the aromatic protons of quinoline and benzene showed at  $\delta\ 8.85$  (dd,  $J = 4.1, 1.6\ \text{Hz}$ , 1H),  $\delta\ 8.40$  (dd,  $J = 8.6, 1.7\ \text{Hz}$ , 1H),  $7.57 - 7.26$  (m, 16H),  $7.17 - 7.13$  (m, 2H) and  $7.01$  (d,  $J = 8.0\ \text{Hz}$ , 1H). Four aliphatic protons between pyrimidinone and benzene ring obtained singlet at  $\delta\ 5.24$  (d,  $J = 12.8\ \text{Hz}$ , 4H). Two aliphatic proton between quinoline and pyrimidinone ring showed singlet at  $\delta\ 4.00$  (s, 2H).

IR spectrum of compound (150) showed peaks at  $3321\text{ cm}^{-1}$  (for -OH), at  $3041\text{ cm}^{-1}$  (aromatic C-H stretching) and at  $1666\text{ cm}^{-1}$  for the presence of -C=O stretching for amide. The mass spectrum showed quasi molecular ion at  $m/z\ 561.73\ [M+H]^+$ . The  $^1\text{H-NMR}$  spectrum of compound (150) offered the aromatic protons of quinoline and benzene appeared at  $\delta\ 8.85$  (dd,  $J = 4.0, 1.6\ \text{Hz}$ , 1H),  $\delta\ 8.40$  (dd,  $J = 8.7, 1.7\ \text{Hz}$ , 1H),  $\delta\ 7.60$  (dd,  $J = 8.4, 5.6\ \text{Hz}$ , 2H),  $\delta\ 7.49$  (dd,  $J = 8.6, 4.1\ \text{Hz}$ , 1H),  $7.37 - 7.15$  (m, 13H) and  $7.01$  (d,  $J = 8.1\ \text{Hz}$ , 1H). Four aliphatic protons between pyrimidinone and benzene ring showed singlet at  $\delta\ 5.22$  (d,  $J = 17.0\ \text{Hz}$ , 4H). Two aliphatic proton between quinoline and pyrimidinone ring appeared singlet at  $\delta\ 4.00$  (s, 2H).

## 4.2. Biological study of compounds

The synthesized derivatives were evaluated for their anti-Alzheimer activities, including AChE, BuChE inhibitory activity, MAO-B inhibition, metal chelation, anti-oxidant activity and cell toxicity study.

### 4.2.1. *In vitro* cholinesterase (AChE and BuChE) and monoamine oxidase (MAO-B) inhibitory studies

The synthesized series of compounds were evaluated for their inhibitory activity against acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), and monoamine oxidase B (MAO-

B). Cholinesterase inhibition assays were conducted using the protocol described by Ellman<sup>5</sup>, while MAO-B inhibition was assessed using the Amplex® Red Monoamine Oxidase Assay Kit (Invitrogen, USA)<sup>6</sup>. All compounds were initially screened at a fixed concentration of 10  $\mu$ M to determine their percentage inhibition. Physostigmine (eserine) served as the standard for cholinesterase inhibition, and pargyline was used as the standard for MAO-B inhibition.

Biological activity data shows that the AChE inhibition activity of compounds **70** (50.7%), **72** (51.4%), **74** (53.3%), **83** (50.9%), and **86** (57.7%) demonstrated moderate inhibition (>50%). Most compounds, such as compounds (**66**, **68**, **71**, **77–79**) exhibited modest activity (20–50%), whereas others, including compounds (**76**, **82**, **87**, **92–95**) displayed negligible inhibition (<10%). Compounds **102** (68.7%) and **105** (67.2%) exhibited the strongest AChE inhibition but remained less potent than physostigmine. Moderate activity was observed for compounds **107** (56.4%), **98** (49%), **99** (44.3%), **100** (42.7%), and **104** (45.6%), while most compounds, such as compounds (**96**, **97**, **110–120**) showed negligible inhibition (<10%), except for **109** (31.7%), **111** (17.3%), and **121** (29%), which displayed weak activity. Compounds **149** (48%), **134** (44%), and **128** (41%) demonstrated moderate inhibition but remained significantly lower than physostigmine. Most compounds, including **123**, **124**, **127**, **137**, **143**, exhibited weak activity (20–40%). The result of compounds summarize in **Table 4.2.1.1**, **Table 4.2.1.2** and **Table 4.2.1.3**.

**Table 4.2.1.1.:** Percentage inhibition of AChE, BuChE and MAO-B. (Comp 66-95)

Compounds	% Inhibition of AChE (10 $\mu$ M)	% Inhibition of BuChE (10 $\mu$ M)	% Inhibition of MAO-B (10 $\mu$ M)
Without Drug	0.0	0.0	0.0
Physostigmine (Positive Control)	99	97	-
Pergyline (Positive Control)	-	-	99
<b>66.</b>	27 $\pm$ 0.31	<10	24.19 $\pm$ 10.17
<b>67.</b>	12 $\pm$ 0.08	<10	<10
<b>68.</b>	30.7 $\pm$ 0.77	28.7 $\pm$ 5.7	<10
<b>69.</b>	15.2 $\pm$ 0.71	27.7 $\pm$ 6.0	<10
<b>70.</b>	50.7 $\pm$ 0.76	17.7 $\pm$ 2.1	17.4 $\pm$ 5.35
<b>71.</b>	28.9 $\pm$ 0.49	13.9 $\pm$ 4.53	23.84 $\pm$ 2.27
<b>72.</b>	51.4 $\pm$ 0.99	13.7 $\pm$ 5.7	31.2 $\pm$ 0.28
<b>73.</b>	39.6 $\pm$ 1.31	17.0 $\pm$ 2.23	<10

74.	53.3 ± 0.14	16.02 ± 3.84	<10
75.	35.5 ± 0.39	<b>94.07 ± 0.19</b>	<10
76.	<10	12.1 ± 1.21	13.32 ± 7.47
77.	26.4 ± 0.45	19.9 ± 5.77	31.4 ± 11.49
78.	31.3 ± 0.95	48.1 ± 4.24	<10
79.	42.6 ± 0.08	14.1 ± 1.85	<10
80.	14.1 ± 0.56	25.1 ± 8.8	<10
81.	14.1 ± 0.30	11.8 ± 7.9	<10
82.	4.9 ± 0.21	21.5 ± 7.4	<10
83.	50.9 ± 1.26	14.2 ± 8.4	38.66 ± 3.89
84.	46.1 ± 1.25	<10	<10
85.	32.8 ± 0.29	14.7 ± 8.2	<10
86.	57.7 ± 1.63	10.4 ± 7.9	<10
87.	15.4 ± 1.45	<10	<10
92.	<10	<10	<10
93.	<10	<10	55.97 ± 0.68
94.	<10	<10	56.81 ± 8.63
95.	<10	<10	<10

\*Data is mean ± standard error of mean (in percentage)

For BuChE inhibitory activity, Compound **75 (94.07%)** emerged as a potent BuChE inhibitor, approaching the efficacy of physostigmine (97%). Moderate inhibition was observed for **68 (28.7%)**, **78 (48.1%)**, and **77 (19.9%)**. Additionally, compound **100 (44.9%)** demonstrated the highest BuChE inhibition among the remaining tested compounds, followed by **109 (25.1%)**, **102 (23.1%)**, and **103 (22.3%)**.

**Table 4.2.1.2.:** Percentage inhibition of AChE, BuChE and MAO-B (**96-121**)

Compounds	% Inhibition of AChE (10 µM)	% Inhibition of BuChE (10 µM)	% Inhibition of MAO-B (10 µM)
Without Drug	0.0	0.0	0.0
Physostigmine (Positive Control)	99	97	-
Pergyline (Positive Control)	-	-	99
<b>96.</b>	<10	<10	<10
<b>97.</b>	<10	<10	<10
<b>98.</b>	49 ± 0.21	14.6 ± 4.09	84.61 ± 3.80
<b>99.</b>	44.3 ± 1.5	11.1 ± 2.92	67.63 ± 3.56
<b>100.</b>	42.7 ± 0.36	44.9 ± 2.19	<10
<b>101.</b>	41.0 ± 0.51	16.3 ± 1.72	79.89 ± 14.25
<b>102.</b>	68.7 ± 1.16	23.1 ± 8.29	80.34 ± 16.31

<b>103.</b>	37.3 ± 0.40	22.3 ± 3.61	78.55 ± 10.00
<b>104.</b>	45.6 ± 0.96	22.5 ± 4.21	67.45 ± 9.6
<b>105.</b>	67.2 ± 0.24	18.8 ± 8.41	69.58 ± 19.07
<b>106.</b>	12.9 ± 0.91	14.9 ± 3.09	<b>90.94 ± 19.08</b>
<b>107.</b>	56.4 ± 1.40	13.1 ± 3.22	<b>99.22 ± 33.63</b>
<b>108.</b>	48.5 ± 0.79	<10	61.37 ± 21.86
<b>109.</b>	31.7 ± 3.5	25.1 ± 3.45	<10
<b>110.</b>	<10	<10	<10
<b>111.</b>	17.3 ± 3.1	<10	<10
<b>112.</b>	<10	<10	<10
<b>113.</b>	<10	21.5 ± 2.43	<10
<b>114.</b>	<10	<10	<10
<b>115.</b>	<10	<10	<10
<b>116.</b>	<10	<10	<10
<b>117.</b>	<10	<10	<10
<b>118.</b>	12 ± 0.21	<10	<b>91.65 ± 1.04</b>
<b>119.</b>	<10	<10	<10
<b>120.</b>	<10	<10	34.54 ± 5.69
<b>121.</b>	29 ± 1.02	<10	66.74 ± 2.58

\*Data is mean ± standard error of mean (in percentage)

Moreover, Compounds **93 (55.97%)** and **94 (56.81%)** exhibited moderate MAO-B inhibition, though their efficacy was significantly lower than the positive control, pargyline (99%). Modest activity was observed for compounds **83 (38.66%)** and **72 (31.2%)**. Notably, **compound 107 (99.22%)** matched the efficacy of pargyline, making it a standout MAO-B inhibitor. Additionally, **compounds 118 (91.65%), 106 (90.94%), 102 (80.34%), and 101 (79.89%)** displayed robust inhibition (>75%). Moderate activity was observed for **98 (84.61%), 105 (69.58%), 99 (67.63%), 104 (67.45%), and 121 (66.74%)**, whereas **120 (34.54%)**. Furthermore, **compound 138 (100%)** matched pargyline's efficacy, emerging as a potent MAO-B inhibitor. Compounds **149 (70.43%), 143 (47.01%), 145 (48.33%), 137 (46.04%), and 135 (46.04%)** demonstrated moderate-to-strong inhibition (>45%).

**Table 4.2.1.3:** Percentage inhibition of AChE, BuChE and MAO-B. (122-150)

Compounds	% Inhibition of AChE (10 µM)	% Inhibition of BuChE (10 µM)	% Inhibition of MAO-B (10 µM)
Without Drug	0.0	0.0	0.0
Physostigmine (Positive Control)	99	97	-
Pargyline (Positive Control)			99

122.	<10	<10	<10
123.	33 ± 2.68	<10	12.05 ± 12.08
124.	26 ± 1.86	<10	16.59 ± 0.39
125.	25 ± 1.44	<10	13.42 ± 7.74
126.	20 ± 1.28	<10	18.10 ± 0.79
127.	25 ± 2.36	<10	18.62 ± 13.31
128.	41 ± 1.46	<10	32.22 ± 2.77
129.	38 ± 3.02	<10	18.33 ± 7.04
130.	19 ± 7.99	<10	11.51 ± 2.39
131.	33 ± 3.90	<10	18.18 ± 5.28
132.	18 ± 6.13	<10	20.91 ± 0.52
133.	13 ± 4.26	<10	18.33 ± 7.04
134.	44 ± 2.12	<10	37.17 ± 9.43
135.	17 ± 4.43	<10	46.04 ± 2.76
136.	21 ± 3.21	<10	40.48 ± 5.14
137.	31 ± 3.92	<10	46.04 ± 2.76
138.	31 ± 5.07	<10	<b>100 ± 1.96</b>
139.	27 ± 10.7	<10	46.39 ± 5.62
140.	21 ± 2.41	<10	36.03 ± 7.25
141.	39 ± 2.65	<10	<10
142.	<10	<10	<10
143.	29 ± 1.17	<10	47.01 ± 10.98
144.	26 ± 2.48	<10	<10
145.	<10	<10	48.33 ± 8.09
146.	<10	<10	33.96 ± 11.7
147.	<10	<10	<10
148.	<10	<10	<10
149.	48 ± 1.27	21 ± 2.34	70.43 ± 2.20
150.	35 ± 2.80	30 ± 3.24	<10

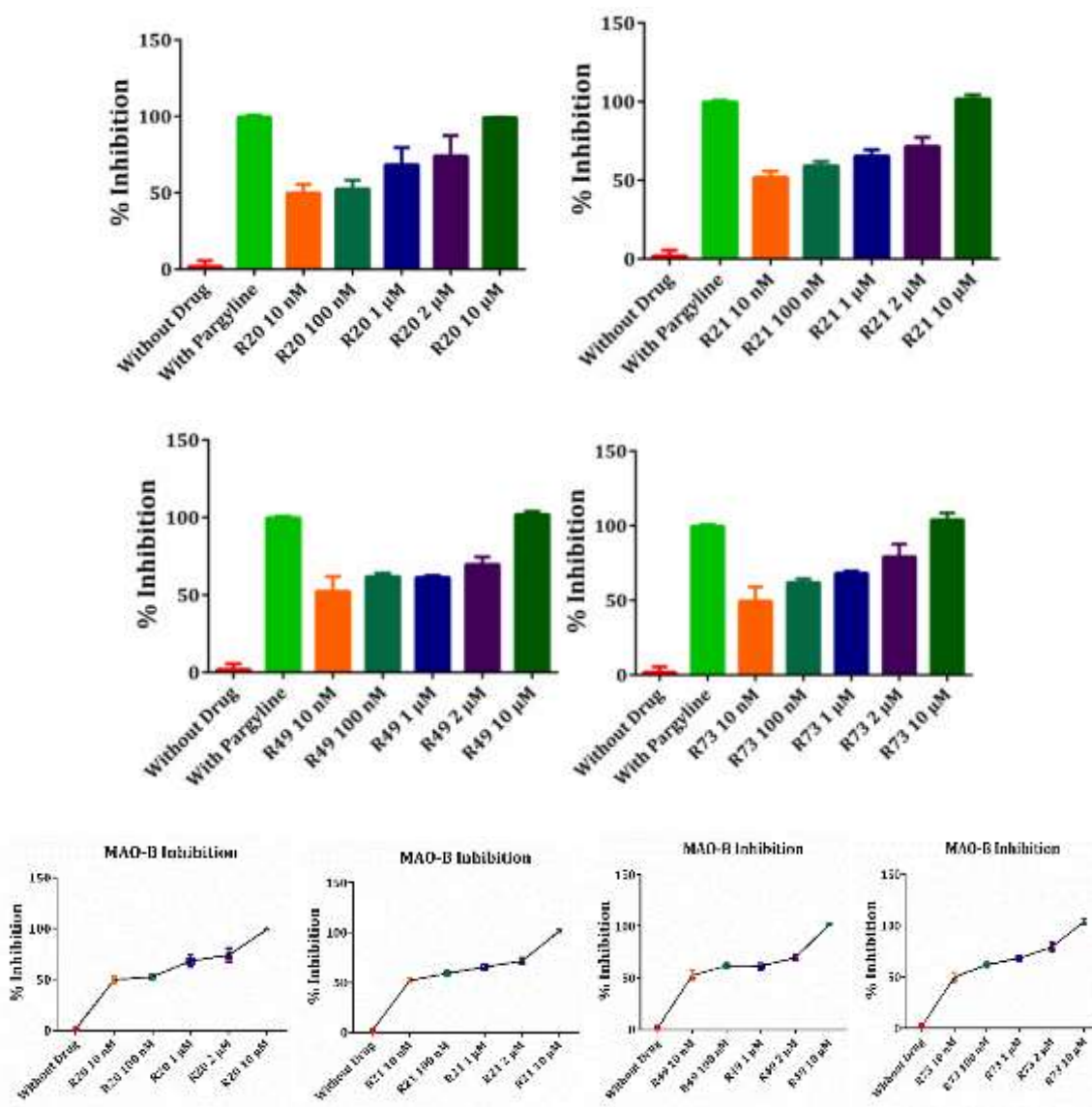
\*Data is mean ± standard error of mean (in percentage)

These findings led to the selection of the four most effective compounds (**106**, **107**, **118** and **138**) for IC<sub>50</sub> analysis. GraphPad Prism, version 6, was used to determine the IC<sub>50</sub> values by utilizing the curves of log (inhibitor) vs. normalized response with a varied slope. For IC<sub>50</sub> evaluation, starting chemical concentrations between 0 and 10 μM were utilized. All the compounds exhibited inhibitory concentration in nanomolar wherein IC<sub>50</sub> of (**118**) was found to be **15.11 ± 8.41 nM** followed by (**106**, **138** and **107**) having IC<sub>50</sub> of **16.02 ± 4.48 nM**, **19.14 ± 11.21 nM** and **26.23 ± 10.56 nM**, respectively (**Table 4.2.1.4 & Figure 4.2.1.4**).

Table 4.2.1.4.: IC<sub>50</sub> Value against MAO-B inhibition of most active compounds.

Compounds	Compound Code	Structure	IC <sub>50</sub> value against MAO-B inhibition (10nM)
106	R20		26.23 ± 10.56 nM
107	R21		16.02 ± 4.48 nM
118	R49		15.11 ± 8.41 nM
138	R73		19.14 ± 11.21 nM

\*Data is mean ± standard error of mean (in percentage)



**Figure 4.2.1.1:** Bar graph represents %MAO-B inhibition of *STHdh*<sup>Q7/Q7</sup> cells at 10 nM, 100 nM, 1 μM, 2 μM and 10 μM concentration for compounds **106 (R20)**, **107 (R21)**, **118 (R49)** and **138 (R73)** compared to negative control (without drug) and pargyline as positive control. Line graph represents %MAO-B inhibition of *STHdh*<sup>Q7/Q7</sup> cells at 10 nM, 100 nM, 1 μM, 2 μM and 10 μM concentration for compounds **106 (R20)**, **107 (R21)**, **118 (R49)** and **138 (R73)** for calibration curvatures of log (inhibitor) vs normalized response with a variable slope.

#### 4.2.2. Metal chelation activity

Furthermore, most active four compounds were considered for evaluating their metal chelation capabilities. In initial investigation, metal-chelating assay using ferrozine and ferrous chloride was performed at a low concentration at 10 μM. A well-known metal chelator and EDTA were used as standards<sup>7,8</sup>. Among the most active four compounds, compound (**118**)

showed good metal chelating activity with  $21.39 \pm 4.30$  % compared to other compounds while EDTA represent  $93.12 \pm 0.24$  % chelating activity. (Table 4.2.2.1).

**Table 4.2.2.1:** Metal chelation activity on ferrozine and ferrous chloride biometals at 10  $\mu$ M concentration

Compound	%MCA	$\pm$ SEM
EDTA	93.12	0.24
106	10.70	1.44
107	11.05	1.82
118	<b>21.39</b>	<b>4.30</b>
138	13.68	3.32

\*Data is mean  $\pm$  standard error of mean (in percentage)

#### 4.2.3. Antioxidant scavenging activity

The compounds were checked for its antioxidant property using DPPH assay<sup>9</sup>. The preliminary testing was performed at a low concentration of 10  $\mu$ M. Compound (118) was found to possess best antioxidant property with % radical scavenging of 5.19% compared to 5.97% of 8-hydroxyquinoline at 10  $\mu$ M (Table 4.2.3.1).

**Table 4.2.3.1:** Antioxidant radical scavenging activity using DPPH assay

Compound	%RSA	$\pm$ SEM
8-HQ	5.973	2.312
106	2.012	1.337
107	-3.082	1.027
118	<b>5.191</b>	<b>1.205</b>
138	-6.350	0.927

\*Data is mean  $\pm$  standard error of mean (in percentage)

#### 4.2.4. Cytotoxic effect of compounds on cell line by MTT Assay

In this study, the cytotoxic effects of selected compounds (106, 107, 118 and 138) were evaluated at varying concentrations on *STHdh*<sup>Q7/Q7</sup> cells. Cell viability was assessed using the MTT assay to determine dose-dependent responses and their significance<sup>10</sup>.

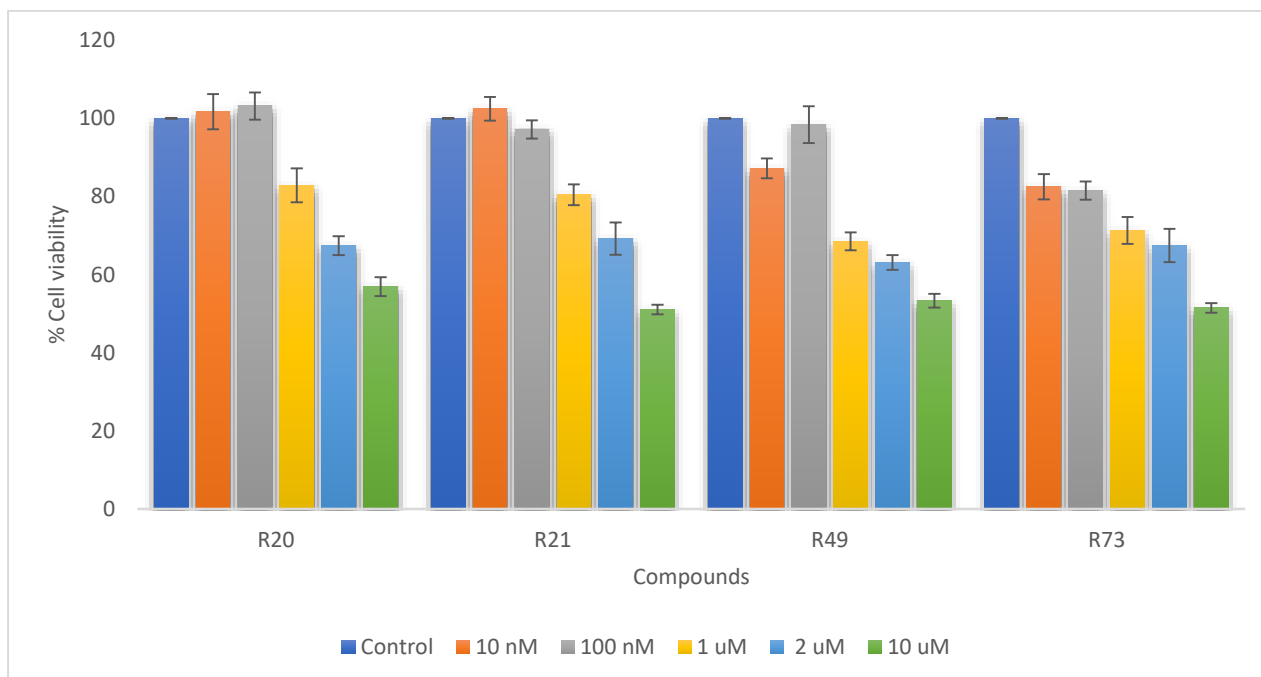
The presented data in Figure 4.2.4.1 represents the results of a cell viability assay conducted on *STHdh*<sup>Q7/Q7</sup> Cells were treated with compounds (106), (107), (118) and (138) at

various concentrations (10 nM, 100 nM, 1  $\mu$ M, 2  $\mu$ M, and 10  $\mu$ M). The control group (0 nM) exhibited 100% cell viability. Treatment with all compounds resulted in a 50% reduction in cell viability at higher concentrations.

**Table 4.2.4.1.:** Percentage cell viability of *STHdh*<sup>Q7/Q7</sup> cells at different concentrations of (106), (107), (118) and (138)

Compound	Compound code	10 nM	100 nM	1 $\mu$ M	2 $\mu$ M	10 $\mu$ M
<b>106</b>	<b>R20</b>	101.69 $\pm$ 4.43	103.17 $\pm$ 3.23	82.85 $\pm$ 4.34	67.43 $\pm$ 2.42	56.92 $\pm$ 2.39
<b>107</b>	<b>R21</b>	102.45 $\pm$ 3.01	97.19 $\pm$ 2.32	80.45 $\pm$ 2.65	69.21 $\pm$ 4.15	51.03 $\pm$ 1.22
<b>118</b>	<b>R49</b>	87.22 $\pm$ 2.54	98.41 $\pm$ 4.69	68.55 $\pm$ 2.28	63.09 $\pm$ 1.88	53.30 $\pm$ 1.77
<b>138</b>	<b>R73</b>	82.49 $\pm$ 3.24	81.53 $\pm$ 2.32	71.31 $\pm$ 3.44	67.45 $\pm$ 4.26	51.44 $\pm$ 1.21

\*Data is mean  $\pm$  standard error of mean (in percentage)



**Figure 4.2.4.1:** % Cell viability from MTT assay following compound treatment - the graph represents the percentage cell viability of *STHdh*<sup>Q7/Q7</sup> cells following treatment with compounds **106 (R20)**, **107 (R21)**, **118 (R49)** and **138 (R73)** at the final concentrations of 10 nM, 100 nM, 1  $\mu$ M, 2  $\mu$ M, and 10  $\mu$ M. The data points represent the mean values from triplicate experiments, and error bars indicate standard error of mean. Cell viability percentages are normalized relative to untreated control cells (0 nM).

However, at lower concentrations (10 nM and 100 nM), the compounds demonstrated nearly negligible effects on viability. A noticeable, dose-dependent decline in cell viability was observed as the concentrations increased (1  $\mu$ M, 2  $\mu$ M, and 10  $\mu$ M), indicating a concentration-related cytotoxic effect. This pattern suggests the compounds are largely non-cytotoxic at lower concentrations, with only moderate effects at higher concentrations.

### 4.3. Computational Study

Molecular docking studies were conducted on the synthesized compounds to evaluate their binding affinity and prioritize their potential activity against AChE and MAO-B enzymes. Based on the highest docking affinity scores, key interactions, and orientation of the designed compounds, the most active candidates were identified and discussed. Grid validation was carried out by redocking co-crystallized ligands into the 3D protein structures of *hAChE* (PDB: 4EY7) and *hMAO-B* (PDB: 2V5Z) at their respective active sites<sup>11,12</sup>. Initially, the co-crystallized ligands were extracted from their binding sites, energy-minimized, and subsequently redocked into the active site to confirm the docking accuracy.

#### 4.3.1 Molecular docking study of pyrazolone based derivatives and

#### 4.3.2 Molecular docking studies of pyrimidinone based derivatives

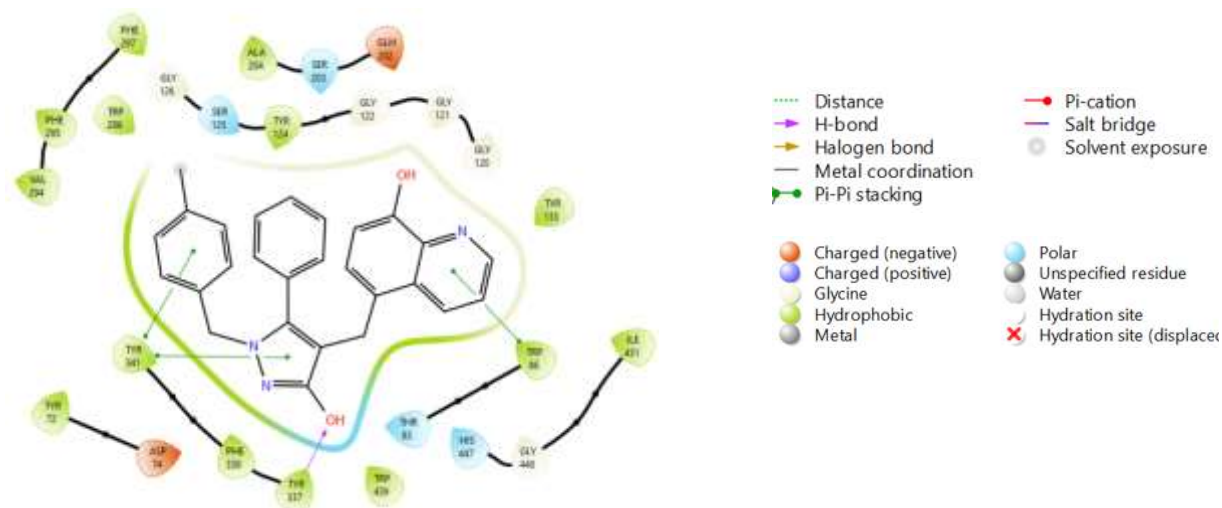
#### 4.3.1 Molecular docking studies of 8-hydroxyquinoline-pyrazolone derivatives

All the designed compounds were subjected to docking studies and analyzed based on their binding energies and receptor-ligand interactions. The interactions of the compounds exhibiting higher affinity within the active sites of *hAChE* and *hMAO-B* are summarized in **Table 4.3.1**.

**Table 4.3.1.** Docking interaction of pyrazolone based compounds against *hAChE* (PDB: 4EY7) and *hMAO-B* (PDB: 2V5Z).

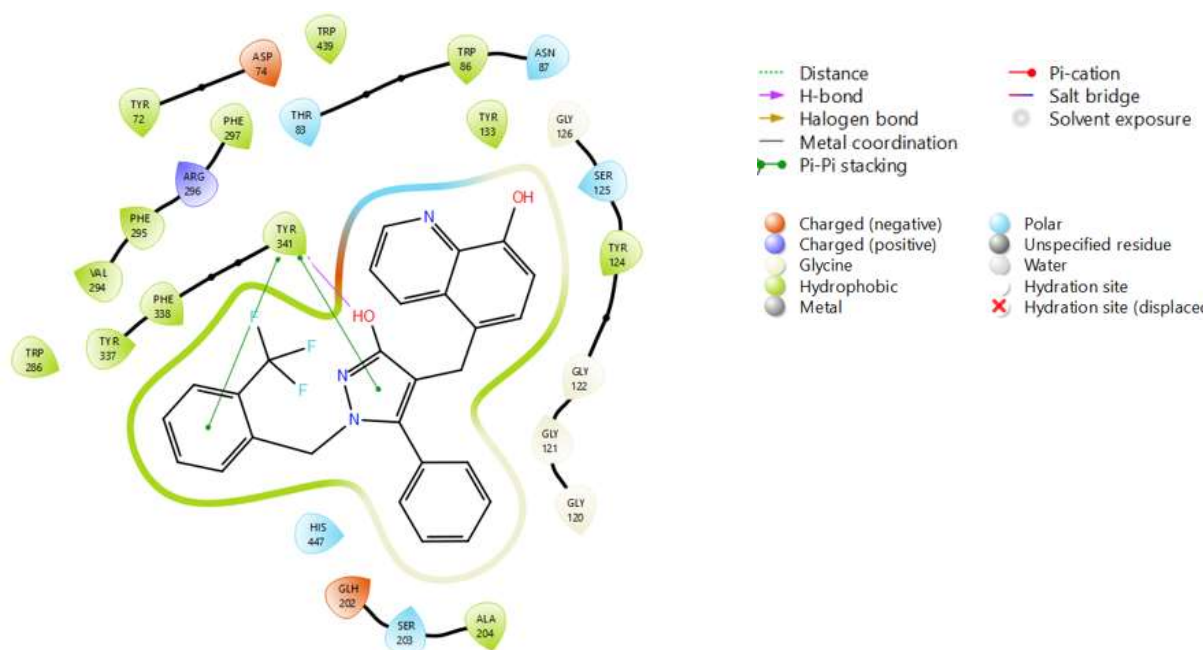
Comp.	<i>hAChE</i> (PDB: 4EY7)		<i>hMAO-B</i> (PDB: 2V5Z)	
	Docking Score (Kcal/Mol)	Interaction	Docking Score (Kcal/Mol)	Interaction
(101)	-10.191	Trp86, Tyr337 Tyr341	-7.051	Trp388, Ser59, Tyr398
(104)	-9.724	Trp86, Tyr337	-8.168	Phe343, Tyr398, Lys296, Trp388
(105)	-10.826	Trp86, Tyr341, Phe338	-6.843	Tyr435, Tyr398
(106)	-8.867	Trp86, Tyr72, Tyr124 Tyr341, Phe338	-8.219	Tyr398, Tyr326, Phe343, Tyr188

(107)	-9.147	Trp86, Tyr72, Tyr341, Tyr337	-8.506	Tyr398, Trp388, Tyr435
(118)	-9.547	Trp286, Tyr72, Tyr341, Val294, Phe295, Ser294	-10.818	Tyr435, Tyr60, Ser59, Tyr398, Phe343



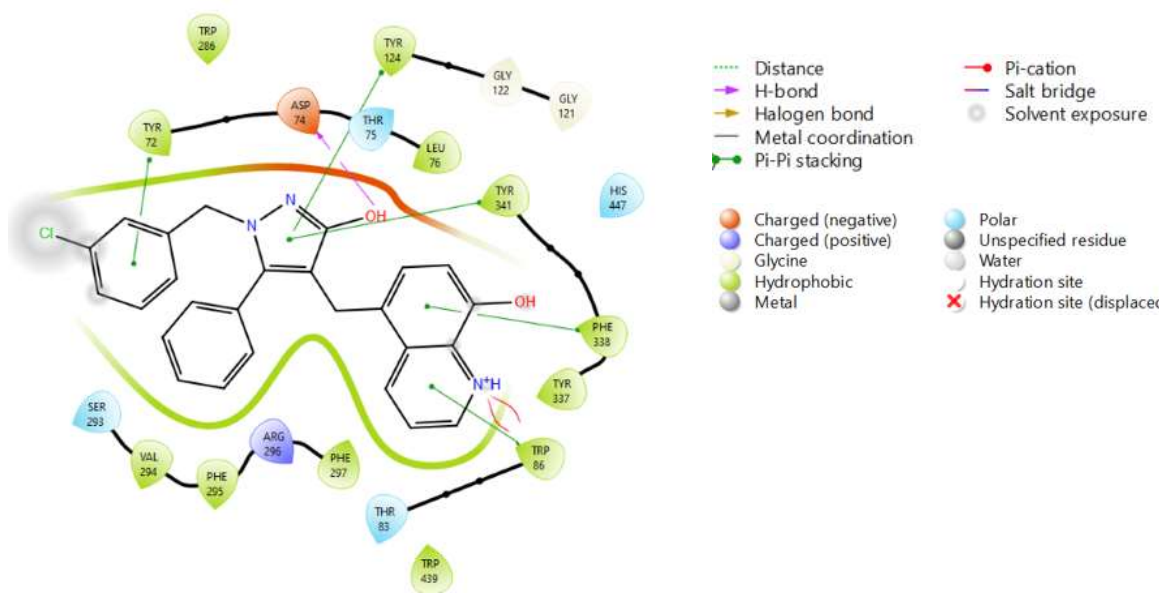
**Figure. 4.3.1.1** 2D interactions of Compound (105) with *hAChE* (PDB Id: 4EY7)

Among the series, compound (105) and (101) exhibited the best binding score with *hAChE* (PDB ID: 4EY7). Compound (105) exhibited favorable interactions with the key amino acids Trp86 and Tyr341 within the binding pocket of the *hAChE* enzyme (Fig. 4.3.1.1). Its orientation closely mirrors that of the reference compound, donepezil, extending from the active site residue Trp86 to the peripheral site residue Tyr286 along the active site cleft. The potent inhibitory effect of dual binding site inhibitors relies heavily on their interactions with these critical amino acids. The quinoline moiety, pyrazolone moiety and benzene ring facilitate  $\pi$ - $\pi$  stacking interactions with Trp86 and Tyr341, respectively. Additionally, the oxygen atom in the pyrazolone moiety forms a H-bond with Tyr337. Furthermore, pyrazolone moiety and benzene ring of compound (101) showed  $\pi$ - $\pi$  stacking interactions with Tyr341. While oxygen of pyrazolone moiety forms a H-bond with Tyr341.



**Figure. 4.3.1.2.** 2D interactions of Compound **101** with *hAChE* (PDB Id: 4EY7)

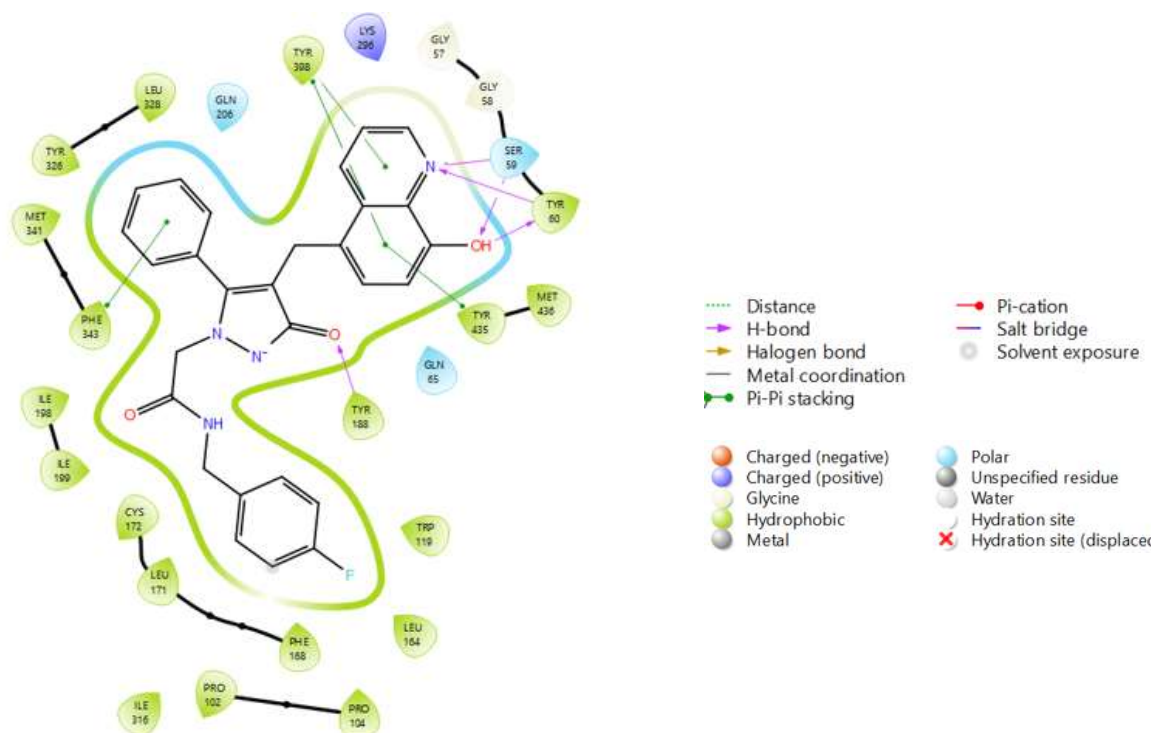
Similarly, **Figure 4.3.1.3** shows interactions of Compound (**106**) with AChE. The quinoline moiety facilitate  $\pi$ - $\pi$  stacking interactions with Trp86 and Phe338, while pyrazolone moiety and benzene ring exhibited interactions towards Tyr124, Tyr341 and Tyr72, respectively. Additionally, the oxygen atom in the pyrazolone moiety forms a H-bond with Asp74.



**Figure. 4.3.1.3** 2D interactions of Compound **106** with *hAChE* (PDB Id: 4EY7)

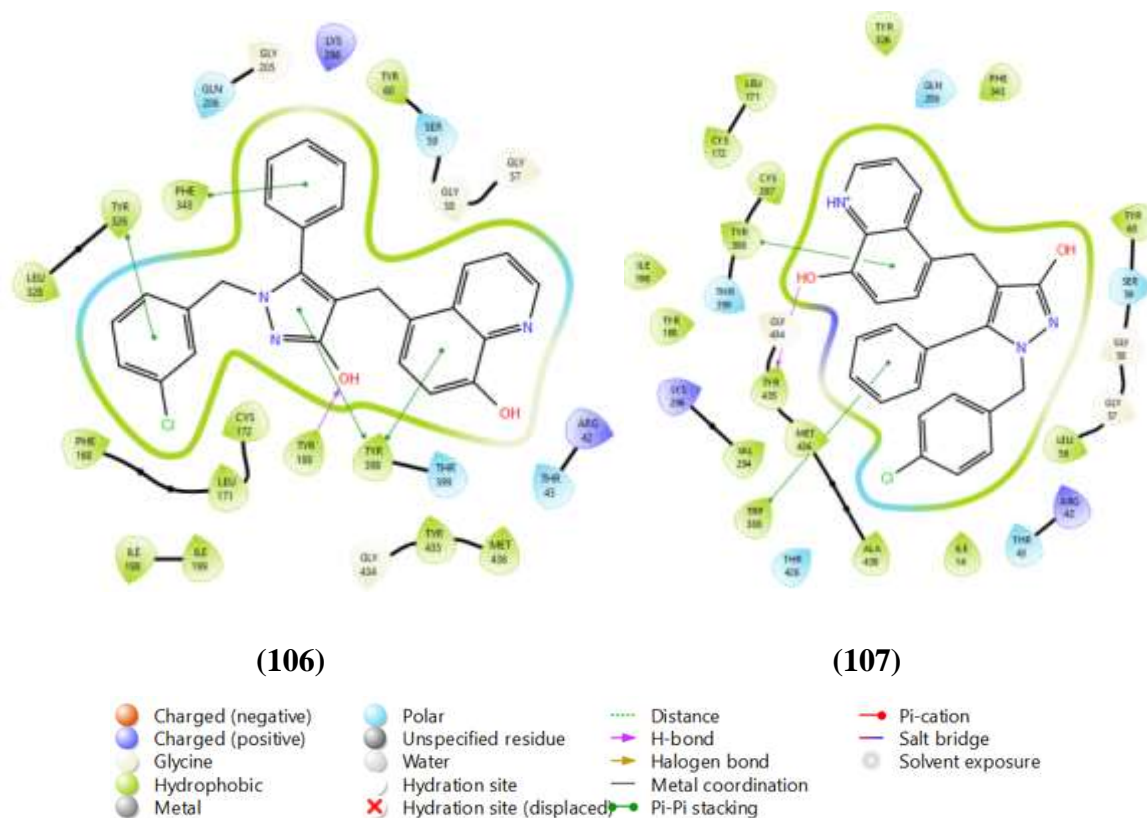
In the docking study of MAO-B, three most active compound (**118**, **106** and **107**) from the series discussed. **Figure 4.3.1.4** showed the interaction of the compound (**118**) within the active site of the *hMAO-B* (PDB: 2V5Z). The quinoline moiety showed the  $\pi$ - $\pi$  stacking

interactions with Tyr398 and Tyr435, while nitrogen and hydroxyl group shared H-bond with the Ser59 and Tyr60. The oxygen of pyrazolone moiety interacted with the H-bond at Tyr188. Pyrazolone substituted benzene ring showed  $\pi$ - $\pi$  stacking interactions with Phe343.



**Figure. 4.3.1.3** 2D interactions of Compound 118 with *h*MAO-B (PDB: 2V5Z).

Similarly, the docking interaction of compound (106) and (107) shown in **Figure 4.3.1.4**. Both quinoline moiety and pyrazolone moiety of the compound (106) exhibited  $\pi$ - $\pi$  stacking interactions with Tyr398, while both pyrazolone linked benzene ring showed interaction with Tyr326 and Phe343. While oxygen of pyrazolone shared H-bond with the Tyr188. Compound (107) showed  $\pi$ - $\pi$  stacking interactions between quinoline moiety and Tyr398, while benzene ring showed  $\pi$ - $\pi$  stacking interactions with Trp388. Hydroxyl group of the quinoline demonstrated H-bond with the Tyr435.



**Figure. 4.3.1.4.** 2D interactions of Compound (106) and (107) with *h*MAO-B (PDB: 2V5Z).

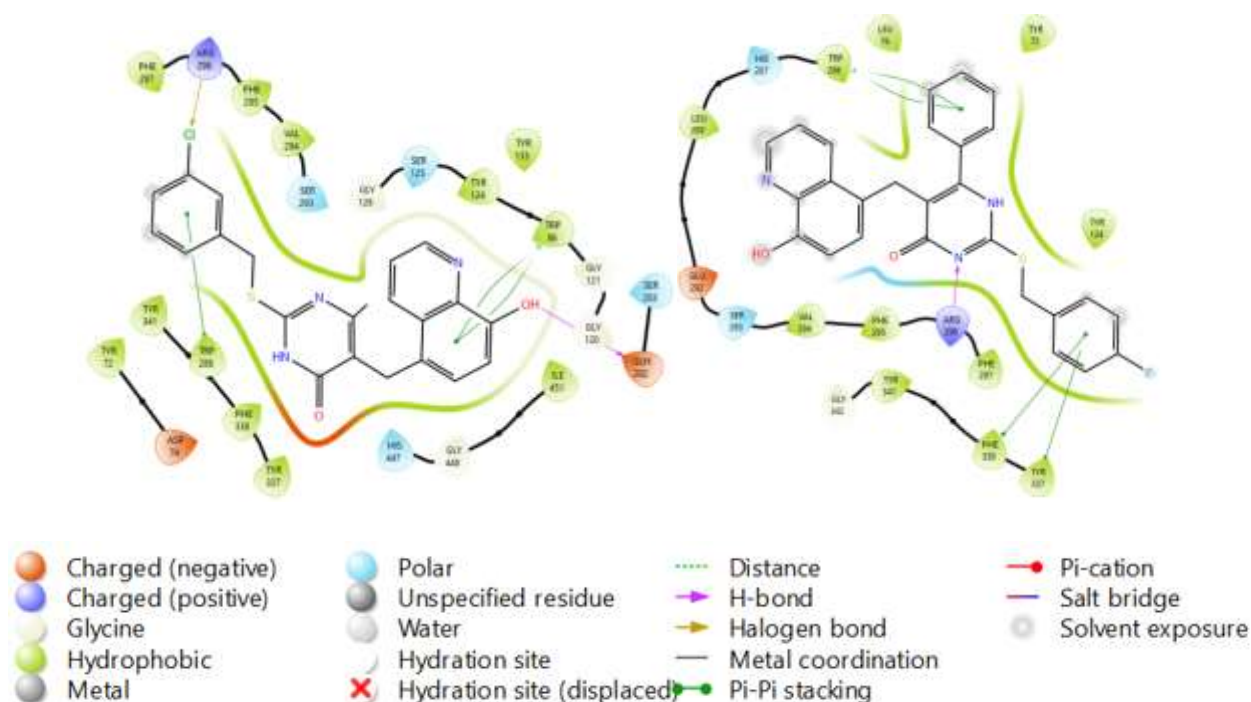
#### 4.3.2 Molecular docking studies of 8-hydroxyquinoline-pyrimidinone derivatives

All the designed compounds were subjected to docking studies and analyzed based on their binding energies and receptor-ligand interactions. The interactions of the compounds exhibiting higher affinity within the active sites of *h*AChE and *h*MAO-B are summarized in Table 4.3.2.

**Table 4.3.2.** Docking interaction of pyrimidinone based compounds against *h*AChE (PDB: 4EY7) and *h*MAO-B (PDB: 2V5Z)

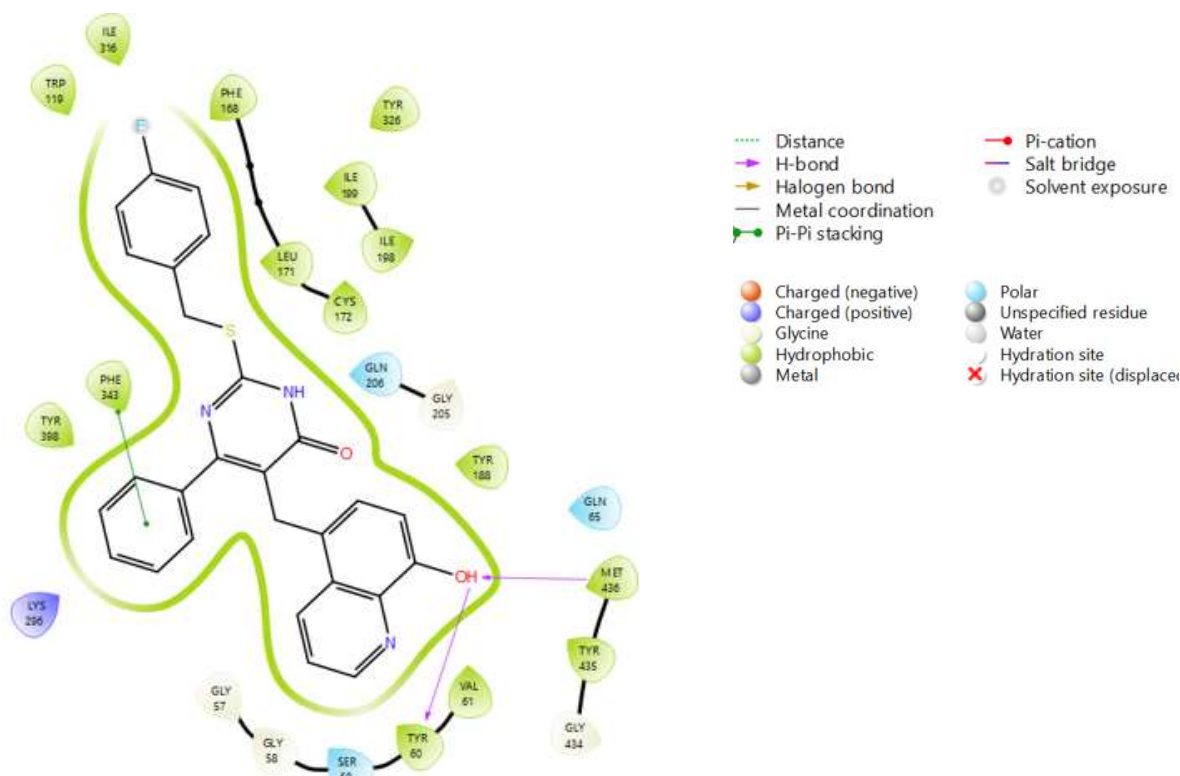
Compound	<i>h</i> AChE (PDB: 4EY7)		<i>h</i> MAO-B (PDB: 2V5Z)	
	Docking Score (Kcal/Mol)	Interaction	Docking Score (Kcal/Mol)	Interaction
(127)	-9.949	Trp86, Trp286, Glh202	-7.051	Tyr435, Tyr60, Tyr398
(133)	-9.904	Trp86, Trp286, Glh202	-8.168	Tyr398, Tyr60
(129)	-9.776	Trp86, Phe338, Trp286, Arg296	-6.843	Tyr435, Met436,
(138)	-8.702	Tyr337, Phe338, Trp286, Arg296	-8.219	Tyr60, Met436, Phe343

**Figure 4.3.2.1.** Represented the docking interaction of compound (127) and (138) with the active site of *hAChE* (PDB Id: 4EY7). Quinoline moiety of the compound showed  $\pi$ - $\pi$  stacking interactions with Trp86, while pyrimidinone linked benzyl ring showed interaction with the Trp286. Chlorine atom at the 3<sup>rd</sup> position of the benzene ring formed H-bond with the Arg296. Moreover, the most active compound among the series, compound (138) showed  $\pi$ - $\pi$  stacking interactions between pyrimidinone substituted benzene ring and Trp286 while another  $\pi$ - $\pi$  stacking interactions observed between fluoro substituted benzene and Phe338 and Tyr337. Amide nitrogen of pyrimidinone shared H-bond with the Arg296.



**Figure. 4.3.2.1.** 2D interactions of Compound (138) with *hAChE* (PDB Id: 4EY7)

Among the series, the most potent compound (138) interaction with the MAO-B (PDB: 2V5Z) demonstrated in **Figure 4.3.2.2**. The hydroxyl group of the quinoline ring formed two H-bond with the Tyr60 and Met436 while pyrimidinone substituted benzene ring showed  $\pi$ - $\pi$  stacking interactions with the Phe343.



**Figure. 4.3.2.1.** 2D interactions of Compound (138) with *h*MAO-B (PDB: 2V5Z).

The molecular docking results of the active compounds demonstrated strong binding interactions with the active sites of both AChE and MAO-B enzymes. These interactions suggest the potential of the compounds as dual inhibitors, which could be beneficial for treatment of AD. The findings highlight their ability to stabilize within the enzyme binding pockets through hydrogen bonding, hydrophobic interactions, and  $\pi$ - $\pi$  stacking, indicating promising inhibitory activity.

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