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# Synthesis and Antibacterial Activity of Some Novel Quinoline Analogues

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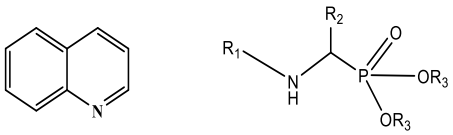
**Abstract**

The synthesis of some new heterocyclic compounds including quinoline moiety. The new 4-chloroacetylaminophenylaminoquinoline derivatives **(5a, 5b)** were synthesized by condensation of 4,7dichloroquinoline **1** with amines **(2a, 2b)** following by acylation with 2-chloro acetyl chloride **4**. Then, 4-chloroacetylaminophenylaminoquinoline derivatives **(5a, 5b)** were reacted with different substituted aniline **(6a,6b,8a,8b)** to afford new 4-acetylaminophenylaminoquinoline derivatives **7(a-c), 9(a-d)**. The one pot reaction with the synthesized 4-acetylaminophenylaminoquinoline derivative **7c**, benzaldehyde **9** and triphenylphosphite **10** in presence of LiClO4 as a Lewis acid catalyst led to the formation of α-aminophosphonate derivative **12** in good yields. The chemical structures of all synthesized compounds were elucidated by the analysis of FT-IR, NMR and MS spectral data. The biological screening data of the newly synthesized compounds were screened for *in vitro* antimicrobial activity towards gram-positive and gram-negative bacteria strains which possess moderate inhibition zones.

**Keywords**: Heterocyclic compounds, 4,7dichloroquinoline, chloro acetyl chloride, substituted aniline, triphenylphosphite, Lewis Acid, α-Aminophosphonate, antimicrobial activity.

## 1. Introduction:

Among heterocyclic compounds, quinolines appear an important construction motif for the development of new drugs. They play an important role in organic chemistry, as exemplified by their extensive application as biologically [1-6], pharmacologically [7-9] and industrially [10, 11] active compounds. They used mainly as an intermediate in the manufacture of many products [12]. Quinoline and their derivatives play important roles for the synthesis of natural products and as therapeutic agents, an important class of compounds for new drug development [13-16]. Furthermore, they were important scaffold in synthetic chemistry [17-19].




**I** **II**

**Figure 1: Quinoline I, α-aminophosphonates II**

They had significant biological activity as anticancer [20, 21], antifungal [22], antibacterial [23, 24], antioxidant [24], antitumor [22], anti-inflammatory [25], antiviral ref and antimalarial [22]. Most quinoline are classified according to their chemical structure or application method. Moreover, hybridization of quinoline moiety with α-aminophosphonates was proved significant synergistic effect on biological activity [26-29]. As amino phosphonate compounds are structural analogues of amino acids in which a carboxylic moiety is replaced by phosphonic acid or related groups [30-32]. Acting as antagonists of amino acids, they inhibit enzymes involved in amino acid metabolism and this affect the physiological activity of the cell. Therefore, the substituted α-amino phosphonate derivatives have important intermediates in the synthesis of large biologically active compounds, which have found wide range applications in medicinal fields [33, 34]. This work covers the synthesis as well as biological activities of

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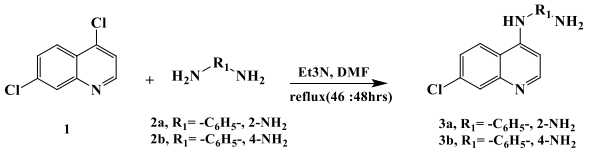
quinoline derivatives towards gram-positive and gram-negative bacterial pathogens.

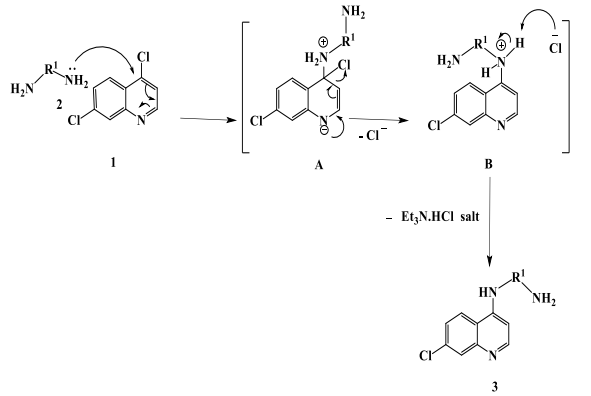
**2. Result and discussion:**

The starting 4-aminophenylaminoquinoline derivatives **3** were obtained in good yields according to the reaction of 4,7-dichloroquinoline **1** with excess amount of 1,2-phenylene diamine **2a** or 1,4-phenylene diamine **2b** dissolved in dimethyl formamide DMF; in presence of triethyl amine $Et_3N$; as a base under refluxing for (46-48hrs) as shown in **Scheme 1**.



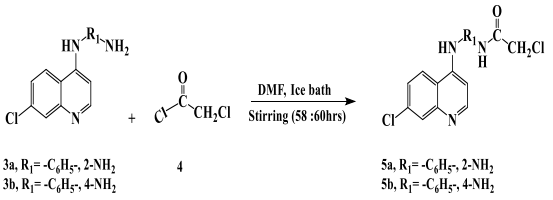

**Scheme 1:** Synthesis of 4-aminophenylaminoquinoline derivatives **3**.

The mechanism of $S_{NAr}$ amination reaction for 4,7 dichloroquinoline at C4 position was illustrated in as shown in **Scheme 2**.



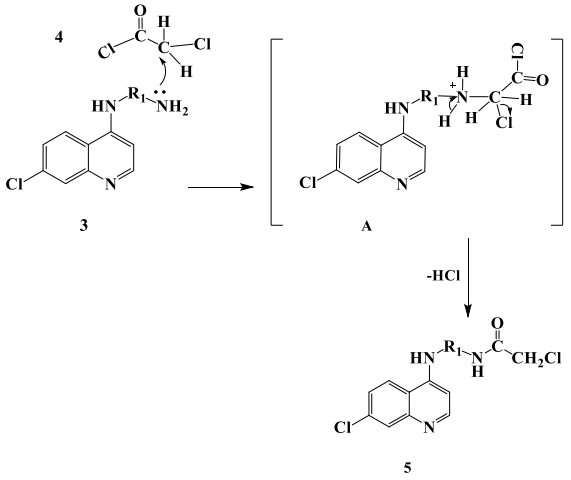

**Scheme 2:** Suggested mechanism for the synthesis of 4-aminophenylaminoquinoline derivatives **3**.

The synthetic method for acylation of 4-aminophenylaminoquinoline derivatives **3** were given in **Scheme 3**. The starting 4-aminophenylaminoquinoline derivatives **3** were reacted with excess amount of 2-chloro acetyl chloride **4** in presence of DMF; through stirring under ice bath for (58-60hrs) to afford quinoline derivatives **5** in good yields as given in **Scheme 3**.




**Scheme 3:** Synthesis of 4-chloroacetyl aminophenyl aminoquinoline derivatives **5**.

The suggested mechanism for formation 4-chloroacetylaminophenylaminoquinoline derivatives **5** is shown in **Scheme 4**. Firstly, the nucleophilic aromatic substitution ($S_{NAr}$) of the amine to the chloride ion at position C-2 is activated by the aminoquinoline ring via negative mesomeric effect through the formation of a resonance-stabilized anion **A**. The new C– N bond formation via charged intermediate **A** lead to the formation of the 4-chloroacetylaminophenylaminoquinoline derivatives **5** as shown in **Scheme 4**.

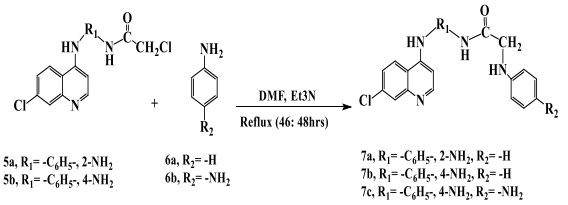



**Scheme 4:** Plausible mechanism for the synthesis of 4-chloroacetylaminophenylaminoquinoline derivatives **5**.

The structure of 4-chloroacetylaminophenylaminoquinoline derivatives **5** was characterized by FT-IR, $^1$H-NMR and mass spectroscopic analysis. The FT-IR of **5a, 5b** showed broad absorption bands at 3285 and 3411 $cm^{-1}$ ;corresponding to NH group. While absorption bands appeared at 2927 and 2926 $cm^{-1}$; corresponding to -$CH_2$ aliphatic. Furthermore, absorption bands appeared at 1607 and 1611 $cm^{-1}$; corresponding to C=O group. Moreover, absorption bands appeared at 1559 and 1576 $cm^{-1}$; corresponding to C=C group and the C=N group appeared at 1509 and 1508 $cm^{-1}$; $^1$HNMR indicated at 3.9 and 3.8 ppm corresponding to -$CH_2$ aliphatic and at 8.21 and 8.38 ppm corresponding to NH groups for compound **5a, 5b**. The mass spectra for compounds **5a, 5b** showed the expected molecular ion peaks, which confirmed the chemical structure.

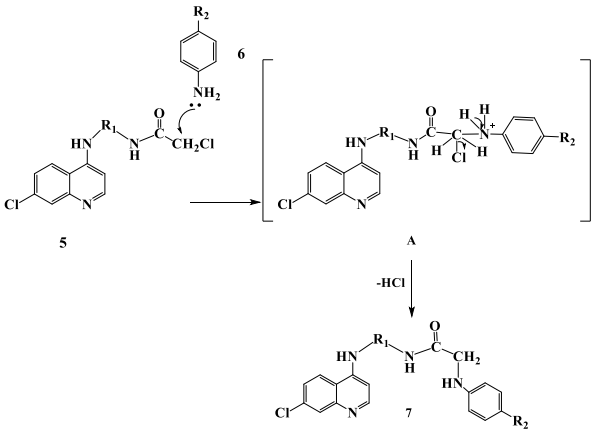
The reaction of new 4-acetylaminophenylaminoquinoline derivatives **7** was depicted in **Scheme 5**. The starting quinoline derivatives **5** were reacted with excess amount of aniline **6a** or 1,4-phenylene diamine **6b** dissolving in DMF; in the presence of triethyl amine $Et_3N$; as a base under reflux for (46-48hrs) to obtain new 4-

acetylaminophenylaminoquinoline derivatives **7** in good yields as shown in **Scheme 5**.




**Scheme 5:** Synthesis of 4-acetylaminophenylaminoquinoline derivatives.

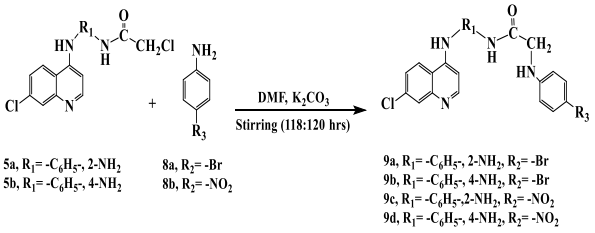
The plausible mechanism for formation 4-acetylaminophenylaminoquinoline derivatives **7** is shown in **Scheme 6**. Firstly, the nucleophilic aromatic substitution ($S_{NAr}$) of the amine to the chloride ion 4-chloroacetylaminophenylaminoquinoline derivatives **5** which is activated via negative mesomeric effect through the formation of a resonance-stabilized anion **A**. The new C– N bond formation via charged intermediate **A** lead to the formation of the expected 4-acetylaminophenylaminoquinoline derivatives **7** as shown in **Scheme 6**.




**Scheme 6:** Proposed mechanism for the synthesis of 4-acetylaminophenylaminoquinoline derivatives **7**.

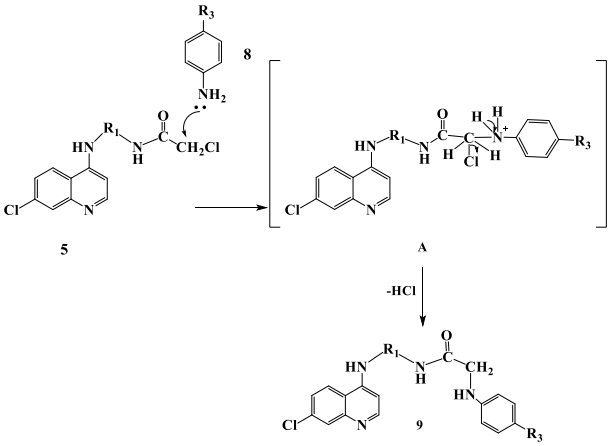
The structure of 4-acetylaminophenylaminoquinoline derivatives **7** elucidated by FT-IR, $^1$H- NMR and mass spectroscopic analysis. The FT-IR of **7a, 7b, 7c** showed broad absorption bands at 3354, 3495 and 3434 cm$^{-1}$; corresponding to NH group. While absorption bands appeared at 2921, 2632 and 2933 cm$^{-1}$ ;corresponding to -$CH_2$ aliphatic. Furthermore, absorption bands appeared at 1608, 1617 and 1624 cm$^{-1}$; corresponding to C=O group. Moreover, absorption bands appeared at 1554, 1544 and 1511 cm$^{-1}$; corresponding to C=C group and the C=N group appeared at 1485, 1415 and 1471 cm$^{-1}$; $^1$HNMR indicated at 4.05, 3.9 and 3.9 ppm corresponding to -$CH_2$ aliphatic for **7a, 7b, 7c** and at 8.83, 8.85 and 9.78 ppm corresponding to NH group for compound **7a, 7b, 7c**. The mass spectra for compounds **7a, 7b, 7c** showed the expected molecular ion peaks, which confirmed the chemical structure.

The starting 4-chloroacetylaminophenylaminoquinoline derivatives **5** were reacted with 4- bromo aniline **8a** or 4- nitro aniline **8b** dissolving in DMF; in the presence of potassium carbonate $K_2CO_3$; as a base under stirring for (118-120hrs) to afford 4-acetylaminophenylaminoquinoline derivatives **9** in good yields as depicted in **Scheme 7**.




**Scheme 7:** Synthesis of 4-acetylaminophenylaminoquinoline derivatives **9**.

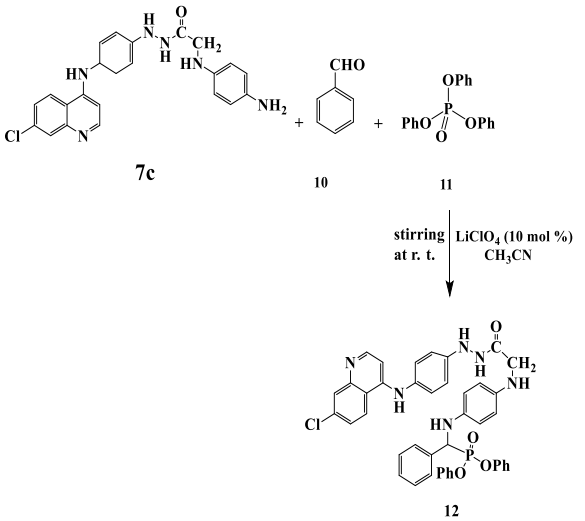
The proposed mechanism for formation 4-acetylaminophenylaminoquinoline derivatives **9** is given in **Scheme 8**. Firstly, the nucleophilic aromatic substitution ($S_{NAr}$) of the amine nitrogen to the chloride ion of 4-chloroacetylaminophenylaminoquinoline derivatives **5** which is activated via negative mesomeric effect through the formation of a resonance-stabilized anion **A**. The new C– N bond formation via charged intermediate **A** lead to the formation of the expected 4-acetylaminophenylaminoquinoline derivatives **9** as shown in **Scheme 8**.




**Scheme 8:** Suggested mechanism for the synthesis of 4-acetylaminophenylaminoquinoline derivatives **9**.

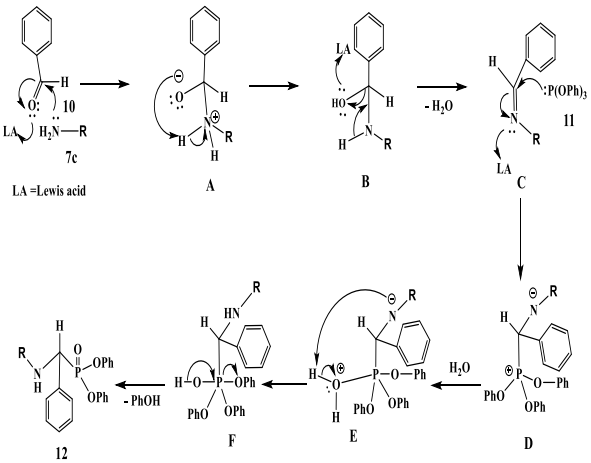
The structure of 4-acetylaminophenyl aminoquinoline derivatives **9** elucidated by FT-IR, $^1$H- NMR and mass spectroscopic analysis. The FT-IR of **9(a-d)** showed broad absorption bands at 3432, 3417, 3445 and 3432 $cm^{-1}$; respectively corresponding to NH group. While absorption bands appeared at 2926, 2925, 2927 and 2922 $cm^{-1}$; respectively corresponding to -$CH_2$ aliphatic for **9(a-d)**. Furthermore, absorption bands appeared at 1606, 1798, 1606 and 1588 $cm^{-1}$; respectively corresponding to C=O group for **9(a-d)** respectively. Moreover, absorption bands appeared at 1507, 1609, 1553 and 1559 $cm^{-1}$; respectively corresponding to C=C group and the C=N group for **9(a-d**) appeared at 1452, 1430, 1413 and 1415 $cm^{-1}$; respectively. $^1$HNMR indicated at 3.87, 3.83, 3.34 and 3.89 ppm respectively corresponding to -$CH_2$ aliphatic for **9(a-d)** and at 5.28, 8.46, 7.95 and 8.45 ppm corresponding to NH group for compound **9(a-d)**. The mass spectra for compounds **9(a-d**) showed the expected molecular ion peaks, which confirmed the chemical structure.

The synthetic method for formation α-aminophosphonate derivative **12** was given in **Scheme 9**. The starting benzaldehyde **10** with triphenyl phosphite **11** and 4-acetylaminophenylaminoquinoline derivative **7c** in equivalent molar ratio was added in acetonitrile then, 10 mmol % of lithium perchlorate as Lewis acid was added to obtain α-aminophosphonate derivative **12** in good yield as presented in **Scheme 9**.




**Scheme 9:** Synthesis of α-aminophosphonate derivative **12**.

The proposed mechanism for formation α-aminophosphonate derivative **12** is given in **Scheme10**. Firstly, the reaction of the bebzaldehyde **10** with the amino-compounds **7c** in the presence of lithum percholorate as a lewis acid (LA) catalyst afforded the corresponding imine- intermediates **C** according to **scheme 10**. Then, the imine intermediate **C** is attacked by nucleophilic phosphite **11** leading to the formation of a phosphonium intermediate **D** and most likely this step is catalyzed by the Lewis acid (LA). Reaction of phosphonium intermediates **D** with water afforded the target α-aminophosphonate derivative **12** after elimination of phenol as shown in **Scheme 10**.




**Scheme 10**: Reaction mechanism of α-aminophosphonate derivative 12

The FT-IR of α-aminophosphonate derivative **12** showed absorption band ranging from 3525 to 3566 $cm^{-1}$; corresponding to NH group. While absorption band appeared at 2434 $cm^{-1}$; corresponding to -$CH_2$ aliphatic. Furthermore, absorption band appeared at 1593 $cm^{-1}$; respectively corresponding to C=O group. Moreover, absorption band appeared at 1498, and 1205 $cm^{-1}$; respectively corresponding to C=C and P=O groups. $^1$HNMR indicated at 3.87, 6.10, 6.85 and 7.78 ppm respectively corresponding to -$CH_2$ aliphatic, -CHP, NH and NH group. The mass spectra showed the expected molecular ion peaks, which confirmed the chemical structure of α-aminophosphonate derivative **12**.

## 3. Antimicrobial Screening

The synthesized compounds **5a, 5b, 7(a-c), 9(a-d)** and **12** were screened in vitro for antibacterial activity against *S. Aureus*, *B. Subtilis*, *E. coli* and *P. aeruginosa*. The effect of synthesized compounds on the several bacterial strains were assayed by Disc diffusion method. The synthesized compounds were allowed to weak diffuse out into the medium and interact in a plate freshly which seeded with the test organisms. The Inhibition zone diameter was measured in mm. Petri-plates containing 20 mL Muller Hinton medium were seeded with 24 h of bacterial strains. The solutions of concentration 100

µg/mL were prepared in dimethyl sulphoxide (DMSO). The diameter of the inhibition zones formed is presented in **table 1**. Also, compounds **5a, 5b, 7a, 7b** and **9(a-d)** exhibited moderate antibacterial activity with inhibition zones as shown in **table 1**.

**Table (1):** Antibacterial activity for compounds **5a, 5b, 7(a-c), 9(a-d)** and **12.**

| Samples | Inhibition zone diameter (mm) | | | |
|---|---|---|---|---|
| | Gram (+) | | Gram (-) | |
| | Bacillus subtilis | Staphylococcus aureus | Escherichia coli | Pseudomonas aeruginosa |
| Ampicillin antibacterial agent | 26 | 21 | 25 | 26 |
| DMSO | 0 | 0 | 0 | 0 |
| 5a | 10 | 12 | 11 | 12 |
| 5b | 0 | 9 | 9 | 0 |
| 7a | 9 | 0 | 0 | 9 |
| 7b | 0 | 10 | 9 | 10 |
| 7c | 0 | 0 | 0 | 0 |
| 9a | 0 | 10 | 0 | 10 |
| 9b | 0 | 11 | 10 | 10 |
| 9c | 10 | 11 | 10 | 10 |
| 9d | 0 | 10 | 9 | 0 |
| 12 | 0 | 0 | 0 | 0 |

## 4. Conclusion:

New 4-chloroacetylaminophenylaminoquinoline derivatives, 4-acetylaminophenylaminoquinoline derivatives and α-aminophosphonate derivative containing quinoline moiety were synthetized and characterized by spectroscopic analysis. They exhibited very good yield. In addition to, biological activity towards gram-positive and gram-negative bacterial species were studied. Most of them showed mild activity in parallel with ampicillin as reference drug.

## 5. Materials:

All NMR spectra were measured at 400 MHz at Faculty of Science, El-Zigzag University, Egypt in which (DMSO-d6) was used as solvent. Chemical shifts were expressed in δ ppm relative to the position respective to the solvent. The mass spectra were performed at Al-Azhar and Cairo University respectively, Egypt. The IR spectra were performed at Al- Spectral Analyses Unit, Faculty of Science, El-Zigzag University, Egypt. The in vitro antibacterial screening was carried out at Micro Analytical Center, Cairo University, Egypt. Melting points were measured and recorded by Stuart scientific melting point apparatus and were uncorrected. All synthetized products were detected by thin layer chromatography (TLC) on kiesel gel F254; precoated plates (Merck). Compound 3 was synthesized according to references [35]. Starting materials, dimethylformamide DMF; triethylamine $Et_3N$; 2-chloro acetyl chloride, potassium carbonate $K_2CO_3$; ethanol EtOH; methanol, hexane, acetonitrile ACN; and lithium perchloride $LiClO_4$; were either commercially available as reported in literature [36].

## 6. Experimental:

### General synthetic procedure for acylation of 4-chloroacetylaminophenylaminoquinoline derivatives [5a, 5b]:

A mixture of 4-aminophenylaminoquinoline derivatives **3a, 3b** and 2-Chloro acetyl chloride **4** (12 mmol) were stirred in ice bath condition for (58-60hrs). The progress of reaction was followed by TLC with hexane and ethanol (5:1) as eluant. The product was cooled to room temperature and poured potion wise into crushed ice. 4-chloroacetylaminophenylaminoquinoline derivatives **5a, 5b** was collected by filtration, washed with distilled water and then dried.

### 2-Chloro-N-(2-((7-chloro quinoline-4-yl) amino) phenyl) acetamide [5a]:

Show the following data m.p = 260-262 °C Yield = 70 %, grey ppt, IR (KBr, $cm^{-1}$): 3285 (-NH), 2927 (-$CH_2$), 1607 (C=O), 1559 (C=C), 1509 (C=N) $cm^{-1}$; $^1$HNMR (DMSO, 400MHz): δ ppm 3.9 (s, H, -$CH_2$), 4,26 (s, H, -$CH_2$), 7,08- 7.31 (m, 7H, $CH_{Ar}$), 7,95 (s, 2H, $CH_{Ar}$), 8.21 (s, 2H, -NH), MS (m/z) : M+2 348.

### 2-Chloro-N-(4-((7-chloro quinoline-4-yl) amino) phenyl) acetamide [5b]:

Show the following data m.p = 278- 280 °C Yield = 72 %, brown ppt, IR (KBr, $cm^{-1}$): 3411 (-NH), 2926 (-$CH_2$), 1611 (C=O), 1576 (C=C), 1508 (C=N) $cm^{-1}$; $^1$HNMR (DMSO, 400MHz): δ ppm 3.8 (s, 2H, -$CH_2$), 6,44- 7.05 (m, 6H, $CH_{Ar}$), 7.27 (s, 1H, $CH_{Ar}$), 7.79 (s, 2H, $CH_{Ar}$), 8.38 (d, J = 8 Hz, 2H, NH). MS (m/z): M+1 347.

### 2.4. General synthetic procedure for 4-acetylaminophenylaminoquinoline derivatives [7(a-c)]:

4-chloroacetylaminophenylaminoquinoline derivatives **5a, 5b** (1 mmol) was refluxed for (46-48hrs) with aniline **6a**, **6b** (2 mmol) in presence of DMF as solvent and 10 eqs. of triethylamine as base. The progress of reaction was followed by TLC with hexane and ethanol (5:1) as eluant. 4-acetylaminophenylaminoquinoline derivatives **7(a-c)** was poured drop wise into crushed ice, then filtered off, washed by distilled water and dried.

### N-(2-((7-Chloro quinoline-4-yl) amino) phenyl)-2-(phenyl amino) acetamide [7a]:

Show the following data m.p = 78- 80 °C Yield = 62 %, white ppt, IR (KBr, $cm^{-1}$): 3354 (-NH), 2921 (-$CH_2$), 1608 (C=O), 1554 (C=C), 1485 (C=N) $cm^{-1}$; $^1$HNMR (DMSO, 400MHz): δ ppm 4.05 (m, 2H, -

CH2), 7.52-7.95 (m, 9H, $CH_{Ar}$), 8.13 (m, 5H, $CH_{Ar}$), 8.26 (s, 1H, NH), 8.82-8.83 (d, J = 9 Hz, 2H, NH). MS (m/z): M 402.

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**N-(4-((7-Chloro quinoline-4-yl) amino) phenyl)-2-(phenyl amino) acetamide [7b]:**

Show the following data m.p = >360ºC Yield = 65 %, brown ppt, IR (KBr, $cm^{-1}$): 3495 (-NH), 2632 (-$CH_2$), 1617 (C=O), 1544 (C=C), 1415 (C=N) $cm^{-1}$; $^1$HNMR (DMSO, 400MHz): δ ppm 3.4 (m, 3H, NH), 3.9 (m, 2H, -$CH_2$), 6.8 (m, 3H, $CH_{Ar}$), 7.1 (m, 6H, $CH_{Ar}$), 7.4 (m, 5H, $CH_{Ar}$) 8.52 (m, 2H, NH), 8.85 (s, 1H, NH). MS (m/z): M+1 403.

**2-((4-Amino phenyl) amino)-N'-(4-((7-chloroquinolin-4-yl) amino) cyclohexa-1,5-dien-1-yl) acetohydrazide [7c]:**

Show the following data m.p = 228- 230 ºC Yield = 63 %, black ppt , IR (KBr, $cm^{-1}$): 3434 (-NH), 2933 (-$CH_2$), 1624 (C=O), 1511 (C=C), 1471 (C=N) and $cm^{-1}$; 1HNMR (DMSO, 400MHz): δ ppm 3.9 (m, 2H, -$CH_2$), 6.82 (m, 3H, $CH_{Ar}$), 7.07 (m, 6H, $CH_{Ar}$), 7.34 (m, 4H, $CH_{Ar}$), 9.78 (m, 5H, NH). NH.MS (m/z): M+2 428.

**2.5. General synthetic procedure for 4-acetylaminophenylaminoquinoline derivatives [9(a-d)]:**

4-chloroacetylaminophenylaminoquinoline derivatives **5a, 5b** (1 mmol) was stirred for (118-120 hrs) with 4-substituted aniline **8a, 8b** (2 mmol) in presence of DMF as solvent and 10 eqs. potassium carbonate as base. Following up reaction by TLC with hexane and ethanol (5:1) as eluant. The desired product was poured drop by drop into crushed ice. 4-acetylaminophenylaminoquinoline derivatives 9(a-d) was filtered off, washed by distilled water and then dried.

**2-((4-Bromo phenyl) amino)-N-(2-((7-achloro quinoline-4-yl) amino) phenyl) acetamide [9a]:**

Show the following data m.p = 230- 232 ºC Yield = 61 %, White ppt, IR (KBr, $cm^{-1}$): 3432 (-NH), 2926 (-$CH_2$), 1606 (C=O), 1507 (C=C), 1452 (C=N) $cm^{-1}$; $^1$HNMR (DMSO, 400MHz): δ ppm 3.87 (m, 2H, -$CH_2$), 4.18 (m, 2H, NH), 5.24 (s, 1H, NH), 6.51 (m, 3H, $CH_{Ar}$), 7.12 (m, 7H, $CH_{Ar}$), 7.81 (m, 3H, $CH_{Ar}$).MS (m/z): M+1 481.

**2-((4-Bromo phenyl) amino)-N-(4-((7-chloro quinoline-4-yl) amino) phenyl) acetamide [9b]:**

Show the following data m.p = 238- 240 ºC Yield = 60 %, brown ppt, IR (KBr, $cm^{-1}$): 3417 (-NH), 2925 (-$CH_2$), 1798 (C=O), 1609 (C=C), 1430 (C=N) $cm^{-1}$. $^1$HNMR (DMSO, 400MHz): δ ppm 3.83 (m, 2H, -$CH_2$), 5.29 (s, 1H, NH), 6.53 (m, 4H, $CH_{Ar}$), 6.87-7.14 (m, 7H, $CH_{Ar}$), 7.36 (m, 2H, $CH_{Ar}$), 8.46 (m, 2H, NH). MS (m/z): M+K 501.

**N-(2-((7-Chloro quinoline-4-yl) amino) phenyl)-2-((4-nitro phenyl) amino) acetamide [9c]:**

Show the following data m.p = >360 ºC Yield = 62 %, Yellow ppt, IR (KBr, $cm^{-1}$): 3445 (-NH), 2927 (-$CH_2$), 1606 (C=O), 1553 (C=C), 1413 (C=N) $cm^{-1}$; $^1$HNMR (DMSO, 400MHz): δ ppm 3.34 (m, 2H, -$CH_2$), 6.58-6.71 (m, 5H, $CH_{Ar}$), 7.09 (m, 5H, $CH_{Ar}$), 7.46 (m, 3H, $CH_{Ar}$), 7.93-7.95 (m, 3H, NH). MS (m/z): M 447.

**N-(4-((7-Chloro quinoline-4-yl) amino) phenyl)-2-((4-nitro phenyl) amino) acetamide [9d]:**

Show the following data m.p = 210 - 212 ºC Yield = 64 %, Dark grey ppt, IR (KBr, $cm^{-1}$): 3432 (-NH), 2922 (-$CH_2$), 1588 (C=O), 1559 (C=C), 1415 (C=N) $cm^{-1}$; $^1$HNMR (DMSO, 400MHz): δ ppm 3.89 (m, 2H, -$CH_2$), 3.9 (s, 3H, NH), 6.6-6.72 (m, 5H, $CH_{Ar}$), 7- 7.08 (m, 4H, $CH_{Ar}$), 7.32 (m, 4H, $CH_{Ar}$), 7.96 (s, 1H, NH), 8.34-8.45 (m, 2H, NH). MS (m/z): M 447.43

**2.6. General synthetic procedure for diphenyl (4-(2- 2- 4- 7-chloroquinolin-4-ylaminophenylhydrazineyl)-(2-oxoethylaminophenylamino)(phenyl)methyl)phosphonate [12]:**

4-acetylaminophenylaminoquinoline derivative **7c** (1 mmol), benzaldehyde **10** (1.2 mmol), triphenyl phosphite **11** (1 mmol) and lithium perchlorate (10 mmol%) in acetonitrile (ACN) (5 mL) were added and refluxed for (72hrs). The reaction was monitored by TLC with hexane and ethanol (5:1) as eluent. The desired product filtered off and crystallized by diethyl ether to yield the corresponding product **12** in good yield.

Show the following data m.p = 360 ºC Yield = 60 %, dark gray ppt, IR (KBr, $cm^{-1}$): 3525-3566 (-NH), 2434 (-$CH_2$), 1593 (C=O), 1498 (C=C), 1205 (P=O). $^1$HNMR (DMSO, 400MHz): 3.87(m, 2H, -$CH_2$), 6.10 (m, 1H, -CHP), 6.58 (m, 2H, NH), 6.73-6.81 (m, 8H, $CH_{Ar}$), 7.10 (m, 7H, $CH_{Ar}$) 7.28 (m, 5H, $CH_{Ar}$), 7.41-7.67(m, 8H, $CH_{Ar}$), 7.78(m, 2H, NH). MS (m/z): M 755.

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