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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL α-AMINOPHOSPHONATES BEARING A QUINOLINE MOIETY

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Keywords:

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ABSTRACT: A novel aminophenylaminoquinoline analogues have been synthesized starting from 4,7 dichloroquinloine and (p-phenylenediamine **2a**, o-phenylenediamine **2b** or m-phenylenediamine **2c**). The one pot reaction with aldehydes and triphenylphosphite in presence of $LiClO_4$ as a Lewis acid catalyst led to the formation of novel α-aminophosphonate derivatives bearing quinoline moiety in good yields. The synthesized compounds have been characterized on the basis of the spectral analysis. All the synthesized compounds were screened for *in vitro* antibacterial activity and most of them showed a potency against both gram positive and gram negative bacteria.

INTRODUCTION: Organ phosphorus compounds have found a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates. [1] α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates. [2, 3] Among α-functional phosphonic acids, α-aminophosphonic acids are an important class of compounds that exhibit a variety of interesting and useful properties. These compounds have already been found to act as α-Aminophosphonic acids I, as structural mimics of α-amino acids II (cf. **Fig. 1**), exhibit a broad spectrum of biological activities.[5-11]

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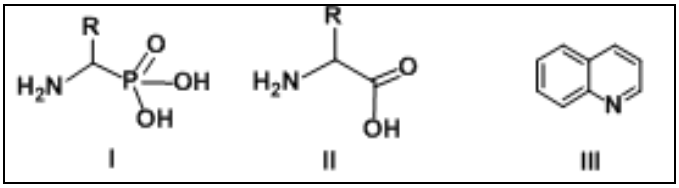


FIG.1: STRUCTURES OF α-AMINOPHOSPHONATES I, α AMINO ACID II AND QUINOLINE III

Antibacterial agents, neuroactive compounds, anticancer drugs, and pesticides, with some of them already commercialized. [11-27] In this context, The therapeutic potential for modified α-aminophosphonates with improved pharmacokinetic properties, potency or spectrum, and lower side effects, prompted us to start a synthetic program to explore new quinoline aminophosphonate conjugates. We focused on quinoline and its derivatives because it is an important class of compounds and attracted widespread attention due to their pharmacological properties, being reported to have a large spectrum of biological effects, especially antimalarial, antibacterial and anticancer properties. In this paper

we would like to present the synthesis of novel quinoline modified α - aminophosphonates conjugates.

Materials:

All 1HNMR experiments (solvent DMSO) were carried out with a 300 MHz at Cairo University, Egypt. Chemical shifts are reported in part per million (ppm) relative to the respective solvent. The mass spectroscopy experiments were performed at Cairo University, Egypt. Melting points were recorded on Stuart scientific melting point apparatus and are uncorrected. The microanalysis were performed in microanalysis laboratory at National Research Centre (NRC), Egypt. All reactions were followed by thin layer chromatography (TLC) on kiesel gel F254 precoated plates (Merck). Starting materials, MeOH, DMF, acetonitrile, CH_2Cl_2, hexane and diethylether were either commercially available as reported in literature.

Procedure for the synthesis N1-(7-chloroquinolin-4-yl)benzene-1,4-diamine (3a) [27]: (1 mmol) 4,7 dichloroquinoline dissolved in MeOH and excess of the appropriate amine (2 mmol) p-phenylenediamine were heated at reflux at 135-155 ºC for 10-15 minutes. TLC monitoring was used to ensure the completion of reaction. The solid formed was collected by filtration.

General procedure for the synthesis N1-(7-chloroquinolin-4-yl) benzene-1, 2 -diamine (3b) and N1-(7-chloroquinolin - 4 - yl)benzene - 1, 3-diamine (3c) [27]: 4,7 dichloroquinoline dissolved in dry DMF and an excess of the appropriate amine o-phenylenediamine or m-phenylenediamine were heated at reflux at 135-155 ºC in presence of 10 eqs. of triethyl amine for 4h. TLC monitoring was used to ensure the completion of reaction. The resulting crude poured into ice water and the solid formed was collected by filtration and dried.

General procedure for the synthesis:

α-aminophosphonate derivatives (6a-g), (7a-c) & (8a-g): Aldehyde (1.2 mmol), aminophenyl aminoquinoline derivatives (1 mmol) and triphenylphosphite were dissolved in acetonitrile (5 ml) and stirred at r.t about 15 minutes. Then the lewis acid, $LiClO_4$ (10 mmol%) was added in one portion. The mixture was stirred at r.t, until TLC analysis showed the complete consumption of aminophenylaminoquinoline derivatives with using hexane and CH_2Cl_2 as eluent. Then for aminophosphonate derivatives of compund **3a** and **3c** the collection of the precipitate by filteration afford the protected α-aminophosphonates in good to excellent yields, but for α-aminophosphonate derivatives of compound **3b**, acetonitrile evaporated and the residue dissolved in diethylether, the product was percipitated from this solution immediately followed by the collection of the precipitate by filteration afford the protected aminophosphonates in good to excellent yields.

N1-(7-chloroquinolin-4-yl) benzene-1,4- diamine (3a): Show the following data m.p = 208-210 °C, Yield = 91 % , Dark yellow solids, The Infra- red spectra of compound show characteristic bands for ν_{NH}at 3430 cm^{-1} and at 3317 cm^{-1} corresponding to ν_{NH}, ^{1}HNMR (DMSO): δ ppm = 6.6(m, 1H, HAr), 6.8(d, *J*=8.4Hz, 1H, HAr), 7.1(d, *J*=9Hz, 2H, HAr), 7.8(d, *J*=8.4Hz, 2H, CHquinoline), 8.1(d, *J*=4.8Hz, 1H, CHquinoline), 8.4(d, *J*=6.9Hz, 1H, CHquinoline), 8.7(d, *J*=9.3Hz, 1H, CHquinoline), 10.7(s, 1H, NH), The mass spectra show the molecular ion peak at m/e = 272 (M+3,7%).

N1-(7-chloroquinolin-4-yl) benzene- 1,2-diamine (3b): Show the following data m.p = 215-217°C, Yield = 85%, Pale brown solids, ^{1}HNMR (DMSO): δ ppm = 6.2 (d, *J*=3.6Hz, 2H, HAr), 6.6 (m, 1H, HAr), 6.9 (m , 1H, CHAr), 7.8 -7.9 (m, 2H, CHquinoline) , 8.1 – 8.2 (m, 3H , CHquinoline), 8.8 (d, *J*=4.5Hz, 1H, NH), The mass spectra show the molecular ion peak at m/e = 270(M+1,23%).

N1-(7-chloroquinolin-4-yl) benzene- 1,3-diamine (3c): Show the following data m.p = 205-207 °C, Yield =76 %, Dark gray solids, The Infra- red spectra of compound show characteristic bands for ν_{NH} at 3276 cm^{-1} and at 3387 cm^{-1} corresponding to ν_{NH} ^{1}HNMR (DMSO): δ ppm = 6.4(m, 1H, HAr), 6.6(m,1H, HAr), 6.9(m, 1H , CHAr), 7.4(m, 1H, CHAr), 7.9 – 8.1(m, 2H, CHquinoline), 8.4(d, *J*=6.3Hz, 1H, CHquinoline), 8.5(d, *J*=7.5Hz, 1H, CHquinoline), 8.9(s, 1H, CHquinoline), 9.1(s, 1H, NH), The mass spectra show the molecular ion peak at m/e = 262 (M+3,6%).

Diphenyl (((4-((7-chloroquinolin-4-yl) amino) phenyl)amino) (phenyl)methyl) phosphonate (6a): Show the following data m.p = 265-267°C Yield = 90%, pale yellow solids, The Infra- red spectra of compound show characteristic bands for ν_{NH} at 3320 cm^{-1} and at 3431 cm^{-1} corresponding to ν_{NH} and at 1227cm^{-1} corresponding to $\nu_{P=O}$ and at 1004 cm^{-1} corresponding to ν_{POC}, ^{1}HNMR (DMSO): δ ppm = 5.8 (s , 1H, CHP), 6.6 (d, *J*=6.9Hz, 2H, HAr) , 6.7 (t, *J*=3Hz, 4H, HAr), 7 – 7.2 (m, 7H, HAr), 7 .3 (m, 6H, HAr) , 7.8 – 8.1 (m, 3H, CHquinoline) , 8.4 (d, *J*=6.9Hz, 1H, CHquinoline) , 8.8 (d, *J*=9.3Hz, 1H, CHquinoline) , 10.9 (s, 1H, NH), The mass spectra show the molecular ion peak at m/e = 595 (M+3,54%).

Diphenyl ([1,1'-biphenyl] – 4 – yl ((4-((7-chloroquinolin-4-yl) amino) phenyl) amino) methyl)phosphonate (6b):
Show the following data m.p =245-248°C Yield =92% , dark yellow solids, The Infra- red spectra of compound show characteristic bands for ν_{NH} at 3318 cm^{-1} and at 3430 cm^{-1} corresponding to ν_{NH} and at 1230cm^{-1} corresponding to $\nu_{P=O}$ and at 1011 cm^{-1} corresponding to ν_{POC}, ^{1}HNMR (DMSO): δ ppm = 6.6 – 6.7(m, 4H, HAr), 6.8 – 6.9(m, 5H, HAr), 7 – 7.7(m, 15H, HAr), 8.1(s, 1H, CHquinoline), 8.4(d, , *J*=6.6Hz, 2H, CHquinoline), 8.7(d, *J*=5.1Hz, 1H, CHquinoline), 8.8(s, 1H, CHquinoline), 10.8 (s, 1H, NH), The mass spectra show the molecular ion peak at m/e = 700 (M+2, 21%).

Diphenyl (((4-((7-chloroquinolin-4-yl) amino) phenyl) amino) (1H – indol – 3 - yl) methyl) phosphonate (6c):
Show the following data m.p = 252-254 °C Yield = 85 %, yellow solids, ^{1}HNMR (DMSO): δ ppm = 6.6(d, *J*=6.9Hz, 3H, HAr) , 6.7(m, 2H, HAr), 6.9 - 7.1(m, 13H, HAr), 7.7 (m, 1H , CHquinoline), 8.1 (d, *J*=1.5Hz, 1H, CHquinoline), 8.4(d, *J*=7.2Hz, 2H, CHquinoline), 8.7(d, *J*=9.3Hz, 1H, CHquinoline), 10.7 (s, 1H, NH), The mass spectra show the molecular ion peak at m/e = 633 (M+2,17%).

Diphenyl (((4-((7-chloroquinolin-4-yl) amino) phenyl) amino) (4-methoxyphenyl) methyl) phosphonate (6d):
Show the following data m.p = 240-243 °C Yield = 88 % **,** dark yellow solids, The Infra- red spectra of compound show characteristic bands for ν_{NH} at 3318 cm^{-1} and at 3430 cm^{-1} corresponding to ν_{NH} and at 1229cm^{-1} corresponding to $\nu_{P=O}$ and at 1018 cm^{-1} corresponding to ν_{POC} , ^{1}HNMR (DMSO): δ ppm = 3.8(d, *J*=3.9Hz, 3H, CH3), 6.6(d, *J*=6.9Hz, 4H, HAr), 6.7(d, *J*=6.5Hz, 3H, HAr), 7(d, *J*=8.1Hz, 11H, HAr), 7.7(d, *J*=8.7Hz, 2H , CHquinoline), 8.1(s, 1H, CHquinoline), 8.4(d, *J*=6.6Hz, 1H , CHquinoline), 8.8(d, *J*=9Hz, 1H, CHquinoline), 10.8 (s, 1H, NH), The mass spectra show the molecular ion peak at m/e = 625 (M+3,38%).

Diphenyl (((4-((7-chloroquinolin-4-yl) amino) phenyl) amino) (2-hydroxynaphthalen-1-yl) methyl) phosphonate (6e):
Show the following data m.p = 274-276°C Yield =93%, yellow solids, ^{1}HNMR (DMSO): δ ppm = 4.8 (s , 1H , CHP), 6.5 – 6.7(m, 4H, HAr), 7.0–7.3(m,16H, HAr), 7.8 - 7.9(m, 2H, CHquinoline), 8-8.1 (m, 2H, CHquinoline) , 8.9(d, *J*=8.7Hz, 1H, CHquinoline), 10.9(s, 1H, NH), The mass spectra show the molecular ion peak at m/e = 661 (M+3,64%).

Diphenyl(((4-((7-chloroquinolin-4 - yl) amino) phenyl) amino) (4-(dimethylamino) phenyl)methyl) phosphonate (6f):
Show the following data m.p = 231-234 °C Yield = 92 %, yellow solids, ^{1}HNMR (DMSO): δ ppm = 5.1(S, 1H, CHP), 6.6(d, *J*=5.4Hz, 4H, HAr), 6.7(d, *J*=7.2Hz, 3H, HAr), 7.1(d, *J*=8.4Hz, 11H, HAr), 7.7 (t, *J*=8.7Hz, 2H , CHquinoline), 8.1(s, 1H, CHquinoline), 8.3(d, *J*=6Hz, 1H , CHquinoline), 8.8(d, *J*=9.3Hz, 1H, CHquinoline), 10.8 (s, 1H, NH), The mass spectra show the molecular ion peak at m/e = 636 (M+1,52%).

Diphenyl ((4-chlorophenyl) ((4-((7-chloroquinolin-4-yl) amino) phenyl) amino) methyl) phosphonate (6g):
Show the following data m.p = 269-271°C Yield =91%, dark yellow solids, The Infra- red spectra of compound show characteristic bands for ν_{NH} at 3329 cm^{-1} and at 3438 cm^{-1} corresponding to ν_{NH} and at 1235cm^{-1} corresponding to $\nu_{P=O}$,^{1}HNMR (DMSO): δ ppm = 6.6(t, *J*=7.2Hz , 2H, HAr), 6.7(m, *J*=7.2Hz, 2H, HAr), 7 – 7.1(m, 3H, HAr), 7.4 – 7.6 (m, 11H, CHAr), 7.8 (d, *J*=9.3Hz, 2H, CHquinoline), 8.1(s, 1H , CHquinoline),

8.4(d, *J*=6.9Hz, 1H, CHquinoline), 8.7(d, *J*=9Hz, 1H, CHquinoline), 10.8 (s, 1H, NH), The mass spectra show the molecular ion peak at m/e = 628 (M+2,60%).

Diphenyl (((2-((7-chloroquinolin-4-yl) amino) phenyl)amino)(phenyl)methyl)phosphonate (7a): Show the following data m.p = 278-279 ˚C Yield = 86 % , pale brown solids, The Infra- red spectra of compound show characteristic bands for ν_{NH} at 3427 cm^{-1} and at 1207cm^{-1} corresponding to $\nu_{P=O}$ and at 1003 cm^{-1} corresponding to ν_{POC}, ^{1}HNMR (DMSO): δ ppm = 5.8 (s, 1H, CHP),7.1(m, 7H, HAr), 7.3 – 7.4(m, 12H, HAr), 7.8(m, 2H, CHquinoline), 8.1 – 8.3(m, 3H, CHquinoline), 8.8(d, *J*=4.5Hz, 1H, NH), The mass spectra show the molecular ion peak at m/e = 595 (M+3,74%).

Diphenyl([1,1'-biphenyl] – 4 – yl ((2-((7-chloro quinolin-4-yl)amino)phenyl) amino) methyl) phosphonate (7b): Show the following data m.p = 289-292 ˚C Yield =80 % , dark brown solids, The Infra- red spectra of compound show characteristic bands for ν_{NH} at 3435 cm^{-1} and at 1207cm^{-1} corresponding to $\nu_{P=O}$ and at 1005 cm^{-1} corresponding to ν_{POC}, ^{1}HNMR (DMSO): δ ppm = 5.8(s , 1H, CHP), 6.7(t, *J*=6.9Hz, 7H, HAr), 7.1(d, *J*=7.5Hz, 6H, HAr), 7.3(m, 10H, HAr), 7.8(t, *J*=9.3Hz, 2H, CHquinoline), 8.1 – 8.2(m, 3H, CHquinoline), 8.9(d, *J*=5.1Hz, 1H, NH), The mass spectra show the molecular ion peak at m/e = 670 (M+2,26%).

Diphenyl (((2-((7-chloroquinolin – 4 - yl) amino) phenyl) amino) (1H-indo l- 3 - yl) methyl) phosphonate (7c): Show the following data m.p = 243-245 ˚C Yield = 92%, dark brown solids, ^{1}HNMR (DMSO): δ ppm = 6.7(d, *J*=8.4Hz , 2H, HAr), 7.1 – 7.3(m, 8H, HAr), 7.5(d, *J*=7.5Hz, 4H, HAr), 7.8(s, 2H, CHquinoline), 8.0 – 8.2(m, 3H , CHquinoline), 9.9(s, 1H, NH), 12.1(s, 1H, NHindol), The mass spectra show the molecular ion peak at m/e = 631 (M,73%).

Diphenyl (((3-((7-chloroquinolin-4-yl) amino) phenyl) amino) (phenyl) methyl) phosphonate (8a): Show the following data m.p = 282-286 ˚C Yield = 86 % , pale gray solids, show characteristic bands for ν_{NH} at 3276 cm^{-1} and at 3426 cm^{-1} corresponding to ν_{NH} and at 1208cm^{-1} corresponding to $\nu_{P=O}$ and at 1000 cm^{-1} corresponding to ν_{POC}, ^{1}HNMR (DMSO): δ ppm = 5.8(s, 1H , CHP), 6.8 – 6.9(m, 4H, HAr), 7 – 7.2(m, 5H, HAr), 7.3 – 7.6(m, 10H, HAr), 7.8 – 7.9(m, 2H, CHquinoline), 8.4 – 8.5(m, 3H, CHquinoline), 9.4 (s, 1H, NH), The mass spectra show the molecular ion peak at m/e = 593 (M+1,56%).

Diphenyl ([1,1'-biphenyl] – 4 – yl ((3-((7-chloroquinolin-4-yl)amino) phenyl) amino) methyl)phosphonate (8b):
Show the following data m.p = 277-279˚C Yield =79 %, pale gray solids, ^{1}HNMR (DMSO): δ ppm = 6.8(d, *J*=6Hz, 4H, HAr), 7 – 7.2 (m, 6H, HAr), 7.3 – 7.6(m, 13H, HAr) ,7.8 – 8(m, 2H , CHquinoline), 8.4 (d, *J*=8.7Hz, 1H , CHquinoline), 8.5(d, *J*=4.8Hz, 2H, CHquinoline), 9.1(s, 1H, NH), The mass spectra show the molecular ion peak at m/e = 670 (M+2,8%).

Diphenyl (((3-((7- chloroquinolin–4 -yl) amino) phenyl) amino) (1H-indol-3-yl) methyl) phosphonate (8c):
Show the following data m.p = 252-255 ˚C Yield = 84 %, pale gray solids, ^{1}HNMR (DMSO): δ ppm = 5.8(s, 1H, CHP), 6.8 -6.9(m, 4H, HAr), 7 – 7.5(m, 15H, HAr), 7.8 – 7.9(m, 2H, CHquinoline), 8.4(d, *J*=8.7Hz, 2H, CHquinoline), 8.5(d, *J*=5.4Hz, 1H, CHquinoline), 9.1(s, 1H, NH), The mass spectra show the molecular ion peak at m/e =634 (M+3,83%).

Diphenyl (((3-((7-chloroquinolin-4-yl) amino) phenyl) amino) (4 - methoxyphenyl) methyl) phosphonate (8d):
Show the following data m.p = 263-267 ˚C Yield = 88 %, pale gray solids, ^{1}HNMR (DMSO): δ ppm = 3.8(m, 3H, CH3), 5.8(s, 1H, CHP), 6.8-6.9(m, 5H, HAr), 7 -7.1(m, 5H, HAr), 7.3(s, 1H, HAr),7.4(d, *J*=8.1Hz, 2H, HAr), 7.5 – 7.6(m, 5H, HAr), 7.9(d, *J*=1.8Hz, 2H, CHquinoline), 8.4(d, *J*=9Hz, 2H, CHquinoline), 8.5(d, *J*=5.1Hz, 1H, CHquinoline), 9.1(s, 1H, NH), The mass spectra show the molecular ion peak at m/e =625 (M+3,31%).

Diphenyl (((3-((7-chloroquinolin-4-yl) amino) phenyl) amino)(2-hydroxynaphthalen – 1 - yl) methyl) phosphonate (8e):
Show the following data m.p = 224-226˚C Yield = 93 % , dark gray solids,^{1}HNMR (DMSO): δ ppm =

6.7(t, *J*=8.1Hz, 4H, HAr), 7-7.1(m, 5H, HAr), 7.3 – 7.7(m, 11H, HAr), 7.9(d, *J*=5.4Hz, 2H, CHquinoline), 8.4 – 8.5(m , 3H, CHquinoline), 9.6(s, 1H, NH), The mass spectra show the molecular ion peak at m/e =657 (M-1, 87%).

Diphenyl (((3-((7-chloroquinolin-4-yl) amino) phenyl) amino) (4-(dimethylamino) phenyl) methyl) phosphonate (8f):

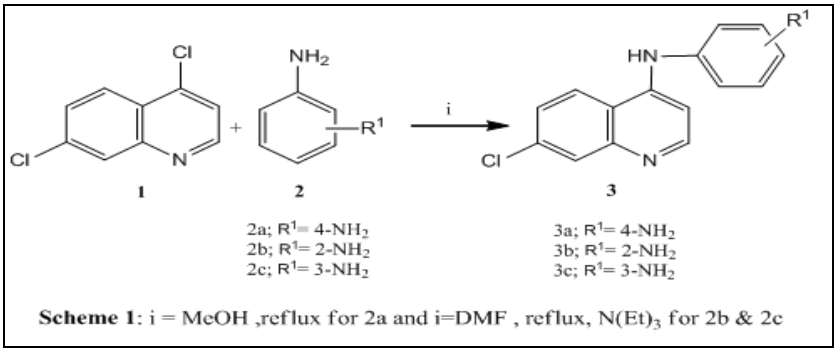
Show the following data m.p = 210-215 ˚C Yield = 82% , dark gray solids, ^{1}HNMR (DMSO): δ ppm = 5.8(s, 1H, CHP), 6.7 – 6.9(m, 5H, HAr), 7-7.2(m, 4H, HAr), 7.3 – 7.6(m, 9H, HAr), 7.8-7.9(m, 2H , CHquinoline), 8.4(d, *J*=8.7Hz, 2H , CHquinoline), 8.5(d, *J*=5.4Hz, 1H, CHquinoline), 9.1(s, 1H, NH), The mass spectra show the molecular ion peak at m/e =636 (M+1,35%).

Diphenyl ((4-chlorophenyl) ((3-((7-chloro quinolin-4-yl) amino) phenyl) amino) methyl) phosphonate (8g):

Show the following data m.p = 274-278 ˚C Yield = 86 %, pale gray solids, ^{1}HNMR (DMSO): δ ppm = 6.7 – 6.8(m, 4H, HAr), 7-7.1 (m, 3H, HAr), 7.3 – 7.6(m, 11H, HAr), 7,9(m, 2H, CHquinoline), 8.4 (d, *J*=8.7Hz, 2H , CHquinoline), 8.5(d, *J*=5.4Hz, 1H, CHquinoline), 9.2(s, 1H, NH), The mass spectra show the molecular ion peak at m/e =626 (M, 17%).

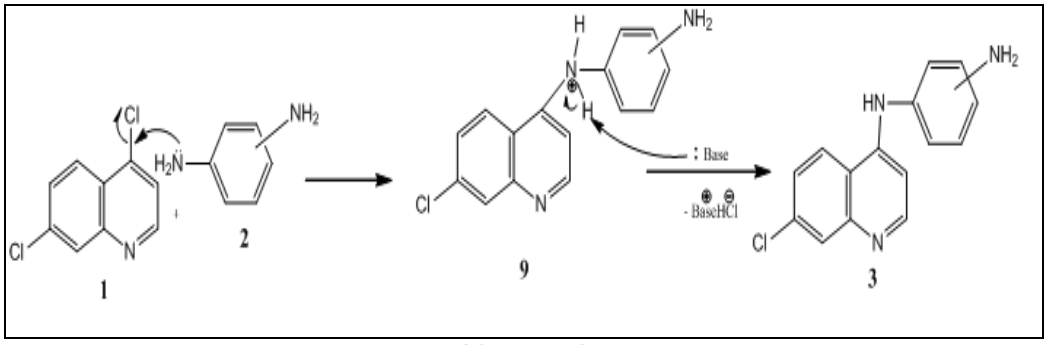
RESULTS AND DISCUSSION:

Chemistry: Our strategy for synthesis of 4,7 dichloroquinoline analogues was based on the amination of 4-chlorosubstituted quinoline compound **1** obtained through **scheme 1**. This method is used for synthesis of quinoline with *N*-substitutions at 4-substitution. Thus, aminophenylaminoquinoline **3a-c** were prepared with various amino- containing groups **2a-c** in position 4, which was aminated via SN_{Ar} in MeOH with the appropriate amines **2a** at high temperature, yielding target compounds **3a**, 4,7dichloroquinoline was aminated via SN_{Ar} in DMF with the appropriate amines **2b,2c** at high temperature, yielding target compounds **3b,3c** as shown in **Schemes 1** and **2**.



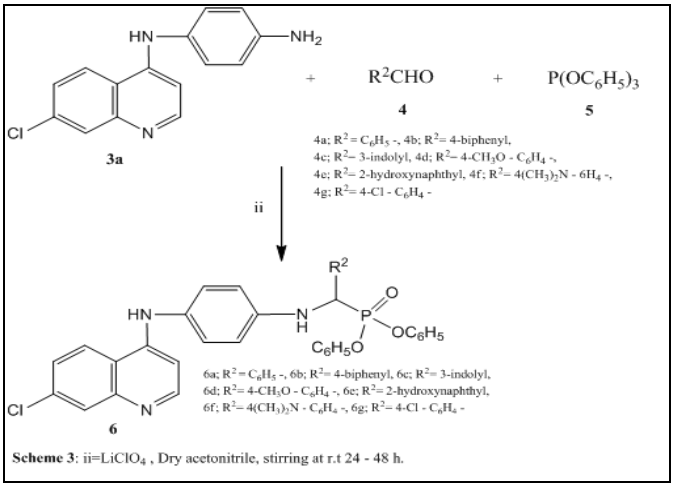
Scheme 1: i = MeOH ,reflux for 2a and i=DMF , reflux, $N(Et)_3$ for 2b & 2c

SCHEME: 1

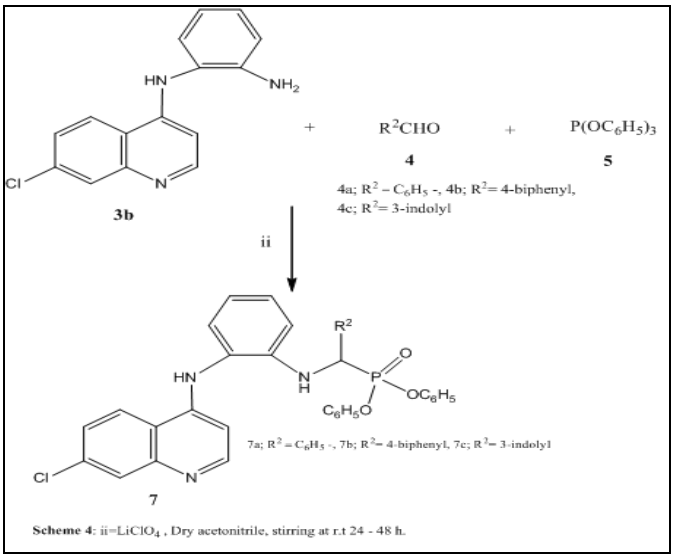


SCHEME: 2

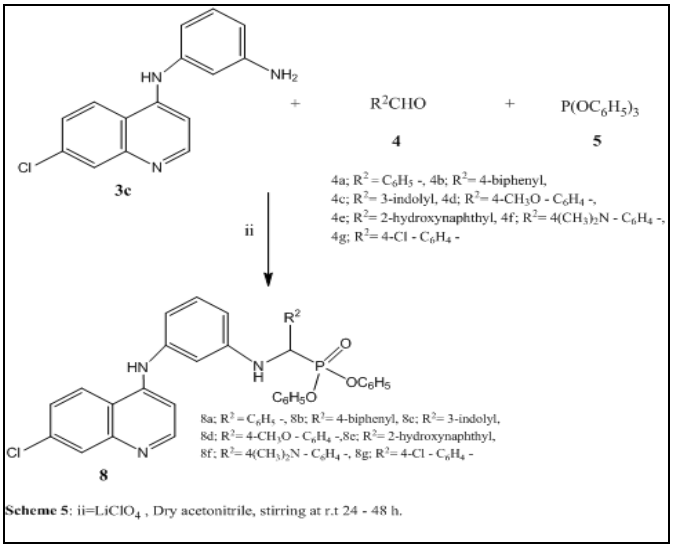
The synthesis of α-aminophosphonates **6**,**7**,**8** bearing quinoline skeleton were accomplished in good yield using aminophenylaminoquinoline **3**, (benzaldehyde, 4-biphenylcarboxaldehyde, indole-3-aldehyde, anisaldehyde, 4-chlorobenzaldehyde, 2-hydroxynaphthaldehyde or 4-Dimethylamino) benzaldehyde) and triphenylphosphite in the presence of a Lewis acid such as $LiClO_4$ and acetonitrile as solvent according to **schemes 3**,**4** and **5.**



SCHEME: 3

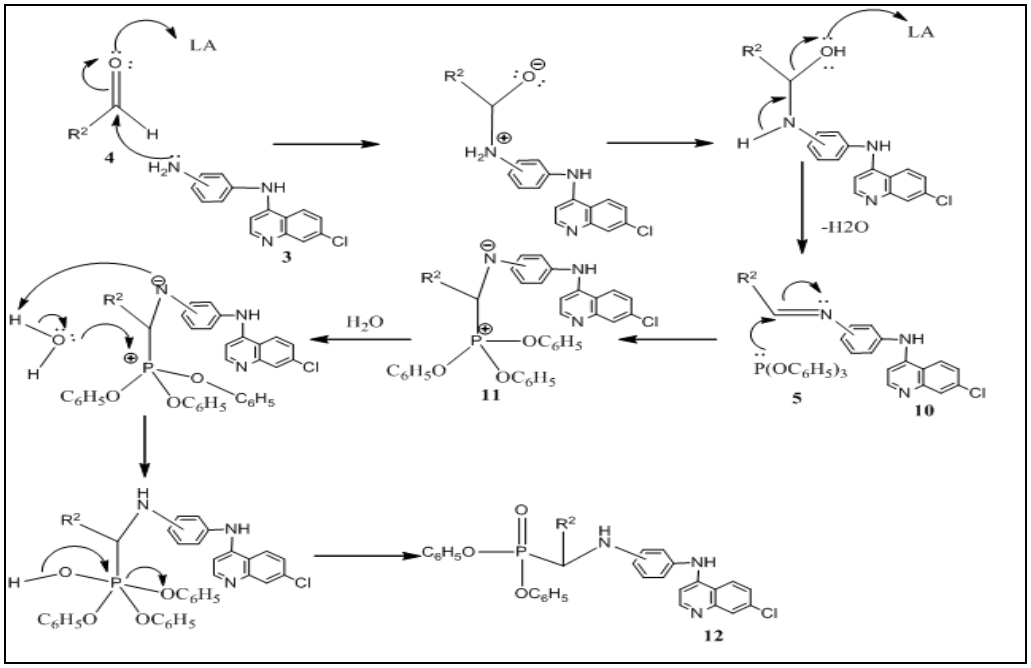


SCHEME: 4



SCHEME: 5

Moreover, the **SCHEME: 5** mechanism of this reaction has not been investigated in detail. However, we firstly proposed that the reaction of the aldehydes **4a-g** with the amino-compounds **3a-c** in the presence of lithum percholorate as a lewis acid (LA) catalyst afforded the corresponding imine- intermediates **10** according to scheme **6**. Then, the imine intermediate **10** is attacked by nucleophilic phosphite **5** leading to the formation of a phosphonium intermediate **11** and most likely this step is catalyzed by the Lewis acid (LA). Reaction of phosphonium intermediates **11** with water afforded the target α-aminophosphonates **12** after elimination of phenol as shown in **Scheme 6**.



SCHEME: 6

Antibacterial Screening:

The diverse biological activities of aminophenylaminoquinoline derivatives and their α-aminophosphonates prompted us to test and study the antibacterial activities of some of the newly synthesized products. Many antimicrobial agents have been introduced into therapy; however the field still needs extensive efforts for the development of new antibacterial agents to overcome the highly resistant strains of microorganisms. The newly synthesized compounds were tested *in vitro* for their antibacterial activity against *Escherichia coli* (Gram -ve bacteria), *Bacillus subtilis* (gram +ve bacteria) and *Staphylococcus aureus* (Gram +ve bacteria), *Klebsiela Spp* (gram –ve bacteria) and *pseudomonas aeruginosa* (gram –ve bacteria). DMSO was used as a control solvent and Cefotaxim, as a reference drug. After 18-24h incubation at 37ºC, the zone of inhibition was measured in mm. The results are depicted in **table 1**. It should be noted that compounds **3b and 7a-c** showed the best antibacterial activity against all tested bacterial strains as shown in **Table 1**. It is worth noting that the presence of α-aminophosphonate moiety at fourth position of the quinoline system significantly increases the antibacterial activity against bacterial strains.

TABLE 1: *IN VITRO* SCREENING OF SAMPLES FOR ANTIMICROBIAL ACTIVITY AFTER SOLUBILITY IN DMSO SOLVENT ON COLD AFTER 24 h:

Sample	Concentration ml/mg	Inhibition zone diameter (millimeter,mm)				
		Gram negative bacteria			Gram positive bacteria	
		E.coli	*pseudomonas aeruginosa*	*Klebsiella*	*bacillus subtilis*	*Staph. aurous*
3a	1	13.0	14.0	17.0	13.0	15.0
6a	1	5.0	11.0	17.0	12.0	16.0
6b	0.85	Nil	14.0	12.0	12.0	Nil
6c	1	Nil	Nil	Nil	11.0	12.0
6d	1	Nil	16.0	12.0	14.0	12.0
6e	1	15.0	Nil	Nil	Nil	13.0
6f	1	Nil	18.0	13.0	15.0	11.0
6g	1	Nil	15.0	12.0	13.0	14.0
3b	1	20.0	20.0	18.0	13.0	20.0
7a	1	6.0	19.0	17.0	19.0	21.0
7b	1	19.0	20.0	11.0	13.0	19.0
7c	0.8	19.0	16.0	19.0	14.0	16.0
3c	1	14.0	14.0	16.0	16.0	14.0
8a	1	Nil	13.0	16.0	14.0	12.0
8b	0.9	Nil	18.0	Nil	12.0	8.0
8c	1	Nil	Nil	Nil	Nil	Nil
8d	1	Nil	11.0	11.0	11.0	Nil
8e	0.95	Nil	15.0	14.0	14.0	14.0
8f	1	11.0	14.0	11.0	19.0	14.0
8g	0.85	Nil	Nil	Nil	14.0	10.0
Control (DMSO)	———	6.0	Nil	5.0	4.0	11.0
Cefotaxim	0.02	Nil	Nil	Nil	Nil	8.0**
Commercial antibiotic	0.05	10.0**	Nil	8.0**	Nil	-
	0.09	-	6.0**	-	Nil	-
	0.15	-	-	-	12.0**	-
	Control (Dist. H_2o)	Nil	Nil	Nil	Nil	Nil

**= MIC For each microorganism(used as stander) Nil= No antimicrobial activity

CONCLUSION: New aminophenyl aminoq uinoline derivatives and their α-aminophosphonates analogues were synthesized and evaluated for their antibacterial activities. Some tested compounds showed strong antimicrobial activity against all tested pathogenic bacteria.

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REFERNECES:

1. For reviews, see: (a) Kukhar VP Hudson H.R: Aminophosphonic and Aminophosphinic Acids John Wiley & Sons:Chichester UK 2000 (b) Kafarski P, Lejczak B.: Aminophosphonic acids of potential medical importance, Curr Med Chem: Anti-Cancer Agents 2001;1:301–312. (c) Berlicki L, Kafarski P.: Computer-aided analysis and design of phosphonic and phosphinic enzyme inhibitors as potential drugs and agrochemicals, Curr Org Chem 2005; 9:1829–1850.
2. (a) Rozenfeld R, Iturrioz X, Okada M, Maigret B, Llorens-Cortes: Contribution of molecular modeling and site-directed mutagenesis to the identification of a new residue, glutamate 215, involved in the exopeptidase specificity of aminopeptidase A. Biochemistry 2003;42: 14785–14793. (b) Lejczak B, Kafarski P, Zygmunt J.: Inhibition of aminopeptidases by aminophosphonates Biochemistry 1989; 28:3549–3555.
3. For a review, see: Kafarski, P., Lejczak, B.: Application of bacteria and fungi as biocatalysts for the preparation of optically active hydroxyphosphonates J. Mol. Catal. B-Enzym 2004; 29:99-104.
4. P. Kafarski, P. Mastalerz, Rocz. Chem.: synthesis of dipeptides containing p-terminal 2-aminoethylphosphonic acid 1977; 51:433.
5. (a) Kafarski, P. Lejczak, B. Mastalerz, P. Szewczyk, J. Wasielewski:C. Phosphonodipeptides: synthesis and separation of diastereoisomers. Can. J. Chem. 1982; 60:3081.
   (b) M.A.kira, M.o. Abdel-Rahman and K.Z. Gadalla: The vilsmeier-haack reaction - III cyclization of hydrazones to pyrazoles, tetrahedeon 1969; lett 2:109.
6. P. Van der Veken, I. El Sayed, J. Joossens, C. V. Stevens, K. Augustyns and A. Haemers: The lewis acid catalyzed synthesis of n-protected diphenyl 1-aminoalkylphosphonates. Synthesis 2005; 634-638.
7. D.M. Shendage, R. Froehlich, G. Haufer: highly efficient stereoconservative amidation and deamidation of α-amino acids, Org. lett. 2004; 6: 3675 – 3678.
8. (a)Schug, K. A.: Lindner: Noncovalent binding between guanidinium and anionic groups: focus on biological- and synthetic-based arginine/guanidinium interactions with phosphonate and sulfonate residues, W. Chem. Rev. 2005;105:64; (b) Moonen, K. Laureyn, I. Stevens C. V.: Synthetic methods for azaheterocyclic phosphonates and their biological activity, Chem. Rev. 2004;104:6177; (c) Palacios, F. Alonso, C. de los Santos: β-phosphono- and phosphinopeptides derived from β-amino-phosphonic and phosphinic acids, J. M. Curr. Org. Chem., 2004;8:1481. (d) X. Rao, Z. Song and L He: Synthesis and antitumor activity of novel α-aminophosphonates from diterpenic dehydroabietylamine, Heteroatom Chem. 2008;19: 512-516.
9. Kafarski, P., Lejczak, B., Tyka, R., Koba, L., Pliszczak, E.: Wieczorek, P. J.: Herbicidal activity of phosphonic, phosphinic, and phosphonous analogues of phenylglycine and phenylalanine, Plant Growth Regul. 1995; 14:199.
10. (a) Gancarz, R.: Chakraborty:A useful method for the preparation of 1-aminoalkanephosphonic acids, S. Synthesis 1977;625, (b) Giannousi, P. P.: Bartlett, P. A.: Phosphorus amino acid analogs as inhibitors of leucine aminopeptidase, J. Med. Chem. 1987;30:1603, (c) Maier, L.: Lea, P. J.: Organic phosphorus compounds 76: synthesis and properties of phosphinothricin derivatives, Phosphorus & Sulfur 1983;17:1, (d) Baylis, E. K. Campbell, C. D. Dingwall, J. G.: 1-Aminoalkylphosphonous acids. part 1. isosteres of the protein amino acids, J. Chem. Soc., Perkin Trans. 1 1984:2845-2853, (e) Hilderbr and, R. L.: The Role of Phosphonates in Living Systems, CRC: Boca Raton, FL, 1982.
11. Atherton, F. R. Hassal, C. H. Lambert, R. W. J.: Synthesis and structure-activity relationships of antibacterial phosphonopeptides incorporating (1-aminoethyl) phosphonic acid and (aminomethyl),phosphonic acid, Med. Chem. 1986; 29: 29-40.
12. Allen, M. C., Fuhrer, W., Tuck, B., Wade, R., Wood: Renin inhibitors. Synthesis of transition-state analogue inhibitors containing phosphorus acid derivatives at the scissile bond, J. M. J. Med. Chem. 1989; 32:1652.
13. Hassal, C. H. In Antibiotics, Hahn, F. E., Ed., Springer:Berlin 1983;Vol. VI:pp 1–11.
14. (a) Rozenfeld R, Iturrioz X, Okada M, Maigret B: Contribution of molecular modeling and site-directed mutagenesis to the identification of a new residue, glutamate 215, involved in the exopeptidase specificity of aminopeptidase A, Llorens-Cortes C. Biochemistry 2003;42:14785–14793.(b) Lejczak B, Kafarski P, Zygmunt J.: Inhibition of aminopeptidases by aminophosphonates, Biochemistry 1989;28:3549–3555.
15. For a review, see: Kafarski P, Lejczak B.: Application of bacteria and fungi as biocatalysts for the preparation of optically active hydroxyphosphontes, J Mol Cat B: Enzym 2004;29:99–104.
16. Maghsoodlou M T, Habibi Khorassani S M, Heydari R, Hazeri N, Sajadikhah S S, Rostamizadeh:$Al(H_2PO_4)_3$ as an Efficient and Reusable Catalyst for One-pot Three-component Synthesis of *α*-Amino Phosphonates under Solvent-free Conditions. M. Chin J Chem 2010; 28:285.
17. Naydenova E D, Todorov P T, Troev K. D.: Recent synthesis of aminophosphonic acids as potential biological importance. Amino Acids 2010; 38:23.
18. Hou J, Gao J, Zhang H: $NbCl_5$: an efficient catalyst for one-pot synthesis of α-aminophosphonates under solvent-free conditions. Appl Organomet Chem 2011; 25:47.
19. Shastri R.: synthesis and antifungal activity of new α-amino phosphonate derivatives containing thiazole moiety. World Journal of Pharmacy and Pharmaceutical Sciences (WJPPS) 2014; 3:1814.
20. Kumari S, Shekhar A, Pathak D.: New Catalyst and Solvent-free Green Synthesis of *α*-Hydroxy Phosphonates and *α*-Aminophosphonates. Chem Sci Trans 2014; 3:45.
21. Badadhe P V, Chavan N M, Ghotekar D S, Mandhane P G, Joshi R S.: Synthesis, Characterization, and Biological Screening of Some Novel Thiazolidin-4-One and α-Aminophosphonate Derivatives. Phosphorous Sulphur and Silicon 2011;186: 2021.
22. Abdel-Megeed M F, Badr B E, Azaam M M, El-Hiti G A.: Synthesis, antimicrobial and anticancer activities of a novel series of diphenyl 1-(pyridin-3-yl)ethylphosphonates Bioorg Med Chem 2012; 20:2252.
23. Nizamov I S, Yambushev F D, Nizamov I D, Voloshina A D, Alfonsov VA.: The Kabachnik–Fields and Pudovik Reactions on the Basis of E,Z-Citral and Its Imines and (R,S)-Citronellal. Heteroatom Chem 2013; 24:36.
24. Reddy S S, Rao V K, Krishna B S, Reddy C S, Rao P V, Raju C N.: Synthesis, Antimicrobial, and Antioxidant

Activity of New α-Aminophosphonates. Phosphorous Sulphur and Silicon 2011; 186:1411.
25. Shafakat A N, Zakir S, Patel M, Farooqui M.: Synthesis of new α aminophosphonate system bearing Indazole moiety and their biological activity. Eur J Med Chem 2012; 50:39.
26. Gandavaram S P, Gollapalli NR. Synthesis of Biologically Active α-Aminophosphonates. J Mod Med Chem 2013; 1:49.
27. Ashok Kumar, Kumkum Srivastava, S. Raja Kumar, M. I. Siddiqi, Sunil K. Puri, Jitendra K. Sexana, Prem M. S. Chauhan: 4-Anilinoquinoline triazines A novel class of hybrid antimalarial agents, European Journal of Medicinal Chemistry 2011;46(2), 11:676-690

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