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SYNTHESIS OF A NOVEL SERIES OF PIPERAQUINE DERIVATIVES

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Abstract
A general and efficient synthesis of piperaquine & its analogues have been achieved by this sequence. All compounds were purified by column chromatography and were characterized by IR, ^{1}H NMR, ^{13}C NMR and by mass spectral analyses.

Keywords: Piperquine, clinical, chloroquine, antimalarial agent

Introduction

Malaria is one of the most abundant parasitic diseases in the world affecting many of the poorest economies. The estimated prevalence is 300 to 700 million clinical episodes each year with up to 3 million deaths. Piperaquine replaced chloroquine as the first line treatment in China for Plasmodium falciparum malaria in the 1970s and was used as mass prophylaxis until the emergence of resistance in the 1990s. It has recently been the object of renewed interest as a partner drug in artemisinin-based combination therapy. Artekin is a fixed oral combination of dihydroartemisinin and piperaquine showing excellent efficacy and tolerability against multi-resistant Plasmodium falciparum malaria. Only a limited number of studies have addressed the clinical pharmacokinetics of piperaquine, none of which have addressed metabolism.

Quinine[i], a member of the cinchona alkaloid family, is one of the oldest antimalarial agents and was first extracted from cinchona tree bark in the late 1600s. The cinchona species is native to the Andean region of South America, but when its therapeutic potential was realised, Dutch and British colonialists quickly established plantations in their south-east Asian colonies. These plantations were lost to the Japanese during World War II, stimulating research for synthetic analogues based on the quinine template, such as the 4-aminoquinoline chloroquine.

A detailed historical review of CQ (in honour of chloroquine's 75th birthday) is available elsewhere[ii]. In short, CQ was first synthesized in 1934 and became the most widely used antimalarial drug by the 1940s[iii].

The presence of impurities, even in small amounts, may influence the quality and safety of the medicine. Impurity profiling (identification and quantification) is now receiving important acute attention from regulatory authorities. The different pharmacopoeias, such as the European Pharmacopoeia (EP), British Pharmacopoeia (BP), and the United States Pharmacopoeia (USP), are slowly incorporating limits to allowable levels of impurities present in the APIs or formulations. The International Conference on Harmonization (ICH) has published guidelines on impurities in new drug substances[iv], products[v], and residual solvents[vi]. Impurity and API reference standards are in good demand for both regulatory authorities and pharmaceutical companies. A number of recent articles[vii-ix] have described a designed approach and guidance for isolating and identifying process related impurities and degradation products using spectral and analytical techniques.

The important step in impurity profiling is the synthesis of the material (impurity standard) with the proposed structure. The synthesized material with the proposed structure is useful for analytical method development and validation. In this perspective, the present paper reports the synthesis and characterization of impurities of piperaquine. These impurities were listed in United States Pharmacopeia and to the best of our knowledge until now the synthesis of these impurities has not been reported in the literature.

Materials and methods

Analytical grade solvents and commercially available reagents were used without further purification. The column chromatography was carried out over silica gel (60-120 mesh), purchased from Sisco Research Laboratories Pvt Ltd. Melting points were determined in open capillaries in electrical melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on 400-MHz Varian spectrometer in DMSO-d_6 or $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ relative to TMS, the coupling constants are given in Hz. Mass spectra were recorded using Agilent 1100 MSD spectrometer in electro spray mode.

Experimental Section

General Procedure for the Preparation of 4, 7-Dichloroquinoline (1).

The mixture of m-chloroaniline (1.27 g, 10 mM) and ethoxymethylenemalonate (2.56 g, 11 mM) in an open round bottom flask. heated on a water bath for a period of 1 h to give 7-Chloro-4-hydroxy-3-quinolinecarboxylic acid. The round bottom flask equipped with an air condenser of Dowtherm is heated vigorous for period of 1 h, during this time most of the compound underwent cyclization and gave crystallization product of 7-chloro-4-hydroxy-3-quinolinecarboxylic acid.

After drying the above contents air-dried acid is suspended in 1 l. of Dowtherm in a flask equipped with a stirrer and a reflux condenser. The mixture is boiled for 1 hour under a stream of nitrogen to assist in the removal of the water. The light-brown solution is cooled to room temperature, and $POCl_3$ (10 ml, 10 mM) is added. The temperature is raised to 145° C, and the mixture is stirred for 1 hour. The reaction mixture is cooled and poured into ether, and the solution is washed with 10% hydrochloric acid. The combined acid extracts are cooled in ice and neutralized with 10% sodium hydroxide to precipitate the 4, 7-dichloroquinoline. The solid is collected, washed thoroughly with water, and dried; the yield is 1.47 g (75%) and m.p. is 85 °C

General Procedure for the Preparation of 7-chloro-4-(piperazin-1-yl)quinoline (7).

KI (1.66 g, 10 mM) was added to a mixture of 4, 7-Dichloroquinoline **(1)** (1.96 g, 10 mM) and piperazine (0.86 g, 10 mM) in isopropyl alcohol (30 mL) and refluxed at 85 ^{0}C for a period of 12 h. After completion of reaction, the mixture is cooled to room temperature and distilled solvent completely under reduced pressure at 50 °C. The final compound was purified by silica gel column chromatography by using 4% MeOH: $CHCl_3$ to obtain white powder. Further it is then recrystallized from ethyl acetate to give pure **(7)** in 82% yield (2.02 g). The TLC system is maintained as 10% MeOH: $CHCl_3$ and Rf value is 0.7.

General Procedure for the Preparation of 7-chloro-4-(4-(3-chloropropyl)piperazin-1-yl)quinoline (8) from 7.

Taken **7** (2.47 g, 10 mM) and DCM (30 mL) solvent into 100 mL round bottomed flask. Added a small amount of methanol (5 mL) for solubility of starting material. Charged TEA (5.56 mL, 50 mM) and 1-bromo-3-chloro-propane (4.6 mL, 45 mM). The reaction mixture under refluxed at 50 °C for a period of 12 h. At the end of this period, the solution was cooled to room temperature and washed with water. The DCM layer dried over sodium sulphate and followed by distilling the solvent completely under reduced pressure. The final compound was purified by silicagel column (100-200 mesh) and eluted with 2% MeOH: DCM to obtain a pure yellow solid of **(8)** in 85 % yield (2.75 g).

^{1}H NMR $CDCl_3$: δ = 8.61 (d, 1H), 8.10 (s, 1H), 8.00 (d, 1H), 7.51 (d, 1H), 6.85 (d, 1H), 3.71 (t, 2H), 3.40 (m, 4H), 2.81 (m, 4H), 2.60 (t, 2H), 2.02 (m, 2H).

General Procedure for the Preparation of 7-chloro-4-(4-(3-(piperazin-1-yl)propyl)piperazin-1-yl)quinoline (9) from 8.

Taken compounds **8** (3.23 g, 10 mM) and piperazine (2.58 g, 30 mM) in a round bottomed (100 mL) flask containing isopropyl alcohol (30 mL). This reaction mixture is heated at 85 °C for a period of 12 h. After completion the reaction by TLC (10% MeOH: $CHCl_3$, Rf = 0.1) the reaction mixture was cooled to room temperature and distilled the solvent by rota vapor under reduced pressure. The crude compound was washed with water and extracted with ethyl acetate. The organic layer dried over sodium sulphate and introduced in a column silicagel (100-200 mesh). Eluted the crude in the presence of 5% MeOH: DCM solvent system to obtain a yellow solid in 75 % yield (2.79 g).

^{1}H NMR $CDCl_3$: δ = 8.70 (d, 1H), 8.10 (s, 1H), 7.90 (d, 1H), 7.50 (d, 1H), 6.80 (d, 1H), 3.65 (m, 4H), 3.41 (m, 4H), 3.10 (m, 2H), 2.71 (m, 4H), 2.50 (m, 8H), 1.80 (m, 2H).

General Procedure for the Preparation of 7-chloro-4-(4-(3-(4-(3-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)propyl)piperazin-1-yl)propyl)piperazin-1-yl)quinoline (10) from 9 & 8.

KI (1.66 g, 10 mM) was added to a mixture of 7-chloro-4-(4-(3-(piperazin-1-yl)propyl)piperazin-1-yl)quinoline **(9)** (3.23 g, 10 mM) and compound **8** (3.73 g, 10 mM) in isopropyl alcohol (100 mL) and refluxed at 85 ^{0}C for a period of 25 h. After completion of the reaction by TLC (MeOH+ 3 drops ammonia, Rf = 0.2), the mixture is cooled to room temperature and distilled solvent completely under reduced pressure at 50 °C. The final compound was purified by silica gel column chromatography by using neutral alumina and eluted in the presence of 5% MeOH: DCM to obtain off-white solid in 70% yield (4.62 g).

^{1}H NMR $CDCl_3$: δ = 8.76 (d, 2H), 8.11 (s, 2H), 7.92(d, 2H), 7.50 (d, 2H), 6.88 (d, 2H), 3.35 (m, 8H), 2.85 (m, 8H), 2.51 (m, 10H), 1.86 (m, 10H).

General Procedure for the Preparation of 7-chloro-4-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)quinoline (11) from 7 & 1.

KI (1.66 g, 10 mM) was added to a mixture of 7-chloro-4-(piperazin-1-yl)quinoline **(7)** (2.47 g, 10 mM) and compound 4,7-dichloroquinoline **(1)** (1.96 g, 10 mM) in isopropyl alcohol (100 mL) and refluxed at 85^0C for a period of 72 h. After completion of the reaction by TLC (10% MeOH+$CHCl_3$, Rf = 0.7), the mixture is cooled to room temperature and distilled solvent completely under reduced pressure at 50 °C. The final compound was purified by silicagel column chromatography and eluted in the presence of 4% MeOH: DCM. Finally compound was recrystalised with ethyl acetate obtained a pure off-white color solid of **(11)** in 70% (2.85 g) yield.

^{1}H NMR $CDCl_3$: δ = 8.81 (d, 2H), 8.10 (s, 2H), 8.01(d, 2H), 7.50 (d, 2H), 7.01 (d, 2H), 3.51 (m, 8H).

General Procedure for the Preparation 3-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)propanoic acid (12) from 7.

To a mixture of K_2CO_3 (1.6 gm, 20 mM) and a catalytic amount of KI (0.42 g, 2.5 mM) in acetone (50 mL), was added **7** (2.47 g, 10 mM) 3-chloro propionic acid (1.62 g, 15 mM). The reaction mixture was refluxed at 80 °C for a period of 12 h. After completion of the reaction by TLC (10% MeOH+$CHCl_3$, Rf = 0.1), the mixture was cooled to room temperature and distilled solvent completely under reduced pressure at 50 °C. The final compound was purified by silicagel column chromatography and eluted in the presence of 20% MeOH: DCM. Finally compound was recrystalised with isopropyl alcohol obtained a pure pale yellow color solid of **(12)** in 68% (2.16 g) yield.

^{1}H NMR $CDCl_3$: δ = 8.73 (d, 1H), 8.02 (m, 2H), 7.60 (d, 1H), 7.02 (d, 1H), 3.25 (m, 4H), 2.80 (m, 6H), 2.50 (m, 2H).

General Procedure for the Preparation 1,3-bis(4-(7-chloroquinolin-4-yl)piperazin-1-yl)propan-2-ol (13) from (7).

To mixture of K_2CO_3 (1.6 gm, 20 mM) and **7** (5.18 g, 21 mM) in DMF (100 mL), 1,3 dichloro-2-propanol (0.93 mL, 10 mM) was added drop wise . The reaction mixture is refluxed at 80 °C for a period of 60 h. After completion of the reaction by TLC (10% MeOH+$CHCl_3$, Rf = 0.2), the mixture was cooled to room temperature and poured into distilled water and extracted with ethyl acetate. The organic layer was washed with brine solution and dried over with sodium sulphate followed by distilled solvent completely under reduced pressure at 50 °C. The crude compound was purified by silicagel column chromatography and eluted in the presence of 5% MeOH: DCM obtain a pure white solid of **(13)** in 75% (4.13 g) yield.

^{1}H NMR $CDCl_3$: δ = 8.75 (d, 2H), 8.10 (d, 2H), 8.02(d, 2H), 7.51 (m, 2H), 6.85 (d, 2H), 4.15 (m, 1H), 3.81 (m, 1H), 3.35 (m, 10H), 2.80 (m, 6H), 2.61 (m, 4H).

General Procedure for the Preparation 7-chloro-4-(4-(3-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)propyl)piperazin-1-yl)quinoline (14) from 8 & 7.

KI (1.66 g, 10 mM) added to a mixture of 7-chloro-4-(4-(3-chloropropyl)piperazin-1-yl)quinoline **(8)** (3.27 g, 10 mM) and a compound of 7-chloro-4-(piperazin-1-yl)quinoline **(1)** (2.47 g, 10 mM) in isopropyl alcohol (100 mL) and refluxed at 85 ^{0}C for a period of 12 h. After completion of the reaction by TLC (5% MeOH+$CHCl_3$, Rf = 0.6), the mixture is cooled to room temperature and distilled solvent completely under reduced pressure at 50 °C. The final compound was purified by silicagel column chromatography and eluted in the presence of 4% MeOH: DCM. Finally compound was recrystalised with ethyl acetate obtained a pure white color solid of **(14)** in 69% (3.68 g) yield.

General Procedure for the Preparation of (15) and (16) from 14.

Dissolved compound **14** (5.34 g, 10 mM) in a solvent mixture of DCM (50 mL) and MeOH (25 mL). piperazine (2.58 g, 30 mM) in a round bottom (250 mL) flask. This reaction mixture is cooled to 10° C and 30% H_2O_2 (2.04 mL, 60 mM)was added drop wise . The reaction mixture was stirred at 10 °C for a period of 72 h. After completion of the reaction by TLC (10% MeOH: $CHCl_3$, Rf = 0.4 & 0.2) distilled the solvent by rota vapor under reduce pressure. The crude compound was purified by column of neutral alumina and was eluted 5% MeOH and 20% MeOH +DCM, obtained the pure compounds of **15** and **16** respectively. The yields of mono N-oxide and di N-oxide were 25% (1.37 g) and 45% (2.52 g).

^{1}H NMR $CDCl_3$: δ = 8.80 (m, 2H), 8.11 (m, 2H), 7.81 (m, 2H), 7.50 (m, 2H), 7.05 (d, 1H), 6.88 (d, 1H), 4.01 (m, 2H), 3.80 (m, 4H), 3.62 m, 2H), 3.51 (m, 2H), 3.31 (m, 4H), 2.85 (m, 4H), 2.79 (m, 2H), 2.49 (m, 2H).

For Compound 16 ^{1}H NMR $CDCl_3$: δ = 8.75 (d, 2H), 8.02 (m, 2H), 7.60 (m, 2H), 7.15 (m, 2H), 3.96 (m, 4H), 3.70 (m, 8H), 3.61 (m, 8H), 3.12 (m, 2H).

Results & Discussion

Preparation of impurities7-chloro-4-(4-(3-(4-(3-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)propyl)piperazin-1-yl)propyl)piperazin-1-yl)quinoline **(10)** &7-chloro-4-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)quinoline**(11)**

4,7-Dichloroquinoline **(1)** has been prepared through well known reported method [12]. m-chloroaniline **(2)** on reaction with ethyl ethoxymethylenemalonate yielded ethyl-α-carbethoxy-β-m- chloroanilinoacrylate **(3)** and was further heated to 250 °C afforded cyclised product **4,** which on hydrolysis in the presence of NaOH/HCl, followed by reaction with $POCl_3$ at 125 °C gave target starting material **(1).** The melting point of the compound matched with the authentic sample.

Treatment of **1** with piperazine in the presence of isopropyl alcohol , at 85 ^{0}C for 12 h without using any catalyst gave a compound which has been identified as 7-chloro-4-(piperazin-1-yl)quinoline **(7)** in 82% yield**.**

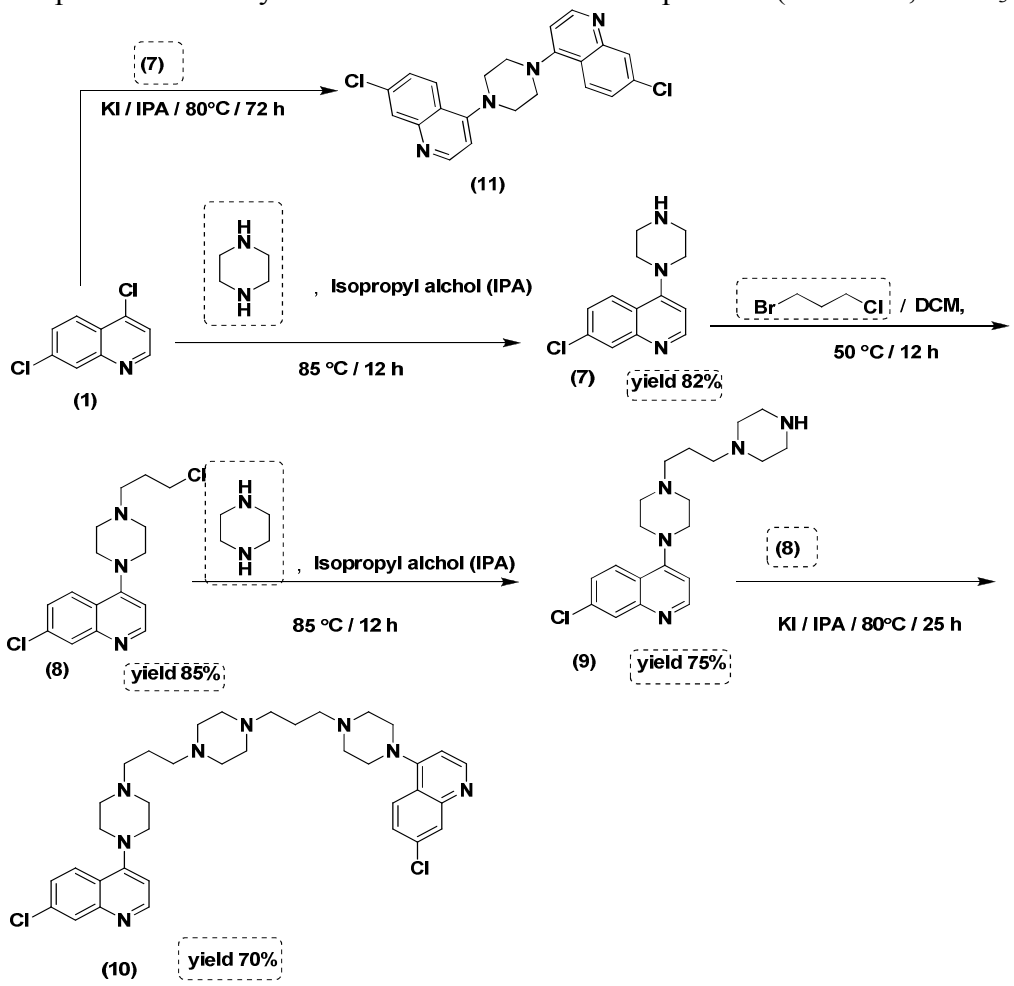
7 on reaction with 1-bromo-3-cholro propane in the presence of DCM under refluxing on water bath at 50 °C for 12 h, gave a yellow color solid of 7-chloro-4-(4-(3-chloropropyl)piperazin-1-yl)quinoline **(8)** in 85% yield. Thus, its IR spectrum in KBr does not showed absorption at 3322 cm^{-1} (due to –NH stretching) and the melting point is 112-114 °C [13]. The structure of this compound has been assigned based on its ^{1}H- NMR spectrum (300 MHz, $CDCl_3$/TMS).

Treatment of **8** with piperazine in the presence of isopropyl alcohol at 85 ^{0}C for 12 h without using any catalyst gave a compound which has been identified as 7-chloro-4-(4-(3-(piperazin-1-yl)propyl)piperazin-1-yl)quinoline **(9)** in 75% yield. The structure of this compound has been assigned based on its spectral and analytical data.

Treatment of 7-chloro-4-(4-(3-(piperazin-1-yl)propyl)piperazin-1-yl)quinoline **(9)** with **8** in the presence of KI in isopropyl alchol,under reflux for a period of 25 h, gave a white color precipitate of 7-chloro-4-(4-(3-(4-(3-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)propyl)piperazin-1-yl)propyl)piperazin-1-yl)quinoline **(10)** in 70% yield. The structure of this compound has been assigned based on its spectral and analytical data. Thus its ^{1}H- NMR spectrum (300 MHz, $CDCl_3$/TMS).

Preparation of compound 7-chloro-4-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)quinoline **(11)** was achieved from the reaction between **7** with **1** in the presence of KI in isopropyl alcohol,

under reflux for a period of 72 h in 70% yield. The structure of this compound has been assigned based on its spectral and analytical data. Thus its ^{1}H- NMR spectrum (300 MHz, $CDCl_3$/TMS).



Scheme-1

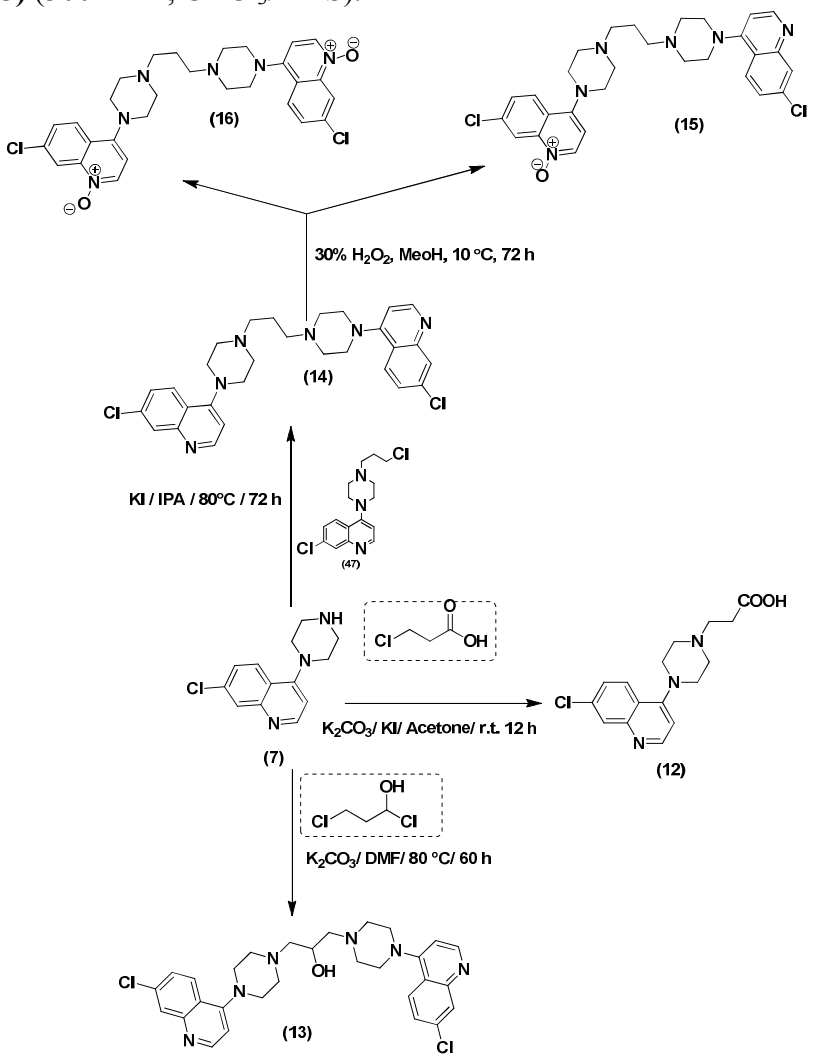
The reaction of **7** with 3-chloropropanoic acid in the presence of KI and weak base i.e. K_2CO_3 in acetone, at room temperature under stirring for a period of 12 h, afforded 3-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)propanoic acid **(11)** in 68% yield. The structure of this compound has been assigned based on its spectral and analytical data.

Treatment of **7** with 1,3-dichloropropan-1-ol in the presence of mild base i.e. K_2CO_3 in DMF solvent and on heating at 80 °C for a period of 60 h. yielded 1,3-bis(4-(7-chloroquinolin-4-yl)piperazin-1-yl)propan-2-ol **(13)** in 70%. The structure of this compound has been assigned based on its spectral and analytical data. Thus its ^{1}H- NMR spectrum (300 MHz, $CDCl_3$/TMS).

The reaction of **8** with **7** in the presence of KI in isopropyl alcohol under reflux at 80 °C for a period of 72 h gave 7-chloro-4-(4-(3-(4-(7-chloroquinolin-4-yl)piperazin-1-yl)propyl)piperazin-1-yl)quinoline (**14**) in 69% yield.

Treatment of **14** with 30% hydrogen peroxide in the presence of MeOH at 10 °C followed by stirring for a period of 72 h afforded quinoline-*N*-oxide of 7-chloro-4-(4-(3-(4-(7-chloro-quinoline-N-oxide-4-yl)piperazin-yl)propyl)piperazin-1-yl)quinoline **(15)** and quinoline *N*-*N*'-dioxide of 7-chloro-4-(4-(3-(4-(7-chloro-quinolin-*N*-oxide-4-yl)piperazin-yl)propyl)piperazin-

el)quinoline-*N*-oxide **(16)** in 25% and 45% yield respectively. Thus its ^{1}H- NMR spectrum of the compound (**15)** (300 MHz, $CDCl_3$/TMS).



Scheme-2

Conclusion

In an effort to understand the SAR Piperquine was synthesized and all of them were pure. The synthesized compounds were characterized by spectral analysis.

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