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SYNTHESIS OF SOME NOVEL PIPERIDONE LINKED BISQUINOLINES

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ABSTRACT

Some novel piperidone linked bisquinolines were synthesized efficiently in 2 steps. In step I, 6-substituted-2-chloro-3-formyl quinolines were prepared by Vilsmeir-Heark reaction. The compounds so formed in step I were treated with ammonium acetate and different ketones in alcohol to yield required piperidone linked bisquinolines. The synthesized compounds were identified by FTIR, ^{1}H and ^{13}NMR spectroscopic techniques.

Key words: Piperidone linked bisquinolines, IR, NMR, Mass spectroscopy.

INTRODUCTION

Bisquinolines, as name suggests are compounds that contain 2 quinoline nuclei combined through an aliphatic or aromatic linker. Bisquinolines are known to be active against chloroquine resistant strains of malaria[1-6] and acts as antimicrobial[7], antimycobacterial[8], antifilarial[9], cytotoxic [10], antileshimanial [11], antiprion [12], haem detoxification[13], antiprotozoal and retroviral[14]. Bisquinolines are prominent compounds against malaria parasites due to their accumulation in the food vacuole of both; cholroquine sensitive and cholroquine resistant parasites[15]. Similarly, piperidones were also reported to possess anticancer [16], analgesic [17], antiinflammatory[18], local anaesthetic [19] and antimicrobial [20] activities.

In view of the above observations, an attempt was made towards the synthesis of piperidone linked bisquinolines to investigate the combination, which could influence the bacterial and fungal activity.

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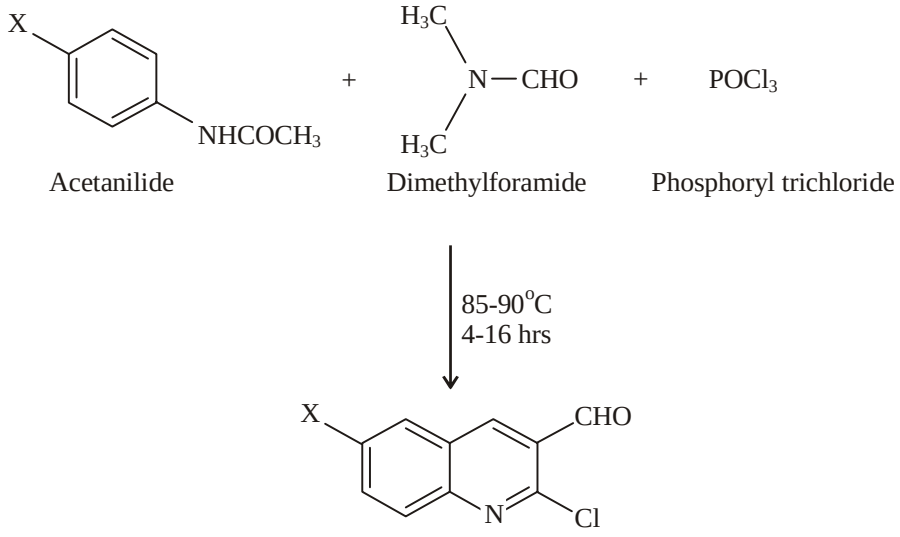
EXPERIMENTAL

All the melting points were determined in Vergo Vmp I melting point apparatus and are uncorrected .The purity of the compounds was determined by TLC on silica gel –G plate. IR spectra were recorded in Perkin-Elmer FTIR spectrophotometer. The ^{1}H NMR spectra were recorded on Bruker spectroscopier 200 MHz using DMSO as solvent and TMS as internal standard .

Synthesis of compounds[21-32]

Step I: Synthesis of 2-choro-3-formyl quinolines

To a solution of acetanilide (5 mmoles) in dry DMF (15 mmoles) at 0-5^{0}C temperature, phosphoryl chloride (60 mmoles) was added dropwise with stirring and mixture was then stirred at 85-90^{0}C for time ranging between 4-16 hours. The mixture was poured onto crushed ice, stirred for 5 minutes and the resulting solid was filtered, washed well with water and dried. The compound was recrystallised from ethyl acetate.



Acetanilide Dimethylforamide Phosphoryl trichloride

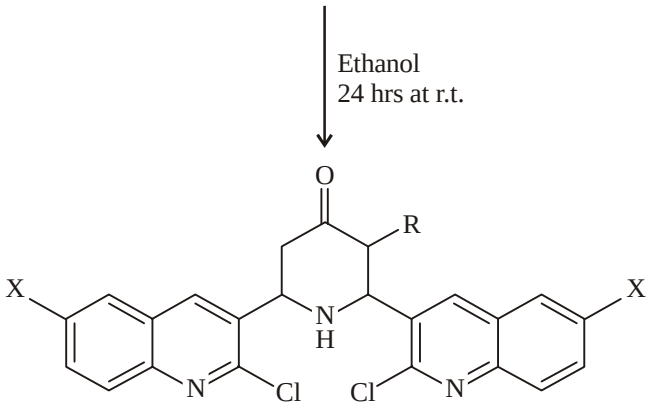
2-Chloro-3-formyl-quinoline

Step II: Synthesis of 3-substituted-2,6-bisquinolinyl-piperidin-4-ones

A mixture of ketone (50 mmoles**),** ammonium acetate (50 mmoles) and substituted 2-chloro-3-formyl quinoline (100 mmoles) in ethanol was heated to simmering carefully. It was kept at room temperature for 24 hours. To a viscous liquid obtained, ether (25 mL) was

added, followed by concentrated hydrochloric acid (15 mL) and cooled in ice water. The precipitated hydrochloride was filtered and washed with ethanol-ether (1 : 5) mixture. The hydrochloride was suspended in acetone and made alkaline using ammonia solution. On dilution with excess of water, the base was precipitated, which was filtered, dried and recrystallised from absolute alcohol.

2-Chloro-3-formyl-quinoline Ammonium acetate

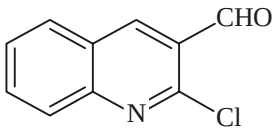


3-Substituted-2,6-bisquinolyl-piperidine-4-one

Spectral analysis

Compound I

2-Chloro-3-formyl quinoline



IR Spectral data (cm^{-1})

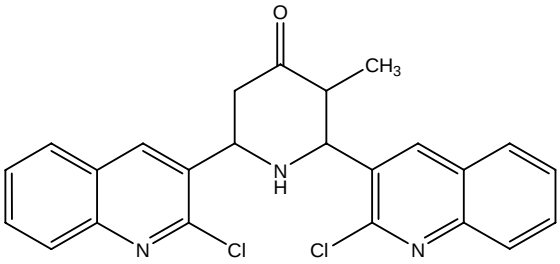
3043.6 (C-H stretching aromatic), 2872.24 (C-H stretching aldehyde), 1688.65 (C=O stretching), 1613.94, 1578.4, 1489.93 (C=C & C=N stretching; aromatic), 1045.74 (C-Cl stretching; aromatic).

NMR Spectral data (δ)

10.57 (strong) Aldehydic proton, 8.77 Heteroaromatic proton, 7.26-8.1 (multiplet) Aromatic hydrogen.

Compound (Ia)

2,6-Bis(2-chloroquinolin-3-yl)-3-methylpiperidin-4-one



IR Spectral data (cm^{-1})

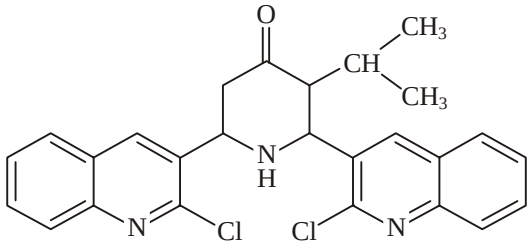
3275.82 (N-H stretching), 2976.74 (C-H stretching; aromatic), 1702.09 (C = O stretching), 1498.34 (N-H bending), 1026.28 (C-Cl stretching; aromatic).

NMR Spectral data (δ)

7.248-8.25 (Aromatic proton; quinoline), 4.06 (Methyne proton; piperidone), 2.39 (Amine proton), 1.185 (Methyl proton).

Compound (Ib)

2,6-Bis(2-chloroquinolin-3-yl)-3-isopropylpiperidin-4- one

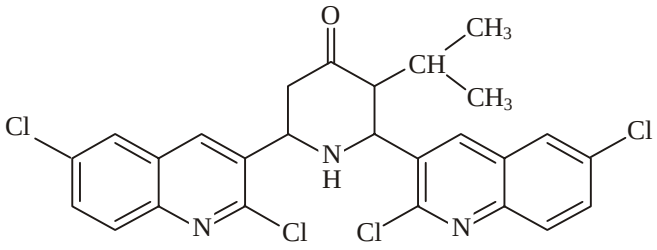


IR Spectral data (cm^{-1})

3423.47 (N-H stretching), 1708.3 (C=O stretching), 1653.75 (N-H Overtone), 1404.08 (C-H bending), 1036.41 (C-Cl stretching; aromatic).

Compound (IIb)

2,6-Bis(2,6-dichloroquinolin-3-yl)-3-isopropylpiperidin-4-one



IR Spectral data (cm^{-1})

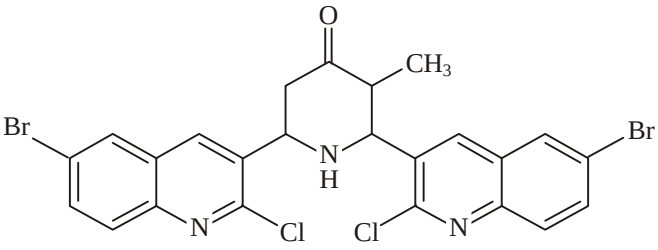
3194.5 (N-H stretching), 1700.2 (C=O stretching), 1504.76 (N-H bending), 1093.67 (C-Cl stretching; aromatic).

NMR Spectral data (δ)

1.2 (Methyl proton), 4.675-4.777 (Methylene proton), 1.76 (Amino proton), 7.26-8.13 (Heteroaromatic hydrogen).

Compound (IIIa)

2,6-Bis(6-bromo-2-chloroquinolin-3-yl)-3- methylpiperidin-4-one

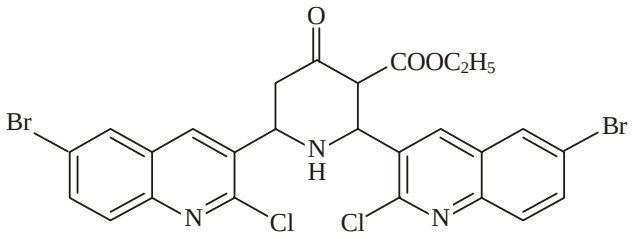


IR Spectral data (cm^{-1})

3414.8 (N-H stretching), 2919.68 (C-H stretching), 1722.67 (C=O stretching), 1392.92 (C-H bending), 1070.82 (C-Br stretching; aromatic).

Compound (IIIc)

Ethyl 2,6-bis(6-bromo-2-chloroquinolin-3-yl)-4- oxopiperidine-3-carboxylate



IR Spectral data (cm^{-1})

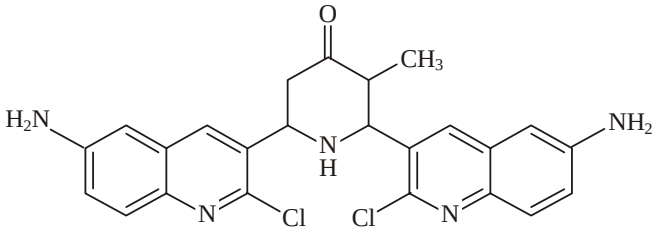
3435.98 (N-H stretching), 2921.89 (C-H stretching), 1770.07 (C=O stretching), 1615.09 (N-H Overtone), 1071.58 (C-Br stretching; aromatic).

NMR Spectral data (δ)

2.93-2.96 (Methyl proton), 3.94-3.99 (Methylene proton; quartet), 2.404 (Amino proton), 6.914-7.525 (Heteroaromatic hydrogen).

Compound (IVa)

2,6-Bis(6-amino-2-chloroquinolin-3-yl)-3- methylpiperidin-4-one

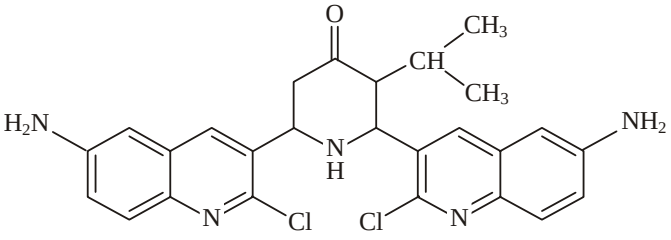


IR Spectral data (cm^{-1})

3414.36 (N-H stretching), 2921.53 (C-H stretching), 1695.53 (C=O stretching), 1615.1 (N-H bending), 1393.03 (C-N stretching; aromatic).

Compound (IVb)

2,6-bis(6-amino-2-chloroquinolin-3-yl)-3-isopropylpiperidin-4-one

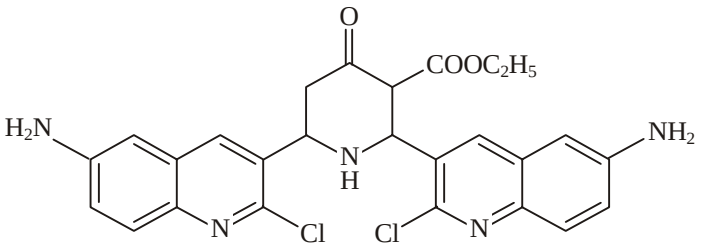


IR Spectral data (cm^{-1})

3421.02 (N-H stretching), 2920.02 (C-H stretching), 1706.07 (C=O stretching), 1614.94 (N-H bending), 1392 (C-N stretching; aromatic).

Compound (IVc)

Ethyl 2,6-bis(6-amino-2-chloroquinolin-3-yl)-4-oxopiperidine-3-carboxylate



IR Spectral data (cm^{-1})

3422.96 (N-H stretching), 2921.88 (C-H stretching), 1706.1 (C=O stretching), 1615.82 (N-H bending), 1392.36 (C-N stretching; aromatic).

Table 1: Physical data of compounds

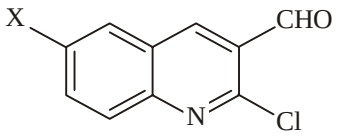
Compound	Molecular formula	Molecular weight	Melting point (^oC)	Yield (%)	R_f value
I	$C_{10}H_6NOCl$	191.66	140	78	0.68
II	$C_{10}H_5NOCl_2$	226.06	161	82	0.74
III	$C_{10}H_5NOClBr$	270.55	176	80	0.71
IV	$C_{10}H_7N_2ClO$	206.63	152	79	0.72
Ia	$C_{24}H_{19}N_3Cl_2O$	435.09	170	60	0.80
Ib	$C_{26}H_{23}N_3Cl_2O$	464.39	195	68	0.75
Ic	$C_{26}H_{21}N_3Cl_2O_3$	494.37	213	65	0.70
IIa	$C_{24}H_{17}N_3Cl_4O$	505.22	210	62	0.76
IIb	$C_{26}H_{21}N_3Cl_4O$	533.28	240	60	0.78

Cont…

Compound	Molecular formula	Molecular weight	Melting point (^{o}C)	Yield (%)	R_f value
IIc	$C_{26}H_{19}N_3O_3Cl_2$	563.26	235	56	0.69
IIIa	$C_{24}H_{17}N_3Cl_2Br_2O$	594.13	264	52	0.81
IIIb	$C_{26}H_{21}N_3Cl_2Br_2O$	622.18	276	58	0.79
IIIc	$C_{26}H_{19}N_3Cl_2Br_2O_3$	648.92	284	50	0.75
IVa	$C_{24}H_{21}N_5Cl_2O$	465.11	232	64	0.26
IVb	$C_{26}H_{25}N_5Cl_2O$	493.14	250	70	0.68
IVc	$C_{26}H_{23}N_5Cl_2O_3$	523.12	245	65	0.62

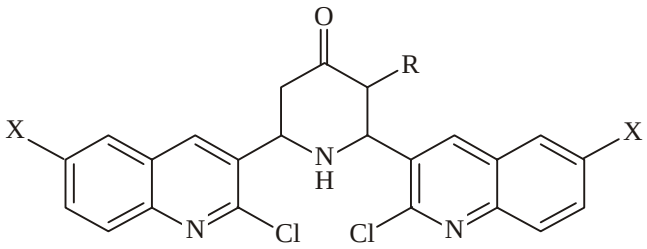
Synthesis of piperidone linked bisquinolines

Step I: Synthesis of 2-chloro-3-formyl quinolines



S. No.	X
I	H
II	Cl
III	Br
IV	NH_2

Step II: Synthesis of 3-substituted-2,6-bisquinolinyl-piperidin-4-ones



3-Substituted-2,6-bisquinolyl-piperidine-4-one

Compd.	X	R
Ia	H	CH_3
Ib	H	$CH(CH_3)_2$
Ic	H	$COOC_2H_5$
IIa	Cl	CH_3
IIb	Cl	$CH(CH_3)_2$
IIc	Cl	$COOC_2H_5$
IIIa	Br	CH_3
IIIb	Br	$CH(CH_3)_2$
IIIc	Br	$COOC_2H_5$
IVa	NH_2	CH_3
IVb	NH_2	$CH(CH_3)_2$
IVc	NH_2	$COOC_2H_5$

RESULTS AND DISCUSSION

Twelve novel piperidone linked bisquinolines were synthesized from the substituted 2-chloro-3-formyl quinoline. The 2-chloro-3-formyl quinolines were synthesized by refluxing acetanilides with Vilsmeir-Haack reagent. The obtained aldehydic quinoline was mixed with ammonium acetate and ketone in ethanol and kept for 24 hours. To this viscous solution, ether and conc. HCl were added and cooled in ice water to get precipitates. Ammonia solution was added to these precipitates. On excess dilution with water, base was liberated, as the desired piperidone linked bisquinoline. The purity of the compounds was checked by TLC using silica gel G as an adsorbent, ethyl acetate and chloroform (9.8 : 0.2) were used as mobile phase. The spot was visualized by iodine vapor or dinitrophenyl hydrazine solution. The structure of the synthesized compounds was characterized by its IR and ^1H NMR spectral analysis, which coincides with the expected values.

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