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Synthesis and characterization and anti-plasmodial activity of Indolo[3,2-c] quinolone derivatives

Rita Yadav, Dr.Dinesh Upadhyay, Dr.Vikas Agarwal, Dr. Birendra Shrivastava

Jaipur National University, Jaipur-302017 (Raj.)
Corresponding Author

Rita Yadav
Address: Jaipur National University, Jaipur- 302017 (Raj.)
E-mail: ritayadav4689@gmail.com

Abstract:
The ultimate goal of modern drug discovery is to identify a therapeutic agent that is effective against a disease. According to a recent study, there is a broad trend in drug research for novel medicines that includes molecular design of compound assemblies and modification of currently used physiologically active matrices. The Indolo[3,2-c] quinolone nucleus represents a noteworthy synthesis strategy for novel drug development. Many important effects, including anti-tubercular, anti-plasmodial, anti-inflammatory, antibacterial, analgesic, and anticancer activity, were revealed by indolo[3,2-c] quinolone derivatives. In retrospect, a number of novel medications and combinations have gradually gained approval for use, including mefloquine (1984), artemisinins (1994), artemether/lumefantrine (1999), atovaquone/proguanil (1999), and chlorproguanil/dapsone (2003). Nevertheless, each of these combinations has shown some limited utility. Thus, there is a pressing need to develop novel, practical, and effective antimalarial drugs.

Keywords: Indolo[3,2-c] quinolone, β-haematin inhibitory activity, anti-plasmodial, anti-malarial.

INTRODUCTION:

The symptoms of malaria to approximately 2700 BC. Many years later, in 1847, German physician Meckel identified significant amounts of dark colored patches from the blood, liver, and spleen of a mentally ill patient that he dubbed "melanin," but he was unable to correlate this unusual Initially, It was thought that the body created this pigment in an effort to fight off the infection. But in 1880, while analyzing recently tainted blood from a patient suffering from malaria, French army surgeon Charles Laveran discovered the missing link between this pigment and the protozoan parasite that was causing it. Decades later, pathologists still utilize this pigment, now known as "hemozoin" (Hz), as a critical component in the diagnosis of this illness [1-3].

The apical complex, a particular organelle that allows parasites to infiltrate their intended host cells, is what makes this genus a member of the *phylum Apicomplexa*. Five species from the genus Plasmodium—*P. falciparum, P. vivax, P. malariae, P. knowelsi, and P. ovale*—are now known to infect humans out of the more than 120 total [4, 5].

WHO World malaria report 2021

Humans can become infected with the potentially lethal malaria parasite through the bites of female mosquitoes. Approximately 3.2 billion individuals, or over half of the world's population, are susceptible to malaria. When they contract malaria, non-immune tourists from malaria-free areas, pregnant women, and young children are most susceptible to the illness. Malaria may be prevented and treated, and more efforts are significantly lowering the disease's prevalence in many regions [6-8]. Globally, the incidence of malaria, or the rate of new cases, decreased by 37% between 2000 and 2021. Malaria death rates decreased by 60% worldwide during that time for all age categories, and by 65% for children under five. The burden of malaria worldwide is disproportionately heavy on Sub-Saharan Africa. 89% of malaria cases and 91% of malaria deaths in 2016 occurred in the region. The malaria parasite *P. falciparum* is the most common in Africa. The majority of malaria-related deaths worldwide are caused by it. *P. vivax* is more widely distributed than P. falciparum, and it is the predominant strain in many non-African nations.

The most recent WHO estimates, which were made public in 2015, state that there were 445000 malaria fatalities and 216 million cases of the disease in 2020 [9, 10]. Approximately 15 nations, mostly in sub-Saharan Africa, are responsible for 78% of malaria fatalities and 90% of cases worldwide. The decrease in malaria incidence in these 15 nations (32%) since 2000 has not kept pace with the global fall in malaria incidence (54%). Children under the age of five are most vulnerable to infection, disease, and mortality in places where malaria transmission is high; in fact, over two thirds (70%) of all malaria deaths occur in this age range. Globally, the under-5 malaria fatality rate decreased by 65% between 2000 and 2020, saving an estimated 5.9 million child lives [11].

MATERIALS AND METHODS:

Selection of compounds for Synthesis: A series of one hundred twenty five derivatives of Indolo[3,2-c] quinolone derivatives were designed on the basis of CoMFA, CoMSIA , HQSAR and Docking studies on fourty nine literature Indolo[3,2-c] quinolone analogues (Ning wang et., al 2014) and its structure activity relationship were predicted. Their predicted activity was calculated from the models generated from CoMFA , CoMSIA and HQSAR. Based on the value of predicted activity fourteen derivatives were selected for synthesis.

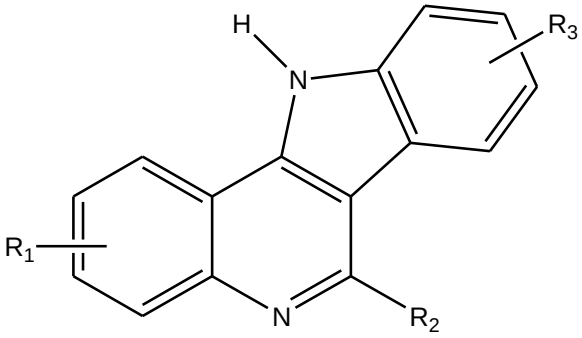


Table 1: List of synthesized fourteen compounds

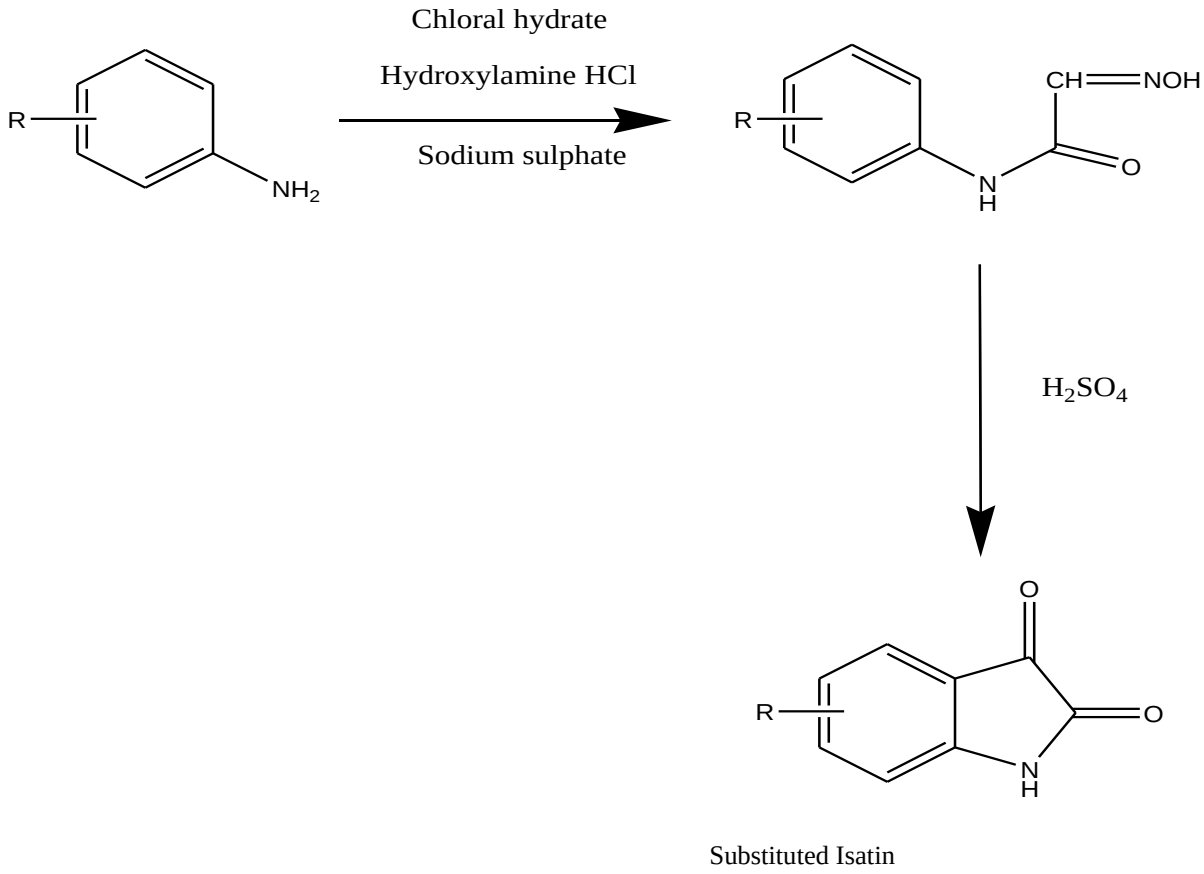
S.N.	Compound number	Compound name	R_1	R_2	R_3	Molecular formula
1	6	DD5	7-chloro	4-(3-amino propylmorpholino)	Chloro	$C_{22}H_{22}Cl_2N_4O$
2	15	DD12	7-methyl	N-methyl piperazino	Chloro	$C_{21}H_{21}ClN_4$
3	16	DD13	7-methyl	N-ethyl piperazino	Chloro	$C_{22}H_{23}ClN_4$
4	17	DD14	7-methyl	Benzyl amino	Chloro	$C_{23}H_{18}ClN_3$
5	18	DD15	7-methyl	N-butyl amino	Chloro	$C_{20}H_{20}ClN_3$
6	20	DD17	7-methyl	3-hydroxy anilino	Chloro	$C_{22}H_{16}ClN_3O$
7	21	DD18	7-methyl	4-hydroxy anilino	Chloro	$C_{22}H_{16}ClN_3O$
8	22	DD19	7-methyl	4-bromo anilino	Chloro	$C_{22}H_{15}BrClN_3$
9	25	DD21	7-methyl	4-fluro anilino	Chloro	$C_{22}H_{15}ClFN_3$
10	28	DD23	7-methoxy	N-methyl piperazino	Chloro	$C_{21}H_{21}ClN_4O$
11	30	DD25	7-methoxy	Benzyl amino	Chloro	$C_{23}H_{18}ClN_3O$
12	33	DD28	7-methoxy	3-hydroxy anilino	Chloro	$C_{22}H_{16}ClN_3O_2$
13	35	DD30	7-methoxy	4-bromo anilino	Chloro	$C_{22}H_{15}BrClN_3O$
14	38	DD32	7-methoxy	4-fluro anilino	Chloro	$C_{22}H_{15}ClFN_3O$

General procedure for synthesis of Isocryptolepine derivatives:

Step-1: Synthesis of Isatin

Substituted aniline (m-anisidine, m-taulidine and 3-chloroaniline)',* (10 g.) in a 1-liter, spherical flask equipped with a stirrer and a thermometer, was covered with 50 cc. of water and 12 cc. of concentrated hydrochloric acid.

Two solutions were added to this combination, which was mechanically stirred: one containing 66 grams of anhydrous sodium sulfate and 10.5 grams of chloral hydrate in 224 cc of water, and the other containing 13 grams of hydroxylamine hydrochloride in 60 cc of water. Over the course of six hours, the well-stirred suspension was progressively heated to roughly 1000C; at 940C, the solids started to turn yellow, and the combination was kept at this temperature for 30 minutes [12-14]. After allowing the reaction to cool while stirring and letting it stand for an entire night, the particles were removed, cleaned with water, and placed in 750 cc of a 1% sodium hydroxide solution. There was a tiny amount of undissolved crude black material that was filtered out and cleaned of concentrated hydrochloric acid diluted with 200 cc. of water, and the white, swollen precipitate was collected, pressed, washed with water, and dried.

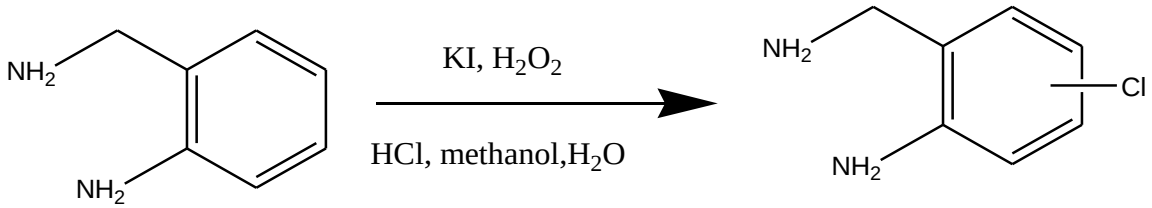


Substituted Isatin

Fig. 1: Synthetic scheme for isatin synthesis

Step 2: Chlorination of 2-AminoBenzylamine

A solution of 2-Amino benzylamine (1.00 g), potassium iodide (1.03 g) and hydrogen peroxide (0.66 ml) was prepared in methanol (5 mL) and water (15 mL). This mixture was treated at room temperature with dilute hydrochloric acid (9.5 mmol) over 40 to 45 minutes and stirred for an additional 2–3 h, diluted with water (15 mL) and extracted with dichloromethane (25 mL×3) [15, 16].



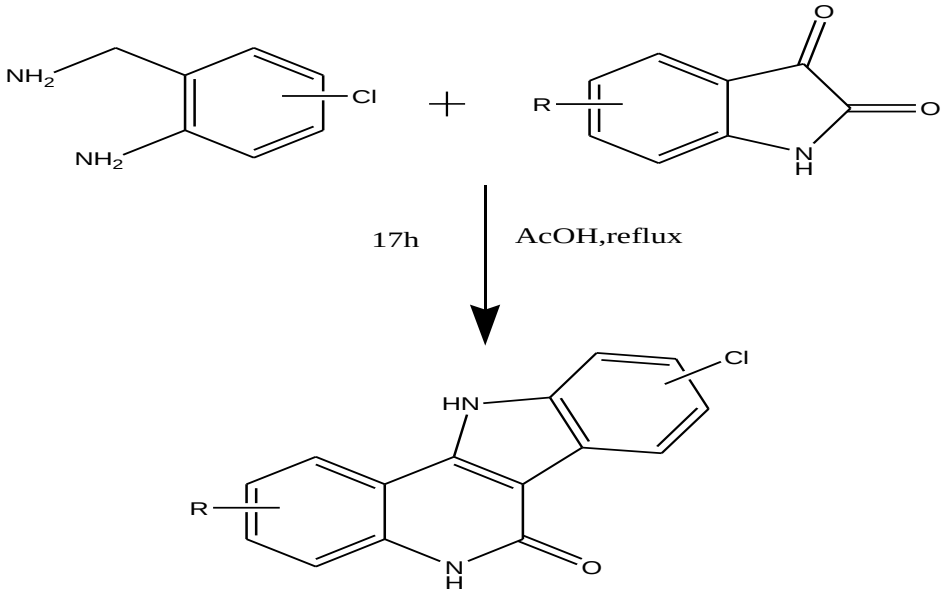
2-amino benzylamine

Chlorinated 2-amino benzylamine

Fig.3: Chlorination of 2-AminoBenzylamine

Step 3: Synthesis of intermediates

Chlorinated Aminobenzylamine and substituted Isatin in equal quantity 1gm each, taken in round bottom flask containing 10ml acetic acid and the reaction mixture allowed to reflux for 17 h. The reaction was monitored by Thin Layer Chromatography [17].

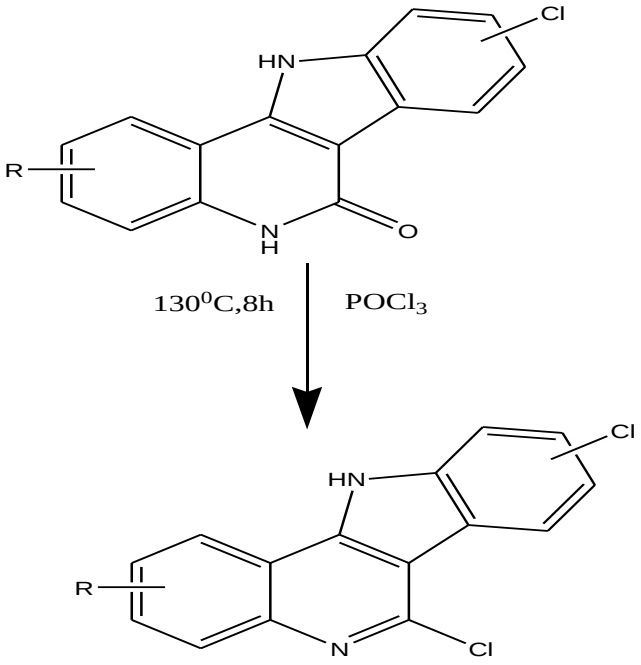


First Intermediate

Fig.4: Synthesis of first intermediates

Step 4: Dehydrative chlorination with $POCl_3$

Clorination of first intermediate was carried by adding 5ml of phosphoryl chloride to the reaction mixture and then the reaction was allowed to refluxed at 130°C for 8h [17, 18].

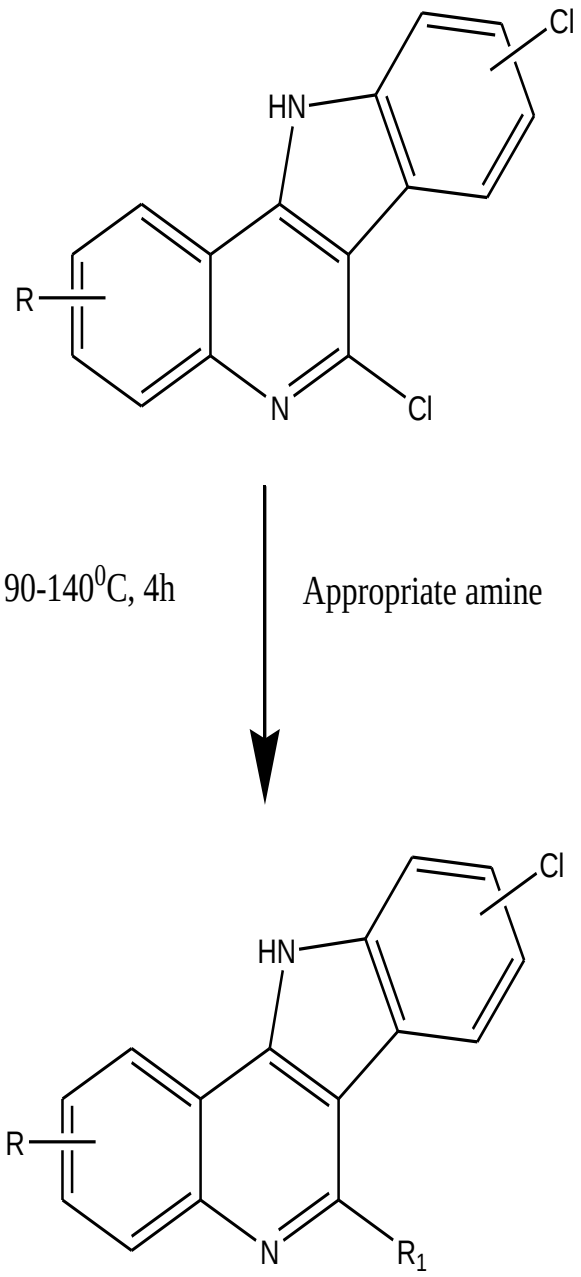


Second Intermediate

Fig.5:.Dehydrative chlorination with $POCl_3$

Step 5: Amine addition

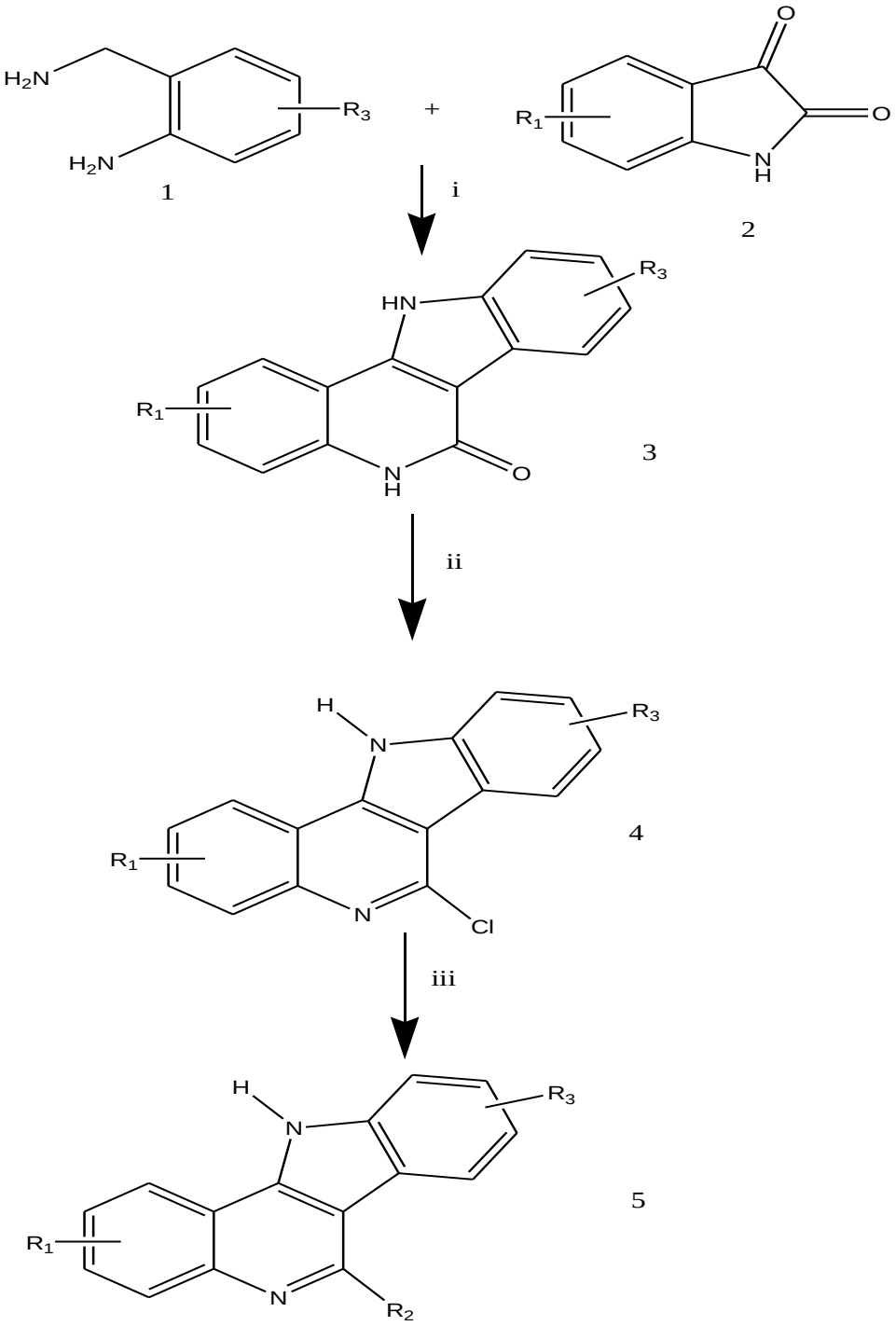
Amino groups were introduced at C-13 by ArSN reaction with various amines. Various amines such as 4-(3-amino propylmorpholino), N-methyl piperazino, N-ethyl piperazino, Benzyl amino, N-butyl amino, 3-hydroxy aniline, 4-hydroxy aniline, 4-bromo aniline [19-21] and 4-fluro aniline introduced at R1 position by heating the reaction mixture at 90-140^{0}C for 4h [22-23].



*R (7-chloro,7-methyl and 7-methoxy)

*R^1 (4-(3-amino propylmorpholino), N-methyl piperazino, N-ethyl piperazino, Benzyl amino, N-butyl amino, 3-hydroxy aniline, 4-hydroxy aniline, 4-bromo aniline and 4-fluro aniline)

Fig.6: Amine addition



(i) Acetic acid ,reflux,8-20h;
(ii) $POCl_3$,130°C,8h;
(iii) appropriate amines ,90-140°C , 20 min-4h

R_1=7-Methyl, 7-Methoxy, 7-Chloro

R_2= N-methyl piperazino, N-ethyl piperazino, Benzyl amino, 4-(3-amino propylmorpholino), 4-hydroxy aniline, 4-bromo aniline, 4-fluro aniline, 2,3dichloro aniline, N-butyl amino

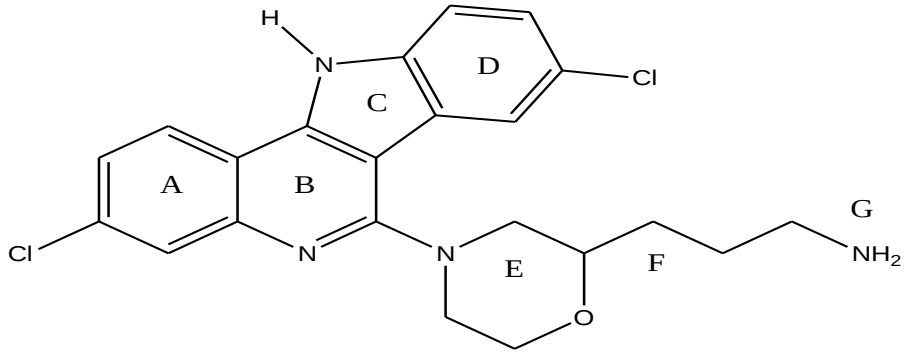
R_3=7-Chloro

Physicochemical Characterization:

Melting Point: Thiele's tube method was used to calculate the melting points, which were then left uncorrected. To determine the purity of the produced compounds, precoated silica gel-G 0.2 mm thick was subjected to thin layer chromatography using several solvent systems. The detecting agents were iodine and UV vapours. FTIR-8400S Shimadzu was used to capture the infrared spectra. Using a Bruker Avance400/AvIII HD-300 (FT NMR) at Punjab University's Sophisticated Analytical Instrument Facility in Chandigarh, 1HNMR and 13CNMR spectra were acquired. Mass spectra were acquired using SAIF/CDRI-lucknow, Alliance Hplc-TQD mass spectrometer, and WATERS.

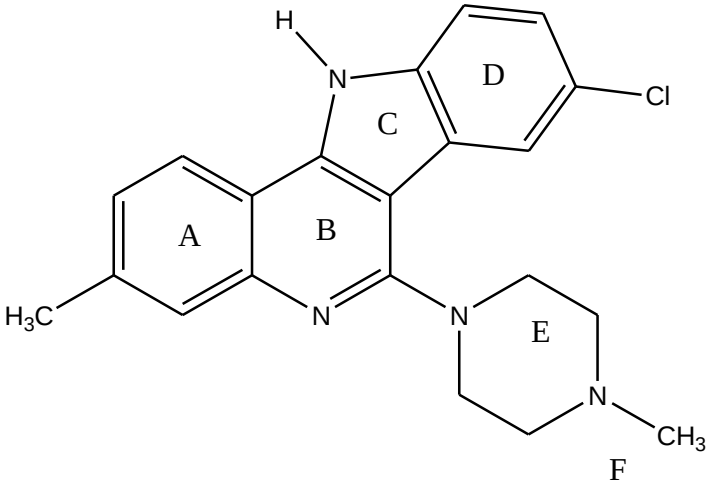
RESULT AND DISCUSSION:

DD-05: 3-(4-(3,8-dichloro-11*H*-indolo[3,2-*c*]quinoli-6-yl)morpholin-2-yl)propan-1-amine



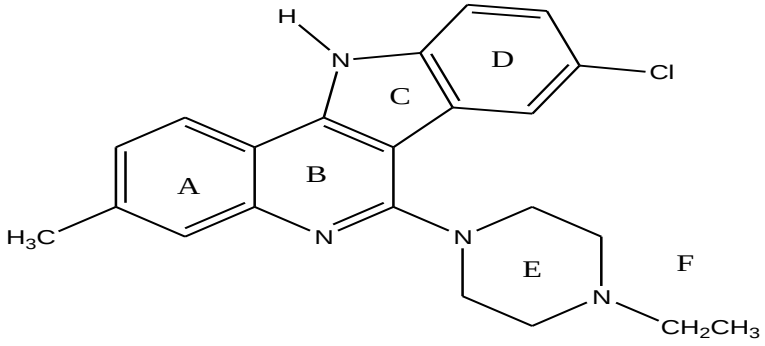
Yield	22.5%
M.P. (˚C)	70 ± 2
Rf value(cm^{-1})	0.6
FTIR(cm^{-1})	C-Cl stretch- 505.80, 602.23,N-H stretch- 3270.56, N-H bend-1559.34,O-H stretch 3600.85,Aromatic C sp^2-3006.82
MASS(m/z)	429(M^+)
^{1}HNMR(δppm)	A ring: 5.0-8.0 (1H,3CH), C ring: 9.93 (1H,1NH), D ring: 5.0-8.0 (1H,3CH), E ring: 2.05-4.5 (1H,3CH_2), F: 2.05-2.54 (1H,3CH_2), G: 2.05 (1H,1NH_2)
^{13}CNMR	A ring: 126.42-157.20, B ring: 111.81-169.69, C ring: 137.74, D ring: 110.68-111.81, E ring: 38.28-38.68, F (aliphatic chain): 23.70
Elemental analysis (%)	C: 52.361, H: 5.168 , N: 8.789

DD-12: 8-chloro-3-methyl-6-(4-methylpiperazin-1-yl)-11*H*-indolo[3,2-*c*]quinoline



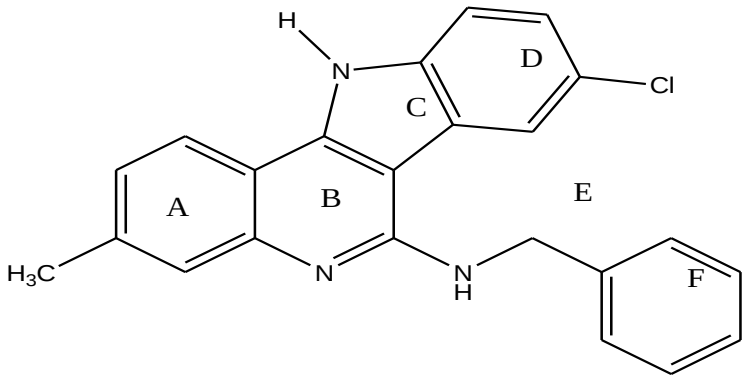
Yield	25.7%
M.P. (˚C)	90± 2
Rf value(cm^{-1})	0.8
FTIR(cm^{-1})	C-Cl stretch- 565.59, 709.76.N-H stretch- 3404.13,C(sp2)-H stretch- 3092.64
MASS(m/z)	294.6
^{1}HNMR(δppm)	A ring: 2.28-2.33 (3H,1CH_3), E ring: 2.05-3.73 (1H,4CH_2), F(CH_3): 2.05-2.54 (3H,1CH_3)
^{13}CNMR	A ring CH_3: 21.05, B ring: 168.39-172.08, E ring: 53.40-53.78, F (CH_3): 44.31-44.41
Elemental analysis (%)	C: 18.620 ,H: 6.245, N: 7.781

DD-13: 8-chloro-6-(4-ethylpiperazin-1-yl)-3-methyl-11*H*-indolo[3,2-*c*]quinoline



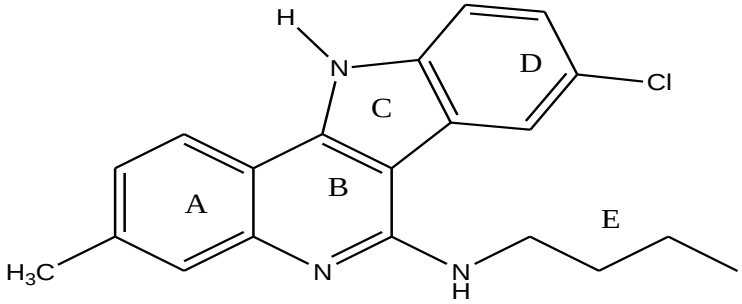
Yield	42.5%
M.P. (˚C)	95± 2
Rf value(cm^{-1})	0.8
FTIR(cm^{-1})	C-Cl stretch- 776.78,N-H bend- 1514.50, Alkanes-C-H stretch- 2816.36, 2880.49,CH3 bend- 1371.78
MASS(m/z)	391.1
^{1}HNMR(δppm)	A ring: 2.26-2.99 (1H,1CH_3), E ring: 2.5-4.5 (1H,4CH_2), F: 1.23-1.77 (1H,1C_2H_5)
^{13}CNMR	A ring CH_3: 22.56-29.05, B ring: 168.93, E ring: 38.12-40.07, F (CH_3CH_2): 13.47-13.62
Elemental analysis (%)	C: 21.161, H: 6.618, N: 6.258

DD-14: *N*-benzyl-8-chloro-3-methyl-11*H*-indolo[3,2-c]quinolin-6-amine



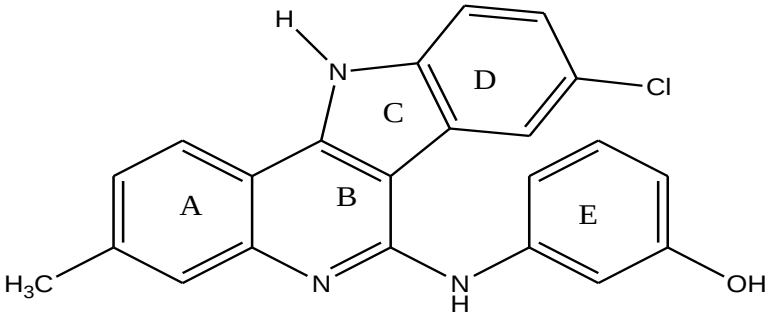
Yield	22%
M.P. (˚C)	88 ± 2
Rf value(cm^{-1})	0.5
FTIR(cm^{-1})	C-Cl stretch- 618.14,Aromatic C=C stretch- 1463.87,C(sp2)-H stretch- 3187.63,
MASS(m/z)	389.6(M+4)
^{1}HNMR(δppm)	A ring: 7.10-7.49(1H,3CH), 2.28-2.54(1H,1CH_3), C ring: 8.45(1H,1NH), D ring: 7.10-7.49 (1H,3CH) E: 3.98 (1H,NH), F: 4.22-4.68(1H,1CH_2), G ring: 7.10-7.49 (1H,5CH)
^{13}CNMR	A ring: 139.43-159.49, A ring CH_3: 17.52-22.47, B ring: 169.50, C ring: 133.95, D ring: 116.30-133.95, E: 40.17-42.21, F ring: 126.35-139.43
Elemental analysis (%)	C: 34.062,H: 4.743,N: 6.341

DD-15: *N*-butyl-8-chloro-3-methyl-11*H*-indolo[3,2-c]quinolin-6-amine



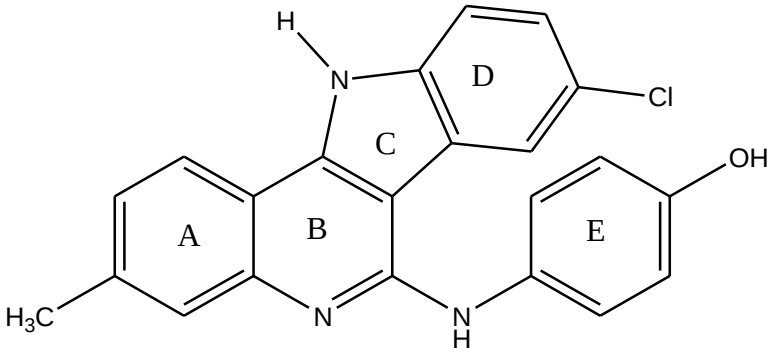
Yield	42%
M.P. (˚C)	55 ± 2
Rf value(cm^{-1})	0.6
FTIR(cm^{-1})	C-Cl stretch- 756.53,Alkane CH3 bend- 1443.62,N-H bend- 1575.25, 1598.88,N-H stretch- 3367.48, 3381.95,Asym.CH3 stretch- 2973.51
MASS(m/z)	299.6(M+4)
^{1}HNMR(δppm)	A ring: 2.05-2.74(1H,1CH_3), E: 4.67-4.72 (1H,1NH), F: 1.11-3.07 (1H,C_4H_9)
^{13}CNMR	A ring: 126.36-131.53, A ring CH_3: 21.01, B ring: 116.25-172.00, C ring: 131.53, D ring: 79.22-131.53, E (aliphatic chain): 10.20-51.07
Elemental analysis (%)	C: 25.934,H: 6.847,N: 8.588

DD-17: 3-(8-chloro-3-methyl-*11*H-indolo[3,2-c]quinolin-6-ylamino)phenol



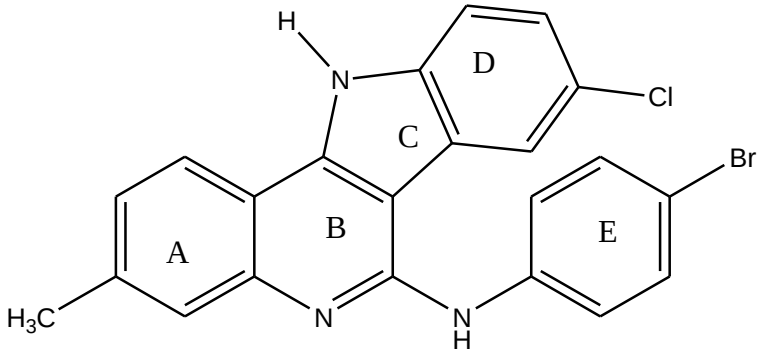
Yield	55%
M.P. (˚C)	99 ± 2
Rf value(cm^{-1})	0.9
FTIR(cm^{-1})	C-Cl stretch- 627.30,Alcohol C-H stretch- 1099.83,N-H bend- 1659.15,Aromatic C-H stretch- 3006.82,N-H stretch- 3338.07
MASS(m/z)	244.51
^{1}HNMR(δppm)	A ring: 7.01-7.43 (1H,3CH), 2.03-2.57(1H,1CH_3), C ring: 10.04 (1H,1NH), D ring: 7.01-7.43 (1H,3CH), -NH-: 4.68 (1H,1NH), E ring: 7.01-7.43 (1H,4CH), -OH-: 4.68 (1H,1OH)
^{13}CNMR	A ring: 126.33-153.61, A ring CH_3: 17.58-23.93, B ring: 110.16-172.11, C ring: 131.45-139.92, D ring: 111.12-131.45, E ring : 103.89-159.09
Elemental analysis (%)	C: 33.722,H: 4.975,N: 6.305

DD-18: 4-(8-chloro-3-methyl-*11*H-indolo[3,2-c]quinolin-6ylamino)phenol



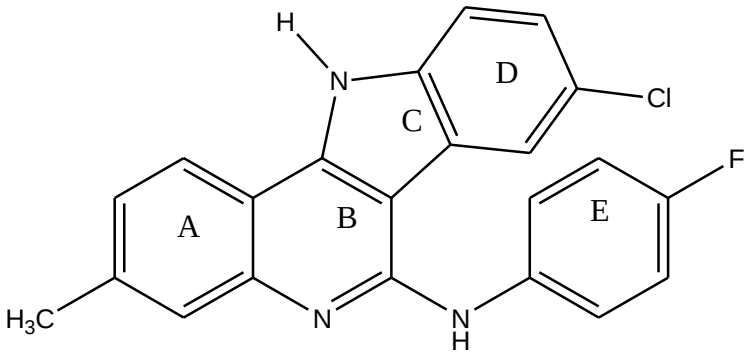
Yield	42.5%
M.P. (˚C)	85± 2
Rf value(cm^{-1})	0.85
FTIR(cm^{-1})	Aromatic C=C stretch- 1591.16,N-H bend- 1607.56,Alcohol O-H stretch- 3352.05,N-H stretch- 3395.45,Aromatic C(sp3)-H stretch- 3067.09
MASS(m/z)	318.512
^{1}HNMR(δppm)	A ring: 7.09-7.18(1H,3CH), 2.24-2.54(1H,1CH_3), D ring: 7.09-7.18 (1H,3CH), -NH-: 4.61 (1H,1NH), E ring: 6.43-7.18 (1H,4CH), -OH: 4.61 (1H,1OH)
^{13}CNMR	A ring: 124.14-143.56, A ring CH_3: 14.78-17.49, B ring: 99.49-159.35, C ring: 131.19, D ring: 115.64-131.19, E ring: 99.49-159.35
Elemental analysis (%)	C: 40.375,H: 4.922,N: 8.340

DD-19: *N*-(4-bromophenyl)-8-chloro-3-methyl-11H-indolo[3,2-*c*]quinolin-6-amine



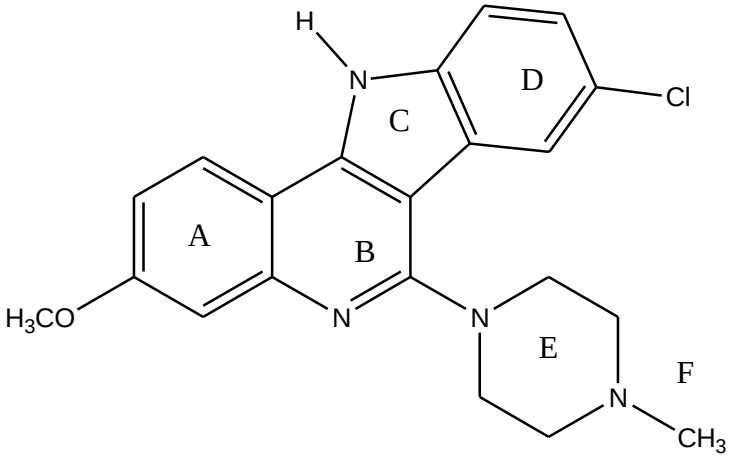
Yield	60%
M.P. (˚C)	140± 2
Rf value(cm^{-1})	0.45
FTIR(cm^{-1})	C-Cl stretch- 673.59, Asymmetric CH3 stretch- 2988.49,N-H stretch- 3391.59.
MASS(m/z)	293.53
^{1}HNMR(δppm)	A ring: 7.41-7.58 (1H,3CH) ,2.06(1H,1CH_3), C ring: 10.05(1H,1NH), D ring: 7.41-7.58(1H,3CH), -NH-: 3.45 (1H,1NH), E ring: 7.41-7.58(1H,4CH)
^{13}CNMR	A ring: 120.82-138.59, A ring CH_3: 23.93, B ring: 114.48-168.35, C ring: 138.35, D ring: 114.48-138.59, E ring: 114.48-138.59
Elemental analysis (%)	C: 41.755,H: 3.373,N: 6.586

DD-21: 8-chloro-*N*-(4-fluorophenyl)-3-methyl-11H-indolo[3,2-c]quinolin-6-amine



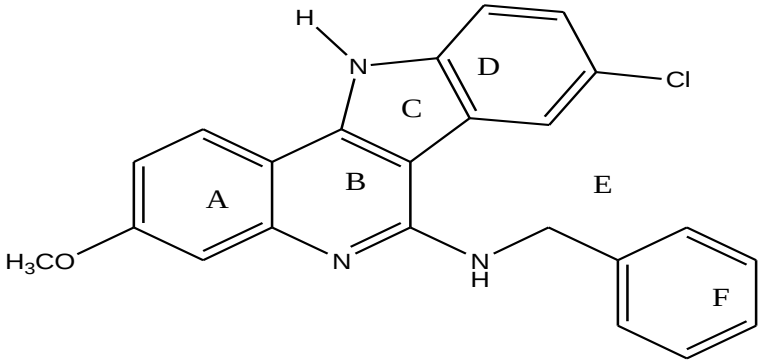
Yield	33%
M.P. (˚C)	140± 2
Rf value(cm^{-1})	0.65
FTIR(cm^{-1})	C-Cl stretch- 740.13,C-F stretch- 1276.31,N-H stretch- 3381.46
MASS(m/z)	294.5
^{1}HNMR(δppm)	A ring: 7.04-7.62(1H,3CH), 2.05(1H,1CH_3), C ring: 10.04 (1H,1NH), D ring: 7.04-7.62 (1H,3CH), -NH-: 3.80 (1H,1NH), E ring: 7.04-7.62(1H,4CH)
^{13}CNMR	A ring: 120.71-156.61, A ring CH_3: 23.71, B ring: 114.74-168.12, C ring: 135.54-135.57, D ring: 114.74-135.57, E ring: 114.74-159.00
Elemental analysis (%)	C: 36.282,H: 4.129,N: 5.769

DD-23: 8-chloro-3-methoxy-6-(4-methylpiperazin-1-yl)-*11*H-indolo[3,2-*c*]quinoline



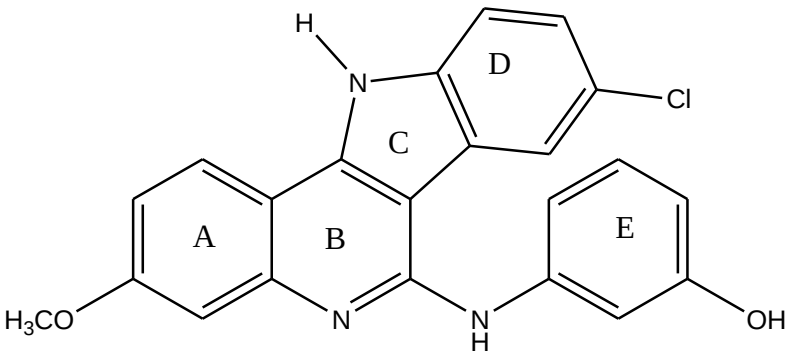
Yield	63%
M.P. (˚C)	75± 2
Rf value(cm^{-1})	0.52
FTIR(cm^{-1})	C-Cl stretch- 783.05,C-N stretch- 1125.39, 1145.64(alkyl),C-O-C stretch- 1282.09,N-H bend- 1631.67
MASS(m/z)	143.5(M+)
^{1}HNMR(δppm)	A ring: 7.08-7.16(1H,3CH), 4.23-4.68(1H,1CH_3O), D ring: 7.08-7.16 (1H,3CH), E ring: 2.02-3.73 (1H,4CH_2), F: 2.74(1H,1CH_3)
^{13}CNMR	A ring: 51.98-131.39, A ring CH_3O: 169.01,B ring: 116.17-169.01,C ring: 131.39, D ring: 116.17-131.39, E ring: 49.28-52.19, F (CH_3): 41.34-42.56
Elemental analysis (%)	C: 21.281,H: 6.403,N: 8.795

DD-25: *N*-benzyl-8-chloro-3-methoxy-11*H*-indolo[3,2-*c*]quinolin-6-amine



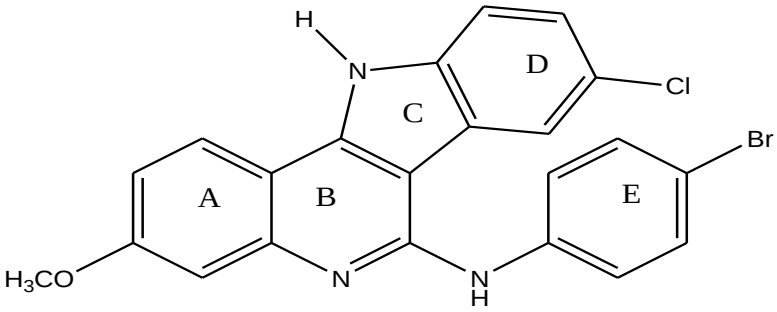
Yield	28%
M.P. (˚C)	190 ± 2
Rf value(cm^{-1})	0.45
FTIR(cm^{-1})	Aromatic C-H bond (mono)- 689.99,C-Cl stretch- 766.17,C-O-C stretch- 1282.13,Aromatic C=C stretch- 1532.82,Aromatic C-H stretch- 3002
MASS(m/z)	262.59(M+)
^{1}HNMR(δppm)	A ring: 7.33-7.52(1H,3CH) ,3.71-3.99 (1H,1CH_3O), C ring: 8.29 (1H,1NH), D ring: 7.33-7.52(1H,3CH), -NH-: 3.99 (1H,1NH), E(-CH_2): 3.99 (1H,CH_2), F ring: 7.33-7.52(1H,5CH)
^{13}CNMR	A ring: 42.25-134.07, B ring: 128.23-134.07, C ring: 134.07, D ring: 132.23-134.07, E ring: 42.25, F ring: 128.23-134.07
Elemental analysis (%)	C: 36.456,H: 5.246,N: 6.319

DD-28: 3-(8-chloro-3-methoxy-*11*H-indolo[3,2-*c*]quinolin-6-ylamino)phenol



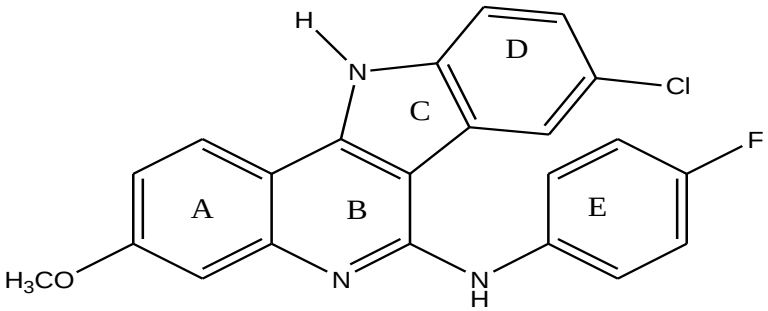
Yield	35.5%
M.P. (˚C)	85± 2
Rf value(cm^{-1})	0.3
FTIR(cm^{-1})	C=C stretch- 1577.66, O-H stretch- 3367.96,N-H stretch- 3488.02.
MASS(m/z)	252.62(M+4)
^{1}HNMR(δppm)	A ring: 7.15-7.17 (1H,3CH) , D ring: 7.15-7.17(1H,3CH), -NH-: 6.73 (1H,1NH), E ring: 7.01-7.43 (1H,4CH) , -OH: 6.76 (1H,1OH)
^{13}CNMR	A ring: 39.27-133.75, A ring CH_3O: 158.04, B ring: 109.41-158.04, C ring: 133.75, D ring: 112.84-133.75, E ring: 109.41-158.04
Elemental analysis (%)	C: 24.071,H: 4.490,N: 5.343

DD-30: N-(4-bromophenyl)-8-chloro-3-methoxy-11*H*-indolo[3,2-*c*]quinolin-6-amine



Yield	32.5%
M.P. (˚C)	120 ± 2
Rf value(cm^{-1})	0.77
FTIR(cm^{-1})	C-O-C stretch- 1244.97,Aryl C-H stretch- 1364.06,N-H bend- 1501.48,Aromatic C(sp2)-H- stretch- 3091.2
MASS(m/z)	339.51(M+)
^{1}HNMR(δppm)	A ring: 7.40-7.58 (1H,3CH), 3.38 (1H,1CH_3O), C ring: 10.16(1H,1NH), D ring: 7.40-7.58(1H,3CH), -NH-: 3.38 (1H,1NH), E ring: 7.40-7.58(1H,4CH)
^{13}CNMR	A ring: 40.15-138.66, A ring CH_3O: 168.38, B ring: 114.40-168.38, C ring: 138.66, D ring: 114.40-138.66 E ring: 114.40-138.66
Elemental analysis (%)	C: 13.596,H: 2.452,N: 2.262

DD-32: 8-chloro-N(4-flurophenyl)-3-methoxy-11H-indolo[3,2-c]quinolin-6-amine



Yield	45%
M.P. (˚C)	65± 2
Rf value(cm^{-1})	0.6
FTIR(cm^{-1})	C-Cl stretch- 684.20,C-F stretch- 1133.10,Alkyl C-N stretch- 1133.10,C-O-C

	stretch- 1048.24,N-H stretch- 3370.86
MASS(m/z)	354.60(M+)
^{1}HNMR(δppm)	A ring: 7.05-7.62(1H,3CH), 3.61(3H,1CH_3O), C ring: 9.96 (1H,1NH), D ring: 7.05-7.62 (1H,3CH), E ring: 7.04-7.62(1H,4CH),-NH-:3.61 (1H,1NH)
^{13}CNMR	A ring: 40.12-156.60, A ring CH_3O: 158.98, B ring: 114.87-168.04, C ring: 135.61-135.63, D ring: 114.87-135.61, E ring: 114.87-156.60
Elemental analysis (%)	C: 52.325,H: 4.618,N: 8.617

ANTIMALARIAL SCREENING:

All the synthesized compounds were screened for antimalarial activity in the Microcare laboratory & TRC, Surat, Gujarat. The in vitro antimalarial assay, which was performed with minor modifications to the microassay protocol of Rieckmann and colleagues, was carried out using a 96-well microtitre plate. The RPMI 1640 medium supplemented with 10% heat-inactivated human serum, 1% D-glucose, 0.23% sodium bicarbonate, and 25 mM HEPES was used to maintain the P. falciparum strain cells. The asynchronous P. falciparum parasites were synchronized upon treatment with 5% D-sorbitol, resulting in the production of solely the ring stage parasitized cells. To conduct the experiment, 200 µ l of medium RPMI-1640 was utilized, and the initial ring stage parasitaemia of 0.8 to 1.5% at 3% haematocrit was determined by Jaswant Singh Bhattacharya (JSB) staining. After that, 50% RBCs (O+) were used to maintain the parasitaemia consistently. Each test sample was generated as a stock solution containing 5 mg/ml in DMSO, and culture medium was used to prepare the subsequent dilutions. The diluted samples in a 20 µ l volume were administered to the test wells in order to achieve final concentrations (at fivefold dilutions) ranging between 0.4 µ g/ml and 100 µ g/ml in duplicate wells containing parasitized cell preparation. The culture plates were incubated at 37°C and stored in a candle jar. After an overnight incubation, thin blood smears from every well were prepared and stained with JSB stain. Under a microscope, the transformation of parasites in the ring stage into trophozoites and schizonts in the presence of different test agent concentrations was observed on the slides. The test concentration that stopped all schizont growth was called the minimal inhibitory concentration (MIC). The usual drug that we used was chloroquine. Minimum inhibitory concentration (MIC) values were used to express the mean number of rings, trophozoites, and schizonts per 100 parasites from triplicate wells after incubation for 38 hours, as well as the percentage of maturation inhibition relative to the control group.

Table 2: Minimum inhibitory concentration of compounds and standards

S.No.	Compound ID	IC_{50} (µg/ml)
1	DD-05	0.86
2	DD-12	0.73
3	DD-13	1.34
4	DD-14	1.27
5	DD-15	1.13
6	DD-17	0.56
7	DD-18	0.77
8	DD-19	1.36
9	DD-21	1.22
10	DD-23	0.86
11	DD-25	0.94
12	DD-28	1.26
13	DD-30	0.54
14	DD-32	0.86
15	Chloroquine	0.020
16	Quinine	0.268

CONCLUSION:

Fourteen compounds have been selected for synthesis and further antimalarial evaluation. Synthesized Indolo[3,2-c] quinolone analogues have showed improved antimalarial activities. This study has shown that some derivatives of Indolo[3,2-c] quinolone, Particularly DD-30 is promising leads in search for new antimalarial agents. Inspection of the data in table allows the following conclusions to be drawn: First, the compounds containing side chain with more aliphatic carbon atoms (e.g., DD-13, DD-14, DD-15)generally present less better antimalarial activity than those with less carbon atoms (DD-17, DD-30 and DD-12). Second, Aromatic basic amine side chain (DD-30) increases the activity then aliphatic amine side (DD-15) chain. Neither, secondary or tertiary ring nitrogen affects antimalarial activity as shown by the IC_{50} values nor cyclic or non-cyclic nitrogen affect the activity.

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