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One Step Conversion of 1-Substituted 3,4-Dihydroisoquinolines to Oxazino [2,3-a] Isoquinolines using DCC

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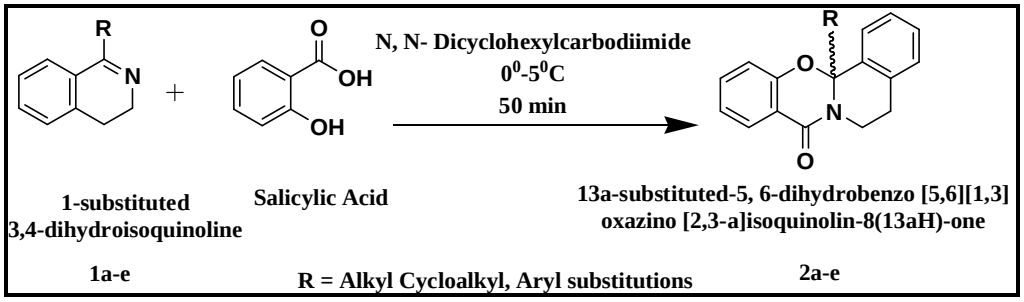
ABSTRACT

Molecular docking study reveals that oxazino [2,3-a] isoquinolines have potential to show activity against dengue. This encourages us for synthesize of tetracyclic oxazino [2,3-a] isoquinolines derivatives. In present work, we have synthesized titled compound using N,N-dicylohexylcarbodiimide (DCC) at 0°-5°C using tetrahydrofuran as solvent in good yield. All synthesized compounds were characterized by FT-IR, NMR and Mass Spectroscopy.

Graphical Abstract



Synthesis of Oxazino [2,3-a] isoquinoline

Keywords: Dengue, Schiff base, DCC, Tetracyclic compounds.

INTRODUCTION

Dengue is mosquito borne viral disease [1]. Currently there is no medicine or therapy available to combat dengue. Tetracyclic compounds like doxorubicin are known to exhibit antidengue activity [2]. In this regard, we have designed several small molecules and docked them against dengue to find their

effectiveness in *silico* using Glide software [3-4]. Recently we have reported oxazino [2,3-a] isoquinolines have potential to show antidengue activity in silico [5].

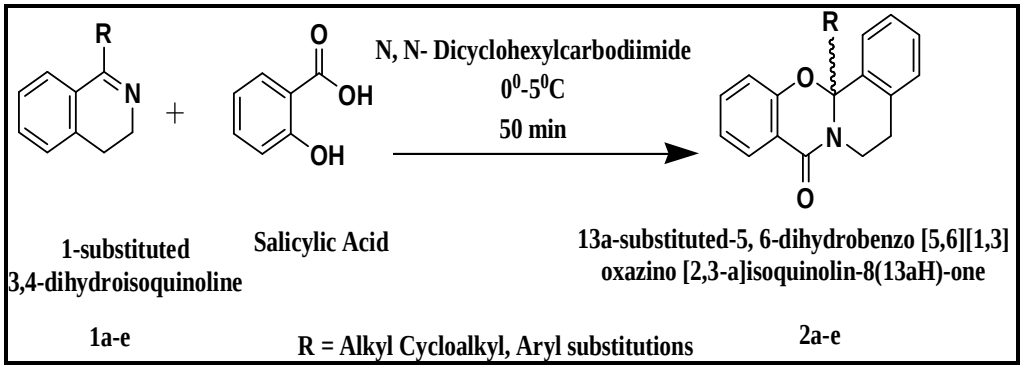
The synthesis of structurally diverse compounds in one pot is key step in synthetic organic chemistry [6]. Herein we report for the synthesis of structurally diverse oxazino [2,3-a] isoquinolines in one step.

Retro synthetic approach suggests combination of 1-substituted 3,4-dihydroisoquinoline and salicylic acid gives oxazino[2,3-a] isoquinolines. Upon examining 1-substituted 3,4-dihydroiso- quinoline is cyclic Schiff base, whose cyclization gives desired product as shown in scheme.

MATERIALS AND METHODS

All Chemicals and reagents were purchased from SD-Fine Chemicals (INDIA) and used without any further purification. Silica gel used for TLC was purchased from Fischer Scientific (Silica gel for TLC).Silica mesh 60-120 were used for column chromatography.The melting points were determined using capillary tube and are uncorrected. Infrared spectras were recorded using Frontier Perkin Elmer IR spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker AVANCE spectrometer (Bruker BioSpin AG, Fällanden, Switzerland) using $CDCl_3$ as solvent and TMS as an internal standard. Chemical shifts (δ) were expressed in terms of ppm. Mass spectra were recorded on a GC-MSQP-1000 spectrometer.

The 1-substituted 3,4-isoquinolines can be synthesized by reported methods [7-9]. The cyclization of Schiff base using thioglycolic acid is reported [10]. One pot synthesis of Oxazino [2,3-a] isoquinolines were achieved successfully using DCC in THF at 0°-5°C in 50 min. The synthesis of Oxazino [2,3-a] isoquinolines is as shown in scheme.



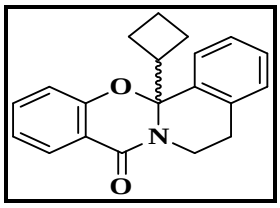
Schem 1 Synthesis of Oxazino [2,3-a] isoquinoline

General Procedure: 1-Substituted 3, 4-dihydroisoquinoline (0.01 mol) **(1a-1e)**, salicylic acid (0.01 mol) were mixed with *N, N*-dicylohexylcarbodiimide (DCC) (1.0 g). The reaction mixture was stirred in tetrahydrofuran (THF) for 50 min at 0°-5°C. The completion of reaction was monitored by TLC. After the completion of reaction, reaction mixture was filtered. Filtrate was extracted with 3x15mL of ethyl acetate. Organic layer was washed with citric acid solution. Ethyl acetate was recovered under reduced pressure. The crude product obtained was purified by column chromatography over silica gel (Petroleum ether: Chloroform 70:30) to afford colourless solid of Oxazino [2,3-a] isoquinolines(**2a-e**). The spectral characterization of newly synthesized compounds is presented below.

RESULTS AND DISCUSSION

Synthesized compounds of oxazino [2,3-a] isoquinolines:

13a-cyclobutyl-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one(2a): White solid. Yield: 70%., M.P:102°C.IR (cm^{-1}): 2937.80, 1647.96, 1465.78, 757.53, ^{1}HNMR ($CDCl_3$): 7.92-7.95, (m,1H,aromatic), 7.64-7.67, (m,1H,aromatic),7.30-7.45,(m,2H, aromatic),7.17-7.20, (m,2H, aromatic),6.98-7.08,(m,2H,aromatic), 1.49-1.56, (m,2H, aliphatic), 1.62-1.74, (m, 4H,aliphatic), 1.85-1.92,(m,1H,aliphatic),2.81-2.86,(dd,1H ,aliphatic, *J*=15Hz), 3.71-3.73,(m,2H,aliphatic), 4.44-4.48, (d, 1H,aliphatic,*J*=12Hz). ^{13}C NMR ($CDCl_3$):17.23, 24.89, 25.31, 27.84, 37.93, 46.09, 91.06, 116.29, 118.00, 121.88, 126.17, 126.53, 127.82, 128.41, 128.42, 134.12, 134.48, 135.09, 155.45, 161.33 (Fig 1-4).



Structure :2a

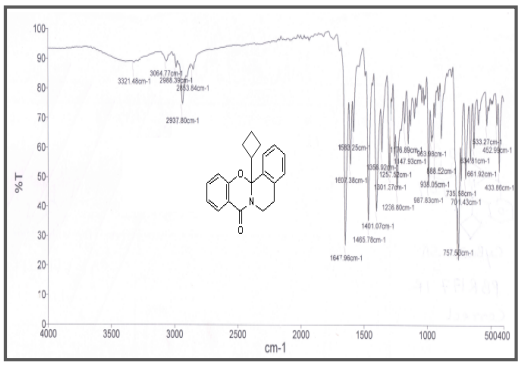


Figure 1. FT IR Spectra of 13a-cyclobutyl-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one

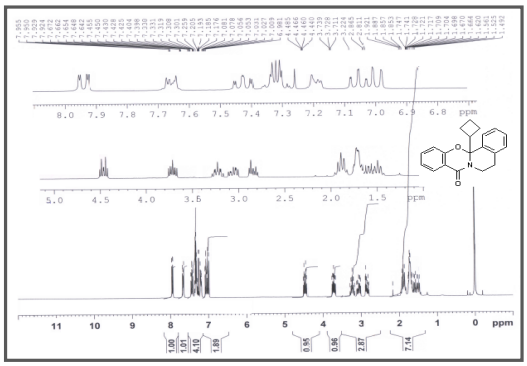


Figure 2.^{1}H NMRSpectra of 13a-cyclobutyl-5,6 dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one

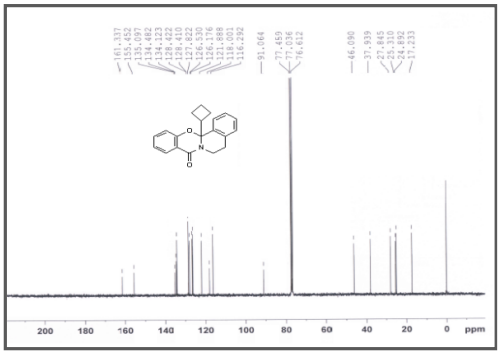


Figure 3.^{13}C NMR Spectra of 13a-cyclobutyl-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one

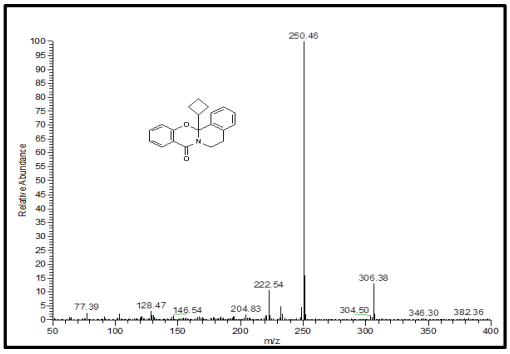
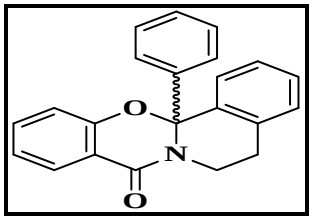


Figure 4. Mass Spectra of 13a-cyclobutyl-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one

13a-phenyl-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one (2b): White solid. Yield: 73%., M.P:87°C.IR (cm^{-1}): 2953.98, 1650.69, 1228.36, 757.88. ^{1}HNMR ($CDCl_3$): 7.99-8.02, (d,1H,aromatic, *J*=9Hz),7.85-7.88, (d,1H,aromatic,*J*=9Hz), 7.27-7.42,(m,5H,aromatic),7.15-7.21, (m, 4H,aromatic),6.94-7.01,(m,2H,aromatic), 2.85-2.90, (ddd,1H,aliphatic, J=15Hz),2.95-3.02,(dd, 1H, aliphatic J=21Hz), 3.92-4.01,(m,1H, aliphatic), 4.37-4.43,(m,1H,aliphatic).^{13}C NMR ($CDCl_3$): 27.50, 40.22, 90.59, 116.99, 119.19, 122.34, 125.12, 126.94, 127.16, 127.86, 127.96, 128.20, 128.38, 128.59, 134.08, 134.49, 137.10, 142.17, 154.77, 162.20 (Fig. 5-8).



Structure:(2b)

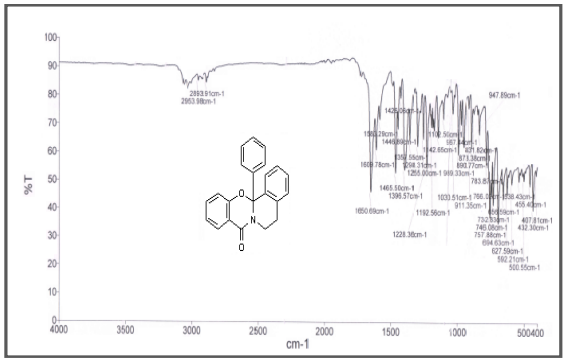


Figure 5. FT-IR Spectra of 13a-phenyl-5,6-dihydrobenzo [5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

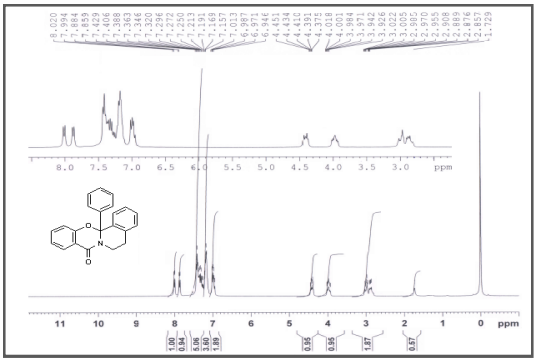


Figure 6. ^{1}H NMRSpectra of 13a-phenyl-5,6-dihydrobenzo [5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

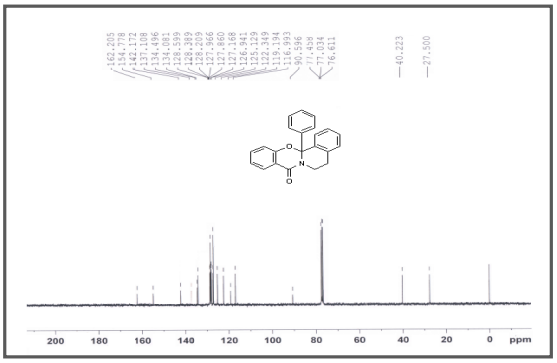


Figure 7. ^{13}C NMR Spectra of 13a-phenyl-5,6-dihydrobenzo [5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

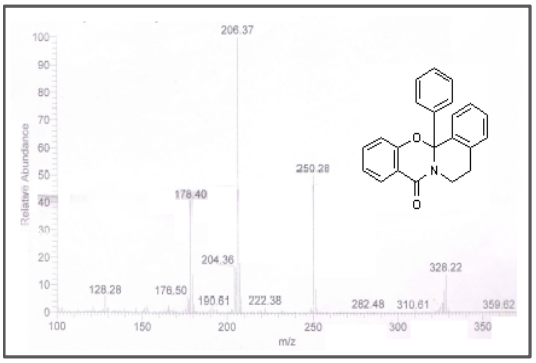
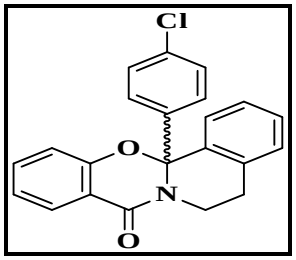


Figure 8. Mass Spectra of 13a-phenyl-5,6-dihydrobenzo [5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

13a-(4-chlorophenyl)-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one(2c): White solid. Yield: 75%, M.P:92°C.IR (cm^{-1}): 2934.77, 1656.89, 1384.85, 747.78. ^{1}HNMR ($CDCl_3$): 7.96-7.98, (d,1H, aromatic *J*=6Hz),7.86-7.89, (d,1H,aromatic, *J*=9Hz),7.40-7.42,(d,2H, aromatic, *J*=6Hz),7.29-7.37, (m, 4H,aromatic), 6.98-7.19, (m,4H,aromatic), 2.78-2.88, (ddd,1H, aliphatic,

J=30Hz)2.96-3.05,(ddd, 1H,aliphatic, *J*=27Hz), 3.89-3.98, (ddd,1H, aliphatic, *J*=27Hz), 4.37-4.45, (ddd,1H,aliphatic, *J*=24Hz).^{13}C NMR ($CDCl_3$):27.49, 40.18, 90.12, 116.98, 119.11, 122.61, 124.94, 127.32, 127.96, 128.07, 128.31, 128.47, 128.82, 134.27, 134.44, 136.67, 140.90, 154.56, 162.05 (Fig. 9-12)



Structure:(2c)

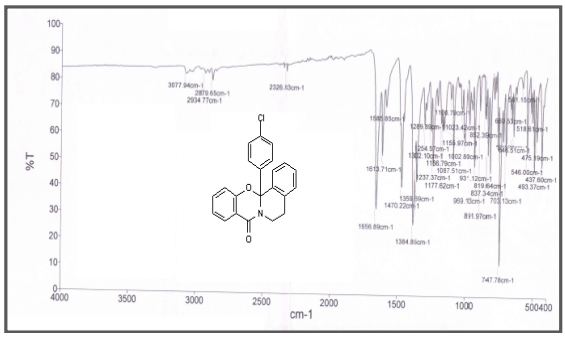


Figure 9. FT IR Spectra of 13a-(4-chlorophenyl)-5, 6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

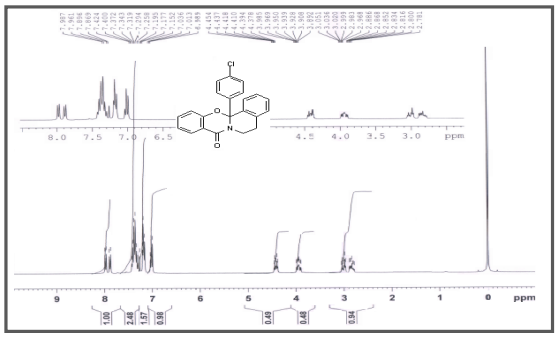


Figure10.^{1}H NMRSpectra of 13a-(4-chlorophenyl)-5, 6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

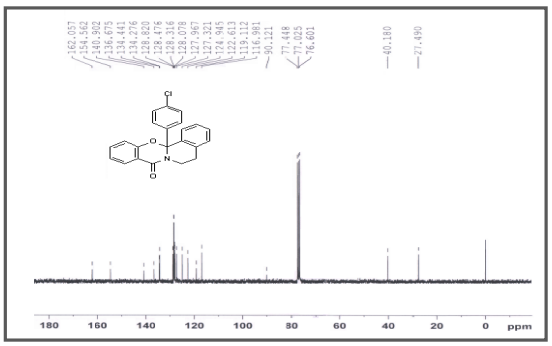


Figure 11.^{13}C NMR Spectra of 13a-(4-chlorophenyl)-5, 6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

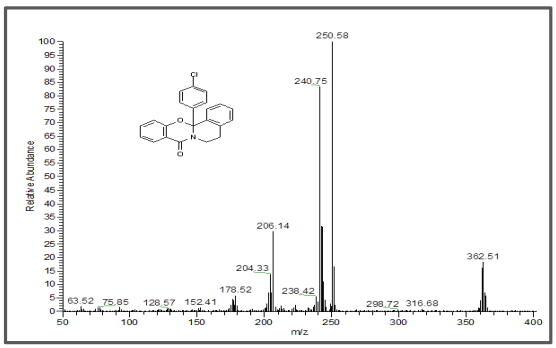
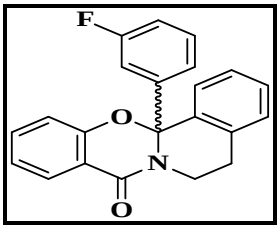


Figure 12. Mass Spectra of 13a-(4-chlorophenyl)-5, 6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

13a-(3-fluorophenyl)-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one(2d):
White solid. Yield: 69%., M.P:89°C. IR (cm^{-1}): 2980.81, 1655.37, 1232.37, 760.95. ^{1}HNMR ($CDCl_3$): 7.97-7.99, (d,1H,aromatic, *J*=6Hz),7.87-7.89, (d,1H, aromatic, *J*=6Hz),7.40-7.42,(d,1H, aromatic, *J*=6Hz), 7.29-7.38, (m,4H,aromatic), 7.19-7.22, (m,1H,aromatic), 7.11-7.17, (m, 2H, aromatic),6.98-7.03,(m,1H, aromatic), 6.84-6.87, (m,1H,aromatic), 2.87-2.92, (ddd,1H, aliphatic, *J*=15Hz), 2.97-3.00,(ddd, 1H,aliphatic, *J*=9Hz), 3.94-3.98, (ddd,1H, aliphatic, *J*=12Hz), 4.40-4.44,(ddd,1H,aliphatic,

J=12Hz). ^{13}C NMR ($CDCl_3$):27.48, 40.14, 76.61, 77.03, 77.45, 89.96, 89.98, 114.14, 114.44, 115.43, 115.71, 116.99, 119.07, 122.55, 122.60, 125.05, 127.35, 127.96, 128.06, 128.85, 129.66, 129.77, 134.28, 134.45, 136.50, 145.00, 145.08, 154.56, 160.98, 162.02, 164.25 (fig. 13-16).



Structure: (2d)

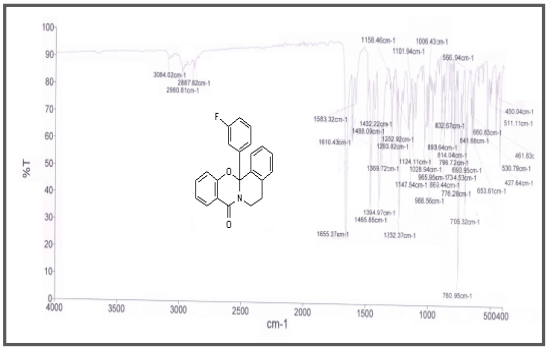


Figure 13. FT IR Spectra of 13a-(3-fluorophenyl)-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

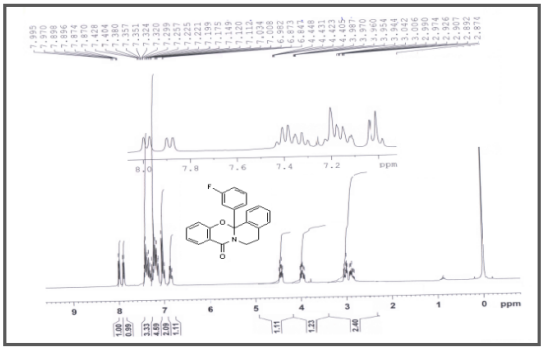


Figure 14. ^{1}H NMRSpectra of 13a-(3-fluorophenyl)-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

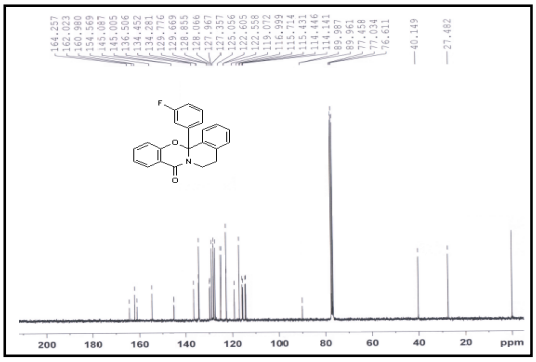


Figure 15. ^{13}C NMR Spectra of 13a-(3-fluorophenyl)-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

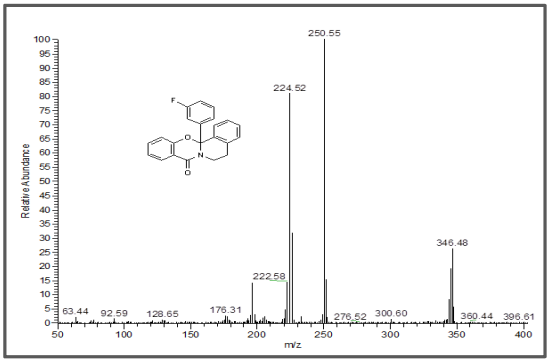
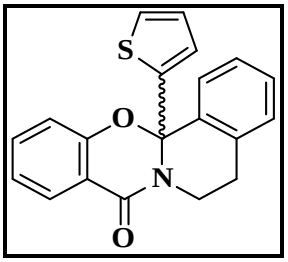


Figure 16. MassSpectra of 13a-(3-fluorophenyl)-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

13a-(thiophen-2-yl)-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one(2e): White solid .Yield: 73%. M.P: 71°C. IR (cm^{-1}):2940.98, 1648.25, 1463.76, 1389.56, 1226.82, 757.99. ^{1}H NMR ($CDCl_3$):2.89-2.96 (m, 1H, aliphatic), 3.02-3.11(m, 1H, aliphatic), 4.00-4.08 (m, 1H, aliphatic), 4.20-4.29 (m, 1H, aliphatic), 6.72-6.74 (m, 1H, aromatic), 6.91-6.92 (m, 1H, aromatic), 7.01-7.19 (m, 4H, aromatic), 7.31-7.44 (m, 4H, aromatic), 7.92-8.00 (m, 1H, aromatic). ^{13}C NMR ($CDCl_3$):27.61, 38.83, 88.88, 117.15, 118.60, 122.61, 125.58, 125.91, 127.05, 127.17, 127.50, 127.87, 128.21, 128.89, 134.24, 136.74, 146.27, 154.54, 161.60(Fig. 17-20)



Structure 5 (2e)

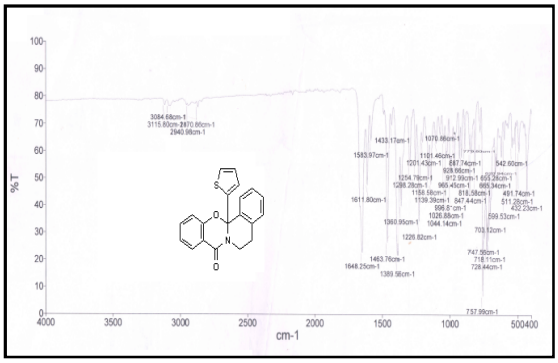


Figure17. FT IR Spectra of 13a-(thiophen-2-yl)-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

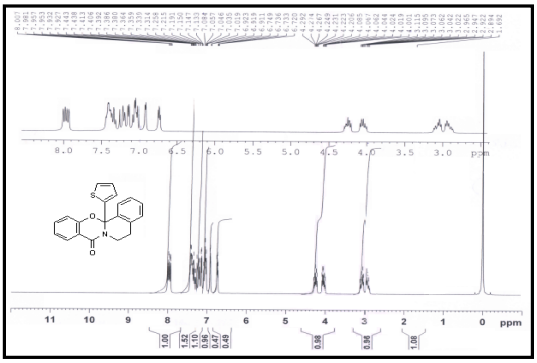


Figure18. [1]H NMR Spectra of 13a-(thiophen-2-yl)-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

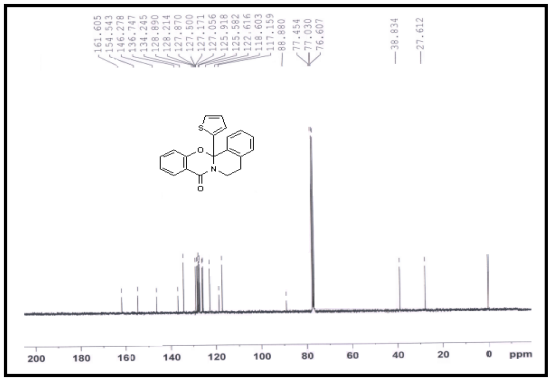


Figure19. [13]C NMR Spectra of 13a-(thiophen-2-yl)-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

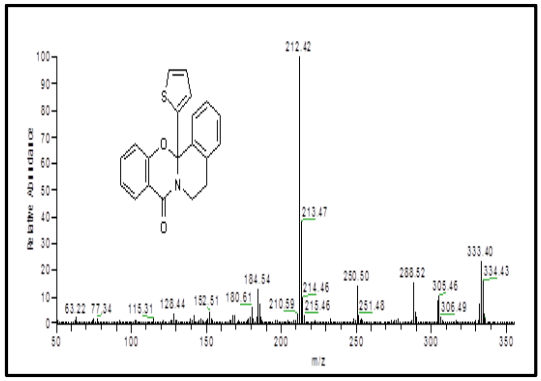


Figure 20. Mass Spectra of 13a-(thiophen-2-yl)-5,6-dihydrobenzo[5,6][1,3]oxazino[2,3-a]isoquinolin-8(13aH)-one.

APPLICATION

This method gives easy and efficient way to cyclize 3,4-dihydroisoquinoline using DCC.

CONCLUSION

Developed successfully the synthesis of structurally diverse tetracyclic oxazino[2,3-a]isoquinolines.

ACKNOWLEDGMENT

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