

SYNTHESIS OF QUINOLINE DERIVATIVES CATALYSED BY YTTERBIUM TRIFLATE (Yb(OTf)₃) AND THEIR ANTI- MICROBIAL ACTIVITIES

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Abstract

Phenanthrene based quinoline derivatives were synthesized using Yb(OTf)₃ catalysed Imino Diels -Alder reactions. The products were tested for anti-microbial activities also. The studies showed that the molecules possess moderate to good antibacterial activity for both gram positive and gram negative bacteria.

Key words: Quinoline derivatives, Yb(OTf)₃, Imino Diels -Alder reaction, Anti-bacterial activity

I. INTRODUCTION

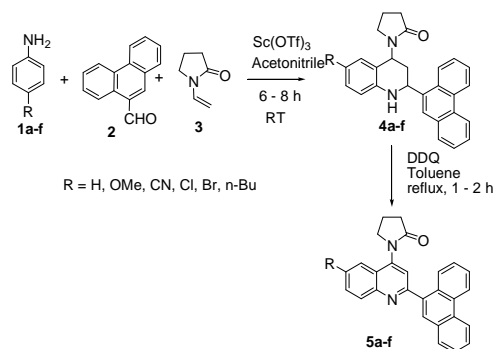
Nitrogen containing heterocycles are indispensable structural units for medicinal chemists. Among the various heterocyclic compounds, quinolines and tetrahydro quinolines^{1,2} occur predominately in nature ascribable to their stability and ease of generation. They exhibit pronounced biological activities such as antioxidant³, antiproliferation⁴, antiinflammation⁵, anticancer activities⁶, etc. Our group initiated a research program on the synthesis of a series of novel quinoline containing heterocycles employing Aza-Diels Alder reaction and screened for antimicrobial activities. Herein we report simple quinoline based organic molecules that can be easily synthesized and used for the anti microbial activity.

The Diels–Alder reaction^{7,8} is a powerful tool in organic synthesis and in the chemical industry. For many years, Diels–Alder reactions have attracted the interest of both experimental and theoretical chemists.⁹⁻¹² The inverse electron-demand Aza-Diels_Alder reaction (IEDDA reaction) is an important acid-catalyzed cycloaddition allowing access to 2,3,4-trisubstituted tetrahydroquinolines from N-aryl imines and electron-rich alkenes.

Indeed quinoline derivatives are an active class of antibacterial agents. Recently, a broad structure-based bio-evaluation of several new chemical entities against various pathogens including *M. tuberculosis* led to the exploration of ring-substituted quinolines as

a new structural class of anti-TB agents. The ring-substituted quinolines inhibit both drug-sensitive and drug-resistant *M. tuberculosis in vitro*.

A simple and convenient method has been adopted for the synthesis of the desired quinoline derivatives. (Scheme 1) Mild conditions using Yb(OTf)₃ catalysed imino Diels-Alder reaction were employed using aniline, phenanthrene aldehydes and vinyl pyrrolidone in acetonitrile at room temperature. Our anti microbial studies using *V. cholera*, *B. subtilis*, *K. pneumonia*, *S. aureus* and *E. coli* species show that almost all of our quinoline derivatives active against both gram positive and gram negative bacteria. This study may be extended to many other strains as well.



Scheme 1

In view of the emerging importance of the use of Lewis acids as efficient catalysts in organic synthesis, we wish to disclose a simple and efficient procedure for the synthesis of quinoline derivatives using

Yb(OTf)₃. Accordingly, treatment of aniline **1a** with phenanthrene-9-carbaldehyde **2** and vinyl **Table 1**: Yb(OTf)₃ mediated one-pot multicomponent synthesis of quinoline derivatives pyrrolidone **3** in the presence of Yb(OTf)₃ in acetonitrile at room temperature resulted in the formation of tetrahydroquinoline derivatives. (**Scheme 1, Table 1, entry 2**) The catalyst offers several advantages including mild reaction conditions, cleaner reactions, shorter reaction times, high yield of the products as well as simple experimental and isolation procedures, which make it

useful for the synthesis of quinoline derivatives. The synthesized tetrahydroquinoline derivatives were oxidized to quinolone derivatives by treatment with DDQ. The structures of tetrahydroquinoline and quinoline derivatives **5a-f** were confirmed by IR, ¹H and ¹³C NMR spectroscopy, mass spectrometry and elemental analysis. The scope of this procedure is illustrated with respect to various substituted anilines **1b-h** for the condensation with phenanthrene-9-carbaldehyde **2** and vinyl pyrrolidone **3**, and the results are summarized in **Table 1**

Table 1 Synthesis of Quinoline derivatives

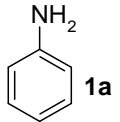
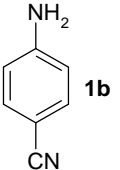
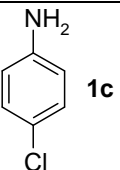
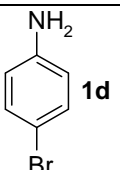
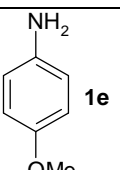
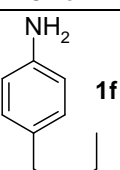
Entry	Aniline	Tetrahydroquinoline	Quinoline	Time (h)	Yield (%) ^a
1	 1a	4a	5a	6	93
2	 1b	4b	5b	6	90
3	 1c	4c	5c	6	86
4	 1d	4d	5d	6	85
5	 1e	4e	5e	6	91
6	 1f	4f	5f	8	90

Table 2: Antibacterial activity with respect to 250 µg of the respective compounds

Compound	Bacterial species				
	<i>B. subtilus</i>	<i>V. cholera</i>	<i>K. pneumonia</i>	<i>S. aureus</i>	<i>E. coli</i>
4a	+	-	-	+	-
5a	+	+	+	-	-
4b	-	-	-	+	-
5b	+	+	+	+	+
4c	-	-	-	-	+
5c	+	+	+	-	+
4d	-	-	-	-	+
5d	+	+	+	-	+
4e	+	-	+	-	-
5e	+	+	+	-	+
4f	-	+	-	-	+
5f	+	+	+	-	+
Ciprofloxacin	+	+	+	+	+

(+) Strongly active, (-) Inactive

All the newly synthesized compounds were screened for their antibacterial activities. The *in vitro* antibacterial activities of synthesized compounds were tested against five human bacterial pathogens such as *V. cholera*, *B. subtilus*, *K. pneumonia*, *S. aureus* and *E. coli*. The antibacterial activities were determined using microdilution broth assay method with modifications reported by Sarker *et al* using resazurin as an indicator. In this method instead of resazurin dye, 2,3-bis[2-methoxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxanilide inner salt (XTT) is used as the indicator for the growth of bacteria or inhibition of bacterial growth. Compound **5b** shows minimum inhibitory concentration (MIC) of 250 µg for *B. subtilus*, *K. pneumonia*, *E. coli*, *V.*

cholera and *S. aureus*. Through this assays, this quinoline derivative compounds has good potent antibacterial activity for various human pathogens. By this modified XTT combined method, MIC value of bacterial pathogens against quinoline derivatives were compared with control antibiotics Ciprofloxacin (mg/ml). The MIC has been calculated using the Muller hinton broth method reported elsewhere.^{13, 14} Based on the MIC values, **5b** is found to show excellent antibacterial activity with a value of 250 µg.

In summary, several derivatives of phenanthrene based quinoline derivatives were synthesized using imino Diels Alder reaction with excellent yield. Based on the biological screening, our hybrid heterocycles incorporated quinoline derivatives displayed moderate to good antibacterial activities for both gram positive and gram negative bacteria.

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- [15] Representative procedure for **4b**: A mixture of 4-cyanoaniline (2.4 mmol), phenanthrene-9-carboxaldehyde (2.4 mmol) in acetonitrile (15 ml) was stirred at room temperature for 30 min followed by *N*-vinyl-2-pyrrolidone (2.5 mmol) and Ytterbium(III) trifluoromethanesulfonate (5 mol%) was added and continued stirred at room temperature until completion of the reaction as evidenced by TLC analysis. After complete the reaction, acetonitrile was concentrated by vacuum and the reaction mixture was extracted with ethyl acetate (2 × 30 mL). Organic layers were separated carefully from the aqueous layer. The combined organic layers were dried over anhydrous Na₂SO₄ by which the water present after the extraction can be removed and further, the organic layer is concentrated in vacuum. The crude was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate / petroleum ether (10:90). Light brown solid. **Isolated Yield: 90%, mp: 264–266 °C**. ¹H NMR (400 MHz, CDCl₃) δ: 2.06-2.13 (m, 2H), 2.27-2.41 (m, 1H), 2.43-2.51 (m, 2H), 2.55-2.61 (m, 1H), 3.20-3.25 (m, 2H), 4.71 (s, 1H, D₂O exchangeable), 5.51 (d, 1H, *J* = 10.8 Hz), 5.81 (dd, 1H, *J* = 5.3, 12.1 Hz), 6.67 (d, 1H, *J* = 10.4 Hz), 7.16 (s, 1H), 7.35 (dd, 1H, *J* = 1.4, 8.3 Hz), 7.60-7.73 (m, 4H), 7.89 (d, 1H, *J* = 7.9 Hz), 7.96 (s, 1H), 8.10 (d, 1H, *J* = 7.7 Hz), 8.68 (d, 1H, *J* = 8.1 Hz), 8.78 (d, 1H, *J* = 7.9 Hz). ¹³C NMR (100 MHz, CDCl₃) δ: 18.5, 31.5, 33.2, 42.6, 48.3, 99.9, 115.3, 119.6, 120.7, 123.0, 124.0, 127.3, 127.4, 127.5, 127.6 (2C), 129.0, 129.5, 130.5, 131.0, 131.2, 131.6, 132.9, 149.7, 176.5. IR (KBr): 3429, 1621, 1579, 1449, 1222, 806 cm⁻¹. Mass (ESI): 318 (M+1). Anal. Calcd for C₂₈H₂₃N₃O: C, 80.55, H 5.55; N, 10.06. Found: C, 80.66; H, 5.51; N, 10.04.
- [16] Representative procedure for **5b**: Compound **4b** (1.1 mmol) was dissolved in toluene (15 ml) and added 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (or DDQ, 2.9 mmol) stirred and heated to 100 °C continued for 1 hr. After complete reaction, toluene was concentrated by vacuum and the reaction mixture was extracted with ethyl acetate (2 × 35 mL). Organic layers were separated carefully from the aqueous layer. The combined organic layers were dried over anhydrous Na₂SO₄ by which the water present after the extraction can be removed and further, the organic layer is concentrated in vacuum. The crude was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate / petroleum ether (15:85). Light

brown solid. **Isolated Yield: 90%, mp: 264–266 °C.** ¹H NMR (400 MHz, CDCl₃) δ: 2.41-2.47 (m, 2H), 2.78 (t, 2H, *J* = 8.0 Hz), 4.04 (t, 2H, *J* = 6.8 Hz), 7.59 (t, 1H, *J* = 7.2 Hz), 7.65 (t, 1H, *J* = 7.2 Hz), 7.71-7.76 (m, 3H), 7.92 (dd, 1H, *J* = 1.6, 8.8 Hz), 7.97 (d, 2H, *J* = 10.4 Hz), 8.11 (d, 1H, *J* = 8.0 Hz), 8.30-8.34 (m, 2H), 8.75 (d, 1H, *J* = 8.4 Hz), 8.81 (d, 1H, *J* = 8.0 Hz). ¹³C NMR (100 MHz, CDCl₃) δ: 19.4, 31.6, 51.0, 110.2, 118.7, 120.0, 122.6, 122.7, 123.2, 126.1, 127.0, 127.1, 127.7, 129.2, 129.4, 129.6, 130.7, 130.8, 130.9, 131.0, 131.6, 136.0, 145.2, 150.4, 162.8, 175.1 IR (KBr): 3429, 1621, 1579, 1449, 1222, 806 cm⁻¹. Mass (ESI): 414 (M+1). Anal. Calcd for C₂₈H₁₉N₃O: C, 81.34, H 4.63; N, 10.16. Found: C, 81.47; H, 4.60; N, 10.14.



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