ORIGINAL ARTICLE

Design, synthesis and antibacterial evaluation of pyrano[3,2-*H*]quinoline carbonitriles

Sravanthi Siliveri[1], T. Radhika[1], V. Harinadha Babu[1], Shiva Raj[2], B. Madhava Reddy[1]

[1]Department of Pharmaceutical Chemistry, G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad, Telangana, India, [2]Department of Chemistry, Osmania University, Hyderabad, Telangana, India

Abstract

Aim: To synthesize novel pyrano quinolines by one-pot multicomponent reaction under noncatalytic conditions, further it was proposed to investigate the reactivity of pyrano quinolines with the oxidizing agent like iodobenzene diacetate (IBD). Synthesized compounds were evaluated for antibacterial activity. **Materials and Methods:** Synthetic procedure: A mixture of aldehyde (1 mmol), malononitrile (1 mmol) in 10 ml of ethanol-water (1:1) was stirred for 10 min and then followed by addition of 8-hydroxy quinoline (1 mmol) and refluxed at 100°C for 1-2 h. The precipitated solid was collected by filtration. In the next step, to a suspension of pyrano[3,2-h]quinoline carbonitrile (1 mmol) in 5 mL of alcohol was added IBD (1.1 mmol) with stirring at room temperature open to air. The reaction mixture immediately became a clear solution followed by the precipitation of the product. The mixture was filtered and washed with the corresponding alcohol to afford the desired product. Antibacterial activity: All the synthesized compounds were screened for antimicrobial activity at a concentration of 100 µg/50 µl using ciprofloxacin as a standard drug. The minimum inhibitory concentrations (MICs) of these compounds were determined using broth microdilution MIC method. **Results and Discussion:** Synthetic studies: At the outset, pyrano[3,2-h]quinoline carbonitrile analogs 1(a-j) were constructed by a catalyst-free protocol via a one-pot, three-component condensation. Further, catalytic oxidative difunctionalization of the chromene double bond was achieved using hypervalent iodine reagents such as IBD in alcoholic medium and total 14 novel compounds 2(a-k) have been synthesized and confirmed on the basis of spectral data (infrared, nuclear magnetic resonance, and mass). Antibacterial activity: Among all the tested compounds, 1g, 1h, 1j, 2d, 2f, 2h, and 2k showed antibacterial activity against both Gram-positive and Gram-negative standard strains, and their MICs ranged between 1.56 and 12.55 µg/mL. **Conclusion:** In summary, an efficient, economical and eco-friendly multicomponent protocol for the construction of pyrano[3,2-h]quinoline carbonitriles has been achieved, and an oxidative difunctionalization of chromene double bond has been studied in the alcoholic solvent medium in the presence of IBD.

Key words: Antibacterial activity, iodobenzene diacetate, multicomponent reaction, synthesis

INTRODUCTION

Quinoline moiety is present in many classes of biologically active compounds.[1,2] The biological activity of these quinoline derivatives depends not only on bicyclic hetero aromatic pharmacophore but also on the nature of peripheral substituent and their spatial relationship. They also exhibit antimalarial,[3] antitumor,[4] antioxidant,[5] and antileishmanial activities.[6] In addition, to this they also function as DNA binding[7] and intercalating carrier.[8] On the other hand, six membered heterocyclic compounds containing oxygen such as 4*H*-pyrans constitute an important class of biologically active, natural and synthetic products, playing a fundamental role in bio organic chemistry.[9] 4*H*-pyran nucleus is a fertile source of biologically important nucleus possessing a wide spectrum of biological and

Address for correspondence:
Sravanthi Siliveri, Department of Pharmaceutical Chemistry, G. Pulla Reddy College of Pharmacy, Osmania University, Hyderabad - 500 028, Telangana, India. Phone: +91-8297222445.
E-mail: sravanthisiliveri@gmail.com

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pharmacological activities such as antimicrobial,[10] antiviral, anthelmintic,[11] hypnotic and insecticidal properties, anticoagulant, spasmolytic, diuretic, antiproliferative,[12,13] sex pheromone, and anti-anaphylactic.[14] Some of the naturally occurring alkaloids (flindersine, oricine, and verprisine) contain both the above heterocycles in the form of pyranoquinoline moiety and possess various biological activities.[15-17] According to literature, there were a variety of three or four component reactions for the construction of different pyrano quinoline carbonitriles.[18] Among them a three component reaction between aromatic aldehyde, malononitrile, and 8-hydroxy quinoline in ethanol was reported with a variety of catalysts.[19-22] Here in we report a simple noncatalytic method for the synthesis of pyrano[3,2-h] quinoline carbonitriles using a mixture of water and ethanol (1:1) as a solvent media. This protocol is persuadable for constructing spiroindoline substituted pyrano[3,2-h] quinoline carbonitriles. A brief review of earlier reports[23] on the reactivity of pyran derivatives reveals that amino chromenes have evolved as very reactive moieties and they react with different reagents to form a variety of heterocyclic scaffolds. Therefore, it was proposed to investigate the reactivity of 2-amino chromenes with the oxidizing agent like iodobenzene diacetate (IBD). Among all hypervalent iodine containing reagents, IBD has pioneered the development of methodologies for oxidative difunctionalizations of olefinic systems,[24] flavonoids, indoles, and pyrans[25-27] which would be a simple convention for obtaining diversely substituted pyrano quinoline carbonitriles. Hence, catalytic oxidative difunctionalization of chromene double bond was envisaged as a reasonable synthetic transformation for obtaining vicinal substitutions.

MATERIALS AND METHODS

All the chemicals used were of synthetic grade obtained from SD Fine, Spectrochem and Aldrich Chemicals. Completion of the reactions was monitored by analytical thin layer chromatography using E-Merck 0.25 mm silica gel plates. Visualization was accomplished with ultraviolet light (256 nm) and iodine chamber. Synthesized compounds were purified by column chromatography. Column chromatography was performed using hexane or a mixture of hexane and ethyl acetate unless otherwise stated. All the solvents were dried using appropriate drying agents before use. By employing standard laboratory techniques, the reagents were purified. Solvents used for column chromatography were distilled before use. ACME grade silica gel was used for column chromatography, unless otherwise mentioned. Melting points were determined on ANALAB melting point apparatus and were uncorrected. All the ^{1}H nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ and dimethyl sulfoxide (DMSO-d_6) solvents unless otherwise mentioned. Chemical shifts are reported on AVANCE 300 MHz and INNOVA 500 MHz spectrometers relative to tetramethylsilane internal standard on the δ-scale. The infrared (IR) spectra were recorded on Shimadzu Fourier transform-IR spectrophotometer using 1% potassium bromide discs. The mass spectra were recorded on quadrupole mass spectrometry.

General Procedure for the Synthesis of Compounds 1(a-i)

A mixture of aldehyde (1 mmol), malononitrile (1 mmol) in 10 mL of ethanol-water (1:1) was stirred for 10 min and then followed by addition of 8-hydroxy quinoline (1 mmol) and refluxed at 100°C for 1-2 h. The precipitated solid was collected by filtration. The structures of the products were assigned on the basis of spectral data.

General Procedure for the Synthesis of Compound 1j

A mixture of isatin (1 mmol), malononitrile (1 mmol) in 10 mL of ethanol-water (1:1) was stirred for 10 min and then followed by addition of 8-hydroxy quinoline (1 mmol) and refluxed at 100°C for 1-2 h. The precipitated solid was collected by filtration.

General Procedure for the Synthesis of Compounds 2(a-k)

To a suspension of 2-amino-4*H*-pyran (1 mmol) in 5 mL of methanol (or ethanol) was added IBD (1.1 mmol) with stirring at RT open to air. The reaction mixture immediately became a clear solution followed by the precipitation of product. The mixture was filtered and washed with the corresponding alcohol to afford the desired product. The structures of the products were assigned on the basis of spectral data.

2'-amino-2-oxospiro[indoline-3,4'-pyrano[3,2-h] quinoline]-3'-carbonitrile (1j)

Yield: 70; m.p.: 230-232°C; IR (KBr disc) in cm^{-1}: 3337, 2181; ^{1}H NMR (300 MHz, DMSO), δ ppm: 6.63 (s, 3H), 6.93-7.11 (m, 3H), 7.40-7.46 (d, 1H, J = 8.768), 7.49-7.60 (m, 2H), 7.70-7.79 (t, 1H), 8.26-8.32 (d, 1H), 10.35 (s, 1H); mass (electrospray ionization mass spectrometry [ESIMS]) (m/z): 341 $(M+H)^+$ analytical calculated for $C_{20}H_{12}N_4O_2$: C, 70.58; H, 3.55; N, 16.46; O, 9.40; found: C, 70.64; H, 3.67; N,16.65; O, 10.01.

3-amino2,2-dimethoxy-4-phenyl-3,4-dihydro-2H-pyrano[3,2-h]quinoline-3-carbonitrile (2a)

Yield: 78%; m.p.: 230-232°C; IR (KBr) cm^{-1}: 3396, 3323, 2228, 1114, 776; ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 9.00 (dd, J = 1.5 Hz, 1H), 8.10 (dd, J = 1.5 Hz, 1H), 7.54-7.28 (m, 7H), 7.00 (d, J = 9.0 Hz, 1H), 4.88 (s, 1H), 3.94 (s, 3H), 3.51 (s, 3H), 1.83 (brs, 2H); mass (ESIMS): 362 $(M+H)^+$

analytically calculated for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63; O, 13.28; found: C, 70.04; H, 5.67; N,11.75; O, 13.41; calculated for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; N, 10.74; O, 16.35; found: C, 67.68; H, 5.55; N,10.55; O, 16.48.

3-amino2,2-diethoxy-4-phenyl-3,4-dihydro-2H-pyrano[3,2-h]quinoline-3-carbonitrile (2b)

Yield: 80%; m.p.: 174-176°C; IR (KBr) cm^{-1}: 3390, 3330, 2231, 1122, 717; ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.96 (d, *J* = 3.9 Hz, 1H), 8.17 (d, *J* = 8.3 Hz,1H), 7.68-7.24 (m, 7H), 6.97 (d, *J* = 8.6 Hz, 1H), 4.87(s, 1H), 4.39-4.19 (m, 2H), 4.04-3.90 (m, 1H), 3.84-3.70 (m, 1H), 1.93 (brs, 2H), 1.42 (t, *J* = 6.9 Hz, 3H), 1.04 (t, *J* = 6.9 Hz, 3H); mass (ESIMS): 330 $(M+H)^+$ analytically calculated for $C_{23}H_{23}N_3O_3$: C, 70.93; H, 5.95; N, 10.79; O, 12.32; found: C, 80.04; H, 5.87; N,11.05; O, 12.41.

3-amino2,2-isopropoxy-4-phenyl-3,4-dihydro-2H-pyrano[3,2-h]quinoline-3-carbonitrile (2c)

Yield: 76%; m.p.: 190-192°C; IR (KBr) cm^{-1}: 3392, 3333, 2229, 1117, 751; ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.25-8.18 (m, 1H), 7.83-7.76 (m, 1H), 7.62-7.30, (8H, m), 5.06-4.96 (m, 1H), 4.93 (s, 1H), 4.63-4.50 (m, 1H), 1.68 (brs, 2H), 1.54 (d, *J* = 6.0 Hz, 3H), 1.47 (d, *J* = 6.2 Hz, 3H), 1.32 (d, *J* = 6.2 Hz, 3H), 0.76 (d, *J* = 6.0 Hz, 3H); mass (ESIMS): 418 $(M+H)^+$; analytically calculated for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.06; O, 11.50; found: C, 72.02; H, 6.87; N,10.25; O, 11.62.

3-amino2,2-dimethoxy-4-(4-methoxyphenyl)-2H-pyrano[3,2-h]quinoline-3-carbonitrile (2d)

White solid; yield: 82%; m.p.: 190-192°C; IR (KBr) cm^{-1}: 3395, 3331, 2230, 1514, 1115, 770; ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.90-8.99 (m, 1H), 8.42-7.95 (m, 5H), 6.95-7.04 (m, 3H), 4.77 (s, 1H), 3.95 (s, 3H), 3.83 (s, 3H), 3.47 (s, 3H), 1.72 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ ppm: 159.7, 145.0, 141.5, 138.5, 138.1, 137.5, 134.5, 132.0, 128.1, 127.5, 124.2, 118.8, 116.0, 114.1, 111.2, 77.4, 76.9, 76.5, 56.9, 55.2, 53.5, 50.7, 49.8; mass (ESIMS): 392 $(M+H)^+$ analytically calculated for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; N, 10.74; O, 16.35; found: C, 67.68; H, 5.55; N, 10.55; O, 16.48.

3-amino2,2-diethoxy-4-(4-methoxyphenyl)-2H-pyrano[3,2-h]quinoline-3-carbonitrile (2e)

Brown solid; yield: 85%; m.p.: 178-180°C; IR (KBr) cm^{-1}: 3395, 3331, 2235, 760; ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 9.05-8.90 (m, 1H), 8.25-7.20 (m, 8H), 4.95 (s, 1H), 4.30-3.50 (m, 4H), 3.15 (s, 3H), 2.00 (brs, 2H), 1.50 (t, 3H), 1.10 (t, 3H); mass (ESIMS): 420 $(M+H)^+$ analytically calculated for $C_{24}H_{25}N_3O_4$: C, 68.72; H, 6.01; N, 10.02; O, 15.26; found: C, 69.04; H, 6.10; N, 10.35; O, 15.48.

3-amino2,2-dimethoxy-4-(4-bromo phenyl)-2H-pyrano[3,2-h]quinoline-3-carbonitrile (2f)

Cream solid; yield: 88; m.p.: 138-140°C; IR (KBr) cm^{-1}: 3384, 3320, 2231, 1110, 820; ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.86-8.80 (1H, m), 8.20-8.36 (1H, m), 7.59-7.29 (5H, m), 7.14 (2H, t, *J* = 8.3 Hz), 4.84 (1H, s), 3.96 (3H, s), 3.47 (3H, s), 1.66 (2H, brs); ^{13}C NMR (75 MHz, $CDCl_3$), δ ppm: 156.9, 148.0, 145.1, 133.6, 132.8, 131.6, 127.5, 126.6, 126.2, 125.8, 124.2, 122.0, 121.0, 120.7, 115.8, 77.4, 76.9, 76.5, 56.6, 53.5, 50.8, 49.9; mass (ESIMS): 442 $(M+2H)^+$; analytically calculated for $C_{21}H_{18}BrN_3O_3$: C, 57.29; H, 4.12; Br, 18.15; N, 9.54; O, 10.90; found: C, 57.40; H, 4.20; Br, 18.35; N, 9.81; O, 11.05.

3-amino2,2-diethoxy-4-(4-bromophenyl)-2H-pyrano[3,2-h]quinoline-3-carbonitrile (2g)

Yellowish brown solid; yield: 90%; m.p.: 158-160°C; IR (KBr) cm^{-1}: 805, 1106, 2230, 3325, 3393; ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.80 (1H, d, *J* = 8.0 Hz), 8.25 (1H, d, *J* = 7.0 Hz), 7.56-7.26 (7H, m), 4.84 (1H, s), 4.33-4.25 (2H, m), 4.01-3.92 (1H, m), 3.74-3.66 (1H, m), 1.74 (2H, brs), 1.44 (3H, t, *J* = 7.0 Hz), 1.05 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$), δ ppm: 151.4, 145.6, 144.4, 143.5, 142.4, 132.7, 132.4, 131.5, 131.2, 130.0, 128.2, 121.7, 121.1, 120.7, 115.1, 77.3, 76.9, 76.5, 61.4, 59.1, 56.8, 50.0 MASS (ESIMS): 469 $(M+H)^+$; analytically calculated for $C_{23}H_{22}BrN_3O_3$: C, 58.98; H, 4.73; Br, 17.06; N, 8.97; O, 10.25; found: C, 59.10; H, 4.51; Br, 17.25; N, 9.05; O, 10.41.

3-amino2,2-dimethoxy-4-(4-nitrophenyl)-2H-pyrano[3,2-h]quinoline-3-carbonitrile (2h)

Brown solid; yield: 80%; m.p.: 138-140°C; IR (KBr) cm^{-1}: 800, 1110, 1351, 1522, 2234, 3315, 3385; ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 9.00-8.80 (3H, m), 7.77 (1H, d, *J* = 7.4 Hz), 7.47-7.70 (4H, m), 7.39 (1H, d, *J* = 8.3Hz), 4.92 (1H, s), 3.95 (3H, s), 3.49 (3H, s), 1.68 (2H, brs).; ^{13}C NMR (75 MHz, $CDCl_3$), δ ppm: 152.1, 148.0, 145.3, 143.6, 133.6, 132.2, 127.6, 126.9, 126.4, 125.7, 124.2, 123.5, 122.3, 120.9, 120.2, 77.4, 76.9, 76.5, 56.4, 53.5, 50.9, 50.5; mass (ESIMS): 407 $(M+H)^+$; analytically calculated for $C_{21}H_{18}N_4O_5$ C, 62.06; H, 4.46; N, 13.79; O, 19.68; found: C, 62.25; H, 4.75; N, 13.81; O, 19.79.

3-amino2,2-dimethoxy-4-(4-methyl phenyl)-2H-pyrano[3,2-h]quinoline-3-carbonitrile (2i)

Buff solid; yield: 78%; m.p.: 135-137°C; IR (KBr) cm^{-1}: 751, 1111, 1400, 2190, 3312, 3392; ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.60-8.75 (d, 1H, *J* = 6.987 Hz), 8.22-8.40 (m, 3H), 7.25-6.93 (m, 5H), 4.79 (s, 1H), 4.72 (brs, 2H), 3.30 (s, 6H), 2.31 (s, 3H); MASS (ESIMS): 376 $(M+H)^+$; analytically calculated for $C_{22}H_{21}N_3O_3$ C, 70.38; H, 5.64; N, 11.19; O, 12.79; found: C, 70.55; H, 5.84; N, 11.31; O, 13.04.

3-amino2,2-dimethoxy-4-(2,4-dimethoxyphenyl)-2H-pyrano[3,2-h]quinoline-3-carbonitrile (2j)

Yellow solid; yield: 85%; m.p.: 140-142°C; IR (KBr) cm^{-1}: 762, 1090, 2201, 3316, 3387; ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.98-8.45 (5H, m), 7.50-7.80 (3H, m), 4.88 (1H, s), 3.98 (3H, s), 3.50 (3H, s), 1.70 (2H, brs); mass (ESIMS): 442 $(M+H)^+$, 444 $(M+Na)^+$; analytically calculated for $C_{23}H_{23}N_3O_5$, C, 65.55; H, 5.50; N, 9.97; O, 18.98; found: C, 65.67; H, 5.74; N,10.05; O, 19.09.

3-amino2,2-dimethoxy-4-(thiphen-2-yl)-2H-pyrano[3,2-h]quinoline-3-carbonitrile (2k)

Brown solid; yield: 80%; m.p.: 158-160°C; IR (KBr) cm^{-1}: 714, 1121, 2224, 3316, 3390; ^{1}H NMR (300 MHz, $CDCl_3$), δ ppm: 8.92-8.99 (1H, m), 8.29-8.22 (1H, m), 7.55-7.43 (2H, m), 7.42-7.34 (2H, m), 7.20 (1H, d, J = 3.0 Hz), 7.11-7.07 (2H, m), 5.13 (1H, s), 3.95 (3H, s), 3.48 (3H, s), 1.89 (2H, brs); ^{13}C NMR (75 MHz, $CDCl_3$), δ ppm: 155.0, 150.5, 144.8, 140.8, 132.5, 131.9, 131.6, 130.6, 130.2, 130.1, 128.0, 121.9, 121.1, 120.5, 115.5, 77.4, 76.9, 76.5, 57.0, 53.5, 50.8, 46.6; mass (ESIMS): 369 $(M+H)^+$; analytically calculated for $C_{19}H_{17}N_3O_3S$, C, 62.11; H, 4.66; N, 11.44; O, 13.06; S, 8.73; found: C, 62.34; H, 4.94; N,11.65; O, 13.26; S, 9.01.

RESULTS AND DISCUSSION

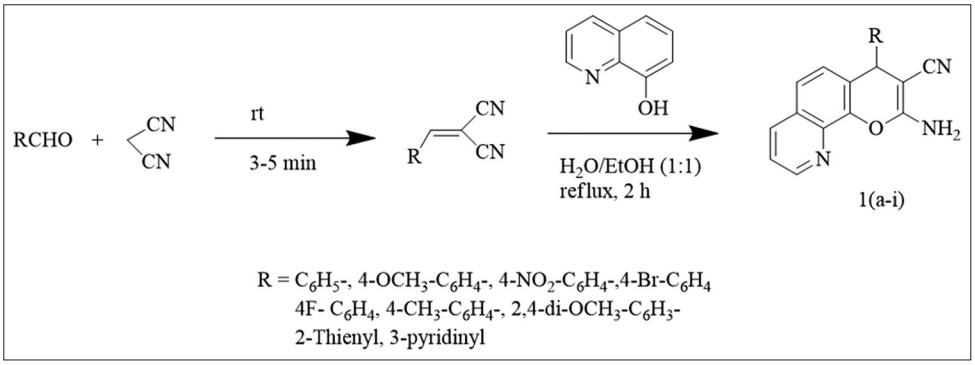
Chemistry

The synthesis of compounds 1(a-i) was depicted in Scheme 1. An one-pot three component reaction was carried out with aromatic aldehyde, malononitrile and 8-hydroxy quinoline in aqueous ethanol medium (1:1) and heated to 100°C. The reaction was completed in 2 h, by cooling the reaction mixture the desired product 1(a-i) was precipitated out in 80% yield. These one-pot multicomponent reactions were endeavored with various aryl and heteroaryl aldehydes, corresponding products were obtained in good yields. Other conspicuous feature of this protocol is that the reaction is very simplistic with the ketone like isatin as shown in Scheme 2.

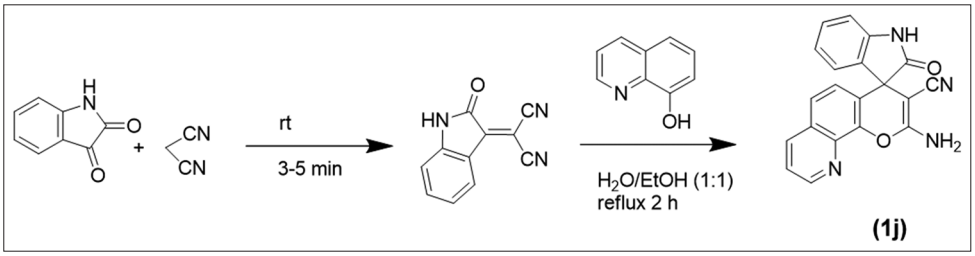
An extension to this compounds 2(a-k) were synthesized via IBD catalyzed a reaction with quinoline carbonitriles as shown in Scheme 3. The structures of newly synthesized compounds were characterized on the basis of spectral data (^{1}H NMR, ^{13}C NMR, MASS, and IR spectroscopy) and those reported compounds by comparing with earlier literature. In IR spectra C≡N absorption band appeared between 2250 and 2150 cm^{-1} and ^{1}H NMR of compounds showed a singlet between δ 3.00 and 4.00 for OCH_3 protons, broad singlet between δ 1.00 and 2.00 for NH_2 protons, singlet for pyran 4*H* proton and peaks for aromatic and quinoline appeared in the range of δ 6.00-9.00 confirmed structures. ^{13}C NMR spectra of compounds showed peaks in the range of δ 40-80 due to OCH_3, pyran 4th carbon and all other aromatic and quinoline carbon appeared in the range of δ 110-160 confirmed the formation of desired compounds. This was more supported by MASS spectral data. The physical and spectral data of individual compounds given under experimental section.

Antibacterial Activity

All the synthesized compounds were screened for antimicrobial activity against four strains of bacteria,



Scheme 1: Construction of various pyrano[3,2-h]quinoline carbonitriles



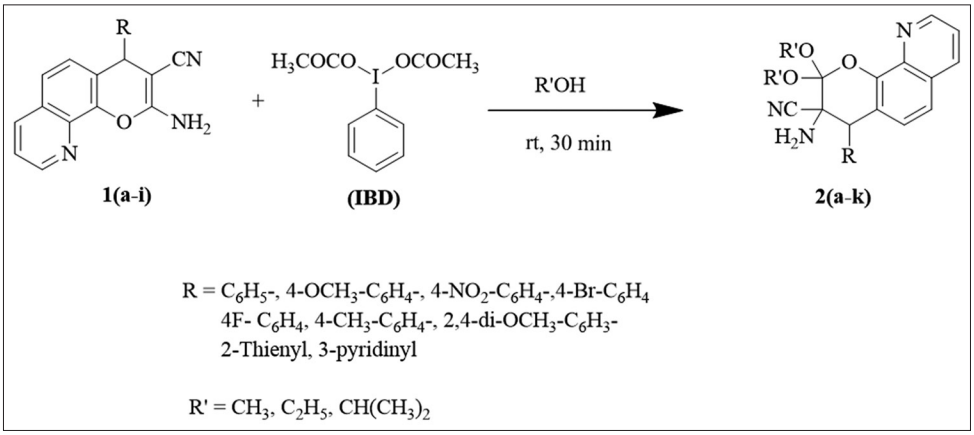
Scheme 2: Construction of spiroindoline substituted pyrano[3,2-h]quinoline carbonitrile

Bacillus subtilis and *Staphylococcus aureus* (Gram-positive), *Escherichia coli,* and *Pseudomonas aeruginosa* (Gram-negative) using ciprofloxacin as a standard drug. The study was conducted by cup-plate method to determine the zone of inhibition (mm) against four strains of bacteria at a concentration of 100 µg/50 µl. Investigation of antibacterial data revealed that compounds 1g, 1h, 1j, 2d, 2f, 2h, 2i, and 2k showed good activity against all four strains of bacteria and minimum inhibitory concentration (MICs) of these compounds were determined at different concentrations 0.39, 0.78, 1.56, 3.125, 6.25, 12.5, 25, 50, and 100 µg/mL using broth microdilution MIC method. All the compounds showed antibacterial activity against all the four strains of bacteria, and their MICs ranged between 1.56 and 12.55 µg/mL. The MICs of these compounds and ciprofloxacin were determined using the standard protocol of National Committee for Clinical Laboratory Standards broth microdilution MIC method,[28] and the results are tabulated in Table 1.

Ciprofloxacin is taken as a standard drug, and its MIC is 1.56 µg/mL against all the four strains.

CONCLUSION

In summary, an efficient, economical and eco-friendly multicomponent protocol for the construction of pyrano[3,2-h]quinoline carbonitriles has been achieved, and an oxidative difunctionalization of chromene double bond has been studied in the alcoholic solvent medium in the presence of IBD. Addition of geminal dialkoxy groups and 1,2-migration of NH_2 occur via an intramolecular aziridination. Pyrano[3,2-h]quinoline carbonitriles have been evaluated for antibacterial activity. Of all the compounds tested, compounds 1g, 1h, 1j, 2d, 2f, 2h, 2i, and 2k have shown significant antibacterial activity. Hence, these compounds are promising lead compounds amenable for further improvisation of antiproliferative activity profile



Scheme 3: Iodobenzene diacetate catalyzed geminal dialkoxylation with 1,2-migration of amino group

Table 1: Antibacterial activity of different compounds by broth microdilution MIC method

µg/mL	Antibacterial activity against standard strains—compounds																													
	1g				1h				1j				2d				2f				2h				2i				2k			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
0.3	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
0.7	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
1.5	+	+	-	-	+	+	+	+	+	+	+	+	+	+	-	+	-	+	-	+	-	-	+	+	+	+	+	+	+	+	+	+
3.1	-	-	-	-	+	+	+	+	-	-	-	+	-	-	-	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
6.2	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-
12.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
25	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
50	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
100	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

1 - *Bacillus subtilis*; 2 - *Staphylococcus aureus;* 3 - *Escherichia coli*; 4 - *Pseudomonas aeruginosa*, +: Resistant; -: Susceptible, MIC: Minimum inhibitory concentrations

and molecular docking as well as absorption, distribution, metabolism, and excretion studies.

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