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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

An efficient synthesis and antimicrobial screening of new hybrid molecules containing coumarin and indenopyridine moiety

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Abstract A novel series of hitherto unknown 3-(4-aryl-5*H*-indeno[1,2-*b*]pyridin-2-yl)coumarin derivatives **3a–r** have been synthesized by the reaction of 3-coumarinyl methyl pyridinium salts **1a-c** with appropriate 2-arylidene-1-indanones **2a–f** under Krohnke's reaction condition so as to investigate their in vitro antimicrobial activity. Structures of the target compounds **3a–r** were characterized by their spectral and elemental analyses. Among the series, compound **3l** displayed an encouraging antibacterial activity profile as compared to the reference drug ampicillin against tested bacterial strains.

Keywords Coumarins · Krohnke's pyridine synthesis · Indenopyridine · Antimicrobial activity

Introduction

Infectious diseases are responsible for great number of deaths in the world population. Today widespread excessive use of antibacterial agents to prevent infectious diseases leads to development of more resistant microorganisms to commonly used antibiotics (Hage *et al.*, 2011). Thus, the infections caused by these microorganisms pose a severe challenge to the medical community and need for an effective therapy has led to a search for novel antimicrobial agents. For this reason, the present work is aimed toward developing molecules with potent antimicrobial activity to tackle this problem.

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Coumarins are subunits of many natural products and a range of relevant pharmaceuticals with distinct biological activities, constituting an important class of heterocycles and widely distributed in nature (Murray *et al.*, 1982). An extensive research has been focused on the biological activities of coumarins such as antitumor (Suzuki *et al.*, 2006), antibacterial (Kayser and Kolodziej, 1999), antifungal (Sharma and Parashar, 1988), anticoagulant (Garazd *et al.*, 2005), anti-inflammatory (Kontogiorgis and Hadjipavlou-Litina, 2005), and antiviral agents (Hwu *et al.*, 2008). On the other hand, coumarin nucleus are present in promising drug applicants such as nonpeptidic HIV protease inhibitors (Thaisrivongs *et al.*, 1996), topoisomerase II (Rappa *et al.*, 2000), and tyrosine kinase (Yang *et al.*, 1999) inhibitors. Many pyridyl-substituted coumarins have a special importance due to their diverse physiological actions. A number of coumarin derivatives having pyridine substituted mainly at 3- or 4-position of the coumarin possess CNS depressant activity, in vitro monoamine oxidase (MAO) inhibition activity, antifungal activity, fish toxicity and bactericidal activity (Moffett, 1964a; Moffett, 1964b; Sreenivasulu *et al.*, 1974). Many other natural and synthetic coumarins have occupied a significant place in drug research.

Indenopyridine and related compounds are a class of heterocyclic compounds endowed with a broad spectrum of biological activity. A simplest member onychnine represents indenopyridine skeleton present in the 4-azafluorene group of alkaloids (Zhang *et al.*, 1987). Certain compounds containing indenopyridine system exhibit cytotoxic (Miri *et al.*, 2004), phosphodiesterase inhibitory (Heintzelman *et al.*, 2002), adenosine A_{2A} receptor antagonistic (Heintzelman *et al.*, 2004), anti-inflammatory/anti-allergic (Cooper *et al.*, 1989), coronary dilating (Vigante *et al.*, 1989), and calcium modulating activities (Safak *et al.*, 1997). Consequently,

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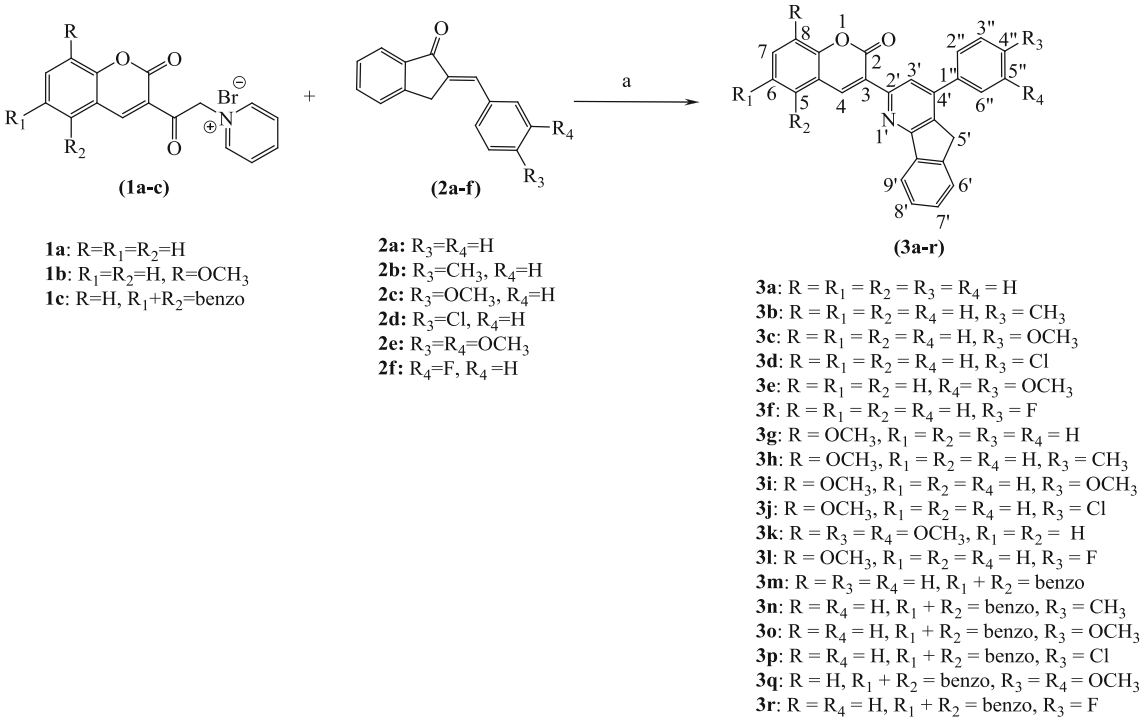

Scheme 1 General synthetic scheme for 3-(4-aryl-5*H*-indeno[1,2-*b*]pyridin-2-yl)coumarins **3a–r**. Reagents and conditions: *a* NH_4OAc, AcOH, 140 °C

hexahydro indenopyridine derivatives are proved to be potential antidepressants (Kunstmann and Fischer, 1984) while the libraries of dihydro indenopyridines also possess antiproliferative properties in a panel of human cancer cell lines (Evdokimov *et al.*, 2011).

The interesting biological properties of coumarin and indenopyridine derivatives prompted us to develop a new molecule which is a hybrid of these two moieties. Therefore, in the present work, we report the synthesis and antimicrobial activity of some 3-(4-aryl-5*H*-indeno[1,2-*b*]pyridin-2-yl)coumarins **3a–r.**

Results and discussion

Chemistry

In the present work, various 3-(4-aryl-5*H*-indeno[1,2-*b*]pyridin-2-yl)coumarins **3a–r** have been synthesized by reacting 3-coumarinyl methyl pyridinium salts **1a–c** with appropriate 2-arylidene-1-indanones **2a–f** in the presence of ammonium acetate in glacial acetic (Scheme 1). The formation of pyridine nucleus in compounds **3a–r** involves Kröhnke's reaction mechanism (Krohnke, 1976). The reaction proceeded smoothly and gave the expected products **3a-r** in moderate to good yield (52–68 %). The structures of the compounds **3a–r** were established on the basis of IR, ^1H, ^{13}C, DEPT NMR, Mass spectroscopy, and elemental analysis.

IR spectra of all the compounds **3a–r** showed a very strong band between 1,701 and 1,737 cm^{-1} for δ-lactone carbonyl (C=O) stretching vibrations. The strong bands for aromatic C=C and C=N stretching vibrations were observed between 1,602–1,626 and 1,433–1,456 cm^{-1}, respectively. The aromatic C–H stretching vibrations were observed between 3,033 and 3,058 cm^{-1} in the form of a medium band.

In the ^1H NMR spectra of all the compounds **3a–r,** the two protons attached at C_5' appeared as singlet in the range of 4.00–4.13 δ. The proton attached at C_4 of coumarin nucleus appeared as a singlet in the most down field region 9.00–9.13 δ in case of compounds **3a–l**, while in case of compounds **3m–r**, it appeared in the region 9.86–9.92 δ due to the peri effect of pyridine nitrogen as well as the deshielding effect of coumarin carbonyl group. In case of compounds **3a–l**, the protons attached at C_9' and C_3' appeared as a poorly resolved doublet of a doublet and a singlet between 8.23–8.42 and 8.45–8.80 δ, respectively, while in case of compounds **3m–r**, these protons are merged with other aromatic protons. The downfield shifting of these protons signals in case of compounds **3a–l** from other aromatic protons is due to the peri effect of coumarin carbonyl and the pyridine nitrogen, respectively. In case of compounds **3a–l**, the aromatic protons (except C_9' and C_3') appeared in

Table 1 Minimum inhibitory concentration (MIC) μg/ml of synthesized compounds **3a–r** against tested bacterial and fungal strains

Compound	Minimum inhibitory concentration (MIC) (μg/ml)					
	Antibacterial activity				Antifungal activity	
	E. coli	*S. typhi*	*S. aureus*	*B. subtilis*	*C. albicans*	*A. niger*
3a	500	500	500	250	1000	500
3b	100	100	200	100	250	500
3c	100	200	250	250	500	200
3d	200	200	500	500	500	–
3e	250	200	500	500	500	500
3f	100	100	200	100	250	1000
3g	200	250	500	250	500	1000
3h	200	250	50	100	250	–
3i	250	200	100	250	500	250
3j	250	250	500	500	250	500
3k	200	250	500	250	500	1000
3l	62.5	100	200	50	200	500
3m	200	200	500	500	–	500
3n	200	500	100	200	250	250
3o	250	500	200	200	500	500
3p	250	200	250	200	1000	1000
3q	250	250	500	250	–	500
3r	100	62.5	200	200	100	250
Ampicillin	100	100	250	250	NT	NT
Nystatin	NT	NT	NT	NT	100	100
Greseofulvin	NT	NT	NT	NT	500	100

– indicate absence of activity; NT, not tested

the form of multiplet between 7.03 and 7.78 δ, while in case of compounds **3m–r**, the aromatic protons appeared between 7.04 and 9.58 δ.

In the ^{13}C NMR spectra, all the compounds **3a–r** showed a signal around 34.00 δ which is due to methylene carbon. The most downfield signal appeared around 160.00 δ can be assigned to the carbonyl carbon of the δ-lactone ring of coumarin, while signals appeared between 116.0 and 160.0 δ can be attributed to the aromatic carbons. In ^{13}C spectra of compounds **3f**, **3l,** and **3r**, the three carbons i.e. C_2'', C_3'' and C_4'' appear as doublets due to the $^3J_{C-F}$, $^2J_{C-F}$, $^1J_{C-F}$ couplings, respectively. The DEPT-135 spectra of compounds **3a–r** showed an inverted signal at around 34.00 δ, which supports the assignment of C_5', while the other signals appeared in the aromatic region correspond to tertiary carbons present in the target compounds.

The selected mass spectrum of compound **3a** showed M^+ peak at *m/z* 387 (100 %) along with other fragments peaks. The appearance of molecular ion peak at 387 mass unit supports the structure of compound **3a**. An analytical and spectral data of all compounds **3a–l** are in full agreement with the proposed structures.

Biological screening

All the synthesized compounds **(3a–r)** were tested in vitro for their antibacterial activity against *Staphylococcus aureus* (MTCC 96) and *Bacillus subtilis* (MTCC 441), Gram positive bacteria, similarly they were tested against *Escherichia coli* (MTCC 443) and *Salmonella typhi* (MTCC 98), Gram negative bacteria, by broth micro dilution method. Reviewing of the antimicrobial activity (Table 1) of all the newly synthesized compounds revealed that compound **3h** (R=OCH_3, R_1=R_2=R_4=H, R_3=CH_3) and **3l** (R=OCH_3, R_1=R_2=R_4=H, R_3=F) showed the highest activity (50 μg/ml) against Gram positive bacterial strain *S. aureus* and *B. subtilis,* respectively. In case of inhibiting Gram negative bacteria *E.coli* and *S. typhi*, compounds **3l** (R=OCH_3, R_1=R_2=R_4=H, R_3=F) and **3r** ($R_1 + R_2$ = Benzo, R=R_4=H, R_3=F) displayed better activity (62.5 μg/ml) against respective bacterial strain.

All the eighteen indenopyridine derivatives were screened for their antifungal activity against *Candida albicans* (MTCC 227) and *Aspergillus niger* (MTCC 282) in DMSO by broth micro dilution method using nystatin and griseofulvin as standard drugs for comparison. Antifungal study (Table 1) reveals that all the synthesized compounds exhibited variable activity against the test organisms. In comparison with standard fungicidal griseofulvin, compounds **3b** (R=R_1=R_2=R_4=H, R_3=CH_3), **3f** (R=R_1=R_2=R_4=H, R_3=F), **3h** (R=OCH_3, R_1=R_2=R_4=H, R_3=CH_3), **3j** (R=OCH_3, R_1=R_2=R_4=H, R_3=Cl), **3l** (R=OCH_3, R_1=R_2=R_4=H, R_3=F), **3n** ($R_1 + R_2$ = Benzo, R=R_4=H, R_3=CH_3) and **3r** ($R_1 + R_2$ = Benzo, R=R_4=H, R_3=F) displayed better activity against *C. albicans*. All the synthesized compounds showed poor activity against *A. niger*.

Compound **3l** (R=OCH_3, R_1=R_2=R_4=H, R_3=F) emerged as the promising antimicrobial member among all the synthesized derivatives. From the series of compounds, it was well concluded that compounds having fluoro substitution (R_3=F), i.e., **3f**, **3l** and **3r** show higher potency against both Gram positive and Gram negative bacterial strains while compounds having methyl substitution (R_3=CH_3) i.e. **3b**, **3h,** and **3n** show higher potency only against Gram positive bacteria as compared to the standard drug.

Experimental section

All the reagents and solvents employed were used without further purification. Melting points were determined by open capillary method and are uncorrected. Infrared spectra (KBr disk) were performed on FTIR-8300 Shimadzu and the frequencies were expressed in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 and 100 MHz, respectively. The chemical shifts (δ) are reported in ppm using chloroform-d as a solvent and TMS signal as an internal standard. Signal multiplicities are represented as s (singlet), d (doublet), dd (doublet of a doublet), and m (multiplet). Elemental analyses were carried out with a Heraeus CHNO analyzer. Mass spectrum of compound **3a** was recorded on Shimadzu QP 2010 spectrometer. Completion of the reaction and the purity of the compounds were checked on Merck precoated silica gel on aluminum sheets (Kieselgel 60, F_{254}, Merck) and spots were visualized with UV light (254 nm) and/or in an iodine chamber. The compounds were purified by column chromatography using silica gel (60–120 mesh) and hexane:ethylacetate as an eluant.

General procedure for the synthesis of 3-coumarinyl methyl pyridinium bromide salts (**1a–c**)

In a 250-ml round-bottom flask fitted with a reflux condenser, a solution of an appropriate 3-(bromoacetyl) coumarin (0.03 mol) in dry toluene (100 ml) was taken and pyridine (0.03 mol) was added. The reaction mixture was refluxed in an oil bath for 2 h. It was then allowed to come to room temperature and was left for 4–5 h. The pyridinium salt was separated out as fine flakes. It was filtered out, washed with hot toluene and dried. It was recrystallized from acetic acid.

*3-Coumarinyl methyl pyridinium bromide salt (**1a**)*

Yield: 93 %, m.p. 218 °C; IR (KBr): 3032, 2361, 1720, 1697, 1188, 764 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.51 (2H, s, methylene protons), 7.48–8.90 (10H, m, aromatic protons). Anal. Calcd. for $C_{16}H_{12}BrNO_3$: C, 55.51; H, 3.49; N, 4.05. Found: C, 55.62; H, 3.46; N, 4.01 (Koelsch, 1950).

*8-Methoxy-3-coumarinyl methyl pyridinium bromide salt (**1b**)*

Yield: 91 %, m.p. 250 °C IR (KBr): 3032, 2361, 1736, 1690, 1188, 733 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.99 (3H, s, OCH_3), 6.55 (2H, s, methylene protons), 7.32–8.96 (9H, m, aromatic protons). Anal. Calcd. for $C_{17}H_{14}BrNO_4$: C, 54.27; H, 3.75; N, 3.72. Found: C, 54.20; H, 3.72; N, 3.76 (Rao and Rao, 1986).

*5,6-Benzo-3-coumarinyl methyl pyridinium bromide salt (**1c**)*

Yield: 84 %, m.p. 179–180 °C (dec.) IR (KBr): 3032, 2361, 1720, 1636, 1196, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.56 (2H, s, methylene protons), 7.56–9.64 (12H, m, aromatic protons). Anal. Calcd. for $C_{20}H_{14}BrNO_3$: C, 60.62; H, 3.56; N, 3.53. Found: C, 60.52; H, 3.60; N, 3.50 (Rao and Rao, 1986).

General procedure for the synthesis of 2-arylidene-1-indanones (**2a–f**)

In a 100-ml three-necked flask equipped with a dropping funnel and magnetic needle, a solution of 4 % ethanolic KOH was placed. A mixture of 1-indanone (0.02 mol) and an appropriate aromatic aldehyde (0.02 mol) in ethanol (20 ml) was added dropwise with stirring at room temperature and stirring continued for further 4 h. The reaction mixture was neutralized with acetic acid, diluted with

water, and stirred for 15 min. The separated solid was filtered, washed with water and then with cold ethanol. It was recrystallized from ethanol to yellow crystals.

*2-Benzylidine-1-indanone (**2a**)*

Yield: 88 %, m.p. 107 °C; IR (KBr): 3046, 1692, 1624, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.08 (2H, s, methylene protons), 7.28–7.95 (10H, m, nine aromatic protons + one olefinic proton). Anal. Calcd. for $C_{16}H_{12}O$: C, 87.25; H, 5.49. Found: C, 87.38; H, 5.43 (El-Rayyes *et al.*, 1987).

*2-(4-Methylbenzylidine)-1-indanone (**2b**)*

Yield: 83 %, m.p. 130 °C; IR (KBr): 3038, 1702, 1615, 826 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.42 (3H, s, CH_3), 4.05 (2H, s, methylene protons), 7.28–7.94 (9H, m, eight aromatic protons + one olefinic proton). Anal. Calcd. for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.01; H, 6.09.

*2-(4-Methoxybenzylidine)-1-indanone (**2c**)*

Yield: 91 %, m.p. 134 °C; IR (KBr): 3028, 1712, 1605, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.89 (3H, s, OCH_3), 4.04 (2H, s, methylene protons), 7.00–7.94 (9H, m, eight aromatic protons + one olefinic proton). Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64. Found: C, 81.68; H, 5.72 (El-Rayyes *et al.*, 1987).

*2-(4-Chlorobenzylidine)-1-indanone (**2d**)*

Yield: 78 %, m.p. 173 °C; IR (KBr): 3041, 1696, 1626, 814 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.05 (2H, s, methylene protons), 7.44–7.95 (9H, m, eight aromatic protons + one olefinic proton). Anal. Calcd. for $C_{16}H_{11}ClO$: C, 75.45; H, 4.35. Found: C, 75.37; H, 4.39 (El-Rayyes *et al.*, 1987).

*2-(3,4-Dimethoxybenzylidine)-1-indanone (**2e**)*

Yield: 83 %, m.p. 181 °C; IR (KBr): 3049, 1690, 1623, 819 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.96 and 3.98 (6H, two s, two OCH_3), 4.04 (2H, s, methylene protons), 6.96–7.93 (8H, m, seven aromatic protons + one olefinic proton). Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.98; H, 5.71. (Rothenberg *et al.*, 2001)

*2-(4-Chlorobenzylidine)-1-indanone (**2f**)*

Yield: 86 %, m.p. 156 °C; IR (KBr): 3033, 1698, 1627, 810 cm^{-1}; ^1H NMR: δ 4.03 (2H, s, methylene protons), 7.15–7.94 (9H, m, eight aromatic protons + one olefinic proton). Anal. Calcd. for $C_{16}H_{11}FO$: C, 80.66; H, 4.65. Found: C, 80.58; H, 4.61.

General procedure for the synthesis of 3-(4-aryl-5*H*-indeno[1,2-*b*]pyridin-2-yl)coumarins (**3a–r**)

In a 100-ml three-necked round-bottom flask equipped with a dropping funnel, condenser, guard tube, and magnetic needle, an appropriate 3-coumarinoyl methyl pyridinium salt **(1a–c)** (0.003 mol) in glacial acetic acid (15 ml) was taken. To this solution, ammonium acetate (0.03 mol) was added with stirring at room temperature. Then a solution of an appropriate 2-arylidene-1-indanone **(2a–f)** (0.003 mol) in glacial acetic acid (15 ml) was added with stirring at room temperature during 15 min. The reaction mixture was further stirred for 1 h at room temperature and then refluxed for 12 h at 140 °C. It was then allowed to come to room temperature and was poured into ice-cold water (75 ml). A crude solid obtained was extracted with chloroform (3 × 30 ml). The organic layer was washed with 5 % sodium bicarbonate solution (3 × 20 ml), water (2 × 20 ml) and dried over anhydrous sodium sulfate. The removal of chloroform under reduced pressure gave crude material which was subjected to column chromatography using silica gel and ethyl acetate–pet. ether (60–80) (2:8) as an eluent to give products **(3a–r)**. The compounds were recrystallized from chloroform-hexane.

*3-(4-Phenyl-5H-indeno[1,2-b]pyridin-2-yl)coumarin (**3a**)*

Yield: 56 %; mp.: 202 °C; IR (KBr): 3053, 2924, 1719, 1607, 1454, 694, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.00 (s, 2H, C_5'–H), 7.31–7.71 (m, 11H, Ar–H), 8.23 (poorly resolved dd, 1H, C_9'–H), 8.48 (s, 1H, C_3'–H), 9.01 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.63(C_5'), 116.27(CH), 119.76(C), 121.23(CH), 121.37(CH), 124.44(CH), 125.05(C), 125.66(C), 127.24(C), 128.41(CH), 128.59(CH), 128.81(C), 128.95(CH), 131.80(CH), 134.16(C), 138.54(C), 140.81(C), 142.12(CH), 144.08(C), 146.08(C), 150.53(C), 153.89(C), 160.34(C), 160.76(CO of coumarin). Mass (*m/z*): 387 (M^+); Anal. Calcd. for $C_{27}H_{17}NO_2$: C, 83.70; H, 4.42; N, 3.62. Found: C, 83.79; H, 4.48; N, 3.59.

*3-(4-p-Methyl-5H-indeno[1,2-b]pyridin-2-yl)coumarin (**3b**)*

Yield: 61 %; mp.: 222 °C; IR (KBr): 3044, 2912, 1711, 1604, 1442, 828 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.48 (s, 3H, CH_3), 4.08 (s, 2H, C_5'–H), 7.36–7.76 (m, 11H, Ar–H), 8.32 (poorly resolved dd, 1H, C_9'–H), 8.47 (s, 1H, C_3'–H), 9.05 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.32(CH_3), 34.79(C_5'), 116.36(CH), 119.75(C),

121.52(CH), 124.25(CH), 124.54(CH), 125.09(CH), 125.38(C), 127.36(CH), 128.36(CH), 128.90(CH), 129.11(CH), 129.43(C), 129.56(CH), 131.95(CH), 134.31(C), 135.48(C), 138.81(C), 140.56(C), 142.48(CH), 144.16(C), 146.48(C) 150.38(C), 153.95(C), 160.40(CO of coumarin); Mass (*m/z*): 401 (M^+); Anal. Calcd. for $C_{28}H_{19}NO_2$: C, 83.77; H, 4.77; N, 3.49. Found: C, 83.67; H, 4.83; N, 3.52.

*3-(4-p-Methoxy-5H-indeno[1,2-b]pyridin-2-yl)coumarin (**3c**)*

Yield: 54 %; mp.: 202 °C; IR (KBr): 3049, 2932, 1737, 1608, 1456, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.92 (s, 3H, OCH_3), 4.06 (s, 2H, C_5'–H), 7.07–7.75 (m, 11H, Ar–H), 8.26 (poorly resolved dd, 1H, C_9'–H), 8.46 (s, 1H, C_3'–H), 9.03 (s, 1H,C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 35.03(C_5'), 55.47(OCH_3), 114.44(CH) 116.37(CH), 119.54(C), 121.67(CH), 122.37(CH), 124.67(CH), 125.03(CH), 127.57(CH), 129.17(CH), 129.58(CH), 129.89(CH), 130.20(C), 131.44(C), 132.23(CH), 134.38(C), 134.70(C), 143.43(CH), 144.24(C), 154.01(C), 157.14(C), 159.77(C), 160.25(C), 160.41(C), 162.15(CO of coumarin); Mass (*m/z*): 417 (M^+); Anal. Calcd. for $C_{28}H_{19}NO_3$: C, 80.56 H, 4.59; N, 3.36. Found: C, 80.51; H, 4.54; N, 3.39.

*3-(4-p-Chloro-5H-indeno[1,2-b]pyridin-2-yl)coumarin (**3d**)*

Yield: 67 %; mp.: 248 °C; IR (KBr): 3040, 2930, 1726, 1610, 1459, 819 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.04 (s, 2H, C_5'–H), 7.35–7.78 (m, 11H, Ar–H), 8.42 (poorly resolved dd, 1H, C_9'–H), 8.53 (s, 1H, C_3'–H), 9.10 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.73(C_5'), 116.41(CH), 119.43(C), 121.70(CH), 122.55(CH), 124.38(CH), 124.48(C), 124.74(CH), 125.10(CH), 127.69(CH), 129.24(CH), 129.74(CH), 129.87(CH), 132.45(CH), 134.60(C), 135.35(C), 136.35(C), 137.07(C), 143.70(CH), 144.11(C), 146.23(C), 149.81(C), 154.05(C), 160.00(C), 160.22(C); Mass (*m/z*): 421 (M^+); Anal. Calcd. for $C_{27}H_{16}ClNO_2$: C, 76.87; H, 3.82; N, 3.32. Found: C, 76.96; H, 3.76; N, 3.29.

*3-(4-(3,4-Dimethoxyphenyl)-5H-indeno[1,2-b]pyridin-2-yl)coumarin (**3e**)*

Yield: 52 %; mp.: 184 °C; IR (KBr): 3044, 2924, 1736, 1607, 1445, 708 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.99 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.08 (s, 2H, C_5'–H), 7.04–7.76 (m, 10H, Ar–H), 8.26 (poorly resolved dd, 1H, C_9'–H), 8.48 (s, 1H, C_3'–H), 9.04 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.87(C_5'), 56.04(OCH_3), 56.13(OCH_3), 111.39(CH), 111.66(CH), 116.35(CH), 119.80(C), 121.16(CH), 121.21(CH), 124.53(CH), 125.09(CH), 127.30(CH), 128.83(CH), 128.96(CH), 131.23(C), 131.89(CH), 133.94(C), 140.90(C), 142.23(CH), 144.03(C), 145.99(C), 149.23(C), 149.57(C), 153.91(C), 160.51(C), 160.86(CO of coumarin); Mass (*m/z*): 447 (M^+); Anal. Calcd. for $C_{29}H_{21}NO_4$: C, 77.84; H, 4.73; N, 3.13. Found: C, 77.77; H, 4.79; N, 3.15.

*3-(4-p-Flouro-5H-indeno[1,2-b]pyridin-2-yl)coumarin (**3f**)*

Yield: 65 %; mp.: 244 °C; IR (KBr): 3048, 2920, 1723, 1606, 1456, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.01 (s, 2H, C_5'–H), 7.21–7.74 (m, 11H, Ar–H), 8.24 (poorly resolved dd, 1H, C_9'–H), 8.45 (s, 1H, C_3'–H), 9.04 (s, 1H, C_4–H); ^{13}C NMR($CDCl_3$, 100 MHz) δ: 34.60(C_5'), doublet centered at 115.86(C_3'' and C_5'', $^2J_{C-F} = 21.0$ *Hz*), 116.34(CH), 119.74(C), 121.25(CH), 124.53(CH), 125.10(CH), 125.58(C), 127.34(CH), 128.85(CH), 129.06 (CH), doublet centered at 130.18(C_2'' and C_6'', $^3J_{C-F} = 9.0$ *Hz*), 131.94(CH), 134.01(C), 134.55(C), 134.58(C), 140.74(C), 142.29(CH), 143.96(C), 145.11(C), 150.64(C), 153.89(C), 160.43(C), 160.89(CO of coumarin), doublet centered at 163.74(C_4'', $^1J_{C-F} = 247.0$ *Hz*); Mass (*m/z*): 405 (M^+); Anal. Calcd. for $C_{27}H_{16}FNO_2$: C, 79.99; H, 3.98; N, 3.45. Found: C, 79.86; H, 4.02; N, 3.42.

*8-Methoxy-3-(4-phenyl-5H-indeno[1,2-b]pyridin-2-yl)coumarin (**3g**)*

Yield: 54 %; mp.: 220 °C; IR (KBr): 3055, 2942, 1701, 1605, 1435, 701, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.02 (s, 3H, OCH_3), 4.06 (s, 2H, C_5'–H), 7.14–7.72 (m, 11H, Ar–H), 8.29 (poorly resolved dd, 1H, C_9'–H), 8.49 (s, 1H, C_3'–H), 9.03 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.66(C_5'), 56.30(OCH_3), 113.75(CH), 120.35(CH), 120.38(C), 121.43(CH), 121.60(CH), 124.34(CH), 125.11(CH), 125.66(C), 127.33(CH), 128.46(CH), 128.69(CH), 128.82(CH), 129.08(CH), 134.35(C), 138.45(C), 140.63(C), 142.60(CH), 143.61(C), 144.17(C), 146.46(C), 146.92(C), 150.43(C), 159.80(C), 160.61(CO of coumarin); Mass (*m/z*): 417 (M^+); Anal. Calcd. for $C_{28}H_{19}NO_3$: C, 80.56; H, 4.59; N, 3.36. Found: C, 80.68; H, 4.67; N, 3.37.

*8-Methoxy-3-(4-p-methyl-5H-indeno[1,2-b]pyridin-2-yl)coumarin (**3h**)*

Yield: 63 %; mp.: 258 °C; IR (KBr): 3051, 2909, 1728, 1602, 1438, 829, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.47 (s, 3H, CH_3), 4.01 (s, 3H, OCH_3), 4.04 (s, 2H, C_5'–H), 7.11–7.62 (m, 10H, Ar–H), 8.25 (poorly resolved dd, 1H, C_9'–H), 8.48 (s, 1H, C_3'–H), 9.00 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.27(CH_3), 34.76(C_5'), 56.31(OCH_3), 113.78(CH), 120.32(CH), 121.46(CH), 124.28(CH), 125.07(CH), 125.75(C), 127.23(CH), 128.35(CH), 128.97(CH), 129.51(CH), 137.17(C),

135.53(C), 138.65(C), 140.63(C), 142.41(CH), 143.61(C), 144.16(C), 146.32(C), 146.94(C), 150.40(C), 159.80(C), 160.56(CO of coumarin); Mass (*m/z*): 431 (M^+); Anal. Calcd. for $C_{29}H_{21}NO_3$: C, 80.72; H, 4.91; N, 3.25. Found: C, 80.81; H, 4.98; N, 3.23.

*8-Methoxy-3-(4-p-methoxy-5H-indeno[1,2-b]pyridin-2-yl)coumarin (**3i**)*

Yield: 65 %; mp.: 244 °C; IR (KBr): 3058, 2931,1717, 1608, 1443, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.92(s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 4.13 (s, 2H, C_5'–H), 7.08–7.72 (m, 10H, Ar–H), 8.41 (poorly resolved dd, 1H, C_9'–H), 8.80 (s, 1H, C_3'–H), 9.13 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 35.27(C_5'), 55.50(OCH_3), 56.41(OCH_3), 114.63(CH), 114.71(CH), 119.88(C), 121.14 (CH), 122.34(CH), 123.79(CH), 124.73(CH), 124.98(CH), 127.98(CH), 129.33(C), 130.12(CH), 130.46(CH), 135.09(C), 143.88(C), 144.48(C), 145.17(CH), 146.94(C), 148.13(C), 158.28(C), 159.41(C), 160.92(C), 165.43(CO of coumarin); Mass (*m/z*): 447 (M^+); Anal. Calcd. for $C_{29}H_{21}NO_4$: C, 77.84; H, 4.73; N, 3.13. Found: C, 77.72; H, 4.79; N, 3.12.

*8-Methoxy-3-(4-chloro-5H-indeno[1,2-b]pyridin-2-yl)coumarin (**3j**)*

Yield: 56 %; mp.: 281 °C; IR (KBr): 3047, 2901, 1713, 1610, 1453, 825 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.03 (s, 3H, OCH_3), 4.05 (s, 2H, C_5'–H), 7.15–7.67 (m, 10H, Ar–H), 8.36 (poorly resolved dd, 1H, C_9'–H), 8.48 (s, 1H, C_3'–H), 9.07 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 35.61(C_5'), 56.64(OCH_3), 109.95(C), 109.97(C), 112.78(C), 115.62(CH), 118.45(CH), 118.98(C), 121.57(CH), 122.41(C), 126.15 (CH), 126.94(CH), 129.25(CH), 129.72(CH), 129.76(CH), 130.14(CH), 132.82(C), 138.24(C), 141.09(C), 143.45(C), 145.85(C), 147.07(C), 148.27(CH), 153.24(C), 160.23(CO of coumarin); Mass (*m/z*): 451 (M^+); Anal. Calcd. for $C_{28}H_{18}ClNO_3$: C, 74.42; H, 4.01; N, 3.10. Found: C, 74.36; H, 4.04; N, 3.13.

*8-Methoxy-3-(4-(3,4-dimethoxyphenyl)-5H-indeno[1,2-b]pyridin-2-yl)coumarin (**3k**)*

Yield: 67 %; mp.: 210 °C; IR (KBr): 3042, 2936, 1720, 1625, 1443, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.99 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.07 (s, 2H, C_5'–H), 7.03–7.62 (m, 9H, Ar–H), 8.25 (poorly resolved dd, 1H, C_9'–H), 8.49 (s, 1H, C_3'–H), 9.02 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.87(C_5'), 56.04(OCH_3), 56.15(OCH_3), 56.32(OCH_3), 111.39(CH), 111.67(CH), 113.74(C), 120.29(CH), 120.46(C), 121.19(CH), 121.33(C), 121.93(C), 124.35(CH), 125.11(CH), 126.04(C), 126.88(C), 127.30(CH), 128.95(CH), 131.23(C), 133.98(C), 140.95(C), 142.38(CH), 143.61(C), 144.07(C), 146.06(C), 146.99(C), 149.22(C), 150.62(C), 159.15(C), 160.84(CO of coumarin); Mass (*m/z*): 477 (M^+); Anal. Calcd. for $C_{30}H_{23}NO_5$: C, 75.46; H, 4.85; N, 2.93. Found: C, 75.54; H, 4.91; N, 2.97.

*8-Methoxy-3-(4-fluoro-5H-indeno[1,2-b]pyridin-2-yl)coumarin (**3l**)*

Yield: 55 %; mp.: 242 °C; IR (KBr): 3050, 2926, 1713, 1605, 1435, 841 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.00 (s, 2H, C_5'–H), 4.01 (s, 3H, OCH_3), 7.11–7.69 (m, 10H, Ar–H), 8.23 (poorly resolved dd, 1H, C_9'–H), 8.46 (s, 1H, C_3'–H), 9.01 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.59(C_5'), 56.27(OCH_3), 113.70(CH), doublet centered at 115.84(C_3'' and C_5'', $^2J_{C-F} = 22.0$ *Hz*), 120.30(CH), 120.37(C), 121.23(CH), 121.28(CH), 124.34(CH), 125.08(CH), 125.72(C), 127.31(CH), 129.02(CH), doublet centered at 130.20(C_2'' and C_6'', $^3J_{C-F} = 7.0$ *Hz*), 134.02(C), 134.57(C), 140.74(C), 142.43(CH), 143.55(C), 143.96(C), 145.11(C), 146.90(C), 150.60(C), 159.84(C), 160.83(CO of coumarin), doublet centered at 163.00(C_4'', $^1J_{C-F} = 244.0$ *Hz*); Mass (*m/z*): 435 (M^+); Anal. Calcd. for $C_{28}H_{18}FNO_3$: C, 77.23; H, 4.17; N, 3.22. Found: C, 77.11; H, 4.10; N, 3.23.

*3-(4-Phenyl-5H-indeno[1,2-b]pyridin-2-yl)benzo[f]coumarin (**3m**)*

Yield: 68 %; mp.: 294 °C; IR (KBr): 3057, 2926, 1720, 1626, 1436, 699, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.35 (s, 2H, C_5'–H), 7.65–9.58 (m, 16H, Ar–H), 9.86 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 35.66(C_5'), 110.18(C), 113.02(C), 113.81(C), 115.84(C), 116.07(CH), 118.67(C), 121.82(CH), 122.37(CH), 126.13(CH), 127.79(CH), 128.50 (CH), 129.12(CH), 129.51(CH), 129.73(CH), 130.18(CH), 130.78(C), 131.64(CH), 133.85(CH), 134.72(CH), 138.18(CH), 138.52(CH), 143.11(C), 143.95(C), 146.02(C), 152.89(C), 155.07(C), 155.59(C), 160.30(CO of coumarin); Mass (*m/z*): 437 (M^+); Anal. Calcd. for $C_{31}H_{19}NO_2$: C, 85.11; H, 4.38; N, 3.20. Found: C, 84.99; H, 4.44; N, 3.23.

*3-(4-p-Methyl-5H-indeno[1,2-b]pyridin-2-yl)benzo[f]coumarin (**3n**)*

Yield: 64 %; mp.: 266 °C; IR (KBr): 3031, 2920, 1719, 1609, 1433, 816 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 2.48 (s, 3H, CH_3), 4.09 (s, 2H, C_5'–H), 7.36–8.61 (m, 15H, Ar–H), 9.90 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.32(CH_3), 34.81(C_5'), 114.05(C), 116.61(CH), 121.47(CH), 122.16(CH), 125.10(CH), 126.10(CH), 127.32(CH), 128.37(CH), 128.99(CH), 129.09(CH), 129.56(CH), 129.68(CH), 130.41(C), 133.41(CH),

134.18(CH), 135.54(C), 138.23(CH), 138.74(C), 139.97(C), 140.68(C), 144.18(C), 144.93(C), 146.43(C), 149.57(C), 150.60(C), 153.78(C), 156.11(C), 160.47(CO of coumarin); Mass (*m/z*): 451 (M^+); Anal. Calcd. for $C_{32}H_{21}NO_2$: C, 85.12; H, 4.59; N, 3.10. Found: C, 85.20; H, 4.61; N, 3.07.

*3-(4-p-Methoxy-5H-indeno[1,2-b]pyridin-2-yl)benzo[f]coumarin (**3o**)*

Yield: 59 %; mp.: 278 °C; IR (KBr): 3046, 2923, 1716, 1621, 1439, 836 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.93 (s, 3H, OCH_3), 4.10 (s, 2H, C_5'–H), 7.08–8.63 (m, 15H, Ar–H), 9.91 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 35.66(C_5'), 55.43(OCH_3), 110.18(C), 113.02(C), 113.81(CH), 115.84 (CH), 116.07(CH), 118.67(C), 121.82(CH), 122.37(CH), 126.13(CH), 127.79(CH), 128.50(CH), 129.12(CH), 129.51(CH), 129.73(CH), 130.18(C), 130.78(C), 131.64(C), 133.85(CH), 134.72(CH), 138.18(C), 138.52(C), 143.11(C), 143.95(CH), 146.02(C), 152.89(C), 155.07(C), 155.59(C), 160.30(CO of coumarin); Mass (*m/z*): 467 (M^+); Anal. Calcd. for $C_{32}H_{21}NO_3$: C, 82.21; H, 4.53; N, 3.00. Found: C, 82.32; H, 4.56; N, 3.01.

*3-(4-Chloro-5H-indeno[1,2-b]pyridin-2-yl)benzo[f]coumarin (**3p**)*

Yield: 61 %; mp.: 280 °C; IR (KBr): 3054, 2930, 1712, 1617, 1444, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.05 (s, 2H, C_5'–H), 7.48–8.61 (m, 15H, Ar–H), 9.92 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 35.58(C_5'), 113.00(C), 113.80(C), 115.83(C), 116.02(CH), 120.67(CH), 121.74 (CH), 122.36(CH), 126.15(CH), 127.88(CH), 129.05(CH), 129.59(CH), 129.83(CH), 130.12(CH), 130.25(CH), 130.84(C), 131.56(C), 133.03(C), 134.07(CH), 138.07(C), 138.42(C), 138.79(CH), 143.14(CH), 143.97(C), 145.89(C), 153.12(C), 154.29(C), 155.15(C), 162.32(CO of coumarin); Mass (*m/z*): 471 (M^+); Anal. Calcd. for $C_{31}H_{18}ClNO_2$: C, 78.90; H, 3.84; N, 2.97. Found: C, 78.99; H, 3.79; N, 3.01.

*3-(4-(3,4-Dimethoxy)-5H-indeno[1,2-b]pyridin-2-yl)benzo[f]coumarin (**3q**)*

Yield: 55 %; mp.: 240 °C; IR (KBr): 3057, 2926, 1718, 1605, 1435, 717 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.00 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.09 (s, 2H, C_5'–H), 7.04–8.58 (m, 14H, Ar–H), 9.89 (s, 1H, C_4–H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 34.77(C_5'), 56.14(OCH_3), 56.23(OCH_3), 114.06(C), 116.61(C), 121.47(CH), 122.17 (CH), 125.10(CH), 126.11(CH), 127.32(CH), 128.37(CH), 129.00(CH), 129.09(CH), 129.57(CH), 129.68(CH), 130.41(C), 133.42(CH), 134.18(CH), 135.54(C), 138.24 (CH), 138.74(C), 139.97(C), 140.68(CH), 144.19(C), 144.93(C), 146.43(C), 149.58(C), 150.60(C), 153.78(C), 156.11(C), 160.48(CO of coumarin); Mass (*m/z*): 497 (M^+); Anal. Calcd. for $C_{33}H_{23}NO_4$: C, 79.66; H, 4.66; N, 2.82. Found: C, 79.73; H, 4.62; N, 2.84.

*3-(4-Fluoro-5H-indeno[1,2-b]pyridin-2-yl)benzo[f]coumarin (**3r**)*

Yield: 64 %; mp.: 204 °C; IR (KBr): 3052, 2932, 1720, 1603, 1442, 833 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 4.06 (s, 2H, C_5'–H), 7.15–8.61 (m, 15H, Ar–H), 9.91 (s, 1H, C_4–H); ^{13}C NMR($CDCl_3$, 100 MHz) δ: 32.31(C_5'), 113.01(C), 113.80(C), doublet centered at 115.93(C_3'' and C_5'', $^2J_{C-F} = 22.0$ *Hz*), 120.67(CH), 121.75 (CH), 122.36(CH), 126.16(CH), 127.88(C), 129.06(CH), 129.59 (CH), 129.83(CH), doublet centered at 130.19(C_2'' and C_6'', $^3J_{C-F} = 8.0$ *Hz*), 130.84(C), 131.57(CH), 133.03(CH), 134.07(C), 138.08(CH), 138.42(C), 138.80(C), 143.14 (CH), 143.99(C), 145.89(C), 153.12(C), 154.29(C), 155.16(C), 160.52(CO of coumarin), doublet centered at 163.24(C_4'', $^1J_{C-F} = 242.0$ *Hz*); Mass (*m/z*): 455 (M^+); Anal. Calcd. for $C_{31}H_{18}FNO_2$: C, 81.75; H, 3.98; N, 3.08. Found: C, 81.64; H, 3.90; N, 3.06.

Antimicrobial Activity

The newly synthesized compounds were screened for their minimum inhibitory concentrations (MICs) by broth micro dilution method. DMSO was used as a diluent to get desired concentration of compounds to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately subcultured(before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 °C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the compound concentrations. The lowest concentration (highest dilution) required to arrest the growth of bacteria was regarded as MIC. All the tubes showing no visible growth (same as control tube) were subcultured and incubated overnight at 37 °C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show (a) similar number of colonies indicating bacteriostatic (b) a reduced number of colonies indicating a partial or slow bactericidal activity (c) no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized compound was diluted obtaining 2,000 μg/ml concentration as a stock solution. In primary screening, 500, 250, and 200 μg/ml

concentrations of the synthesized compounds were taken. The active synthesized compounds found in this primary screening were further tested in a second set of dilution against all microorganisms. The compounds found active in primary screening were similarly diluted to obtain 100, 62.5, and 50 μg/ml concentrations. The highest dilution showing at least 99 % inhibition is taken as MIC.

Conclusion

The present research study reports the successful synthesis of a novel series of indenopyridine substituted coumarin derivatives along with their antimicrobial screening against different pathogenic strains. Among this series, compounds, **3h** and **3l** are the most potent against *S. aureus* and *B. subtilis,* respectively, while rest of the compounds are moderate to antibacterial and antifungal activity with respect to other analogous.

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