

Synthesis and Characterization of Some New Azetidin-2-ones Containing Coumarin Moiety and Their Antimicrobial Study

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Abstract

A series of novel azetidinones **5a-i** have been synthesized by cyclocondensation of various Schiff bases of coumarin with chloro acetyl chloride in presence of triethyl amine. The reaction of 4-hydroxy coumarin with POCl₃ yielded 4-chloro coumarin **2** and 4-chloro-3, 4', 3', 4"-tercoumarin **2a**. Compound **2** was reacted with *p*-phenylene diamine to yield 4-[(4-aminophenyl)amino]-2*H*-chromen-2-one. Various Schiff bases of coumarin were synthesized by condensation of 4-[(4-aminophenyl)amino]-2*H*-chromen-2-one with different aldehydes. The structures of the newly synthesized compound were confirmed by IR, ¹H NMR, ¹³C NMR and C, H, N analysis. The Schiff bases and azetidin-2-one derivatives were evaluated for their anti bacterial and antifungal activity by broth dilution method.

Keywords: Coumarin, Schiff bases, Azetidinones, Antibacterial, Antifungal

1. Introduction

2-Azetidines have been extensively investigated by the organic chemists due to their close association with various types of biological activities (Sharma, M.C. et. al 2009). Azetidine-2-ones also have great importance because of the use of β -lactam derivatives as antibacterial agents (Toraskar, M. et. al 2010). Recently, some other types of biological activity beside the antibacterial activity have been reported in compounds containing 2-azetidinone ring. Such biological activities include antimicrobial, anti tubercular, anti inflammatory, anticonvulsant, local anesthetics, and hypoglycemic agents (Kumar, V. et. al 2009, Rajasekaran, A. et. al 2010).

Coumarin and its derivatives represent one of the most active classes of compound possessing a wide spectrum of biological activity (Zuo, H. et.al 2008, Lee, S. et.al 2006, Moghadam, K. et.al 2004). Novobiocin and chlorobiocin are established antimicrobials containing a coumarin skeleton (Deklc, S.V. et.al 2007). Many of these compounds found to be active as, antibacterial (El-Saghier, A.M. et.al 2000, Musicki, B. et.al 2000, Azizian, J. et.al 2008), antifungal (Satyanarayan, V.S. et.al 2008), anti inflammatory (Garazd, M.M. et.al 2007),

anticoagulant (Smitha, G. et.al 2004), anti-HIV (Kotali, A. et.al 2008), and antitumor (Hamdi, N. et.al 2006), In addition, these compounds are used as additives to food and cosmetics (Maheswara, M. et.al 2006). Coumarin derivatives are commonly used as optical whiteners, luminescence dyes (Rajitha, B. et.al 2006), active media for lasers (Zabradnik, M. et.al 1992) and solar collector (Sizova, Z.A. et.al 2002). Various analogues of 4-substituted coumarin such as 4-chlorocoumarins exhibit antimicrobial activity. From the above line of reasoning we directed our work towards synthesis of various coumarin derivatives of biological interest using 4-chloro coumarin as a key starting material.

The aim of the present work was to synthesize new azetidine-2-one derivatives containing coumarin moiety in order to find new biologically active compound. Thus, synthesis of novel azetidine-2-one derivatives has been achieved.

2. Experimental

All the chemicals used in the synthesis were of analytical grade. The melting points were determined in open capillary on Veego (Model: VMP-D) electronic apparatus and are uncorrected. The IR spectra of synthesized compounds were recorded on Shimadzu 8400-S FT-IR spectrophotometer using potassium bromide. To monitor the reactions, as well as, to establish the identity and purity of reactants and products, thin layer chromatography was performed on microscopic glass slides (2x7.5 cm) coated with silica gel-G, using toluene-acetone and chloroform-methanol, as the solvent systems and spots were visualized under UV radiation. Nuclear magnetic resonance spectra were recorded on Varian 400 MHz model spectrometer using DMSO as a solvent and TMS as internal reference (Chemical shifts in δ ppm). All new compounds were analyzed for C, H, and N and the results are in acceptable range.

2.1 Material: 4-Hydroxy coumarin, triethyl amine (TEA), POCl_3 , *p*-phenylene diamine, aldehydes, chloro acetyl chloride.

2.2 Synthesis of 4-chloro coumarin (2)

4-Hydroxycoumarin 1 (30 g, 0.185 mol) and 60 mL POCl_3 were refluxed for 1h, cooled, and slowly poured into crushed ice (700 g) with vigorous stirring. The solid was collected by filtration and washed successively with ice-water. Azeotropic distillation with *n*-hexane, hot filtration of the by-product (15 g, 17 %), followed by evaporation of solvent and crystallization yielded (21.9 g, 65%) of 4-chloro coumarin with m.p. 87-89 °C (Kováč, M. et.al 2001); IR (KBr, cm^{-1}) 1664.62(C=O of coumarin), 773.48(Ar-C-Cl); $^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 7.30-7.91 (m, 3H, Ar-H), 7.93 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3 of coumarin); $^{13}\text{C NMR}$ 117.22, 118.14, 124.87, 125.84, 130.18, 146.04, 149.04, 149.22, 161.23. Anal. Calcd. For $\text{C}_9\text{H}_5\text{ClO}_2$: C, 59.86; H, 2.79. Found C, 59.88; H, 2.76.

4-chloro-3, 4', 3', 4"-tercoumarin (by-product) (**2a**): crystallization from acetic acid gave yellowish crystals, m.p. 322-327 °C. IR (KBr, cm^{-1}) 769.62(C-Cl), 1718 (C=O), 1593-1625 (Aromatic -CH str.), 3039-3080 (C=C), 1187 (C-O str.); $^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 7.46-7.92 (m, 9H, Ar-H), 7.27 (s, 1H, 3'-H); $^{13}\text{C NMR}$ 114.56, 117.60, 118.01, 118.30, 118.83, 118.96, 120.05, 123.40, 124.83, 125.55, 126.00, 126.10, 126.52, 126.69, 132.59, 133.32, 136.13, 149.96, 151.12, 151.95, 156.75, 157.00, 161.80, 163.25. Anal. Calcd. For $\text{C}_{27}\text{H}_{13}\text{ClO}_6$: C, 69.16; H, 2.79. Found C, 69.20; H, 2.75.

2.3 Synthesis of 4-[(4-Aminophenyl)amino]-2H-chromen-2-one (3)

To a boiling solution of the 4-chloro coumarin (10 g, 0.05mol) and little amount of Triethyl amine in ethanol (30 mL) was added to a boiling solution of *p*-phenylene diamine (6.09 g, 0.05mol) in ethanol (30 mL). The mixture was refluxed for 1h and left at room temperature for 4-5 h. The precipitate was separated and recrystallized from DMF. Yield: 78 %; m.p. 265-273 °C; IR (KBr, cm^{-1}) 3341.78 (NH str. for 2^0), 3290.67, (NH for 1^0), 1664.62(C=O of coumarin); $^1\text{H-NMR}$ (400 MHz, $\text{DMSO}-d_6$) δ 6.53-7.26 (m, 7H, Ar-H), 3.31(s, 2H, NH_2), 3.76 (s, 1H, C-NH), 7.93 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3 of coumarin); $^{13}\text{C NMR}$ 88.22, 116.51, 118.91, 121.80, 123.59, 124.25, 125.79, 131.84, 132.55, 145.13, 149.08, 155.32, 161.98. Anal. Calcd. For $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2$: C, 71.42; H, 4.79; N, 11.10. Found C, 71.40; H, 4.82; N, 11.06.

2.4 General procedure for the synthesis of Schiff bases (4a-i)

To a solution of compound **3** (1.36g; 0.01mol) in absolute ethanol (50 mL), containing a catalytic amount of piperidine, equimolecular amount of the appropriate aldehydes (for e.g. benzaldehyde) was added. The reaction mixture was heated under refluxed for 5-6 h. It was then cooled at room temperature, poured into crushed ice, filtered, washed, dried and recrystallized from DMF to yield 4-[(4-{[(*E*)-phenylmethylidene]amino}phenyl)amino]-2H-chromen-2-one. Other Schiff bases were obtained in similar manner.

2.5 General procedure for the synthesis of spiro β -lactum derivatives (5a-i)

A mixture of different Schiff bases (**4a-i**) (0.002mol) and triethylamine (TEA) (0.004mol) was dissolved in 1, 4-dioxane (50 mL) and cooled and stirred. To this well stirred solution chloro acetyl chloride (0.004mol) was added drop wise within a period of 20 minute. The reaction mixture was then stirred for further 3h and then refluxed for 8h. The resultant mixture was concentrated, cooled, then poured into ice-cold water and then extracted with ethyl acetate. The solvent was evaporated and the product thus obtained was purified by column chromatography over silica gel using 15% ethyl acetate: 85% benzene as eluent. Recrystallisation from ether/n-hexane yields azetidinone derivatives (**5a-i**).

2.5.1 Characterization data of synthesized compound

3- Chloro-1-[4-(2-oxo-2H-chromen-4-ylamino)-phenyl]-4-phenyl-azetidin-2-one(**5a**).

Yield: 73%; m.p. 252-254⁰C ; IR (KBr,cm⁻¹) : 3296.46 (N-H str.), 1718.63 (C=O of β -lactum), 1664.62 (C=O of coumarin), 806.27(C-Cl bending); ¹H -NMR (400 MHz, DMSO- *d*₆) δ 6.55-7.68 (m,12H,Ar-H); 3.76 (s,1H,C-NH); 7.93 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3 of coumarin), 4.97 (d,1H, CH-Cl of azetidinone), 5.19 (d,1H, CH-Ar of azetidinone); ¹³C NMR 55.67, 60.45, 88.22, 116.11, 117.50, 120.85, 123.59, 124.25, 125.79, 128.52, 130.36, 132.55, 135.40, 136.09, 136.45, 140.96, 149.08, 155.26, 161.23,162.59. Anal. Calcd. For C₂₄H₁₇ClN₃O₅: C, 62.41; H, 3.49; N, 9.10. Found: C, 62.40; H, 3.47; N, 9.10.

3-Chloro-4-(4-nitrophenyl)-1-{4-[(2-oxo-2H-chromen-4-yl)amino]phenyl}azetidin-2-one(**5b**).

Yield: 68%; m.p. 256-259⁰C ; IR (KBr,cm⁻¹) : 3296.46 (N-H str.), 1718.63 (C=O of β -lactum), 1664.62 (C=O of coumarin), 823.63 (C-Cl bending), 1552.75 cm⁻¹(N=O str.); ¹H -NMR (400 MHz, DMSO- *d*₆) δ 6.53-7.70 (m,11H,Ar-H); 3.76 (s,1H,C-NH); 7.93 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3 of coumarin), 4.97(d,1H, CH-Cl of azetidinone), 5.19(d,1H, CH-Ar of azetidinone); ¹³C NMR 52.26, 85.38, 117.75, 123.11, 123.40,124.04, 124.32, 125.79, 126.16, 128.45, 130.19, 132.99, 137.74, 142.09, 148.37, 152.84, 153.93,159.26, 162.06. Anal. Calcd. For C₂₄H₁₇ClN₃O₅: C, 62.41; H, 3.49; N, 9.10. Found: C, 62.40; H, 3.47; N, 9.10.

3-Chloro-4-(3-nitrophenyl)-1-{4-[(2-oxo-2H-chromen-4-yl)amino]phenyl}azetidin-2-one(**5c**).

Yield: 65%; m.p. 273--275⁰C ; IR (KBr,cm⁻¹) : 3296.46 (N-H str.), 1716.70 (C=O of β -lactum), 1664.62 (C=O of coumarin), 833.28(C-Cl bending), 1536.35 cm⁻¹(N=O str.) ; ¹H -NMR (400 MHz, DMSO- *d*₆) δ 6.55-7.69 (m,11H,Ar-H); 3.76 (s,1H,C-NH); 7.93 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3 of coumarin), 4.97(d,1H, CH-Cl of azetidinone), 5.19(d,1H, CH-Ar of azetidinone); ¹³C NMR 52.30, 85.38, 117.65, 123.11, 123.40,124.04, 124.38, 125.77, 126.10, 127.50, 130.15, 132.95, 136.08, 142.05, 147.49, 152.80, 153.97,159.20, 162.10. Anal. Calcd. For C₂₄H₁₇ClN₃O₅: C, 62.41; H, 3.49; N, 9.10. Found: C, 62.40; H, 3.47; N, 9.10.

3-Chloro-4-(3,4-dimethoxy-phenyl)-1-[4-(2-oxo-2H-chromen-4-ylamino)-phenyl]-azetidin-2-one(**5d**). Yield: 70%; m.p. 281-285⁰C ; IR (KBr,cm⁻¹) : 3296.46 (N-H str.), 1716.70 (C=O of β -lactum), 1664.62 (C=O of coumarin), 842.92 (C-Cl bending), 1286.56 cm⁻¹(Ar-OCH₃) ; ¹H -NMR (400 MHz, DMSO- *d*₆) δ 6.58-7.60 (m,10H,Ar-H); 3.76 (s,1H,C-NH); 7.93 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3 of coumarin), 3.38 (S,3H,-OCH₃), 4.97(d,1H, CH-Cl of azetidinone), 5.19(d,1H, CH-Ar of azetidinone); ¹³C NMR 55.96, 56.15, 85.38, 115.00, 117.55, 122.37, 123.30, 124.11, 126.36, 129.52,129.66, 136.20, 149.20, 149.70, 149.81, 152.81, 152.40, 153.89, 159.82, 160.72, 161.99. Anal. Calcd. For C₂₆H₂₁ClN₂O₅: C, 65.48; H, 4.44; N, 5.87 Found: C, 65.47; H, 4.45; N, 5.85.

3-Chloro-4-(4-chloro-phenyl)-1-[4-(2-oxo-2H-chromen-4-ylamino)-phenyl]-azetidin-2-one(**5e**).

Yield: 78%; m.p. 270-272⁰C ; IR (KBr,cm⁻¹) : 3296.46 (N-H str.), 1703.20 (C=O of β -lactum), 1664.62 (C=O of coumarin), 827.70.70 (C-Cl bending), 751.30 cm⁻¹(Ar- C-Cl); ¹H -NMR (400 MHz, DMSO- *d*₆) δ 6.56-7.66 (m,11H,Ar-H); 3.76 (s,1H,C-NH); 7.93 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3 of coumarin), 4.97(d,1H, CH-Cl of azetidinone), 5.19(d,1H, CH-Ar of azetidinone); ¹³C NMR 60.45, 65.10, 85.30, 116.11, 117.50, 118.91, 120.85, 123.59, 124.25, 125.79, 129.08, 129.23, 131.84, 135.76, 136.09, 140.96, 149.08, 155.26, 161.23, 162.59. Anal. Calcd. For C₂₄H₁₆Cl₂N₂O₃: C, 63.87; H, 3.57; N, 6.21. Found: C, 63.89; H, 3.55; N, 6.21.

3-Chloro-4-(4-methylphenyl)-1-{4-[(2-oxo-2H-chromen-4-yl)amino]phenyl}azetidin-2-one(**5f**).

Yield: 72%; m.p. 258-260⁰C ; IR (KBr,cm⁻¹) : 3296.46 (N-H str.), 1700.31 (C=O of β -lactum), 1664.62 (C=O of coumarin), 821.70 (C-Cl bending), 1454.38 cm⁻¹(Ar-CH₃); ¹H -NMR (400 MHz, DMSO- *d*₆) δ 6.58-7.69 (m,11H,Ar-H), 3.76 (s,1H,C-NH), 7.93 (d, 1H, H at C-5 of coumarin), 2.16 (S,3H,CH₃), 4.97(d,1H, J=2.2 Hz CH-Cl of azetidinone), 5.19(d,1H, J=2.3 Hz CH-Ar of azetidinone); ¹³C NMR 21.15, 59.45, 60.04, 85.35, 116.11, 117.50, 118.91, 120.85, 123.59, 124.25, 125.79, 129.49, 130.44, 132.19, 133.25, 136.09, 140.96, 149.08, 155.26,

161.23, 162.26. Anal. Calcd. For $C_{25}H_{19}ClN_2O_3$: C, 69.69; H, 4.44; N, 6.50. Found: C, 69.65; H, 4.42; N, 6.49.

2-(3-Chloro-4-oxo-1-{4-[(2-oxo-2H-chromen-4-yl)amino]phenyl}azetidin-2-yl)benzaldehyde (**5g**).

Yield: 75%; m.p. 289-291°C; IR (KBr, cm^{-1}): 3296.46 (N-H str.), 1716.47 (C=O of β -lactum), 1664.62 (C=O of coumarin), 842.78 (C-Cl bending), 2951.19 (Ar-CHO Str); 1H -NMR (400 MHz, DMSO- d_6) δ 6.55-7.66 (m, 11H, Ar-H), 3.76 (s, 1H, C-NH), 7.93 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3 of coumarin), 10.22 (s, 1H, CHO), 4.97 (d, 1H, CH-Cl of azetidinone), 5.19 (d, 1H, CH-Ar of azetidinone); ^{13}C NMR 55.40, 56.72, 86.45, 116.11, 117.50, 118.91, 120.85, 123.59, 124.25, 125.79, 128.56, 133.43, 134.71, 135.07, 135.41, 136.09, 140.96, 141.26, 149.08, 155.26, 161.23, 162.59, 191.59. Anal. Calcd. For $C_{25}H_{17}ClN_2O_4$: C, 67.50; H, 3.85; N, 6.30. Found: C, 67.48; H, 3.84; N, 6.30.

3-Chloro-4-naphthalen-1-yl-1-[4-(2-oxo-2H-chromen-4-ylamino)-phenyl]-azetidin-2-one (**5h**).

Yield: 68%; m.p. 297-300°C; IR (KBr, cm^{-1}): 3296.46 (N-H str.), 1691.63 (C=O of β -lactum), 1664.62 (C=O of coumarin), 840.10 (C-Cl bending); 1H -NMR (400 MHz, DMSO- d_6) δ 6.53-7.90 (m, 14H, Ar-H), 3.76 (s, 1H, C-NH), 7.93 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3 of coumarin), 4.97 (d, 1H, CH-Cl of azetidinone), 5.19 (d, 1H, CH-Ar of azetidinone); ^{13}C NMR 54.48, 85.57, 116.11, 117.50, 118.91, 120.85, 123.59, 124.25, 125.79, 126.27, 127.12, 127.19, 127.38, 128.66, 132.29, 136.09, 138.18, 140.96, 149.08, 155.26, 161.23, 162.59. Anal. Calcd. For $C_{28}H_{19}ClN_2O_3$: C, 72.03; H, 4.10; N, 6.00. Found: C, 72.02; H, 4.13; N, 6.02.

3-Chloro-4-(2-chloro-quinolin-3-yl)-1-[4-(2-oxo-2H-chromen-4-ylamino)-phenyl]-azetidin-2-one (**5i**).

Yield: 79%; m.p. 289-292°C; IR (KBr, cm^{-1}): 3296.46 (N-H str.), 1697.41 (C=O of β -lactum), 1664.62 (C=O of coumarin), 823.63 (C-Cl bending), 753.23 (Ar-C-Cl); 1H -NMR (400 MHz, DMSO- d_6) δ 6.54-7.80 (m, 12H, Ar-H), 3.76 (s, 1H, C-NH), 7.93 (d, 1H, H at C-5 of coumarin), 5.75 (s, 1H, H at C-3 of coumarin), 4.97 (d, 1H, CH-Cl of azetidinone), 5.19 (d, 1H, CH-Ar of azetidinone); ^{13}C NMR 58.85, 68.30, 85.32, 116.11, 117.50, 118.91, 120.85, 123.59, 124.25, 125.79, 128.66, 128.84, 130.08, 132.55, 136.09, 138.80, 140.96, 144.75, 148.26, 149.08, 155.26, 161.23, 162.28. Anal. Calcd. For $C_{27}H_{17}Cl_2N_3O_3$: C, 64.55; H, 3.41; N, 8.36. Found: C, 64.51; H, 3.40; N, 8.35.

2.6 Antimicrobial activity

All the synthesized compounds were tested for their antibacterial and antifungal activity (MIC-minimum inhibition concentration) in vitro by broth dilution method with two gram positive bacteria *S. aureus* and *B. subtilis* and gram negative bacteria *E. coli*, *P. aeruginosa*, and fungi species like *C. albicans*, *A. niger* organisms taking ciprofloxacin, ampicillin, chloramphenicol, norfloxacin, flucanazole, griseofulvin, and nystatin. Muller Hinton broth was used as nutrient medium to grow and dilute the drug suspension for test. DMSO was used as a diluent which not effected the growth of microbes.

3. Results and Discussion

All the reactions were carried out under conventional methods. 4-[(4-Aminophenyl)amino]-2H-chromen-2-one **3** was a key intermediate that required to prepare the target product. 4-Chloro coumarin **2** was prepared from 4-hydroxy coumarin **1**. The selectivity of the reaction of **1** with $POCl_3$ was low, because a considerable amount of 4-chloro-3, 4', 3', 4"-tercoumarin was formed as a byproduct. In this method n-hexane was used to improve the yield of 4-chloro coumarin and significantly decreased yield of the by product. The key intermediate 4-[(4-aminophenyl)amino]-2H-chromen-2-one **3** was easily prepared from 4-chloro coumarin using little amount of triethyl amine. The IR spectra of compound **3** revealed a strong band at 3290.67 cm^{-1} confirming the presence of 2^0 -NH group and band at 3341.78 cm^{-1} indicating the presence of 1^0 -NH₂ group. The IR spectrum of compound **3** showed a band at 1664.62 cm^{-1} which is the characteristic for C=O of coumarin. The 1H NMR of compound **3** showed signal between 6.53-7.26 δ ppm for aromatic protons. Compound **4b** showed a characteristic band at 3290 cm^{-1} observed for 2^0 -NH group which indicate the disappearance of -NH₂ gr. of **3** and confirmed the formation of Schiff base. Stretching vibration for C=N of Schiff base present at 1473-1602 cm^{-1} . The 1H NMR showed signal between 6.55-7.52 δ ppm for aromatic protons. All the Schiff bases reacted with chloro acetyl chloride to afford azetidinone derivatives. Compound **5b** showed a characteristic band at 1718.63 cm^{-1} confirming the presence of C=O group and C-Cl present at 831.35 cm^{-1} of azetidinone. The 1H NMR of **5b** showed signal between 6.53-7.70 for aromatic protons and doublet at 4.97 for CHCl of azetidinone. ^{13}C NMR of **5b** showed characteristic peak at 52.26, 35.38, 117.75, 123.11, 123.40, 124.04, 124.32, 125.79, 126.16, 128.45, 130.19, 132.99, 137.74, 142.09, 148.37, 152.84, 153.93, 159.26, and 162.06. All the compound **5a-i** was synthesized diastereoselectively. In compound **5f** J=2.2 Hz (CHCl of azetidinone) and J=2.3 Hz (CH-Ar of azetidinone).

All the newly synthesized compounds were screened for their antimicrobial activity. Azetidinone derivatives with Ar gr. such as 4-chloro phenyl, 4-methy phenyl and 2-chloro quinonyl found to be more active than others.

From the result in table 1 Schiff base **4e** showed excellent activity when compared with ampicillin and chloramphenicol; while **5a**, **5e**, **5f** and **5i** demonstrated good activity against *E.coli* and **5f**, **5i** significant activity against *P.aeruginosa*; while **4c**, **5b**, **5e**, **5i** showed good activity against *S.aureus* and **5g** and **5i** demonstrated significant activity against *B.subtilis* when compared with standard drug ampicillin.

From the MIC results of fungal activity, Schiff base **4d** was found equipotent to Nystatin; while **4a**, **4c**, **4e**, **4f**, **4g**, **4h**, **4i** demonstrated significant activity. The azetidinones **5c**, **5d**, **5e**, **5f**, **5g**, **5h**, **5i** demonstrated good activity against *C. albicans* when compared with Griseofulvin. All remaining compounds demonstrated good to moderate activity against remaining fungal specie (*A. niger*).

4. Conclusion

A series of coumarin based azetidine-2-one compounds were successfully synthesized and tested for their in vitro antimicrobial activity. Overall conclusion made for synthesized compounds are that most of the compounds were more active against *E. coli*, *S. aureus* and *B. subtilis*. Some of the compounds were found equipotent to ampicillin and chloramphenicol such as **5e**, **5f**, **5i** and found less active than other standard drugs. Most of the compounds demonstrated antifungal activity for *C. albicans* similar to that of Griseofulvin and found less active than other fungal specie (*A. niger*).

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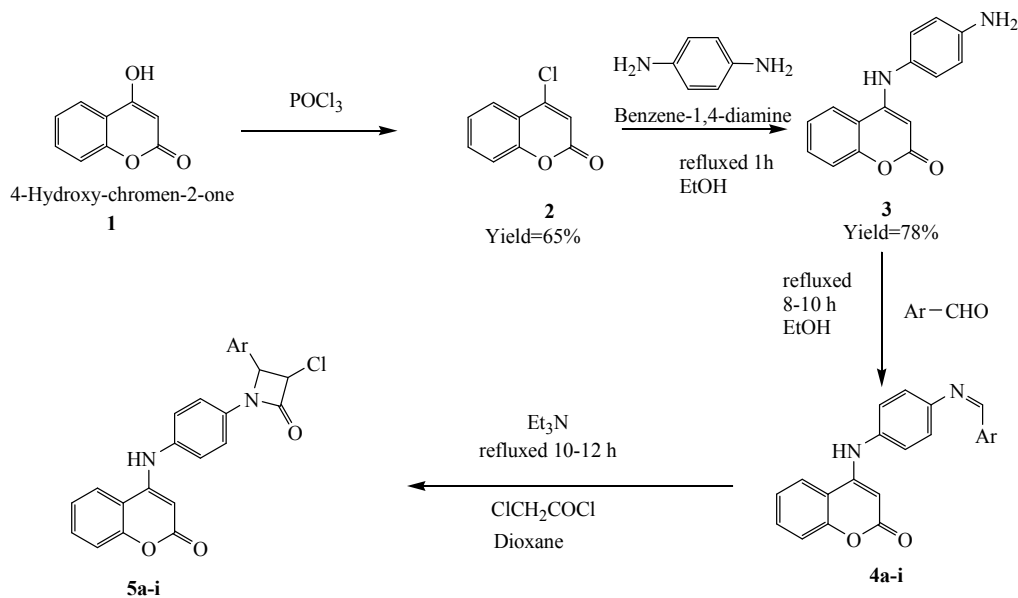
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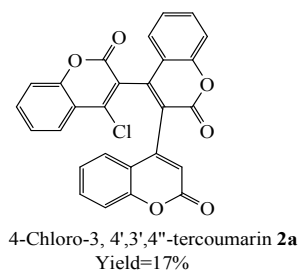
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Table 1. Antimicrobial study (MIC µg/mL) of synthesized compound **4a-5i**. Minimum inhibitory concentration

Comp. no.	Ar	Gram negative		Gram positive		Fungal species	
		<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>B. subtilis</i>	<i>C. albicans</i>	<i>A. niger</i>
4a	Phenyl	500	1000	500	1000	500	1000
4b	4-Nitro phenyl	200	200	500	1000	800	1000
4c	3-Nitro phenyl	500	200	100	200	500	1000
4d	3,4-dimethoxy phenyl	200	500	1000	200	100	500
4e	4-chloro phenyl	50	100	200	100	500	>1000
4f	4-methyl phenyl	100	200	1000	500	200	500
4g	Phenyl-2-carboxaldehyde	500	1000	800	100	500	1000
4h	Naphthyl	500	250	800	100	400	1000
4i	2-chloro quinonyl	250	400	500	100	400	>1000
5a	Phenyl	200	200	250	500	1000	1000
5b	4-Nitro phenyl	500	250	200	100	1000	500
5c	3-Nitro phenyl	250	500	1000	200	500	>1000
5d	3,4-dimethoxy phenyl	500	1000	1000	400	200	500
5e	4-chloro phenyl	50	200	200	200	400	500
5f	4-methyl phenyl	100	150	500	200	100	1000
5g	Phenyl-2-carboxaldehyde	200	200	500	50	200	>1000
5h	Naphthyl	500	1000	250	100	200	500
5i	2-chloro quinonyl	100	150	200	50	200	500
Ampicillin		100	100	250	100	-	-
ciprofloxacin		25	25	50	50	-	-
chloramphenicol		50	50	50	50	-	-
Norfloxacin		10	10	10	10	-	-
Griseofulvin						500	100
Nystatin						100	100
Flucanazole						10	10



Scheme: Synthesis of azetidine-2-ones derivatives



	Ar
a	Phenyl
b	4-Nitro phenyl
c	3-Nitro phenyl
d	3,4-dimethoxy phenyl
e	4-chloro phenyl
f	4-methyl phenyl
g	Phenyl-2-carboxaldehyde
h	Naphthyl
i	2-chloro quinonyl