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RESEARCH ARTICLE

Synthesis and Antimicrobial Studies of Schiff's Bases of 2-Carboxy Benzaldehyde and their Azetidinone Derivatives

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ABSTRACT

A series of novel Schiff's bases of 2-carboxy benzaldehyde containing azetidinones 4(a-e) were synthesized by reaction of corresponding Schiff's bases 3(a-e) with chloroacetyl chloride in the presence of TEA. The structures of the newly synthesized compounds 4(a-e) were established on the basis of their elemental analyses, IR, 1HNMR, 13 C NMR and mass spectral data. All the title compounds were subjected to *in vitro* antibacterial testing against four pathogenic strains and antifungal screening against two fungi.

KEYWORDS

Schiff' Base, Carboxy Benzaldehyde, Chloroacetyl Chloride, Antibacterial, Antifungal

INTRODUCTION

Schiff's bases are considered as a very important class of organic compounds, which have wide applications in many biological aspects.[1] Schiff's bases are compounds containing C=N group, which are usually synthesized from the condensation of primary amines with compounds having active carbonyl groups.

The biological activities of Schiff's bases have attracted considerable attention to organic and medicinal researchers for many years. Schiff's bases are now well known for their importance in biological fields such as antibacterial, anticonvulsant, anti inflammatory activities.[2] In addition some Schiff's bases show pharmacologically useful activities like anti cancer, anti hypertensive and hypnotic activities.[3,4]

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Azetidinones and their derivatives are an important group of heterocyclic compounds which have also been recognized as TACE inhibitors[5], and biological activities such as anti cancer[6], anticonvulsant[7], anticoccidal[8], cardiovascular[9], antiviral[10], mutagenic property[11] and anti-inflammatory[12].

EXPERIMENTAL

Melting points were recorded in open capillary and were uncorrected. Column chromatography was performed using silica-gel (100–200 mesh size) purchased from Thomas Baker, and thin-layer chromatography (TLC) was carried out using aluminium sheets precoated with silica-gel 60F254 purchased from Merck. IR spectra (KBr) were obtained using a Bruker WM-4(X) spectrometer (577 models). ^{1}H NMR (400MHz) and ^{13}C NMR (100MHz) spectra were recorded on a Bruker WM-400 spectrometer in DMSO-d_6 with TMS as an internal standard. Mass spectra (ESI) were carried out on a JEOL SX-102 spectrometer. CHN analysis was done by the Carlo Erba EA 1108 automatic elemental analyzer. The chemicals and solvents used were of commercial grade and were used without further purification unless otherwise stated.

General Procedure for the Synthesis of Schiff's Bases 2(A-E)

The mixture of compound 2-carboxy benzaldehyde 1(10 m mol), substituted amines 2(a-e) (10 m mol) and triethylamine (12 m mol) were mixed in methanol (25 mL). The mixture was refluxed with agitation for 4-5 h (monitored by TLC). After completion, the reaction mixture was cooled, solid separated, which was filtered and recrystallized from methanol.

General Procedure for Synthesis of 2-(Substituted -4-Oxoazetidin-2yl) Benzoic Acids 4(A-E)

Schiff's bases (0.01mol) in benzene were taken into RB flask, cooled to 0-5^{0}C. To this added a solution of triethylamine (0.012mol) and chloroacetylchloride (0.012 mol) slowly, after addition the reaction mixture was refluxed for 12-15 h (monitored by TLC). The residue obtained after removal of benzene under vacuo, which was recrystallized from ethanol.

2-(3-Chloro-1-(2,5-Dihydrothiazol-2-Yl)-4-Oxoazetidin-2-Yl)Benzoicacid (4a)

Yield:72%, m. p. 213–216 ^{0}C; IR (KBr,cm^{-1}): 3206, 1796, 1690, 1592, 1326; ^{1}H NMR (400MHz, DMSO-d_6): δ 2.42-2.52(d,2H,-CH_2), 4.68(s,1H,-CH), 4.82(d,1H,-CH), 5.12(d,1H,-CH),7.32(t,1H,Ar-H),7.38(d,1H,Ar-H),7.52(t,1H,-CH),7.62(t,1H,Ar-H),8.12(d,1H,Ar-H),11.2 (s, 1H,-COOH); ^{13}C NMR (100MHz, DMSO-d_6): δ 45.8, 49.2, 79.2, 126.8, 127.2, 128.9, 129.8, 131.2, 133.6, 134.2, 161.2, 165.5, 167.6; MS *(m/z)* 311(M+1)+. Anal. Calcd for $C_{13}H_{11}Cl\ N_2O_3S$: C, 50.24; H, 3.57; N, 9.01. Found: C, 50.89; H, 3.61; N, 9.38 %.

2(3-Chloro-1-(3-Carboxy-4-Hydroxyphenyl)-4-Oxoazetidin-2-Yl) Benzoic Acid (4b)

Yield:79%, m. p. 198–200 ^{0}C; IR (KBr,cm^{-1}): 3216, 1792, 1692, 1592 ; ^{1}H NMR (400MHz, DMSO-d_6):δ 4.82(d,1H,-CH),4.92(br,s,1H,-OH),5.13(d,1H,-CH),7.08(d,1H,-CH),7.29 (d,1H,Ar-H), 7.32(t,1H,Ar-H),7.36(d,1H,-CH),7.62(t,1H,Ar-H),7.88(s,1H,Ar-H),8.12(d,1H,Ar-H), 10.2 (s, 1H,-COOH); ^{13}C NMR (100MHz, DMSO-d_6): δ 56.9, 62.4, 111.2, 116.8, 122.4, 125.6, 125.9, 126.8, 129.2, 129.8, 131.2, 131.5, 132.4, 132.8, 133.6, 159.3, 170.2; MS *(m/z)* 362(M+1)+.Anal. Calcd for $C_{17}H_{12}ClNO_6$: C, 56.45; H, 3.36; N, 3.87. Found: C, 57.29; H, 3.61; N, 3.92 %.

2(3-Chloro-1-(2-Carboxyphenyl)-4-Oxoazetidin-2-Yl) Benzoic Acid (4c)

Yield:69%, m. p. 212–213 ^{0}C; IR (KBr,cm^{-1}): 3226, 1798, 170.2, 1597 ; ^{1}H NMR (400MHz, DMSO-d_6):δ 4.88(d,1H,-CH), 5.10(d,1H,-CH),7.24(t,1H,Ar-H),7.28 (d,1H,Ar-H), 7.36(d,1H,Ar-H), 7.52 (t,1H,Ar-H),7.62(t,1H,Ar-H),7.72(t,1H,Ar-H),8.02(d,1H,Ar-H), 8.20 (d,1H,Ar-H),10.8 (s, 1H,-COOH), 11.2(s,1H,-COOH);^{13}C NMR (100MHz, DMSO-d_6): δ 54.2, 61.4, 117.6, 120.4, 124.2, 124.8, 125.2, 126.4, 130.2, 131.2, 132.6, 134.3, 135.7, 140.6, 163.2, 169.8; MS *(m/z)* 346(M+1)+ .Anal. Calcd for $C_{17}H_{12}ClNO_5$: C, 59.06; H, 3.50; N, 4.05. Found: C, 59.27; H, 3.62; N, 4.22 %.

2(3-Chloro-1-(2,6-Dimethylphenyl)-4-Oxoazetidin-2-Yl) Benzoic Acid (4d)

Yield:59%, m. p. 167–169 ^{0}C; IR (KBr,cm^{-1}): 3292, 1788, 169.7, 1595 ; ^{1}H NMR (400MHz, DMSO-d_6):δ 2.32(s,3H,-CH_3), 2.34(s,3H,-CH_3), 4.82(d,1H,-CH), 5.21(d,1H,-CH), 6.98-7.10 (m,3H,Ar-H),7.32(t,1H,Ar-H),7.40(d,1H,Ar-H),7.68(t,1H,Ar-H),,8.22(d,1H,Ar-H), 10.8 (s, 1H,-COOH), ^{13}C NMR (100MHz, DMSO-d_6): δ 16.2, 59.2, 62.8, 121.4, 127.2, 127.5, 128.4,129.4, 131.2, 133.4, 134.8, 135.2, 143.6, 163.6, 170.2; MS*(m/z)* 330(M+1)+ .Anal. Calcd for $C_{18}H_{16}ClNO_3$: C, 65.56; H, 4.89; N, 4.25. Found: C, 65.97; H, 4.93; N, 4.39 %.

2(3-Chloro-1-(4-Chloro-2-(2,2,2-Trfluoro-1,1-Dihydrooxyethyl)Phenyl)-4-Oxoazetidin-2-Yl) Benzoic Acid (4e)

Yield:67%, m. p. 217–219 ^{0}C;IR(KBr,cm^{-1}):3232, 1794, 170.7, 1593; ^{1}H NMR (400MHz, DMSO-d_6):δ 2.40(br,s,1H,-OH), 4.92(d,1H,-CH), 5.12(d,1H,-CH), 7.24-

7.32 (m,3H,Ar-H), 7.35 (t,1H,Ar-H),7.42(d,1H,Ar-H),7.60(t,1H,Ar-H), 8.10(d,1H,Ar-H),11.02(s, 1H,-COOH), ^{13}C NMR (100MHz, DMSO-d_6): δ 56.6, 62.3, 95.2, 124.4, 127.2, 127.9 128.2, 128.9, 129.4, 131.4, 132.0, 133.9, 134.9, 135.6, 137.4, 141.0 164.5, 170.0; MS(*m/z)*451(M+1)+.Anal. Calcd for $C_{18}H_{12}Cl_2F_3NO_5$: C, 48.02; H, 2.69; N, 3.11. Found: C, 48.85; H, 2.63; N, 3.32 %.

RESULTS AND DISCUSSION

The synthetic strategies adopted for the synthesis of the target compounds are depicted in Scheme-1. The starting materials such as Schiff's bases prepared by the condensation of 2-carboxy benzaldehyde 1 with substituted amines 2(a-e) in presence of TEA in methanol to give corresponding Schiff's bases 3(a-e), which on reaction with chloroacetyl chloride in presence of TEA in benzene yielded the corresponding 2-(substituted-4-oxoazetidin-2yl) benzoic acids 4(a-e). The structures of all the newly synthesized compounds were elucidated on the basis of their spectral data. The synthesized compounds 4(a-e) were also assayed for their antimicrobial activities.

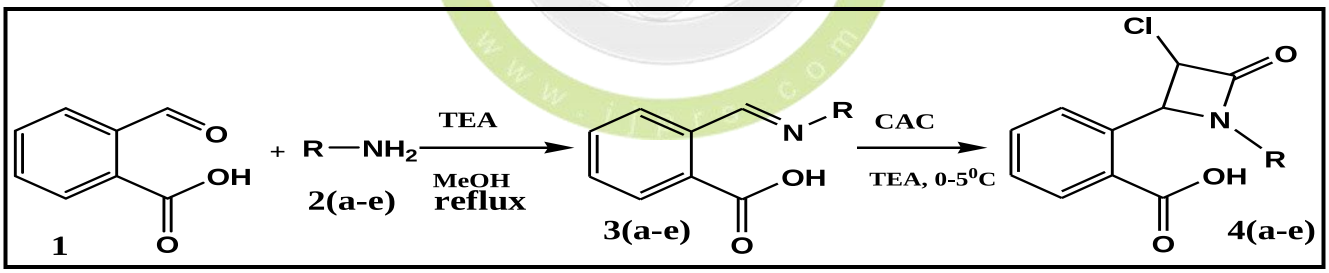
Antimicrobial Activity

The antibacterial activity of the synthesized compounds 4(a–e) was screened against the Gram-positive bacteria such as Bacillus subtilis and Staphylococcus aureus and the Gram-negative bacteria, that is, Pseudomonas aeruginosa and Escherichia coli using nutrient agar medium. The antifungal activity of the compounds was tested against Candia albicans and Aspergillus niger using Potato dextrose agar (PDA) medium. The minimum inhibitory concentration (MIC) was carried out using micro dilution susceptibility method[13].

Ciprofloxacin was used as a standard antibacterial drug, and fluconazole was used as a standard antifungal drug. The observed data on the antimicrobial activity of compounds and control drugs are given in Table 1.

The MIC values were determined as the lowest concentration that completely inhibited visible growth of the microorganisms.

The investigation of antibacterial screening (Table 1) revealed that some of the newly synthesized compounds showed moderate-to-



Scheme-1

Table1: Minimum inhibitory concentration (MIC, μg/mL) of the synthesized compounds 4(a–e)

Compound	Gram positive bacteria		Gram negative bacteria		Fungi	
	B. subtilis	S. aureus	P. aeuroginosa	E. coli	C. albicans	A. niger
4a	400	400	200	400	200	200
4b	25	100	100	50	100	50
4c	100	50	200	100	50	200
4d	200	100	50	100	200	50
4e	25	100	100	25	50	100

good inhibition at 25–100 μg/mL in DMSO. Amongst all of the compounds, compounds 4b and 4e exhibited good activities against B. subtilis (MIC: 25 μg/mL) and E. coli (MIC: 50 and 25 μg/mL) and moderate activities against S. aureus and P. aeruginosa. Compound 4c displayed good activity against S. aureus (MIC: 50 μg/mL), whereas compound 4d exhibited good activity against P. aeuroginosa (MIC: 50 μg/mL). The investigation of antifungal screening (Table 1) revealed that some of the newly synthesized compounds showed moderate-to-good inhibition at 25–100 μg/mL in DMSO. Among the tested compounds, compounds 4b, and 4d were found to be more active than other compounds against A. niger (MIC: 50 μg/mL). Compounds 4c and 4e possess good activities against C. albicans (MIC: 50μg/mL). Remaining compounds showed moderate-to least activity against both bacteria and fungi.

CONCLUSION

In summary, a series of novel Schiff's bases of 2-carboxybenzaldehyde containing azetidinones have been synthesized and characterized by spectral and elemental analyses. All of the newly synthesized compounds were screened for their *in vitro* antimicrobial activities. Among the screened samples, 4b, 4e, 4c, and 4d showed significant antibacterial and antifungal activities compared with other tested samples.

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