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Synthesis, Characterization and Antimicrobial Studies of New Chiral Amide-Schiff Base Derivatives

Yeni Kiral Amid-Schiff Baz Türevlerinin Sentezi, Karakterizasyonu ve Antimikrobiyal Çalişmalari

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ABSTRACT

In this study, new chiral Schiff bases (3-9) were synthesized via the reaction of chiral amide derivatives with various substituted aromatic aldehydes. The structures of the newly synthesized compounds were characterized by FTIR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis. All of these Schiff bases were tested in vitro against *Staphylococcus aureus, Bacillus cereus, Escherichia coli, Salmonella thyphimirium, Klebsiella pneumoniae, Enterococcus faecalis, Pseudomonas aeruginosa, Candida albicans* for their antibacterial and antifungal activities. All compounds have shown moderate to good antibacterial activity against Gram-positive and Gram-negative bacteria. Among the tested compounds compound **7** was found to show the most potent inhibitory action against test organisms.

Key Words

Amino acid, amide, schiff base, antimicrobial.

ÖZ

Bu çalışmada, kiral amid türevlerinin farklı sübstitüe aromatik aldehitler ile reaksiyonu yoluyla elde edilen yeni kiral Schiff bazları (3-9) sentezlendi. Yeni sentezlenen bileşiklerin yapıları FTIR, ^{1}H-NMR, ^{13}C-NMR ve elementel analiz ile karakterize edildi. Bu Schiff bazlarının tümü *Staphylococcus aureus, Bacillus cereus, Escherichia coli, Salmonella thyphimirium, Klebsiella pneumoniae, Enterococcus faecalis, Pseudomonas aeruginosa, Candida albicans*'a karşı antibakteriyel ve antifungal etkilerine karşı in vitro olarak test edildi. Tüm bileşikler, Gram pozitif ve Gram negatif bakterilere karşı orta ile iyi derecelerde antibakteriyel aktivite göstermiştir. Test edilen bileşikler arasında bileşik **7** test organizmalarına karşı en güçlü inhibe edici etkiyi göstermiştir.

Anahtar Kelimeler

Amino asit, amit, schiff bazı, antimikrobiyal.

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INTRODUCTION

Schiff base was first synthesized by Hugo Schiff in 1864 as a result of the reaction between an aldehyde and an amine. Schiff bases are one of the most preferred groups of compounds in organic chemistry due to their easy synthesis methods and high reaction yields. They have been used as pigment and dyes [1], catalysts in various biological systems [2], catalysts in photoelectrochemical processes, electrode materials and micro-electronic equipment [2], cation carriers in potentiometric sensors, corrosion inhibitors and photostabilizers [3]. Schiff bases exhibit many biological activities such as anti-cancer, anti-viral, anti-microbial, anti-convulsant, anti-depressant, anti-inflammatory and anti-glycation activity [4].

Amino acids and their derivatives are excellent ligand candidates due to their ability to complex with different metals and their biological significance. Amino acid-based Schiff bases have been one of the major study subject in organic chemistry because their biological activities and structures can be easily modified.

In recent years, considerable interest has been developed in synthesis of amino acid-Schiff base and amide-Schiff base derivatives. Geeta et al [5] have reported on the synthesis, characterization and antibacterial activity of Schiff base-amide derivative obtained by template condensation of o-phthalaldehyde with glycyl-glycine. Sakıyan et al [6] carried out the synthesis and evaluation of novel Schiff bases derived from the reaction of 2-hydroxy-1-naphthaldehyde with different amino acids against Gram-positive, Gram-negative bacteria and the fungus *Candida albicans*. In 2013, the antibacterial and antifungal activities of the amino acid-Schiff base derivatives against *Escherichia coli, Pseudomonas aeruginosa, Basillus cereus, Penicillium purpurogenium, Aspergillus flavus* and *Trichotheium rosium* were reported by Abdel-Rahman et al [7].

In most of the previous studies [6-12], Schiff base derivatives were synthesized by the reaction of amino acids directly with aldehydes. Whereas, Schiff bases derivatives were synthesized from aromatic amide derivatives of amino acids in this study. The aim of the study is to synthesize some derivatives of chiral Schiff bases. Since amide-derived compounds are also known to be biologically active, the synthesized Schiff base derivatives contain amide structures. In this work, we have used chiral amino acids and substituted aromatic aldehyde to prepare Schiff base derivatives (3-9). Their structures were confirmed by FTIR, ^{1}H-NMR, ^{13}C-NMR and elemental analysis. These new Schiff bases were also tested against some Gram-positive (*Staphylococcus aureus and Bacillus cereus), Gram-negative (Escherichia coli, Salmonella thyphimirium, Klebsiella pneumoniae, Enterococcus faecalis* and *Pseudomonas aeruginosa*) bacteria and Candida albicans as a yeast-like fungus.

MATERIALS and METHODS

Materials

All reagents and starting compounds were obtained from commercial sources. Solvents were obtained from industrial grade solvents which were further purified by distillation. Melting points of synthesized compounds were measured by Gallenkamp electrothermal melting points device. TLC analyses were carried out on Silica gel 60 F254 (Merck) plates. FTIR spectra were obtained by Perkin Elmer Spectrum 100 FTIR Spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were carried out using 400 MHz Varian spectrometer. The elemental analyses were performed using a Leco CHNS-932 analyzer.

General procedure for the synthesis of amide compounds

Chiral amide derivatives were prepared from amino acids through two-step sequence: *N*-Boc protection and then treatment with o-phenylenediamine according to the previously reported procedure [13]. Valine, isoleucine, phenyl glycine and phenyl alanine were selected as the starting amino acids.

General procedure for the synthesis of Schiff base

Chiral amide compound (1 equiv) was dissolved in 15 mL of methanol. Substituted aldehyde (1 equiv) was added and the mixture was stirred at room temperature for 48 hours. When the reaction was complete, methanol was evaporated under vacuum. Residue was purified by a silica-gel column chromatography (Hexane / EtOAc, 2:1) to afford a product.

(R)-tert-butyl 2-(2-(4-nitrobenzylideneamino) phenylamino)-2-oxo-1-phenylethylcarbamate (3)

Yellow solid. 52 % yield. mp: 177-179 °C. IR (NaCl, cm^{-1}): 3329, 2970, 1662, 1518, 1449, 1269, 1168, 759. ^{1}H NMR (600MHz, $CDCl_3$, ppm): δ= 1.39 (s, 9H), 5.35 (s, 1H), 5.90 (s, 1H), 7.11 (t, 1H, J=7.4 Hz), 7.21 (d, 1H, J=7.5 Hz), 7.26

(s, 1H), 7.32 (t, 2H, J=6.6 Hz), 7.36 (t, 2H, J=6.6 Hz), 7.45 (d, 2H, J=6.6 Hz), 7.88 (d, 2H, J=7.3 Hz), 8.34 (d, 1H, J=7.9 Hz), 8.48 (d, 1H, J=8.1 Hz), 8.58 (s, 1H), 8.88 (s, 1H). ^{13}C NMR (600MHz, $CDCl_3$, ppm): δ= 28.1, 29.8, 59.7, 80.5, 116.2, 119.6, 124.5, 127.5, 128.7, 129.3, 130.2, 133.6, 136.9, 140.6, 149.5, 155.7, 167.8, 193.7. Anal. Calc. For $C_{26}H_{26}N_4O_5$: C, 65.81; H, 5.52; N, 11.81. Found: C, 64.46; H, 5.27; N, 11.63.

(R)-tert-butyl 2-(2-(4-chlorobenzylideneamino) phenylamino)-2-oxo-1-phenylethylcarbamate (4)

Yellow solid. 40 % yield. mp: 180-182°C. IR (NaCl, cm^{-1}): 3341, 2975, 1678, 1490, 1449, 1368, 1272, 1165, 754. ^{1}H NMR (600MHz, $CDCl_3$, ppm): δ= 1.41 (s, 9H), 5.32 (s, 1H), 5.93 (s, 1H), 6.74 (s, 1H), 7.07 (m, 1H), 7.15 (d, 1H, J=7.3 Hz), 7.20-7.36 (m, 4H), 7.44 (m, 3H), 7.68 (d, 1H, J=6.7 Hz), 8.44 (s, 2H), 8.90 (s, 1H). ^{13}C NMR (600MHz, $CDCl_3$, ppm): δ= 28.1, 59.7, 80.2, 116.2, 119.3, 124.1, 127.0, 128.1, 128.4, 129.1, 130.0, 133.2, 134.1, 137.9, 138.3, 155.2, 157.3, 167.6, 190.9. Anal. Calc. For $C_{26}H_{26}ClN_3O_3$: C, 67.31; H, 5.65; N, 9.06. Found: C, 66.45; H, 6.17; N, 9.18.

(R)-tert-butyl 2-(2-(4-bromobenzylideneamino) phenylamino)-2-oxo-1-phenylethylcarbamate (5)

Yellow solid. 32 % yield. mp: 179-181°C. IR (NaCl, cm^{-1}): 3334, 2972, 1671, 1510, 1449, 1270, 1166, 755. ^{1}H NMR (600MHz, $CDCl_3$, ppm): δ= 1.38 (s, 9H), 3.47 (s, 1H), 4.11 (s, 1H), 5.32 (s, 1H), 5.93 (s, 1H), 6.73 (s, 1H), 7.11-7.53 (m, 6H), 7.58 (s, 2H), 8.44 (d, 1H, J= 9.1 Hz), 8.90 (s, 1H). ^{13}C NMR (600MHz, $CDCl_3$, ppm): δ= 28.1, 59.8, 80.2, 116.5, 119.4, 124.3, 127.2, 128.5, 129.0, 130.2, 133.4, 135.8, 140.8, 155.3, 167.8, 192.3. Anal. Calc. For $C_{26}H_{26}BrN_3O_3$: C, 61.42; H, 5.15; N, 8.27. Found: C, 60.26; H, 5.33; N, 8.26.

(2S,3S)-tert-butyl-3-methyl-1-(2-(-4-nitrobenzylideneamino)phenylamino)-1-oxopentan-2-ylcarbamate (6) Yellow solid. 34 % yield. mp: 189-191°C. IR (NaCl, cm^{-1}): 3318, 2974, 1668, 1518, 1447, 1344, 1273, 1165, 750. ^{1}H NMR (600MHz, $CDCl_3$, ppm): δ= 0.93 (t, 3H, J=7.2 Hz), 1.00 (d, 3H, J=5.5 Hz), 1.39 (s, 9H), 1.57 (s, 2H), 2.03 (s, 1H), 4.18 (s, 1H), 5.13 (s, 1H), 7.13 (t, 1H, J=7.4 Hz), 7.26 (s, 1H), 7.33 (t, 1H, J=7.5 Hz), 8.14 (d, 2H, J=7.2 Hz), 8.36 (d, 2H, J=7.7 Hz), 8.55 (s, 1H), 8.69 (s, 1H), 9.12 (s, 1H). ^{13}C NMR (600MHz, $CDCl_3$, ppm): δ= 11.5, 14.0, 15.6, 28.1, 37.1, 60.2, 80.2, 116.0, 119.8, 123.9, 124.2, 129.1, 129.5, 130.4, 133.9, 141.0, 149.4, 155.8, 169.5, 190.1. Anal. Calc. For $C_{24}H_{30}N_4O_5$: C, 63.42; H, 6.65; N, 12.33. Found: C, 62.73; H, 6.36; N, 12.11.

(R)-tert-butyl 1-(2-(4-nitrobenzylideneamino) phenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (7)

Yellow solid. 28 % yield. mp: 182-184°C. IR (NaCl, cm^{-1}): 3331, 2917, 1681, 1515, 1341, 1162, 749. ^{1}H NMR (600MHz, $CDCl_3$, ppm): δ= 1.38 (s, 9H), 1.67 (m, 2H), 2.04 (s, 1H), 4.18 (s, 1H), 5.14 (s, 1H), 7.12 (t, 1H, J=7.6 Hz), 7.20-7.41 (m, 3H), 8.14 (d, 3H, J=8.3 Hz), 8.35 (d, 3H, J=8.1 Hz), 8.55 (d, 1H, J=8.1 Hz), 8.68 (s, 1H), 9.13 (s, 1H). ^{13}C NMR (600MHz, $CDCl_3$, ppm): δ= 28.1, 29.6, 38.4, 58.2, 79.1, 113.6, 116.4, 119.8, 124.1, 128.5, 129.7, 132.5, 134.0, 135.6, 138.4, 148.0, 151.0, 154.5, 166.1, 173.2, 192.7. Anal. Calc. For $C_{27}H_{28}N_4O_5$: C, 66.38; H, 5.78; N, 11.47. Found= C, 65.39; H, 5.74; N, 11.18.

(R)-tert-butyl 1-(2-(4-chlorobenzylideneamino) phenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (8)

Yellow solid. 50 % yield. mp: 181-184°C. IR (NaCl, cm^{-1}): 3319, 2924, 1675, 1516, 1449, 1364, 1272, 1165, 757. ^{1}H NMR (600MHz, $CDCl_3$, ppm): δ= 1.34 (s, 9H), 3.15 (m, 2H), 4.47 (m, 2H), 5.13 (s, 1H), 7.09 (d, 1H, J=6.2 Hz), 7.17 (s, 1H), 7.19 (d, 3H, J=10.3 Hz), 7.27 (d, 2H, J=9.5 Hz), 7.45 (d, 2H, J=7.2 Hz), 7.78 (d, 2H, J=7.2 Hz), 8.43 (s, 1H), 8.95 (s, 1H). ^{13}C NMR (600MHz, $CDCl_3$, ppm): δ= 28.1, 38.6, 56.5, 80.0, 115.8, 119.3, 123.7, 127.2, 128.5, 129.2, 130.2, 133.2, 136.2, 137.4, 157.2, 168.8, 191.0. Anal. Calc. For $C_{27}H_{28}ClN_3O_3$: C, 67.85; H, 5.90; N, 8.79. Found: C, 67.35; H, 6.05; N, 8.73.

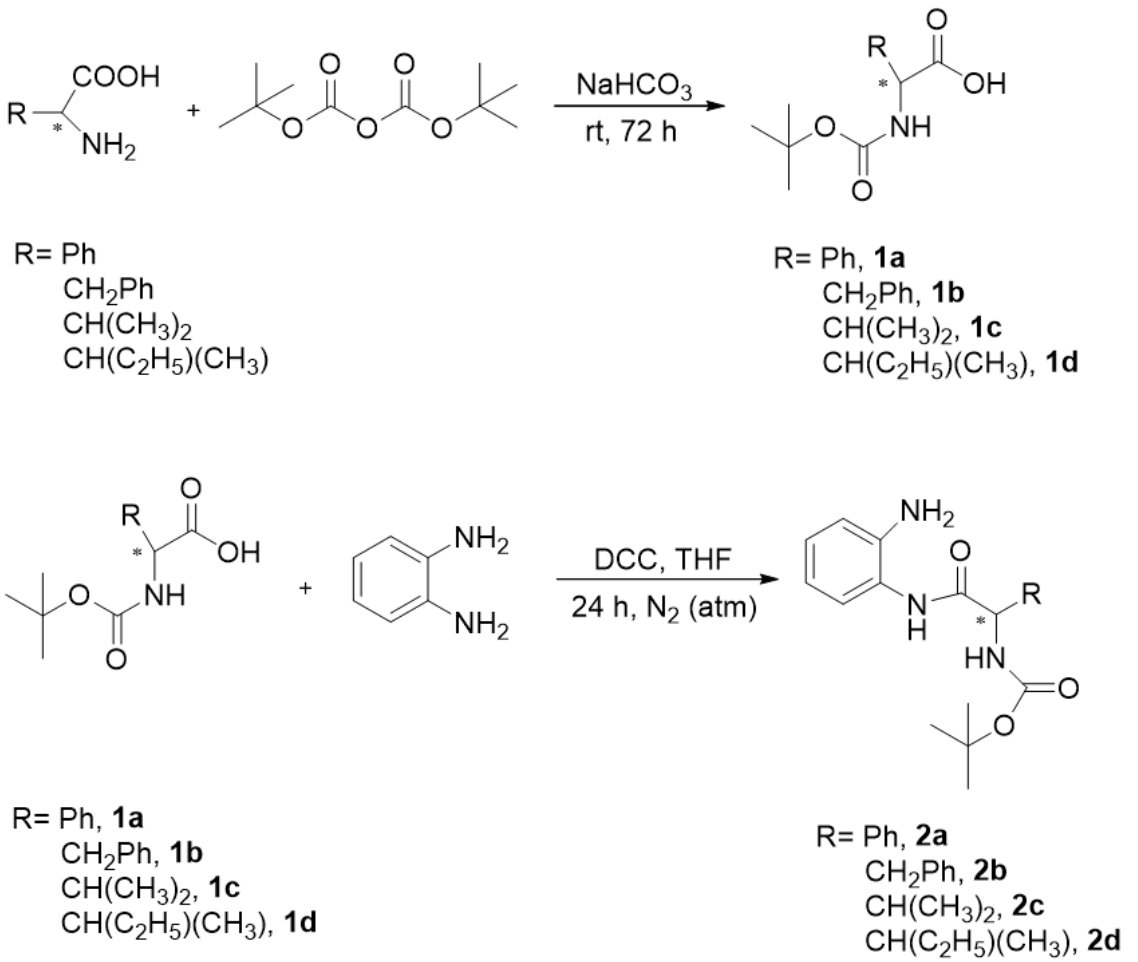
(S)-tert-butyl 3-methyl-1-(2-(4-nitrobenzylideneamino)phenylamino)-1-oxobutan-2-ylcarbamate (9)

Yellow solid. 30 % yield. mp: 185-187°C. IR (NaCl, cm^{-1}): 3320, 2972, 1664, 1516, 1448, 1345, 1270, 1162, 752. ^{1}H NMR (600MHz, $CDCl_3$, ppm): δ= 1.00 (s, 3H), 1.03 (d, 3H, J=7.4 Hz), 1.38 (s, 9H), 2.29 (d, 1H, J=6.9 Hz), 4.12 (s, 1H), 5.12 (s, 1H), 7.13 (t, 1H, J=7.5 Hz), 7.26 (s, 1H), 7.34 (t, 1H, J=7.7 Hz), 8.14 (d, 2H, J=7.2 Hz), 8.36 (d, 2H, J=8.1 Hz), 8.56 (s, 1H), 8.68 (s, 1H), 9.13 (s, 1H). ^{13}C NMR (600MHz, $CDCl_3$, ppm): δ= 19.2, 28.3, 29.6, 61.1, 113.8,

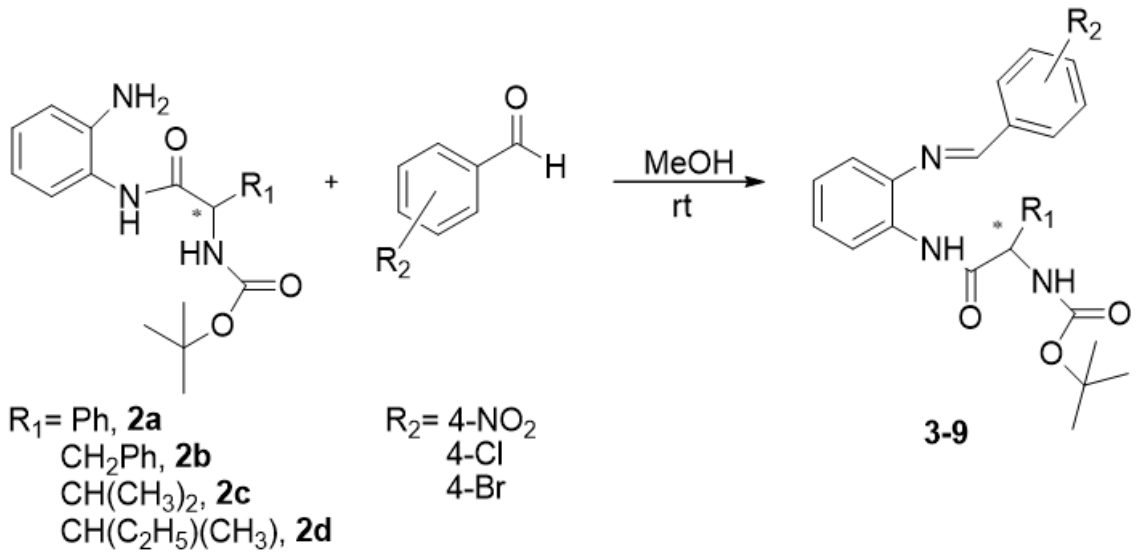
115.9, 119.8, 124.0, 128.0, 129.1, 130.4, 134.0, 141.3, 149.4, 155.8, 169.4, 190.1. Anal. Calc. For $C_{23}H_{28}N_4O_5$: C, 62.71; H, 6.41; N, 12.72. Found: C, 62.82; H, 6.53; N, 12.29.

Antimicrobial assay

The antimicrobial activities of the synthesized new Schiff bases (3-9) were evaluated in vitro against *Staphylococcus aureus* (ATCC 6538-P), *Bacillus cereus* (ATCC 6633) as Gram-positive bacteria, *Escherichia coli* (ATCC 12228), *Salmonella thyphimirium* (CCM 5445), *Klebsiella pneumoniae* (CCM 2318), *Enterococcus faecalis* (ATCC 29212), *Pseudomonas aeruginosa* (ATCC 27853) as Gram-negative bacteria, and *Candida albicans* (ATCC 10239) as a yeast-like fungus. Test microorganisms were activated in Muller Hinton Broth (MHB) in a shaking water bath at 37°C for 20 h. The minimum inhibitory concentrations (MICS) of the compounds were determined using 96-well microplates and broth microdilution technique. Microorganisms were incubated in Muller Hinton Broth (MHB) at 37°C for 18-20 hours [14]. The test compounds were prepared with different concentrations using 10% aqueous DMSO. 100 µL of test microorganisms prepared in 1/100 dilutions of the double cuvette MHB were transferred to the wells in parallel. Then 100 µL of tested compounds were added to these wells to give a final volume of 200 µL. After 24 hours of incubation, 50 µL of 0.5% TTC (triphenyl tetrazolium chloride) solution was added to the wells and incubated for a further 2 hours. At the end of the incubation time the red formazan compound, formed by the reduction of TTC, was considered as an indicator of growth and was used to determine the MIC value [15]. The MIC value is expressed as the lowest concentration of the substance without growth. While



Scheme 1. Synthesis of chiral amide derivatives (2a-d).



Scheme 2. SSynthesis of chiral amide-Schiff base derivatives (3-9).

gentamicin and clotrimazole were used as reference antibiotics, 10% aqueous DMSO was used as the negative control for all experiments.

RESULTS and DISCUSSION

Chemistry

The syntheses of chiral amide derivatives were carried out according to the literature [8]. The selected amino acids were reacted with di-tert-butyl dicarbonate to obtain *N*-Boc protected amino acids (**1a-d**). Then chiral amide derivatives (**2a-d**) were synthesized by the reaction of *N*-Boc protected amino acids, o-phenylenediamine and *N,N'*-dicyclohexylcarbodiimide under nitrogen atmosphere for 24 hours (Scheme 1).

Molecular structures of synthesized Schiff base derivatives were elucidated by various spectral methods. The data obtained from the analyses were proved to be compatible with the structures. Accordingly, the FTIR results observed for the all synthesized compounds showed N-H bands in the 3319–3341 cm^{-1} range. The band at the region of 1662-1681 cm^{-1} is assignable to carbon-nitrogen double bond which is characteristic band for Schiff base. Additionally, C-N peak were observed at 1490-1518 cm^{-1} for all synthesis products.

In the ^{1}H-NMR spectral data, the peaks observed at 1.34-1.41 ppm ascertain the presence of Boc-protecting group with a total of 9 protons. The secondary amine protons signals have been observed approximately about 5 to 6 ppm for the all synthesised compounds. The signals observed at 6.73-8.68 ppm showed the presence of aromatic ring in all the structures. The synthesized schiff base compounds showed single peak at about 8.88 to 9.13 ppm which is assigned to the presence of proton of azomethine group.

In the ^{13}C NMR spectra of the synthesised Schiff bases (3-9), the peaks for amide carbonyl carbons were observed at about 190 ppm and the peaks for azomethine carbons at about 166 to 170 ppm. The aromatic ring carbons gave signals at 113-157 ppm and the peak signals observed at about 28 ppm indicated the presence of methyl carbons in Boc-protecting group.

Biological Activity

The MIC values of the tested Schiff base derivatives (**3–9**) against to the microorganisms are presented in Table 2. All of the tested compounds showed a remarkable biological activity against test organisms in different ratios (0.125-1 µg/ml). It was appeared to be that the most effective compound was the compound **7**. It showed activity against all the organisms apart from *S. Aureus*.

Table 1. Physical data of chiral amide-Schiff bases (3-9).

Entry	R_1	R_2	Product	Yield [%a]	M.p. (°C)
1	Ph	4-NO_2	3	52	177-179
2	Ph	4-Cl	4	40	180-182
3	Ph	4-Br	5	32	179-181
4	CH(C_2H_5)(CH_3)	4-NO_2	6	34	189-191
5	CH_2Ph	4-NO_2	7	28	182-184
6	CH_2Ph	4-Cl	8	50	181-184
7	CH(CH_3)$_2$	4-NO_2	9	30	185-187

a Isolated yield after silica gel chromatography.

Compounds **3, 4, 6, 9** were also active against Albicans which is an opportunistic patogen yeast.

Compounds 6 and 9 have alkyl groups attached to the sterogenic center whereas the other compounds with phenyl ring. It appears to be alkyl groups attached to the chiral center reduces the microbial effect of the molecule. The results of these antimicrobial studies show that the electronic and steric effects of substituted groups dominantly affect the overall biological behaviour of the compounds, which are potent against bacterial strains.

As a result it was concluded that these newly syntesized 7 compounds (**3-9**) have anti-microbial effect and might also have potential to be used with therapeutic purpose.

Molecular structures of synthesized Schiff base derivatives were elucidated by various spectral methods. The data obtained from the analyses were proved to be compatible with the structures. Accordingly, the FTIR results observed for the all synthesized compounds showed N-H bands in the 3319-3341 cm^{-1} range. The band at the region of 1662-1681 cm^{-1} is assignable to carbon-nitrogen double bond which is characteristic band for Schiff base. Additionally, C-N peak were observed at 1490-1518 cm^{-1} for all synthesis products.

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Table 2. MIC values of amide-Schiff base derivatives (3-9) against bacteria and C. albicans (µg/ml).

Compound	*E. coli*	*S. aureus*	*P. aureginosa*	*S. thyphimirium*	*E. faecalis*	*K. pneumoniae*	*B. cereus*	*C.albicans*
3	-	-	-	0.5	1.0	-	-	0.125
4	0.25	0.125	0.5	0.5	-	1.0	-	0.125
5	-	0.5	-	-	-	-	-	-
6	-	0.5	-	-	1.0	-	-	0.5
7	0.125	-	1.0	0.125	0.5	1.0	1.0	0.5
8	-	-	-	-	-	-	1.0	-
9	0.125	-	0.5	0.25	0.5	0.5	-	0.25
Gentamisin	1.25	1.25	2.5	2.5	n.t.	2.5	1.25	1.25
Clotrimazole	n.t.	n.t.	n.t.	n.t.	0.75	n.t.	n.t.	n.t.

n.t= Not tested

zed schiff base compounds showed single peak at about 8.88 to 9.13 ppm which is assigned to the presence of proton of azomethine group.

In the ^{13}C NMR spectra of the synthesised Schiff bases (**3-9**), the peaks for amide carbonyl carbons were observed at about 190 ppm and the peaks for azomethine carbons at about 166 to 170 ppm. The aromatic ring carbons gave signals at 113-157 ppm and the peak signals observed at about 28 ppm indicated the presence of methyl carbons in Boc-protecting group.

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Compounds **6** and **9** have alkyl groups attached to the sterogenic center whereas the other compounds with phenyl ring. It appears to be alkyl groups attached to the chiral center reduces the microbial effect of the molecule. The results of these antimicrobial studies show that the electronic and steric effects of substituted groups dominantly affect the overall biological behaviour of the compounds, which are potent against bacterial strains.

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