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Synthesis, Characterization and Anti-Bacterial Evaluation of Novel Heterocyclic Compounds Derived From Some Amino Acids

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Abstract

Vanillin as a natural compound has been used for the synthesis of two new Schiff's bases derived from the amino acids L-asparagine and 4-aminobutanoic acid in the presence of NaOH as a catalyst. 1,3-Oxazepine derivatives have been synthesized by reaction of M1 and M2 with succinic anhydride while one tetrazole derivative has been synthesized by reaction of M2 with sodium azide. The synthesized compounds have been identified by using FT-IR and ^{1}H-NMR spectroscopies , the anti-bacterial study was showed good- moderate results.

Keyword: Heterocyclic compounds, 1,3-Oxazepines, Tetrazoles, Schiff's bases

INTRODUCTION

Schiff's bases are compounds containing imine or azomethine (–C=N–) functional group. Which are produced through the condensation reaction of primary amines with carbonyl-containing compounds and they were firstly reported by Hugo Schiff [1,2], Schiff's bases have been found to possess a wide-spread pharmacological activities such as antibacterial [3], antifungal [4],anti-tubercular [5], antimicrobial[6], antimalarial[7] and anti-cancer [8]. Recently, heterocyclic molecules with seven-membered ring structures have been a quickly gained the curiosity and attention of the chemists in comparison to five and six-membered heterocyclic compounds. Increasing the size of the ring means more range of compounds can be derived via altering the type and or number of the heteroatoms [9]. Seven-membered heterocyclic compounds containing two heteroatoms are important compounds used in many applications. Oxazepine derivatives are one of such seven-membered heterocyclic compounds [10], Oxazepine derivatives have been attracted a considerable attention due to the large variety of biological activities such as anti-bacterial[11], hypnotic muscle relaxant [12], anti-inflammatory [13] and anti-epileptic [14].

MATERIALS AND METHODS

The chemicals that used are obtained from Merck, Fluka and Aldrich companies without applying further purification. The uncorrected melting points were measured by using an (Electro thermal) melting point apparatus. FT-IR spectra were measured with SHIMADZU FTIR-4800S Infrared spectrophotometer by using KBr disk.^{1}H-NMRspectra were recorded by using 300 MHz JNM ECP-600 spectrometer and DMSO-*d6* was the solvent and tetramethylsilane (TMS) was the internal standard

General method for the synthesis of M1and M2

L-asparagine (0.01 mol, 1.32g) or 4-aminobutanoic acid (0.01 mol, 1.03 g) and NaOH (0.01 mol, 0.4 g) were dissolved in a mixture of distilled water and absolute ethanol (1:3). The mixture was stirred for 15 minute then vanillin (0.01 mol, 1.52 gm) dissolved in 20 mL absolute ethanol was added and the reaction mixture was heated at 60 ^{o}C with continuous stirring for 6 h, compound M2 was acidified by 0.1 M HCl, the precipitate was collected, washed with small portions of ethanol and dried over $CaCl_2$ desiccator.

Synthesis of Sodium 3-carbamoyl-2-[(4-hydroxy-3-methoxy-benzylidene)-amino]-propionate [M1]

Light red solid, Yield 76 %, m.p 115-117 ^{o}C, MW 288. FT-IR (KBr, cm^{-1}) : 3354(phenolic OH), 3194(C-H aromatic), 2939(C-H aliphatic), 1672(amidic C=O), 1641(C=N) 1591(aromatic C=C), 1514, 1355 (asymmetric and symmetric -COONa). ^{1}H-NMR (DMSO-*d6*): 9.6(s, 1H, phenolic OH), 8.4(s, 1H, CH=N), 7.2-7.5(m, 3H, Ar-H), 6.1(s, 2H, -NH_2), 4.3(t, 1H ,-CH-COONa), 3.4(s , 3H , -OCH_3), 2.4(d, 2H, -CH_2-). Elemental analysis (%) for $C_{12}H_{13}N_2NaO_5$ calculated: C(50.00), H(4.55), N(9.72), found: C(49.99), H(4.54), N(9.72).

Synthesis of 4-[(4-Hydroxy-3-methoxy-benzylidene)-amino]-butyric acid [M2]

Red oily, Yield 81 %, MW 237. FT-IR (KBr, cm^{-1}): 3332(OH), 3150(C-H aromatic), 2976(C-H aliphatic), 1704(C=O of COOH), 1651(C=N), 1558(aromatic C=C). ^{1}H-NMR (DMSO-*d6*): 13.3(s, br, 1H, CO<u>OH</u>), 9.5(s, 1H, phenolic OH), 8.3(s, 1H, CH=N), 7.6-7.8(m, 3H, Ar-H), 4.3-4.7(t , 2H, -CH_2CO), 3.5(s , 3H, -OCH_3), 2.1-2.3(t, 2H , -CH_2N), 1.3-1.6(m , 2H ,-CH_2-<u>CH_2</u>-CH_2). Elemental analysis (%) for $C_{12}H_{15}NO_4$ calculated: C(60.75), H(6.37), N(5.90), found: C(60.76), H(6.35), N(5.92).

General method for the synthesis of M3 ,M4 and M5

A mixture of Schiff's base M1(0.001 mol, 0.288 g) or M2(0.001 mol, 0.237g) and succinic anhydride (0.001 mol, 0.1g) in 20 mL DMF was heated at 70^{o}C for (8-10 h), the solvent was removed by the rotary evaporator, the obtained product was washed with benzene and diethyl ether.

Synthesis of sodium3-carbamoyl-2-[2-(4-hydroxy-3-methoxy-phenyl)-4,7-dioxo-1,3-oxazepan-3-yl]-propionate [M3]

Brown solid, Yield 88 %, m.p 127-129 ^{o}C, MW 388. FT-IR (KBr, cm^{-1}) : 3482(phenolic OH) 3355 and 3332 (syn NH_2), 1748(C=0 lactone), 1681(C=O lactam), 1672(C=O amide), 1577(aromatic C=C),1562 and 1400(asymmetric and symmetric COONa). ^{1}H-NMR (DMSO-*d6*): 9.6(s, 1H, phenolic OH), 9.3(s, 1H, CH-N), 7.3-7.6(m, 3H, Ar-H), 6.6(d, 1H , =CH-CON-cyclic), 6.5(d, 1H, =CHCOO- cyclic), 6.1(s, 2H, -NH_2), 4.4(t, 1H , -CH-COONa), 3.4(s , 3H , -OCH_3), 2.4(d, 2H, -CH_2-). Elemental analysis (%) for $C_{16}H_{17}N_2NaO_8$ calculated: C(49.49), H(4.41), N(7.71), found: C(49.51), H(4.40), N(7.70).

Synthesis of 4-[2-(4-Hydroxy-3-methoxy-phenyl)-4,7-dioxo-1,3-oxazepan-3-yl]-butyric acid [M4]

Gray solid, Yield 63 %, m.p 137-139 ^{o}C, MW 337. FT-IR (KBr, cm^{-1}) : 3376(OH), 1722(C=0 lactone), 1705(COOH), 1665(C=O lactam), 1586(aromatic C=C). ^{1}H-NMR(DMSO-*d6*): 13.2(s, br, 1H, CO<u>OH</u>), 9.5(s, 1H, phenolic OH), 9.3(s, 1H, -CH-N cyclic), 7.2-7.5(m, 3H, Ar-H), 4.5(t , 2H, -CH_2CO), 3.5(s , 3H , -OCH_3), 2.6(t, 2H, CH_2CON- cyclic), 2.5(t, 2H, CH_2-COO-cyclic), 2.2(t, 2H, -CH_2N), 1.4(m, 2H ,-CH_2-<u>CH_2</u>-CH_2). Elemental analysis (%) for $C_{16}H_{19}NO_7$ calculated: C(56.97), H(5.68), N(4.15), found: C(56.99), H(5.67), N(4.17).

Synthesis of 4-[5-(4-Hydroxy-3-methoxy-phenyl)-2,5-dihydro-tetrazol-1-yl]-butyric acid [M5]

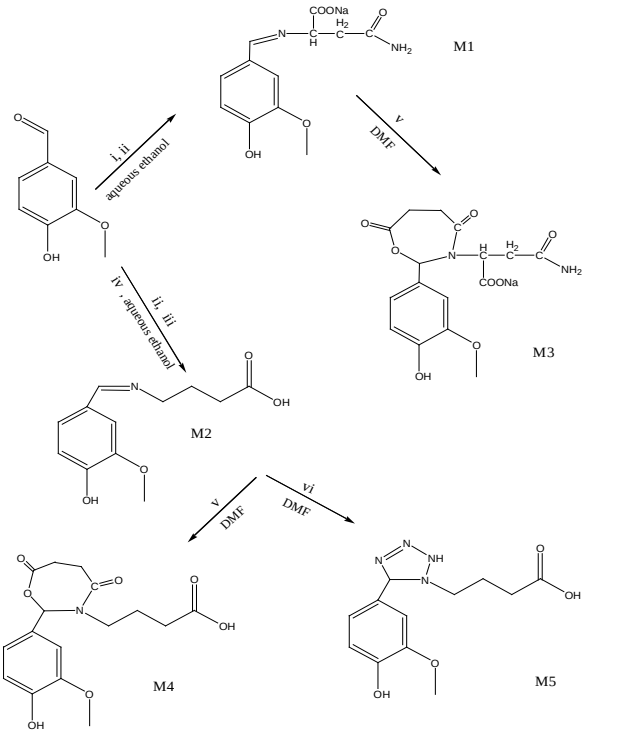
A mixture of Schiff's base M2 (0.001 mol, 0.237 g) and sodium azide (0.001 mol, 0.065 g) in 20 ml DMF was heated at 80 ^{o}C for 24 h, after cooling at RT acetone(15 ml) was added to

deposit the product, the product was obtained by vacuum filtration, washed with small portions of water.

Wight yellow, Yield 60 %, m.p 130-132 ^{o}C, MW 280. FT-IR (KBr, cm^{-1}): 3365(phenolic OH) 3185(NH), 1700(C=O carboxylic acid), 1593(C=C aromatic), 1518(-N=N-) ^{1}H-NMR (DMSO-*d6*): 14.1(s, br, 1H, COOH), 9.8(s, 1H, phenolic OH), 8.9(s, 1H, -CH-N cyclic), 8.1(s, br, -NH),7.2-7.5(m, 3H, Ar-H), 4.5(t , 2H, $-CH_2CO$), 3.5(s , 3H , $-OCH_3$), 2.2(t, 2H, $-CH_2N$), 1.4(m, 2H ,$-CH_2-CH_2-CH_2$). Elemental analysis (%) for $C_{12}H_{16}N_4O_4$ calculated: C(51.42), H(5.75), N(19.99), found: C(51.41), H(5.75), N(20.01).

Anti-bacterial activity

The anti-bacterial activity was performed by using a reported method [15].



i = L-asparagine , ii = NaOH , iii = 4-aminobutyric acid , iv = HCl , v = succinic anhydride

vi = sodium azide

Scheme 1: Synthesis of compounds (M1-M5) from vanillin

RESULT AND DISCUSSION

The Schiff's bases (M1, M2) were prepared by reaction of vanillin with L-asparagine and 4-aminobutyric acid respectively in solution of ethanol (aqueous) as shown in Scheme 1. Due to amino acids are exist as a zwitterion in aqueous solvent the primary amino group is protected, as a result deprotonating agent must be used. The first attempt was performed via using sodium acetate but the yield was very low, the deprotonating of the protected amino group converts sodium acetate into acetic acid in a considerable amount, the later could be reversibly protonates the amino group consequently the yield was low. Our second attempt was performed via using NaOH, the yield was good. The synthesized Schiff's bases were reacted with succinic anhydride to produce two 1,3-oxazepane derivatives (M3, M4), the reaction proceeds according to (5 + 2) cycloaddition strategy, because of the low solubility of the produce Schiff's bases DMF was used as a solvent. On the other hand compound M2 was used for the synthesis of one tetrazole derivatives (M5), the reaction proceeds according to (3 + 2) cycloaddition strategy which is considered as 1,3 dipolar cycloaddition. The above prepared compounds were screened for their anti-bacterial activity against gram positive (*Staphylococcus aureus*) and gram negative (*Escherichia coli*) by using disc diffusion method, the compounds was dissolved in DMSO (1mg in 1ml) and the solvent was showed no inhibition zone, the results are shown in Table 1.

Table 1: The inhibition zone (mm) of the prepared compounds (M1-M5)

Compounds	*Staph.*	*E-Coli*
M1	23	18
M2	20	16
M3	21	19
M4	15	12
M5	25	22

CONCLUSION

The present work describes the synthesis of two Schiff's bases, two 1,3-oxazepane derivatives and one tetrazole derivative. Compound M1 has been used in its salt form without acidification in the synthesis of compound M3 while compound M2 was acidified by 0.1 M HCl, the yield of the compounds that derived from the acidified Schiff's base was lower than the non-acidified one. The synthesized compound were showed excellent anti-bacterial activity except compound M4 (moderate activity), also they were freely soluble in water. These bio-based compounds could be medicinally promised with this two features.

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