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NEW HETEROCYCLIC SCHIFF BASE AND AZETIDINONE AS ANTIBACTERIAL AGENTS

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ABSTRACT: *New heterocyclic Schiff base were synthesized from metronidazole and aldehyde, further this heterocyclic Schiff base was converted into 2-azetidinone by the action of chloroacetyl chloride. The biological screening data of the synthesized compounds were also presented.*

KEYWORDS: Schiff base, 2-Azetidinone, Antibacterial

INTRODUCTION

The chemistry of Schiff base plays a vital role in the progress of chemistry science (1, 2), synthesis of Schiff base through classical condensation of aldehydes (or ketone) and imines were pursued (3, 4) Schiff base are characterized by the N=CH- (imine) group which is important in elucidating the mechanism of transformation in biological systems. Due to great flexibility and diverse structural aspects, wide range of Schiff bases has been synthesized and their complexion behavior was studied (5). Furthermore, Schiff base are reported to show a variety of interesting biological activities, including antibacterial (6), antifungal (7), anticancer (8, 9), and herbicidal activities (10).

2-Azetidinone compounds are characterized by the ring system (amide) (11). These compounds are shown to possess make biological activities (12-15). 2-Azetidinone has been synthesized by the condensation of chloroacetyl chloride with Schiff base, the compound has been characterized on the base of analytical and spectral data. It has been screened of antibacterial activity against staphylococcus and E.coli.

Experimental

Melting point were determined in Gallen Kamp melting point apparatus and were uncorrected, Elemental analysis (CHN) were recorded in EA300 Euro-Vector in University of Al-albyat in Jordon. FT-IR Spectra were recorded on Shimadzu FT-IR 8400 Fourier Transformer infrared as KBr disk. Ultraviolet spectra were recorded in spectro scan 80 in the wavelength 200-800 nm. 1HNMR and 13CNMR spectra were recorded on Brucker spctrospin ultra shield magnets 400MHz instrument using tetramethyl silane (TMS) as an internal standard and DMSO-d6 as a solvent in university of Tabriz-Iran. Thin layer chromatography were performed on pre-coated sheets with 0.25 mm layer of Slica Gel GF254 of the Merck Company.

Synthesis of Compounds

Synthesis of 2-methyl-5-nitro-1-ethyl bromide imidazole (A)

A mixture of (1mmole,1.57gm) from metronidazole in 20ml ethanol and (1mmole, 1.18gm) of potassium bromide in 20ml water, then added 10ml of 10% sulphuric acid and refluxed in hotplate in 100oC for 3hrs. This reaction was monitored by TLC. The mixture was cooled in ice to participate the solid crystal, the participate solid was filtered and recrystallized from Tetrahydrofuran (THF), yield 76%. Melting point 124-126oC, CHN analysis that formula C5H6BrN3O2 calculated C, 27.293 H, 2.574 N, 19.105; Found C, 27.132 H, 2.533 N, 18.924. Ultraviolet spectra λmax 245, 270nm. FT-IR spectra νmax 3013, 1440.1255, 960cm-1.

Synthesis of 2-methyl-5-amino-1-ethyl bromide imidazole (B)

(1mmole, 2.2gm) of compound (A) was added to the 40 ml of concentrated hydrochloric acid solution of stannous chloride (1mmole, 1.9gm) an heating at 6hrs in 75oC to reduce nitro group. The solution was evaporated white crystal of compound (2) hydrochloride was obtained by addition of liquid ammonia and recrystallization by tetra hydro furan. yield 65% melting point 145-147oC, CHN analysis that formula C5H8BrN3 calculated C, 31.603 H, 4.245 N, 22.112 ; Found C, 31.446 H, 4.105 N, 22.007. Ultraviolet spectra λmax 242, 273nm. FT-IR spectra νmax 3200, 3010, 1475, 870cm-1.

Synthesis of 2-methyl-5-amino-1-ethyl bromide imidazole Schiff base (C)

A mixture of aldehyde (1mmole, 1.37gm) and compound B (1mmole, 1.9gm) were dissolved in ethyl alcohol (25ml), three drop of acetic acid was added and was refluxed for 3hrs, and this reaction was monitored by TLC. The resultant solution was cooled and poured in cold water. The separated solid was filtered ,crystallized from ethyl alcohol to give crystalline yellow, yield 79%, Melting point 212-214oC, CHN analysis that formula C12H10BrN3O2 calculated C, 46.783 H, 3.275 N, 13.642 ; Found C, 46.721 H, 3.254 N, 13.611. Ultraviolet spectra λmax 240, 255 and 292nm. FT-IR spectra νmax 2964, 1618, 1454, 1217, 752cm-1.1HNMR spectra δppm, (2.1, 3H) t, (2.3, 3H) t, (6.7, 5H), and (8.2, 1H) s.13CNMR spectra δppm, 14, 17, 21, 114, 127, 128, 129, 132,138, 140, 141, 164, 183.

Synthesis of 2-azetidinone (D)

A mixture of (1mmole, 3.06gm) Schiff base (C) and chloroacetyl chloride (10ml) in 40ml dioxane, drops of triethylamine was added slowly and reflexed for 6hrs, This reaction was monitored by TLC. The resultant solution was cooled and poured in cold water. The separated solid was filtered, crystallized from ethyl alcohol to give crystalline yellow. yield 82%, Melting point 266-268oC, CHN analysis that formula C14H11BrClN3O3 calculated C, 43.722 H, 2.881 N, 9.227 ; Found C, 43.645 H, 2.772 N, 9.018. Ultraviolet spectra λmax 245, 265 and 295nm. FT-IR spectra νmax 3105, 1691, 1523, 1251, 854cm-1. 1HNMR spectra δppm, (2,2H) t, (2.7, 3H) t, (3.8, 1H) s, (4,1H) s and (7.3, 5H) .13CNMR spectra δppm, 14, 17, 56, 110, 112, 114 123, 126, 128,133, 140, 149, 151, 163, 183.

RESULT AND DISCUSSION

Metronidazole derivatives form a group of generally less investigated compounds. However, recently growing efforts are made to synthesize and characterized these compounds. Many metronidazole derivatives possess very promising properties regarding biological activities as

shown in literature survey. In the present research, project the conventional methods to prepare some metronidazole compounds with expected biological activity.

Scheme (1)

The objective of this work is the synthesis of new heterocyclic compound by using percyclic reaction between new imine with chloroacetyl chloride (16-18) in dioxane; these compounds may have biological effects besides being prepare for this time. The reaction of replacement hydroxyl group is by protonation and then nucleophilic attack of potassium bromide. Reduction of metronidazole was occur by using stannous chloride in the presence of hydrochloric acid to give 1-ethyl bromide-2-amino imidazole. Then the aromatic aldehyde were condensate with the amine compound to give Schiff base according to well-known procedure (19,20)was reacted with chloroacetyl chloride to produce four membered heterocyclic compound of azetidinone it show in scheme (1) .

Mechanism of the percyclic reaction between an imine group and chloroacetyl chloride for preparing azetidinone ring systematically investigated as (2+2) cycloaddition (21). The breaking and formation of bonds occur simultaneously and thus the reaction proceeds via a single cyclic as show in scheme (2).

Scheme (2)

All new synthesis compounds have been characterized by their melting points, UV spectra, FT-IR spectra, (CHN) analysis, 1HNMR and 13CNMR, these results are compared with those obtained earlier. Elementary analysis showed good agreement of the calculated and found percentages. Compound (A) and (B) characterized with UV spectrum(22) which showed the two band at (240-275)nm were due to transition (π-π^*) aromatic heterocyclic ring. While the compound (C) and (D) which showing three band at (240-295) nm were due to interferences transition (π-π^*) aromatic heterocyclic ring with aromatic benzene ring.

Compound (A) characterized with FT-IR spectrum(23,24) which showed disappearance of hydroxyl group in 3400cm-1, While the compound (B) which showed appearance new double band in 3200-3300cm-1 were due to asymmetric and symmetric vibration of amino group. Compound (C), which showed disappearance of carbonyl group of aldehyde and amino group of amine compound, and showed appearance new band of azomethane group in 1620cm-1. Compound (D) which showed appearance new band in 1690cm-1 were due to symmetric carbonyl group of amide.

Compound (C) characterized with 1HNMR and 13CNMR spectra (25-26). 1HNMR spectra showed the signals in the region (6.8-7-7) ppm due to interferences of five protons (three of benzene and 2 of imidazole) difference in chemicals environment, the signal in the region 8.2ppm due to of one proton of azomethane. The final signal in the region (2-3.5) ppm due to ethyl group. 13CNMR spectra showed the 13 signals due to 13-carbon atom difference in chemicals environment.

1HNMR spectra of compound (D) showed the signals in the region (6.5-7-5) ppm due to interferences of five protons (three of benzene and two of imidazole), the signal in the region (2-

3.5) ppm due to ethyl group. The signal in the region 3.5ppm due to of proton attach the carbon which carrying chloride. Finally, the signal in the region 5ppm due to of proton attach the carbon, which attach the nitrogen atoms. 13CNMR spectra showed the 15 signals due to 15-carbon atom difference in chemicals environment. The solvent (DMSO) showed the signals in the region (2.5) ppm in 1HNMR and appears that signals in the region 40ppm in 13CNMR.

Biological Activities

The antibacterial (27, 28) activities of the series (A-D) have been carried out against some strain of bacteria. The result (table 1) showed that prepared compounds are toxic against the bacteria. The compounds (C) and (D) were found more active against the above microbes. The comparison of the antibacterial activity of these compounds with penicillin shows that these compounds have almost similar activity.

Table (1): The antibacterial activities of the compounds (A-D)
% of zone inhibition

Compound	Staphylococcus aurous(gram +ve)	E. Coli (gram –ve)
A	54	42
B	63	51
C	77	66
D	75	72
penicillin	63	73

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