SYNTHESIS AND CHARACTERIZATION OF NEW DERIVATIVES IMIDES FROM METOCLOPRAMIDE

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ABSTRACT

This study includes synthesis and characterization of new imide derivatives (R or Ar-2-(N-phthalimido acetyl, N-(2-aminoacetyl substituted benzothiazole, via of the reaction from 3-chloro-4-(2-chloroacetamido)-N-(2-(ethyl (methyl) amino) ethyl)-6-methoxycyclohex-1-ene-1-carboxamide with potassium phthalimide or potassium succinimide and substituted-2-aminobenzothiazole. Using absolute ethanol as a solvent. This mixture was refluxed for (6 - 8) hrs. While maintaining the pH at 6. The prepared compounds were characterized by melting point, FT-IR and 1H-NMR spectroscopy

Key words: 2-aminobenzothiazole, Derivatives imides, metoclopramide drugs and biological activity.

INTRODUCTION

Metoclopramide (MCP), monohydrate of 4-amino-5- chloro-N-[(2-diethyl amino)ethyl]-2-methoxy benzamide mono hydrochloride (Figure 1) is a substituted benzamide and commonly used as an anti-emetic in the management of some forms of nausea and vomiting and for stimulating the motility of the upper gastrointestinal tract [1][2]. Benzothiazole belongs to the family of bicyclic heterocyclic compounds having benzene nucleus fused with five - membered ring comprising nitrogen and sulfur atoms[3]. Being a hetero cyclic compound, benzothiazole finds use in research as a starting material synthesis of larger, usually bioactive structures. Its, aromaticity makes it relatively stable; although as a heterocycle, it has reactive sites, which allow for function alization[4][5][6]. Benzothiazole is a colorless, lightly viscous liquid with a melting point of (2 ) and boiling point of (227-228) . The density of benzothiazole is (1.24 g/mL), and its molecular, mass is (135.19 g/mol). Benzothiazole has no house hold, use. It is used in industry and research [7][8][9] . Cyclic imides and their derivatives have been found to be an important moiety in creation of novel medical materials. In the view of their broad spectrum of biological applications [10]. Numerous derivatives containing extensively studied and many of these compounds have proved to be active as antibacterial, antifungal, anti-cancer and anti-inflammatory agents and some of them are expansively used as analgesic and anti-nociceptive agents [11]. Succinimide is an organic compound with the formula (CH2)28(CO)2NH This white solid is used in a variety of organic syntheses, as well as in some industrial silver plating processes. The compound is classified as a cyclic imide. It may be prepared by thermal, decomposition of ammonium succinate [12][13]. The molecule are obviously, responsible for electrostatic interactions. The atomic charges give a qualitativeunderstanding of the structure and reactivity of molecule and they are used for the description of the molecular polarity of the molecules [14][15][16]
II. MATERIALS AND METHODS

Detection Equipment

The melting points were determined in open capillary tubes method. The FT-IR spectra were recorded on FT-IR spectrophotometer, Shimadzu at Abn siena Company- ministry and metal. 1H-NMR Spectra of some prepared derivatives were recorded on a Varian-Mercury 300MHZ Spectrometer, CDCL3 use as a solvent in 1H-NMR Spectra.

Synthesis of (2-Chloroacetyl) Mcp

Place in round –bottom flask (0.02 mol) Metoclopramide(M) and (15ml) Diethyl ether with (0.025 mol) triethylamine, then added (0.025 mol) choro acetyl chloride drop-wise at 5-10°C, and stirred for 6 hours. left the reaction mixture at room temperature for 24 hours then poured into crushed ice. The solid separated was dried and recrystallized from (1:1) ethanol and water. Physical properties are listed in Table (3).

Synthesis of Potassium Phthalimide and Succinimide(M1-M2)

(0.01 mol) of Phthalimide or succinimide has been dissolved in (20 ml) of absolute ethanol then was heated in water bath . The obtained clear solution has been added to alcoholic potassium hydroxide solution with continuous stirring and cooling then the resulted precipitate has been filtered and dried. Melting points, yield% data are listed in Table (3).

Synthesis of 4-(N-Phthalimido (or succinimido) acetyl)MCP (M3-M4)

MCP (M1-M2) and 2-(N-Phthalimido (or succinimido) acetyl),M (0.01 mol) has been dissolved in (25 ml) of absolute ethanol then (0.01mol) of prepared potassium phthalimide or potassium succinimide has been added gradually with stirring. The resulted mixture was refluxed for six hours with continuous stirring then has been cool edit room temperature . The formed precipitate was filtered, washed with (10%) NaHCO3 solution then with water, and finally purified by recrystallization from acetone. Physical properties are listed in Table (3).

Synthesis of N-(2-aminoacetyl substituted benzothiazole)MCP  (M5-M9)

Compound (M) (0.008 mol) in (15 ml) absolute ethanol and (0.008 mol) potassium carbonate anhydrous was refluxed and added dropwise to a solution of (0.008 mol) odisubstituted-2-amino benzothiazole in (20 ml) of absolute ethanol, The reaction mixture was refluxed for (8-10) hours after cooling then the precipitate was separated, filtered, and recrystallized from ethanol as solvent. Physical properties are listed in Tables (3).

Antibacterial activity of chemical samples by agar well diffusion method:

Mueller-Hinton agar plates were inoculated with 0.1ml of 1.5x108 CFU/ml (McFarland tube No. 0.5) of pathogenic bacterial isolates. Sterile cork borer was used to make wells with diameter of 10 mm. The wells were filled with 100 μl of each sample (conc. 1000 Mg / ml). The plates were incubated at 37°C for 24 hours. After incubation, inhibition zones were measured.

III. RESULTS AND DISCUSSIONS

The new derivatives were prepared following the reaction sequences in (scheme 1). Preparation salt from reaction the different primary aromatic amine (aniline and p-aminoacetonaphone) with salicylaldehyde to gave new derivatives of salt (M1-M2), indicated by disappearance of NH2 stretching band at (3230)cm-1 and appearance (1566-1550) cm-1 due to N=N stretching vibration respectively (M1-M2),shown in table (1). Preparation of substituted-2-aminobenzothiazole, by the reaction of (ortho, para and 2,4-) disubstituted aromatic primary), amine with Ammonium thiocyanate, bromine, and glacial acetic acid as catalyst . Metoclopramide has been convert to 4(2-chloroacetyl) Metoclopramide(M) by the reaction with Chloroacetyl chloride at (5-10) °C in the presence of triethylamine and Diethylether as asolvents as shown in the following equation(1) :

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The mechanism for these reactions involves nucleophilic attack of amino group in Metoclopramide on reaction with carbonyl group in chloroacetychloride which gives the final product (M).

Mechanism 1

The FT-IR spectra show the (C=O) amide group band at (1658, 1701) cm$^{-1}$, (C-CL) at (856, 39) cm$^{-1}$ which is a good indication of successful) condensation listed in table (1).

The $^1$H-NMR spectra of compound (M) showed the signal at $\delta$(2.6)(t,2H,CH$_2$-N),$\delta$(4.32)(s,2H,CH$_2$C=O),$\delta$(8.1)(s,1H,NH),$\delta$(10.8)(s,1H,NHC=Oamid),$\delta$(7.55)(d,2H,CHaromatic),$\delta$(3.95)(s,3H,CH$_3$O),$\delta$(3.59)(t,2H,CH$_2$CH$_2$),$\delta$(2.2)(s,3H,CH$_3$-N),$\delta$(2.6)(t,2H,CH$_2$-N),$\delta$(2.3)(q,2H,CH$_2$N),$\delta$(1.06)(t,3H,CH$_3$-CH2)these spectra are shown in table (2).

Table (1): The FT-IR spectra data cm$^{-1}$ of the prepared compounds(M)

<table>
<thead>
<tr>
<th>Comp. No</th>
<th>Structure</th>
<th>$\delta$(N-H)</th>
<th>$\delta$(C=O)</th>
<th>$\delta$(C=N)</th>
<th>$\delta$(C-O)</th>
<th>$\delta$(C-CL)</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td></td>
<td>3113</td>
<td>1701</td>
<td>1546</td>
<td>1481</td>
<td>1238</td>
<td>856</td>
</tr>
</tbody>
</table>

3-chloro-4-(2-chloroacetamido)-N-(2-(ethyl(methyl)amino)ethyl)-6-methoxycyclohex-1-ene-1-carboxamide

Table (2): $^1$H-NMR spectral data for compound (M)

<table>
<thead>
<tr>
<th>Comp. No</th>
<th>Structure</th>
<th>$^1$H-NMRspectra data( ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M</td>
<td></td>
<td>$\delta$(2.6)(t,2H,CH$_2$-N),$\delta$(4.32)(s,2H,CH$_2$C=O),$\delta$(8.1)(s,1H,NH),$\delta$(10.8)(s,1H,NHC=Oamid),$\delta$(7.55)(d,2H,CHaromatic),$\delta$(3.95)(s,3H,CH$_3$O),$\delta$(3.59)(t,2H,CH$_2$CH$_2$),$\delta$(2.2)(s,3H,CH$_3$-N),$\delta$(2.6)(t,2H,CH$_2$-N),$\delta$(2.3)(q,2H,CH$_2$N),$\delta$(1.06)(t,3H,CH$_3$-CH2)</td>
</tr>
</tbody>
</table>
Preparation of Potassium Phthalimide and Succinimide (M1, M2)

The compounds (M) have been synthesized from the conversion of succinimide or phthalimide to potassium phthalimide or succinimide by the reaction with alcoholic potassium hydroxide and heated in water bath. The FT-IR spectra show the absence at (3213) cm⁻¹ for imide (NH) in the phthalimide and (3240) cm⁻¹ in the succinimide and appear at (1751 cm⁻¹) for (C=O), (3043 cm⁻¹) for (C-H aromatic) in the phthalimide, at (1708 cm⁻¹) for (C=O) in succinimide.

Preparation of 4-(N-Phthalimido (or succinimido) acetyl), Metoclopramide (M3, M4)

The reaction compound (M) with potassium phthalimide or potassium succinimide and absolute ethanol as solvent. The FT-IR spectra show that compounds (M3-M4) give absorption band at (1771, 1774) cm⁻¹ for (C=O) Imide, (1654, 1604) cm⁻¹ (C=O) Amide, (1558, 1543) cm⁻¹ (C=C) and (1307, 1300) cm⁻¹ (C-N) are listed in table(34). The 1H-NMR spectrum of compound (M4) show the signal δ(2.9) (t, 2H, CH2-N), δ(3.0) (d, 2H, CH2-O), δ(4.2-4.8) (t, 2H, CH2C=O), δ(8.2-8.3) (d, 1H, NH), these spectral.

Preparation of Substituted 2-Aminobenzothiazole

Aniline derivatives have been reacted with Ammonium thiocyanate with the addition of bromine in the presence of glacial acetic acid as solvent. The FT-IR spectra show compounds (M5-M9) which give absorption bands at (3406-3479) cm⁻¹ for (NH2) group, (1616-1728) cm⁻¹ (C=N), (856-964) cm⁻¹ (C-S) and (1550-1620) cm⁻¹.

Synthesis of N-(2-aminoacetyl Substituted Benzothiazole-2-yl)Metoclopramide (M10-M14)

The reaction compound (M) with 2-amino benzothiazole derivatives in the presence of potassium carbonate anhydrous and Diethyl ether as solvent. The FTIR spectra show that compounds (M10-M14) have absorption bands at (3116-3298) cm⁻¹ for (N-H), (3024-3100) cm⁻¹ (C-H) aromatic, (1631-1766) cm⁻¹ (C=O) and (1581-1697) cm⁻¹ (C=N) listed. The 1H-NMR spectra of compound (M10) showed the signal at δ(1.4-2.4) (d, 2H, CH2-N), δ(3.0) (s, 2H, CH2-O), δ(3.3) (s, 1H, NH), δ(7.2) (s, 2H, CH2C=O), δ(7.3) (m, 3H, aromatic), δ(9.7-9.9) (s, 1H, OH) these spectra.

Result of Biological Activity

As shown in table (4), only three isolates were affected by chemical samples with diameters of inhibition zones ranged from (11-15) mm, while Proteus sp. was not affected by any one of them.
Table (3): Physical Properties and Structures of The Compounds (M-M14)

<table>
<thead>
<tr>
<th>Comp.no</th>
<th>structures</th>
<th>Yield %</th>
<th>Color</th>
<th>M.P °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>90</td>
<td>pink</td>
<td>158-160</td>
</tr>
<tr>
<td>M2</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>95</td>
<td>Off White</td>
<td>310-312</td>
</tr>
<tr>
<td>M3</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>90</td>
<td>White</td>
<td>254-256</td>
</tr>
<tr>
<td>M4</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>80</td>
<td>Off White</td>
<td>160-162</td>
</tr>
<tr>
<td>M5</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>85</td>
<td>White</td>
<td>186-188</td>
</tr>
<tr>
<td>M6</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>70</td>
<td>White</td>
<td>202-204</td>
</tr>
<tr>
<td>M7</td>
<td><img src="image7.png" alt="Structure" /></td>
<td>60</td>
<td>Green</td>
<td>78-80</td>
</tr>
<tr>
<td>M8</td>
<td><img src="image8.png" alt="Structure" /></td>
<td>90</td>
<td>White</td>
<td>78-80</td>
</tr>
<tr>
<td>M9</td>
<td><img src="image9.png" alt="Structure" /></td>
<td>66</td>
<td>Orang</td>
<td>84-86</td>
</tr>
<tr>
<td>M10</td>
<td><img src="image10.png" alt="Structure" /></td>
<td>53</td>
<td>White</td>
<td>198-200</td>
</tr>
<tr>
<td>M11</td>
<td><img src="image11.png" alt="Structure" /></td>
<td>85</td>
<td>Yellow</td>
<td>162-164</td>
</tr>
<tr>
<td>M12</td>
<td><img src="image12.png" alt="Structure" /></td>
<td>98</td>
<td>Orang</td>
<td>138-140</td>
</tr>
<tr>
<td>M13</td>
<td><img src="image13.png" alt="Structure" /></td>
<td>90</td>
<td>Off White</td>
<td>170-172</td>
</tr>
<tr>
<td>M14</td>
<td><img src="image14.png" alt="Structure" /></td>
<td>80</td>
<td>Off White</td>
<td>174-176</td>
</tr>
</tbody>
</table>
Table (4): Antibacterial activity of chemical samples against some pathogenic bacteria by agar well diffusion method

<table>
<thead>
<tr>
<th>Sample concentration (2000 Mg/ml)</th>
<th>Antibacterial activity against pathogenic bacteria (diameters of inhibition zones, mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. coli</td>
</tr>
<tr>
<td>M3</td>
<td>12</td>
</tr>
<tr>
<td>M10</td>
<td>12</td>
</tr>
<tr>
<td>M13</td>
<td>13</td>
</tr>
<tr>
<td>M14</td>
<td>11</td>
</tr>
</tbody>
</table>

Antagonistic activity of different materials against pathogenic bacteria is usually detected by agar well diffusion assay[17]

Figure (1): FT-IR spectrum of compound (M)

Figure (2): FT-IR spectrum of compound (M4)

Figure (3): FT-IR spectrum of compound (M13)
Figure (4): 1H-NMR Spectral of compound (M)

Figure (5): 1H-NMR Spectral of compound (M\textsubscript{5})

Figure (6): 1H-NMR Spectral of compound (M\textsubscript{12})

REFERENCES


