Synthesis, identification and evaluation of antibacterial activity for some new heterocyclic derivatives from 4-methoxy-2-nitroaniline

Authors Names
a. Sabah Matrood Mezaal
b. Shaimaa Adnan

Article History
Received on: 21/6/2021
Revised on: 10/7/2021
Accepted on: 11/7/2021

Keywords:
schiff base, Oxazepine, Quinazoline, Thiazine

DOI: https://doi.org/10.29350/jops.2021.26.4.1383

ABSTRACT
This research involved synthesis novel heterocyclic derivatives (quinazoline and thiazinone) derivatives, this compounds prepared from starting react (4-methoxy-2-nitroaniline) with 2,4-dimethoxycetophenone to gate azo derivative (A), (A) interact with aromatic amine derivatives to produce imine compounds (B1-B2), imine derivatives interact with (anthranilic acid, 2-mercaptopbenzoic) to get heterocyclic derivatives quinazoline (C1-C2) and thiazinone (D1-D2). All these compound characterized by 13C-NMR, FT-IR, 1HMNR. Then that, we studies the biological properties for all heterocyclic derivatives, to ward two different kind of bacteria.

1. Introduction
Heterocyclic compounds that have (N,S) as hetero atoms are very important because of the applications (1). Heterocyclic compounds forms a part of large number of pharmaceutical relevant molecule and have major biological significance (2). Organic heterocyclic compounds currently account for about 70% of all clinically used drugs (3). Azo, compounds, or dyes are characterized, by, the, presence of the, Azo, moiety (−N=N−), in their, structure, conjugated with two, distinct or, identical, , mono- or, poly-cyclic, aromatic, or heteroaromatic systems (4). The biological importance of, Azo, compounds is well known due to their use as, inflammatory, (5), antibacterial, (6), anti-diabetic, (7), and antifungal (8). Schiff bases are condensation products of primary amines and carbonyl compounds and they were discovered by Hugo Schiff in 1864 (9). A, Schiff base, is the nitrogen, analogue of, aldehyde in, which the
C=O group, is replaced by a C=N group \(^{(10)}\). There are numbers of biologically important Schiff bases have been noted in previous studies possessing antibacterial, antifungal, antimicrobial, anticonvulsant, antitumor, anti-inflammatory, and anti-HIV activities \(^{(11)}\). Quinazolines and thiazine derivatives, have six-membered containing \((N\text{, and } S)\), respectively such as antitubercular, anti-inflammatory, antimicrobial, antipyretic, anti-HIV, analgesic, antitumor, and calcium channel modulatory activities \(^{(12)}\). Thiazine derivatives that exhibit various biological activities such as anti-tubercular, antifungal \(^{(13)}\), insecticidal, and pesticidal \(^{(14)}\). Studies of heterocycles containing heteroatoms such as sulphur and nitrogen, are definite, one of the supreme targeted areas in heterocyclic chemistry. They are extensively used in several studies of natural products and pharmaceutical agent’s synthesis. Thiazine ring systems are considered a significant heterosystem in heterocyclic chemistry \(^{(15)}\). Quinazoline nucleus is an interesting molecule among the most important classes of aromatic bicyclic compounds with two nitrogen atoms in their structure. It is consisting of aromatic benzopyrimidine system, synthesis \(^{(16)}\) made up of two fused six-membered aromatic rings, benzene, and pyrimidine rings \(^{(17)}\). Researchers have already determined many therapeutic activities of quinazoline derivatives, including antitumor \(^{(18)}\), antiviral \(^{(19)}\), antimalarial \(^{(20)}\).

2. Materials

\"(FTIR,) Spectra, \((400.\text{ to } 4000 . \text{ cm}^{-1})\), in KBr, disk were recorded on SHIMADZU FTIR-8400S, Fourier transform. \(^{13}\)C-NMR, and \(^{1}H\)NMR were recorded on varian agilent USA at \((500. \text{ MHz})\) with \((\text{DMSO-}d_6)\) measurement were made at Department of Chemistry, Tehran University, Iran.\"

2.1 Preparation of compound A \(^{(21)}\)

\((0.01) (1.68 \text{ g})\) of 4-methoxy-2-nitro aniline, was dissolved in a solution consisting of \((10 \text{ ml})\) hydrochloric acid with the mixture cooled to \((0\text{, to } 5)^\circ\text{C}\) and then added sodium nitrite \((0.8 \text{ g})\) \(\text{NaNO}_2\) with a brown color drop as a drop to a solution consisting of \((1.8 \text{ g})\) \((0.01 \text{ mol})\) of 2,4-dimethoxyacetophenone and \((2 \text{ g})\) of \(\text{NaOH}\) dissolved in \((130 \text{ ml})\) distilled and cooled water to \((20 {^\circ}\text{C})\) and \((10 \text{ ml})\) ethanol was observed. The Azo composite deposit is dark brown color after completing the addition process. This process was carried out in \(\text{PH} = 5\) and the solution is left for \(24 \text{ hours}\) after which the precipitate was filtered and then the precipitate was collected after filtering and washed with distilled water, and dried and recrystallized with ethanol.

2.2 Preparation of compound \((B1-B2)\) \(^{(22)}\)

In a double-beaker flask, \((1 \text{ g})\) \((0.00278 \text{ mol})\) of derivative (A) was mixed with \((0.03 \text{ g})\) \((0.00278 \text{ mol})\) of \(\text{p-amino phenol, \(\text{p}, \text{ and } 2\)-amino phenol, compound with } (20 \text{ ml})\) of ethyl alcohol added to it (three drops) of glacial acetic acid and the mixture up and left. For a period of two hours at a temperature \((78 {^\circ}\text{C})\) and then cool the mixture and leave it for \((24 \text{ hours})\) and then re-crystallize it with absolute ethyl alcohol.
2.3 Preparation of compound (C1-C2):

(0.00150mol) (0.7 g) of dissolved schiff base B1 and B2 compound was mixed in (1-4-dioxane (20ml) with (0.213g) of (anthranilic acid) or (0.00150mol)(0.7 g) of Schiff base B2, was mixed in (1-4-dioxane (20ml) with (0.205g) of (anthranilic acid) was mixed in (1-4-dioxane (20ml) with (0.213g) of (anthranilic acid) then add drops of (DMF) and reflex of (36 Hour) and then re-crystallized the product with absolute ethanol.

2.4 Preparation of compound (D1-D2):

(0.7g) (0.00155mol) of Schiff baseB1, B2 compound was mixed in (22ml) of benzene with (0.239g) of 2-mercapto benzoic acid (3ml) of DMF then add drops of triethylamine to the reaction mixture and from Then reflex of (10 hours), then the product was filtered and re-crystallized with absolute ethanol.
Scheme(1) prepare of some heterocyclic compounds

3. Results and Discussion

Derivative (A)

(E)-1-(6,2-dimethoxy-3-(4-methoxy-2-nitrophenyl)diazanylphenyl)-N-(4-nitrophenyl)ethan-1-imine C4,C

FT-IR spectrum data for derivative (A), show peak at 3000 cm⁻¹ for (Ar-H), 2980 cm⁻¹ for (C-H) in CH₃, 1700 cm⁻¹ for (C=O), 1650 cm⁻¹ for (C=C), (1521-1357) cm⁻¹ for (NO₂). HNMR spectrum data of derivative (A) show 2.52ppm (DMSO), 3.78ppm (3H, (OCH₃)), 3.87ppm (3H, (OCH₃)), 3.98ppm (s, 1H, CH₃), 6.3-7.6ppm (M, 5H, Ar-H), 9.4PPm. The C13-NMR
spectrum data (DMSO) compound (A) show: 197 ppm (C_{17}), 79 ppm (C_{16}), 56 ppm (C_{15}), 55 ppm (C_{14}), 31 ppm (C_{13}), 164 ppm (C_3), 161 ppm (C_4, C_7), 98-132 ppm (C_{Arom}).
Derivative (B1) 4-(((Z)-1-{2,4-dimethoxy-5-((E)-(4-methoxy-2-nitrophenyl)diazenyl)phenyl)ethylidene) amino)phenol

FT-IR spectrum data for derivative (B1) show peak at 3025 for (Ar – H), 2988 cm\(^{-1}\) for (C- H) in CH\(_3\), 1456 for N=N, 1652 cm\(^{-1}\) for C=C\(_{\text{arom}}\), 1500, 1350 cm\(^{-1}\) for NO\(_2\), 1650 cm\(^{-1}\) for C=O. \(^1\)HNMR spectrum data of derivative (B1) show 2.52 ppm (DMSO), 2.9 (S, 3H, (OCH\(_3\))\(_1\)), 3.9 (S, 3H, (OCH\(_3\))\(_2\)), 3.7 (S, 3H, (OCH\(_3\))\(_3\)), 3.8 ppm (s, 1H, CH), (6.5-7.6) ppm (m, 9H, (Ar-H)). The C13-NMR spectrum data (DMSO) compound (B1) show: 79 ppm (C\(_{21}\)), 55ppm (C\(_{20}\)), 79ppm (C\(_{21}\)), 31ppm (C\(_{22}\)), 161ppm (C\(_{13}\)), 164ppm (C\(_{4-7}\)), 196ppm (C\(_{17}\)), 34 ppm (C\(_{19}\)).
Fig(4) FT-IR spectrum of compound (B1)

Fig(5) $^{1}$H-NMR spectrum of compound (B1)
Compound (B2) 2-(((Z)-1-(2,4-dimethoxy-5-((E)-(4-methoxy-2-nitrophenyl)diazenylphenyl) ethylidene)amino)phenol

FT-IR spectrum data for derivative (B2) show band at 3300 cm\(^{-1}\) for (O – H) 3080 for (Ar – H), 2985 cm\(^{-1}\) for (C- H) in CH\(_3\), 1600 cm\(^{-1}\) for (C=N), 1593 cm\(^{-1}\) for (C=C), 1470 cm\(^{-1}\) for (C=N), 1325 cm\(^{-1}\) for (C=C), 1130 cm\(^{-1}\) for (C=O). 1\(^{\text{H}}\)NMR spectrum data of derivative (B2) show 2.52 ppm (DMSO), 1.9 ppm (DMSO), 3.9 ppm (DMSO), 3.8 ppm (DMSO), 2.01 ppm (DMSO), 9.1 ppm (DMSO), 6.5-7.6 ppm (m, 9H, Ar-H). The C13-NMR spectrum data (DMSO), compound (B1) show: 79 ppm (C\(_{21}\)), 72 ppm (C\(_{20}\)), 56 ppm (C\(_{21}\)), 161 ppm (C\(_{22}\)), 31 ppm (C\(_{23}\)), 164 ppm (C\(_{4}\), C\(_{7}\)), 196 ppm (C\(_{17}\)).
Fig(7) FT-IR spectrum of compound (B2).

Fig(8) $^1$H-NMR spectrum of compound (B2).
**Fig. (9) (\(^{13}\)C-NMR,) spectrum of compound (B2)**

**Compound (C1) and ((E)-2-(2,6-dimethoxy-3-((4-methoxy-2-nitrophenyl)diazenyl)phenyl)-3-(4-hydroxyphenyl)-2-methyl-2,3-dihydroquinazolin-4(1H)-one**

FT-IR; spectrum data; for derivative (C1) show, peak at 1,420 for (N=N), 3078 for (Ar – H), 2947 cm\(^{-1}\) for (C- H) in CH\(_3\), 1670 cm\(^{-1}\) for (C=O), 1620 cm\(^{-1}\) for (C=C), 3425 cm\(^{-1}\) for (N-H). 1HMNR spectrum; data, of derivative (C1) show 4.0 ppm (s, 1H, NH), 2.6 ppm (s, 3H, OCH\(_3\)) 30, 3.8 ppm (s, 3H, OCH\(_3\)) 28, 2.8 ppm (s, 3H, OCH\(_3\)) 29, 1.2 ppm (s, 1H, CH), 1.8 ppm (s, 2H, CH\(_2\)), 6.5-7.8 ppm 13H, (Ar-H), 8.4 ppm (s, 1H, OH), 4.1 ppm 9s, 1H, NH). C\(_{13}\)_NMR spectrum data (DMSO) compound (C1) show: 79 ppm (C\(_{27}\)), 56 ppm (C\(_{28}\)), 56.2 ppm (C\(_{29}\)), 32 ppm (C\(_{30}\)), 31 ppm (C\(_{19}\)), 164 ppm (C\(_{3}\)), 63 ppm (C\(_{13}\)), 196 ppm (C\(_{14}\)), 164-98 ppm (CArom).
Fig. (10): (FT-IR) spectrum of compound (C1)

Fig. (11): ($^1$H NMR) spectrum of compound (C1)
Compound \((C2)\) \((E)\)-2-(2,6-dimethoxy-3-\((4\text{-methoxy-2-nitrophenyl})\text{diazenyl})(phenyl)-3-(2-hydroxyphenyl)-2-methyl-2,3-dihydroquazolin-4(1H)-one

FT-\(\text{IR}\) spectrum data for derivative \((C2)\) show peak at 3325 cm\(^{-1}\) for \((O-H)\), 3060 for \((Ar-H)\), 2920 cm\(^{-1}\) for \((C-H)\) in CH\(_3\), 1680 cm\(^{-1}\), for \((C=O)\), 1600 cm\(^{-1}\), for \((C=C)\), 1550 cm\(^{-1}\), \((C=N)\), \((1500\text{-}1360)\) cm\(^{-1}\) NO2. 1HMN, spectrum data of \((DMSO)\) compound \((C2)\) show: 2.8 ppm \((S, 3H, OCH3)\), 2 ppm \((S, 3H, OCH3)\), 3.9 ppm \((S, 3H, OCH3)\), 0.8 ppm \((s, 3H, CH3)\), 6.3 ppm \((s, 3H, CH3)\), \(-8.4 ppm (m, 13H, Ar-H)\), 4.4 ppm \((s, 1H, N-H)\). The C\(_{13}\)_NMR spectrum data \((DMSO)\) compound \((C2)\) show: 31 ppm \((C29)\), 32 ppm \((C28)\), 56.05 ppm \((C27)\), 36 ppm \((C26)\), 56.28 ppm \((C25)\), 167 ppm \((C23)\), 162 ppm \((C21)\), 164 ppm \((C5\text{-}C7)\), 164-96 ppm \((CArom)\), 196 ppm \((C=O)\).
Fig(13): (FT-IR) spectrum of compound (C2)

Fig(14): ($^1$H-NMR) spectrum of compound (C2)
Compound (D1): \((E)-2-(2,6\text{-dimethoxy}-3-((4\text{-methoxy}-2\text{-nitrophenyl})\text{diazenyl})\text{phenyl})-3-(4\text{-hydroxyphenyl})-2\text{-methyl}-2,3\text{-dihydro}-4\text{-H}-\text{benzo[\text{e}]1,3}\text{-thiazin}-4\text{-one}\)

FT-IR spectrum: data for derivative (D1) show: peak at 3090 cm\(^{-1}\) for (Ar-H), 2910 cm\(^{-1}\) for (C-H) in CH\(_3\), 1680 cm\(^{-1}\) for (C=O), 1412 cm\(^{-1}\) for (N=N), 1600 cm\(^{-1}\) for (C=C), (1550-1396) cm\(^{-1}\) for (NO\(_2\)).

\(^1\)H NMR spectrum: data of compound (D1) show 1.2 ppm (s, 3H, OCH\(_3\)), 0.8 ppm (s, 3H, CH\(_3\)), 1.2 ppm (s, 3H, OCH\(_3\)), 3.8 ppm (s, 3H, OCH\(_3\)), 2.4 ppm (s, 3H, OCH\(_3\)), 6.5-7.9 ppm (s, 13H, Ar-H). The C\(^{13}\)NMR spectrum data (DMSO) compound (D1) show: 16.6 ppm (C\(_{28}\)), 56 ppm (C\(_{30}\)), 153 ppm (C\(_{4}\), C\(_{14}\), C\(_{17}\)), 191 ppm (C\(_{31}\)), 111-134 ppm (C\(_{Arom}\)).
Fig(16): (FT-IR): spectrum of compound (D1)

Fig(17): -H NMR, spectrum of compound (D1)
Compound (D2) (E)-2-(2,6-dimethoxy-3-((4-methoxy-2-nitrophenyl)diazenyl)phenyl)-3-(5-hydroxy-4-methylpyrimidin-2-yl)-2-methyl-2,3-dihydro-4H-benzo[ae][1,3]thiazin-4-one

FT-IR spectrum data for derivative (D2) show band at 3332 cm\(^{-1}\), for (O–H), 3080 cm\(^{-1}\), for (Ar–H), 2931 cm\(^{-1}\), for (C–H) in CH\(_3\), 1700 cm\(^{-1}\), for (C=O), 1458 cm\(^{-1}\), for (N=N), 1600 cm\(^{-1}\), for (C=C), 1650 cm\(^{-1}\), for (C=N), (1535-1537) cm\(^{-1}\), for (NO\(_2\)). \(^1\)HMNR spectrum data of compound (D2) show 0.8 ppm (s, 3H, CH\(_3\)), 1.2 ppm (s, 3H, OCH\(_3\)), 2.4 ppm (s, 3H, OCH\(_3\)), 3.8 ppm (s, 3H, OCH\(_3\)), 8.4 ppm (s, 1H, OH), 6.5-7.6 ppm (m, 10H, Ar-H). The C\(^{13}\)-NMR spectrum data (DMSO) compound (D2) show: 196 ppm (C\(_{14}\)), 36 ppm (C\(_{29}\)), 32 ppm (C\(_{28}\)), 32 ppm (C\(_{26}\)), 38 ppm (C\(_{27}\)), 56 ppm (C\(_{25}\)), 67 ppm (C\(_{13}\)), 30 ppm (C\(_{30}\)), 164 ppm (C\(_4\), C\(_7\)).
Fig(19): (FT-IR) spectrum of compound (D2)

Fig(20): (1H-NMR) spectrum of compound (D2)
4. Biological activity

4.1 antibacterial

The results show that, derivatives reduce significant antibacterial effectiveness against bacteria "staphylococcus aureus" and Escherichia coli. The compounds that show good activity are (A,B1,C1,C2, D1) against (staphylococcus aureus), and compound that show very good activity are (A-D1), against (Escherichia coli); the results of the antibacterial activity are shown in the fig (6). The results show that derivatives reduce significant antibacterial effectiveness against bacteria "staphylococcus aureus and Escherichia coli" the compounds that show good activity are (A,B1,B2,C1,C2,D1,D1) against (staphylococcus aureus), and compound that show very good activity are (A-D1) against (Escherichia coli), the results of the antibacterial activity are shown in the fig (6).
**Fig. (30)** effect: compounds (Staph Aureus) against and (E.Coli) against

**Table (1)** the results of the antibacterial activity for (A-D3) derivatives

<table>
<thead>
<tr>
<th>Comp No</th>
<th>Staph aureus</th>
<th>Mm</th>
<th>E.Coli</th>
<th>Mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>+++</td>
<td>37</td>
<td>+++</td>
<td>40</td>
</tr>
<tr>
<td>B1</td>
<td>+++</td>
<td>45</td>
<td>+++</td>
<td>30</td>
</tr>
<tr>
<td>B2</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>Zero</td>
</tr>
<tr>
<td>C1</td>
<td>-</td>
<td>Zero</td>
<td>+++</td>
<td>45</td>
</tr>
<tr>
<td>C2</td>
<td>-</td>
<td>Zero</td>
<td>-</td>
<td>Zero</td>
</tr>
<tr>
<td>D1</td>
<td>++</td>
<td>22.3</td>
<td>+++</td>
<td>30</td>
</tr>
<tr>
<td>D2</td>
<td>+++</td>
<td>30.5</td>
<td>-</td>
<td>Zero</td>
</tr>
</tbody>
</table>

(-)No discouragement!

"+= (5-10)mm , =slightly,:active, ++=, (11-20)mm moderately +++= More,than ,20: good,active"

**Table (2)** Proaratese of derivtive (A-D3) derivetives
<table>
<thead>
<tr>
<th>Comp</th>
<th>M.F M.wat</th>
<th>m.p</th>
<th>Rf</th>
<th>Colour</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>C_{17}H_{19}N_{4}O_{6} 359.11</td>
<td>45</td>
<td>0.5</td>
<td>Brown</td>
<td>72</td>
</tr>
<tr>
<td>B1</td>
<td>C_{23}H_{22}N_{4}O_{6} 450.5</td>
<td>120</td>
<td>0.47</td>
<td>Black</td>
<td>90</td>
</tr>
<tr>
<td>B2</td>
<td>C_{23}H_{22}N_{4}O_{6} 450.5</td>
<td>115</td>
<td>0.5</td>
<td>Brown</td>
<td>93</td>
</tr>
<tr>
<td>C1</td>
<td>C_{30}H_{29}N_{5}O_{7} 569.6</td>
<td>180</td>
<td>0.4</td>
<td>Black</td>
<td>90</td>
</tr>
<tr>
<td>C2</td>
<td>C_{30}H_{27}N_{5}O_{7} 569.6</td>
<td>134</td>
<td>0.3</td>
<td>Brown</td>
<td>87</td>
</tr>
<tr>
<td>D1</td>
<td>C_{30}H_{28}N_{5}O_{8}S 615.6</td>
<td>160</td>
<td>0.2</td>
<td>Black</td>
<td>79</td>
</tr>
<tr>
<td>D2</td>
<td>C_{29}H_{28}N_{6}O_{8}S 602.6</td>
<td>182</td>
<td>0.29</td>
<td>Black</td>
<td>85</td>
</tr>
</tbody>
</table>

References


