



Synthesis of Some New Phenazine Derivatives as Antifungal Agents

Islam Ragab*



Department of Mathematics, College of Science and Arts, Qassim University, Riyadh Al Khabra,
Saudi Arabia

Abstract

2-Methyloxazolo[4,5-b]phenazine (**2**) was obtained through the cyclocondensation of 3-aminophenazin-2-ol (**1**) with acetic anhydride. Oxazolophenazine derivatives (**3a-d**) were synthesized by oxidatively adding 3-aminophenazin-2-ol (**1**) to aromatic aldehydes. The addition of 3-aminophenazin-2-ol (**1**) to activated acrolein resulted in the formation of the 2-methylene-2H-[1,4]oxazino[2,3-b]phenazine (**5**). Alkylation and subsequent cyclization of aminophenazin-2-ol (**1**) using phenacyl bromide and/or ethyl acetochloroacetate produced 2-phenyl-4H-[1,4]oxazino[2,3-b]phenazine (**7**) and 3-acetyl-2H-[1,4]oxazino[2,3-b]phenazin-2-one (**9**), respectively. The cyclocondensation of aminophenazin-2-ol (**1**) with cyanoacetamide led to the synthesis of 2-amino-1H-pyrrolo[2,3-b]phenazine-3-carbonitrile (**10**). 2H-[1,4]oxazino[2,3-b]phenazin-2-one (**11**) was generated through the alkylation of aminophenazin-2-ol (**1**) in pyridine followed by cyclization. The antifungal activity of oxazine derivatives (**9**), (**10**), and pyrrole derivatives (**11**) was evaluated against two fungal species, *Candida albicans* and *Aspergillus niger*. The tested compounds exhibited varying degrees of antifungal activity against the two fungal strains.

Keywords: Synthesis (chemical), Aminophenazinol, oxazolophenazine, pyrrolophenazine Antifungal activity.

1. Introduction

Phenazines and quinoxalines represent significant classes of benzoheterocycles with notable implications in the fields of chemistry and biology [1-5]. Phenazine, a nitrogen-containing heterocyclic compound, belongs to a group of antibiotic agents [6-14] which exhibit a diverse range of biological properties, such as , antifungal, antibacterial, antimicrobial, anti-oomycete activity, genotoxicity, cytotoxicity, antioxidant, antitumor and antimalarial [15-18]. The synthesis of quinoxaline and phenazine derivatives has been achieved [19, 20]. Various methods have been employed for synthesizing phenazines, such as oxidative cyclization of 1,2-diaminobenzene/diphenylamines, condensation of 1,2-diaminobenzenes with 2C-units, the Wohl-Aue method, reductive cyclization of diphenylamines, Pd-catalyzed N-arylation, Beirut method and multicomponent approaches [15]. In this study, our aim was to join a heterocyclic nucleus with potential biological activities through the heteroannulation of phenazine derivatives bearing o-amino hydroxyl groups using readily available laboratory reagents.

2. Experimental

Melting points were determined using Electro Thermal IA 9,100 series digital melting point apparatus in capillaries without any corrections applied. Infrared (IR) spectra were

recorded in KBr using a Shimadzu spectra 200-91506 spectrophotometer. ¹H-NMR spectra (Proton nuclear magnetic resonance) were acquired DMSO-d₆ as the solvent, utilizing a Varian 90 MHz instrument with TMS as the internal reference. Elemental analysis was performed at the Microanalytical Unit, Cairo University, Giza, Egypt.

3-Aminophenazin-2-ol (**1**):

3-Aminophenazin-2-ol was prepared according to reported procedures [21, 22] ; from finely powdered o-phenylenediamine. (**1**); yellow crystal from ethanol with yield=35%, m.p. = >300°C, IR (KBr), ν , cm⁻¹: revealed bands at 1480 (C=C) aromatic; 1580 (C=N), 3090 (CH) aromatic, 3320-3395 (NH₂) and 3450 broad (OH) group. ¹HNMR (DMSO-d₆): 6.29 (2H, s, NH₂) disappear by deuteration with D₂O, 6.69 (2H, s, Ar), 8.62 (1H, s, OH), 7.56 (2H, m, Ar) and 7.91 (2H, m, Ar). Calculated C₁₂H₉N₃O (211.07), %: C, 68.24; H, 4.29; N, 19.89. Found, %: C 68.11; H 4.20; N 19.80.

2-Methyloxazolo [4,5-b]phenazine (**2**):

A suspension of 3-aminophenazin-2-ol (0.21g, 1 m mole), in acetic anhydride (12ml) was heated for 30 minutes under reflux, resulting in the formation of a dark yellow solution. Subsequently, the solution was cooled. The resulting product was filtered off and recrystallized from acetic acid ;

*Corresponding author email: chem_islam82@yahoo.com, is.mohamed@qu.edu.sa; (Islam Ragab).

EJCHEM use only: Received date 11 December 2023; revised date 11 January 2024; accepted date 13 January 2024

DOI: 10.21608/EJCHEM.2024.254620.8978

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A colorless crystal with yield= 68%, m.p.= 231-232°C, IR (KBr), ν , cm^{-1} : revealed bands at 1480 (C=C) aromatic; 1580 (C=N), 2926 (CH) aliph, 3090 (CH) aromatic. ^1H NMR (DMSO- d_6): 2.42 (3H, s, CH_3), 7.16, 7.37 (2H, s, Ar), 7.67 (2H, m, Ar) and 7.86 (2H, m, Ar). Calculated $\text{C}_{14}\text{H}_9\text{N}_3\text{O}$ (235.07), %: C 71.47, H 3.86 N 17.87. Found, %: C 71.35; H 3.70; N 17.74.

General procedure for compound 3:

An aryl aldehyde (1 mmole) was added drop wise at room temperature to a solution of compound **1** (0.21g, 1 mmole) in nitrobenzene or DMF (10 ml). The mixture was stirred for 30 minutes and then refluxed for 8 hours. Afterward, it was left to cool overnight at room temperature. The resulting precipitate was collected, washed with ether, and recrystallized from DMF, resulting in the desired oxazolophenazine derivatives (**3a-d**).

2-Phenyloxazolo[4,5-b]phenazine (3a);

Yellow crystal with yield= 71%, m.p. = 245-247 °C, IR (KBr), ν , cm^{-1} : revealed bands at (1154 C-O-C, 1580 C=N) for oxazole system, 1740 for 5-membered ring and 3100 (CH) arom. ^1H NMR (DMSO- d_6): 7.62-7.83 (4H, m, Ar), 8.64 (2H, s, Ar), 7.52-7.93 (5H, m, Ar). Calculated $\text{C}_{19}\text{H}_{11}\text{N}_3\text{O}$ (297.31), %: C 76.76; H 3.73; N 14.13. Found, %: C 76.68; H 3.60; N 14.05.

2-(4-Chlorophenyl)oxazolo[4,5-b]phenazine (3b);

A pale yellow crystal with yield= 71%, m.p. = 260-262 °C, IR (KBr), ν , cm^{-1} : revealed bands at (1154 C-O-C, 1580 C=N) for oxazole system, 1740 for 5-membered ring and 3100 (CH) arom. ^1H NMR (DMSO- d_6): 7.62-7.83 (4H, m, Ar), 8.14 (2H, s, Ar) and 7.52-7.65(4H, m, Ar). Calculated $\text{C}_{19}\text{H}_{10}\text{ClN}_3\text{O}$ (331.08), %: C 68.79; H 3.04; N 10.69. Found, %: C 68.70; H 2.90; N 10.55.

2-(4-Nitrophenyl)oxazolo[4,5-b]phenazine (3c);

A pale yellow crystal with yield= 71%, m.p. = 305-307 °C IR (KBr), ν , cm^{-1} : revealed bands at (1154 C-O-C, 1580 C=N) for oxazole system, 1740 for 5-membered ring, 1540 NO_2 and 3100 (CH) arom. ^1H NMR (DMSO- d_6): 7.62-7.83 (4H, m, Ar), 8.14 (2H, s, Ar), 7.55-7.77 (4H, m, Ar), Calculated $\text{C}_{19}\text{H}_{10}\text{N}_4\text{O}_3$ (342.08), %: C 66.67; H 2.94; N 16.37. Found, %: C 66.55; H 2.80; N 16.25.

2-(4-Methoxyphenyl)oxazolo[4,5-b]phenazine (3d);

A colorless crystal with yield= 71%, m.p. = 291-292 °C, IR (KBr), ν , cm^{-1} : revealed bands at (1154 C-O-C, 1580 C=N) for oxazole system, 1740 for 5-membered ring, 2930 (CH) aliph., and 3100 (CH) arom. ^1H NMR (DMSO- d_6): 3.94 (3H, s, OCH_3), 7.14 (2H, m, Ar), 7.62, 7.93 (4H, m, Ar), 8.24 (2H, m, Ar) and 8.32 (2H, s, Ar). ^{13}C NMR (DMSO- d_6): 63 (OCH_3), 123, 129, 134, 137, 137, 137, 137, 138, 138, 138, 138, 149, 149, 151, 151, 170 and 173 (Ar-C, C=N).

Calculated $\text{C}_{20}\text{H}_{13}\text{N}_3\text{O}_2$ (327.10), %: C 73.38; H 4.00; N 12.84. Found, %: C 73.30; H 3.90; N 12.70

General procedure for compound 5, 7 and 9:

A mixture of 3-aminophenazin-2-ol (0.21g, 1 mmole) and acrolein **4**, phenacyl bromide **6** and/or ethyl acetochloroacetate **8** (1 mmole) in 20 ml of acetic acid was refluxed for a period of 3-5 hours. The resulting solid was separated by filtration and recrystallized using a suitable solvent to give (**5**, **7** and **9**) respectively.

2-Methylene-2H-[1,4]oxazino[2,3-b]phenazine (5);

A brown crystal from ethanol with yield= 70%, m.p. = 243-245 °C, IR (KBr), ν , cm^{-1} : revealed bands at 1170 (C-O-C), 1475 (C=C), 1610 (C=N), 3120 (CH) aromatic. ^1H NMR (DMSO- d_6): 5.5, 5.6 (2H, dd, $=\text{CH}_2$), 6.94, 7.24 (2H, s, Ar), 7.2 (1H, s, H-C=N), 7.56 (2H, m, Ar.), 7.92 (2H, m, Ar). ^{13}C NMR (DMSO- d_6): 112, 119, 107, 129, 129, 129, 129, 136, 137, 139, 142, 142, 146 and 147 (Ar-C, $=\text{CH}_2$ and C=N). Calculated $\text{C}_{15}\text{H}_9\text{N}_3\text{O}$ (247.07), %: C 71.48; H 3.86; N; 17.86. Found, %: C 71.40; H 3.81; N 17.75.

2-Phenyl-4H-[1,4]oxazino[2,3-b]phenazine (7);

Yellow crystal from chloroform with yield= 65%, m.p. = 225-227 °C, IR (KBr), ν , cm^{-1} : revealed bands at 1170 (C-O-C), 1475(C=C), 1610 (C=N), 3120 (CH) aromatic and 3450 broad (NH) cyclic. ^1H NMR (DMSO- d_6): 5.82 (1H, s, $\text{CH}=\text{C}$), 7.12, 7.33 (2H, s, Ar), 7.62, 7.83 (4H, m, Ar), 7.34, 7.45 (5H, m, Ar) and 11.43 (1 H, br., NH) which disappear in D_2O . Calculated $\text{C}_{20}\text{H}_{13}\text{N}_3\text{O}$ (311.11), %: C 77.12; H 4.21; N 13.50. Found, %: C 77.05; H 4.10; N 13.40.

3-Acetyl-2H-[1,4]oxazino[2,3-b]phenazin-2-one (9);

white-brown crystal from DMF/ H_2O with yield= 62%, m.p. = 310-312 °C, IR (KBr), ν , cm^{-1} : revealed bands at 1170 (C-O-C), 1480 (C=C), 1585 (C=N), 1170 (C-O), 1735 (C=O), 2950 (CH) aliph. ^1H NMR (DMSO- d_6): 3.45 (3H, s, COCH_3) 5.5, 5.6 (2H, dd, $=\text{CH}_2$), and 7.8, 8.1 (4H, m, Ar). Calculated $\text{C}_{16}\text{H}_9\text{N}_3\text{O}_3$ (291.06), %: C 70.08; H 4.50; N; 14.43. Found, %: C 70.02; H 4.40; N 14.30.

2-Amino-1H-pyrrolo[2,3-b]phenazine-3-carbonitrile (10)

A mixture of compound **1** (0.21g, 1 mmole), cyanoacetamide (1 mmole) and (5 ml) acetic anhydride in 30 ml of acetic acid arid was refluxed for 4 hours. The resulting solid was separated by filtration and recrystallized from DMF/ H_2O ;Yellow crystal from DMF/ H_2O with yield= 58%, m.p. = 236-238 °C, IR (KBr), ν , cm^{-1} : revealed bands at 1485 (C=C), 1620 (C=N), 2210 (C \equiv N), 3320 -3400 (NH_2) and 3470 broad (NH). ^1H NMR (DMSO- d_6): 6.46 (2 H, s, NH_2), 7.22 (2H, s, Ar), 7.62 (2H, m, Ar), 7.96 (2H, m, Ar), and 12.63 (1 H, br. (s), NH) disappear by dutration with D_2O). ^{13}C NMR (DMSO- d_6): 67, 124 (C=C), 113 (C=N), 126,

129.3, 129.3, 129.4, 129.4, 129.6, 129.6, 129.6, 142, 142, 144 and 144 (Ar-C, C=N). Calculated $C_{15}H_9N_5$ (259.09), %: C 69.48; H 3.50; N; 27.10. Found, %: C 69.38; H 3.40; N 27.05.

2H-[1,4]oxazino[2,3-b]phenazin-2-one (11):

A mixture of compound **1** (0.21g, 1 mmole) and chloroacetic acid (1 mmole) in dry pyridine (25ml) was refluxed for 5 hours. The reaction mixture was then cooled and poured over an ice/water mixture. The resulting solid was separated by filtration and recrystallized DMF/H₂O; A pale yellow crystal with yield= 59%, m.p. = 325-327 °C, IR (KBr), ν , cm^{-1} : revealed bands at 1490 (C=C), 1510 (C=N), 1735 (C=O), 3110 (CH) aromatic. ¹H-NMR (DMSO-d₆): 7.22 (1H, s, H-C=N), 7.96 (2H, s, Ar) and 7.63, 7.84 (4H, m, Ar). ¹³C-NMR (DMSO-d₆): 142, 145, 145.5 (C=N), 119, 129, 129, 129.5, 130, 132, 141, 141, 150 and 195 (Ar-C, C=N, C-O, C=O). Calculated $C_{14}H_7N_3O_2$ (249.05), %: C, 72.87, H 3.67; N 16.99. Found, %: C 72.70; H 3.50; N 16.85.

3. Discussion

3-1. Chemistry

Phenazine under investigation bearing a suitable located functionality for further functionalization and heteroannulation using simple available laboratory reagents thus, the condensation of 3-aminophenazin-2-ol **1** with

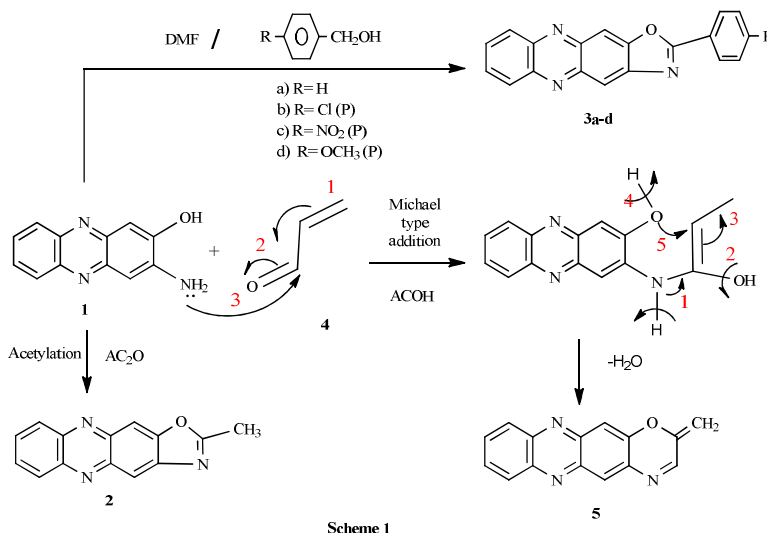
variously substituted aromatic aldehydes namely, benzaldehyde, p-chlorobenzaldehyde, p-nitrobenzaldehyde, p-methoxybenzaldehyde, in nitrobenzene or DMF, resulted in oxazole cyclization affording 2-aryl-oxazolo[4,5-b]phenazine derivatives (**3a-d**). The formation of **3** from **1** may be proceed through the formation of non-isolable acyclic shiff base followed by oxidative cyclization, (**scheme 1**).

Another type of oxazolocyclization was achieved by acylation of amino compound **1** with acetic anhydride producing 2-methyl-oxazolo [4,5-b] phenazine **2** (**scheme1**).

IR of compound **2** showed absorption frequency at 1580 and 1165 cm^{-1} for (C=N), (C=C) and (C-O-C) respectively. In ¹H-NMR showed singlet signals at (7.1, 7.3), and multiplet signals at (7.67 , 7.8) and the aliphatic CH₃ proton was detected as a single signal at 2.68 ppm.

Oxazine derivative **5** was achieved by Michael addition [23, 24] of acrolein to compound **1** followed by cyclisation (**scheme 1**).

IR of compound **5** showed absorption frequencies at 1170, 1475, 1610 and 3120 cm^{-1} for (C-O-C), (C=C), (C=N) and (CH) aromatic respectively. ¹H-NMR revealed signal at 5.5, 5.6 for (=CH₂). ¹³C NMR showed sp^2 carbon of C=N at 142 ppm and for C-O at 146ppm.

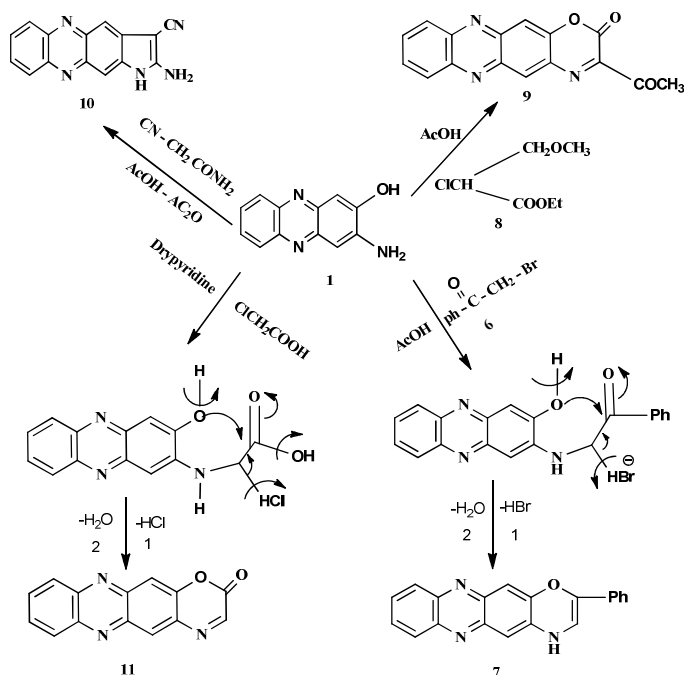


The synthesis of condensed oxazine (**7**, **9** and **11**) was achieved by alkylation followed by intramolecular

cyclocondensation using phenacyl bromide, ethyl acetochloroacetate and chloroacetic acid as cyclizing agent, (**scheme 2**). cyclodehydration of compound **1** with cyanoacetamid affording pyrrolophenazine **10** (**scheme 2**).

IR of compound **10** showed absorption frequencies at 3470, 3320-3400, 2210, 1620 and 1485 cm^{-1} for (NH), (NH_2), ($\text{C}\equiv\text{N}$), ($\text{C}=\text{N}$) and ($\text{C}=\text{C}$) respectively. ^1H NMR displayed downfield signals at 12.6 ppm for NH disappear by deuteration with D_2O and 6.46 ppm for NH_2 . ^{13}C NMR showed sp^2 carbon of $\text{C}=\text{N}$ and $\text{C}\equiv\text{N}$ at 142 and 113 ppm respectively.

IR of compound **11** showed absorption frequencies at 1490, 1510, 1735 and 3110 for ($\text{C}=\text{C}$), ($\text{C}=\text{N}$), ($\text{C}=\text{O}$) and (CH) aromatic respectively. ^1H NMR showed signals at (7-8) for CH aromatic protons. ^{13}C NMR showed sp^2 carbon of $\text{C}=\text{O}$ at 195 ppm and 150 ppm for $\text{C}-\text{O}$.



Scheme 2

3-2. Antifungal activity:

The tested compounds (**9**), (**10**), and (**11**) demonstrated distinct antifungal activities against *Candida albicans* and *Aspergillus niger*. To assess their preliminary antifungal activity, the cup plate method was employed. Each compound was dissolved in 5 mL of dimethyl sulfoxide (at a concentration of 50 $\mu\text{g}/\text{mL}$). A control group consisting of dimethyl sulfoxide and a standard drug, ketoconazole (at a concentration of 50 $\mu\text{g}/\text{mL}$), were also included. The diameter of the resulting zone of inhibition was measured in millimeters [25]. Data was found in table (1); showed that compound **11** have value more than Ketoconazole (standard) with *Candida Albicans*. While compound (**9**) have higher value with *Aspergillus Niger*, which have value lower than Ketoconazole.

Table 1: Antifungal Activities of the three tested compounds 9, 10 and 11

| Drug | <i>Candida Albicans</i> | <i>Aspergillus Niger</i> |
|-------------------------|-------------------------|--------------------------|
| Ketoconazole (standard) | 8.25 | 7.25 |
| 9 | 5.3 | 6.8 |
| 10 | 7.35 | 4.5 |
| 11 | 8.65 | 3.9 |

4. Conclusions

Our study focus the synthesis of new oxazolophenazine, oxazine and pyrrolophenazine derivatives. This synthesis was achieved using 3-aminophenazin-2-ol **1** as the starting material. The resulting products **9**, **10** and **11** exhibited diverse structural features and displayed varying levels of antifungal activity against *Candida albicans* and *Aspergillus niger*.

5. Author Contributions

I.R: supervision, project administration, conceptualization, investigation, writing-original draft, visualization, formal analysis, data curation and writing- review.

6. Conflicts of interest:

There are no conflicts to declare

7. Acknowledgements:

Researcher would like to thank the Deanship of Scientific Research, Qassim University for funding publication of this project.

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