Synthesis of New Heterocyclic Compounds with Biological Activity against Pathogenic Microbes in the Albaha Area

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Abstract

Several new heterocyclic derivatives containing fused pyrazoloxazine moieties were synthesized via cycloaddition reactions of bi-nucleophilic dentates, including hydrazine hydrate and its derivatives as well as active methylene compounds and aniline derivatives, resulting in novel five-, six- and seven-membered heterocyclic compounds. Due to increased microbial resistance to currently available drugs accentuate a real problem, so novel antimicrobial drugs are needed. Pyrazoles are good candidate as antimicrobial agents, where they have low-molecular-weight compounds, nonvolatile and chemically stable. The novel synthesized five-, six- and seven-membered heterocyclic compounds were tested for their antimicrobial activity against different pathogenic microorganisms inside Albaha area. Bacterial species included Staphylococcus aureus, Staphylococcus epidermidis, Salmonella enteritidis, Streptococcus faecalis, Streptococcus agalactiae, Klebsiella pneumonia, Proteus mirabilis, Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterobacter aerogenes. However, the following fungi were tested: Aspergillus niger, Aspergillus fumigates, Penicillium chrysogenium, Trichophyton rubrum and Candida albicans. The zones of inhibition ranged from 40 to 14 mm/disc for these organisms. The current study demonstrates that the newly synthesized pyrazoloxazine derivatives have a good inhibition capacity against most tested pathogenic bacterial and fungal species.

Keywords: Pyrazole-Oxazine; Five-Six and Seven-Membered Heterocycles; Microorganisms; Pathogenic Microbes; Antimicrobials; Albaha

Introduction

Increased microbial resistance to currently available drugs is a major cause of morbidity and mortality throughout the world. Thus, novel antimicrobial drugs are needed. The use of heterocyclic agents is an attractive alternative. Compared to conventional antimicrobials, they are low-molecular-weight compounds that are nonvolatile and chemically stable and do not easily permeate the skin. Pyrazoles, also called as azoles, are five-membered ring heterocyclic compounds with two adjacent nitrogen atoms [1]. Recently, pyrazole derivatives have been found in nature [1]. For example, β-[1-pyrazolyl] alanine was isolated from watermelon seeds (Citrullus lanatus). The most common use for pyrazoles is to treat inflammation and inflammation-associated disorders such as arthritis [2]. Pyrazole derivatives are the subject of many studies due to their potential antimicrobial [3], Antiviral [4], Antitumor [5,6], Antihistaminic [7], Antidepressant [8], Insecticidal and fungicidal properties [9]. Pyrazole derivatives function as 5-α-reductase inhibitors [10]. In addition to having antiproliferative [11], Antiparasitic [12] and herbicidal properties [13]. Several pyrazoles have also been reported to have anti-inflammatory [14] and antiprotozoal effects [15,16].

Which render them valuable as medicinal and plant-protecting agents? Furthermore, the current literature indicates that 1; 2-pyrazole derivatives possess various biological activities [17]. Recently, acyclonucleosides, which are heterocyclic compounds bound to an acyclic sugar moiety, have gained worldwide attention because of their high potential as chemotherapeutics [18,19]. Substituted pyrazole and its analogs have been used as precursors for the synthesis of various biologically active molecules. Recently,
improvements in microwave chemistry have dramatically reduced reaction times, which have been demonstrated in several fields of organic chemistry [20]. Additionally, microwave-assisted organic synthesis has shown significant improvement in the generation of combinatorial small molecule libraries [21].

The goal of this study was to synthesize novel pyrazoloxazine derivatives and to determine their antimicrobial activity with the cooperation of the Blood Bank in Albahe, Saudi Arabia. We chose the most common pathogenic microorganisms (bacteria and fungi) from Albahe county, including Staphylococcus aureus (skin-wound-abscess infections, hospital-acquired pneumonia, gastroenteritis), Staphylococcus epidermidis (endocarditis, urinary tract infections, skin-wound-abscess infections), Salmonella enteritidis (gastroenteritis), Streptococcus faecalis (urinary tract infections, wound, and soft issue infections), Streptococcus agalactiae (bacterial septicaemia in newborns, leading to death or long-term sequelae), Klebsiella pneumonia (urinary tract infections), Pseudomonas aeruginosa (hospital-acquired pneumonia), Proteus mirabilis (urinary tract infections) and Acinetobacter baumannii (hospital-acquired pneumonia). Enterobacter aerogenes is an opportunistic pathogen associated with nosocomial infections, including urinary tract infections (especially in catheterized patients), respiratory tract infections, and bacteremia in elderly or debilitated patients. The following fungi were tested: Aspergillus niger, Aspergillus fumigates, Penicillium chrysogenum, Trichophyton rubrum and Candida albicans 157. Aspergilli cause aspergillosis and Candida albicans causes candidiasis.

**Materials and Methods**

**Chemicals**

We synthesized novel heterocyclic derivatives based on a fused pyrazoloxazine moiety. This moiety was synthesized via cycloaddition reactions of bi-nucleophilic dentates (including hydrazine hydrate and its derivatives, active methylene compounds, and aniline derivatives), resulting in novel five-, six- and seven-membered heterocyclic compounds. Novel heterocyclic compounds, which are versatile starting materials, were also prepared. The following heterocyclic derivatives were obtained:

- a) 4-isonitroso-3-methyl-1-phenylpyrazole-5-one (oxime).
- b) 5-cyano-3-methyl-1-phenylpyrazolo[4,3-b][1,4]oxazine-6-one (oxazine).
- c) 1,6-diphenyl-5-imino-3-methylpyrazolo[4,3:2,3]oxazino[5,6-c]pyrazole (compound 3).
- d) 5-imino-3-methyl-1-phenylpyrazolo[4,3:2,3]oxazino[5,6-c]-6-[2,4-dinitro-phenylpyrazole (compound 4).
- e) 1,6-diphenyl-5-imino-3-methylpyrazolo[4,3:2,3]oxazino[5,6-c]oxazole (compound 5).
- f) 5-amino-3-methyl-1-phenylpyrazolo[4,3:2,3]oxazino[4,5-b]pyrimidine-7-one (compound 6).
- g) 6-amino-5-imino-3-methyl-1-phenylpyrazolo[4,3:2,3]oxazino[4,5-b]-pyrimidine-7-thione (compound 8).
- h) 5-imino-3-methyl-1-phenylpyrazol[4,3:2,3]oxazino[5,6-b][1,4]benzoepine (compound 9).
- i) 5-cyano-3-methyl-1-phenylpyrazolo[4,3-b][1,4]oxazine-6-[(ethylcyano-acetate] (compound 10).
- j) 5-cyano-3-methyl-1-phenylpyrazolo[4,3-b][1,4]oxazino-6-(4-nitro-iminophenyl) (compound 13).
- k) 5-cyano-3-methyl-1-phenylpyrazolo[4,3-b][1,4]oxazino-6-(4-methoxy-iminophenyl) (compound 24) and,
- l) 5-cyano-3-methyl-1-phenylpyrazolo[4,3-b][1,4]oxazino-6-imino-(1-aminohexane) (compound 25).

Details of compound synthesis and characterization are presented elsewhere. Pyrazoloxazine derivatives 1, 3, 4, 5, 6, 8, 9, 10, 13, 21, 24, 25, 2Y, Ox2, Ox1, oxime and oxazine were chosen for the evaluation of antimicrobial activity against the obtained microbial strains.

**Microbial Organism Source**

The microorganisms were previously isolated and identified in patients from the Blood Bank, Albahe from different hospitals and health centers in Albahe County. Infected patient urine samples, throat swabs, vaginal swabs, wound swabs, sputum, and breath samples were cultivated in Mueller Hinton agar (for bacteria) and Sadourad dextrose medium (for fungi). These pathogens were identified after purification using Vitek2 (Biomerieux 3584, USA). Purified organisms were grown on slants in the appropriate media and stored at 4°C until further use.

**Antimicrobial Activity**

**Preparation of Inoculum**

The Gram positive (S. aureus 119, S. faecalis, S. agalactiae, S. enteritidis, and S. epidermidis) and Gram negative bacteria (K. pneumonia, P. aeruginosa, P. mirabilis, A. baumannii, and E. aerogenes 157) were pre-cultured overnight in nutrient broth in a rotary shaker at 37°C and then centrifuged at 10,000 rpm for 5 min. The pellet was re-suspended in double distilled water, and the cell density was standardized and used to inoculate Mueller Hinton medium. Petri dishes were inoculated in triplicate, and the average zone of inhibition was calculated. The fungal inocula (A. niger, A. fumigates, P. chrysogenum, T. rubrum and C. albicans 157) were prepared from 5- to 10-day-old cultures grown on potato dextrose agar. Petri dishes were flooded with 8 to 10 mL of distilled water, and the conidia were scraped using a sterile spatula. The spore suspension used for fungal inoculation was harvested.

**Anti-bacterial Activity Determined Using the Agar Cup Method**

The antibacterial activities of the pyrazoloxazine derivatives (1, 3, 4, 5, 6, 8, 9, 10, 13, 21, 24, 25, 2Y, Ox2, Ox1, oxime and oxazine) were determined using the agar cup method [22,23]. Nutrient broth was used as a basal medium for testing bacteria. Overnight bacterial cultures were spread evenly over the surface of the solidified Mueller Hinton Petri dishes. The selected bacterial culture and the inoculated plates were percolated to form wells.
Historically, microbial infections have been a major cause of death in humans. During the 19th century, tuberculosis, diarrhea, urinary tract infections, diphtheria and pneumonia were the main causes of human morbidity. Heterocyclic pyrazole is a well-known five-membered ring with two adjacent nitrogen atoms. This compound recently received major interest for medical applications. E. coli and S. enteritidis showed complete resistance to all of the tested synthesized pyrazoloxazine derivatives (1, 3, 4, 5, 6, 8, 9, 10, 13, 21, 24, 25, 2Y, Ox2, Ox1, oxime and oxazine) at 20 mg per well of culture media. S. aureus, S. epidermidis, S. faecalis, S. agalactiae, K. pneumonia, P. aeruginosa, P. mirabilis, A. baumannii 116 and E. aerogenes 157 showed susceptibility or resistance to the pyrazole compounds (Table 1). Among heterocyclic compounds, pyrazoles constitute a large group with a broad spectrum of biological activity [26].

**Table 1:** Zone of inhibition (mm) for different pyrazoloxazine derivatives against pathogens isolated from patients inside Al Alba County.

| Microorganism name | Compound number | Staphylococcus aureus 119 | Staphylococcus epidermidis | Salmonella enteritidis | Streptococcus faecalis | Streptococcus agalactiae | Klebsiella pneumoniae | Pseudomonas aeruginosa | Proteus mirabilis | Acinetobacter baumannii 116 | Enterobacter aerogenes 157 | Escherichia coli |
|-------------------|----------------|---------------------------|---------------------------|-----------------------|------------------------|------------------------|---------------------|----------------------|----------------|-----------------------------|-----------------------------|----------------|
| 1                 | 1              | 15±1.0                    | 20±2.0                    | 0.0                   | 0.0                    | 0.0                    | 10±1               | 20±2.0               | 10±1           | 0.0                         | 0.0                         | 0.0           |
| 3                 | 0.0            | 0.0                       | 0.0                       | 0.0                   | 0.0                    | 0.0                    | 0.0                 | 12±1.0               | 0.0             | 0.0                         | 0.0                         | 0.0           |
| 4                 | 0.0            | 15±1.0                    | 0.0                       | 15±1.0                | 0.0                    | 0.0                    | 0.0                 | 0.0                  | 0.0             | 0.0                         | 0.0                         | 0.0           |
| 5                 | 24±2.0         | 15±1.2                    | 0.0                       | 0.0                   | 15±1.0                | 24±2.0                 | 0.0                 | 0.0                  | 0.0             | 0.0                         | 0.0                         | 0.0           |
| 6                 | 25±3.0         | 20±2.0                    | 0.0                       | 0.0                   | 15±1.2                | 20±2.0                 | 0.0                 | 21±2.2               | 0.0             | 0.0                         | 0.0                         | 0.0           |
| 8                 | 24±1.5         | 20±1.0                    | 0.0                       | 0.0                   | 0.0                    | 0.0                    | 0.0                 | 15±2.0               | 0.0             | 0.0                         | 0.0                         | 0.0           |
| 45                | 20±2.0         | 10±1.0                    | 0.0                       | 0.0                   | 0.0                    | 0.0                    | 0.0                 | 10±1.0               | 0.0             | 0.0                         | 0.0                         | 0.0           |
| 10                | 26±2.0         | 15±2.0                    | 0.0                       | 0.0                   | 0.0                    | 10±1.0                 | 0.0                 | 0.0                  | 0.0             | 0.0                         | 0.0                         | 0.0           |
| 21                | 30±2.1         | 20±2.0                    | 0.0                       | 0.0                   | 0.0                    | 15±2.0                 | 0.0                 | 15±1.0               | 15±1.0         | 0.0                         | 0.0                         | 0.0           |
| 24                | 25±1.0         | 15±1.0                    | 0.0                       | 0.0                   | 0.0                    | 10±1.0                 | 10±1               | 20±2.0               | 16±1.2         | 10±1                         | 0.0                         | 0.0           |
| 25                | 0.0            | 0.0                       | 0.0                       | 0.0                   | 0.0                    | 0.0                    | 0.0                 | 0.0                  | 0.0             | 0.0                         | 0.0                         | 0.0           |
| 0Y                | 0.0            | 0.0                       | 0.0                       | 0.0                   | 0.0                    | 0.0                    | 0.0                 | 0.0                  | 0.0             | 0.0                         | 0.0                         | 0.0           |
| 0X2               | 0.0            | 0.0                       | 0.0                       | 0.0                   | 0.0                    | 0.0                    | 0.0                 | 0.0                  | 0.0             | 0.0                         | 0.0                         | 0.0           |
| 0X1               | 0.0            | 0.0                       | 0.0                       | 0.0                   | 0.0                    | 0.0                    | 0.0                 | 0.0                  | 0.0             | 0.0                         | 0.0                         | 0.0           |
| Oxime             | 0.0            | 15±1.0                    | 0.0                       | 0.0                   | 0.0                    | 20±2.0                 | 0.0                 | 20±2.0               | 15±1.2         | 0.0                         | 0.0                         | 0.0           |
| OxAzine           | 20±2.0         | 15±1.0                    | 0.0                       | 0.0                   | 0.0                    | 15±1.0                 | 0.0                 | 10±1.0               | 0.0             | 10±1                         | 0.0                         | 0.0           |
| Rifampin*         | 32±2.0         | 45±4.1                    | 0.0                       | 0.0                   | 20±2.0                 | 20±1.5                 | 20±2.0             | 15±1.0               | 17±1.0         | 15±2.0                      | 15±2.0                      | 15±2.0 |

These compounds are present in nature and are constituents of nucleic acids, amino acids, alkaloids and hormones. Thus, pyrazoles may be misincorporated during synthesis of the aforementioned compounds, leading to an incorrect structure and loss of function. Additionally, pyrazoles can inhibit the enzymes responsible for its synthesis, such as nucleic acid gyrase in bacteria [27]. The maximum and minimum recorded inhibition zones were 40 and 10 mm, respectively, for all tested pyrazoles against the pathogenic bacteria species (Table 1). S. aureus 119 exhibited a 40 mm zone of inhibition after contact with the synthesized pyrazoloxazine derivatives 1, 5, 8, 10, 13 and 24. S. enteritidis and E. coli were completely resistant to all of the synthesized pyrazole derivatives. K. pneumonia and E. aerogenes 157 were the least affected bacteria and exhibited zones of inhibition between 10 and 12 mm (Table 1).
Recently [28] Stated that pyrazole compounds exhibit their activity against specific targets (including bacteria), protein targets (including DNA gyrase, fatty acid synthetase, and glutamate racemase) and RNA to cause bacterial cell death. The growth inhibition pattern of different pyrazole compounds tested against P. aeruginosa were approximately equal for compounds 4, 6, 8, 10 and 24 and were the largest zones of inhibition for all of the tested compounds (Table 2). The order of effectiveness of the compounds against P. aeruginosa was (from greatest to least) 5, 6, 8, 10, 24, 9, oxime, oxazine, 1, and 4. However, compounds 3, 4, 25, 2Y, Ox2 and Ox1 had no effect on P. aeruginosa. The order of compound effectiveness against P. mirabilis was (from greatest to least): 4, 24, 1, 6, 8, 13, 12, oxime, 3 and oxazine. P. mirabilis showed complete resistance to all of the other synthesized pyrazole compounds. S. agalactiae was highly resistant to the synthesized pyrazoloxazine derivatives except for three compounds (from greatest to least inhibition): 24, 13, and 21 Compound 25 was the most potent pyrazoloxazine derivative tested against S. epidermidis, which exhibited a 24 mm zone of inhibition.

Table 2: Antifungal activity of the synthesized pyrazoloxazine derivatives.

| Compound number | Aspergillus niger | Aspergillus fumigatus | Penicillium chrysogenum | Trichophyton rubrum | Candida albicans 178 |
|-----------------|------------------|----------------------|------------------------|--------------------|----------------------|
| 1               | 0.0              | 0.0                  | 0.0                    | 0.0                | 10 ± 0.1             |
| 3               | 30 ± 2.0         | 32 ± 3.0             | 25 ± 2.0               | 32 ± 2.3           | 0.0                  |
| 4               | 40 ± 3.0         | 37 ± 3.0             | 30 ± 2.4               | 0.0                | 0.0                  |
| 5               | 0.0              | 0.0                  | 0.0                    | 0.0                | 10 ± 0.12            |
| 6               | 0.0              | 0.0                  | 0.0                    | 0.0                | 10 ± 0.1             |
| 8               | 0.0              | 0.0                  | 0.0                    | 0.0                | 10 ± 0.1             |
| 9               | 0.0              | 0.0                  | 0.0                    | 0.0                | 10 ± 0.1             |
| 10              | 0.0              | 0.0                  | 0.0                    | 0.0                | 20 ± 0.2             |
| 13              | 0.0              | 0.0                  | 0.0                    | 0.0                | 0.0                  |
| 21              | 0.0              | 0.0                  | 0.0                    | 0.0                | 0.0                  |
| 24              | 0.0              | 0.0                  | 0.0                    | 0.0                | 0.0                  |
| 25              | 25 ± 1.0         | 22 ± 2.0             | 20 ± 1.3               | 30 ± 2.5           | 0.0                  |
| 2Y              | 20 ± 2.0         | 19 ± 1.0             | 20 ± 1.3               | 24 ± 2.0           | 0.0                  |
| OX2             | 15 ± 1.0         | 14 ± 1.2             | 20 ± 2.0               | 23 ± 2.0           | 0.0                  |
| OX1             | 17 ± 2.0         | 20 ± 2.0             | 16 ± 1.0               | 20 ± 2.0           | 0.0                  |
| Oxime           | 0.0              | 0.0                  | 0.0                    | 0.0                | 0.0                  |
| Oxazine         | 0.0              | 0.0                  | 0.0                    | 0.0                | 0.0                  |
| Nystatin*       | 20 ± 2.0         | 18 ± 1.0             | 15 ± 1.0               | 25 ± 2.0           | 7 ± 0.5              |

Figure 1: Antimicrobial activity of the pyrazoloxazine derivatives 24 and 25 on Staphylococcus aureus 119, and Candida albicans 178.

The order of effectiveness was as follows: 1, 6, 8, 13, 4, 5, 10, 21, oxime, oxazine, and 9. the other synthesized pyrazoloxazine derivatives showed no activity against S. epidermidis the inhibition pattern effectiveness of different pyrazoloxazine derivatives against A. baumannii 116 was 24, 2, and 1. The other compounds showed no activity against A. baumannii 116. The synthesized pyrazoloxazine derivatives resulted in variable zones of inhibition for S. aureus 119 (Table 1) and (Figure 1). A. Niger, A. fumigatus, P. chrysogenum and T. Rubrum were used to assess antifungal activity. Pyrazoloxazine derivatives 3, 4, 25, 2Y, Ox1 and Ox2 inhibited all of the fungi tested. The zones of inhibition ranged from 40 to 14 mm/disc. However, the pyrazoloxazine compounds 1, 5, 6, 8, 9, 10, 13, 21, 24, oxime and oxazine had no activity against fungi [29].

Stated in his study of the enzymatic basis of drug–drug interactions with systemic triazole antifungals that these compounds inhibit the enzyme in sterol biosynthesis that inhibits ergosterol synthesis (the main cytoplasmic cell membrane fungal sterol), leading to fungal death, We are interesting to decipher the mode of action of these active pyrazoloxazine compounds to increase its inhibition efficiency in near future. Where we are doing a lot of work in find out efficient antimicrobial compounds based on different strategy [30,31]. Finally, we could conclude that this study
has shown that the newly synthesized pyrazoloxazine derivatives have a potent inhibition capacity against most examined pathogenic bacterial and fungal species that might be used for infections treatments (Table 3).

Table 3: Antifungal activity of the synthesized pyrazoloxazine derivatives.

| Microorganism name | Aspergillus niger | Aspergillus fumigatus | Penicillium chrysogenum | Trichophyton rubrum | Candida albicans 178 |
|--------------------|------------------|-----------------------|------------------------|-------------------|----------------------|
| Compound number    |                  |                       |                        |                   |                      |
| 1                  | 0.0              | 0.0                   | 0.0                    | 0.0               | 10 ± 0.1             |
| 3                  | 30 ± 2.0         | 32 ± 3.0              | 30 ± 2.4               | 32 ± 2.3          | 0.0                  |
| 4                  | 40 ± 3.0         | 37 ± 3.0              | 30 ± 2.4               | 0.0               | 0.0                  |
| 5                  | 0.0              | 0.0                   | 0.0                    | 0.0               | 10 ± 0.12            |
| 6                  | 0.0              | 0.0                   | 0.0                    | 0.0               | 10.1                 |
| 8                  | 0.0              | 0.0                   | 0.0                    | 0.0               | 11 ± 0.1             |
| 9                  | 0.0              | 0.0                   | 0.0                    | 0.0               | 10 ± 0.1             |
| 10                 | 0.0              | 0.0                   | 0.0                    | 0.0               | 20 ± 0.2             |
| 12                 | 0.0              | 0.0                   | 0.0                    | 0.0               | 0.0                  |
| 21                 | 0.0              | 0.0                   | 0.0                    | 0.0               | 15                   |
| 24                 | 0.0              | 0.0                   | 0.0                    | 0.0               | 16                   |
| 25                 | 25 ± 1.0         | 22 ± 2.0              | 20 ± 1.3               | 30 ± 2.5          | 0.0                  |
| 2Y                 | 20 ± 2.0         | 19 ± 1.0              | 20 ± 1.3               | 24 ± 2.0          | 0.0                  |
| OX2                | 15 ± 1.0         | 14 ± 1.2              | 20 ± 2.0               | 23 ± 2.0          | 0.0                  |
| OX1                | 17 ± 2.0         | 20 ± 2.0              | 16 ± 1.0               | 20 ± 2.0          | 0.0                  |
| Oxime              | 0.0              | 0.0                   | 0.0                    | 0.0               | 0.0                  |
| Oxazine            | 0.0              | 0.0                   | 0.0                    | 0.0               | 0.0                  |
| Nystatin*          | 20 ± 2.0         | 18 ± 1.0              | 15 ± 1.0               | 25 ± 2.0          | 7 ± 0.5              |

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