Synthesis, spectroscopic and molecular docking studies on new schiff bases, nucleosides and \( \alpha \)-aminophosphonate derivatives as antibacterial agents

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**Abstract**

New Nucleosides, analogues derived from 1, 3, 4-oxadiazole, arylidene analogues and \( \alpha \)-aminophosphonate were prepared. Infrared (IR), elemental analysis and \(^1\)HNMR elucidated nucleosides; arylidines and phosphonate derivatives. The prepared derivatives were purified and allowed to test against bacteria strains. Phosphonate derivative \( 12a \) showed the higher antibacterial against \( E. \) coli with inhibition zone 35 mm, \( P. \) aeruginosa with inhibition zone 30 and \( S. \) aureus with inhibition zone 22 while compounds \( 4, 6d, 9a, 9c \) and \( 12c \) showed moderate to weak activity against these bacteria species with inhibition zones ranged from 12 mm to 24 mm. The molecular docking studies was applied on compound \( 12a \), which showed the binding at the active DNA Gyrase.

**1. Introduction**

Analogues of nucleoside are used as antibiotics as antiviral strains to treat cancer have been source of investigation for therapies and drug development to treat cancer and other pathogens (Jordheim et al., 2013). They possess properties of anticancer, antiviral and antibacterial (Ding et al., 2010). The main components of deoxyribonucleic acid and ribonucleic acid are nucleotides, it consists of nucleosides and phosphate group, also responsible for the production of proteins, also responsible for the production of proteins, acts as cofactor in many metabolic pathways; lipid and polyamine biosynthesis (Yssel et al., 2017). Nucleosides are metabolites excreted from RNA, composed of nucleobases which are covalently attached to ribose or deoxyribose. The aromatic heterocyclic nucleobases contain nitrogen in the ring with purine or pyrimidine. (Dudley, 2009). All pro-drugs derived from nucleoside are undergo chemical modification, to add phosphorous group to activate sites in many cellular processes during nucleotide and nucleic acid metabolism (Tsesmetzis et al., 2018). Development of nucleoside-analogue; Acyclic nucleosides such as zidovudine (AZT), Didanosine (DDL) and Zalcitabine (ddC) were effective antiviral analogues used for treating human immunodeficiency virus (HIV) infection but due to its toxicity has led to desertion (Seley-Radtke & Yates, 2018). Phthalazines heterocycle containing nitrogen is a novel drug possess antitumor, antihypertensive and antidiabetic activities (Sangshetti et al., 2019; EL-Hashasha et al., 2017; Haikal et al., 2003; Demirayak et al., 2004; Lenz et al., 2002; Dogruer et al., 2004; Watanabe et al., 1998). Purine and Pyrimidines as nucleotides and nucleosides are energy carriers show various bioactivity such as bactericidal, fungicidal, insecticidal properties (Thomson & Lamont, 2019).

**2. Material and methods**

**2.1. Chemistry**

Melting points were analyzed on kofler block apparatus and were uncorrected \(^1\)HNMR was recorded on spectrometer (400 MHz), chemical shifts are referenced from tetramethylsilane...
2.1.1. Ethyl 2-(4-nitrophenoxoy) acetate (2) (Amer et al., 2018)
Equivalent amounts of 4-nitrophenol (1) (1.39 gm, 0.01 mol), ethylchloroacetate (1.225 gm, 0.01 mol) and K₂CO₃ (1.38 gm, 0.01 mol) were dissolved in 50 ml of acetone and then, refluxed for 6 h. The solvent evaporation took place at low pressure. The final product was collected, dried and heated to yield 92% of a yellow powder. m.p. 221–222 °C. IR spectra (KBr) (v, cm⁻¹): 3250 (OH), 3050 (Ar-H), 2990 (CH aliphatic), 1575, 1385 (NO₂), 2860 (CH₂); ¹HNMR (400 MHz, CDCl₃): δ = 5.00 (2H, s, CH₂), 7.20–8.10 (12H, m, CH aromatic), 8.65 (1H, s, CH); MS: m/z (%) 416 (M+).

2.1.2. 2-(4-Nitrophenoxoy) acetohydrazide (3) (Amer et al., 2018)
Equivalent amounts of 2 (2.25 gm, 0.01 mol) and hydrazine hydrate (1.5 gm, 0.03 mol) were dissolved in 40 ml ethanol and then, refluxed for 10 h. Solvent has been evaporated by halving it and put in the fridge one day; A white powder was collected in 70% yield of brown crystal, m.p. 221–222 °C. IR spectra (KBr) (v, cm⁻¹): 3460, 3505 (NH₂), 1645 (CO); ¹HNMR (CDCl₃): δ = 2.65 (2H, t, J = 7.2 Hz, CH₂), 5.40 (1H, brs, OH), 7.00–8.12 (12H, m, CH aromatic), 8.65 (1H, s, CH); MS: m/z (%) 226 (M⁺+H).
yield, m.p. = 227–229 °C, RF = 0.75 (7% CH₂OH in CHCl₃). IR spectra (KBr) (ν, cm⁻¹): 3345 (OH), 3052 (Ar-H), 1632 (C=N), 1570, 1380 (NO₂), 1445 (CH₂); ¹H NMR (400 MHz, DMSO-d₆): δ: 3.52 (2H, d, 2xOH), 3.60 (2H, d, 2xOH), 3.97 (1H, d, J = 2.5 Hz, H-1), 4.13 (1H, brs, NH), 4.62 (2H, s, 2H), 3.55–3.90 (6H, m, H-2, H-3, H-4, H-5, H-6), 6.49–7.62 (4H, m, Ar-H), 7.23 (2H, dd, J = 7.2 Hz, CH), 8.10 (2H, dd, J = 4.9 Hz, CH); MS: m/z (%) 476 (M+2H)². Anal. Calc'd for C₂₉H₂₂N₄O₁₃: C, 54.21; H, 4.73; N, 7.82. Found C, 54.55; H, 4.43; N, 7.63.

2.1.6. General procedure for the synthesis of acetylated nucleosides 9a-d

Equivalent amounts of nucleoside derivatives 8a-d (4.44 gm, 0.01 mol), 4,6-diacetyl-2-deoxy-α-D-ribofuranose (4.44 gm, 0.01 mol) and acetic anhydride (6.02 gm, 0.01 mol) were dissolved in appropriate amount of anhydrous pyridine and the stirring of produced solution was occurred at 25 °C for 24 h. The blend is poured onto ice to create a light brown precipitates. The resulting products were purified to produce 80–85% of acetylated nucleosides 9a-d.

2.1.6.1. 4-(2, 3, 5-Tri-O-acetyl)-N-arabinofuranosylamino-phenyl-4 - (2-(4-nitrophenoxy) methyl) – 1, 3, 4-oxadiazole (9a). Pale brown powder, 85% yield, m.p. = 194–196 °C, IR spectra (KBr) (ν, cm⁻¹): 3400 (NH), 3050 (Ar-H), 1735 (COCH₃), 1625 (C=C), 1575, 1383 (NO₂), 1445 (CH₂); ¹H NMR (400 MHz, DMSO-d₆): δ: 2.01–2.19 (9H, m, 3xCOCH₃), 4.05 (1H, brs, NH), 2.95–4.75 (7H, m, H-2, H-3, H-4, H-5), 4.76 (2H, s, CH₂), 4.94 (1H, d, J = 5.5 Hz, H-1), 6.90–7.45 (8H, m, Ar-H); Anal. Calc'd for C₃₉H₃₇N₄O₁₄: C, 54.74; H, 4.59; N, 9.82. Found C, 54.41; H, 4.87; N, 9.65.

2.1.6.2. 4-(2, 3, 5, 6-Tetra-O-acetyl)-N-galactopyranosylamino-phenyl-4 - (2-(4-nitrophenoxy) methyl) – 1, 3, 4-oxadiazole (9b). Pale brown powder, 85% yield, m.p. = 201–203 °C, IR spectra (KBr) (ν, cm⁻¹): 3400 (NH), 3050 (Ar-H), 1735 (COCH₃), 1625 (C=C), 1575, 1383 (NO₂), 1445 (CH₂); ¹H NMR (400 MHz, DMSO-d₆): δ: 2.10–2.27 (12H, m, 4xCOCH₃), 4.10 (1H, brs, NH), 2.92–4.78 (7H, m, H-2, H-3, H-4, H-5, H-6), 4.63 (2H, s, CH₂), 5.10 (1H, d, J = 5.5 Hz, H-1), 6.96–7.41 (8H, m, Ar-H); MS: m/z (%) 642 (M⁺). Anal. Calc'd for C₄₀H₄₀N₄O₁₄: C, 52.41; H, 4.71; N, 8.72. Found C, 54.41; H, 4.87; N, 8.45.

2.1.6.3. 4-(2, 3, 5, 6-Tetra-O-acetyl)-N-glucopyranosylamino-phenyl-4 - (2-(4-nitrophenoxy) methyl) – 1, 3, 4-oxadiazole (9c). Pale brown powder, 80% yield, m.p. = 230–232 °C, IR spectra (KBr) (ν, cm⁻¹): 3400 (NH), 3050 (Ar-H), 1735 (COCH₃), 1625 (C=C), 1575, 1383 (NO₂), 1445 (CH₂); ¹H NMR (400 MHz, DMSO-d₆): δ: 2.12–2.30 (12H, m, 4xCOCH₃), 4.05 (1H, brs, NH), 2.98–4.68 (6H, m, H-2, H-3, H-4, H-5, H-6), 4.63 (2H, s, CH₂), 5.00 (1H, d, J = 5.5 Hz, H-1), 6.48–7.50 (8H, m, Ar-H); MS: m/z (%) 642 (M⁺). Anal. Calc'd for C₄₀H₄₀N₄O₁₄: C, 52.41; H, 4.71; N, 8.72. Found C, 54.65; H, 4.92; N, 8.85.

2.1.6.4. 4-(2, 3, 5, 6-Tetra-O-acetyl)-N-mannopyranosylamino-phenyl-4 - (2-(4-nitrophenoxy) methyl) – 1, 3, 4-oxadiazole (9d). Pale brown powder, 85% yield, m.p. = 180–182 °C, IR spectra (KBr) (ν, cm⁻¹): 3400 (NH), 3055 (Ar-H), 1735 (COCH₃), 1630 (C=C), 1575, 1383 (NO₂), 1445 (CH₂); ¹H NMR (400 MHz, DMSO-d₆): δ: 2.07–2.24 (12H, m, 4xCOCH₃), 4.00 (1H, brs, NH), 2.90–4.72 (6H, m, H-2, H-3, H-4, H-5, H-6), 4.60 (2H, s, CH₂), 5.12 (1H, d, J = 5.5 Hz, H-1), 6.50–7.62 (8H, m, Ar-H); MS: m/z (%) 642 (M⁺).
resistant bacterial strains. All strains were freshly subcultured on suitable media before beginning of the experiment.

### 2.2.2. Antimicrobial assay

The antimicrobial assay was conducted on synthesized compounds 4, 6b, 6d, 8a, 8c, 9b, 9d, 12a, 12b, 12c and 12d by using minor modifications on agar well diffusion method (Valgas et al., 2007). The inoculations in the Mueller agar plate of the measured minority modifications on agar well diffusion method (Valgas et al., 2007) were cultivated and put in incubator for 24 h at 37 °C. Amoxicillin (10 μg/ml) and Ciprofloxacin (5 μg/ml) for Pseudomonas aeruginosa and E. coli. Vancomycin (10 μg/ml) and Amoxicillin (10 μg/ml) for S. aureus were included in the test. Finally, the experiment was repeated three times with duplicates and the inhibition zone was measured.

### 2.3. Computational study

#### 2.3.1. Preparation of small molecule

Synthesized compounds to reduce their energy PM3 was used via MOPAC then DFT through B3LYP/6-311 G. The semi-empirical Hamiltonian molecular orbital calculation MOPAC16 kit was used for all Quantum chemical calculations were done. (Stewart, 2013), basis on implementation of MOE 2015 package (Molecular Operating Environment (MOE), density function theory in Gaussian 09 W program with the Becke3-Lee-Yang-parr (B3LYP) level using 6-311G∗ was employed. (Frisch et al., 2013). Geometry for molecular structures has been optimized to understand of the chemical structures, geometry for molecular structures has been optimized.

#### 2.3.1.1. Selection of proteins structures

Docking tests for the active target site in DNA Gyrase B (ID: 4uro) and and Cathepsin B (ID: 4uro) were evaluated using MOE 2015 (Version 2009.10). (Dale et al., 1999, Greenspan et al., 2003). Later, MOE was corrected for the structures with errors of active sites. Subsequently hydrogens were added and partial charges (Amber12; EHT) were calculated. MOE Site Finder program was implied to identify the binding site of each receptors in protein; method based on alpha spheres (convex hulls) (Soga et al., 2007).

#### 2.3.2. MOE stepwise docking methods

Crystal structures of enzymes were obtained by removal of Water and inhibitors molecule, addition of hydrogen atoms. The site finder module of MOE was used to generate alpha-site spheres. Triangular matcher placement method was used to generate optimized 3D structures of ligands. A random triplet of alpha sphere center was used to decide the pose in each iteration to generate by aligning ligand triplets of atoms in three alpha spheres defined at the receptor level. The poses developed by MMFF94x forcefield with treating solvation effects.

### 3. Results and discussions

#### 3.1. Chemistry

The ester derivative 2 in 92% yield was obtained when P-nitrophenol was reacted with ethylchloroacetate and KOH in dry acetone under reflux. 95% acid hydrazide 3 yield was obtained, when synthesized ester 2 was reacted in ethanol reflux with hydrazine hydrate. The derivative of 1, 3, 4-oxadiazole 4 in 70% yield was prepared with reaction of hydrazide 3, p-aminobenzoic acid and phosphorus oxychloride under reflux. Compound 4 IR spectra showed the appearance of (NH₂) group at 3460, 3505 cm⁻¹ and (CO) group at 1645 cm⁻¹ and disappearance of (NH) group. ¹H NMR spectra peaks at 4.60, 6.05, 6.56–8.50 and 8.53 for CH₂, NH₂, eight protons of aromatic system and NH respectively; mass spectra with the molecular ion peak at 312 [M⁺] (Scheme 1).

Oxadiazole derivative with amino group 4 was reacted under reflux in ethanol with different aldehyde derivatives 7a-d and acetic acid under heat in the presence of condenser to give Schiff bases 6a-d in 90–93% yields, the IR spectra of compounds 6a-d showed NO₂ (1572, 1380 cm⁻¹), CH₂ (1465 cm⁻¹), CH (aromatic) (3050–3070 cm⁻¹) and OH group (3250 cm⁻¹). ¹H NMR spectra peaks around 4.60 for CH₂ group, broad peak at 5.40. OH group had (CH) group of shift bases around 8; the molecular ion peaks showed by mass spectra at 450 and 416 [M⁺] for 6a and 6b, 615 [M+2H⁺] for 6c and 401 [M+Na⁺] for 6d (Scheme 2) with no NH₂ group.

Oxadiazole with amino group 4 reacted with different sugar (aldohexoses) derivatives 7a-d and acetic acid in absolute ethanol under reflux to give nuclosides 8a-d in 80–90% yields, the IR spectra of compounds 8a-d; (NO₂) at 1570, 1380 cm⁻¹, (CH₂) at 1450 cm⁻¹, (CH aromatic) at the range of 3050 to 3060 cm⁻¹ and (OH) group at 3330 cm⁻¹. ¹H NMR spectra peaks for (NH) at 4.05–4.13, (CH₂) at 4.60, the disappearance of (NH₂), peaks for (OH) at 3.52 to 3.60 peaks (CH-Sugars) at 3.55–3.92, (CH- aromatics) at 6.52 to 7.75; the molecular ion peaks for 8a showed by mass spectra at 444 [M⁺], for 8b at 475 [M+H⁺] and for 8c and 8d at 476 [M+2H⁺]. The nuclosides 8a-d were acetylated to give acetylated nuclosides 9a-d in 80–85% yields, the disappearance of peak for (OH) around 330 cm⁻¹ and the appearance of peak for (COCH₃) at 1735 cm⁻¹ showed by IR spectra of compounds 9a-d, this change is due to that acetylation of the nuclosides 8a-d by acetic anhydride to the corresponding acetylated nuclosides 9a-d; the ¹H NMR spectra showed that the disappearance of peaks for (OH) groups of nuclosides around 3.52 to 3.60 and appearance of peaks for (COCH₃) groups at the range from 2.02 to 2.30 which were acetylated nuclosides 9a-d; mass spectrum molecular ion peaks at 581 [M+Na⁺] for 9a and 642 [M⁺] for 9b, 9c and 9d (Scheme 3).

2-(4-Nitrophenoxo) acetohydrazide (3) reacted with triphenylphosphite (10), aldehyde derivatives 11a-d (pyridine-3-carboxaldehyde, salisaldehyde, p-chlorobenzaldehyde and 5-methylfurfuraldehyde respectively) and perchloric acid in acetonitrile gives 8-aminophosphonate derivatives 12a-d in 70–82% yields, the IR spectra of 12a-d showed (CO) at 1705 cm⁻¹, (NO₂) at 1572, 1380 cm⁻¹, (CH₂) at1460 cm⁻¹, and (OH) at 3420 cm⁻¹; ¹H NMR spectra peaks at 4.60 for CH₂ group, (OH) at 5.10 group, (CH) group of shift bases around 5.88, the appearance of aromatic protons around 6.30 to 8.22 and (NH) group around 9.05 to 9.10; ¹³C disappearance of (NH₂) group. NMR spectra of the synthesized phosphonates 12a-d; (CH—P—) at 61.43 to 68.02; ³¹P NMR spectra

![Scheme 1.](image-url)
of the synthesized derivatives 12a-d showed that the appearance of peaks for phosphorus of phosphonates (O=P–CH–) at 19.73, 18.86, 19.22 and 18.53 for 12a, 12b, 12c and 12d respectively; mass spectra; molecular ion peaks at 534 [M+] for 12a, 550 [M+H+] for 12b, 567 [M+] for 12c and 539 [M+] for 12d (scheme 4).

3.2. Microbiology

There is increasing high mortality rate related to increasing infections due to multidrug-resistant bacteria. When treating such infections, the therapeutical impact of widely used antibiotics frequently fails because of their transition to the antibiotics used by mechanisms of inducible resistance to antibiotics and regulatory bacterial gene mutations (Fowler et al., 2004). Twelve synthesized compounds (4, 6a, 6b, 8c, 8d, 9a, 9b, 9c, 12a, 12b, 12c and 12d) were subjected to antibiogram activity against three bacterial strains. The results showed that the substance 12a used in concentration (50 mg / ml dimethylsulphoxide). It was the most important destructive compound against E. coli, P. aeruginosa and S. Aureus with inhibition zone (35, 30 and 22 mm) respectively. E. coli isolates were sensitive to 4, 6a, 6b, 9a, 9b, 9c, 12b, 12c and 12d with zone size 20, 15, 13, 18, 22, 10, 24, 17 and 22 mm respectively. P. aeruginosa was sensitive to 4, 9a, 9b, 9c, 12b, 12c and 12d with zone size 16, 16, 18, 14, 20, 12, and 10 mm respectively. S. aureus was sensitive to 6a, 6b, 8c, 8d, 9a, 9b, 9c, 12b, 12c and 12d with zone size 12, 16, 10, 24, 14, 18, 16, 15 and 18 mm respectively meanwhile, 12a showed the highest effect against three bacterial strains (Table 1). Previous studies show that multiple classes of flavonoids have antimicrobial activity and have been reviewed extensively (Batovska & Todorova, 2010). The activity of synthesized derivatives is most likely attributed to the existence of hydroxy groups in different nucleoside positions and the phosphorous movement. (Lewis & Jorgensen, S.H. Alotaibi and H.H. Amer Saudi Journal of Biological Sciences 27 (2020) 3481–3488

| Inhibition zone (mm) of 50 mg/ml | Compound no. | E. coli | P. aeruginosa | S. aureus |
|----------------------------------|--------------|---------|---------------|-----------|
|                                   |              | E. coli | P. aeruginosa | S. aureus |
| 4                                 | 20           | 16      | nz            | 12        |
| 6a                                | 15           | nz      | 12            |
| 6b                                | 13           | nz      | 12            |
| 8c                                | nz           | nz      | 16            |
| 8d                                | nz           | nz      | 10            |
| 9a                                | 18           | 16      | 24            |
| 9b                                | 22           | 18      | 14            |
| 9c                                | 10           | 14      | 18            |
| 12a                               | 35           | 30      | 22            |
| 12b                               | 24           | 20      | 16            |
| 12c                               | 17           | 12      | 15            |
| 12d                               | 22           | 10      | 18            |
| Ciprofloxacin                     | Nz           | <6      | 24            |
| Amoxicillin                       | Nz           | Nz      | <6            |
| Vancomycin                        | Nt           | Nt      | 18            |

Table 1
Antimicrobial activity of tested synthesized compounds and antibiotics on three clinical isolated bacteria. Nz: no zone, Nt: not tested.
Phosphonate qualities that are better suited to therapeutic use than widely used antibiotics (Anandhi et al., 2014).

### 3.3. Docking studies

Docking experiment is most commonly used to design drug due to its efficiency in predicting the potency of molecule towards the reaction energy associated with potential binding conformations of an active site of biological strains; evaluation of target enzyme for evaluating the binding convergence at its catalytic site. The largest variation in the synthesized \( \alpha \)-aminophosphonate derivative of Gibbs-free energy (after G) is the strongest binding convergence with the penicillin binding protein, involved in bacterial-cell wall maturation and cell-form development. The crystallographic structure of 2EX6 contained the amino acid residues with ampicillin as the attached ligand at the binding pocket. The synthesized compound 12a molecular docking research revealed (\( \Delta G = -5.645 \) Kcal/mol) (Table 2). Amino acid residues; Ser420 and Ser398 has H-bond with target Compound (see Table 3).

#### 3.3.1. Structure activity relationship (SAR)

Compound 12a molecular docking results showed as antimicrobial. Due to pyridine moiety core in parent phosphonate derivative. Perpendicular arrangement of phosphonate and pyridine with Ser420, this compound is stabilized in binding pocket. The ampicillin was used as reference for binding into the active DNA Gyrase (Fig. 1). Hydrophilic amino acids serve as backbone in binding site (Figs. 2, 3, and 4). Due to hydrophobicity in nature is

### 4. Conclusion

The nucleoside derivatives, \( \alpha \)-aminophosphonates and aryli- dene analogues derived from 4-aminophenol were designed, prepared and elucidated by different spectroscopic analysis, physically studied by molecular docking of \( \alpha \)-aminophosphonate derivative 12a showed most effective antibacterial activity against all bacterial strains in this study with inhibition zones (35, 30 and 22 mm) respectively and the theoretical binding with DNA of bacteria.

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**Table 2**

| PDB: 4uro | | | | | | |
|---|---|---|---|---|---|
| mol E.d,\( \alpha \) | E_conf | E_place | E_sur | Eele | rmsd |
| 12 a | -5.645 | 183.702 | -84.595 | -10.953 | -18.486 | 3.006 |
| PDB:1gmy | | | | | | |
| mol E.d,\( \alpha \) | E_conf | E_place | E_sur | Eele | rmsd |
| 12a | -6.657 | 210.339 | -82.132 | -10.086 | -21.099 | 1.889 |

**Table 3**

| Ligand | Atom | Receptor | Amino acid residues | Interaction | Distance (\( \AA \)) | E (kcal/mol) |
|---|---|---|---|---|---|---|
| PDB: 4uro | 12 a | N12 | OD2 | ASP57 | H-donor | 3.01 | -4.8 |
| | | O10 | N | GLY125 | H-acceptor | 3.18 | -5.2 |
| | | O20 | N | GLY125 | H-acceptor | 3.45 | -1.1 |
| | | O39 | N | GLY85 | H-acceptor | 3.12 | -1.8 |
| PDB:1gmy | 12 a | O10 | SG | CYS29 | H-donor | 3.44 | -1.2 |
| | | N12 | O | GLY74 | H-donor | 3.06 | -1.9 |

**Fig. 1.** The binding of ampicillin into the active DNA Gyrase.
Fig. 2. The binding mode of 12a into the active DNA Gyrase.

Fig. 3. The binding mode of 12a into the active 1GMY.

Fig. 4. The binding mode of 12a into the active 1NJE.
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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Amer, H.H., Ali, O.M., Salama, A.A., El-gendy, M.S., Houssin, O.K., 2018. Synthesis of some new 1, 3, 4-oxadiazole derivatives bearing sugars and α-aminophosphonate derived from 4-nitrophenol as anticancer agents. Natl. J. Physiol. Pharm. Pharmacol. 8 (9), 1275–1286.

Anandhi, D., Srinivasan, P.T., Praveen, G.K., Jagatheesh, S., 2014. DNA fragmentation induced by the glycosides and flavonoids from C. coriaria. Int. J. Curr. Microbiol. Appl. Sci. 3, 666–673.

Batovska, D.I., Todorova, I.T., 2010. Trends in utilization of the pharmacological potential of chalcones. Curr. Clin. Pharmacol. 5 (1), 1–29.

Dale, G.E., Kostrewa, D., Gsell, B., Steiger, M., D’Arcy, A., 1999. Crystal engineering: deletion mutagenesis of the 24 kDa fragment of the DNA gyrase B subunit from Staphylococcus aureus. Acta Crystallogr. D Biol. Crystallogr. 55 (9), 1626–1629.

Demirayak, S., Karaburun, A.C., Beis, R., 2004. Some pyrrole substituted aryl pyridazinone and phthalazinone derivatives and their antihypertensive activities. Eur. J. Med. Chem. 39 (12), 1080–1095.

Ding, Q.-B., Ou, L., Wei, D.-Z., Wei, X.-K., Xu, Y.-M., Zhang, C.-Y., 2010. Enzymatic synthesis of nucleosides by nucleoside phosphorylase co-expressed in Escherichia coli. J. Zhejiang Univ. Sci. B 11 (11), 880–888.

Degrues, D.S., Kupeli, E., Yasuda, S., Chiravic, F., 2004. Synthesis of new 2-[1(2H)-phthalazin-2-yl]acetamide and 3-[1(2H)-phthalazin-2-yl)propanamide derivatives as antiviral and anti-inflammatory agents. Arch. Pharm. Pharm. Med. Chem. 337 (6), 303–310.

El-Hashaia, M., Rizk, S., El-Bassiouny, F., Guirguis, D., Khairy, S., Guirguib, L., 2017. Facile synthesis and structural characterization of some phthalazin-1(2H)-one derivatives as antimicrobial nucleosides and reactive dye. Egypt. J. Chem. 0 (0), 0.

Fowler Jr., V.G., Sakoulas, G., McIntyre, L.M., Meka, V.G., Arbeit, R.D., Cabell, C.H., et al., 2004. Persistent bacteremia due to methicillin-resistant Staphylococcus aureus infection is associated with agr dysfunction and low-level in vitro resistance to thrombin-induced platelet microparticle protein. J. Infect. Dis. 190 (6), 1140–1149.

Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R., et al., 2013. Gaussian 03, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004. There is no corresponding record for this reference. [Google Scholar].

Greenspan, P.D., Clark, K.L., Cowen, S.D., McGuire, L.W., Tommasi, R.A., Farley, D.L., Quadros, E., Coppa, D.E., Du, Z., Fang, Z., Zhou, H., Doughty, J., Toscano, K.T., Wigg, A.M., Zhou, S., 2003. N-Arylamidomimetics as bioavailable peptidomimetic inhibitors of cathepsin B. Bioorg. Med. Chem. Lett. 13 (22), 4121–4124.

Haikal, A.Z., El Ashry, E.S.H., Banoub, J., 2003. Synthesis and structural characterization of 1-(d-glycosoxy)phthalazines. Carbohydr. Res. 338 (22), 2291–2299.

Jordheim, L.P., Durantel, D., Zouloum, F., Dumontet, C., 2013. Advances in the development of nucleoside and nucleotide analogues for cancer and viral diseases. Nat. Rev. Drug. Discov. 12 (6), 447–464.

Lenz, E.M., Wilson, J.D., Wright, B., Partridge, E.A., Rodgers, C.T., Haycock, P.R., Lindon, J.C., Nicholson, J.K., 2002. A comparison of quantitative NMR and radiolabelling studies of the metabolism and excretion of Statin® (3-(4-bromo-2-fluorobenzyl)-4-oxo-3H-phthalazin-1-ylacetic acid) in the rat. J. Pharm. Biomed. Anal. 28 (1), 31–43.

Lewis, J.S., Jorgensen, J.H., 2005. Inducible clindamycin resistance in staphylococci: should clinicians and microbiologists be concerned?. Clin. Infect. Dis. 40 (2), 280–285.

Dudley, E.D., 2009. In: Mass Spectrometry of Nucleosides and Nucleic Acids. CRC Press, pp. 163–194. https://doi.org/10.1201/9781420044034-c5.

Sangshetti, J., Pathan, S.K., Patil, R., Akher Ansari, S., Chhajed, S., Arote, R., Shinde, D.B., 2019. Synthesis and biological activity of structurally diverse phthalazine derivatives: a systematic review. Bioorg. Med. Chem. 27 (18), 3979–3997.

Seley-Radtke, K.L., Yates, M.K., 2018. The evolution of nucleoside analogue antivirals: a review for chemists and non-chemists. Part 1: Early structural modifications to the nucleoside scaffold. Antiviral Res. 154, 66–86.

Soga, S., Shirai, H., Kobori, M., Hirayama, N., 2007. Use of amino acid composition to predict ligand-binding sites. J. Chem. Inf. Model. 47 (2), 400–406.

Stewart, J.J.P., 2013. Optimization of parameters for semiempirical methods VI: more modifications to the NDDO approximations and re-optimization of parameters. J. Mol. Model. 19 (1), 1–32.

Thompson, J.M., Lamont, E.L., 2019. Nucleoside analogues as antibacterial agents. Front. Microbiol. 10, 952.

Tssetmetzis, N., Paulin, C.B., Rudd, S.G., Herold, N., 018. Nucleobase and nucleoside analogues: resistance and re-sensitisation at the level of pharmacokinetics, pharmacodynamics and metabolism. Cancers 10 (7), 240.

Valgas, C., Souza, S.M.D., Smânia, E.F., Smânia Jr, A., 2007. Screening methods to predict ligand-binding sites. J. Chem. Inf. Model. 47 (2), 400–406.

Wigg, A.M., Zhou, S., 2003. N-Arylaminonitriles as bioavailable peptidomimetic derivatives as antimicrobials and reactive dye. J. Chem. Phys. 0 (0), 0.

Yssel, A.E.J., Vanderleyden, J., Steenackers, H.P., 2017. Repurposing of nucleoside- and nucleobase-derived drugs as antibiotics and biofilm inhibitors. J. Antimicrobial. Chemother. 72 (8), 2156–2170.