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Synthesis and Antimicrobial Activity of Novel Phthalazineamino phosphonate Scaffold Hybrids

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Abstract

The 1-aminophthalazine derivatives (**7a-d)** were prepared by the reaction of 1-chloro-4-(4`-methoxyphenyl) pthalazine compound **5** with 1, 2-phenylene diamine **6a** or 1, 3-phenylene diamine **6b** dissolved in DMF while ethylenediamine **6c** or 1,4-diaminobutane **6d** dissolved in ethanol. The resulting new α-aminophosphonate compounds **(10a-f)** were produced by combining derivative of 1-aminophthalazine derivatives **7,** aldehyde **8** and triphenyl phosphite **9** then $LiClO_4$ as a Lewis acid catalyst was added. The chemical structures of all the produced compounds were determined by IR, ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, and mass spectroscopic methods. The antimicrobial activities of the synthesized compounds were *in vitro* screened against gram-positive bacteria, gram-negative bacteria and fungi pathogens. The majority of synthesized compounds have moderate to good antimicrobial efficacy.

Keywords: phthalazine, α-aminophosphonate, antimicrobial activity.

1. Introduction

The most privileged pharmacophore in medicinal chemistry, phthalazine and its functional analogs have a variety of biological applications [1-7]. Due to its numerous biological applications, aminophthalazine's pharmacological usefulness has long been recognized and has attracted the interest of numerous researchers [8-10]. Bioisosteres of naturally occurring amino acids, aminophosphonates have a wide range of therapeutic applications [11-34]. Numerous analogs are presented as antiviral, antifungal, antibacterial, and anticancer medicines [35,36]. The function of physiologically active cells is affected by the action of α-aminophosphonates, which work as amino acid antagonists by inhibiting the enzymes involved in amino acid metabolism. Consequently, the derivatives of substituted α-aminophosphonate are crucial as they serve as intermediate in the synthesis of large physiologically active compounds, which have numerous applications in the medical field [37-40]. To improve pharmaceutical accessibility and reduce the problem of drug-resistant microorganisms, novel compounds with robust antibacterial activities can still be synthesized. Given the aforementioned information, it is predicted that combining two intrinsically biologically active scaffolds, such as aminophthalazine derivatives and aminophosphonates moieties, will have a synergistic effect on the hybrid's structure when compared to each moiety separately. To find the most effective substitution and activity for the synthesized hybrids, a number of novel phthalazine-aminophosphonate hybrids will be created and tested for their antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria and fungi, **figure 1**[41-44].

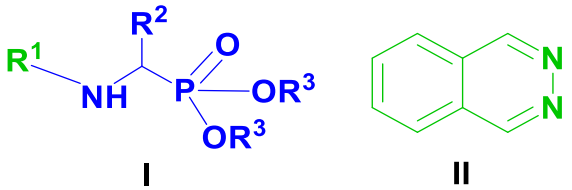

Fig. 1: I α-aminophosphonates, II phthalazine.

2. Result and discussion

Incorporating phthalazine heterocyclic nucleus for synthesis of new α-aminophosphonate derivatives **(10a-10f)**, a mixture (5gm, 0.003 moL) of phthalic anhydride **1**, (25 mL, 0.2 moL) of anisol **2** was heated under reflux for 2h, (9g, 0.6 mol) of $AlCl_3$ anhydrous was added gradually and refluxed on sand bath for 2h, The mixture was then acidified with 100 mL of dilute HCl, the anisol was evaporated, then the mixture was cooled, filtered and washed with dilute water. The residue was then dissolved in saturated sol Na_2CO_3 and precipitated with dilute HCl to produce compound **3**. Compound **3** was treated in boiled ethanol with hydrazine hydrate. This mixture was refluxed for two hours on a sand bath, filtered and dried to produce

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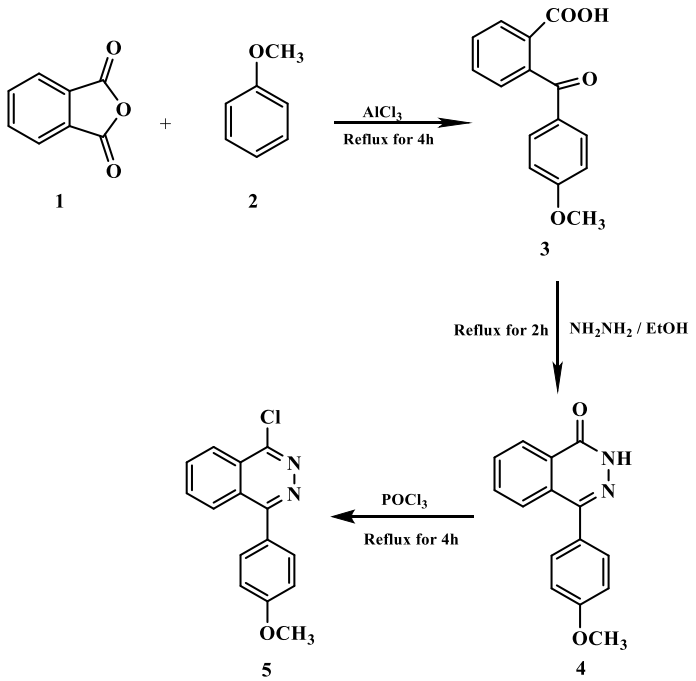
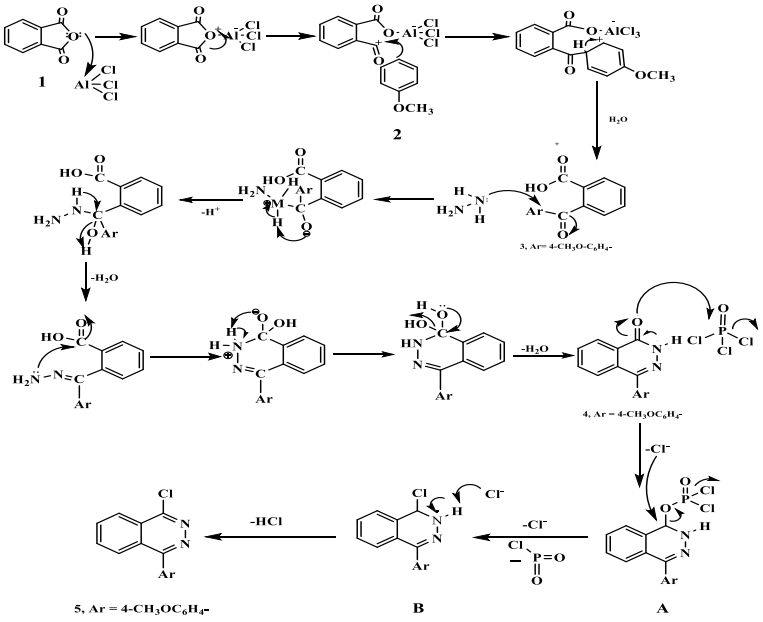
compound **4**. Compound **5** is produced through the chlorination of compound **4** with $POCl_3$ in a refluxing reaction for four hours, neutralisation with saturated sol Na_2CO_3, filtration, washing with water and drying as shown as in **scheme 1**[8].



Scheme 1: Synthesis of 1-chloro-4-(4`-methoxyphenyl) phthalazine compound 5.

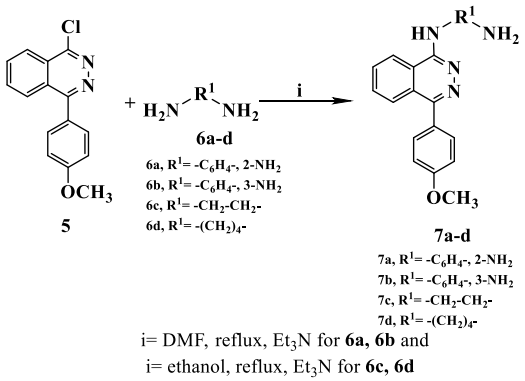
Scheme 2 provide illustration of 1-chloro-4-(4`-methoxyphenyl) phthalazine **5**, The possible mechanism for compound **3** could be explained by the nucleophilic addition of the nucleophilic hydrazine nitrogen on the electrophilic carbonyl carbon atom to give the corresponding hydrazone, followed by the cyclization process via the nucleophilic addition of the second amino group on hydrazine on the carbonyl carbon atom of compound **3** to afford the cyclized product via dehydration after heating to afford Phthalazinone **4**. The mechanism for the conversion of **4** into **5** involves the displacement of one atom of chlorine and the production of the phosphorylated intermediate **A** after the carbonyl oxygen lone pair in phthalazinone **3** is first attacked by a nucleophile to generate pentacoordinate phosphorus in $POCl_3$. By dehydroxy chlorination and deprotonation at the intermediate of **B**, as indicated in **Scheme 2**, it was possible to convert the phosphorylated intermediate **A** to the equivalent chlorophthalazine **5**, which is represented by the chlorophthalazine **5**[8].



Scheme 2

1-Aminophthalazine derivatives **(7a-d)** synthesis was illustrated. The 1-chloro-4-(4`-methoxyphenyl) pthalazine compound **5** as a starting material reacted with excess amounts of 1,2-phenylene diamine **6a** or 1,3-phenylene diamine **6b** dissolved in dimethyl formamide DMF parallel with triethyl amine Et_3N, while ethylenediamine **6c** or 1,4-diaminobutane **6d** dissolved in

ethanol parallel with triethyl amine Et_3N as a base then those mixtures were refluxed for 6 hours to produce new 1-aminoaphthalazine derivatives **(7a-d)** in good yields as shown in **scheme 3**.



Scheme 3: Synthesis of new 1-aminophthalazine derivatives (7a-d)

IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectroscopic analyses were done to know the structure of the new phthalazine derivatives **7**. The measurements 2975, 2899, 2928 and 3274 cm^{-1}, that refer to the NH group. There are absorption bands 1602, 1601, 1594 and 1599 cm^{-1} which refer to C=N group. ^{1}HNMR spectra were measured in DMSO-d6 solvent. The presence of peak at δ: 8.45, 8.9, 8.67 and 9.58 ppm affirmed the presence of NH. ^{13}C-NMR spectra showed peaks related to the expected carbon for both aliphatic and aromatic carbon. The mass spectra of **(7a-d)** compounds gave molecular ion peaks (*cf.* Experimental)**.** For compound **7a** its fragmentation pattern is illustrated in **chart 1**.

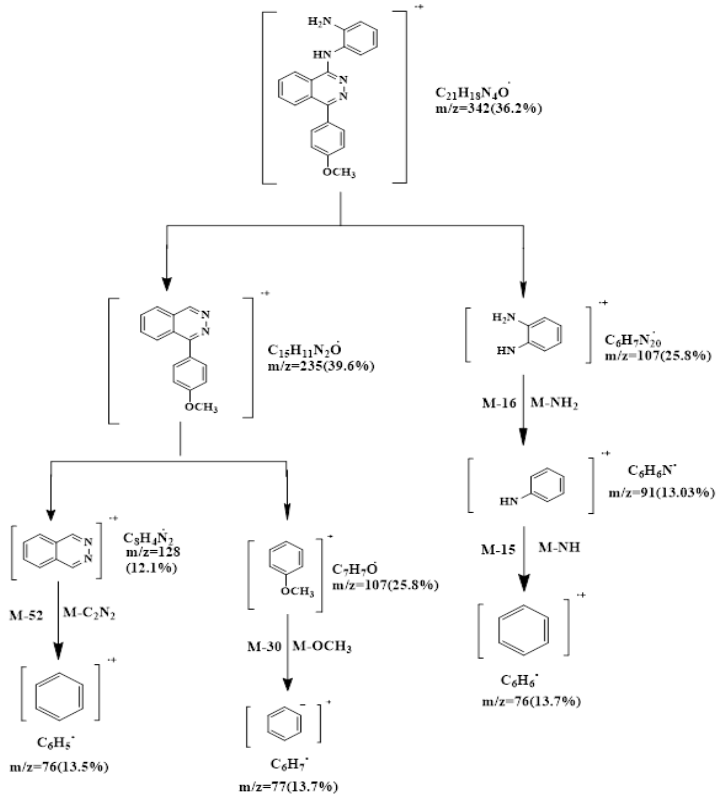
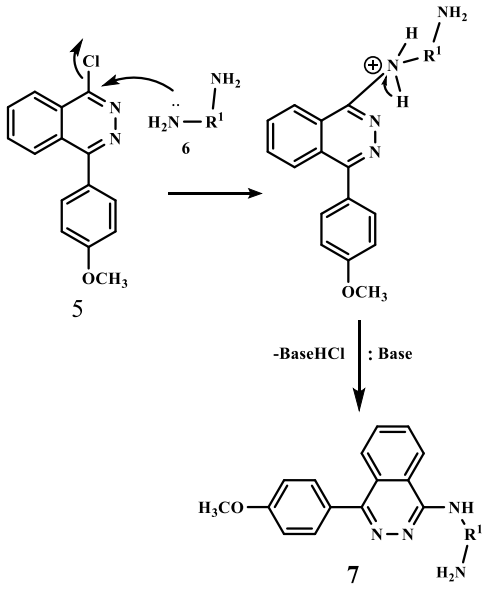


Chart 1

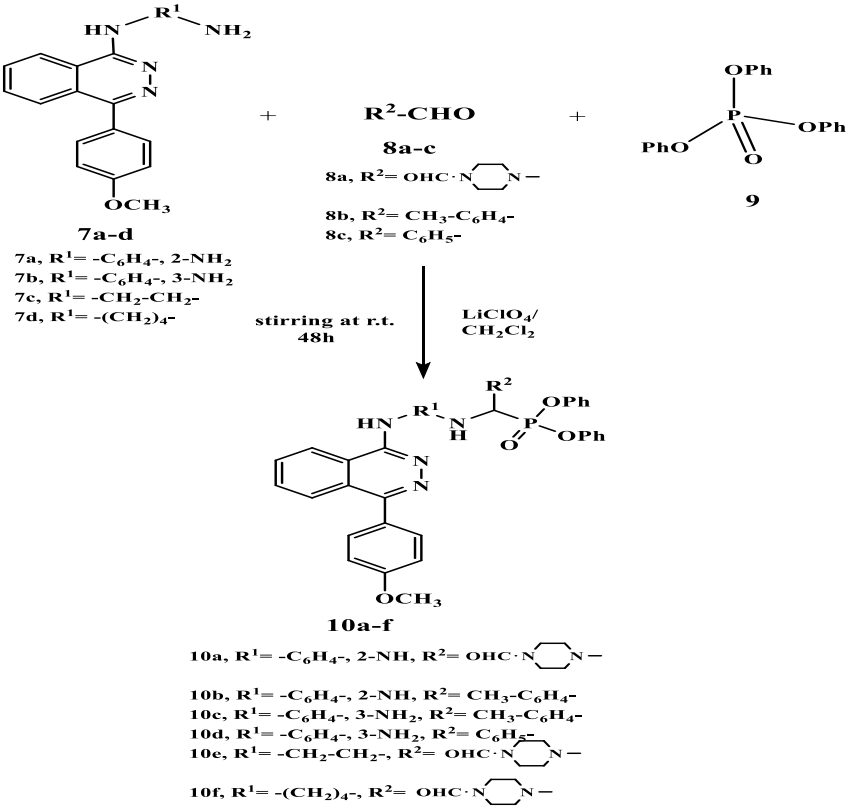
Then, the mechanism of the S_{NAr} amination reaction for new 1-aminophthalazine derivatives **7** was proposed in **Scheme 4**.



Scheme 4

The one pot reaction for α-aminophosphonate derivatives **10a, 10b** were done by 1,4-Piperazinedicarboxaldehyde **8a** or p-tolualdehyde **8b**, triphenyl phosphite **9**, and 1-aminophthalazine derivative **7a** addition to methylene chloride in an equivalent molar ratio, with 10 mmol% of lithium perchlorate as a Lewis acid to produce the α-aminophosphonate derivatives **10a, 10b** in a good yield as in **Scheme 5**. This reaction required stirring for [48hrs]. While we added p-tolualdehyde **8b** or benzaldehyde **8c**, triphenyl phosphite **9**, 1-amino phthalazine derivative **7b** and 10 mmol% of lithium perchlorate as a Lewis acid and then stirred in methylene chloride for [48hrs]. This reaction is done as one pot reaction. α-Aminophosphonate derivatives **10c, 10d** were produced in a good yield as in **Scheme 5.**

The one pot reaction for α-aminophosphonate derivatives **10e, 10f** was performed. The addition of new 1-aminophthalazine derivatives **(7c,d),** 1,4-Piperazinedicarboxaldehyde **8a**, triphenyl phosphite **9** and 10 mmol% of lithium perchlorate as a Lewis acid were added to methylene chloride in an equivalent molar ratio. This reaction led to produce the α-aminophosphonate derivatives **10e, 10f** in a good yield as in **Scheme 5**.



Scheme 5: Synthesis of α-aminophosphonate derivatives 10.

After IR, ^{1}H-NMR, ^{13}C-NMR, ^{31}P-NMR, and mass spectroscopic analyses for compounds **(10a-f),** the structure of the α-aminophosphonate derivatives **(10a-f)** was identified. Broad absorption bands at (3306, 3254), (3467, 3393), (3388, 3027), (3339, 3243), (3388, 3262) and (3381,3267) cm^{-1}, which belong to the NH group, were visible in the IR, additionally, P=O-corresponding absorption bands at range 1251, 1241, 1267, 1267, 1114 and 1110 cm^{-1} were seen. ^{1}HNMR spectra were captured in DMSO-d6 solvent. The presence of broad at (8.43, 8.6), (5.07, 8.91), (8.91, 9.36), (6.73, 9.32), (8.09, 9.67) and (8.45, 9.6) ppm confirmed the presence of NH. Corresponding to ^{13}C-NMR spectra, the expected chiral carbon (P-C-H) was confirmed by displaying peaks at range from 45.7 to 60.8 ppm. The production of the α-aminophosphinates moiety was known with ^{31}P-NMR spectra, which showed a distinct signal at -0.09, 16.78, 16.42, 15.96, -3.1 and -2.38 ppm[35,37]. The molecular ion peaks confirmed the molecular formula of the synthesized compounds through the mass spectra analysis (*cf*. Experimental)**.**For compound **10d** its fragmentation pattern is illustrated in **chart 2**.

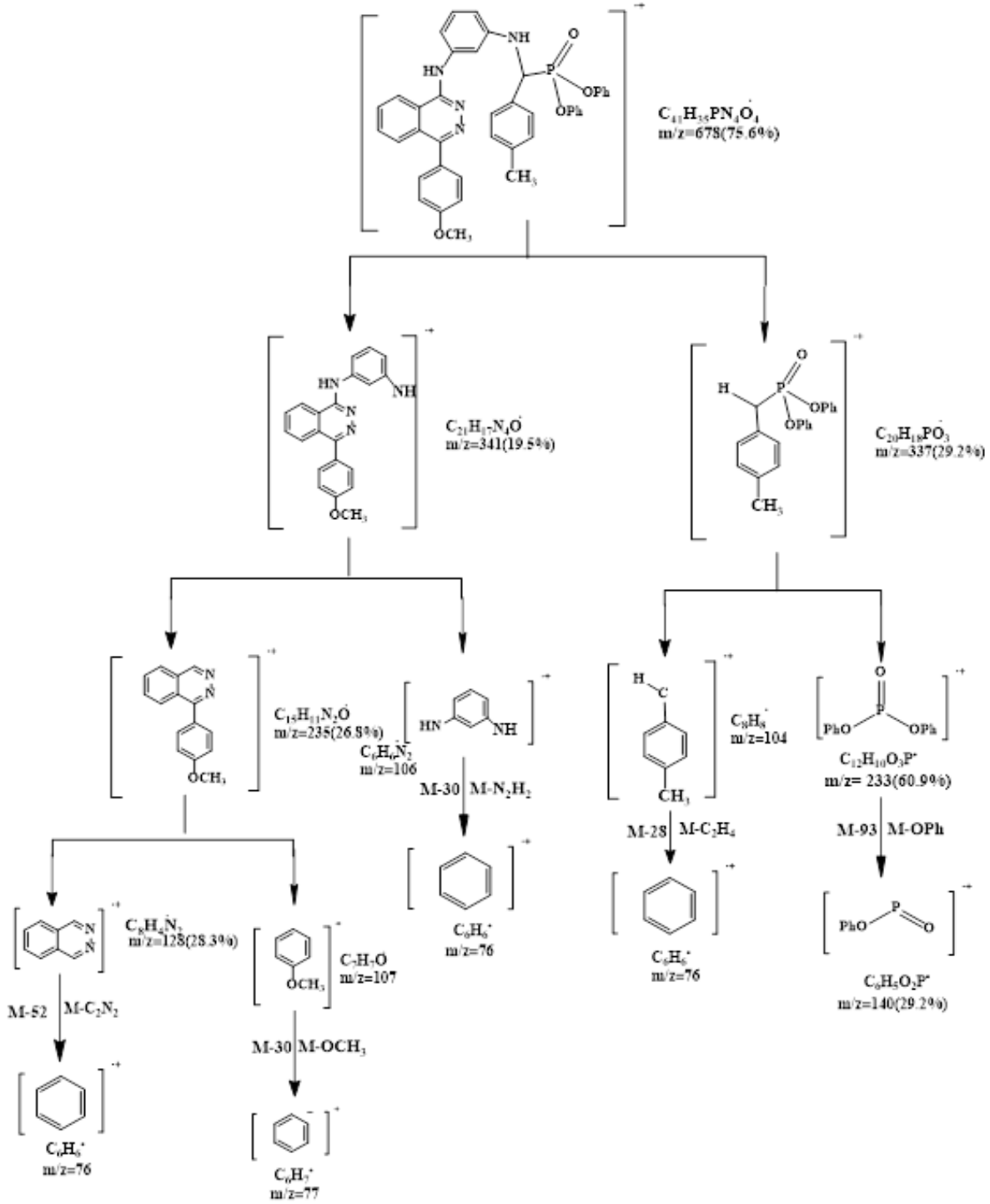


Chart 2

Fragmentation pattern of compound **10f** is described in **chart 3**.

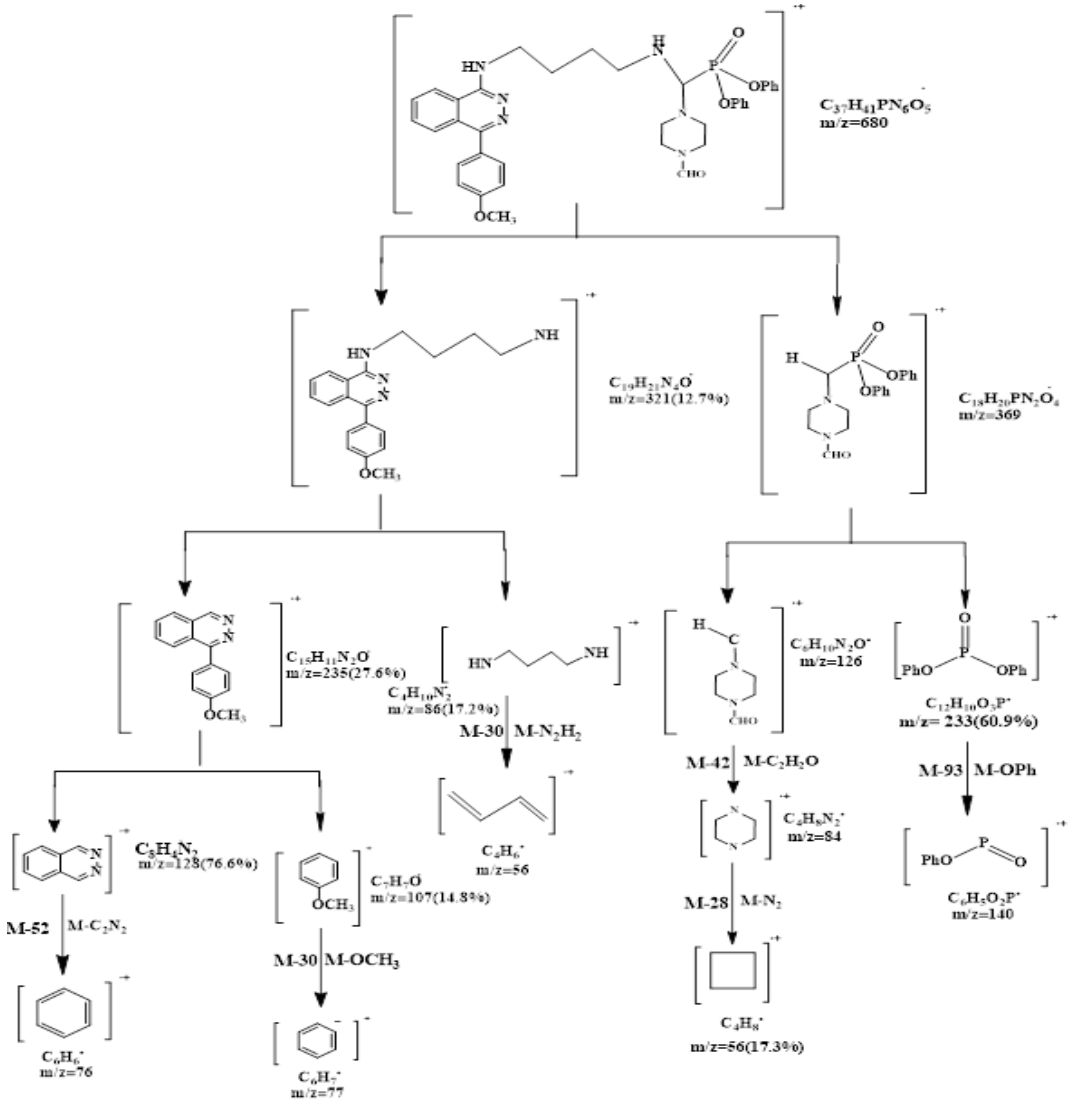


Chart 3

3. *In-vitro* Antimicrobial screening of the synthesized compounds

The synthesized compounds were examined and tested *in-vitro* for their ability to inhibit the growth of gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*), gram-negative (*Escherichia coli* and *Proteus vulgaris*) and fungi (*Aspergillus fumigatus* and *Candida albicans*). Additionally, we employed DMSO as the control substance and (ketoconazole and gentamycin) as the reference medications for comparison. We assessed the inhibition zone of all synthetic drugs, which were measured in mm, after a 24-hour incubation time at 37°C for bacteria and a 48-hour incubation period at 28°C for fungi. We noticed that the compound **10a** was the most biologically effective against gram- positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*) according to **Table 1**. We used *Escherichia coli* and *Proteus vulgaris* as gram-negative bacteria for antimicrobial screening, so the compound **7c** has the highest antimicrobial activity against those gram-negative bacteria according to **Table 1**.

We evaluated the antimicrobial activity of all produced compounds against *Aspergillus fumigatus* and *Candida albicans* as fungi, and found that compound **10b** was the most highly effective, depending on **Table 1.** We came to the conclusion that the synthesized compounds exhibit moderate to good antimicrobial action against gram-positive bacteria, gram-negative bacteria and fungi (*cf.* the supplementary material).

Table 1: *In Vitro* Screening of Samples for Antimicrobial Activity.

Compound	The inhibition zone (mm)					
	Gram + Bacteria		Gram - Bacteria		Fungi	
	Staphylococcus aureus	Bacillus subtilis	Escherichia coli	Proteus vulgaris	Aspergillus fumigatus	Candida albicans
7a	13	12	11	10	0	11
7b	0	12	10	9	11	11
7c	12	16	14	17	10	14
7d	10	11	13	15	0	13
10a	15	15	12	16	10	11
10b	13	15	14	15	12	11
10c	13	0	10	0	0	0
10d	0	10	9	10	0	10
10e	14	11	13	16	10	10
10f	13	16	11	14	9	15
Ketoconazole	--	--	--	--	17	20
Gentamycin	24	26	30	25	--	--
DMSO	0	5	0	0	0	3

Using EXCEL software, we carried out the statistical analysis of antimicrobial activity as shown in **Figure 2**.

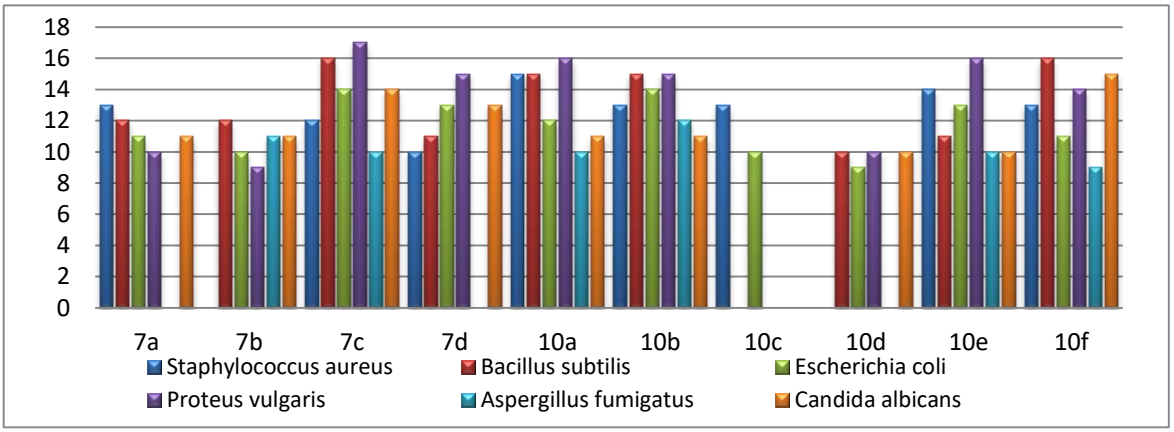


Fig. 2: The statistical analysis of antimicrobial activity

4. Conclusion

New phthalazine derivatives and their α-aminophosphonate conjugates were created, characterized by spectroscopic analysis and evaluated for their biological effects on gram-positive, gram-negative bacteria and fungi. For the most part, their antimicrobial activity was moderate to good effect.

5. Materials

^{1}HNMR, ^{13}CNMR, and ^{31}PNMR spectra were measured at the faculty of science at El-Zigzag University, Egypt in the presence of (DMSO-d6) as a solvent. In relation to the location of the solvent, chemical shifts were calculated in ppm. IR spectra were obtained at the Menoufia University in Egypt, faculty of science. The mass spectra were measured and *in vitro* antimicrobials were evaluated at Azhar University in Egypt. We used Stuart Scientific's melting point device to measure and record the melting points which may be uncorrected. Monitoring all synthesised products were done by using thin layer Chromatography(TLC). Dimethylformamide (DMF), triethylamine (Et_3N), ethanol, methylene chloride, lithium perchloride ($LiClO_4$), Aluminium chloride ($AlCl_3$), hydrochloric acid (HCl), sodium carbonate ($NaCO_3$) and the starting components that were either commercially accessible or listed in the literature.

6. Experimental

General procedure of Synthesis of a1-aminophthalazine derivatives (7a-d):

1-chloro-4-(4`-methoxyphenyl) pthalazine compound **5** (1 mmol) and 1,2-phenylene diamine **6a** (2 mmol) or 1,3-phenylene diamine **6b** (2 mmol) dissolved in dimethyl formamide DMF parallel with triethyl amine Et_3N, while ethylenediamine **6c** (2

mmol) or 1,4-diaminobutane **6d** (2 mmol) dissolved in ethanol parallel with triethyl amine Et_3N as a base then those mixtures were refluxed for 6 hours to produce 1-aminophthalazine derivatives **(7a-d)** in good yields. TLC monitoring was used to ensure that the reaction was finished. The solid precipitate that formed after the crude was submerged in freezing water was then gathered and dried.

N1-(4-(4-methoxyphenyl)-1,2-dihydrophthalazin-1-yl)benzene-1,2-diamine (7a)

Product **7a** was separated as brown solid, m.p =203-206 °C, Yield =67%, IR (KBr, cm^{-1}): 3335 (NH_2), 2975(NH), 1602(C=N). ^{1}HNMR (DMSO d6, 400MHz): δ ppm = 3.64 (s, 3H, -OCH_3), 3.81-3.96 (m, 2H, -NH_2), 6.38 – 6.66(m, 6H, -H_{Ar}), 6.81 – 6.93(m, 2H, -H_{Ar}), 7-7.39(m, 2H, -H_{Ar}), 7.86-8.13 (m, 4H, -H_{Ar}), 8.45(m, 1H, -NH). ^{13}C-NMR (DMSO d6, 100MHz): δ =159.1, 151.8, 134.7, 132.6, 130.4, 128, 127.8, 126.2, 126.1, 124.3, 117.4, 117.1, 114.9, 114.3, 113.9, 90.8, 55.1, 45.4. MS (m/z): 344(M+2, 10%).

N1-(4-(4-methoxyphenyl)-1,4-dihydrophthalazin-1-yl)benzene-1,3-diamine (7b)

Product **7b** was separated as dark gray solid, m.p =231-233 °C, Yield =65%, IR (KBr, cm^{-1}): 3345 (NH_2), 2899(NH), 1601(C=N). ^{1}HNMR (DMSO d6, 400MHz): δ ppm = 3.65 (s, 3H, -OCH_3), 3.85 (s, 2H, -NH_2), 5.89 – 6.46(m, 4H, -H_{Ar}), 6.78 – 6.87(m, 2H, -H_{Ar}), 7.13 – 7.41 (m, 2H, -H_{Ar}), 7.58-8.43(m, 6H, -H_{Ar}), 8.9(s, 1H, -NH). ^{13}C-NMR (DMSO d6, 100MHz): δ =169.1, 159.4, 152.3, 149.8, 139.5, 135.1, 132.9, 129.9, 129.8, 129.5, 126.5, 125.6, 124.6, 124.5, 124.4, 114.1, 113.7, 111.2, 110.9, 110.1, 109.6, 108.4, 107, 106.4, 91.1, 55.5, 55.3, 55.1. MS (m/z): 345(M+3, 6.9%).

N1-(4-(4-methoxyphenyl)-1,4-dihydrophthalazin-1-yl)ethane-1,2-diamine (7c)

Product **7c** was separated as orange solid, m.p =199-202 °C, Yield =69%, IR (KBr, cm^{-1}): 3443(NH_2), 2928(NH), 1605(C=N). ^{1}HNMR (DMSO d6, 400MHz): δ ppm = 3.85-3.98 (m, 3H, -OCH_3), 5.78(s, 2H, -NH_2), 6.76 – 7.33(m, 2H, -H_{Ar}), 7.58-7.64(m, 2H, -H_{Ar}), 7.83 – 7.89(m, 2H, -H_{Ar}), 8.1-8.46 (m, 2H, -H_{Ar}), 8.67 (s, 1H, - NH). ^{13}C-NMR (DMSO d6, 100MHz): δ =161.3, 159.3, 132.8, 128.2, 126.4, 125.5, 124.5, 114, 113.7, 75.5, 56.1, 55.3, 45.9, 44.9. MS (m/z): 294(M, 28.7%).

N1-(4-(4-methoxyphenyl)-1,4-dihydrophthalazin-1-yl)butane-1,4-diamine (7d)

Product **7d** was separated as dark red solid, m.p =141-143 °C, Yield =70%, IR (KBr, cm^{-1}): 3400(NH_2), 3274(NH), 1599(C=N). ^{1}HNMR (DMSO d6, 400MHz): δ ppm = 1.47 (s, 4H, -CH_2), 2.62 (s, 4H, -CH_2), 3.84 (m, 2H, -NH_2), 6.75 – 7.18(m, 2H, -H_{Ar}), 7.25-7.48(m, 2H, -H_{Ar}), 7.61-8.44 (m, 4H, -H_{Ar}), 9.58 (s, 1H, - NH). ^{13}C-NMR (DMSO d6, 100MHz): δ =168.8, 159.2, 152.1, 134.8, 133.8, 132.8, 129.9, 129.6, 128.1, 126.2, 125.5, 124.1, 113.7, 107.6, 91.1, 71, 55.5, 28.1. MS (m/z): 324(M+2, 28.3%).

General procedure of α-aminophosphonate derivatives (10a-f):

The one pot reaction of Lithium perchlorate (10 mmol%), 1,4-Piperazinedicarboxaldehyde **8a** or p-tolualdehyde **8b** (1.2 mmol each), triphenyl phosphite **9**(1 mmol) and 1-aminophthalazine derivative **7a** (1 mmol) were done by addition and stirring in 5 mL of methylene chloride (48hrs) to give α-aminophosphonate derivatives **10a**, **10b**, while for formation of α-aminopho sphonate derivatives **10c, 10d** using the one pot reaction, we added 1-aminophthalazine derivative **7b** (1 mmol), p-tolualdehyde **8b** or benzaldehyde **8c** (1.2 mmol each), triphenyl phosphite **9** in 5 mL of methylene chloride then added Lithium perchlorate (10 mmol%). We used TLC monitoring to guarantee the completion of the reaction. The required product was gathered, produced in a good yield. The same one pot reaction was also done here. So, we added new 1-aminophthalazine derivatives **7c, 7d** (1 mmol), 1,4-Piperazine dicarboxaldehyde **8a** (1.2 mmol) and triphenyl phosphite **9** (1 mmol) in 5 mL of methylene chloride then added Lithium perchlorate (10 mmol%). We used TLC monitoring to affirm that the reaction was finished. Likewise, the required product was gathered, produced in a good yield.

Diphenyl (4-formylpiperazin-1-yl) (2-(4-(4-methoxyphenyl)-(1,4-dihydrophthalazin-1-yl) amino) phenyl)amino)methyl) phosphonate (10a)

Product **10a** was separated as dark brown gum, Yield =63%, IR (KBr, cm^{-1}): 3306 (NH), 3254(NH), 1602(C=N), 1251(P=O), 800(POC), 716 (PCH). ^{1}HNMR (DMSO d6, 400MHz): δ ppm = 3.64(s, 8H, -CH_2), 3.84-3.89 (m, 3H, -OCH_3), 5.35 (s, 1H, -CHP), 6.37 – 6.92(m, 14H, -H_{Ar}), 7.06-7.9 (m, 8H, -H_{Ar}), 8.11 (s, 1H, -CHO), 8.43(s, 1H, - NH), 8.6(s, 1H, - NH). ^{13}C-NMR (DMSO d6, 100MHz): δ =169, 159.2, 152.3, 130.1, 129.2, 128.9, 127.9, 126.5, 125.2, 118.5, 117.65, 116.9, 114.7, 114, 91.3, 71.7, 55.7, 55.5, 45.7, 45.5, 45.4. ^{31}P -NMR (DMSO, 162MHz) δ: -0.09 ppm. MS (m/z): 703(M+3, 50%).

Diphenyl (((2-((4-(4-methoxyphenyl)-1,4-dihydrophthalazin-1-yl)amino) phenyl)amino) (*p*-tolyl)methyl) phosphonate (10b)

Product **10b** was separated as red brown gum, Yield =68%, IR (KBr, cm^{-1}): 3467(NH), 3393 (NH), 1601(C=N), 1256(P=O), 821(POC), 621(PCH). ^{1}HNMR (DMSO d6, 400MHz): δ ppm = 5.07- 5.27(m, 1H, - NH), 5.9 (s, 1H, -CHP), 6.06 – 6.26(m, 8H, -H_{Ar}), 6.33-6.6 (m, 8H, -H_{Ar}), 6.88-6.92(m, 6H, -H_{Ar}), 7.01-8.17 (m, 4H, -H_{Ar}), 8.91 (s, 1H, - NH). ^{13}C-NMR (DMSO d6, 100MHz): δ =153.1, 150.6, 150.3, 149.2, 145.9, 141.2, 138.8, 138.1, 129.5, 129.3, 111.1, 111, 110.9, 110, 109.9, 109.6, 109.2, 108.3, 106.9, 106.4, 103.3, 100.2, 96.8, 91, 55.3, 45.5, 10.1, 10, 9.9. ^{31}P -NMR (DMSO, 162MHz) δ: 16.78 ppm. MS (m/z): 678(M, 60.1%).

Diphenyl (((3-((4-(4-methoxyphenyl)-1,4-dihydrophthalazin-1-yl)amino) phenyl) amino) (phenyl)methyl) phosphonate (10c)

Product **10c** was separated as black solid, m.p = 289-292 °C, Yield =71%, IR (KBr, cm^{-1}): 3388 (NH), 3027(NH), 1605(C=N), 1267(P=O). ^{1}HNMR (DMSO d6, 400MHz): δ ppm = 3.63-3.89(m, 3H, -OCH_3), 5.89 (s, 1H, -CHP), 6.13 – 6.95(m, 15H, -H_{Ar}), 7.18- 7.38 (m, 6H, -H_{Ar}), 7.64- 8.18 (m, 6H, -H_{Ar}), 8.91 (s, 1H, - NH), 9.36 (s, 1H, - NH). ^{13}C-NMR (DMSO d6, 100MHz): δ =159.3, 157.3, 132.8, 132.7, 130.3, 129.9, 129.5, 129.2, 128.7, 128.2, 126.3, 124.5, 120.6, 118.9, 115.3, 114.1, 55.32, 40.2, ^{31}P -NMR (DMSO, 162MHz) δ: 16.42 ppm. MS (m/z): 665(M, 6.3%).

Diphenyl (((3-((4-(4-methoxyphenyl)-1,4-dihydrophthalazin-1-yl)amino)phenyl)amino) (p-tolyl)methyl) phosphonate (10d)

Product **10d** was separated as black solid, m.p = 279-281 °C, Yield =60%, IR (KBr, cm^{-1}): 3339 (NH), 3243(NH), 1602(C=N), 1264(P=O), 811(POC), 622 (PCH). ^{1}HNMR (DMSO d6, 400MHz): δ ppm = 2.4(s, 3H, -CH_3), 6.73 (s, 1H, -NH), 6.75 – 7.02(m, 10H, -H_{Ar}), 7.08-7.46(m, 10H, -H_{Ar}), 7.79-7.82 (m, 6H, -H_{Ar}), 9.32 (s, 1H, - NH). ^{13}C-NMR (DMSO d6,

100MHz): δ =157.4, 150.98, 150.94, 14.94, 149.9, 149.8, 145.4, 134, 130.4, 130.2, 129.8, 129.7, 129.5, 129.2, 129,126, 125.3, 124.7, 120.6, 120.5, 120.4, 120, 119.9, 118.9, 115.3, 45.8, 21.44, 21.3, 20.8. ^{31}P -NMR (DMSO, 162MHz) δ: 15.96 ppm. MS (m/z): 681.9(M+2, 24.4%).

Diphenyl ((4-formylpiperazin-1-yl)((2-((4-(4-methoxyphenyl)-1,4-ihydrophthalazin-1-yl) amino) ethyl)amino)methyl) phosphonate (10e)

Product **10e** was separated as dark orange solid,m.p = 241-243 °C,Yield =64%, IR (KBr,cm^{-1}): 3388 (NH), 3262(NH), 1601(C=N), 1114(P=O), 810(POC), 624 (PCH). ^{1}HNMR (DMSO d6, 400MHz): δ ppm = 2.71-2.87(m, 4H, -CH_2), 6.75-6.92(m, 10H, -H_{Ar}), 7.16-7.44(m, 6H, - H_{Ar}), 7.64-7.89 (m, 6H, - H_{Ar}), 8.01 (s, 1H, - CHO), 8.09 (s, 1H, - NH), 9.67 (s, 1H, - NH). ^{13}C-NMR (DMSO d6, 100MHz): δ =169.3, 161.9, 159.5, 157.5, 152.4, 146.1, 135.3, 134.2, 133, 132.2, 130.6, 130.1, 129.6, 129.1, 128.8, 128.3, 127.9, 126.6, 126.3, 125.7, 124.9, 124.6, 124.5, 120.2, 120.1, 119.1, 115.8, 115.5, 114.6, 114.2, 113.8, 108.1, 91.3, 71.6, 55.6, 55.5, 55.2, 37.1. ^{31}P-NMR (DMSO, 162MHz) δ: -3.1 ppm. MS (m/z): 654(M+2, 9.2%).

Diphenyl ((4-formylpiperazin-1-yl) ((4-((4-(4-methoxyphenyl)-1,4-dihydrophthalazin-1-yl) amino) butyl)amino)methyl)phosphonate (10f)

Product **10f** was separated as red black gum, Yield =64%, IR (KBr, cm^{-1}): 3381 (NH), 3267(NH), 1598(C=N), 1110(P=O), 821(POC), 621 (PCH). ^{1}HNMR (DMSO d6, 400MHz): δ ppm = 1.42(s, 4H, -CH_2), 2.59(s, 4H, -CH_2), 3.63 (s, 8H, -CH_2), 3.84-95 (m, 3H, -OCH_3), 5.95 (s, 1H, -CHP), 6.75-6.77(m, 5H, -H_{Ar}), 6.93-7.02(m, 5H, - H_{Ar}), 7.15-7.29(m, 4H, - H_{Ar}), 7.45-7.72 (m, 4H, - H_{Ar}), 7.83-8.09 (m, 4H, - H_{Ar}), 8.19 (s, 1H, - CHO), 8.45(s, 1H, - NH), 9.6(s, 1H, - NH). ^{13}C-NMR (DMSO d6, 100MHz): δ =168.9, 159.4, 158.5, 157.2, 152.2, 134.8, 133, 129.8, 129.4, 128.7, 128.4, 127.6, 125.4, 124.3, 121.9, 119.8, 118.7, 115.4, 114.1, 113.4, 107.8, 91.2, 71.2, 60.8, 55.5, 55.1, 40.5, 36.3, 28.1. ^{31}P-NMR (DMSO, 162MHz) δ: -2.38 ppm. MS (m/z): 685(M+4, 9.9%).

7. Conflicts of interest

In carrying out this work, the authors affirm that there were no conflicts of interest.

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