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Synthesis, and phytopathological application of some novel amino acid, dipeptide and diphenylphosphonic acid derivatives of 2-aminopyrimidine

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ABSTRACT

A new series of 2-[N-(Tos- or Pht-)aminoacyl- p-substituted phenylmethyleneamino]-pyrimdines (V-XII) was synthesized via the reaction of Schiff bases, 2-(4-substituted benzylidene)aminopyrimdines (I,II) with the requisite tosyl or phthalylaminoacyl chlorides. Elongation of these amino acid derivatives to form the corresponding dipeptides (XVII-XXIV) were synthesized starting with 2-[glycyl or Dl-valyl- p-substituted phenylmethyleneamino]-pyrimdines (XIII-XVI). Diphenylphosphonic acid ester derivatives (III,IV) also be synthesized. All the prepared compounds were characterized by elemental analyses, IR, ^{1}H-NMR and mass spectral studies. The resulting novel amino acid derivatives were screened for their (In Vitro) antimicrobial activity against Gram-positive and negative bacteria as well as for their antifungal activity and (In Vivo) application against plant pathogenic fungus Botrytis cinerea , the causal agent of cucumber plant (Cucmis. sativa L) gray mold disease.

Key words: Schiff bases, diphenylphosphonic acid esters, *N*-aminoacyl and dipeptidyl derivatives, antimicrobial activity, phytopathogen, *Botrytis cinerea* Cucumber plant *Cucmis. Sativa.*

INTRODUCTION

Pyrimidine and their derivatives are considered to be important for drugs and agricultural chemicals. Pyrimidine derivatives possess several interesting biological activities such as antimicrobial [1-3], antitumour [4-6], and antifungal [7-9]. Many pyrimidine compounds are used for thyroid drugs and leukemia [10]. Antibacterial, antifungal, antitumor, anticancer [11-15] and insecticidal [16] activities of some Schiff bases have been reported and they are found to be active against a wide range of organisms [17]. Moreover, organo-phosphorus compounds have many interesting biological properties. They are used as herbicides, insecticides and enzyme inhibitors [18]. In recent times biological

control of plant pathogenic fungi has received a considerable attention, as it has several advantages such as possibility of multiple pathogen suppression, low cost and promotion of soil fertility [19]. It was mentioned that biocontrol by fungi may be enhanced if the procedure involves the use of chemical protector [20]. In view of these observations and in continuation of our previous work on structure–activity relationship (*SAR*) of amino acid and peptide derivatives [21-24], the present study aims at the synthesis and phytopathological evaluation of 2-[*N*-(tosyl or phthalyl)-aminoacyl- or dipeptidyl- *p*-substituted phenylmethyleneamino]-pyrimdines as a novel class of antimicrobial agents that have many biological applications, as environmentally safe weapons for controlling the most potent destructive plant diseases caused by different phytopathogens and others.

EXPERIMENTAL SECTION

Melting points were uncorrected and meassured on electric melting point apparatus SMP1. Thin layer chromatography (tlc, R_f) was run on plastic sheets coated with silica gel-60 (Merck) and developed with *n*-butanol- acetic acid- water (4:1:1, v/v) and detected under UV light. The infrared spectra (ν_{max} in cm^{-1}) were taken in KBr discs using FTIR-2000 instrument. ^{1}H-NMR spectra (δ, ppm) were measured in DMSO-d_6 or $CDCl_3$ using FX90Q Fourier Transform NMR spectromrter. The mass spectra, m/e (intensity %) were performed using Shimadzu-GC-MS-QP 100 Ex by the direct inlet system. Elemental analysis were carried out at Microanalytical Uint, Faculty of Science, Cairo University, Cairo, Egypt.

Synthesis of 2-(4-substituted benzylidene)-aminopyrimdine derivatives (I,II):

A mixture of equimolar amounts of 2-aminopyrimidine and benzaldehyde or *p*-chloro-benzaldehyde (0.1 mole) in absolute ethanol (40 ml) containing few drops of gl.acetic acid was refluxed for 3-4 h and then left to cool. The progress of the reaction was followed by tlc. The precipitate was filtered off, washed several times with diethyl ether, dried and was then recrystallized from the proper solvent. **I**, IR: 3067,1596(CH, and C=C, aro), 2832 (CH, ali), 1622 (CH=N). ^{1}H-NMR: 6.87-8.47 (m, 8H, phenyl & pyrimdine-H), 8.72 (s,1H,N=CH). **II**, IR: 3084,1601 (CH, and C=C, aro), 2954, 2860 (CH, ali), 1626 (CH=N).

Synthesis of [*p*-substituted phenyl-(2-pyrmidinylimino)methyl]-phosphonic acid diphenyl ester derivatives (III,IV):

A solution of diphenylchlorophosphate (0.001 mole) was added, in small portions to a well–stirred solution of (I-II, 0.001 mole) containing TEA (0.002 mole) in dry benzene. After complete addition, the reaction mixture was refluxed for 5 h under anhydrous conditions. The solid obtained $Et_3N.HCl$ after cooling was removed by filtration and the filtrate was then evaporated under reduced pressure. The residual substance was purified by recrystallization from benzene-ether. **III**,IR: 3026,1599 (CH and C=C,aro), 1610 (C=N), 1178 (P=O). ^{1}H-NMR: 6.72-7.31 (m, 15H, Ar-H), 8.04-8.46 (3H, pyrimi-dine-H). **IV**,IR:3013,1591 (CH and C=C,aro),1612 (C=N), 1172 (P=O) and 734 (C-Cl).

Synthesis of 2-[*N*-(Tos- or Pht-)aminoacyl- *p*-substituted phenylmethyleneamino]-pyrimdine derivatives (V-XII):

A solution of freshly prepared *N*-(Tos- or Pht-)amino acid chloride[26] (0.003 or 0.02 mole respectively) in anhydrous THF was added portionwisely to a stirred solution of Schiff base (I-II, with corresponding molar ratio) in dry dioxane containing Et_3N (0.006 or 0.04 mole respectively). After complete addition, the reaction mixture was heated under reflux for 4-6 h and then kept overnight at room temperature. The solid formed $Et_3N.HCl$ was removed and the filtrate was evaporated under reduced pressure. The residual substance was purified by

recrystallization from the proper organic solvent. All the product were chromatographically homogeneous when detected under UV light. **V** ,IR: 3287 (NH), 3052,1598 (CH and C=C, aro), 2966 (CH,ali), 1691(C=O), 1626 (C=N), 1328,1156 (SO_2). ^{1}H-NMR: 2.33 (s, 3H, CH_3), 4.45 (s,2H,CH_2), 7.30- 8.46 (m,12H, Ar-H & pyrimidine-H), 9.09 (s,1H,$NHSO_2$). **VI**, IR: 3263 (NH), 3085,1598 (CH and C=C, aro), 2979(CH,ali), 1701(C=O), 1618 (C=N), 1344,1164 (SO_2). **VII**, IR: 3034 (CH, aro), 2981 (CH,ali), 1683 (C=O), 1619 (C=N). ^{1}H-NMR: 2.32 (s,3H,CH_3), 4.39 (s,2H, CH_2), 7.23-8.46 (m, 11H,Ar-H & pyrimidine-H), 9.23 (s,1H,$NHSO_2$). **IX**, IR: 3023, 1592 (CH and C=C, aro), 2947 (CH,ali), 1774, 1719 (C=O, phthalyl), 1701 (C=O), 1629 (C=N). **X**, IR: 3067 (CH, aro), 2951(CH,ali), 1771 (C=O, phthalyl), 1701 (C=O), 1629 (C=N). MS m/e : 412 (M^+, 3.12%), 369 (M-43,1.90%), 290(11.45%), 197(100%), 155(27.13%). **XI**, IR: 3033 (CH, aro), 2977,2883 (CH,ali),1774,1718 (C=O, phthalyl), 1689 (C=O), 1616 (C=N) ,738(C-Cl). **XII**, ^{1}H-NMR :0.93 (d,6H, 2CH_3), 2.31(h,1H,CH),4.34 (d,1H, CH), 7.21-8.41 (m,11H, Ar-H & pyrimidine-H).

Synthesis of some hydrochloride salts of 2-[glycyl or Dl-valyl- *p*-substituted phenyl-methyleneamino]pyrimdine derivatives (XIII-XVI):

2-[*N*-(Pht-)aminoacyl- *p*-substituted phenylmethyleneamino]pyrimdine**s** (IX-XII, 0.01 mole) was dissolved in methanol and treated with 85% hydrazine hydrate (0.02 mole). The reaction mixture was refluxed for 2h at 60-70°C, left to cool and then evaporated to dryness *in vacuo*. The residual solid was warmed for 15 min with dilute HCl (40 ml) and then left to cool. The insoluble phthalylhydrazide was filtered off and the filtrate was evaporated .The residual oil or solid was recrystallized from water-methanol. The IR spectra of these derivatives showed the following characteristic bands at ~ 3061, 1603 (CH,and C=C, aro.), 2976, 2854 (CH,ali), 3391-3123 (broad NH_3^+), 1628 (C=N).

Synthesis of 2-[*N*-(Tos-)dipeptidyl- *p*-substituted phenylmethyleneamino]-pyrimdine (XVII-XX):

To a cold solution of *N*-(Tos)-glycyl hydrazide (0.001 mole) in a mixture of acetic acid (8ml), HCl (5N, 2ml), and water (10 ml) was added a solution of $NaNO_2$ (0.0024 mol) in cold water (3 ml). The reaction mixture was stirred at -5°C for 15 min. The yellow syrup formed was extracted with cold ethyl acetate (30 ml), washed successively with cold 3% $NaHCO_3$, H_2O and finally dried over anhydrous Na_2SO_4. To this solution, a previously stirred solution of the hydrochloride salts (XIII-XVI, 0.0012 mole) in dry ethyl acetate (25 ml) containing Et_3N (0.0024 mole) for 30 min at room temperature was added. The reaction mixture was stirred at -5°C for 6 h, then at room temperature for 24 h. The solution was washed with cold water, dried over anhydrous Na_2SO_4. The solution was evaporated in vacuo to dryness and the residue was recrystallized from the proper solvent to give the desired product. **XVII**, IR: 3311 (NH), 3032 (CH,aro), 2985 (CH,ali), 1702 (C=O), 1631 (C=N), 1345,1162 (SO_2). MS m/e: 451 (M^+,1.37%), 372 (M-$C_4H_3N_2$, 5.02%), 269 (9.23%), 183(100%), 155 (27.12%), 91 (38.78 %) , 76 (56.23%). **XVIII**, ^{1}H-NMR: 0.94 (d,6H,2CH_3), 2.31(s,3H,CH_3-Ph), 4.21(d, 1H, CH), 4.32 (s,2H ,CH_2) , 7.27-8.45 (m,12H, Ar-H & pyrimidine-H), 9.11(s,1H,$NHSO_2$). **XIX**, IR: 3271 (NH), 3040,1605 (CH and C=C, aro), 2959 (CH,ali), 1707 (C=O), 1621 (C=N), 1339,1161 (SO_2). MS m/e: 485 (M^+,2.19 %), 442(10.21%), 363 (7.10%), 197 (100%), 155 (32.10 %), 91(34.13%). **XX**, IR: 3278 (NH), 3019,1599 (CH and C=C, aro), 2967,2845 (CH,ali), 1694 (C=O), 1624 (C=N).

Synthesis of 2-[*N*-(Pht-)dipeptidyl- *p*-substituted phenylmethyleneamino]-pyrimdine (XXI-XXIV):

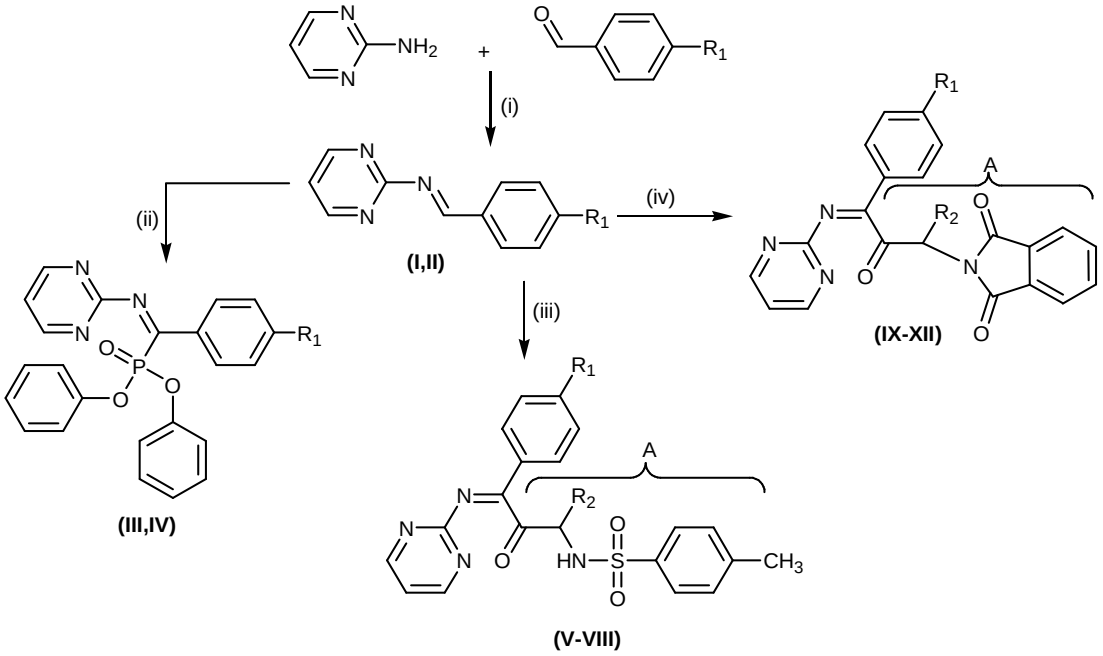
A solution of freshly prepared *N*-(Pht)-glycyl chloride (0.002 mole) in anhydrous THF (15

ml) was added dropwisely to a previously stirred solution of the hydrochloride salts (XIII-XVI, 0.0022 mole) in dry dioxane (25 ml) containing Et_3N (0.0044 mole) for 30 min at room temperature. .The reaction mixture was stirred for additional 4h at room temperature and then kept overnight. The precipitated $Et_3N.HCl$ was filtered off and the solvent was removed *in vacuo*. The crude dipeptide derivatives (XXI-XXIV) were purified by recrystallization from the proper solvent. **XXI**, ^{1}H-NMR: 4.19 (s,2H,CH_2), 4.33 (s, 2H, CH_2), 7.20-8.44 (12 H, Ar-H& pyrimidine-H). **XXI**,IR: 3286, 3178 (NH), 30231(CH, aro), 2960,2852 (CH,ali), 1765, 1711 (C=O, phthalyl and amide), 1624 (C=N). **XXIII**, IR, 3254 (NH), 3009,1600(CH, and C=C, aro), 1770, 1723, 1689(C=O, phthalyl and amide). ^{1}H-NMR: 4.20 (s,2H,CH_2), 7.24 - 8.42 (11H, Ar-H & pyrimidine-H). **XXIV,** MS m/e: 503 (M^+,1.05%), 460 (M-43,19.10%), 314 (6.21%), 272(11.09 %), 135(100%).

RESULTS AND DISCUSSION

Chemistry

2-Aminopyrimidine was reacted with various aromatic aldehydes in abs. ethanol to obtain the starting 2-(4-substituted benzylidene)-aminopyrimdine compounds (I,II) in a good yield (76-83 %). The IR spectra were recorded using KBr pellets in the range of 4000-400 cm^{-1}. The absorption bands at 3067 - 3084 cm^{-1} are assigned to the aromatic C-H stretch. The appearance of a medium to strong absorption bands at ~1626 cm^{-1} are attributed to a stretching vibration of the azomethine (-HC=N-) which confirming the condensation of the reactants. Furthermore, ^{1}H-NMR signal that observed at δ 8.72 chaacteristic for azomethine proton supports the proposed structure .



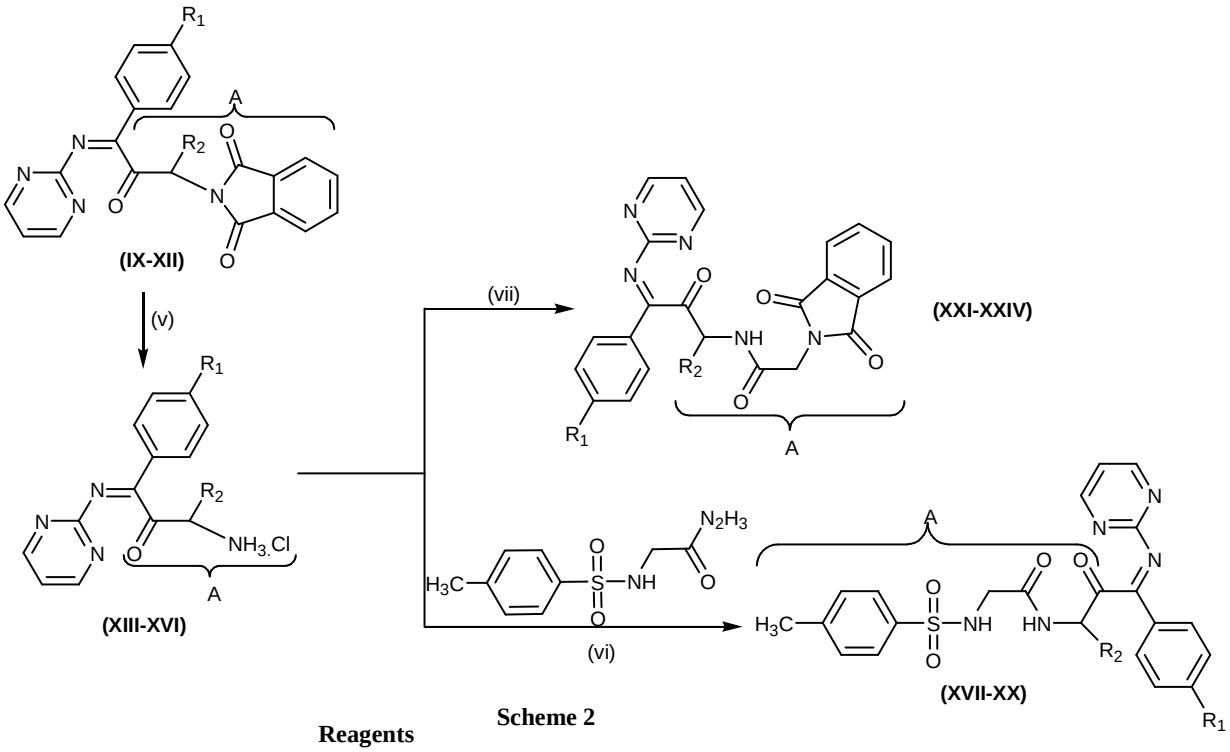
Scheme 1

Reagents
(i) = Ethanol /reflux
(ii) = Diphenylchlorophosphonic acid in dry bnezene-TEA/ Reflux
(iii) = Tosylaminoacyl chloride in THF-TEA/reflux
(iv) = Phthalylaminoacyl chloride in THF-TEA/reflux

Interaction of Schiff bases (I,II) with diphenylchlorophosphate in equimolar amounts in the presence of a hydrogen ion acceptor such as triethylamine in dry benzene results in the formation of the replacement products, [*p*-substituted phenyl- (2-pyrmidinyl-imino)methyl]-

phosphonic acid diphenyl esters (III,IV) for which the elemental and spectral analyses are compatible with their proposed structures [25]. Infrared spectra of these compounds showed the following characteristic stretching vibaretions at ~1610 and 1172 cm^{-1} corresponding to (C=N) and (P=O) respectively. The proton NMR spectral data revealed the disappearance of a resonance signal assigned to the CH=N in (I,II) derivatives which confirming the replacement reactions.

In the same manner, 2-[*N*-(Tos- or Pht-)aminoacyl- *p*-substituted phenylmethylene-amino]pyrimdines (V-XII) were prepared via the replacement reaction of azomethine proton in (I,II) with tosyl (Tos-) or phthalyl (Pht-)aminoacyl chlorides in dry benzene -triethylamine medium. The products were isolated, purified and recrystallized and obtained in (51-73%) yield and were chromatographically homogeneous. The time required for completion of the reaction (4-6 h) was controlled by tlc (Scheme 1).



Scheme 2

Reagents
(v) = Hydrazine hydrate 85% - methanol/reflux
(vi) = Tosylglycyl hydrazide/azide coupling method
(vii) = Phthalylglycyl chloride in THF-TEA/stir

Mild hydrazinolysis conditions of phthalylglycyl or Dl-valyl derivatives of Schiff bases (IX-XII) led to removal of the protecting phthalyl group and formation of hydrochloride salts of 2-[glycyl or Dl-valyl- *p*-substituted phenylmethyleneamino]-pyrimdine (XIII-XVI) in (71-82%) yield.

Elongation of the amino acid derivatives (XIII-XVI) to produce the corresponding Tos-dipeptide derivatives (XVII-XX) was carried out using the azide method [26] in which Tos-glycyl azide, resulting from the reaction of the corresponding hydrazide compound with cold solution of nitrous acid; was treated with freshly prepared cold solution of free 2-[glycyl or DL-valyl - *p*-substituted phenylmethyleneamino]-pyrimdine (XIII-XVI) in dry ethyl acetate containing Et_3N. The time required for completion of the reaction was monitered by tlc. The resulting purified Tos-dipeptides were chromatographically homogeneous and obtained (51-62%) yield.

On the other hand, for preparation of Pht-dipeptide derivatives (XXI-XXIV), the requisite 2-[glycyl or DL-valyl - *p*-substituted phenylmethyleneamino]pyrimdine hydro-chloride (XIII-XVI), firstly treated with TEA to liberate the free amine compound which then coupled with phthalylglycine in presence of slightly molar excess of TEA using the acid chloride procedure [26]. All the products were isolated, purified and recry-stallized and obtained in (58-71%) yield and were found to be chromatographically homogeneous (Scheme 2). The spectral data of (XIII-XXIV) were found to be consistent with the formulations.

Table (1): Physical data of the prepared derivatives (I-XXIV)

Compd No	R	A	Cryst. solv*	M.P. °C	Yield %	R_f	Mol.Formula**
I	H	---	a	207-208	76	0.86	$C_{11}H_9N_3$
II	Cl	---	b	45-46	83	0.66	$C_{11}H_8ClN_3$
III	H	---	c	187-190	43	0.64	$C_{23}H_{18}N_3O_3P$
IV	Cl	---	c	113-114	56	0.69	$C_{23}H_{17}ClN_3O_3P$
V	H	Tos-Gly	a	165	66	0.89	$C_{20}H_{18}N_4O_3S$
VI	H	Tos-DL-Val	d	177-179	51	0.60	$C_{23}H_{24}N_4O_3S$
VII	Cl	Tos-Gly.	d	114-116	63	0.72	$C_{20}H_{17}ClN_4O_3S$
VIII	Cl	Tos-DL-Val	b	187-188	57	0.81	$C_{23}H_{23}ClN_4O_3S$
IX	H	Pht-Gly.	d	250	70	0.71	$C_{21}H_{14}N_4O_3$
X	H	Pht-DL-Val	a	197-198	57	0.87	$C_{24}H_{20}N_4O_3$
XI	Cl	Pht-Gly.	a	199-201	73	0.81	$C_{21}H_{13}ClN_4O_3$
XII	Cl	Pht-DL-Val	b	179-182	54	0.84	$C_{24}H_{19}ClN_4O_3$
XIII	H	Gly.HCl	e	178-181	82	0.62	$C_{13}H_{13}ClN_4O$
XIV	H	DL-Val.HCl	e	98-100	75	0.71	$C_{16}H_{19}ClN_4O$
XV	Cl	Gly.HCl	e	163-163	79	0.67	$C_{13}H_{12}Cl_2N_4O$
XVI	Cl	DL-Val.HCl	e	122-124	71	0.64	$C_{16}H_{18}Cl_2N_4O$
XVII	H	Tos-GlyGly	a	124-125	62	0.79	$C_{22}H_{21}N_5O_4S$
XVIII	H	Tos-Gly-DL-Val	d	114-116	54	0.90	$C_{25}H_{27}N_5O_4S$
XIX	Cl	Tos-GlyGly	b	136-137	57	0.84	$C_{22}H_{20}ClN_5O_4S$
XX	Cl	Tos-Gly-DL-Val	d	167-169	51	0.87	$C_{25}H_{26}ClN_5O_4S$
XXI	H	Pht-GlyGly	a	148-149	71	0.87	$C_{23}H_{17}N_5O_4$
XXII	H	Pht-Gly-DL-Val	a	233	58	0.80	$C_{26}H_{23}N_5O_4$
XXIII	Cl	Pht-GlyGly	f	200-202	63	0.85	$C_{23}H_{16}ClN_5O_4$
XXIV	Cl	Pht-Gly-DL-Val	a	186-188	64	0.86	$C_{26}H_{22}ClN_5O_4$

Cryst.solv.: a =methanol, b = ethanol / H_2O, **c = benzene / ether, d = acetic acid / H_2O, e = H_2O / methanol, f = Benzene / pet.ether 60-80. ** All compounds gave satisfactory C,H, and N analysis*

Biological activity

Due to the need to diminish the amount of pesticides used, alternative ways of controlling fungal disease have to be developed [27]. Accordingly, studies on some 2-aminopyrimidines to form Schiff bases proved that they are significantly active against bacteria and fungi [28]. Fortunately, the results obtained from tables (2 & 3) are running parallel with those held *in vitro*. On the other hand, *in vivo* results obtained from table (4) revealed that, in spite of the deleterious effect of the phytopathogen *B .cinerea* exerted up on the host plant *Cucmis. sativa* L [29], the use of newly formed amino acid derivatives XX and XXI was able to minimize the drastic action of the phytopathogen by reducing the infection percentage from 88 % down to (17 & 22 %) respectively, and this considered as the first application of such newly formed compounds. Amazingly, the second applicable side can be detected in table (5) by using these newly formed amino acid derivatives XX and XXI can be collectively improving the growth parameters measured up on the cucumber host plant cultivated even under pathogenicity conditions and the obtained results are backed by many authors [30].

Antimicrobial activities of the prepared compounds (I-XXIV).

For testing antimicrobial activity of compounds (I-XXIV), we used more than one test organisms to increase the range of antibiotic detection in the tested materials by using filter paper disc method [31]. A filter paper discs must be of uniform thickness and size and containing an equal and graded amount of the agent to be tested for its antimicrobial activity. The method was performed by dissolving 5 mg. of the sample in 1ml. of solvent solution, *N*,*N*-dimethylformamide then a sterile filter paper discs were dipped into this solution. After absorption, each disc was dried and placed on bacterial or fungal test organisms seeded plates to be tested for their antimicrobial activity. The inhibition zone were measured in millimeters at the end of incubation period.

Pathogenecity test:

1-Fungal isolate and plant material .

A pure strain of cucumber plants (*Cucmis sativa L*.) and virulent pathogenic isolate of *Botrytis cinerea* used in this study was kindly provided by the Agriculture Research Center (A.R.C), Ministry of agriculture, Giza -Egypt.

2-Cultivation, inoculation ,and treatment of Cucumber plants :

According to the method previously reported [32], the pathogenecity test of *Cucmis sativa L c*onducted under green-house conditions by using a uniform lot of susceptible cucumber seeds cultivar (American-105) that were surface sterilized, and sown in 25 cm.diameter pots containing 2 Kg. of soil , as three plants per each pot were used in triplicate. Then all plants were kept in natural conditions .

Four sets of pots were established :

A) Uninoculated plants sprayed with distilled water were used as control.
B) Cucumber plants treated with amino acid derivative XX compd.(at 10 ppm. conc.).
C) Cucumber plants inoculated with the pathogen *Botrytis cinerea* spore suspension (Contain 1000000, spores ml^{-1}).
D) Cucumber plants inoculated with both the pathogen and XX and XXI respectively.
All plants were then covered with cage of polyethylene sheet for 12 h to increase high relative humidity necessary for fungal infection .

3- Phytopathological analysis :

Disease symptoms was assessed using a scale of five classes ; 0= no symptoms , 1= Slight and few lesions, 2= moderate lesions, 3= leaves wilted ,and 4= plants was completely destroyed. Disease index was calculated according to the method described earlier [33] by using the formula: DI = (1 n1 + 2 n2 +3 n3 + 4 n4) 100 / 4Nt where n1 ~ n4 is the No. of plants in indicated classes and Nt is the total No. of plants

Determination of Chlorophyll contents : Chlorophyll content was determined according to the method described by [34]. The pigment was extracted by grinding 1 gm of fresh leaves with a suitable amount of 100 ml. of 80 % aqueous acetone as, (v/ v) . The optical density of the extract was measured using Carl Zeiss Colorimeter at two wave lengths (649 and 665 nm). The pigment content was calculated using the equation of this method and expressed as mg /g fresh weight.

The results show a considerable antimicrobial responses of some newly formed amino acid derivatives against the most potent clinically isolated strains of bacteria (*in vitro*). Any way, the inhibition potential of the newly formed amino acid derivatives tested, were more up on

both Gram positive and negative bacteria tested than filamentous plant pathogenic fungi. However, this may give an indication that the mechanism of the inhibition that exerted by these newly formed amino acid derivatives up on filamentous fungi as Eukaryotic representative class is completely different from that upon bacteria as Prokaryotic representative class .Secondary, the *In Vivo*, results show that, some of the newly formed amino acid derivatives as XX ,and XXI can be successfully inhibit the growth of plant pathogenic fungus *Botrytis cinerea* in a different degrees resulted in reducing the infection percentage from, 88 % down to only (17 &22 %) respectively.

Table (2):The antibacterial activity of biologically active synthetic derivatives

Compd No.	Mean diameter of inhibition zone(mm)				
	B.subtilis **NCTC10400**	***S.aureus*** **TCC25923**	***E.coli*** **ATCC25922**	***P.vulgaris*** **NCTC4175**	***P.aeruginosa*** **ATCC10425**
I	3	4	0	0	0
II	4	5	2	0	0
III	16	14	23	18	16
IV	12	19	24	18	11
V	8	10	6	8	0
VII	14	12	13	9	0
VIII	17	16	12	11	0
XV	12	14	13	9	0
XVI	15	11	10	7	0
XVII	7	7	6	7	0
XVIII	0	0	0	0	0
XIX	10	8	8	7	0
XX	9	7	10	7	0
XXI	0	4	0	5	0
XXII	4	5	0	0	0

Table (3) : The antifungal activity of biologically active synthetic derivatives

Compd .No.	Mean diameter of inhibition zone(mm)		
	Candida albicans	***Botrytis cinerea***	***Aspergillus flavus***
III	13	11	0
IV	11	10	0
V	6	4	0
VII	5	5	0
VIII	8	6	0
X	4	2	0
XIII	6	5	0
XIV	5	3	0
XX	24	23	0
XXI	22	20	0

Collectively, some of the newly formed amino acid derivatives compounds exhibited a good antimicrobial activity when compared with other compounds in the series against the tested pathogenic bacterial and fungal strains that may lead to more promising applicable sides.

Table (4): Effect of different treatments on *Cucmis sativa L*. plant infected by the fungal pathogen *,Botrytis cinerea*

Treatment	Severity Classes					Disease index	Infection %
	0	1	2	3	4		
Control (untreated plants).	16	2	0	0	0	3	11
Control + (XX) Compd .	17	1	0	0	0	2	6
Plants infected with *Botrytis cinerea* (I.P)	2	0	1	4	11	80	88
I.P + (XX) Compd	15	3	0	0	0	4	17
I.P + (XXI) Compd	14	3	0	0	0	7	22

Table (5): Effect of different treatments on the growth parameters of Cucumber plants inoculated with *B. cierea*

No.	Treatment	Shoot Fresh Weight /gm.	Leaf Width /cm.	Total Chlorophyll Content. mg /g Fresh weight
1	Control (untreated plants).	38	6.3	17.8
2	Control + (XX) compd.	41	6.5	18.5
3	Plants infected with *Botrytis cinerea* (I.P)	25	4	11
4	I.P + (XX) Compd.	36	6	16.8
5	I.P + (XXI) Compd .	31	5.1	15.6

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