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Synthesis and Antimicrobial Activity of some New α N-Phthilimido Amino Acids Analogues

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Abstract: The aim of the study was to design, synthesize and investigate the antimicrobial & fungal activity of some α N-Phthilimido derivatives of amino acids. The chemical structures of the titled compound were confirmed by IR, 13CNMR and elemental analysis. All the compounds are screened for antimicrobial activity against gram positive, gram negative bacteria (Escherichia coli, Klebsiella, Staphylococcus epidermitis, Bacillus cereus, Micrococcus leteus, Staphylococcus aureus) and fungal strains (Candida albicans, Aspergillus niger)

Key words: α N-Phthilimido, Antimicrobial Activity.

Introduction

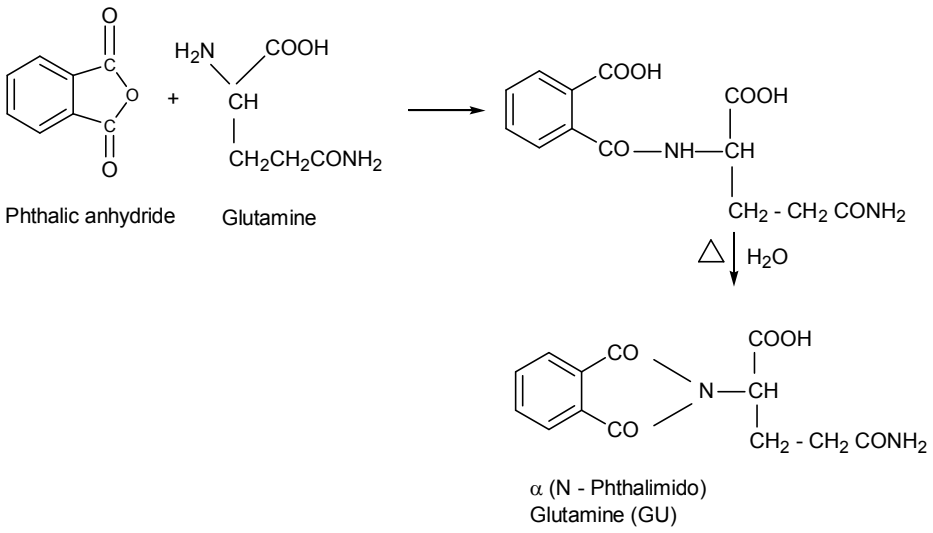
In view of the importance of amino acids in nutrition, metabolic processes and translation of information, they have been an important target in the design of antimeatabolites[10]. However the number of amino acid analogs, that have been shown to have significant chemotherapeutic activity is rather small. This may be due, in part, to the high serum concentration that is needed, which is difficult to maintain over long periods, and the possibility of inter conversions among amino acids, which help to overcome metabolic blocks easily. Because of their resemblance with natural amino acids[9] (valine, alanine, serine, etc.,), these amino acid inhibitors are thought to interfere with amino acid metabolism.

Experimental[3]

Melting point of all synthesized compound were determined by using open capillary method and are uncorrected. The precoated alumina plates with silica gel GF254 (E.Merck) were used for purity determination and pet: ethyl acetate (1:2) was employed as irrigate. IR spectra were recorded in (cm^{-1}) ABB BOMEM FT-IR Spectrometer using KBr pellet technique. ^{1}H-NMR[11] and ^{13}C-NMR were recorded (in δppm) on BRUKER AV 400 using TMS as internal standard[11].

Synthesis of α N-Phthilimido Glutamine [1](1)

Equimolar quantities of Phthalic anhydride[4], Glutamine and distilled water. The above was mixed well and heated on a heating mantle and refluxed for two & half-hours. After reflux, the hot mixture was transferred and kept in a beaker at room temperature, over night. The crystalline product, which was found to be insoluble in benzene and chloroform but soluble in hot water, was collected by filtered & dried to remove moisture. The unreacted raw materials were removed by repeatedly shaking with 50ml portions of benzene A.R. and then with 50ml portions of chloroform A. R. filtered, dried and recrystallised from hot water. The pure product was collected by filtration and dried to remove moisture.



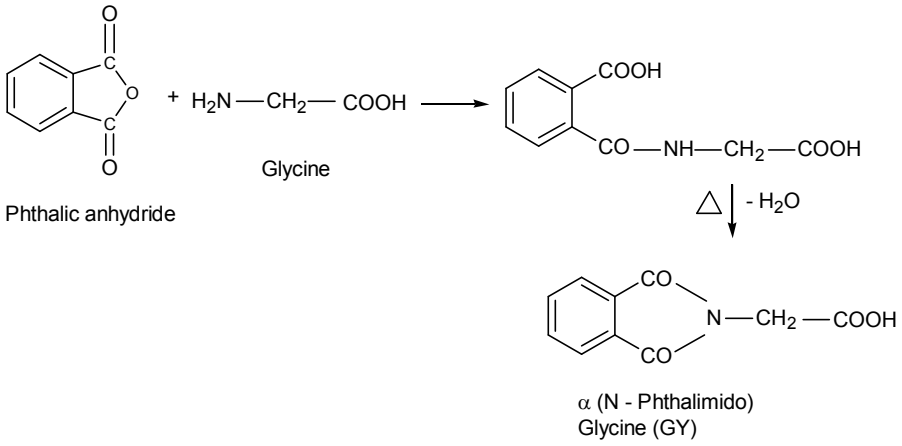
Synthesis of α N-Phthilimido Glycine[1] (2):

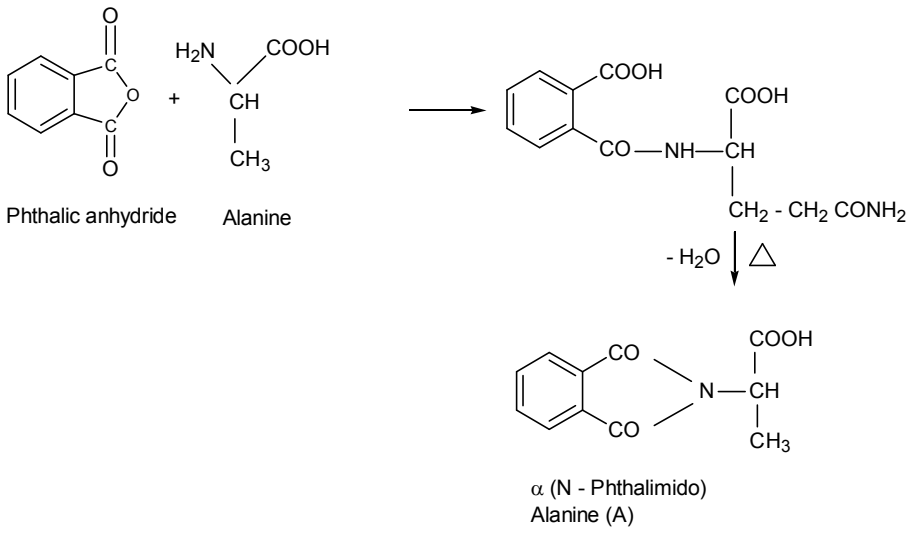
Equimolar quantities Phthalic anhydride[4], Glycine and distilled water. The above was mixed well and heated on a heating mantle and refluxed for two & half-hours. After reflux, the hot mixture was transferred and kept in a beaker at room temperature, over night. The crystalline product, which was found to be insoluble in benzene and chloroform but soluble

in hot water, was collected by filtered & dried to remove moisture. The unreacted raw materials were removed by repeatedly shaking with 50ml portions of benzene A.R. and then with 50ml portions of chloroform A. R. filtered, dried and recrystallised from hot water. The pure product was collected by filtration and dried to remove moisture.

Synthesis of α N-Phthilimido Alanine[1](3):

Equimolar quantities of Phthalic anhydride[4], Alanine and distilled water. The above was mixed well and heated on a heating mantle and refluxed for two & half-hours. After reflux, the hot mixture was transferred and kept in a beaker at room temperature, over night. The crystalline product, which was found to be insoluble in benzene and chloroform but soluble in hot water, was collected by filtered & dried to remove moisture. The unreacted raw materials were removed by repeatedly shaking with 50ml portions of benzene A.R. and then with 50ml portions of chloroform A. R. filtered, dried and recrystallised from hot water. The pure product was collected by filtration and dried to remove moisture.





Antimicrobial activity

All synthesized compound were screed for antimicrobial activities by Disc Diffusion method using Mueller-Hinton agar medium to study the preliminary antibacterial activity against Escherichia coli, Klebsiella, Staphylococcus epidermitis, Bacillus cereus, Micrococcus leteus, Staphylococcus aureus. The agar medium was purchased in HI media laboratories Ltd., Mumbai, India. Nutrient broth, subculture, base layer medium, agar medium and peptone water were prepared as per the standard procedure. Each test compound was dissolved in 5ml of Dimethyl Sulfoxide (1000ug/ml) Volume of 0.05ml and 0.1ml of each compound were used for testing.

The cup plate method using PDA medium was employed to study the preliminary antifungal activity of C. albicans, A. niger. The PDA medium was purchased from HI media laboratories Ltd., Mumbai, India. Nutrient broth, subculture, base layer medium, agar medium and peptone water were prepared as per the standard procedure. Each test compound was dissolved in 5ml of Dimethyl Sulfoxide (1000ug/ml) Volume of and 1mg/ml of each compound were used for testing. Ciprofloxacin and Ketocanazole were used as standard drug (50 & 100ug/ml) and dimethyl sulfoxide as a control. The observed zone of inhibition was measured in mm and results are present in table1 and2.

Table 1:Antibacterial Activity of Antimetabolites

Drugs	**Conc.**	E.coli	**Kieb.**	**S.Epid**	**B.cereus**	**M.leteus**	**S.aureus**
Ciproflaxacin (Standard)	1mg/ml	-	20	22	20	24	22
Sample: Glutamine Analog (Gu)	1 mg/ml	15	13	15	13	12	12
Glycine Analog (Gy)	1 mg/ml	13	13	13	15	13	12
Alanine Analog (A)	1 mg/ml	12	12	12	13	12	15
Control	DMSO	-	-	-	-	-	-

Table 2: Antifungal Activity of Antimetabolites

Drug	Concentration	Candida albicans	Aspergillus Nigar
Ketaconazole (standard)	1mg/ml	8.25	7.25
Samples: GlutamineAnalog (Gu)	1mg/ml	-	5.25
GlycineAnalog (Gy)	1mg/ml	-	5.21
Alanine Analog (A)	1mg/ml	-	5.40
Control	DMSO	-	-

Results and discussion

In present study a series of amino acid analogs are synthesized. Phthalic anhydride, amino acids and distilled water are used to produce α N-Phthilimido of amino acids(scheme 1,2,3). The structure of the compound was characterized by IR, ^{13}C NMR. All the synthesized compound are active against all micro organisms when compared to standards. From the result it is evident that the compounds Gu, Gy and A exhibit significant antibacterial activity at concentration of 1mg/ml with reference to ciprofloxacin at a 1mg/ml concentration. The compound show significant effect with Aspergillus nigar and on effective against Candid albicans with reference to Ketaconazole at a 1mg/ml concentration.

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