Research Article

[Kumar & Fazal, 2(12): Dec., 2011]

ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

Synthesis, characterization and anti bacterial activity of some novel tryptamines bearing pyrrolidin-2-one moiety

S. Senthil Kumar [1]* and Fazal Mohamed M. I.[2]

1, Department of Chemistry, Srinivasan Engineering College, Perambalur - India

2, Department of Chemistry, Jamal Mohamed College, Tiruchirappalli - India

Abstract

A series of Novel pyrrolo tryptamines were synthesized,characterized and screened for their anti-bacterial activities. The structures of the synthesized compounds were established by 1H-NMR AND ^{13} C-NMR spectroscopic analyses. The anti-bacterial activities of compounds were studied by disc diffusion method. All compounds were tested against three Gram positive and three Gram-negative bacteria. All compounds revealed better results against Gram positive as compared to Gram-negative bacteria. But 4-Amino-5-(5-hydroxy-1H-indol-3-yl)-pyrrolidin-2-one was found most potent compound showing broad spectrum activity when compared with other compounds.

Key-Words: Synthesis, Tryptamines, Pyrrolidin-2-one moiety, Anti-bacterial activity, Disc diffusion method

Introduction

The chemistry of heterocyclic compounds has attracted attention in recent time due to its increasing importance in the field of pharmaceuticals and industries. The substituted tryptamine moiety is an example.Tryptamines are a broad range of compounds that share a common indole ring structure and are found in a wide variety of plant and animal sources[1].Some are naturally occurring neurotransmitters (Serotonin) while the majority are psychoactive hallucinogens (Psilocin, DMT, 5-MeO-DMT).

The presence of pyrrolidine ring is responsible for antimicrobial activity. A survey of the literature revealed that no synthesis of pyrrolidine annulated tryptamine had been reported.

Tryptamine derivatives are used to design β-carbolines, which have a wide diversity of important biochemical effects and pharmacological properties via pictet-spengler[2-6] and Bischler-Napieralski[7-10] condensation reactions.

These observations have stimulated our interest in designing pyrrolidine annulated tryptamines with the hope to get better antibacterial agents. This paper describes work aimed at preparing a series of new pyrrolidine annulated tryptamines. All the synthesized compounds were characterized through various spectral techniques and screened for anti-bacterial activity.

*** Corresponding Author:**

E-mail: senswaan@gmail.com

Material and methods

General

All chemicals and solvents used for this work were of analytical grade and distilled before use. Melting points are determined in open capillaries and are uncorrected. Purity of the compounds was checked by thin layer chromatography (TLC) and spots were developed using iodine vapours as visualizing agents.The 1H NMR and 13C NMR were recorded on Bruker AMX-500 spectrometer operating at 400 MHz using $CDCl_3$ as solvent.

Synthesis of N-Phthalimido-α-hydroxy acetic acid ($C_{10}H_7NO_5$) (1)

Phthalimide (10 g, 68 mmol) was dissolved in THF (200 cm^3) at room temperature with stirring. 50 wt% Glyoxalic acid (30.20 g, 0,204 mol) was added to this solution. The reaction mixture was heated to reflux for 3 Hrs. Evaporation to dryness under reduced pressure produced a cream solid.This was recrystallised from ethyl acetate yielding N-Phthalimido-α-hydroxy acetic acid .**(Scheme-I).**

1:Yield:87%,White powder,m.p 190^O C-191^O C PMR Spectra (CDCl3): δ (ppm) 7.72-8.14 (1H, aromatic),6.32 (-CH), 2.3 (-OH);11.2(-COOH) CMR Spectra (CDCl3): δ (ppm) 127.2-133(benzene), 80.5 (- CH,aliphatic), 177.2(-COOH), 166.1 (C=O of amide)

Synthesis of N-Phthalimido-α-chloro acetic acid ($C_{10}H_6NO_4Cl$) (2)

N-Phthalimido-α-hydroxy acetic acid(2.00 g, 9.0 mmol) was dissolved in dry THF (100 cm^3) at room

temperature with stirring under N_2 atmosphere. The solution was then cooled to 0^{O}C.Thionyl chloride (3.37 g, 28.0 mmol) was added to this solution in a dropwise manner.

Evolution of an acidic gas was observed. The reaction mixture was allowed to warm to room temperature overnight. Ice (10 g) was added and the mixture stirred for 3 Hrs.The solution was extracted using ethyl acetate (3 X 50 cm^3) . The combined organics were dried using MgSO4, filtered and evaporated to give a cream solid. Recrystallisation of the cream solid from Dichloro methane afforded N-Phthalimido-α-chloro acetic acid .**(Scheme-II).**

2:Yield:43%,White powder**,**m.p 147^{O} C-148^{O} C PMR Spectra (CDCl3): δ (ppm) 7.7-8.15 (1H, aromatic),6.43 (-CH), 11.1(-COOH) CMR Spectra (CDCl3): δ (ppm) 127.3-132.4(benzene), 72.3 (-CH,aliphatic), 171.2(-COOH), 166.3 (C=O of amide)

Direct reduction of N-Phthalimido-α-chloro acetic acid in to N-Phthalimido-α- chloro acetaldehyde($C_{10}H_6NO_3Cl$) (3)

N-Phthalimido-α-chloro acetic acid (0.01 mole) was dissolved in dilute acetic acid. To this an equimolar amount of Hexamine (0.01 mole) was added and refluxed in water bath for 2 hrs. The crude N-Phthalimido-α- chloro acetaldehyde was isolated and crystallized from ethyl acetate.

3: Yield:78%,White powderM.P 127ºC-129ºC :PMR Spectra (CDCl3): δ (ppm) 7.70-8.14 (1H, aromatic),6.41 (-CH), 9.73(-CHO) CMR Spectra (CDCl3): δ (ppm) 127.3-132.3(benzene), 80.3 (-CH,aliphatic), 192.2(-CHO), 166.3 (C=O of amide)

General procedure for the synthesis of 2-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-1-chloro-2-(1H-indol-3-yl)-ethyl]-isoindole-1,3-diones(4a-c)

N-Phthalimido-α-chloro acetaldehyde(47.15mmol) was dissolved in 250 cm^3 of CH_3CN and to this solution appropriate indole(47.15mmol),Meldrum's acid and D,L-proline (2.36 mmol) were added under N_2 atmosphere.The reaction mixture was stirred at room temperature for 48 Hrs. The resulting solution was evaporated to dryness under reduced pressure yielded crude product. Purification of the crude product was done by Column chromatography on silica gel.

2-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-1-chloro -2-(1H-indol-3-yl)-ethyl]-isoindole-1,3-dione 4a ($C_{24}H_{19}N_2O_6Cl$) **:**Yield:75%,yellow solid,mp 153ºC-155^{O}C PMRSpectra (CDCl3): δ (ppm) 7.15-8.16 (1H, aromatic),10.2 (-NH), 3.55-4.32(-CH,aliphatic), 1.81(CH_3) CMR Spectra (CDCl3): δ (ppm) 111.2-136.3(aromatic), 38.3-52.4 (-CH,aliphatic), 172.2(-COO),167.5 (C=O of amide) ,26.2(CH_3),

2-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-1-chloro-2-(5-hydroxy-1H-indol-3-yl)-ethyl]-isoindole-1,3-dione 4b($C_{24}H_{19}N_2O_7Cl$) **:**Yield:73%,yellow solid,mp 196ºC-198^{O}C PMRSpectra (CDCl3): δ (ppm) 6.65-8.18 (1H, aromatic),10.1 (-NH),5.1 (-OH) 3.51-4.32(- CH,aliphatic), 1.81(CH_3) CMR Spectra (CDCl3): δ (ppm) 106.7.0-150.3(aromatic), 38.3-52.4 (- CH,aliphatic),172.1(-COO),167.6 (C=O of amide) ,26.2(CH_3),

2-[2-(2,2-Dimethyl-4,6-dioxo-[1,3]dioxan-5-yl)-1-chloro -2-(5-methoxy-1H-indol-3-yl)-ethyl]-isoindole-1,3-dione

4c($C_{25}H_{21}N_2O_7Cl$) **:**Yield:72%,yellow solid,mp 162ºC-164^{O}C PMRSpectra (CDCl3): δ (ppm) 6.71-8.17 (1H, aromatic),10.1 (-NH), 3.52-4.33(- CH,aliphatic), 1.78(CH_3),3.71(-OCH_3) CMR Spectra (CDCl3): δ (ppm) 105.2-155.3(aromatic), 38.3-52.4 (-CH,aliphatic), 172.2(-COO),167.2 (C=O of amide) ,26.3(CH_3),56.1(-OCH_3)

General procedure for the synthesis of 4-1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-4-chloro-3-(1H-indol-3-yl)-butyramides (5a - c)

The appropriate trimolecular adduct[12] (1 mmol) was dissolved in 20 cm^3 of CH_3CN.To this an equimolar amount of NH_3 solution in THF (1 mmol) was added**.** The reaction mixture was stirred under N_2 at 70ºC.The solvent was evaporated under reduced pressure yielded the crude product.Purification was done by column chromatography on silica gel.

4-(3-Allylidene-2,5-dioxo-pyrrolidin-1-yl)-4-chloro-3-(1H-indol-3-yl)-butyramide

5a ($C_{20}H_{16}N_3O_3Cl$)**:** Yield:73%,brown solid , mp 237ºC -239ºC PMR Spectra (CDCl3): δ (ppm) 6.7-8.12 (1H, aromatic),10.1 (-NH), 2.43(-CH_2)3.4-4.1(CH,aliphatic),6.1(amide) CMR Spectra (CDCl3): δ (ppm) 111.2-136.2 (aromatic),39.2(-CH_2,aliphatic) 41.3-55.2 (- CH,aliphatic), 167.6(-C=O),176.6 (amide)

4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-4-chloro-3-(5-hydroxy-1H-indol-3-yl)-butyramide

5b($C_{20}H_{16}N_3O_4Cl$)**:** Yield:72%,brown solid , mp 284ºC -286ºC PMR Spectra (CDCl3): δ (ppm) 6.66-8.14 (1H, aromatic),10.0 (-NH), 2.41(-CH_2)3.3-4.07(CH,aliphatic),6.1(amide),5.1(-OH) CMR Spectra (CDCl3): δ (ppm) 106.8-150.4 (aromatic),39.2(-CH_2,aliphatic) 41.1-55.3 (- CH,aliphatic), 167.4(-C=O),176.6 (amide)

4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-4-chloro-3-(5-methoxy-1H-indol-3-yl)-butyramide

5c($C_{21}H_{18}N_3O_4Cl$) **:** Yield:74%,brown solid , mp 252ºC -254ºC PMR Spectra (CDCl3): δ (ppm) 6.67-8.13 (1H,

aromatic),10.1 (-NH), 2.42(-CH_2)3.3-4.03(CH,aliphatic),6.1(amide),3.72(-OCH_3) CMR Spectra (CDCl3): δ (ppm) 105.2-155.2(aromatic), 39.1(-CH_2,aliphatic) 41.1-55.1 (- CH,aliphatic), 167.5(-C=O),176.6 (amide) ,56.2(-OCH_3)

General procedure for the synthesis of 2-[2-(1H-Indol-3-yl)-5-oxo-pyrrolidin-3-yl]-isoindole-1,3-diones (6a - c)

To a stirred solution of the corresponding butyramide (20 mmol) in dimethylformamide (50 cm^3) at 60°C , was added potassium carbonate (14 mmol).During the stirring (1 Hr) the mixture first cleared up and then the cyclization product began to separate. Water (50 cm^3) was poured to the cooled mixture and the product was filtered off. Yield: 64% of the product recrystallized from chloroform-diethyl ether, m.p.: 248-251 °C.

2-[2-(1H-Indol-3-yl)-5-oxo-pyrrolidin-3-yl]-isoindole-1,3-dione

6a($C_{20}H_{15}N_3O_3$)**:** Yield:66%,brown solid , mp 279°C -281°C PMR Spectra (CDCl3): δ (ppm) 6.82-8.13 (1H, aromatic),10.1 (-NH), 2.45(-CH_2)3.38-3.97(CH,aliphatic),8.1 (-CONH) CMR Spectra (CDCl3): δ (ppm) 111.2-136.6 (aromatic),44.2(-CH_2,aliphatic) 34.3-46.2 (- CH,aliphatic), 167.7(-C=O),174.5 (-CONH)

2-[2-(5-Hydroxy-1H-indol-3-yl)-5-oxo-pyrrolidin-3-yl]-isoindole-1,3-dione

6b($C_{20}H_{15}N_3O_4$)**:** Yield:63%,brown solid , mp 327°C -329°C PMR Spectra (CDCl3): δ (ppm) 6.62-8.14 (1H, aromatic),10.3 (-NH), 2.45(-CH_2)3.38-3.96(CH,aliphatic), 5.0(-OH), 8.1 (-CONH) CMR Spectra (CDCl3): δ (ppm) 106.6-150.2 (aromatic),44.3(-CH_2,aliphatic) 34.5-46.3(-CH,aliphatic), 167.5(-C=O),174.4 (-CONH)

2-[2-(5-Methoxy-1H-indol-3-yl)-5-oxo-pyrrolidin-3-yl]-isoindole-1,3-dione

6c($C_{21}H_{17}N_3O_4$)

: Yield:65%,brown solid , mp 293°C -295°C PMR Spectra (CDCl3): δ (ppm) 6.67-8.14 (1H, aromatic),10.2 (-NH), 2.46(-CH_2)3.37-3.96(CH,aliphatic), 3.6(-OCH_3), 8.0 (-CONH) CMR Spectra (CDCl3): δ (ppm) 105.3-155.2 (aromatic),44.2(-CH_2,aliphatic) 34.5-46.2 (-CH,aliphatic), 167.7(-C=O),174.5 (-CONH), 56.2(-OCH_3)

General procedure for the synthesis of 4-Amino-5-(1H-indol-3-yl)-pyrrolidin-2-ones (7a - c)

The corresponding 2-[2-(1H-Indol-3-yl)-5-oxo-pyrrolidin-3-yl]-isoindole-1,3-diones (1 mmol) were dissolved in 20 cm^3 of n-butyl amine and stirred at 50° C for 24 Hrs under N_2. The solvent was evaporated and the residue was purified by column chromatography on silica gel.

4-Amino-5-(1H-indol-3-yl)-pyrrolidin-2-one

7a($C_{12}H_{13}N_3O$) **:** Yield:64%,brown solid , mp 220°C -222°C PMR Spectra (CDCl3): δ (ppm) 6.82-7.16 (1H, aromatic),10.0 (-NH), 2.46(-CH_2)3.62-4.92(CH,aliphatic), 2.1(-NH_2) ,8.1(-CONH) CMR Spectra (CDCl3): δ (ppm) 111.2-136.6 (aromatic),41.5(-CH_2,aliphatic) 36.6-62.5 (-CH,aliphatic), 174.5 (-CONH)

4-Amino-5-(5-hydroxy-1H-indol-3-yl)-pyrrolidin-2-one 7b($C_{12}H_{13}N_3O_2$) **:** Yield:62%,brown solid , mp 271°C -273°C PMR Spectra (CDCl3): δ (ppm) 6.64-7.03 (1H, aromatic),10.3 (-NH), 2.45(-CH_2)3.62-4.93(CH,aliphatic), 5.1(-OH),2.0 (-NH_2) ,8.2 (-CONH) CMR Spectra (CDCl3): δ (ppm) 106.6-150.3 (aromatic),41.2(-CH_2,aliphatic) 36.3-62.3 (-CH,aliphatic), 174.6 (-CONH)

4-Amino-5-(5-methoxy-1H-indol-3-yl)-pyrrolidin-2-one 7c($C_{13}H_{15}N_3O_2$): Yield:62%,brown solid , mp 232°C -234°C PMR Spectra (CDCl3): δ (ppm) 6.68-7.09 (1H, aromatic),10.2 (-NH), 2.46(-CH_2)3.61-4.92(CH,aliphatic), 3.5(-OCH_3), 2.1(-NH_2),8.2(-CONH) CMR Spectra (CDCl3): δ (ppm) 105.3-155.3 (aromatic),41.3(-CH_2,aliphatic) 36.5-62.2 (CH,aliphatic), 174.5 (-CONH), 56.1(-OCH_3)

Anti-bacterial activity

The antimicrobial activity of newly synthesized compounds was evaluated according to the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS, 1997) using the agar disc diffusion method .Briefly, pyrrolo tryptamines (7a-c) were dissolved in DMSO (2%) to obtain concentration of 10mg/ml. The solutions (0.02ml) were impregnated on sterile paper disc of 6mm diameter and discs were let to dry to remove any residual solvent which might interfere with the determination. The solvent control (DMSO (2%) did not show any antimicrobial activity. Seeded agar plates were prepared and inoculated with 0.1ml of inoculum; discs were then placed on the seeded agar plates. Plates were incubated at 35 °C for 18-20 hours. The zones of growth inhibition around the disc were measured after 18-20 hours of incubation. Experiment was performed in duplicate.

Results and Conclusion

Chemistry

N-Phthalimido-α-hydroxy acetic acid[11] **1** was conveniently prepared by the reaction between Phthalimide and Glyoxalic acid(scheme 1).The acid was then chlorinated with thionyl chloride to give the corresponding chloro substituted acid **2** (scheme 2).The aldehyde **3** was obtained by the reduction of **2** with hexamine in aqueous acetic acid medium(scheme 3). Condensation of N-Phthalimido-α-chloro

acetaldehyde with indole and Meldrum's acid smoothly gave the trimolecular adduct[12] **4, in** good yield (scheme 4).Transformation of **4** in to amide **5** through Nucleophilic cleavage of the Meldrum's ring was achieved by aminolysis(scheme 5). Cyclo dehydrochlorination[13] of **5** with potassium carbonate in DMF yielded the cyclization product **6**(scheme 6). Deprotection of the phthalimido group of **6** yielded the corresponding pyrrolidine annulated tryptamines[14-17].Their structures were confirmed by analytical and spectral data. The proton magnetic resonance spectra of the prepared compounds (7a-c) shows signal at 2 δ for amine proton,a signal at10 δ for -NH protons in the pyrrole ring and a signal at 8 δ confirms the presence of -NH protons in the pyrrolidine ring . All other signals are at their respective positions in the PMR spectrum. The CMR spectra of the compounds also show the signal at 174 δ and 41 δ for -CONH and $-CH_2$ in the pyrrolidine ring respectively .All other signals appeared at their respective positions.

Table 1: Physicochemical data of the synthesized pyrrolo tryptamines

Compound no.	Molecular formula	M.P. °C	% Yield
7a	$C_{12}H_{13}N_3O$	220°C - 222°C	64%,
7b	$C_{12}H_{13}N_3O_2$	271°C - 273°C	62%,
7c	$C_{13}H_{15}N_3O_2$	232°C - 234°C	62%

The results of the antibacterial screening of the synthesized pyrrolo tryptamines are shown in table.

The antibacterial activity was evaluated by disc diffusion method[18]. All compounds were tested against three Gram positive and four Gram- negative bacterial strains.

According to the table compound **7b** showed good activity against all tested Gram-positive and Gram-negative bacteria.

These results indicated that presence of hydroxyl functional group in phenyl ring is not only responsible for the antibacterial activity, but also showing good effect indicating by greater inhibition zone.

All the experiments reported here together with the previous studies of others have left no room for doubt that the compounds (7a,7b,7c) reported in this study are newly designed compounds.

The results of anti-bacterial screening of the synthesized compounds revealed that the observed increase in ant-bacterial activity of 7b is attributed to the presence of hydroxyl group in phenyl ring.

This study may also provide a route for designing1, 2, 3, 4-tetrahydro- or 3, 4-dihydro-β-carbolines having pyrrolidine moiety via pictet-spengler and Bischler-Napieralski condensation reactions.

Acknowledgements

The authors are grateful to the Head, SAIF, IIT-Madras for providing spectral and analytical data of the compounds. They are greatly acknowledging the support from Dept. of Microbiology, Periyar College of Pharmaceutical Sciences for Girls, Trichy for anti-bacterial activity assessment.

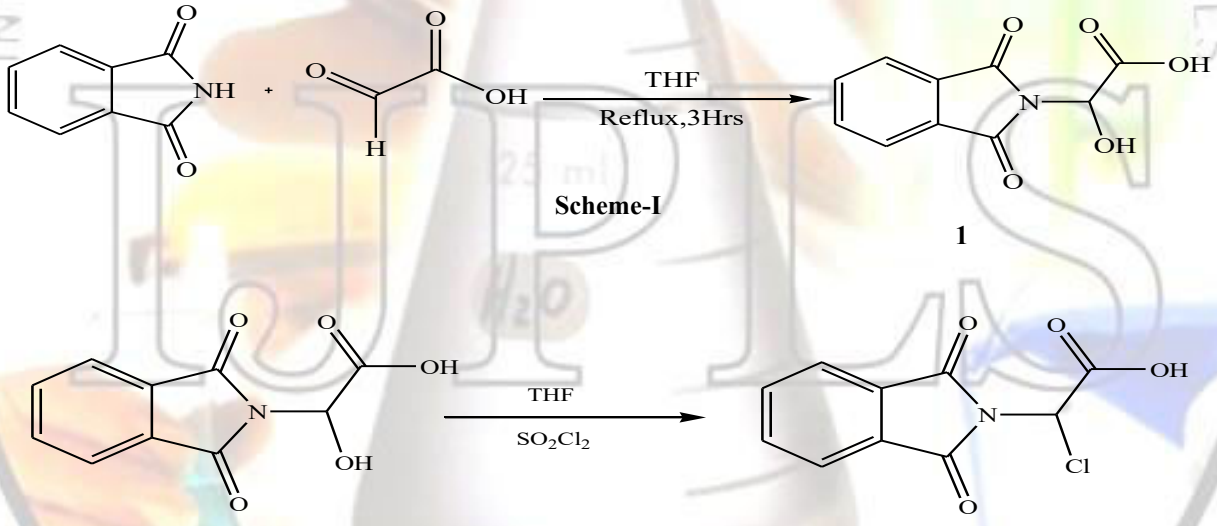
References

1. Shulgin Alexander and Perry W.E. (2002).Transform Press, Berkeley, CA A. Pictet, T. Spengler, *Chem. Ber.*, **44**: 2030
2. Whaley W. M. and Govindachari T. R. (1951). *Organic Reactions*, 6: 151
3. Cox E. D. and Cook J. M. (1995). *Chem. Rev.* **95**: 1797**.**
4. Larghi E. L., Amongero M., A. Bracca B. J. and Kaufman T. S. (2005). *ARKIVOC*, **12**: 98**.**
5. Lewis S. E. (2006). *Tetrahedron*, **62**: 8655.
6. Bischler A. and Napieralski B. (1893). *Chem.Ber*., **26:** 1903-1908.
7. Kayed A. Abu-Safieha, Mustafa M. El-Abadelaha, Salim S. Sabria, Wolfgang Voelterb, Cäcilia M. Mössmerc, and Markus Stroebelec *Z.* (2002). *Naturforsch*. **57b**: 1327-1332
8. Marcos D. Garc´ıa, A. James Wilson, Daniel P. G. Emmerson, Paul R. Jenkins, Sachin Mahale and Bhabatosh Chaudhuri (2006). *Org. Biomol. Chem.*, **4**: 4478–4484
9. Movassaghi M. and Hill M. D (2008). *Org. Lett.*, ***10*****:** 3485-3488.
10. Peter S Hadfielda, Lorraine A Caseya, Ronald H B Galtb, Bartholomew Vilanovaa and Michael I Pagea (2002). *ARKIVOC* **(6)**: 125-144
11. Boisbrun M,Jeannin L, Toupet L and Laronze JY (2000). *Eur J Org Chem ,* 3051.
12. Hesek D and Rybfir A (1994). *Monatshefte fiir Chemie,* **125**: 1273-1278
13. Jeannin L, Nagy T, Vassileave E, Sapi J, Laronze (1995). *Tetrahedron Lett* **36**, 2057
14. Renault J, Fabis F, Dauphin F, Lebranchu M, Le Roche M, Butt S, Uriac P and Rault S (2001). *J Pharm Pharmacol* **53**: 969
15. Hinschberger A, Gillard AC, Dauphin F, Rault S. (2000). *Pharm Pharmacol Commun* **6**: 67.

16. Hinschberger A,Butt S,Lelong V,Boulouard M,Dumuis A,Dauphin F, Bureau R,Pfeiffer B, Renard P, Rault S (2003). *J Med Chem,* **46**: 138.
17. National Committee for Clinical Laboratory Standards. *NCCLS Approved Standard M27-A.*
18. Wayne: Pennsylvania, PA, USA, 1997.

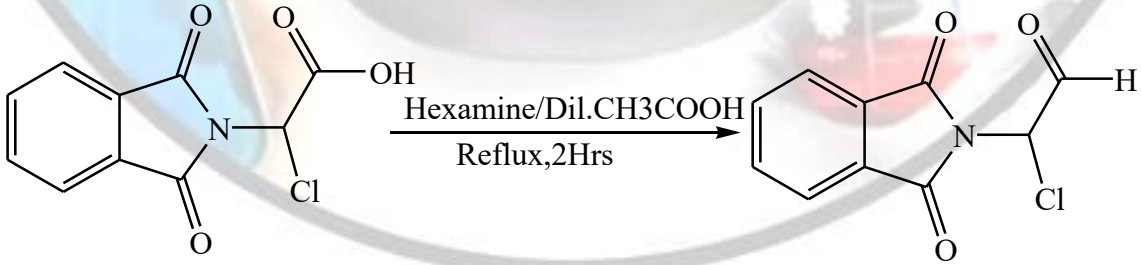
Table 2: Anti-bacterial activity of pyrrolo tryptamines by disc diffusion method

Microorganisms	Values of diameters of inhibition zones in mm		
Gram Positive	7a	7b	7c
Bacillus subtilis	6	19	12
Corneybacterium diphteriae	10	20	14
Staphylococcus aureus	9	17	11
Gram Negative			
Escherichia coli	9	18	15
Salmonella typhi	5	15	10
Klebsiella pneumoniae	8	16	11



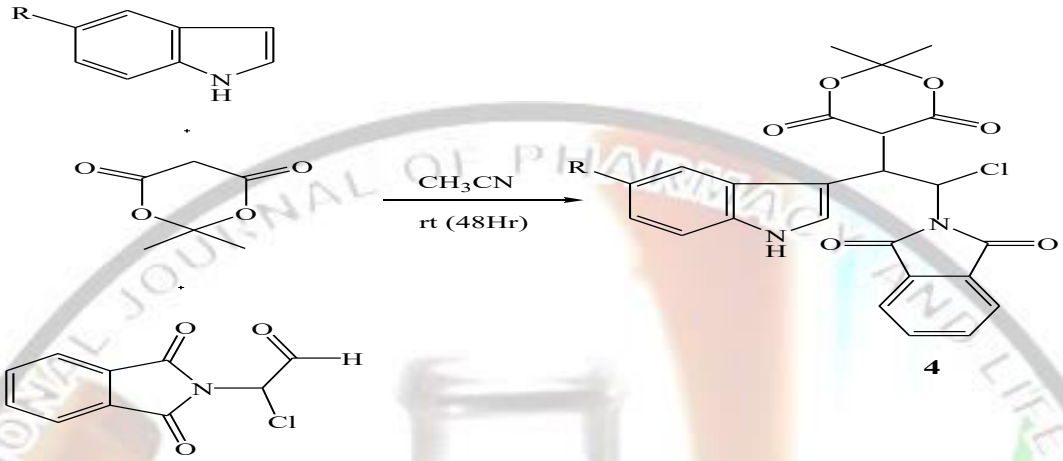
Scheme-I **1**

Scheme-II **2**



Scheme-III **3**

ISSN: 0976-7126



4

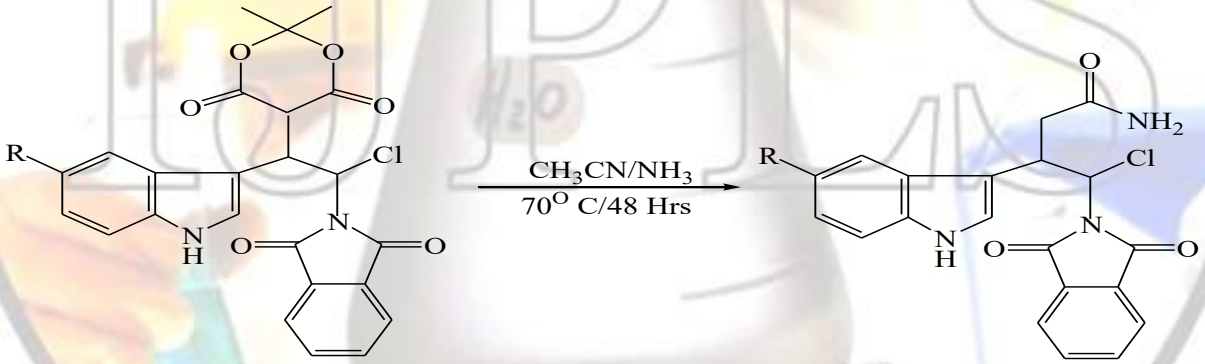
R = H,OH,OCH_3

R=H ; 4a

R=OH ; 4b

R=OCH_3 ; 4c

Scheme-IV



5

R = H,OH,OCH_3

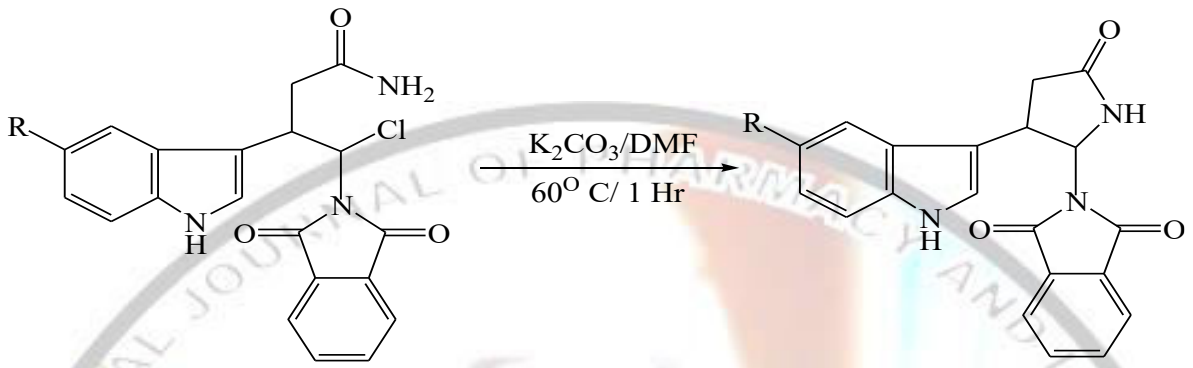
R=H ; 5a

R=OH ; 5b

R=OCH_3 ; 5c

Scheme-V

ISSN: 0976-7126



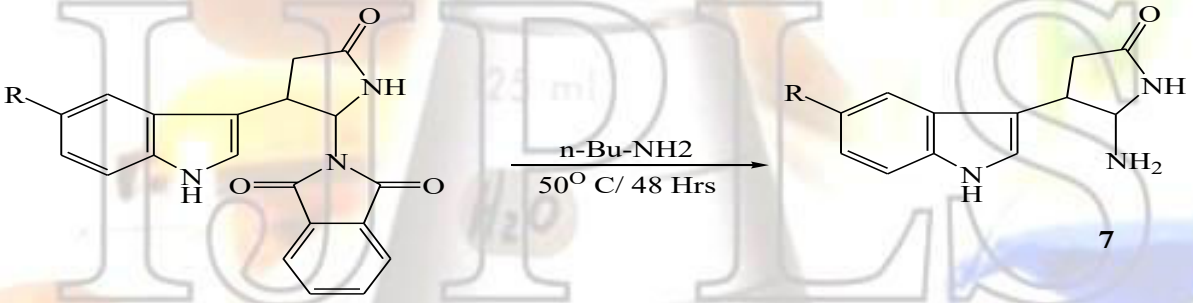
6

R=H ; 6a

R=OH ; 6b

R=OCH3 ; 6c

Scheme-VI



7

R = H,OH,OCH_3

Scheme-VII

R=H ; 7a

R=OH ; 7b

R=OCH3 ; 7c