International Journal of Researches In Biosciences, Agriculture & Technology | Feb. 2015 Special Issue-1 | ISSN No. (Online) 2347-517X

Route A Facile Of 8-[2/-(3//, 5//-Dimethyl-4//-Ethoxy Carbonyl Pyrrolyl) Hydrazine] Substituted Phenothiazines Derivatives

M. N. Narule[1], K. M. Baste[2],Tasneem K.H. Khan[3], Y. A. Hatwar[4] and S. V. Garhate[5]

[1]Vidya Vikas Art, Commerce andScience College, Samudrapur, Dist-Wardha, 442305, India
[2]*Pravara Rural Engineering College, Loni.*
[3]Anjuman Engineering college, Nagpur.
[4]*Mata Mahakali polytechnic College, Chandrapur.*
[5]*Hislop college, Nagpur.*
meghasham_n@rediffmail.com

Abstract:

A short facile synthesis of 8-[2/-(3//, 5//-dimethyl-4//-ethoxy carbonyl pyrrolyl) hydrazine] substituted phenothiazines from 2-arylamin benzal-2-(3′, 5′- dimethyl - 4′ - ethoxy carbonyl pyrrole) hydrazines in presence of sulphur and iodine. These compounds were screened for their antibacterial activity against S. aureus and E. coli as well as for their antifungal activity against C. albicans and A. niger. The synthesized compounds are characterized by FTIR, ^{1}H NMR,C^{13}NMR, elemental and chemical properties.

Keywords: 4′-diethoxy carbonyl pyrrole, iso-semicar bazide, treated, E. coli.

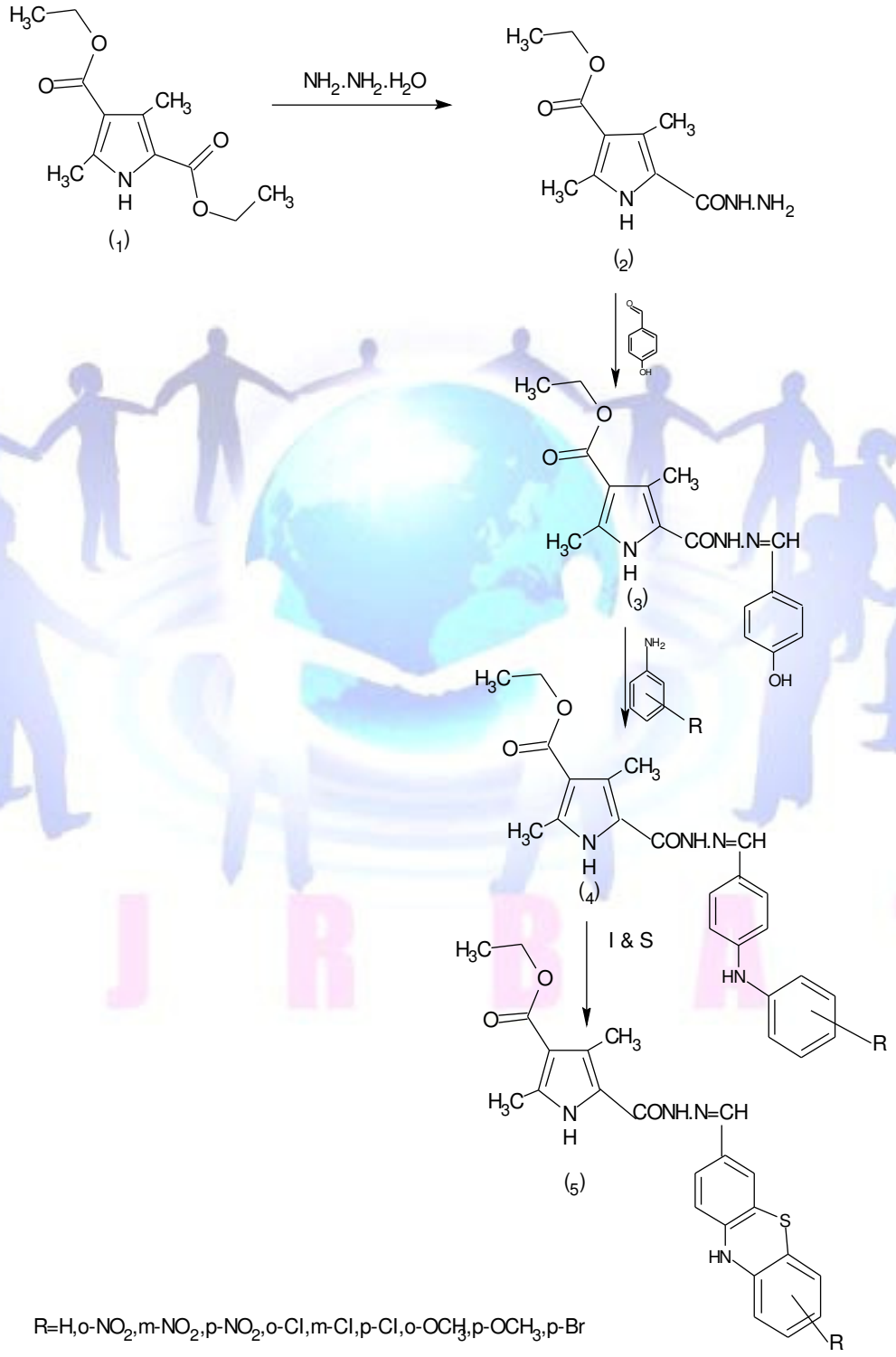
Introduction:

Heterocyclic compounds are organic compounds containing at least one atom of carbon and at least one element other than carbon, such as sulfur, oxygen or nitrogen within a ring structure. Since in heterocycles non-carbons usually are considered to replace carbon atoms, they are called heteroatoms e.g. different from carbon and hydrogen. A ring with only heteroatoms is called homocyclic compound and heterocycles are the counterparts of homocyclic compounds. Heterocyclic chemistry is one of the branches of Medicinal Chemistry and large numbers of heterocyclic compounds are successfully used as antimicrobial agents. Heterocyclic systems are encountered in many groups of organic compounds possessing great applicability in several industries as well as other aspects of life. Pyrroles exhibit interesting biological properties[1-3]. Inaddition, Phenothiazines are well known CNS depressant compounds and have emerged as an important area of research for the biological activities like antiparkinsonian[1], anticonvulsant[2], antihistaminic[3], antihelmatic[4-5], antiviral[6], anti-parasitic activities[8]. In view of these observations it was thought worthwhile to synthesized and investigate the compounds in which pyrrole derivative have been linked with phenothiazine moiety. We report in this paper, thesynthesis and pharmacological investigation of 8-[2/-(3//, 5//-dimethyl-4//-ethoxy carbonyl pyrrolyl) hydrazine] substituted phenothiazines **(5) (scheme-I)**.

Result and Discursion:

The required starting material 3′, 5′-dimethyl-2′, 4′-diethoxy carbonyl pyrrole **(1)** has been prepared by reported method[15]. The compound **(1)** was refluxed with hydrazine hydrate to yield 2-(3′, 5′ dimethyl-4′- ethoxy carbonyl pyrrole) acid

hydrazide **(2)**.The compound (2) which reacts with 4-hydroxy benzaldehyde in presence of ethanol for 8 hr to get the desired iso-semicar bazide **(3).** The compound **(3)** was condensed with different aryl amines by refluxing in ethanol to get 2-arylamin benzal-2-(3′,5′-dimethyl-4′-ethoxy carbonyl pyrrole) hydrazine **(4).** The compound (4) was treated with sulphur and iodine to yield 8-[2/-(3//, 5//-dimethyl-4//-ethoxy carbonyl Pyrrolyl) hydrazine] substituted Phenothiazines **(5a-j).**



Scheme-I

Biological Activities:

Comparative study of 3, 5 dimethyl-2, 4-diethoxy carbonyl pyrrole **(1)** and 1-Phenothiazine-2--(3′, 5′dimethyl-4′ethoxy carbonyl pyrrolyl) hydrazines **(5a-j)** have been observed by using Norfloxacine and Griseofulvine as standards. The enhancement in biological activity of compound **(1)** as compared with the newly synthesized **(5a-j)** has been observed. The synthesized compounds were tested at 100□g/ml concentration against *Escherichiacoli, Staphylococcusaureus*, *Ps. acruginosa*, *P.vulgaris*, *A.niger* and *C. albicans* for its antibacterial and antifungal screening as shown in Table-I.

2-(3', 5'-Dimethyl-4'-ethoxy carbonyl pyrrole) acid hydrazide (2)

3, 5-Dimethyl-2, 4-diethoxy carbonyl pyrrole (1) (0.05 mole), hydrazine hydrate (1.0mL, 99%), and ethanol (20mL) were taken in a 100mL round bottom flask. The reaction mixture was refluxed for 4hr.on water bath. The reaction was checked by thin layer chromatography. The mixture was evaporated to its half and left over night. The product precipitated was filtered, washed with water, dried and crystallized from ethanol. Yield 70%: M.P.216°C: IR (KBr): 3153(NH), 1621(CONH), 1712($COOC_2H_5$), 1322($-CH_3$):^{1} HNMR (300MHz DMSO) δ7.82–7.91(m, 3H, $CONHNH_2$), 8.9(1H, s, Pyrrole - NH).

4-Hydroxybenzal-2-(3′, 5′dimethyl-4′ethoxy carbonyl pyrrolyl) hydrazines (3)

A mixture of 2-(3′, 5′-dimethyl-4′-ethyl carbonyl pyrrole) acid hydrazide**2** (0.01 mole) and p-hydroxy aldehyde in appropriate amounts in excess of DMF was magnetically stirred for 8 hours. The resulting mixture was allowed to stand for 1 hour keeping the internal temperature between 5 – 10°C. The mixture was refluxed for 3 hours. The solvent was removed under vacuum to obtain the crude product which was washed with water followed by ethanol (10ml) and crystallized from appropriate solvents (70% aqueous ethanol).M.P. 187°, yield 72%. ; IR(KBr): 3393.0(OH), 3306.3 (N-H), 1693.8 (C=O, ester), 1682 (C=N, azomethine), 1573.5(-CONH).□$_H$ 2.10(6H, s, 2 x CH_3), 3.31(5H, m, COO CH_2CH_3), 3.42 (1H, s, CH=N), 8.93(1H, s, 2-OH), 8.1(4H, ArH); ^{13}C NMR(300MHz, DMSO-d_6) 36.93, 39.20, 39.48, 39.76, 40.03, 77.74, 78.18, 78.62, 116.13, 117.4, 118.9, 131.09, 132.51, 158.60, 163.02.

2-Aryl amine benzal-2-(3′, 5′dimethyl-4′ethoxy carbonyl pyrrolyl) hydrazines (4)

A mixture of 4-hydroxy benzal-2-(3′, 5′dimethyl-4′ethoxy carbonyl pyrrolyl) hydrazines(3) (0.05mole) and an aromatic primary amine (0.05mole) in absolute ethanol (100ml) was heated under reflux in the presence of anhyd. $ZnCl_2$ (0.5g) for 3 hr. on a water bath.On cooling a solid mass separated out which was washed repeatedly with acidified water to remove inorganic materials. It was filtered off, dried and crystallized from ethanol. (M. P. 170° yield 72%.). IR(KBr): 3342.6(N – H-pyrrole), 1792.9(CONH), 1712($COOC_2H_5$), 1650(-C=O, ester). !649 (N-H-Bridge) 1322($-CH_3$); H^{1}NMR (300MHz DMSO) δ 2.56(6H, s, 2 x CH_3), 4.28(5H, q, $COOCH_2CH_3$), 3.54(1H, s, -CONH); ^{13}C NMR(300MHz, DMSO-d_6), 11.3, 13.4, 13.9,

27.0, 38.9, 39.2, 39.5, 39.7, 40.0, 40.3, 58.5, 76.8, 77.2, 77.6, 111.8, 119.1, 126.2, 137.3, 162.2, 165.0.

8-[2/-(3//, 5//-dimethyl-4//-ethoxy carbonyl pyrrolyl) hydrazine] substituted phenothiazines (5a)

A mixture of **(4)** (0.01mole) sulphur (0.1 mole) and Iodine (0.5 g) was rapidly heated at 180^{0}c in an oil bath and this temperature was maintained for 2 hr. The hot melt was rapidly poured in to a mortar and crushed to a fine powder. It was washed with water dried and crystallized from ethanol containing animal charcoal. (M. P. 215° yield 80%). IR(KBr): 3344.6 (N – H-pyrrole), 3320 (N-H-phenothiazine), 2967 (C-H-Aromatic stretch), 1792.9 (CONH), 1714 ($COOCH_2CH_3$), 1650 (-C=O, ester), 1332 ($-CH_3$), 785 (C-S); H^1NMR (300MHz DMSO) δ 2.56(6H, s, 2 x CH_3), 4.28(5H, q, COO CH_2CH_3), 3.54(1H, s, -CONH); ^{13}C NMR(300MHz, DMSO-d_6) 12.3, 13.4, 13.9, 27.0, 38.9, 39.2, 39.5, 39.7, 40.0, 40.3, 58.5, 76.8, 77.2, 77.6, 111.8, 119.1, 126.2, 137.3

5b: (M. P. 224° yield 65%). IR(KBr): 3342.6(N – H-pyrrole),3323 (N-H-phenothiazine), 2965 (C-H-Aromatic stretch), 1792.9(CONH), 1714 (COO CH_2CH_3), 1650(-C=O, ester), 1555 ($-NO_2$)1514 ($-NO_2$) 1332($-CH_3$), 785 (C-S); H^1NMR (300MHz DMSO) δ 2.56(6H, s, 2 x CH_3), 4.28(5H, q, COO CH_2CH_3), 3.54(1H, s, -CONH); ^{13}C NMR(300MHz, DMSO-d_6) 14.3, 13.5, 13.6, 22.0, 37.9, 38.2, 34.5, 39.4, 40.0, , 58.5, 76.8, 77.2, 77.6, 111.8, 159.1, 126.2, 137.3, 162.2, 162.1.

5c: (M. P. 212° yield 62%). IR(KBr): 3342.6(N – H-pyrrole),3324 (N-H-phenothiazine), 2967 (C-H-Aromatic stretch), 1792.9(CONH), 1714 ($COOC_2H_5$), 1650(-C=O, ester), 1552 ($-NO_2$), 1332($-CH_3$), 785 (C-S); H^1NMR (300MHz DMSO) δ 2.56(6H, s, 2 x CH_3), 4.28(5H, q, COO CH_2CH_3), 3.54(1H, s, -CONH); ^{13}C NMR(300MHz, DMSO-d_6), 11.3, 13.4, 13.9, 27.0, 38.9, 39.2, 39.5, 39.7, 40.0, 40.3, 58.5, 76.8, 77.2, 77.6, 111.8, 119.1, 126.2, 137.3, 162.2, 165.0.

5d (M. P. 267° yield 68%). IR(KBr): 3346.(N – H-pyrrole),3324 (N-H-phenothiazine), 2967 (C-H-Aromatic stretch), 1792.9(CONH), 1714 (COO CH_2CH_3), 1650(-C=O, ester), 1553 (-NO2), 1336($-CH_3$), 785 (C-S); H^1NMR (300MHz DMSO) δ 2.56(6H, s, 2 x CH_3), 4.28(5H, q, COO CH_2CH_3), 3.54(1H, s, -CONH);^{13}C NMR(300MHz, DMSO-d_6) 11.3, 13.4, 13.9, 27.0, 38.9, 34.2, 39.5, 39.7, 40.0, 40.3, 58.5, 76.8, 77.2, 77.6, 111.8, 119.1, 126.2, 137.3, 162.2, 164.6.

5e (M. P. 238° yield 70%). IR(KBr): 3442.6 (N – H-pyrrole),3327 (N-H-phenothiazine), 2967 (C-H-Aromatic stretch), 1792.9 (CONH), 1714 ($COOC_2H_5$), 1650 (-C=O, ester), 1332 ($-CH_3$), 785 (C-S), 706 (-Cl); H^1NMR (300MHz DMSO) δ 2.56 (6H, s, 2 x CH_3), 4.28 (5H, q, COO CH_2CH_3), 3.54 (1H, s, -CONH);^{13}C NMR(300MHz, DMSO-d_6), 11.3, 13.4, 13.9, 27.0, 38.9, 34.2, 39.5, 39.7, 40.0, 40.3, 58.5, 76.8, 77.2, 77.6, 111.8, 119.1, 126.2, 137.3, 162.2, 165.3.

5f (M. P. 245° yield 58%). IR(KBr): 3342.6 (N – H-pyrrole),3320 (N-H-phenothiazine), 2960 (C-H-Aromatic stretch), 1792.9 (CONH), 1714 (COO CH_2CH_3), 1650 (-C=O, ester), 1332 ($-CH_3$), 785 (C-S) 736 (-Cl); H^1NMR (300MHz DMSO) δ 2.56 (6H, s, 2 x CH_3), 4.28 (5H, q, COO CH_2CH_3), 3.54(1H, s, -CONH); ^{13}C

NMR(300MHz, DMSO-d_6), 11.3, 13.4, 13.9, 27.0, 38.9, 39.2, 39.5, 39.7, 40.0, 40.3, 58.5, 76.8, 77.2, 77.6, 111.8, 119.1, 126.2, 137.3, 162.2, 165.1.

5g (M. P. 217° yield 55%). IR(KBr): 3348.6(N – H-pyrrole),3326 (N-H-phenothiazine), 2967 (C-H-Aromatic stretch), 1792.9(CONH), 1714 (COO CH_2CH_3), 1650(-C=O, ester), 1332(-CH_3), 785 (C-S),726 (-Cl); H^1NMR (300MHz DMSO) δ 2.56(6H, s, 2 x CH_3), 4.28(5H, q, COO CH_2CH_3), 3.54(1H, s, -CONH); ^{13}C NMR(300MHz, DMSO-d_6), 11.3, 13.4, 12.9, 25.0, 38.9, 39.2, 39.5, 39.7, 40.0, 40.3, 58.5, 76.8, 77.2, 77.6, 111.8, 119.1, 123.2, 137.3, 164.2, 165.3.

5h (M. P. 209° yield 66%). IR(KBr): 3452.6 (N – H-pyrrole),3352 (N-H-phenothiazine), 2969 (C-H-Aromatic stretch), 1792.9(CONH), 1714 (COO CH_2CH_3), 1650 (-C=O, ester), 1332 (-CH_3), 785 (C-S); H^1NMR (300MHz DMSO) δ 2.56(6H, s, 2 x CH_3), 4.28(5H, q, $COOCH_2CH_3$), 3.54 (1H, s, -CONH); ^{13}C NMR(300MHz, DMSO-d_6), 11.3, 13.4, 13.9, 27.0, 38.9, 39.2, 39.5, 39.7, 40.0, 40.3, 58.5, 76.8, 77.2, 77.6, 111.8, 119.1, 126.2, 137.3, 162.2, 165.0.

5i (M. P. 251° yield 92%). IR (KBr): 3362.6 (N – H-pyrrole), 3390 (N-H-phenothiazine), 2967 (C-H-Aromatic stretch), 1792.9 (CONH), 1714 (COO CH_2CH_3), 1650 (-C=O, ester), 1339 (-CH_3), 785 (C-S). H^1NMR (300MHz DMSO) δ 2.56 (6H, s, 2 x CH_3), 4.28 (5H, q, COO CH_2CH_3), 3.54 (1H, s, -CONH),^{13}CNMR(300MHz,DMSOd_6),11.3,13.4,13.9,27.0,38.9,39.2,39.5,39.7,40.0,40.3,58.5,6.8,77.2,77.6,111.8,119.1,126.2,137.3,162.2..

5j (M. P. 218^{0}yield 71%). IR (KBr): 3362.6(N – H-pyrrole),3332 (N-H-phenothiazine), 2961 (C-H-Aromatic stretch), 1792.9(CONH), 1714 (COO CH_2CH_3), 1650(-C=O, ester), 1332(-CH_3), 785 (C-S), 518 (-Br); H^1NMR (300MHz DMSO) δ 2.56(6H, s, 2 x CH_3), 4.28(5H, q, COO CH_2CH_3), 3.54(1H,s,CONH);^{13}CNMR(300MHz,DMSOd_6),11.3,13.4,13.9,7.0,38.9,9.2,39.5,39.7, 40.0,40.3,58.5,76.8,77.2,77.6,111.8,119.1,126.2,137.

Table. 2 - Characterization of data of Newly synthesized compounds

Compound	Molecule Formula	Mol. Wt.	RF Value	R	M.P. (°C)	Yield (%)	Analysis (Cal) (found)		
							C	H	N
5a	$C_{23}H_{22}O_3N_4S$	434.06	0.36	H	215°	80%	65.70 (65.8)	5.0 (5.95)	12.9 (12.0)
5b	$C_{23}H_{21}O_5N_5S$	479.06	0.24	2-NO_2	224°	65%	56.61 (56.9)	4.3 (4.20)	14.6 (14.7)
5c	$C_{23}H_{21}O_5N_5S$	479.06	0.91	3-NO_2	212°	62%	56.61 (56.9)	4.3 (4.20)	18.70 (18.7)
5d	$C_{23}H_{21}O_5N_5S$	479.06	0.71	4-NO_2	267°	68%	56.61 (56.9)	4.3 (4.20)	18.70 (18.7)
5e	$C_{23}H_{21}O_3N_4SCl$	468.06	0.37	2-Cl	238°	70%	58.9 (58.7)	4.4 (4.3)	11.9 (11.4)
5f	$C_{23}H_{21}O_3N_4SCl$	468.06	0.48	3-Cl	245°	58%	58.9 (58.7)	4.4 (4.3)	11.9 (11.4)
5g	$C_{23}H_{21}O_3N_4SCl$	468.06	0.36	4-Cl	217°	55%	58.9 (58.7)	4.4 (4.3)	11.9 (11.4)

5h	$C_{24}H_{23}O_4N_4S$	463.06.	0.87	2-OCH_3	209°	66%	62.1 (62.0)	4.9 (4.9)	12.09 (12.6)
5i	$C_{24}H_{23}O_4N_4S$	463.06.	0.11	4-OCH_3	251°	92%	62.1 (62.0)	4.9 (4.9)	12.09 (12.6)
5j	$C_{23}H_{20}O_3N_4SBr$	511.96	0.92	4-Br	218⁰	71%	53.9 (53.6)	3.9 (3.4)	10.9 (10.7)
* Eluents for TLC : ethyl acetate – acetone (6 : 4) for **5a, 5b, 5c,5e** ; ethyl acetate – chloroform (8:2) for 5d, 5f, 5g , 5h, 5i, 5j. ★ Solvent for crystallization ; aq. ethanol for **5a –j.**									

Table. I– Data for in vitro antibacterial and anti Fungal activities (in mm) (NA=not active, --=no inhibition of growth)

Comp.	Minimum inhibitory concentration's µg/ml					
	E. *Coli*	S. *aurous*	Ps. *aeruginoa*	P. *Vulgaris*	A.*niger*	C. *albicans*
5a		10	15	14	16	15
5b	11	9	10	12	22	12
5c	16	10	11	13	19	NA
5d	13	9	10	11	17	NA
5e	14	12	13	-	12	22
5f	15	11	-	9	-	21
5g	9	-	7	-	-	-
5h	NA	10	5	8	NA	11
5i	12	9	NA	10	18	NA
5j	17	7	-	14	12	-

Conclusion:

A series of 8-[2/-(3//, 5//-dimethyl-4//-ethoxy carbonyl pyrrolyl) hydrazine] substituted phenothiazines**(5a-j)**from 2-arylamin benzal-2-(3′, 5′-dimethyl-4′-ethoxy carbonyl pyrrole) hydrazines**(4)**in presence of sulphur and iodine. These compounds were screened for their antibacterial activity against *S. aureus* and *E. coli* as well as for their antifungal activity against *C. albicans* and *A. niger* Showing good result.

Acknowledgement:

One of the author M. N. Narule is thankful to Dr. R. R. Bobhote, principal, VidyaVikas Arts, Commerce and Science College, Samudrapur for providing necessary facility for the complexion of this research work. The authors are also thankful to the Head, Department of Pharmaceutical Science Nagpur University for screening anti-microbial activities, Head RSIC, CDRI, Lucknow for providing the spectral data of the compounds.

References:

[1] **Sundberg R. J,** The chemistry of indoles, (Academic press, New york), (970).

[2] **Hibino S and Chazi T,** Nat prod. Rep. 66, (2001).

[3] **Ayd (IIr) FJ,** Disease of nervous system, 23, 29-32, (1968).

[4] (a) **Clane NT, Witten LK and Eilmer DS,**Austver J, 23, 344, (1947).
(b) **Clane NT,**Aust vet J, 23, 340-344, (1947).

[5] **Douglass JR, Baker NF and Langhwest MW,** Am J. vet, Res,17, 318-321, (1956).

[6] **Ddhlbom R and Ekstramd T,** Arch Intern pharmacodynamics, 159,70-74, (1966).

[7] **Well CS,** Biometrics, 8, 249-252, (1952).

[8] **Collier H OJ,** Nature.146, 232-236, (1940).

[9] **Karreman G, Isenberg I and Szent-Gyorgyi A**, science, 130, 1191-1193, (1959).

[10] **Harwood PD, Jestad AC and swanson LE,** J parasital, 24, 16-18, (1938).

[11] **Kalinowsky LB and Hoch PH** somatic treatment in phychiatry (Grune and Stratton) New York, London. (1961).

[12] **Fischer H,**Org.Syn. Coll. Vol-II, 202(1943).