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SYNTHESIS OF TRIAZOLE SUBSTITUTED PHENOTHAZINE DERIVATIVE FOR THEIR ANTIMICROBIAL AND ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT

The synthesis, structure and biological activity of phenothiazine derivative. The triazole substituted phenothiazine has been of keen interest biological activity such as antimicrobial, anti inflammatory. The antimicrobial activity of synthesized compound had been done by using cup plate agar diffusion method and anti inflammatory activity of synthesized compound had been done by using carrageenan induced Rat hind paw method.

KEYWORDS: Antimicrobial activity, Anti-inflammatory activity, carrageenan induced Rat hind paw method, cup plate agar diffusion method.

INTRODUCTION

Inflammation- This is the complex biological response of vascular tissue to harmful stimuli such as pathogen damaged cells, irritants, Inflammation is protective by the organism to remove the injurious stimuli as well as initiate the healing process for the tissue.

Antimicrobial- Initially the term chemotherapeutics agent was restricted to synthesis compound but now since many antibiotic and their analogues have been synthesized this criterion has become irrelevant, both synthetically and microbiologically produced.[1-3]

MATERIALS AND METHODS

Reagents: All the chemicals were purchased from Merck research chemicals pvt. Ltd. all are of synthesis grade.

Synthesis of 4-(cyclohexylidine domino) benzoic acid

Equimolar amount of substituted p-amino benzoic acid added to cycloxexanone and heated under refluxed for 1 hr, cool the mixture by addition of water.

Synthesis of ethyl 4(cyclohexylidine domino) benzoate

Equimolar amount of substituted 4-(cyclohexylidine domino) benzoic acid was added to ethyl alcohol and heated under refluxed for 1 hr.; cool the mixture by addition of water.

Synthesis of4 (cyclohexylidinedomino) benzohydrazide

Equimolar amount of substituted ethyl 4-(cyclohexylidine domino) benzoate was added to hydrazine hydrate and heated under refluxed for 1 hr, cool the mixture by addition of water.

Synthesis of 10H –phenothiazine -carbohydrazide

Equimolar amount of substituted 4(cyclohexylidine domino) benzohydrazide- was added to sulfur and heated under refluxed for 1 hr., cool the mixture by addition of water.

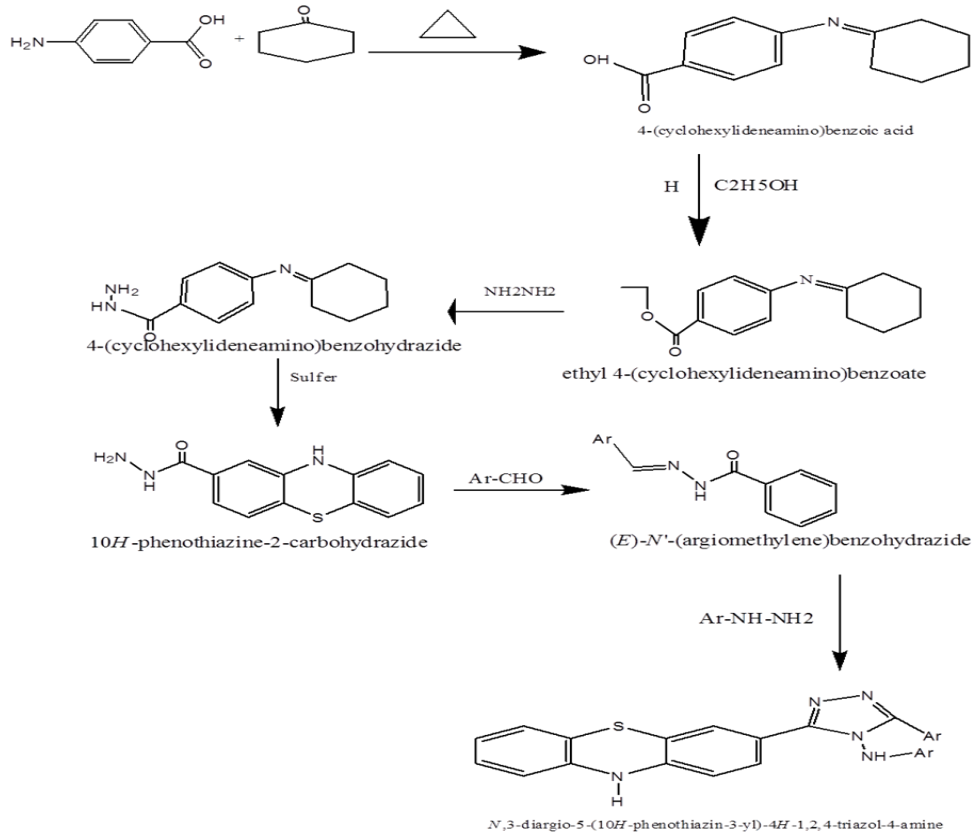
Synthesis of (E) N' (argiomethyline) 10H –N-3 diargio-5phenothiazine -carbohydrazide

Equimolar amount of substituted 10H –phenothiazine –carbohydrazide was added to 4 methoxy benzaldehyde and heated under refluxed for 1 hr., cool the mixture by addition of water.

Synthesis of N-3 diargio-5 (10-H-yl)-4H 1, 2, 3 triazol-4 amine

Equimolar amount of substituted (E) N (argiomethyline) 10H-N-3 diargio-5phenothazine- carbohydrazinene added different aimed and under refluxed for 1hr, cool the mixture by addition of water.

SCHEME



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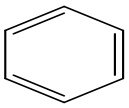
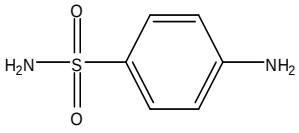
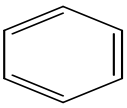
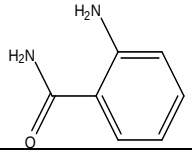
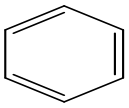
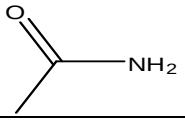
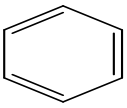
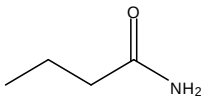
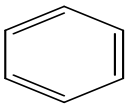
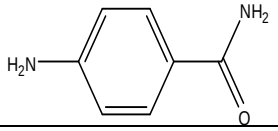
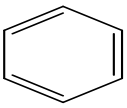
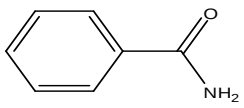
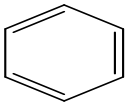
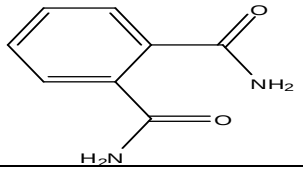
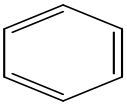
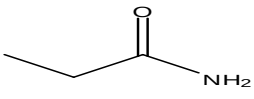
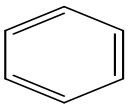
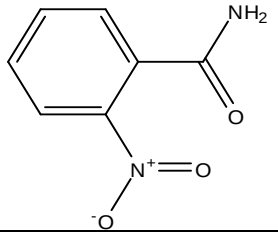
A_1			**A6**		
A2			**A7**		
A3			**A8**		
A4			**A9**		
A5					

Antibacterial activity

In radial or 2 D technique petri dishes of agar are prepared by pouring melted agar media previously inoculated with selected microorganism after the solidification of agar cups are made with the help of borer and cups are filled with solution of suitable conc. Of sample and standards respectively and are inoculated at37Oc for 24 hr. the anti-microbial agent diffuses through the agar around its cup and produces a characteristic zone of inhibition of the microorganism sensitive to the sample, the diameter of which can be measured.

Anti-inflammatory activity

In vitro anti-inflammatory activity

Inhibition of protein denaturation

The standard drug and synthesised compound were dissolve in minimum quantity of dimethyl form amide (DMF) diluted with phosphate buffer (0.2m,ph 7.4)final concentration of DMF in all solution was less than 2.5% test solution S(1ml) containing different conc. Of drug was mixed with 1ml of 1Mm albumin solution in phosphate buffer and incubated at 27oc +1oc in BOD incubator for 15 min. denaturation was induced by keeping the reaction mixture are 60o+1oc in water bath for 10min.after cooling, the turbidity was measured at 600nm(UV-visible spectrophotometer)per4centage of inhibition of denaturation was calculated from control where no drug was added each experiment was done in triplicate and average is taken. Then ibuprofen was use as standard drug. The percentage inhabitation of denaturation was calculated by using following formula.

Percentage of inhibition =100*(1-Vt/Vc)

Where,

Vt: mean absorbance of test sample Vc: mean absorbance of test control.

Table no. 01: Analytical & Physicochemical data of the synthesized compounds (A1-A9)

Comp.	Mol. Formula	Mol. Wt.	M.P. °C	Yield %	Elemental analyses Calculated		
					C	H	N
A_1	$C_{25}H_{20}N_7O_2S_2$	539	260-265	61	66.70	5.21	11.80
A_2	$C_{21}H_{16}N_6OS$	400	255-260	56	72.14	5.19	11.40
A_3	$C_{26}H_{18}N_7O_2S$	492	280-285	62	60.70	5.20	9.53
A_4	$C_{26}H_{20}N_7OS$	478	265-270	59	67.84	5.21	10.95
A_5	$C_{27}H_{18}N_7O_2S$	504	250-255	63	73.22	4.48	11.15
A_6	$C_{26}H_{20}N_7OS$	478	265-270	49	68.32	4.32	10.81
A_7	$C_{22}H_{16}N_6OS$	412	230-235	58	63.11	4.30	11.52
A_8	$C_{26}H_{19}N_6OS$	463	245-250	60	68.56	4.20	10.70
A_9	$C_{23}H_{16}N_7OS$	424	270-275	57	63.20	4.70	11.85

Spectral Data (A1-A12)

A1: IR (cm-1): 3310.43 (-CH=CHStr.), 3213.45(-NHStr.),3010.23(Ar-CHStr.),1682.11(-C=O-)1525.32(-C-O-).[1]HNMR: CH6.61 1.50 methine, CHPhenothazine 9.68(OH-Aromatic).

A2: IR (cm-1) 3310.43 (-CH=CH-), 3010.23(Ar-CHStr.), 1682.11 (C=O-), 1245.36(-C-N-Str.)1325.42(-C-O-). [1]HNMR: CH7.11 7.26 benzene, CH 3 3.83 0.86 methyl, 9.4 OH (aromatic-OH).

A3: IR (cm-1):3310.43(-CH=CHStr), 3010.23(Ar-CHStr), 1682.11(-C=O-) 1245.36(-C-N-), 3213.45(-NHStr).1340(-C-O-) [1]HNMAR: benzene CH7.02 7.29, CH 7.41 6.91 Phenothiazine, 9.86(OH aromatic).

A4: IR (cm-1): 3213.45 (-NHStr.), 3010.23 (Ar-CH Str) 1682.11(-C=O-Str) 1245.36.

(-C-N-).[1]HNMR: CH 7.00 7.26 Phenothiazine, CH2 2.56 1.37 methylene, CH6.61 1.50 methane CH 7.407.26benzene

A5: IR (cm-1) 3010.23 (Ar-CH), 1682.11(-C=O-Str), 1245.36 (-C-N-Str), 3250.23(-N-HStr). [1]HNMR: CH7.41 Phenothiazine 9.43(Aromatic OH), CH3 1.50 benzene.CH 5.25 ethyline.

A6: IR (cm-1): 3213.45 (-NHStr.), 3010.23 (Ar-CH Str.), 1682.11(-C=O-Str.)1245.36 (-C-N-Str.)[1]HNMR: 9.45 (Aromatic –OH), 6.94 benzene, CH 7.41 CH3 2.34 methyl.

A7: IR (cm-1): 3213.45(-NH-Str.)3010.23(Ar-CH Str.), 1682.11(-C=O-), 1245.36 (-C-N-). [1]HNMR: CH 7.41 6.91 Phenothiazine, OH 9.68 aromatic (C-OH) CH 7.73 7.26 benzene.

A8: IR (cm-1): 3010.23 (Ar-CH Str.), 1682.11(-C=O-Str.)1245.36 (-C-N-Str.) 1682.11(-C=O-) 1 [1]HNMR: CH 7.41 CH3 2.34 methyl. 9.45 (Aromatic –OH), CH 5.25 ethyline.

A9: IR (cm-1): 1260.36 (-C-N str.), 3259.23 (-N-H str.), 1335.32 (-C-O str.) 1682.11(-C=O-) 3010.23(Ar-

CHStr.), ^{1}HNMR: CH 7.00 7.26 Phenothiazine, CH2 2.56 1.37 methylene, CH6.61 1.50 methineCH7.407.26benzene.

Table No 02: Antibacterial activity of synthesized compounds (A1-A9)

Compounds	Zone of inhibition at 200µcg/Ml (in mm.)				
	E.coil	***B. Subtilis***	***S. aureus***	***A. niger***	***C. albicans***
A_1	24	25	26	15	22
A_2	20	23	25	16	21
A_3	20	24	25	19	22
A_4	25	26	23	20	21
A_5	24	23	26	21	22
A_6	20	22	24	18	23
A_7	21	23	22	20	21
A_8	22	24	25	20	22
A_9	21	23	22	20	21
Levofloxacin	26	25	26	-	-
Amphotericin B	-	-	-	22	23

Table No.03: Anti-inflammatory activity of synthesized compounds (A1-A9)

Treatment	Mean increase in paw volume (ml)±SEM									
	Time in min									
	0	**% Inh**	**30**	**% Inh**	**60**	**% Inh**	**90**	**% Inh**	**120**	**% Inh**
Carrageenan (Control)	0.22±0.01	0	0.44±0.03	0	0.76±0.09	0	0.83±0.12	0	0.87±0.14	0
Ibuprofen	0.25±0.03	0	0.32±0.07	36.41	0.31±0.07	62.53	0.28±0.06	69.23	0.27±0.13	71.78
A_1	0.25±0.01	0	0.35±0.03	29.16	0.36±0.01	56.12	0.34±0.01	62.17	0.29±0.01	67.29
A_2	0.25±0.02	0	0.34±0.03	32.25	0.33±0.01	59.97	0.31±0.01	65.70	0.33±0.02	69.53
A_3	0.24±0.01	5.16	0.35±0.01	30.16	0.39±0.01	52.28	0.39±0.02	56.29	0.30±0.01	65.04
A_4	0.25±0.02	0	0.34±0.01	32.25	0.34±0.02	58.69	0.32±0.02	64.52	0.31±0.02	68.41
A_5	0.24±0.01	5.16	0.33±0.01	34.33	0.35±0.01	57.41	0.33±0.01	63.35	0.33±0.03	67.29
A_6	0.25±0.02	0	0.36±0.01	28.08	0.40±0.02	51	0.39±0.01	56.29	0.31±0.01	65.04
A_7	0.24±0.02	5.16	0.34±0.01	32.25	0.36±0.02	56.12	0.35±0.02	61	0.31±0.02	67.29
A_8	0.25±0.02	0	0.34±0.02	32.25	0.36±0.03	56.12	0.32±0.02	64.52	0.31±0.02	67.29
A_9	0.24±0.03	5.16	0.34±0.02	32.25	0.35±0.01	57.41	0.33±0.02	63.35	0.31±0.02	67.29

RESULT AND DISCUSSION

Antibacterial activity

The compound A_1, A_2, A_3, A_5, A_8 has excellent Antibacterial activity *S.aureus*, the compound A_1 have shown Antibacterial activity *B.subtilis*, while A_4 show Antibacterial activity against *E.coil*, when compared with standard Levofloxacin.

Anti-inflammatory activity

All the compounds were evaluated of Anti-inflammatory activity by carrageenan induced Rat hind paw method. The synthesised compound A_2, A_4, A_5, A_6 and A_8 show better Anti-inflammatory activity found comparable with standard drug Ibuprofen (70.78% inhibition) at the same dose (100µg/kg).

CONCLUSION

The present research work is a bonafide novel for the synthesis of Triazole substituted phenothiazine. The method of synthesis of these heterocycles starting from different substrate had been established. Around nine newer derivatives of mentioned hetrocycles were synthesized. The purity of synthesized compounds was checked with the help of TLC. The physical constants (M.P.) of the synthesised compounds were determined using open capillary method. The structures of the synthesized compounds were established by using IR, H^{1}-NMR and CHN analysis. The synthesis compounds were screened for their anti-inflammatory and antibacterial activities. Some of the compounds shows significant biological activity which can be explore as drug candidate in future.

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