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Research Article

ANTIMICROBIAL AND ANTIFUNGAL STUDY OF NOVEL 2-CHLORO-4-METHYL-3H-BENZO[β][1,5]DIAZEPINE DERIVATIVES

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ABSTRACT

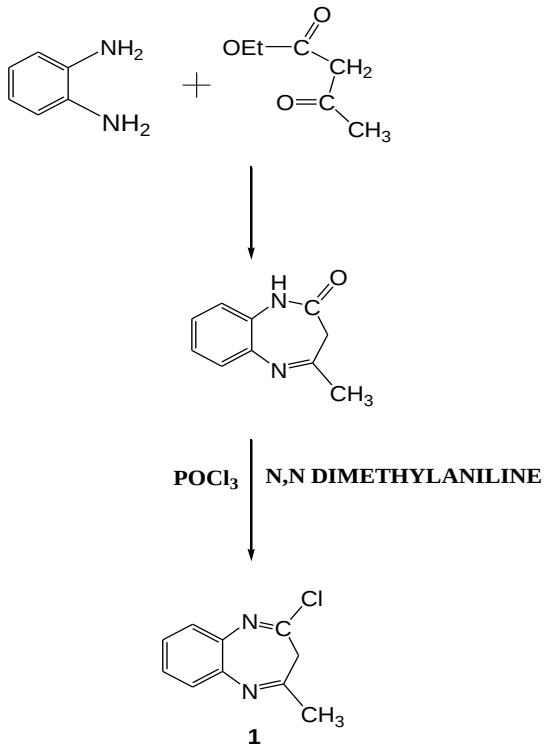
Heterocyclic compounds containing 1,5-benzodiazepines have accelerated interest in various fields like medicinal chemistry, polymer industry, etc. The preparation of 2-chloro-4-methyl-3H-benzo[β][1,5]diazepine by the reaction of 1,2-diaminobenzene and ethylactoacetate that gives the intermediate 4-methyl-1H-benzo[β][1,5]diazepine-2[3H]-one, and it reacts with N,N-dimethylaniline and $POCl_3$. 2-chloro-4-methyl-3H-benzo[β][1,5]diazepine forms a number of derivatives by further reactions. The compounds 2, 3, 4, 5, 6, 7, 8, 9 were screened for their antimicrobial, antifungal activities.

Keywords: Heterocyclic, 1,5-benzodiazpine, Antimicrobial, Antifungal study.

INTRODUCTION

Benzodiazepines have attracted attention as an important class of heterocyclic compounds in the field of drugs and pharmaceuticals. These compounds are widely used as anticonvulsant, anti-anxiety, analgesic, sedative, antidepressive and hypnotic agents,[1] as well as anti-inflammatory agents.[2] Other than their biological importance, benzodiazepines derivatives are also commercially used as dyes for acrylic fibers.[3] Moreover, 1,5-benzodiazepines derivatives are valuable synthons that can be used in the preparation of other fused ring compounds, such as triazolo, imidazo-, benzimidazo-, oxadiazolo-, pyrazolo-, isoxazolo-, azepino-, pyrimidino-, thiadiazolo or furano-benzodiazepines.[4] Generally, these compounds are synthesized by the condensation of o-phenylenediamines with α,β-unsaturated carbonyl compounds,[5] β-haloketones or ketones.[6] A variety of reagents, such as BF_3-etherate, $NaBH_4$, polyphosphoric acid, or SiO_2, $MgO/POCl_3$, $Yb(OTf)_3$, $Sc(OTf)_3$, Al_2O_3/P_2O_5, or AcOH under microwave and in ionic liquids[7] have been utilized for the condensation reaction. Most recently, this condensation has also been reported to proceed in the presence of CAN, bromodimethylsulfonium bromide, organic acids and $AgNO_3$.[8]

In present work, novel 1,5benzodiazpine derivatives of the 2-chloro-4-methyl-3H-benzo[β][1,5]diazepine are studied for their antibacterial and antifungal activity. An attempt has been made to highlight the antibacterial and antifungal activity of 2-chloro-4-methyl-3H-benzo[β][1,5]diazepine derivatives by testing their antibacterial and antifungal action against several types of bacteria and fungi.



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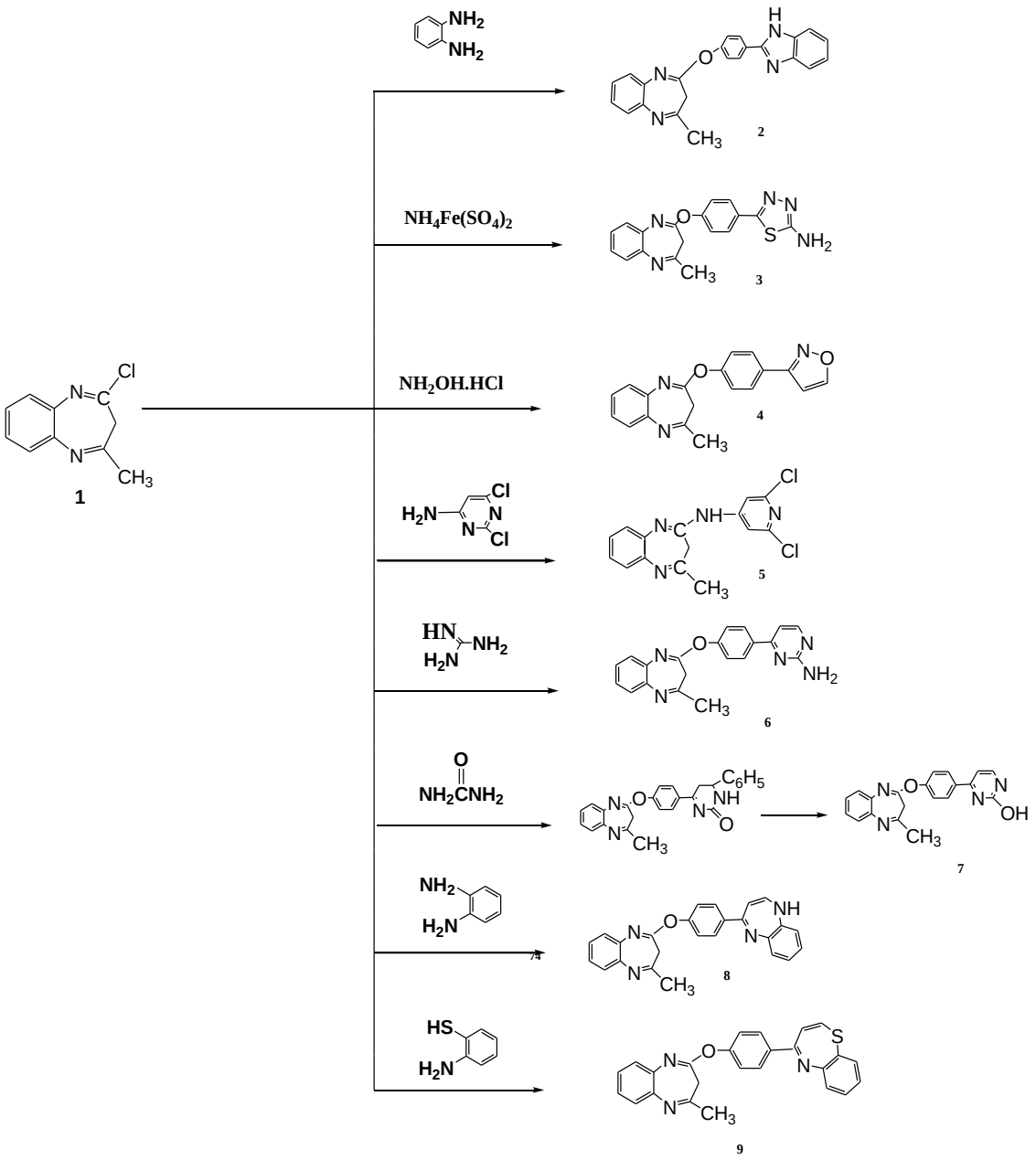
Scheme-1

Scheme 1: Synthesis of intermediate and target compounds



Scheme 2

MATERIALS AND METHODS

Antimicrobial and Antifungal Activities of Compounds

The newly synthesized 1,5-benzodiazepine derivatives compounds were screened for antifungal activity against *Aspergillus niger* and *Candida albicans* and antimicrobial activity against *E.coli and Bacillus* by the deep well method. Fluconazole and Ampilicine were used as standards for comparison of the antifungal and antimicrobial activities, respectively. The results indicate that these compounds were active against all the four organisms. The results of the antimicrobial and antifungal activity reported in the given table-1.

Methodology

Growth medium (Disc diffusion method)

Preparation of media

The media used for testing of antibacterial activity had the following composition (for one litre solution). Nutrient agar was developed for the microbes to grow by settling over petridishes in the compositions given below

Peptone : 5.0gm

NaCl : 5.0gm

Meat extract : 3.0gm

Distilled water : 1000ml

The media, which was used for testing of antifungal activity, had the following compositions (for one litre solution). The composition of potato dextrose (Hi-Media) was developed for the microbes to grow by settling over petridishes.

Glucose : 20gm

Peptone : 10gm

Agar-agar : 15gm

Distilled water : 1000ml

In this method all the components were mixed and dissolved in one litre of distilled water by hating the mixture. The pH of the media was adjusted to 5.0.The media was then sterilized in the

autoclave along with the glassware's petridishes, pipettes etc. at 1 lb pressure and 120^{0}C for half an hour. The sterilized nutrient agar solution was taken out by micro-pipettes and a large number of petridishes were prepared by pouring agar solution to it, between two burners (for media and solvent control) in Laminar Air Flow 0.5-0.3 cm. The plates were then tightly tapped and kept at room temperature. Under aseptic conditions, the sterilized filter paper discs dipped in the diluted test solutions with different concentrations in DMF were placed in the petridishes in the LAF. All the agar plates with different organisms and disc of test solutions were accordingly utilized. Then the plates, properly cupped, were placed in an incubator at 37^{o}C for 12 hours for bacteria and 28±2ºC for 48 hours for fungi.

Analysis and Interpretation of Data

After 24 hours of incubation, the plates were analyzed and the diameter of the zones of complete inhibition was measured to the nearest whole millimeter with a sliding callipers. The newly synthesized 1,5-benzodiazepine derivatives compounds were screened for antifungal activity against Aspergillus niger and Candida albicans.and antimicrobial activity against E.coli and Bacilus by the deep well method. Fluconazole and Ampilicine were used as standards for comparison of the antifungal and antimicrobial activities, respectively. The results indicate that these compounds were active against all the four organisms. The results of the antimicrobial and antifungal activity reported in the given table 1.

RESULTS AND DISCUSSION

The objective of this study was to synthesize and investigate the antimicrobial and antifungal activity of novel 1,5-benzodiazepines derivatives. These compounds were subjected to in-vitro antibacterial and antifungal screening. The obtained data revealed that ten compounds namely 2, 3, 4, 5, 6, 7, 8, 9 exhibited promising antimicrobial activities against tested organisms. It is to be noted down that, among the tested pyrimidine compound was found to be the most potent member. It showed a broad spectrum of antimicrobial activity with special high activity against E. coli, and Bacillus. On the other hand, compound no. 9 (aminothiadiazole derivative) were found to be the most potent member among the benzodiazepine series. Further investigation of such compounds represents a fruitful matrix for the development of more potent antimicrobial agents.

CONCLUSION

In summary, we have demonstrated a novel, mild, efficient method for the synthesis of 2-chloro-4-methyl-3H-benzo [β][1,5]diazepine derivatives. Novel 1,5-benzodiazpine derivatives of the 2-chloro-4-methyl-3H-benzo[β][1,5]diazepine were studied for their antibacterial and antifungal activity.

Table 1

S. No.	Conc. (mg/ml)	*E.coli*		*B. subtilis*		*A. niger*		*F. solani*	
		Zone of Inhibition (mm)	% activity Compared To the standard	Zone of Inhibition (mm)	% activity Compared To the standard	Zone of Inhibition (mm)	% activity Compared To the standard	Zone of Inhibition (mm)	% activity Compared To the standard
2	400	14.4	58.23	9.6	52.00	8.3	32.21	13.8	45.25
(A)	200	10.3	55.50	6.2	54.38	5.2	28.52	12.7	58.57
	100	8.6	50.00	3.3	46.77	3.3	25.88	8.9	48.50
3	400	18.6	74.30	12.2	65.00	23.1	85.07	21.1	68.06
(B)	200	11.2	60.00	5.4	48.23	17.8	88.52	14.2	65.09
	100	6.3	44.60	4.1	55.66	13.6	90.24	11.3	60.50
4	400	15.9	64.00	11.9	63.50	24.3	89.36	11.4	37.75
(C)	200	9.5	51.50	8.2	69.77	17.1	85.52	8.6	39.74
	100	3.9	29.60	4.6	61.22	12.6	84.00	5.1	29.50
5	400	12.3	50.10	10.6	54.00	12.2	46.14	22.7	73.06
(D)	200	8.6	47.00	4.9	44.38	9.8	50.14	15.5	70.73
	100	5.8	41.45	2.6	39.00	6.6	46.50	12.3	65.00
6	400	11.2	45.90	10.4	56.00	15.5	57.93	12.4	40.88
(E)	200	7.0	39.00	5.3	47.47	10.5	53.76	9.1	42.91
	100	3.5	27.10	3.2	45.67	7.1	49.63	5.9	33.50
7	400	18.4	73.23	14.6	77.00	26.3	95.21	24.8	80.25
(F)	200	14.3	77.50	7.2	62.38	17.2	86.52	18.7	82.57
	100	10.6	72.00	5.3	67.77	12.3	80.88	14.9	76.00
8	400	21.6	84.30	13.2	71.00	19.1	71.07	26.1	84.06
(G)	200	15.2	82.00	8.4	72.23	13.8	66.52	19.2	87.09
	100	11.3	76.60	4.1	54.66	7.6	54.00	13.3	69.50
9	400	21.9	8500	17.9	89.50	14.3	53.36	19.4	62.75
(H)	200	16.5	85.50	10 .2	85.77	9.1	48.52	14.6	65.74
	100	11.9	79.60	6.6	76.22	6.6	47.00	9.1	50.00
*Std.	400	25	100	19	100	-	-	-	-
Antibact.	200	19	100	12	100				
	100	15	100	8	100				
*Std.	400	-	-	-	-	27	100	31	100
Antifungal.	200					20	100	22	100
	100					15	100	19	100

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