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BIOLOGICAL APPLICATIONS (ANTIBACTERIAL ACTIVITY) OF BAYLIS-HILLMAN ADDUCTS DERIVED FROM BENZOXEPINE DERIVATIVES (AGAR DIFFUSION ASSAY)

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ABSTRACT

The simple an efficient protocol using a cyclic reaction for the novel synthesis of benzoxepine derivatives connecting a tandem building of C–O and C–C bonds using Baylis–Hillman adducts with paraformaldehyde under the catalist of H2SO4 was successfully realised. We also established that these 2-benzoxepine results are useful for constructing wide variety of benzoxe herecyclic compounds in very good yields. Since benzoxepines and its derivatives are well known for their biological properties, the newly synthesized benzoxepines and its derivatives also may exhibit significant bioactivities.

Keywords: Baylis-Hillman reaction, Benzoxepine, antibacterial activity, Pseudomonos aeruginosa, Klebsiella pneumonia.

1. INTRODUCTION

Minimum inhibitory concentration (MIC) of benzoxpin derivatives against human pathogens (µg/mL). The newly synthesized connected thiazepine derivative resolved with 40% DMSO has been evaluated in studies of vitro antibacterial activity against microorganisms, and the results are explained. Research into organic activity was opposed to bacteria, Staphylococcus aureus, subspecies, cyanoplasia Pseudomonos, pneumoniasis, and E. coli. Thiazepinderivats against the above microorganisms. Approximately 15 mL of nutritional maker was poured into petrimesh (9 cm diameter) and inoculated with each test organism. The wells are made from cork drills on solid agar and loaded with test connections with 50, 75, 100 µg/100 µg/tetracycline as control and control as 40% DMSO. Petri dishes were incubated at 37ºC for 24 hours and the average diameter of the surrounding zone of inhibition was measured according to the specified incubation period.

The percentage of inhibition zone was calculated by using following formula.

$$\% \text{ of Inhibition zone} = \frac{\text{Zone of inhibition (diameter in mm)}}{\text{Diameter of the petri plate in mm}}$$

The antibacterial activity of thiazepines was assessed via agar differentiation for five human pathogenicities: subsilicon, pneumococcus, Staphylococcus aureus, Pseudomonas aeruginosa, and E. coli. All connections have been tested, with efficacy in inhibiting tested pathogenicity (human pathogen) growth at 50 µg, 75 µg, and 150 µg/well concentrations, respectively.

Material and Methods

Thiazepine derivatives inhibit the growth of subspecies, pneumococcus, Pseudomonas aeruginosa, Staphylococcus aureus, and E. coli E. coli (Tables 1 and 2). The thiazepine derivative system showed good antibacterial activity against each test bacteria using 100 raw/borehole concentrations. Furthermore, the connections of 2B, 2D, 2F, 2H, and 2I inhibited the growth of five human pathogenic bacteria. Connected 2D showed better activity against gram (-) and gram (+) bacteria than other compounds (Table 1). Connections 2B, 2F, and 2H showed significant activity as connections 2C and 2D for subspecies. Among the derivatives, 2E showed no significant activity. All connections 2a-i showed effective antibacterial activity against aeruginos and Staphylococcus aureus than other human pathogenic bacteria.

Results and Discussion

The **2f** compounds showed good activity against all bacterial pathogens while compared to rest compounds.

Human pathogens	Compound test using well diffusion methods									
	2a	**2b**	**2c**	2**d**	**2e**	**2f**	**2g**	**2h**	**2i**	**2j**
Bacillus subtilis	+++	+++	++	++	-	+++	+++	+++	+++	+++
Staphylococcus areus	+++	+++	+++	+++	++	+++	+++	+++	+++	+++
Escherichia coli	+++	+++	-	++	++	+++	++	++	+++	-
Pseudomonas argenosa	+++	+++	+++	++	++	+++	+++	+++	+++	+++
Klebciella pneumonia	+++	+++	++	++	-	+++	-	+++	+++	-

Note:

+++ = Excelent

++ = Moderate

\- = No activity

Thiazepines (µg/well)		*Bacillus subtilis* (mm)	*Escherichia coli* (mm)	*Staphylococcus aureus* (mm)	*Pseudomonas argenosa* (mm)	*Klebciella pneumonia* (mm)
2a	50	12	20	12	16	NA
	75	16	22	16	20	NA
	100	20	24	20	24	NA
Positive control		24	26	24	26	21
2b	50	14	10	16	12	8
	75	14	12	18	20	12
	100	16	20	20	26	14
Positive control		24	26	24	26	21
2c	50	6	NA	14	10	6
	75	8	NA	16	12	10

	100	12	NA	20	14	12
	PC	24	26	24	26	21
2d	50	6	8	10	6	4
	75	8	10	18	8	4
	100	10	12	18	10	6
Positive control		24	26	22	26	21
2e	50	NA	10	8	6	NA
	75	NA	11	10	8	NA
	100	NA	12	12	12	NA
Positive control		24	26	24	26	21
2f	50	16	14	16	14	13
	75	17	17	18	15	15
	100	18	20	20	18	17
Positive control		24	26	24	26	21
2g	50	10	10	17	15	NA
	75	11	11	18	16	NA
	100	13	12	19	16	NA
Positive control		24	26	24	26	21
2h	50	13	NA	13	13	13
	75	15	10	14	15	14
	100	17	12	17	17	15
Positive control		24	26	24	26	21
2i	50	12	11	13	10	14
	75	16	12	13	12	16
	100	17	16	15	15	17
Positive control		24	26	24	26	21
2j	50	NA	NA	13	11	NA
	75	10	NA	14	13	NA
	100	13	NA	15	14	NA
Positive control		24	26	24	26	21

NA = No activity

Positive control = tetracycline

1. *Bacillus subtilis*; 2. *Escherichia coli*; 3. *Staphylococcus aureus*; 4. *Pseudomonas aeruginosa*; 5. *Klebsella pneumonia*

a-control; b-positive control; c-50µg/ml; d-75µg/ml; e-100µg/ml

Fig Bioactive studies of diazepine derivatives

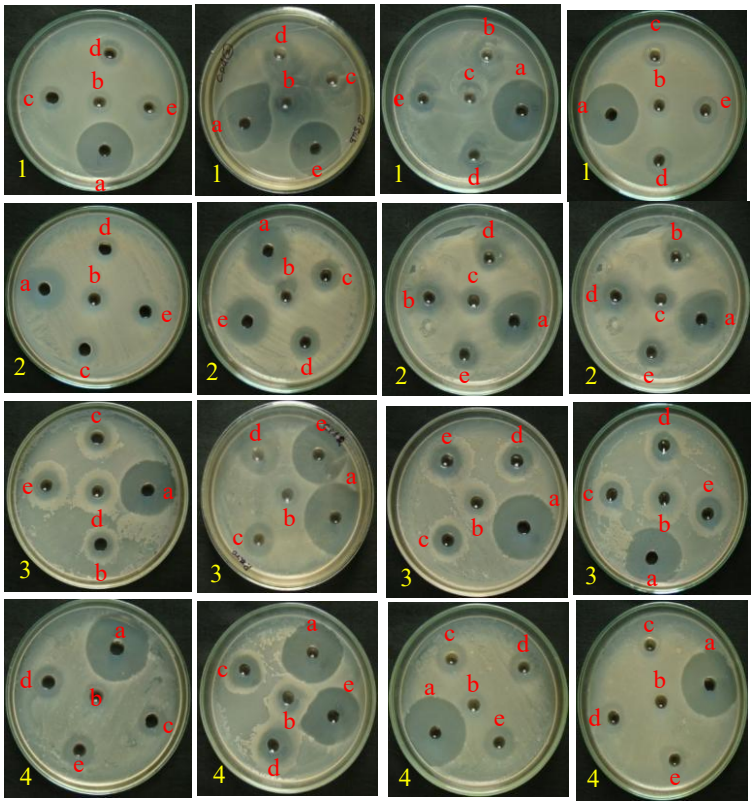
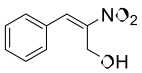
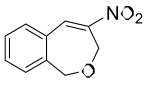
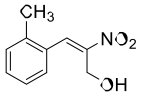
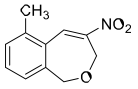
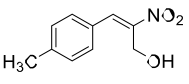
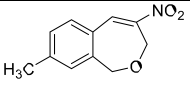
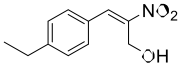
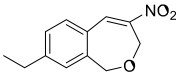
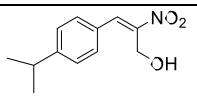
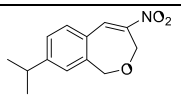
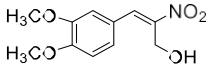
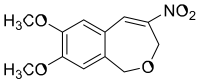
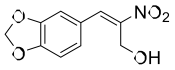
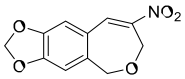
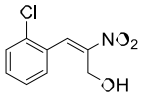
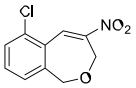
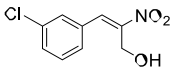
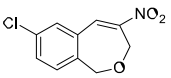
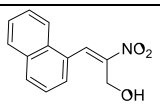
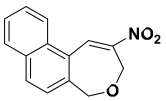


Table 1. Synthesis of novel benzoxepine derivatives from Baylis-Hillman adducts

Entry	BH Adducts	Benzoxepine[a, b]	Time	Yield (%)[C]
1	 **1a**	 **2a**	1	65
2	 **1b**	 **2b**	2	71
3	 **1c**	 **2c**	1	67
4	 **1d**	 **2d**	1	62

5	 **1e**	 **2e**	2	65
6	 **1f**	 **2f**	2	60
7	 **1g**	 **2g**	2	61
8	 **1h**	 **2h**	2	62
9	 **1i**	 **2i**	2	65
10	 **1j**	 **2j**	2	71

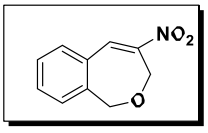
2. CONCLUSION

In summary, the tandem buildings made with C-bonds with Baylis-Hillman-Adducts are successfully combined with Paraformdehyde under the catalonist of H_2SO_4, which can be said to be a simple and efficient protocol using cyclic reactions for the new synthesis of benzoxpine derivatives. It has also been found that the results of these 2-benzoxoccipins are useful in constructing various benzox tight ring compounds in very good yields. Because Benzoxpine and its derivatives are known for their biological properties, newly synthesized benzoxpine and its derivatives can have important organic activity.

Typical experimental procedure for the synthesis of (*E*)-1,3-dihydro-4 nitrobenzo[*c*]oxepine

A mixture of (*E*)-2-nitro-3-phenylprop-2-en-1-ol (0.36g, 2 mmol) in DCM (30 ml), paraformaldehyde (0.06g, 2 mmol) was added at room temperature. After stirring for about 10 minutes at 0ºC, con H_2SO_4 (2 equiv) was added drop wise. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure. The crude product was diluted with water (10 ml) and extracted with ethylacetate (20 ml). The organic layer thus obtained was washed with brine solution (10 ml) and concentrated under reduced pressure. Then the crude sample was purified by column chromatography to provide the desired pure product as yellow colour solid in 62% (0.29g) yield.

(*E*)-1,3-Dihydro-4-nitrobenzo[*c*]oxepine Yellow crystalline solid



Yield : 65%

M. P : 98-100 ^{0}C

IR (KBr) : 1650, 1516, 1319 cm^{-1}

^{1}H NMR ($CDCl_3$, 300 MHz) : δ 4.74 (s, 2H), 5.03 (s, 2H), 7.19-7.54 (m, 4H), 8.17 (s, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz) : δ 71.30, 74.17, 127.86, 128.65, 129.15, 131.20, 134.54, 134.88, 141.62, 148.83.

MS (m/z) : 192 (M^++1).

Elemental Analysis for $C_{10}H_9NO_3$

Calculated	: C, 62.82; H, 4.74; N, 7.33.
Found	: C, 62.77; H, 4.72; N, 7.29.

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