

ANTIBACTERIAL ACTIVITY OF SOME NOVEL TETRASUBSTITUTED PYRIMIDINONES DERIVATIVES

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ABSTRACT

Several tetra substituted pyrimidinones were conveniently prepared by the Diels-Alder reaction. The constitution of the products was supported by IR, PMR and mass spectral study. The compounds synthesized were tested in vitro against Gram positive microorganisms, *Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*, *Enterococcus faecalis* and Gram negative microorganism *Escherichia coli* and *Pseudomonas aeruginosa*. Standard drugs were also tested under identical conditions for comparing the results and a significant level of activity was observed.

Keywords: Antibacterial, Pyrimidinones, Diels-Alder, Gram Positive Bacteria, Gram Negative Bacteria

INTRODUCTION

The emergence and spread of bacterial resistance represent a severe global problem¹. The escalating resistance has led to the appearance of multiresistant *staphylococci*, *enterococci* and *pneumococci* in nosocomial and community acquired infections. Therefore, there is an urgent need for the development of novel chemical entities that are particularly effective against Gram-positive and Gram-negative pathogens including the multi resistant strains. In the last few years, various pyrimidinone derivatives substituted at the C-5 position have emerged in the field of chemotherapy. In this context these derivatives showed selective antitumour² antiviral³ antitubercular⁴ and antifungal⁵ activities. Although, there are numerous reports concerning β -lactam derivatives, the four membered cyclic amides acting as potential antibacterial agents⁶, however, there are few scattered reports⁷ in which six member cyclic amides *viz.* pyridones, pyrimidinones have been tested for the antibacterial activity against gram positive and gram negative strains. In view of these observations and our continuous efforts in developing heterocycles^{8,9} of biological interest, it was thought worthwhile to synthesize variedly substituted pyrimidinones for evaluation of their antibacterial activity. Previously, we have reported the convenient routes for the synthesis of 5-dienyl pyrimidinone and 3-butadienyl-2-azetidinone *via* [4+2] and [2+2] cycloaddition reactions of butadienylketene with 1, 3-diazabuta-1, 3- dienes¹⁰ and imines¹¹ respectively. Since a vast library of C-5 substituted pyrimidinone derivatives for assessment for their antibacterial activity, can be easily prepared by their Diels-Alder cycloaddition reactions with various dienophiles, it was thought worthwhile to design, synthesize and evaluate variedly substituted 5-substituted pyrimidinone derivatives for evaluation of their antibacterial activity. This prompt us to develop Lewis acid promoted regio- and diastereoselective DA cycloaddition reactions of 5-dienyl pyrimidinone derivatives with various dienophiles, for the construction of vast variety of 5-

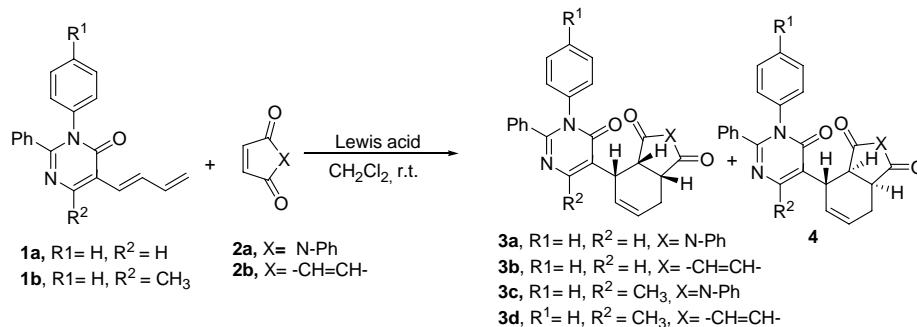
substituted pyrimidinones derivatives and the present communication describe the design synthesis and evaluation of diastereomerically pure 1, 2, 4, 5-tetrasubstituted-pyrimidinone derivatives for their antibacterial activities.

EXPERIMENTAL

Chemistry

The starting substrate 5-dienyl pyrimidinones were prepared by previous reported methods. The common dienophiles *viz.* *N*-phenyl maleimide, benzoquinone, methyl acrylate and methyl vinyl ketone were utilized in these DA cycloaddition reactions. The common Lewis acids *viz.* aluminium (III) chloride, titanium(IV) chloride and tin(IV) chloride were examined for their comparative effects on the yields and desired diastereoselectivity in these Diels-Alder reactions. Interestingly, the use of all these Lewis acids promoted high diastereoselectivity and high resolution ¹H NMR spectra (300MHz) of even crude reaction mixture of adducts did not show the presence of detectable amount of other diastereoisomer.

Best results in terms of yields and selectivity were obtained with the use of titanium (IV) chloride as catalyst. Thus the reactions of **1a-c** with *N*-phenylmaleimide **2a** as dienophile using titanium (IV) chloride as catalyst resulted in the good yields (90%) of the corresponding "endo"adducts. (Table 1; entries 3, 4). The Diels-Alder cycloaddition reactions of **1a-b** with benzoquinone **2b** resulted in the exclusive formation of the "endo" adducts in good yields (34-81%) (Table 1; entries 7-12). However, with the use of titanium (IV) chloride and tin (IV) chloride, the yields of adducts significantly increased especially when the reaction were conducted at -78°C (Table 5; entries 10, 12). However all reactions showed deterioration of adducts with the use of aluminium(III) chloride possibly, owing to its strong acidity (Table-1; entries 1, 2, 7, 8).



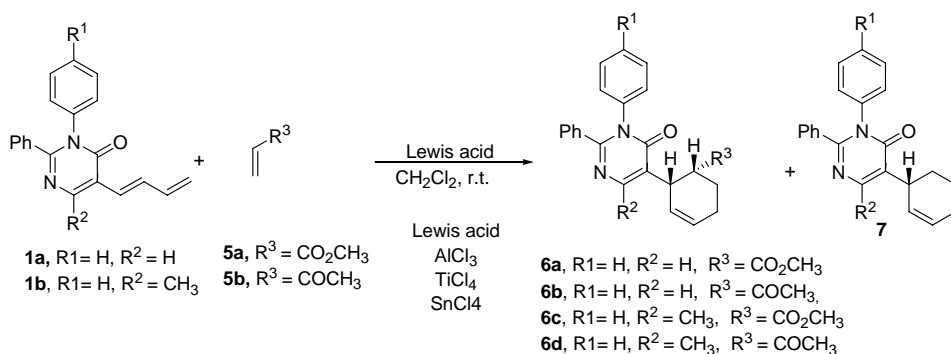
Scheme-1

The diastereomerically pure adducts thus obtained, were characterized with the help of analytical data and spectral evidences, the details of which are described in the experimental section while the salient features are discussed here. The 4-(4-Methyl-6-oxo-1,2-diphenyl-1,6-dihydro-pyrimidin-5-yl)-2-phenyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione **3e**, for example, analyzed for $C_{31}H_{25}N_3O_3$ showed a molecular ion peak at m/z 487 in its mass spectrum. Its IR spectrum showed a strong absorption peak at 1678 cm^{-1} due to the carbonyl group of pyrimidinone ring. Its high resolution 1H NMR (300MHz) spectrum showed characteristic

singlet at δ 2.57 corresponding to the methyl of pyrimidinone ring, a doublet of doublet (ddd, $J=2.7, 6.6, 15.9$ Hz) at δ 3.01 corresponding to H_{11} of the cyclohexenyl ring, a doublet of doublet of doublet ($J= 5.2, 6.6$ Hz) at δ 3.34 due to H_{15} and another doublet of doublet of doublet ($J= 3.1, 5.2, 15.2$ Hz) at δ 4.1 assigned to H_7 of the cyclohexenyl ring. The coupling constant of $J= 5.2$ Hz between H_7 and H_{15} established the *cis* stereochemistry between these protons. Its ^{13}C NMR spectrum showed the presence of three carbonyl carbons at δ 161.2, δ 176.7, δ 178.2 corresponding to C_4, C_{12} and C_{14} respectively.

Table1: Lewis acid catalyzed reaction of 1a-c with 2a-b

Entry	Pyrimidinones	Dienophile	LA	Temp (°C)	Yield (%)
1	1a/b	2a	$AlCl_3$	r.t.	54/59
2	1a/b	2a	$AlCl_3$	-78	75/71
3	1a/b	2a	$TiCl_4$	r.t.	48/43
4	1a/b	2a	$TiCl_4$	-78	76/79
5	1a/b	2a	$SnCl_4$	r.t.	41/47
6	1a/b	2a	$SnCl_4$	-78	81/75
7	1a/b	2b	$AlCl_3$	r.t.	46/57
8	1a/b	2b	$AlCl_3$	-78	67/62
9	1a/b	2b	$TiCl_4$	r.t.	78/85
10	1a/b	2b	$TiCl_4$	-78	82/79
11	1a/b	2b	$SnCl_4$	r.t.	51/47
12	1a/b	2b	$SnCl_4$	-78	59/54



Scheme-2

In continuation of our studies and in an attempt to generalize the above methodology, the Diels-Alder cycloaddition reactions of **1a-b** were further examined with various unsymmetrical dienophiles viz. methyl acrylate **5a** and methyl vinyl ketone **5b** in the presence of different Lewis acids. As expected, the use of different Lewis acids promoted high regio- and diastereoselectivity. The reactions of **1a-c** with methyl acrylate **5a** resulted in the good yields of the corresponding cycloadducts **5a** in good yields (**Table-6; entries 1-6**) in the presence of different Lewis acids. The DA cycloaddition

reactions of **1a-c** with methyl vinyl ketone **2b** resulted in good yields of cycloadducts in the presence of tin(IV) chloride at low temperature (**Table-6; entries 11, 12**). However, the reaction of **1a-c** with methyl vinyl ketone **5b** resulted in the low yield of their adducts in the presence of aluminium(III) chloride and titanium(IV) chloride, possibly owing to the strong binding of the Lewis acid with the carbonyl of the dienophiles (**Table-2; entries 9, 10, 11, 12**).

Table-2 Lewis acid catalyzed reaction of 1a-c with 5a-b

Entry	Pyrimidinones	Dienophile	LA	Temp	Yield (%)
1	1a/b	5a	$AlCl_3$	r.t.	Quantitative
2	1a/b	5a	$AlCl_3$	-78	Quantitative
3	1a/b	5a	$TiCl_4$	r.t.	Quantitative
4	1a/b	5a	$TiCl_4$	-78	Quantitative
5	1a/b	5a	$SnCl_4$	r.t.	Quantitative
6	1a/b	5a	$SnCl_4$	-78	Quantitative
7	1a/b	5b	$AlCl_3$	r.t.	46/57
8	1a/b	5b	$AlCl_3$	-78	67/62
9	1a/b	5b	$TiCl_4$	r.t.	78/85
10	1a/b	5b	$TiCl_4$	-78	82/79
11	1a/b	5b	$SnCl_4$	r.t.	51/47
12	1a/b	5b	$SnCl_4$	-78	59/54

Antimicrobial Activity

The antibacterial activity of the test compounds was determined by agar well diffusion method as recommended by the National Committee for Clinical Laboratory Standards 19-21 against Gram positive microorganisms, *Bacillus subtilis* MTCC 121, *Bacillus cereus*

MTCC 1272, *Staphylococcus aureus* MTCC 1430, and Gram negative microorganism *Eseherichia coli* MTCC 42, *Pseudomonas aeruginosa* MTCC 1034, at 1 mg/ml concentration, using dimethyl sulfoxide (DMSO) as solvent. The bacteria were subcultured on Mueller Hinton Agar Medium. Standard antibacterial ciprofloxacin was also screened under similar conditions for comparison. The Petri dishes

were incubated at 37°C for 48 h to know the bacterial growth inhibition developed around the hole and was measured in millimeter for particular test solution with particular organism. The results are presented in Figure-1 and Figure-2 and Figure-3.

RESULTS AND DISCUSSION

It has been observed that the test compounds (**1a-b**, **3a-d** & **6a-d**) exhibited interesting antibacterial activity, however with a degree of variation. Results reveal that the starting compounds 5-dienyl pyrimidinones **1a** & **1b** have shown very less antibacterial activity as compared to the ciprofloxacin. Moreover **1a** do not show antibacterial activity against *B. subtilis*. The compound **3c**, **6a** do not show

antibacterial activity against *S. aureus* and *B. cereus* respectively. However, **6b** showed significant activity against *B. subtilis*, *B. cereus*, *S. aureus*, *E. coli* and *P. aeruginosa* as compared to ciprofloxacin. The substitution of the methyl group at the C-4 of the pyrimidinones in **6d** markedly reduced their antibacterial activity. Moreover the change of the substituent from methyl ketone to ethyl ester in compounds **6a** & **6c** markedly reduced the antimicrobial activity. Moreover, the C-5 naphthoquinone substituted pyrimidinones **3b** & **3d** have also shown reasonable amount of antibacterial activity. Solvent DMSO did not show any antibacterial activity. Moreover, the compound **3d** do not show antibacterial activity against gram negative bacteria viz. *E. coli* and *P. aeruginosa*.

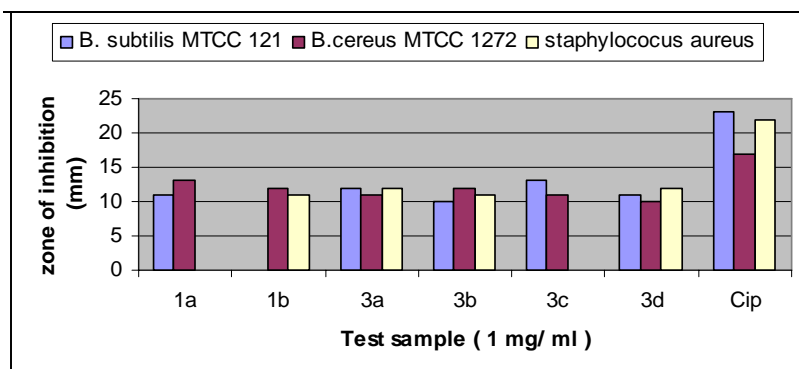


Fig. 1: Antibacterial activity of compound 1a-b & 3a-d

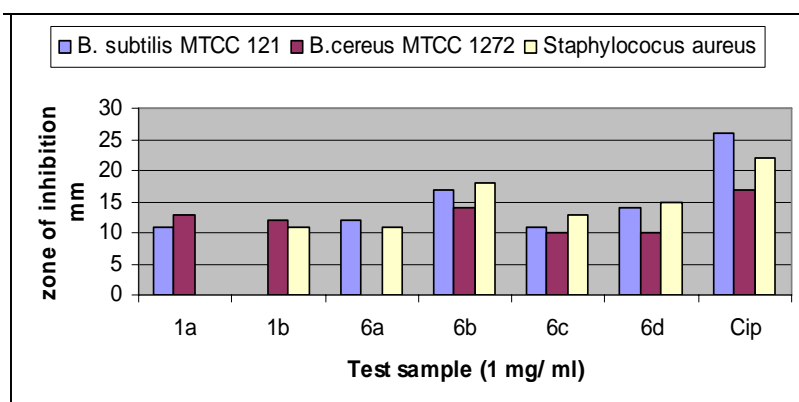


Fig. 2: Antibacterial activity of compounds 1a-b & 6a-d

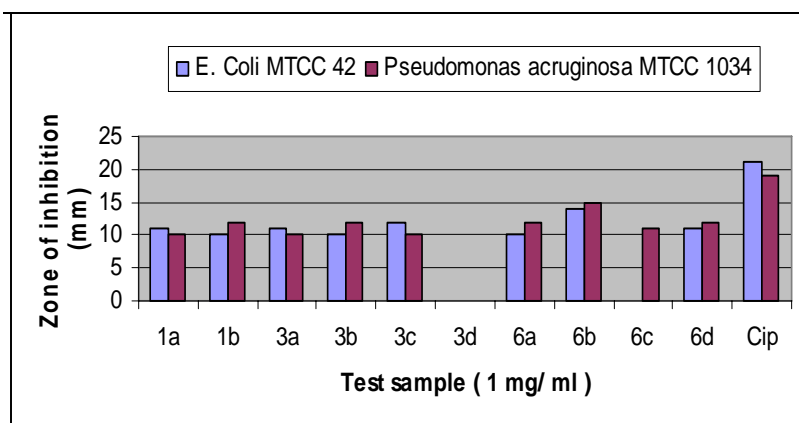


Fig. 3: Antibacterial activity of compound 1a-b, 3a-d & 6a-d

CONCLUSION

The microbiological results of the present study show a good antibacterial profile in comparison to standard. Compounds possessing *p*-methyl -COCH₃ moiety is among the most active compounds in our studies. Moreover, substitution of methyl group at the C-4 of the pyrimidinones markedly reduced the antibacterial activity. Hence, a new class of tetrasubstituted pyrimidinones has been made available as potential antimicrobial agent.

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