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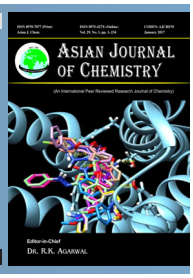

Antibacterial Evaluation of Benzo[b]pyrazolo[3,4-b]-1,6-naphthyridines, Pyrazolo[3,4-b]pyrido-[2',3'-b]-1,6-naphthyridines and Dipyrazolo[3,4-b];3',4'-h]-1,6-naphthyridines

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Antibacterial screening of benzo[b]pyrazolo[3,4-b]-1,6-naphthyridines, pyrazolo[3,4-b]pyrido[2',3'-b]-1,6-naphthyridines and dipyrazolo-[3,4-b];3',4'-h]-1,6-naphthyridines has been performed by dics diffusion method. Cefotaxime, enoxabid and dibkacin were used as a reference and antibacterial activity was assessed by measuring the diameter of the growth-inhibition zone.

Keywords: Pyrazoles, Pyridines, 1,6-Naphthyridines, Antibacterial activity.

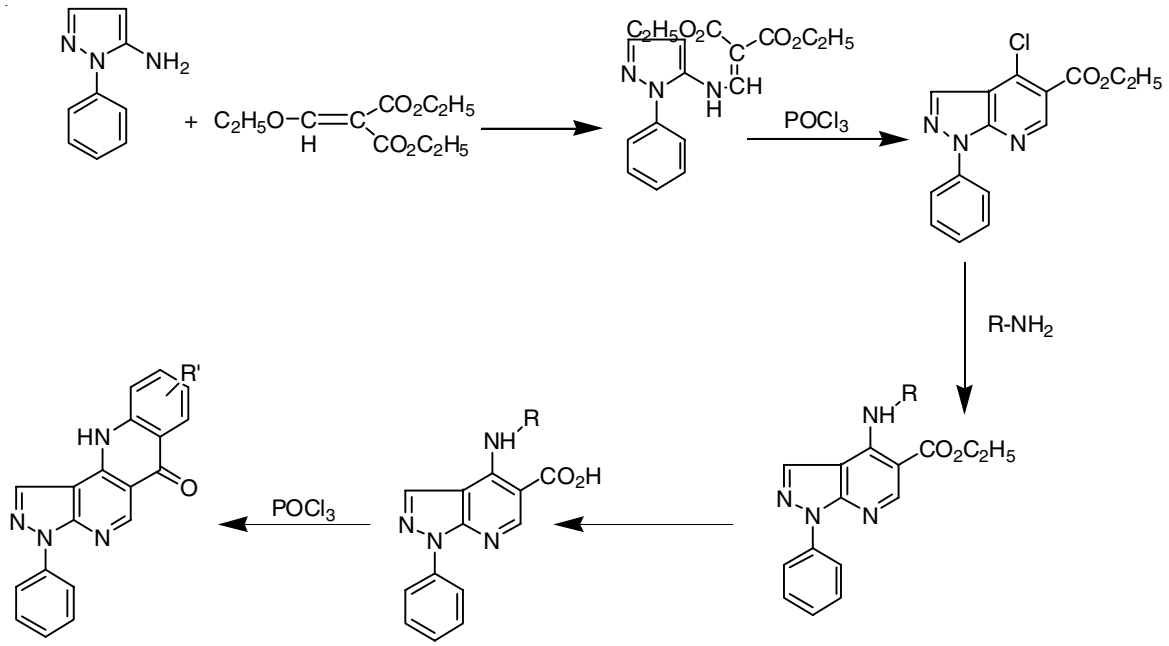
INTRODUCTION

Naphthyridine have received considerable attention over the past years because of their wide range of biological activities including antitumor [1-3], anti-inflammatory [4,5], and antifungal [6] activities. Pyridopyrimidine is one of the most important "privileged medicinal scaffolds," used for the development of pharmaceutical agents for diverse applications. A large variety of pyridopyrimidine derivatives have been used as antitumor [7], antibacterial [8], anti-inflammatory [9], antifungal [10] and antileishmaniasis [11] agents. Therefore, the synthesis of these molecules has attracted considerable attention. Gangjee and co-workers [3] have described the construction of pyrimidonaphthyridine skeleton *via* multistep reaction. However, the continued development of diversity synthesis of compounds library, including pyrimidonaphthyridine, benzonaphthyridine, pyrazolonaphthyridine and azabenzo[*b*]fluorene frameworks, is still strongly desired, because of their profound chemical and biological significance. In this paper, we would like to report highly efficient synthesis of compounds library containing benzo[b]pyrazolo[3,4-b]-1,6-naphthyridines, pyrazolo[3,4-b]pyrido[2',3'-b]-1,6-naphthyridines and dipyrazolo[3,4-b];3',4'-h]-1,6-naphthyridines (**1-17**).

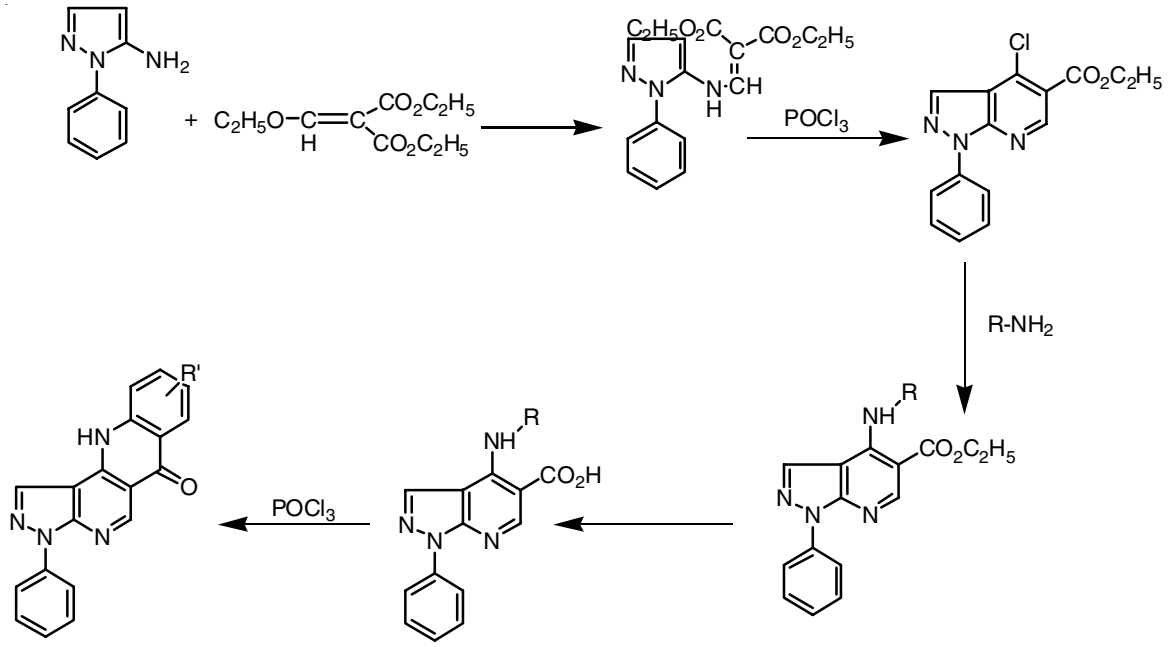
EXPERIMENTAL

Synthesis of benzo[b]pyrazolo[3,4-*b*]-1,6-naphthyridines (1-9): These were prepared according to the method already reported in our earlier commnication [12]. 5-Amino-1-phenylpyrazole by successive condensation with diethyl ethoxymalonate in ethanol followed by the thermal cyclization (Gould-Jacobs reaction) provided ethyl 4-oxo-1-phenylpyrazolo[3,4-b]pyridine-5-carboxylate. A clorodesoxygenation with $POCl_3$ gives the corresponding 4-chloro derivative which in turn reacts with various anilines to give the 4-anilino intermediate. This intermediate on tandem hydrolysis and cyclization provides the desired compounds (**1-9**) (**Scheme-I**).

Synthesis of pyrazolo[3,4-b]pyrido[2',3'-b]-1,6-naphthyridines and dipyrazolo[3,4-b];3',4'-h]-1,6-naphthyridines (10-17): These were prepared according to the method already reported in our previous commnication [12]. 5-Amino-1-phenylpyrazole by successive condensation with diethyl ethoxymalonate in ethanol followed by the thermal cyclization (Gould-Jacobs reaction) provided ethyl 4-oxo-1-phenylpyrazolo[3,4-b]pyridine-5-carboxylate. A chlorodesoxygenation with $POCl_3$ gives the corresponding 4-chloro derivative which in turn reacts with various amino pyridines and amino pyrazoles to give 4-anilino intermediate. This



Scheme-I



Scheme-II

intermediate on tandem hydrolysis and cyclization provides the desired compounds (**10**-**17**) (**Scheme-II**).

Antibacterial activity: The antibacterial activity of the 80 % methanolic, ethonolic and acetone extracts of different parts of *C. spinosa* and *C. decidua* was determined by disc diffusion method (NCCLS, 1997). Briefly, 100 µL of suspension containing 108 colony-forming units (CFU)/mL of bacteria cells were spread on petri plates containing NA medium (50 mL media/plate). The paper discs (6 mm in diameter) were separately impregnated with 15 µL of each extract placed on the agar, which had previously been inoculated with the selected test bacteria. Cefotaxime, enoxabid and dibkacin were used as a positive reference for bacteria. Discs without samples were used as a negative control. Plates were kept at 4 °C for 1 h. The plates were incubated at 37 °C for 24 h for bacteria. Antibacterial activity was assessed by measuring the diameter of growth-inhibition zone in millimeters (including disc diameter of 6 mm) for the test organisms comparing to the controls.

RESULTS AND DISCUSSION

Antibacterial activity: Antibacterial activity of benzo-[b]pyrazolo[3,4-b]-1,6-naphthyridines, pyrazolo[3,4-b]-pyrido[2',3'-b]-1,6-naphthyridines and dipyrazolo[3,4-b];3',4'-h]-1,6-naphthyridines (**1-17**) was tested by Agar plate disc diffusion method [13] against four different bacterial strains; *S. aureus* (Gram +ve), *Pseudomonas* (Gram -ve), *E. coli* (Gram -ve) and *Proteus* (+) (Gram +ve). The paper discs (6 mm in diameter) were separately impregnated with 15 µL of each extract placed

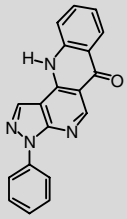
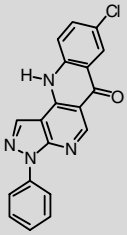
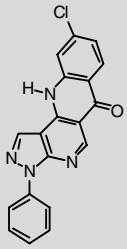
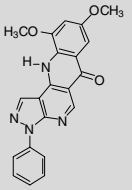
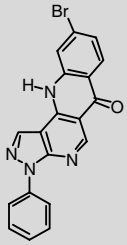
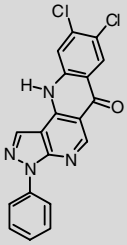
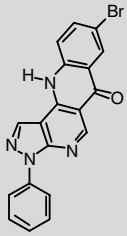
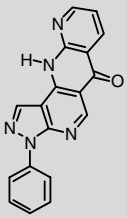
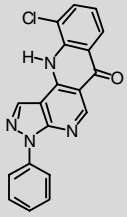
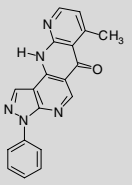
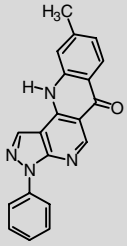
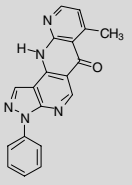
on the agar, which had previously been inoculated with the selected test bacteria. Cefotaxime, enoxabid and dibkacin were used as a positive reference for bacteria. Discs without samples were used as a negative control. Plates were kept at 4 °C for 1 h. The plates were incubated at 37 °C for 24 h for bacteria.

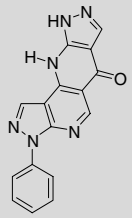
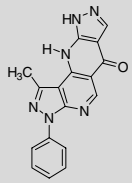
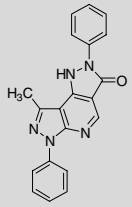
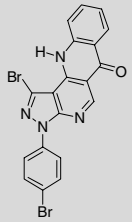
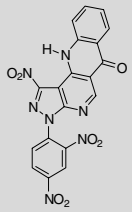
In case of antibacterial activity of synthesized compounds (**1-17**), different compound showed good activity against *S. aureus*, *Pseudomonas*, *Pseudomonas* and *E. coli*. Compounds **1**, **3**, **4**, **5**, **8**, **12**, **13**, **16** and **17** showed good results when compared with standards. The results of antibacterial activity are given in Table-1.

Conclusion

Antibacterial activity of benzo[b]pyrazolo[3,4-b]-1,6-naphthyridines, pyrazolo[3,4-b]pyrido[2',3'-b]-1,6-naphthyridines and dipyrazolo[3,4-b];3',4'-h]-1,6-naphthyridines (**1-**

TABLE-1
ANTIBACTERIAL ACTIVITY OF BENZO[b]PYRAZOLO[3,4-b]-1,6-NAPHTHYRIDINES, PYRAZOLO[3,4-b]PYRIDO[2',3'-b]-1,6-NAPHTHYRIDINES AND DIPYRAZOLO[3,4-b];3',4'-h]-1,6-NAPHTHYRIDINES

Compd. No.	Structure	SA	EC	P (+)	P (–)	Compd. No.	Structure	SA	EC	P (+)	P (–)
1		27	27	18	22	**7**		15	20	10	15
2		14	16	6	15	**8**		16	24	10	20
3		18	21	10	18	**9**		27	20	6	
4		13	28	4	12	**10**		12	22	-	12
5		17	30	9	16	**11**		20	4		14
6		15	20	15	18	**12**		24	14	15	3

Compd. No.	Structure	SA	EC	P (+)	P (–)
13		18	22	12	18
14		10		13	
15		30	26	6	10
16		20	30	5	18
17		21	28	12	14
	Enoxabid	15	–	12	13
	Cefotaxime	18	20	20	18
	Dibkacin	20	–	15	16

SA = *Staphylococus aureus* (+); EC = *E. coli* (+); P (+) = *Proteus* (+); P(–) = *Pseudomonas* (–)

17) were tested and found satisfactory results when compared with standards.

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