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Synthesis and biological activity of novel antibacterial quinazolines

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Abstract—Novel quinazolines, having interesting antibacterial activity have been prepared, characterized and tested against a panel of susceptible and resistant Gram positive and Gram negative organisms.

1. Introduction

The rapid rise in bacterial resistance to the traditional antibiotics such as Penicillins[1] and tetracyclines[2] has encouraged a continuing search for new classes of compounds with novel modes of antibacterial activity. The quinolone antibacterials have emerged as an area of immense interest because of their broad spectrum of in vitro activity and their in vivo chemotherapeutic efficiency.[3–6] However, the current quinolones suffer from some drawbacks such as limited activities against a number of clinically important Gram positive such as *Streptococcus pneumonia*, *Streptococcus pyrogens*, *Staphylococcus aureus* and *Enterococcus*, low activity against anaerobes and increasing quiolones resistance among many pathogens.[7] In view of the above, the design and synthesis of newer antimicrobials is an area of immense significance and continues to attract the attention of increasing number of medicinal chemists. Quinazolines exhibit a wide range of activity such as anthelmintic,[8] antimicrobial,[9–11] CNS depressant,[12] neuroleptic,[13] hypnotic[14] and analgesic.[15] In continuation of our work on heterocycles[16–20] with biological interest, we wish to report here in some new title quinazolines in order to study their antibacterial activities.

2. Chemistry

A novel series of 6-methyl-2-aryl/secondary amino-4-aryl-quinazolines were conveniently prepared[21] by the microwave condensation reactions of N-imidoyl iminophosphorane **4** with aldehydes **5**. The iminophosphoranes **4** in turn were obtained from the corresponding N-aryl benzamidine/guanidines **1** by their initial conversion to N-chlorobenzamidine/guanidine **2** followed by treatment with triphenylphosphine. The exposure of a mixture of N-imidoyliminophosphorane **4** and aldehyde **5** to microwave radiation at a power of 300 W for a period of 10–15 min (5 cycles of 3 min each) resulted in the excellent yields of quinozolines **6** (Scheme 1), which were purified by column chromatography using a mixture of ethyl acetate and hexane (1:10). The quinazolines so obtained (**6a–e**) were characterized on the basis of analytical data and spectral evidences.

3. Antimicrobial activity

The antibacterial activity of all the synthesized compounds was determined by agar well diffusion method as recommended by the National Committee for Clinical Laboratory Standards[22–24] against Gram positive microorganisms *Bacillus subtilis* MTCC 121, *Bacillus cereus* MTCC 1272, *Staphyloccocus aureus* MTCC 1430, *Enterococcus faecalis* MTCC 439 and Gram negative microorganisms *Escherichia coli* MTCC 42, *Pseudomonas aeruginosa* MTCC 1034, *Proteus* vulgaris MTCC 744, *Klebsiella pneumoniae* MTCC 109 and *Shigella sonnei* MTCC 2957 at 50 μg/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. Solvent control was also maintained under similar conditions. The

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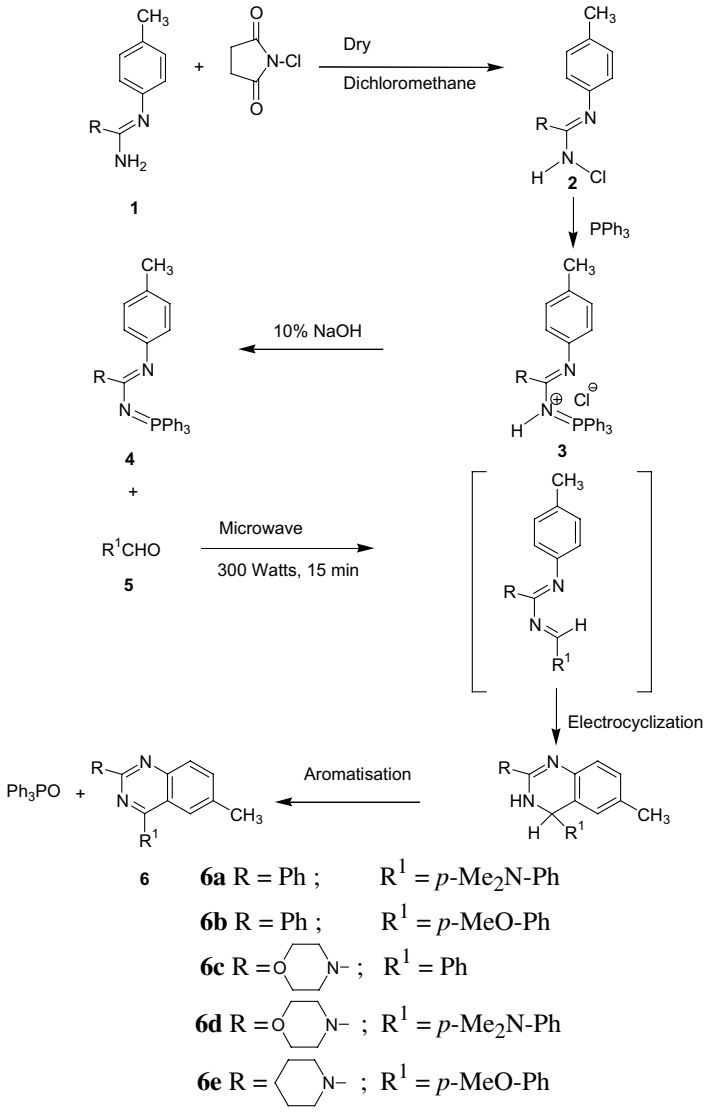

Scheme 1. Synthesis of 6-methyl-2-aryl/secondary amino-4-aryl-quinazolines.

Table 1. Antibacterial activity of compounds **6a**–**e** against Gram positive and Gram negative bacterial strains

Bacterial Strain	Diameter growth of inhibition area (mm)						
	Compound						
	6a	**6b**	**6c**	**6d**	**6e**	DMSO	Ciprofloxacin
B. subtilis MTCC 121	15	12	16	18	21	0	22
B. cereus MTCC 1272	14	13	15	19	16	0	17
S. aureus MTCC 1430	11	0	12	22	19	0	21
E. faecalis MTCC 439	12	12	16	17	16	0	16
P. aeruginosa MTCC 1034	18	16	19	16	15	0	18
P. vulgaris MTCC 744	17	15	18	18	18	0	19
K. pneumoniac MTCC 109	19	17	19	20	20	0	18
S. sonnei MTCC 2957	16	15	20	19	21	0	21
E. coli MTCC 42	18	16	21	20	19	0	22

Petri dishes were incubated at 37 °C for 48 h to know the bacterial growth inhibition developed around the hole and was measured in millimetre for particular test solution with particular organism. The results are presented in Table 1.

4. Results and discussion

It has been observed that the test compounds (**6a**–**e**) exhibited interesting antibacterial activity, however with a degree of variation. Results reveal that compounds **6d**

and **6e** showed significant activity against *K. pneumoniae* as compared to ciprofloxacin. Moreover, the introduction of *p*-methoxy phenyl group in compound **6b**, decreases its antibacterial activity against Gram positive and Gram negative bacterial strains. However compound **6b** did not show any activity against Gram positive *S. aureus*. Antibacterial data indicated that compound **6c** showed maximum activity against *S. sonnei* as compared to the standard and exhibited significant activity against *E. faecalis* and *P. aeruginosa* as compared to ciprofloxacin. It is interesting to note that by the introduction of morpholino and piperidino moieties in compounds **6d** and **6e**, increases their antibacterial activity against Gram positive and Gram negative bacterial strains. Compound **6d** was superior in action against *S. aureus*, *E. faecalis* and *K. pneumoniae* over the standard ciprofloxacin, where as compound **6e** containing piperidino moiety showed maximum activity against *K. pneumoniae* as compared to ciprofloxacin. Solvent DMSO did not show any antibacterial activity. Therefore the results of antibacterial screening of compounds revealed that quinazolines having morpholino and piperidino heterocycles showed significant activity comparable to standard drug against Gram positive and Gram negative bacterial strains. The other chemical moiety found to be favourable towards antibacterial activity was *p*-dimethylamino phenyl followed by *p*-methoxy phenyl in the quinazoline ring system.

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