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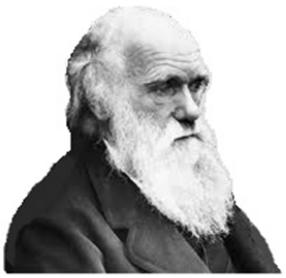

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Design and Antimicrobial evaluation of 1-(2-(2,3,5-triphenylcyclopenta-2,4-dien-1-yl)ethyl)piperazine and their derivatives

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ABSTRACT

A total of six of 1,2,4,5-tetrasubstituted imidazoles were prepared by multicomponent cyclo-condensation of benzil, aromatic aldehyde, aminoethylpiperazine and ammonium acetate. The prepared compounds were screened for their antibacterial activity against *S. aureus, S. typhi, E.coli* and *Pseudomonas* and antifungal activity against *A. niger, C. albicans, Rhizopus* sp, and *Mucor*. They exhibited better activities against all the tested bacterial and fungal strains.

***Keywords*:** imidazoles, multicomponent, piperazine, antibacterial studies, antifungal studies

1. INTRODUCTION

The battle to control bacterial and other microbial infectious diseases has continued all through mankind's history. Over hundreds of years, epidemics, such as cholera and plague have at times been prevalent and widespread, occasionally ensuing in dramatic local inhabitants

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decreases [1]. Pneumonia – was depicted as "the captain of the men of death" in the 19th Century [2]. Tuberculosis (TB) is another common and often deadly infectious disease in humans, with more than 1.5 million deaths per year worldwide [3]. One of the significant advances in clinical science in the course of the only remaining century has been the improvement of antimicrobials. Notwithstanding, an outcome of their across the board use has been the development of medication safe populaces of microorganisms.

Disease, by such medication safe pathogens, has become a significant reason for harshness and mortality overall indeed: in an ongoing update from the Infectious Diseases Society of America [4]. There is obviously a requirement for the improvement of new antimicrobials; yet more critically, there is the requirement for the advancement of new classes of antimicrobials, as opposed to drugs essentially dependent on analogs of known frameworks. Protection from anti-microbials is one of the most difficult issues related with the treatment of irresistible infections today [5-7]. To beat horribleness and mortality because of antimicrobial safe contamination and to protect the viability of antimicrobial specialists, the method for treatment is to be changed through the improvement of new procedures.

Heterocycles, as favored structures in drug discovery, comprise one of the most critical territories of research in medicinal science [8]. Writing review featured the importance of imidazole mixes. The imidazole heterocycle which goes about as an auxiliary subunit of increasingly complex common items and medications is omnipresent in nature [9]. Imidazole-containing derivatives exhibit diverse biological activities and pharmacological properties, such as anti-bacterial [10, 11], anti-alzheimer [12], anti-fungal [13], anti-HCV [14], anti-HIV [15], anti-malarial [16, 17] and anti-cancer [18] activities, play a pivotal role in drug discovery. Right now, we aimed to produce a progression of imidazoles as prodrugs. A series of substituted benzhydrazide, comprising diverse electron-withdrawing and electron attracting groups were chosen. After being prepared, the compounds are screened for their antibacterial and antifungal activities against standard bacterial and fungal strains.

2. MATERIALS AND METHODS

2. 1. Reparation of 1-(2-(2,3,5-triphenylcyclopenta-2,4-dien-1-yl)ethyl)piperazine and their derivatives

1-(2-(2,3,5-triphenylcyclopenta-2,4-dien-1-yl)ethyl)piperazine (1-6) are prepared by multicomponent condensation of benzil, aromatic aldehyde, aminoethylpiperazine and ammonium acetate using sulphated yttria as a catalyst in ethanol. The detailed synthetic method is given in literature [19].

2. 2. Antibacterial activity by disc diffusion method

Nutrient agar plates were prepared under sterile conditions and incubated overnight to detect contamination. About 0.2 mL of working stock culture was transferred into separate nutrient agar plates and spread thoroughly using a glass spreader. Whatmann No.1 discs (6 mm in diameter) were impregnated with the test compounds dissolved in DMSO (200 mg/mL) for about half an hour. Commercially available drug disc *(Ciprofloxacin* 10 µg/disc) was used as a positive reference standard. Negative controls were also prepared by impregnating the disc of same size in DMSO solvent.

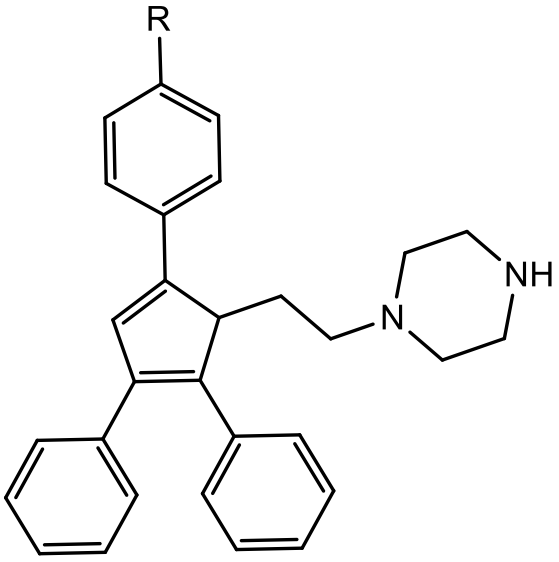
The discs were placed on the inoculated agar plates and incubated at 37 ±1 °C for about 18-24 h. Antibacterial activity was evaluated by measuring the zone of inhibition against the test organism.

2. 3. Antifungal activity by disc diffusion method

Sabouraud's dextrose agar (SDA) medium was used for the growth of fungi and testing was done in Sabouraud's dextrose broth (SDB) medium. The subculture and the viable count were carried out by the same procedure used in antibacterial studies except the temperature, which should be maintained at 28 ±1 °C for about 72 h. Similarly, for disc diffusion method, the petridishes were incubated at 28 ±1 °C for about 72 h. The same concentration of the test compound, solvent (DMSO) and *Cetramazole* (standard) prepared previously were used for the antifungal studies.

2. 4. Minimum Inhibitory Concentration (MIC)

The lowest concentration of the test compounds which caused apparently the inhibition of growth of organism, was taken as the minimum inhibitory concentration (MIC). The minimum inhibitory concentration was recorded by visual observation after 24 h (bacteria) and 72-96 h (fungi) of incubation. The sterile distilled water and DMSO did not show any inhibition.



Entry	R
1	H
2	F
3	Cl
4	Br
5	CH_3
4	OCH_3

Fig. 1. Numbering scheme of imidazoles

3. RESULTS AND DISCUSSION

3. 1. Chemistry

1,2,4,5-tetrasubstituted imidazoles (1-6) were prepared by condensation of benzil, aromatic aldehyde, aminoethylpiperazine and ammonium acetate [19]. Numbering scheme of imidazoles are given in **Fig. 1**.

3. 2. Antibacterial studies

Table 1 shows the *in vitro* antibacterial activities of the substituted imidazoles 1-6 and of *ciproflocin* taken as the reference drug on a panel of bacterial strains, such as *S. aureus, S. typhi, E. coli* and *Pseudomonas* as minimum inhibitory concentration (MIC, μg·mL^{-1}).

Table 1. Minimum inhibitory concentration (μg/mL) of imidazoles (1-6)

Compound	Minimum inhibitory concentration in μg·mL^{-1}							
	S. aureus	*S. typhi*	*E. coli*	*Pseudomonas*	*A. niger*	*C. albicans*	*Rhizopus* sp	*Mucor*
1	50	6.25	100	50	100	25	12.5	100
2	12.5	6.25	12.5	100	6.25	12.5	50	50
3	25	25	25	25	25	50	50	25
4	6.25	12.5	12.5	25	12.5	12.5	100	50
5	12.5	25	12.5	12.5	100	25	12.5	25
6	100	12.5	12.5	25	50	100	50	200
Ciproflocin	6.25	6.25	6.25	6.25				
Amphotericin					12.5	12.5	12.5	12.5

The percentage of antimicrobial potency of the tested compounds, compared with reference, was calculated by adopting the following equation:

$$\text{Antimicrobial potency (\%)} = \frac{MIC(\mu g mL^{-1}) of\ reference\ compound}{MIC(\mu g mL^{-1}) of\ test\ compound} \times 100$$

The compound **1** showed excellent activity against *S. typi*, while poor activity was noted against the remaining tested strains. Introduction of a fluoro group at *para* position of the phenyl group at 5 position in imidazoles (compound **2**) exerted activity at against *S. aureus, S. typhi* and *E. coli*, while against *Pseudomonace* showed a poor activity.

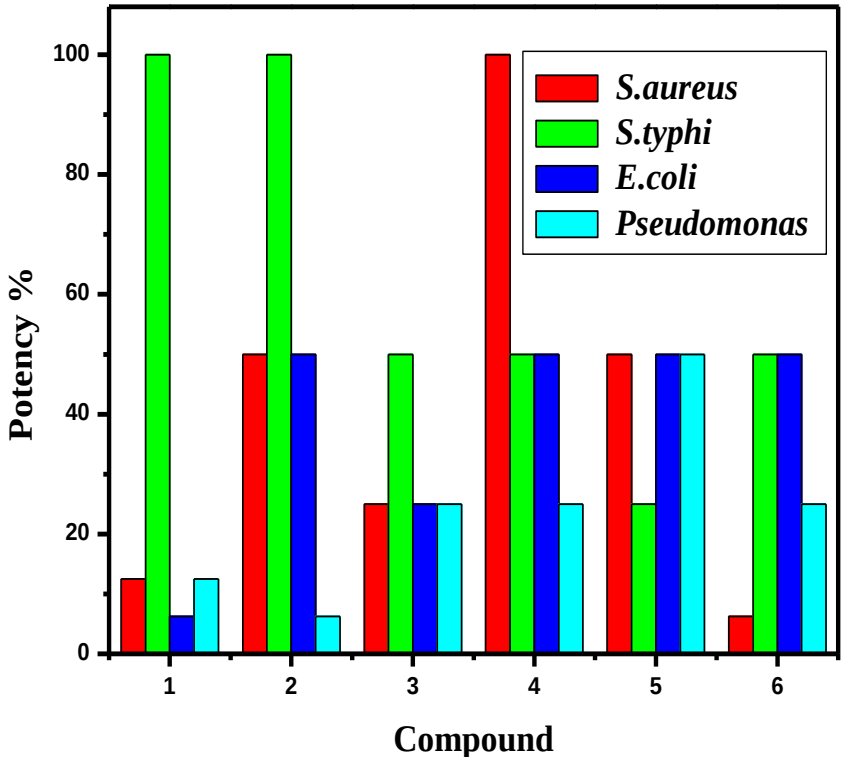


Fig. 2. Potency diagram of antibacterial activity of compounds (**1-6**)

Replacement of fluoro group by chloro group in compound 2 (compound 3) exhibited moderate activity against all the tested bacterial strains. Introduction of a bromo group at *para* position of the phenyl moiety at 5 position in imidazoles (compound 4) exhibited excellent activity against *S. typhi* and good activity against *S. aureus* and *E. coli*, whereas poor activity against *Pseudomonaces*. Substitution of a methyl group in 1 (compound 5) showed a good activity against *S. aureus*, *E. coli* and *Pseudomonace*, while the activity was reduced towards *S. typhi*. Substitution of a methoxy group at *para* position of the phenyl group at 5 position in imidazoles (compound 5). Instead of methyl functionality, substitution of methoxy group in compound 5 (compound 6) showed good activity against *S. typhi* and *E. coli* and moderate activity (**Fig. 2**) against *Pseudomonace* and moderate activity against *Pseudomonace*, whereas poor activity was noted against *S. aureus* [20].

3. 3. Antifungal activity

Table 1 shows the *in vitro* antifungal activities of the tetra substituted imidazoles 1-6 and of *Amphotericin* taken as the reference drug on a panel of fungi such as *A. niger, C. albicans, Rhizopus* sp., and *Mucor* as minimum inhibitory concentration (MIC, $\mu g \cdot mL^{-1}$). Against all the fungal strains, compound 1 showed poor antifungal activity except *Rhizapus* sp. (**Fig. 3**).

The introduction of fluoro function at *para* position of the phenyl group at 5 position in imidazoles compound 1 (compound 2) exhibited excellent activity against *Rhizapus* sp. and *mucor*. *Para* chloro substituted compound 3 showed moderate activities against all the tested fungal strains.

Para bromo substituted compound 4 exhibited excellent activities against *A. niger* and *C. albicans* whereas poor activity was noted against *Rhizapus* sp and mucor. Compound 5 exhibited good antifungal activity against *A. niger* and *C. albicans* while against *Rhizapus* sp. and mucor poor activities were noted. Introduction of methoxy phenyl group at C-2 and C-6 position in compound 1 (compound 6) showed a good activity against all the tested antifungal strains.

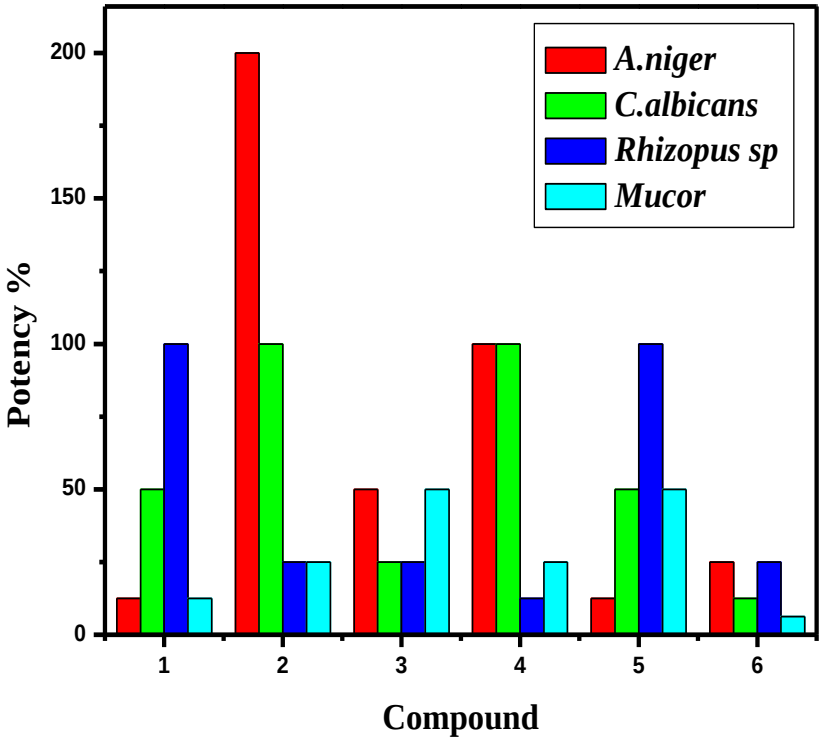


Fig. 3. Potency diagram of antifungal activity of compounds (**1-6**)

4. CONCLUSIONS

Overall, the 1,2,4,5-tetrasubstituted imidazoles (1-6) were prepared by mixing of benzil, aromatic aldehyde, aminoethylpiperazine and ammonium acetate. The imidazoles (1-6) were monitored for their antibacterial activity against *S. aureus*, *S. typhi*, *E. coli* and *Pseudomonas* and antifungal activity against *A. niger*, *C. albicans*, *Rhizopus* sp, and *Mucor*. The compound 1 showed an excellent activity against *S. typi*, while poor activity was noted against the remaining tested strains, and in the case of antifungal activity, compound 2 exhibited excellent activity against *Rhizapu* sp. and *mucor*.

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