Evaluation of the antimicrobial activity of some novel α substituted hydroxylamine derivatives

Sir,

Diazepines, imidazoles, several heterocyclics, alpha substituted hydroxylamine derivatives and related compounds are known to possess important pharmacological properties.\textsuperscript{1-3} Some new compounds were formulated by substitutions of functional groups in these compounds. A preliminary study of the antimicrobial activity of the novel α substituted hydroxylamine derivatives was done in order to determine the effect of substitutions on their antimicrobial activity. The present communication reports the findings of the preliminary study of the antimicrobial activity of the following compounds.

1. Phthalamidobenzimidazolyl ethanoate
2. Benzamidobenzimidazolyl ethanoate
3. Benzophenoneoximinobenzimidazolyl ethanoate
4. Benzophenoneoximimidazolyl ethanoate
5. 2,3-(Bisoxypthalimido) imidazolyl ethanoate
6. 3-(Ethoxypthalimido) pentane\textsubscript{2}, \textit{4} dione
7. 3-(Ethoxymino) pentane\textsubscript{2}, \textit{4} dione salt
8. 3-(Ethoxy)-(p-chlorophenyl) biguanidinonpentane\textsubscript{2}, \textit{4} dione
9. Ethyl (2-ethoxypthalimido) butanoate
10. Diethyl (2-ethoxypthalimido) propane dicoate
11. Diethyl (2-butoxypthalimido) propane dicoate
12. Diethyl (2-ethoxyamino) propane dicoate
13. 3N-[Butoxypthalimido] \textsubscript{2}, \textit{4} dimethyl 1,5 benzodiazepine
14. 3N-[Ethoxy-5-N-(p-chlorophenyl) biguanidino]pentane 2,4 dione
15. 3N-[Butoxypthalimido] \textsubscript{2}, \textit{4} dimethyl 1,5 benzodiazepine
16. 5N-cabazolylethoxyphthalimide

Structures of the above, synthesized, compounds were confirmed on the basis of their infrared (KBr), \textit{1}H nuclear magnetic resonance, mass spectral data and elemental analysis. Compounds 1-4 were prepared by the condensation of different heterocycle alkanoyl halides with N-hydroxyphthalimide, benzohydroxamic acid and benzophenoneoxime. Compound 5 was prepared by bromination of imidazolyl propene followed by condensation with N-hydroxyphthalimide. Compounds 7 and 8 were prepared by the condensation of bromoethoxy (p-chlorophenyl) biguanide with monosodio pentane\textsubscript{2}, \textit{4} dione. Compound 9 was prepared by treating bromoalkoxyphthalimide with ethylacetocacetate, whereas Compounds 10 and 11 were obtained by treatment with diethylmalonate. Condensation of \textit{ω}-bromoaminooxy salt with sodium diethylmalonate yielded Compound 12. Cyclization of suitable reactive methylene compounds with O-phenylenediamine gave corresponding diazepine derivatives. Bromoalkoxyphthalimide on reaction with carbazole/NaH gave Compound 16.

The antimicrobial activity of all compounds was tested at 250, 500, 750 and 1000 ppm. Optimum inhibition was observed at 1000 ppm and the results at this concentration are given in Table 1. Inhibition activity was tested against clinical Pseudomonas aeruginosa (Org.1), Escherichia coli (Org.2), Proteus mirabilis (Org.4), Klebsiella pneumoniae (Org.4), Salmonella typhi (Org.5), Bacillus subtilis (Org.6), Aspergillus niger (Org.7), Candida albicans (Org.8), Aspergillus fumigatus (Org.9), Trichopyton rubrum (Org.10) and Cladosporium sps. (Org.11).

Antimicrobial activity was first confirmed by tube dilution method\textsuperscript{4} in nutrient broth. Sensitivity test was done by cup or

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well method and zone of inhibition was taken as an indication of inhibition activity. 500 μl of 1000 ppm stock solution of test compound was filled in each well.

Antifungal activity was observed on Sabouraud dextrose agar and assayed using well method. Scoring was done on the basis of zone of inhibition as follows:

| (-) | Absence of inhibition |
| (+) | zone of inhibition up to 10 mm |
| (+++) | zone of inhibition >10 and > 15 mm |

Extract-free control and three repetitions of each experiment were maintained. It is evident from the given table that significant inhibition of Organism 1 was shown by Compounds 2, 3, 4 and 5. Compounds 8, 12 and 15 were seen to be more inhibitory as compared to standard (Streptomycin) for Organism 2. None of the compounds was found to be inhibitory for Organisms 3 and 5. Compound 7 showed significant inhibition of growth of Organism 4. Except for five compounds i.e. 2, 10, 11, 15 and 16, which showed comparable inhibition with standard (Streptomycin), all other compounds were found to be ineffective. Compounds 7, 11, 12, 14 and 15 showed maximum inhibition of Organism 7. Compound 7 also showed severe inhibition of Organism 8. Compound 3 severely inhibited growth of Organisms 9 and 11. Growth of Organism 11 was also severely restricted by Compound 13.

It can be concluded that most of the heterocyclic compounds used showed appreciable antimicrobial activity. Compounds show enhanced activity when phthalimidoxy, aminooxy and alkoxybiguanides derivatives of benzimidazole and imidazole show better antibacterial inhibition.

The presence of the benzophenone oxime group in the molecule increases both the antifungal and antibacterial activity of benzimidazole. Benzodiazipine derivatives of phthalimidoxy and biguanides showed better activity than the standard used. The activity of carbozoles increases when substituted with alkoxyphthalimide. The presence of aminooxy moiety in reactive methylene compounds increases the activity to an appreciable extent (54% larger zone of inhibition for Compound 14 and 36% for Compound 15) as compared to streptomycin.

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