Antimicrobial activity of some pyridazinoquinoline derivatives

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\textbf{Abstract}: Some pyridazinoquinoline derivatives have been synthesized and screened for their possible antimicrobial activity. Compound 1c exhibited significant activity against \textit{S. aureus}, 1d and 1f exhibited significant activity against \textit{E. coli}; whereas 1a and 1b exhibited pronounced activity against fungi \textit{C. albicans}.

\textbf{Keywords}: Antimicrobial activity, heterocycles, quinoline derivatives.

Quinoline derivatives constitute an important class of heterocyclic molecules. Various substituted quinolines are reported to elicit a wide range of biological activities\textsuperscript{1}. The immunity developed by malaria parasites against almost all the available drugs, urged the scientific community to look for newer derivatives possessing significant activity against such dreaded parasites. In our search for the synthesis of some biologically active heterocycles, we report herein some pyridazinoquinoline derivatives possessing anti-bacterial and anti-fungal activity.

\textbf{Results and discussion}

The title compounds were synthesized from our laboratory as per the reported procedure\textsuperscript{2}. The screening of the compounds for activity against microorganisms has been made on the basis of their solubility in DMSO. It has been observed that 1e exhibited almost comparable activity with respect to Chloramphenicol against \textit{Staphylococcus aureus}, whereas 1d and 1f exhibited significant activity against \textit{E. coli}. Further, the screening of 1a and 1b for antifungal activity against \textit{Candida albicans} using Clotrimazole as the standard exhibited pronounced activity (Table 1). Decrease in the concentration level below 1000 µg/mL, prevented its activity. Analysis of the activity data with respect to the structure reveals that the two ends of the molecule as indicated in structure 1 govern the activity and is absolutely dependent on the relative polarizability of the molecule. For \textit{Staphylococcus aureus} presence of the -NO\textsubscript{2} group in the \textit{meta} position of aromatic ring-B deactivates the molecule and thus the activity of the molecule is less than that of the unsubstituted molecule. On the contrary, the relative polarizability of the molecule is more when the NO\textsubscript{2} group is not placed in \textit{meta} position of the aromatic ring-B. The substitution on \textit{para} positions of both rings neutralizes each other polarizability and thus the molecule behaves at par with the unsubstituted molecule. This evidently suggests that the directional polarizability in connection with the activity could have been enhanced with the substitution of electron releasing group in one of the ring there by establishing the donor-acceptor concept. Unfortunately, the molecules with similar substitutions were insoluble in DMSO.

Analysis of the activity with respect to the different substitutions shows a linear relation as per the Hammett plot for both \textit{S. aureus} and \textit{E. coli}. However, for \textit{Candida albicans} neither the unsubstituted one nor compounds with both \textit{p}-substitutions displayed any activity. This further, emphasizes two factors, (i) presence of -NO\textsubscript{2} group in \textit{para} positions of both the rings neutralizes each other polarizability and behaves as if the molecule is unsubstituted; (ii) for \textit{Candida albicans} substitution at \textit{meta} position enhances the activity quite significantly.

\textbf{Materials and methods}:

\textit{Synthesis of the title compound (1)}: \textit{General procedure}:
To a mixture of amyl nitrate (0.06 mol) and HCl (5 mL) at 0 °C, substituted/unsubstituted aniline in amyl alcohol was added under stirring. To the resulting mixture a solution of 2-methyl-4-oxoquinoline (0.05 mol) in 5 \textit{N} NaOH solution (20 mL) was added and stirred for 30 min. The reaction mass was neutralized with ice-cold solution of 5 \textit{N} HCl, the resulting solid was collected, washed with water and recrys-
tallized from ethanol. To the synthetic quinoline derivatives (0.01 mol) in benzene (50 mL) was added phenylpropionic acid (0.01 mol) and was refluxed for 8 h. Removal of the solvent gave a solid which was recrystallized from ethanol to give the desired product.

The individual chemicals to be tested were weighed and dissolved in DMSO to prepare a clear solution, to make a concentration of 1000 µg/mL. They were sterilized by filtration using satorious 0.22 mm cellulose membrane filters.

Chloramphenicol solution was prepared by dissolving it in ethanol to give a final solution of concentration 1000 µg/mL. This was used as standard chemical against the bacteria species. Clotrimazole solution was prepared by dissolving it in ethanol to make a concentration of 1000 µg/mL.

The zone of inhibition for each chemical was determined by using cup plate method as described in the literature3.

| Compd. | R    | R'   | S. aureus (nm) | E. coli (nm) | C. albicana (nm) |
|--------|------|------|----------------|--------------|-----------------|
| 1a     | m-NO₂| m-NO₂| 9              | –            | 13              |
| 1b     | H    | m-NO₂| 9              | 10           | 13              |
| 1c     | m-NO₂| H    | 13             | –            | 12              |
| 1d     | H    | H    | 10             | 12           | –               |
| 1e     | p-NO₂| m-NO₂| 12             | 9            | –               |
| 1f     | p-NO₂| p-NO₂| 10             | 11           | –               |
| Chloramphenicol | –   | –   | 16             | 14           |                 |
| Clotrimazole      | –   | –   | –              | –            | 15              |

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