Revista Argentina de Clínica Psicológica
2016, Vol. XXV, N°2, 204-206
DOI: 10.53555/03276716.2016.01



# Antibacterial and Antifungal activity of novel naphthyridine derivatives

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Received: 24/02/2016 Accepted:17/05/2016

**Abstract**
With the rising antimicrobial resistance (AMR) within the microbial populations and limited effectiveness of existing antibiotics, discovery of antimicrobial agents has become crucial across the globe. To this end, we have tested the efficacy of five novel Naphthyridine compounds towards antibacterial and antifungal activity. Among the novel molecules tested, compounds [(8,10-Dibromo-6-phenyl-6a,7,10,12-tetrahydro-1,7,12a-triaza-benzo[a]anthracen-12-one)] displayed better antibacterial and antifungal properties compared to others. Thus, the newly derived molecule may better help in combating microbes which have developed antibiotic in the recent past.

**Key words:** Naphthyridines, antimicrobial activity, DNA gyrase,

**Introduction:**
As per the World Health Organization Data (WHO) the death rate in hospitals is alarming due to the bacterial infections and is listed as top ten causes of death of patients across the globe (WHO 2016). On the other hand, the fungal resistance (antimicrobial resistance, AMR) has attained special status as they are prone to kill patients particularly that are immune-compromised wherein the fungal species like *Aspergillus niger* and *Mucor mycosis* are proven to be fatal. By 2050, it is estimated that all the AMR strains may affect millions of patients in the world leading to at least ten millions of deaths annually with a major prediction of deaths in Asia and Africa (Blair et al. 2015). Therefore, pharmaceutical industry in the recent past has made a special focus on developing antimicrobial compounds for effective control of AMR strains. However, with the evolution of resistance mechanisms by AMR population the discovery of novel drugs has become only alternative to combat antimicrobial resistance to save millions of lives (Blair et al., 2015).
Naphthyridines since last decades were known for their anti-asthmatic, antimicrobial and antimalarial activities besides their wide-spectrum of antimicrobial activity (Enguehard and Gueiffier 2007; Zhu et al. 2009). Naphthyridine compounds especially 2-Pyridones were featured as novel antimicrobial molecules due to stable, efficient nature and wide spectrum of antimicrobial activity (Hooper 1995). To this end, we tested five novel napthyridine derivatives (synthesized in our laboratory) and tested their AMR levels against selected bacteria and fungi.

**Materials and Methods:**
**Antimicrobial Screening:** All the chemicals that are used in the current study are of analytical grades and were procured from Himedia. The microorganisms (bacteria and fungi) are procured from National Chemical Laboratory, Pune and are subcultured periodically under aseptic conditions and preserved as glycerol stocks in deep refrigerators for further use. Five novel naphthyridine compounds (NNC) used in the study (Table 1) were obtained from the Department of Chemistry, Kakatiya University, Warangal.

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**Table 1**. Nomenclature of naphthyridine compounds as per IUPAC

| Code* | COMPOUND |
|---|---|
| ND1 | 8,10-Dibromo-6-(4-chloro-phenyl)-10,12-dihydro1,7,12a-triaza-benzo[a]anthracen-12-one |
| ND2 | 8,10-Dibromo-6-(4-methoxy-phenyl)-1,7,12a-triaza-benzo[a]anthracen-12-one |
| ND3 | 8,10-Dibromo-6-phenyl-6a,7,10,12-tetrahydro-1,7,12a-triaza-benzo[a]anthracen-12-one |
| ND4 | 6-(4-Methoxy-phenyl)-5,6-dihydro-1,7,12a-triaza-benzo[a]anthracen-12-one |
| ND5 | 6-phenyl-5,6-dihyro-1,7,12a-triaza-benzo[a]anthracen-12-one |

* ND stands for Novel Napthyridine derivatives

All the strains that are used for antimicrobial study were grown on simple nutrient agar media for bacteria and potato dextrose agar media for fungi. (David and Richard 2001; Wonarxvaduz and Cramer 1974). To test the efficacy of novel napthyridine derivatives we have maintained two control samples (antibiotics) i.e., Streptomycin and amphotericin B at two concentrations (250 and 500 μg $mL^{-1}$). Prior to surface streaking on the above said medium for bacteria and fungi, the microorganisms were checked for their purity by serial dilution. Following incubation period, a single colony of each microbial population was selected and the same was used in AMR studies. The newly synthesized napthyridine derivatives were dissolved in acetone (1mg/ml) to make a stock solution.For all disc studies, with the help of cork borer we have prepared discs (0.5 cm) from whatman filter paper and following this these were sterilized as per standard conditions. From the above stock solutions, an aliquot of 250 μL and 500 μL was taken from each napthyridine derivative samples and was transferred into different tubes where in each one disc was transferred to soak. All the tubes were kept in water bath at 60°C until the entire acetone got evaporated (Spooner and Skyes 1972; Hugo and Russel 1987). Thus the discs with different concentrations (250 μg or 500 μg) different napthyridine concentrations were made and placed on lawns of different microorganisms on their respective media. Zone of inhibition around each NNC disc was measured Hiantibiotic zone scale™ ( Himedia, India) following incubation at 37°C + 1°C for 24 hours. All the experiments were carried out in triplicates and the mean values of the three were used in the conclusion drawing.

**Results and Discussion:**

For obtaining accurate results, we have maintained two controls (one with microorganism and other without microorganism) and the zone of inhibition was recorded both in bacterial and fungal cultures as per the standard methods (Table-2).

**Table 2: Antimicrobial results of novel napthyridines against selected bacteria and fungi**

| Microorganism | μg / disc | S* | A* | Naphthyridine Derivatives (ND) | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | ND1 | ND2 | ND3 | ND4 | ND5 |
| *Escherichia coli* | 250 | 3 | 0 | 0 | 0 | 0.5 | 0 | 1 |
| | 500 | 5 | 0 | 10 | 0 | 1.5 | 0 | 2 |
| *Pseudomonas aeruginosa* | 250 | 2 | 0 | 3 | 0 | 1 | 0 | 1 |
| | 500 | 6 | 0 | 7 | 0 | 3 | 0 | 2 |
| *Staphylococcus aureus* | 250 | 3 | 0 | 0 | 0 | 2 | 0 | 0 |
| | 500 | 7 | 0 | 0 | 0 | 2.5 | 0 | 0 |
| *Aspergillus niger* | 250 | 0 | 3 | 0 | 0 | 3 | 0 | 3 |
| | 500 | 0 | 4 | 3 | 0 | 9 | 0 | 7 |
| *Aspergillus niger* | 250 | 0 | 2 | 0 | 2 | 4 | 0 | 2 |
| | 500 | 0 | 4 | 0 | 5 | 5 | 0 | 4 |
| *Fusarium oxysporum* | 250 | 0 | 1 | 0 | 0 | 7 | 0 | 0 |
| | 500 | 0 | 3 | 0 | 7 | 8 | 0 | 9 |

*S-Streptomycin; A-Amphotericin B

The molecular structural analysis of the napthyridine compounds reveal that the molecule, which ever possessed the halogen group atom were found to be showing the antimicrobial activity (ND 3) and the molecules which did not possessed halogen group has not shown any antimicrobial activity (ND4). Further, the position of halogen in the molecule displayed greater influence on the activity spectrum. The napthyridine derivatives comprising of halogen at C-8 and C- 10 (ND2) position were found to be showing high level of antimicrobial activity. In addition to the above, it is interesting to note that the halogen type

showed profound impact on (Table-2). Interestingly the napthyridine derivative ND4 with iodine atom at C-8 position showed complete antimicrobial activity against all the species tested in the current study. The ND1 at higher concentration (500 μg / disc) has showed higher antimicrobial activity on *Escherichia coli* and *Pseudomonas aeruginosa* and without any effect on *Staphylococcus aureus.* On the other hand ND3 and ND5 displayed high antifungal activity compared to other napthyridine derivatives with a clue that these molecules may be potentially used for antifungal compounds in future for human kind. Particularly the ND3 and ND5 molecules have showed antifungal property against *Aspergillus niger* and *Fusarium oxysporum.* Interestingly the ND4 have not shown any antibacterial nor antifungal activity. From the above studies it is evident that the compounds ND1 to ND5 as mentioned in the Table 2 might disrupt the cytoplasmic membranes and impact the replication machinery as observed in several other studies (Higgins 1978). Such studies are well documented wherein the inhibition of DNA replicative enzymes such as gyrase which is responsible for supercoiling of the genomic DNA shall lose its function leading to uncontrolled synthesis of mRNA and protein (Uri and Actor 1985; Gellert et al. 1976; Wang 1974; Wang 1985).

The current study for the first time resulted in a broad spectrum antimicrobial property against important microbial species and further research on such compounds shall definitely throw light on health industry to combat with AMR species.

**Acknowledgements**:

Thanks to the Head, Department of Biotechnology, Telangana University for providing the facilities in carrying out antimicrobial work with novel napthyridine molecules.

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