



Promising activity of tetrahydroisoquinolines against multidrug-resistant clinical *Salmonella* isolates and cytotoxicity against monkey kidney cells



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INTRODUCTION

Salmonella infections are a major cause of morbidity and mortality in humans. Each year, an estimated 1.3 billion cases resulting to about 3 million deaths occur worldwide due to salmonellosis (Kirk *et al.*, 2015).

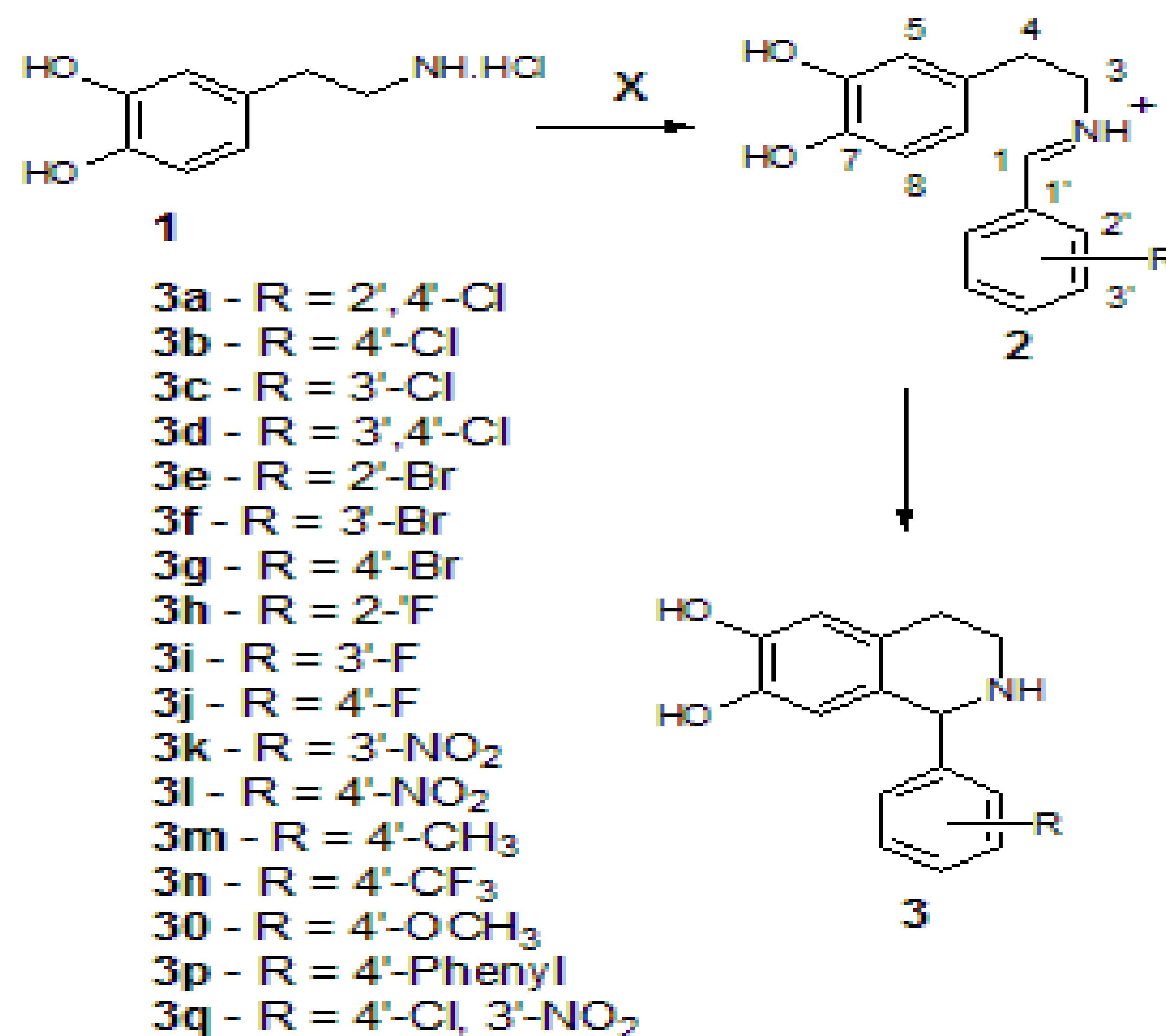
Current oral typhoid vaccines Typhim Vi and Ty21a, unfortunately display low efficacy (Gamazo *et al.*, 2007). Since decades, also antibiotics are applied (Paul *et al.*, 2017). However, antimicrobial resistance is presently a global concern due to resistant strains of *Salmonella* species that have emerged (Akoachere *et al.*, 2009; Njukeng *et al.*, 2019) showing high rates of resistance to current antibiotics (Paul *et al.*, 2017; Crump *et al.*, 2015). Thus, increasing anti-*Salmonella* resistance justifies the search for new efficacious drugs. Presently, several strategies are employed in the discovery of antibacterials including screening of synthetic compounds derived from medicinal chemistry. Notably, tetrahydroisoquinolines (THIQs) (Pyne *et al.*, 2020). Medicinal chemistry exploration of this scaffold has yielded analogues with application in cardiovascular, central nervous system, inflammatory, endocrine, metabolic, and infectious diseases covering antitubercular, antibacterial, antifungal, antiviral action. In this study, we report the antibacterial activity of a synthetic series of 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline analogues against resistant clinical strains of *Salmonella* using a cell-based screening (Matano *et al.*, 2016).

BIOLOGICAL SCREENING

- *In vitro* screens of the target compounds against multidrug-resistant strains of *Salmonella* using standard methods were carried out in the collaborating Biotechnology Unit Research Laboratories, Department of Biochemistry and Molecular Biology, Faculty of Science, University of Buea.

- Cytotoxicity was performed against monkey kidney epithelial cell line LLC-MK2 (ATCC, Virginia, USA)

SYNTHESIS



Reagents: X = Benzaldehyde or substituted benzaldehyde, triethylamine and ethanol, reflux

CONCLUSION AND PRESPECTIVE

- Based on the diameter of the zone of inhibition, two of the seventeen compounds (**3b** and **3n**) showed moderate to high activity against all multidrug-resistant clinical isolates of *Salmonella* with MICs comparable to recommended treatment antibiotics for *Salmonella* infections favourable to warrant further investigation

- On the basis of our findings, we suggest that: The optimization of the R substituent on the phenyl side chain of the isoquinoline scaffold should be the point of focus for future investigations.

Cytotoxicity and selectivity index of selected compounds based on lowest MIC value.

Compound	Lowest MIC (µg/mL)	CC ₅₀ (µg/mL)	Selectivity Index value
3b	16	9.8 x10 ⁻³	6 x 10 ⁻⁵
3c	16	121.9	7.6
3d	16	127.1	7.9
3e	16	8.755	0.5. x 10 ⁻¹
3j	256	904.9	353
3n	16	2592	162
3o	32	134.1	8.4
3q	16	22.06	1.4