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In Silico Design and Docking of Novel Benzimidazole Derivatives as Inhibitors Targeting AcrB Efflux Pump and NDM-1 Carbapenemase: Strategies to Combat Antibiotic Resistance

Yusuf Jimoh*, Ummulkhair Sani, Abdullahi Ahmad

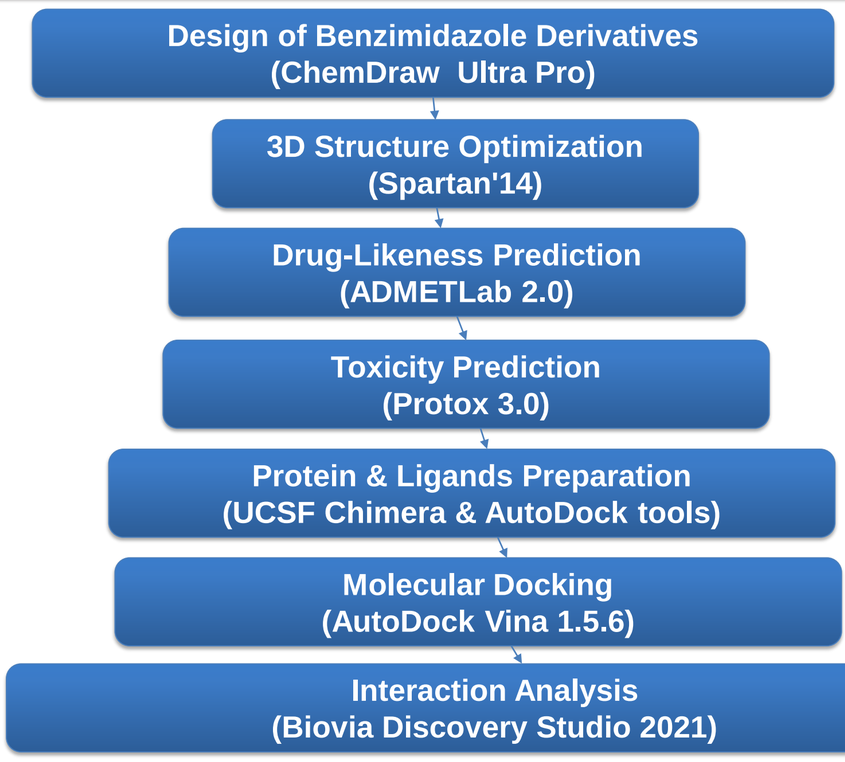
Department of Pharmaceutical and Medicinal Chemistry, Ahmadu Bello University, Zaria 810107, Nigeria

INTRODUCTION & AIM

- Antibiotic resistance, driven by AcrB efflux pumps and NDM-1 carbapenemases, threatens global health, potentially causing 10 million deaths annually by 2050 [1].
- AcrB expels antibiotics from Gram-negative bacteria (e.g., *E. coli*), while NDM-1 hydrolyzes carbapenems, a last-resort treatment [4,5]. Dual-action inhibitors targeting both mechanisms are needed to restore antibiotic efficacy.
- Benzimidazole derivatives have gained attention in medicinal chemistry for their versatile pharmacological properties, including antibacterial activity [9].

Aim: Design and evaluate novel benzimidazole derivatives as dual inhibitors of AcrB and NDM-1 using *in-silico* methods to combat multidrug-resistant bacteria.

METHOD



RESULTS & DISCUSSION

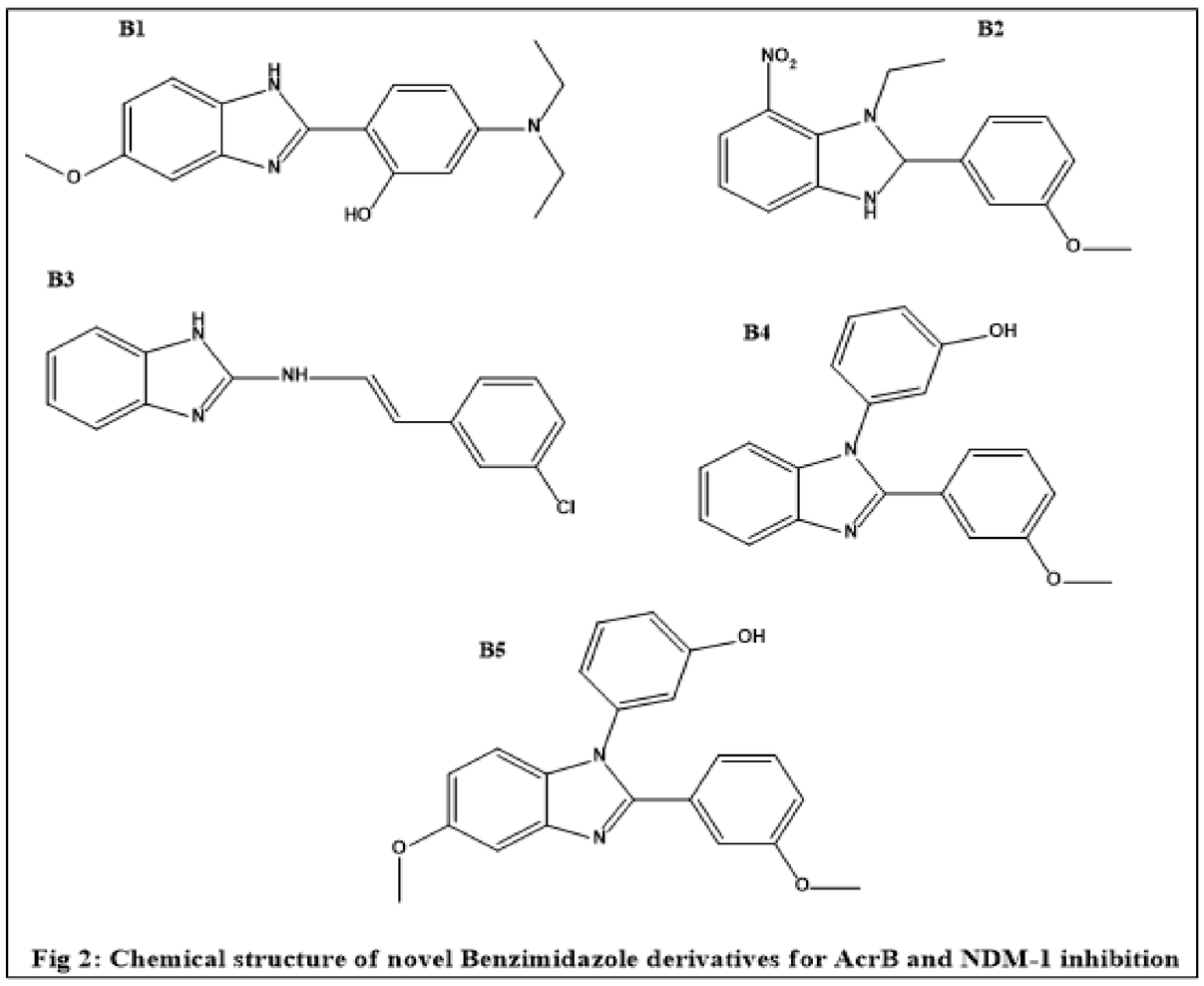


Fig 2: Chemical structure of novel Benzimidazole derivatives for AcrB and NDM-1 inhibition

RESULTS & DISCUSSION…

Table 1: Bioavalabilty and toxicity of novel benzimidazole derivatives based on lipinski's rule of five, GI absorption, LD_{50}, and toxicity class

Compound ID	Lipinski's rule of five[b]							
	Mol.Wt[a]	HbA	HbD	MLogP	GI	Inference	LD_{50} (mg/kg)	Toxicity Class
B1	311.16	5	2	4.49	High	Pass	800	4
B2	299.13	6	1	3.82	High	Pass	500	1
B3	268.00	2	2	4.53	High	Pass	729	4
B4	316.12	4	1	3.93	High	Pass	3420	5
B5	346.13	5	1	4.00	High	Pass	2000	4

(a) Molecular weight in g/mol, (b) [20] (Mwt ≤ 500, MLogP ≤ 5, HbA ≤ 10, and HbD ≤ 5

Table 2: Binding Energies of novel benzimidazole derivatives and co-crystallized ligands for AcrB and NDM-1

Compound ID	6KZL (Kcal/mol)	5ENO (Kcal/mol)
E1C	-5.8	-
5QG	-	-11.0
B1	-6.9	-9.5
B2	-6.5	-8.7
B3	-6.7	-11.1
B4	-6.7	-11.0
B5	-7.0	-10.6

PDB ID: 6KZL = NDM-1 Carbapenemase- matallo-beta-lactamase, PDB ID: 5ENO= AcrB Efflux Pump Gram-negative bacterial, E1C and 5QG are the co-crystallized ligands for the respective enzyme

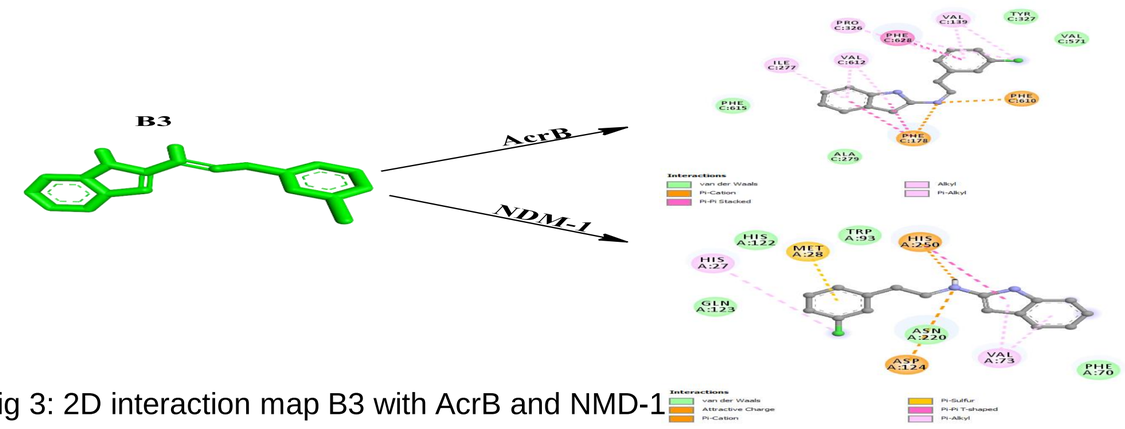


Fig 3: 2D interaction map B3 with AcrB and NMD-1

CONCLUSION

Five novel benzimidazole derivatives (B1–B5) show promise as dual-action inhibitors of AcrB and NDM-1, with favorable drug-likeness, low toxicity (B4: LD_{50} 3420 mg/kg), and strong binding affinities (B3: -11.1 kcal/mol AcrB, B5: -7.0 kcal/mol NDM-1). Key interactions (hydrogen bonds, pi-pi stacking) support their inhibitory potential. *In-silico* methods highlight their value in drug discovery. Experimental validation is needed to advance these candidates against antibiotic-resistant bacteria.

FUTURE WORK / REFERENCES

Synthesize B3, B4, B5 for *in-vitro/in-vivo* testing against resistant *E. coli and K. pneumonia.*

References

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