SYNTHESIS, ANTIMICROBIAL ACTIVITY AND ADMET PROFILING OF 2-SUBSTITUTED THIAZOLO[3,2-b][1,2,4]TRIAZOL-7-IUM HEXABROMOTELLURATES

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The thiazolo[3,2-b][1,2,4]triazol-7-ium hexabromotellurate derivatives **1–3** were synthesized via electrophilic heterocyclization of methallyl thioether precursors using an in situ generated Te(IV) reagent (TeO_2/HBr in CH_3CN) (Fig. 1). This one-step transformation simultaneously constructs the fused heterocyclic core and forms the biologically active $TeBr_6^{2-}$ counterion, ensuring good atom economy and synthetic efficiency.

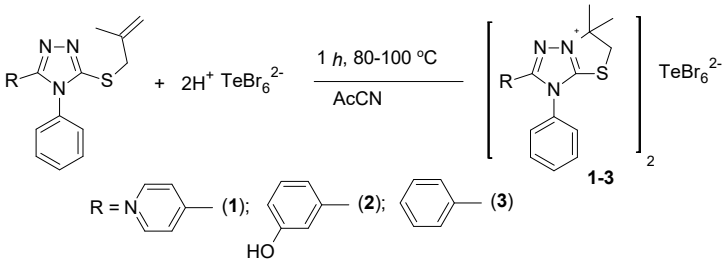

Fig. 1. Synthesis of compounds **1-3**.

The antimicrobial and antifungal activities of compounds **1–3** were evaluated against *Staphylococcus aureus*, *Candida albicans*, *Klebsiella pneumoniae*, *Escherichia coli*, and *Pseudomonas aeruginosa* using MIC/MBC assays (Table 1).

Table 1. Antimicrobial and antifungal activities of compounds **1–3**

Compound	Substituent	MIC/MBC, μg/mL				
		C. albicans	*S. aureus*	*K.pneumoniae*	*E. coli*	*P.aeruginosa*
1	4-Pyridyl	15.625 / 62.5	125 / 250	125 / 125	31.25 / 62.5	125 / 125
2	3-Hydroxy-phenyl	15.625 / 31.25	62.5 / 250	125 / 125	125 / 125	125 / 250
3	Phenyl	62.5 / 125	125 / 250	125 / 125	125 / 125	125 / 125

Structure–activity relationship (SAR) analysis revealed:

• Introduction of polar aromatic substituents at C-2 significantly enhances antifungal activity.

• Compounds **1** (4-pyridyl) and **2** (3-hydroxyphenyl) exhibited fourfold lower MIC values against *C. albicans* (15.63 μg/mL) compared to the phenyl analogue **3**.

• Compound **2** showed the best activity against *S. aureus* (MIC 62.5 μg/mL), suggesting that hydrogen-bonding functionality improves Gram-positive efficacy.

• Compound **1** demonstrated selective potency toward *E. coli* (MIC 31.25 μg/mL), likely due to the protonatable pyridine nitrogen facilitating penetration through the Gram-negative outer membrane.

• Activity against *K. pneumoniae* and *P. aeruginosa* remained moderate (MIC ≥ 125 μg/mL), indicating that permeability barriers limit efficacy.

Comparative analysis with previously reported aliphatic analogues confirmed that incorporation of polar or π-conjugated substituents provides broader and more balanced antimicrobial profiles than simple alkyl groups.

In silico ADMET profiling (ADMETlab) showed that all cations comply with Lipinski's rule of five (MW < 325 Da; logP 2.6–3.2; nHD ≤ 1). However, predicted intestinal absorption is extremely low due to permanent cationic charge and poor permeability (Caco-2 logPapp < −5).

Compound **1** displayed higher predicted solubility and unbound fraction, but stronger CYP inhibition risk. Compound **2** showed slightly lower predicted toxicity scores. Compound **3** was the most hydrophobic and strongly protein-bound (> 98 %).

All compounds are predicted to inhibit P-gp and BSEP transporters and exhibit moderate probabilities of hepatotoxicity and genotoxicity (Table 2).

Table 2. Physicochemical and absorption descriptors for compounds **1–3**

Descriptor	**Compound**		
	1	**2**	**3**
Molecular weight (MW, Da)	309.12	324.12	308.12
H-bond donors/acceptors (nHD/nHA)	0 / 4	1 / 4	0 / 3
Topological polar surface area (TPSA, Å²)	34.59	41.93	21.7
# Rotatable bonds / rings / hetero atoms	2 / 4 / 5	2 / 4 / 5	2 / 4 / 4
Fraction of sp³ carbons (Fsp3)	0.235	0.222	0.222
Predicted solubility logS	-3.73	-4.67	-4.07
Predicted lipophilicity logP	2.61	3.15	3.06
Caco-2 permeability (log cm/s)	-5.19	-5.43	-5.02
MDCK cell permeability (log cm/s)	-4.53	-4.81	-4.63
Predicted human intestinal absorption (HIA)	≈ 0	≈ 0	≈ 0
Blood–brain barrier (BBB) permeability	0.114	0.006	0.181
P-gp inhibition / substrate	inhibitor ≈1; substrate ≪1	inhibitor ≈1; substrate ≈0.01	inhibitor ≈1; substrate ≈0.0046
BCRP / BSEP	moderate BCRP (0.51–0.62) and strong BSEP inhibition (≈1) for all	similar for all	potential for biliary transport inhibition

Overall, polarity and hydrogen-bonding capacity at C-2 are key determinants of antifungal and Gram-positive activity, whereas balanced polarity and basicity are crucial for *E. coli* inhibition. Although the scaffold demonstrates promising antimicrobial potential, further optimisation should focus on improving permeability and reducing predicted toxicity.