Sequencing [4+1]-cycloaddition and aza-Michael addition reactions: Tandem cascades for the rapid and modular access of unique collections of anticancer and anti-superbugs motifs

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Representative examples of biologically active imidazo[1,5-a]quinolone and imidazopyridines/thiazole derivatives

1. *Eur. J. Med. Chem.* **2009**, *44*, 1570-1578; 2. *Anti-Infective Agents*, **2016**, *14*, 110-120; 3. *J. Chin. Pharm. Sci.* **1998**, *7*, 62-68; 4. CN 106478625, Mar 8, **2017**; 5. *Chem. Eur. J.* **2013**, *19*, 12249-53; 6. *Chem. Commun.* **2015**, *51*, 1555-75; 7. *Br. Vet. J.* **1974**, *130*, 501-4; 8. *Asian J. Org. Chem.* **2017**, *6*, 1830-1837

Three directional build/couple/pair protocol for the rapid construction of diverse molecular shapes

One-pot synthesis of pyrido[2,1:2,3]imidazo[1,5-a]quinolones

^aReaction conditions: step-1- Aldehyde (**3**, 0.5 mmol), Amine (**4**, 0.5 mmol), DCM, MS, -78 °C 1h, and then Sc(OTf)₃ (20 mol%), *tert*-Butyl isocyanide (0.55 mmol), -78 °C to rt, 5h; step-2- Sc(OTf)₃ (20 mol%), rt, 10h

Diastereoselective synthesis of various pyrido/thiazo[2,1:2,3]imidazo[1,5-a]quinolone derivatives

^aReaction conditions: step-1- Aldehyde (**3a**, 0.5 mmol), Amine (**4/7**, 0.5 mmol), DCM, MS, -78 °C 1h, and then Sc(OTf)₃ (20 mol%), *tert*-Butyl isocyanide (0.55 mmol), -78 °C to rt 5h; step-2- Sc(OTf)₃ (20 mol%), rt, 10h.

Diastereoselective synthesis of various pyrido/thiazo[2,1:2,3]imidazo[1,5-a]morpholine derivatives

Diastereoselective synthesis of polycyclic imidazo[1,5-d][1,4]oxazinium scaffolds

^aReaction conditions: step-1- Aldehyde (**3c**, 0.5 mmol), Amine (**4/7**, 0.5 mmol), DCM, MS, -78 °C 1h, and then Sc(OTf)₃ (20 mol%), *tert*-Butyl isocyanide (0.55 mmol), 78 °C to rt, 5h; step-2- Sc(OTf)₃ (20 mol%), rt, 10h

Diastereoselective synthesis of polycyclic imidazo[1,5-d][1,4]oxazinium scaffolds

^aReaction conditions: step-1- Aldehyde (**3d**, 0.5 mmol), Amine (**4/7**, 0.5 mmol), DCM, MS, -78°C 1h, and then $\text{Sc}(\text{OTf})_3$ (20 mol%), *tert*-Butyl isocyanide (0.55 mmol), -78°C to rt, 5h; step-2- $\text{Sc}(\text{OTf})_3$ (20 mol%), rt, 10h

Proposed regiochemical analysis for the formation of the aza-Michael addition products 12/14

Anticancer activities against a panel of human cancer cell lines

Compound	IC ₅₀ (μM) ^a			
	MCF7	A549	HeLa	HCT116
8d	2.1	4.4	2.88	1.7
10c	3.1	4.5	5.4	3.64
10d	2.5	7.4	1.2	3.0
14a	6.9	11.2	2.1	6.1
14b	9.1	14.6	5.1	9.4
Doxorubicin	0.17	0.12	0.29	0.09

^aBreast cancer (MCF-7), lung cancer (A549), cervical cancer (HeLa), colon cancer (HCT116).

IC₅₀ = Half-maximal inhibitory concentration.

Antibacterial activity of compound 8d

Compound	MICs ($\mu\text{g/ml}$)				
	Staphylococcus aureus (strain ATCC 25923)	MRSA-1	MRSA-2	MRSA-3	Escherichia coli (strain ATCC 25922)
8d	25	12.5	12.5	25	Non-active
Ciprofloxacin	0.125	32	16	2	0.008