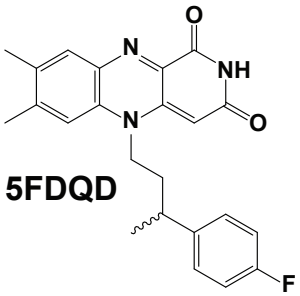
Breaker Laboratory

Molecule of the Year 2015

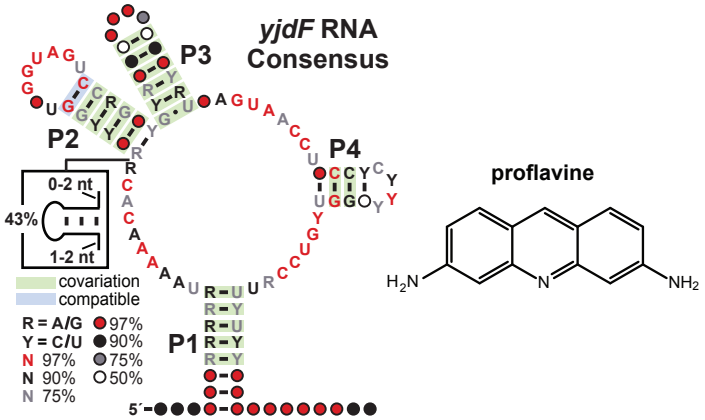
5FDQD
Clostridium difficile Antibiotic

Fig. 1. Chemical structure of the compound 5FDQD (5-(3-(4-fluorophenyl)butyl)-7,8-dimethylpyrido[3,4-b]-quinoxaline-1,3(2H,5H)-dione). This compound binds FMN riboswitches and causes transcription termination.



Azaaromatic Riboswitches

Fig. 2. The former *yjdF* motif (left) was considered an orphan riboswitch candidate since its discovery in 2010. New evidence suggests this riboswitch RNA responds to a broad collection of azaaromatic compounds such as proflavine (right).



In recognition of the development[1] of riboswitch-targeting compounds that cure animals of *C. difficile* infection, and in recognition of the surprisingly broad ligand specificity for azaaromatic riboswitches,[2] the status of Breaker Laboratory "Molecule of the Year" is conferred upon these findings.

5FDQD (Fig. 1) was initially identified and pursued at BioRelix as compound BRX2102, and its properties were established through studies both at BioRelix and in the Breaker Laboratory.[1] This compound represents the first known riboswitch-targeting compound that can cure animals of an otherwise lethal human disease. 5FDQD and many of its close analogs exhibit high selectivity for inhibiting the target pathogen while permitting beneficial bacteria to thrive.

Orphan riboswitches, or those whose ligands remain to be established, constitute some of the most interesting and challenging noncoding RNAs to study. They have remained orphans most likely because little information is available regarding the biology they regulate. Therefore, establishing their natural ligands can reveal new and important aspects of microbial biochemistry and physiology. One very common orphan riboswitch, called *yjdF* (Fig. 2), almost exclusively regulates a gene coding for a protein of unknown function. We discovered[2] that members of this riboswitch class broadly recongize azaaromatic compounds. This suggests that a group of unknown natural ligands with this general chemical structure might be the natural ligands for this riboswitch.

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1. *K. F. Blount, et al. (2015) Novel riboswitch-binding flavin analog that protects mice against Clostridium difficile infection without inhibiting cecal flora. Antimicrob. Agents Chemother. 59:5736-5746.*

2. *S. Li, X. Y. Hwang, S. Stav, R. R. Breaker. (2016) The yjdF riboswitch candidate regulates gene expression by binding diverse azaaromatic compounds. RNA (in press).*