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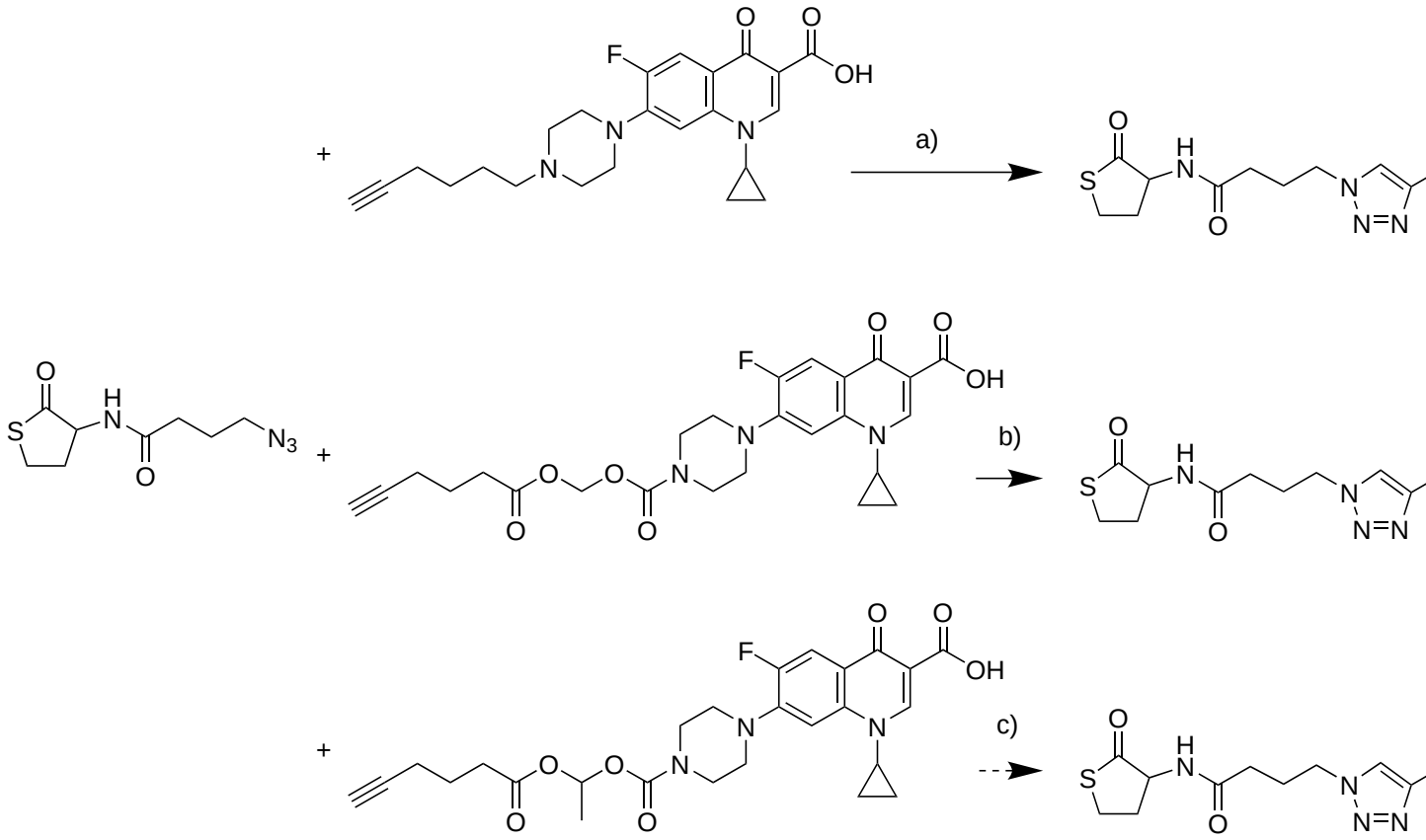
0.1 Cleavable linkers

In the series of ciprofloxacin-AHL containing cleavable linkers synthesised by Prof. Eddy Sotelo-Perez, the linker is designed with the hope that the linker will be stable under the extracellular assay conditions, but will be cleaved upon entry into the cell by intracellular esterases. It is hoped that the attached AHLs will facilitate increased uptake into the cells. However, initial results in YM64 (a PAO1 mutant lacking efflux pumps) show that the one compound that may show comparable results to ciprofloxacin is a control compound with a benzyl group attached. However, both compounds completely inhibited bacterial growth at all concentrations tested, so it is not clear if the compound is better than ciprofloxacin. Testing in PAO1 should be completed this week; as antibiotics are usually in this wild-type strain the difference between ciprofloxacin and the conjugate should show up without lowering the concentration.

For the series of compounds with cleavable linkers, in buffered water conditions they are expected to be stable for '> 3 yrs under optimal conditions', based on the hydrolysis studies of similar compounds in a study by Gogate.[1] The optimum conditions for slowest cleavage of these compounds is 4oC and around pH 4.7, whereas LB may reach around pH 8.5[?] after 24 hours of bacterial growth and the reaction is run at 30oC, so the degradation rate might be markedly increased under experimental conditions.[?]

In this study the hydrolysis of a secondary amine prodrug is dependent on ester hydrolysis rate in the range $1 =< \text{pH} =< 9$, therefore the cleavage rate can be tuned by the portion of the molecule between the ester and the triazole, and by the presence of a methyl, hydrogen or other group between the ester and amide.[?]



Scheme 1: a) CuI, DIPEA, DCM, Ar, r.t., 1 d, ? %, LMO-2-022, went to completion after adding more CuI. b) CuI, DIPEA, DCM, Ar, r.t., 1 d, ? %, LMO-2-023, didn't go to completion, columned anyway. c) CuI, DIPEA, DCM, Ar, r.t., 1 d, LMO-2-024, didn't go to completion OR CuSO4, NaAsc, THPTA, H2O, tBuOH, r.t., 1.5 d, LMO-2-027, went to completion but too little recovered for NMR

1 References

[1] U. Gogate, a. Repta and J. Alexander. N-(Acyloxyalkoxycarbonyl) derivatives as potential prodrugs of amines. I. kinetics and mechanism of degradation in aqueous solutions. *International Journal of Pharmaceutics*, 40(3):235–248. 1987.

Todo list