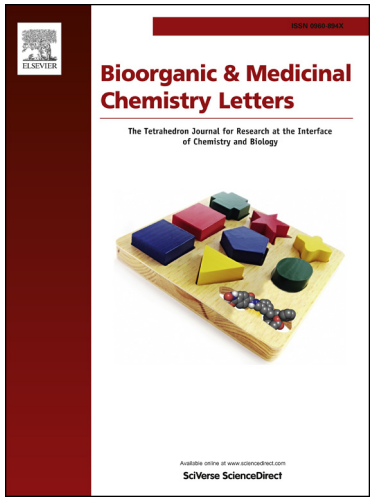

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Optimization of diarylazines as anti-HIV agents with dramatically enhanced solubility

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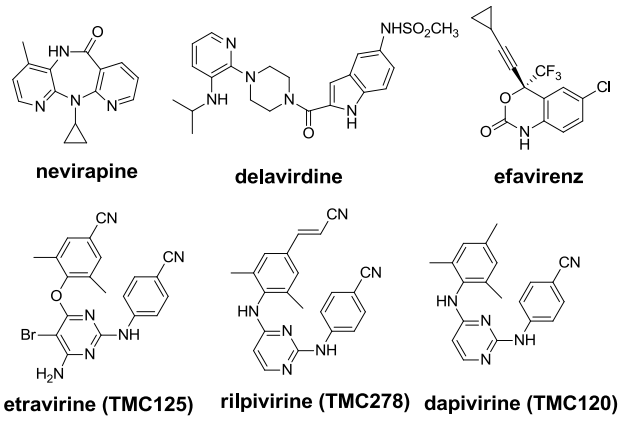
Abstract— Non-nucleoside inhibitors of HIV-1 reverse transcriptase are reported that have ca. 100-fold greater solubility than the structurally related drugs etravirine and rilpivirine, while retaining high anti-viral activity. The solubility enhancements come from strategic placement of a morpholinylalkoxy substituent in the entrance channel of the NNRTI binding site. Compound **4d** shows low-nanomolar activity similar to etravirine towards wild-type HIV-1 and key viral variants.

The use of non-nucleoside inhibitors of HIV-1 reverse transcriptase (NNRTIs) is commonplace for treatment of HIV infection.[1,2] Among the five FDA-approved drugs in the class, the most recent introductions have been etravirine and rilpivirine. These diarylpyrimidines provide much improved performance in cell assays against variant forms of HIV-1 that incorporate mutations in the vicinity of the NNRTI binding site.[3,4] The earliest approved NNRTIs, nevirapine and delavirdine, are debilitated by most common mutations. Though the second-generation compound, efavirenz, performs well against variants bearing the clinically prevalent Tyr181Cys mutation, resistance arises from other common variants such as those including Lys103Asn.[2-4] The clinical significance of efavirenz and rilpivirine is particularly great since they are incorporated into the once-a-day combination therapies Atripla and Complera, respectively.[5] The other two active components of the pills are the same, the nucleosides emtricitabine and tenofovir. Though the performance in cell-based assays is far better for rilpivirine than for efavirenz, surprisingly more virologic failure is observed for patients under treatment with Complera than Atripla.[5-7] Thus, from this observation and the desire to further diminish dosages and side effects, improvements are still possible for the NNRTI class.

A particular issue with aminoazine NNRTIs has been poor solubility, which often has undesirable



ramifications including low bioavailability, difficulties in formulation, and accumulation in fatty tissues.[8,9] Most oral drugs have an aqueous solubility (S) in the range 10^{-5} to 10^{-2} M, which for a drug with a molecular weight of 400, corresponds to 4 to 4,000 μg/mL. It is very rare for an FDA-approved oral drug to have a solubility near neutral pH below 10^{-6} M.[9] However, rilpivirine "is practically insoluble in water (20 ng/mL at pH 7.0)",[4] which translates to an S of 5 x 10^{-8} M. It appears to have an unusual absorption mechanism involving aggregates.[10] For etravirine, the solubility is also "<<1 μg/mL", and extensive formulation work was needed to bring the daily dosage to 0.4 g per day.[11] Furthermore, in view of its low solubility, dapivirine is being evaluated as a vaginal microbicide.[12] This was