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Pyrrolo[1,2-*a*][1,4]benzodiazepine: A novel class of non-azole anti-dermatophyte anti-fungal agents

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Abstract—Broad screening revealed compound **1a** to be a novel anti-fungal agent with high specificity towards dermatophytes. The anti-fungal structure–activity relationship of this novel class of 5,6-dihydro-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines is described together with its mode of action that appeared to be the inhibition of squalene epoxidase. Preliminary in vivo results of the most active compounds are also reported.

In view of the increasing resistance to existing azole anti-fungals,[1] and the lack of sufficient chemical diversity in the existing classes of anti-fungals, the need for new anti-fungals remains high.[2] Although potent systemic broad-spectrum anti-fungals are preferred, there is ample room for compounds with a more focused application. In fact, the largest branch of the anti-fungal market is dermatology. It includes conditions such as onychomycosis, athlete's foot, tinea corporis and the like, that can be treated by both topical and oral regimes. Two major classes are dominating this market: the azole anti-fungals (14-α-demethylase inhibitors) such as ketoconazole,[3] itraconazole[4] and fluconazole,[5] and squalene epoxidase inhibitors such as thiocarbamates (e.g., tolnaftate)[6], naftifine,[7] terbinafine[8] and butenafine[9] (Scheme 1).

As well as target directed projects, general in vitro screening of the corporate compound library on yeast and mould species was conducted, revealing compound **1a** to be a novel molecule with specific activity against dermatophyte species, *Aspergillus fumigatus* and *Candida parapsilosis*. In this communication, we would like to report on the preliminary structure–activity relationship of this novel class of anti-fungals.

Compound **1a** has a 5,6-dihydro-4-(4-ethylphenyl)-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine structure, which is scarcely described in the literature,[10] and the potential anti-infective activity of this heterocyclic class has not been reported. The synthesis of this novel template is easily achieved via a four-step synthesis depicted in Scheme 2. Substituted 2-amino-benzonitriles are commercially accessible or easily accessible via synthetic routes described in the literature.[11] The amine was cyclized in good yield via a modified Hantzsch pyrrole synthesis using 2,5-diethoxytetrahydrofurane in refluxing acetic acid. Then the nitrile was reduced using lithium aluminium hydride in dry tetrahydrofuran. Finally, the corresponding 2-*N*-pyrrolobenzyl amine was treated with the selected aldehyde to give the corresponding imine. This immediately gave an intramolecular Mannich reaction upon treatment with dry acid,

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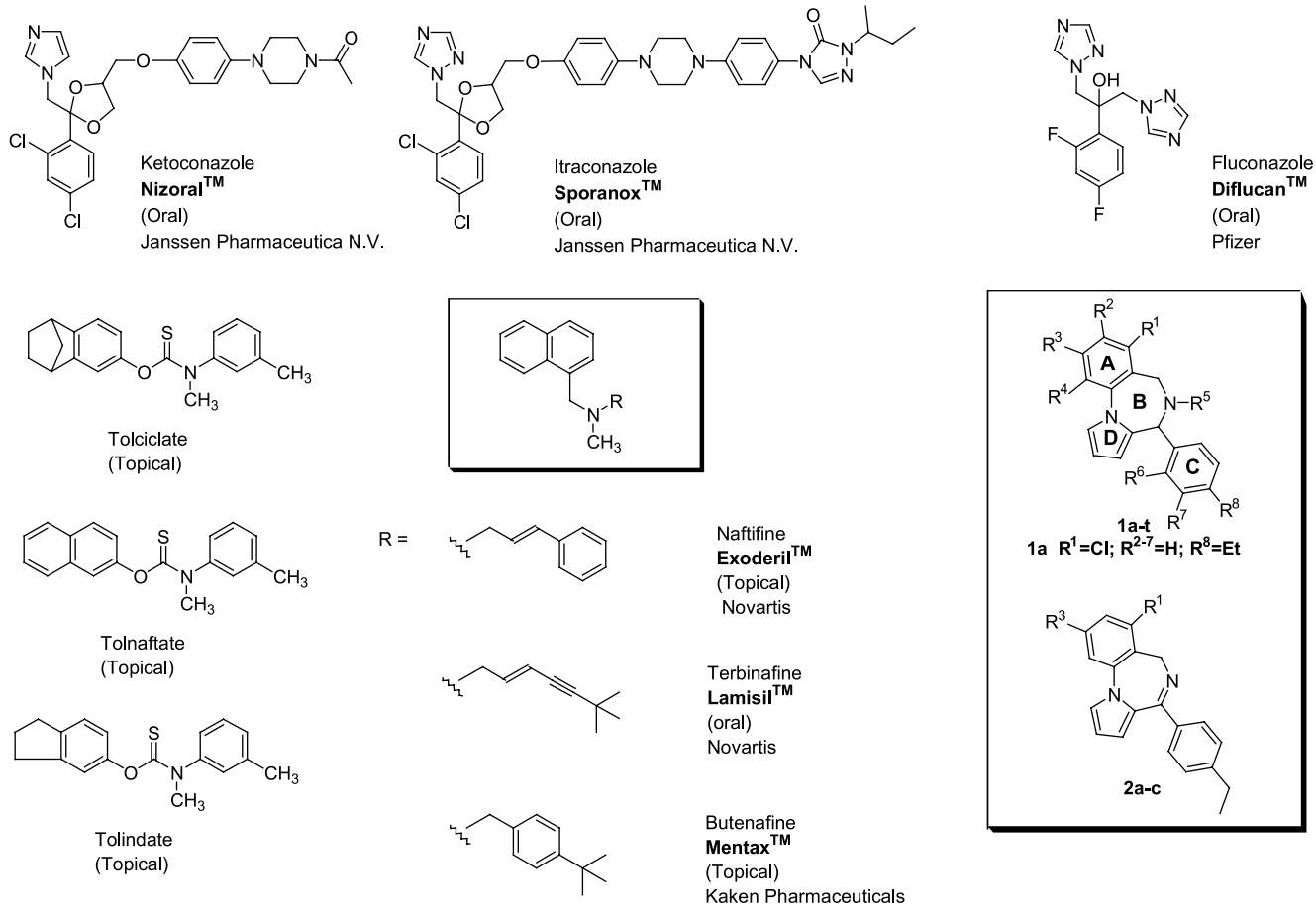
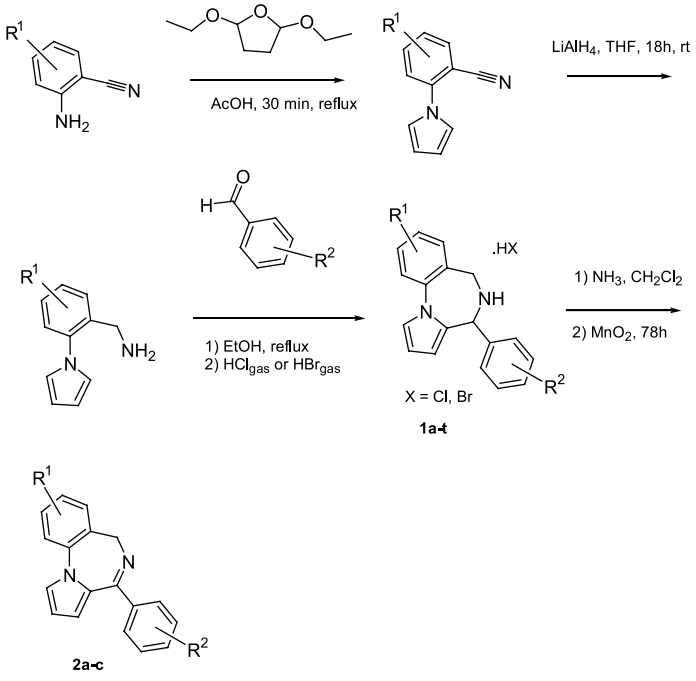


Scheme 1.



Scheme 2.