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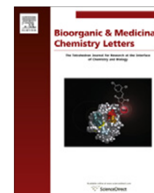

Influence of pK_a on the biotransformation of indene H_1-antihistamines by CYP2D6

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ABSTRACT

Structure–activity relationship studies were conducted to reduce CYP2D6-mediated metabolism in a series of indene H_1-antihistamines. Reductions in pK_a via incorporation of a β-fluoro substituent or a heteroaryl moiety were shown to reduce contributions to metabolism through this pathway. Several compounds, including **8l**, **8o**, and **12f** were identified with promising primary in vitro profiles and reduced biotransformation via CYP2D6.

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Novel and selective H_1-antihistamines with appropriate exposure are of potential interest as an alternative to current medications for the treatment of insomnia. Such agents enhance sleep during the latter third of the night and improve sleep efficiency.[1] Unlike current $GABA_A$ hypnotics,[2] these antihistamines are likely to have low abuse potential. Recently, derivatives of H_1-antihistamine *R*-dimethindene (**1**),[3] namely **2a** and **2b**, were identified as highly selective compounds for the H_1 receptor with sedating properties (Fig. 1).[4]

Analysis of the metabolism of compound **2a** in human liver microsomes (HLM) showed a similar metabolite profile to *R*-dimethindene (**1**),[5] the major metabolite being the 6-hydroxyindene (**3**) (Fig. 2). Semi-quantitative analysis of the enzymatic pathways associated with this metabolism indicated that the enzyme responsible for the vast proportion of metabolism (>90% in human liver microsomes, HLM) was CYP2D6.[6] Analysis of compound **2b** indicated a similar metabolite profile to **2a**. The characterization of these compounds as predominant CYP2D6 substrates presented two issues. In addition to the liability of drug–drug interactions, heterogeneity of CYP2D6 activity within the general population raised the concern of extreme variability in pharmacokinetics for candidate compounds.[7] This was of particular concern for a sleep agent as extended duration of action would be expected in CYP2D6 poor metabolizers resulting in undesirable next day residual effects. We previously described an approach in which modifications to the 6-position of the indene core was utilized to identify a backup candidate, **4**, with significantly reduced biotransformation through the CYP2D6 pathway.[6]

In this Letter, we describe an alternative approach to reduce biotransformation via CYP2D6 in the indene series. Previous reports demonstrated the critical importance of Asp 301 in the CYP2D6 enzyme for substrate transformation,[8] suggesting that binding of the basic amine within compounds such as **2a** and **2b** is important for metabolism. Indeed modulation of pK_a in some basic compounds has been shown to affect metabolism by this enzyme.[9] While indenes **2a** and **2b** are basic (measured pK_a 9.1 for

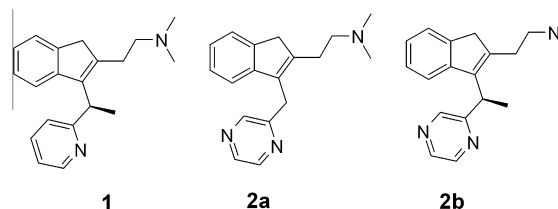

Figure 1. *R*-Dimethindene (**1**), and analogs **2a** and **2b**.

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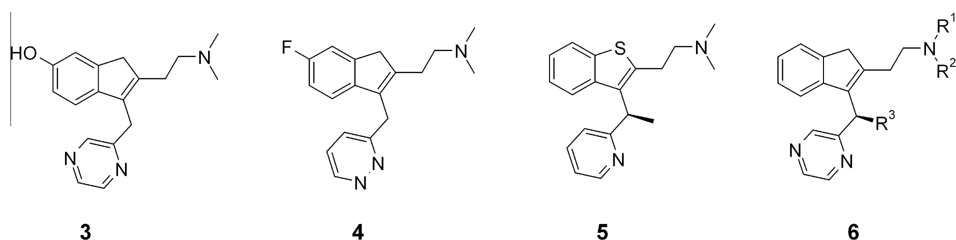


Figure 2. Major metabolite (**3**) of **2a**, backup compound (**4**), clinical compound (**5**), and series described in this Letter (**6**).

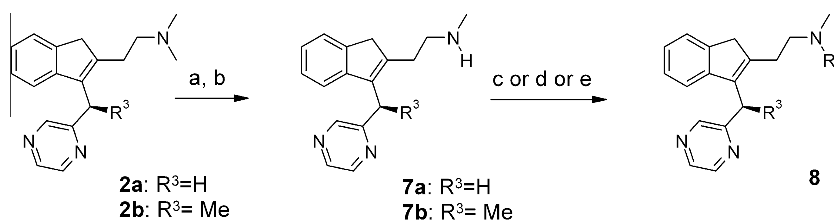
both, calcd pK_a 9.6)[6] and primary substrates for CYP2D6, benzothiophene **5** is less basic (measured pK_a 8.6, calcd pK_a 9.2)[10] and is metabolized by a variety of CYP450 enzymes.[11] We hypothesized that we could reduce susceptibility to metabolism via the CYP2D6 pathway in the indene class by reduction of pK_a through modification of the NR_1R_2 in the general substructure **6**.

Assessment of the biotransformation was measured through a screening strategy previously described using quinidine, a known specific CYP2D6 inhibitor.[6,12] Contributions from CYP2D6 biotransformation to overall compound metabolism vary significantly between normal and poor metabolizer populations. We estimated that a contribution from CYP2D6 greater than 70% could lead to exposure variabilities ⩾3–10-fold. Therefore, to limit PK variability to ⩽2–3-fold, we estimated that CYP2D6 contributions to compound metabolism should not exceed 60%.

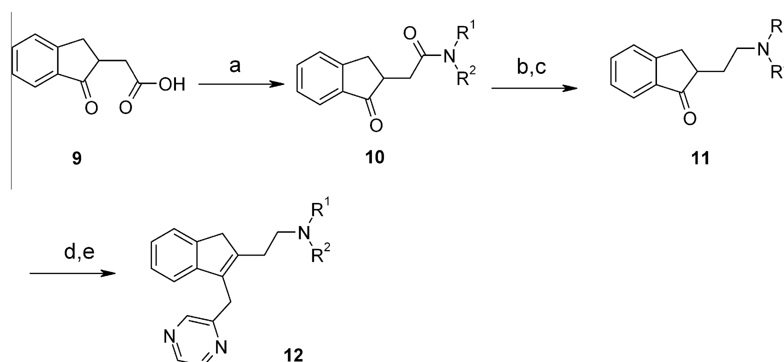
Our objective was to make small modifications to the amine in general structure **6** that maintained H_1 affinity and selectivity, yet reduced pK_a of the basic function. Compounds of interest would then be evaluated for their ability to reduce biotransformation via CYP2D6. To achieve similar selectivity to that described earlier,[4,12] candidate compounds were required to demonstrate high H_1 binding affinity ($K_i \leqslant 10$ nM) with at least 100-fold binding selectivity versus the representative muscarinic M_1 receptor. Initially, selectivity in the range of 100–1000-fold was considered acceptable for CYP enzyme inhibition. It is well known that several antihistamines are potent inhibitors of the hERG channel,[13] implicated in prolongation of cardiac QTc and leading to cardiac arrhythmias. A preliminary assessment of hERG affinity would also be conducted.

Two synthetic schemes were employed to generate indenes (**6**). Indenes **2a**, **2b**[4] were demethylated to **7** under standard conditions and N-alkylated by reductive amination or alkylation to yield **8** (Scheme 1). When the NR^1R^2 fragment in **6** was a cyclic amine, a different route was employed. Indanone **9** was coupled to an amine to give intermediate **10**, as previously reported.[12] A simultaneous reduction of the amide and ketone functionalities with $LiALH_4$, followed by a subsequent oxidation, yielded indanone **11**. Addition of methyl pyrazine to **11**, followed by dehydration afforded indene **12**. (Scheme 2)

Compounds were tested in a histamine H_1 receptor binding assay.[4] To confirm initial selectivity, compounds were subsequently tested for inhibition of cytochrome P450 enzymes CYP2D6 and CYP3A4.[4] Preliminary selectivity over the hERG channel was evaluated using the high-throughput dofetilide binding assay.[14] Representative compounds were also assessed for M_1 affinity.[4] Estimates of biotransformation through CYP2D6 were made through comparison of the predicted intrinsic clearance in HLM with and without the specific CYP2D6 inhibitor quinidine.[12] The



Scheme 1. Reagents and conditions: (a) ACE-Cl, DIPEA, 1,2-DCE, 1 h, 45 °C; (b) MeOH, rt; (c) $NaBH(OEt)_3$, HOAc, R^2(=O)H; (d) BH_3·Pyr, MeOH, R^2(=O)H; (e) R^2X, K_2CO_3, DMF, 70 °C.



Scheme 2. Reagents and conditions: (a) HNR^1R^2, EDCI, HOBt, DIPEA, DCM; (b) $LiAlH_4$, THF, 0 °C then reflux 3 h; (c) Ph_2CO, ^{t}BuOK, benzene, 120 °C, 3 h; (d) methyl pyrazine, LDA, THF, 0 °C; (e) 20% HCl, reflux.

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