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Novel benzothiophene H_1-antihistamines for the treatment of insomnia

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ABSTRACT

SAR of lead benzothiophene H_1-antihistamine 2 was explored to identify backup candidates with suitable pharmacokinetic profiles for an insomnia program. Several potent and selective H_1-antihistamines with a range of projected half-lives in humans were identified. Compound **16d** had a suitable human half-life as demonstrated in a human microdose study, but variability in pharmacokinetic profile, attributed to metabolic clearance, prevented further development of this compound. Compound **28b** demonstrated lower predicted clearance in preclinical studies, and may represent a more suitable backup compound.

Histamine elicits effects on arousal through central action at the H_1 and H_3 receptor subtypes.[1] While first generation H_1-antihistamines are sedating and are used in over-the-counter sleep aids, these agents are functional antagonists of muscarinic (M) receptors,[2] a property thought to cause undesirable side effects such as dry mouth, blurred vision, constipation, tachycardia, urinary retention, and memory deficits.[3,4] Next-day impairment, presumed to result from protracted CNS exposure and a consequence of long plasma half-life, has also been seen with these compounds.[5,6] Thus, selective H_1-antihistamines with appropriate duration of CNS exposure may provide an alternative to current medications for the treatment of insomnia.

Previously, we described the use of the selective (−)-*R*-dimethindene (**1**)[7] as a starting point to generate novel series of selective and brain penetrating H_1-antihistamines with pharmacokinetic profiles suitable for use as night time sleep aids.[8] The benzothiophene analog (**2**) was selected as a lead compound with a suitable receptor selectivity profile and, based on modeling of its clearance profile, a projected half-life in a desirable range of 5–18 h (Fig. 1).

In this Letter, we describe the SAR of benzothiophene series **3**. The objective of this study was to identify backup compounds with similar or improved selectivity to **2**, but with differences in clearance profiles and hence projected half-life.[8] Backup compounds with a range of projected half-lives that model optimal plasma exposure over time as a function of dose were desirable to mitigate any risk of next day residual effects should they be observed in our lead.

From our previous observations, a pyridyl or other heteroaryl was required for R^3 in **3** to confer selectivity versus cytochrome CYP2D6 inhibition.[8] We also demonstrated that variation of the heteroaryl provided subtle changes to clearance in preclinical models. The importance of the chiral center for binding affinity and selectivity in **3** had also been established.[8,9]

Initial efforts described in this Letter focused on subtle modifications of the pyridyl moiety (R^3) and amine substituents (R^1R^2) in **3**. To achieve a selectivity profile comparable to **2**,[8] candidate compounds were required to demonstrate potent H_1 affinity (K_i <10 nM) and acceptable selectivity versus other receptor targets (M_1, M_3, H_3, serotonin $5HT_{2A}$, >100-fold) and CYP2D6 and CYP3A4

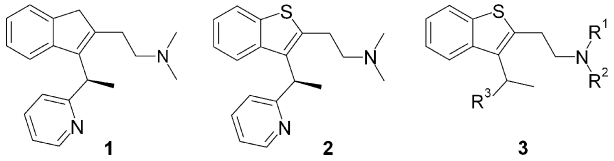

Figure 1. (−)-*R*-Dimethindene (**1**), its direct benzothiophene analog (**2**) and series (**3**) described in this communication.

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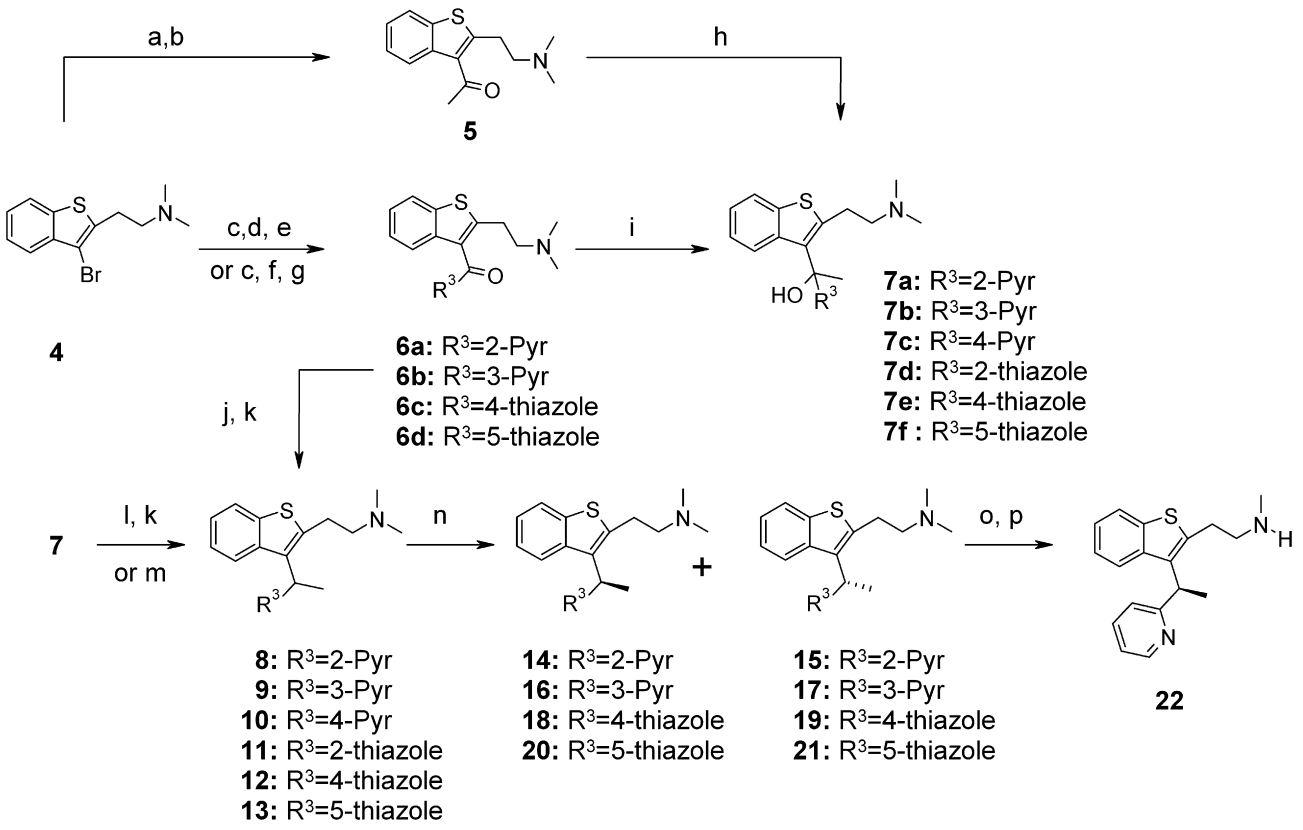
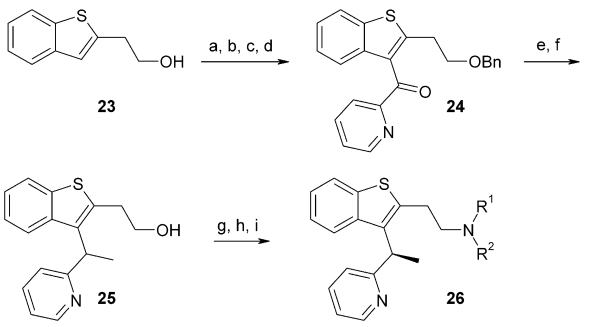


Scheme 1. Reagents and conditions: (a) $CH_3(CH_2)_3OCH{=}CH_2$, $Pd(OAc)_2$, P(o-Tol)$_3$, Et_3N, CH_3CN, 100 °C; (b) 10% HCl in THF; (c) *n*-BuLi, TMEDA, toluene or DCM, −78 °C; (d) R^3CN; (e) 6 N HCl, MeOH; (f) R^3CHO; (g) MnO_2, DCM; (h) R^3Br or R^3H/ *n*-BuLi, −78 °C, DCM; (i) MeMgCl or MeLi, toluene, −78 °C; (j) PPh_3MeBr, *t*-BuOK, THF; (k) Pd/C or $Pd(OH)_2$ in MeOH, H_2; (l) H_2SO_4 in TFA or MsOH in DCM; (m) NaI, TMSCl, CH_3CN, reflux; (n) fractional crystallization, chiral HPLC or chiral SFC; (o) $Cl(CO)OCH(CH_3)Cl$, DIPEA, DCE, 40 °C; (p) MeOH.

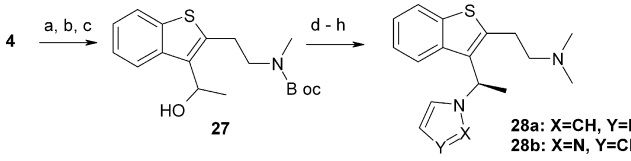
enzymes (>1000-fold). Since **2** lacked an in vivo cardiovascular risk,[8] despite weak hERG channel inhibition, we reasoned that compounds with hERG IC_{50}/H_1 K_i selectivity of 400 or greater would be acceptable for lead candidates. To minimize the risk associated with next day impairment, only H_1-antihistamines with a projected half-life of 18 h or less were considered acceptable.[10]

Various synthetic schemes were employed to generate benzothiophenes **3** (Schemes 1–3) dependent on the availability of relevant starting materials. A Heck reaction of bromide **4**[8] with *n*-butyl vinyl ether, followed by hydrolysis, gave the acetyl intermediate **5**.[11] Addition of a lithium heteroaryl, generated in situ from the heteroarene or heteroaryl bromide, yielded alcohol **7**. Alternatively, lithium–halogen exchange of bromide **4**, followed by the addition of a heteroaryl nitrile and subsequent acidic hydrolysis, afforded the heteroaryl ketone **6**, which was converted to the alcohol **7** by addition of MeLi or MeMgBr. An alternative route to ketone **6** was developed involving lithium–halogen exchange of bromide **4**, followed by treatment with a heteroaryl aldehyde and a subsequent oxidation. Compound **7** was either dehydrated with a strong acid followed by hydrogenation, or directly deoxygenated with in situ TMSI to yield **8–13**.[12] Alternatively, ketone **6** was subjected to a Wittig reaction, followed by hydrogenation to yield **8, 9, 12** and **13**. Fractional crystallization or chiral chromatography (HPLC or SFC) of racemic **8–13** afforded the enantiomers **14–21**.[13] Demethylation of **14** to generate the secondary amine **22** was accomplished with 1-chloroethyl chloroformate followed by treatment with methanol. (See Supplementary data for specific synthetic steps to each final compound.)

Benzothiophenes, containing a cyclic amine, were generated through an alternative sequence (Scheme 2). Alcohol **23** was treated with bromine, protected with a benzyl group and subjected to a lithium–halogen exchange. Reaction with 2-pyridinecarbonitrile followed by hydrolysis afforded the ketone intermediate **24**. After



Scheme 2. Reagents and conditions: (a) Br_2, $CHCl_3$; (b) NaH, BnBr, DMF, 0 °C (c) *s*-BuLi, TMEDA, PyrCN, toluene, −78 °C; (d) 6 N HCl, MeOH; (e) MeLi or MeMgBr, toluene, −78 °C; (f) TMSCl, NaI, CH_3CN, reflux; (g) MsCl, Et_3N, DCM, 0 °C; (h) R^1R^2NH, IPA, 85 °C; (i) chiral HPLC.



Scheme 3. Reagents and conditions: (a) (i) $Cl(CO)OCH(CH_3)Cl$, DIPEA, DCE, 40 °C; (ii) MeOH; (b) Boc_2O, DCM; (c) *n*-BuLi, TMEDA, $CH_3C(O)H$, toluene, −78 °C; (d) MsCl, DIPEA, DCM, 0 °C; (e) HetAryl/NaH, DMF, rt to 80 °C; (f) 50% TFA in DCM, 0 °C; (g) aq HC(=O)H, $NaBH(OEt)_3$, THF; (h) Chiral HPLC or SFC.