Bioorganic & Medicinal Chemistry Letters 20 (2010) 2316–2320

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Novel benzothiophene H_1-antihistamines for the treatment of insomnia

Wilna J. Moree *, Florence Jovic, Timothy Coon, Jinghua Yu, Bin-Feng Li, Fabio C. Tucci, Dragan Marinkovic, Raymond S. Gross, Siobhan Malany, Margaret J. Bradbury, Lisa M. Hernandez, Zhihong O'Brien, Jianyun Wen, Hua Wang, Samuel R. J. Hoare, Robert E. Petroski, Aida Sacaan, Ajay Madan, Paul D. Crowe, Graham Beaton *

Neurocrine Biosciences, 12780 El Camino Real, San Diego, CA 92130, USA

ARTICLE INFO

Article history:
Received 30 December 2009
Revised 27 January 2010
Accepted 28 January 2010
Available online 2 February 2010

Keywords:
H1 receptor
H1-antihistamines
Insomnia
Benzothiophenes
Histamine

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

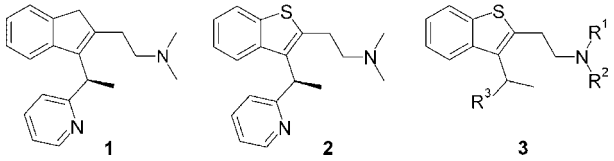
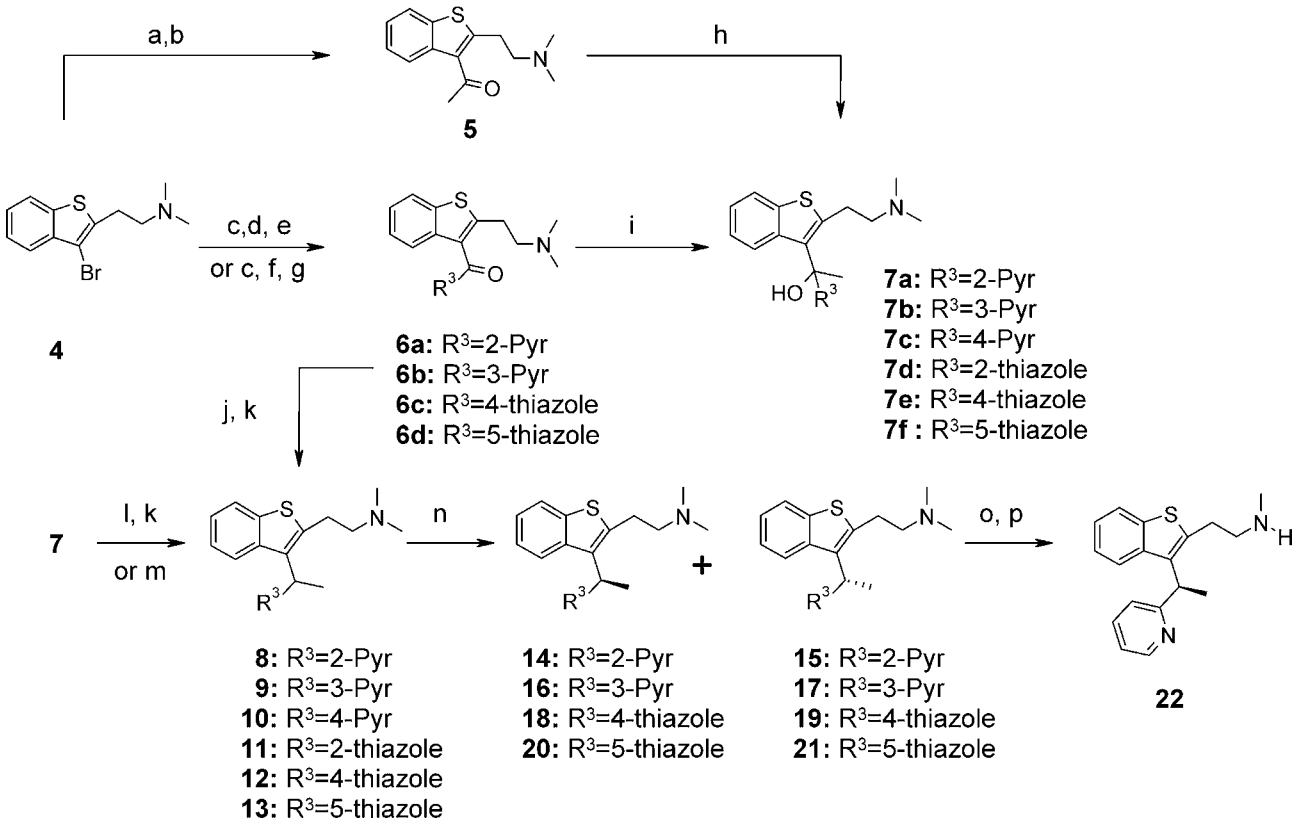


Figure 1. (−)-*R*-Dimethindene (**1**), its direct benzothiophene analog (**2**) and series (**3**) described in this communication.

* Corresponding authors. Tel.: +1 858 336 4479 (W.J.M.); +1 858 337 1801 (G.B.).
E-mail addresses: wilna.moree@gmail.com (W.J. Moree), beaton.graham@gmail.com (G. Beaton).

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.01.134

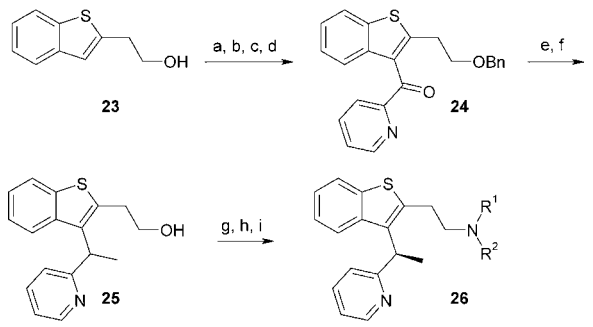


Scheme 1. Reagents and conditions: (a) $CH_3(CH_2)_3OCH{=}CH_2$, $Pd(OAc)_2$, P(o-Tol)$_3$, Et_3N, CH_3CN, 100 °C; (b) 10% HCl in THF; (c) *n*-BuLi, TMEDA, toluene or DCM, −78 °C; (d) R^3CN; (e) 6 N HCl, MeOH; (f) R^3CHO; (g) MnO_2, DCM; (h) R^3Br or R^3H/ *n*-BuLi, −78 °C, DCM; (i) MeMgCl or MeLi, toluene, −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.

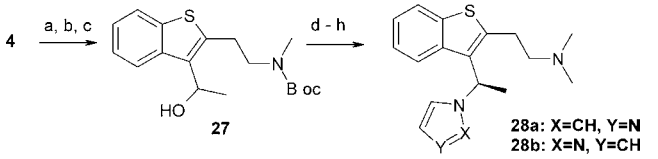
enzymes (>1000-fold). Since **2** lacked an in vivo cardiovascular risk,[8] despite weak hERG channel inhibition, we reasoned that compounds with hERG IC_{50}/H_1 K_i selectivity of 400 or greater would be acceptable for lead candidates. To minimize the risk associated with next day impairment, only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

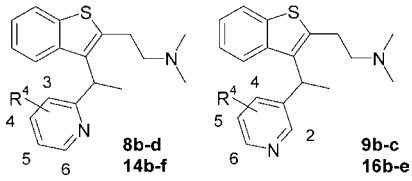
addition of MeLi, treatment with TMSCl/NaI resulted in both deoxygenation and removal of the protecting group to yield alcohol **25**. Conversion of the alcohol to the mesylate, displacement with cyclic amines followed by chiral HPLC, gave the desired (−)-*R* enantiomers **26**.

N-Linked heterocycle substituted benzothiophenes **28** (Scheme 3) were prepared from **4** by a sequence that involved a temporary conversion of $-NMe_2$ to –NMeBoc via demethylation and Boc protection. Subsequent lithium–halogen exchange and addition of acetaldehyde yielded **27**. This alcohol was converted to the mesylate and reacted with the sodium salts of different heterocycles. Removal of the Boc group and reinstallment of the Me moiety by reductive amination, followed by chiral HPLC gave the (−)-*R* enantiomers **28**. The NMeBoc group was required to prevent intramolecular cyclization of the mesylate intermediate. More efficient syntheses were developed for compounds **28** with promising in vitro profiles.[14]

Compounds were tested in an histamine H_1 receptor binding assay.[8] To confirm initial selectivity, compounds were assessed for M_1 receptor binding affinity[8] and inhibition of CYP2D6 and CYP3A4.[8] Selectivity over the hERG channel was evaluated using the high-throughput dofetilide binding assay.[15] Compounds of interest were subsequently tested in an hERG patch clamp functional assay.[8] (Tables 1–4).

Benzothiophene **2**,[8] was a high affinity H_1-antihistamine with a good selectivity profile and moderate hERG activity. Similar to dimethindene,[7] the (+)-*S* enantiomer (**15a**) showed significantly lower affinity and selectivity for H_1 than its (−)-*R* enantiomer. This observation was consistent in all the enantiomeric pairs we studied. A tertiary amine was more potent and selective than a secondary amine as exemplified by comparison of **2** to **22**. Incorporation of cyclic amines at NR^1R^2 position (**26a, 26b**) yielded compounds with similar affinity to **2** and promising in vitro profiles albeit with a slight increase in hERG inhibition. Examination of the role of the nitrogen position in the pyridine indicated that the 3-pyridine (**16a**) had a very similar profile to **2** with marginally lower selectivity for the hERG channel. The racemic 4-pyridine (**10**) did not appear to offer an advantage with respect to H_1 affinity and selectivity, and therefore the enantiomers were not profiled.

Table 2
SAR profiles of substituted 2- and 3-pyridyl-benzothiophenes

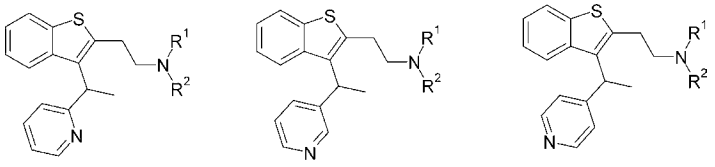


Compd	Isomer	R^4	H_1[a,b] K_i (nM)	CYP2D6[c] IC_{50}(μM)	hERG[e] IC_{50} (μM)
8b	*rac*	4-Me	390 ± 15	NT[d]	NT
8c	*rac*	6-OMe	59 ± 10	NT	NT
8d	*rac*	6-F	38 ± 4	NT	NT
14b	(−)-*R*	3-Me	9.3 ± 0.8	5.5	0.91
14c	(−)-*R*	3-OMe	5.0 ± 2.0	9.5	3.0
14d	(−)-*R*	3-F	2.7 ± 0.3	4.0	0.33
14e	(−)-*R*	3-Cl	8.0 ± 1.3	1.5	NT
14f	(−)-*R*	5-F	13 ± 2	>10	0.24
9b	*rac*	6-Me	69 ± 8	NT	NT
9c	*rac*	6-OMe	120 ± 15	NT	NT
16b	(−)-*S*	2-Me	17 ± 1	>10	NT
16c	(−)-*S*	2-OMe	2.9 ± 0.2	9.6	1.8
16d	(−)-*S*	2-F	1.7 ± 0.2	7.5	2.3
16e	(−)-*S*	2-Cl	2.9 ± 0.5	9.5	1.5

[a] SEM for K_i values derived from dose–response curves generated from triplicate or more data points.
[b] M_1 K_i > 10 μM for all compounds except for **14d** (K_i = 2.2 μM).
[c] CYP3A4 IC_{50} > 10 μM.
[d] NT = not tested.
[e] In dofetilide binding assay: hERG K_i > 5 M for all compounds except for **14f** (K_i = 2.5 μM).

Subsequent SAR focused on the substituent effect of Me, OMe, F, and Cl in both the 2-pyridyl and 3-pyridyl moieties. Initially, the racemates were assessed for H_1 binding and when affinity was sufficient (K_i <25 nM), the (−) enantiomers were isolated and profiled against H_1, M_1, CYP2D6, CYP3A4 and hERG (Table 2). These data indicated that substitution in the 4- (**8b**) or 6-position (**8c**, **8d**) of the 2-pyridyl moiety reduced H_1 binding. In contrast, substitution at the 3-position of the 2-pyridine was tolerated (K_i of racemates <20 nM). Of the enantiomers, the 3-F analog (**14d**) had highest H_1

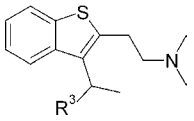
Table 1
Primary profile of unsubstituted pyridyl-benzothiophenes



Compd	Isomer	R^1	R^2	H_1[b] K_i (nM)	M_1[c] K_i (μM)	CYP2D6[d] IC_{50} (μM)	hERG[e] K_i (μM)	hERG[f] IC_{50} (μM)
8a	*rac*	Me	Me	12 ± 1.5	1.4	6.9	>5	NT[g]
2	(−)-*R*	Me	Me	4.0 ± 0.5	5.3	28	>5	1.4
15a	(+)-*S*	Me	Me	256 ± 16	0.99	3.3	>5	NT
22	(−)-*R*	H	Me	32 ± 6	3.7	9.8	>5	6.5
26a	(−)-*R*	$-(CH_2)_4-$		6.1 ± 1.2	5.8	2.7	1.1	NT
26b	(−)-*R*	$-(CH_2)_3-$		3.9 ± 0.9	>10	>10	4.2	0.73
9a	*rac*	Me	Me	10 ± 2	4.7	7.3	>5	NT
16a	(−)-*S*[a]	Me	Me	3.5 ± 0.6	28	5.2	>5	0.49
17a	(+)-*R*[a]	Me	Me	79 ± 4	>10	2.0	>5	NT
10	*rac*	Me	Me	23 ± 2	5.6	0.85	1.8	NT

[a] *R*/*S* nomenclature inverted.
[b] SEM for K_i values derived from dose–response curves generated from triplicate or more data points.
[c] K_i values derived from dose–response curves generated from duplicate data points.
[d] CYP3A4 IC_{50} >10 μM except for **16a** (IC_{50} = 4.0 μM) and **10** (IC_{50} = 2.8 μM).
[e] Dofetilide binding assay.
[f] Patch clamp analysis.
[g] NT = not tested.

Table 3
SAR profiles of pyridine isosteres



Compd	Isomer	R^3	H_1[a] K_i (nM)	M_1[b] K_i (nM)	CYP2D6[c] IC_{50} (nM)	hERG[d] IC_{50} (μM)
11	*rac*		35	2072	856	NT[e]
18	(−)-*R*		4.6 ± 4	4759	4926	1.7
20	(−)-*R*		5.2 ± 2	>10,000	>10,000	NT
28a	*rac*		122	NT	8012	NT
28b	(−)-*R*		4.4 ± 3	>10,000	>10,000	2.0

[a] SEM for K_i values derived from dose–response curves generated from triplicate or more data points.
[b] Ki values derived from dose response curves generated from duplicate data points.
[c] CYP3A4 IC_{50} values >10 μM for all compounds, except for **28a** CYP3A4 IC_{50} = 5.2 μM.
[d] In dofetilide binding assay: hERG K_i >5 μM for all compounds.
[e] NT not tested.

Table 4
hERG Selectivity and pharmacokinetic parameters for key compounds[a]

Compd	hERG IC_{50}/H_1 K_i	Pred hClsys (ml/min/kg)	[P][b] 4 h (ng/mL)	[B][b] 4 h (ng/g)	B/P[b] 4 h	hClsys[c,e] (ml/min/kg)	Human[c] AUC_{0-t} (h ng/mL)
2	339	9.7	2.8	23	8	6.2 (5.8–7.2)	2.78 (1.90–4.23)
16c	629	14.8	37.5	347	9	NT[d]	NT
16d	1370	13.5	3.0	83	26	12.1 (4.6–18.5)	0.64 (0.21–1.86)
28b	443	6.0	0.6	11	20	NT	NT

[a] All compounds highly permeable (Caco-2: Papp > 21.7×10^{-6} cm/s; A > B/B > A > 0.7), no evidence for pGP substrate.
[b] Rat 30 mpk oral.
[c] Microdose of 0.1 mg/kg; data are median values of four individual subjects; data in parentheses are the range of four subjects (for full details see Ref. 17).
[d] NT not tested.
[e] Calculated for an average weight of 60 kg.

affinity. However, hERG inhibition for this and the 5-F analog **14f** was increased compared to **2**. The 3-OMe analog (**14c**) had comparable H_1 affinity to **2** with a marginally improved selectivity versus hERG. These data along with the profile of methyl analog (**14b**) suggested an electronic effect at the 3-position on hERG affinity. In the case of the 3-pyridyl moiety, substitutions at the 6-position were not tolerated (**9b**, **9c**) whereas substitutions at the 2-position met the defined criteria for affinity. Interestingly, in the 3-pyridyl subseries the 2-OMe, 2-F and 2-Cl compounds (**16c, 16d, 16e**) all demonstrated improved in vitro profiles. H_1 affinities were comparable to **16a**, while selectivities versus hERG were significantly improved. In contrast, the 2-Me substituent (**16b**) resulted in an H_1-antihistamine with reduced binding. Electronic effects were not apparent for this subseries, resulting in improved selectivity profiles for these compounds compared to the 2-pyridyl subseries.

Compounds **3** with pyridine isosteres (R^3) were also investigated (Table 3). The racemates of either a 4- or 5-thiazolyl moiety were tolerated in the H_1 pharmacophore (K_i <20 nM), whereas the 2-thiazolyl analog (**11**) had reduced binding. While introduction of a *N*-1 pyrazole moiety was acceptable, the corresponding imidazolyl modification (**28a**) negatively impacted H_1 binding. The primary profiles of the enantiomers for the active racemates (**18, 20, 28b**) were comparable to **2**, with the pyrazole **28b** demonstrating acceptable selectivity versus hERG (hERG/ H_1 K_i = 443).

Compounds with the best primary profiles (**16c**, **16d** and **28b**) were subsequently screened against other receptor off-targets (M_3, H_3 and $5HT_{2A}$) and assessed for pharmacokinetic parameters (Table 4) to determine how they compared to **2**.[8] Compounds exhibited >1000-fold selectivity over these three off-target receptors, except **16c** (400-fold selective over $5HT_{2A}$) and **28b** (200-fold selective over H_3). Predicted microsomal stability in humans (HLM assay[8]) indicated that both **16c** and **16d** showed higher clearance, whereas **28b** appeared more stable relative to **2**. Like benzothiophene **2**[8], compounds **16c**, **16d** and **28b** were unstable in rat liver microsomes with projected clearances approaching hepatic blood flow rate (Pred. systemic clearance >67 ml/min/kg). Discrete oral PK studies of these compounds in rat at a relatively high dose (30 mpk) indicated that each of these compounds was brain-penetrating as judged by B/P ratios (4 h post dose) with brain levels sufficient to produce efficacy in a rat EEG/EMG model.[16] Subsequently, efficacy was demonstrated for **16c** and **16d** and found to be comparable to **2** (See Supplementary data).[8]

As a higher clearance alternative with lower projected half-life, **16d** was selected for comparison of pharmacokinetic profile to **2** in

a human microdose study.[17] While clearance projections from allometric scaling were reasonably predictive (predicted clearance: 13.5 mL/min/kg, measured mean clearance: 12.1 mL/min/kg), the measured human half-life for **16d** was longer than anticipated (13 h vs the estimate of 1.6 h predicted from allometry) and longer than for **2** (6.8 h). This discrepancy in half-life prediction was attributed to both an underestimate of the volume of distribution of **16d** (V_{ss} measured as 5.6 L/kg in humans[16] versus 1.7 L/kg from allometric scaling) and an overestimate of clearance. Even though a small sample size was used in the microdose study, **16d** showed an increasing trend to high variability in exposure compared to **2** following both iv (hClsys, Table 4) and oral dosing ($AUC_{0\text{-}t}$, Table 4). PK variability in our leads was considered a significant issue because of the potential for varying exposures to adversely impact duration of action. Although a specific mechanism for the higher variability remains unclear, the higher clearance of **16d** compared to **2**, coupled with lower bioavailability (23% vs 47% for **2**) is consistent with mechanistic expectations that reduced metabolic stability generally contributes to increased variation in PK profile.[17] Based on these human PK data, neither compound **16d** nor **2** was pursued further. The more stable **28b** may therefore represent a more suitable backup to **2** and warrants further assessment.

In summary, discrete modifications around a lead benzothiophene **2** provided several compounds with a comparable in vitro profile and a small improvement in hERG selectivity. From rat PK studies, compounds with a range of projected human half-lives were identified. Compound **16d** was chosen as a representative high clearance compound and assessed in a human microdose study. In contrast to allometric projections, this compound had a longer half-life in humans compared to **2**. Unfortunately, both compounds **2** and **16d** showed a trend to high PK variability indicating neither analog was suitable for further development. Compound **28b**, with improved metabolic stability, may represent the more promising backup candidate.

Acknowledgments

The authors wish to thank Michael Johns for permeability determinations, John Harman, Shawn Ayube and Chris DeVore for analytical support. Dr. Tao Hu and Mila Lagman for chiral separations and Dr. John Saunders, Dr. Paul Conlon, Dr. H. Bozigian, and Dr. Wendell Wierenga for program support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.01.134.

References and notes

1. Barbier, A. J.; Bradbury, M. J. *CNS Neurol. Disord. Drug Targets* **2007**, *6*, 31.
2. Kubo, N.; Shirakawa, O.; Kuno, T.; Tanaka, C. *Jpn. J. Pharmacol.* **1987**, *43*, 277.
3. Kay, G. G.; Abou-Donia, M. B.; Messer, W. S., Jr.; Murphy, D. G.; Tsao, J. W.; Ouslander, J. G. *J. Am. Geriatr. Soc.* **2005**, *53*, 2195.
4. Meoli, A. L.; Rosen, C.; Kristo, D.; Kohrman, M.; Gooneratne, N.; Aguillard, R. N.; Fayle, R.; Troell, R.; Townsend, D.; Claman, D.; Hoban, T.; Mahowald, M. *J. Clin. Sleep Med.* **2005**, *1*, 173.
5. Kay, G. G.; Berman, B.; Mockoviak, S. H.; Morris, C. E.; Reeves, D.; Starbuck, V.; Sukenik, E.; Harris, A. G. *Arch. Intern. Med.* **1997**, *157*, 2350.
6. Kay, G. G.; Plotkin, K. E.; Quig, M. B.; Starbuck, V. N.; Yasuda, S. *Am. J. Manag. Care* **1997**, *3*, 1843.
7. Nicholson, A. N.; Pascoe, P. A.; Turner, C.; Ganellin, C. R.; Greengrass, P. M.; Casy, A. F.; Mercer, A. D. *Br. J. Pharmacol.* **1991**, *104*, 270.
8. Moree, W. J.; Li, B.; Jovic, F.; Coon, T.; Yu, J.; Gross, R. S.; Tucci, F.; Marinkovic, D.; Malany, S.; Bradbury, M. J.; Hernandez, L. M.; O'Brien, L.; Wen, J.; Wang, H.; Hoare, S. R. J.; Petroski, R. E.; Sacaan, A.; Madan, A.; Crowe, P. D.; Beaton, G. *J. Med. Chem.* **2009**, *52*, 5307.
9. The corresponding achiral analog of **2** with a methylene moiety instead of the –$CH(CH_3)$ group had H_1 K_i = 30 nM and CYP2D6 IC_{50} = 2157 nM.
10. (a) Roth, T.; Rogowski, R.; Hull, S.; Schwartz, H.; Koshorek, G.; Corser, B.; Seiden, D.; Lankford, A. *Sleep* **2007**, *30*, 1555; (b) Virtanen, R.; Scheinin, M.; Iisalo, E. *Acta Pharmacol. Toxicol.* **1980**, *47*, 371.
11. (a) Barcia, J. C.; Cruces, J.; Estevez, J. C.; Estevez, R. J.; Castedo, L. *Tetrahedron Lett.* **2002**, *43*, 5141; (b) Vallin, K. S. A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 4340.
12. Toudic, F.; Ple, N.; Turck, A.; Queguiner, G. *Tetrahedron* **2002**, *58*, 283.
13. Key chiral products were characterized by chiral SFC and/or optical rotation. Crystallographic data were obtained for compounds **2**[8], and **26b** to confirm absolute stereochemistry.
14. Larger quantities of pyrazole **28b** were synthesized from **5** by treatment with NH_2NH_2/EtOH at 100 °C, followed by a reduction with $NaCNBH_3$ in 50% aq HOAc to yield the hydrazine, and a cyclization using malonaldehyde bis(dimethyl acetal) in conc. HCl/EtOH at 95 °C and subsequent chiral SFC separation.
15. Coon, T.; Moree, W. J.; Li, B.; Yu, J.; Zamani-Kord, S.; Malany, S.; Santos, M. A.; Hernandez, L. M.; Petroski, R. E.; Sun, A.; Wen, J.; Sullivan, S.; Haelewyn, J.; Hedrick, M.; Hoare, S.; Bradbury, M. J.; Crowe, P. D.; Beaton, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4380.
16. Unpublished data has indicated that compounds that achieve brain concentrations >10 ng/g during this time period produce significant increases in nonrapid eye movement (NREM) sleep.
17. Madan, A.; O'Brien, Z.; Wen, J.; O'Brien, C.; Farber, R. H.; Beaton, G.; Crowe, P. D.; Oosterhuis, B.; Garner, R. C.; Lappin, G.; Bozigian, H. P. *Br. J. Clin. Pharmacol.* **2009**, *67*, 288.