Bioorganic & Medicinal Chemistry Letters 24 (2014) 2079–2085

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Discovery of dual orexin receptor antagonists with rat sleep efficacy enabled by expansion of the acetonitrile-assisted/diphosgene-mediated 2,4-dichloropyrimidine synthesis

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ARTICLE INFO

Article history:
Received 12 February 2014
Revised 14 March 2014
Accepted 17 March 2014
Available online 26 March 2014

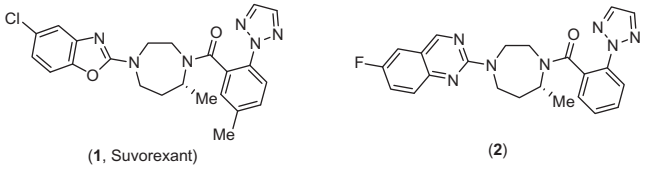
Keywords:
Orexin
Antagonist
Sleep
Bioactivation
Pyrimidine

ABSTRACT

Recent clinical studies have demonstrated that dual orexin receptor antagonists (OX_1R and OX_2R antagonists or DORAs) represent a novel treatment option for insomnia patients. Previously we have disclosed several compounds in the diazepane amide DORA series with excellent potency and both preclinical and clinical sleep efficacy. Additional SAR studies in this series were enabled by the expansion of the acetonitrile-assisted, diphosgene-mediated 2,4-dichloropyrimidine synthesis to novel substrates providing an array of Western heterocycles. These heterocycles were utilized to synthesize analogs in short order with high levels of potency on orexin 1 and orexin 2 receptors as well as in vivo sleep efficacy in the rat.

The discovery of novel orexin receptor antagonists has evolved rapidly in the past decade from the generation of novel peptide analogs[1] to small molecule clinical candidates[2] to the NDA filing of suvorexant (**1**, Fig. 1) in 2012 for the treatment of patients suffering from insomnia.[3] Suvorexant (**1**) and DORA **2** antagonize the action of wake-promoting orexin peptides (orexin A and B) at orexin 1 (OX_1R) and orexin 2 (OX_2R) receptors, hence, they are categorized as dual orexin receptor antagonists (DORAs). Several reviews have been published detailing the pharmacology and therapeutic utility associated with orexin antagonism and are beyond the scope of this manuscript.[4] Herein we report the expansion of the acetonitrile-assisted, diphosgene-mediated 2,4-dichloropyrimidine synthesis as it applies to the discovery of orexin antagonists.

As shown in Figure 1, Suvorexant and DORA **2** are both potent antagonists of OX_1R and OX_2R with nanomolar to subnanomolar binding potency and high levels of functional antagonism as determined in the FLIPR (fluorometric imaging plate reader) assay.[5] DORA **2** possessed similar in vivo efficacy in rat sleep studies compared to suvorexant, however, bioactivation concerns were confirmed through glutathione (GSH) trapping studies in microsomal incubations.[2c] Through additional diazepane core and heterocycle modifications and GSH trapping experiments, the 6-fluoroquinazoline moiety was determined to be the substructure responsible for the observed bioactivation. These findings encouraged us to examine the SAR of potential 6-fluoroquinazoline replacements. In order to effectively examine this new SAR, we sought an efficient synthesis of appropriately functionalized bicyclic pyrimidines.



OX_1R K_i (IC_{50}) = 0.6 nM (50 nM)
OX_2R K_i (IC_{50}) = 0.4 nM (56 nM)

OX_1R K_i (IC_{50}) = 1.8 nM (27 nM)
OX_2R K_i (IC_{50}) = 0.2 nM (27 nM)

Figure 1. Potent, optimized diazepane-containing dual orexin receptor antagonists (DORAs) suvorexant (**1**) and **2** that have demonstrated excellent sleep efficacy.

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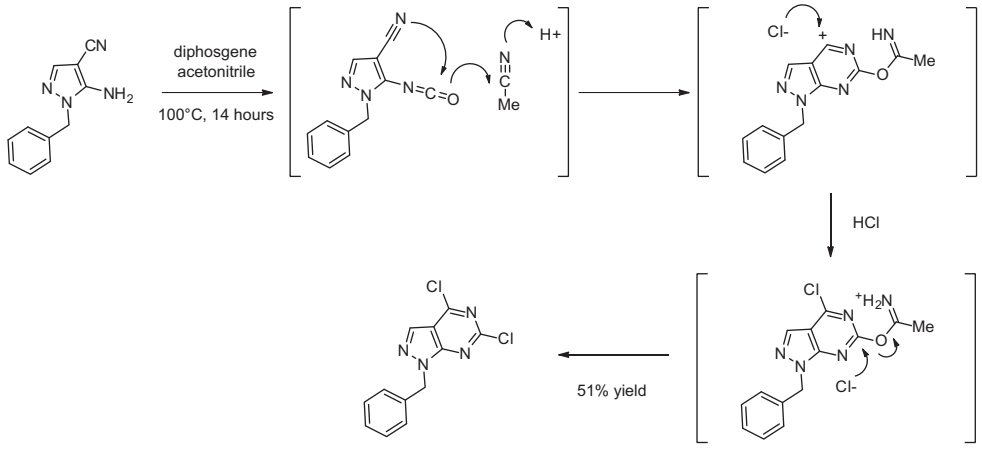
http://dx.doi.org/10.1016/j.bmcl.2014.03.052
0960-894X/



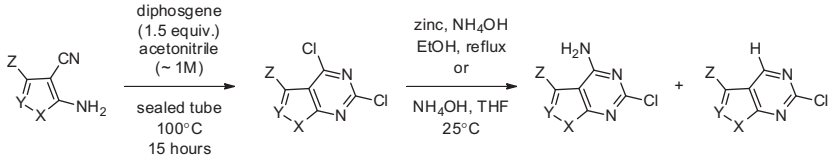
Scheme 1. Mechanism proposed by Chi et al. for their acetonitrile-assisted fused 2,4-dichloropyrimidine synthesis.

Chi and co-workers published a synthesis of 2,4-dichloroquinolines and 2,4-dichloroquinazolines in a single step from 2-ethynylanilines or anthranilonitriles, respectively, using diphosgene in acetonitrile.[6] A single example of a five-membered ring substrate, 5-amino-1-benzyl-1*H*-pyrazole-4-carbonitrile, demonstrated that this methodology would also provide fused pyrimidine heterocycles that could serve as interesting quinazoline replacements for the diazepane series shown in Figure 1. The mechanism proposed by Chi and co-workers for this transformation is depicted in Scheme 1, and it involves isocyanate formation, ring closure assisted by acetonitrile, and two subsequent chloride ion attacks to afford the final products in modest yield. Our group sought to further evaluate the scope of this reaction and to test its application toward the synthesis of DORAs with diminished bioactivation potential compared to DORA **2**.[7]

A series of commercially available five-membered heterocyclic 2-aminocarbonitriles were subjected to the conditions described in Scheme 1 and the results are shown in Table 1. Truncated pyrazole substrates **3** and **7** provided fused dichloropyrimidines **4** and **8** in slightly reduced yields (39% and 24%, respectively) compared to the pyrazole substrate exemplified in Scheme 1. Substituted thiophene scaffolds were also competent substrates under the reaction conditions with precursors **11** and **15** affording products **12** and **16** in 52% and 65% yields, respectively. Substrate **18**, 2-aminothiophene-3-carbonitrile, provided the desired product with less overall yield (19%). Finally, substituted furans **21** and **25** performed well giving rise to products **22** and **26** in acceptable to good yields.

Standard nucleophilic substitution reactions (S_NAr) of 2,4-dichloropyrimidines using secondary amines such as our diazepane substrates provide 4-substituted products with high regioselectivity.[8] In order to afford the 2-substituted analogs similar to DORA **2**, bicyclic 2,4-dichloropyrimidine substrates were subjected to a variant of known conditions for selective dechlorination of the 4-position. Treatment with excess elemental zinc and ammonium hydroxide in refluxing ethanol afforded a mixture of desired dechlorinated-, aminated-, and ethoxy substituted products.[9] In

Table 1
Acetonitrile-assisted synthesis of 2,4-dichloropyrimidines and subsequent amination/dechlorination



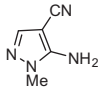
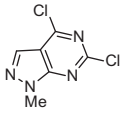
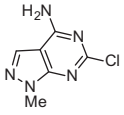
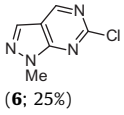
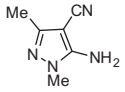
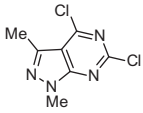
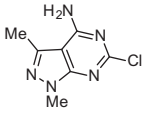
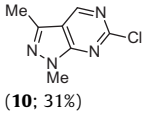
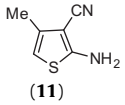
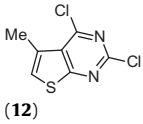
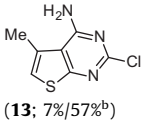
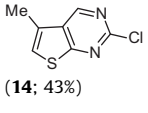
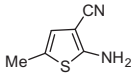
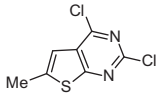
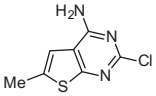
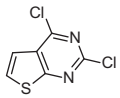
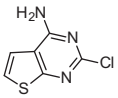
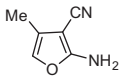
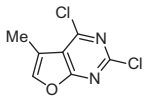
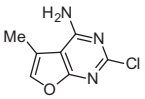
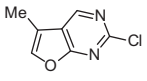
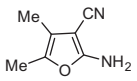
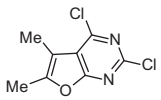
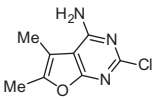
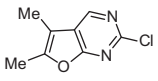
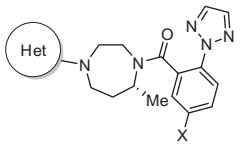
Substrate	Product	Yield (%)	Amine substitution (yield)[a]	Dechlorination (yield)[a]
 (**3**)	 (**4**)	39	 (**5**)	 (**6**; 25%)
 (**7**)	 (**8**)	24	 (**9**; 51%)	 (**10**; 31%)
 (**11**)	 (**12**)	52	 (**13**; 7%/57%[b])	 (**14**; 43%)

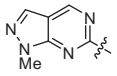
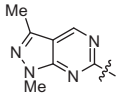
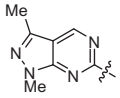
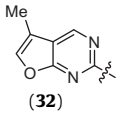
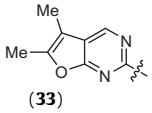
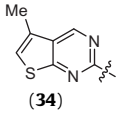
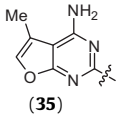
Table 1 (*continued*)

Substrate	Product	Yield (%)	Amine substitution (yield)[a]	Dechlorination (yield)[a]
 (**15**)	 (**16**)	65	 (**17**; 57%[b])	NS
 (**18**)	 (**19**)	19	 (**20**; 18%[b])	NS
 (**21**)	 (**22**)	38	 (**23**; 23%)	 (**24**)
 (**25**)	 (**26**)	75	 (**27**; 3%)	 (**28**; 6%)

Reagents and conditions: (a) zinc (8 equiv), ammonium hydroxide (5 equiv), ethanol (0.15 M), reflux, 30 min; (b) ammonium hydroxide (5 equiv), THF (0.2 M), 25 °C; NS = not synthesized.

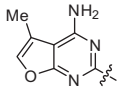
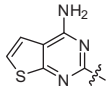
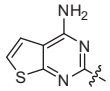
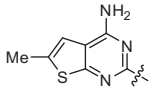
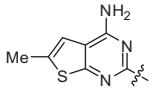
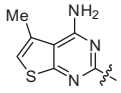
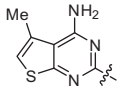
Table 2
Potent diazepane-containing DORAs[a,b]



Heterocycle (compound #)	X	OX_2R K_i[a] (nM)	OX_1R K_i[a] (nM)	OX_2R IC_{50}[a] (nM)	OX_1R IC_{50}[a] (nM)
 (**29**)	Me	2	49	92	70
 (**30**)	Me	0.8	3.7	119	85
 (**31**)	H	4.5	92	200	280
 (**32**)	Me	0.2	0.6	45	34
 (**33**)	Me	0.5	0.5	67	42
 (**34**)	Me	0.3	0.2	37	35
 (**35**)	Me	1.8	5	195	160

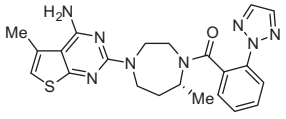
(*continued on next page*)

Table 2 (*continued*)

Heterocycle (compound #)	X	OX_2R K_i[a] (nM)	OX_1R K_i[a] (nM)	OX_2R IC_{50}[a] (nM)	OX_1R IC_{50}[a] (nM)
 (**36**)	H	1.8	25	195	210
 (**37**)	Me	0.5	0.7	26	34
 (**38**)	H	0.9	9.2	15	35
 (**39**)	Me	0.4	0.4	47	35
 (**40**)	H	0.7	1.5	31	34
 (**41**)	Me	0.3	0.3	53	43
 (**42**)	H	0.3	1.2	28	29

[a] See Ref. 2c for the details of these assays. All compounds listed were assayed as single enantiomers.
[b] All data reported as an average value from $n \geqslant 2$; for $n > 2$, standard deviation is <40% in all cases.

order to provide additional SAR, the aminated products (Table 1, row 4), targeting improved physiochemical properties, and dechlorinated products (Table 1, row 5) were isolated and the yields are shown in Table 1. It was also found that the aminated products could be synthesized more efficiently using ammonium hydroxide in tetrahydrofuran at ambient temperature (products **13**, **17**, and **20**).[10] Both diazepane cores for DORAs **1** and **2** and the heterocycles above were used to synthesize the analogs displayed in Table 2.[2c] These analogs were synthesized under standard S_NAr conditions of heterocycle (1.2 equiv), diazepane core (1.0 equiv), Hunig's base or triethylamine (2.5 equiv), in dimethylformamide (~0.3 M) at 100–180 °C in a microwave reactor for 10–40 min.



DORA **42**

Plasma Protein Binding
Human: 98.5%
Rat: 98.9%
Dog: 97.8%

CNS Properties
Pgp ratio (BA/AB): 1.2(h); 1.8(r)
Papp: 31 cm * 10^{-6}/s
HPLC log D: 2.0
PSA: 96 Å^2

Figure 2. Additional properties of DORA **42**.

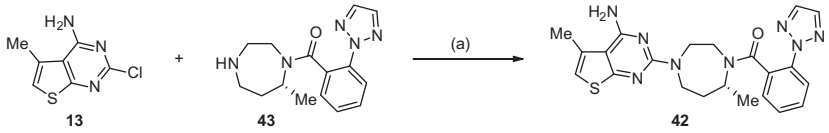
Analysis of the SAR for the new compounds revealed that pyrazolopyrimidine **29** showed diminished binding and functional potency on both OX_1R and OX_2R when compared with lead DORA **2** as shown in Table 2. Substitution of the pyrazole motif with a methyl group (**30**) improved OX_1R binding potency, however, functional potency on both receptors decreased slightly. Removal of the methyl group on the benzamide generally decreases potency on both receptors for compounds in this series,[11] and this was observed for des-methyl analog **31**. Furopyrimidines **32** and **33** demonstrated subnanomolar binding potency for both orexin receptors and functional potency similar to DORA **1**. Given the improved functional potency for mono-methyl furopyrimidine **32**, thienopyrimidine **34** was synthesized. This analog possessed exquisite binding potency on both OX_2R (0.3 nM) and OX_1R (0.2 nM) and functional potency similar to DORA **2**. Unfortunately, compound **34** suffered from high plasma protein binding (PPB: 99.4% human; 99.3% rat) and high log *D* (3.8; HPLC method[12]) which precluded additional pharmacokinetic or in vivo studies.

Luckily, 4-amino substituted heterocycles were available from the synthetic studies in Table 1 allowing the production of analogs that might provide improved physiochemical properties (Table 2). Amino-substituted furopyrimidines **35** and **36** displayed reduced binding and functional potency when compared to des-amino analog **32**. Surprisingly, amino-substituted thienopyrimidines **37** to **42** all demonstrated low to subnanomolar binding affinity and excellent functional potency for OX_2R and OX_1R. While analogs **37** and

Table 3
Pharmacokinetics of DORA **42** in rat and dog

	IV[a]				Dose (mg/kg)	PO[b]			
Species	Dose (mg/kg)	Cl (mL/min/kg)	Vd_{ss} (L/kg)	$T_{1/2}$ (h)		AUC (μM h)	T_{max} (h)	C_{max} (μM)	*F* (%)
Rat	2	22	0.3	0.2	10	2.8	0.3	3.8	17
Dog	0.5	13	0.7	0.8	3	3.1	0.6	1.2	34
Rat[c]	NA	NA	NA	NA	25	6.1	0.5	2.5	15

[a] Vehicle = 100% DMSO in rat and dog ($n = 2$).
[b] Dosed as the hydrochloride salt in 100% PEG200 ($n = 2$).
[c] Dosed as hydrochloride salt in 20% VitE TPGS in water; satellite rats for sleep study pharmacokinetics ($n = 3$).



Scheme 2. Gram scale synthesis of compound **42**. Reagents and reaction conditions: (a) triethylamine, DMF, 185 °C, 40 min, microwave, 39% (7.5 mmol scale; 1.3 grams produced). See Ref. 2c for the synthesis of diazepane core **43**.

38 possessed excellent potency profiles, the unsubstituted thiophene motif is a known substrate for bioactivation.[13] Precedent suggested that substitution on the thiophene motif can reduce this liability.[14] Since DORA **42** demonstrated the best balance of binding potency, functional potency, and theoretical bioactivation potential of the final four analogs (**39**–**42**), this compound was selected for additional profiling (Fig. 2).

The 4-amino substituent present in DORA **42** improved free fraction to measurable levels across species and decreased log*D* by 1.8 units compared to compound **34** (Table 2). In addition, the compound was highly permeable and not a substrate for rat or human P-glycoprotein efflux. Compound **42** possessed polar surface area in an acceptable range for brain penetrant small molecules.[15] Pharmacokinetic properties were evaluated for compound **42** (dosed as a hydrochloride salt) and these data are displayed in Table 3. In the rat and the dog, this compound had moderate clearance, a short half-life, and bioavailability of 17% and 34%, respectively. Since this compound was suitable for oral administration, it was scaled up for additional in vivo characterization in rat sleep studies. The gram scale synthesis is shown in Scheme 2.

Figure 3 displays the results of sleep studies from active phase radiotelemetric recordings in the rat over the two hour period directly following compound administration using methods previously described.[16] Upon dosing the hydrochloride salt of compound **42** in rats at 25 mg/kg (p.o. in 20% Vitamin E TPGS), immediate and significant reduction in active wake and concomitant increases in slow wave sleep (SWS) and REM sleep were observed over the two hour period immediately following treatment. The sleep efficacy of compound **42** in the rat was accompanied by a C_{max} of 2.5 μM, T_{max} of 30 min, and an AUC of 6.1 μM h (Table 3). The C_{max} data for compound **42** coincided nicely with results from ex vivo occupancy studies in transgenic rats which overexpress human OX_2R demonstrating 88% receptor occupancy at a plasma concentration of 2.0 μM.[17] These findings follow the same occupancy/efficacy relationship as compounds **1** and **2**. In fact, Compound **42** induced a sleep architecture profile nearly identical to that observed for compound **2** administered at 30 mg/kg (C_{max}: 2.0 μM; T_{max}: 1.3 h; AUC: 4.5 μM h), as previously described for this structure as well as compound **1**.[2c]

Finally, DORA **42** and DORA **2** were directly compared for bioactivation potential via our GSH trapping assay in rat and human microsomal incubations.[18] DORA **42** and DORA **2** demonstrated similar levels of bioactivation in rat and human experiments as determined by AUC measurements of all GSH adducts relative to an internal standard (Fig. 4). Although precedent suggested that substituted thiophene analogs could reduce bioactivation potential relative to their unsubstituted counterparts,[14] the direct comparison between phenyl and thiophene isosteres is less well studied. The bioactivation potential of DORA **42** precluded further development of thiophene-containing DORAs.

Expansion of an acetonitrile-assisted, diphosgene-mediated synthesis of bicyclic 2,4-dichloropyrimidines enabled the expeditious production of analogs of DORA **2**. These efforts afforded DORAs with excellent binding and functional potency on OX_1R and OX_2R as well as improved physiochemical properties. DORA **42** was identified as an advanced compound with superb potency and rat sleep efficacy comparable to DORA **2**. Unfortunately, the bioactivation potential of DORA **42** precluded further development

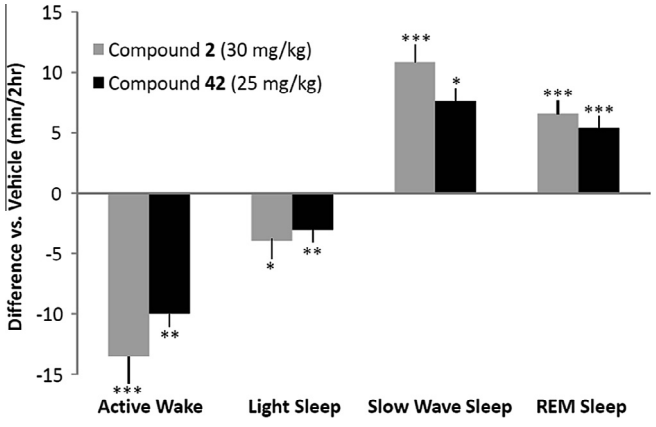


Figure 3. Sleep architecture effects of DORA **42** and DORA **2** in rat sleep dosed during their active phase. (a) Mean change in active wake, light sleep, SWS and REM sleep time relative to vehicle (20% Vitamin E TPGS) in rats monitored for two hours following p.o. administration of compound **2** (30 mg/kg) and compound **42** (25 mg/kg). Treatment occurred at Zeitgeber Time 16:00 (4 h after lights off) in a balanced cross-over design such that each subject received drug and vehicle (3 or 7 days of consecutive treatment, compounds **2** and **42**, respectively). Values represent the mean of within-subject differences between vehicle and compound treatment (±SEM). Mean times for the compound condition in experiments evaluating compound **2** and compound **42** experiments, respectively (min): AW: 58, 53; LS: 14, 12; SWS: 41, 46; REM: 7, 9. Data were analyzed using within-subject ANOVA to determine main effects and one sample *t*-test to compare to vehicle ($N = 14$, 8 for studies evaluating compounds **2** and **42**, respectively; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$).

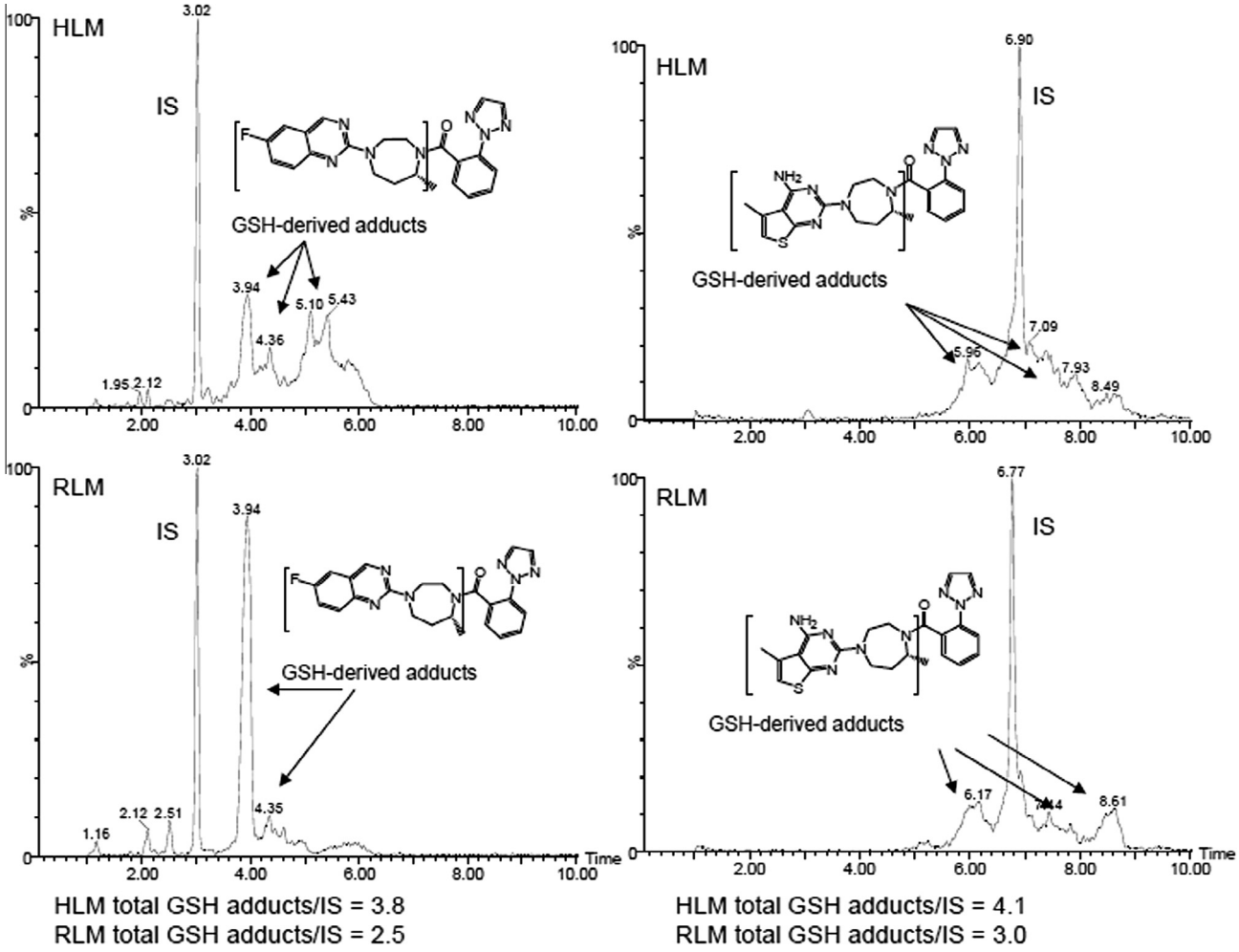


Figure 4. GSH trapping studies in rat and human liver microsomes. Ratios are AUC measurements normalized to the AUC of an internal standard (IS = labetalol). AUC = area under curve; RLM = rat liver microsomes; HLM = human liver microsomes.

of thiophene-containing DORAs. Studies focused on additional strategies to reduce bioactivation of diazepane amide DORAs will be published in due course.

Acknowledgments

We thank Dr. Charles W. Ross III and Joan S. Murphy for analytical studies in support of this manuscript. We would like to thank Michael J. Bogusky for NMR support. We would like to thank Joseph G. Bruno and Rodney A. Bednar for assay support.

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18. See Ref. 2c for an experimental description of the GSH-trapping assay in microsomal preparations.