Synthesis and Antiinflammatory Activity of Certain 5,6,7,8-Tetrahydroquinolines and Related Compounds

William Calhoun,† Richard P. Carlson,† Roger Crossley, Louis J. Datko,† Scott Dietrich,† Kenneth Heatherington, Lisa A. Marshall,† Peter J. Meade, Albert Opalko,* and Robin G. Shepherd

Department of Medicinal Chemistry, Wyeth Research (U.K.) Ltd., Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 OPH, United Kingdom, and Wyeth-Ayerst Research, CN-8000, Princeton, New Jersey 08543-8000

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Modification of some 8-benzylidene-5,6,7,8-tetrahydroquinolines, which have good antiulcer activity, led to three distinct classes of compounds with good *in vivo* antiinflammatory activity. Initial efforts led to a series of alkenes derived from 5,6,7,8-tetrahydroquinolines substituted at the 8-position. A second approach concentrated on replacing the CH linkage of these 8-benzylidene-substituted compounds with other spacer groups and increasing the size of the cycloalkyl ring from a six- to seven-membered ring, which provided 6,7,8,9-tetrahydro−5*H*-cyclohepta[*b*]pyridine analogues. Finally, the substituent was switched from the cycloalkyl ring to the 2-position of the pyridine ring. Variation of the 2-substituent was also examined. Optimal antiinflammatory activity after oral administration was found in both the rat carrageenan paw edema and rat developing adjuvant arthritis models with 2-substituted 6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridines, and of particular interest was **27** (WY-28342).

The current treatment for rheumatoid arthritis and other inflammatory diseases still involves the use of nonsteroidal antiinflammatory drugs (NSAIDs).[1] These agents manifest their action by the inhibition of the enzyme cyclooxygenase (CO), which results in a decrease in prostaglandins, and although this is a very effective mechanism as demonstrated by their wide clinical use, there are a number of drawbacks such as gastrointestinal ulceration, bleeding, and nephrotoxicity.[2] The prostaglandins have been shown to be antisecretory and cytoprotective,[3] and so the inhibition of cyclooxygenase results in their reduction and consequently an increase in gastric irritation. Inhibition of 5-lipoxygenase (5-LO) produces a decrease in leukotrienes, and there are reports that these substances may also have a pathophysiological role in the production of gastrointestinal ulceration.[4] Besides the gastrointestional side effects, leukotrienes also promote inflammation,[5] and so a combined inhibition of both the CO and LO pathways may result in antiinflammatory agents with an improved safety profile.

A number of combined LO/CO inhibitors have been identified and studied as antiinflammatory agents,[6] and recent approaches to identifying dual inhibitors, by modifying selective CO inhibitors, have led to the discovery of compounds such as **1**[7] and **2**,[8] Figure 1. Another approach has focused on the use of antioxidants in which a 2,6-di-*tert*-butylphenol is linked either directly[9] or to a two-carbon chain linkage[10] or is part of a benzylidene, **3**, attached to a heterocyclic ring.[11]

In a previous gastrointestinal project, we had prepared a series of compounds, **4**–**7**, which have useful antiulcer activity[12] but which did not mediate this effect through an antisecretory mechanism. An attempt was made to determine their mode of action, and because prostaglandins are known[13] to be implicated in the pathology of ulcer formation, we examined these 8-substituted benzylidenetetrahydroquinolines for their effects on the arachidonic acid pathways and found they had both LO and CO activity.[14] As these compounds are basic, unlike conventional NSAIDs, and were derived from an antiulcer series, we felt that these compounds would offer a useful starting point for our investigation. We soon established that they had good oral antiinflammatory activity, and so we concentrated on the elaboration of this novel lead. The range of compounds we studied can be divided into three main structural classes, outlined in Tables 1–3. In this paper we describe their synthesis and examine both their *in vitro* and *in vivo* antiinflammatory activity.

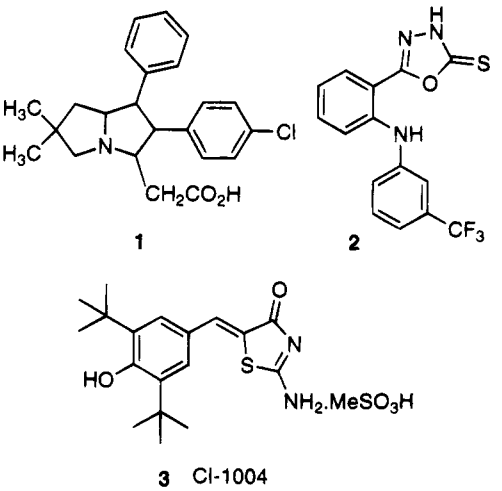

Figure 1. Combined 5-LO/CO inhibitors.

Chemistry

The majority of compounds **4**–**13** described in Table 1 were prepared by one of two main methods, and these are outlined in Scheme 1. The first of these, method A, involved refluxing the appropriate tetrahydroquinoline with the required benzaldehyde in acetic anhydride[15] to give the benzylidenes **4**–**7** with *E*-stereochemistry.

The second method of preparation was through the Peterson reaction[16] (method B) which is more versatile,

† Wyeth-Ayerst Research.
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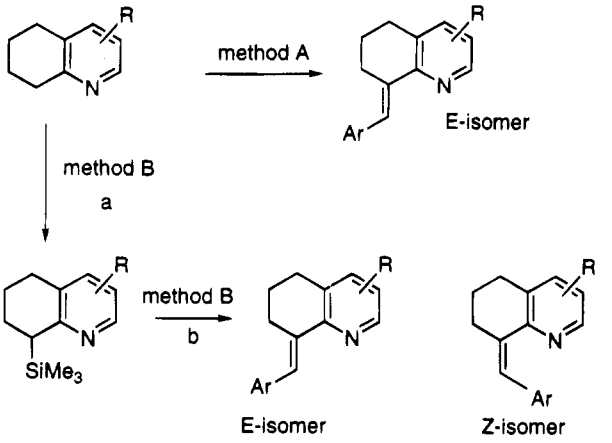
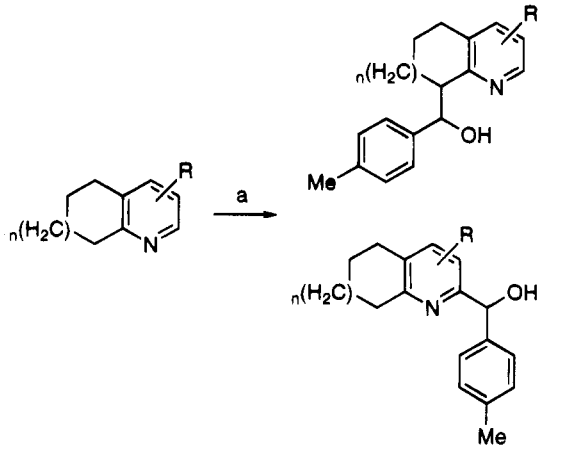
Scheme 1[a]



[a] Reagents: method A ArCHO, $ZnCl_2$ in Ac_2O; method B, (a) *n*-BuLi, Me_3SiCl, (b) *n*-BuLi, ArCHO, H^+.

Scheme 2[a]



[a] Reagents: (a) *n*-BuLi, ArCHO, H^+.

as it allows the preparation of both the (*E*)- (**8** and **11**) and (*Z*)-benzylidene (**9**, **10**, and **13**) derivatives. This method entailed the preparation of the organosilane, by forming an anion of the tetrahydroquinoline[17] with *n*-butyllithium followed by reaction with trimethylsilyl chloride.[18] The silane was then reacted with another equivalent of *n*-butyllithium, and the resulting anion was treated with an aldehyde or ketone to form a β-hydroxysilane. Elimination occurred when the hydroxysilane was treated with acid to give a mixture of both (*E*)- and (*Z*)-alkenes, and these were separated by column chromatography.

The benzylidene derivative **7** was prepared by acid hydrolysis of an acetoxy group to give the phenol, and **12** was prepared by the dehydration of the alcohol **21** (Table 2), also under acidic conditions. Only the alkene with *Z*-stereochemistry was isolated, presumably because the steric effects of the flanking dimethyl substituents interfere in the formation of the (*E*)-alkene.

Other compounds were prepared (Table 2) where the alkene CH functionality was replaced by other bridging groups (**14**–**25**), such as $NHSO_2$, CO, S, SO, SO_2, or CH(OH). The sulfonamide **14** was prepared by allowing the corresponding amine[19] to react with *p*-toluenesulfonyl chloride in dichloromethane. The ketones **15**–**17** were formed by reacting the lithium anion of the tetrahydroquinoline with a suitably substituted benzonitrile (method C). The thioether **18** was prepared by reacting the anion of the tetrahydroquinoline with diphenyl disulfide, and **18**[20] was subsequently oxidized to the sulfinyl compound **19**, which was further oxidized to the sulfonyl compound **20**, also with *m*-chloroperbenzoic acid.

The alcohols **21**–**25** were prepared by reacting the respective tetrahydroquinoline or cyclohepta[*b*]pyridine with *n*-butyllithium and then quenching with *p*-tolualdehyde. Treatment of the tetrahydroquinoline (see Scheme 2, $n = 1$) gave only products where anion formation at the 8-position was observed, and only the 8-substituted alcohols **21**–**23** were isolated. However, with the cyclohepta[*b*]pyridine (Scheme 2, $n = 2$), the 2-substituted derivative **26** was unexpectedly formed as well as the 9-substituted analogues **24** and **25**, presumably reflecting the relative stability of the corresponding anions and kinetic vs thermodynamic control of the anion formation in cyclohepta[*b*]pyridines. Such anion migration is known between alkyl substituents on pyridines and cycloalkyl-fused pyridines (ref 21 and previous papers), but this is the first example of such a migration to the 2-aryl position of a cyclohepta[*b*]pyridine.

Isolation of **26** led to the elaboration of a third class of compounds, **26**–**41** (Table 3), based on 2-substituted cyclohepta[*b*]pyridines. In order to prepare the 2-substituted cyclohepta[*b*]pyridines in good yield and in a more consistent manner, a new synthetic method was devised. This required the use and preparation of 2-bromo-3-methylcyclohepta[*b*]pyridine[22] and subsequent formation of the 2-lithio species prior to derivatization. Under these circumstances no equilibration of the anion to the 9-position was observed.

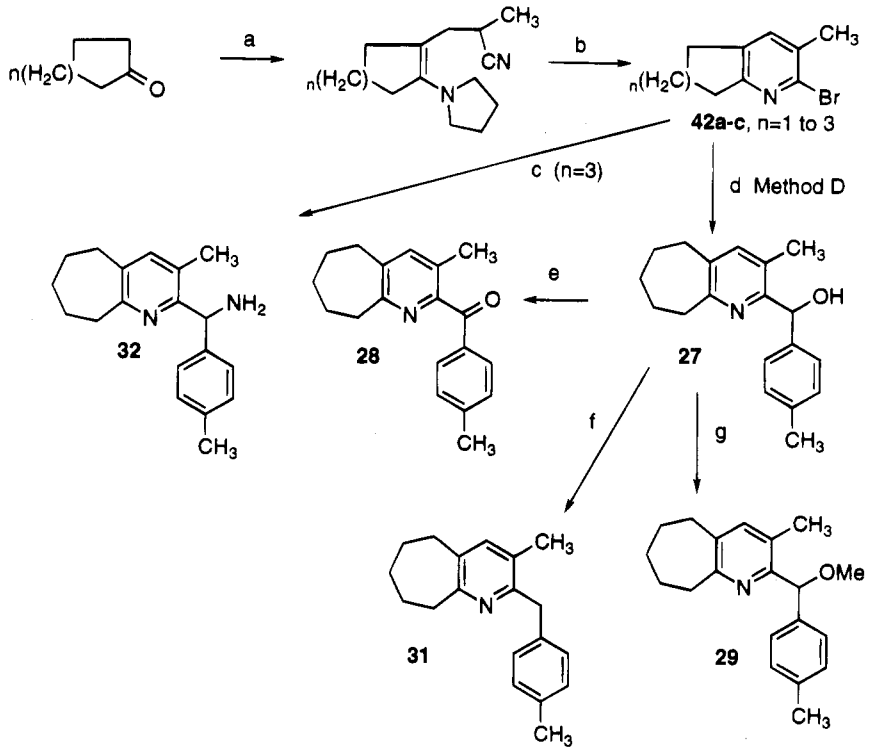
The various 2-bromo-substituted analogues were prepared by treating the appropriate cyclic ketone with pyrrolidine and then allowing the subsequent enamine to react with methacrylonitrile. This Michael adduct was hydrolyzed back to a ketone and then cyclized by treatment with bromine to give the desired bromo compounds **42a**–**c** directly. The general procedure is described in Scheme 3 and the Experimental Section.

In order to prepare the alcohols of Table 3, the required bromo derivative **42** was treated with *n*-butyllithium and the resulting anion was then quenched with an aldehyde or ketone (method D, Scheme 3). The homologous alcohol (**41**) of **27** was prepared by forming the anion of 2-methylcyclohepta[*b*]pyridine[23] in toluene and reaction with 4-tolualdehyde. The ketone **28**, ether **29**, and alkane **31** were then prepared from the alcohol **27** using standard chemistry as outlined in Scheme 3. The corresponding amine analogue (**32**) of alcohol **27** was prepared by reacting the required bromo compound (**42b**, $n = 2$) with *n*-butyllithium and subsequently with benzonitrile. The resulting imine was reduced with sodium borohydride to give the amine **32**.

Biological Investigations

Approximately 40 compounds were examined for both their *in vitro* and *in vivo* biological activity. The *in vitro* effect of each compound was evaluated in the rat polymorphonuclear leucocyte (PMN) assay,[24] and the antiulcer compounds **4**–**6** were tested for the inhibition of the 5-LO pathway, by measuring for their effects in inhibiting the formation 5-hydroxy-(6*E*,8*Z*,11*Z*,14*Z*)-eicosatetraenoic acid (5-HETE), and the CO pathway, by measuring for their effects in inhibiting the formation of thromboxane B_2 (TXB_2), both at 50 μM. Following the initial assay of these three compounds, the screening

Scheme 3[a]



[a] Reagents: (a) (i) pyrrolidine, (ii) methacrylonitrile; (b) Br_2; (c) (i) *n*-Bu-Li, (ii) ArCN, (iii) $NaBH_4$, (iv) H^+; (d) method D, (i) *n*-BuLi, (ii) ArCHO; (e) MnO_2; (f) H_2, 10% Pd/C, H^+; (g) (i) NaH, (ii) MeI.

protocol was modified and the rest of the compounds were tested at 10 μM in the rat PMN assay[24] for their effects in inhibiting the formation of leukotriene B_4 (LTB_4) and 5-HETE on the 5-LO pathway, and TXB_2 and prostaglandin E_2 (PGE_2) levels on the CO pathway. The *in vivo* effects of these compounds were evaluated orally in two ways. These were in the rat carrageenan paw edema assay[25] at 50 mg/kg po and the rat developing adjuvant arthritis assay[26] at 30 mg/kg po. A small number of compounds were evaluated in the rat yeast-induced fever assay[26] and rat acute gastric irritation assay (see the Experimental Section).

Results and Discussion

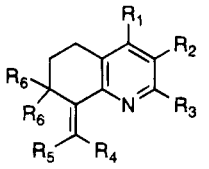
The starting point for this study were compounds **4**–**7**, which were originally prepared as antiulcer agents. Compounds **5** and **6** totally inhibited both 5-LO and CO in the rat PMN assay at 50 μM and had good activity in the rat carrageenan paw edema model but displayed poor activity in the developing adjuvant arthritis assay. These results were especially interesting because it was unusual for compounds with effects on prostaglandin synthesis to show antiulcer actvity; indeed in general CO inhibitors are ulcerogenic.[27] It is assumed that the antiinflammatory activity and the lack of ulcerogenic properties of these compounds are due to their effects in inhibiting both 5-LO and CO. The 4-methylphenyl analogue **4** had almost the same profile but was less potent against 5-LO.

These initial compounds had the *E*-stereochemistry. As noted above, using the Peterson reaction it was possible to prepare compounds with both *E*- and *Z*-stereochemistry, and a number of analogues were synthesized in both isomeric forms. Both (*E*)- and (*Z*)-alkenes had good antiinflammatory activity in the rat carrageenan paw edema model, as demonstrated by compounds such as **4**–**6** and **12**. However, the only compounds which had significant activity in the rat developing adjuvant arthritis assay had the *Z*-stereochemistry, namely the pyridyl analogue **10** and the quinolyl analogue **13**.

Interestingly, the *E*-isomer **11** was not as effective as its corresponding *Z*-isomer **10** in the adjuvant arthritis model. Both had no activity in the rat carrageenan model, but both compounds did stimulate the formation of PGE_2, and this may be attributed to the inhibition of thromboxane A_2 synthase by these compounds. The general structural requirement for thromboxane synthase A_2 inhibition is a basic heterocyclic ring (normally 1-imidazolyl or 3-pyridyl) separated from a polar function which is normally carboxylic acid,[28] with less potent compounds just having the heterocyclic moiety. Compounds **10** and **11** both have the required 3-pyridyl function. Additionally, **10** (50 mg/kg po) had significant antipyretic activity in the rat yeast-induced fever[26] assay.

As some of the (*Z*)-alkenes were more potent than the (*E*)-alkenes in the developing adjuvant arthritis assay, the spatial arrangement of the aryl ring with the tetrahydroquinoline was examined further. Accordingly, we varied the substituent at the 8-position of the tetrahydroquinoline or the 9-position of the cyclohepta[*b*]pyridines (Table 2). Initially, attention was given to the nature of the bridging group, and the vinylic CH of the benzylidene was replaced by a variety of other bridging systems. Of these, the more potent compounds were found when A was CH(OH). Also, when A is CH(OH), two diastereoisomers could be prepared, and so both diastereoisomers of the six- and seven-membered ring analogues **23**–**25** were isolated and examined for biological activity. The *R**,*S** analogues of the tetrahydroquinoline **21** and the cyclohepta[*b*]pyridine **24** had

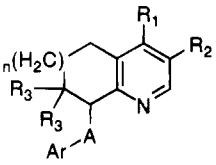
Table 1. Physical Data and Biological Activity for 8-(Phenylmethylene)tetrahydroquinoline Analogues



												rat PMN[d]					
												5-LO		CO		rat	
no.	R_1	R_2	R_3	R_6	R_4	R_5	method[a]	yield (%)	mp (°C)[b]	formula[c]		LTB_4	5-HETE	TXB_2	PGE_2	cargn edema[e]	dev AA[f]
4	H	Me	H	H	H	4-MeC_6H_4	A	15	105–7	$C_{18}H_{19}N$			−28[g]		−100[g]	−47[h]	17
5	H	−$(CH)_4$−		H	H	4-AcO-3-$MeOC_6H_3$	A	74	127–8	$C_{23}H_{21}NO_3$			−100[g]		−100[g]	−39[h]	14
6	Me	H	H	H	H	4-AcO-3-$MeOC_6H_3$	A	32	111–3	$C_{20}H_{21}NO_3$			−100[g]		−100[g]	−45[h]	23
7[i]	H	Me	H	H	H	4-OH-3-$MeOC_6H_3$	*j*	94	256–8	$C_{18}H_{19}NO_2$·HCl						−36[h]	−1
8	Me	H	H	H	Me	4-MeC_6H_4	B	7	231–5	$C_{19}H_{21}N$·HCl		−18	1	−57	−49	−15	0
9	Me	H	H	H	4-MeC_6H_4	Me	B	19	89–93	$C_{19}H_{21}N$		−22	7	−22	7	−15	−14
10	Me	H	H	H	4-pyridyl	H	B	25	213–5	$C_{16}H_{16}N_2$·2HCl·H_2O		−25	−17	−87	191	−17	−49[h]
11	Me	H	H	H	H	4-pyridyl	B	29	118–20	$C_{16}H_{16}N_2$		−4	9	−75	142	−15	3
12	H	Me	H	Me	4-MeC_6H_4	H	*j*	39	153–5	$C_{20}H_{23}N$·HCl		86	97	−66	−56	−48[h]	8
13	Me	H	H	H	4-quinolyl	H	B	19	90–1	$C_{20}H_{18}N_2$·0.5H_2O		−23	−5	−18	−15	−36[h]	−38[h]

[a] Methods A and B are general conditions described in the Experimental Section (see Scheme 1). [b] Uncorrected. [c] Compounds were analyzed for C,H,N ±0.4% for formula indicated. [d] Rat polymorphonuclear leucocyte assay, percent change at 10 μM. [e] Rat carrageenan edema assay, percent change at 50 mg/kg po (3 h edema). [f] Rat adjuvant arthritis (developing model) assay, percent change at 30 mg/kg po (uninjected paw at day 16). [g] Rat polymorphonuclear leucocyte assay, percent change at 50 μM. [h] $P \leq 0.05$ from control. [i] Not tested in rat PMN assay. [j] See the Experimental Section for preparation.

Table 2. Physical Data and Biological Activity of 8-Substituted Tetrahydroquinolines and 9-Substituted Cyclohepta[*b*]pyridines



												rat PMN[d]					
												5-LO		CO		rat	
no.	*n*	R_1	R_2	R_3	Ar	A	method[a]	yield (%)	mp (°C)[b]	formula[c]		LTB_4	5-HETE	TXB_2	PGE_2	cargn edema[e]	dev AA[f]
14	1	H	Me	H	4-MeC_6H_4	$NHSO_2$	*g*	42	204–14	$C_{17}H_{20}N_2O_2S$·HCl		2	−16	−9	2	−33[h]	77
15	1	Me	H	H	4-MeC_6H_4	CO	C	49	240–2	$C_{18}H_{19}NO$·HCl		−34	−41	−15	−18	−12	19
16	1	Me	H	H	3,4-diMeC_6H_3	CO	C	53	237–9	$C_{19}H_{21}NO$·HCl		−53	−50	−4	7	−25	−28
17	1	H	H	H	3-MeC_6H_4	CO	C	41	211–3	$C_{17}H_{17}NO$·HCl		−11	23	8	37	−6	−16
18	1	H	Me	H	Ph	S	*g*	96	173–6	$C_{16}H_{17}NS$·HCl		−39	−50	−19	−10	−21	−27
19	1	H	Me	H	Ph	SO	*g*	52	123–8	$C_{16}H_{17}NOS$		13	50	30	18	−25	13
20	1	H	Me	H	Ph	SO_2	*g*	90	84–6	$C_{16}H_{17}NO_2S$		6	0	18	16	−22	−2
21	1	H	Me	Me	4-MeC_6H_4	CH(OH) *R*,S**	*g*	24	111–3	$C_{20}H_{25}NO$		8	27	−2	27	−19	−39[h]
22	1	H	Me	H	4-MeC_6H_4	CH(OH) *R*,R**	*g*	40	91–3	$C_{18}H_{21}NO$		−48	−49	53	36	−33[h]	49
23	1	H	Me	H	4-MeC_6H_4	CH(OH) *R*,S**	*g*	16	140–2	$C_{18}H_{21}NO$		−11	−27	31	16	−15	−3
24	2	H	H	H	4-MeC_6H_4	CH(OH) *R*,S**	*g*	9	205–7	$C_{18}H_{21}NO$·HCl		−37	−37	−24	19	−33[h]	−42[h]
25	2	H	H	H	4-MeC_6H_4	CH(OH) *R*,R**	*g*	11	216–7	$C_{18}H_{21}NO$·HCl·0.75H_2O		−37	−31	−18	−17	−26	−32[h]

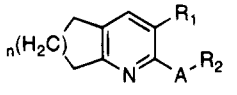
[a] Method of preparation is described in the Experimental Section. [b] Uncorrected. [c] Compounds were analyzed for C,H,N ±0.4% for formula indicated. [d] Rat polymorphonuclear leucocyte assay, percent change at 10 μM. [e] Rat carrageenan edema assay, percent change at 50 mg/kg po (3 h edema). [f] Rat adjuvant arthritis (developing methods) assay, percent change at 30 mg/kg po (uninjected paw at day 16). [g] See the Experimental Section for preparation. [h] $P \leq 0.05$ from control.

activity in the adjuvant arthritis assay. As to the more potent diastereoisomer, the *R*,S** form **24** was slightly more potent than the *R*,R** form **25**. No attempt was made to separate or prepare the enantiomers of these compounds.

Development of a third series based on 2-substituted cyclohepta[*b*]pyridines occurred with the identification of the 2-substituted cyclohepta[*b*]pyridine **26**. With these compounds a number of factors were varied including the aryl residue R_2, the size of the cycloalkyl ring, and the nature of the bridging group A.

Substitution of phenyl with the 4-methyl group (i.e., from **26** to **27**) led to an enhancement in *in vivo* antiinflammatory activity. Next, the nature of the linking group A was examined, and this was varied from CH(OH) (**27**) to C=O (**28**), CH(OMe) (**29**), C(Me)OH (**30**), CH_2 (**31**), and $CH(NH_2)$ (**32**) or the higher homologue with $CH_2CH(OH)$ (**41**), but all these substitutions led to less potent compounds than **27**. Then, the size of the cycloalkyl ring was reduced from seven to five (i.e., $n = 3$ to 1) while keeping A as CH(OH) and R_2 as 4-methylphenyl, and this also led to less potent compounds as demonstrated by the superior antiinflammatory activity of **27** over **33** and **34**. Finally, further analogues (**35**–**40**) were prepared in which substituents were varied on the phenyl ring R_2 or it was replaced with a heterocycle, but these all led to much less potent compounds. The pyridyl analogue **39** like **10** and **11** also stimulated formation of PGE_2. It therefore ap-

Table 3. Physical Data and Biological Activity of 2-Substituted Cyclohepta[*b*]pyridines and Analogues



									rat PMN[d]					
									5-LO		CO		rat	
no.	*n*	R_1	R_2	A	method[a]	yield (%)	mp (°C)[c]	formula[c]	LTB_4	5-HETE	TXB_2	PGE_2	cargn edema[e]	dev AA[f]
26	3	H	4-MeC_6H_4	CH(OH)	*g*	10	168–70	$C_{18}H_{21}NO{\cdot}HCl{\cdot}0.25H_2O$	−25	−28	−3	7	−26	−33
27	3	Me	4-MeC_6H_4	CH(OH)	D	91	143–5	$C_{19}H_{23}NO$	−43	−49	−15	−18	−58[h]	−49[h]
28	3	Me	4-MeC_6H_4	CO	*g*	80	172–4	$C_{19}H_{21}NO{\cdot}HCl$	−52	−49	−82	−68	−59[h]	−26
29	3	Me	4-MeC_6H_4	CH(OMe)	*g*	59	144–6	$C_{20}H_{25}NO{\cdot}HCl$	−12	−10	−21	−3	−9.5	−26
30	3	Me	4-MeC_6H_4	CMe(OH)	D	28	162–4	$C_{20}H_{25}NO{\cdot}HCl{\cdot}0.75H_2O$	−13	−14	−14	9	2.5	−4
31[j]	3	Me	4-MeC_6H_4	CH_2	*g*	15	172–4	$C_{19}H_{23}N{\cdot}HCl$	−57	−37	−63	−52	−26	*i*
32	3	Me	4-MeC_6H_4	$CH(NH_2)$	*g*	20	178–80	$C_{19}H_{24}N_2{\cdot}2HCl{\cdot}H_2O$	−29	−23	6	37	−10	−3
33	2	Me	4-MeC_6H_4	CH(OH)	D	75	88–90	$C_{18}H_{21}NO$	−23	−44	−8	−2	−12.5	−34[h]
34	1	Me	4-MeC_6H_4	CH(OH)	D	56	123–4	$C_{17}H_{19}NO$	−43	−45	−32	−11	−3.5	−2
35	3	Me	Ph	CH(OH)	D	16	130–2	$C_{18}H_{21}NO$	−4	−29	6	−3	−45[h]	−45[h]
36	3	Me	3-ClC_6H_4	CH(OH)	D	57	123–5	$C_{18}H_{20}ClNO$	−51	−42	−15	8	−28	30
37	3	Me	3-$MeOC_6H_4$	CH(OH)	D	59	104–6	$C_{19}H_{23}NO_2$	−50	−34	−14	−7	−28	−14
38	3	Me	4-$CF_3C_6H_4$	CH(OH)	D	60	131–3	$C_{19}H_{20}F_3NO$	40	5	62	42	−24	−18
39	3	Me	3-pyridyl	CH(OH)	D	64	124–6	$C_{17}H_{20}N_2O$	9	−5	−83	389	−14	18
40	3	Me	2-thienyl	CH(OH)	D	65	102–4	$C_{16}H_{19}NOS$	34	37	−13	−8	−9.5	−6
41	3	H	4-MeC_6H_4	$CH_2CH(OH)$	*g*	38	184–6	$C_{19}H_{23}NO{\cdot}HCl$	−29	−14	11	26	−41	28

[a] Method D is described in the Experimental Section (see Scheme 4). [b] Uncorrected. [c] Compounds were analyzed for C,H,N ±0.4% for formula indicated. [d] Rat polymorphonuclear leucocyte assay, percent change at 10 μM. [e] Rat carrageenan edema assay, percent change at 50 mg/kg po (3 h edema). [f] Rat adjuvant arthritis (developing model) assay, percent change at 30 mg/kg po (uninjected paw at day 16). [g] See the Experimental Section for preparation. [h] $P \leq 0.05$ from control. [i] Not tested in rat adjuvant arthritis assay (developing model).

Table 4. Comparison of WY-28342 (**27**) to Standard Cyclooxygenase (CO), 5-Lipoxygenase (5-LO), and Dual LO/CO Inhibitors

	rat PMN IC_{50} (μM)						
	5-LO		CO		oral ED_{50} (mg/kg)		oral UD_{50}[a]
compd	LTB_4	5-HETE	TXB_2	PGE_2	cargn edema	rat dev AA	rat acute gast irritn
WY-28342 (**27**)	14	27	33	>50	40	30	no effect (300 mg/kg)
BW 755C	11	10	4	18	72	38	*c*
zileuton	0.4[b]	0.3[b]	*c*	16[b]	*c*	*c*	*c*
naproxen	>100	>100	0.1	0.3	25	8	15
ibuprofen	>50	>50	0.6	*c*	56	95	42

[a] Ulcerogenic dose (50% of animals tested had at least one lesion). [b] See ref 29. [c] No data reported.

pears that in the 2-substituted series optimum activity is obtained with the alcohol **27**.

As WY-28342 (**27**) had good activity in both the rat carrageenan and adjuvant arthritis models, it was evaluated further and compared with some standard CO (naproxen, ibuprofen), 5-LO (zileuton), and dual LO/CO (BW 755C) inhibitors, and these results are summarized in Table 4. Comparison of **27** with standard antiinflammatory compounds which work through a variety of mechanisms indicates that **27** had a profile of action which was similar to the dual LO/CO inhibitor BW 755C, but there are differences which probably reflect the underlying mechanisms. **27** was slightly less effective against TXB_2 than BW 755C and inactive against PGE_2 synthase in comparison with BW 755C which has respectable potency. Most notably, WY-28342 (**27**) had no gastric irritation liability up to 300 mg/kg unlike standard CO inhibitors. WY-28342 (**27**), therefore, appears to have considerable advantages when compared with standard antiinflammatory agents and adds support to our original hypothesis.

In conclusion we have described the synthesis of some novel tetrahydroquinolines and cyclohepta[*b*]pyridines, and a number of these have *in vivo* antiinflammatory activity, comparable to NSAIDs, but unlike these agents they do not appear to have any liability to produce gastric irritation.

Experimental Section

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Spectra were recorded for all compounds and are consistent with the assigned structures. ^1H NMR spectra were recorded on a Bruker WP200 spectrometer at 200 MHz, and the chemical shifts are reported in δ (ppm) values downfield from a tetramethylsilane as internal standard. IR spectra were recorded with a Perkin Elmer model 983G spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240B elemental microanalyzer, and all compounds in Tables 1–3 are within 0.4% of the theoretical value. Spectroscopic and microanalytical data were obtained by the Physical Chemistry Department (Taplow). Noncommercially available tetrahydroquinolines such as 5,6,7,8-tetrahydro-4-methylquinoline,[30] 5,6,7,8-tetrahydro-3,7,7-trimethylquinoline,[31] 8-amino-5,6,7,8-tetrahydro-3-methylquinoline,[19] 1,2,3,4-tetrahydroacridine,[32] and 6,7,8,9-tetrahydro-2-methyl-5*H*-cyclohepta[*b*]pyridine[33] were prepared by the application of standard methods described in the literature.

Compounds 4–6. The procedure given for the synthesis of **4** (method A) was used for the preparation of compounds **5**, **6**, and (*E*)-5,6,7,8-tetrahydro-8-[(4-acetoxy-3-methoxyphenyl)-methylene]-3-methylquinoline (used in the preparation of **7**).

Method A. (*E*)-5,6,7,8-Tetrahydro-8-[(4-methylphenyl)-methylene]-3-methylquinoline (4). To 5,6,7,8-tetrahydro-3-methylquinoline (6.5 g, 44 mmol) were added *p*-tolualdehyde (6.6 g, 55 mmol) and zinc chloride (0.4 g, 3 mmol) in acetic anhydride (10 mL), and the solution was heated at reflux, under nitrogen (N_2), for 20 h. The solvent was removed under reduced pressure, and the residue was washed with diethyl ether and recrystallized from acetonitrile to give **4** (1.6 g, 15%

yield): mp 105–7 °C; ^{1}H NMR ($CDCl_3$) δ 8.29 (d, J = 2 Hz, 1H), 7.86 (t, J = 1 Hz, 1H), 7.34 (d, J = 8 Hz, 2H), 7.20 (d, J = 2 Hz, 1H), 7.18 (d, J = 8 Hz, 2H), 2.86 (m, 2H), 2.80 (t, J = 7 Hz, 2H), 2.36 (s, 3H), 2.30 (s, 3H), 1.82 (m, 2H). Anal. ($C_{18}H_{19}N$) C, H, N.

(*E*)-5,6,7,8-Tetrahydro-8-[(4-hydroxy-3-methoxyphenyl)-methylene]-3-methylquinoline, Hydrochloride (7). A mixture of (*E*)-5,6,7,8-tetrahydro-8-[(4-acetoxy-3-methoxyphenyl)methylene]-3-methylquinoline (3 g, 9.3 mmol; prepared as in method A from 5,6,7,8-tetrahydrdo-3-methylquinoline and vanillin) and 2 M HCl (50 mL) was heated at 100 °C for 1 h. After cooling, the resulting yellow crystals were removed by filtration, washed with Et_2O, and dried to give 2.5 g (94%) of **7**: mp 256–8 °C; ^{1}H NMR (DMSO-d_6) δ 8.48 (d, J = 1 Hz, 1H), 8.13 (d, J = 1 Hz, 1H), 7.88 (s, 1H), 7.12 (d, J = 1 Hz, 1H), 7.05 (dd, J = 8, 1 Hz, 1H), 6.90 (d, J = 8 Hz, 1H), 3.81 (s, 3H), 2.90 (m, 4H), 2.42 (s, 3H), 1.80 (m, 2H). Anal. ($C_{18}H_{19}NO_2$·HCl) C, H, N.

Compounds 8–11 and 13. The procedure used for the synthesis of **10** and **11** (method B) was also used in the preparation of compounds **8**, **9**, and **13**.

Method B. (*Z*)- and (*E*)-5,6,7,8-Tetrahydro-8-(4-pyridiylmethylene)-4-methylquinoline (10 and 11). 5,6,7,8-Tetrahydro-4-methylquinoline (2.12 g, 14.4 mmol) in tetrahydrofuran (THF) (10 mL) was added to a solution of *n*-BuLi (10.6 mL, 1.36 M in hexane, 14.4 mmol) in THF (10 mL) maintained at 0 °C. After 0.5 h, this solution was blown over with N_2 into a solution of trimethylsilyl chloride (1.56 g, 14.4 mmol) in THF (10 mL) at 0 °C. Further *n*-BuLi (10.6 mL, 1.36 M in hexane, 14.4 mmol) was added at −5 °C, and after 0.5 h the anion was blown with N_2 onto a solution of 4-pyridinecarboxaldehyde (2.5 g, 23 mmol) in THF (10 mL) at 0 °C. After 10 min, 2 M HCl (25 mL) was added. The aqueous extract was washed with hexane and then basified (Na_2CO_3 solution) and the product extracted into dichloromethane (CH_2Cl_2). The CH_2Cl_2 layer was dried over $MgSO_4$ and then evaporated to give a mixture of *E*- and *Z*-isomers. These were separated by chromatography on silica gel using ethyl acetate (EtOAc) as eluent. The *E*-isomer **11** eluted first (0.98 g, 29%): mp 118–20 °C; ^{1}H NMR (DMSO-d_6) δ 8.93 (d, J = 5 Hz, 2H), 8.57 (d, J = 5 Hz, 1H), 8.17 (s, 1H), 8.09 (d, J = 5 Hz, 2H), 7.64 (d, J = 5 Hz, 1H), 2.90 (m, 4H), 2.45 (s, 3H), 1.90 (m, 2H). Anal. ($C_{16}H_{16}N_2$) C, H, N. The *Z*-isomer **10** followed. The solid **10** was dissolved in isopropyl alcohol (IPA) and treated with ethereal HCl and the solid recrystallized from IPA (1.05 g, 25%): mp 213–5 °C; ^{1}H NMR (DMSO-d_6) δ 8.73 (d, J = 5 Hz, 2H), 8.21 (d, J = 5 Hz, 1H), 7.74 (d, J = 5 Hz, 2H), 7.65 (d, J = 5 Hz, 1H), 7.06 (s, 1H), 2.92 (t, J = 7 Hz, 2H), 2.72 (t, J = 7 Hz, 2H), 2.44 (s, 3H), 2.12 (m, 2H). Anal. ($C_{16}H_{16}N_2$·2HCl·H_2O) C, H, N.

(*R,*S**)-5,6,7,8-Tetrahydro-3,7,7-trimethyl-α-(4-methylphenyl)-8-quinolinemethanol (21).** *n*-BuLi (13 mL, 1.36 M in hexane, 17 mmol) was added to a solution of 5,6,7,8-tetrahydro-3,7,7-trimethylquinoline (3 g, 17 mmol) in THF (50 mL) at 0 °C. After 5 min a solution of 4-tolualdehyde (3 g, 25 mmol) in THF (3 mL) was added rapidly and the mixture stirred at room temperature for 0.25 h. Water and Et_2O were added, and the organic phase was separated. The organic phase was extracted with 2 M HCl and separated. The aqueous phase was basified with K_2CO_3 solution and extracted with Et_2O. The combined Et_2O extracts were dried ($MgSO_4$) and evaporated to give a yellow oil (5.5 g). The residue was chromatographed on silica gel using diisopropyl ether as eluent to give the *R**,*S** isomer **21** which was recrystallized from diisopropyl ether (1.2 g, 24%): mp 111-3 °C; ^{1}H NMR ($CDCl_3$) δ 8.28 (d, J = 1 Hz, 1H), 7.22 (d, J = 1 Hz, 1H), 7.0 (br s, 1H), 6.86 (d, J = 8 Hz, 2H), 6.36 (d, J = 8 Hz, 2H), 5.09 (d, J = 4 Hz, 1H), 3.19 (d, J = 4 Hz, 1H), 2.59 (ddd, J = 16, 11, 7 Hz, 1H), 2.35 (s, 3H), 2.28 (ddd, J = 16, 6, 2 Hz, 1H), 2.22 (s, 3H), 1.20 (s, 3H), 0.96 (d ddd, J = 14, 7, 2, 1 Hz, 1H), 0.92 (s, 3H), 0.84 (ddd, J = 14, 11, 6 Hz, 1H). Anal. ($C_{20}H_{25}NO$) C, H, N.

(*Z*)-5,6,7,8-Tetrahydro-3,7,7-trimethyl-8-[(4-methylphenyl)methylene]quinoline, Hydrochloride (12). 21 (3.4 g, 11.5 mmol) in benzene (50 mL) was treated with concentrated H_2SO_4 (7 mL) and stirred at room temperature for 1.25 h, and the mixture was then washed with Na_2CO_3 solution (50 mL). The organic phase was separated, washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to give a gum. This was purified by chromatography on silica gel using $CHCl_3$ as eluent to give an oil (2.7 g). The oil was dissolved in Et_2O, treated with ethereal HCl, and evaporated. The yellow gum was triturated with diisopropyl ether to give a yellow solid, which was recrystallized from Et_2O to give 1.4 g (39%) of **12**: mp 153–5 °C; ^{1}H NMR (DMSO-d_6) δ 8.30 (s, 2H), 7.08 (d, J = 8 Hz, 2H), 6.95 (s, 1H), 6.90 (d, J = 8 Hz, 2H), 3.02 (t, J = 7 Hz, 2H), 2.44 (s, 3H), 2.27 (s, 3H), 1.90 (s, 6H), 1.81 (t, J = 7 Hz, 1H). Anal. ($C_{23}H_{23}N$·HCl) C, H, N.

4-Methyl-*N*-(5,6,7,8-tetrahydro-3-methyl-8-quinolinyl)-benzenesulfonamide (14). 8-Amino-5,6,7,8-tetrahydro-3-methylquinoline (3.07 g, 18.9 mmol) was dissolved in CH_2Cl_2 (250 mL), and *p*-toluenesulfonyl chloride (2.68 g, 14 mmol) was added in CH_2Cl_2 (25 mL) followed by Et_3N (25 mL) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at room temperature until thin layer chromatography showed all the starting material to have reacted (1 h). The solvent was removed under reduced pressure, and the residue was dissolved in 2 M HCl (200 mL) and extracted with Et_2O (2 × 100 mL). The acid solution was then basified with solid K_2CO_3 and extracted with CH_2Cl_2 (3 × 100 mL). The extracts were dried ($MgSO_4$) and evaporated to low volume under reduced pressure. The residue was treated with ethereal HCl to give a white solid which was recrystallized from EtOH to give **14** (2.1 g, 42%): mp 204–14 °C; ^{1}H NMR ($CDCl_3$) δ 8.90 (br s, 1H), 8.81 (d, J = 1 Hz, 1H), 7.88 (d, J = 8 Hz, 2H), 7.78 (d, J = 1 Hz, 1H), 7.24 (d, J = 8 Hz, 2H), 4.82 (m, 1H), 3.0–2.7 (m, 2H), 2.47 (s, 3H), 2.38 (s, 3H), 2.2–1.5 (m, 4H). Anal. ($C_{17}H_{20}N_2O_2S$·HCl) C, H, N.

Compounds 15–17. The procedure given for the synthesis of **15** (method C) was also used for the preparation of compounds **16** and **17**.

Method C. (4-Methylphenyl)(5,6,7,8-tetrahydro-4-methyl-8-quinolinyl)methanone (15). 5,6,7,8-Tetrahydro-3-methylquinoline (1.47 g, 10 mmol) in THF (20 mL) was treated with *n*-BuLi (7.5 mL, 1.36 M in hexane, 10 mmol) at 0 °C and left to stand for 0.75 h. 4-Methylbenzonitrile (1.4 g, 12 mmol) in THF (5 mL) was added rapidly. After 0.5 h, 2 M HCl (30 mL) was added and the aqueous phase was then washed with hexane. The aqueous layer was basified (K_2CO_3) and then extracted with $CHCl_3$. The product was purified on silica gel using Et_2O as eluent and then converted into the hydrochloride with ethereal HCl in Et_2O to give **15** (1.5 g, 49%): mp 240–2 °C; ^{1}H NMR (DMSO-d_6) δ 8.68 (d, J = 5 Hz, 1H), 7.98 (d, J = 8 Hz, 2H), 7.84 (d, J = 5 Hz, 1H), 7.42 (d, J = 8 Hz, 2H), 5.56 (m, 1H), 3.0–2.6 (m, 2H), 2.52 (s, 3H), 2.42 (s, 3H), 2.4–1.4 (m, 4H). Anal. ($C_{18}H_{19}NO$·HCl) C, H, N.

5,6,7,8-Tetrahydro-3-methyl-8-(phenylthio)quinoline (18). *n*-BuLi (90 mL, 1.25 M in hexane, 112.5 mmol) was added to a stirred mixture of 5,6,7,8-tetrahydro-3-methylquinoline (7.4 g, 50 mmol) and diisopropylamine (10 mL, 50 mmol) in THF (200 mL) at −78 °C. The reaction mixture was stirred for 0.5 h. Then a solution of diphenyl disulfide (10.9 g, 50 mmol) in THF (100 mL) was added dropwise over 0.75 h. The mixture was stirred for 1 h while allowing it to warm up to room temperature. The reaction was quenched with water and the mixture concentrated and partitioned between Et_2O and water. The organic layer was washed with 2 M NaOH. The organic layer was extracted into 2 M HCl, basified, extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated to obtain **18** (12.25 g, 96%). The solid was converted into the hydrochloride by dissolving in EtOAc and then treating with ethereal HCl, and the resulting salt was recrystallized from EtOAc/MeOH: mp 173–6 °C; ^{1}H NMR (DMSO-d_6) δ 8.64 (d, J = 1 Hz, 1H), 8.15 (d, J = 1 Hz, 1H), 7.65 (m, 2H), 7.40 (m, 3H), 4.96 (m, 1H), 3.0–2.7 (m, 2H), 2.43 (m, 3H), 2.2–1.8 (m, 4H). Anal. ($C_{16}H_{17}NS$·HCl) C, H, N.

5,6,7,8-Tetrahydro-3-methyl-8-(phenylsulfinyl)quinoline (19). To a stirred solution of **18** (3.8 g, 15 mmol) in CH_2Cl_2 (30 mL) at 0 °C was added *m*-chloroperbenzoic acid (3 g, 17.4 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 0.5 h. Then the mixture was washed with 2 M NaOH, dried ($MgSO_4$), and concentrated. The residue was triturated with Et_2O and the resulting precipitate collected by filtration to obtain the title compound **19** which was recrystallized from CH_2Cl_2/Et_2O (2.1 g, 52%): mp 123–8 °C;

^{1}H NMR ($CDCl_3$) δ 8.39 (d, J = 1 Hz, 1H), 7.5–7.0 (m, 5H), 7.15 (d, J = 1 Hz, 1H), 4.68 (t, J = 6.5 Hz, 1H), 2.6–2.4 (m, 1H), 2.33 (s, 3H), 2.2–2.0 (m, 3H), 1.6–1.4 (m, 1H), 1.3–1.1 (m, 1H). Anal. ($C_{16}H_{17}NOS$) C, H, N.

5,6,7,8-Tetrahydro-3-methyl-8-(phenylsulfonyl)quinoline (20). A solution of *m*-chloroperbenzoic acid (1.4 g, 8 mmol) in CH_2Cl_2 (25 mL) was added to a stirred solution of **19** (1.87 g, 6.9 mmol) and trifluoroacetic acid (1.2 mL) in CH_2Cl_2 (25 mL). After stirring at ambient temperature for 1 h, the reaction mixture was washed with 2 M NaOH, dried over $MgSO_4$, and evaporated to give a solid. After chromatography on silica gel eluting with Et_2O, the product **20** was recrystallized from diisopropyl ether affording white crystals (1.78 g, 90%): mp 84–6 °C; ^{1}H NMR ($CDCl_3$) δ 8.07 (d, J = 1 Hz, 1H), 7.8–7.4 (m, 5H), 7.25 (d, J = 1 Hz, 1H), 4.53 (dd, J = 6.6, 3.2 Hz, 1H), 3.0–2.6 (m, 3H), 2.5–2.0 (m, 2H), 2.27 (s, 3H), 2.27 (s, 3H), 1.8–1.6 (m, 1H). Anal. ($C_{16}H_{17}NO_2S$) C, H, N.

(*R,*R**)- and (*R**,*S**)-5,6,7,8-Tetrahydro-α-(4-methylphenyl)-3-methylquinoline-8-methanol (22 and 23).** To a solution of 5,6,7,8-tetrahydro-3-methylquinoline (5.88 g, 40 mmol) in THF (30 mL) at −20 °C, under N_2, was added *n*-BuLi (25 mL, 1.6 M in hexane, 40 mmol), and the mixture was left to stir at −20 °C for 0.25 h. 4-Methylbenzaldehyde (4.32 g, 40 mmol) in THF (15 mL) was added and the mixture allowed to warm to room temperature. Water was added followed by Et_2O and the organic phase separated and extracted with 2 M HCl. The aqueous acid extract was basified with aqueous K_2CO_3 and extracted with $CHCl_3$, which was separated, dried ($MgSO_4$), and evaporated. The oil was purified by chromatography on silica gel using diisopropyl ether as eluent to give the *R**,*R** isomer **22**. This was recrystallized from *n*-hexane to give a white solid (4.26 g, 40%): mp 91–3 °C; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, J = 1.5 Hz, 1H), 7.33 (d, J = 8 Hz, 2H), 7.27 (d, J = 1.5 Hz, 1H), 7.16 (d, J = 8 Hz, 2H), 4.64 (d, J = 10 Hz, 1H), 2.97 (d t, J = 10, 6 Hz, 1H), 2.68 (m, 2H), 2.35 (s, 3H), 2.29 (s, 3H), 1.9–1.1 (m, 4H). Anal. ($C_{18}H_{21}NO$) C, H, N. The second component was the *R**,*S** isomer **23**. This was recrystallized from diisopropyl ether to give a white solid (1.75 g, 16%): mp 140–2 °C; ^{1}H NMR ($CDCl_3$) δ 8.24 (d, J = 1.5 Hz, 1H), 7.0 (d, J = 8 Hz, 2H), 7.16 (d, J = 1.5 Hz, 1H), 6.98 (d, J = 8 Hz, 2H), 5.15 (d, J = 4.5 Hz, 1H), 3.43 (m, 1H), 2.52 (m, 2H), 2.29 (s, 3H), 2.26 (s, 3H), 2.0–1.4 (m, 4H). Anal. ($C_{18}H_{21}NO$) C, H, N.

(*R,*S**)- and (*R**-*R**)-6,7,8,9-Tetrahydro-α-(4-methylphenyl)-5*H*-cyclohepta[*b*]pyridine-9-methanol (24 and 25) and 6,7,8,9-Tetrahydro-α-(4-methylphenyl)-5*H*-cyclohepta[*b*]pyridine-2-methanol (26).** 6,7,8,9-Tetrahydro-5*H*-cyclohepta[*b*]pyridine (7.4 g, 50 mmol) in THF (100 mL) was cooled to −10 °C and treated wth *n*-BuLi (32 mL, 1.57 M in hexane, 50 mmool) and then stirred at −10 °C for a further 0.5 h. 4-Tolualdehyde (10 g, 83 mmol) in THF (10 mL) was added rapidly and the mixture allowed to warm to room temperature, and then water and Et_2O were added. The combined Et_2O extracts were treated with 2 M HCl, and the separated aqueous acid extract was basified with solid Na_2CO_3 and then extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, dried ($MgSO_4$), and evaporated to give an oil. This was purified by chromatography using silica gel, eluted with diisopropyl ether, and then further purified by chromatography using silica gel and elution with $CHCl_3$. Three pure products were isolated, and these were converted into the hydrochloride salts by dissolving in ether and treating with ethereal HCl to give *R**,*S** isomer **24** (1.4 g, 9%): mp 205–7 °C; ^{1}H NMR (DMSO-d_6) δ 8.43 (dd, J = 5, 1 Hz, 1H), 8.27 (dd, J = 8, 1 Hz, 1H), 7.71 (dd, J = 8.5 Hz, 1H), 7.20 (d, J = 8 Hz, 2H), 7.02 (d, J = 8 Hz, 2H), 5.26 (d, J = 7.5 Hz, 1H), 3.70 (m, 1H), 3.3–2.9 (m, 2H), 2.2–1.4 (m, 6H), 2.22 (s, 3H). Anal. ($C_{18}H_{21}NO$·HCl) C, H, N. **26** (1.5 g, 10%): mp 168–70 °C; ^{1}H NMR (DMSO-d_6) δ 8.22 (d, J = 8 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 7.40 (d, J = 8 Hz, 2H), 7.17 (d, J = 8 Hz, 2H), 6.15 (s, 1H), 3.30 (m, 2H), 2.95 (m, 2H), 2.27 (s, 3H), 2.0–1.5 (m, 6H). Anal. ($C_{18}H_{21}NO$·HCl·0.25H_2O) C, H, N. *R**,*R** isomer **25** (1.7 g, 11%): mp 216–7 °C; ^{1}H NMR (DMSO-d_6) δ 8.67 (dd, J = 5, 1 Hz, 1H), 8.38 (dd, J = 8, 1 Hz, 1H), 785 (dd, J = 8, 5 Hz, 1H), 7.47 (d, J = 8 Hz, 2H), 7.22 (d, J = 8 Hz, 2H), 5.40 (d, J = 10.5 Hz, 1H), 3.75 (m, 1H), 3.3–3.0 (m, 2H), 2.32 (s, 3H), 2.0–1.3 (m, 6H). Anal. ($C_{18}H_{21}NO$·HCl·0.75H_2O) C, H, N.

General Method for the Preparation of 2-Bromocycloalkeno[*b*]pyridines 42a–c. The method used for the preparation of **42a** was used for **42b,c** also.

2-Bromo-3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]-pyridine (42a). (a) Cycloheptanone (84.1 g, 0.75 mol), pyrrolidine (53.34 g, 0.75 mol), and *p*-toluenesulfonic acid (0.1 g) in toluene (500 mL) were refluxed under N_2 and refluxed over a soxhlet apparatus containing 4 Å molecular sieves (250 g) for 3 h. The toluene was removed under reduced pressure, and the resulting enamine was dissolved in absolute EtOH (400 mL), treated with methacrylonitrile (50.32 g, 0.75 mol), and refluxed under N_2 for 18 h. The solvent was removed under reduced pressure and the residue hydrolyzed with water (300 mL) for 3 h, and Et_2O (500 mL) was added. After stirring for a further 3 h, the organic phase was separated, dried ($MgSO_4$), and evaporated to give an oil which was distilled (bp 100 °C/0.02 mmHg) to give a colorless liquid (94 g, 70%).

(b) The above product (88.6 g, 0.5 mol) in AcOH (1 L) was treated with Br_2 (26 and 0.5 mL) over 15 min maintaining an internal temperature of ca. 15 °C. The mixture was allowed to warm to room temperature overnight. The solvent was evaporated under reduced pressure and the residue partitioned between water and CH_2Cl_2. The organic phase was dried ($MgSO_4$) and evaporated to give a solid which was purified by chromatography on silica gel using CH_2Cl_2. The resulting solid was recrystallized from hexane to give the title compound as white needles (30.9 g, 26%): mp 68–70 °C; ^{1}H NMR ($CDCl_3$) δ 7.2 (s, 1H), 2.96 (m, 2H), 2.66 (m, 2H), 2.29 (s, 3H), 1.9–1.6 (m, 6H). Anal. ($C_{11}H_{14}BrN$) C, H, N.

2-Bromo-3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohexa[*b*]-pyridine (42b). This compound was prepared in 20% overall yield as described above: mp 50–2 °C; ^{1}H NMR ($CDCl_3$) δ 7.17 (s, 1H), 2.85 (t, J = 6 Hz, 2H), 2.67 (t, J = 6 Hz, 2H), 2.29 (s, 3H), 2.7–2.0 (m, 4H). Anal. ($C_{10}H_{12}BrN$) C, H, N.

2-Bromo-3-methyl-6,7,8,9-tetrahydro-5*H*-cyclopenta[*b*]-pyridine (42c). This compound was prepared as a white hydrochloride in Et_2O using ethereal HCl in 15% yield as described above for the preparation of **42a**: mp 204–6 °C; ^{1}H NMR (DMSO-d_6) δ 14.3 (br s, 1H), 7.94 (s, 1H), 3.53 (t, J = 8 Hz, 2H), 3.05 (t, J = 8 Hz, 2H), 2.52 (s, 3H), 2.33 p, J = 8 Hz, 2H). Anal. ($C_9H_{10}BrN$·HCl) C, H, N.

Compounds 27, 30, and 33–40. The method used for the preparation of **27** (method D) was used for all these compounds using as starting material 2-bromocycloalkeno[*b*]pyridine.

Method D. 6,7,8,9-Tetrahydro-α-(4-methylphenyl)-3-methyl-5*H*-cyclohepta[*b*]pyridine-2-methanol (27). To a solution of *n*-BuLi (78 mL, 1.6 M in hexane, 125 mmol) in toluene (100 mL) at −15 °C under N_2 was added slowly 2-bromo-3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (30 g, 125 mmol) in toluene (100 mL). The mixture was left to stand at −20 °C for 0.25 h and then was blown over into a solution of 4-methylbenzaldehyde (3.7 g, 27 mmol) in toluene (100 mL) kept at −15 °C. The mixture was allowed to warm up to room temperature, and water was added. The organic layer was separated and then extracted with 2 M HCl. The aqueous acid was basified with solid K_2CO_3 and then extracted into CH_2Cl_2. The organic extract was dried ($MgSO_4$) and evaporated to give a solid which was recrystallized from diisopropyl ether to give **27** (32 g, 91%): mp 143–5 °C; ^{1}H NMR ($CDCl_3$) δ 7.20 (d, J = 7 Hz, 2H), 7.15 (s, 1H), 7.10 (d, J = 7 Hz, 2H), 6.3 (br s, 1H), 5.61 (s, 1H), 3.08 (t, J = 6.5 Hz, 2H), 2.73 (t, J = 6.5 Hz, 2H), 2.30 (s, 3H), 2.0–1.5 (m, 4H), 1.98 (s, 3H). Anal. ($C_{19}H_{23}NO$) C, H, N.

(4-Methylphenyl)(6,7,8,9-tetrahydsro-3-methyl-5*H*-cyclohepta[*b*]pyridin-2-yl)methanone (28). A suspension of **27** (2.0 g, 7 mmol) and manganese dioxide (6.1 g, 70 mmol) in toluene (50 mL) was heated under reflux for 15 h and water collected in a Dean–Stark apparatus. The cooled solution was filtered and the solvent evaporated under reduced pressure to give a gum. This dissolved in Et_2O and treated with ethanolic HCl, and the precipitated solid was collected by filtration and dried to give **28** (1.8 g, 80%): mp 172–4 °C; ^{1}H NMR (DMSO-d_6) 8.11 (s, 1H), 7.71 (d, J = 7 Hz, 2H), 7.40 (d,

J = 7 Hz, 2H), 3.23 (m, 2H), 2.95 (m, 2H), 2.52 (s, 3H), 2.19 (s, 3H), 1.9–1.6 (m, 4H). Anal. ($C_{19}H_{21}NO$·HCl) C, H, N.

6,7,8,9-Tetrahydro-2-[methoxy(4-methylphenyl)methyl]-3-methyl-5*H*-cyclohepta[*b*]pyridine (29). **27** (2.0 g, 7 mmol) was added to sodium hydride (0.35 g, 50% dispersion in oil, 7 mmol, washed with 40–60 petroleum ether) suspended in dimethylformamide (20 mL). After evolution of hydrogen had ceased, methyl iodide (0.5 mL) was added and the mixture stirred at room temperature for 0.5 h. Water was added and the mixture extracted with Et_2O. The combined Et_2O extracts were treated with 2 M HCl. The aqueous acid solution was separated, basified with solid Na_2CO_3, and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on silica gel and eluted with $CHCl_3$ to give **29** as a gum. This was dissolved in Et_2O and treated with ethereal HCl to give the white crystalline hydrochloride salt (1.4 g, 59%): mp 144–6 °C; ^{1}H NMR (DMSO-d_6) δ 8.17 (s, 1H), 7.30 (d, J = 7 Hz, 2H), 7.20 (d, J = 7 Hz, 2H), 6.36 (s, 1H), 3.50 (m, 2H), 3.40 (s, 3H), 2.95 (m, 2H) 2.29 (s, 3H), 2.20 (s, 3H), 1.9–1.5 (m, 4H). Anal. ($C_{20}H_{25}NO$·HCl) C, H, N.

6,7,8,9-Tetrahydro-3-methyl-2-[(4-methylphenyl)methyl]-5*H*-cyclohepta[*b*]pyridine (31). **27** (3.0 g, 10.7 mmol) was dissolved in EtOH (150 mL) and added to 10% Pd/C (1 g) under nitrogen. H_2SO_4 (2 M, 5 mL) was added and the mixture hydrogenated at 50 psi until hydrogen uptake had ceased. The catalyst was removed by filtration and the EtOH removed under reduced pressure. The residue was treated with Na_2CO_3 solution and then extracted with $CHCl_3$. The combined $CHCl_3$ extracts were dried ($MgSO_4$) and evaporated to give an oil. The product was separated from **27** by chromatography on basic alumina and elution with $CHCl_3$. The resulting oil was dissolved in Et_2O and acidified with ethereal HCl to give **31** as a white crystalline solid (0.47 h, 15%): mp 172–4 °C; ^{1}H NMR (DMSO-d_6) δ 8.14 (s, 1H), 7.2–7.1 (m, 4H) 4.53 (s, 2H), 3.45 (m, 2H), 2.95 (m, 2H), 2.25 (s, 3H), 2.23 (s, 3H), 1.9–1.5 (m, 4H). Anal. ($C_{19}H_{23}N$·HCl) C, H, N.

6,7,8,9-Tetrahydro-3-methyl-α-(4-methylphenyl)-5*H*-cyclohepta[*b*]pyridine-5-methanamine (32). To a solution of n-BuLi (16.5 mL, 1.6 M in hexane, 25 mmol) in toluene (20 mL) at −20 °C under N_2 was added a solution of 2-bromo-3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (6.0 g, 25 mmol) in toluene (30 mL), and the mixture was kept at −20 °C for 0.25 h. The solution was blown over onto a solution of 4-methylbenzonitrile (3.2 g, 27 mmol) in toluene (30 mL) at −20 °C and then allowed to warm to room temperature. The solvent was removed under reduced pressure and EtOH (150 mL) added followed by small portions of sodium borohydride (1.2 g, 32 mmol). After the mixture had stirred at room temperature for 0.75 h, 2 M HCl was added until hydrogen evolution had ceased. The solvent was removed under reduced pressure and the residue treated with $NaHCO_3$ solution and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on basic alumina, eluted with $CHCl_3$ to give an oil. This was dissolved in Et_2O and treated with ethereal HCl to give **32** as a dihydrochloride, monohydrate (1.93 g, 20%): mp 178–80 °C; ^{1}H NMR (DMSO-d_6) δ 8.85 (br s, 3H), 7.43 (s, 1H), 7.29 (d, J = 7 Hz, 2H), 7.21 (d, J = 7 Hz, 2H), 5.15 (m, 1H), 3.15 (m, 2H), 2.80 (m, 2H), 2.28 (s, 3H), 1.9–1.5 (m, 4H). Anal. ($C_{19}H_{24}N_2$·HCl·H_2O) C, H, N.

6,7,8,9-Tetrahydro-α-(4-methylphenyl)-5*H*-cyclohepta[*b*]pyridine-2-ethanol (41). To a solution of n-BuLi (7.2 mL, 1.6 M in hexane 11.5 mmol) in toluene (25 mL) at −20 °C under N_2 was added a solution of 2-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridine (1.7 g, 10 mmol) in toluene (5 mL). The solution was left to stir at −20 °C for 0.75 h and then blown over into a solution of 4-methylbenzaldehyde (1.5 g, 12.5 mmol). The solution was allowed to warm to room temperature and water added. The toluene phase was extracted with 2 M HCl, and this was basified with solid K_2CO_3 and then extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with water, dried ($MgSO_4$), and evaporated to give an oil. This was purified by chromatography on basic alumina using diisopropyl ether as eluent to give **41** as an oil. This was dissolved in Et_2O and treated with ethanolic HCl to give a white crystalline hydrochloride salt (1.2 g, 38%): mp 184–6 °C; ^{1}H NMR (DMSO-d_6) δ 8.24 (d, J = 8 Hz, 1H), 7.65 (d, J = 8 Hz, 2H), 7.36 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 5.05 (dd, J = 8, 3 Hz, 1H), 3.50 (m, 2H), 3.45 (dd, J = 11, 3 Hz, 1H), 3.17 (dd, J = 11, 8 Hz, 1H), 2.95 (m, 2H), 2.29 (s, 3H), 1.9–1.5 (m, 6H). Anal. ($C_{19}H_{23}NO$·HCl) C, H, N.

Biological Methods. Rat PMN Assay.[24] Glycogen-elicited peritoneal cells were collected from female Wistar rats (150–250 g) by lavaging the peritoneal cavity with 50 mL of Hank's balanced salt solution (HBSS) (without Ca^{2+} or Mg^{2+}). Cells were suspended in HBSS (Mg^{2+}, Ca^{2+}, 10 mM cysteine) such that the cell concentration = 10^7/mL. One milliliter aliquots of cells were then incubated with drug (delivered in 10 μL of dimethyl sulfoxide (DMSO)) for 10 min in a 37 °C shaking water bath. Samples then received 2.0 μCi of [^{3}H]-arachidonic acid (AA), 1 μM AA, and 1 μM A23187 (delivered in a total of 20 μL of DMSO) and were incubated for 10 min in a 37 °C shaking water bath. The reaction was stopped by centrifugation (500g, 10 min, 4 °C), and the supernatant fluid was injected directly onto an RCSS-C18 guard column (Waters). The major eicosanoids were separated on a Supelcosil LC-18 HPLC column (15 cm, 3 μm particle size; Supelco, Bellefont, PA) using a binary gradient that started with solvent A [17 mM H_2PO_4:CH_3CN (70:30, v/v)] and progressed to 90% solvent B (CH_3CN) in 45 min via the following gradient scheme: 100% A, 0–15 min; 65% A, 15–40 min; 5% A, 40–45 min. Radiolabeled eicosanoids were detected by an in-line radioactivity detector (Ramona LS-4; IN/US, Fairfield, NJ).

Rat Carrageenan Paw Edema Assay[25] (Acute inflammation). Groups of six male Sprague–Dawley rats (Charles River), weighing between 150 and 165 g, were used in these experiments. Drugs were administered po in 0.5% methyl cellulose (400 centipoise). One hour after administering drugs or vehicle, 0.1 mL of 1% carrageenan was injected subplantar into the right hind paw. Right hind paw volumes (mL) were measured prior to carrageenan injection, the right hind paw volumes were remeasured, paw edema was calculated for each rat by subtracting the zero time reading from the 3 h reading, and the percent change in paw edema was calculated. Dunnett's test was used to determine statistical significance, $P \leq 0.05$.

Rat Developing Adjuvant Arthritis[26] (Chronic inflammation). Groups of 10 male Lewis rats (Charles River), weighing between 150 and 170 g, were injected sc into the right hind paw with heat killed desiccated *Mycobacterium butyricum* (0.5 mg/0.1 mL) suspended in light mineral oil. Drugs were administered orally in 0.5% methyl cellulose. The following dosing regimen was used; rats were dosed daily po from day 0 to 15 except for weekends. Both hind paw volumes (mL) were measured by an automated mercury plethysmography at the time of injection of adjuvant (day 0). Later, paw volumes were measured at day 16 (uninjected paw) to determine the immunologically induced (T-cell-mediated) inflammation. Drug effects were expressed as a percentage change from vehicle-treated arthritic controls. Dunnett's test was used to determine statistical significance, $P \leq 0.05$.

Yeast-Induced Fever in Rats.[26] Male Sprague–Dawley rats (Charles River), weighing 180–200 g, were injected sc with 2 mL of a 7.5% suspension of brewer's yeast in 0.5% methyl cellulose. Rectal temperatures were recorded 18 h later. Rats developing a satisfactory pyrexia (viz., a 1.5–2 °C increase over nonfevered control animals) were divided into groups of six. Drugs were administered orally in 0.5% methyl cellulose immediately thereafter, and the mean rectal temperatures were then recorded at 0.5, 1.0, 1.5, and 2 h. A temperature index was calculated for each rat as the sum of the decreases in temperature (°C) for each of the readings after drug administration. Dunnett's test was used to determine statistical significance, $P \leq 0.05$.

Rat Acute Gastric Irritation Assay. Male Sprague–Dawley (CD) rats (190–220 g) from Charles River were fasted for 18 h prior to drug administration. Rats were divided into groups of 8 and coded (i.e., observer of gastric lesions was not aware of drug treatment). Drugs were dissolved or suspended in 0.5% Tween 80 and administered by gastric intubation in a volume of 1 mL/100 g of body weight; control rats received

only Tween 80. Four hours after drug administration, rats are evaluated by recording the incidence and severity of gastroirritation using the following scoring systems: (0) no irritation or lesions, (1) irritation (redness), (2) ≤5 lesions, and (3) >5 lesions. Dunnett's test ($\alpha = 0.05$) was used to calculate the mean ± SE of each test group and the statistical significance.

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