N-Substituted Dibenzoxazepines as Analgesic PGE_2 Antagonists

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8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic acid, 2-acetylhydrazide (1, SC-19220) has been previously reported by us and others to be a PGE_2 antagonist selective for the EP_1 receptor subtype[1] with antinociceptive activities.[2] Analogs of SC-19220, in which the acetyl moiety has been replaced with pyridylpropionyl groups and their homologs, have been synthesized as illustrated by compounds **13** and **29**. These and other members of this series have been shown to be efficacious analgesics and PGE_2 antagonists of the EP_1 subtype. This report discusses the structure activity relationships within this series.

Introduction

Pain upon exposure to noxious stimuli is thought to occur through the intermediacy of several autacoids including histamine, bradykinin, serotonin, norepinephrine, prostaglandin E_2 (PGE_2), leukotrienes, and other agents of nociception released at the site of injury.[3] Relief of mild to moderate pain is achieved with over-the-counter and prescription nonsteroidal antiinflammatory drugs (NSAIDs). The antinociceptive actions of the NSAIDs are believed to occur through the inhibition of the action of cyclooxygenase on arachidonic acid.[4] This microsomal enzyme complex converts arachidonate, liberated by lipolytic enzymes, to a myriad of eicosanoids which exhibit a variety of bioactivities. Ferreira suggested that the effectiveness of NSAIDs against the pain accompanying inflammation and tissue injury is due specifically to the inhibition of PGE_2 formation from arachidonate.[4b] More particularly, NSAIDs block the production of PGE_2, a prostanoid, which causes pain, hyperalgesia, and potentiates the action of bradykinin in pain transmission.[3] Two decades of research by several groups have provided evidence supporting this view.[5]

While NSAIDs are considered generally safe, untoward effects do accompany their administration. The most notable and most prevalent are the gastric side effects including dyspepsia and heartburn.[6] In addition, NSAIDs elicit long lasting disturbances in platelet function, CNS toxicity at high doses, and anaphylaxis. Full-blown anaphylaxis is not common in the general population but occurs in 25% of middle-aged patients suffering from asthma or nasal polyps. Chronic use of NSAIDs often results in severe damage to gastric and intestinal mucosa which can lead to frank bleeding requiring emergency intervention. Due to their side effects, chronic administration of NSAIDs is contraindicated for long-term management of pain and inflammation.

The rationale of our analgesia program is based on the hypothesis that PGE_2-induced hyperalgesia occurring in inflamed tissue would be attenuated by selective blockade of PGE_2 receptors in the periphery and in the CNS. Additionally, analgesics based on PGE_2 antagonism would obviate the problems associated with NSAIDs, particularly their gastric side effects.

Sanner has observed that SC-19220 is a functional antagonist of PGE_2-elicited contractions in select tissues *in vitro*.[1a] Hammond et al. have demonstrated that antagonists of PGE_2 such as SC-19220 and pinadoline (**5**) are analgesic.[2] We now report on our research on PGE_2 antagonists which are modeled on SC-19220 and its congeners. Previous research on the group (R) (Table II) distal to the dibenzoxazepine was restricted to alkyl, haloalkyl, and alkylphenyl groups.[7] In order to enhance PGE_2 antagonism and analgesic activity, a broader scope of functionality for R in this class of compounds has been studied. Minimal research has been done modifying the alkylaromatic analog, **4**. We sought to explore the impact of heteroaromatic systems as well as alkyl chain length on the PGE_2 antagonism and analgesia which has been observed in this series. Described in this article are a series of compounds in which the alkylphenyl group of **4** has been replaced with various alkylpyridyl moieties.

The length of R seems to play a pivotal role in PGE_2 antagonism of the N-substituted dibenzoxazepines as can be seen in Table II. The progression of R from methyl (**1**) to *n*-pentyl (**3**) results in increasing PGE_2 antagonism but with a concomitant decrease in selectivity.[7] Bearing this in mind, a chain, from the carbonyl distal to the ring, intermediate in length between **4** (8.22 Å) and **3** (11.16 Å) was sought to maximize PGE_2 antagonism without a loss in selectivity. In addition to enhanced antinociceptive and PGE_2 antagonism activity, desirable physicochemical properties in this chemical class were sought particularly aqueous solubility. Compounds **1–5** have proven difficult to test *in vivo*. The initial target was the 3-(2-pyridyl)-propyl analogs which provided compounds with the desired lengths (9.8 Å) and preferred physicochemical properties.

Chemistry

Syntheses of 8-chlorodibenzoxazepine, **6**, as well as two key intermediates, **7** and **8**, have been described previously.[8] Functionalizing **7** or **8** with various pyridyl acid moieties required several strategies using the appropriate acids, esters or monoacylhydrazines as seen in Schemes I–VI.

Scheme I illustrates the synthesis of the 3-(2- or 4-pyridyl)propanoates and their attachment to the dibenzoxazepine. The syntheses via Wittig chemistry of ethyl 3-(2- and 4-)pyridylpropanoates proceeded uneventfully in good yield. The subsequent acylhydrazine was attached to the ring via **7** to generate **12** and **13**. The unsaturated chains were also appended to the 8-chlorodibenzoxazepine

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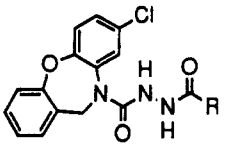
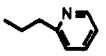
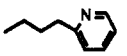
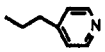
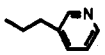
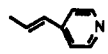
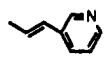
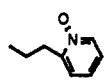
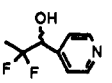
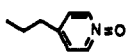
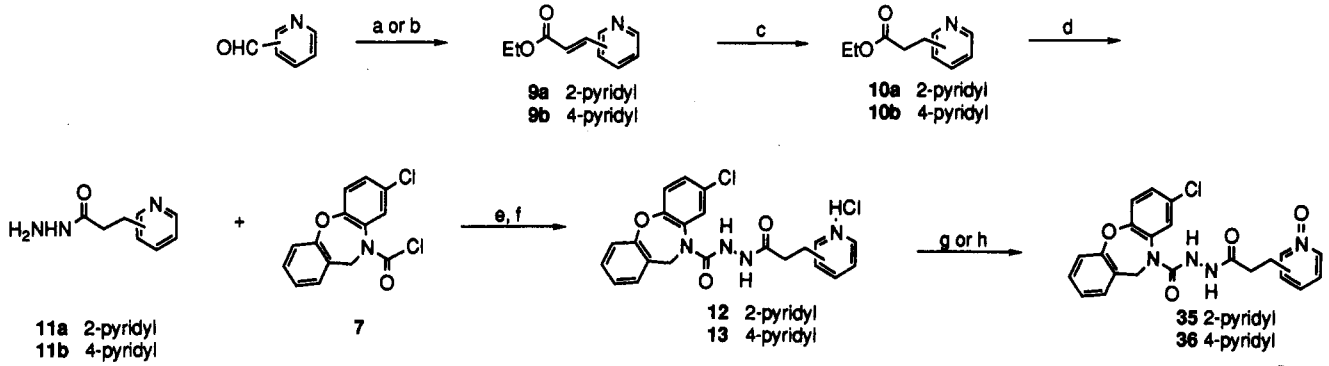
Table I. Phenylbenzoquinone Writhing Assay in Mouse



no.	R	ED_{50} (mg/kg)[a] ig	sc	no.	R	ED_{50} (mg/kg)[a] ig	sc
	aspirin	42.3 (20.8–63.3)					
	ibuprofen	4.8 (1.7–9.2)		25		6/10	9.7 (3.7–25.2)
12[b]		5.8 (2.4–10.0)	9.8 (5.5–17.1)	26[b]		4/10	5/10
13[b]		6.8 (1.7–12.9)	6.3 (3.7–11.3)	19[b]		3/10	2/10
29[b]		9.1 (3.7–21.2)	7.1 (1.5–30.2)	20[b]		3/10	1/10
18[b]		6/10	5/10	21[b]		1/10	2/10
14[b]		1/10	2/10	22[b]		2/10	2/10
15[b]		2/10	4/10	23[b]		3/10	5/10
17		6/10	5/10	24[b]		3/9	1/10
35		1/10	3/10	30[b]		12.3 (8.0–19.3)	5/10
36		5/10	nt[c]	34[b]		9.7 (3.7–25.2)	nt

[a] The initial screening dose of test compound is 30 mg/kg. Values in parentheses are confidence limits determined at 95% ($p < 0.05$). [b] Hydrochloride salt. [c] Not tested.

Scheme I[a]



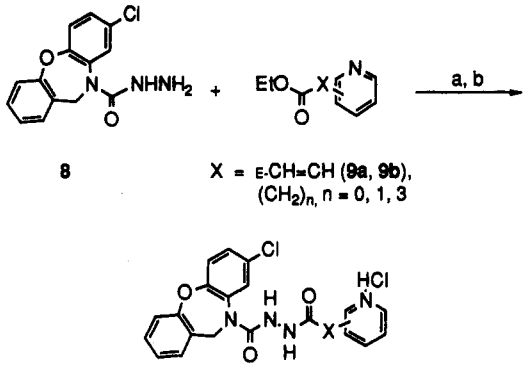
[a] (a) $Ph_3P{=}CHCOOEt$, THF, room temperature, 16 h; (b) $(EtO)_2P(=O)CH_2COOEt$, NaH, $MeO(CH_2)_2OMe$, 20–50 °C, 3h; (c) H_2, 5% Pd/C, EtOH; (d) NH_2NH_2, i-PrOH, 82 °C, 16 h; (e) Et_3N, DMF, room temperature, 20 h. (f) 6N HCl/dioxane; (g) H_2O_2, HOAc, 90 °C, 19 h; (h) *m*-chloroperbenzoic acid, DCM, 16 h, room temperature.

as shown in Scheme II. To secure the 3-(3-pyridyl)-propionyl analog, the commercially available *trans*-3-(3-pyridyl)acrylic acid was reduced under catalytic hydrogenation conditions to provide 3-(3-pyridyl)propanoic acid, **16**. The saturated acid, **16**, and unsaturated acid were attached to **8** using carbodiimide coupling conditions as seen in Scheme III to generate **17** and **18**.

As seen in Scheme II, the pyridyl carboxylates, the 2-pyridylacetates, and 4-(4-pyridyl)butanoate were attached to **8** using Weinreb amidation conditions to afford **14**, **15**, **19-25**.[9] Although the yields were modest and unoptimized, the desired compounds were isolated and characterized. The attractiveness of this approach lay in that it avoided the occasional problems associated with activation and attachment of the pyridyl acids to the semicarbazide, **8**. The 4-(2-pyridyl)butanoic acid[10] was attached to the **8** via acid activation employing carbonyldiimidazole as the activating agent, as illustrated in Scheme IV to yield **26**.

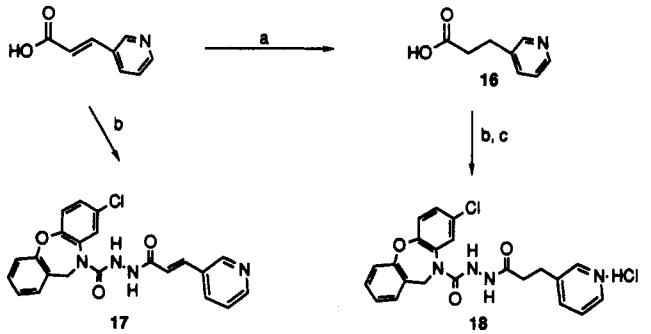
Fluorine on the carbon α to a carbonyl group has a substantative effect on that group in that it enhances the Lewis acidity of the carbonyl moiety.[11] Seeking to determine the implication of fluorine in the alkylpyridyl chain, the syntheses of **29**, **30**, and **34** were undertaken. The strategies for the syntheses of these analogs are illustrated in Schemes V and VI. The ethyl 3-hydroxy-2,2-difluoro-3(2-pyridyl)propanoate, **27**, was synthesized via the Hallinan–Fried variation of the Reformatsky reaction.[12] Formation of the monoacylhydrazine proceeded more facilely than formation of the analogous

Scheme II[a]



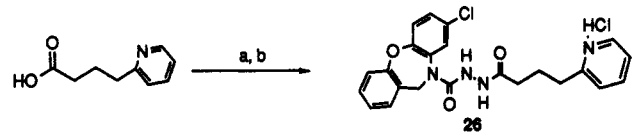
[a] (a) $AlMe_3$, toluene, 110 °C; (b) HCl/EtOH.

Scheme III[a]



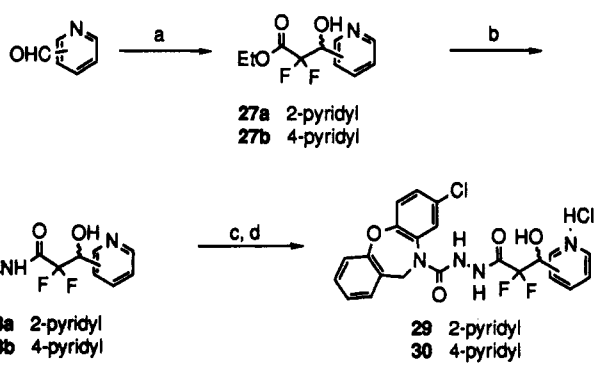
[a] (a) H_2, 5% Pd/C, EtOH; (b) 8, $Me_2N(CH_2)_3N{=}C{=}NCH_2CH_3$, $i\text{-}Pr_2EtN$, DMF, 5-20 °C, 16 h; (c) HCl/dioxane.

Scheme IV[a]



[a] (a) 8, 1,1'-carbonyldiimidazole, DMF, room temperature, 16 h; (b) HCl/EtOH.

Scheme V[a]

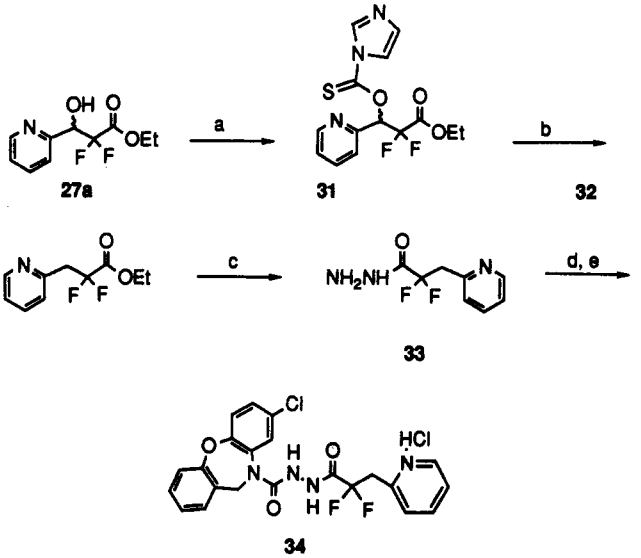


[a] (a) Zn, $BrCF_2COOEt$, THF, 67–20 °C, 16 h; (b) $NH_2NH_2{\cdot}H_2O$, EtOH, room temperature, 16 h; (c) 7, DMF, TEA, room temperature, 16 h; (d) 1 N HCl.

unsubstituted alkylpyridyl acylhydrazine, indicating an ester moiety more susceptible to nucleophilic attack. Subsequent functionalization of **28a** with **7** followed in good yield.

The synthesis of ethyl 2,2-difluoro-3-(2-pyridyl)propanoate, **32**, from **27a** was troublesome. Initially, **27a** proved intractable to deoxygenation using a variety of reductive techniques. As shown in Scheme VI, conditions

Scheme VI[a]



[a] (a) 1,1'-Thiocarbonyldiimidazole, (*N,N*-dimethylamino)pyridine, $ClCH_2CH_2Cl$, room temperature, 1 h; (b) *n*-Bu_3SnH, toluene/DCM, 2 h, Δ; (c) $NH_2NH_2{\cdot}H_2O$, EtOH, 1 h, room temperature; (d) 7, DMAc, TEA, 20 h, room temperature; (e) 1 N HCl.

for generating **32** employed those reported recently.[13] The Barton–Motherwell method using tri-*n*-butyltin hydride to reduce thioimidazolate was utilized. The thioester, **31**, was unstable and, once chromatographed, had to be reduced immediately to generate **32**. Formation of the hydrazide, **33**, and functionalization of **7** smoothly provided **34**.

To study the effect of reduced basicity on biological activity, the pyridyl nitrogens of **12** and **13** were oxidized as shown in Scheme I. Reaction of the 2-pyridyl group of **12** with peracetic acid gave a poor yield of **35**. Thus, the 4-pyridyl group of **13** was oxidized with *m*-chloroperbenzoic acid to give **36** in excellent yield.

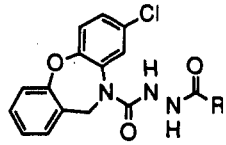
Pharmacology

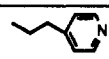
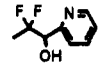
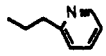
The phenylbenzylquinone writhing assay in mouse was used to evaluate the antinociceptive effectiveness of these compounds.[14] PGE_2 antagonism in PGE_2-stimulated guinea pig ileum muscle strips was confirmed in those compounds which are active in the writhing assay.[1] In order to establish that PGE_2 is the mechanism of analgesic action, a few analogs that showed little analgesic activity were tested for their PGE_2 antagonism activity. To unambiguously demonstrate that PGE_2 antagonism and not cyclooxygenase inhibition was the mechanism of action, **13** and **29** were screened by Panlabs in their cyclooxygenase inhibition assay and found to have no cyclooxygenase inhibition activity.[15] On the other hand, Panlabs confirmed antinociceptive activity in the writhing assay and the lack of overt toxicity at analgesic doses.

Results and Discussion

As seen in Tables I and II, the original synthetic objective, **12**, is a good analgesic and has PGE_2 antagonism activity. Exploration of analogs of **12** led to **13** and **29** which are the most active members of the series. Both are analgesic and PGE_2 antagonists. The 2- and 4-pyridyl positional isomers, **12** and **13**, have comparable activity while the 3 positional isomer, **18**, is less active. In order to investigate the conformational requirements of the alkylpyridyl chain, the *E*-olefin was introduced. Con-

Table II. PGE_2 Antagonism in Guinea Pig Ileum



no.	R	pA_2[a]	no.	R	pA_2[a]
1	Me	5.5 ± 0.5	13[c]		6.5 ± 0.2
2	$(CH_2)_2CH_3$	6.0[b]	29[c]		7.5 ± 0.3
3	$(CH_2)_4CH_3$	6.6[b]	14[c]		inactive
4	CH_2Ph	6.0[b]	19[c]		inactive
5	$(CH_2)_4Cl$	6.2 ± 0.2	20[c]		inactive
12[c]		6.4 ± 0.4	21[c]		inactive
			22[c]		inactive

[a] pA_2 determined based on the dose ratio at 3 μM. [b] Reference 7. [c] Hydrochloride salt.

straining the conformational flexibility of **12** and **13** results in a loss of analgesic activity as seen with **14** and **15**. However, the unsaturated 3-pyridyl analog, **17**, showed no difference in its analgesic action when compared with its saturated analog, **18**, in that both have only modest antinociceptive activity. Since **12** and **13** were analgesic, the function of basicity of the pyridyl group was explored. Oxidation of the pyridyl moiety to the *N*-oxides, **35** and **36**, reduced basicity which resulted in a concomitant reduction in biological activity and aqueous solubility.

Surprisingly, little tolerance for chain length variation with retention of analgesic activity was seen in this series. The 4-(pyridyl)butyl analogs, **25** and **26**, yielded longer compounds that resulted in a lessening of analgesic activity. Shortening the alkyl chain as seen in analogs **19-24** resulted in almost complete abolition of analgesic activity.

The introduction of a 3-hydroxy-2,2-difluoro functionality into the pyridylpropionyl chain as exemplified by **29** resulted in a compound with analgesic and PGE_2 antagonism activity.[16] The para positional isomer, **30**, is not as robust an analgesic as its subcutaneous activity is reduced. The lack of hydroxyl in **34** demonstrates that the geminal fluorines alone in the 3-(pyridyl)propyl group are sufficient for analgesic activity. Additional testing of **13** and **29** in several models of antinociception, mouse hot plate, mouse tail flick, and rat formalin assays showed them to be broadly efficacious analgesics.[17]

Both **13**, SC-51089,and **29**, SC-51234A, were considered as potential clinical candidates. As an analgesic, SC-51234A is more potent than SC-51089. Given that SC-51234A is racemic and its synthesis is more complex, SC-51089 was chosen as a development candidate. SC-51089 was subsequently dropped from development when issues around its metabolism arose, i.e., release of hydrazine which we had not seen previously in other members of this class of compounds.

Conclusion

The original objective of this research was to identify structurally novel analgesics that were PGE_2 antagonists. By replacing the benzyl group of **4** with alkypyridyl moieties of narrowly defined lengths, we have found compounds that meet that criteria. Compounds **13** and **29** are broadly efficacious analgesics and PGE_2 antagonists and displayed little overt toxicity at analgesic doses.

Experimental Section

All experiments were performed under either dry nitrogen or argon. All solvents and reagents were used without further purification unless otherwise noted. The routine workup of the reactions involved the addition of the reaction mixture to a mixture of either neutral, or acidic, or basic aqueous solutions and organic solvent. The aqueous layer was extracted *n* times (×) with the indicated organic solvent. The combined organic extracts were washed *n* times (×) with the indicated aqueous solutions, dried over anhydrous Na_2SO_4, filtered, concentrated in vacuo, and purified as indicated. Separations by column chromatography were achieved with conditions described by Still.[18] The hydrochloride salts were made from 1 N HCl, HCl in ethanol (EtOH), or 6 N HCl in dioxane. Thin-layer chromatograms were run on 0.25 mm EM precoated plates of silica gel 60 F254. High-performance liquid chromatograms (HPLC) were obtained from C-8 or C-18 reverse-phase columns which were obtained from several vendors. Analytical samples were dried in an Abderhalden apparatus at either 56 or 78 °C. ^1H NMR spectra were obtained from either General Electric QE-300 or Varian VXR 400 MHz spectrometer with tetramethylsilane as an internal standard. ^{13}C NMR were obtained from a Varian spectrometer at 125.8 MHz with tetramethylsilane as an internal standard. In polar solvents such as DMSO, a major and a minor rotamer (4:1) about the diacylhydrazine group of the final products were seen. These rotamers were not separable under any chromatographic condition. Earlier reports indicate that this phenomenon is known.[19] NMR signals reported here are that of the major rotamer. This mixture of rotamers was not observed in $CDCl_3$.

The syntheses of 8-chloro-10,11-dihydrodibenz[*b,f*][1,4]-oxazepine (**6**), 8-chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-10-carbonyl chloride (**7**), 8-chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic acid, hydrazide (**8**)have been reported previously.[8]

Ethyl 3-(4-Pyridinyl)-(2*E*)-propenoate (9b). To a mechanically stirring suspension of NaH (7.4 g, 0.16 mol) in 100 mL of ethylene glycol dimethyl ether maintained at 20–25 °C was added, dropwise over 40 min, a 30-mL ethylene glycol dimethyl ether solution of ethyl diethylphosphonoacetate (33.6 g, 0.15 mol). After the mixture was stirred for 1 h at ambient temperature, a 40-mL ethylene glycol dimethyl ether solution of 4-pyridine carboxaldehyde (16 g, 0.15 mol) was added dropwise. After the mixture was stirred for 2 h at ambient temperature and 40 min at 50 °C, 600 mL of brine was added to the reaction mixture which was extracted with 3 × 300 mL of Et_2O. The combined organic solution was washed 1 × 250 mL of brine and worked up in the usual manner. The yellow precipitate was recrystallized from 10% Et_2O–hexanes to yield 18.6 g (70.0%) of desired product which was used in the next step.

Ethyl 4-Pyridinepropanoate (10b). The product from example **9b** (18.7 g, 105 mmol)was reduced under catalytic hydrogenation conditions using 5% Pd/C at 5 psi H_2 in EtOH for 4 h. The yield of product was 18 g (95.2%): bp 90 °C (0.6 Torr). Anal. ($C_{10}H_{13}NO_2$) C, H, N.

3-(4-Pyridyl)propanoic Acid Hydrazide (11b). Anhydrous hydrazine (16.8 mL, 0.53 mol) was added to **10b** (18.0 g, 0.10 mol) dissolved in 200 mL of 2-propanol. After being heated at reflux for 16 h, the solvent was removed *in vacuo*. To the resulting gum was added ethanol and the solution was concentrated *in vacuo*. Hexanes (300 mL) was added to the product. The following day, the resulting crystals were filtered, washed with hexanes, and dried under vacuum. The yield was 16.5 g (100%). Anal. ($C_8H_{11}N_3O$) C, H, N.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-[1-Oxo-3-(4-pyridinyl)propyl]hydrazide, Monohydrochloride (13). To a stirring solution of **11b** (10.0 g, 60.5 mmol) and triethylamine (21 mL, 151 mmol) in 150 mL of dimethylformamide (DMF) was added **7** (17.8 g, 60.5 mmol). After 20 h, triethylamine hydrochloride was filtered from the reaction mixture and the filtrate concentrated *in vacuo*. The

residue was taken up in 200 mL of DCM. The product crystallized. After collecting, the product was washed 2× with hot acetone to yield 18.6 g (73%). To form the hydrochloride, the product was treated with 6 N HCl in dioxane and precipitated with Et_2O and collected: ^1H NMR (DMSO-d_6) 9.68 (d, 1H, J = 1.0 Hz), 8.79 (d, 2H, J = 6.5 Hz), 8.54 (d, 1H, J = 1.0 Hz), 7.92 (d, 2H, J = 6.5 Hz), 7.0–7.4 (m, 7H), 4.84 (s, 2H), 3.10 (t, 2H, J = 7.5 Hz), 2.56 (t, 2H, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) 170.3, 161.7, 155.4, 153.3, 151.3, 140.7, 134.1, 129.2, 128.7, 128.3, 128.2, 127.6, 126.9, 126.1, 123.2, 122.9, 120.0, 48.7, 32.2, 30.4. Anal. ($C_{21}H_{17}N_4O_3Cl\cdot HCl\cdot H_2O$) C, H, N, Cl.

Ethyl 3-(2-Pyridinyl)-2(*E*)-propenoate (9a). (Carbethoxymethylene)triphenylphosphorane (1.74 g, 5 mmol) was added to a stirring solution of 2-pyridinecarboxaldehyde (0.54 g, 5 mmol) in 25 mL of tetrahydrofuran (THF). After 6 h, the reaction had changed from a gray-green to a bright yellow. After 24 h, the reaction solvent was removed under vacuum. The residue was triturated with hexanes. The solid was collected on a sintered-glass funnel. The filtrate containing the product was concentrated under reduced pressure to give a quantitative yield (0.89 g). The product was used immediately without further purification.

Ethyl 3-(2-Pyridinyl)propanoate (10a). The product from example **9a** was reduced under catalytic hydrogenation conditions using 5% Pd/C as described for **9b**. The yield of product was 0.68 g (76%). The product was used immediately without further purification.

3-(2-Pyridyl)propanoic Acid Hydrazide (11a). **11a** was prepared in the same manner described for **11b**.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-[1-Oxo-3-(2-pyridinyl)propyl]hydrazide, Monohydrochloride (12). **12** was prepared on a 1.3-mmol scale in the same manner as described for **13** to yield 0.34 g (61%) of **12**: ^1H NMR (DMSO-d_6) 9.72 (s, 1H), 8.76 (d, 1H, J = 7.3 Hz), 8.55 (s, 1H), 8.41 (dt, 1H, J = 1.4, 7.9 Hz), 7.91 (d, 1H, J = 8.0 Hz), 7.82 (t, 1H, J = 6.8 Hz), 7.0–7.4 (m, 7H), 4.84 (s, 2H), 3.23 (t, 2H, J = 7.3 Hz), 2.68 (t, 2H, J = 7.4 Hz). Anal. ($C_{22}H_{19}N_4O_3Cl\cdot HCl$) C, H, N, Cl.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-[1-Oxo-3-(2-pyridinyl)-2(*E*)-propenyl]hydrazide, Monohydrochloride (14). To a suspension of **8** (1.5 g, 5.18 mmol) and **9a** (1.3 g, 7.34 mmol) in toluene (250 mL) was added trimethylaluminum (6 mL of 2 M solution, 12 mmol), and the resulting yellow solution was refluxed for 6 h. The reaction mixture was allowed to cool to room temperature followed by the addition of methanol (7 mL). The reaction mixture was extracted with 2 × 200 mL of 1 M NaOH. The aqueous extracts were combined and extracted with 3 × 200 mL of EtOAc. The organic solutions were combined and worked up in the usual manner. The product was chromatographed to yield 0.90 g (41%) of product as the free base. To a solution of the free base in EtOH (25 mL) was added HCl in EtOH (9.5 M, 5 mL). The solvent volume was reduced, and a white precipitate formed which was collected by filtration to yield 0.83 g of **14**. Anal. ($C_{22}H_{17}N_4O_3Cl\cdot HCl\cdot 0.25H_2O$) C, H, N, Cl.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-[1-Oxo-3-(4-pyridinyl)-2(*E*)-propenyl]hydrazide, Monohydrochloride (15). A solution of **8** (3.5 mmol) and **9b** (3.5 mmol) in toluene (250 mL) was reacted under the same conditions described for **14**. The product was chromatographed to yield 0.33 g (23%) of product as the free base. To a solution of the free base in EtOH (25 mL) was added HCl in EtOH (9.5 M, 5 mL); the solvent volume was reduced. A white precipitate formed, was collected by filtration, and was dried to yield 0.29 g of **15**: ^1H NMR (DMSO-d_6) 10.17 (s, 1H), 8.85 (m, 3H), 8.05 (d, 2H, J = 6.8 Hz), 7.65 (d, 1H, J = 16.0 Hz), 7.51 (d, 1H, J = 2.4 Hz), 7.0–7.4 (m, 7H), 4.89 (s, 2H). Anal. ($C_{22}H_{17}N_4O_3Cl\cdot HCl\cdot 0.2H_2O$) C, H, N.

3-(3-Pyridyl)propanoic Acid (16). 3-(3-pyridyl)acrylic acid (3.0 g, 20.0 mmol) was reduced using 5% Pd/C as catalyst as described for **9b** to yield, upon removal of solvent, 3.0 g (99%) of product. Anal. ($C_8H_9NO_2$) C, H, N.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-[1-Oxo-3-(3-pyridinyl)-2(*E*)-propenyl]hydrazide (17). To a stirring solution of **8** (2.82 g, 9.7 mmol) in 25 mL of dimethylformamide (DMF) cooled in an ice bath was added 3-(3-pyridyl)acrylic acid (1.54 g, 9.7 mmol). To the stirring suspension were added *N,N*-diisopropylethylamine (1.74 mL, 10 mmol) and [(*N,N*-dimethylamino)propyl]ethylcarbodiimide hydrochloride (1.92 g, 10 mmol). After being stirred over night at ambient temperature, the reaction mixture was added to 100 mL of ethyl acetate (EtOAc) and 100 mL of a saturated $KHCO_3$ solution. The layers were separated. The organic layer was washed 3× with saturated $KHCO_3$ solution and 2× with H_2O and was worked up in the usual manner. The resultant solid was chromatographed. The yield of isolated product was 2.16 g (53%). Anal. ($C_{22}H_{17}N_4O_3Cl$) C, H, N, Cl.

8-chlorodibenz[b,f][1,4]oxazepine-10(11H)-carboxylic acid, 2-[1-oxo-3-(3-pyridinyl)propyl]hydrazide, monohydrochloride (18). The reaction described for example 17 was repeated on a 5-mmol scale with 8 and 3-(3-pyridyl)propionic acid. The yield of the reaction was 0.75 g (34%). The free base was dissolved in 5 mL of acetic acid (HOAc) and filtered. To the filtrate was added 5 mL of 6 N HCl/dioxane. The hydrochloride salt was precipitated from the reaction by the addition of Et_2O. The resultant solid was collected by filtration and dried. Anal. ($C_{22}H_{20}N_4O_3Cl\cdot HCl$) C, H, N, Cl.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-(2-Pyridinylcarbonyl)hydrazide, Monohydrochloride (19). **19** was prepared on a 3.5-mmol scale as described in **14** to yield 0.50 g (36%) of the free base and 0.35 g of the hydrochloride: ^1H NMR (DMSO-d_6) 10.28 (s, 1H), 8.76 (s, 1H), 8.64–8.65 (m, 1H), 8.00 (dd, 2H, J = 3.2, 1.9 Hz), 7.62 (m, 1H), 7.54 (d, 1H, J = 2.4 Hz), 7.2–7.4 (m, 5H), 7.07 (t, 1H, J = 7.4 Hz), 4.89 (s, 2H). Anal. ($C_{20}H_{15}N_4O_3Cl\cdot HCl\cdot 0.1EtOH$) C, H, N, Cl.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-(3-Pyridinylcarbonyl)hydrazide, Monohydrochloride (20). **20** was prepared in the same manner as **14** on a 3.5-mmol scale to yield 0.65 g (48%) of product as the free base and 0.54 g as the hydrochloride. Anal. ($C_{20}H_{15}N_4O_3Cl\cdot HCl$) C, H, N, Cl.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-(4-Pyridinylcarbonyl)hydrazide, Monohydrochloride (21). **21** was synthesized in the same manner as **14** on a 3.5-mmol scale to yield 1.0 g (72.3%) of product as the free base and 0.740 g of the hydrochloride: ^1H NMR (DMSO-d_6) 10.62 (s, 1H), 9.12 (s, 1H), 8.89 (m, 2H), 8.46 (d, 1H, J = 1.6 Hz), 8.43 (dd, 1h, J = 1.4, 4.6 Hz), 7.68 (td, 1H, J = 2.0, 7.8 Hz), 7.0–7.4 (m, 8H), 4.84 (s, 2H), 3.45 (s, 2H). Anal. ($C_{20}H_{15}N_4O_3Cl\cdot HCl$) C, H, Cl; N: calcd, 12.99; found, 12.24.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-(2-Pyridinylacetyl)hydrazide, Monohydrochloride (22). **22** was prepared in the same fashion as **14** on a 3.5-mmol scale to yield 0.52 g (36%) of product as the free base and 0.35 g of the hydrochloride: ^1H NMR (DMSO-d_6) 10.17 (s, 1H), 8.81 (d, 1H, J = 5.0 Hz), 8.73 (s, 1H), 8.45 (m, 1H), 7.8–8.0 (m, 2H), 7.0–7.5 (m, 7H), 4.86 (s, 2H), 4.03 (s, 2H). Anal. ($C_{21}H_{17}N_4O_3Cl\cdot HCl\cdot 0.3H_2O$) C, H, N, Cl.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-(3-Pyridinylacetyl)hydrazide, Monohydrochloride (23). **23** was prepared in the same manner as **14** on a 3.5-mmol scale to yield 0.26 g (18%) of product as the free base and 0.12 g of the hydrochloride: ^1H NMR ($CDCl_3$) 9.88 (s, 1H), 8.60 (s, 1H), 8.46 (d, 1H, J = 1.6 Hz), 8.43 (dd, 1H, J = 1.4, 4.6 Hz), 7.68 (td, 1H, J = 2.0, 7.8 Hz), 7.0–7.4 (m, 8H), 4.84 (s, 2H), 3.45 (s, 2H). Anal. ($C_{21}H_{17}N_4O_3Cl\cdot 1.1HCl\cdot 0.2H_2O$) C, H, N, Cl.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-(4-Pyridinylacetyl)hydrazide, Monohydrochloride (24). **24** was prepared in the manner described for **14** on a 3.5-mmol scale to yield 0.26 g (18%) of product as the free base and 0.070 g of the hydrochloride. Anal. ($C_{21}H_{17}N_4O_3Cl\cdot 1.1HCl$) C, H, Cl; N: calcd, 12.48; found, 12.96.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-[1-Oxo-4-(4-pyridinyl)butyl]hydrazide (25). **25** was prepared in the same manner as **14** on a 3.5-mmol scale from methyl 4-(4-pyridyl)butanoate[10] to yield 1.3 g (57%) of product as the free base: mp 173 °C; ^1H NMR (DMSO-d_6) 9.51 (s, 1H), 8.50 (s, 1H), 8.48 (d, 1H, J = 1.6 Hz), 7.0–7.5 (m, 9H), 4.85 (s, 2H), 2.60 (t, 2H, J = 8.1 Hz), 2.08 (t, 2H, J = 7.2 Hz), 1.80 (m, 2H). Anal. ($C_{23}H_{22}N_4O_3Cl$) C, H, N, Cl.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-[1-Oxo-4-(2-pyridinyl)butyl]hydrazide, Monohydrochloride (26). To a stirring solution of 4-(2-pyridyl)butanoic

acid[10] (1.0 g, 6 mmol) in DMF (50 mL) was added carbonyldiimidazole (1.1 g, 6.8 mmol). After the mixture was stirred for 15 min, 8 (1.43 g, 5 mmol) was added. After 16 h, the solvent was removed, and the residue was taken up in 250 mL of EtOAc and extracted with 1 × 125 mL of brine, 1 × 125 mL of saturated $NaHCO_3$, and 125 mL of 1 N HCl. The aqueous acid solution was neutralized with 1 N NaOH and extracted with 2 × 125 mL of EtOAc. The combined organic solution was worked up in the usual fashion to yield 0.40 g (15%) of product as the free base and 0.32 g of the hydrochloride. Anal. ($C_{23}H_{22}N_4O_3$-Cl·1.15HCl·3H_2O) C, N, Cl; H: calcd, 5.50; found, 4.95.

Ethyl α,α-Difluoro-β-hydroxy-3-(2-pyridinyl)propanoate (27a). Freshly etched Zn (6.55 g, 100 mmol) was suspended in 200 mL of THF (distilled or a newly opened bottle) to which was added ethyl bromodifluoroacetate (15.22 g, 75 mmol). When the Zn adduct began to form in the refluxing reaction, a solution of pyridinecarboxaldehyde (5.35 g, 50 mmol) in 50 mL of THF was added dropwise. Once the addition was complete, the reaction mixture was removed from the heat and stirred for 16 h. To the reaction mixture was added 125 mL of 1 M $KHSO_4$. The aqueous acid was neutralized with 250 mL of saturated $KHCO_3$ which was extracted with 2 × 250 mL of EtOAc. The organic phase was dried over Na_2SO_4. Since normal chromatographic conditions result in product loss, the EtOAc layer was filtered through a 10- × 3-cm pad of EM silica gel topped with a 10- × 1-cm layer of charcoal. The pad was washed with EtOAc to ensure no loss of product. The organic phase was concentrated *in vacuo* to yield 10.32 g (93%) of a pale yellow gum which on standing darkened: ^{1}H NMR ($CDCl_3$) 8.61 (d, 1H, J = 4.6 Hz), 7.77 (dt, 1H, J = 1.4, 7.5 Hz), 7.44 (d, 1H, J = 7.8 Hz), 7.35 (dd, 1H, J = 5.1, 7.2 Hz), 5.18 (dd, 1H, J = 4.9, 17.5 Hz), 4.36 (q, 2H, J = 7.1 Hz), 1.36 (t, 3H, J = 7.1 Hz).

α,α-Difluoro-β-hydroxy-3-(2-pyridinyl)propanoic Acid, Hydrazide (28a). To a stirring solution of **27** (2.91 g, 12.6 mmol) in 15 mL of EtOH was added hydrazine hydrate (1.26 g, 25.2 mmol). After 16 h, a yellow precipitate was filtered, washed with a minimum of EtOH, and dried. The yield of product was 1.98 g (72%). Anal. ($C_8H_9N_3O_2F_2$) C, H, N.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-[2,2-Difluoro-3-hydroxy-1-oxo-3-(2-pyridinyl)propyl]hydrazide, Monohydrochloride (29). **29** was prepared in the same manner as **13** on a 24-mmol scale to yield 7.2 g (59%) of the free base. Hydrochloride was prepared by dissolving in 1 N HCl and lyophilizing: ^{1}H NMR (DMSO-d_6) 10.53 (s, 1H), 8.87 (s, 1H), 8.64 (d, 1H, J = 4.6 Hz), 8.07 (t, 1H, J = 7.5 Hz), 7.74 (d, 1H, J = 8 Hz), 7.58 (broad t, 1H, J = 7.5 Hz), 7.0–7.4 (m, 7H), 5.31 (dd, 1H, J_{CCCF} = 6.0, 17.5 Hz), 4.36 (dd, 2H, J = 15, 20 Hz); ^{13}C NMR (DMSO-d_6) 161.7 (t, J_{CCF} = 27.5), 154.8, 153.2, 151.4, 133.8, 129.3, 128.7, 128.5, 128.4, 127.7, 125.9, 125.7, 125.1, 123.2, 122.9, 120.1, 114.9 (dd, J_{CF} = 256, 263 Hz), 69.9 (dd, J = 24, 29 Hz), 48.7. Anal. ($C_{22}H_{17}N_4O_4F_2$-Cl·HCl·1.2H_2O) C, H, N, Cl.

Ethyl α,α-Difluoro-β-hydroxy-3-(4-pyridinyl)propanoate (27b). **27b** was prepared in the same manner as **27a** on a 20-mmol scale to yield 4.14 g (90%).

α,α-Difluoro-β-hydroxy-3-(4-pyridinyl)propanoic Acid, Hydrazide (28b). **28b** was prepared in the same manner as described for example **28a** on a 20-mmol scale to yield 2.7 g (62%). **28b** was used immediately.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-[2,2-Difluoro-3-hydroxy-1-oxo-3-(4-pyridinyl)propyl]hydrazide, Monohydrochloride (30). The free base of **30** was prepare in same manner as **29** on a 1.75-mmol scale for a yield of 0.098 g (12%). A 0.049-mg amount of the hydrochloride salt was isolated. Anal. ($C_{22}H_{17}N_4O_4F_2$-Cl·HCl·0.25H_2O) C, H, N.

1*H*-Imidazole-1-carbothioic Acid, *O*-[2,2-Difluoro-1-(2-pyridinyl)-3-ethoxy-3-oxopropyl] Ester (31). Thiocarbonyldiimidazole (1.78 g, 10 mmol) and (dimethylamino)pyridine (0.06 g, 0.5 mmol) were added to a stirring solution of **27a** (1.16 g, 5 mmol) in 10 mL of 1,2-dichloroethane. After 1 h, the reaction mixture was applied to a column of silica gel for purification to yield 1.04 g (59%) of **31**: ^{1}H NMR ($CDCl_3$) 8.62 (d, 2H, J = 5.0 Hz), 8.44 (s, 1H), 7.55 (dt, 1H, J = 2.0, 8.1 Hz), 7.72 (s, 1H), 7.43 (d, 1H, J = 9.5 Hz), 7.34 (m, 1H), 7.10 (s, 1H), 6.96 (t, 1H, J = 11 Hz), 4.38 (q, 2H, J = 7.5 Hz), 1.33 (t, 3H, J = 7.5 Hz).

Ethyl α,α-Difluoro-2-pyridinepropanoate (32). **31** (0.51 g, 1.5 mmol) in 10 mL of toluene–DCM (4:1) was added dropwise to a refluxing solution of tri-*n*-butyltin hydride (0.88 g, 3.0 mmol) in 10 mL of toluene. After 2 h, the reaction mixture was filtered through a pad of silica gel which was sequentially washed with DCM and EtOAc. The EtOAc solution was concentrated *in vacuo* to yield 0.18 g (56%) of **32**.

α,α-Difluoro-2-pyridinepropanoic Acid, Hydrazide (33). To a stirring solution of **32** (0.18 g, 0.8 mmol) in 5 mL of EtOH was added NH_2NH_2·H_2O (0.08 g, 1.7 mmol). After 1 h, the reaction mixture was concentrated *in vacuo* and the solid filtered to yield 70% of **33**.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-[2,2-Difluoro-1-oxo-3-(2-pyridinyl)propyl]hydrazide (34). To a stirring solution of **33** (0.31 g, 1.5 mmol) in 5 mL of dimethylacetamide were added **7** (0.45 g, 1.5 mmol) and triethylamine (0.42 mL, 3.0 mmol). After 20 h, the reaction mixture was added to 25 mL of EtOAc and 25 mL of H_2O. The organic layer was washed with 1 × 25 mL of H_2O and 1 × 25 mL of brine. The organic phase was worked up in the usual fashion, and the residue was chromatographed to yield 0.35 g (51%) of the free base. The hydrochloride salt was prepared from 1 N HCl: ^{1}H NMR (DMSO-d_6) 10.61 (s, 1H), 8.81 (s, 1H), 8.70 (d, 1H, J = 9.5 Hz), 8.12 (t, 1H, J = 4.9 Hz), 7.6–7.7 (m, 2H), 7.0–7.4 (m, 8H), 4.87 (s, 2H), 3.74 (t, 2H, J = 20 Hz). Anal. ($C_{22}H_{17}N_4O_3$-ClF_2·0.75HCl·0.5H_2O) C, H, N, Cl.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-[1-Oxo-3-(2-pyridinyl)propyl]hydrazide, *N*-Oxide (35). **35** was prepared by treating the free base of **12** (2 mmol) in 6 mL of HOAc with 0.37 mL of 30% H_2O_2 (3.6 mmol) and heating at 90 °C for 1h. An additional 3.6 mmol of H_2O_2 was added and the reaction heated for an additional 18 h. After the solvent was removed *in vacuo*, the product was chromatographed and recrystallized to yield 0.083 g (9%): ^{1}H NMR (DMSO-d_6) 9.61 (s, 1H), 8.52 (s, 1H), 8.23 (d, 1H, J = 4.7 Hz), 7.0–7.4 (m, 10H), 4.85 (s, 2H), 2.98 (t, 2H, J = 7.3 Hz), 2.51 (t, 2H, J = 7.3 Hz). Anal. ($C_{22}H_{19}N_4O_4Cl$) C, H, N.

8-Chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylic Acid, 2-[1-Oxo-3-(4-pyridinyl)propyl]hydrazide, *N*-Oxide (36). To a stirring suspension of the free base of **13** (22 g, 52 mmol) in 2.5 L of DCM was added dropwise *m*-chloroperbenzoic acid (13.3 g, 87 mmol) in 135 mL of DCM. After 16 h, the reaction mixture was washed sequentially with 1 × 600 mL of 3% Na_2CO_3 and 1 × 600 mL of H_2O. The organic layer was worked up in the usual manner. The residue was treated with ethanol. After 2 h, the crystals were collected and dried to yield 19.65 g (86%) of **36**: mp 193 °C; ^{1}H NMR (DMSO-d_6) 9.57 (s, 1H), 8.51 (s, 1H), 8.07 (d, 2H, J = 6.7 Hz), 7.0–7.45 (m, 9H), 4.84 (s, 2H), 2.80 (t, 2H, J = 7.5 Hz), 2.39 (t, 2H, J = 7.5 Hz). Anal. ($C_{22}H_{19}N_4O_4Cl$) C, H, N, Cl.

***In Vivo* Characterization: Mouse Writhing Assay.**[14] The writhing test was performed using male albino mice (Charles River Laboratories, CD-1/HAM/1LR) weighing between 20 and 30 g. Twenty-five minutes after subcutaneous (sc) or intragastric (ig) administration of the test compound (0.1 mL/10 g body weight), 0.025% (w/v) phenylbenzoquinone was injected intraperitoneally (0.1 mL/g body weight). Five minutes later, each mouse was placed in a large glass beaker, and the number of writhes that occurred in the subsequent 10 min was counted. A test compound was considered to have produced antinociception in a mouse if the number of writhes elicited by phenylbenzoquinone was equal to or less than half the median number of writhes recorded for the saline-treated group that day. Each dose, 30 mg/kg, of test compound was administered to 10 mice, and the results were expressed as the number of mice (out of a possible 10) in which the test compound produced antinociception. The ED_{50}'s were determined on those compounds in which 7 out of 10 mice responded. The ED_{50} value, defined as the dose that inhibited writhing in 50% of the mice, and 95% confidence limits were calculated using a maximum likelihood function.

***In Vitro* Characterization: PGE_2 Antagonism Assay Utilizing the Guinea Pig Ileum.** Male Hartley guinea pigs were sacrificed by cervical dislocation. The distal 40 cm of ileum was removed and was flushed with a modified Tyrode solution consisting of following: NaCl (137.68 mM), KCl (2.68 mM), $CaCl_2$ (0.90 mM), $MgCl_2$ (1.05 mM), NaH_2PO_4 (0.42 mM), dextrose

(5.55 mM), $NaHCO_3$ (11.90 mM). Atropine sulfate (0.14 μM) and pyrilamine maleate (2.5 μM) were added to inhibit cholinergic and histaminergic activation, respectively. The ileum was cut into 2-cm segments and mounted in 10-mL organ baths bubbled with 5% CO_2 in 95% O_2 maintained at 37 °C. The tissues were equilibrated for 1 h with the buffer with flushing every 15 min. Following the preequilibration, 1 g of tension was applied to the tissue, which was briefly exposed to a test dose of PGE_2 to ensure that the tissues were responding. The tissues were exposed to increasing PGE_2 concentrations for 2 min for each dose to allow for maximum tension to develop in response to each dose. Over this brief time, the maximum tension was elicited with no observable desensitization to the agonist. Each dose of PGE_2 was then removed via three consecutive bath washes. After acquiring the dose–response data in the absence of drug, the same tissues were reequilibrated in the presence of test compound and the rightward shifts in the dose–response data were acquired. Experiments were conducted and the data captured by a Buxco STC-400 automated tissue bath controller. If the dose ratio between the control and treated tissues was greater than 2 at a concentration of antagonist less than 30 μM, the experiment was repeated and EC_{50}'s were calculated using the Graded Dose–Response method.[20]

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