128104-36-9; **20** amidoxime, 128104-37-0; **21**, 774-14-1; **21** amidoxime, 128104-92-7; **22**, 63625-95-6; **22** amidoxime, 128104-88-1; **23**, 128104-99-4; **23** amidoxime, 139346-95-5; **24**, 83-33-0; **25a**, 10426-30-9; **25b**, 10381-08-5; **26**, 26452-99-3; **26** amidoxime, 139346-96-6; **27**, 3262-03-1; **28**, 128104-82-5; **29**, 128104-83-6; **29** amidoxime, 128104-84-7; **30**, 128104-43-8; **31**, 128104-42-7; **32**, 128104-44-9; **33**, 128104-47-2; **34**, 128104-41-6; **35**, 128104-40-5; **36**, 128104-51-8; **37**, 128104-52-9; **38**, 128104-98-3; **39**, 128105-08-8; **40**, 128105-10-2; **41**, 128105-02-2; **42**, 128105-11-3; **43**, 128105-09-9; **44**, 128105-12-4; **45**, 128105-17-9; **46**, 128105-06-6; **47**, 139346-97-7; **48**, 139346-98-8; **49**, 128105-16-8; **50**, 128105-15-7; **51**, 128129-37-3; **52**, 128105-14-6; **53**, 128105-05-5; **54**, 128104-89-2; **55**, 128105-04-4; **56**, 128105-13-5; **57**, 139346-99-9; **58**, 139347-00-5; **59**, 128129-36-2; **60**, 128105-03-3; **61**, 128105-01-1; $(EtO)_2P(O)CH_2CN$, 50586-62-4; benzyl bromide, 100-39-0; 2-phenylethanol, 60-12-8; 2-tetralone, 530-93-8; (4-hydroxyphenyl)acetonitrile, 14191-95-8.

Synthesis and Antiulcer Activity of Novel 5-(2-Ethenyl substituted)-3(2*H*)-furanones

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In order to investigate new antiulcer agents, spizofurone 1 (AG-629) was fragmented and reassembled to generate 5-phenyl-2,2-dimethyl-3(2*H*)-furanone (bullatenone, **2**). Because of the antiulcer activity of **2**, 5-phenyl-substituted 2,2-dimethyl-3(2*H*)-furanones (**3–6**) were made and shown to have poor activity. Insertion of an ethenyl link between the furanone and phenyl rings gave 5-(2-phenylethenyl)-2,2-dimethyl-3(2*H*)-furanone (**7**). This compound had better activity than **2**. Compounds **8–41** were synthesized to evaluate the SAR in 5-(2-ethenyl substituted)-3(2*H*)-furanones. Electron-withdrawing substituents on the aromatic ring (**8**, **10**, **19**, and **20**) gave 2–3-fold higher activity. Further increases in the activity were found when the phenyl ring was replaced by heterocyclic nuclei. Compounds that contained a thiophene (**29**), pyridine (**24–26**), or quinoline ring (**32**) had the best activity. Replacement of the methyl group on the furanone ring with a phenyl (**34**) or *p*-fluorophenyl (**40**) substituent in the 2-pyridine series gave compounds with activity that ranked with the best obtained in this study. The best compounds from the above SAR studies were evaluated in the ethanol-necrosis model for duration of cytoprotection action. Compounds **19**, **24**, and **29**, which had the best duration of action, were tested with AG-629 in the acidified aspirin and indomethacin-induced lesion models. Only compound **24** had equivalent activity with AG-629 in both models.

Introduction

The stomach is constantly subjected to a variety of pathogenetic factors, including its own acid-pepsin secretion, microorganisms and, sometimes, alcohol and irritant drugs. Nevertheless, until recently, the primary strategy in ulcer therapy had focused on only the inhibition of gastric acid secretion. One successful approach to decreasing stomach acid secretion is to antagonize the parietal cell H_2 (histamine) receptor. Considerable drug discovery efforts led to the development of several H_2 antagonists as marketable drugs, which controlled 90% of the 1988 antiulcer market.[1] Although the therapeutic and commerical success of H_2 antagonists has been remarkable, some ulcer patients do not respond to gastric secretion inhibitors. Furthermore, it is well known that most patients with gastric ulcers or gastritis have acid secretory rates in the normal range.[2] Also, many gastric ulcer patients with normal or lower than normal acid secretion have deficient mucosal bicarbonate barrier[3] or mucosal blood flow.[4]

Concurrent with the development of H_2 antagonists, Robert[5,6] observed that the property of certain prostaglandins to inhibit gastric secretion and to protect against experimentally-induced lesions could be separated from each other by dose. When the prostaglandin dose caused mucosal protection but no gastric secretion inhibition, this phenomenon was called cytoprotection.[7] This initial concept has been redefined to designate the target area, such as gastroprotection or gastric mucosal protection, because an absolute mucosal cell preservation has not been demonstrated.[2,8] The inability of some patients to respond to most inhibitors of gastric acid secretion, coupled with the above observations, stimulated interest in the search for antiulcer drugs that might act by strengthening gastric and duodenal mucosal defenses. This premise was realized in sucralfate,[9] which captured 10% of the 1988 antiulcer market.[1] Another gastroprotective agent, spizofurone (AG-629, **1**), is also reputed to be a weak antisecretory agent with strong gastroprotective properties.[10] This drug

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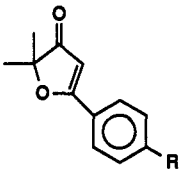
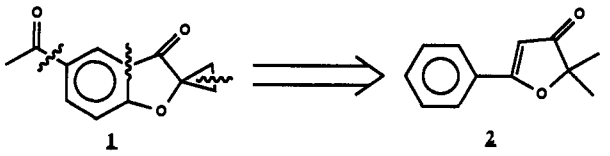
Table I. 5-Phenyl-2,2-dimethyl-3(2*H*)-furanone Analogues



compd	R	mp, °C	formula	% yield	purificn[a]	ethanol-induced lesions[b] dose, mg/kg po	% inhibn	ED_{50} (95% CI)
AG-629	-	-	-	-				10 (5.1-11.8)
2	H	67-68.5	$C_{12}H_{12}O_2$	79	A			19 (10.7-32.7)
3	Cl	133.5-135	$C_{12}H_{11}ClO_2$	46	B	25	29	
4	Br	144.5-145.5	$C_{12}H_{11}FO_2$	58	B	25	36	
5	CF_3	78.5-79	$C_{13}H_{11}F_3O_2$	60	B	25	39	
6	MeO	94-95	$C_{13}H_{14}O_3$	56	C	25	30	

[a] Recrystallization used (A) hexane, (B) hexane/ethyl acetate mixtures, (C) petroleum ether/ethyl acetate mixtures, or (D) EtOH. Silica gel column chromatography used (E) petroleum ether/ethyl acetate mixtures, (F) hexane/ethyl acetate mixtures, or (G) hexane/diethyl ether mixtures. Trituration used (H) diethyl ether/petroleum ether mixtures or (I) diethyl ether/hexane mixtures. [b] Absolute ethanol was administered 1 h after oral dosing of the compounds.



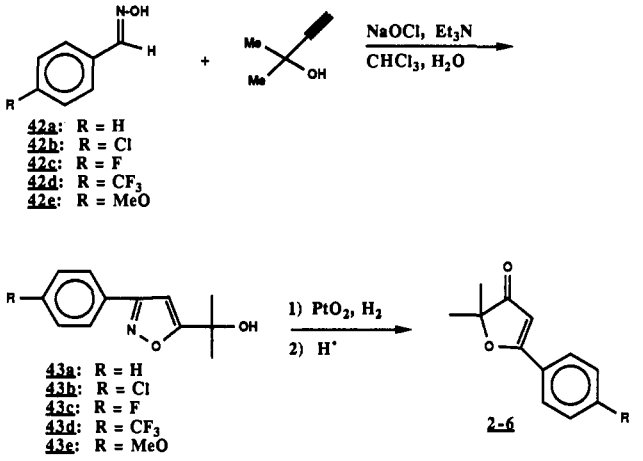
1 2

Figure 1.

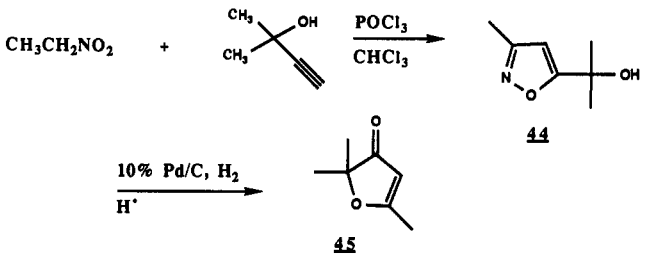
was launched in Japan as Maon by Takeda.[11] Maon's protective action on gastric mucosa has been attributed to its ability to increase gastric mucosal blood flow, a phenomenon which also enhances ulcer healing.[12] The prophylactic and curative properties of these gastroprotective agents suggested a desirable alternative to gastric acid secretory inhibition alone.

Our goal was to discover a potential drug candidate that had a similar profile to AG-629, but with higher potency and longer duration of action. Looking for a key pharmacophore in AG-629 that would allow the synthesis of potentially novel drug candidates, the molecule was fragmented and reassembled (Figure 1) to yield 5-phenyl-2,2-dimethyl-3(2*H*)-furanone (bullatenone, **2**). To test the validity of the structural alteration, bullatenone was synthesized and tested versus AG-629 in the ethanol-induced lesion model (Table I). Kinney et al.[13] have shown that gastroprotectants demonstrate better activity in this model than H_2 antagonists. Therefore, potential antiulcer candidates with activity in this model may complement existing treatments. The resulting ED_{50} values of bullatenone and AG-629, 19 and 10 mg/kg, respectively, provided encouragement for further exploration of the 3(2*H*)-furanone family as antiulcer agents. During the initial investigation of 3(2*H*)-furanones, 5-phenyl-substituted 2,2-dimethyl-3-

Scheme I



Scheme II



(2*H*)-furanones (**3-6**) were found to have less activity than bullatenone. Insertion of an ethenyl link between the aromatic and furanone ring (compound **7**) was beneficial. Therefore, compound **7** became the lead structure for a program devised to systematically appraise 5-(2-substituted ethenyl)-3(2*H*)-furanones as potential antiulcer drug candidates. The results of this program are described in this paper.

Chemistry

Synthetic pathways for target molecules (**2-41**) are outlined in Schemes I-IV. 5-Phenyl-substituted 2,2-dimethyl-3(2*H*)-furanones (**2-6**) were prepared by first converting commercially available benzaldehydes to their corresponding oximes (**42a-e**) by standard methods.[14]

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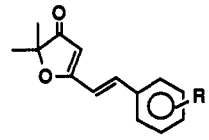
Table II. 5-(2-Phenylethenyl)-2,2-dimethyl-3(2*H*)-furanone Analogues



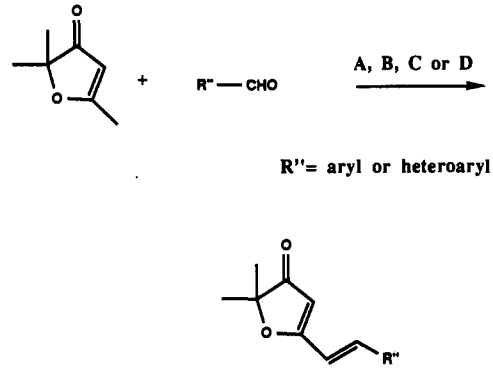
compd	R	mp, °C	formula	% yield	purificn[a]	method[c]	ethanol-induced lesions[b] dose, mg/kg, po	% inhibn	ED_{50} (95% CI)
7	H	77–78	$C_{14}H_{14}O_2$	71	A	K			17 (1–28)
8	4-Cl	91–92	$C_{14}H_{19}ClO_2$	65	E	J			10.3 (7.1–14.8)
9	4-Br	109–110	$C_{14}H_{13}BrO_2$	39	A	J			18 (9–36)
10	4-F	55–57	$C_{14}H_{13}FO_2$	45	A	L			11 (7.4–16.1)
11	2,4-F_2	98–100	$C_{14}H_{12}F_2O_2$	65	E	J			11 (7.1–17.1)
12	3,4-F_2	105–106	$C_{14}H_{12}F_2O_2$	50	H	L	25	47	
13	2,4-Cl_2	154–156	$C_{14}H_{12}Cl_2O_2$	70	H	L	25	20	
14	3,4-Cl_2	100–102	$C_{14}H_{12}Cl_2O_2$	56	E	L	25	45	
15	3,5-Cl_2	129–131	$C_{14}H_{12}Cl_2O_2$	45	E	L	25	63	
16	4-CF_3	94–95	$C_{15}H_{13}F_3O_2$	71	E	J	25	30	
17	4-MeS	98–99.5	$C_{15}H_{16}O_2S$	48	E	J	25	5	
18	4-$MeSO_2$	159–160	$C_{15}H_{16}O_4S$	76	E	L	25	56	
19	4-CN	169.5–170.5	$C_{15}H_{13}NO_3$	59	E	L			12 (8.6–18.1)
20	3-CN	155–157	$C_{15}H_{13}NO_3$	43	B	L	10	68	

[a,b] See Table I for details. [c] Synthesis used (J) 1. LDA, HMPA, THF; 2. TFAA, Et_3N, CH_2Cl_2, (K) NaOH/EtOH, (L) 1N NaOH/EtOH or (M), DBU/EtOH.

These oximes were treated with an aqueous sodium hypochlorite solution as described by Lee[15] in the presence of 2-methyl-3-butyn-2-ol to effect a 3 + 2 cycloaddition and form the penultimate isoxazoles (**43a–e**). The resulting isoxazoles underwent hydrogenolysis to vinylogous amide intermediates which were not isolated. Acidification effected cyclization and subsequent ammonia expulsion to give the desired furanones **2–6** (Scheme I).

A synthesis of starting 2,2,5-trimethyl-3(2*H*)-furanone (**45**) was readily achieved when nitroethane underwent a 3 + 2 cycloaddition to 2-methyl-3-butyn-2-ol when treated with phosphorus oxychloride in chloroform. The resulting isoxazole **44** was hydrogenated in the presence of 10% palladium on charcoal and then acidified with aqueous hydrochloric acid to yield the desired intermediate **45** (Scheme II). The synthesis of the 5-(2-substituted ethenyl)-3(2*H*)-furanones (**7–41**) proved to be more problematic. The literature is replete with examples of lithium diisopropyl amide-induced aldol reaction followed by a variety of dehydration methods.[16] Despite the modest results obtained by others, we examined the lithium diisopropyl amide-catalyzed aldol reaction. We found that the addition of HMPA to the reaction increased the yield and suppressed the competition of α vs γ condensation on 2,5,5-trimethyl-3(2*H*)-furanone as observed by Smith.[16a] Notwithstanding the improved regioselectivity afforded by HMPA, a more straightforward approach was desired to facilitate rapid synthesis of analogs for evaluation. Further investigation revealed that the aldol reaction required milder conditions than the use of lithium amide bases. Powdered sodium hydroxide, 1 N aqueous sodium hydroxide, or DBU (1,8-diazobicyclo[5.4.0]undec-7-ene) in ethanol effected the aldol condensation between aryl or heteroaryl aldehydes and 2,2,5-trimethyl-3(2*H*)-furanone to yield 5-(2-ethenyl substituted)-2,2-dimethyl-3(2*H*)-furanones **7–33** (Scheme III). NMR data indicated that the *E* olefin was formed exclusively.

Scheme III[a]



7-33

[a] (A) 1. LDA, HMPA, THF 2. TFAA, Et_3N, CH_2Cl_2. (B) NaOH, EtOH. (C) 1 N NaOH, EtOH. (D) DBU, EtOH.

To allow for modifications of the furanone ring in the 2-position, a universal intermediate, 5-acetyl-3-methylisoxazole (**47**), was synthesized (Scheme IV). This ketone was made by a series of steps beginning with the 3 + 2 cycloaddition of acetaldoxime to 3-butyn-2-ol in the presence of aqueous sodium hypochlorite. The resulting secondary alcohol **46** was oxidized with Jones reagent to give the desired isoxazole **47** which was treated with an appropriate Grignard reagent to yield intermediates **48a,b**. These tertiary alcohols were subjected to the hydrogenolysis–dehydration sequence described above to afford the penultimate furanones **49a,b**. A pH 7 phosphate buffer was used in the Grignard addition quench to minimize elimination of the tertiary alcohol to the olefin. Treatment of these furanones with a variety of aldehydes in the presence of DBU or 1 N aqueous sodium hydroxide in ethanol gave the desired 5-(2-substituted ethenyl)-3-(2*H*)-furanones (**34–41**).

Results and Discussion

As previously discussed, weak gastric secretion inhibition would be a desirable property in conjunction with gastroprotective activity in new antiulcer agents. Therefore,

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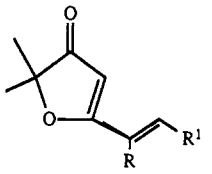
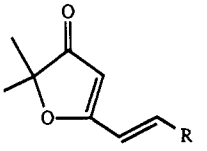
Table III. Other 5-(Ethenyl substituted)-2,2-dimethyl-3(2*H*)-furanone Analogues



compd	R	R¹	mp, °C	formula	% yield	purificn[a]	ethanol-induced lesions[b] method[c]	dose, mg/kg po	% inhibn
21	H	2-naphthyl	150–152	$C_{18}H_{16}O_2$	77	E	L	25	43
22	Me	phenyl	99–101	$C_{15}H_{16}O_2$	86[d]	F	L	10	0
23	H	2-(*p*-chlorophenyl)ethenyl	95–96	$C_{16}H_{15}ClO_2$	36	E	L	10	33

[a,b] See Table I for details. [c] See Table II for details. [d] A 4:1 ratio of *E* to *Z* isomers as observed in NMR.

Table IV. 5-(2-Heterocyclic ethenyl)-2,2-dimethyl-3(2*H*)-furanone Analogues



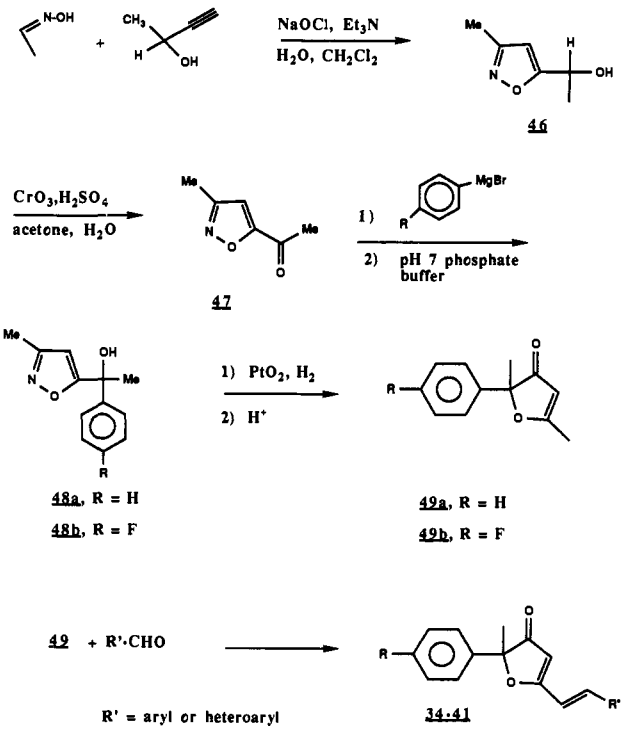
compd	R	mp, °C	formula	% yield	purificn[a]	method[c]	ethanol-induced lesions[b] dose, mg/kg po	% inhibn	ED_{50} (95% CI)
24	2-pyridinyl	87.5–89	$C_{13}H_{13}NO_2$	75	G	L			10 (7.2–15.1)
25	3-pyridinyl	68–70	$C_{13}H_{13}NO_2$	53	E	L			9 (3.2–27.4)
26	4-pyridinyl	94–96	$C_{13}H_{13}NO_2$	32	E	J			4 (2.6–6.1)
27	2-pyrazinyl	120.5–121.5	$C_{12}H_{12}N_2O_2$	44	F	M	10	56	
28	2-thienyl	75–77	$C_{12}H_{12}O_2S$	43	A	L	25	1	
29	3-thienyl	79–80	$C_{12}H_{12}O_2S$	72	E	L			4 (1.9–6.6)
30	3-furanyl	79–80	$C_{12}H_{12}O_3$	74	F	L	10	35	
31	1-methyl-2-pyrrolyl	98.5–100	$C_{13}H_{15}NO_2$	65	E	L	10	32	
32	4-quinolinyl	117–118	$C_{17}H_{15}NO_2$	32	E	L			2.5 (1.6–4.0)
33	2-benzo[*b*]thien-2-yl	103.5–104.5	$C_{16}H_{14}O_2S$	58	F	L	10	17	

[a,b] See Table I for details. [c] See Table II for details.

compound **7**, which had activity in the ethanol-necrosis model, was tested in the pylorus-ligated rat model. As expected, the latter activity was poor (38% inhibition at 50 mg/kg po) relative to ranitidine (ED_{50} = 2.4 mg/kg).[17] Thus, this activity would not be a factor in the investigation of furanones as antiulcer agents and focus would be on the ethanol-necrosis model. To this end, the initial structure–activity relationship study was carried out to determine the effect of aromatic substitution on activity in compound **7** versus activity (Table II). In general, electron-withdrawing substituents on the aromatic ring gave the best results. When the 4-chloro, 4-fluoro, 4-cyano, and 3-cyano compounds were tested (**8**, **10**, **19**, and **20**, respectively), these compounds had 2–3-fold higher activity than **7**. Attempts to maximize the halogen effect on the ring resulted in the preparation of a number of dihalo species (**11–15**). However, no further increase in activity was observed. Other modifications to compound **7**, such as a second aromatic ring (**21**), another methyl group (**22**), or an additional double bond (**23**) gave less active compounds (Table III).

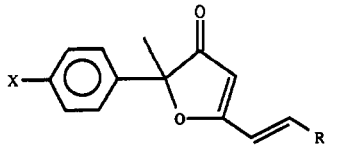
Because only modest increases in activity were obtained in the first study, another structure–activity relationship study was initiated which substituted various heterocyclic nuclei for the aromatic ring (Table IV). The pyridinyl and 3-thienyl furanone derivatives (**24–26**, and **29**, respectively) were more potent than furan- and pyrrole-substituted compounds (**30** and **31**). The former compounds had the best activity observed. Heteroatom orientation in the ring was critical for activity. In the pyridine series, the ED_{50} of the 2- or 3-substituted pyridine (**24** and **25**) was twice as high as the 4-substituted pyridine (**26**).

Scheme IV



(17) DiJoseph, J. Unpublished results.

Table V. 2-Phenyl-2-methyl-5-(2-ethenyl substituted)-3(2H)-furanone Analogues



compd	X	R	mp, °C	formula	% yield	purificn[a]	method[c]	ethanol-induced lesions[b] dose, mg/kg po	% inhibn	ED_{50} (95% CI)
34	H	2-pyridinyl	74.5–76	$C_{18}H_{15}NO_2$	40	I	M			5 (3–8.2)
35	H	3-pyridinyl	106–108	$C_{18}H_5NO_2$	36	E	L	10	44	
36	H	4-pyridinyl	165–166	$C_{18}H_{15}NO_2$	37	E	M			6 (3.2–11.4)
37	H	3-thienyl	75–76	$C_{17}H_{14}O_2S$	71	E	L	10	0	
38	H	4-cyanophenyl	187–188	$C_{20}H_{15}NO_2$	42	D	L	10	4	
39	F	4-cyanophenyl	140–142	$C_{20}H_{14}FNO_2$	38	E	L	10	1	
40	F	2-pyridinyl	70–72	$C_{18}H_{14}FNO_2$	59	E	M			3.5 (2.4–5.2)
41	F	3-thienyl	97–98	$C_{17}H_{13}FO_2S$	62	E	L	10	22	

[a,b] See Table I for details. [c] See Table II for details.

Table VI. Duration of Action in Ethanol-Necrosis Model

compd	ED_{50}, mg/kg po vs EtOH	ED_{50}, mg/kg po vs dose	duration of cytoprotective effect: % inhibition of ulceration[a] 4 h after dosing	6 h after dosing	8 h after dosing
AG-629	10	100	72	44	0
8	10	40	51	NT	NT
10	11	50	61	50	25
11	11	100	42	NT	NT
19	12	50	NT	NT	66
24	10	40	67	NT	76
25	9	40	43	60	40
26	4	20	NT	46	NT
29	4	16	NT	NT	62
34	5	40	28	NT	NT
36	6	24	31	NT	NT

[a] Absolute ethanol was administered at 4, 6, or 8 h after dosing the compounds. NT = not tested.

In the thienyl compounds, the 3-substituted thienyl derivative (29) was dramatically more active than 2-substituted thienyl derivative (28). Aromatic ring appendage to the heterocycle gave mixed results. Whereas, the 4-quinolinyl compound (32) was more active than the 4-pyridinyl derivative (26), the 2-benzothienyl compound (33) showed no advantage over the 2-thienyl compound (28). To further increase activity in these new compounds, a methyl group on the furanone was replaced by an aromatic ring (Table V). This structural change only increased activity in the 2-substituted pyridine series (34 and 40). The activity ranked with the best obtained in the study.

A number of compounds with ED_{50} values between 4 and 12 mg/kg were generated from the above SAR studies. In order to delineate the better candidates, the duration of action of these compounds was evaluated in the ethanol–necrosis model (Table VI). A number of compounds still showed cytoprotective activity when ethanol was administered 8 h after drug dosing. This characteristic is lacking in AG-629. Compounds 19, 24, and 29, which had the best duration of action, were further tested with AG-629 in other lesion models (Table VII, acidifed aspirin and indomethacin induced). These tests gave mixed results. Both compounds 19 and 29 had less activity than AG-629 in the acidified aspirin model, but 19 had equivalent activity in the indomethacin model. Only compound 24 had similar activity to AG-629 in both screens.

In conclusion, this investigation has identified a number of 5-(2-ethenyl substituted)-3(2H)-furanones as novel antiulcer agents. Several members have shown better duration of action than AG-629 in the ethanol-necrosis model and good activity in other lesion models. Further studies are underway to profile these new compounds in other lesion models as well as elucidate a mechanism of action.

Table VII. Further Evaluation in Different Models

compd	ED_{50} vs EtOH[a]	% inhibition, mg/kg po acidified aspirin	indomethacin induced
AG-629	10	78 (40)	95 (100)
19	12	23 (50)	70 (120)
24	10	77 (40)	72 (111)
29	4	0 (16)	65 (40)

[a] Absolute ethanol was administered 1 h after oral administration of the compounds.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded on either a Varian XL-200 or a Brucker AM-400 spectrometer using tetramethylsilane as an internal standard. The chemical shifts are reported in parts per million (δ) relative to TMS, and coupling constants are reported in hertz (Hz). Mass spectra were recorded on a Hewlett-Packard 5995A spectrometer or a Finnigan 8230 high-resolution instrument. Elemental analyses (C, H, N) were measured on either a Perkin-Elmer 240 or 2400 analyzer. All compounds are within ±0.4% of theory unless otherwise noted. All yields were unoptimized. Aryl or heteroaryl aldehydes were commercially available except for pyrazinecarboxaldehyde,[18] 2-benzothiophenecarboxaldehyde,[19] and *p*-chlorocinnamaldehyde.[20] Organic extracts were dried over magnesium sulfate and were concentrated in vacuo with a rotary evaporator. Column chromatography was done using 230–400 mesh silica gel. Thin-layer chromatography was performed on silica gel 60 F-254 (0.25-mm thickness) plates. Visualization was accomplished with UV light, I_2 vapor, and/or 10% phosphomolybdic acid.

Preparation of 2–6. Compounds 2–6 were prepared according to the representative procedures illustrated for 3.

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5-(4-Chlorophenyl)-2,2-dimethyl-3(2*H*)-furanone (3). The starting oxime was prepared by a modified literature procedure.[14] To a solution of *p*-chlorobenzaldehyde (14.1 g, 100 mM), hydroxylamine hydrochloride (7.35 g, 110 mM), ice/water (75 mL), and 95% ethanol (25 mL) at 0–10 °C was added 50% aqueous sodium hydroxide (20 g, 250 mM) dropwise. The resulting solution was stirred 1 h. Then the reaction was washed with diethyl ether (150 mL) and the organic layer discarded. The mixture was cooled to 0 °C and acidified with concentrated hydrochloric acid to pH 4–5. The acid solution was extracted with dichloromethane (2 × 150 mL). The combined dichloromethane washes were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford a yellow crystalline oxime **42b** (13.3 g, 86%, mp 105.5–107.0 °C, lit.[21] mp 110–111 °C). The product was used without further purification.

To a solution of 5.25% aqueous sodium hypochlorite (bleach, 104 g), triethylamine (0.6 mL, 4.0 mM), and 2-methyl-3-butyn-2-ol (5.8 mL, 60 mM) in chloroform (60 mL) at 0 °C was added a solution of oxime **42b** (6.2 g, 40 mM) in chloroform (40 mL) dropwise. After addition, the reaction mixture was allowed to warm to room temperature and was stirred overnight. The aqueous layer was then saturated with sodium chloride and extracted with chloroform (3 × 100 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give yellow crystalline isoxazole **43b** (8.0 g, 83%, mp 93–95 °C) which was used without purification: ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 2.6 Hz, 2 H), 7.35 (d, J = 2.5 Hz, 2 H), 6.48 (s, 1 H), 2.33 (br s, 1 H), 1.70 (s, 6 H).

A mixture of isoxazole **43b** (5.00 g, 20.9 mM), platinum oxide (0.5 g), and Raney nickel (100 mg) in methanol (60 mL) and water (15 mL) was hydrogenated at 1 atm for 1 day. The mixture was filtered after degassing, and the resulting solution was concentrated under reduced pressure. Aqueous hydrochloric acid (2 N, 30 mL) and tetrahydrofuran (40 mL) was then added, and the resulting mixture was stirred overnight. The reaction was cooled to 0 °C, and solid sodium bicarbonate was added until a pH 8 was achieved. The aqueous layer was extracted with chloroform (3 × 30 mL). The combined chloroform extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow solid. Recrystallization of the crude product from hexane/ethyl acetate gave analytically pure, white crystalline **3** (2.18 g, 46%, mp 133.5–135 °C, lit.[22] mp 132–133 °C): ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J_1 = 8 Hz, J_2 = 2 Hz, 2 H), 7.46 (d, J = 8 Hz, 2 H), 5.95 (s, 1 H), 1.49 (d, J = 0.5 Hz, 6 H); MS (EI) m/e 222 (M^+), 136 (100); IR (KBr) 3100, 2980, 1692, 1620, 1170, 1045, 830 cm^{-1}. Anal. ($C_{12}H_{11}ClO_2$) C, H, N.

2,2,5-Trimethyl-3(2*H*)-furanone (45). To a solution of 2-methyl-3-butyn-2-ol (675 mL, 6.97 M), triethylamine (1.50 L, 10.8 M), and nitroethane (350 mL, 4.90 M) in chloroform (4 L) at 10 °C was added a solution of phosphorus oxychloride (438 mL, 4.72 M) in chloroform (1.5 L) dropwise over 8 h. After the addition, the reaction was allowed to warm to room temperature and was stirred overnight. The solution was then washed with water (2 × 2 L) and saturated aqueous sodium bicarbonate (2 × 2 L), dried over sodium sulfate, and filtered. After the solvent was removed under reduced pressure, the dark residual oil was distilled (85–86 °C, 1 mm) to give a dark orange liquid **44** (343 g, 49.7%): ^{1}H NMR ($CDCl_3$) δ 6.05 (s, 1 H), 3.08 (brs, 1 H), 2.16 (s, 3 H), 1.54 (s, 6 H).

To a solution of 10% palladium on charcoal (50 g) in methanol (800 mL) under nitrogen was added a solution of isoxazole **44** (109 g, 0.77 M) in methanol (200 mL). The reaction mixture was hydrogenated at 30 psi in a Parr hydrogenation apparatus to the point of no more hydrogen uptake. The catalyst was filtered under nitrogen and washed with methanol (2 × 100 mL). The resulting filtrate was concentrated under reduced pressure to yield a white crystalline solid (106.2 g). This product was suspended in water (200 mL) and 1 N aqueous hydrochloric acid (400 mL) and stirred for 2 h. The mixture was then neutralized with solid sodium bicarbonate and saturated with sodium chloride. The aqueous solution was extracted with diethyl ether (5 × 100 mL). The combined ethereal extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow liquid (82.7 g, 85% from the isoxazole). This procedure was repeated, and the combined crude products were distilled (bp = 100–120 °C at 1 mm) to yield a clear liquid **45** (140 g, 72%). The NMR data was consistent with published data:[23] ^{1}H NMR ($CDCl_3$) δ 5.36 (s, 1 H), 2.21 (s, 3 H), 1.40 (s, 6 H).

Preparations of 8, 9, 11, 16, 17, and 26. Compounds **8**, **9**, **11**, **16**, **17**, and **26** were synthesized by method J. The following procedures for compound **16** are representative of method J.

2,2-Dimethyl-5-[2-[4-(trifluoromethyl)phenyl]ethenyl]-3-(2*H*)-furanone (16). To a solution of dry diisopropylamine (5.00 mL, 35.7 mM) in dry tetrahydrofuran (150 mL) at −78 °C was added a 2.3 N solution of *n*-butyllithium in hexane (15.5 mL, 35.7 mM) dropwise. After the reaction solution was stirred 15 min, a solution of furanone **45** (3.00 g, 23.8 mM) in tetrahydrofuran (25 mL) was added dropwise. After 30 min, hexamethylphosphoramide (6.40 mL, 35.7 mM) was added dropwise. Finally, a solution of *p*-(trifluoromethyl)benzaldehyde (4.0 g, 28.5 mM) in tetrahydrofuran (25 mL) was added in one portion. The reaction solution was stirred 15 min when trifluoroacetic anhydride (10.5 mL, 76 mM) was added. Again the reaction was stirred 15 min when triethylamine (5.9 mL, 48 mM) was added and was allowed to warm to room temperature. The reaction was partitioned between diethyl ether (50 mL) and saturated aqueous sodium chloride (100 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate (2 × 25 mL) and saturated aqueous sodium chloride (50 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced vacuum to give an amber liquid. The crude product was purified by chromatography (petroleum ether/ethyl acetate) to give a yellow crystalline **16** (3.20 g, 71%, mp 94–95 °C): ^{1}H NMR ($CDCl_3$) δ 7.65 (s, 4 H), 7.49 (d, J = 16 Hz, 1 H), 6.92 (d, J = 16 Hz, 1 H), 5.63 (s, 1 H), 1.45 (s, 1 H); MS (EI) m/e 282 (M^+), 196 (100). Anal. ($C_{15}H_{13}O_2F_3$) C, H, N.

Preparation of 7. Compound **7** was obtained by method K. The following procedure is illustrative of method K.

2,2-Dimethyl-5-(2-phenylethenyl)-3(2*H*)-furanone (7).[24] To a solution of benzaldehyde (3.00 g, 28.2 mM) and furanone **45** (3.20 g, 25.5 mM) in ethanol (150 mL) was added sodium hydroxide (0.57 g, 14.1 mM). The resulting solution was stirred 24 h. The solution was concentrated under reduced pressure to dryness. The resulting solid was partitioned between diethyl ether (200 mL) and saturated aqueous sodium chloride (50 mL). After the layers were separated, the ethereal layer was washed with saturated aqueous sodium chloride (50 mL), dried over magnesium sulfate, filtered, and concentrated to a dark yellow solid. Recrystallization from hexane afforded a light yellow solid **7** (4.00 g, 71%, mp 77–78 °C): ^{1}H NMR ($CDCl_3$) δ 7.54 (m, 2 H), 7.49 (d, J = 4 Hz, 1 H), 7.39 (m, 3 H), 6.85 (d, J = 4 Hz, 1 H), 5.58 (s, 1 H), 1.45 (s, 6 H); IR (KBr) 2960, 1695, 1630, 1555, 1380, 975, 690 cm^{-1}; MS (EI) m/e 214 (M^+), 128 (100). Anal. ($C_{14}H_{14}O_2$) C, H, N.

Preparation of 10, 12–15, 18–25, 28–33, 35, 37–39, and 41. Compounds **10**, **12–15**, **18–25**, **28–33**, **35**, **37–39**, and **41** were prepared by method L. The following procedure for compound **18** is typical for method L.

2,2-Dimethyl-5-[2-[4-(methylsulfonyl)phenyl]ethenyl]-3-(2*H*)-furanone (18). A solution of furanone **45** (1.50 g, 11.9 mM), *p*-(methylthio)benzaldehyde (2.20 g, 14.3 mM) and 1 N aqueous sodium hydroxide (1.20 mL, 1.20 mM) in ethanol (30 mL) was stirred 16 h at room temperature. The reaction mixture was diluted with saturated aqueous sodium chloride (200 mL) and was extracted with diethyl ether (3 × 100 mL). The combined ethereal extracts were washed with saturated aqueous sodium chloride (50 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow solid. The

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crude product was dissolved in dichloromethane (200 mL), and then *m*-chloroperbenzoic acid (6.15 g, 35.6 mM) was added, and the reaction solution was stirred 4 h at room temperature. Then the solution was washed with 0.5 M aqueous sodium sulfite (50 mL) and saturated aqueous sodium bicarbonate (2 × 50 mL). The resulting solution was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow solid. The crude product was purified by column chromatography (petroleum ether/ethyl acetate) to afford a pale yellow crystalline 18 (1.76 g, 76% from ketone, mp 159–160 °C): ^{1}H NMR ($CDCl_3$) δ 7.81 (d, J = 8.4 Hz, 2 H), 7.73 (d, J = 8.4 Hz, 2 H), 7.52 (d, J = 16 Hz, 1 H), 7.00 (d, J = 16 Hz, 1 H), 5.68 (s, 1 H), 3.09 (s, 3 H), 1.47 (s, 6 H); MS (EI) m/e 292 (M^+), 127 (100). Anal. ($C_{15}H_{16}O_4S$) C, H, N.

3-Methyl-5-acetoxyisoxazole (47). To a solution of acetaldoxime (44.5 g, 0.75 M), 3-butyn-2-ol (52.9 g, 0.75 M) and triethylamine (10.5 mL, 0.075 M) in dichloromethane (1.75 L) at 0 °C was added a 5% aqueous solution of sodium hypochlorite (bleach, 1.94 kg) over 3 h. The reaction was allowed to warm to room temperature and allowed to stir overnight. The layers were separated, and the aqueous layer was extracted with dichloromethane (500 mL). The combined dichloromethane extracts were washed with saturated aqueous sodium chloride (500 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow oil 46 (47.7 g, 50%) that was used without further purification: ^{1}H NMR ($CDCl_3$) δ 6.25 (s, 1 H), 4.95 (q, J = 5 Hz, 1 H), 2.25 (s, 3 H), 1.53 (d, J = 5 Hz, 3 H).

To a solution of tertiary alcohol 46 (47.6 g, 367 mM) in acetone (2 L) at 0 °C, a solution of chromic anhydride (93.3 g, 933 mM), 6 N aqueous sulfuric acid (186 mL, 1.1 M), and water (186 mL) was added over 2 h. After the reaction mixture was allowed to warm to room temperature, saturated aqueous sodium chloride (500 mL) was added to the reaction. The aqueous layer was extracted with dichloromethane (3 × 400 mL). The combined organic extracts were washed with saturated aqueous sodium sulfite (2 × 300 mL) and saturated aqueous sodium chloride (2 × 300 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give a yellow powder 47 (27.8 g, 60%) that was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.55 (s, 1 H), 2.65 (s, 3 H), 2.43 (s, 3 H).

Preparation of 49a,b. Compounds **49a,b** were made according to the representative procedures shown for **49b**.

2-Methyl-2-(4-fluorophenyl)-5-methyl-3(2*H*)-furanone (49b). To a solution of isoxazole 47 (0.5 g, 4.0 mM) in diethyl ether (25 mL) at 0 °C was added a 2 N solution of (*p*-fluorophenyl)magnesium bromide in diethyl ether (2.4 mL, 4.8 mM) dropwise. After addition, the reaction mixture was stirred 30 min. When pH 7 buffer (10 mL) was added, the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 25 mL). The combined ethereal extracts were washed with saturated aqueous sodium chloride (10 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to give an amber oil **48b** (0.8 g, 91%) that was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.4 (dd, J_1 = 6 Hz, J_2 = 2.5 Hz, 2 H), 7.0 (t, J = 5 Hz, 2 H), 5.95 (s, 3 H), 2.25 (s, 3 H), 1.88 (s, 3 H).

The catalyst (10% Pd/C, 15 g) was suspended in methanol (400 mL), when a solution of tertiary alcohol **48b** (15.0 g, 73.8 mM) in methanol (100 mL) was added. The mixture was hydrogenated under 20 psi until there was no uptake in hydrogen. After the reaction solution was degassed, the catalyst was filtered and the filtrate was concentrated under reduced pressure. The crude product was dissolved in 1 N aqueous hydrochloric acid (100 mL) and methanol (100 mL) and stirred 1 h. Then the solution was neutralized with solid sodium bicarbonate and diluted with saturated aqueous sodium chloride (100 mL). The aqueous solution was extracted with diethyl ether (4 × 100 mL). The combined ethereal extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford a yellow oil **49b** (10.7 g, 67%) that was used without further purification: ^{1}H NMR ($CDCl_3$) δ 7.49 (dd, J_1 = 6 Hz, J_2 = 2.5 Hz, 2 H), 7.02 (t, J = 8 Hz), 5.42 (s, 1 H), 2.35 (s, 3 H), 1.72 (s, 3 H).

Preparation of 27, 34, 36, and 40. Compounds **27, 34, 36,** and **40** were synthesized by method M. The following procedures for compound **40** demonstrate method M.

2-Methyl-2-(4-fluorophenyl)-5-[2-(2-pyridinyl)ethenyl]-3(2*H*)-furanone. (40). To a solution of 2-pyridinecarboxaldehyde (1.26 g, 10.2 mM) and furanone **49b** (2.00 g, 9.80 mM) in ethanol (100 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.20 mL, 1.30 mM). The reaction mixture was heated at 80 °C for 4 h. After the reaction solution was allowed to cool to 20 °C, saturated aqueous sodium chloride (400 mL) was added. The aqueous layer was extracted with diethyl ether (3 × 100 mL). The combined ethereal extracts were washed with saturated aqueous sodium chloride (50 mL), dried over magnesium sulfate, filtered, and concentrated to give a yellow liquid. The crude product was purified by chromatography (petroleum ether/ethyl acetate) to yield a yellow solid **40** (1.70 g, 59%, mp 70–72 °C): ^{1}H NMR ($CDCl_3$) δ 8.69 (dd, J_1 = 4 Hz, J_2 = 1 Hz, 1 H), 7.76 (dt, J_1 = 7.5 Hz, J_2 = 1.8 Hz, 1 H), 7.65 (d, J = 16 Hz, 1 H), 7.52 (d, J = 16 Hz, 1 H), 7.51 (dd, J_1 = 9 Hz, J_2 = 5.2 Hz, 2 H), 7.47 (d, J = 8 Hz, 1 H), 7.31 (dd, J_1 = 4.4 Hz, J_2 = 2.8 Hz, 1 H), 7.05 (t, J = 8.8 Hz, 2 H), 5.71 (s, 1 H), 1.80 (s, 3 H); MS (EI) m/e 295 (M^+), 129 (100). Anal. ($C_{18}H_{14}FNO_2$) C, H, N.

Ethanol-Induced Gastric Lesions.[5] Male Sprague-Dawley rats (180–210 g) were deprived of food but not water for 18–24 h prior to use. Rats were dosed orally with drug or vehicle 1, 4, 6, or 8 h before absolute ethanol administration (1 mL per rat po). One hour after ethanol administration, the rats were sacrificed by CO_2 asphyxiation. The stomachs were removed and kept moist with saline until the lesions were scored by an investigator unaware of the treatment groups (single blind). The grading of gastric ulcers took into account the size of the ulcers (in mm^2) and the number of ulcers in each size category. The mean ulcer score for each treatment group was compared to the mean score of the vehicle-treated group, and the percent inhibition of ulcer formation was calculated.

Acidified Aspirin-Induced Lesions.[25] Male Sprague-Dawley rats (120–180 g) were fasted for 18–24 hours (water available ad libitum). Acidified aspirin was prepared by grinding aspirin into a fine powder and then adding the appropriate amount of 0.35 M HCl. Test compounds or vehicle were administered (10 ml/kg po) 30 minutes prior to acidified aspirin (5 ml/kg po). Five hours after aspirin administration, the rats were sacrificed with CO_2 (g), the abdomens opened, and the stomachs excised and examined grossly. Gastric lesions were graded as above.

Indomethacin-Induced Lesions.[26] Male Sprague-Dawley rats (120–170 g) were fasted for 18 hr (water ad libitum) prior to use. The test compound was administered orally 30 min prior to indomethacin treatment (20 mg/kg po). Four hours after indomethacin administration, the rats were sacrificed by cervical dislocation. The stomach was removed, opened along the greater curvature, and rinsed with tap water. Gastric lesions were graded as above.

Statistics. In single dose tests, the mean score of each treatment group (±SEM) was compared with that of the control group and expressed as a percentage inhibition. Each group consisted of 10 rats or more. Statistical significance was determined by Dunnett's multiple comparison technique ($p < 0.01$). In multidose (minimum 3 dose levels) experiments, values for ED_{50} with 95% confidence limits were calculated by standard regression analysis of the dose–response data.

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