2.08
Furans and their Benzo Derivatives: Applications

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2.08.1 INTRODUCTION

This chapter describes various applications of furan and benzo furan derivatives since 1982. The subject matter concentrates on the actual use of molecules that contain one or more of the following ring systems: a furan ring, dihydro- and tetrahydro furan ring, 2(5H)- and 3(2H)-furanones, five-membered anhydrides, benzo furans, isobenzo furans, dibenzofurans, benzofuranones, benzoanhydrides, polyarylfurans (and derivatives thereof), and their hydro derivatives. This chapter is not an exhaustive review of the literature since 1982 due to the large number of references found on this topic and the page limitation imposed upon this chapter. Thus, what appears is a selection. There were too many references to simple compounds like tetrahydrofuran, maleic anhydride, succinic
anhydride, and phthalic anhydride, so for the most part, they are not discussed in detail. The reader is referred to Chemical Abstracts for references related to these compounds. It was very difficult to distinguish whether compounds described in patents had an actual application or were being listed as the subject of claim. Therefore, molecules whose claim of application would be of general interest have been included. Again, due to space restrictions biologically active molecules isolated from natural sources have not been included.

2.08.2 FURAN DERIVATIVES

2.08.2.1 Agrochemical Bioregulators

Some monosubstituted aryl and alkyl furans have exhibited beneficial properties. Furfuryl triazine (1) was shown to have detrimental effects on larval survival when introduced into adult female house flies, Musca domestica <85M 208-01>. It was found that, although females deposit eggs and the eggs hatch, the larvae fail to pupate. The results were dependent upon when the eggs were treated with (1) and the concentration injected. The distribution, elimination, and metabolism of 14C-labeled (1) has also been studied on the common house fly <86M 208-01>. Ring opening of the furan moiety to yield a saturated dihydroxy derivative appears to be the major metabolic pathway. Furfuryl triazine (1) suppressed the population of T. granarium <91M 208-01>. Larvas treated with (1) provided adults with small legs and incomplete wing pads. The solubility of the widely used fungicide fuberidazole (2) in water-surfactant systems was measured as a function of pH to help determine how it degrades in the environment. <92M 208-01> Finally, a mixture of furan (3), the salt of kasugamycin, white carbon, lauryl sulfate, calcium ligninsulfonate, and clay (20:1:20:1:2:54 wt. parts) were shown to protect rice seeds from infection by Gibberella fujikuroi and Pseudomonas glumae <91JAP(K)0313907>.

![Chemical Structures](image_url)

A variety of 2-nitrofuran derivatives have shown interesting activity. 2-Nitrofuran (4) has been used to control barnacles and mussels at levels as little as 0.1 ppm <83JAP(K)58015902>. Venters et al. has tested a variety of 5-substituted-2-nitrofuran derivatives <90M 208-01>. Thus, furan (5) was shown to be an effective agent against houseflies and rice weevils, nitrile (6) was active against bean spider mites, carbonitrile (7) was a plant growth regulator and herbicide, and compounds (8) and (9) were fungicides. In addition, 40 other derivatives of 5-nitrofuran have been prepared and assayed for their fungicidal activity <90M 208-02>. Silyl-containing amides of acid (10) showed the best success against Phytophthora on tomato and gray rot of beans. Furan (11) gave >90% inhibition of five species of fungi; a spray of as little as 0.3% gave good control of blue mold of tobacco in pot experiments <85M 208-02>. Furadantin (12) has been shown to act as a chemosterialant on the lesser bandicoot rat <82M 208-01>. An improved synthesis of 2-(2-bromo-2-nitroethyl)furan (13) has been reported, since it has been shown to be active against a wide variety of microbes <89MIP8911793>. Synergistic effects have been noted when furan (13) is mixed with other compounds. Thus, a mixture of (13) with 2-bromo-2-nitropropane-1,3-diol is an effective industrial microbicide and algicide <91USP5045104>, while with glutaraldehyde and didecyldimethylammonium chloride the mixture controls the bacteria K. pneumoniae in aqueous systems, such as cooling waters and in paper manufacturing <92USP5158973, 92USP5158973>. Derivatives of furan-2-carbaldehyde and 2- and 3-furoic acid have shown interesting properties. The copper complex of compound (14) possesses herbical activity <89M 208-01>. The complex was more active than the parent compound (14). 2-Furoic acid (15) increased hypoxic stress resistance in wheat, thus increasing the yield and quality of the crop <92JAP(K)04342507>. The feryl furanones (16)–(18) <87CZP246434> and indanylfuran (19) <87JAP(K)62249066> have shown promise as antifungal agents. The latter exhibited 100% control of Rhizoctonia solani at 12.5–100 ppm. Furan (20) is a
seed-disinfectant fungicide when mixed with N-methyl-2,3-dichloromaleimide \(\langle 85\text{EGP}218261 \rangle\). A formulation of 30% maleimide and 10% \(\langle 20 \rangle\) applied as a seed dressing, at 4 g kg\(^{-1}\), synergistically controlled \(H.\) gramineum on barley.

Furan \(\langle 21 \rangle\) when mixed with Sanplas \(\langle 22 \rangle\) acted as a wood preservative and inhibited the growth of \(Coriolus \langle 93\text{JAP(K)}05112406 \rangle\).

Compound \(\langle 23 \rangle\) has exhibited some very interesting synergistic effects. Mixtures of \(\langle 23 \rangle\) with 1,1,1,2,6,7,7-octachloro-4-oxaheptane when added to plywood adhesives were effective in controlling termites \(\langle 87\text{JAP(K)}62016402 \rangle\). Mixing \(\langle 23 \rangle\) with isopropargyl derivatives \(\langle 86\text{JAP(K)}61091109 \rangle\) or 2-iodo-N-phenylbenzamide \(\langle 84\text{GEP(O)}3316007 \rangle\) provided good fungicidal wood preservatives. Adding phenyl salicylate to \(\langle 23 \rangle\), when used as a wood preservative, retarded photodegradation \(\langle 86\text{JAP(K)}61060676 \rangle\). Finally, structure–activity relationships of a variety of mono-, di-, and trimethyl-furan carboxamides have been tested against the succinate dehydrogenase complex (SDC) activity in mitochondria isolated from sporidia of a wild-type strain and a moderately carboxin-resistant mutant strain of \(U.\) maydis (corn smut). Furan \(\langle 24 \rangle\) had the highest affinity for the mutant SDC \(\langle 88\text{MI}208-01 \rangle\).

Maleic anhydride was the active ingredient in a synergistic microbicide; 15 mg ml\(^{-1}\) of maleic anhydride controlled the growth of slime in paper manufacturing \(\langle 89\text{JAP(K)}01221302 \rangle\). In addition, industrial microbicides containing both maleic acid and maleic anhydride have been useful for controlling microbial growth in water and prevented slime formation in textile lubricating oils, paints, adhesives, latex, glues, leather, lumber, paper goods, bamboo, and in paper manufacturing \(\langle 89\text{JAP(K)}01050803 \rangle\). The dimethylphosphono derivative \(\langle 25 \rangle\) is an excellent insecticide. \(Musca domestica\) was completely killed when exposed to a film of 0.01% of \(\langle 25 \rangle\) \(\langle 87\text{EGP}246023 \rangle\).

A number of furanones have been reported to exhibit interesting properties. Many papers have been published describing the ability of \(2(5H)\)-furanone \(\langle 26 \rangle\) to stimulate seedling vigor, enhance root and foliage growth, and increase the grain yield of corn \(\langle 83\text{MI}208-01, 88\text{MI}208-02, 89\text{MI}208-02,\)
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90MI 208-03, 91MI 208-02. Two 3,4-dichloro derivatives of 2(5H)-furanone have been used as fungicides with seeds. Compound (27) compared favorably with the fungicide Vitavax (88CZP248215), while (28) was successful with rye seeds (88CZP254669). Furanone (29) was shown to be secreted by Trichoderma harzianum, which inhibits the growth of microorganisms (92P485). Compound (30) was a powerful fly attractant (81JAP(K)8113201) and furanones (31) and (32) showed inhibition of the microbe Pyricularia oryzae (90JAP(K)02255669, 91JAP(K)03099058). The dithiophosphate derivatives (33) and (34) are aphicides (90URP1578133), while the methylated derivative (35) (and others) have been shown to be good herbicides (88JAP(K)63174983).

A series of analogues of strigol (36), a potent weed seed germination regulator, have been prepared and tested. It has been shown that the A, B, and C rings of strigol are not necessary for germination stimulation of Striga and Orobanche seeds. This is illustrated by the simple compound (37) exhibiting almost the same activity as the complex molecule (38) (92M1 208-02). Pepperman and Cutler have prepared a variety of 5-alkoxy-3-methyl-2(5H)-furanones and screened them for plant growth regulating activity. Interestingly, strigol did not inhibit the growth of etiolated wheat coleoptiles, but epistrigol (39) did at 1 mM concentrations (91MI 208-03). 5-Hydroxy-3-methyl-2(5H)-furanone was shown to stimulate the germination of dormant cheat and nondormant perennial ryegrass and sorghum seeds, while 5-allyloxy-3-methyl-2(5H)-furanone showed a similar activity against witchweed as strigol did. In general, the 5-alkoxy-3-methyl derivatives of butenolid were less effective in stimulating seed germination than the multiring systems (88M1 208-03).

(20) R = H, R¹ = cyclohexyl
(21) R = H, R¹ = Ph
(22) R = OMe, R¹ = cyclohexyl

(26) R = R¹ = R² = H
(27) R¹ = Cl, R² = O=C(O)CH=CHPh (E)
(28) R¹ = Cl, R² = OCH(Me)CH²Cl
(29) R = CH₂CH(OH)Me, R¹ = H
R² = CH₂CH=CHCH=CHMe (E, E)
(30) R = OH, R¹ = Me, R² = Et
(31) R = Me, R¹ = CO₂H, R² = H
(32) R = Me, R¹ = CO₂CH²Ph, R² = H

(33) R = Cl
(34) R = OMe

R = \beta\text{-OH} (strigol)
R = \alpha\text{-OH}

R = \beta\text{-OH} (strigol)
R = \alpha\text{-OH}

R = \beta\text{-OH} (strigol)
R = \alpha\text{-OH}
A variety of tetrahydro-2-oxofurans have exhibited beneficial properties. Lettuce seeds when treated with acid (40) showed almost no germination \( \langle 91 \text{JAP(K)03251505} \rangle \). A combination of the sex attractant formation of lactone (41) with a PEP—eugenol mixture caught significantly more *Popillia japonica* than either alone. More male beetles were trapped during the period of heavy adult emergence \( \langle 81 \text{MI 208-01} \rangle \). The structure of (41) is similar to the female sex pheromone (42) which has an additional double bond in the C(3)—C(4) position. The latter has been used to assess the population of the Japanese beetle (*J. japonica*) in the Azores \( \langle 88 \text{MI 208-04} \rangle \).

Compound (43) has been shown to possess antifeedant activity against *Phytophthora infestans* on tomato plants \( \langle 85 \text{MIP544086} \rangle \), while (44) controlled nut sedge (*Cyperus rotundus*) and barnyard grass (*Echinochloa crus-galli*) \( \langle 86 \text{EUP178101} \rangle \). Bakkenolide A (45) showed very good antifeedant activity against a variety of insects \( \langle 84 \text{MI 208-01} \rangle \).

A variety of 3(2H)-furanone derivatives have been synthesized and tested for activity. Sandmann and Boeger have performed structure—activity studies on 26 derivatives of (46) for inhibition of colored carotenoids in cultures of *Synechococcus*. The most active compound was found to have structure (47) \( \langle 93 \text{ZN(C)312} \rangle \). Other groups over the past ten years have been studying various analogues of compound (46) for their herbicidal activity and a few patents have been granted. Compounds (47)–(52) have shown good herbicidal activity. Compound (47) controlled spurred anoda and prickly sida and partially controlled yellow foxtail with no phytotoxicity to peanuts and cotton \( \langle 93 \text{USP5180415} \rangle \). Compounds (48) and (51) were active against crabgrass, wild oats, lambsquarter, and mustard \( \langle 86 \text{USP4568375}, 86 \text{USP4568377} \rangle \), while mustard and pigweed was controlled by (49) \( \langle 86 \text{USP4568378} \rangle \). Furanones (50) and (52) were active against a variety of common weeds \( \langle 85 \text{USP4537623}, 87 \text{MI 208-01} \rangle \). In addition, (52) possesses potent bleaching activity and is postulated to act through inhibition of carotenoid biosynthesis. Peanuts and sorghum are tolerant to postemergence applications, while potatoes, barley, peas, safflower, and cucumbers show some degree of tolerance to (52).

Compound (53) acts as a cockroach attractant. Baits containing (53), food and insecticide were tested on a variety of common cockroaches. This mixture showed more activity than the control bait (COMBAT) \( \langle 89 \text{EUP319757} \rangle \). On the other hand, compound (54) acted as a cockroach repellent. It was more active than eugenol, and the effect lasted for greater than five days \( \langle 89 \text{JAP(K)01242503} \rangle \).
Finally, the 2,4-dione (55) controlled a variety of perennial weeds including broadleafed perennials \(\langle 90\text{EUP}351020\rangle\).

A few tetrahydrofuran-containing molecules have exhibited useful properties. Compounds (56) and (57) have shown herbicidal activity against a number of common weeds such as barnyard grass, Johnson grass, yellow foxtail, yellow millet, and blackgrass \(\langle 86\text{USP}4594094, 88\text{EUP}264978\rangle\). Tetrahydrofuran (58) has shown insecticidal activity when applied to eggs and pupae of a variety of insects \(\langle 88\text{MI}208-05\rangle\). The tetrahydrofuranyl ether of 8-hydroxymenthol is a long-lasting insect repellent. When applied to the arms of humans, mosquitoes were repelled even six hours later. This was 55% better than the control compound (60) \(\langle 92\text{JAP}(K)04210685\rangle\). Compound (59) may also be useful as an antifouling agent since it was shown to repel mollusks.

2.08.2.2 Fermentation and Bioindustrial Chemistry

A number of furan derivatives have been used or detected in the fermentation and bioindustrial area. A nutrient substrate for growing yeast has been prepared by hydrolyzing plant raw material and steam distilling the remains to provide a furfural (61)-containing condensate, which was subsequently treated with ozone, and a hydrolysate. Mixing this ozone treated furfural condensate with the hydrolysate increased the yield of the yeast. \(\langle 90\text{URP}1558983\rangle\). Furfural has also been degraded to methane and carbon dioxide under anaerobic conditions. Methane was produced at a 80% yield of the theoretical expected biogas when furfural was continuously added to a continuously stirred tank reactor containing the biomass pretreatment liquor \(\langle 91\text{MI}208-04\rangle\). 2-Acetoxyfuran (62) has been isolated from the volatiles of various invert sugars. It is suggested that the detection of (62) in wines could be used as a measure of whether inverted sucrose solutions have been added to wine \(\langle 83\text{MI}208-02\rangle\). Disulfide (63), which has a burnt odour, was reduced in whisky (from grain spirit) by passing oxygen through the solution. Bubbling nitrogen gas increased the concentration of disulfide (63). The reduced burnt smell was confirmed by a nosing panel \(\langle 88\text{BRP}2204878\rangle\). Furans (64)–(67)
were produced by fermentation of *Streptomyces* strains DSM 4349, 4355, 4200, and 4211 and were found to be active against *staphyl-* and *streptococci* \(\langle 89\text{EUP}337152\rangle\).

![Chemical structures](image)

\(\text{(61)} \ R = \text{CHO}, \ R^1 = \text{H} \)
\(\text{(62)} \ R = \text{OAc}, \ R^1 = \text{H} \)
\(\text{(63)} \ R = \text{Me}, \ R^1 = \text{SSMe} \)

Sotolone (68) is the key substance in the aroma of sugar cane and was detected in botrytized wine. When sotolone was added to normal wine, a sweet, honey-like flavour was detected \(\langle 84\text{ABC}2707\rangle\). Wine tasters have also associated the presence of sotolone (68) with an aftertaste of a nutty flavour \(\langle 92\text{MI} 208-03\rangle\). Furanone (69) was produced by a shake-culture of *Scedosporium* sp. SPC-15549 and shown to inhibit acyl CoA-cholesterol acyltransferase with an ID\(_{50}\) of 0.29 \(\mu\)g ml\(^{-1}\) \(\langle 92\text{JAP(K)04356475}\rangle\). Furanones (70) and (71) have been found to be useful as taste and flavour enhancers for food. The yeast *Zygosaccharomyces rouxii* ATCC 13356, when cultured in a medium containing sucrose, salts, the sodium salt of D-xylulose 5-phosphate, and the barium salt of D-ribose 5-phosphate produced a mixture of furanones (70) and (71) \(\langle 91\text{JAP(K)04183490}\rangle\). Finally, it has been reported that *Bacillus thermolysin*, a metallo-protease which is used in the preparation of peptide sweeteners, is acylated with maleic anhydride (72) to improve its heat stability \(\langle 90\text{JAP(K)02286084}\rangle\).

![Chemical structures](image)

\(\text{(68)} \)
\(\text{(69)} \ R = \text{Me}, \ R^1 = \text{Et} \)
\(\text{(70)} \ R = \text{Et}, \ R^1 = \text{Me} \)

### 2.08.2.3 Food and Feed Chemistry

A number of furan derivatives have been used in the food and feed industry, mainly as taste enhancers. Three reviews have appeared in the literature since 1982 on the use of furans in this area. The first two deal with specifications, safety data, and so on, of furanones and sulfur containing furans, respectively, used in flavouring materials \(\langle 83\text{MI} 208-03, 84\text{MI} 208-02\rangle\). The third discusses the use of furan derivatives as fragrant additives in food products \(\langle 87\text{MI} 208-02\rangle\). Furfural (61) has been shown to be a major component of the furans essential for the formation of important coffee aroma constituents \(\langle 89\text{MI} 208-03\rangle\). In addition, when furfural is mixed with aspartame, the mixture tastes like sucrose \(\langle 90\text{JAP(K)02276553}\rangle\).

Dithiolane (73) at a concentration of 2.5 ppm deepened the chicken taste and added a light onion aftertaste when added to chicken broth \(\langle 85\text{USP4515968}\rangle\), while disulfide (74) exhibited a meaty flavor \(\langle 90\text{MI} 208-04\rangle\). 2-Undecylfuran (75) has been detected in tonka beans and it has been proposed that furan (75) be used as an indicator for the detection of illegal tonka bean products in food \(\langle 91\text{MI} 208-05\rangle\). Furanone (53) has been detected as a volatile component in strawberries, pineapples, grapes, and wines. It has also been used as a food additive, in racemic form, since it has a strawberry flavor \(\langle 83\text{MI} 208-04\rangle\); however, furan (53) has been reported to induce micronuclei chromatid exchanges in germ cells of male mice and therefore may not be a safe food additive \(\langle 92\text{MI} 208-04\rangle\). Furanone (76) has also been isolated from strawberries, and only the racemic form possesses the taste of strawberries. The individual enantiomers have different odor and sensory characteristics \(\langle 92\text{MI} 208-05\rangle\).

Furanones (70) and (71) have been used as artificial sweeteners in beverages \(\langle 86\text{JAP(K)61035761}\rangle\) as a sweetener enhancer with sucrose \(\langle 92\text{JAP(K)04008264}\rangle\). Furanones (77) helped remove the unpleasant odor of goat milk, while not reducing the nutritional value of the milk \(\langle 86\text{MI} 208-02\rangle\). Finally, some five-membered lactones have been detected or used in the food and feed industry. Lactone (78), which imparts a caramel-like sweet odor, has been detected in nonfermented sausages.
stored at 10°C 〈93MI 208-01〉. Lactones (79)–(81) inhibit the growth of food microorganisms such as *Salmonella infantis*. Thus, 0.1% of (79) inhibited the growth of salmonella in a trypticase soy broth at pH 5 (37°C) 〈83EUP72202〉.

2.08.2.4 Textiles and Fibers

Maleic anhydride (72) has been used extensively in the textiles and fibers industry. Some representative examples are given below. Cellulosic fabrics (i.e., cotton knits) have been treated with a mixture of maleic anhydride and a polyoxyalkylene co-polymer to improve hygroscopicity and softness with good washfastness 〈92JAP(K)04174774〉. Hygroscopic, flat yarns have been prepared for use with electrical cables, water-retaining sheets for agricultural goods, and medical instruments by sandwiching a polypropylene extrudate between two extrudates of maleic anhydride-grafted linear polyethylene 〈89JAP(K)01156578, 89JAP(K)01162874〉. High density fibers with high bending strength have been prepared by spinning polypropylene (50 parts), maleic anhydride modified polypropylene (20 parts), cellulose pulp (45 parts), and silicone rubber (5 parts) at 120°C 〈91JAP(K)03224713〉. Maleic anhydride and Glauber’s salt (sodium sulfate decahydrate) are useful additives for dyeing wool. Wool, dyed with a mixture of Palatine Fast Blue, maleic anhydride, a wetting agent and Glauber’s salt at 100°C for 1–1.5 h provided fibers with blue shades which were no more sensitive to alkali than raw wool 〈90MIP150368〉. Polypropylene fibers with improved dyeability were prepared by spinning isotatic polypropylene with 1–25% aminotriazole containing copolymers. These copolymers were prepared by the condensation of furans (82) or (83) with hydrazine hydrate (containing water) in the presence of various aliphatic or aromatic monocarboxylic acids and ε-aminocaproic acid 〈81CZP192298〉.

Cellulose esters have been prepared by the esterification of cellulose hydrate fibers with acid chlorides (84) and (85). The resulting fibers exhibited antimicrobial properties 〈85MI 208-03〉. To make environmentally friendly paper substitutes, weather degradable fibers have been prepared by melt spinning poly(2,3-dihydrofuran) (86) at 285°C. When the spun polymer was used with poly(vinyl alcohol) fibers in a paper substitute, the paper showed marked degradation after 40 d of weathering 〈91JAP(K)03206113〉. Finally, carbon fiber strength was improved by impregnating pitch-
based carbon fibers with a 90:10 mixture of furfuryl alcohol and furfural-modified furfuryl alcohol resin containing 2% BF₃·EtNH₃. The tensile strength of the fiber increased from 11.0 g denier⁻¹ for untreated carbon fibers to 14.2 g denier⁻¹ (EUP251596).

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\begin{align*}
\text{(84)} & \\
\text{(85)} & \\
\text{(86)} & 
\end{align*}
\]

2.08.2.5 Dyes and Photosensitizers

A few furan rings have been incorporated into molecules which have shown useful properties as dyes and photosensitizers. Furan (87) was reacted with diazotized p-nitroaniline to produce a reddish blue dye which has been used to color polyester fibers (GEPO2910806). Polyamide fibers were dyed yellow to brown shades by furans (88) (88MI 208-06), while furans (89) provided dyes ranging in colour from blue-green to violet (86MI 208-03). Some furan derivatives have been used to dye polyesters. The highly conjugated lactone (90) provided a fast red shade (88BRP2205324) while the furluy coumarin derivative (91) was found to enhance the whitening effect of polyesters (85DP331).

Finally, the furan salts (92) have been reported to be photosensitizers, which enhance the photosensitive properties of poly(vinylcarbazole). Unfortunately, no data were given (85Ml 208-04).

\[
\begin{align*}
\text{(87)} & \\
\text{(88)} & \quad R = \text{Cl, NO₂, CO₂H, or SO₃H} \\
\text{(89)} & \quad R = \text{Br, I, or NO₂} \\
\text{(90)} & \\
\text{(91)} & \\
\text{(92)} & \quad R = \text{H or Me} \\
& \quad R¹ = p-\text{NO₂, m-NO₂, o-NO₂, p-Cl} \\
& \quad X = \text{Br or I}
\end{align*}
\]

2.08.2.6 Cellulose, Lignin, Paper, and Other Wood Products

A number of interesting property changes are possible in wood and paper products by the addition of furan-containing compounds during manufacturing processes. Furfuryl alcohol (93) has been used numerous times, along with other additives, in the preparation of particleboard. Particleboard made from the flakes of Abies concolor, when oxidized with nitric acid and then treated with a cross-linking agent consisting of ammonium lignosulfonate, furfuryl alcohol (93), maleic anhydride (72), and water (in a ratio of 4.2:1.8:1.0:5.2 per 100 g of wood) gave a constant thickness swelling of approximately 14–16% in a 2 h boiling test. A similar treatment with hydrogen peroxide failed the boiling test (83Ml 208-05). However, if paraformaldehyde was used in place of maleic anhydride, good strength properties and resistance to swelling were observed (82Ml 208-02). Flakes from a
Douglas fir tree, when treated with hydrogen peroxide and a cross-linking agent consisting of ammonium lignosulfonate, furfuryl alcohol (93), maleic acid, and ferric chloride produced boards with strength properties and boiling resistance comparable to or better than those obtained from phenolic resin binders. (82M1 208-03). Evenly colored black birch veneer was produced when the wood was impregnated with 10% furfuryl alcohol (93) then immersed in an aqueous p-toluenesulfonic acid solution for 5 s and dried at 170°C (87JAP(K)62160202). It has been claimed that the properties of some phenolic resins can be improved by the addition of either furfuryl alcohol (93) or poly(vinyl alcohol) to the phenol during the polymerization process; however, no details were provided (88M1 208-07).

A mixture of sulfuric acid and furan (94) was found to increase the uniformity of wetting of cotton husks, which resulted in a fourfold decrease of the acidity value of the raw material. In addition, the yield of furfural increased by approximately 5% (85M1 208-05).

Maleic anhydride (72) has been used extensively in the paper and wood industry. There have been numerous reports in which maleic anhydride is added to the emulsions used for the sizing of paper (88MIP145090, 90MIP201190, 91JAP(K)03234892). Generally, emulsions containing some maleic anhydride (among other additives) give paper showing good Stoeckigt sizing. Enhanced water-proofing and frictional properties of wrapping paper have been reported when the paper is treated with an emulsion containing a mixture of ricinoleic acid, linoleic acid, and maleic anhydride (83MIP27736). The impact strength of modified wood is increased by adding triethylene glycol dimethacrylate containing styrene and 2-5 wt.% maleic anhydride. It was reported that the processability of the wood was also improved (82URP795400). The dimensional stability of wood and weather resistance is improved by adding anhydrides to the hydroxy groups present on the outer layer of wood and then treating the wood with epoxy compounds at 60–150°C. Thus, a piece of Japanese cypress was dipped into molten maleic anhydride containing N,N-dimethylbenzylamine at 100°C for 3 h and then treated with epichlorohydrin at 120°C for 3 h. The resulting wood showed improved stability and discolored to an other color after 800 h exposure in a Sunshine weatherometer. Untreated wood turned reddish brown (88JAP(K)63054204). Wood impregnated with maleic anhydride and glycerol in water or alcohol, followed by hot pressing gave improved plywood with excellent gloss, surface smoothness, water resistance, dimensional stability, and durability (89JAP(K)01226302).

Interestingly, maleic anhydride has been used in the ink industry both to prepare inks and to deink paper. Printing inks giving sharp images and high gloss have been prepared by heating resins (100 parts) with maleic anhydride (1–20 parts) at 150–250°C, adding diprimary diamines and heating to 130–250°C, followed by adding polyols and heating to 200–300°C. A mixture of the above resin, linseed oil, and mineral oil was used as a printing ink (90GEP(O)3837520). A deinking agent was obtained by the reaction of a wood resin–ethylene oxide/proplylene oxide (24:16) block co-polymer adduct with maleic anhydride (92JAP(K)04202880). Succinic anhydride (95) has also been used to prepare a deinking agent for use with recycled paper by treating succinic anhydride with ethylene oxide, propylene oxide, and 12-hydroxystearic acid (92JAP(K)04202881).

Maleic anhydride has been polymerized with a variety of alkenes to form copolymers. These copolymers have found wide use in the paper industry as sizing agents for paper. For example, copolymers of maleic anhydride with styrene (84USP4448884), C_{12-40} monoalkenes (93GEP(O)4133123), phthalic anhydride–propylene glycol copolymer (90JAP(K)02142814), norbornene (84EGP210695), diisobutylene (84USP4481319), and x-monoalkenenes (83GEP159077) have been reported.

Furan (96), when added to paints, provided good wood preservatives, which had good wood penetration and temperature stability (86GEP(O)3610189). Thus, wood destruction by termites was reduced (83GEP(O)3130675), and attack by Coniophora puteana, Poria monticola or Coriolus versicolor was prevented (83GEP(O)319252). Cycloalk(en)ylsuccinic anhydrides have good dispersibility and sizing effects on paper (88JAP(K)63227894). Thus, handsheets sized with cyclohexenylsuccinic anhydride had a sizing degree of 36 s, versus 27 s when sized with dodecenylsuccinic anhydride. Furanes (98), where R' or R'' is any substituent that does not attack the furanone ring, reduces the brightness reversion of high-yield wood pulps which have been bleached with Na_{2}S_{2}O_{8} (89USP4871423). Finally, a two-stage emulsion polymerization of butadiene (25 parts), styrene (49
parts), methyl methacrylate (15 parts), acrylonitrile (8 parts), itaconic acid (2 parts), and acrylic acid (1 part) with 2,5-dihydrofuran (99) (2.5 parts) gave latexes with good adhesion and printability on paper 〈91JAP(K)03227304〉.

Finally, a review has been published on the manufacturing of furan and furan derivatives from biomass and papermaking wastes 〈87MI 208-03〉.

\[
\begin{align*}
(96) \\
(97) n = 4-10 \\
(98) \\
(99)
\end{align*}
\]

2.08.2.7 Industrial Organic Chemicals, Leather, Fats, and Waxes

Only three compounds were found to be useful in this category. Furan (100) has shown good antioxidant properties for fats and oils. Thus, when 1% (by weight) of furan (100) is mixed with methyl linolate and heated to 45°C for 2 d, the amount of oxidation of methyl linolate was reduced 〈89JAP(K)64003192〉. Succinic anhydride (95) has been used to prepare a flux for soldering. A mixture of succinic anhydride (95), tetrahydrophthalic anhydride and pyromellitic anhydride when combined with trimethylolpropane and heated for 1 h at 150–160°C gave a poly(half)ester. When this ester is mixed with hydrogenated rosin and isopropanol a soldering flux was obtained with good working properties 〈92JAP(K)04200992〉. Finally, good manganese and cobalt catalysts are obtained when a limonene/maleic anhydride co-polymer or β-pinene/maleic anhydride copolymer are complexed with Mn²⁺ or Co²⁺ ions. The catalysts effectively oxidized n-hexadecanoic acid 〈93MI 208-02〉.

2.08.2.8 Surface Active Agents and Detergents

A few furan derivatives have found a use in the detergent industry. A copolymer (1:1) of MeO(C₂H₄O)₉CH₂CH═CH₂ and maleic anhydride (72) (20 000 ppm) when mixed with potassium nitrate (1100 ppm), magnesium sulfate (520 ppm), calcium dihydrogen phosphate (310 ppm), and ammonium sulfate (140 ppm) provided a good cleaning agent for plants and trees 〈90JAP(K)02067400〉. A dispersant was obtained for α-ferric oxide and titanium dioxide when 1-heptene/maleic anhydride co-polymer and polyethylene glycol (mol. wt. 2000) were heated to 70°C and cooled to room temperature. The dispersant showed a higher affinity than conventional sulfonated petroleum salts, fatty acid calcium salts, or partially oxidized polyethylene wax 〈89JAP(K)01004228〉. Oxidized co-polymers of furan and maleic anhydride have been reported to have a good sequestering capacity for calcium ions. The co-polymers have found a use as filters in detergent compounds when used for laundering and general cleaning 〈91USP5061396, 92USP5087682〉. Diacyloxydihydrofurans (101) are activators for inorganic peroxoxygen compounds. Thus, the bleaching power of a laundry detergent containing hydrogen peroxide was enhanced by the addition of 2,5-diacetoxy-2,5-dihydrofuran (102) 〈91JEP(O)4015859〉. Finally, mixtures containing ≥50% of furan derivatives (103) (double bonds at C₂-3 and C₄-5), dihydrofuran derivatives of (103) (double bond at C₂-3, C₄-5, or C₃-4) or tetrahydrofurans derivatives (103) with 0.1–30% surfactants have been found useful for the defluxing of printed circuit boards 〈91JAP(K)03062898〉.
2.08.2.9 Fossil Fuels, Derivatives, and Related Products

A number of furan derivatives have been used as additives in the fuel and oil industry. Tetrahydrofuran (104) has been found to improve ignition in ethanol-based diesel fuels. In a similar manner, the cetane number of diesel fuels is increased by the addition of 0.05–0.5 wt.% of furans (105)–(107). Not surprisingly, maleic anhydride has been used as an additive in fuels. A mixture of maleic anhydride (72), Jeffamine M-300 (a polyoxyalkylene monoamine), and Duomeen T (a hydrocarbyl polyamine) have been found to inhibit engine octave requirement increase (ORI) and carburetor deposit formation. While copolymers of maleic anhydride with C₂₀–₅₀-alkenes have been added to Otto fuels as anticorrosion–antiwear additives. Furan (94) or branched C₁₋₅-alkyl derivatives promote flame propagation for internal-combustion engines. Furfuryl alcohol (93), furfuryl amine (108), and esters of furico acid (109) are effective antiknock agents (at 0.1 M levels) in unleaded gasolines. Finally, succinic anhydride dimers (110) have been added to diesel and heating fuels to improve the low-temperature fluidity of the fuels. Thus, the reaction product of epoxidized C₂₄₋₂₅-alkenes, di(hydrogenated tallow) amine, and (110) when added to a base fuel gave a pour point of −40°C.

Maleic anhydride has also been used as an additive for oils. Various effects by the addition of maleic anhydride to the oils have been reported (or claimed) and are listed below. Asphaltenic flocculation in unstable heavy oils is decreased by the addition of maleic anhydride in the presence of an amine. An effective corrosion inhibitor for iron metals was obtained when the Diels–Alder adduct between maleic anhydride and 2,3-poly(allocimene) was added to petroleum oil or grease. A mixture of polyaniline dispersants, prepared by the mixing of polyisobutylene substituted phenol, formaldehyde, tetraethylene pentamine, and oleic acid) and maleic anhydride is effective in maintaining a high level of dispersancy in lubrication oils. In addition, fluoro hydrocarbon seals were observed not to deteriorate. Maleic anhydride was grafted onto an ethylene–propylene copolymer and then added to a lubricating oil (2.0 wt.%). Testing in a 2.3 L 4-cylinder Ford Ranger truck engine showed the additive to have a dispersancy and seal compatibility superior to a commercial polyisobutenyl succinimide additive. Maleic anhydride onto Shellvis 200 or an ethylene/propylene copolymer. The addition of furfuryl alcohol and formaldehyde to assist with the cross-linking of the water soluble acrylamide/sodium 2-acrylamido-2-methylpropane sulfonate/N-vinyl-2-pyrrolidone copolymer provides not only long-term stability of the resulting gel in subterranean formations having an ambient temperature of 93°C, but also delays the gelling process giving the fluid more time to travel down the wellbore. Finally, the addition of furfuryl alcohol to a raffinate (obtained from the selective purification of petroleum oils in the presence of Al-Co–Mo or Al-Ni–Mo catalysts, followed by depaaffination) prior to hydrotreatment provided an improved lubricating oil basestock.

\[
\begin{align*}
(101) &\text{ } R = C_8 \text{ alkyl, phenyl} \\
(102) &\text{ } R = \text{Me} \\
(103) &\text{ } R = C_8 \text{ alkylene} \\
&\text{ } X = H, \text{alkyl, acyl} \\
&\text{ } n = 0–10
\end{align*}
\]

\[
\begin{align*}
(104) &\text{ } R = H \\
(105) &\text{ } R = \text{NO}_2 \\
(106) &\text{ } R = H \\
(107) &\text{ } R = \text{NO}_2 \\
(108) &\text{ } R = \text{CH}_2\text{OH} \\
(109) &\text{ } R = \text{CO}_2\text{Me or CO}_2\text{Et} \\
(109) &\text{ } R = 32–36
\end{align*}
\]

\[
\begin{align*}
(111) &\text{ } X = \text{H}
\end{align*}
\]
2.08.2.10 Essential Oils and Cosmetics

Polymers have been used extensively in the essential oil/cosmetic industry. A few examples are provided herein. Maleic anhydride has been polymerized with \( \text{CH}_2=\text{CHCH}_2\text{O(C}_2\text{H}_4\text{O)}_3\text{Me} \) to provide a copolymer, which when mixed with floral perfumes, propylene glycol, ethanol, water, gelatin, and sucrose gave a transparent air freshener gel with good physical properties [91JAP(K)03197531]. Similar gels prepared from various alkene/maleic anhydride copolymers have also been used in the manufacturing of pet repellents and detergents [89JAP(K)01297484]. Nonaqueous sunscreen oils have been prepared by mixing a 1-octadecene/maleic anhydride copolymer with Lipovol MOS-70, benzyl alcohol, propylparaben, octyldimethyl PABA, benzophenone, homomenthyl salicylate, octyl \( \beta \)-methoxycinnamate, silicone oil, and fragrance. The sunscreens exhibited a high sun-protection factor [90USP4940574]. A neutralized cross-linked maleic anhydride/C\(_1\)_4 alkyl vinyl ether copolymer is the gel forming agent in some shaving gels. Thus, a mixture of 0.2–5.0% gel forming agent, 3–15% soap and 80–97% water provided a useful shaving gel. [91USP5034220]. Finally, a nail polish has been prepared (colored or not colored), which is not toxic to skin, by mixing poly(tetrahydrofuran) (8 g), nitrocellulose (12 g), dibutyl phthalate (4 g), camphor (2 g), and a 2:1 mixture of butyl acetate and ethyl acetate (up to 100 g). The poly(tetrahydrofuran) (mol. wt. 110000) was prepared by the polymerization of tetrahydrofuran in the presence of silver hexafluoroantimonate under a nitrogen atmosphere [83GEP(O)3243291].

A variety of highly conjugated furan derivatives (112) and (113) have been prepared and used as UV absorbers in sunscreens. Unfortunately, no data was provided on how active the compounds were as UV absorbers [87JAP(K)62138206, 88USP4740369].

\[
\begin{align*}
\text{(112)} & \quad R = \text{H, Me, OH, or OMe} \\
R^1 & = \text{H or Me} \\
R^2 & = \text{H or OH}
\end{align*}
\]

\[
\begin{align*}
\text{(113)} & \quad R = \text{alkyl, alkenyl, aryl, alkylaryl, or OR}^3 \\
R^3 & = \text{alkyl, alkenyl, aryl, or alkylaryl} \\
R^1 & = \text{H, Me, CH}_2\text{CH}_2\text{OH, OMe, OEt,}
\text{OPh}
\end{align*}
\]

A derivative of vitamin C, furan (114), has been prepared, which exhibited better skin-lightening effects than vitamin C itself. Furan (114) was applied to skin as a mixture of glycerin, pyrrolidonecarboxylic acid, pyridoxin • HCl, ethanol, dipropylene glycol, poly(oxyethylene) hydrogenated castor oil, and water [88JAP(K)63198674]. Lactones (115) and (116) have been shown to stimulate hair growth in synergy with skin peripheral vasodilators, such as vitamin E nicotinate, and capronium chloride. The mode of action is believed to be by the inhibition of testosterone-5α-reductase [88JAP(K)63275514].

\[
\begin{align*}
\text{(114)} & \quad \text{HO}_2\text{C(CH}_2\text{)}_7 \\
\end{align*}
\]

\[
\begin{align*}
\text{(115)} & \quad R = \text{alkyl, double bond at } C_{3-4} \\
\text{(116)} & \quad R = \text{alkyl}
\end{align*}
\]

Compound (117) has a long-lasting hay-like odor and has been used to create a fragrance having a rose-like odor. A large number of chemicals have been mixed to produce the rose-smelling fragrance. The chemicals are listed to give the reader an idea of the large number of chemicals involved in the preparation of some fragrances. Thus, furanone (117) (40 g) was mixed with 960 g of a composition of chemicals. This latter composition was made up of 2-phenylethanol (200 g), geraniol (50 g), heliotropin (20 g), citronellol (10 g), nerol (100 g), hydroxycitronellal (30 g), methylphenylcarbinyl acetate (25 g), geranium oil (10 g), linalool (30 g), benzyl acetate (35 g), benzyl alcohol (20 g), rosephenone (10 g), rhodinol (280 g), rose oil (10 g), \( \beta \)-ionone (50 g), benzyl salicylate (40 g), cyclopentadecanolide (30 g), and guaiawood oil (50 g). As can be seen above, the furan compound plays a minor role in the creation of the fragrance of rose [88JAP(K)63313719]. Furanones
Furans have been used as UV absorbents in cosmetics and plastics, by effectively absorbing UVA light 〈90JAP(K)02164817〉.

\[
\begin{array}{c}
\text{(117) } R = H \\
\text{(118) } R = \text{OC}_{1-4} \text{alkyl}
\end{array}
\]

Tetrahydrofurans (119) and (120) have been used as additives in perfumes to create a citrus-like floral aroma 〈87JAP(K)62270573, 89JAP(K)01261384〉. Similarly, tetrahydrofuran (121) has been added to perfumes in Russia. Unfortunately, no data regarding the aroma of compound (121) was provided 〈85URP1169971〉.

\[
\begin{array}{c}
\text{(119) } R = \text{Et, } R^1 = \text{Me or Eth} \\
\text{(120) } R = \text{vinyl, } R^1 = H
\end{array}
\]

A large number of papers have appeared in the last 12 years regarding the search for suitable analogues of Ambrox (122), which is reported to be major compound responsible for the woody scent with unique fixative properties indicative of the ambergris-type odorants 〈B-82MI 208-04〉. Ambrox (122) is presumably formed from the oxidation of (−)-ambrein (123), which is present in the gut of the blue sperm whale Physeter macrocephalus L. 〈90PAC1377〉. The need in the perfume industry for ambergris-type odorants, coupled with the almost worldwide ban on whaling has led to a plethora of papers related to Ambrox (122) and derivatives thereof. Ambrox (122) and tetrahydrofurans (124) and (125) have been produced by the microorganism Hyphozyma roseoniger. The latter two compounds have demonstrated an ambergris-type odor 〈86SAP8504306, 89USP4798799〉. Russian workers have prepared tetrahydrofuran (126) and used it in perfume solutions 〈83URP1049490〉. Finally, an elegant enantioselective total synthesis of (−)-9-epi-ambrox (127) has been achieved by Paquette and Maleczka using an anionic oxy-Cope rearrangement as the key step in the synthesis 〈91JOC912〉.

2.08.2.11 Pharmaceuticals

A wide variety of pharmaceuticals have been prepared which incorporate a five-membered ring containing one oxygen atom. A number of compounds have been reported which contain a furan
ring. Ranitidine (128) has been mixed with either tartaric or citric acid and complexed with bismuth(III) to provide salts which are very effective for the treatment of gastrointestinal disorders \(90\text{BRP2220937}, 93\text{MIP9317679}, 93\text{EUP533281}\). It has been reported that the antimicrobial activity of a variety of drugs can be extended beyond the expected shelf life when the drugs are mixed with furan (129) and a carrier solvent comprising of propylene carbonate and/or ethylene carbonate \(92\text{USP5122301}\). Some 5-substituted-2-furoic acid derivatives (130)–(132) have shown some pharmaceutical potential. Thus, furan (130) has exhibited antiinflammatory and analgesic properties \(84\text{EUP123546}\), furan (131) was effective as an antiseborrhea agent via a topical application \(92\text{GEP(O)4033563}\), and furan (132) was very useful as a snake bite antidote. The latter furan (132) was effective when topically applied onto the hemorrhages caused by various snake venoms in mice \(82\text{USP4347255}\). Interestingly, polysilasesquioxane (133) has demonstrated useful antitumor properties \(85\text{JAP(K)60169390}\), while \(N^1\)-(2-furanyl)-5-fluorouracil (134) has been shown to be useful for the treatment of basaloma \(91\text{URP1697814}\).

Furyl sulfonic acid (135) was isolated from earthworms \((Lumbricus rubellus)\) and found to be useful as an anticoagulant, a blood platelet aggregation inhibitor, an ulcer inhibitor, and a vasconstriction inhibitor. Thus, furan (135) showed a 100% inhibition of collagen-induced blood platelet aggregation in human blood at a concentration of \(1.1 \times 10^{-4}\text{M} \quad 88\text{JAP(K)63005088}\). Furano-germenone (136) was isolated from a ginger extract and found to be an excellent antiulcer agent. Thus, when furan (136) was given orally to mice \((500\text{ mg kg}^{-1})\) and the mice immobilized, placed in water and subjected to stress, gastric ulcers did not appear \(86\text{JAP(K)61227523}\). Donetidin (137) has been shown to be an effective agent against gingivitis or periodontitis by topical administration to gingival tissues in the mouth. Donetidin is believed to act as a H2 histamine antagonist \(93\text{MIP9320815}, 94\text{USP5294433}\).

A steroid and three penicillin derivatives containing a furan ring have exhibited some interesting properties. The Shering Corporation has reported that the steroid derivative (138) possessed greater antiinflammatory activity than Valisone (139) in the croton oil ear edema test in mice \(84\text{USP4472393}\). The stability of amoxicillin (140) was enhanced by treatment of (140) with furfural to give furan derivative (141). The bactericidal activity was not affected by the addition of the furfural moiety \(82\text{USP4327105}\). Furans (142) and (143) are reported to be improved oral cephalosporin-type antibiotics when administered at the rate of 100–3000 mg d\(^{-1}\) \(85\text{EUP(O)3500090}\). The final three compounds containing a furan ring also possess two or more complex heterocyclic rings. Janssen has patented both barmastine (144) and the citrate salt of noberastine (145) as antihistaminic agents \(85\text{EUP144101}, 92\text{EUP464927}\). The citrate salt of noberastine (145) exhibited superior light stability compared to noberastine and noberastine dimaleate. The hydrochloride salt
of furan (146) was reported to prevent ventricular tachycardia or ventricular fibrillation in animals at 0.5 mg kg\(^{-1}\). The compound was administered by preparing a capsule containing furan (146) (70 parts), mannitol (300 parts), corn starch (450 parts), lactose (200 parts), calcium stearate (10 parts), and hydroxypropyl cellulose (30 parts) \(<87\text{EUP209089}\>.

Two lactones have shown promise in the pharmaceutical industry. \(\gamma\)-Butyrolactone (147) and its salt was reported as an allergy inhibitor showing very little side effects \(<85\text{AP(K)60011415}\>\). Etoposide diethylphosphate (148) was effective for the treatment of small cell lung cancer and refractory testicular tumors. The diethyl ester lost very little potency over an eight-week period when heated to 50 °C \(<93\text{EUP537555}\>\). Interestingly, the prodrug etoposide 4-phosphate (149) can be delivered to a tumor site by the administration of a tumor-specific antibody–enzyme conjugate. Thus, mice with H3347 tumors were treated with an alkyl phosphatase enzyme covalently linked to the monoclonal antibody L6.96.5 through a thioether linkage followed by etoposide 4-phosphate (149). Six out of eight mice showed complete tumor regression and the prodrugs were apparently less toxic than the alkylated drugs \(<89\text{EUP302473}\>\). The half-amide : half-amide copolymers obtained from ethylene and maleic anhydride derivatives \((a : b = 1 : 2\text{–}5\) decreased the cytotoxic side effects of adriamycin (150). No lethality in mice was shown after 30 d when the mice were treated with 1700 mg of (151) per kg
of mouse concomitantly with 21 mg of adriamycin (150). Mice treated with 21 mg kg\(^{-1}\) of adriamycin died within 5 d in the absence of the co-polymer (151) \(\langle 90\text{EUP393575} \rangle\).

\[
\begin{align*}
\text{(147)} \\
\text{(148) R}^1 = \text{Et} \\
\text{(149) R}^1 = \text{H} \\
\text{(150)} \\
\text{(151)}
\end{align*}
\]

Since the report in 1986 that 3’-azido-3’-deoxythymidine (AZT, now called zidovudine) (152) was effective against human retroviruses \(\langle 86\text{GEP03608606} \rangle\), a plethora of ribonucleoside derivatives have been prepared and their pharmaceutical properties studied and reported. Only a few representative examples (152)–(164) are discussed here; space limitations do not allow for a comprehensive overview.

Over 195 patents have been filed since 1986 in which zidovudine (152) is mentioned. Potent side effects preclude the widespread use of zidovudine against the AIDS virus. In addition to having activity against the AIDS virus, zidovudine has activity against the feline leukemia virus and gram-negative bacterial infections \(\langle 86\text{EUP199451}, 86\text{EUP217580} \rangle\).

Alavudine (153), sorivudine (154), and stavudine (155) possess antiviral activity \(\langle 88\text{EUP254268}, 88\text{EUP273277}, 91\text{EUP439117} \rangle\). In addition, monoclonal antibodies to sorivudine (154) have been prepared by the hybridoma method and used in radioimmunoassays and enzyme-linked immunosorbent assays for detecting (154) \(\langle 91\text{EUP439117} \rangle\). Fialuridine (156) has exhibited very good activity against herpes infections when given concomitantly with acyclovir \(\langle 92\text{MIP9209287} \rangle\). Fialuridine (156) and flacitabine (157) were effective for the treatment of hepatitis B infections \(\langle 93\text{EUP565412} \rangle\). Thus (156) at 0.1 mg kg\(^{-1}\) decreased the hepatitis B viral DNA serum levels by 88% in patients. The triphosphate analogue of compound (158) showed good activity against human and Woodchuck hepatitis viruses \(\langle 93\text{USP5246924} \rangle\). The geminally substituted difluoro compound gemcitabine (159) was active against the herpes simplex virus \(\langle 84\text{RBP2136425} \rangle\), while the 2’,3’-dideoxy derivative zalcitabine (160) was active against the HTLV-III B virus \(\langle 89\text{EUP31110} \rangle\). Purine derivatives (161) and (162) exhibited anticancer and anti-HIV activity, respectively \(\langle 92\text{MIP9210198}, 93\text{MIP9314013} \rangle\). Compound (163) has been used successfully in combination with other drugs against strains of HIV-I which are resistant to reverse transcriptase inhibitors such as zidovudine, pyridinone, and foscarinet. Combinations of drugs were found to be more effective than the drugs used singly \(\langle 94\text{MIP9402149} \rangle\). Finally, it has been shown that a mixture of compound (164) and uracil effectively delivers 5-fluorouracil to cancer tissues in warm-blooded animals \(\langle 82\text{USP4328229} \rangle\).

A mixture of alfavuzosin hydrochloride (165) and diltiazem (166) act synergistically as an effective antihypertensive agent. Thus, rats treated with combination of 30–160 mg of diltiazem and 0.1–10 mg of alfavuzosin showed a decrease in blood pressure which was more than that shown by the drugs alone \(\langle 86\text{FRP2570275} \rangle\). Alfavuzosin hydrochloride (165) has also reduced the pressure at the neck of the urinary bladder by 44% in patients with neurological dysuria \(\langle 86\text{EUP204597} \rangle\) and stimulated hair
growth \(<88\text{BRP2197589}\). A hair-growth lotion contained alfuzosin hydrochloride (0.3 g), 13-cis-retinoic acid (0.025 g), ethanol (95 g), and propylene glycol (4.675 g). A formulation of amiprilose hydrochloride (167), cellulose, starches, and magnesium stearate provided good antirheumatic activity. A preferred dose of 2–200 mg kg\(^{-1}\) day\(^{-1}\) of amiprilose hydrochloride is recommended \(<89\text{JAP(K)01042436}\).

Elfamycin (168) is an antibiotic produced by \textit{Streptomyces lactamdurans} NRRL 3802 and possesses growth promoting activity. A suitable feed additive was formulated by adding the sodium salt of efrotomycin (735 mg) in ethanol (5 ml) to corn cob grits (8,265 g) followed by solvent evaporation and a coating of the solids with 10\% tristearin (glyceryl tristearate) \(<88\text{SAP706440}\).

A dental cement has been prepared by mixing an acrylic acid–maleic acid copolymer 7500 (44 parts), water (44 parts), and tetrahydrofuran-2,3,4,5-tetracarboxylic acid (169) (12 parts). This mixture (1 g) when mixed with dental cement powder (1.4 g) had a setting time of 4–6 min and a crushing strength of 1490 kg cm\(^{-2}\) as compared with 4–8 min and 700 kg cm\(^{-2}\) for regular cement.
2,5-Dimethoxy-2,5-dimethyl-2,5-dihydrofuran (170) has been used as a disinfectant. Furan (170) was active against *Staphylococcus aureus, Pseudomonas aeruginosa,* and *Candida albicans* in minimum inhibitory concentrations of 250, 1000, and 1000 ppm, respectively. The lignin derivative (171), when given orally to mice at 30 mg kg⁻¹, showed a 64% inhibition of gastric secretion. Finally, the bis(tetrahydrofuran) containing compound (172) exhibited anticancer activity against the murine leukemia cell L1210 with an ED₅₀ of 0.5 µg ml⁻¹. Mice treated with compound (172) at levels of up to 0.5 g kg⁻¹ d⁻¹ showed no lethal side effects.

### 2.08.2.12 Miscellaneous

Compounds (173)–(176) have been added to nitrogen fertilizers, at 2–4%, to inhibit nitrification. During the manufacturing of the fodder additive furan (177) explosive by-products are formed, which can be removed by a 20% NaOH wash. Furan (178), prepared by the asymmetric reduction of [1-²H]-furfural, has been used as a precursor in the synthesis of both (R)- and (S)-[2-²H]-glycine.

Maleic anhydride (72) when mixed with triphenylbismuthine in a ratio ranging from 1:1 to 1:1.5 provided a curing catalyst for a propellant composite comprising an oxidizer, isocyanate curing agent, and a hydroxy-terminated polymer binder. The resulting composite showed improved modulus and/or stress values for use with propellants.

A peptide, conjugated using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride to a maleic anhydride-derived lysozyme, provided a polyclonal antibody with increased cross-reactivity with maleimidobenzoyl-N-hydroxysuccinimide ester-derived hemocyanin. A sandwich enzyme immunoassay for rabbit IgG has been developed. Thus, the enzyme labeling of a goat antibody to rabbit IgG with β-D-galactosidase was possible using the crosslinker N-(γ-maleimidobutyryloxy)succinimide.

### 2.08.3 BENZOFURAN DERIVATIVES

#### 2.08.3.1 Agrochemical Bioregulators

There is a great deal of activity in the synthesis of 2,2-dimethylbenzofurans such as Carbofuran (179). Carbofuran is a systemic insecticide active against flies, aphids, larvae, and mosquitos.
A similar example is the insecticide Benfuracarb (180) \(\langle 83\text{JAP}(K)5826804\rangle\). Derivative (181) is a water-soluble analogue of Benfuracarb active against bean aphid, southern armyworm, and tobacco caterpillar among others \(\langle 86\text{USP}4605667\rangle\). Hydroxybenzofuran (182) and its 3-keto derivative are components in a mixture that regulated plant growth \(\langle 84\text{MIP}8403419\rangle\). Urea (183) gave control of barnyard grass \(\langle 88\text{EUP}293839\rangle\).

\[
\begin{align*}
\text{CONHMe} & \quad \text{O} \\
\text{O} & \quad \text{CONHMe} \\
\text{O} & \quad \text{CONHMe} \\
\text{O} & \quad \text{CONHMe}
\end{align*}
\]

(179) \(R = \text{Pr}, R' = \text{CH}_{2}\text{CH}_{2}\text{COEt}\) 
(180) \(R = \text{Me}, R' = \text{CONHCH}_{2}\text{COH}\) 
(181) \(R = \text{Me}, R' = \text{CONHCH}_{2}\text{COH}\) 
(182) 
(183)

Several 3,3-dimethylbenzofurans exhibit pesticidal activity. Ethofumesate (184) is an herbicide for the control of peas, mustard, flax, corn, oats, and rye grass \(\langle 89\text{USP}4587259, 85\text{USP}4550121\rangle\). Hemiacetal (185) gave high preemergent control over four weeds without damaging rice seedlings \(\langle 92\text{JAP}(K)04368376\rangle\). Triflate (186) gave 100% preemergent control of several weeds in the protection of rice crops with less damage \(\langle 92\text{JAP}(K)04235178\rangle\).

\[
\begin{align*}
\text{MeSO}_3 & \quad \text{O} \\
\text{O} & \quad \text{CF}_3\text{SO}_3 \\
\text{O} & \quad \text{OH} \\
\text{O} & \quad \text{NH}_{2}\text{SO}_2\text{NMe}_2
\end{align*}
\]

(184) 
(185) 
(186)

Triazole (187) acts as a plant growth regulator found to be effective in reducing the height of summer rape \(\langle 83\text{GEP}3139250\rangle\). Hyrazide (188) and a related diazine were found to be more effective against spotted spider mites (on bean) than parathion \(\langle 86\text{USP}4587259, 85\text{USP}4550121\rangle\). Rotenone (189) is a natural insecticide found in derris root \(\langle B-71\text{MI}208-01\rangle\). Oxime (190), derived from \(\beta\)-rotenone, and another analogue (191) have analgesic activity in addition to insecticidal activity \(\langle 88\text{JAP}(K)63243087, 88\text{JAP}(K)6383088\rangle\).

\[
\begin{align*}
\text{Bu} & \quad \text{OH} \\
\text{N} & \quad \text{N} \\
\text{N} & \quad \text{H}_2\text{N}\text{CO}_2\text{Me}
\end{align*}
\]

(187) 
(188) 
(189) 
(190) 
(191)

In 1976, Merck, Sharp, and Dohme discovered the Avermectins, a class of macrolides which contain a benzofuran unit as part of the macrolide ring \(\langle 90\text{PAC}1231, 91\text{CSR}211\rangle\). A dihydro-derivative, Ivermectin (192) \(\langle 22,23\text{-Dihydro}\text{avermectin} B_{1a}\rangle\), has emerged as one of the most useful anthelmintics currently available \(\langle 77\text{GEP}(O)2717040, 89\text{CBR}692\rangle\). It kills a range of parasites in cattle, sheep, pigs, and horses and also has insecticidal activity against lice and mites. Its 13-\text{epi} isomer is reported to be just as potent but less toxic \(\langle 92\text{JMC}3873\rangle\). Closely related are the milbemycins, many of which
exhibit similar biological activity. One example discovered in this class is Nemadectin α (193), isolated from *Streptomyces cyanogriseus* ssp. noncyanogenus <87CC402>. The development of milbemycin analogues is a very active area and has been reviewed <91CSR21>. Variations include RNHaR-CH₃CH₂S—<91EUP430884> or aryl ether <91EUP444964> substituents at the 13-position (where the disaccharide is located in Ivermectin). Another example (13-F, 23-C==NOH) prevented the pupation of housefly larvae <91EUP423445>.

Triazine (194) is a herbicide useful in protecting rice paddies <87EUP216259>. Another example (195) gave complete control of *Cyperus serotinus* and *Echinochloa crus-galli* without crop damage <89JAP(K)01246279>. Hydroxybenzofuran (196) is a preemergent herbicide active against *Echinochloa crus-galli*, *Monchoria vaginalis*, and other weeds <90JAP(K)0477487>. Phenoxybenzofuran (197), active against nine weeds, is a postemergent herbicide used to protect rice <92BRP2253847>.

Dibenzofuran (198) protected paprika from damage by *Botrytis cinerea* <90GEP(O)3825840>. Another dibenzofuran (199) is a herbicide that gave 85% control over *Galium aparine* <91GEP(O)4021503>. R-11 (200) is best known as an insect repellant, though the original work also mentions utility as a plasticizer and a bactericide <57USP2795592>.

Lactone (201) is an antifungal compound active against yeast and also has antileukemic activity <91PHA742>. Quinone (202) is a bactericide <91CCC706>. Phenoxyphthalide herbicide (203) gave 95–100% preemergent herbicidal effect on five weeds <87EUP306095>. Pyrimidine derivative (204) gave
preemergent and postemergent control of barnyard grass, pigweed, goosefoot, and umbrella sedge <93JAP(K)0592971>.

Tetrachlorophthalide (205) has been used in a fungicidal composition that controlled *Piricularia oryzae* on rice <83JAP(K)59154506>. Dimethylhexahydrophthalide (206) is an useful insect repellant. With its tetrahydro analogue, it was found to be twice as effective against mosquitoes as *N*)N-diethyl-3-methylbenzamide (DEET) <91CP2022491>. Compound (207) is an agrochemical fungicide which gave control of *Rizoctonia solani* <89EUP3i5502> and is a synergistic antimicrobial which controlled *Piricularia oryzae* in rice <91JAP(K)03284601>.

2.08.3.2 Dyes and Photographic Materials

Phthalide derivatives are of major importance in the dye industry, particularly in the area of recording material color formers. Pressure-sensitive carbonless copy paper and thermal recording paper are typical applications. Five principal structural classes have been developed extensively: the xanthen e dyes (fluorans (208)), 3,3-diarylphthalides (209), spirofu renes (210), 3,3-bis(diarylethylene)phthalides (211), and 3-substituted phthalides <84MI 208-03>. Some of these structures are common to many familiar acid/base indicators, dyes, biological stains, or laser dyes such as fluorescein (212) and phenolphthalein (213) <B-91MI 208-07>.

Fluoran (214) gave a dark violet image on contact with silica gel and a black image on bisphenol
A (84JAP(K)5915452). Fluroan (215) (93JAP(K)05221142) and its “acyclic” counterpart (216) (92JAP(K)04191093) have both been patented for use in recording materials. Diaryl phthalide (217) and spiroflourene (218) are electron-donating couplers in thermal and pressure-sensitive papers (86JAP(K)6122076).

![Chemical Structures](image)

Monosubstituted phthalide (219) was used in a pressure-sensitive copy paper (93JAP(K)05177827), while disubstituted phthalide (220) was used in thermal recording paper (88JAP(K)6362777). Indole (221), a less common example, gave an intense yellow color in a composition used for preparing pressure-sensitive copy paper (91EUP437185). Phthalide (222) is a color former in heat-sensitive recording materials (88GEP3727201). Compound (223), which incorporates a benzophenylene system, develops a grey–green color in contact with a clay-coated developing layer (88BRP2192637).

![Chemical Structures](image)

Bis(sulfobenzofuranyl)biphenyls such as (224) have been used as fluorescent brighteners in stable bleach solutions (90EUP395588). Some examples (R = H) survived much longer than stilbenedisulfonic acid derivatives (89GEP(O)3900651). Derivatives of polyheterocycle (225) were used to whiten polyester textiles (83GEP(O)3311092). In combination with zinc salicylate and 2-phenylindole,
bis(phthalide) (226) was used as a dye coating on facsimile paper \(<90\text{EUP}395588\)\. Bis(oxepane) (227) has been patented for use in recording materials \(<89\text{JAP(K)}01211591\)\. 

\[
\begin{align*}
\text{(224)} \quad R &= \text{H or Me} \\
\text{(225)} \quad \text{(226)} \\
\text{(227)} \\
\end{align*}
\]

Benzodifurandiones (228) and naphthodifurandione (229) \(<92\text{EUP}574118\) are polyester dyes. Compound (228; \(R = \text{H, } R' = \text{O-allyl}\) dyed aromatic polyester dyes a fast, bright red \(<86\text{EUP}182507\)\, while another example (\(R = \text{Et, } R' = \text{NH}_2\) dyed polyesters blue \(<93\text{EUP}575056\)\. Indandione (230), of similar structure, is a dye in a dye-diffusion thermal transfer printing process \(<93\text{EUP}535842\)\. Benzofuranquinones find application as dyes in liquid crystal mixtures. Hydroxyquinone (231) had high dichroic property with good photoresistance \(<92\text{JAP(K)}04290880\)\. Analogue (232) was developed as a dichroic dye useful for liquid-crystal displays in electronic devices \(<91\text{JAP(K)}03264575\)\.

\[
\begin{align*}
\text{(228)} \\
\text{(229)} \\
\text{(230)} \\
\text{(231)} \\
\text{(232)} \\
\end{align*}
\]

Benzyldibenzofuran (233) was used in a thermal recording material \(<92\text{JAP(K)}0485078\)\. Nitroso-dibenzofuran (234) is a dye intermediate \(<89\text{JAP(K)}01193261\)\. A dialkylaminodibenzofuran has been employed as a charge-transporting agent in electrophotographic photoconductors \(<90\text{JAP(K)}02178670\)\. Bisazo compound (235) is a charge-generating agent in an electrophotographic photoreceptor \(<93\text{JAP(K)}05173344\)\. Diphenylisobenzofuran (236) and several substituted derivatives have also been used in this way \(<88\text{JAP(K)}6360453\)\. Bibenzofuranyl (237) is used as a dye in thermal recording material \(<93\text{JAP(K)}05294977\)\.

Benzo[\(\text{f}\)]uranone (238) is part of a color developer for thermal recording materials which colors at higher temperature and are particularly good for multicolor recording. The compound is an alter-
native to bisphenol A (88JAP(K)6317083). Naphtho[h]furan (239) is used to prepare presensitized lithographic plates (93JAP(K)0534904). Tri(t-butyl)isobenzofuran (240) has been patented as a photochromic substance useful in preparing optical recording materials (87JAP(K)6220188).

2.08.3.3 Polymers

Phthalide (241) has been used as an additive used to prepare polyesters with low molten viscosity (91JAP(K)0320089). Phthalic anhydride (242), prepared by the oxidation of o-xylene, is of major importance to the chemical industry with 1992 production over 400000 tonnes (93CEN38). It is used as a monomer in the preparation of alkyd resins (a polyester with glycerol and other polyols) and thermosetting polymers (with maleic anhydride and polyols). Another important application is in the production of dioctyl phthalate (243), which is used as a plasticizer for PVC (1991 production, 123000 tonnes). Over 400 references pertaining to the use of phthalic anhydride in polymer compositions have appeared since 1982. Tetrabromophthalic anhydride (244) has been used to prepare flame-retardant bisphthalimides as polymer additives (90JAP(K)02145568).

Trimellitic acid anhydride (245), which has an additional carboxyl group available for cross-
linking, has also found wide application in the polymer area \(<91\text{JAP(K)0361954}\). In addition, it is also used to prepare bisanhydrides useful as polyimide monomers. Pyromellitic dianhydride (246) has been used often, for example, in the preparation of membranes for liquid separation \(<91\text{EUP418883}\).

\[
\begin{align*}
\text{(245)} & \quad \text{HO}_2\text{C} & \quad \text{O} \\
\text{(246)} & \quad \text{O} & \quad \text{O}
\end{align*}
\]

A series of hydro- and bicyclic derivatives of phthalic anhydride have been employed as hardeners in epoxy resins used for optical recording disks \(<88\text{JAP(K)6383701}\), and in a urethane composition to prepare a wire coating with good insulating, thermal shock resistance and adhesion \(<86\text{JAP(K)61200164}\).

A wide variety of bisanhydrides have also been popular as monomers, especially for polyimide preparation. A particularly interesting example (for the purposes of this review) involved combination of bisanhydrides such as (247) and (248) with benzofuranamine (249). The resulting polyimides had good glass transition temperatures and solvent resistance \(<88\text{EUP264836}\). Fluorenic bisanhydride (250) has been developed as a polyimide monomer \(<91\text{USP5061809}\). There are many examples of the use of bisanhydride (248). One example, in which the anhydride was polymerized with an aminosiloxane, gave a polyimide with good adherence to silicon wafers \(<90\text{MI 208-05}\). A hexabromo derivative of (247; \(R = S, \text{CH=CH, others}\)) has been used in ABS plastic to improve flame retardancy \(<93\text{EUP549021}\).

\[
\begin{align*}
\text{(247)} & \quad R = O \text{ or } S \\
\text{(248)} & \quad R = \text{C}=\text{O}
\end{align*}
\]

\[
\begin{align*}
\text{(249)} & \quad \text{H}_2\text{N} & \quad \text{NH}_2 \\
\text{(250)} & \quad \text{O} & \quad \text{O}
\end{align*}
\]

More elaborate examples of bisanhydrides include (251; \(R = \text{CPh}_3\)) which, when polymerized with aryldiamines, gave polyether-polyimides useful for the manufacture of heat and moisture resistant optical disks \(<90\text{JAP(K)0251527}\). Another series (\(X = \text{spirocyclohexyl or } p\text{-C(Me)}_2\text{PhC(Me)}_2\)) were used to prepare heat-resistant polyether-polyimides that are useful for electronic parts \(<89\text{JAP(K)0120637}\). Bisanhydride (252), prepared from styrene and maleic anhydride, is useful as a hardener for epoxy resins, and as a polyester and polyimide monomer \(<91\text{JAP(K)03264574}\).

\[
\begin{align*}
\text{(251)} & \quad \text{O} & \quad \text{O} & \quad \text{O} \\
\text{(252)} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

Trimellitic acid anhydride (245) was used to prepare sulfone (253). Not surprisingly, polymers prepared with this monomer have high thermal stability \(<89\text{EUP315592}\).

 Peroxide (254) was developed as a cross-linking and vulcanization agent and also serves as a vinyl polymerization initiator \(<90\text{JAP(K)02117670}\). Pseudoester (255) is a photopolymerization initiator \(<89\text{JAP(K)01180587}\).

Phenolphthalein (213) and its derivatives have found application in the polymer area. Phenolphthalein itself (213) and substituted derivatives were polymerized with 2,6-dichlorobenzonitrile to form heat-resistant polycyanoaryl ethers \(<89\text{JAP(K)01225631}\). A tetrabromo derivative (256) was polymerized with epichlorohydrin to form flame-retardant epoxy resins. The phthalide-derived
polymers had better flame retardancy than those formed from 3,3',5,5'-tetramethylbiphenol A \( \langle 84 \text{JPS(A)1707} \rangle \). The fluorinated derivative (257) has enhanced solubility in fluoropolymers making it a useful additive in coating materials \( \langle 93 \text{JAP(K)0543569} \rangle \). An alkylated phenolphthalein (258) was polymerized with tere- and isophthaloyl chlorides to form a polyester \( \langle 87 \text{USP4652608} \rangle \). A phenolphthalein homologue (259) has been used to prepare polyurethanes in reaction with 2,4-toluenediisocyanate \( \langle 88 \text{MI 208-08} \rangle \). Compound (260) has been used to prepare polyamides and polyimides which form flexible, transparent films \( \langle 94 \text{JPS(A)423} \rangle \).

Chlorophthalide (261) undergoes homopolymerization to form an interesting polyphthalide (262) \( \langle 90 \text{MAC1477} \rangle \). The monomer was prepared in two steps from phthalic anhydride and biphenyl followed by reaction with SOCl\(_2\). Metal halides such as SbCl\(_3\) or InCl\(_3\) were used as catalysts for the Friedal–Crafts polymerization \( \langle 84 \text{MI 208-04} \rangle \). A bifunctional example (263; \( R = \text{PhOPh (para), PhSPh (para), dibenzofurandiy} \)) was highly reactive in electrophilic polymerization and could also be polymerized with bisphenol A \( \langle 90 \text{DOK(311)127} \rangle \).

Several arylidenephthalide derivatives have been used in various polymers. Benzalphthalide itself (264) was found to act as a UV stabilizer in aromatic polyesters and polycarbonates
Benzodifuran (265) was reacted with 4,4’-(diaminophenyl)ether and a diacid to form a polyimide–polyamide copolymer \( \langle 90 \text{USP}4918153 \rangle \). Bisbenzal phthalide (266; \( R = \text{CO-PhOPhCO} \) (para)) was condensed with diamines to give a variety of polyimides \( \langle 83 \text{JPS(A)}1241, 84 \text{JAP(K)}5927884 \rangle \).

Methylene-1,4,6-trioxaspiro[4,4]nonane (267) (BMTN), an orthoester synthesized from phthalide and epichlorohydrin, underwent radical ring-opening polymerization to form an aromatic polyketoester (268) with high thermal stability \( \langle 83 \text{JPS(A)}353 \rangle \).

Despite its similarity to styrene, benzfuran (269) does not see extensive application in the polymer area. It has been used as an electron-rich vinyl monomer \( \langle 86 \text{PB405} \rangle \) and copolymerized with maleic anhydride (73) \( \langle 82 \text{MI}208-05 \rangle \). It appears in a review on electroanodic polymerization \( \langle 87 \text{CLY673} \rangle \).

Interest in the preparation of conducting polyphenylenes led to the development of poly(4,7-benzofuran vinylene) (270). It was prepared from 4,7-dimethylbenzofuran (271) and was found to have a band gap of 2.76 eV. The corresponding thiophene polymer had a slightly larger band gap of 2.92 eV \( \langle 94 \text{JPS(A)}65 \rangle \).

Isobenzofuran (272) (benzo[c]furan) is a reactive polyene and is unstable at room temperature. There are no examples of a poly(isobenzofuran). Two related species, the theoretical bis(isobenzofuran) (273), and napthobifuran (274) have been used to prepare an intriguing Diels–Alder ladder polymer (275) \( \langle 92 \text{MAC2829} \rangle \).

Polymerization of \( o \)-cyanobenzaldehyde has been reported to give poly(nitriloisobenzofuran-1,3-diyl) (276), which has good thermal stability. The proposed structure is startling, given the instability of isobenzofuran, particularly when electron-donating groups are present. A more plausible structure may be tautomer (277) \( \langle 82 \text{MI}208-06 \rangle \).

Bislactone (278) is a stabilizing agent used to improve the melt index of polypropylene \( \langle 93 \text{BRP2257140} \rangle \). Other 3-phenyl-2-benzofuranones (279) are useful polymer additives for their anti-
oxidant properties <93EUP543778>, for instance, in the manufacture of optical recording disks <86JAP(K)61138648>.

Diol (280) has been used as an alternative to bisphenol A in the preparation of thermoplastic polyethers with good fire- and heat-resistant properties <89EUP329029>. It has also been used as a comonomer with bisphenol A (281) in a polymerization with 4,4'-difluorobenzophenone <89EUP329029>.

Phenylbenzofuran (282) was used to protect polyphenylene ether resins against damage from UV radiation <87USP4665112>. As a nucleating agent, benzofuran-2-carboxylic acid (283) was found to improve the properties of an ethylene/4-methyl-1-pentene copolymer <84JAP(K)5919746>.

2.08.3.4 Pharmaceuticals

Hydroxybenzofuran (284) has found application in the treatment of melasma as a topical skin depigmentation agent <93EUP524108>. An isomer (285) has been used as a coupling agent for oxidative hair dyes <92EUP06549>. Acid (286), extracted from Cnidium monnierri, reportedly enhanced sexual activity in mice. It has been patented for use in the treatment of physical and mental stress <92JAP(K)0459733>.

Cloridarol (287) has use in the treatment of lipidemia and as an anticoagulant. It was found to be less toxic than the similarly active clofibrate <61GEPO3029421>. Benzyl derivative (288) is an inhibitor of leukotriene biosynthesis <88EUP295851>. Oxazolidine (289) is a promising hypoglycemic; it was found to lower blood sugar levels in obese mice. The benzofuran system was found to greatly enhance the activity of various alternative analogues, phenyl for example <91JMC1538>. A similar example (290) has been patented as an antidiabetic and hypolipemic <89EUP299620>. Ethyl ester (291) is an inhibitor of arachidonic acid-induced platelet aggregation, potentially useful in treating a variety of cardiac ailments <92JAP(K)04225972>.

A host of aroylbenzofurans have medical applications. Amiodarone (292) is an antiarrhythmic and antiischemia drug <85BE900138> and has also been patented as a component in a skin wrinkle cream <92USP5118707>. Analogues of Amiodarone are (293) <89USP4831054> and thiophene (294) <90MIP9002743> which have similar activity. Another example (295) is an antiarrhythmic which was superior to lidocaine in animal tests <90USP4975458>. Other benzofuran drugs have similar structures; benzbrumarone (296) is a uricosuric drug <57BE9553621>, while benzaron (297) is a capillary protectant <61USP3012042>. Compound (298) promotes the excretion of uric acid and is useful for
Furans and their Benzo Derivatives: Applications

Hydroxybenzofuran (301) is an estrogen inhibitor ⟨83GEP(O)4117512⟩. Quinolinones (302) and (303) are bone growth stimulants useful in the treatment of osteoporosis ⟨89JAP(K)01242585, 90EUP370760⟩. Sulfide (304) and its analogues are bladder control agents ⟨89EUP306226⟩. Ester (305) has been used to treat dermatological conditions ⟨88FRP2614618⟩, while the triazinyl derivative (306) finds use as a sunscreen ⟨93EUP570845⟩.

Several synthetic polyheterocyclic compounds are angiotensin II antagonists. Bromobenzofuran (307) is reportedly useful in the treatment of cognitive disorders ⟨92EUP514216⟩. Other examples are (308) ⟨92EUP520724⟩ and (309); the latter is potentially useful for the treatment of coronary and circulatory diseases ⟨93EUP546449⟩.

Medical applications of a series of amine benzofuran derivatives have been explored. Brofaromine (310) has been developed as a nootropic for the treatment of degenerative nervous system diseases ⟨92EUP499586⟩. Etofuradine (311) is an antitussive and antihistamine ⟨68BEP704705⟩. Coumazoline
Furans and their Benzo Derivatives: Applications

(301) R = H, R1 = OH

(302) R = CH2CH2NMe2, R1 = H

(303) R = CH2CH2NMe2, R1 = H

(304) MeO

(305) R = H

(306) R = CH2CH2NMe2

(307) R = H

(308) R = CH2CH2NMe2

(309) R = H

(312) is a peripheral vasoconstrictor useful as a nasal decongestant ⟨72GEP(O)2203373⟩, while the related faroxan (313) exhibits K channel blocking activity for the treatment of diabetes ⟨92MIP9205171⟩. Prifuroline (314) is an antiarrhythmic with low toxicity ⟨86AF1761⟩. Pyridorine (315) is an antidepressant ⟨74GEP(O)2423835⟩ as is befuraline (316), which also possesses analgesic properties ⟨74GEP(O)2240665⟩. Becliconazole (317) is antifungal and antifungal with activity against Staphylococcus aureus and Pseudomonas aeruginosa ⟨88EUP257171⟩.

Carocainide (318) is a cardiac drug that reversed ouabain-induced ventricular tachycardia in dogs ⟨78GEP(O)2730593⟩. Enadoline hydrochloride (319) is an analgesic that also has diuretic and cerebrovascular activity ⟨90EUP393696⟩. In mice, amide (320) was found to protect the liver from acetaminophen-induced damage ⟨93JAP(K)05320169⟩.

Many carboxylic acid derivatives of benzo furans have important activity. Benfurodil hemi-succinate (321) is a cardiotonic and vasodilator ⟨65FRP1408721⟩, while sulfanamide (322) and furacrinic acid (323) are antihypertensives ⟨72GEP(O)2227423, 89MI 208-05⟩. A pyridinyl derivative (324) (sodium furegrelate) is an inhibitor of thromboxane synthetase ⟨83EUP6952⟩. Several compounds have analgesic activity. Raxofelas (325), for example, is an antiinflammatory and antioxidant ⟨90BRP2221463⟩. Sodium tifurac (326) was found to be more effective than aspirin in mice ⟨85EUP132130⟩. Furprofen (327) is an analogue of the well-known Ibuprofen ⟨82GEP(O)3026402⟩.
Furans and their Benzo Derivatives: Applications

(310)

(311)

(312)

(313)

(314)

(315)

(316)

(317)

(318)

(319)

(320)

(321)

(322)

(323)

(324)

(325)

(326)

(327)
Great interest has been taken in khellin (328) and its derivatives. Khellin, which has lipid-altering activity and is a coronary vasodilator, is isolated from the seeds of Ammi visnaga (83JOC3863). Like khellin, iprocrolol (329) is a coronary vasodilator (71FRP2077694). Analogs such as butocrol (330) are antiarrhythmics and effective local anesthetics (75FRP2232311). Azaspirium chloride (331) is a khellin derivative that offers the advantage of water solubility (71GEP(O)2019570). Compound (332) (83USP4412071) and bis(khellin) (333) (90MIP9002129, 90JMC2685) have both been developed for the treatment of atherosclerosis.

![Chemical structures of 328, 329, 330, 331, 332, 333, and 339](image)

Psoralen (334) and its derivatives exhibit a wide range of activity (86MI 208-04). Methoxsalen or xantotoxin (335) and ester (336), have been used in the treatment of psoriasis and other skin disorders (83SZP638978). The psoralen derivative (337) has been patented for the prevention and treatment of retroviral infections (HIV-1 or HIV-2) (93FRP2691629). Sulfonamide derivatives (338) show antimicrobial activity superior to methoxsalen (88JIC422). Trioxsalen (339) is a synthetic psoralen that offers skin protection against UVB erythema and is an orally active tanning and pigmentation agent useful in the treatment of vitiligo (59USP2889337).

![Chemical structures of 334, 335, 336, 337, 338, and 339](image)

The photochemical activity (phototoxicity) of several psoralen derivatives has potential application in several areas. Biotin derivative (340), for example, is a neoplasma inhibitor; it inhibited the growth of lymphocytes by 99% in the presence of near UV light (87MIP705805). Compounds (341) and (342) both displayed photochemical antibacterial activity (87MI 208-04). Benzopsoralen (343) is a DNA photoonent (86HCl1405).

Griseofulvin (344) is an antifungal antibiotic (89JAP(K)01258668). Phenyl analogues (345) have also been found to be active (92MI 208-06). Spirofurone (346) is an antiulcerative which gave 48% inhibition of gastric acid secretion in rats (79EUP3084); analogues (347) and (348) share this activity (89JAP(K)01246273, 89JAP(K)01246279).

The rifamycins, isolated from the fermentation broths of Streptomyces mediterranei, are an important class of antibiotics which have a naphtho[2,1-b]furan system as part of a macrolide. Rifamide (349) (Rifamycin B amide) was reported to be active against gram-positive bacteria and Mycobacterium tuberculosis (63BEP632770). Many analogues have been prepared, presenting a broad spectrum of antibiotic activity. An example is rifaximin (350), which incorporates a fused benzimidazole (81BEP888895). Another analogue (351) was more active against Mycobacterium
tuberculosis than rifampicin \textlangle K0310168 \rangle. Prepared analogs of Rifamycin S have been reported to lower blood cholesterol levels \textlangle 92EUP475896 \rangle.

Upjohn has developed two antineoplastic drugs that are analogues of CC-1065. Adozelesin (352) and carzelesin (353) show antileukemia activity in mice \textlangle 88MIP8804659 \rangle.

Pyridine (354) is a hypoglycemic shown to reduce blood glucose levels in starved rats \textlangle 91MIP9100862 \rangle. Piperidine (355) is an antihypertensive, psychotropic agent \textlangle 90EUP98413 \rangle.
Pyrrolidine (356) is an anticholinergic agent \(91\text{MIP}\,9110651\). Thioester (357) is an antioxidant, mucolytic and antieschismic agent which gave significant protection against carbon tetrachloride-intoxicated liver lipoperoxide formation in rats \(91\text{EUP}\,413668\). The D-form of amine (358) is a dopaminergic agent \(88\text{EUP}\,286515\). Bisbenzofuran (359) is an antinflammatory and analgesic; tested for the inhibition of edema in rats. It showed greater potency than Ibuprofen \(91\text{JAP(K)}\,03157383\).

Amides (360; \(R = \text{Bu}^n\) and \(R = \text{CH}_2\text{CH}_2\text{CH}_2\text{Ph}\)) are psychotropic drugs useful in the treatment of nerve and mental disorders such as schizophrenia, dystrophy, and others \(91\text{MIP}\,9117144, 92\text{JAP(K)}\,04364181\). An earlier example (361) was patented as an antiemetic for cancer chemotherapy patients \(89\text{EUP}\,314483\).

The antioxidant activity of 5-hydroxybenzofurans makes them useful in the inhibition of biochemical oxidations. Sulfide (362) is an inhibitor of leukotriene \(B_4\) biosynthesis \(90\text{BRP}\,2221680\). Long-chain alcohol (363) was found to be a better inhibitor of lipid autooxidation than vitamin E \(93\text{JAP(K)}\,05178848\). Alcohols (364) and (365) are antioxidants; the former tested against luminol-induced chemiluminescence \(90\text{EUP}\,398142\) and the latter in an \textit{in vitro} test against the oxidation of ethyl linolate \(89\text{JAP(K)}\,6388173\). Alkylated benzofuran (366) inhibited Fe–ADP–adriamycin complex-induced liposome oxidation \(90\text{JAP(K)}\,02121975\). A series of compounds (367) has been evaluated as inhibitors of leukotriene biosynthesis \(89\text{JMC}\,1006\). Two other examples have medicinal application: fluoride (368) is a cardiovascular and antiallergy agent \(88\text{EUP}\,273647\) and amine (369) is useful for the treatment of central nervous system disorders \(88\text{EUP}\,281261\).

In a study of structure–activity relationships, it was found that the (+)-enantiomer of (370) was responsible for its uricosuric activity \(87\text{CPB}\,3195\). Alcohol (371) and acid (372) are also diuretics \(89\text{JAP(K)}\,01246277, 92\text{CPB}\,2597\). Ketone (373) was developed for the treatment of brain injury \(87\text{USP}\,4654365\), while lactone (374) is a drug for the treatment of hypoxia \(87\text{USP}\,4654365\).

Cabnegrin A-I (375) and its regiosomer cabnegrin A-II are orally active antidotes against snake venoms, isolated from a South American plant. They are members of the pterocarpin (376) family \(83\text{EUP}\,8929\). Compound (377) is an aflatoxin analogue which has modest anticoagulant activity \(90\text{JIC}\,917\).

Rocaglamide (378) is a natural product isolated from the roots and stems of \textit{Aglaia elliptofolea} Meer. (Meliaceae). It displays antileukemic activity against P388 lymphocytic leukemia in mice and
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\[
\begin{align*}
\text{PhS} & \quad \text{HO} \quad \text{PhS} \\
\text{(362)} & \quad \text{(363)} & \quad \text{(364)} \\
\text{HO} & \quad \text{Pr}^1 & \quad \text{HO} \\
\text{alkyl} & \quad \text{alkoxy} & \quad \text{R} \\
\text{(365)} & \quad \text{(366)} & \quad \text{(367) R = alkyl or alkoxy} \\
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{F} \\
\text{HO} & \quad \text{HO} \\
\text{(368)} & \quad \text{(369)} \\
\end{align*}
\]

\[
\begin{align*}
\text{Me}_2\text{NSO}_2 & \quad \text{Cl} \quad \text{Cl} \quad \text{Cl} \\
\text{(370)} & \quad \text{(371)} & \quad \text{(372)} \\
\text{Cl} & \quad \text{Cl} \\
\text{(373)} & \quad \text{(374)} \\
\text{MeO} & \quad \text{PhCO}_2 \\
\text{(375)} & \quad \text{(376)} & \quad \text{(377)} \\
\end{align*}
\]
has in vitro activity against KB cell carcinoma \(82\text{CC1150}\). Several analogues derived from (378) have also been prepared and evaluated for their activity \(85\text{USP459414}\).

Oxyacetic acid derivative (379) was developed for use in treating brain trauma \(88\text{USP4769379}\). A similar ring system is a component in a new penicillin derivative (380), which was active against Staphylococcus aureus 209P \(92\text{JAP(K)04187689}\). Taziprinone hydrochloride (381) is an antitussive \(75\text{GEP(O)2518289}\).

\[
\text{\[378\]}\,\text{\[379\]}
\]

Kadsurenone (382) is a highly specific agonist of platelet-activating factor with a \(K_i\) of \(5.8 \times 10^{-8}\) M. It is found in the Chinese herb Piper futokadura (heifenteng) \(85\text{JAP(K)6097972, 86TL309}\). Similarly, active analogue (383) and other derivatives have been patented \(87\text{SAP8606273}\).

\[
\text{\[380\] R = N\text{-penicillinamide}}\]

\[
\text{\[381\]}
\]

Several prostaglandin analogues of PGI\(_2\) incorporate benzofurans, for example (384) and (385) \(87\text{JCS(P1)1825, 88MI 208-09}\). Another such derivative, beraprost (386), is an inhibitor of platelet aggregating factor \(82\text{EUP100449}\), and analogue (387) has antiluier activity \(87\text{EUP232776}\).

A series of Gossypol derivatives were tested for inhibitory activity of aldose reductase. Lactone (388) showed the best inhibition \(91\text{JMC3301}\). Clofurac (389) has analgesic, antipyretic activity and inhibits blood platelet aggregation, edema, and inflammation \(76\text{GEP(O)2608697}\).

The well-known phenanthrofuran alkaloids such as codeine, morphine, and heroin (390: R = Me, OH, and CH\(_3\)CO, respectively) are very important narcotic analgesics, heroin being famous for its abuse. Many derivatives have been developed as antinarcotics and/or appetite suppressants. Examples are (391) \(92\text{JAP(K)04342529}\) and (392) \(87\text{JAP(K)62283976}\). The morphine-like compound (393) had a high affinity for opiate receptors \(89\text{EJM385}\), while (394) had analgesic properties and was a narcotic antagonist \(89\text{URP869288}\).

A variety of polycyclic benzofurans have anticancer activity. Dibenzofuranol (395) \(88\text{EUP257701}\), quinone (396) \(92\text{JAP(K)04139177}\), dichloride (397) \(90\text{MIP9008142}\), and aminoalcohol (398) \(91\text{EUP447703}\) have all been prepared as anticancer agents. Indole (399) has antitumor and antiviral activity \(90\text{KFZ44}\). Hydroxylamine (400) is a lipoxygenase inhibitor, useful as an antiinflammatory \(88\text{USP4769387}\).

Azabenzo[\(\alpha\)furan (401) (as the hydrochloride) is a platelet-activating factor receptor antagonist and antitumor agent \(91\text{USP4992428}\).

For an apparently simple compound, butylphthalide (402) exhibits a surprising range of activity. Along with its 4,5-dihydro derivative, it was found to have anticonvulsant activity \(84\text{MI 208-05}\) and it has been used in skin cosmetics \(92\text{JAP(K)0469314}\). With its analogues, (402) has also been used as part of a stress-controlling fragrance \(90\text{JAP(K)02184683}\), and it reportedly enhances the activity of
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acetyl cholinesterase \( \langle 93 \text{JAP(K)05247022} \rangle \). Addition of a methoxy group to the 4-position gives a compound (403) which is a prostaglandin \( F_{2\alpha} \) inhibitor \( \langle 89 \text{JAP(K)01199958} \rangle \). Tetrahydrophthalide (404) is useful in the treatment of Alzheimer’s disease \( \langle 92 \text{JAP(K)04334378} \rangle \).

Another alkylphthalide (405) was an active ingredient in a hair tonic that increased the amount of anagen-phase hair in volunteers over a six-month period \( \langle 91 \text{JAP(K)03135907} \rangle \), while isoamylphthalide (406) is found in a dentifrice active against periodontal disease \( \langle 92 \text{JAP(K)0469325} \rangle \).

Mycophenolic acid (407), a phthalide produced by Penicillium brevi-compactum; \( P. \) stoloniferum, has antibiotic, antitumor, and immunosuppressive activity \( \langle 69 \text{BRPH57099} \rangle \). A derivative, Mycophenolate mofetil (408), has been applied to the problem of transplant rejection as an immunosuppressive agent \( \langle 93 \text{ANY(685)309} \rangle \) and has been reported to have antiinflammatory and virucidal activity \( \langle 88 \text{USP4727069} \rangle \). Several side-chain variants of mycophenolic acid (409) have been prepared, and a study of their structure–activity relationships has appeared \( \langle 90 \text{JMC833} \rangle \). A very similar compound, vinyl ketone (410), was isolated from Hericium erinaceum. It was found to possess activity as a uterocervical cancer inhibitor \( \langle 91 \text{JAP(K)03157379} \rangle \). Several derivatives, such as (411), have been applied to the treatment of rheumatoid arthritis \( \langle 87 \text{USP4686234} \rangle \).
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Altoqualine (412) and tritoqualine (413) are antihistamines and antinausea agents related to the alkaloids hydrastine (414) and noscapine (415).

Lactol benzodifuran (416), a sesquiterpene isolated from Stachybotrys sp. K76, was found to be useful for the treatment of noninsulin-dependent diabetes. Lactol ester talniflumate (417) is an analgesic and antiinflammatory.

Podophyllotoxin (418) (sometimes referred to as VP-16), isolated from Podophyllum peltatum, and its diastereomers continue to be of substantial interest owing to their antineoplastic activity. As a topical antiviral, podophyllotoxin was shown to be effective in the treatment of genital warts. Etoposide (419) and teniposide (420) are semisynthetic derivatives that are also antineoplastics. Podophyllotoxin and its esters have shown significant activity against P-388 lymphocytic leukemia. Many more derivatives of podophyllotoxin have been prepared. Hydroxyalkyl (421), thioester (422), amino (423), and benzylamino (424)
derivatives are typical examples. In many instances, the compounds (421)–(424) showed greater activity than either compounds (419) or (420).

Justicidin A (425) and justicidin B (426) are known piscicidal agents. Analogue have been patented for use in the treatment of osteoporosis.

Phthalan citalopram (427) and its analogues are antidepressants. Cicletanine (428), an antihypertensive, was found to have diuretic activity in rats and was a hypolipemic in rabbits. Barucainide (429) is a novel antiarrhythmic agent.

2.08.3.5 Miscellaneous

Cram has prepared a host system consisting of four linked dibenzofurans (430). One variation was found to form a complex with guanine in methanol. Bisdibenzo furan (431), a derivative of Kagan's ether, is a molecular tweezer that binds to trinitrobenzene.

The spirolactone fluorescamine (432) reacts with primary amines to form highly fluoroscent products making it a useful analytical reagent for the fluorometric determination of primary amines. Diphenylisobenzofuran (433) continues to be useful as a trap for singlet oxygen and reactive alkenes. An example is its reaction with cyclopropabenzene (434), which is postulated to
occur via a diradical mechanism to produce (435) \( \langle 91TL593 \rangle \). Benzofuran (436) has a musk odor and is used as a perfume component \( \langle 90FRP2634203 \rangle \).