Synthesis and Biological Evaluation of 14-Alkoxymorphinans. 2.[1] (−)-*N*-(Cyclopropylmethyl)-4,14-dimethoxymorphinan-6-one, a Selective μ Opioid Receptor Antagonist

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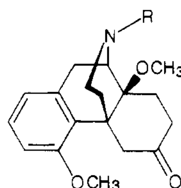
(−)-*N*-(Cyclopropylmethyl)-4,14-dimethoxymorphinan-6-one (**2**) was synthesized with 4,14-dimethoxy-*N*-methylmorphinan-6-one (**1**) as starting material. In vivo and in vitro experiments show **2** (cyprodime) to be a pure opioid receptor antagonist. Some of these tests (opioid receptor binding assays, guinea pig ileal longitudinal muscle preparation, rat and mouse vas deferens preparation, acetic acid writhing antagonism test) indicate that **2** is a selective μ opioid receptor antagonist.

In a series of 14-methoxy-*N*-methylmorphinan-6-ones found to possess opioid agonistic properties, 4,14-dimethoxy-*N*-methylmorphinan-6-one (**1**) was one of the most potent derivatives.[1] These findings prompted us to replace the *N*-methyl group of **1** by a cyclopropylmethyl group to obtain a potential opioid antagonist (**2**). We speculated that **2** might exhibit considerable opioid antagonist properties since a 14-methoxy group in morphinan-6-ones enhances the opioid receptor affinities not only in opioid agonists[1] but also in opioid antagonists.[2]

Chemistry

The starting material, 4,14-dimethoxy-*N*-methylmorphinan-6-one (**1**), was synthesized as described from oxymorphone in six steps.[1,3] N-Demethylation of **1** was achieved via the 2,2,2-trichloroethyl carbamate (**3**), which was cleaved reductively with Zn/NH_4Cl in MeOH to give the *N*-normorphinanone **4**. Alkylation with cyclopropylmethyl chloride in DMF provided the desired compound **2** (will now be refered to as cyprodime).



1: R = CH_3
2: R = $CH_2CHCH_2CH_2$ (cyprodime)
3: R = $CO_2CH_2CCl_3$
4: R = H

Pharmacological Results

In Vitro Studies. Cyprodime was evaluated in vitro for opioid agonistic and antagonistic properties in opioid receptor binding assays, in the isolated guinea pig ileal longitudinal muscle preparation (GPI), in the mouse vas deferens preparation (MVD), and in the rat vas deferens preparation (RVD). The ligands used in the binding assays were [^{3}H]naloxone (nonselective antagonist), [^{3}H]tifluadom (κ-selective agonist), and [^{3}H]D-Ala^2,D-Leu^5-enkephalin (DADLE) (δ-selective agonist). In the GPI, the inhibitory effect of cyprodime and naloxone was tested against normorphine (μ-selective agonist) and ethylketocyclazocine (EKC) (κ-selective agonist). In the MVD, normorphine, EKC, and DADLE were used as ligands. In the RVD, normorphine and DADLE were used. The RVD was set up in Krebs solution containing only 50% of the normal

Table I. Effects of Cyprodime and Reference Drugs in Opioid Receptor Binding Assays

	[^{3}H]naloxone[a]				
	+NaCl	−NaCl	ratio +/−NaCl	[^{3}H]tifluadom[a]	[^{3}H]DADLE[a]
cyprodime (**2**)	4.5	90	0.05	170	628
levallorphan	1.1	0.54	2.0	0.67	2.6
naloxone	2.0	2.0	1.0	9.0	127
naltrexone	0.5	0.62	0.8	2.6	12
U-50,488	12000	2150	5.6	5.0	3100

[a] The values are IC_{50} in nM with the exception of the ratio. The unlabeled drugs were examined with at least five concentrations in duplicate in two independent determinations in the presence of ^{3}H-labeled ligands.

Table II. Potencies of Cyprodime and Naloxone in the GPI, MVD, and RVD

	K_e, nM			selectivity ratio	
	NM[a] (μ)	EKC[b] (κ)	DADLE[c] (δ)	κ/μ	δ/μ
cyprodime					
GPI	31	1157		37	
MVD	55.4	1551	6108	28	110
RVD	61.6		4556		74
naloxone					
MVD	1.4	15.9	9.6	12	7

[a] NM = normorphine. [b] EKC = ethylketocyclazocine. [c] DADLE = D-Ala^2,D-Leu^5-enkephalin.

Ca^{2+} concentration to enhance the δ agonist activity.[4]

In the binding assays, cyprodime exhibited about one-tenth the potency of naltrexone to displace [^{3}H]naloxone in the presence of NaCl. Cyprodime yielded in this test the lowest ratio (with NaCl/without NaCl) of all drugs tested, indicating pronounced antagonistic activity. In displacing [^{3}H]tifluadom from its binding sites, cyprodime was much less effective than naloxone, naltrexone, and U-50,488. Cyprodime was also weak in displacing [^{3}H]-DADLE binding, suggesting selectivity for μ opioid receptors (Table I).

The antagonist activity and the selectivity for μ receptors was confirmed in the GPI, MVD, and RVD. Cyprodime shows good κ/μ and especially good δ/μ selectivity ratio (Table II).

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Table III. Activities of Cyprodime and Reference Drugs in the Respiratory Activity Test (Rabbits) and in the Withdrawal Jumping Precipitation Test (Mice)

	respiratory activity			withdrawal jumping: ED_{50}, mg/kg	
	dose, mg/kg iv	% change (±SE) of volume	% change (±SE) of rate	sc	po
cyprodime	1.0	+21 (±5.2)	−6.9 (±10)	0.60	9.2
naloxone	0.1	+23 (±12)	+7.3 (±5.8)	0.044	2.9
naltrexone	0.1	+36 (±7.8)	+7.5 (±9.0)	0.018	0.44
U-50,488	0.1	+42 (±6.2)	+29 (±15)	HDT[a] 10:0%	

[a] HDT is the highest dose tested in mg/kg sc.

Table IV. Antagonist Potencies of Cyprodime and Reference Drugs in the Acetic Acid Writhing Antagonism Test (Mice)

		% reduction of analgesia induced by	
	mg/kg sc	morphine: 10 mg/kg sc	U-50,488: 15 mg/kg sc
cyprodime (2)	10	100	6.5
naloxone	1	87	83
naltrexone	0.1	94	19

The lack of any opioid agonist potency of cyprodime is indicated by the fact that no depression of electrically induced twitch response was obtained up to concentrations of 10 μM in either the GPI (very sensitive to μ and κ agonists) or the MVD (very sensitive to δ agonists).

In Vivo Studies. Opioid agonism was determined in the acetic acid writhing test and in the hot plate test in mice. Cyprodime did not show antinociception at doses up to 10 and 30 mg/kg sc, respectively.

Opioid antagonism was studied in the opioid-type withdrawal jumping precipitation test in mice, in the respiratory activity test in rabbits, and in the acetic acid writhing antagonism test against morphine (μ-selective agonist) and U-50,488 (κ-selective agonist) in mice.

In the respiratory activity test, cyprodime produced a similar increase in respiratory volume as naloxone, but at a 10 times higher dose, indicating the antagonistic action of **2** (Table III).

The antagonistic potency of cyprodime in the withdrawal jumping precipitation test was about $^1/_{14}$ that of naloxone when administered subcutaneously. After oral administration, cyprodime had about one-third the potency of naloxone and about $^1/_{20}$ the potency of naltrexone. These results also show the antagonistic action of cyprodime (Table III).

In the acetic acid writhing antagonism assay, the potency of cyprodime in counteracting morphine-induced analgesia was about one-tenth that of naloxone. In contrast to this reference drug, cyprodime was virtually inactive against U-50,488-induced analgesia, indicating relatively pure μ opioid antagonism (Table IV).

Discussion and Conclusion

In the binding assays, *N*-(cyclopropylmethyl)-4,14-dimethoxymorphinan-6-one (**2**, cyprodime) demonstrated marked opioid antagonistic activity and selectivity for μ opioid receptors. This pure and selective μ opioid antagonism was verified in the GPI, MVD, and RVD where an especially good δ/μ selectivity ratio was found.

The in vitro findings correlate well with the results found in vivo. Cyprodime showed an antagonistic potency about one-tenth that of naloxone. The acetic acid writhing antagonism test confirmed the in vitro results concerning selective μ opioid antagonism, in that cyprodime did not suppress antinociception induced by the κ opioid agonist U-50,488.

Although a number of pure opioid antagonists have been synthesized and characterized over the past 10 years, resulting in some very selective competitive κ (e.g. norbinaltrorphimine[5-7]) and δ antagonists (e.g. naltrindol[8]), the only nonpeptide, competitive μ antagonists available with high affinity for the μ receptor show only 10–15 times higher affinity at μ compared to δ receptors in functional isolated tissue studies. For μ/δ selectivity with competitive nonpeptide antagonists, naloxone and naltrexone are still probably the antagonists of choice. β-FNA has been widely used as a selective μ antagonist,[9] but this is a noncompetitive compound which may well interact with sites adjacent to the μ receptor and certainly in isolated tissue studies there is a marked difference in the sensitivity of the μ receptor blockade by β-FNA in different tissues. The μ receptors in the RVD are much more resistant to blockade by β-FNA than those in the MVD.[10] This difference is not seen with competitive antagonists. A selective competitive antagonist is therefore arguably an easier and safer tool to use than a noncompetitive antagonist.

Because cyprodime is structurally similar to naltrexone, it is quite likely the compound will distribute in the whole animal in a similar way; therefore, restricted access to the CNS, etc., would not be expected to be a problem. Probably the main problem with cyprodime is that its relatively low affinity at the μ site means that quite large doses (ca. 10 times that of naloxone) are required for in vivo experiments.

Experimental Section

Chemistry. Melting points were determined with a Kofler melting point microscope and are uncorrected. IR spectra were recorded on a Beckman Accu Lab 2 apparatus. ^{1}H NMR spectra were determined by using a JEOL JNM-PMX 60 spectrometer and are reported in parts per million relative to tetramethylsilane as internal reference (s = singlet, m = multiplet). Electron-ionization (EI) and chemical-ionization (CI) mass spectra were obtained from a Finnigan MAT 44S apparatus. Optical rotations (concentrations (g/100 mL, solvent) were measured by using a Perkin-Elmer 141 polarimeter. Alumina basic (70–230-mesh ASTM) from Merck was used for column chromatography. Elemental analyses were performed at the Analytical Department of Hoffmann-La Roche & Co Inc., Basle.

(−)-4,14-Dimethoxy-*N*-[(2,2,2-trichloroethoxy)carbonyl]-morphinan-6-one (3). 2,2,2-Trichloroethyl chloroformate (15.5 mL, 0.11 mol) was added dropwise to a refluxing mixture of 1 (4.35 g, 13.79 mmol), anhydrous $KHCO_3$ (12.0 g, 0.12 mol), and 120 mL of $CHCl_3$ (EtOH-free) under N_2 during a period of 10 min. The resulting mixture was stirred and refluxed for an additional 2 h.

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The inorganic solid was filtered off and washed with $CHCl_3$ (EtOH-free), and the filtrate was evaporated at 80 °C (bath temperature) and 0.1 Torr to afford 6.45 g of a crystalline solid, which was treated with diisopropyl ether to give 6.0 g (91%) of **3**. An analytical sample was obtained by recrystallization of a small portion from MeCN: mp 179–182 °C; $[\alpha]^{20}_D$ −113.2° (*c* 1.00, $CHCl_3$); IR (KBr) 1745 (ester), 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.06–6.56 (m, 3 H, Ar H), 4.75 (s, 2 H, OCH_2), 3.80 (s, 3 H, C-4 OCH_3), 3.29 (s, 3 H, C-14 OCH_3); MS (EI), *m/e* 476 (M^+), 478 (M^+ + 2), 480 (M^+ + 4). Anal. ($C_{21}H_{24}Cl_3NO_5$) C, H, N, Cl.

(−)-4,14-Dimethoxymorphinan-6-one (4). Activated zinc powder (11.0 g, 168 mmol) was added in portions to a refluxing mixture of **3** (5.5 g, 11.5 mmol), NH_4Cl (11.0 g, 0.20 mol), and 100 mL of MeOH within 5 min. The resulting mixture was refluxed for additional 30 min, filtered, and washed with MeOH, and the filtrate was evaporated. The oily residue was partitioned between concentrated NH_4OH and CH_2Cl_2, and the organic layer was washed with brine, dried, and evaporated to give 3.2 g (92%) of **4** as a crystalline residue. An analytical sample was prepared by recrystallization of a small amount from EtOH: mp 155–157 °C; $[\alpha]^{20}_D$ −41.4° (*c* 1.31, $CHCl_3$); IR (KBr) 3410 (NH), 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.10–6.55 (m, 3 H, Ar H), 3.76 (s, 3 H, C-4 OCH_3), 3.30 (s, 3 H, C-14 OCH_3); MS (CI), *m/e* 302 (M^+ + 1). Anal. ($C_{18}H_{23}NO_3$) C, H, N.

(−)-*N*-(Cyclopropylmethyl)-4,14-dimethoxymorphinan-6-one Hydrobromide (2·HBr). A mixture of **4** (600 mg, 1.99 mmol), anhydrous K_2CO_3 (600 mg, 4.35 mmol), cyclopropylmethyl chloride (0.20 mL, 2.16 mmol), and 8 mL of anhydrous DMF was stirred at 100 °C (bath temperature) under N_2 for 16 h. The inorganic solid was filtered off and washed with CH_2Cl_2, the filtrate was evaporated, and the oily residue was partitioned between CH_2Cl_2 and H_2O. The CH_2Cl_2 phase was washed with brine, dried, and evaporated to give 700 mg of an oil, which was converted into the hydrobromide salt **2·HBr** (580 mg, 67%) in the usual way: mp 269–271 °C dec (MeOH/Et_2O); $[\alpha]^{20}_D$ −82.9° (*c* 1.03, 95% EtOH); IR (KBr) 3420 (^+NH), 1705 (CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.50 (br s, ^+NH), 7.20–6.60 (m, 3 H, Ar H), 3.68 (s, 3 H, C-4 OCH_3), 3.30 (s, 3 H, C-14 OCH_3); MS (EI), *m/e* 355 (M^+). Anal. ($C_{22}H_{29}NO_3$·HBr·0.5MeOH) C, H, N, Br.

Pharmacology. Materials and Methods. Drugs Used. Cyprodime (**2**) was used as the HBr salt. Other compounds and their sources included DADLE (D-Ala^2,D-Leu^5-enkephalin) (Cambridge Research Biochemicals), ethylketocyclazocine mesylate (Sterling Winthrop), levallorphan tartrate, normorphine, U-50,488 and [^{3}H]tifluadom (Roche), morphine hydrochloride (Sandoz), naloxone hydrochloride (Endo), [^{3}H]naloxone (New England Nuclear), and naltrexone hydrochloride (Endo). For in vitro experiments the compounds were dissolved in distilled water. For in vivo experiments they were dissolved in saline for parenteral injection and tap water for oral (po) administration; sometimes 1 N HCl had to be added in order to obtain a solution. The volume of injection was 10 mL/kg in mice and 1.5 mL/kg in rabbits.

Opioid Receptor Binding Assays. [^{3}H]Naloxone binding was performed essentially as described by Pert and Snyder.[11] Briefly, male rats Fü-albino (SPF) with 140–180 g body weight were decapitated. Whole brain without cerebellum was homogenized in 100 vol of ice-cold buffer (50 mmol/L Tris·HCl, pH 7.4, with or without NaCl (0.1 mmol/L) with a polytron and centrifuged 18000*g* for 10 min. Pellets were rehomogenized and incubated with [^{3}H]naloxone (1 nmol/L; sp act. 40 Ci/mmol) at 25 °C. After a 30-min incubation, the homogenate was filtered (Whatman GF/B) and washed three times with 3 mL of cold buffer. Specific binding was calculated by substracting the nonspecific binding in the presence of 1 μmol/L levallorphan.

[^{3}H]Tifluadom and [^{3}H]DADLE binding was performed in homogenates of guinea pig cerebellum as previously described by Burkard et al.[12] and Gillan et al.,[13] respectively. IC_{50} values were determined graphically or by a computer program assisted least-squares fit of sigmoid curves. All experiments, performed in duplicate, were replicated at least once with similar results.

Mouse Vas Deferens Preparation (MVD). Vasa deferentia from adult male mice (strain MFI/OLA) of weight greater than 30 g were set up in a 50-mL organ bath containing oxygenated (95% O_2 and 5% CO_2) magnesium-free Krebs solution (mM: NaCl, 118; KCl, 4.75; $CaCl_2$, 2.54; $NaHCO_3$, 25; KH_2PO_4, 0.93; glucose, 11) thermostatically controlled at 30 °C. The preparations were field stimulated between platinum electrodes at 0.1 Hz with 3.0-ms rectilinear pulses at a voltage of 30–50 V (measured across the electrodes with an oscilloscope) delivered from a computer-controlled stimulator made in the equipment development department at Reckitt and Colman. Dose–response curves were constructed by the cumulative addition of agonist to the organ bath. Contractions of the tissue were recorded with a Statham Goldcell Isometric Transducer connected to a Smiths Servoscribe flat bed potentiometric recorder.

Guinea Pig Ileal Longitudinal Muscle Preparation (GPI). Male Duncan Hartley guinea pigs of weight > 300 g were killed by a blow on the head, and the ileum was dissected out. The last 15 cm from the ileocecal junction was discarded and the rest was placed in warm (36 °C) Krebs solution gassed with 95% O_2/5% CO_2. After the lumen was washed with warm Krebs solution, a piece of ileum approximately 4 cm long was removed and set up in oxygenated Krebs solution at 30 °C in a 50-mL organ bath between two platinum electrodes. One electrode was situated intraluminally and the other extraluminally. The tissue was stimulated with 1-ms square wave pulses at a rate of 0.1 Hz and just maximal voltage with a BBC microcomputer controlled stimulator developed in the Equipment Development Laboratory at Reckitt and Colman. Agonist dose–response curves were constructed by using a cumulative dosing method.

Rat Vas Deferens Preparation (RVD). All experiments were performed in Krebs solution containing only 50% the normal calcium concentration. The Krebs solution formula used was as follows (mM): NaCl 113.8, KCl 4.7, $CaCl_2$ 1.2, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25, and glucose 11.4. The solution was gassed with 95% O_2 and 5% CO_2 and maintained at 30 °C. Contractions were recorded with a Statham Goldcell Isometric Transducer (Model UTC 3) connected to a Smiths Servoscribe pen recorder (Model R52E). The vasa deferentia were stimulated via platinum electrodes placed above and below the tissue at 40 V, 3 ms, and 0.1 Hz with a BBC microcomputer controlled stimulator, developed in the Equipment Development Laboratory at Reckitt and Colman. The output impedance of the stimulator was 100 ohms.

Sprague–Dawley rats (OLAC) weighing 200–300 g were killed by cervical dislocation, and the vasa deferentia were dissected out, desheathed, and suspended in a 50-mL organ bath containing Krebs solution. A 30–45-min period of equilibration under continuous stimulation, with washing every 10 min, was allowed before construction of agonist dose–response curves.

Cumulative dose–response curves were constructed to the test agonist by successively increasing the agonist concentration in the organ bath by approximately 3 times after the maximum inhibitory effect of the previous concentration was established. The Krebs solution was then changed for Krebs solution containing the antagonist to be investigated and at least 30-min contact time was allowed before another agonist dose–response curve was constructed. In many experiments the effect of the antagonist on the dose–response curves to two or more agonists was determined in the same preparation.

Determination of K_e Values. Antagonist K_e values were determined by constructing dose–response curves to the agonists in the presence and absence of a known concentration of the antagonist and measuring the dose ratios produced. The K_e values were calculated from the dose ratio by using the formula employed by Kosterlitz and Watt:[14] $K_e = a/\mathrm{DR} - 1$, where a = molar concentration of the antagonist and DR = dose ratio (i.e. ratio of equiactive concentrations of the test agonist in the presence and absence of the antagonist). At least four dose–response curves were constructed on each preparation to each agonist before and after the addition of the antagonist. In all cases K_e values were derived with concentrations of the antagonist which produced dose ratios between 3 and 12.

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Acetic Acid Writhing Test. This test was performed as described by Witkin et al.[15]

Hot Plate Test. This test was performed as described by Woolfe et al.[16]

Opioid-Type Withdrawal Jumping Precipitation Test.[17] Mice were made physically dependent on morphine as described.[1] Three days after implantation of the morphine pellet, eight mice (21–28 g body weight) per dose were administered the test compound and observed for withdrawal jumping. The number of jumps was counted individually for each mouse during a period of 60 min. The ED_{50} value for precipitation of withdrawal jumping was calculated by using the method of cubic splines and represents the dose at which the number of jumps was 50% of the control group value obtained with 0.1 mg/kg naloxone.[1]

Respiratory Activity Test. This test was performed as described earlier.[1]

Acetic Acid Writhing Antagonism Test. The test procedure corresponds to the acetic acid writhing test,[15] except that 20 min after the opioid agonist (morphine or U-50,488) was administered, the test compound was given.

Acknowledgment. We thank the Analytical Department of Hoffmann-La Roche & Co. Inc., Basle, for elemental analyses and Dr. K.-H. Ongania (Institute of Organic and Pharmaceutical Chemistry) for performing the mass spectra.

Registry No. 1, 92055-59-9; 2, 118111-54-9; 2·HBr, 118111-51-6; 3, 118111-52-7; 4, 118111-53-8; cyclopropylmethyl chloride, 5911-08-0.

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Studies on Hindered Phenols and Analogues. 1. Hypolipidemic and Hypoglycemic Agents with Ability To Inhibit Lipid Peroxidation

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A series of hindered phenols were investigated as hypolipidemic and/or hypoglycemic agents with ability to inhibit lipid peroxidation. 1,3-Benzoxathioles (**9** and **22**), phenoxypentanoic acid (**34**), phenoxypentanol (**35a**), phenoxynonanol (**35b**), phenylchloropropionic acid having a chromanyl group (**25**), and a thiazolidine compound (**27**) derived from **25**, all having a hindered phenol group, were prepared and examined. Compound **27** showed the expected biological properties in vivo and in vitro without any liver weight increase. Biological activities of the analogous thiazolidine compounds, **43–58**, were compared. Thus, (±)-5-[4-[(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl)methoxy]benzyl]-2,4-thiazolidinedione (**27**) (CS-045) was found to have all of our expected properties and was selected as a candidate for further development as a hypoglycemic and hypolipidemic agent.

There have been many reports that described the relationship of lipid peroxides (LPO) to angiopathy.[1–4] On macroangiopathy, Glavind et al. showed a relationship of LPO with arteriosclerosis in 1952.[1] Several years later, Fukuzumi et al. confirmed the presence of LPO in the atherosclerotic aorta.[2] According to Yagi, the accumulation of the complex of LPO with protein was one of the pathogenic causes of arteriosclerosis.[3] On microangiopathy, which is associated with diabetic complications, Yagi et al. have reported that the average level of LPO in plasma is higher in diabetics than in normals.[4]

Concerning such angiopathy, some reports describe experimental trials for lowering the serum LPO level by vitamin E,[5,6] which is a type of hindered phenol and therefore plays a role as a radical trapping agent.[7] However, vitamin E has been reported to not improve the

Chart I

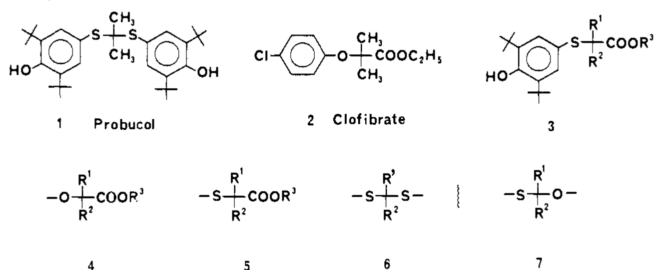


Chart II

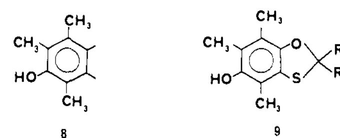
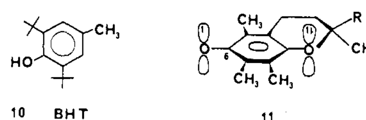


Chart III



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