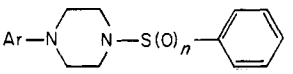
Table III[a]



no.	Ar	n	mp,[b] °C	yield,[c] %	formula	anal.[d]	indirect hypotensive screen[e]
9a	C_6H_5	1	101–104	74	$C_{16}H_{18}N_2OS$	C, H, N	83 (50), 42 (25), 22 (10)
9b	2-pyridyl	1	83–86	62	$C_{15}H_{17}N_3OS$	C, H, N	80 (50), 59 (25), 36 (10)
10a	C_6H_5	2	138–141	90	$C_{16}H_{18}N_2O_2S$	C, H, N	26 (50), 33 (25)
10b	2-pyridyl	2	154–157	89	$C_{15}H_{17}N_3O_2S$	C, H, N	5[f] (50)

[a-d] See corresponding footnotes in Table I. [e] Spontaneous hypertensive rat; drop of systolic pressure, mmHg, on day 3, 2 h postdrug (dose mg/kg po). [f] See footnote *g* in Table I.

effect in the unanesthetized dog at 20 mg/kg po.

Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 457 or 727) and ^1H NMR (JEOL C60HL; in $CDCl_3$ relative to an internal Me_4Si standard). Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Labs, Skokie, Ill. Results are within ±0.4% of theoretical values.

4-Benzoylpiperidine-1-benzenesulfenamide (4). To a mixture of 4.51 g (0.02 mol) of 4-benzoylpiperidine hydrochloride and 4.55 g (0.045 mol) of triethylamine in 100 mL of dichloromethane was added dropwise with stirring under nitrogen a solution of 3.18 g (0.022 mol) of benzenesulfenyl chloride in 40 mL of dichloromethane. The reaction mixture was stirred for 2.5 h at room temperature, diluted with 150 mL of dichloromethane, and washed with 150 mL of water and 150 mL of 1 N NaOH solution. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo to a brown oil. This oil was chromatographed on 100 g of silica gel using 5% MeOH/$CHCl_3$ as eluent. Evaporation of the solvent in vacuo afforded 3.23 g of a yellow oil, which partially crystallized on standing. Trituration with 4:1 petroleum ether/ether and cooling gave 2.06 g (35%) of a slightly yellow crystalline solid. Recrystallization from ethanol afforded 0.79 g (13.2%) of 4 as fine white crystalline solid, mp 74–76 °C.

1-Phenylpiperazine-4-benzenesulfenamide (7a). A mixture of 12.98 g (0.08 mol) of *N*-phenylpiperazine and 20.42 g (0.08 mol) of *N*-(phenylthio)phthalimide (8) in 400 mL of benzene was heated at reflux under nitrogen for 17 h, cooled to room temperature, and filtered to remove precipitated solid. The solid was washed with a small quantity of benzene, and the combined filtrate and washing were evaporated in vacuo to a yellow solid. Recrystallization from ethanol afforded 18.74 g (87%) of **7a** as fine colorless leaflets, mp 79.5–82 °C. The properties of compounds **2**, **3**, **5**, **6**, and **7b–l**, prepared in an analogous manner, are included in Tables I and II.

1-Phenylpiperazine-4-benzenesulfinamide (9a). To a solution of 4.87 g (0.03 mol) of *N*-phenylpiperazine in 150 mL of dichloromethane containing 4.59 mL (0.033 mol) of triethylamine was added dropwise with stirring under nitrogen a solution of 4.82 g (0.03 mol) of benzenesulfinyl chloride in 50 mL of dichloromethane. The reaction mixture was stirred for 3 h at room temperature, diluted with 100 mL of dichloromethane, and washed with 150 mL of water and 100 mL of 5% aqueous K_2CO_3 solution. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo to a nearly colorless crystalline solid. Recrystallization from ethanol afforded 6.37 g (74%) of **9a** as a nearly colorless crystalline solid, mp 101–104 °C. The properties of compounds **9b**, **10a**, and **10b**, prepared in an analogous manner, are included in Table III.

SHR Test for Antihypertensive Activity. The assay was conducted and the data were analyzed as described in ref 2.

Acknowledgment. The authors express their appreciation to Marc N. Agnew, David R. Claire, Jr., Eugene C. Dombrowski, and Yorum R. Shatz for spectral data and to the staffs of Mr. Wilker and Dr. Woodward for performing pharmacological assays. We also gratefully acknowledge June D. Baird for library research and Rose Marie Boysen for assistance in preparation of the manuscript.

Synthesis and Analgesic Properties of Some Conformationally Restricted Analogues of Profadol

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N-Methylspiro[5-hydroxytetralin-1,3'-pyrrolidine] (**2j**) and *N*-methylspiro[7-hydroxytetralin-1,3'-pyrrolidine] (**2n**), conformationally restricted analogues of profadol, were synthesized via initial reaction of the appropriately substituted 1-tetralone with ethyl cyanoacetate to give the ethyl 1-tetralylidenecyanoacetate derivative (**3**), which was then reacted with KCN to give the corresponding 1-cyano-1-(cyanomethyl)tetralin (**4**). Treatment of 4 with either HBr in dry ether–dichloromethane or acetic acid–sulfuric acid afforded the spiro[tetralin-1,3'-pyrrolidine-2',5'-dione] derivative (**5**), which was then reduced with $LiAlH_4$–THF and N-methylated with HCHO–HCO_2H to give the appropriately substituted spiro[tetralin-1,3'-pyrrolidine] (**2**). Both **2j** and **2n** and the isomeric 6-hydroxy derivative **21** all showed no significant analgesic activity in hot-plate and writhing tests. However, spiro[tetralin-1,3'-pyrrolidine] (**2a**) and its *N*-methyl derivative (**2b**) both possessed codeine-level analgesic activity.

The 3-alkyl-3-arylpyrrolidine derivative profadol (1) is the most potent analgesic in its structural class[1,2] and its enantiomers have been studied extensively both in animals and in man.[3-7] Numerous structure–activity studies of profadol derivatives have concentrated mainly on varying

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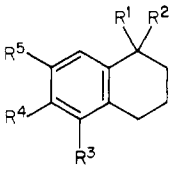
Table I. 1,1-Disubstituted Tetralin Derivatives



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no.	R^1	R^2	R^3	R^4	R^5	formula[a]	yield,[b] %	mp or bp (mmHg), °C
7a	=C(CN)CO$_2$Et		H	H	H	$C_{15}H_{15}NO_2$[c]	60	164-168 (0.3)
7b	=C(CN)CO$_2$Et		OCH_3	H	H	$C_{16}H_{17}NO_3$[c]	55	186-189 (1.5)
7c	=C(CN)CO$_2$Et		H	OCH_3	H	$C_{16}H_{17}NO_3$[c]	54	192-203 (0.2)
7d	=C(CN)CO$_2$Et		H	H	OCH_3	$C_{16}H_{17}NO_3$[c]	52	172-184 (0.5)
7e	CN	CH_2CN	H	H	H	$C_{13}H_{12}N_2$	82	65-69
7f	CN	CH_2CN	OCH_3	H	H	$C_{14}H_{14}N_2O$	73	92-95
7g	CN	CH_2CN	H	OCH_3	H	$C_{14}H_{14}N_2O$	83	102-105
7h	CN	CH_2CN	H	H	OCH_3	$C_{14}H_{14}N_2O$	73	74-76
7i	-CONHCOCH$_2$-		H	H	H	$C_{13}H_{13}NO_2$	82	158-159
7j	-CONHCOCH$_2$-		OCH_3	H	H	$C_{14}H_{15}NO_3$	67	178-181
7k	-CONHCOCH$_2$-		H	OCH_3	H	$C_{14}H_{15}NO_3$	91	163-165
7l	-CONHCOCH$_2$-		H	H	OCH_3	$C_{14}H_{15}NO_3$	89	128-130

[a] All compounds were analyzed for C, H, and N. [b] Yields are of purified product and are not maximal. [c] Isolated as a mixture of geometrical isomers.

N-substitution,[1,8-10] 3-alkylation,[2,11] and the aromatic substitution pattern.[1,2,10] However, these studies have not given rise to more active compounds. The 3-alkyl-3-arylpyrrolidines are conformationally mobile and are thought to exist predominantly in the half-chair conformation.[12] In addition, free rotation of the aryl group is possible. In view of this, it was thought of interest to prepare analogues of profadol in which conformational and rotational mobility was restricted and to determine the effect of this upon biological activity. We now report on the synthesis and initial central nervous system (CNS) screening of some spiro[tetralin-1,3'-pyrrolidine] derivatives. Within this structural class, *N*-methylspiro[5-hydroxytetralin-1,3'-pyrrolidine] (**2j**) and *N*-methylspiro-[7-hydroxytetralin-1,3'-pyrrolidine] (**2n**) are compounds of particular interest, since they may be regarded as conformationally restricted rotamers of profadol about the C(1)–C(3') bond.

Chemistry. The procedure adopted for the synthesis of the spiro[tetralin-1,3'-pyrrolidine] derivatives (**2a**) is outlined in Scheme I. Formation of the tetralylidene derivative (**7a**) from 1-tetralone was carried out using the method of Cope[13] and incorporating a modified procedure described by Cragoe.[14] Hydrocyanation of **7a** followed by decarboxylation afforded the dinitrile derivative (**7e**). Intramolecular cyclization of **7e** with HBr in anhydrous ethanol and subsequent hydrolysis of the intermediate imino salt (**6**) in aqueous DMF afforded **7i** in good yield. Cyclization of the methoxy derivatives **7f–7h**, which were prepared as described above from the corresponding 1-tetralone, was best achieved in aqueous H_2SO_4–CH_3CO_2H, cyclization in HBr–ethanol resulting in partial demethylation of the aromatic methoxy group (see Table I). Reduction of the appropriately substituted spirosuccinimide (**5**) with $LiAlH_4$/THF gave the corresponding spiro[tetralin-1,3'-pyrrolidine] (**2**). N-Methylations were carried out in formic acid–formaldehyde solution, and O-demethylations were achieved in 48% aqueous HBr under nitrogen (see Table II).

Analgesia was determined by the writhing[15] and hot-

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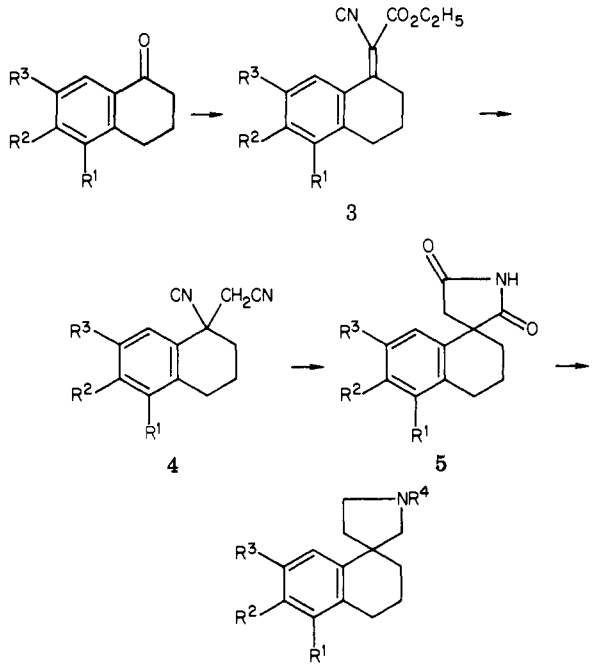
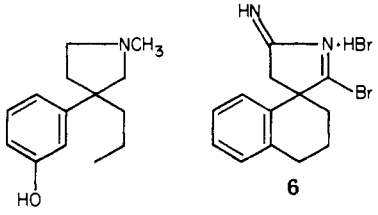
Scheme I



2a, $R^1 = R^2 = R^3 = R^4 = H$
b, $R^1 = R^2 = R^3 = H$; $R^4 = CH_3$
c, $R^1 = OCH_3$; $R^2 = R^3 = R^4 = H$
d, $R^1 = OCH_3$; $R^2 = R^3 = H$; $R^4 = CH_3$
e, $R^1 = R^3 = R^4 = H$; $R^2 = OCH_3$
f, $R^1 = R^3 = H$; $R^2 = OCH_3$; $R^4 = CH_3$
g, $R^1 = R^2 = R^4 = H$; $R^3 = OCH_3$
2h, $R^1 = R^2 = H$; $R^3 = OCH_3$; $R^4 = CH_3$
i, $R^1 = OH$; $R^2 = R^3 = R^4 = H$
j, $R^1 = OH$; $R^2 = R^3 = H$; $R^4 = CH_3$
k, $R^1 = R^3 = R^4 = H$; $R^2 = OH$
l, $R^1 = R^3 = H$; $R^2 = OH$; $R^4 = CH_3$
m, $R^1 = R^2 = R^4 = H$; $R^3 = OH$
n, $R^1 = R^2 = H$; $R^3 = OH$; $R^4 = CH_3$



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6

plate[16] tests in mice (see Table II). The lack of analgesic activity in **2j** and **2n** is noteworthy and may reflect the importance of the correct orientation of the 3-*n*-propyl group in the profadol–receptor interaction. Of interest also is the weak, codeine-level analgesia exhibited by **2a** and **2b**, which suggests that absorption, distribution, and/or metabolic factors may also be responsible for the lack of analgesia shown by the aromatic hydroxylated derivatives.

None of the compounds tested possessed any other significant CNS activity as determined by reserpine-induced hypothermia, maximal electroshock, metrazole shock, locomotor activity, and stationary rod tests.

Experimental Section

Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of Manchester. Analytical results obtained for all compounds were within ±0.4% of theoretical values. The IR, UV, and NMR spectra of all reported compounds were consistent with their proposed structures. 1-Tetralone and 5-methoxy-1-tetralone were purchased from Koch-Light Laboratories; 6-methoxy-1-tetralone[17] and 7-methoxy-1-tetralone[18] were prepared by literature procedures.

Synthesis of Ethyl 1-Tetralylidenecyanoacetates 3. A mixture of the appropriate 1-tetralone (0.26 mol), ethyl cyanoacetate (0.26 mol), ammonium acetate (0.052 mol), glacial acetic acid (0.21 mol), and benzene (70 mL) was heated under reflux with a Dean and Stark water trap for 7 h. The cooled reaction mixture was diluted with ether (500 mL) and washed with water (2 × 100 mL), and the washings were extracted with ether (2 × 100 mL). The combined organic liquors were dried ($MgSO_4$), the solvent was evaporated, and the resulting oil distilled in vacuo to give a clear oil consisting of a mixture of **3** and its geometrical isomer (see Table I).

Synthesis of 1-Cyano-1-(cyanomethyl)tetralins 4. A solution of sodium or potassium cyanide (0.25 mol) in water (35 mL) was added to a stirred solution of the appropriate ethyl 1-tetralylidenecyanoacetate (0.1 mol) in absolute ethanol (200 mL), and the reaction mixture was stirred at 65 °C for 16 h. The solvent was then evaporated under reduced pressure, and the residue was suspended in water (200 mL) and extracted with ether (3 × 200 mL). The ethereal layers were combined and the solvent was evaporated to give either a brown oil or a brown solid. Crude oils were vacuum distilled to afford pale yellow to colorless viscous liquids which slowly crystallized on standing. Solids were recrystallized from ether (see Table I).

Synthesis of Spiro[tetralin-1,3'-pyrrolidine-2',5'-diones] 5. Method 1. 1-Cyano-1-(cyanomethyl)tetralin (3.92 g, 0.02 mol) was dissolved in a mixture of CH_2Cl_2 (5 mL) and anhydrous ether (145 mL), and the solution cooled to 0 °C with stirring. Dry HBr gas was passed through the solution until precipitation of the intermediate spiro[tetralin-1,3'-(2'-bromo-5'-imino-Δ^1-pyrrolidine)] hydrobromide salt (**6**) was complete. This salt is unstable in air and was therefore quickly filtered, the precipitate was immediately dissolved in a mixture of DMF (25 mL) and water (50 mL), and the solution was heated on a steam bath for 2.5 h. When the solution cooled, a white crystalline precipitate of spiro[tetralin-1,3'-pyrrolidine-2',5'-dione] (**7i**) was obtained, which was filtered off, washed with cold water, and dried in vacuo using a P_2O_5 trap: NMR (Me_2SO-d_6) δ 8.74 (br s, 1, exchangeable with D_2O, NH), 7.26–6.87 (m, 4, Ph), 3.06–2.65 (m, 2, C-4 H_2), 2.84 (s, 2, C-4' H_2) 2.76–1.81 (m, 2, C-2 H_2).

Method 2. The appropriate aromatic-substituted 1-cyano-2-(cyanomethyl)tetralin (0.1 mol) was suspended in a mixture of glacial acetic acid (50 mL) and 78% (v/v) sulfuric acid (17 mL), and the mixture was heated on an oil bath at 125 °C for 1 h. When the mixture cooled, the acetic acid was removed under reduced pressure and the resulting mass was suspended in water (50 mL) and extracted with ethyl acetate (3 × 500 mL). The combined organic liquors were washed with saturated $NaHCO_3$ solution (2 × 200 mL) and water (100 mL) and then dried ($MgSO_4$) and concentrated to afford a buff-white powder. Recrystallization of the product from absolute ethanol gave the corresponding spiro[tetralin-1,3'-pyrrolidine-2',5'-dione] as white crystals (see Table I): NMR of the 5-methoxy derivative (**7j**) δ (Me_2SO-d_6) 9.12 (br s, 1, exchangeable with D_2O, NH) 7.70–6.57 (m, 3, Ph), 3.74 (s, 3, OMe), 2.96–2.52 (m, 2, C-4 H_2), 2.85 (s, 2, C-4' H_2), 2.47–1.44 (m, 4, C-2 H_2 and C-3 H_2).

Synthesis of Spiro[tetralin-1,3'-pyrrolidines] 2. The appropriate spiro[tetralin-1,3'-pyrrolidine-2',5'-dione] was slowly added to a stirred suspension of $LiAlH_4$ (0.03 mol) in anhydrous THF (100 mL), and the mixture was heated under reflux for 24 h. The excess $LiAlH_4$ was decomposed by careful addition of water. Anhydrous $MgSO_4$ was added, the mixture was filtered, and the filtrate was concentrated to afford a pale yellow oil. The oil was taken up in ether (10 mL) and extracted with 5% (w/v) HCl (3 × 10 mL). The aqueous layer was separated, basified (NH_4OH), and extracted with ether (3 × 20 mL), and the combined organic extracts were washed with water and dried ($MgSO_4$).

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Table II. Spiro[tetralin-1,3'-pyrrolidine] Derivatives 2a-n

compd	formula[a]	yield,[b] %	mp, °C	writhing test, mg/kg po	hot-plate test: ED_{50}, mg/kg po[g]
2a	$C_{13}H_{18}NCl$[c]	79	164-176	30, ++++	13.3 (10.5-15.7)
2b	$C_{14}H_{20}NCl$[c]	81	202-210	30, ++++	12.1 (8.4-14.3)
2c	$C_{17}H_{21}NO_5$[d]	85	182-189	30, ++	48.6 (30.3-57.6)
2d	$C_{18}H_{23}NO_5$[d]	92	132-136	100, +++	ND[f]
2e	$C_{14}H_{20}NOCl$[c]	90	174-192	100, +	ND[f]
2f	$C_{18}H_{23}NO_5$[d]	92	147-151	100, ++	ND[f]
2g	$C_{14}H_{20}NOCl$[c]	78	162-169	100, +	ND[f]
2h	$C_{18}H_{23}NO_5$[d]	85	129-135	30, ++	>50
2i	$C_{13}H_{18}NOBr$[e]	60	230-232	30, ++	>50
2j	$C_{14}H_{20}NOBr$[e]	88	255-259	100, +	ND[f]
2k	$C_{13}H_{18}NOBr$[e]	39	195-203	100, ++	ND[f]
2l	$C_{14}H_{20}NOBr$[e]	50	218-230	30, ++	>50
2m	$C_{13}H_{18}NOBr$[e]	67	258-261	100, ++	ND[f]
2n	$C_{14}H_{20}NOBr$[e]	52	182-193	30, ++	42.8 (35.6-49.4)
morphine hydrochloride				10, ++++	1.2 (0.9-1.5)
profadol				10, ++++	3.9 (2.5-5.9)

[a, b] See corresponding footnotes in Table I. [c] Isolated as the hydrochloride salt and recrystallized from ethanol-ether. [d] Isolated as the fumarate salt and recrystallized from ethanol. [e] Isolated as the hydrobromide salt and recrystallized from ethanol. [f] Not determined. [g] Confidence limits in parentheses.

Evaporation of the solvent afforded a yellow oil, which was distilled in vacuo to afford the appropriate spiro[tetralin-1,3'-pyrrolidine] as a colorless oil. Bases were converted immediately to their hydrochloride or fumarate salts.

Synthesis of *N*-Methylspiro[tetralin-1,3'-pyrrolidines]. The appropriate spiro[tetralin-1,3'-pyrrolidine] (1.1 g, 0.005 mol), HCO_2H (2.5 mL), and HCHO (37%, 1.0 mL) were heated together on a water bath for 7 h. After evaporation of the solution to dryness, the residual oil was dissolved in 5% HCl, washed with ether, basified with 10% NaOH, extracted with ether, and dried ($MgSO_4$). After evaporation of the solvent, the residual oil was distilled in vacuo to give the corresponding *N*-methyl derivative as a clear, colorless oil. The free base was converted to either the hydrochloride or fumarate salt (see Table II).

O-Demethylation of Compounds 2c-h. As a general procedure, the appropriate spiro[methoxytetralin-1,3'-pyrrolidine] (0.01 mol) was refluxed under nitrogen for 2 h at 125 °C in 48% aqueous hydrobromic acid (25 mL). The resulting yellow-brown solution was evaporated to dryness under nitrogen, and the residue was taken up in absolute ethanol. On addition of ether and refrigeration, buff crystals of the crude O-demethylated product were obtained. Recrystallization from ethanol-ether afforded a purer product (see Table II).

Pharmacology. Analgesia was determined by the acetic acid writhing test[15] in groups of six mice. Each group was dosed orally with either vehicle ("Dispersol") or compound under test and injected intraperitoneally 30 min later with dilute acetic acid (0.4 mL, 0.25%). The total number of writhes was recorded, and the protection afforded was expressed as a percentage of control values according to the following scale: ++++, 100% inhibition; +++, 75-99% inhibition; ++, 50-74% inhibition; +, 25-49% inhibition. Compounds showing 50% or more inhibition at 30 mg/kg in the above test were also tested for analgesia in mice by the hot-plate[16] method (see Table II).

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Relationship of Octanol/Water Partition Coefficient and Molecular Weight to Rat Brain Capillary Permeability

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The rat brain capillary permeability coefficient was determined for 27 compounds. The relationship of permeability to octanol/water partition coefficient and molecular weight was found to be predictable for drugs with molecular weights less than 400.

It is generally believed that the blood-brain barrier (BBB) is restrictive for small molecules at capillary endothelial cells and for large molecules at the interendothelial tight junctions. Although a great deal has been learned about the effects of BBB physiology on the passage of electrolytes and hydrophobic nonelectrolytes, a limited amount of information that correlates lipophilicity, molecular size, and the ability to cross the BBB has been published.[1-3]

We report the brain capillary permeability coefficient (P_c) determined in ether-anesthetized rats for 27 compounds for which the octanol/water partition coefficients are known.

Experimental Section

Isotopes. ^{14}C-labeled urea, creatinine, 5-fluorouracil, sodium ascorbate, and sucrose, ^{3}H-labeled water, glycerol, and galactitol, and $^{24}NaCl$ were purchased from New England Nuclear Corp. and/or Amersham-Searle, Inc. Radiopurity was satisfactory by manufacturer's specifications. ^{14}C-Labeled dianhydrogalactitol, dibromodulcitol, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea (PCNU), *N*-(1-methylethyl)-4-[(2-methylhydrazino)methyl]benzamide monohydrochloride (procarbazine), Baker's antifol, adriamycin,

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