Notes

6,7-Dihydroxy-3-chromanamine: Synthesis and Pharmacological Activity of an Oxygen Isostere of the Dopamine Agonist 6,7-Dihydroxy-2-aminotetralin

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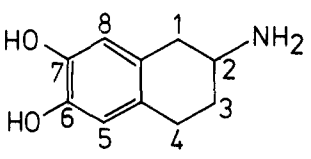
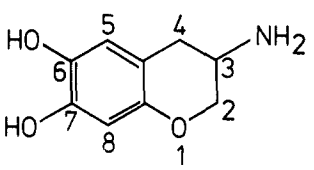
6,7-Dihydroxy-3-chromanamine, the oxygen isostere of 6,7-dihydroxy-2-aminotetralin (6,7-ADTN), has been synthesized and its dopaminergic activity in various test systems determined. Following bilateral injection into the rat nucleus accumbens, a pattern of locomotor activity similar to that produced by 6,7-ADTN was observed. Its ability to displace *N*-*n*-propyl[^{3}H]norapomorphine binding to homogenates of rat brain corpus striatum was found to be about 15 times weaker than 6,7-ADTN and apomorphine. Like 6,7-ADTN it failed to influence dopamine metabolism following an intraperitoneal injection. It is suggested that in addition to the 2-aminotetralins, the 3-chromanamines may be a potential source of new dopamine receptor agonists.

There has been considerable recent interest in preparing oxygen-containing isosteres of various dopamine (DA) agonists.[1-3] Due to our own interest in the synthesis of DA agonists related to the 2-aminotetralins,[4,5] in particular 6,7-dihydroxy-2-aminotetralin (6,7-ADTN, **1a**), we decided to prepare an isostere of this compound with the methylene group at C-4 replaced by an oxygen atom, i.e., 6,7-dihydroxy-3-chromanamine (**1b**).



1a

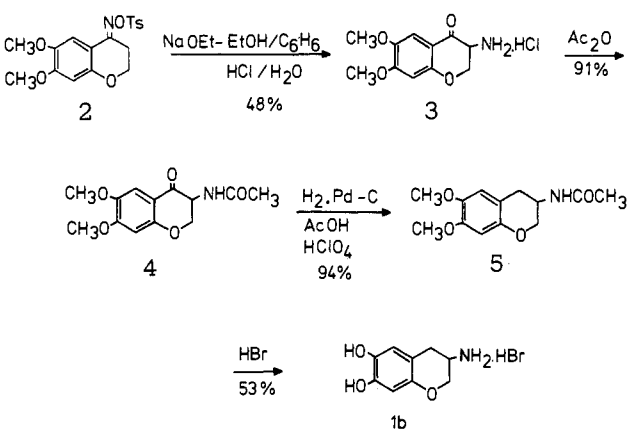


1b

The pharmacological activity of this compound was evaluated in vivo by studying the induction of locomotor activity in rats following injections into the nucleus accumbens and also for its effects on DA metabolism. Its in vitro activity was investigated by examining its ability to displace the specific binding of *N*-*n*-propyl[^{3}H]norapomorphine ([^{3}H]NPA) to homogenates of rat brain corpus striatum. In all cases, 6,7-ADTN was used as the reference compound. Various 3-chromanamine analogues have been shown to possess β-adrenergic,[6] psychostimulant,[7,8] and antipsychotic-antidepressant[9] activity. However, to our knowledge, this is the first report of dopaminergic activity in this series.

Chemistry. Although many 3-chromanamines are known in the literature,[9,10] 6,7-dihydroxy-3-chromanamine (**1b**) has not been previously synthesized. Our initial approach was via reductive amination of the corresponding 3-chromanone. However, the syntheses of 3-chromanones are long[11] and give low yields.[12] An additional problem was the protection of the catechol group in the presence of the cyclic ether. Early attempts using benzyl functions for this purpose were unsuccessful due to difficulties in preparing the starting material, 3,4-bis(benzyloxy)phenol. We therefore chose a method described by Lockhart,[8] which introduces the amino function via a Neber rearrangement. The catechol group was protected as the dimethyl ether. Compound **1b** was thus prepared as outlined in Scheme I.

Scheme I



3-Amino-6,7-dimethoxy-4-chromanone hydrochloride (**3**·HCl) was obtained in 48% yield by the Neber rear-

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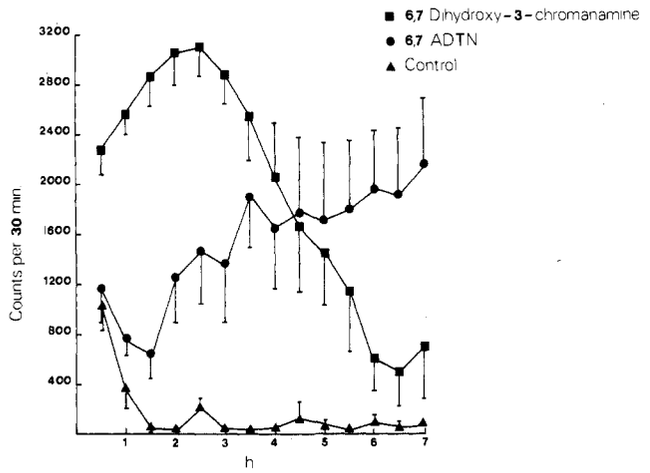

Figure 1. Effects of the DA agonists on rat locomotor activity. 6,7-ADTN and 6,7-dihydroxy-3-chromanamine (20 μg) were injected bilaterally (total dose 40 μg) into the rat nucleus accumbens via cannulae. The total locomotor activity over a 30-min period was then registered. Each point represents the mean ± SEM for six independent experiments. The saline controls are the mean ± SEM for five experiments.

rangement of **2**, as previously reported by Sugihara and Sanno.[6] Changing from NaOEt to KOEt[6] or to a higher temperature did not result in a higher yield. Direct hydrogenation of the keto amine **3** via a method described by Rosenmund and Karg[13] failed; therefore, **3** was first converted into its acetamide **4**. Hydrogenation in acetic acid with perchloric acid and Pd–C as a catalyst gave 3-acetamido-6,7-dimethoxychroman (**5**) in 94% yield. When the hydrogenation was incomplete (lower hydrogen pressure), the 4-acetoxy derivative of **5** could be isolated as a byproduct, while hydrogenation in ethanol rapidly gave the 4-hydroxy analogue of **5**. As it is known that benzyl acetates are hydrogenated much faster than benzyl alcohols,[14] the hydrogenation probably proceeds via the former intermediate. The dimethoxy amide **5** was hydrolyzed in 48% HBr to give the hydrobromide salt of 6,7-dihydroxy-3-chromanamine (**1b**). Anchimeric assistance between the catechol ethers is probably responsible for the ease of hydrolysis.

Pharmacology and Discussion

Due to the fact that, because of its lipophobicity and metabolic instability 6,7-ADTN is inactive following parenteral administration,[15] it was expected that this would also be a problem with the oxygen isostere. We therefore decided to initially evaluate the compound following intracerebral injection and in an in vitro binding assay in order to avoid these complications.

It is known that 6,7-ADTN produces long-lasting locomotor activity in rats following direct injection into the dopamine-rich nucleus accumbens.[16] Similar activity was found for the oxygen isostere (Figure 1); thus a bilateral injection of 20 μg produced locomotor activity that was more rapidly induced and of a greater intensity than with an equivalent dose of 6,7-ADTN. However, the duration of this effect was longer with 6,7-ADTN than with its isostere. These effects could be antagonized by pre-

Table I. Effects of DA Agonists on in Vitro [^{3}H]NPA Binding to Rat Corpus Striatum

drug	IC_{50},[a] nM	K_i,[b] nM
6,7-dihydroxy-3-chromanamine	259 ± 0.76	144.0
6,7-ADTN	24.5 ± 0.59	12.0
apomorphine	22.6 ± 0.55	10.5

[a] IC_{50} values are presented as the mean values ± SEM of three independent experiments, each determined over the concentration range 10^{-11}–10^{-5} M in triplicate. The final concentration of [^{3}H]-NPA was 0.50 nM. The IC_{50} value is defined as the concentration required to reduce the specific binding of [^{3}H]NPA by 50%. [b] The apparent inhibitory constant, K_i, was derived from the Cheng–Prusoff equation using a K_D value for [^{3}H]NPA of 0.46 nM.

treatment with the neuroleptic pimozide (1 mg/kg, ip). Bearing in mind the high dopaminergic innervation of the area under study,[16] the structural resemblance of the two drugs to DA, and the antagonism of the effects by the DA-receptor blocker pimozide,[16] it seems reasonable to conclude that the oxygen isostere is a DA agonist.

A direct measure of the affinity of this compound for DA receptors in homogenates of the rat corpus striatum was obtained from binding studies with *N*-*n*-propyl[^{3}H]-norapomorphine ([^{3}H]NPA). As can be seen in Table I, the chromanamine was about 15 times weaker than 6,7-ADTN and apomorphine.

The problem of passage through the blood–brain barrier was clear from the outcome following an intraperitoneal (ip) dose of 100 μmol/kg of the compound. Thus, even at this high dose there was no apparent effect on behavior up to 45 min after injection. In addition, this dose produced no significant changes in the levels of the DA metabolites HVA or DOPAC or of DA itself in the striatum (Table II). It is known that most DA agonists cause a lowering of the levels of HVA and DOPAC.[17] Similar negative results have previously been reported following peripheral administration of 6,7-ADTN.[18]

The concentration in the corpus striatum after 15 min, although in fact higher than that achieved with an equivalent dose of 6,7-ADTN[19] (0.13 nmol/g), was, bearing in mind the dose, very low, i.e., 0.34 nmol/g. Similar differences were also found in the cerebellum (values not shown). This difference in the brain concentrations of the two compounds was probably mainly due to their differing partition coefficients. Thus in an octanol–phosphate buffer system at pH 7.4, **1a** and **1b** had log *p* values of −1.88 ± 0.17 and −1.39 ± 0.17 (mean ± SD, $n = 6$), respectively.

In principle, a DA agonist that does not readily pass the blood–brain barrier could be very useful as a starting point in the current search for new antihypertensive drugs acting on DA receptors.[20] With this in mind we carried out some preliminary experiments on peripheral DA receptors.[21] On the DA_1 receptor (renal vasodilation) in the dog, **1b** was 20–30 times less active than DA and the effect could be blocked by sulpiride. In the dog femoral vascular bed (DA_2) preparation, it was virtually inactive. 6,7-ADTN is known to be a potent agonist in both preparations.[20,22]

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Table II. Effects of 6,7-Dihydroxy-3-chromanamine on Rat DA Metabolism and Striatal Concentrations following 100 μmol/kg ip

time, min	DOPAC, μg/g	HVA, μg/g	DA, μg/g	6,7-dihydroxy-3-chromanamine,[b] nmol/g
0	1.05 ± 0.07 (8)[a]	0.91 ± 0.05 (8)[a]	9.87 ± 0.63 (8)[a]	
15	0.97 ± 0.04 (8)	0.83 ± 0.03 (8)	10.47 ± 0.30 (8)	0.34 ± 0.03 (8)
45	1.02 ± 0.04 (8)	1.02 ± 0.09 (8)	10.84 ± 0.30 (8)	0.20 ± 0.02 (8)

[a] The values for DOPAC, HVA, and DA are shown as the mean ± SEM with the number of determinations in parentheses. These values are not corrected for recovery. [b] The concentrations of 6,7-dihydroxy-3-chromanamine are presented as the mean ± SEM for eight determinations; the values have been corrected for a recovery of 78.8%.

This particular isosteric replacement therefore appears to be unfavorable with regard to activity at certain peripheral DA receptors.

In conclusion, we have shown that 6,7-dihydroxy-3-chromanamine like its isostere 6,7-ADTN is inactive following peripheral administration to rats but that it has considerable activity if it is injected into the brain. Thus the chromanamine moiety may represent a useful ring system for the development of new centrally active DA agonists, and efforts are currently underway in our group to achieve better brain penetration by molecular manipulation.

Experimental Section

Melting points (uncorrected) were determined on a Mettler FP-2 apparatus. Infrared spectra were recorded on a Unicam SP-200 infrared spectrophotometer, and only the important absorptions are given in reciprocal centimeters. The 60-MHz ^{1}H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24B spectrometer. Chemical shifts are denoted in ppm relative to tetramethylsilane (Me_4Si) as an internal standard. A Nicolet NT-200 or a Varian XL 100 spectrometer was used for ^{13}C NMR spectra, with chloroform-*d* ($CDCl_3$) as an internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were obtained on an AEI MS-902 instrument (voltage 70 eV, accelerating voltage 8 kV, DI temperature 100–120 °C). Elemental analyses were performed in the microanalytical section of the Chemistry Department, Groningen, and are within ± 0.3% of the theoretical values.

6,7-Dimethoxy-4-chromanone *O*-(*p*-Tolylsulfonyl)oxime (2). To an ice-cooled solution of 4.90 g (22 mmol) of 6,7-dimethoxy-4-chromanone oxime[6] in 20 mL of dry pyridine was added 4.62 g (24.2 mmol) of *p*-toluenesulfonyl chloride in portions over a period of 40 min. After 19 h at 0 °C the reaction mixture was poured into 150 mL of water. The orange oil that separated slowly solidified. The solid was filtered off, washed with cold MeOH, and dried over P_2O_5 in vacuo: yield 7.15 g. (86%), white crystalline solid; mp 155–157 °C dec (lit.[6] mp 158–159 °C); IR (Nujol) 1590 (Ar, C=N), 1370 (SO_2), 1200 (SO_2), 1160 (CO); ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3 H), 2.86 (t, 2 H), 3.77 (s, 6 H), 4.03 (t, 2 H), 6.23 (s, 1 H), 7.00 (s, 1 H), 7.20 (d, 2 H), 7.79 (d, 2 H); ^{13}C NMR ($CDCl_3$) δ 21.40 (q), 24.56 (t), 55.74 (q), 55.97 (q), 64.49 (t), 100.37 (d), 105.60 (d), 106.40 (s), 128.68 (d, tosyl), 129.24 (d, tosyl), 132.50 (s, tosyl), 144.09 (s, tosyl), 144.81 (s), 153.48 (s), 153.75 (s, 4-C), 156.65 (s).

3-Amino-6,7-dimethoxy-4-chromanone Hydrochloride (3·HCl). Under a nitrogen atmosphere, 530 mg (23 mmol) of sodium was dissolved in 20 mL of absolute EtOH (ice cooling). To this ice-cooled solution was added dropwise a suspension of 7.5 g (20 mmol) of **2** in 25 mL of dry benzene. The reaction mixture was kept at 0 °C for 24 h. The solid (TsO^-Na^+) was then filtered off and washed with benzene; 50 mL of 4 N HCl solution was added to the yellow filtrate and stirring was continued for 1 h. The water layer was separated, washed with Et_2O, and evaporated to dryness under reduced pressure. The crude product was recrystallized from EtOH. From the organic layers 3.05 g of starting material was recovered: yield 1.65 g (48%), light-yellow crystals; mp 233 °C dec (lit.[6] mp 237 °C); IR (Nujol) 3000 (NH_3^+), 1665 (C=O), 1510 (CN); ^{1}H NMR (Me_2SO-d_6) δ 3.72 (s, 3 H), 3.81 (s, 3 H), 4.46 (m, 2 H), 4.78 (m, 1 H), 6.65 (s, 1 H), 7.10 (s, 1 H), 8.95 (br, 3 H); MS, *m/e* 223 (M^+), 181 (base).

3-Acetamido-6,7-dimethoxy-4-chromanone (4). To a well-stirred solution of 1.50 g (5.8 mmol) of 3·HCl and 3.1 g NaOAc in 27 mL of EtOAc and 8 mL of water was added 5 mL of Ac_2O. The heterogeneous reaction mixture was stirred for 4 h at room temperature. Then, additional EtOAc and water were added and the layers were separated. The organic layer was evaporated to dryness under reduced pressure and the yellow residue was recrystallized from benzene (50 mL): yield 1.40 g (91%), colorless needles; mp 205–206 °C; IR (Nujol) 3300 (NH), 1680 and 1640 (C=O); ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3 H), 3.80 (s), 3.85 (s), 3.7–4.1 (m, together 7 H), 4.8 (m, 2 H), 6.25 (br) and 6.35 (s, together 2 H), 7.15 (s, 1 H); MS, *m/e* 265 (M^+), 181 (base). Anal. ($C_{13}H_{15}NO_5$) C, H, N.

3-Acetamido-6,7-dimethoxychroman (5). A 1.35-g (5.0 mmol) sample of 4 in 17 mL of AcOH was hydrogenated at 3 atm with 500 mg of Pd–C (5%) and 1 mL of $HClO_4$ (70%) for 24 h. The solution was then filtered and the Pd–C washed with 200 mL of EtOH. The combined filtrates were evaporated under reduced pressure and, after addition of water, neutralized with solid $NaHCO_3$. The aqueous solution was extracted with $CHCl_3$ (4 × 25 mL). The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated under reduced pressure to yield the slowly crystallizing product: yield 1.16 g (94%), white crystalline solid; mp 170–172 °C; IR (Nujol) 3300 (NH), 1675 (C=O), 1525 (CN), 1195 and 1130 (CO); ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3 H), 2.55 (br d, ^2J = 16 Hz, 1 H), 3.05 (d + d, ^2J = 16 Hz and ^3J = 5 Hz, 1 H), 3.76 (s, 6 H), 4.05 and 4.40 (m, 3 H), 5.9 (br, 1 H), 6.33 (s, 1 H), 6.42 (s, 1 H); MS, *m/e* 251 (M^+), 192 (base). Anal. ($C_{13}H_{17}NO_4$) C, H, N.

6,7-Dihydroxy-3-chromanamine Hydrobromide (1b·HBr). Under a nitrogen atmosphere, 1.00 g (4.0 mmol) of **5** was treated with 30 mL of 48% (v/v) HBr solution at 140 °C for 2 h. After cooling, the solution was concentrated under reduced pressure ($T < 40$ °C) and dried over P_2O_5. The residue was recrystallized under nitrogen from $EtOH/Et_2O$: yield 550 mg (53%), tan crystals; mp 280 °C dec; IR (Nujol) 3300 (br, NH and OH), 1620 (Ar), 1500 (CN), 1275 (Ar–O), 1180 (CO); ^{1}H NMR (Me_2SO-d_6) δ 2.9 (m, 2 H), 3.80 and 4.15 (m, 3 H), 6.0 (br, ±2 H), 6.35 (s, 1 H), 6.55 (s, 1 H), 8.25 (br, ±3 H); ^{13}H NMR (D_2O + MeOH as a reference) δ 27.59 (t), 44.75 (d), 63.93 (t), 104.58 (d), 109.45 (s), 117.11 (d), 138.90 (s), 144.41 (s), 146.98 (s); MS, *m/e* 181 (M^+ – HBr, base). Anal. ($C_9H_{12}NO_3Br$) C, H, N.

Pharmacology. Locomotor Activity. Male rats (250 g) of a Wistar-derived strain (C.D.L., Groningen) were used. The bilateral implantation of the stainless steel cannulae into the rat nucleus accumbens and the administration of the drugs was carried out according to the method of Elkhawad and Woodruff.[16] Solutions of the drugs were prepared in physiological saline containing 0.1% sodium metabisulfite as an antioxidant. Locomotor activity was measured with Automex activity boxes (Columbus Instruments, Columbus, OH). After injection of the test drug or saline, the rat was placed in the Automex cage, one rat per cage. The counts were summated and recorded on a printer. Pimozide (1 mg/kg, ip) was administered 30 min before the intra-accumbens injections in certain experiments.

Displacement of *N*-*n*-Propyl[^{3}H]norapomorphine ([^{3}H]-NPA) Binding to Rat Brain Corpus Striatum Homogenates. The [^{3}H]NPA binding assay was performed in a manner analogous to that described by Leysen and Gommeren[23] (1981) for [^{3}H]-

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apomorphine. Striatal tissue was obtained from male rats weighing 200–225 g. The incubation mixture consisted of 15 mM Tris-HCl buffer, pH 7.5, containing 1 mM EDTA and 0.01% ascorbic acid, and the final volume was 1.0 mL. The concentration of the striatal tissue was 2.5 mg (wet weight) and the final concentration of [^{3}H]NPA (specific activity 58.8 Ci/mmol) was 0.50 nM. Incubations were carried out at 25 °C for 20 min. Nonspecific binding was determined in the presence of 1 μM *d*-butaclamol.

Determination of the Striatal Concentrations of DA, DOPAC, HVA, and 6,7-Dihydroxy-3-chromanamine. Female rats (180–200 g) were injected ip with a dose of 100 μmol/kg of 6,7-dihydroxy-3-chromanamine dissolved in physiological saline solution containing sodium metabisulfite (0.1%) as an antioxidant. After periods of 15 and 45 min, the animals were sacrificed, the brains were rapidly removed, and the striatal and cerebellar tissues were dissected and immediately frozen on dry ice and stored at −80 °C. DA, DOPAC, and HVA in the corpus striatum were determined by reversed-phase HPLC (Nucleosil 5 C_{18}) with amperometric detection after isolation on Sephadex G-10 columns according to the method of Westerink and Mulder.[24] The cerebellar tissues of control rats were used as blanks and as tissue for recovery experiments. The recoveries were 86–89% and the values were not corrected for recovery.

The striatal concentrations of 6,7-dihydroxy-3-chromanamine following the administration of 100 μmol/kg, ip were determined after 15 and 45 min by using a previously reported HPLC/electrochemical detection method for 6,7-ADTN.[19] Slight modifications of the mobile phase, i.e., 0.1 M phosphate–acetate buffer, pH 4.5, were found to be necessary. Concentrations were calculated with the aid of a standard. Recoveries were estimated by assaying spiked brain samples from untreated rats. The recovery was 78.8 ± 3.8% (n = 5), mean ± SD.

Determination of the Partition Coefficients of 1a and 1b. The partition coefficients (log p values) in an octanol–phosphate buffer system (pH 7.4) were determined according to the method of Feenstra et al.[25] using the above analytical methodology.

Registry No. 1a, 53463-78-8; 1b, 90990-80-0; 2, 64173-08-6; 3, 64139-42-0; 4, 90990-81-1; 5, 90990-82-2; dopamine, 51-61-6; 6,7-dimethoxy-4-chromanone oxime, 64139-41-9.

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Total Chemical Synthesis and Antitumor Evaluation of 4-Demethoxy-10,10-dimethyldaunomycin

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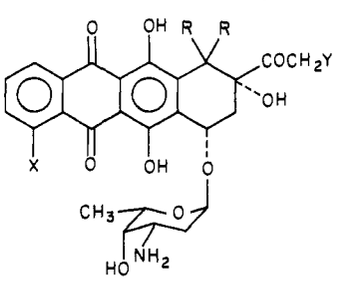
The novel anthracycline analogue 4-demethoxy-10,10-dimethyldaunomycin was prepared in nine chemical steps from 5,8-dimethoxy-2-tetralone. It proved to be inactive as an antitumor agent in the mouse P388 lymphocytic leukemia model.

Synthetic studies on anthracycline antitumor antibiotics such as daunomycin (1) and doxorubicin (2) have been pursued intensively.[1,2] Present interest is turning increasingly to total synthesis of unnatural analogues inaccessible from fermentation-derived substrates in the hope of producing drugs with significantly altered biological properties.[1-6] In this context we report here our experiences in the total synthesis and antitumor evaluation of 4-demethoxy-10,10-dimethyldaunomycin (3).



1, X = OCH_3; R = Y = H
2, X = OCH_3; R = H; Y = OH
3, X = Y = H; R = CH_3

Previous knowledge of structure–activity relationships at the C-10 position of anthracycline antibiotics is relatively sparse. Natural congeners are limited to those possessing a C-10β-CO_2CH_3[7-11] and C-10β-OH[12,13] moiety. These are known to retain significant antitumor activity, but they have not been commercialized. From chemical transformation of daunomycin and doxorubicin, it is known that dehydration produces $\Delta^{9,10}$-analogues that proved to be toxic to mice and did not cure their tumors (L1210).[4,14,15]

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