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**Short communication**

# Synthesis and pharmacological evaluation of mercapto and thioacetyl analogues of cannabidiol and $\Delta^8$-tetrahydrocannabinol

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**Summary** — A series of novel mercapto and thioacetyl derivatives of $\Delta^8$-tetrahydrocannabinol ($\Delta^8$-THC, **5**), and cannabidiol (**1**) were synthesized. Treatment of 10-hydroxy-cannabidiol (**2**) with thioacetic acid in the presence of a complex of diisopropylazodicarboxylate and triphenylphosphine in dry THF gave 10-thioacetyl-cannabidiol (**3**). Further treatment with $LiAlH_4$ converted **3** into 10-mercapto-cannabidiol (**4**). Using a similar sequence, 11-mercapto-$\Delta^8$-THC (**8**) was synthesized from the metabolite 11-hydroxy-$\Delta^8$-THC (**6**) *via* the corresponding thioacetyl derivative (**7**). Similarly, the 12$\beta$-thioacetyl derivative (**10**) of $\Delta^8$-THC was prepared. Although **8** is a derivative of a pharmacologically active cannabinoid (**6**), **8** proved to be inactive in 4 different pharmacological evaluations in the mouse. Similarly, **10** and **4** were also inactive. Additionally, **7** was inactive except for the production of hypothermia, but was more than 3-fold less potent than $\Delta^8$-THC. None of these cannabinoids was able to antagonize the effects of $\Delta^9$-THC. These data indicate that there are specific structural requirements for the production of cannabimimetic activity, which tends to suggest that activity is determined, in part, *via* specific molecular interactions such as those observed in receptor-, enzyme-, ion channel-, or other protein-mediated events.

**Résumé — Synthèse et évaluation pharmacologique d'analogues mercapto et thioacétylés des cannabidiol et $\Delta^8$-tetrahydrocannabinol.** *On a analysé une série de dérivés nouveaux de mercapto et thioacétylés du $\Delta^8$-tétrahydrocannabinol ($\Delta^8$-THC, **5**) et cannabidiol (**1**). Le traitement de l'hydroxy-10 cannabidiol (**2**) avec de l'acide thioacétique en présence d'un complexe du diisopropylazodicarboxylate et triphénylphosphine dans du THF sec a donné le thioacetyl-10 cannabidiol (**3**). Un traitement supplémentaire avec $LiAlH_4$ a changé **3** en mercapto-10 cannabidiol (**4**). En utilisant une séquence semblable, on a synthétisé le mercapto-11-$\Delta^8$-THC (**8**) à partir d'un métabolite l'hydroxy-11-$\Delta^8$-THC (**6**) avec le concours du dérivé thioacétylé (**7**). De même, on a préparé le dérivé 12$\beta$-thioacétylé (**10**) du $\Delta^8$-THC. Bien que **8** soit un dérivé d'un cannabinoïde actif pharmacologiquement (**6**) on l'a trouvé inactif dans quatre différentes évaluations pharmacologiques chez la Souris. De même, **10** et **4** ont été inactifs. De plus, **7** a été inactif sauf pour la production d'hypothermie, tout en étant trois fois moins fort que le $\Delta^8$-THC. Aucun de ces cannabinoïdes n'a pu antagoniser les effets de $\Delta^9$-THC. Ces faits indiquent qu'il y a des demandes structurales spécifiques pour la production de l'activité cannabimimétique, ce qui suggère que l'activité est determinée, en partie, par des interactions moléculaires spécifiques comme celles observées dans des récepteurs, enzymes, canaux ioniques ou tout autre cas d'interpositions de protéines.*

**$\Delta^8$-tetrahydrocannabinol / cannabidiol / mercapto analogue / thioacetyl analogue / mouse behavior / antagonism**

## Introduction

$\Delta^9$-Tetrahydrocannabinol ($\Delta^9$-THC) and some of its analogues (*e.g.*, $\Delta^8$-THC, 11-hydroxy-$\Delta^8$-THC) produce characteristic psychotropic responses in humans, as well as specific behavioral alterations in laboratory animals [1]. The pharmacological effects of the cannabinoids have been hypothesized to be mediated by a variety of mechanisms including general membrane perturbation, such as occurs with general anesthetics [2, 3], or other more specific alterations of membrane fluidity [4, 5], as well as possible interactions with a hypothetical THC receptor [6–8]. Evidence

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suggesting that the cannabinoids act *via* a specific receptor include structure–activity relationships (SAR) indicating that subtle changes in structure can greatly alter potency or activity [9–11].

One noticeable aspect of cannabinoid chemistry is that this class of compounds does not contain a nitrogen atom. Therefore, many have investigated the effects of substitutions of functional groups with nitrogen-containing moieties, as well as the pharmacology of nitrogen-containing heterocyclic analogues of $\Delta^9$-THC. However, except for alterations at the C-1 phenolic hydroxy group, no cannabinoids have been synthesized with a sulfur-containing functional group attached, though a small number of sulfur-containing heterocyclic analogues of $\Delta^9$-THC have been determined to possess cannabimimetic activity [11–13].

If cannabinoids produce pharmacological effects *via* partitioning into, and disruption of lipid membranes (which is probably a function of their extreme lipophilicity), then substitution of an –SH for the –OH group of 11-hydroxy-$\Delta^8$-THC (which would increase lipid solubility) should increase potency. Alternately, if cannabinoids produce effects *via* a mechanism requiring specific molecular interactions, then the simple –SH substitution would likely either decrease or not alter activity, though substitutions of greater bulk (*e.g.*, $-SCOCH_3$) would probably produce sufficiently large steric hindrances to reduce potency. Therefore, a group of novel sulfur-containing derivatives of $\Delta^8$-THC were synthesized and evaluated pharmacologically in order to further evaluate the SAR of the cannabinoids. Additionally, because of interest in developing an inactive analogue which might possess antagonistic properties, a 10-mercapto-cannabidiol derivative was also prepared.

## Chemistry

We previously reported [14] a practical synthesis of 10-hydroxy-cannabidiol (**2**) from cannabidiol (**1**). We have now found that treatment of **2** with thioacetic acid in the presence of a complex of diisopropylazodicarboxylate and triphenylphosphine in dry THF gives 10-thioacetyl-cannabidiol (**3**) in 57% yield. Further treatment of **3** with $LiAlH_4$ formed the mercapto derivative **4** in 36% yield. By following a similar sequence, 11-hydroxy-$\Delta^8$-THC (**6**)* the major metabolite of $\Delta^8$-THC (**5**), was converted into the sulfur analogues **7** and **8** in 69% and 67% yields, respectively. The 12$\beta$-thioacetyl derivative **10** of $\Delta^8$-THC was similarly prepared from 12$\beta$-hydroxy-$\Delta^8$-THC (**9**) in 23% yield. The yield in this case was lower, presumably, because the 12$\beta$-hydroxyl group in **9** is not allylic and is somewhat hindered. This sequence appears to be of general application in cannabinoids for the conversion of alcohols to thiol esters and thiols, and hence extends the scope of the original report of Volante [15] for the preparation of mercapto derivatives from alcohols.

*This was prepared by $SeO_2$ oxidation of $\Delta^8$-THC acetate using the conditions described by Inayama S., Sawa A. & Hosoya E. (1974) *Chem. Pharm. Bull.* 22, 1519–1525, followed by $LialH_4$ reduction. For other references on the synthesis of the metabolite **6** see Razdan R.K. (1981) *in: Total Synthesis of Natural Products, Vol. 4* (Apsimon J., ed.), Wiley & Sons, New York, pp. 185–262.

## Pharmacology and Discussion of results

*Agonistic activity*

The pharmacological evaluations of **4**, **7**, **8**, and **10** are shown in Table I. Unlike either $\Delta^8$- or $\Delta^9$-THC, none of the analogues produced a dose-dependent depression of spontaneous activity at doses up to 10–30 mg/kg. In contrast, the $ED_{50}$'s for depression of spontaneous activity by $\Delta^9$- and $\Delta^8$-THC were 2.9 and 10 mg/kg, respectively (data not shown). There was a statistically significant increase in spontaneous activity by **7** at a dose of 1 mg/kg. However, no biological significance can be inferred from single dose effects.

Analogues **4**, **8**, and **10** also failed to produce a dose-dependent depression in rectal temperature at doses up to 10–30 mg/kg, yet $\Delta^9$- and $\Delta^8$-THC reduced rectal temperature beyond control values by 4.0 and 3.9°C, respectively, at a dose of 10 mg/kg (data not shown). Only analogue **7** significantly altered rectal temperature, but doses of 10–30 mg/kg were required and only minor decreases in temperature occurred, which suggested **7** was a weak cannabinoid of at least 3-fold less potency than $\Delta^9$- or $\Delta^8$-THC.

The ability of **4**, **7**, **8**, **10** to produce antinociception is presented in Table I as the % maximum possible effect (% *MPE*). Only **10** produced a statistically significant degree of antinociception at a dose of 1 mg/kg, but the effect was not dose dependent. Similarly, **8** produced antinociception at 10–30 mg/kg, yet the effect was not dose dependent. In contrast, **7** produced a large degree of antinociception in a dose-dependent fashion. However, the $ED_{50}$ of $\Delta^9$-THC in the tail-flick procedure was 1.3 mg/kg (data not shown), suggesting that **7** is approximately 100-fold less potent than $\Delta^9$-THC. Analogue **4** failed to produce antinociception at doses up to 10 mg/kg.

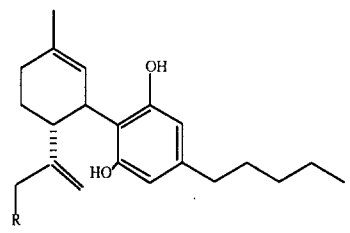
The ability of **7**, **8**, and **10** to produce catalepsy is presented in Table I as the % immobility. $\Delta^8$-THC produced maximal catalepsy (39%) at 10 mg/kg, while $\Delta^9$-THC produced maximal catalepsy (42%) at 6 mg/kg (data not shown). Only **7** produced a significant degree of catalepsy (10 and 30 mg/kg), yet appears to be more than 3-fold less potent than $\Delta^9$- or $\Delta^8$-THC. Analogue **8** produced some catalepsy at 30 mg/kg, but only at this single high dose, so biological significance cannot be inferred. Analogue **10** was inactive at 10 mg/kg, and **4** was not tested.

*Antagonistic properties*

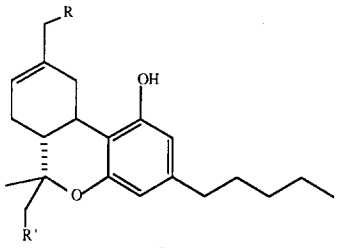
The above data indicate that **4**, **7**, **8**, and **10** either possess no cannabimimetic activity, or only posses minimal activity. Therefore, these analogues were evaluated for their ability to antagonize the pharmacological effects of 6 mg/kg of $\Delta^9$-THC.

Figure 1 indicates that the 10 mg/kg **4**/vehicle treatment failed to produce a significant effect *versus* the vehi-

**Table I.** Dose–response data (mean ± SEM) for cannabinoid analogs.




| | | R |
|---|---|---|
| 1 | (cannabidiol) | H |
| 2 | | -OH |
| 3 | | $-SCOCH_3$ |
| 4 | (10-mercapto-cannabidiol) | -SH |




| | | R | R' |
|---|---|---|---|
| 5 | ($\Delta^8$-THC) | H | H |
| 6 | | -OH | H |
| 7 | | $-SCOCH_3$ | H |
| 8 | (11-mercapto-$\Delta^8$-THC) | -SH | H |
| 9 | | H | -OH |
| 10 | | H | $-SCOCH_3$ |

| | Spontaneous activity (total counts) | | | | Rectal temperature (°C) | | | | % Maximum possible effect (tail-flick) | | | | Catalepsy (% immobility) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cannabinoid | **8** | **7** | **10** | **4** | **8** | **7** | **10** | **4** | **8** | **7** | **10** | **4** | **8** | **7** | **10** | **4** |
| Dose (mg/kg) | | | | | | | | | | | | | | | | |
| 0 | 61 ± 9 | 47 ± 5 | 44 ± 6 | 44 ±10 | −0.8 ±0.2 | −0.9 ±0.2 | −1.2 ±0.3 | −1.5 ±0.3 | 6 ± 2 | 9 ± 2 | 8 ± 2 | 9 ± 3 | 4 ± 1 | 4 ± 1 | 4 ±1 | NT[a] |
| 1 | 68 ±11 | 81* ± 9 | 32 ±10 | 62 ±14 | −0.5 ±0.3 | −0.6 ±0.3 | −2.0 ±0.7 | −2.2 ±0.5 | 9 ± 4 | 7 ± 3 | 39* ±11 | 6 ± 5 | NT | NT | NT | NT |
| 3 | 48 ± 5 | 67 ±12 | 51 ± 8 | 76 ±11 | −1.1 ±0.3 | −0.8 ±0.2 | −0.4 ±0.2 | −1.4 ±0.4 | 3 ± 2 | 6 ± 3 | 25 ±10 | 11 ± 3 | NT | NT | NT | NT |
| 10 | 60 ± 9 | 32 ± 5 | 45 ± 6 | 70 ±14 | −1.1 ±0.3 | −1.9* ±0.3 | −1.5 ±0.4 | −1.8 ±0.5 | 23* ± 5 | 37* ± 7 | 29* ± 6 | 10 ± 3 | 16 ± 5 | 22* ± 4 | 9 ±2 | NT |
| 30 | 56 ±14 | 21 ± 7 | NT | NT | −1.3 ±0.4 | −2.3* ±0.3 | NT | NT | 25* ± 6 | 55* ± 8 | NT | NT | 22* ± 4 | 34* ± 4 | NT | NT |

*Significantly different ($P<0.05$) *versus* vehicle (0 mg/kg) by ANOVA with Dunnett's *t*-test. ($N=12-24$). [a]NT, not tested.

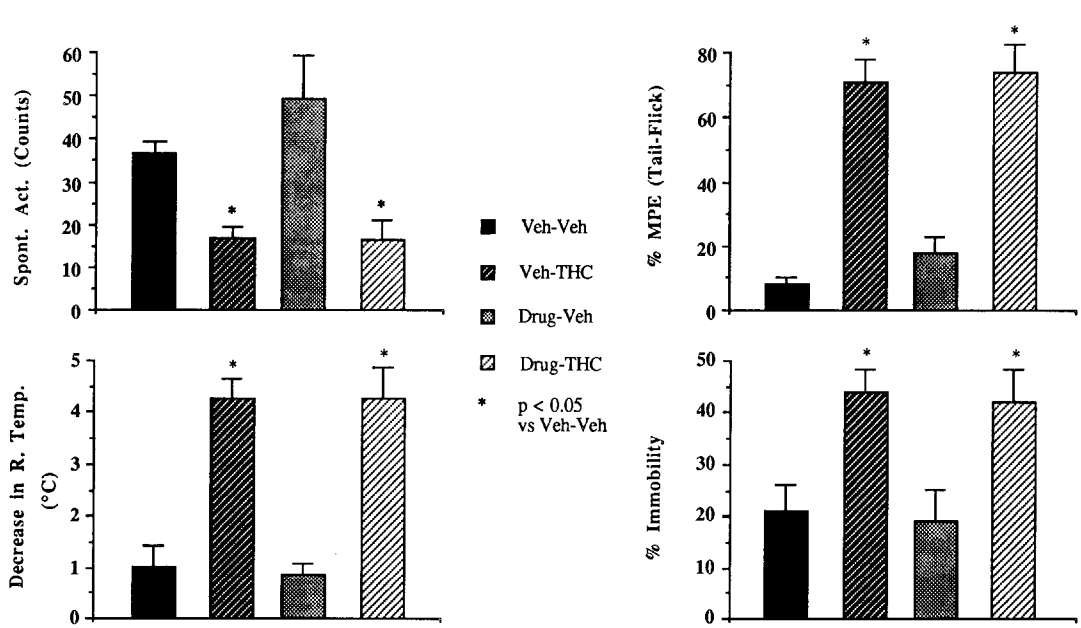



**Fig. 1.** Lack of antagonism of the effects of $\Delta^9$-THC. Alteration by 10 mg/kg **4** pretreatment on 6 mg/kg $\Delta^9$-THC-induced decrease in spontaneous activity (total counts/10 min), decrease in rectal temperature (°C), antinociception (tail-flick % *MPE*), and catalepsy (% immobility). The various dual-injection treatment groups ($N=12-18$) were: vehicle/vehicle (solid background), vehicle/$\Delta^9$-THC (solid with light cross-hatching), **4**/vehicle (stippled), and **4**/$\Delta^9$-THC (light background with dark cross-hatching). Multiple comparisons performed using analysis of variance and *post hoc* evaluation with the Schefe *F*-test. *$P < 0.05$ *versus* vehicle/vehicle control.

cle / vehicle control, and did not after the effects of $\Delta^9$-THC on spontaneous activity, rectal temperature, tail-flick % *MPE*, or % immobility. Additionally, *post hoc* statistical analysis also showed that the combination treatment of vehicle / $\Delta^9$-THC was not different from **4** / $\Delta^9$-THC treatment in any of the evaluations (suggesting no antagonism by **4**). Thus, these data indicate that analogue **4** failed to antagonize the effects of $\Delta^9$-THC. Analogues **7**, **8**, and **10** were similarly tested at doses of 3, 10, and 10 mg / kg of cannabinoid, respectively, and also did not significantly alter the effects of $\Delta^9$-THC on spontaneous activity, rectal temperature, % *MPE*, or % immobility.

## Conclusions

The earliest reported investigation of a sulfur-containing heterocyclic cannabinoid by Dewey *et al.* [13] indicated this cannabinoid possessed an interesting pharmacological profile. It was active in the mouse and in the dog static-ataxia model, but did not alter the cardiovascular parameters of anesthetized dogs. In contrast, substitution of an −SH group for the phenolic −OH of $\Delta^9$-THC produces inactive analogues, even if lipid solubility is increased by altering the 5-carbon side chain [16, 17]. Similarly, substitution of an $-SO_3K$ or $-NHSO_2CH_3$ group at the C-1 position also produces inactive canabinoids [17, 18]. However, substitutions of sulfur-containing groups at sites other than the C-1 position of the cannabinoid structural nucleus have not been investigated until this report. Only **7** showed any activ-ity, yet this analogue was between 3- and 100-fold less potent than $\Delta^9$- or $\Delta^8$-THC. Simple -SH substitution for the −OH group at the C-11 position of 11-OH-$\Delta^8$-THC (**6**) produced the inactive cannabinoid **8**. This was an unexpected result, since 11-OH-$\Delta^8$-THC (**6**) is approximately 2.5-fold more potent than $\Delta^9$-THC [11]. Thus, the reason for the inactivity of **8** is unclear. Similarly, **10** was also inactive, as was **4** (which was expected since it is an analogue of the relatively inactive cannabidiol). Thus, even minor substitutions or additions of sulfur-containing functional groups upon the basic cannabinoid structural nucleus resulted in a tremendous loss of activity. These data would tend to suggest that specific structural requirements, and not lipophilicity alone, is of primary importance in determining cannabimimetic activity. However, it is still possible that a high degree of lipophilicity is a necessary, though not a sufficient, characteristic for the production of cannabimimetic effects. Lastly, though these analogues were inactive, none were found to antagonize the effects of $\Delta^9$-THC.

## Experimental protocols

### Chemistry

The infrared spectra were recorded on a Perkin−Elmer Model 1320 spectrophotometer and the NMR spectra were measured on a Varian T-60 spectrometer with tetramethylsilane as an internal standard. Elemental analysis was performed by Atlantic Microlab, Inc. (Atlanta, GA). Mass spectra were obtained with a Hewlett−Packard 5988 mass spectrometer using direct insertion probe. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

*10-Thioacetyl-cannabidiol* ***3***

To a well-stirred solution of 2.20 g (8.86 mmol) of triphenylphosphine in 22 ml of dry THF at 0°C was added 1.8 ml (9.06 mmol) of diisopropylazodicarboxylate, which produced a white solid precipitate. After stirring the heterogeneous mixture for 30 min at 0°C, a solution of 489 mg (1.47 mmol) of triol **2** and 0.22 ml (2.94 mmol) of thioacetic acid in 11 ml of dry THF was added dropwise to the reaction mixture over 10 min while maintaining the temperature at 0°C. During the addition, initially a brownish colored mixture was formed which changed to green towards the end of the addition. After stirring for 1 h at 0°C and then 30 min at room temperature, the reaction mixture was diluted with 100 ml of water and extracted with 4 50-ml portions of ether. The combined ether extracts were washed with 100 ml of brine, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residual solid was purified by flash chromatography using $CH_2Cl_2$ / hexane 1:1 as eluant to provide 330 mg (57% yield) of thioacetate **3** as a yellow gum; NMR ($CDCl_3$) $\delta$ 0.85 (t, 3 H, $\omega$-$CH_3$), 1.78 (s, 3 H, H-7), 2.09 (s, 3 H, $SCOCH_3$), 3.45 (s, 2 H, H-10), 3.96 (m, 1 H, H-3), 4.95 (m, 2 H, H-9), 5.60 (br s, 1 H, H-2), 5.63 (br s, 2 H, exchangeable with $D_2O$), 6.23 (s, 2 H, Ar H).

*10-Mercapto-cannabidiol* ***4***

To a mixture of 129 mg (3.39 mmol) of lithium aluminum hydride in 15 ml of dry ether at 0°C was slowly added a solution of 330 mg (0.85 mmol) of thioacetate **3** in 20 ml of dry ether over 5 min. The ice bath was removed and the reaction mixture was stirred at room temperature for 30 min. Water was added dropwise to the reaction mixture with cooling, and it was stirred for 10 min at room temperature. The reaction mixture was then made acidic with 1 N HCl and extracted with 3 50-ml portions of ether, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residual solid was purified by flash chromatography using $CH_2Cl_2$ / petroleum ether 1:1 as eluant to provide 106 mg (36% yield) of **4** as a yellow foam; NMR ($CDCl_3$) $\delta$ 0.86 (t, 3 H, $\omega$-$CH_3$), 1.80 (s, 3 H, H-7), 2.95 (d, 2 H, H-10, doublet changed to singlet when exchanged with $D_2O$), 3.96 (m, 1 H, H-3), 4.90 (s, 1 H, H-9), 5.07 (s, 1 H, H-9), 5.60 (s, 1 H, H-2), 6.29 (s, 2 H, Ar H); MS *m / e* 346 ($M^+$); Anal. ($C_{21}H_{30}O_2S$) C, H, S.

*11-Thioacetyl-*$\Delta^8$*-THC* ***7*** *and 11-mercapto-*$\Delta^8$*-THC* ***8***

With use of the same procedure as described for **3**, treatment of 164 mg (0.49 mmol) of 11-hydroxy-$\Delta^8$-THC (**6**) with 87 $\mu$l (1.21 mmol) of thioacetic acid in the presence of 0.4 ml (2.03 mmol) of diisopropylazodicarboxylate and 521 mg (1.98 mmol) of triphenylphosphine followed by purification by chromatography ($CH_2Cl_2$ / hexane 1:1) gave **7** as a yellow gum (134 mg; 69% yield); homogeneous by TLC ($CH_2Cl_2$ / hexane 1:1); NMR ($CDCl_3$) $\delta$ 0.88 (t, 3 H, $\omega$-$CH_3$), 1.10 and 1.40 (s, 3 H, gem $CH_3$'s), 2.40 (s, 3 H, $SCOCH_3$), 3.59 (s, 2 H, H-11), 5.76 (br s, 1 H, H-8), 6.11 (br s, 1 H, H-2), 6.30 (br s, 1 H, H-4); IR $\nu_{max}$ (film) 3400, 1650 $cm^{-1}$; MS *m / e* 388 ($M^+$); Anal. ($C_{23}H_{32}O_3S \cdot 1/4\ H_2O$) C, H, S.

Further treatment of 134 mg (0.34 mmol) of **7** with 52 mg (1.36 mmol) of $LiAlH_4$ in 15 ml of ether, as in the preparation of **4**, gave a gum which was purified by chromatography ($CH_2Cl_2$ / hexane 1:1). Compound **8** was obtained as a light yellow foam (81 mg; 67% yield); NMR ($CDCl_3$) $\delta$ 0.88 (t, 3 H, $\omega$-$CH_3$), 1.13 and 1.43 (s, 3 H, gem $CH_3$'s), 3.35 (s, 2 H, H-11), 5.74 (br s, 1 H, H-8), 6.13 (br s, 1 H, H-2), 6.33 (br s, 1 H, H-4); MS *m / e* 346 ($M^+$). Anal ($C_{21}H_{30}O_2S \cdot 1/4\ H_2O$) C, H.

*12*$\beta$*-Thioacetyl-*$\Delta^8$*-THC* ***10***

With use of the same procedure as described for **3**, treatment of 100 mg (0.3 mmol) of **9** with 53 $\mu$l (0.7 mmol) thioacetic acid in the presence of 0.24 ml (1.21 mmol) of diisopropylazodicarboxylate and 318 mg (1.21 mmol) of triphenylphosphine followed by purification by chromatography ($CH_2Cl_2$ / hexane 1:1) gave **10** as a light yellow gum (27 mg; 23% yield); homogeneous by TLC ($CH_2Cl_2$ / hexane 1:1); NMR ($CDCl_3$) $\delta$ 0.88 (t, 3 H, $\omega$-$CH_3$), 1.17 (s, 3 H, H-13), 1.72 (s, 3 H, H-11), 2.41 (s, 3 H, $SCOCH_3$), 3.35 (d, 2 H, H-12), 5.48 (br s, 1 H, H-8), 6.21 (br s, 1 H, H-2), 6.36 (br s, 1 H, H-4); MS *m / e* 388 ($M^+$); Anal. ($C_{23}H_{32}O_3S \cdot 1/2\ H_2O$) C, H, S.

### Pharmacology

*Materials*

Male ICR mice (22−30 g), obtained from Dominion Laboratories

(Dublin, VA), were maintained on a 12-h light:dark cycle, and received food and water *ad libitum*. $\Delta^8$- and $\Delta^9$-THC were obtained from the National Institute on Drug Abuse.

*Drug preparation and administration*
The procedure of Olson *et al.* [19] was used to prepare suspensions suitable for injection, resulting in a final vehicle of ethanol:emulphor:saline (1:1:18), which was administred *via* tail-vein injection (0.1 ml / 10 g).

*Behavior evaluation*
Spontaneous activity, antinociception, hypothermia, and catalepsy were evaluated by previously reported methods [20]. $ED_{50}$ values were generated by the method of Litchfield and Wilcoxon [21]. Possible antagonistic properties of the cannabinoids were also determined by previously reported methods [22]. Mice were pretreated with 3 mg / kg (analog **7**) or 10 mg / kg (analogs **4**, **8**, and **10**) of the sulphur-containing drug 10 min prior to administration of 6 mg / kg $\Delta^9$-THC. Statistical analysis was performed using ANOVA (with Dunnet's *t*-test for comparisons to control, and Schefe's *F*-test for multiple comparisons), and differences considered significant at the $P < 0.05$ level (two-tailed).

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