Use of a Potential Rabbit Model for Structure–Behavioral Activity Studies of Cannabinoids

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Using the genetically unique tetrahydrocannabinol-seizure susceptible (THC-SS) rabbit, the behavioral effects of 14 cannabinoids or related structures were determined and compared to the effects of 11 previously tested cannabinoids. Relative potencies of the cannabinoid-induced convulsions in THC-SS rabbits were generally comparable to reported relative potencies of cannabinoid-produced psychoactivity in humans and other behavioral activity in monkeys or other species. These data suggest that the THC-SS rabbit may represent an experimentally convenient and reliable animal model for studies of structure–psychoactivity relationships of marijuana-like compounds.

Recently, we have summarized in detail the data concerning a new, putative animal model of marijuana psychoactivity, the tetrahydrocannabinol-seizure susceptible (THC-SS) rabbit.[1] Briefly, because of a homozygous expression of a single autosomal gene (*thc*) in our rabbit colony (Uaz:NZW-*thc*),[2] THC-SS rabbits exhibit nonfatal, behavioral convulsions when injected with (−)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC, **1a**), the major psychoactive ingredient in marijuana.[1-7] Members of our rabbit colony without this genetic background are THC-seizure resistant. In THC-SS rabbits, convulsions are elicited with other cannabinoids known to be psychoactive in humans[1,3] but not with nonpsychoactive cannabinoids or noncannabinoid psychoactive drugs.[1,3] Also, other major correlates exist between cannabinoid-induced behavioral responses in THC-SS rabbits and cannabinoid-produced psychoactivity in humans, i.e., Δ^9-THC dose–effect relationships,[4] comparability of minimally effective doses of Δ^9-THC to elicit the behaviors,[1,4] reversible tolerance development with chronic Δ^9-THC administration,[3,5] electroencephalographic correlates with Δ^9-THC,[6] and the ability of the nonpsychoactive cannabidiol (CBD, **8**) to block the Δ^9-THC-produced behaviors.[7] Moreover, the convulsant potencies of 11 cannabinoids (**1a–d**, (−)-**2a,c**, **3a**, **5a**, **6**, **8**, and **10**) in THC-SS rabbits correlate well with the psychoactive potencies of these compounds in humans.[1]

In this paper we describe the behavioral effects in THC-SS rabbits of 14 additional cannabinoids (**1e,f**, (+)-**2a**, **2b,d,e**, **3b**, **4**, **5b,c**, **7**, **9**, 11 and the γ-morpholinobutylate ester of **1a**). The relative potencies of all 25 compounds (structures 1–11) to cause convulsions in THC-SS rabbits are listed (Table I) and discussed in terms of their reported behavioral activities in other species.

Results

Inspection of Table I reveals that the capability of the compounds tested to induce convulsions in THC-SS rabbits is confined to those possessing a nearly planar benzopyran ring system, i.e., 1–7. Thus, structures with an open pyran (e.g., cannabidiol, **8**) or terpenoid (e.g., cannabichromene, **10**) ring structure are inactive. Cannabicyclol (**9**), a highly nonplanar tetracyclic structure, is similarly inactive. Olivetol (11), a partial structural component of most cannabinoids, is also inactive. The two cannabinoids that are believed to be responsible, in part, for the psychoactive properties of marijuana, (−)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC, **1a**, the major constituent[8,9]) and (−)-*trans*-Δ^8-tetrahydrocannabinol (Δ^8-THC, **2a**, a minor constituent[10]) are both very active in the test, with

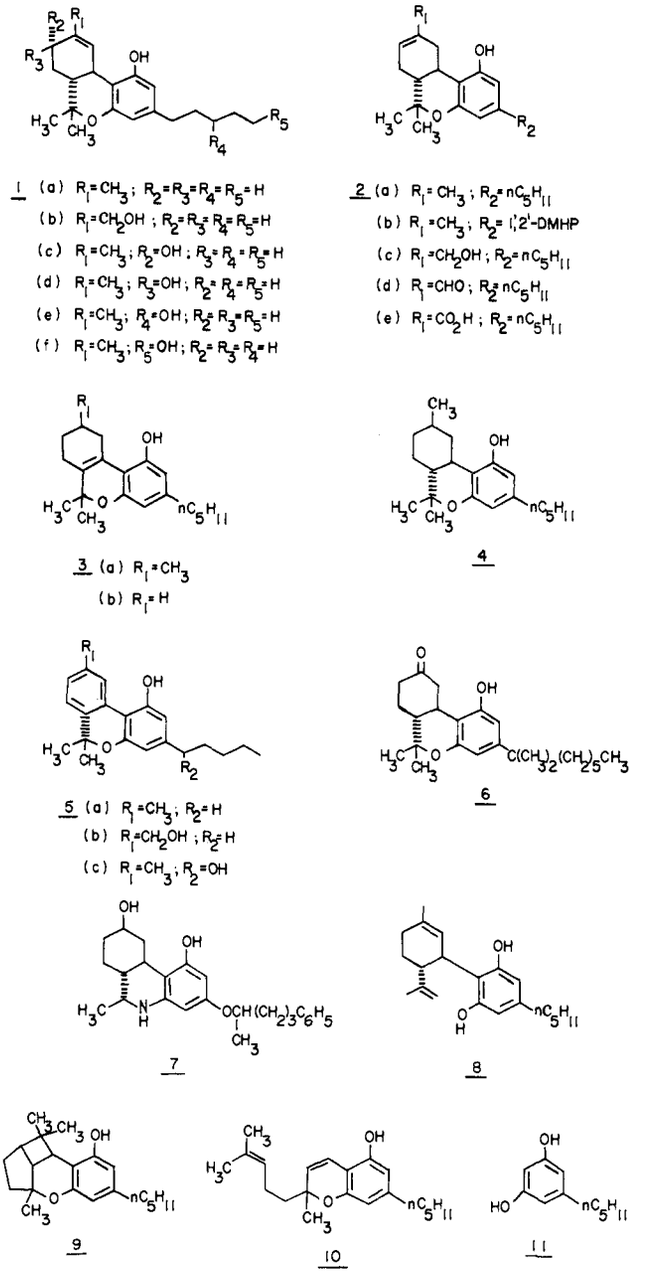

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Table I. Relative Potency of Δ^9-THC (= 100%) and Other Cannabinoids for Causing Convulsions in THC-SS Rabbits

cannabinoid	dose(s), mg/kg iv	no. of rabbits convulsed/no. tested	rel potency[a]
(−)-nantradol (7)	0.005; 0.01	3/4; 2/2	750
nabilone (6)	0.005; 0.01; 0.1	3/4; 4/4; 4/4	750
11-OH-Δ^9-THC (1b)	0.01; 0.05; 0.1; 0.25	3/4; 4/4; 4/4; 5/5	375
Δ^8-THC-1',2'-DMHP (2b)	0.01; 0.05	3/4; 3/3	375
11-OH-Δ^8-THC (2c)	0.01; 0.05; 0.25; 0.5; 1	2/4; 4/4; 1/1; 1/1; 1/1	250
3'-OH-Δ^9-THC (1c)	0.01; 0.05	2/4; 4/4	250
Δ^9-THC (1a)	0.01; 0.05; 0.1; 0.5; 0.9; 10	0/4; 14/14; 10/10; 20/20; 9/9; 1/1	100
11-oxo-Δ^8-THC (2d)	0.01; 0.05; 0.5	0/4; 4/4; 4/4	100
5'-OH-Δ^9-THC (1f)	0.05; 0.1	2/4; 4/4	50
(−)-Δ^8-THC [(−)-2a]	0.05; 0.1; 0.5	2/4; 4/4; 7/7	50
hexahydro-CBN (4)	0.05; 0.1; 0.5; 1; 5	2/4; 1/1; 1/1; 3/3; 1/1	50
SP111-A[b]	0.1; 0.25; 0.5; 1	0/1; 0/5; 3/4; 6/6	7.5
$\Delta^{6a(10a)}$-THC (3a)	0.1; 0.5; 0.9	0/2; 2/3; 4/4	6.7
8β-OH-Δ^9-THC (1c)	0.1; 0.9; 5; 10	0/2; 0/1; 2/2; 1/1	1
11-OH-CBN (5b)	0.5; 1; 2; 4	0/1; 1/4; 2/2; 1/1	1
(+)-Δ^8-THC [(+)-2a]	5; 20	2/4; 1/1	0.5
cannabinol (CBN, 5a)	10; 15	4/6; 10/10	0.3
11-nor-9-carboxy-Δ^8-THC (2e)	1; 5; 10; 20	0/3; 0/1; 0/1; 2/2	0.3
11-nor-$\Delta^{6a(10a)}$-THC (3b)	0.9; 20	0/3; 1/3	0.1
cannabichromene (10)	8; 15; 20	0/2; 0/1; 1/4	0.1
8α-OH-Δ^9-THC (1d)	0.1; 0.9; 20	0/1; 0/1; 0/2	0
cannabicyclol (9)	8; 20	0/1; 0/2	0
1'-OH-CBN (5c)	5; 10	0/1; 0/1	0
cannabidiol (CBD, 8)	15; 20	0/7; 0/6	0
Olivetol (11)	20	0/4	0

[a] Calculated by the following formula: lowest effective dose of Δ^9-THC (0.05 mg/kg)/lowest effective dose of cannabinoid × percent of rabbits convulsed = relative potency. [b] γ-Morpholinobutyrate ester of Δ^9-THC.

Δ^9-THC exhibiting twice the potency of Δ^8-THC. Furthermore, the behavioral response is apparently also specific for the naturally occurring cannabinoid stereoisomers, since (+)-Δ^8-THC [(+)-**2a**, prepared according to the procedure of Mechoulam et al.[11]] is much less active than (−)-Δ^8-THC [(−)-**2a**].[12]

The metabolism of THC's in laboratory animals and in man has been extensively studied and reviewed.[13-16] Numerous oxygenated metabolites have been isolated and identified. Several have been shown to elicit THC-like behavioral changes in various animal species, including man,[15,16] raising the question of whether the psychoactive effects are primarily due to the THC's themselves or to one or more of their metabolites. Five oxygenated metabolites of Δ^9-THC have been evaluated in THC-SS rabbits thus far: three ring-hydroxylated derivatives (**1b–d**) and two side-chain hydroxylated derivatives (**1e,f**). 11-Hydroxy-Δ^9-tetrahydrocannabinol (**1b**) was found to be 3–4 times more potent than Δ^9-THC. On the other hand, 8β-hydroxy-Δ^9-tetrahydrocannabinol (**1c**) and its 8α-hydroxy isomer (**1d**) exhibited relatively low activity in the doses tested. The two side-chain metabolites 3'-hydroxy-Δ^9-tetrahydrocannabinol (**1e**) and 5'-hydroxy-Δ^9-tetrahydrocannabinol (**1f**) were both significantly active; the former was 2.5 times and the latter 0.5 times the potency of Δ^9-THC. Three oxygenated metabolites of Δ^8-THC were evaluated: the 11-hydroxy-, 11-oxo-, and the 11-nor-9-carboxy derivatives, **2c–e**, respectively. Both **2c** and **2d** were more active, 5 and 2 times, respectively, than Δ^8-THC. The carboxylic acid derivative (**2e**), on the other hand, was virtually inactive.

Cannabinol (CBN, **5a**) and two of its metabolites, 11-hydroxycannabinol (**5b**) and 1'-hydroxycannabinol (**5c**), were also evaluated and, as expected, found to be much less active than Δ^9-THC. Again, the 11-hydroxy metabolite **5b** was more potent than CBN itself, paralleling the situation observed in the Δ^8- and Δ^9-THC's. Side-chain metabolite **5c** was inactive at the doses tested, suggesting that oxidation at the 1' position is a mechanism for metabolic inactivation.

Several synthetic cannabinoids have been tested in our THC-SS rabbit model. These include the 1',2'-dimethylheptyl side-chain derivative of Δ^8-THC (**2b**), two members of the Δ^6-tetrahydrocannabinol series (**3a** and **3b**), nabilone (**6**), and levonantradol (**7**). The 1',2'-dimethylheptyl analogue of Δ^8-THC (**2b**) was found to be 7–8 times more potent than Δ^8-THC, paralleling the increased central nervous system potency generally observed with this side-chain modification in cannabinoids.[17,18] The $\Delta^{6a(10a)}$-THC derivatives, $\Delta^{6a(10a)}$-tetrahydrocannabinol (**3a**) and 11-nor-$\Delta^{6a(10a)}$-tetrahydrocannabinol (**3b**), caused behavioral convulsions in THC-SS rabbits but were 15 and 1000 times less active, respectively, than Δ^9-THC. Among the more interesting of our results is the very great potency observed for the synthetic cannabinoid analogues, nabilone (**6**, Lilly compound 109514)[19] and levonantradol (**7**, Pfizer compound CP-50,556).[20] Both were found to be 7.5 times

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Table II. Comparison of the Cannabinoid Activities Relative to Δ^9-THC for Producing Behavioral Convulsions in THC-SS Rabbits and Their Behavioral Effects in Rhesus Monkeys (RM), Dogs (D), Rats (R), Mice (M), or Pigeons (P)

cannabinoid	THC-SS rabbit[a]	other species	ref
(−)-nantradol (7)	>	> (R, M)	31, 20
nabilone (6)	>	> (D, R)	31, 32
11-OH-Δ^9-THC (1b)	>	> (R, P); = (RM)	31, 35, 17
Δ^8-THC-1',2' DMHP (2b)	>	> (RM)	17
11-OH-Δ^8-THC (2c)	>	> (R, M); = (RM)	33, 35, 17, 28
3'-OH-Δ^9-THC (1e)	>	>, analogue (RM)	34
11-oxo-Δ^8-THC (2d)	=	> (M); =, analogue (RM)	33, 30
5'-OH-Δ^9-THC (1f)	<	<, analogue (RM)	34
(−)-Δ^8-THC [(−)-2a]	<	< (RM)	17
hexahydro-CBN (4)	<	< (RM)	17
SP111-A[b]	<	< (R, P)	35
$\Delta^{6a(10a)}$-THC (3a)	<	< (RM)	17
8β-OH-Δ^9-THC (1c)	0	< (RM)	29
11-OH-CBN (5b)	0	0 (RM)	25
(+)-Δ^8-THC [(+)-2a]	0	0 (RM)	17
cannabinol (CBN) (5a)	0	0 (RM)	17, 27
11-nor-9-carboxy-Δ^8-THC (2e)	0	0 (RM)	30
11-nor-$\Delta^{6a(10a)}$-THC (3b)	0	0 (D); <,>, analogues (D, M)	36, 37
cannabichromene (10)	0	0 (RM)	17, 27
8α-OH-Δ^9-THC (1d)	0	< (RM)	17, 29
cannabicyclol (9)	0	0 (RM)	17, 27
1'-OH-CBN (5c)	0	not tested (?)	
cannabidiol (CBD, 8)	0	0 (RM)	17, 27
olivetol (11)	0	not tested (?)	

[a] Activity taken from Table I. [b] γ-Morpholinobutylate ester of Δ^9-THC (1a): >, more active than Δ^9-THC; =, equal in activity to Δ^9-THC; <, less active than Δ^9-THC; 0, inactive or virtually inactive (less than 5% of the activity of Δ^9-THC).

more active than Δ^9-THC as inducers of convulsions in THC-SS rabbits.

Discussion

The combined data of Table I illustrate the relative potencies of several cannabinoids for inducing behavioral convulsions in THC-SS rabbits compared to that of Δ^9-THC (**1a**). In general, these relative potency relationships appear to be congruent with reported data of relative cannabinoid potencies for inducing behavioral changes in other animal species. A particularly salient measure for comparison is human psychoactivity itself, i.e., the constellation of subjective, mental perturbations that are purportedly characteristic of the marijuana-induced "high".[23] In this regard, we have previously shown[1] that there is a positive and highly significant correlation between the potencies of cannabinoids (i.e., **1a–d, 2a,c, 3a, 5a, 6, 8,** and **10**) for causing seizures in THC-SS rabbits and the potencies of these same 11 cannabinoids for eliciting psychoactivity in humans. Additionally, levonantradol (**7**) is a potent convulsant in our rabbits (Table I). Although no direct comparative studies with Δ^9-THC have been published, levonantradol has recently been reported to produce Δ^9-THC-like psychoactivity in humans at relatively low doses.[21,22] To our knowledge, the other cannabinoids listed in Table I have not yet been similarly evaluated in humans.

While the effects of various cannabinoids have been reported for a host of behavioral measures in a multitude of other species,[24] cannabinoid alteration of normal, Rhesus monkey behavior is generally thought to be particularly reflective of marijuana-induced psychoactivity.[11,17,24,26] Indeed, Mechoulam and co-workers[17,24] have provided the most extensive analysis of structure–activity relationships of cannabinoids using primarily Rhesus monkey behaviors[26] and, to a lesser extent, dog ataxia[26] as models. Thus, Table II and the following discussion primarily emphasize comparisons of the present data in THC-SS rabbits with that of the latter, previously reported data in monkeys. Additional comparisons, as indicated (in Table II and the following discussion), are derived from selective cannabinoid effects in other species, where appropriate.

Although there are some exceptions, for the most part the monkey behavioral data are comparable to the data obtained from the THC-SS rabbit with respect to the relative activity of cannabinoids. As was demonstrated in the THC-SS rabbit, CBD (**8**), cannabicyclol (**9**), and cannabichromene (**10**) were inactive in producing Δ^9-THC-like behavioral alterations in monkeys.[17,27] Similarly, CBN (**5a**), 11-nor-9-carboxy-Δ^8-THC (**2e**), and (+)-THC [(+)-**2a**] were inactive in monkeys[17,27,30] and inactive, or virtually inactive, in THC-SS rabbits. Compared with (−)-Δ^9-THC [(−)-**1a**], (−)-Δ^8-THC [(−)-**2a**] was slightly less active in monkey[17] and rabbit tests. Parallels are also seen with some of the rabbit and monkey responses to cannabinoid metabolites. Thus, 8β-hydroxy- and 8α-hydroxy-Δ^9-THC (**1c** and **1d**) were both less active than Δ^9-THC in monkeys[17,29] and in THC-SS rabbits. The metabolite, 5'-hydroxy-Δ^9-THC (**1f**) was half as active, whereas the 3'-hydroxy side-chain metabolite of Δ^9-THC (**1e**) was found

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to be 3 times more active than the parent compound in THC-SS rabbits. While these latter metabolites of Δ^9-THC have not been tested in monkeys, the corresponding 5′-hydroxy analogue of Δ^8-THC has been reported to be slightly less active than Δ^8-THC and 3′-hydroxy-Δ^8-THC more potent than Δ^8-THC.[34] The activities of 11-hydroxy-Δ^9-THC and 11-hydroxy-Δ^8-THC were equally active to one another and to Δ^9-THC in monkeys.[17] This is discrepant with our data that show these hydrolyated metabolites to be more potent than Δ^9-THC. In this instance, our results in THC-SS rabbits are more similar to those found in rodents and pigeons.[31,33,35] In addition, 11-oxo-Δ^8-THC (**2d**), one of the most active compounds tested (i.e., equal in potency to that of Δ^9-THC) in our rabbits, was not tested in monkeys, but 1-acetoxy-11-oxo-Δ^8-THC has been reported to exhibit the same level of activity as Δ^8-THC in this species.[30] However, 11-oxo-Δ^8-THC (**2d**) has recently been shown to be more active than Δ^8-THC in mice.[33]

In monkeys, cannabinol (CBN, **5a**) was inactive, its 11-hydroxy metabolite (**5b**) virtually inactive, and hexahydrocannabinol (**4**) less active than Δ^9-THC.[17,25,27] In THC-SS rabbits, **4** was 2 times less active and **5a** and **5b** were 100 times less active than Δ^9-THC. To our knowledge, 1′-hydroxy-CBN (**5c**) has not been tested in animal species other than the THC-SS rabbits, where it is inactive.

The synthetic 1′,2′-dimethylheptyl-Δ^8-THC analogue (**2b**) was more active than Δ^9-THC in monkeys (i.e., had a longer duration of effect),[17] and this greater activity (expressed as relative potency) was also seen in THC-SS rabbits. $\Delta^{6a(10a)}$-THC (**3a**) was less active in monkeys[17] and about 14 times less active in THC-SS rabbits, compared with Δ^9-THC. The 11-nor-$\Delta^{6a(10a)}$-THC derivative (**3b**), on the other hand, was virtually inactive in dogs[36] as it was in THC-SS rabbits (corresponding monkey activity data of **3b** are apparently not available). However, other 11-nor cannabinoids have varying degrees of THC-like activities, depending upon the pharmacological test used. For example, 11-nor-Δ^9-THC and 11-nor-Δ^8-THC were less active in producing dog ataxia and mouse hypoactivity, but were more active in producing tolerance to behavioral effects in dogs, than Δ^9-THC.[37] The synthetic cannabinoid nabilone (**6**) has been shown in animal tests of dog and rat behaviors to be about 3–10 times more active than Δ^9-THC.[31,32] This is in agreement with our findings of an 8-fold increase in potency of **6** over Δ^9-THC. Also, levonantradol (**7**) is a potent analgesic agent,[20] and its activity in rat behavioral tests is about 10 times that of Δ^9-THC.[31] This agrees with our findings where **7** was 7.5 times more active than Δ^9-THC in THC-SS rabbits. Finally, the synthetic, water-soluble salt of Δ^9-THC (SP111-A) has been shown to be from 2 to 6 times less potent than Δ^9-THC in rat and pigeon behaviors,[35] and the reduced potency of this compound agrees with that observed in THC-SS rabbits.

In summary, the THC-SS rabbit model has been shown to provide a measure of the relative psychoactive potencies of a large number and wide diversity of cannabinoid structures, including the psychoactive cannabinoids found in marijuana (Δ^9-THC, Δ^8-THC, and CBN), nonpsychoactive marijuana constituents (CBD, cannabichromene, and cannabicyclol), oxidized nuclear and side-chain metabolites of Δ^9-THC and Δ^8-THC, and several synthetic cannabinoids. In general, the results obtained in THC-SS rabbits correlate very well with data obtained from the evaluation of the relatively few compounds in humans, as well as with the data from the testing of a larger number of compounds in monkeys or other species. The THC-SS rabbit thus appears to be a convenient and relatively inexpensive model for assessing the psychoactive potential of cannabinoid-like compounds in structure–behavioral activity studies. Moreover, considering the pharmacogenetic implications of THC-SS rabbits, the model may provide valuable insights on the mechanism of action of psychoactive cannabinoids.

Experimental Section

Olivetol was purchased from Aldrich Chemical Co. (+)-Δ^8-THC was synthesized in our laboratory according to published procedures.[11] Commercial and other sources (see Acknowledgment) supplied us with levonantradol, nabilone, SP111-A, 11-nor-$\Delta^{6a(10a)}$-THC, $\Delta^{6a(10a)}$-THC, cannabichromene, cannabicyclol, and the other cannabinoids used. The behavioral tests have been described in detail previously.[1-4] Briefly, adult THC-SS rabbits (2–4 kg) were injected, intravenously, with a cannabinoid (prepared in a vehicle of 10% polysorbate 80 and 90% physiological saline solution), and the presence or absence of behavioral convulsion was recorded within a 20-min period. Essential criteria for convulsion included the presence of limb extension, clonus, and thrashing (all cannabinoid convulsions are composed of these end points). Most convulsions also consist of head tuck, extreme mydriasis, and nystagmus as well. The data in Table I are comprised of the test results from 109 rabbits of both sexes. More than one compound and/or dose of a compound was tested in the same animal, but at least 7 days separated the trials. Treatments were given randomly, but all rabbits were given at least one treatment with 0.05 mg/kg of Δ^9-THC (all adult THC-SS rabbits convulse to this dose of Δ^9-THC). We attempted to administer each cannabinoid dose to four rabbits. The THC-SS rabbits are bred exclusively in our laboratory and were not available in substantial numbers to permit a more extensive study of the rabbit response to cannabinoids. In addition, many of the cannabinoids which we tested were not available to us in large quantities, placing further limitations on the number of rabbits tested in the present investigation. However, because the behavioral convulsion induced by Δ^9-THC and other cannabinoids in the THC-SS rabbits is such a reliable response, the available animals and drugs were sufficient for the experimental determinations. The potencies of the cannabinoids were determined relative to the lowest dose of Δ^9-THC that produces convulsions in 100% of the THC-SS rabbits, i.., 0.05 mg/kg. This was set at 100%. Relative potencies were then calculated by dividing 0.05 mg/kg by the lowest effective dose of a given cannabinoid and multiplying this by the percentage of THC-SS rabbits exhibiting convulsions at this latter dose.

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