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DuP 747: SAR STUDY[1]

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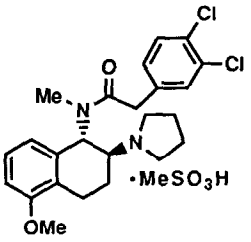
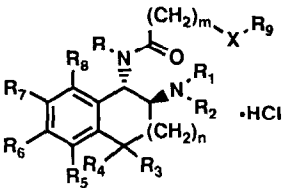
Abstract: The results of a detailed study of the structure-activity relationships in the series of compounds represented by DuP 747 are described.

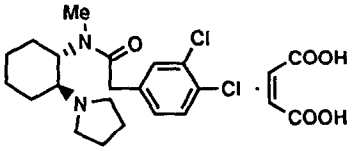
The synthesis and pharmacology of racemic *trans*-3,4-dichloro-N-methyl-N-[5-methoxy-2-(pyrrolidin-1-yl)-1,2,3,4-tetrahydronaphthalen-1-yl]benzeneacetamide methanesulfonate (**DuP 747, 1**) was described in the preceding letter A number of analogues of this novel, kappa selective analgesic was prepared to develop a structure-activity relationship in this series of compounds represented by the general structure **2**. The result of the study is the subject of this letter



1 (DuP 747)



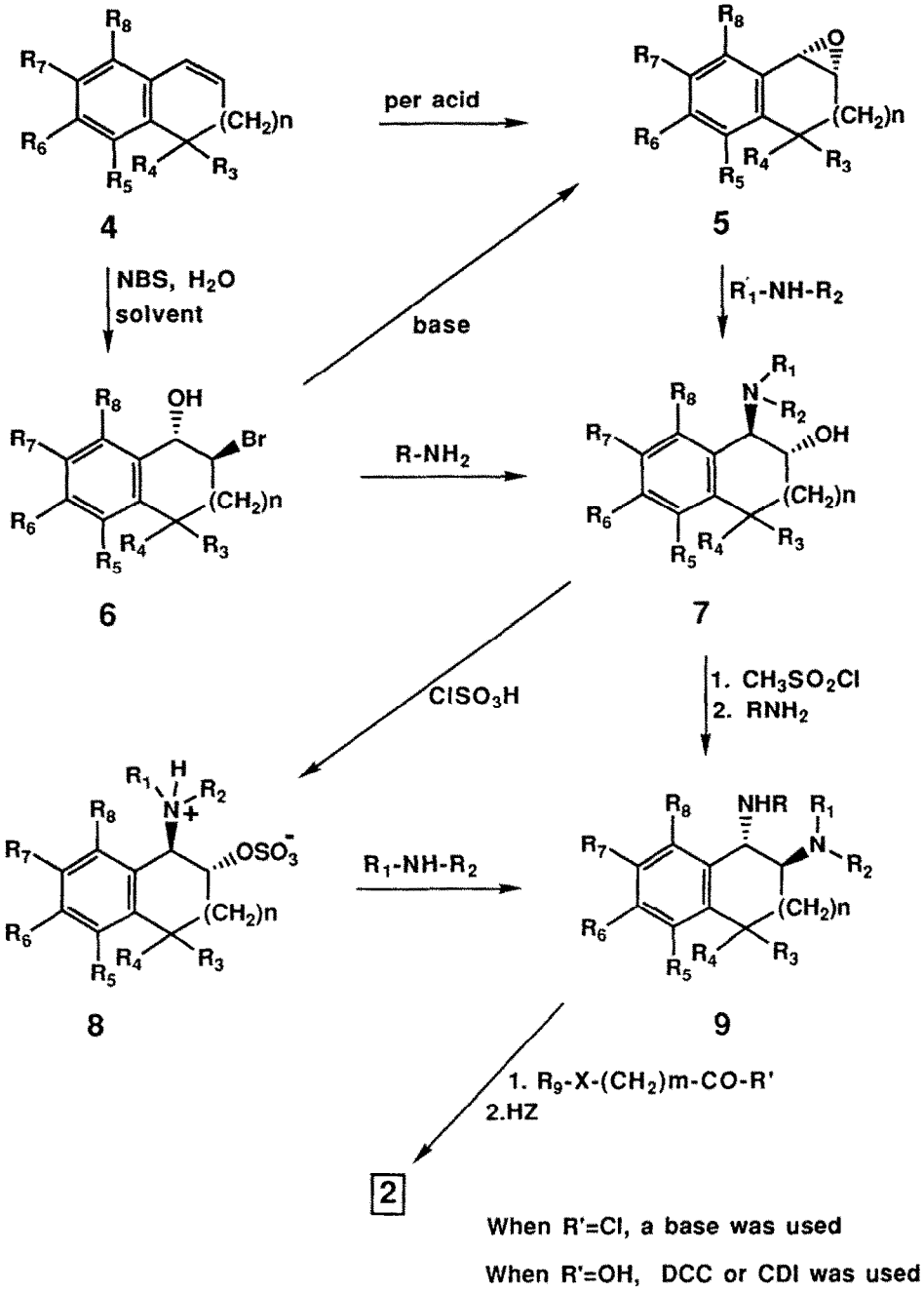
2



3 (U-50,488 H)

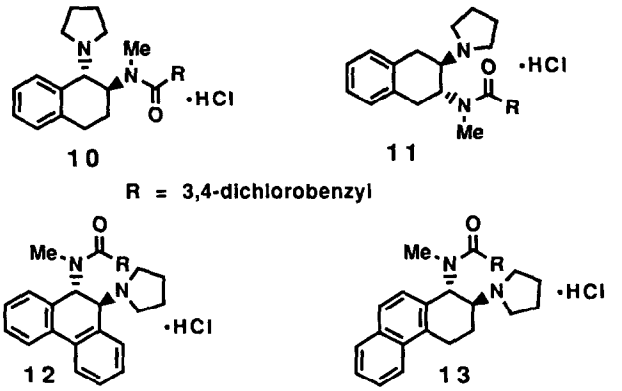
CHEMISTRY: The methods employed for the synthesis of compounds of the type **2** are depicted in Scheme 1 and are fairly straightforward The preferred route to the aminoalcohols **7** was through the bromohydrins **6** The epoxide route (**5**➡**7**), though successful in a few cases, was not dependable in that the epoxidation of the alkenes of the type **4** was capricious,being sensitive to the substituent on the benzene ring The chlorosulfonic acid route[3] to the diamines (**7**➡**8**➡**9**) was clean and of general applicability. It was particularly useful when the amino group of the aminoalcohols **7** was secondary because the alternate route (**7**➡**9**) involving methanesulfonyl chloride would lead, in this case, to a sulfonamide useless for further elaboration The starting material for **12** was 9,10-epoxy-9,10-dihydrophenanthrene[4] and that for **13** was 3,4-dihydrophenanthrene[5] The resolution of DuP 747 (**1**) was

SCHEME 1


per acid
NBS, H_2O
solvent
base
R_1-NH-R_2
R-NH_2
$ClSO_3H$
1. CH_3SO_2Cl
2. RNH_2
R_1-NH-R_2
1. R_9-X-(CH_2)m-CO-R'
2.HZ
4
5
6
7
8
9
2
When R'=Cl, a base was used
When R'=OH, DCC or CDI was used

carried out using (+)- and (-)- dibenzoyltartaric acids. The structure of the analogues **10** to **13** are shown in Chart 1 and the other analogues are listed in Table 1 under the general structure **2**.

Chart 1



PHARMACOLOGY: For SAR purposes the tests employed were limited *in vitro* to kappa and mu receptor binding and *in vivo* to the mouse phenylquinone writhing (PQW) antagonism[6] tests. The standards chosen for comparison were the selective mu receptor agonist morphine and the selective kappa receptor agonist U-50,488H (**3**). The data are shown in Table 2.

STRUCTURE-ACTIVITY RELATIONSHIP: Early in our SAR study, it was decided, on the basis of the structure of U-50,488[7], to restrict the amide and amino functions at the 1- and 2- positions of the tetralin system of **2** to the N-(3,4-dichlorophenylacetyl)-N-methylamino and the pyrrolidino groups, respectively. It was then quickly demonstrated that transposing the amide and the amine functions at the 1- and 2- position, respectively, resulted in undesirable mu selectivity (entry **10**) and that moving the amide group from the 1- to the 3-position led to reduced mu selectivity and analgesic activity only by the s.c. route (entry **11**)[8]. Mono- or disubstitution at the 4-position of **2** (entries **17** and **16**, respectively) reduced kappa selectivity and destroyed analgesic activity. Annelation of a benzene ring to the 3,4-positions (entry **12**) of **2** eliminated both kappa affinity and *in vivo* activity while fusing it to the 5,6-positions (entry **13**) retained both, albeit to a lesser extent. Also, any substituent on the benzene ring of the tetralin moiety other than alkyl, alkoxy, hydroxymethyl or hydroxy groups and their esters generally brought about a reduction or complete elimination of both kappa binding and *in vivo* activity (entries **18** to **42**). Although the 6-hydroxy derivative (entry **22**) was by far the most potent both in terms of affinity to the kappa receptor and analgesic potency, it exhibited a high degree of affinity to the mu receptor as well. A methoxy substituent at the 5-position seemed to be ideal for kappa selectivity and analgesic potency. The optimal substituents and the substitution pattern on the aromatic and aliphatic rings of structure **2** having thus been established, the variations of the amino function at the 2-position and of the amide group at the 1-position were then systematically investigated. As can be seen (entries **43** to **48**), replacing the pyrrolidino group with any amine other than 3-pyrroline (entry **46**) led to

reduced kappa selectivity and complete loss of *in vivo* activity. Even with the 3-pyrrolino substitution, reduced kappa selectivity was evident.

With regard to the amide group at the 1-position, even changing the methyl group on the nitrogen to an ethyl abolished both kappa selectivity and *in vivo* activity (entry **50**). Removal of the methylene group between the amide carbonyl function and the benzene ring or addition of a methylene thereto (entries **48** and **49**, respectively) reduced both kappa selectivity and analgesic potency. Introduction of an oxygen between the methylene and the benzene ring (entry **51**) retained both kappa selectivity and analgesic activity whereas a sulfur in the place of oxygen (entry **52**) reduced kappa selectivity and eliminated *in vivo* activity. With a few exceptions, the benzene ring of the amide function tolerated both electron withdrawing and electron donating groups as well as mono-, di- and trisubstitutions (entries **53** to **71**) without much loss of kappa selectivity and parenteral activity. Replacing the benzene ring of the amide function with 4-thianaphthyl group retained both kappa selectivity and analgesic potency (entry **76**), while replacing it either with 1-naphthyl group or with some heteroaromatic rings generally resulted in a decrease of both properties (entries **72** to **77**). Decreasing the aliphatic ring size of the tetralin unit by one carbon led to retention of both kappa selectivity and analgesic potency (entry **14**), while increasing it by one carbon resulted in retention of selectivity but a decrease in potency (entry **15**) However, almost all of these analogues elicited only moderate to poor activity when administered orally.

The kappa affinity and analgesic activity of DuP 747 (**1**) resides exclusively in the (+)-S,S-diastereomer (the fourth entry in Table 2).

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8 This compound has also been described by Freeman *et al* (Ref.13, preceding letter).

9. Satisfactory analytical and spectral data were obtained for all the new compounds described in this letter.

TABLE 1

Compd.	R	R1 R2	R3	R4	R5	R6	R7	R8	R9	X	m	n
9	Me	-$(CH_2)_4$-	H	H	H	H	H	H	3,4-dichlorphenyl	bond	1	1
14	Me	-do-	H	H	H	H	H	H	-do-	-do-	1	0
15	Me	-do-	H	H	H	H	H	H	-do-	-do-	1	2
16	Me	-do-	Me	Me	H	H	H	H	-do-	-do-	1	1
17	Me	-do-	H	Ph	H	H	H	H	-do-	-do-	1	1
18	Me	-do-	H	H	H	Me	H	H	-do-	-do-	1	1
19	Me	-do-	H	H	OH	H	H	H	-do-	-do-	1	1
20	Me	-do-	H	H	OEt	H	H	H	-do-	-do-	1	1
21	Me	-do-	H	H	H	OMe	H	H	-do-	-do-	1	1
22	Me	-do-	H	H	H	OH	H	H	-do-	-do-	1	1
23	Me	-do-	H	H	H	H	OMe	H	-do-	-do-	1	1
24	Me	-do-	H	H	H	H	OH	H	-do-	-do-	1	1
25	Me	-do-	H	H	CH_2OH	H	H	H	-do-	-do-	1	1
26	Me	-do-	H	H	CH_2OMe	H	H	H	-do-	-do-	1	1
27	Me	-do-	H	H	$OCOC_2H_5$	H	H	H	-do-	-do-	1	1
28	Me	-do-	H	H	OCOPh	H	H	H	-do-	-do-	1	1
29	Me	-do-	H	H	OCH_2COOH	H	H	H	-do-	-do-	1	1
30	Me	-do-	H	H	OCH_2CONH_2	H	H	H	-do-	-do-	1	1
31	Me	-do-	H	H	OMe	OMe	H	H	-do-	-do-	1	1
32	Me	-do-	H	H	OH	OH	H	H	-do-	-do-	1	1
33	Me	-do-	H	H	H	OH	OH	H	-do	-do-	1	1
34	Me	-do-	H	H	OMe	H	H	OMe	-do-	-do-	1	1
35	Me	-do-	H	H	Me	OH	H	H	-do-	-do-	1	1
36	Me	-do-	H	H	Me	OMe	H	H	-do-	-do-	1	1
37	Me	-do-	H	H	H	F	OMe	H	-do-	-do-	1	1
38	Me	-do-	H	H	OMe	H	Cl	H	-do-	-do-	1	1
39	Me	-do-	H	H	OMe	NO_2	H	H	-do-	-do-	1	1
40	Me	-do-	H	H	OMe	H	H	NO_2	-do-	-do-	1	1
41	Me	-do-	H	H	NO_2	OH	H	H	-do-	-do-	1	1
42	Me	-do-	H	H	H	H	H	H	-do-	-do-	1	1
43	Me	Me Me	H	H	H	H	H	H	do-	-do-	1	1
44	Me	-$(CH_2)_5$-		H	H	OMe	H	H	H	-do-	1	1
45	Me	$(CH_2)_2$-N-$(CH_2)_2$- (Me)		H	H	OMe	H	H	H	-do-	1	1
46	Me	CH_2-CH=CH-CH_2		H	H	OMe	H	H	H	-do-	1	1
47	Me	Me CH_2Ph	H	H	OMe	H	H	H	- do	-do-	1	1
48	Me	-$(CH_2)_4$-		H	H	OMe	H	H	H	-do-	0	1
49	Me	-do-	H	H	OMe	H	H	H	-do-	-do-	2	1
50	Et	-do-	H	H	OMe	H	H	H	-do-	-do-	1	1
51	Me	-do-	H	H	OMe	H	H	H	-do-	O	1	1
52	Me	-do-	H	H	OMe	H	H	H	-do-	S	1	1
53	Me	-do-	H	H	OMe	H	H	H	2,6-dichlorophenyl	bond	1	1
54	Me	-do-	H	H	OMe	H	H	H	4-fluorophenyl	-do-	1	1
55	Me	-do-	H	H	OMe	H	H	H	2-chlorophenyl	-do-	1	1
56	Me	-do-	H	H	OMe	H	H	H	3-chlorophenyl	-do-	1	1
57	Me	-do-	H	H	OMe	H	H	H	4-chlorophenyl	-do-	1	1
58	Me	-do-	H	H	OMe	H	H	H	4 bromophenyl	-do-	1	1
59	Me	-do-	H	H	OMe	H	H	H	2-nitrophenyl	-do-	1	1
60	Me	-do-	H	H	OMe	H	H	H	3-nitrophenyl	-do-	1	1
61	Me	-do-	H	H	OMe	H	H	H	4-nitrophenyl	-do-	1	1
62	Me	-do-	H	H	OMe	H	H	H	4-aminophenyl	-do-	1	1
63	Me	-do-	H	H	OMe	H	H	H	4-trifluoromethylphenyl	-do-	1	1
64	Me	-do-	H	H	OMe	H	H	H	4-methylmercaptophenyl	-do-	1	1
65	Me	-do-	H	H	OMe	H	H	H	4-methoxyphenyl	-do-	1	1
66	Me	-do-	H	H	OMe	H	H	H	3,4-methylenedioxyphenyl	-do-	1	1
67	Me	-do-	H	H	OMe	H	H	H	3,4-dimethylphenyl	-do-	1	1
68	Me	-do-	H	H	OMe	H	H	H	3,4-dimethoxyphenyl	-do-	1	1
69	Me	-do-	H	H	OMe	H	H	H	2,4-dichlorophenyl	-do-	1	1
70	Me	-do-	H	H	OMe	H	H	H	3,4-difluorophenyl	do-	1	1
71	Me	-do-	H	H	OMe	H	H	H	2,3,6-trichlorophenyl	-do-	1	1
72	Me	-do-	H	H	OMe	H	H	H	3-pyridyl	-do-	1	1
73	Me	-do-	H	H	OMe	H	H	H	4-pyridyl	-do-	1	1
74	Me	-do-	H	H	OMe	H	H	H	3-thienyl	-do-	1	1
75	Me	-do-	H	H	OMe	H	H	H	3-thianaphthyl	-do-	1	1
76	Me	-do-	H	H	OMe	H	H	H	4-thianaphthyl	-do-	1	1
77	Me	-do-	H	H	OMe	H	H	H	1 naphthyl	-do	1	1

TABLE 2

Entry	Receptor binding (nM) Kappa	mu	Mouse PQW antagonism ED_{50} (mg/kg) s.c.	p.o.
U-50488H	15	825	1.2	13
Morphine	1870	38	1 0	3.8
DuP 747 (1)	6	304	0.46	6.2
(+)-S,S-DuP747	7	750	0.15	5.2
(-)-R,R-DuP747	350	260	>81	>81
9	10	453	2.7	13
10	2760	453	0.16	>81
11	20	615	46.8	>81
12	1000	6175	>81	>81
13	56	4100	3.6	15.6
14	7	756	1.5	30
15	87	6750	24.2	53.6
16	857	277	>81	>81
17	190	1200	>81	>81
18	70	700	8.1	47
19	5	260	0.33	7.4
20	7	1630	2.2	19
21	8	430	1 5	6.5
22	1	21	0 03	4.2
23	94	1300	3	19
24	3	45	0.46	16
25	5	4380	0 71	6.4
26	19	>10,000	4.5	13
27	4	530	0.24	10
28	14	7800	0.71	6.4
29	7900	>10,000	>81	>81
30	15	335	5.2	>81
31	32	2000	8.1	16
32	9	568	0.89	8.1
33	1	29	0 19	3.3
34	7	630	8.1	24
35	32	1020	>81	>81
36	-	-	4.2	19
37	400	6400	16	47
38	18	975	4 5	13
39	49	>10,000	>81	>81
40	-	-	3.4	16
41	5	662	1.5	13
42	10	545	2.7	13
43	870	2310	0.46	6.2
44	150	2300	>81	>81
45	620	9100	>81	>81
46	10	330	0.24	3.4
47	3700	>10,000	>81	>81
48	20	-	47	81
49	1500	>1000	38	81
50	120	680	47	>81
51	10	540	0.46	10
52	680	4930	47	>81
53	3250	1345	>81	>81
54	19	1840	12	32
55	35	2500	10	38
56	12	1600	1.2	16
57	66	2200	3.4	30
58	34	540	8.1	54
59	39	3600	19	47
60	6	510	0.89	19
61	10	1200	0.72	18
62	140	>10,000	47	81
63	12	1200	4.2	24
64	15	690	>81	>81
65	20	900	6.5	47
66	14	775	5.2	30
67	8	775	2.3	27
68	120	2660	22	47
69	12	450	5.2	30
70	7	1465	0.72	>81
71	14	350	1 3	10
72	230	10,000	38	54
73	15,263	33,480	>81	>81
74	144	21,700	16	>81
75	15	245	>81	>81
76	8	285	0.46	16
77	13	207	27	>81