Bioorganic & Medicinal Chemistry Letters, Vol.2, No.7, pp. 715-720, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

DuP 747: A NEW, POTENT, KAPPA OPIOID ANALGESIC. SYNTHESIS AND PHARMACOLOGY[1].

P. Rajagopalan*, R.M. Scribner, P. Pennev, W.K. Schmidt, S.W. Tam, G.F. Steinfels, and L. Cook

CNS Diseases Research, The Du Pont Merck Pharmaceutical Company, Wilmington DE 19880-0353

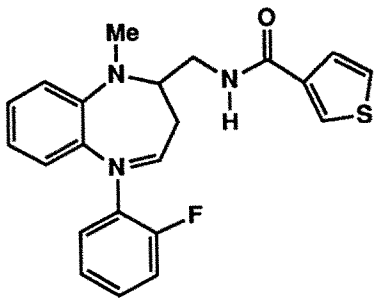
(*Received* 20 *April* 1992)

Abstract: The synthesis and pharmacology of (±)-*trans*-3,4-dichloro-N-methyl-N-[5-methoxy-2-(pyrrolidin-1-yl)-1,2,3,4-tetrahydronaphthalen-1-yl]benzeneacetamide methanesulfonate (**DuP 747**), a novel kappa agonist analgesic, are described.

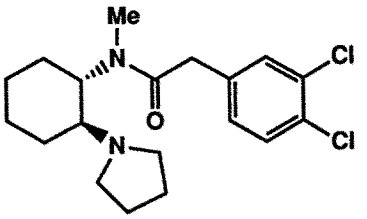
The presence of mu, kappa, and delta opioid receptors in the central and peripheral nervous system of many mammalian species has been convincingly demonstrated[2] since the concept of multiple opioid receptors was propounded about sixteen years ago[3]. Of these, the kappa receptor seems to be unique in that agonists that selectively bind to it are postulated to be potent centrally acting analgesics bereft of the undesirable narcotic side effects and addiction liability elicited by the mu selective agonists.

In our ongoing search for new and potent analgesics, we had, a few years ago, initiated a program directed toward the design and synthesis of compounds that would be selective agonists of the kappa receptor. At that time, the only selective kappa agonists described in the literature were tifluadom (**1**)[4] and U-50,488 (**2**)[5]. Ethylketocyclazocine (**3a**) and bremazocine (**3b**), though endowed with a high degree of affinity to the kappa receptor, are not selective to that receptor alone in that they exhibit an equal preference to the mu receptor as well - the former as an agonist and the latter as an antagonist[6].

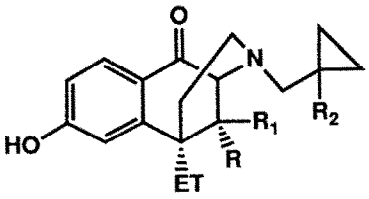
Since the 2-aminotetralin unit of **4**, which has been reported to be a potent narcotic analgesic[7], is a part of morphine and, hence, of ethylketocyclazocine (**3a**) molecular framework, it was of interest to combine the structural features of **2** and **4** into a single unit as **5** or **6** either or both of which could be expected to display kappa agonist specificity and analgesic activity. Accordingly, the racemic trans-3,4-dichloro-N-methyl-N-[2-(pyrrolidin-1-yl)-1,2,3,4-tetrahydro-napthalen-1-yl]benzene-acetamide (**5**) was synthesized starting with 1,2-dihydronapthalene (**7**) as outlined in Scheme 1. The epoxide (**8**) obtained from **7** by



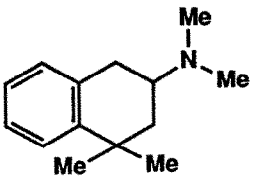
1



2

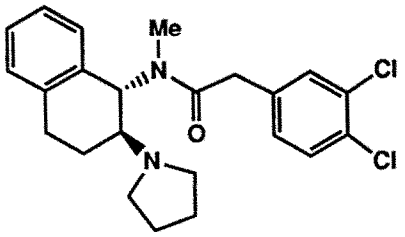


3

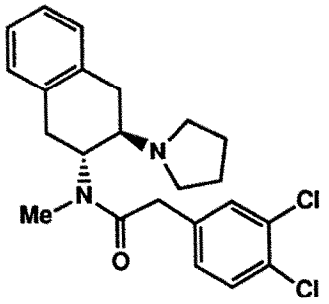


4

a) R=Me, R_1=R_2=H
b) R=R_1=Me, R_2=OH

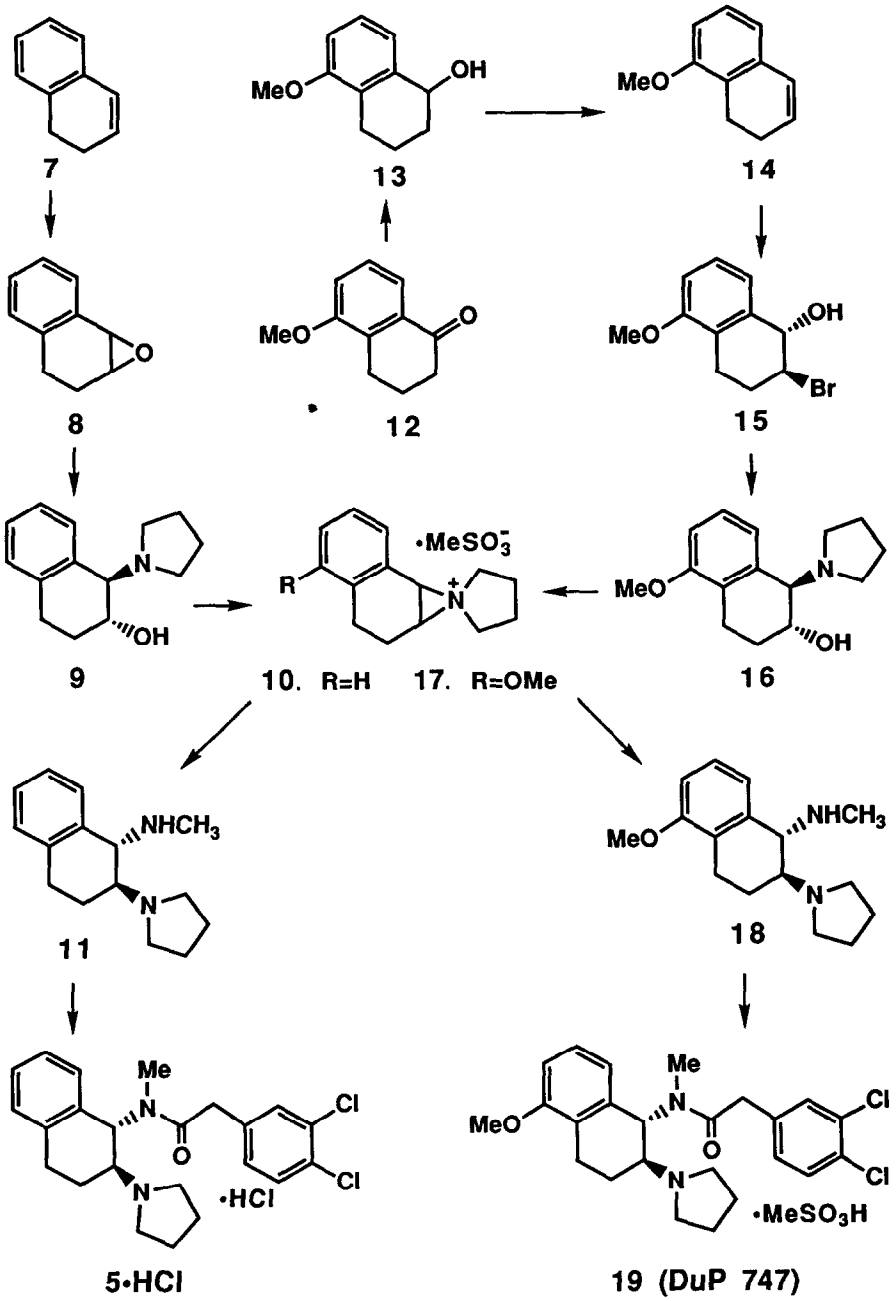


5



6

SCHEME 1


7
13
14
8
12
15
9
10. R=H
17. R=OMe
16
11
18
5•HCl
19 (DuP 747)
MeO
OH
Br
R
•MeSO3-
NHCH3
Me
Cl
•HCl
•MeSO3H

oxidation with 3-chloroperoxybenzoic acid, furnished **9** upon treatment with excess of pyrrolidine in ethanol. The aziridinium intermediate (**10**) formed when (**9**) was exposed to methanesulfonyl chloride in the presence of triethylamine, was, without isolation, treated with an excess of methylamine in ethanol to yield the diamine (**11**). Acylation of **11** with 3,4-dichlorophenylacetyl chloride afforded **5** which was isolated and characterized as the hydrochloride. The regio- and stereochemistry assigned to the product (**5**) was arrived at by detailed NMR analysis and confirmed by single crystal X-ray structure determination[8].

Our expectations were more than fulfilled when **5** displayed a high degree of kappa selectivity (Table 1) and also elicited potent *in vivo* antinociceptive activity in the mouse and rat phenylquinone writhing antagonism (PQW) test[9] (Table 2). It was, however, inactive in the rat tail-flick assay[10] which is a test for strong analgesic activity, even when administered subcutaneously.

A minor modification of structure **5** led to **DuP 747** (**19**) as the compound of choice for development. A slightly different route was followed for the synthesis of **19** which is also depicted in Scheme 1. Reduction of 5-methoxytetralone (**12**) with sodium borohydride followed by dehydration of the resulting carbinol (**13**) yielded 5-methoxy-3,4-dihydronapthalene (**14**) which was converted to the bromohydrin (**15**) by treatment with N-bromosuccinimide in aqueous acetone. When exposed to an excess of pyrrolidine in ethanol, **15** yielded **16** the formation of which can be rationalized by the *in situ* generation and susequent opening of the corresponding epoxide by the base. Mesylation of **16** furnished the aziridinium intermediate (**17**) which, without isolation, was converted to the diamine (**18**) as described earlier. Coupling of **18** with 3,4-dichlorophenylacetic acid in the presence of 1,1'-carbonyldiimidazole and treatment of the product with methanesulfonic acid furnished the title compound (**19**) designated as **DuP 747**. Its pharmacology is outlined in Tables 1 and 2.

Table 1. Opioid Receptor Binding Ki (nM).

Compound	Kappa	Mu	Delta	Sigma
5.HCl	10	545	10,000	10,000
5 (from ref. 13)	5.2	>1000	-	-
DuP 747	6	304	2,090	5,160
U-50488H	15	825	21,000	696
Morphine	1,900	38	51	>10,000

Table 2. Analgesic Activity in Mice and Rats

	Mouse PQW ED_{50} (mg/kg)		Rat Tail-Flick ED_{50} (mg/kg)	
Compound	s.c.	p.o.	s.c.	p.o.
5.HCl	2.7	13	>54	not tested
5 (from ref. 13)	1.1	-	2	-
DuP 747	0.46	6.2	9.4	42
U-50,488H	1.2	13	19	not tested
Morphine	0.98	3.8	4.9	54

DuP 747 (19) is a selective kappa agonist analgesic which elicits antinociceptive response in mice, rats, and dogs by parenteral as well as oral routes of administration. It is as selective as U-50,488 in its affinity to the kappa receptor and is nearly equipotent with morphine against chemically-induced pain in the mouse PQW test (table 2). It is also active against heat-[10] (table 2) and pressure-induced pain in rats[11] (ED_{50}=31 mg/kg for uninflamed paw and 26 mg/kg for inflamed paw, respectively) and electrically stimulated tooth pulp pain[12] in rats and dogs (ED_{50}=3.2 mg/kg and 1.3 mg/kg, respectively). Chronic treatment with analgesic doses of **DuP 747** produces less tolerance than is achieved by equi-analgesic doses of morphine. **DuP 747** is not cross-tolerant to **DuP 747** in morphine-tolerant mice and morphine is not cross-tolerant to **DuP 747**-tolerant mice. Mice treated with a three-day continuous infusion of **DuP 747** showed no withdrawal symptoms following abrupt discontinuation of treatment. In cross-dependence tests, it failed to substitute for morphine.

In conclusion, we have demonstrated that the fusion of a benzene ring to the cyclohexane ring of U-50,488 in a proper orientation is tolerated well by the kappa receptor leading to a novel series of potent, kappa agonist analgesics of which **DuP 747** is the best representative. The results of the detailed study of structure-activity relationship in this series are reported in the following letter.

A recent publication by J.P. Freeman et al[13] which describes an independent synthesis of **5** and related compounds followed our patent disclosure[14] and also the posters that we presented at the 200th Meeting of the American Chemical Society[1]

ACKNOWLEDGEMENTS

We thank Maria Marynowski, Kimberly Cornwell, William Keim, Carla Maciag, Anne Marshall, Carol Morgan, and Bonni Rule for biological evaluations.

REFERENCES AND NOTES

1. Part of two posters presented at the 200th Meeting of the American Chemical Society, Washington,DC, August **1990**; Division of Medicinal of Chemistry, Abstracts No. 58 and 59.

2. Lord, J.A.H.; Waterfield, A.A.; Hughes, J.; Kosterlitz,H.W. Nature, **1977**, 267, 495.

3. (a) Martin, W.R.; Eades, C.G.; Huppler, R.E.; Gilbert, P.E.; J. Pharmacol. Exp. Ther. **1976**, 197, 517; (b) Gilbert, P.E.; Martin, W.R. Ibid, **1976**,198,66.

4. Romer, D.; Buscher, H.H.; Hill, R.C.; Maurer, R.; Petcher, T.J.; Zeugner, H.; Benson, W.; Finner, E.; Milkowski, K.I.; Thies, P.W. Nature, **1982**, 298, 759.

5. Szmuszkovicz, J.; Von Voigtlander, P.F. J. Med. Chem. **1982**, 25, 1125.

6. Von Voigtlander, P.F.; Lahti, R.A.; Ludens, J.H. J. Pharmacol. Exp. Ther. **1983**, 224, 7.

7. Martin, A.R.; Parulkar, A.P.; Gusseck, D.J.; Anderson, L.J.; Grunewald, G.L.; White, J. J. Pharm. Sci. **1969**, 58, 340.

8. We thank Dr. J.C. Calabrese, Central Research and Development, E.I. Du Pont de Nemours and Company, Wilmington, DE, for the single crystal X-ray analysis of **5**.HCl.

9. Blumberg, H.; Wolf, P.S.; Dayton, H.B. Proc. Soc. Exp. Biol. Med. **1965**, 118, 763

10. D'Amour, F.E.; Smith, D.L. J. Pharmacol. Exp. Ther. **1941**, 72, 74.

11. Randall, L.O.; Sellito, J.J. Arch. Int. Pharmacodyn. **1957**, 111, 409.

12. Steinfels, G.F.; Cook, L. J. Pharmacol. Exp. Ther. **1986**, 236, 111.

13. Freeman, A.P.; Michalson, E.T.; D'Andrea, S.V.; Baczynskyj, L.; Von Voigtlander, P.F.; Lahti, R.A.; Smith, M.W.; Lawson, C.F.; Scahill, T.A.; Mizsak, S.A.; Szmuszkovicz, J. J. Med. Chem. **1991**, 34, 1891.

14. Pennev, P.; Rajagopalan, P.; Scribner, R.M. Eur. Pat. Appl. 260,555; Chem. Abstr. **1989**, 110, 8036b.

15. Satisfactory analytical and spectral data were obtained for all the new compounds described in this letter. Compounds 7,8,9, and 11 have also been described in the paper by Freeman *et al.* (ref. 13).