PIPERIDYL AND QUINUCLIDINYL ESTERS OF 1-BENZANILIDO-CYCLOHEXANE CARBOXYLIC ACIDS AS ANALGESICS

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SUMMARY: A series of N-methyl-3-piperidyl, N-methyl-4-piperidyl and 3-quinuclidinyl esters of 1-benzanilidocyclohexane carboxylic acids (3a-k) was prepared and examined for their analgesic potential.
Key Words: Piperidyl esters, quinuclidinyl esters, cyclhexanecarboxylic acid esters, analgesics.

INTRODUCTION

Recent studies by Aboul-Enein *et al.* (1983) have shown that ester 1 possesses analgesic activity by the hot-plate assay, and displays no morphine-like physical dependence liability.

Also, previous investigations by Waters (8) and Cheng *et al.* (4) revealed that substituted benzoic acid esters of 1 methyl-4-piperidinol 2 elecit antinociceptive activity in the range of morphine and codeine with no physical dependence.

Consequently, it was of interest to extend our study to the piperidyl and quinuclidinyl esters 3, with the aim to augment the analgesic potential of 1. The syenthesis of the desired esters 3 a-k (Table 1) is illustrated in Scheme 1.

Aroylation of 1-anilincyclohexane carboxylic acids 4 with the appropriate aroyl chloride in benzene-triethylamine medicum afforded 1-benzanilidocyclohexanecarboxylic acids 5. Subsequent estrification of 5 with N-methylpiperidinols and 3-quinuclidinol following the mixed anhydride technique using trifluoroacetic anhydride led to the basic esters 3 a-k, (Table 1).

MATERIALS AND METHODS

Melting points were determined on Buchi 510 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckmann Infracord, model 4220. The microanalytical data were obtained from the National Research Centre, Dokki, Cairo. The analytical results deviated maximally ±0.4% from the theoritical values for C, H and N. The ^{1}H-NMR ($CDCl_3$, TMS) were recorded on VARIAN (90 MHz^{1}H). The mass spectra were obtained on VARIAN CH-5 and CH-7 spectrometers. Mass spectra were performed at the Institute für Pharmazeutische Chemie, Universität Munster, FRG.

1. Anilinocyclohexane carboxylic acids 4 a and b were prepared according to the procedures of Aboul-enein *et al.* (1, 2) and Betts *et al.* (3).

1. Benzanilidocyclohexane carboxylic acids 5a-d

To a solution of 0.05 mol of acid 4 and 15 g (0.15 mol) of triethylamine in 50 ml of dry benezene was added dropwise under stirring and cooling 0.05 mol of the appropriate acid chloride. Thereafter, the reaction mixture was refluxed for 12 h. The precipitated triethylamine hydrochloride was filtered off, and the filtrate evaporated under reduced pressure. The residual solid was recrystallized from the appropriate solvent.

5a and b were previously synthesized by Aboul-Enein *et al.* (1). 5c was recrystallized from ethanol: water, m.p. 186-8°C Yield 56% Anal. ($C_{21}H_{23}NO_3$):

	C	H	N
Calc.	74.75	6.87	4.15
Found.	74.66	6.91	4.08

5d was recrystallized from ethanol: water. m.p. 187-9°C Yield 81%. Anal. ($C_{22}H_{25}NO_3$):

	C	H	N
Calc.	75.19	7.17	3.99
Found.	75.12	7.22	4.05

General Procedure for piperidyl and quinuclidinyl esters 3 a-k (Table 1):

To a suspension of 0.01 mol of 5 a-d in dry benzene (40 ml) was added 0.01 mol of trifluoroacetic anhydride at room temperature. The reaction mixture was stirred for 5 minutes after which 0.011 mol of the appropriate piperidinol or quinclidinol was added

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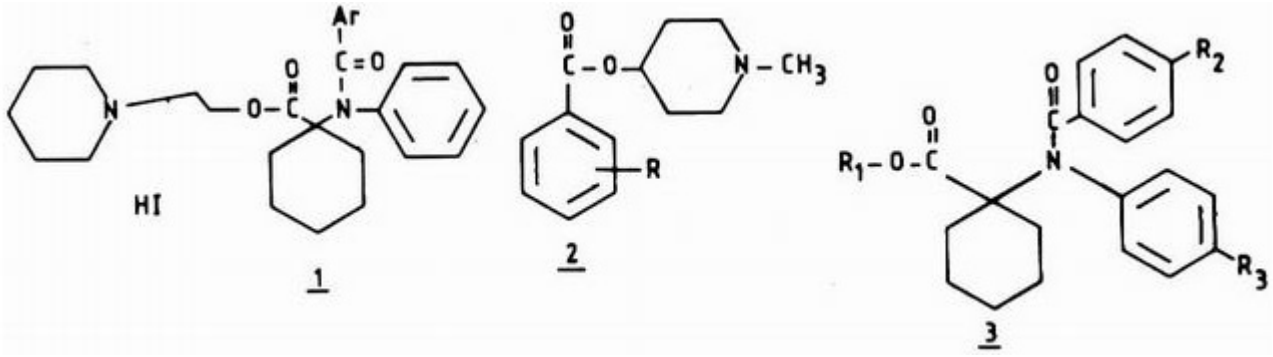
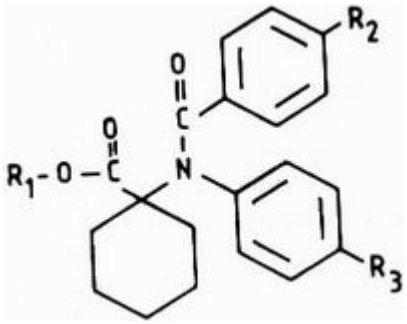


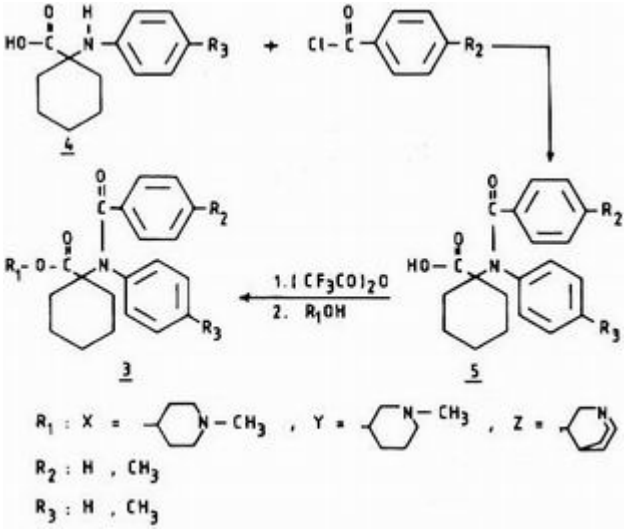
at 50°C. Stirring was continued for further 2 hours at room temperature. Thereafter, the solvent and volatile substances were removed in vacuo. The residue was treated with 5% Na_2CO_3 solution and extracted with methylene chloride. The organic extract was dried (Na_2SO_4) and evaporated to give 3 a-k.

3f: MS (m/z): 434 (M^+ $C_{27}H_{34}N_2O_3$, 2%) base peak 97 (M^+ - 337, $C_6H_{11}N^+$, 100%); 292(M^+-142, $C_{20}H_{22}NO^+$, 12%). ^{1}H-NMR ($CDCl_3$, TMS): δ (ppm)= 2.25 (s, 3H, CH_3-C_6H_4), 2.29 (s, 3H, N-CH_3); 4.98 (m, C - 4 piperidine H), 7.10 (M, 9H, aromatic H).



No.	R_1	R_2	R_3	M.p. °C	Yield %	Cryst solvent	Formula (mol. Wt.)		Microanaly			ED_{50} mg/Kg (Confidence Limit)
									C	H	N	
3a	X	H	H	95-6	51	A	$C_{26}H_{22}N_2O_3.2/3H_2O$ (432.66)	Calc. Found.	72.18 72.12	7.77 8.04	6.48 6.52	18.1 (10.11-32.39)
3b	Y	H	H	87-8	42	A	$C_{26}H_{32}N_2O_3$ (420.55)	Calc. Found.	74.26 73.39	7.67 7.63	6.66 6.25	25.2 (14.82-44.20)
3c	Z	H	H	268-70(2)	47	B	$C_{27}H_{33}ClN_2O_3.6/5\ H_2O$ (490.65)	Calc. Found.	66.10 66.21	7.27 7.36	5.71 5.12	-
3d	X	CH_3	H	125-6	39	A	$C_{27}H_{34}N_2O_3$ (434.58)	Calc. Found.	74.62 74.55	7.89 7.93	6.45 6.36	17.2 (9.50-31.13)
3e	Y	CH_3	H	90-2	31	A	$C_{27}H_{34}N_2O_3$ (434.58)	Calc. Found.	74.62 74.70	7.89 7.82	6.45 6.39	26.4 (20.31-34.32)
3f	X	H	CH_3	112-4	55	A	$C_{27}H_{34}N_2O_3$ (434.58)	Calc. Found.	74.62 73.91	7.89 8.01	6.45 7.24	44.0 (34.1-56.76)
3g	Y	H	CH_3	Oil (3)	31		$C_{27}H_{34}N_2O_3$ (434.58)	Calc. Found.	74.62 75.00	7.89 7.40	6.45 6.60	52.1 (35.93-75.51)
3h	Z	H	CH_3	118-9	58	C	$C_{28}H_{34}N_2O_3$ (446.59)	Calc. Found.	75.31 75.40	7.67 7.29	6.27 6.41	-
3i	X	CH_3	CH_3	146-7	50	C	$C_{28}H_{36}N_2O_3$ (448.61)	Calc. Found.	74.97 76.46	8.09 8.74	6.25 6.35	40.1 (28.64-56.14)
3j	Y	CH_3	CH_3	95-6	51	C	$C_{28}H_{36}N_2O_3$ (448.61)	Calc. Found.	74.97 75.13	8.09 7.95	6.25 6.12	65.6 (50.85-84.64)
3k	Z	CH_3	CH_3	248-50(2)	25	B	$C_{29}H_{37}ClN_2O_3$ (497.08)	Calc. Found.	70.07 70.13	7.50 7.42	5.64 5.70	-
1												21.8 (17.30-27.39)
Morphine hydrochloride												7.3 (5.79-9.20)

(1) x=4-methyl-piperidyl, Y=3 -methyl-piperidy, Z=3-quinuclidinyl.; (2) Hydrochloride. ; (3) Purified by column chromotography using neutral alumina. Petroleum ether (40:60) is used to pack the column. The compound was obtained sufficiently pure on using petroleum ether (40:60): chloroform (7:3). A: Petroleum ether (60:80) -ether; B: 2-Propanol-ether; C: Petroleum ether



3g: ^{1}H-NMR ($CDCl_3$, TMS): δ (ppm)= 2.30 (s, 3H, $CH_3C_6H_4$); 2.33 (s, 3H, N-CH_3), 4.88 (m, C-3 piperidine H), 7.33 (m, 9h, aromatic H).

Pharmacology

Analgesic activity: The mouse hot-plate technique was performed for the determination of the analgesic potency. Male Swiss Webster mice (20-25 g) were used. The test compounds were administered i.p. as hydrochlorides, dissolved in distilled water and the final concentration was adjusted to the required dose. The maximum volume injected did not exceed 0.05 ml/20g. Using groups of six mice the reaction time is measured 10 and 5 minutes before and 15,30,45,60,75,90,120 and 180 minutes after administration of the test compounds. If the control value exceeded 15 seconds, or the difference between the two control measurements was greater than 4 seconds, the animal was rejected. The mice were considered positive for analgesia if the reaction time was increased by at least 2.5 times of the corresponding control value. Each group was observed for at least five different doses from subanalgesic to 100 mg/kg. The analgesic activity of the screened compounds peaked about 30-60 minutes after i.p. treatment. The data obtained at the peak time were used for statistical evaluation.

RESULTS AND DISCUSSION

Analgesic Activity

The test compounds 3a-k were evaluated for their analgesic activity using the hot-plate technique as described by Janssen *et al.* (5) and Portoghese *et al.* (7), and morphine as reference. The dose producing analgesic activity 50% of mice (ED_{50} and 95% confidence limits) was calculated by the graphical method of Litchfield and Wilcoxon (6), (Table 1).

The 4-methyl piperidyl moiety in esters 3 a, d, f and i enhances the analgesic activity more than the 3-methyl piperidyl one in esters 3 b, e, g and j, while the quinclidinyl group abolisches such activity. Compound 3 d displayed the highest activity in the current series and it possessed more analgesic potency than ester 1 and 0.42 of that of morphine. Regarding the SAR of the 4-methyl piperidyl esters, the data in Table (1) revealed that the 4-CH_3 group in the benzoyl moiety in ested 3 d daugments such activity, while esters 3 a, f and i indicated the following potency order reference: 3a>3i>3f. Ester 3b is the most active one in the 3-methyl piperidyl series, it posessed 0.29 of the morphine analgesic potency. The order of activity of these esters is: 3b>3e>3g>3j. None of these esters induced any marked CNS manifestions. Also, none of them showed the straub-tail phenomenon, which is an index of addiction potential.

Conclusively the introduction of the 4-methyl piperidyl moiety in the present esters 3 augments the analgesic activity in comparison with ester 1.

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