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Structure-Activity Studies of Fentanyl

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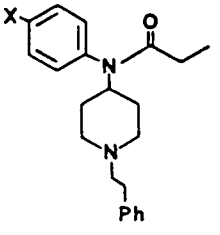
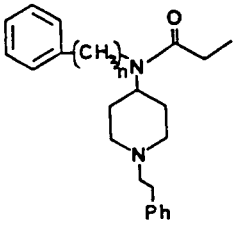
Abstract—The preparation of analogues of fentanyl with *para* substituents in the anilino aromatic ring, anilino nitrogen separated from phenyl by methylene or bimethylene, and phenacyl replacing propionyl as the N-acyl substituent is reported. Although all *para* substituents examined depressed antinociceptive potency in rats, most analogues of this kind were more effective than morphine and the p-F, I, and Me derivatives were only a few-fold less active than fentanyl. Separation of anilino nitrogen from phenyl lowered potency with N-phenethyl analogues retaining reasonable levels of activity (> morphine). All the phenacyl analogues were of low potency or inactive. Diagnostic details of the mass spectra of analogues likely to be encountered as 'designer drugs' are appended.

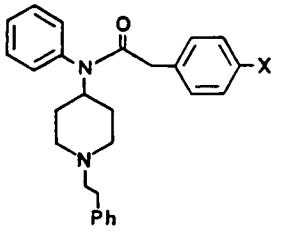
In this paper we report data which extend knowledge of the structure-activity relationships of the potent opioid analgesic fentanyl (1,X = H) (review, Casy & Parfitt 1986). The types of structural variant investigated were those with *para* substituents in the anilino aromatic ring (**1**), anilino nitrogen insulated from phenyl by methylene or bimethylene (**2**), and with phenacyl replacing propionyl as the *N*-acyl substituent (**3**), plus the miscellaneous products **4–6**.



1 a) X = F, b) Cl, c) Br, d) I, e) Me, f) CF_3, g) NHCOEt.



2 a) n = 1, b) n = 2



3 a) X = H, b) X = OMe

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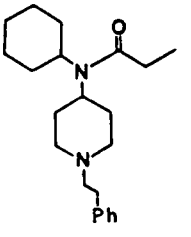
Chemistry

Derivatives **1a–1f** were obtained by condensing 1-methyl-4-piperidone (used rather than the 1-phenethyl analogue for reasons of economy) with the appropriate substituted aniline to give the corresponding Schiff bases which were reduced with sodium borohydride without isolation to the secondary amines. The related propionamides, obtained by heating the intermediate amines with propionic anhydride, were smoothly *N*-demethylated with cyanogen bromide (methiodide by-products were not encountered) and the resultant nor-compounds were alkylated with phenethyl bromide to yield the required fenanyl analogues. Use of cyclohexylamine



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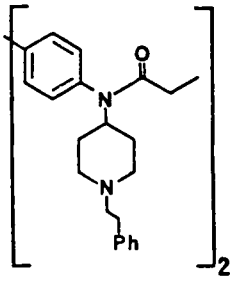

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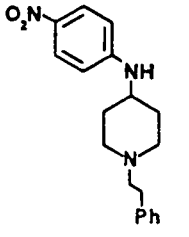

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and *p*-phenylenediamine in this procedure led to the cyclohexyl (**4**) and "di-fentanyl" (**5**) analogues, respectively.

Since *p*-nitroaniline failed to condense with the 4-piperidone, the penultimate secondary amine **6** was prepared by reaction between 4-amino-1-phenethylpiperidine (itself made by reduction of a 4-piperidone oxime with lithium aluminium hydride) (Harper & Chignell 1964) and 1-fluoro-4-nitrobenzene. Unfortunately the amine **6** resisted *N*-propionylation, even in the presence of strong bases (BuLi, Lithium diisopropylamide or dicyclohexylcarbodiimide-propionic acid). The reactivity of the anilino nitrogen was restored when nitro of **6** was reduced (H_2,Pd-C) to amino, and the resultant triamine gave the diacyl derivative **1g** with propionic anhydride. A one-pot procedure of preparing intermediate secondary amines by reductive amination of 4-piperidone with aniline and sodium cyanoborohydride, as described by Borne et al (1984), proved unsuitable when applied to 1-methyl-4-piperidone.

Compounds **2a** and **2b** were prepared by acylation of 4-amino-1-phenethylpiperidine with benzoyl chloride and phenacyl chloride respectively, and reducing the resultant amides with diborane to amines which were *N*-propionylated as usual. The *N*-phenacyl derivatives **3** were obtained by treating the corresponding secondary amines with an arylacetic acid with dicyclohexylcarbodiimide (DCC) as coupling reagent—this route avoided use of *p*-methoxyphenacetyl chloride which is difficult to prepare (Simon et al 1967).

Pharmacology and Discussion

All novel fentanyl derivatives were examined as antinociceptive agents in rats by the tail-withdrawal test and some in mice by hot-plate, tail-flick and phenylquinone writhing procedures. Tail-withdrawal ED50 values for series **1** and **4–6** are given in Table 1. Introduction of a *para* substituent in the anilino phenyl group of fentanyl depresses antinociceptive potency in rats but, except for **1g**, all derivatives were more effective than morphine and some only few-fold less active than the parent, notably the *para* fluoro, iodo and methyl derivatives. Most of these analogues are now classified by the Home Office as "designer drugs" which before April 1987 were exempt from the Misuse of Drugs Regulations. Thus this loophole in drugs legislation (Observer 12 January 1986) has now been closed. Apart from the *meta* hydroxy and methoxy congeners of fentanyl (both with only a tenth or less of the affinity of fentanyl for rat brain opioid receptor sites) (Lobbezoo et al 1981), no other analogues of type **1** appear to have been reported.

The response of rats to the non-acylated p-nitroderivative **6** was unexpected since no other active fentanyl derivative lacking an *N*-acyl substituent is known. In mice ED50 values (mg kg^{-1} s.c.) for **6** were 15·5 (tail-flick) and 0·9 (writhing), cf. pethidine 7·8 (tail-flick) and 0·8 (writhing), and the compound was inactive at 5 and 20 mg kg^{-1} in the hot-plate test. The result for **4** demonstrates the crucial nature of the anilino (aromatic) substituent in fentanyl ligands, while that for **5** shows that this "dimer-type" compound is unable to bridge a pair of opioid receptor sites. Duplication of the otherwise key propionylamido feature of fentanyl as in **1g** also abolished activity.

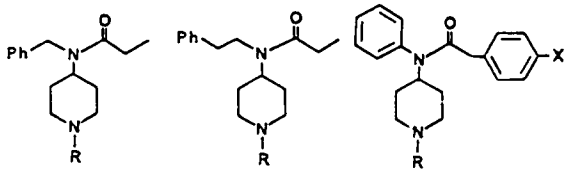
Table 1. Antinociceptive ED50 values of some fentanyl analogues (HCl salts) in rats by the tail-withdrawal test (Janssen et al 1963)

Structure	ED50 (mg kg^{-1} i.v.)
1 X = H (fentanyl)	0·01[a]
1a X = F	0·02
1b X = Cl	0·63
1c X = Br	1·25
1d X = I	0·16
1e X = Me	0·31
1f X = CF_3	1·25
1g X = NHCOEt	Inactive at 2·5[b]
6	2·5
5 ("di-fentanyl")	Inactive at 2·5
4 (cyclohexyl analogue)	Inactive at 2·5
Morphine	3·15[a]

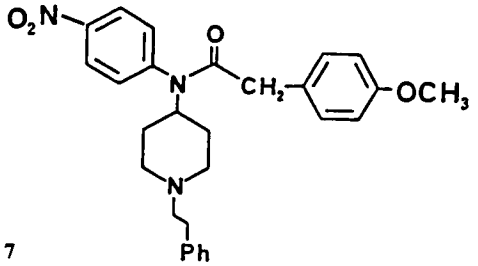
[a] Ref. Van Daele et al (1976)
[b] Failure of compound to elicit antinociceptive response at this dose level indicates that its ED50 is very high.

Antinociceptive activity data in rats for series **2** and **3** are presented in Table 2. Insertion of a one or two carbon chain between phenyl and nitrogen of the anilino unit of fentanyl depressed potency in all cases although the *N*-phenethyl analogues retained reasonable levels of activity; that of series A (5 × morphine) also exceeded morphine in potency in mice

Table 2. Antinociceptive ED50 values of some fentanyl analogues (HCl salts) in rats by the tail-withdrawal test.



Series	R	X	ED50 (mg kg^{-1} i.v.)
	Me	—	1·25
A	$PhCH_2$	—	Inactive at 2·5
	$Ph(CH_2)_2$	—	0·63
	Me	—	Inactive at 2·5
B	$PhCH_2$	—	Inactive at 2·5
	$Ph(CH_2)_2$	—	2·0
	Me	OMe	Inactive at 2·5
C	$Ph(CH_2)_2$	OMe	2·5
	$Ph(CH_2)_2$	H	insoluble: inactive at 10 orally)



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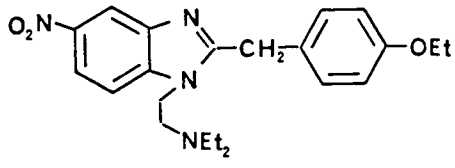

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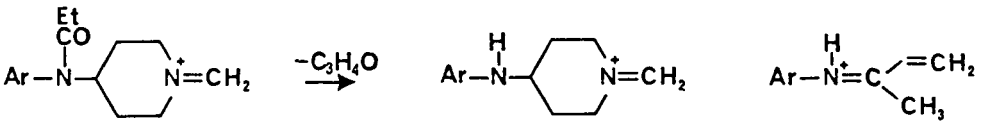

a *b* *c*

(ED50 mg kg^{-1}, s.c. tail-flick 1·7, writhing 0·2 cf. morphine tail-flick 5·8, writhing 0·23). The phenacyl analogues (C of Table 2) differ radically in potency from fentanyl. The compound of most promise (**3b**) fell below the potency of pethidine in mice (ED50mg kg^{-1} s.c. tail-flick 9·8, writhing 1·2). Nevertheless the corresponding *p*-nitro analogue (**7**) remains a worthwhile target compound in view of its possible relationship to the highly potent analgesic etonitazene (**8**) (Casy & Parfitt 1986), an objective so far frustrated by the resistance of the precursor amine **6** to *N*-acylaction. None of the compounds of Tables 1 and 2 exhibited antagonism to fentanyl-induced effects in rats at a dose level of 2·5 mg kg^{-1}.

Mass spectrometric (MS) details for fentanyl and its *para*substituted derivatives of type **1** ("designer drugs") are presented in Table 3 since they have value in forensic analysis in addition to providing evidence in support of outcome of the present syntheses. Molecular ions were only observed in chemical ionization (CI, isobutane) spectra where they had high intensities or were the base peak. Under the usual electron impact conditions (70eV) diagnostic ions are those with *m/z* values corresponding to M-91 (*a*), M-91-56 (*b*), and M-190 (*c*), cf. MS analysis of α-methyl fentanyl ("China White") (Cheng et al 1982).

Preparative work

Melting points are uncorrected. Spectroscopic data (IR, ^1H and ^{13}C NMR) and MS (Table 3) support structures in all cases. Microanalyses were performed by Butterworth Laboratories Ltd, Teddington, UK.

Propionylamides (1) (General procedure)

1-Methyl-4-piperidone (25 mmol) in toluene (50 mL) was added dropwise to a solution of the appropriate substituted aniline (28 mmol) and *p*-toluene sulphonic acid (10 mg) in toluene (50 mL) at the reflux temperature contained in a flask attached to a Dean-Stark trap for water removal. After a 7 h reflux the solution was cooled and molecular sieve 4A (20g) added. The mixture was refluxed overnight, cooled, filtered, and the filtrate concentrated under vacuum. The residue in hot methanol (60 mL) was treated with sodium borohydride (28 mmol) added cautiously over 0·5 h and the product heated under reflux for 2 h. The cooled product was concentrated under vacuum to about 20 mL, diluted with water (50 mL) and extracted several times with toluene. The organic phase was separated, dried ($MgSO_4$), filtered and concentrated. A mixture of the residual amine and propionic anhydride 120 mmol) in toluene (50 mL) was heated under reflux overnight; if TLC analysis showed the presence of starting material a further quantity of anhydride (10 mmol) was added and refluxing continued for 6 h. The cooled product was extracted with 20% sodium hydroxide in water (3 × 20 ml), washed with water and dried ($MgSO_4$). Residual products **1**, isolated as usual, were purified as HCl salts. For **1f** (X = CF_3) prior purification by column chromatography was necessary. Products obtained from *p*-phenylenediamine (**5**) and cyclohexylamine (**4**) were also prepared by this method.

Table 3. 70eV Electron impact mass spectrometric features of fentanyl and some *p*-substituted derivatives (**1**)*.

Compound	*m/z* value of diagnostic ions (ion type followed by intensity in parentheses)
1 (X = H) fentanyl 336†	245 (*a* 100), 189 (*b* 60, 146 (*c* 70)
1a (X = F) 354	263 (a 100), 207 (b 25), 164 (*c* 30)
1b (X = Cl) 370/372	279/281 (*a* 100/33), 223/225 (*b* 23/7), 180/182 (*c* 20/6)
1c (X = Br) 414/416	323/325 (*a* 100/100), 267/269 (*b* 30/30), 224/226 (*c* 20/20)
1d (X = I) 462	371 (*a* 100), 315 (*b* 20), 272 (*c* 18)
1e (X = Me) 350	259 (a 100), 203 (*b* 22), 160 (*c* 38)
1f (X = CF_3) 404	313 (*a* 100), 257 (*b* 55), 214 (*c* 35)

* Recorded with a 7070E VG Analytical instrument: we thank Mr. C. Cryer for these data.
† Molecular weight.

N-*demethylation and* N-*alkylation*

Cyanogen bromide (4 equivalents) was added to the appropriate N-methylpiperidine (**1**) in toluene (30 mL per g of **1**) and the solution heated to about 60°C for 2 h. If TLC showed the presence of starting material a further portion of cyanogen bromide (2 equivalents) was added and heating continued. When the reaction was complete the mixture was cooled and washed several times with brine. The residue recovered from the dried organic layer as usual was washed with light petroleum (bp40–60°C) to give the *N*-cyano products as pale yellow crystals (ν_{NCN}2200 cm^{-1}). These materials were hydrolysed by heating to reflux for 6h with 50% acetic acid in water (50 mL g^{-1} of substrate). After the reaction mixture had stood overnight it was concentrated under vacuum and the residual oil extracted with chloroform. The extract was washed with NH_3-H_2O, dried ($MgSO_4$), filtered and evaporated. A mixture of the residual secondary amine (9 mmol), phenethyl bromide (9·2 mmol) and acetonitrile (20 mL) was treated with anhydrous Na_2CO_3 (40 mmol) and a few crystals of KI and the mixture heated under reflux for 24 h. The cooled product was filtered, evaporated, and the residue dissolved in 10% HCl-H_2O (30 mL). The acidic solution was washed with ether, made alkaline with 10% NH_3-H_2O and extracted with chloroform. The base recovered from the organic phase as usual was converted to a HCl salt. Melting point and microanalytical data are given in Table 4.

4-(4-Nitrophenylamino)-1-(2-phenethyl)piperidine and reduced product

A mixture of 4-amino-1-(2-phenethyl)piperidine (2 g) (de-

Table 4. Melting point and microanalytical data.

Compound	M.P(°C)	Molecular formula	Microanalyses (required % age in parentheses)
1a	104	$C_{23}H_{27}FN_2O$ HCl H_2O	C 64·59 (64·62); H 7·51 (7·40) N 6·49 (6·85); F 4·76 (4·65)
1b	195–196	$C_{22}H_{27}ClN_2O$ HCl H_2O	C 62.41 (62·12); H 7·14 (7·11) N 6·71 (6·54); Cl 8·10 (8·33)
1c	241	$C_{22}H_{27}BrN_2O$ HCl H_2O	C 56·68 (56·24); H 6·04 (6·44) N 6·20 (5·96); Br 16·91 (17·01)
1d	227	$C_{22}H_{27}IN_2O$ HCl H_2O	C 51·49 (51·11); H 5·59 (5·85) N 5·78 (5·42); I 24·41 (24·55)
1e	236	$C_{23}H_{30}N_2O$ HCL H_2O	C 68·14 (68·21); H 7·87 (7·47) N 6·91 (6·92)
1f	237	$C_{23}H_{27}F_3N_2O$ HCl H_2O	C 60·43 (60·20); H 6·29 (6·57) N 6·41 (6·10)
1g	199	$C_{25}H_{33}N_3O_2$ HCl H_2O	C 65·30 (64·99); H 7·64 (7·85) N 9·10 (9·10)
6	81–82	$C_{19}H_{23}N_3O_2$ HCl	C 62·83 (63·06); H 6·31 (6·68) N 11·60 (11·61)
4	160–161	$C_{22}H_{34}N_2O$ HCl	C 69·16 (69·72); H 9·33 (9·31) N 7·06 (7·39)
5	289–300 dec	$C_{38}H_{50}N_4O_2$ 2HCl $4H_2O$	C 62·04 (61·71); H 7·57 (8·18) N 8·00 (7·58)
2a	237 dec	$C_{23}H_{30}N_2O$ HCl H_2O	C 68·58 (68·21); H 7·76 (8·21) N 6·82 (6·92)
N-Methyl analogue of 2a	178–179	$C_{16}H_{24}N_2O$ HCl	C 71·14 (71·22); H 9·10 (9·33) N 10·44 (10·38)
N-Benzyl analogue of 2a	222	$C_{22}H_{28}N_2O$ HCl	C 70·72 (70·85); H 7·75 (7·84) N 7·09 (7·51)
2b	174	$C_{24}H_{32}N_2O$ HCl H_2O	C 67·71 (67·80); H 8·28 (8·42) N 6·98 (6·69)
N-Methyl analogue of 2b	196–197	$C_{17}H_{26}N_2O$ HCl H_2O	C 61·98 (62·08); H 8·64 (8·89) N 8·43 (8·52)
N-Benzyl analogue of 2b	220	$C_{23}H_{30}N_2O$ HCl	C 71·04 (71·38); H 8·02 (8·07) N 6·84 (7·23)

rived from HCl m.p. 274–275°C, Harper & Chignell 1964 give m.p. 273–274°C), 1-fluoro-4-nitrobenzene (1·4 g), propan-1-ol (50 mL), KI (10 mg) and Na_2CO_3 (1·2 g) was heated under reflux for 24 h. The cooled product was filtered, the filtrate concentrated and the residue in benzene (100 mL) washed with aqueous NaOH (10%, 3 × 20 mL). The residue isolated from the dried organic phase was purified by flash column chromatography using methanol as eluant to give **6** (2·1 g) as pale yellow crystals from 2-propanol (Table 4). The nitro compound **6** (1 g) in methanol (50mL) was hydrogenated in the presence of 10% Pd/C (0·5 g) at 100 psi (approx.) overnight. The 4-amino base (0·87 g), recovered as a deep red oil, was acylated in the usual manner to give 1 g HCl (Table 4).

*4-Benzylamido-(**2a**) and 4-phenylacetamidopiperidines (**2b**).* A mixture of the appropriate 4-aminopiperidine (40 mmol), sodium bicarbonate (12·1 g, 144 mmol) and chloroform (100 mL), cooled to 0°C, was treated with benzoyl chloride or phenylacetyl chloride (48 mmol). The product was maintained at the reflux temperature until disappearance of starting material was observed by TLC (24 h approx.). The cold product was filtered and the amide products isolated from the filtrate. Diborane (30 mL of M solution) was added over 0·5 h to the appropriate amide (10 mmol) in tetrahydrofuran cooled to 0°C under nitrogen. The mixture was then heated under reflux until all starting material was absent (by TLC). Solvent was evaporated under vacuum and the residue heated under reflux for 4 h with methanol (50 mL) and 2 M HCl (5 mL). The cooled product was made alkaline with aqueous ammonia and extracted with chloroform. Amine products, recovered as usual were acylated with propionic anhydride, as before, and the amides isolated as HCl salts (Table 4).

N-Phenacyl analogues of fentanyl (**3**). Dicyclohexylcarbodiimide (DCC, 1·85 g), followed by the appropriate carboxylic acid (5 equivalents) was added to an *N*-substituted 4-phenylaminopiperidine (0·5 g) in methylene dichloride (50 mL). The clear mixture was heated under reflux for 4 h, cooled and filtered, and the filtrate washed with aqueous NaOH (20%, 3 × 10 mL). The resultant amides (**3**), recovered from the organic phase, were isolated as HCl salts (Table 4).

Acknowledgements

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