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New heteroaryl derivatives of fentanyl

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Abstract—The preparation of analogues of fentanyl with *N*-phenyl replaced with a heterocyclic aromatic ring, and with *N*-alkyl/arylalkyl *N*-acyl substituents is reported. Only those compounds carrying an *N*-phenylethyl substituent were active in the rat tail-withdrawal test. Fentanyl (1) is the prototype of the 4-anilidopiperidine class of opioid analgesics (Casy & Parfitt 1986). Several recent publications (Casy & Huckstep 1988; Bagley et al 1989) on this series have dealt with heterocyclic and aromatic modifications of the fentanyl molecule. Although the antinociceptive potency of most novel derivatives was greater than that of morphine, they had reduced activity when compared with fentanyl itself. To acquire further information on the structure-reactivity relationships of the series, new heteroaryl derivatives have been prepared and tested for antinociceptive activity.

Chemistry

The intermediate 4-(heteroanilido)-piperidines were obtained by treating the 4-amino-*N*-substituted piperidine with the appropriate heterocyclic halide. Acylation of these products with the corresponding acid chloride in the presence of triethylamine (Lobezoo et al 1980) yielded the required fentanyl analogues 2–13 (Table 1). Infra-red spectroscopy, ^{1}H-NMR spectroscopy and elemental analysis confirmed the structures shown.

Preparative work

Melting points are uncorrected. Spectroscopic data (IR, ^{1}H-NMR) support structures in all cases. Microanalyses were performed on a Perkin-Elmer 240 by CSIC laboratories (Madrid Spain).

5-Bromo and 8-bromoquinolines were prepared as described by Butler & Gordon (1975), 5-bromoisoquinoline as described by Gordon & Pearson (1964), 9-chloroacridine as described by Atwell et al (1984), and 7-chlorobenzo[b][1,8] phenanthroline as described by Elslager & Tendrick (1962). 1-Methyl-4-aminopiperidine and 1-phenylethyl-4-aminopiperidine were prepared by reduction of the corresponding 4-piperidone oximes with lithium aluminium hydride by the standard procedure (Harper & Chignell 1964).

4-Heteroanilido-piperidines (general procedure). A mixture of 4-aminopiperidine-*N*-substituted (40 mmol), heteroaryl halide (20 mmol), copper powder (20 mmol) and triethylamine (5 mL) in 1-pentanol (30 mL) was stirred at the reflux temperature for 4 h. The mixture was concentrated in-vacuo and the solid was added to 10% HCl (50 mL). The suspension was stirred and the melt was poured slowly into an excess of ice and concentrated ammonium hydroxide (150 mL) and extracted with ether (4 × 100 mL). The organic layer was washed with water and dried over anhydrous sodium sulphate. The crude products were purified by column chromatography and recrystallized.

4-Heteroanilido-4-acyl-piperidines (2–13) (general procedure). To a mixture of 4-heteroanilidopiperidine (20 mmol) in chloroform (30 mL) and triethylamine (5 mL) was added dropwise a solution of the acid chloride (30 mL) in chloroform (5 mL). The reaction mixture was stirred at reflux temperature for 1 h. The mixture was concentrated in-vacuo and the residue was extracted with 10% HCl–ether (1 : 1) (50 mL). The aqueous layer was alkalinized with concentrated ammonium hydroxide (100 mL) and extracted with chloroform (4 × 100 mL), washed with water and dried over anhydrous sodium sulphate. The products were purified by recrystallization.

Pharmacology and discussion

The antinociceptive activities of fentanyl and its analogues were assessed in rats by the tail-withdrawal test (Janssen et al 1963, Table 1). When the *N*-phenylethyl and *N*-propionyl substituents were present (compounds 2-5), the antinociceptive activity decreased while a complete lack of activity at 2·5 mg kg^{-1} was observed for compound 6 with an increased steric bulk (Series 5A). The *N*-heteroaryl analogues have potencies greater than that of morphine, with significant differences between 5- and 8-quinolyl isomers (2,3) indicating that the heterocyclic conforma-

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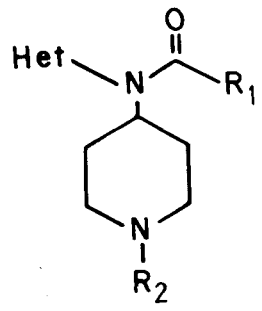
Table 1. Structure, characterization and properties of fentanyl analogues.



Compound (Fentanyl)	Heterocycle	R_1	R_2	m.p. °C	Elemental analysis (theoretical) C	H	N	EC50 (mg kg^{-1})
A 1	C_6H_5	C_2H_5	$(CH_2)C_6H_5$					0·03
2	5-Quinolyl	C_2H_5	$(CH_2)C_6H_5$	183–184	77·31 (77·48)	7·76 (7·54)	10·63 (10·84)	0·19
3	8-Quinolyl	C_2H_5	$(CH_2)C_6H_5$	202–203	77·51 (77·48)	7·48 (7·54)	10·91 (10·84)	1·96
4	5-Isoquinolyl	C_2H_5	$(CH_2)C_6H_5$	176	77·62 (77·48)	7·42 (7·54)	11·01 (10·84)	0·65
5	9-Acridinyl	C_2H_5	$(CH_2)C_6H_5$	212–213	79·45 (79·60)	7·32 (7·14)	9·42 (9·60)	1·42
6	7-Benzo(b) (1,8) phenanthrolyl	C_2H_5	$(CH_2)C_6H_5$	260	78·78 (78·65)	6·51 (6·60)	11·52 (11·46)	>2·5
B 7	5-Quinolyl	C_2H_5	CH_3	146–147	72·80 (72.69)	7·60 (7·79)	14·30 (14·12)	>2·5
8	8-Quinolyl	C_2H_5	CH_3	158–159	72·49 (72·69)	7·83 (7·79)	14·02 (14·12)	>2·5
9	5-Acridinyl	CH_3	CH_3	166–167	76·28 (76·04)	7·11 (7·25)	12·21 (12·09)	>2·5
C10	5-Quinolyl	CH_3	$(CH_2)C_6H_5$	177	77·32 (77·17)	7·09 (7·28)	11·37 (11·25)	1·45
3	8-Quinolyl	CH_3	$(CH_2)C_6H_5$	186	77·22 (77·17)	7·17 (7·28)	11·30 (11·25)	2·35
4	5-Isoquinolyl	CH_3	$(CH_2)C_6H_5$	169–170	77·04 (77·17)	7·35 (7·28)	11·10 (11·25)	1·85
5	9-Acridinyl	CH_3	$(CH_2)C_6H_5$	195	79·59 (79·40)	6·79 (6·90)	10·02 (9·92)	>2·5
Morphine								3·15

tion has relevance for the opiate-receptor interaction. The structural rigidity of these compounds compared with fentanyl may explain the lack of activity as attempts to restrict the conformational flexibility of fentanyl have been shown to lead to decreased activity (Berger et al 1977; Borne et al 1984; Fifer et al 1984).

Replacement of *N*-propionyl by *N*-acetyl in the active compounds 2–5 depressed the potency. However, in these compounds (Series C, 10–12) the antinociceptive activity at 2·5 mg kg^{-1} lower doses was maintained which is surprising because the *N*-propionyl group in fentanyl and its derivatives seems to be essential for the opiate-receptor interaction (Lobezoo et al 1980; Lobezoo & Soudijn 1981). The explanation may lie in a substantial increase of opiate receptor affinity for the heteroaromatic ring region or a capacity of the opiate receptor to bind structurally different morphinomimetics in different orientations.

Lack of activity up to at least 2·5 mg kg^{-1} on *N*-methyl substitution of the piperidine ring was observed (Series B) indicating that the *N*-phenylethyl group is necessary for the interaction with opiate receptor(s). This is in agreement with the report of Fifer et al (1984). None of the compounds exhibited antagonism to fentanyl-induced effects in rats at doses of 2·5 mg kg^{-1}. Finally, the property of several of these derivatives in sharing antinociceptive activity indicates that substitution with a heteroaromatic ring and the lack of an *N*-propionyl group does not lead to a complete loss of antinociceptive activity in this series of opioids.

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