Supplementary material

Fentanyl-related compounds and derivatives: current status and future prospects for pharmaceutical applications

Ruben S. Vardanyan, Victor J. Hruby

Department of Chemistry and Biochemistry, University of Arizona, Tucson, AZ 85721, USA

Supplement 1.

9 Opioids have been introduced into the medicinal practice during the last five decades, and they are: pentazocine (1967), fentanyl (1968), butorphanol (1978), nalbuphine (1979), buprenorphine (1981), sufentanil (1984), alfentanil (1986), tramadol (1995) and remifentanil (1996). (Fig.1S.)

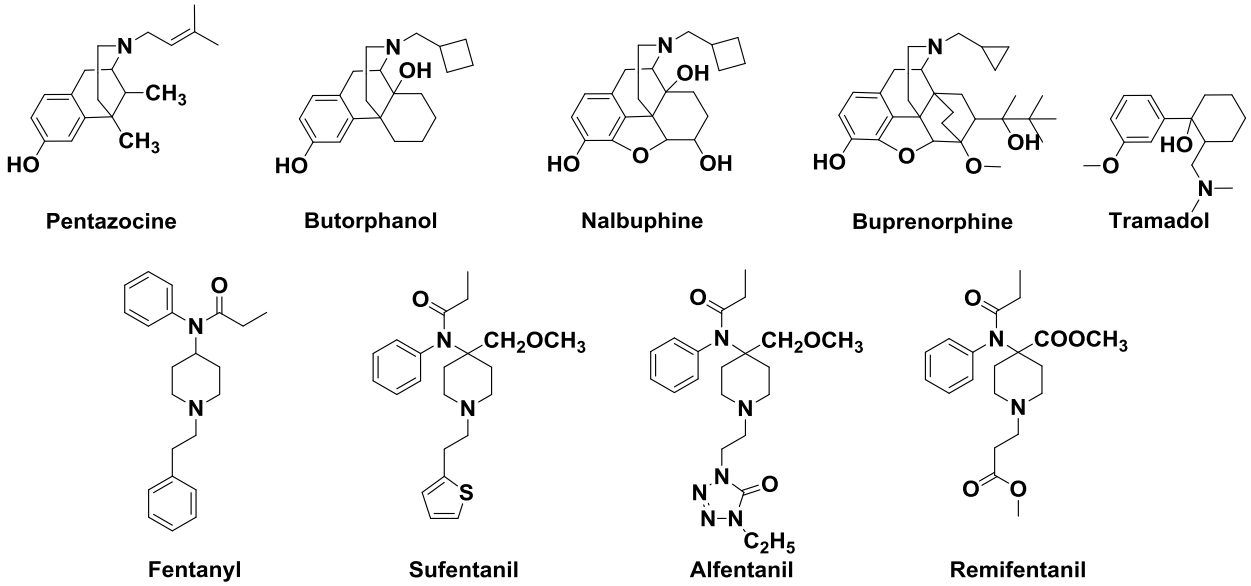


Fig. 1S.

Supplement 2.

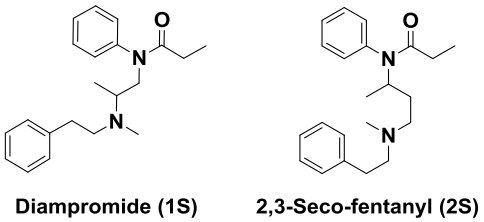


Fig. 2S. Structures of diampromide (**1S**) and 2,3-seco-fentanyl (**2S**)

Supplement 3.

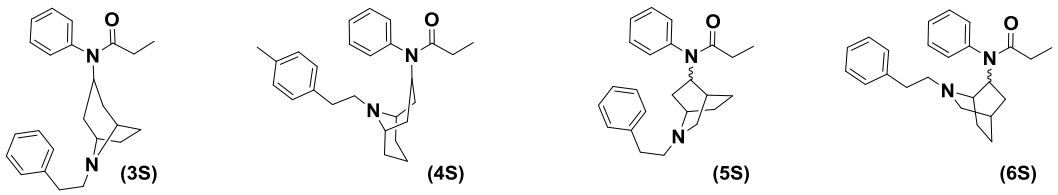


Fig. 3S. Structures of conformationally restricted, semirigid analogues of fentanyl

Supplement 4.

The synthesis of 2-methyl-fentanyl.

2-Methyl- derivatives were proposed to be prepared from 2-methylpyridine N-oxide (**7S**). On interaction with phosphorous oxychloride (**7S**) was transformed to 4-chloro-2-methylpyridine hydrochoride (**8S**), which on heating with aniline gave 4-anilino-2-methylpyridine (**9S**). Then (**9S**) was acylated by propionic anhydride to give compound (**10S**). Hydrogenation of (**10S**) using Pd/C catalyst yielded 2-methyl-4-(N-phenylpropanamido)piperidine (**11S**), which after benzylation gave product (**12S**), which on reductive amination in the presence of phenylacetaldehyde gave the desired (**25**), possessing analgesic activity in the rat with an ED_{50} of 0.665 mg/kg [82]. (Scheme 6.) The question of why authors avoided direct alkylation with reagents like phenylethylbromide remains open. This synthesis of 3-methyl-fentanyl (**26**) using the same approach was patented [83].

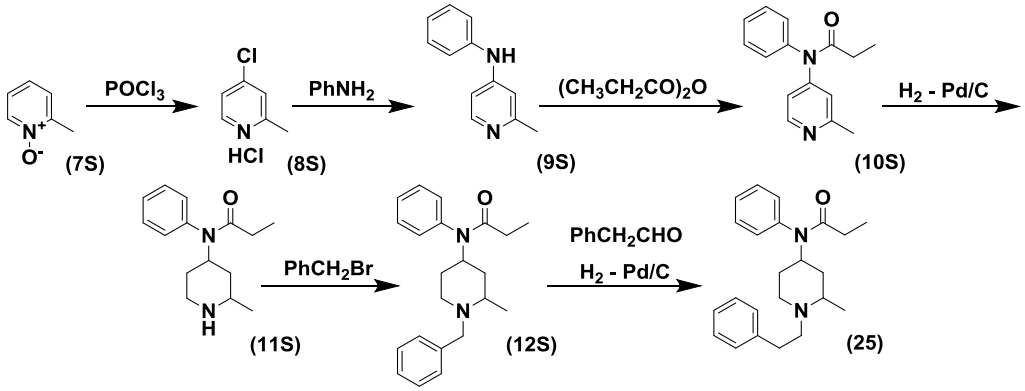


Fig. 4S. The synthesis of 2-methyl-fentanyl.

Supplement 5.

Publication [82] was followed with another one with a different approach to the synthesis of 3-methylfentanyl derivatives [84]. This method (Fig. 5S) started with 3-methyl-4-oxopiperidinecarboxylate (**13S**) which was condensed with aniline and the obtained imine was reduced to the amine, which were propionylated to afford a mixture of cis-(±) and trans-(±) methyl 3-methyl-4-[N-(1-propionoxy)-N-phenylamino]-l-piperidinecarboxylates (**14S**), which were separated by fractional crystallization (isomers with equatorial 3-Me group were defined as

trans-, with axial 3-Me cis-). The N-carbalkoxy groups of the obtained cis-(±) and trans-(±) isomers were removed by brief refluxing in 48% HBr giving the corresponding cis-(±) and trans-(±) diastereoisomers (**15S**), which were separated to enantiomers by fractional crystallization of their tartaric salts. The D-tartaric acid salt of cis-(±)-(**15S**) was converted to free base to give optically pure cis-(-) (**15S**). Similarly, the L-tartaric acid salt of cis-(±)-(**15S**) afforded the corresponding cis-(+) (**15S**). Alkylation of the obtained 3-methylpiperidineamines (**15S**) with 2-phenylethyl bromide yielded the corresponding 3-methyl-l-(2-phenylethyl)-N-phenyl-4-piperidineamines respectively cis-(±)-(**16S**), cis-(-)-(**16S**), cis-(+)-(**16S**), and trans-(±)-(**16S**). Treatment of the obtained isomers of (**16**) with propionic anhydride afforded the end products cis-(±)-(**26**), trans-(±)-(**26**), cis-**(**-)-(**26**) and cis-(+)-(**26**). The structure assignments were confirmed by NMR spectroscopy using differences in the splitting pattern of the 4-proton of the piperidine ring, and assuming a chair conformation for the piperidine ring, the most predominant conformer would have an equatorial 4-N-phenylpropanamide group.

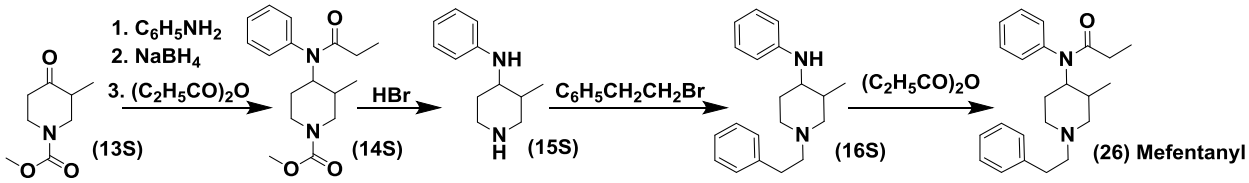


Fig. 5S. The synthesis of 3-methyl-fentanyl.

The cis-(+)-N-(3-methyl-l-(2-phenylethyl)-4-piperidyl]-N-phenylpropan-amide (**26**) is an extremely potent analgesic agent with an ED_{50} 0.00058 mg/kg, which is up to 6700 times higher than that of morphine. It has a fast onset of action, a shorter duration of action, and a high safety margin.

A general conclusion is that the trans- compound (**26**) is more potent than fentanyl, while the corresponding cis- diastereoisomer (**26**) is approximately eight times more active than fentanyl. The analgesic activity of (**26**) as expected is mainly due to one enantiomer, namely the cis-(+) compound (**26**)**,** which is about 16 times more potent than fentanyl, while its cis-(-) counterpart is 120 times less potent than the cis-(+). It was of interest to know the absolute configuration of product with maximal activity**.** The absolute configuration of the isomers are: cis-(+)-(**26**) as (3R,4S), cis-(-)-**26**) as (3S,4R), trans-(+)-(**26**) as (3S,4S), trans-(-)-(**26**) as (3R,4R) [84]. Isomeric α-methylfentanyl (**27**), obtained by the same synthetic method but containing an additional methyl group in the side chain in the α position to the basic nitrogen, also displayed high activity (ED_{50} 0.0085 mg/kg) close to that of fentanyl (ED_{50} 0.011 mg/kg). Insertion of two methyl groups simultaneously (**28**) in this position led to enhancement of activity depending on orientation of the 3-methyl substitution in the compounds with ED's_{50} from 0.011 for the (+)-cis, to 0.00075 mg/kg for the (-)-cis- isomers [84]. (Fig.6S)

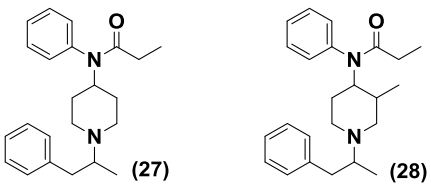


Fig.6S. Structures of α-methylfentanyl (**27**) and its 3-methyl analogue (**28**).

Another method for the synthesis of cis- and trans-3-alkylfentanyl analogs was developed [85] (Fig. 7S). In this case the N-phenethyl-4-piperidone (**7**) was converted to the cyclohexylimine derivative (**17S**), which was α-deprotonated with butyllithium and the resulting imine anion was alkylated with alkyl halides to give a variety of piperidin-4-ones (**18S**), which were reacted with aniline to form the corresponding Schiff bases (**19S**). Reduction of (**19S**) with $LiAlH_4$ yielded mixtures of cis-/trans- 3-alkyl-4-anilinopiperidines (**20S**). The diastereoisomers were separated by column chromatography to yield the pure cis- and trans-isomers. Finally, N-propionylation of the obtained amines afforded twelve new fentanyl analogs (**22S**). Except for the known (±)-cis-3-methylfentanyl and the novel (±)-cis-3-ethylfentanyl, the others were inactive or less active than fentanyl itself.

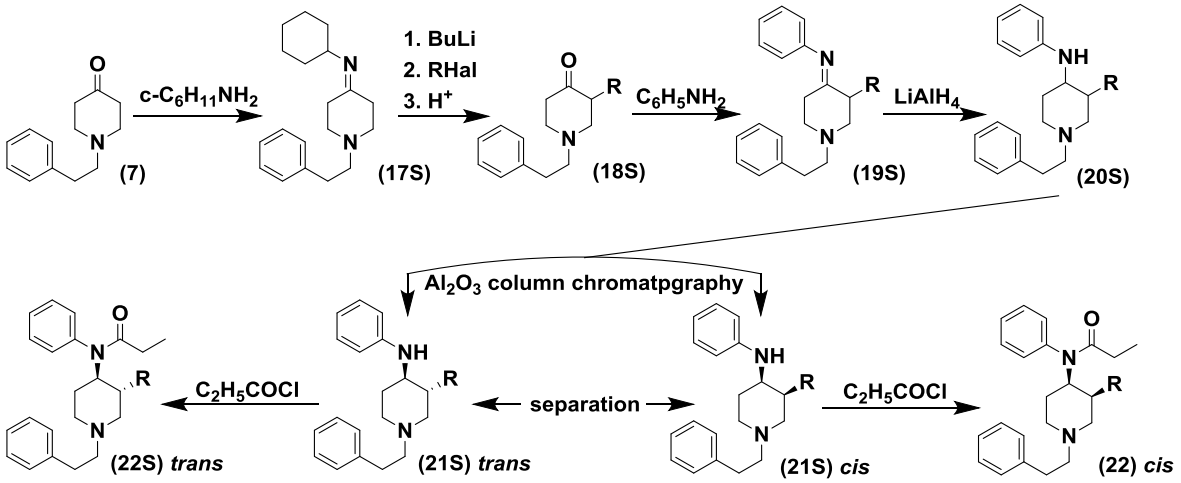


Fig. 7S. Synthesis of trans-3-alkylfentanyls.

Supplement 6.

The synthesis of 2.5-dimethyl-fentanyl - Phenaridine (**29**) started with 2-methylhex-5-en-3-yn-2-ol (**23S**), which underwent dehydration forming dienyne (**24S**). Triple bond hydration and simultaneous rearrangement of the intermediate allyl- compound gave dienone (**25S**), which via interaction with phenethylamine was cyclized to desired piperidinone-4 (**26S**). It was converted to the 2.5-dimethyl-fentanyl by the known protocol via consequential reactions with aniline, followed by hydrogenation to amine and, finally propionylation to give desired (**29**) as a mixture of isomers [86,87].

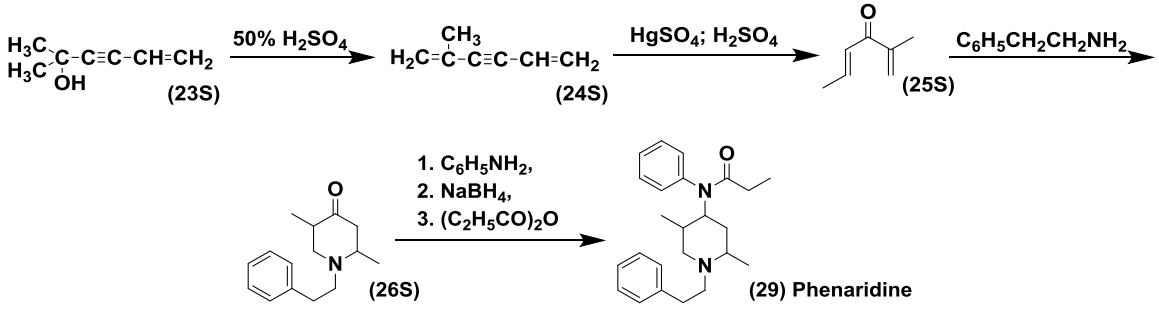


Fig. 8S. Synthesis of 2.5-dimethyl-fentanyl – phenaridine (**29**).

Supplement 7.

An original method of synthesis of 3.5-dimethyl-fentanyl (**30**) and its analogs (**33S, 34S**) has been proposed (Fig.9S.) starting from methyl-substituted benzylaminodipropionate (**27S**), which underwent Dieckman condensation to give 5-methyl-4-oxopiperidine-3-carboxylate (**28S**). Then (**28S**) was condensed with aniline and the double bond in the formed imine was hydrogenated with sodium cyanoborohydride to yield aminoester (**29S**). The last was reduced with lithium aluminum hydride providing aminoalkohol (**30S**), which reaction with methanesulfonyl chloride yielded mesyl derivative (**31S**). Compound (**31S**) was reduced with lithium aluminum hydride to give 1-benzyl-3,5-dimethyl-N-phenylpiperidin-4-amine (**32S**). Acylation of (**32S**) with appropriate acid chlorides or anhydrides gave anilides, which were debenzylated by hydrogenolysis on palladium hydroxide catalyst. Further alkylation of the obtained secondary amine with appropriate 1-(2-aryl, (heteroaryl)-ethyl halogenides gave desired fentanyl analogues (**33S**). The cis- and trans- isomers were separated at various stages of the reaction scheme. The most convenient is the separation after reduction of the ester to form (**30S**). The compounds (**33S**) as obtained diastereomers or as mixtures, were tested for analgesic activity on mouse hot plate test and the majority of the compounds displayed good activity. The most promising was N-(phenyl)-N-[1-(2-(1H-pyrazol-1-yl)ethyl)-3,5-dimethyl)-4-piperidinyl]methoxyacetamide (**34S**) with an ED_{50} 0.0025 mg/kg [94].

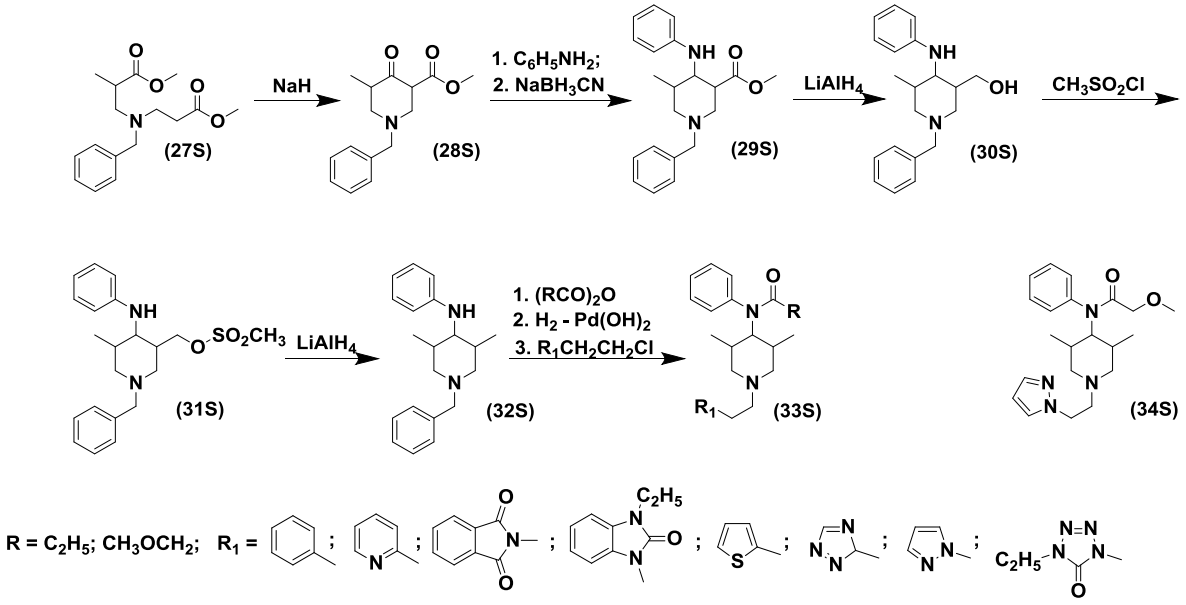


Fig. 9S. Synthesis of 3.5-dimethyl-fentanyl analogues.

2,3-Dimethyl-fentanyl - (**31**) to our knowledge is not described in the literature. Decahydro-quinoline analogue (**32**) and other derivatives of the same series were synthesized starting from the 4-oxodecahydroquinoline showed low analgesic activities (ED_{50} 25-50 mg/kg) [95]. (Fig.10S.)

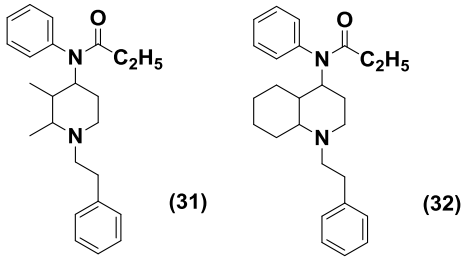


Fig. 10S.

Supplement 8. Structures of 2,3-Dimethyl-fentanyl - (**31**) and its decahydro-quinoline analogue.

A simple and efficient synthesis of 4-methylfentanyl was proposed recently [96] (Fig. 11S.). N-Carbethoxypiperidin-4-one (**15**) was involved in Grignard reaction with MeMgI to yield tertiary alcohol (**35S**). The Ritter reaction of (**35S**) with propionitrile afforded amide (**36S**). The phenylation of N-metalated amide was accomplished with diphenyliodonium chloride in the presence of 18-crown-6 ether, which improved the yields giving piperidine-1-carboxylate (**37S**). The carbamate group in amide (**37S**) was removed, using trimethylsilyl iodide to give secondary amine (**38S**). The obtained intermediate was alkylated with phenethyl iodide giving the desired 4-methyl fentanyl (**33**). The potency of 4-methyl fentanyl (**70**) was found to have an ED_{50} 0,0028 mg/kg in rats, which is approximately four times greater than that of fentanyl (ED_{50} 0,0105 mg/kg), while the time peak and the duration of action are the same as fentanyl's .

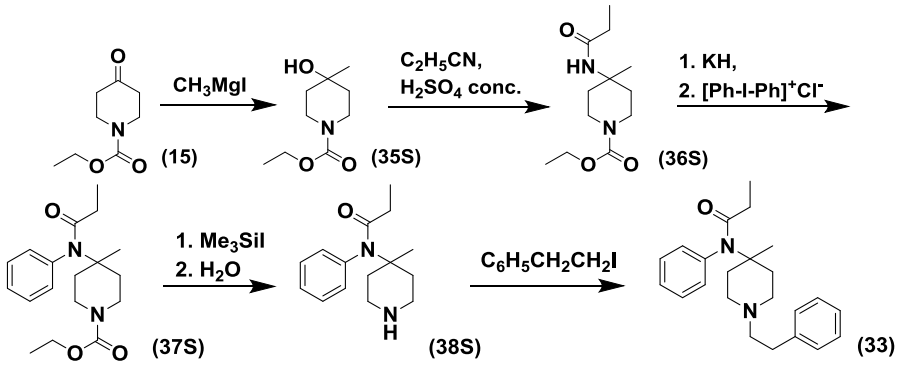
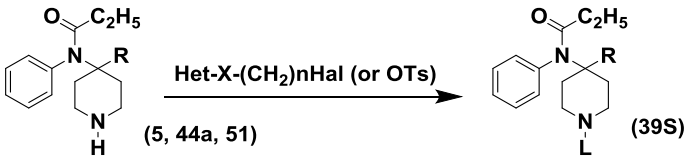


Fig. 11S. Synthesis of 4-methyl-fentanyl analogue.

Supplement 9.

In an attempt to prepare novel analgesics in the fentanyl series, studies were initiated [107] to create new 1-(heterocyclyalkyl)-4-(propionanilido)-4-piperidinyl methyl esters and methylene methyl ethers (**93**) where aromatic β-substituent (benzene, thiophene, tetrazole) at the first position of piperidine ring was replaced for a variety of other possible heterocyclic substituents (pyrroles, pyrazoles, imidazoles, triazoles, tetrazoles, thiophenes, furans, thiazoles, other pentacyclic heterocycles, pyridines and other hexacyclic heterocycles, benzo-fused pentacyclic heterocycles, benzo-fused hexacyclic heterocycles, xantines, naphtalimides and others). The new compounds (**39S**) have been synthesized by alkylating of the intermediate amines (**5)**, N-dezalkylated (**44) – (44a)** and (**51**) with appropriate electrophiles [107]. (Fig. 12S.)



R = H (5); $COOCH_3$ (44a); CH_2OCH_3 (51);
L = -(CH_2)n-X-Heterocycle (n = 1,2. X = O, S, or direct bond

Employed hetetocycles:

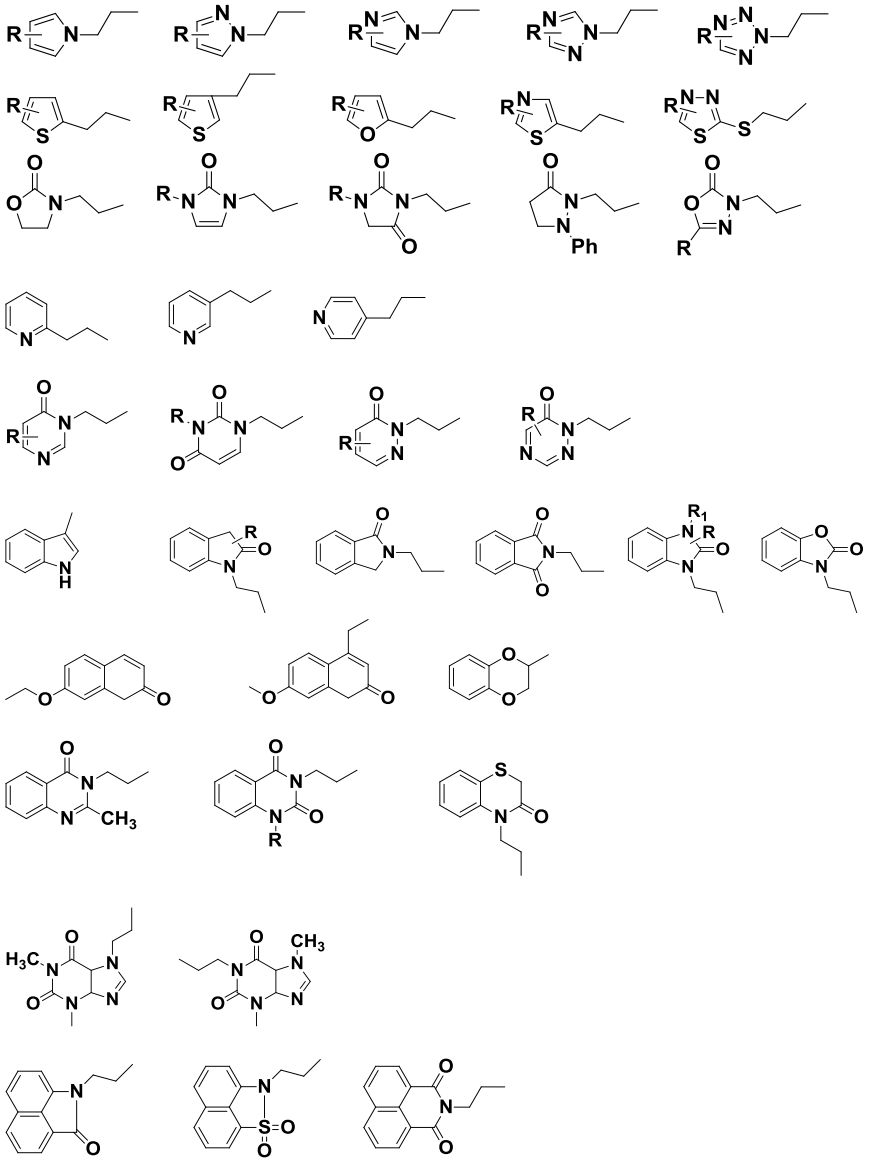


Fig. 12S. General method for the synthesis of compounds with various aromatic β-substituents.

The compounds above were tested in the mouse hotplate test. Most of the compounds exhibited an analgesia (ED_{50} < 1 mg/kg) superior to that of morphine. New interesting compounds like the pyrazolylethyl derivative (**40S**) (Fig. 13S.) (ED_{50} 0.0099 mg/kg), were obtained which exhibited

appreciable μ-opioid receptor affinity, were more potent and short-acting analgesics than alfentanil and less respiratory depression in the rat and phthalimidoethyl compounds (**41S**) (ED_{50} 0.056 mg/kg) and (**42S**) (ED_{50} 0.119 mg/kg), which exhibited no affinity for opioid receptors associated with the mediation of nociceptive transmission (i.e., μ-, δ-, and κ-subtypes). Nonetheless they showed analgesic efficacy in all antinociception tests. In addition, (**42S**) showed a superior motor coordination following from full anesthetic doses in the rat rotarod test. (Fig. 13S).

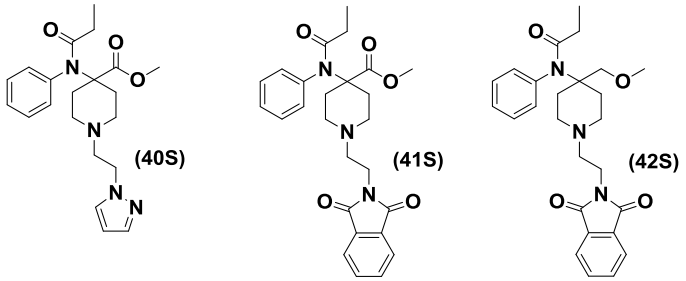


Fig. 13S. Structures of fentanyl analogues (**40S**), (**41S**) and (**42S**).

Supplement 10.

The first synthesis of this series of compounds was proposed from (piperidin-4-yl)-N-phenylpropionamide (**5**), N-(4-(methoxymethyl) piperidin-4-yl)-N-phenylpropionamide (**51**) and methyl 4-(N-phenylpropionamido)piperidine-4-carboxylate (**44**a), which were prepared according to methods of synthesis of fentanyl, sufentanil and alfentanil starting from N-benzyl piperidin-one-4 [105,108-111].

Compounds **5, 44a** and **51** underwent Michael addition with appropriate acrylates, or alkylation reaction with 2-bromoacetates, 4-bromobutenoates or 4-bromopentenoates to give compounds of general formula (**43S**) [112,113]. (Fig. 14S.)

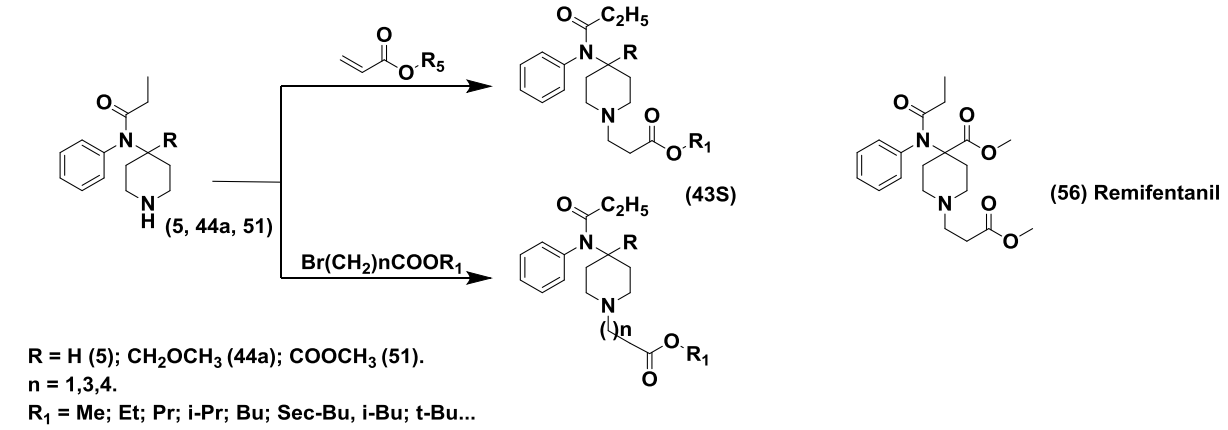


Fig. 14S. Synthesis of remifentanil and analogues.

As a result of these investigations it has been shown that replacement of the fentanyl nucleus, R = H, with the carfentanil nucleus, R = CO_2CH_3, enhances the analgesic potency of these compounds. Use of the sufentanil nucleus, R = CH_2OCH_3, gave weak opioid agonists.

By changing the length of the methylene tether, it was found that two methylene units between the piperidine nitrogen and the methyl ester were the best for enhanced potency and decreased duration of action. Compound (**56**) remifentanil now is a drug on the market.
The carboxylic acid, resulting from hydrolysis of esters in first position of the piperidine ring was about 1000 times less potent than compound (**56**), which provided insights into the effects of the alkyl ester moiety on potency and duration of action. All of the esters were potent μ opioid agonists. However, variations in the size and substitution patterns of the ester led to effects on both in vivo and in vitro potency. The most potent compounds were those which have a tertiary or quaternary carbon alpha to the ester oxygen. For straight chain esters the potencies decreased as the chain length increased from ethyl to octyl. Durations of action ranged from extremely short to long (5 to 85 min) depending upon the the alkyl group of the ester.
In vivo experiments with (**56**) demonstrated also that the major μ opioid side effects: respiratory depression, bradycardia, and muscle rigidity, were of short duration. Thus a unique drug (**56**) remifentanil with a high degree of analgesic potency (ED_{50} 0.0044 mg/kg) and ultra-short duration of action (15 min.) became a clinically useful addition to the fentanyl family of analgesics [112]. Later other data appeared in literature [114], according to which ED_{50} and 95 % confidence limits of analgesic effect of remifentanil on mice were 0.73 (0.64-0.84) mg/kg and 0.19 (0.12-0.31) mg/kg, respectively in hot-plate and clam-tail tests. Analgesic effects of remifentanil on rat were 2.70 (1.15-6.34) mg/kg and 5.21 (2.11-12.85) mg/kg, respectively in formaldehyde and swing-tail methods. The analgesic action of remifentanil was the strongest at 1 min after intravenous injection. The action was weakened after 6 min., and disappeared after 12 min. Remifentanil (**56**) occupied its own place in the arsenal of opioid analgesics and described and discussed in many pharmacological reviews [115-124] including an originally titled review "Remifentanil: do we need another opioid?" [116]. Many modifications of the scheme of synthesis were proposed [125-129], among which is an interesting approach which applies the Ugi reaction for the synthesis of remifentanil (**56**) and caefentanil (**45**) [129] (Fig. 15S.).
The first step of this approach is just mixing together methyl 1-(2-carbomethoxyethyl)-piperidine-4-one (**44S**), aniline, propionic acid and cyclohexenylisocyanide in methanol for 24 hours a 55^{o}C to get product (**45S**) in 86% yield which was hydrolysed in 10% acetic acid methanol solution to give the desired remifentanil (**56**). (The method has been employed for mg scales and includes HPLC purification. But, probably on appropriate development, it'll be possible to expand it to an industrial scale.

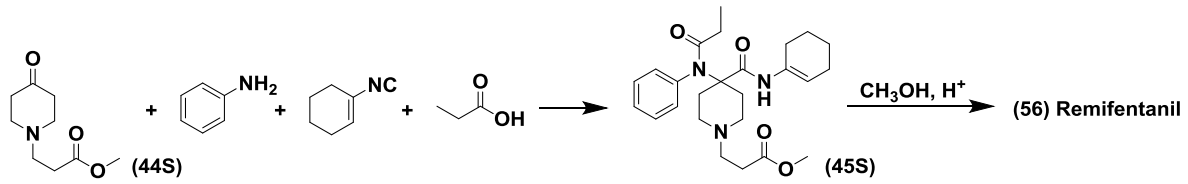


Fig. 15S. Alternative synthesis of remifentanil.

Supplement 11.

Another set of analogue compounds (**71**) was prepared by the condensation of aminoalkohol (**48**) with 1,l'-carbonyldiimidazole and the only obtained monocondensed adduct (**46S**) was treated with an alcohol in the presence of a catalytic amount of acid giving carbonates (**47S**). Further acylation of the anilido nitrogen afforded the compounds (**48S**), which were subjected to

hydrogenolysis, giving (**49S**). The resulting amines were alkylated with arylethyl halogenides to give the desired compounds (**71**). (Fig. 16S.)

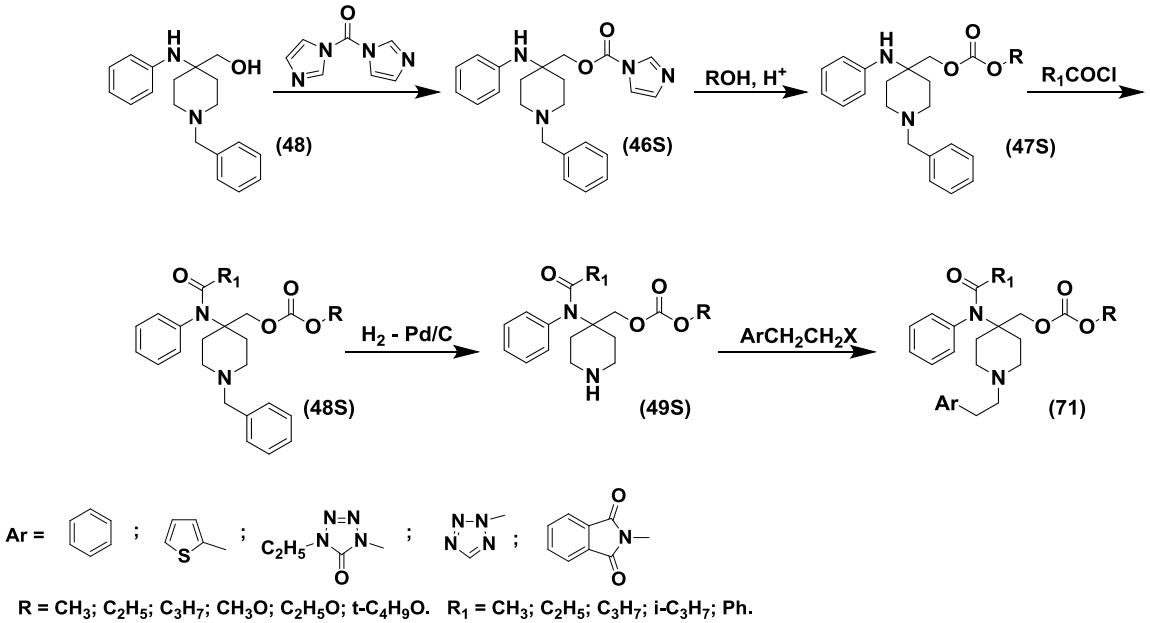


Fig. 16S. Alternative synthesis of 4-acyloxymethyl - fentanyls.

For the series of arylethyl derivatives the phenethyl and the thienylethyl substituents were found to be the most effective as analgesics (ED_{50} 0.06-0.1 mg/kg, whereas the tetrazolo- and phthalimido- derivatives were all of diminished potency, and corresponding N-benzyl analogues were found to be inactive. The thienyl- derivatives were often were found to be more potent and shorteracting than their corresponding phenethyl analogues. On the other hand, lengthening or branching of either the amide or the ester substituents (R and R_1) leads to diminishing potency and increasing duration of analgesia. Replacement of the ester acetyl (R) for a propionyl group led to a decrease in analgesic activity. In the group of carbonates (**71**) change from a methyl to an ethyl carbonate led to diminished analgesic activity, but longer duration of action [130].

Supplement 12.

The preparation of other groups of fentanyl analogs (**52S**, **54S**, **56S**, **58S**) is described starting from 1-methyl-piperidin-4-one (**50S**) with the corresponding substituted anilines followed by the reduction of obtained imines (**51S**, **53S**, **55S**, **57S**), their N-acylation, demethylation with cyanogene bromide and further N-alkylation. All obtained compounds (**52S**, **54S**, **56S**, **58S**) expressed antinociceptive potency in rats that were better than morphine. The p-F, I, and CH_3 derivatives of (**52S**) were only slightly less active than fentanyl. “Difentanyl” (**54S**), the cyclohexyl analog (**58S**) and compound (**52S** X = $NHCOC_2H_5$) were inactive. Among compounds of the series (**58S**) all benzyl derivatives ($R_1 – C_6H_5CH_2$) were inactive. All N-phenethyl analogs (**52S**) retaining reasonable levels of activity less than that of fentanyl but more than that of morphine [131]. (Fig. 17S.)

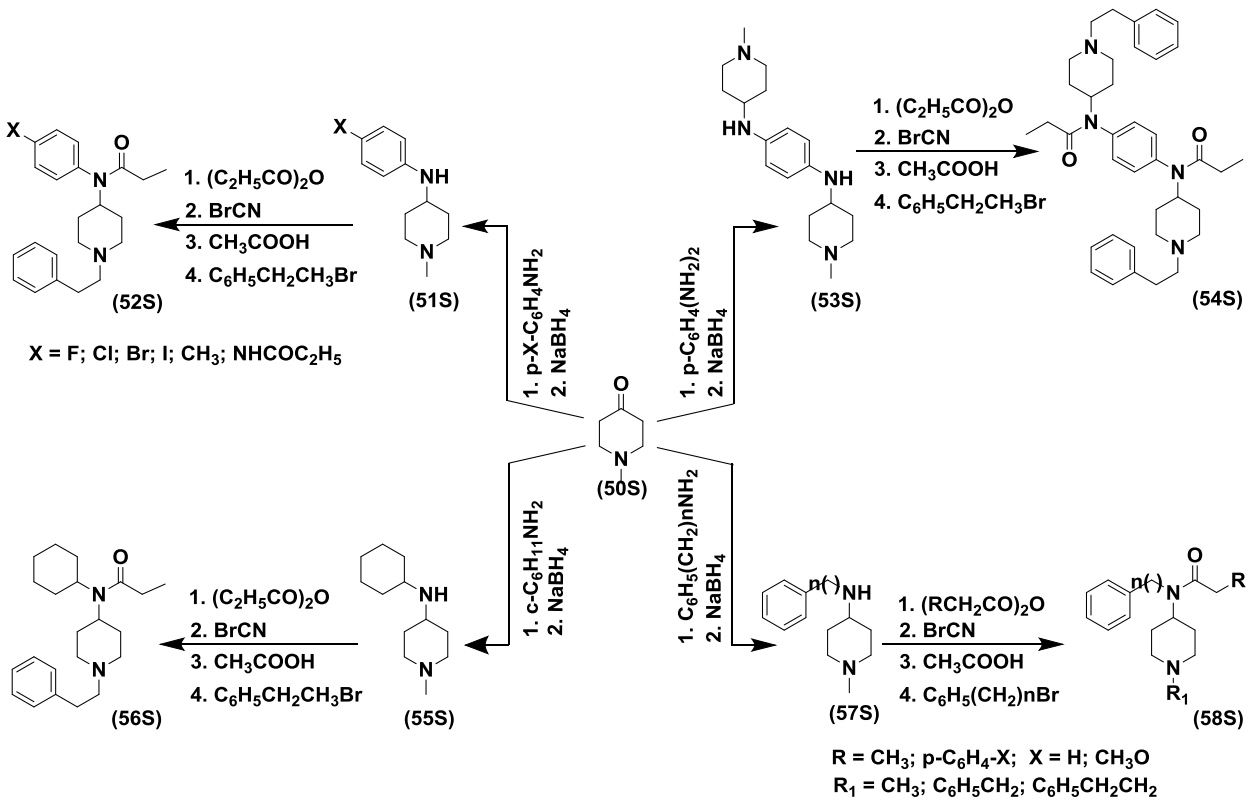


Fig. 17S. Variations in 4-anylino- fragment of fentanyl.

Standard scheme of synthesis (Fig. 1.) starting from N-benzyl-4-piperidone (**1**) and substituted anilines such as 3,4-difluoroaniline and substituted (2-halogenoethyl)benzenessuch as 2-(4-fluorophenyl)ethyl bromide have been employed to synthesize a variety of new fentanyl derivatives. The obtained compounds were tested in a binding assay using human recombinant opiate μ receptors showing activity of below 1 to 100 μM range. For example, compound (**131**) showed 91% inhibition at 10 μM [132] (Fig. 18S.).

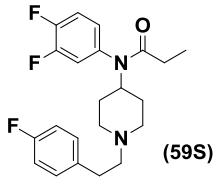


Fig. 18S. Fluoro- derivative of fentanyl.

Supplement 13.

Another research approach was based on modifications of the 4-anilido- fragment and its replacement by a variety of heterocycles. The 4-(heteroani1ino)-piperidines (**62S**) have been prepared by two major methods as depicted in. Condensation of 1-phenethyl-4-piperidon (**7**) with heterocyclic amines provided imines (**60S**), (Scheme 24.) which were reduced to amines (**62S**). Alternatively, intermediates of the same type were prepared by coupling of 1-phenethyl-4-aminopiperidin (**61S**) with the appropriate heteroarylchlorides. Acylation of (**62S**) afforded the target compounds (**63S**) [133]. (Fig. 19S.)

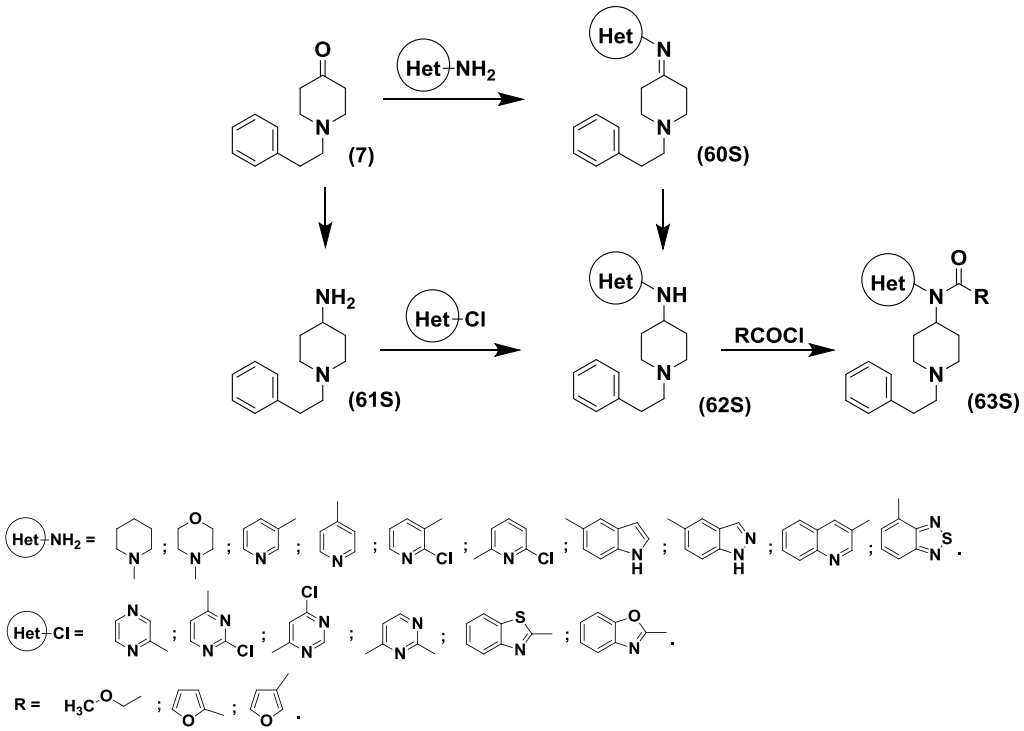


Fig. 19S. Replacements of phenyl group of 4-anylino-fragment of fentanyl for heterocycles.

Observations, which have been done in this research allowed one to make important conclusions. One of them is substitution of the phenyl ring of the propionanilido group of fentanyl for heterocycles, resulted in a significant diminition of analgesic activity. The sole exception was the 2-pyridino derivative (**64S**) which shows agonistic activity comparable with fentanyl. Another observation deserves much more attention. The compounds of described series were also screened as opioid antagonists. The majority of these compounds (80%) were morphine antagonists, and they selectively antagonized respiratory depression. The compounds with the 2-pyridinyl, 4-pyridinyl, and 2-pyrimidinyl rings were found to be inactive as antagonists. Variations of an acyl- chain within the amido- substructure of 4-(heteroani1ido)-piperidines likely play a larger role. Among the compounds, bearing a methoxymethyl chain attached to the amide carbonyl group opioid antagonists was not found. In contrast, 2- or 3-fury1 compounds were antagonists. Moreover, most of furan containing compounds selectively reverse respiratory depression. Two compounds (**65S** and 72) (Fig. 20.) which were antagonists, displayed different antagonistic profiles. Compound (**64S**) resembled naloxone in inhibiting both morphine-induced analgesia and respiratory depression. Compound (**72**) mirfentanil, however, inhibited morphine analgesia slightly, but completely reversed respiratory depression. These findings are difficult to explain. Another important observation was that antagonistic activity remains even in the absence of a 4-(heteroani1ido) substituent e.g. (**66S**, **67S**), but when the furan group was removed, there was no activity [133].

Making parallel comparisons of chemical structures of opioid agonists, it is possible to conclude that practically every chemical class of compounds with opioid-agonist activity has a structurally similar opioid-antagonist compound. Agonist-antagonist transformation in these cases takes place as a result of small changes in the structure of the agonist. The only exceptions, where the corresponding change for agonist-antagonist transformations has not been found are the

compounds of the fentanyl series. Pharmacological evaluation of (**72**), (ED_{50} = 0.07 mg/kg, rat tail-flick test) showed that it had minimal cardiovascular and respiratory depression compared to fentanyl.
Thus, these structurally unique fentanyl analogues provide a new gate into the area of creation of new powerful opioid antagonists [133,134]. The possibility of creation of opioid antagonists in the fentanyl has been patented [135].

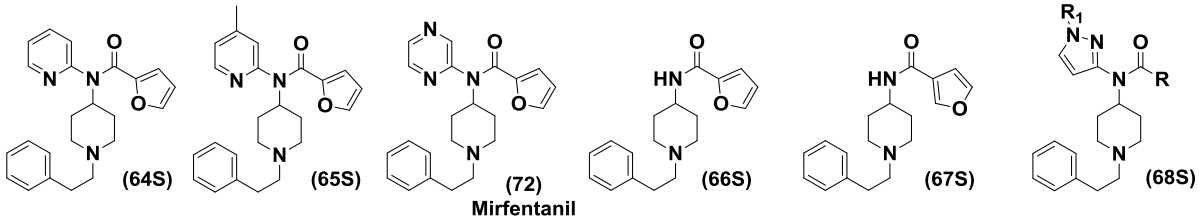


Fig. 20S. Structures of some unique fentanyl analogues with opioid antagonist activity.

Other fentanyl analogs in which the benzene ring of the propioanilido group was changed to a heterocyclic substituent, particularly for phenylpyrazole group also have been described [136-139]. Obtained compounds e.g. (**68S**) (R = C_2H_5, CH_2=CH-; R_1 =Ph, p-F-Ph), showed more potent analgesic properties than morphine, but less than fentanyl with longer duration of action. Compound with (R = CH_2=CH-, R_1 = H) showed reduced ability to induce dependence [139]. (Fig. 20S.)

Supplement 14.

It was proposed that imidazoline receptor agonists combined with opioid agonists could produce antinociceptive synergy. Thus fentanyl derivatives which incorporate guanidinium and 2-aminoimidazolinium groups were designed and synthesized which incorporate both – μ-opioid and I_2- imidazoline receptors pharmacophores [140,141]. Probably this publication was the first attempt for creation of bivalent ligands based on fentanyl as the μ- component. The synthesis of designed compounds, e.g. (**71S**, **72S**, **74S**, **75S**) (Fig. 21S.) have been performed applying the usual method of preparation of fentanyl derivatives (ketone-imine-amine-amide sequence) based on piperidine-4-one (**7** → **69S**) and (**7** → **73S**). The synthesis started by condensation of (**7**) with appropriate amines, followed by their transformation to the designed amines (**69S**) and (**73S**) which further underwent guanidinylation with N,N-di(tert-butoxycarbonyl) thiourea, in the presence of mercuric chloride and triethylamine which provided (**71S**) and (**75S**) respectively. Treatment of the same amines with 2-(methylthioimidazolinium) iodide, led to aminoimidazoline derivatives (**145**) and (**147**) [140,141].
Binding assays indicate that guanidinium compounds (**136**) and (**140**) are potent μ opioid ligands. Particularly compound (**144**) showed binding affinities similar to that of fentanyl, but displays moderate analgesic properties in vivo. The results for the I_2-imidazoline receptor are less significant and the compounds (**72S**) and (**74S**) showed only low affinity.

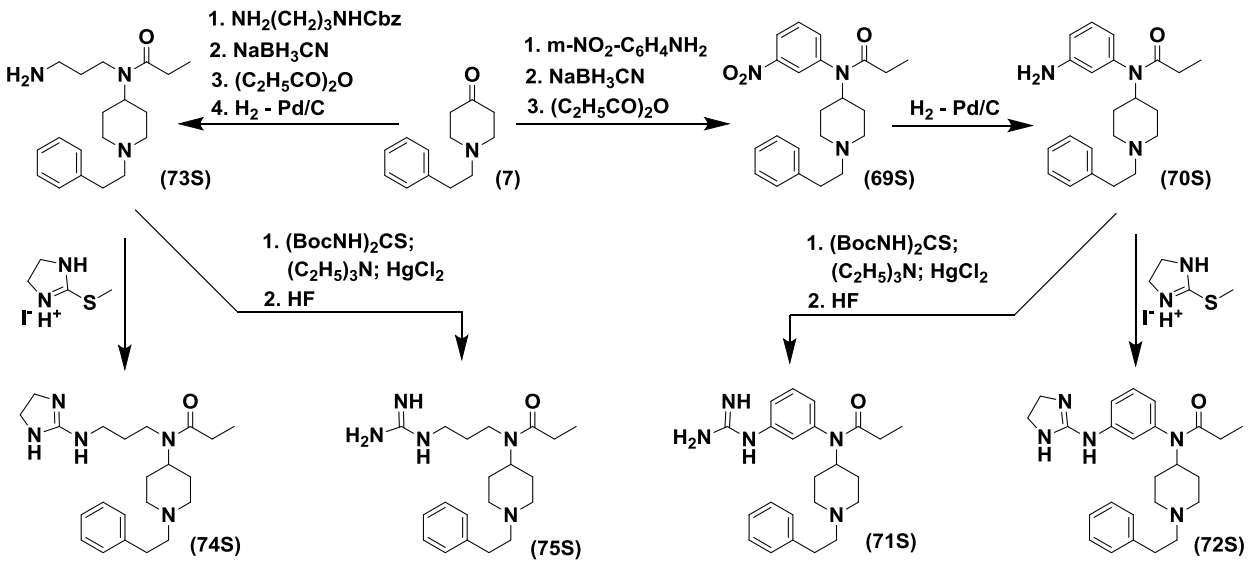


Fig. 21S. Synthesis of some guanidinium derivatives of fentanyl.

Supplement 15.

Here should be noted attempts to synthesize 3-methoxy- (**79S**) and 3-carbmethoxy- (**84S**) analogues of fentanyl. 3-Methoxy-fentanyl analogue (**79S**) has been prepared by traditional scheme (ketone-imine-amine-amide sequence) starting from 1-(2-phenylethyl)-3-methoxypiperidine-4-one (**7**) (Scheme 26.). Thus piperidine-4-one (**7**) was oxidized with iodobenzene diacetate to give 3-hydroxy-piperidine-4-one dimethyl ketal (**76S**), which was methylated to give 3-methoxy-piperidine-4-one ketal (**77S**). The ketal was reconverted to ketone (**78S**) which was further subjected to transformation to 3-methoxy-fentanyl (**76S**). The effective dose (ED_{50} 0.00064 mg/kg) was obtained for the cis-isomer of (**76S**) [142]. (Fig. 22S.)

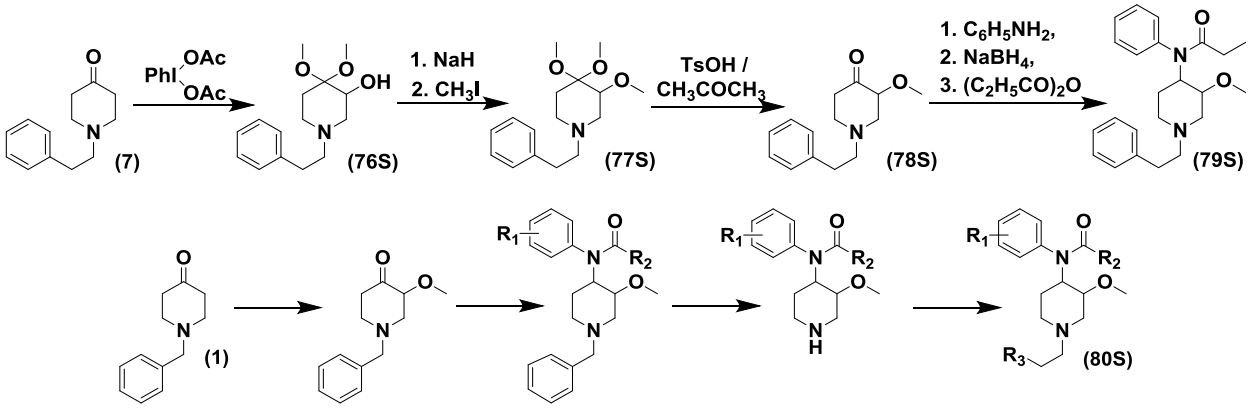


Fig. 22S. Synthesis of 3-methoxy-derivative of fentanyl.

Using the regular scheme for the synthesis, starting from N-benzylpiperidine-4-one (**1**), and separating on different stages cis- and trans- isomers, led to the synthesis of a plethora of highly active analgesics (**80S**) (ED_{50} 0.00046 - 0.0019 mg/kg). (Fig. 22S.)

Supplement 16.

The synthesis of 3-carbomethoxy fentanyl or iso-carfentanil (Scheme 27.) has been accomplished starting from dipropanoate (**81S**), which underwent Dieckman reaction to give (**82S**), followed with aniline condensation, reduction of obtained compound (**83S**) and it's subsequent propionylation (**84S**). Both (±) cis- (carbmethoxy group orientated axial - ED_{50} 0.023 mg/kg) and (±) trans- (carbmethoxy group orientated equatorial - ED_{50} 0.1 mg/kg) isomers of separated 3-carbomethoxy-fentanyl (**84S**) revealed significant but substantially reduced potency compared to fentanyl (ED_{50} 0.011 mg/kg), the trans in particular [143,144]. (Fig. 23S.)

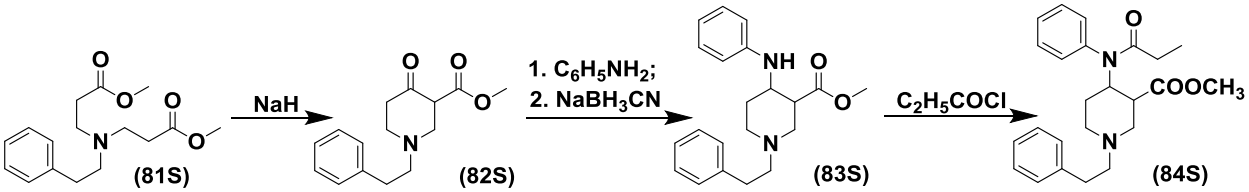


Fig. 23S. Synthesis of 3-carbmethoxy-derivative of fentanyl.

Supplement 17.

Attempts to functionalize the second position of fentanyl have been made. Thus, 1-benzyl-4-N-propinoylanilinopiperidine (**4**) was cyanated in the α-position by N-oxidation with m-chloroperoxybenzoic acid. The N-oxide was treated with CF_3COOH, and the obtained iminium intermediate (**85S**), both sides of double bond which were equally accessible for nucleophilic attack reacted with KCN surprisingly giving only one trans- diastereoisomer with axial orientation of the cyano- group (**86S**). During the transformation to amide conducted with KOH in t-BuOH, epimerization took place and practically pure cis- isomer of corresponding amide (**87S**) was obtained. The N-debenzylation gave cis- (**88S**), which underwent reductive amination with phenylacetaldehyde and sodium cyanoborohydride to give the desired (**89S**) [145]. Compound (**89S**) was 110 and 450 times less potent than fentanyl in the GPI and MVD assays respectively. (Fig. 24S.)

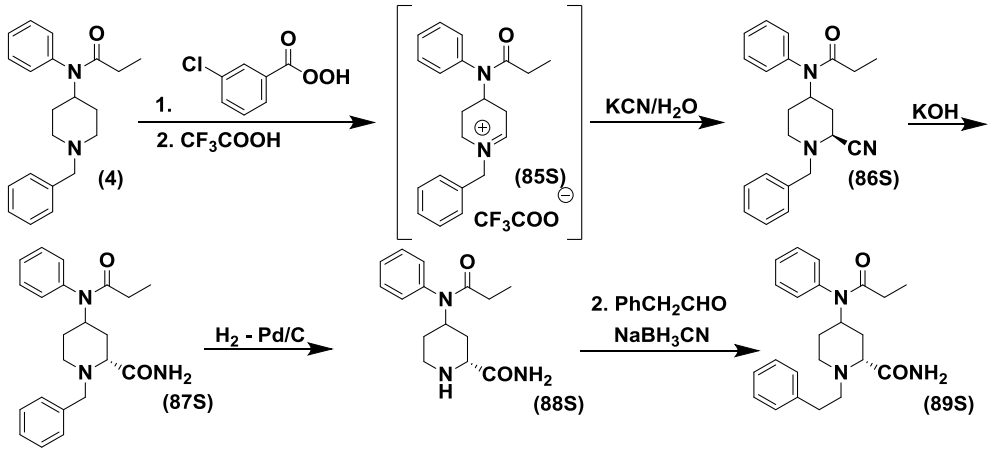


Fig. 24S. Synthesis of -carboxamide derivative of fentanyl.

Other types of functionalization of the 2nd position of the piperidine ring have been examined and lactam analogs of fentanyl were synthesized. In the first step, aminopropanoate (**90S**) was reacted with dimethyl malonate yielding compound (**91S**), which further subjected to Dieckmann cyclization to produce the corresponding 3-methoxycarbonylpiperidine-2,4-dione (**92S**). Acid hydrolysis and decarboxylation furnished piperidine-2,4-dione (**93S**) after which the fentanyl analog (**94S**) with a carbonyl group in the second position of piperidine ring was prepared in the regular way.
At the same time alkylation of the N-phenethylpiperidine-2,4-dione with Me iodide gives the 3,3-di-Me derivative (**97S**). After condensation of obtained product with aniline, the imine double bond and the lactam carbonyl was readily reduced ($NaBH_3CN$) providing access to 3,3-di-Me fentanyl analog (**95S**) [146,147]. (Scheme 29.) The same compound was obtained when dimethyl 2,2-dimethylmalonate was used in the reaction (**90S** →**97S**). Results of pharmacological studies are not given. (Fig. 25S.)

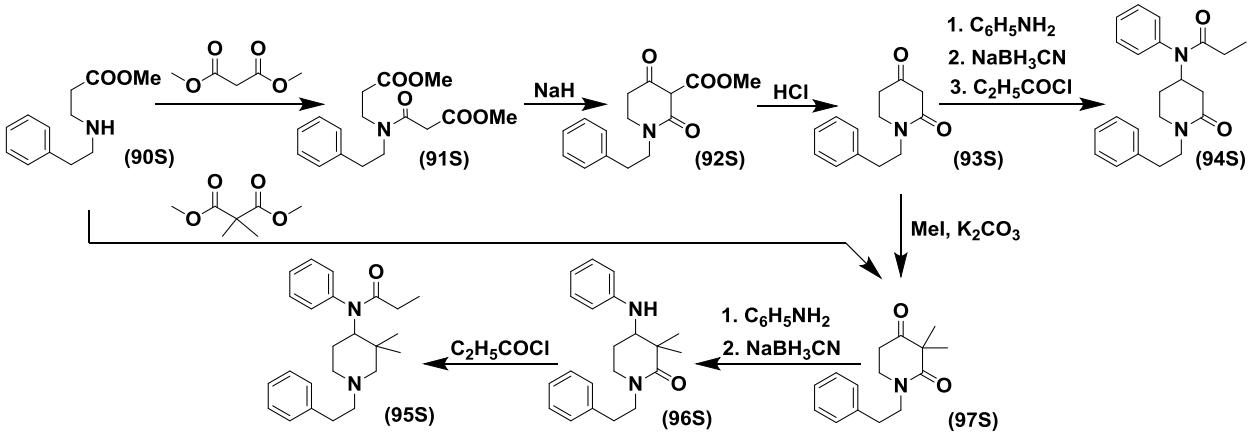


Fig. 25S. Synthesis of 3,3-dimethyl-fentanyl.

Supplement 18.

A number of "ring-closed" analogues of fentanyl (**172**, **174**, **175**, **179**) were prepared.
The first publication is probably that which described (4-piperidinyl)-2-indolinones (n = 1) and quinolinone (n = 2) (**72**). The synthetic approach is very simple and includes reductive alkylation of 2-amino-phenylacet(propion)amides with piperidin-4-one (**7**) and further acid catalyzed cyclization of obtained product (**98S**) [148]. The second approach includes condensation of 2-indolinone with the same piperidin-4-one (**7**) to obtain piperidylidene-2-indolinone (**73**) and reduction of double bond in the formed product to desired (**74**) [149,150]. Benzofuran derivative (**78**) was obtained via condensation of o-methoxyphenylacetonitrile with the same piperidin-4-one (**7**), reduction of the double bond of the synthesized product (**99S**) and demethylation of the obtained product (**100S**) with BBr_3 in chloroform during which cyclization to (**179**) occurred [150]. The affinities (IC_{50}) of the the indolinone derivative (**171**) (n = 1) and quinolinone derivative (**171**) (n = 2) are respectively 250 and 100 times less than that of fentanyl. The affinity of indolin-2-one (**175**) 500 to 800 times less. The affinity of the benzofuran derivative (**78**) is similar to that of the parent none rigid compound (**101S**) in which replacement of the amide

nitrogen in fentanyl by a carbon atom causes a sharp decline in receptor affinity and a complete loss of analgesic activity [150]. (Fig. 26S.)

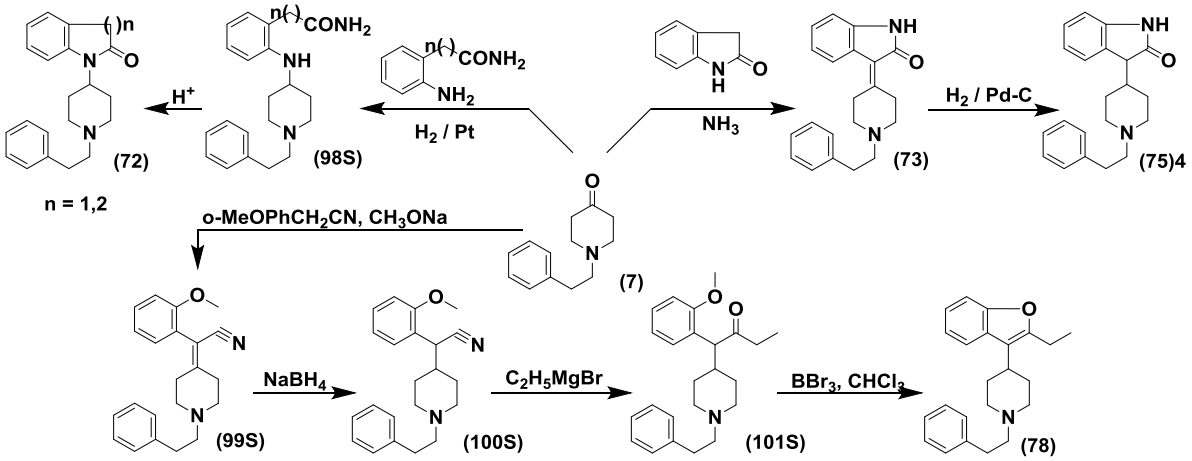


Fig. 26S. Synthesis of some "ring-closed" analogues of fentanyl.

Another series of "ring-closed" analogues of fentanyl as (4-piperidinyl)-benztriazole (**75**) and benzimidazoles (**76**, **77**) were obtained via heterocyclization of easily synthesized (piperidin-4-yl)benzene-1,2-diamine (**104S**). (Fig. 27S.)

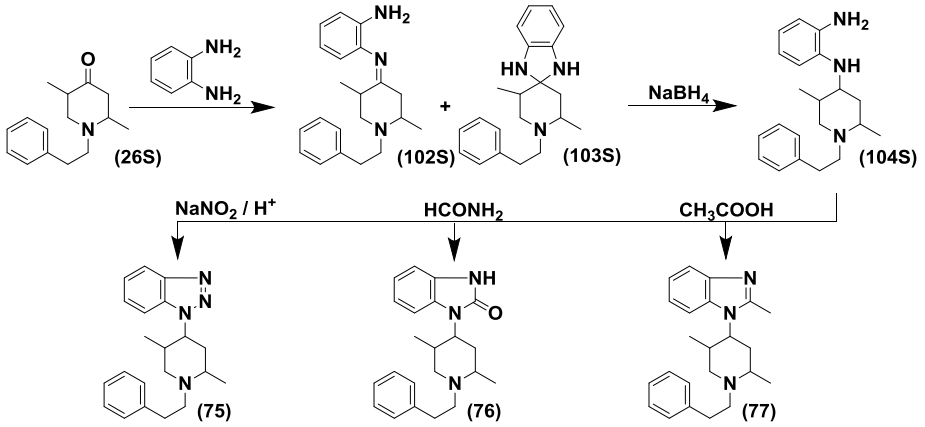


Fig. 27S. Another example of "ring-closed" analogues of fentanyl.

Supplement 19.

Insertion of a methyl group in the N-substituent in the α–position to the basic nitrogen, also displayed high activity close to that of fentanyl, as mentioned above [84]. According to the first fentanyl patent [52] compound with methyl group in the β–position to the basic nitrogen has no advantages on fentanyl itself. Insertion of hydroxyl group in the β–position to the basic nitrogen in general enhances the potency of compounds of these series. But the most impressive results were obtained with the synthesis of ohmefentanyl (**95**), one of the most potent opioids known (Fig. 1.).

The two main synthetic approaches to ohmefentanyl started from the previously separated cis- and trans- 3-methyl-N-phenylpiperidin-4-amines (**15S**) which were separated transforming the

diastereoisomeric mixture to the action of fumaric acid, which allowed one to separate cis- fumarate, converting the mother liquor back to base and turning it into oxalate, which allowed to separate the trans- oxalate. The resolution of racemic cis- and trans- isomers was realized by fractional crystallization of their tartrates. In one of proposed methods, (+)-cis- and (-)-cis- isomers of (**15S**) were alkylated with (R)-(+)- or *(S)*-(-)-styrene oxide, which afforded four stereoisomers of (1**05S**) in high regioselectivity. These were propionylated to give esters (1**06S**) followed with their selective hydrolysis to give desired optically active ohmefentanyls (**95**) [161]. In the other method, the separated isomers of (+)-cis- and (-)-cis- amine (**15S**) were alkylated with 2-bromoacetofenone, which gave amines (**107S**) which were propionylated to (**108S**). The keto- group which was hydrogenated with $NaBH_4$ to give the diastereoisomeric mixture of alcohols (95) separated by fractional crystallization to give the same set of isomeric ohmefentanyls [162]. (Fig. 28S.)

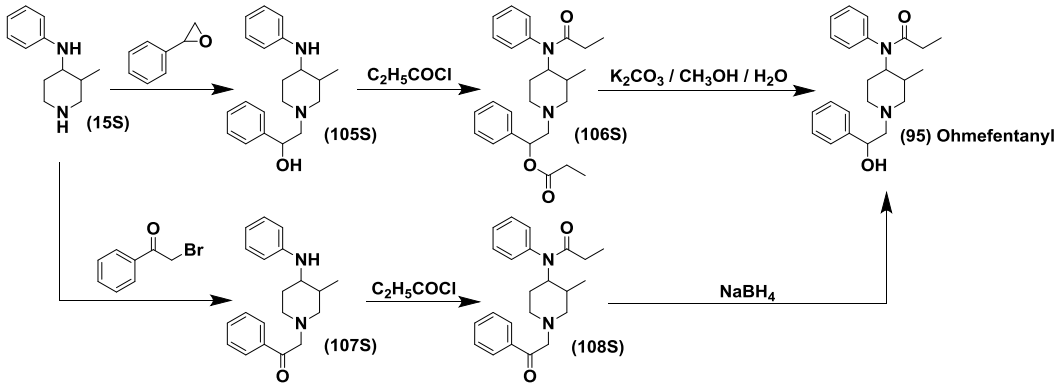


Fig. 2S. Synthesis of ohmefentanyl.

For the four stereoisomers of (±)-cis-N-[l-(2-hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-N phenylpropanamides: (**95a**)-(2S,3R,4S) had an ED_{50} 0.0001 mg/kg; (**95b**)-(2R,3R,4S) had an ED_{50} 0.0013 mg/kg; (**95c**)-(2R,3S,4R) had an ED_{50} 0.08 mg/kg and (**95d**)-(2S,3S,4R) had an ED_{50} 2.1 mg/kg. Ohmefentanyl had an ED_{50} of 0.0002 mg/kg. (Fig. 29S.).

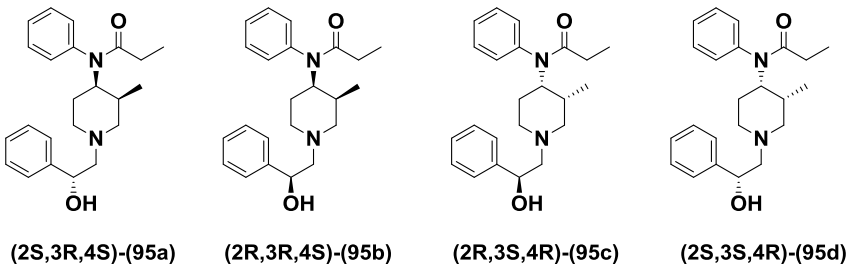
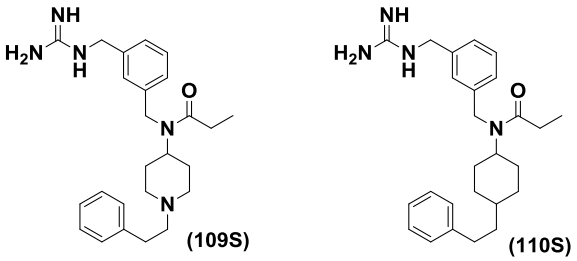


Fig. 29S. Four stereoisomers of ohmefentanyl.

The individual activities of (**95a,b,c,d**) were examined in a variety of binding and pharmacological assays. The binding studies showed that the highest affinity and selectivity for the μ receptors were isomers (**95b**) and (**95c**). At the same time, obtained data on the mouse vas deferens test showed potencies in the order (**95a**) > (**95b**) > (**95c**) > (**95d**) with concentrations in the fentomolar range. According to the mouse data, isomer (**207a**) was 21,000 times more potent

than (**95d**). Isomers (**95b**) and (**95c**) had similar opiate activities in vivo. The potency of (**95a**) was from 20,000 to 50,000 times higher than that of morphine, which makes this isomer one of the most potent opiates known [161,162].

Supplement 20.



(Fig. 30S.). Replacement of anilino- moiety for benzylamino group in fentanyl.