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COMPREHENSIVE SYNTHESIS OF 20 FENTANYL DERIVATIVES FOR THEIR RAPID DIFFERENTIATION BY GC-MS ANALYSIS

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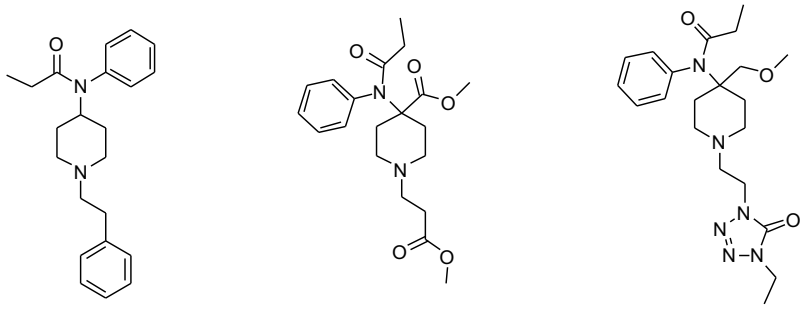
Abstract – Fentanyl, a selective agonist of opioid μ receptors, is a broadly used clinical agent for anesthesia and pain relief. Despite its clinical benefits, the abuse of fentanyl and its derivatives causes a number of health concerns, which are increasing at an alarming rate; its abuse has become a serious social problem. These compounds are often difficult to obtain as reagents, which hinders forensic toxicological analysis. Therefore, it is important to address their unavailability by synthesizing the structural derivatives of fentanyl. In this study, we synthesized 20 fentanyl derivatives, such as *o*- or *p*-fluorofentanyl and furanylfentanyl, and determined their purities using HPLC (95.2%−100%). Moreover, the GC-MS analysis of the synthesized fentanyl derivatives was performed for the rapid differentiation of the synthesized fentanyl derivatives. We demonstrate that our method achieves a convenient and efficient synthesis of fentanyl derivatives.

INTRODUCTION

Fentanyl (**1**), a selective agonist of opioid μ receptors, is broadly used as a clinical agent for anesthesia and pain relief. Because of its utility in pain management, over 1400 derivatives of fentanyl have been reported for legitimate medical use.[1-4] Among them, remifentanil (**2**) and alfentanil (**3**) display a rapid onset and recovery time;[5,6] hence, these have been approved for sedation during surgery (Figure 1). Conversely, the

number of health problems resulting from the abuse of synthetic fentanyl has increased rapidly, which has become a serious social problem. An overdose of fentanyl derivatives can cause the depression of respiratory rate and could be potentially fatal.[7] Moreover, several fentanyl derivatives have been recreationally used instead of fentanyl to avoid the detection of illegal consumption through standard drug tests.[8] Fentanyl derivatives are categorized into 5 classes (Figure 2) based on: (A) the replacement of the propionyl group with other acyl groups (*p*-fluorobutylfentanyl (**4**), valelylfentanyl (**5**), crotonylfentanyl (**6**), cyclopropylfentanyl (**7**), cyclopentylfentanyl (**8**), methoxyacetylfentanyl (**9**) and furanylfentanyl (**10**)), (B) a substitution on the aromatic ring with functional groups such as halogens (*p*- and *o*-fluorofentanyl (**11** and **12**)) or replacement of the phenethyl group with other heterocycles (thiofentanyl (**13**) and furanylethylfentanyl (**14**)), (C) the possession of quaternary carbon (remifentanil (**2**), alfentanil (**3**), and sufentanil (**15**)), (D) the substitution of the piperidine ring with an alkyl group (3-methyfentanyl (**16**), 3-methylthiofentanyl (**17**), and β-hydroxy-3-methylfentanyl (**18**)), and (E) the introduction of a functional group (α-methylfentanyl (**19**), α-methylthiofentanyl (**20**), and α-methylacetylfentanyl (**21**)). These compounds are often difficult to obtain as reagents, which causes a hindrance to forensic toxicological. To investigate a rapid, sensitive, and highly selective method for the differentiation of fentanyl derivatives, we describe the synthesis of 20 fentanyl derivatives through our improved synthetic route, as shown in Figure 2, and evaluate their purity using high-performance liquid chromatography (HPLC) analysis. Moreover, the gas chromatography-mass spectrometry (GC-MS) analysis of the synthesized fentanyl derivatives was performed for their rapid differentiations.



Fentanyl (**1**) Remifentanil (**2**) Alfentanil (**3**)

Figure 1. Pharmaceutical fentanyl and fentanyl derivatives

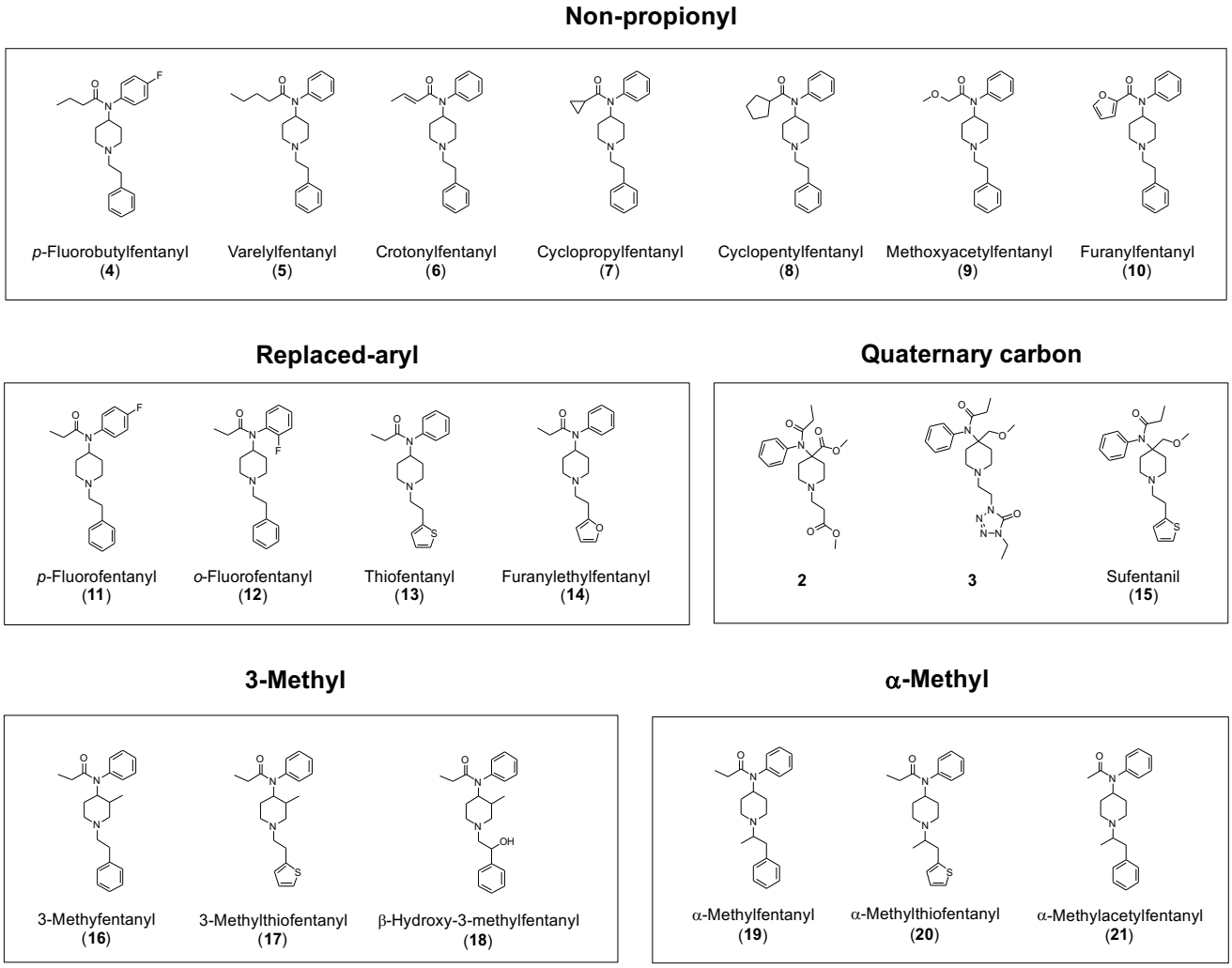


Figure 2. Structural classification of synthesized fentanyl derivatives

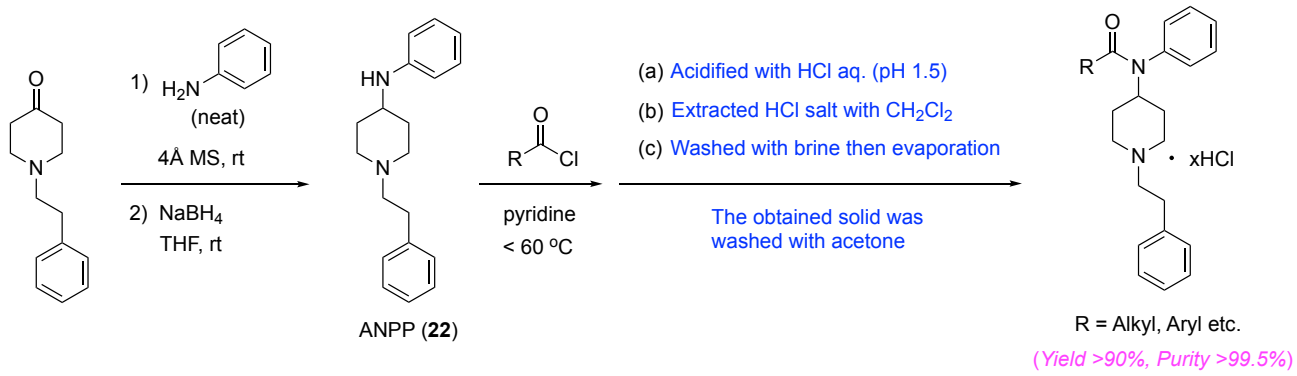
RESULTS AND DISCUSSION

Chemistry

Fentanyl derivatives were mostly synthesized using previously reported methods. α-methylfentanyl derivatives and 4-anilino-*N*-phenethylpiperidine (ANPP, **22**) derivatives were prepared as intermediates and were converted to fentanyl derivatives by *N*-acylation with the corresponding acyl chlorides. The synthesis of fentanyl was originally patented by Janssen in 1964.[9] Since then, several synthetic routes have been reported for the production of fentanyl derivatives. Kumar *et al*. performed the one-pot synthesis of fentanyl derivatives as a convenient preparation method.[10] Recently, it has been reported that bipiperidinyl-type impurities are generated in this method.[11] Valdez *et al*. reported the optimized synthesis for several fentanyl derivatives via the general three-step strategy using ANPP as a synthetic intermediate.[12] Although their synthetic route (Valdez method) provides a variety of acyl derivatives of fentanyl,[12] the final step in the synthesis, i.e., the acylation reaction using a combination of diisopropylethylamine (DIPEA)/acyl chlorides, requires purification by silica gel column chromatography, resulting in low-to-moderate yields

depending on the derivative.[13] Another synthetic strategy for fentanyl derivatives, the Siegfried method, involves acylating **22** using acyl chloride (Scheme 1).[14] This procedure, particularly the combined Siegfried/Valdez method, is widely used for the preparation of various fentanyl derivatives.[15-17]

Non-propionyl and Replaced-aryl: In the original Siegfried method, **22** was treated with acyl chloride in pyridine at < 60 °C. After the completion of the reaction, the reaction mixture was acidified, extracted with CH_2Cl_2, and evaporated to obtain the crude product. Washing this crude product with acetone afforded a hydrochloride form of the fentanyl derivatives with high yield (> 90%) and high purity (> 99.5%).[14] This protocol is useful for the preparation of hydrochloride salts of fentanyl derivatives without chromatographic purification.

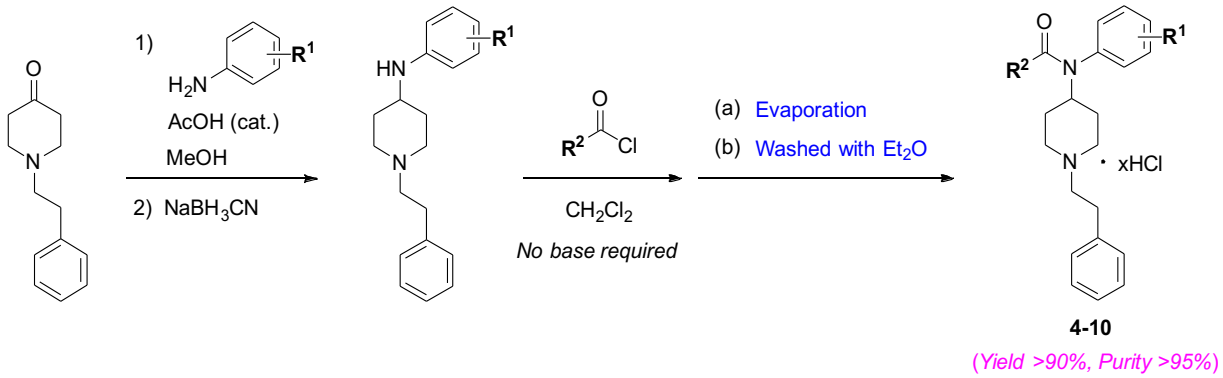


Scheme 1. Preparation of fentanyl hydrochloride using the Siegfried method

Similarly, in our study, the *N*-acylation of the ANPP derivative with acyl chloride was employed in the final step for all fentanyl derivatives (Scheme 2). We further improved the Siegfried method to obtain various non-propionyl fentanyl derivatives more efficiently. In our protocol, ANPP derivatives were treated with two equivalents of acyl chloride in CH_2Cl_2 without any base, at room temperature (< 30 °C). The hydrochloric acid generated in this reaction was trapped by the ternary amino group on the piperidine ring, resulting in the formation of fentanyl hydrochloride salts.

After the completion of the reaction, the reaction mixture was concentrated under reduced pressure to remove volatile compounds, and the resulting residue was washed with diethyl ether to remove the excess acyl chloride, yielding fentanyl derivatives as a hydrochloride salt. UPLC-MS analysis confirmed that the purity of the obtained fentanyl hydrochlorides, **4**–**10**, was high enough (> 95%) to be used as analytical samples without further purification (Table 1). This method requires no addition of bases to the reaction mixture or in the extraction process, rather it simply employs concentrating and washing processes, leading to the facile and rapid synthesis of fentanyl hydrochlorides. Indeed, the synthesis of **10** with a furoyl group,

11 with a fluorine at the *p*-position on an aniline, and **13** with the thiophene moiety were carried out using the Valdez method, but the yields of each derivative were 61%, 74% and 63%, respectively. These results were presumably due to the requirement of liquid separation operation and inconvenience of the handling of oil-like compounds. Moreover, our method was applicable for the synthesis of **12** with fluorine at the *o*-position on the aniline ring and **14** with the furan moiety, indicating that the method can be utilized for wide substrates.

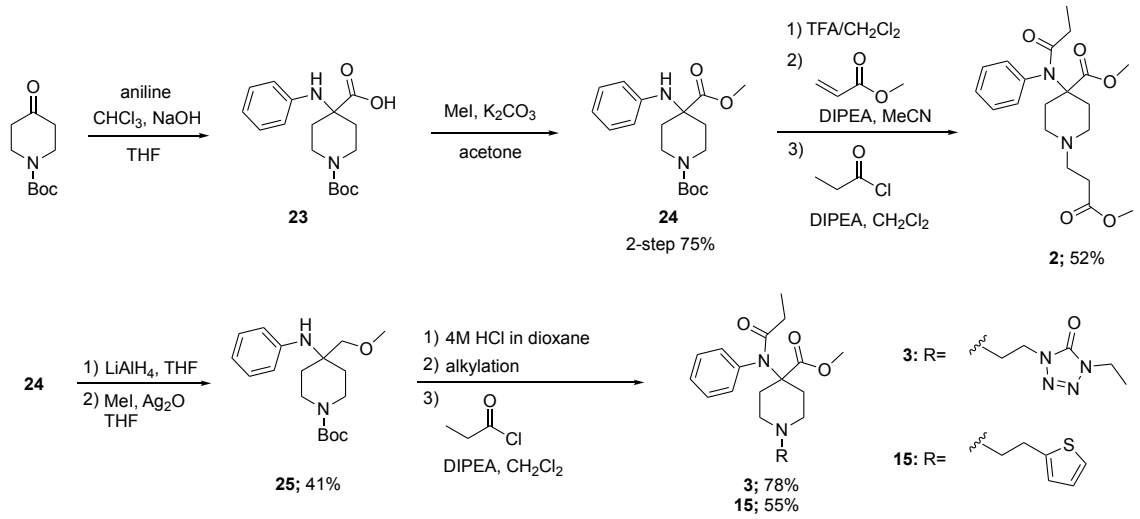


Scheme 2. Preparation of fentanyl hydrochloride by modified Siegfried method (Current study)

Table 1. Yield (%) and purity (%) of the obtained product using the modified Siegfried method

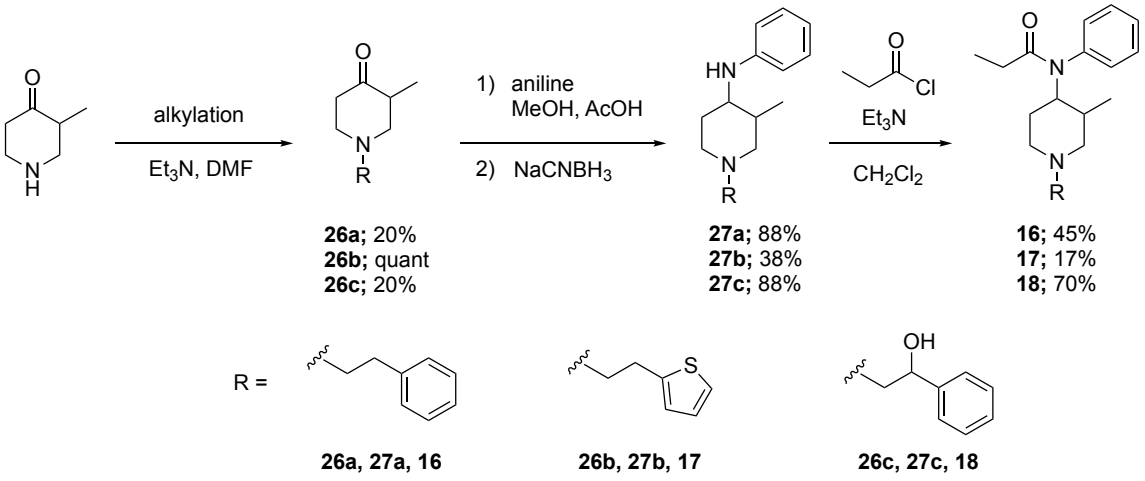
Compound	Yield from **22** (%)	Purity (%)
4	95	98.2
5	98	99.3
6	95	98.4
7	98	99.5
8	92	100
9	100	98.6
10	94	100

Quaternary carbon: Fentanyl derivatives **2**, **3** and **15** with a quaternary carbon were synthesized according to Scheme 3. The intermediate **23** was prepared by the Bargellini reaction using 4-Boc-piperidone as a starting material. **23** was converted to methyl ester **24** using a combination of MeI, K_2CO_3 and acetone. Remifentanil (**2**) was synthesized from **24** by Boc deprotection with TFA, *N*-alkylating with methyl acrylate, followed by propionylation. Alfentanil (**3**) and sufentanil (**15**) were also prepared from **24** as a common intermediate by the similar procedure for **2** using the corresponding alkylating agent.



Scheme 3. The synthesis of quaternary carbon derivatives **2**, **3**, and **15**

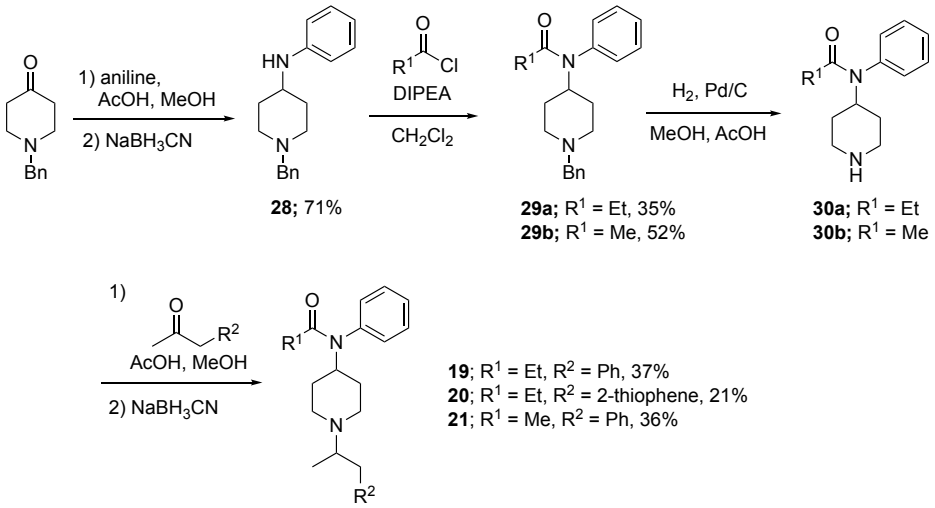
3-Methyl: The synthesis of 3-methyl derivatives **16**–**18** was carried out by conventional methods using 3-methylpiperidone as a starting material. Each derivative was synthesized by *N*-alkylation on piperidone to afford **26a**–**c** followed by reductive amination to introduce anilines. Further propionylation was performed in the obtained intermediate **27a**–**c**, to obtain the target products **16**–**18** as a mixture of diastereomers (Scheme 4).



Scheme 4. The synthesis of 3-methyl derivatives **16-18**

α-Methyl: The fentanyl derivatives with methyl group on an α-position, **19**–**21**, were synthesized according to Scheme 5. The starting material of *N*-benzylpiperidone was converted to **28** by reductive amination using aniline. After converting **28** to **29a** or **29b** by acylation, the *N*-benzyl group was deprotected by hydrogenation using Pd/C in the presence of AcOH to afford **30a** and **30b**, respectively. The deprotected amine was then alkylated by reductive amination with the corresponding ketones to give an α-methyl-

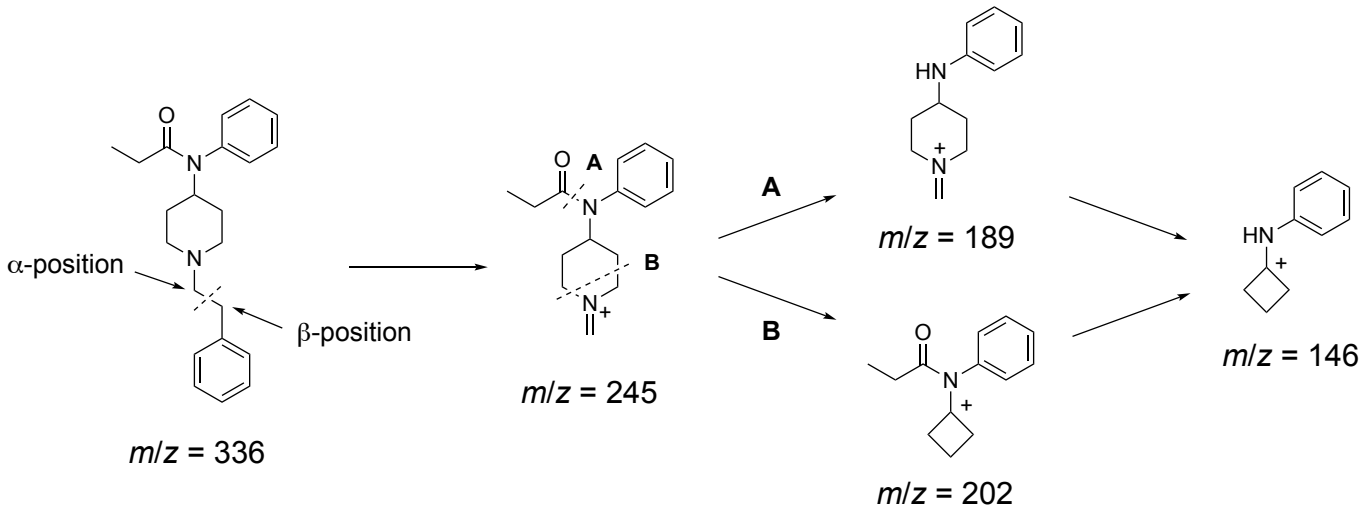
substituted products **19**−**21**. Although we first attempted to synthesis the target product by the *N*-alkylation of **30a** and **30b** using the corresponding alkyl bromide in this step, the reaction did not progress.



Scheme 5. The synthesis of α-methylfentanyl derivatives **19-21**

Finally, the GC-MS analysis for the rapid determination of the synthesized fentanyl derivatives was performed. It has been reported that the fragment ion (*m*/*z* = 245) can be detected as the base peak of fentanyl by the cleavage between α- and β-position of the phenethyl group (Scheme 6). Additional cleavage of the amide bond (A) and/or piperidine group (B) removes an acyl group (*m*/*z* = 189) or a cyclobutyl ring (*m*/*z* = 202) is formed. Based on these knowledges, we investigated whether the specific fragment ion derived from each synthesized fentanyl derivative could be detected by GC-MS analysis. For example, all derivatives (**1**−**21**) showed a cleavage at between α- and β-positions similar to that of fentanyl, giving the corresponding fragment ions. The resulting fragment ions were detected as the base peak and could be identified by differences of the acyl group (**4**−**10**) or fluorine on the phenyl group (**11** and **12**) or the α-methyl group (**16**−**18**) or the 3-methyl group (**19**−**21**). On the other hand, thiofentanyl (**13**) and furanylethylfentanyl (**14**) derivatives generated the same fragments as fentanyl, thus, it is impossible to make the identification from the base peak. In that case, it was possible to distinguish these derivatives by detection of fragments containing the thiophene or furan moiety, which is formed by cleavage of the bond between the nitrogen atom on the piperidine ring and the α-position (**13**; *m*/*z* = 111, **14**; *m*/*z* = 95) (Table 2). As shown in Table 2, the GC-MS spectra demonstrated that the specific fragment ions of each fentanyl derivative were detected. On the other hand, the fentanyl derivatives **16**, **17** and **18** are a mixture of stereoisomers, giving similar retention times (Rt.) and fragment ions were observed for each isomer in GC-MS analysis, making discrimination of each derivative difficult. In order to identify such mixture

compounds, reference materials including both isomers are required, hence the synthesis methods described in this study is useful for preparing the reference materials.



Scheme 6. The detectable fragment peak of the fentanyl by GC-MS analysis. (A) Removal of acyl group, (B) cleavage of piperidine group to form cyclobutyl group.

Table 2. The GC-MS analysis of the synthesized fentanyl derivatives **1**-**21**. The number in parentheses represent relative ion intensities compared to the base peak.

No.	Name	Formula	Accurate mass (Da)	Rt. (min)	Fragments (relative ion intensities)
1	Fentanyl	$C_{22}H_{28}N_2O$	336.2202	21.61	245(100), 146(51), 189(34), 246(18), 105(15), 42(11), 202(11), 57(9), 77(8), 132(8)
2	Remifentanil	$C_{20}H_{28}N_2O_5$	376.1998	18.98	168(100), 227(69), 212(47), 303(34), 140(25), 57(24), 42(23), 142(22), 55(14), 228(14)
3	Alfentanil	$C_{21}H_{32}N_6O_3$	416.2536	27.10	289(100), 268(39), 140(23), 222(21), 290(19), 170(15), 93(13), 235(12), 108(10), 110(8)
4	*p*-Fluorobutylfentanyl	$C_{23}H_{29}FN_2O$	368.2264	22.33	277(100), 164(30), 207(27), 278(18), 43(13), 105(10), 91(7), 42(7), 96(6), 71(6)
5	Valerylfentanyl	$C_{24}H_{32}N_2O$	364.2515	26.72	273(100), 146(53), 189(42), 105(21), 274(20), 57(19), 91(14), 42(14), 96(13), 41(11)
6	Crotonylfentanyl	$C_{23}H_{28}N_2O$	348.2202	24.58	257(100), 69(55), 189(51), 146(46), 105(21), 41(20), 258(18), 42(18), 91(17), 96(16)
7	Cyclopropylfentanyl	$C_{23}H_{28}N_2O$	348.2202	24.19	257(100), 189(39), 146(29), 258(18), 69(18), 41(12), 105(12), 91(10), 77(8), 42(7)
8	Cyclopentylfentanyl	$C_{25}H_{32}N_2O$	376.2515	31.12	285(100), 69(65), 189(53), 146(42), 105(25), 41(24), 286(21), 42(16), 91(15), 96(15)

9	Methoxyacetylfentanyl	$C_{22}H_{28}N_2O_2$	352.2151	24.06	261(100), 218(17), 262(17), 158(15), 45(14), 105(12), 91(9), 132(7), 77(7), 96(7)
10	Furanylfentanyl	$C_{24}H_{26}N_2O_2$	374.1994	30.22	283(100), 95(67), 240(44), 284(20), 42 (18), 96(17), 105(14), 158(12), 77(11), 91(10)
11	*p*-Fluorofentanyl	$C_{22}H_{27}FN_2O$	354.2107	21.01	263(100), 164(36), 207(26), 264(17), 105(10), 220(9), 57(8), 42(7), 44(6), 96(6)
12	*o*-Fluorofentanyl	$C_{22}H_{27}FN_2O$	354.2107	21.23	263(100), 164(40), 207(29), 264(17), 105(10), 57(10), 42(8), 91(7), 96(6), 150(6)
13	Thiofentanyl	$C_{20}H_{26}N_2OS$	342.1766	21.83	245(100), 146(48), 189(35), 246(17), 202(11), 42(7), 111(7), 132(7), 57(6), 77(6)
14	Furanylethylfentanyl	$C_{20}H_{26}N_2O_2$	326.1994	18.35	245(100), 146(86), 189(59), 246(18), 202(17), 147(10), 42(9), 95(9), 158(9), 96(8)
15	Sufentanil	$C_{22}H_{30}N_2O_2S$	386.2028	23.43	289(100), 290(20), 140(15), 110(8), 106(7), 111(7), 132(6), 93(4), 42(4), 77(3)
16	3-Methylfentanyl-1	$C_{23}H_{30}N_2O$	350.2358	21.75	259(100), 260(18), 160(18), 105(10), 42(7), 110(7), 203(7), 216(6), 132(6), 77(6)
	3-Methylfentanyl-2	$C_{23}H_{30}N_2O$	350.2358	22.62	259(100), 160(40), 203(32), 216(20), 260(18), 105(14), 132(9), 42(7), 57(7), 77(7)
17	3-Methylthiofentanyl-1	$C_{21}H_{28}N_2OS$	356.1922	21.93	259(100), 160(20), 260(18), 110(10), 42(9), 111(8), 216(8), 203(8), 93(7), 57(7)
	3-Methylthiofentanyl-2	$C_{21}H_{28}N_2OS$	356.1922	22.93	259(100), 160(46), 203(36), 216(23), 260(18), 111(10), 132(9), 110(9) 42(8), 57(8)
18	β-Hydroxy-3-methylfentanyl-1	$C_{23}H_{30}N_2O_2$	366.2307	26.17	259(100), 260(18), 160(16), 77(7), 42(7), 216(6), 203(6), 132(5), 57(5), 110(5)
	β-Hydroxy-3-methylfentanyl-2	$C_{23}H_{30}N_2O_2$	366.2307	27.70	259(100), 160(41), 203(30), 216(21), 260(18), 77(12), 93(9), 132(9), 42(8), 57(8)
19	α-Methylfentanyl	$C_{23}H_{30}N_2O$	350.2358	22.80	259(100), 260(18), 91(13), 110(12), 56(11), 146(10), 203(6), 57(6), 202(4), 58(4)
20	α-Methylthiofentanyl	$C_{21}H_{28}N_2OS$	356.1922	23.04	259(100), 260(18), 110(13), 56(13), 146(12), 97(8), 203(7), 57(7), 58(5), 77(4)
21	α-Methylacetylfentanyl	$C_{22}H_{28}N_2O$	336.2202	21.62	245(100), 246(17), 91(13), 56(13), 110(13), 146(9), 188(8), 43(5), 77(4) 58(4)

CONCLUSION

We described novel synthetic routes for 20 fentanyl derivatives. Fentanyl and its derivatives were synthesized using the Siegfried method, which involved acylation using acyl chloride and piperidine. Additionally, we demonstrated the acylation using only acyl chloride under heating condition, suggesting that fentanyl derivatives can be synthesized as hydrochloride salts without any extraction process. Moreover,

HPLC analysis revealed that the synthesis of these fentanyl derivatives was achieved with high yield and purity (95.2%−100%). The GC-MS analysis demonstrated that the specific fragment ions corresponding to the synthesized fentanyl were detected and could be applicable for the rapid differentiation. Furthermore, stereoisomers that were difficult to distinguish by mass spectra could also be identified based on the difference in retention time using the synthesized compounds in this study. Our synthetic methods are convenient and can be used to obtain fentanyl derivatives with high purities and contribute to curbing the abuse of fentanyl derivatives.

EXPERIMENTAL

Safety and Legal matters

Caution : *Unauthorized preparation could be considered a criminal offence*.

Fentanyl derivatives are potentially toxic and addictive, and as such rigorous protective measures are required to work safely with them as they need to be handled with care. All work performed during chemical synthesis of fentanyl derivatives were performed in a laboratory with an appropriately equipped fume hood by well-trained staff. All glassware and laboratory consumables used in the preparation of these compounds were appropriately disposed of after use.

General

All chemicals were purchased from Sigma-Aldrich Co. LLC, Kanto Chemicals Co. Inc., Tokyo Chemical Industry Co. Ltd., FUJIFILM Wako Pure Chemical Industries Ltd., and were used without further purification. Reactions were followed by thin-layer chromatography (TLC) (60 F_{254}, Merck), and spots were visualized by UV irradiation with a handheld UV lamp (254 nm) (UVP) and iodine vapor or ninhydrin reagent. Silica gel for column chromatography was packed columns for medium pressure column chromatography (Inject column / Hi-Flash column, Si or NH) (Yamazen). ^{1}H and ^{13}C NMR spectra were measured on an ECZ 600R spectrometer (JEOL) using deuterated solvents. Chemical shift values (ppm) are expressed in δ (ppm) with tetramethylsilane (TMS, 0.00 ppm for ^{1}H NMR in $CDCl_3$) or residual solvent peak (^{1}H NMR : 2.50 ppm for DMSO-d_6 and 3.31 ppm for MeOH-d_4 ; ^{13}C NMR : 77.16 ppm for $CDCl_3$, 39.52 ppm for DMSO-d_6 and 49.00 ppm for MeOH-d_4) as internal standards. High-resolution mass spectrometry (HRMS) was measured by electrospray ionization using Shimadzu IT-TOF MS (Shimadzu). HPLC-PDA (ACQUITY UPLC I-Class, Waters, Milford, MA, USA) were used for purity check. The analyses were performed using an ACQUITY HSS T3 column (2.1 mm i.d. x 100 mm, 1.8 μm, Waters) with Van Guard Pre-Column HSS T3 (2.1 mm i.d. x 5 mm, 1.8 μm, Waters). The column temperature was maintained at 40 °C, and the following isocratic system was used with a mobile phase A (1% formic acid), mobile phase B (1% formic acid/acetonitrile) delivered at 0.3 mL/min and the analysis time was 30 min.

The composition ratio of isocratic mobile phase A for each compound measurement is as follows; *p*-fluorobutylfentanyl (**4**), cyclopropylfentanyl (**7**), *o*-fluorofentanyl (**12**), sufentanil (**15**), 3-methyfentanyl (**16**) and methylthiofentanyl (**17**): A 75%, valerylfentanyl (**5**) and cyclopentylfentanyl (**8**): A 72%, crotonylfentanyl (**6**): A 77%, methoxyacetylfentanyl (**9**), furanylfentanyl (**10**), *p*-fluorofentanyl (**11**), thiofentanyl (**13**), alfentanil (**3**), β-hydroxy-3-methylfentanyl (**18**), α-methylfentanyl (**19**), α-methylthiofentanyl (**20**) and α-methylacetylfentanyl (**21**): A 80%, furanylethylfentanyl (**14**): A 82%, remifentanil (**2**) A 85%. The injection volume was 2 μL of 1 mg/mL methanol solution and the wavelength of the PDA detector was set from 210 to 450 nm.

The GC–EI–MS was performed on an Agilent 7890 B GC system with a 5977 mass-selective detector (Agilent Technologies, Santa Clara, CA, USA) using a capillary column (HP-1MS, 30 m × 0.25 mm i.d., 0.25-μm film thickness; Agilent Technologies) with helium gas carrier flowing at 1.0 mL/min. The conditions were as follows: electron energy, 70 eV; injector temperature, 220 °C; injection mode, splitless mode for 1.0 min; transfer line temperature, 280 °C; scan range, *m*/*z* 40-600. The oven temperature was held at 100 °C for 1 min, and then increased at 10 °C/min to 250 °C, where it was held for 15 min. Finally, it was increased at 10 °C/min to 310 °C, where it was held for another 5 min.

General procedure to prepare fentanyl hydrochloride: modified-Siegfried method

To a solution of ANPP derivative (1.0 mmol) in CH_2Cl_2 (5 mL) was added dropwise acyl chloride (2.0 mmol) at room temperature, and the reaction mixture was stirred at 40 °C for 1 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to remove the volatiles. The residue was suspended in Et_2O, and the resulting precipitate was collected by filtration, washed with Et_2O, dried under vacuum to afford analytically pure hydrochloride salt of fentanyl derivatives.

ACKNOWLEDGEMENTS

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SUPPORTING INFORMATION

Supplementary (synthesis of the starting azides, HPLC chromatograms, IR, 1H and 13C NMR, MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27784/106/1.

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