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Synthesis and Identification of A Novel Fentanyl Analog

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Abstract. In the background of the growing popularity of synthetic opioids in the field of narcotics, this study explores the synthesis and identification of a novel fentanyl analog, trifluoromethyl fentanyl (TFMF). Utilizing advanced analytical techniques for qualitative analysis, such as NMR Spectroscopy, LC and GC-MS. The synthesis process highlights the method starting with N-tert-butoxycarbonyl-4-piperidone with a final product yield of 53%. Characterization through 1H-NMR reveals the successful incorporation of the trifluoromethyl group into the fentanyl structure. Liquid chromatography and melting point analysis confirms the high purity of the synthesized compound. GC-MS analysis provides essential qualitative data, identifying characteristic ion peaks that uniquely define TFMF. This study adds to existing knowledge of novel fentanyl analogues and highlights the importance of analytical techniques in addressing the opioid crisis.

Keywords: Fentanyl analogs; Trifluoromethyl fentanyl (TFMF); Synthetic opioids.

1. Introduction

Fentanyl analogs, as third-generation new psychoactive substances, have been extensively studied and used since the 1960s for their potent analgesic properties. These compounds are not only used in the medical field for the treatment of severe pain, have also been misused in the illegal drug market due to their high efficacy and low cost [1]. Since fentanyl was first synthesized by Paul Jensen in 1960 in Belgium, various fentanyl analogs such as sufentanil and alfentanil have been developed to provide more efficient pain management solutions [2,3]. However, the misuse and illegal production of these compounds have led to a public health crisis, the overdose of fentanyl and its analogs has become a major concern [4,5]. International control over fentanyl and its analogs has been strengthened, but the rapid emergence of new synthetic opioids presents unprecedented challenges to regulatory and law enforcement efforts [6,7]. In this study, a new fentanyl analog, trifluoromethyl fentanyl (TFMF), was synthesized by chemical group modification. It was characterized and qualitatively analyzed by advanced technologies such as NMR spectroscopy, liquid chromatography and gas chromatography-mass spectrometry. The aim is to provide a scientific basis for the identification and analysis of new synthetic opioids, while offering a new perspective on addressing the current opioid abuse crisis.

2. Materials and Methods

2.1. Main Instruments

Nuclear Magnetic Resonance Spectrometer (Bruker Avance NEO 400MHz, Germany Bruker); Gas Chromatography-Mass Spectrometer (Trace-1300-TSQ-7000, Thermo Fisher Scientific); Liquid Chromatograph (LC-20AR, Shimadzu); Micro Melting Point Apparatus (X4B, Shanghai Yidian Physical Optical).

2.2. Synthesis of new fentanyl analogs

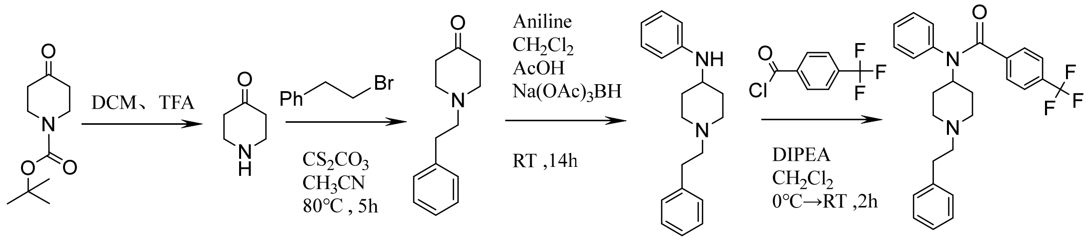

Fig. 1 Synthesis Process of TFMF

Start with N-tert-butoxycarbonyl-4-piperidone dissolved in dichloromethane, add trifluoroacetic acid at 0°C, and stir at room temperature for 3 hours to form a yellow oily liquid. Introduce cesium carbonate and β-bromostyrene to the mixture, reflux in an 80°C oil bath for 5 hours, then extract and wash the resultant mixture to obtain another yellow oily liquid. Dissolve the compound in dichloromethane, add acetic acid, aniline, and sodium triacetoxyborohydride, and allow the reaction to proceed overnight. After purification, a pale yellow solid is obtained. Dissolve the solid in dichloromethane, react with trifluoromethylbenzoyl chloride at 0°C, and after stirring, extraction, and purification, obtain the final product, a white solid (TFMF), with a yield of 53%.

2.3. Characterization and Identification

2.3.1. NMR spectroscopy

Nuclear Magnetic Resonance Spectroscopy (NMR) is one of the most powerful instruments for the compositional and qualitative analysis of substances, leveraging the inherent properties of the atomic nuclei that make up molecules. In this study, Methanol-d4 was used as the solvent and tetramethylsilane (TMS) as the standard for ^{1}H-NMR testing.

2.3.2. Liquid Chromatography

Liquid chromatography is used for testing the purity of compounds. Dilute the TFMF to a concentration of 100 μg/mL in methanol. The mobile phase is methanol and H_2O (7:3), with an ultraviolet detection wavelength of 254 nm, column temperature of 25°C, flow rate of 0.8 mL/min, and a run time of 10 minutes.

2.3.3. Melting Point

The micro melting point apparatus allows for the observation of physical changes such as deformation, color change, and phase transitions of a substance upon heating, to determine the melting point range.

2.3.4. Gas Chromatography-Mass Spectrometry

The chromatographic column: Thermo Scientific TG-5SILMS (30m x 0.25mm x 0.25μm). The carrier gas: high-purity helium, with a flow rate of 1.5 mL/min; the vaporization chamber temperature: 280°C. The column temperature program started at 60°C, holding for 1 minute, then increased to 300°C at a rate of 30°C/min, holding for 5 minutes. Mass spectrometry conditions included an EI ionization source, electron energy of 70eV, ion source temperature of 300°C. Tuning was performed automatically, with a multiplier voltage of 1073V and an emission current of 100μA. A full scan mode was used for detection, scanning from 40 to 550 m/z.

3. Results and Discussion

3.1. NMR Spectrum

In the NMR spectrum (400 MHz, Methanol-d4), the hydrogens are evident at δ7.48-7.42 (4H) and δ7.33-7.14 (10H), suggesting the presence of benzene rings. A distinct signal at δ4.80 (1H) is identified as a tertiary carbon hydrogen, linked to both the piperidine ring and a secondary amine, highlighting a specific structural feature. The methylene hydrogens adjacent to nitrogen atoms show up at δ2.88-2.82 (4H) and δ2.64-2.58 (2H), alongside δ3.34-3.27 (2H), indicating their positions on the piperidine ring close to nitrogen. Additional methylene groups on the piperidine ring are observed at δ1.87-1.68 (2H) and δ2.16-2.04 (2H), completing the structural analysis.

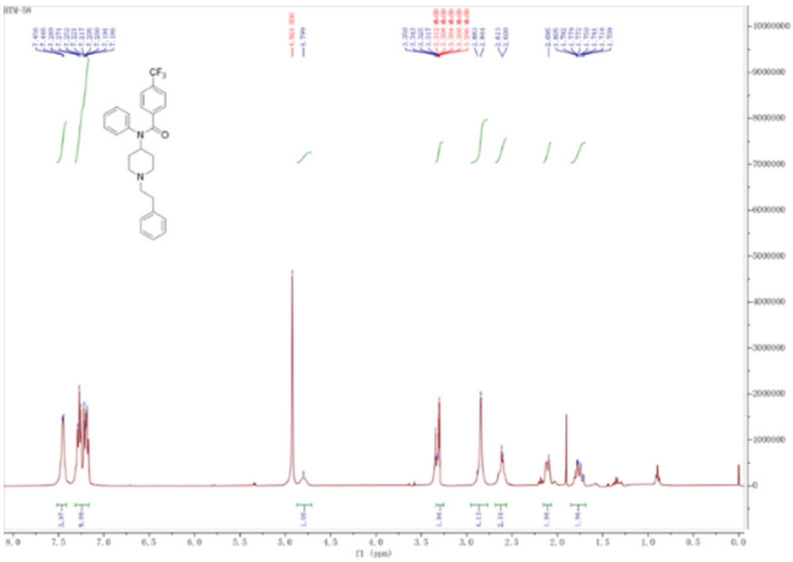

Fig. 2 ^{1}H-NMR Spectrum of TFMF

3.2. Product Purity Analysis

Melting Point Test Results: The melting point of TFMF was found to be 235.1-235.8°C, with the temperature range from the beginning of melting to complete melting being within 1°C, indicating a high purity of the product. And the results of the liquid chromatography are presented in Table 1 and Figure 3.

Table 1. Results of Liquid Chromatography

Component	Retention Time/min	Peak Area	Percentage/%
1	2.526	35072	0.320
2	3.298	10930915	99.680

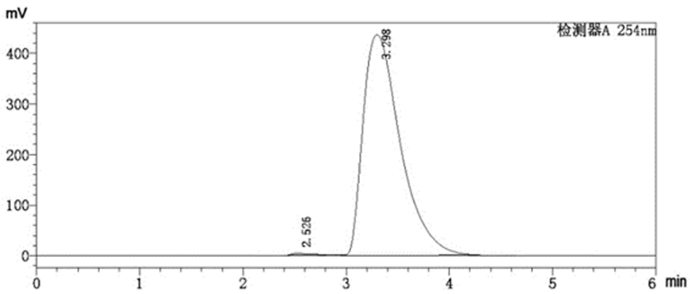

Fig. 3 Liquid Chromatography Chromatogram

3.3. Gas Chromatography-Mass Spectrometry

1mg/mL TFMF in methanol was prepared for GC-MS analysis. The total ion chromatogram and mass spectrum are shown in Figure 4. Under the set analysis conditions, the retention time was 13.003 min, with the main characteristic ion peaks in the mass spectrum being: m/z 173 (base peak), 361, and 145.

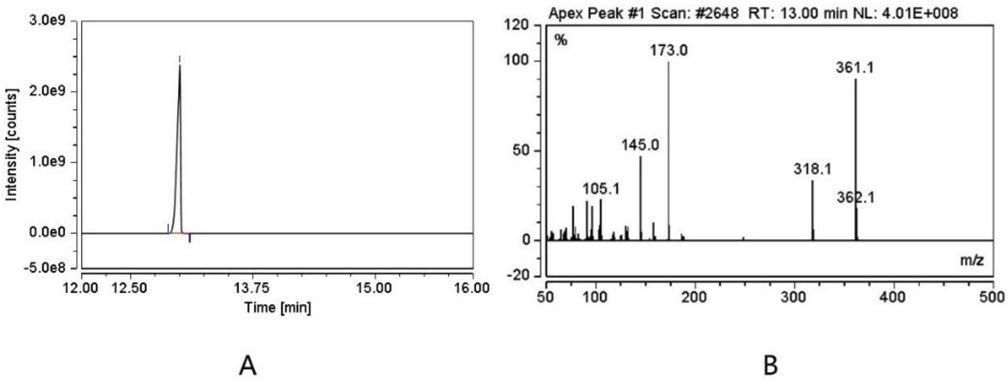

Fig. 4 GC-MS Analysis of TFMF: Total Ion Chromatogram (A) and Mass Spectrum (B)

4. Conclusion

In conclusion, this study enhances the scientific understanding of the synthesis, characterization, and analysis of new fentanyl analogs, aiding law enforcement in tracing the origins to combat drug abuse and the opioid crisis. The findings from this research can aid in the development of more effective strategies for monitoring, regulating, and ultimately preventing the illicit use of powerful synthetic opioids. As the fight against drug abuse evolves, scientific research must keep pace, providing the knowledge and tools necessary to protect society and save lives.

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