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Review: Synthetic Routes from 1-(2-phenylethyl)-4-piperidinone (PPD) to Fentanyl; A Short Review

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ABSTRACT

Fentanyl, a potent synthetic opioid widely used in clinical anesthesia and pain management, has attracted sustained attention due to both its therapeutic significance and public health concerns.

Central to its preparation is the key intermediate 1-(2-phenylethyl)-4-piperidinone (PPD), which serves as the strategic starting point for nearly all reported synthetic routes.

This mini-review provides a focused overview of the major pathways leading from PPD to fentanyl, highlighting the classical approach through 4-anilino-N-phenethylpiperidine (4-APPD), subsequent optimizations aimed at improving yield and operational simplicity, and recent innovations including continuous-flow methodologies.

Rather than offering an exhaustive account, this concise review emphasizes the recurring role of PPD as a pivotal hub in synthetic design, as well as the implications for pharmaceutical development, process control, and forensic monitoring. By centering on PPD-derived routes, this work aims to provide a compact yet informative perspective on the state of fentanyl citrate synthesis.

Introduction

Fentanyl is a potent synthetic opioid widely used in anesthesia and pain management due to its rapid onset, high potency, and controllable pharmacokinetics [1]. Its therapeutic value is paralleled by significant challenges related to public health, regulatory oversight, and abuse potential [2]. The development of fentanyl derivatives relies heavily on the strategic use of key intermediates, particularly 1-(2-phenylethyl)-4-piperidinone (PPD), which serves as a central hub in various synthetic strategies (References available in Table 1). Understanding these intermediates is crucial not only for efficient pharmaceutical production but also for regulatory monitoring, analytical characterization, and ensuring reproducibility. Reviewing the evolution of

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PPD-based synthetic strategies provides insights into the design principles of opioid chemistry, historical developments, and emerging trends in process optimization, setting the stage for a concise mini-review focused on the critical chemical and strategic aspects of fentanyl citrate synthesis.

PPD's chemical versatility enables multiple pathways to fentanyl citrate, encompassing both classical multi-step sequences and more modern continuous-flow or catalytic processes. Each approach offers trade-offs between yield, operational simplicity, scalability, and control of by-products, reflecting broader considerations in active pharmaceutical ingredient (API) development [3,4]. The design of efficient synthetic routes generally requires careful optimization of intermediates, reagents, and reaction conditions, with attention to safety and reproducibility [5]. These principles are widely applied across pharmaceutical chemistry and have been documented in several studies, including process optimization and scalable synthesis of various APIs [6–10]. By understanding these overarching strategies, researchers can implement systematic process improvements while maintaining compliance with regulatory standards and quality control requirements.

Historically, fentanyl synthesis has emphasized the modular use of intermediates and stepwise transformations to maximize yield and control impurities [3-5]. Classical approaches typically convert PPD to 4-anilino-N-phenethylpiperidine (4-APPD) before forming the citrate salt, reflecting a common theme in medicinal chemistry where strategic intermediates facilitate multiple derivative pathways [11-13]. Over time, efforts to improve efficiency, reduce environmental impact, and enhance safety have guided the evolution of synthetic routes [14,15]. These trends mirror broader developments in pharmaceutical process chemistry, highlighting the importance of reaction optimization, scalable methodologies, and analytical characterization of intermediates to ensure reproducible, high-quality API production.

Recent innovations, including continuous-flow techniques and catalytic methods, demonstrate enhanced control over reaction parameters, scalability, and safety in handling intermediates. Such advances not only improve operational efficiency but also contribute to reproducible and robust production processes, which are essential for both research and industrial applications. This mini-review focuses specifically on PPD-derived pathways to fentanyl citrate, comparing classical and modern strategies, analyzing historical development, and highlighting emerging trends. Insights gained from these studies may guide future research in opioid chemistry and broader API synthesis, promoting safer, more efficient, and scalable approaches to pharmaceutical production.

Key Synthetic Pathways of Fentanyl Citrate

Since the first introduction of fentanyl by Janssen et al. (1961–1962), numerous laboratory and industrial routes have been developed to improve the efficiency, selectivity, and environmental profile of its synthesis. The classical route involves the aminomethylation of 4-piperidone derivatives with β-phenethyl chloride under basic conditions (Na_2CO_3, KI) in ketone solvents such as hexanone, typically affording yields of 40–50%. This original process, described in US3141823 and FR1517671, established the industrial foundation for fentanyl but suffered from long reaction times (≈27 h), formation of by-products, and purification difficulties [11].

A significant improvement was achieved by Richter et al. (HU157325, 1970), who employed copper powder catalysis in aromatic solvents (toluene or xylene) with sodium carbonate. Their use of 1-(2-phenylethyl)-4-piperidinone instead of unsubstituted piperidones markedly enhanced the overall yield to ≈72%, while reducing the thermal load and reaction duration [12].

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During the late 1970s and 1980s, further optimization focused on reducing steps and improving selectivity. Jonczyk et al. (1978) introduced a two-step reductive pathway using $NaBH_4$ and propionyl chloride, achieving around 65% yield, while Brine et al. (1989) employed p-toluenesulfonic acid catalysis followed by selective reduction to obtain purer fentanyl bases [13,14].

The early 2000s saw the advent of one-pot and reductive amination approaches. Gupta et al. (2005) demonstrated a three-step synthesis using $NaBH(OAc)_3$ in acetic media, achieving over 40% yield with high selectivity [15]. Subsequent advances by Saidi et al. (2010) and Watson et al. (2011) introduced Ir- and Ru-catalyzed systems under aqueous or microwave-assisted conditions (Figure 1), reaching yields between 68–77%, marking a significant step toward green and efficient synthesis [16,17].

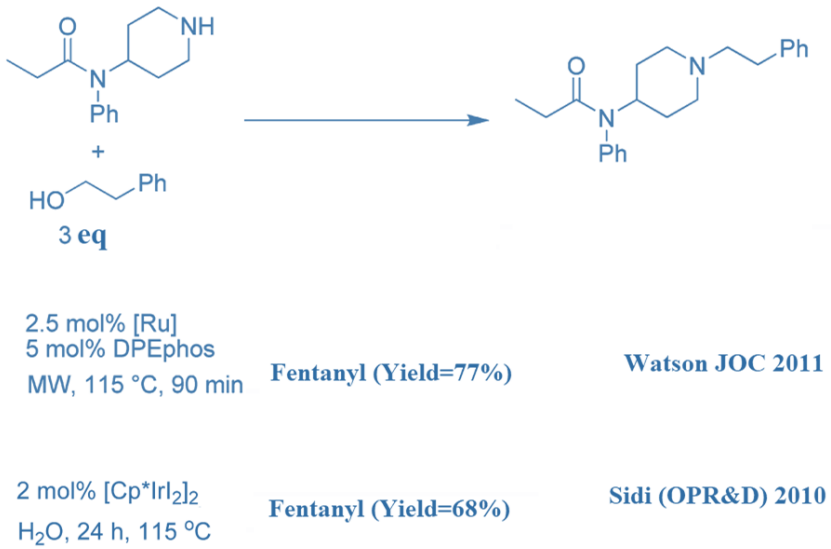


Figure 1. Synthesis of fentanyl via N-phenyl-N-(piperidin-4-yl)propionamide as the key intermediate

After 2014, research emphasized metal replacement, catalytic efficiency, and eco-compatibility. Valdez et al. (2014) achieved 91–95% yields via mild reductive amination using sodium triacetoxyborohydride and bulky amines, under ambient conditions [18]. Zhang et al. (2016) extended this to high-pressure palladium-catalyzed systems (yield ≈96%), while Ghaffarzadeh (2012) developed silanol-mediated transformations (yield ≈86%) [19,20]. Finally, Braga et al. (2022) introduced a photocatalytic flow system employing $[Ru(bpy)_3]Cl_2$, 3-mercaptopropionic acid, and ascorbic acid, producing stepwise yields of 84% and 92%. This represents the modern pinnacle of fentanyl synthesis methodology [21].

Overall, the historical development of fentanyl citrate synthesis reflects a steady evolution from harsh, low-yield conditions toward highly selective, environmentally friendly methods with near-quantitative efficiency (≈95%).

Synthesis Routes from the Intermediate PPD (1-(2-phenylethyl)-4-piperidinone)

The intermediate PPD has emerged as the central structural unit for modern fentanyl syntheses (Figure 2) since its first use by Richter (1970) [12]. Its reactivity and stability make it an ideal precursor for reductive amination–acylation strategies leading to the final N-phenethyl-N-propionamide framework. Gupta et al. (2005) [15] and later Valdez et al. (2014) [18] exploited PPD to construct fentanyl and its citrate salts through selective reductive amination. In Valdez's method, $NaBH(OAc)_3$ achieved yields up to 95% under mild, scalable conditions (room temperature, 2 h) [18].

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Table 1. The key routs for production of fentanyl (especially related to PPD as precursor)

Researcher	Year	Route Type (precursor)	Reagents/ condition	Conceptual Yield (%)
Janssen [11]	1961-1962	4-piperidyl)-propionanilide	Na_2CO_3, KI, hexone, Reflux of 27h	40-50
Richter et al. [12]	1970	1-(2-phenylethyl)-4-piperidinone	Cu powder, Na_2CO_3, toluene/xylene	72
Jonczyk et al. [13]	1978	4-piperidinone	$NaBH_4$, propionyl chloride, 2-phenethyl bromide	65
Brine A et al. [14]	1989	1-(2-phenylethyl)-4-piperidinone	A: p-toluenesulfonic acid monohydrate, 2) $NaBH_4$ / 1) toluene, 22 h, reflux, 2) ethanol, rt, 3 h B: toluene / 2 h / Heating	57
Gupta PK et al. [15a]	2005	PPD	A: $PhNH_2$, $NaBH(OAc)_3$, AcOH, 24 hrs B: EtCOCl	More than 40
Gupta PK et al. [15b]	2009	4-anilinopiperidine	acetic acid; zinc / 24 h / 20 - 70 °C	More than 60
Saidi O et al. [16]	2010	N-phenyl-N-(piperidin-4-yl)propionamide	[Cp*IrI$_2$]2 **In** water at 115°C; for 24h; Inert atmosphere	68
Watson AJA et al. [17]	2011	N-phenyl-N-(piperidin-4-yl)propionamide	[Ru(p-cymene)Cl$_2$]2; DPEPhos at 115°C; for 1.5h; Inert atmosphere; Microwave irradiation; Neat (no solvent);	77
Ghaffarzadeh et al. [20]	2012	N-(1-phenethylpiperidin-4-ylidene) aniline	triethylsilane; zinc In tetrahydrofuran at 20°C; for 1h	86
Valdez CA et al. [18]	2014	PPD	A: acetic acid; sodium tris(acetoxy)borohydride / DCM / 2 h / 20 °C / Cooling with ice B: N-ethyl-N,N-diisopropylamine / DCM / 2 h / 0 - 20 °C	A: 91 B: 95
Zhang G et al. [19]	2016	1-phenethyl-N-phenylpiperidin-4-amine	bis(η3-allyl-μ-chloropalladium(II)); hydroxylamine hydrochloride; 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene at 120°C; for 24h; Autoclave; High pressure	96
Walz et al. [22]	2017	PPD	sodium tetrahydroborate; Dichloroethane ; 24 h, RT	85
Robertson, et al. [23]	2019	PPD	A: sodium tris(acetoxy)borohydride B: triethylamine	A: 91 B: 33
Kanamori T et al. [24]	2021	PPD	A: Molecular sieve B: sodium tetrahydroborate	A: 75 B: 95
Braga FC et al. [21]	2022	PPD	A: [Ru(bpy)3]Cl2.6H2O; 3-mercaptopropionic acid; ascorbic acid / methanol / 6 h / 25 °C / Schlenk teczInert atmosphere; Flow reactor; Irradiation B: N-ethyl-N,N-diisopropylamine / dichloromethane / 2 h / 25 °C	A: 84 B: 92

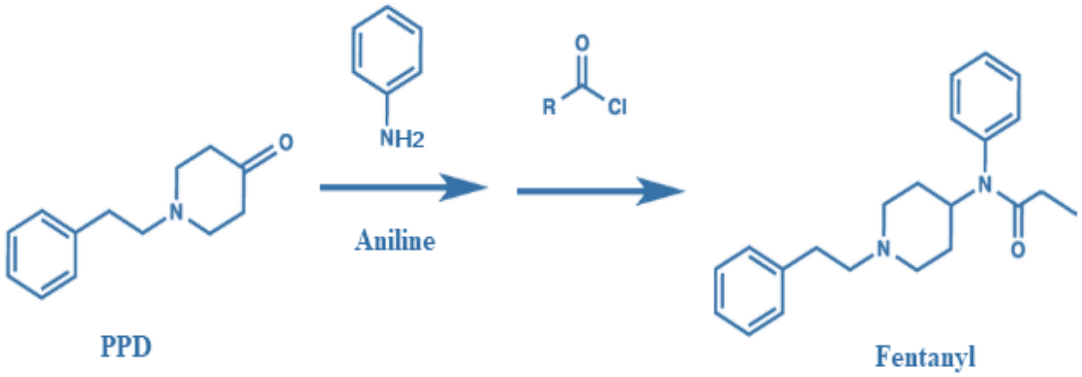


Figure 2. Synthesis of fentanyl via PPD as the key intermediate

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Subsequent work explored various reducing agents, including $NaBH_4$, $NaBH(OAc)_3$, and combinations with molecular sieves. Kanamori et al. (2021) reported yields ranging from 75–95% by carefully controlling reaction moisture and employing sequential reduction steps [24].

Walz & Hsu (2017) proposed a simplified version using only $NaBH_4$ in 1,2-dichloroethane (DCE) at ambient temperature, with an 85% yield [22].

Robertson et al. (2019) later introduced a practical two-step approach utilizing $NaBH(OAc)_3$ and Et_3N, giving successive yields of 91% and 33%, suitable for mid-scale pharmaceutical preparation [23].

Finally, the Braga et al. (2022) photocatalytic system marked a transformative step. Utilizing visible-light catalysis in a continuous-flow reactor with $[Ru(bpy)_3]Cl_2$ and ascorbic acid, they achieved stepwise yields of 84% and 92%, offering high safety, reproducibility, and green scalability [21].

Discussion

Over six decades of fentanyl research reveal a clear evolution from primitive condensation reactions to sophisticated, catalytically controlled, and environmentally compliant methodologies. Each synthetic era, from Janssen's (1961) early chloride-based alkylations to Braga's (2022) visible-light photocatalysis, reflects a deeper understanding of mechanistic control and kinetic optimization in the construction of the piperidinone–amide scaffold. The transition from hazardous reagents to selective borohydride reductions, transition-metal catalysis, and ultimately photo- or flow-assisted green chemistry demonstrates an outstanding example of how synthetic strategy has converged toward higher efficiency, reproducibility, and safety. However, despite these achievements, several challenges remain. Current transition-metal systems, although efficient, often suffer from catalyst recovery difficulties, trace metal contamination, and limited recyclability. Therefore, the next logical stage in the evolution of fentanyl synthesis will likely involve superparamagnetic nanocatalysts that combine high surface reactivity with facile magnetic separation. These hybrid catalysts, composed of Fe_3O_4 cores functionalized with Ru, Pd, or Ir complexes or even funcionalized with organic acids or amines [26can enable heterogeneous versions of reductive amination, acylation, and hydrogenation reactions with minimal waste and complete catalyst recovery.

In principle, superparamagnetic catalysts could merge the selectivity of homogeneous systems with the recyclability and stability of heterogeneous media, significantly reducing cost and environmental impact. Furthermore, when applied under continuous-flow photoreactors, they can provide dynamic control over reaction kinetics, enhance photon absorption, and minimize side-product formation ideal conditions for pharmaceutical-grade fentanyl analog synthesis. Thus, the future of fentanyl chemistry lies in integrating superparamagnetic catalysis, green solvents, and automated flow technology into one sustainable, high-yield platform. Such hybrid systems not only promise scalability and safety but also align with the next generation of intelligent drug manufacturing, where reaction optimization, energy efficiency, and environmental compatibility become inseparable.

Conclusion

In summary, over the past six decades, fentanyl synthesis has evolved from classical alkylation of 4-piperidone derivatives to highly efficient, selective, and environmentally benign methods, including borohydride-mediated reductive aminations, transition-metal catalysis, and photocatalytic flow processes. The introduction of 1-(2-phenylethyl)-4-piperidinone (PPD) as a key intermediate enabled consistently high yields and operational simplicity, while modern methodologies minimize hazardous reagents and improve scalability. Looking forward, superparamagnetic nanocatalysts offer a promising avenue to combine the selectivity of homogeneous catalysis with the

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recyclability and stability of heterogeneous systems, particularly in continuous-flow and photochemical setups. Such innovations could establish a sustainable, high-yield platform for pharmaceutical-grade fentanyl and related analogues, aligning synthetic efficiency with environmental and operational safety.

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Authorship
All authors contributed to the study's conception and design, conducted the literature review, and participated in drafting and critically revising the manuscript. All authors reviewed and approved the final version for submission.

Conflicts of interest
No potential conflict of interest relevant to this article was reported.

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