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Review

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Synthetic strategies toward nefopam: a short review

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In memory of Prof. Janusz Zachara (1955–2024): An inspiring crystallographer, an exceptional educator, and an outstanding mentor to generations of students

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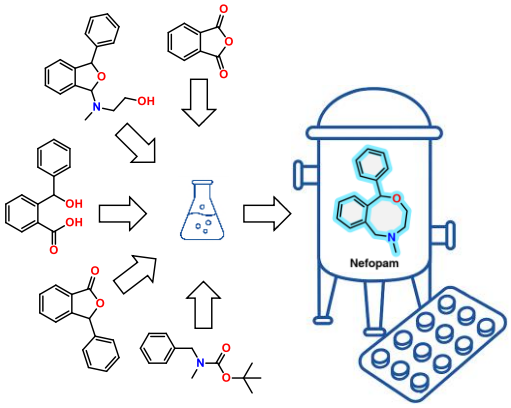
Abstract

Nefopam is a centrally acting, non-opioid, and non-steroidal analgesic with both oral and parenteral bioavailability. Its clinical utility arises from a favorable side-effect profile relative to conventional analgesics, which has led to its adoption in the management of acute postoperative, dental, and renal pain, as well as for the prevention of postoperative shivering and treatment of intractable hiccups. Although nefopam has demonstrated efficacy in selected chronic pain conditions, such as migraine and facial pain, its therapeutic use remains predominantly restricted to acute pain settings.

This short review provides a concise overview of synthetic strategies developed for nefopam and its structural analogues, with particular emphasis on their potential for adaptation to industrial-scale synthesis. The survey encompasses peer-reviewed research articles and patent documentations published between 1969 and 2025.



Keywords: Nefopam, non-opioid analgesic, non-steroidal painkiller, active pharmaceutical ingredient (API).

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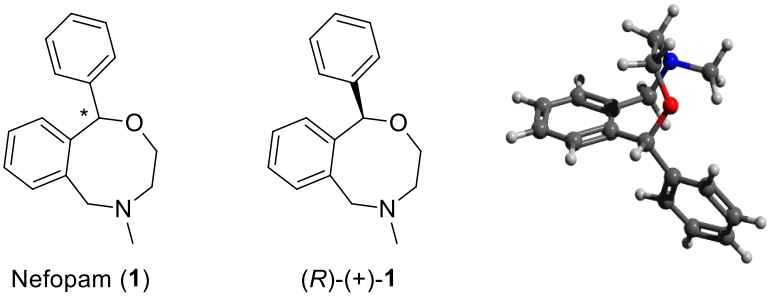
1. Introduction

Nefopam (**1**, Figure 1), sold under the brand name Acupan™, is a centrally acting, non-opioid, and non-steroidal analgesic that has gained increasing interest in recent years owing to its distinct mechanism of action and favorable safety pharmacological profile.[1,2] In contrast to conventional non-steroidal anti-inflammatory drugs (NSAIDs) and opioid-based analgesics, nefopam (**1**) does not function through inhibition of cyclooxygenases (COXs) and/or modulation of opioid receptors (ORs).[3]



Nefopam (**1**) (*R*)-(+)-**1**

Figure 1. Chemical structure of racemic nefopam (**1**), its eutomer (*R*)-5-methyl-1-phenyl-3,4,5,6-tetrahydro-1*H*-benzo[*f*][1,4]oxazocine [(*R*)-(+)-**1**], and 3D model of (*R*)-(+)-**1** generated and optimized by Avogadro vs. 1.2.0. (http://avogadro.cc/). The asterisk indicates the stereocenter.

Instead, its analgesic effect is primarily attributed to the inhibition of reuptake of endogenous monoamines [specifically serotonin (5-HT), dopamine (NA), and norepinephrine (DA)] in the central nervous system (CNS), suggesting a multimodal mechanism of action on monoaminergic neurotransmission.[4] Nefopam (**1**) also modulates *N*-methyl-D-aspartate (NMDA) receptor activity, which is associated with central sensitization and chronic pain development.[5] By indirectly reducing glutamatergic transmission, nefopam (**1**) helps dampen central sensitization and neuropathic components of pain. This unique pharmacological profile renders nefopam (**1**) effective in the treatment of both acute and chronic pain, including postoperative pain,

dental and renal colic, migraine, and neuropathic disorders.[6] Clinically, 20 mg of nefopam (**1**) has been reported to provide analgesic efficacy comparable to that of 6–12 mg of morphine, while 30 mg of **1** is approximately equivalent in potency to 8 mg of oxycodone.[7] However, at doses exceeding 60 mg/day, a ceiling effect, which is typical for NSAIDs, has been observed.[8] Notably, co-administration of **1** with strong opioids such as fentanyl allows significant dose reduction of the opioid component,[6] an approach that holds particular promise for optimizing postoperative pain management while minimizing opioid-related side effects, such as respiratory depression, severe hypotension, or a risk of dependence, tolerance, and addiction. In addition to its analgesic effects, nefopam (**1**) has shown efficacy in preventing postoperative shivering and treating severe hiccups—further broadening its clinical applications.[5] Importantly, its reduced potential for gastrointestinal irritation, respiratory depression, or dependence positions nefopam (**1**) as an attractive alternative in multimodal pain management strategies.[9] On the other hand, among the most prevalent, possible drug-related side effects of nefopam (**1**) are insomnia and dryness of the mouth; however these were found over 12 weeks of drug administration with the dose of 60 mg 3 times/day.[10]

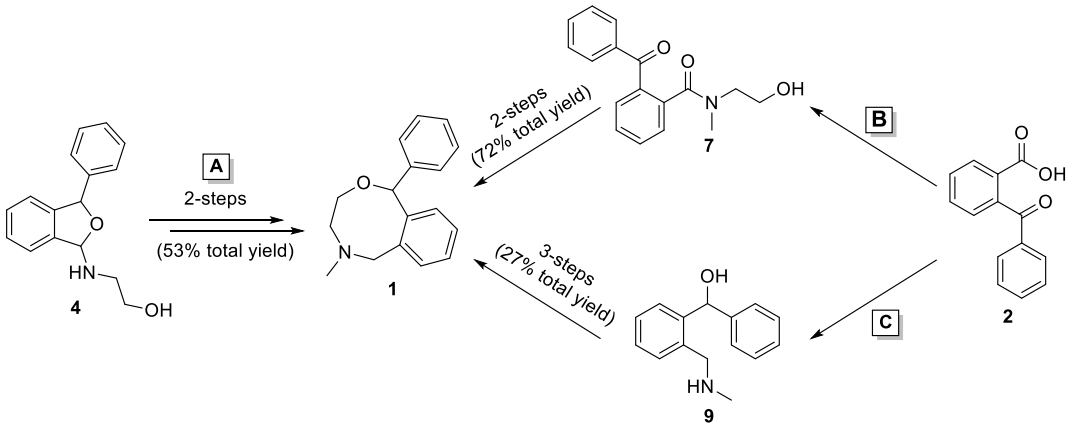
From a chemical standpoint, nefopam (**1**, 5-methyl-1-phenyl-1,3,4,6-tetrahydro-2,5-benzoxazocine) belongs to the class of chiral benzoxazocine derivatives. Formally nefopam (**1**) is a cyclized analogue of orphenadrine and diphenhydramine, bearing a single asymmetric carbon atom situated in a doubled benzylic position. Although nefopam (**1**) is manufactured and administered only as a racemic mixture, several pharmacological and pharmacokinetic studies revealed that (+)-enantiomer exhibits significantly higher biological activity compared to (–)-enantiomer,[11] particularly with respect to its analgesic properties[12] and antinociceptive activity.[13,14] Moreover, (+)-nefopam [(*R*)-(+)-**1**] is reported to be better tolerated by patients and may exhibit increased selectivity in binding to receptors associated with its antidepressant effect, primarily through modulation of monoamine neurotransporters.[15,16] In this context, two other studies revealed that the potency of nefopam's antinociceptive activity[17] and its effects on synaptosomal uptake of monoamines[18] are enantiomer-dependent, following the trend: (*R*)-(+)-**1** > *rac*-**1** > (*S*)-(–)-**1**. Interestingly, both of these pharmacological activities (analgesic and antidepressant) were not originally anticipated; only the muscle relaxant effects were initially taken into account. As mentioned above, on the basis of the recent studies, it is considered that nefopam's analgesic activity is also connected with the interaction with the glutamatergic system, most probably because of effective modulation of NMDA effects;[19] however, this mechanism of action remains under investigation.

From a synthetic perspective, the preparation of nefopam (**1**) presents several challenges due to the structural complexity of its tricyclic scaffold and the formation of the eight-membered benzoxazocine ring. Over the past few decades, various synthetic strategies have been developed to improve the efficiency, scalability, and environmental sustainability of its production, with the aim of facilitating adaptation to industrial-scale manufacturing. This review aims to provide a comprehensive overview of the known synthetic approaches to the active agent nefopam (**1**), highlighting key methodologies and offering critical insights into their advantages and disadvantages with respect to suitability for large-scale industrial application. Special attention is given to green chemistry principles and metrics, transition-metal-catalyst-free conditions, and other valuable transformations, such as sequential one-pot/multi-steps cascade operations that limit laborious isolation and purification procedures—all of which collectively reflect modern trends in pharmaceutical synthesis. At the end of this article, we present several promising examples of structural modifications of the parent nefopam (**1**) molecule aimed at generating novel lead compounds that may contribute to the advancement of modern medicinal chemistry in the development of improved and safer non-opioid analgesics.

2. Results and Discussion

2.1. Historical perspective on nefopam (1)

The earliest reported syntheses of nefopam (**1**)—though not yet referred to by this name—appeared in the 1960s in a patent filed by *Rexall Drug and Chemical Company*,[20] describing the preparation of phenylbenz(*f*)-2,5-oxazocine derivatives and their homologues. Three synthetic routes to the target **1** were disclosed therein (Scheme 1A–C).



Scheme 1. Seminal work by the *Rexall Drug and Chemical Company* reporting the synthesis of nefopam (**1**).

The first route involved a two-step reaction sequence starting from *N*-(2-hydroxyethyl)-3-phenyl-1-phthalanamine (**4**), affording nefopam (**1**) in an overall yield of 53% (Scheme 1A). In the second approach, *N*-(2-hydroxyethyl)-*N*-methyl-*o*-benzoylbenzamide (**7**), derived from 2-benzoylbenzoic acid (**2**), served as the key intermediate, whereas the desired product was obtained *via* a two-step sequence in 72% overall yield (Scheme 1B). The third method employed a three-step reaction sequence starting from 2-(*N*-methylaminomethyl)benzhydrol (**9**), also derived from **2**, and afforded the titled API **1** in a 27% overall yield (Scheme 1C).

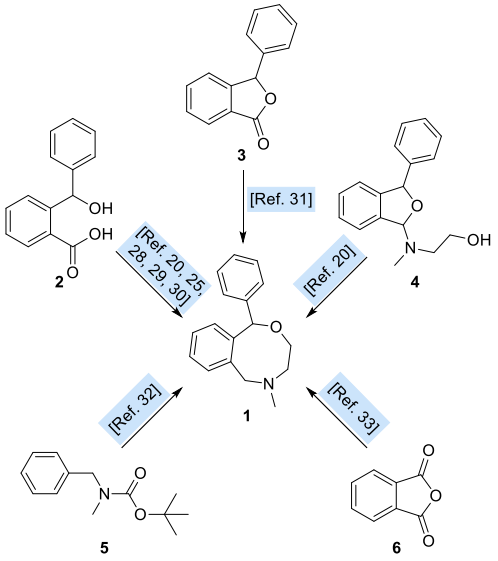
In 1969, Bassett et al.[21] introduced pharmacological investigations of the compound under its provisional name, fenazoxine. Their studies indicated that the molecule exhibited catecholamine reuptake inhibition similar to that of cocaine and desmethylimipramine, and showed anti-noradrenaline activity at higher concentrations. According to Kim and Abdi,[7] the name "fenazoxine" was ultimately replaced by "nefopam" in the early 1970s. Interestingly, initial pharmacological evaluations primarily focused on its muscle relaxant[22] and antidepressant[23] properties, before subsequent research began to reveal its potent analgesic effects.

Nefopam (**1**) was first marketed under the trade name Acupan™ by *Riker Laboratories, Inc.*, and is currently distributed globally under various names including Ajan™, Silentan™, Nefadol™, Lenipan™, Nefam™, and Oxadol™. According to data deposited in the IQVIA database (formerly IMS Health and Quintiles),[24] global consumption of nefopam (**1**) reached 4.3 metric tons (MT) in Q2 2024 (July 2023–June 2024), marking a 12% increase year-over-year, with Europe accounting for 81% of this demand. The total market value of nefopam-based medicinal products for this period amounted to approx. USD 60 mln (14% annual increase). Interestingly, the United Kingdom (UK) led in terms of overall volume of nefopam (**1**) manufacturing (1998 kg), whereas France dominated value share, representing 58.7% of global sales. These trends underscore nefopam's growing significance as an active pharmaceutical ingredient and its increasing impact in the global analgesics market.

2.2. Synthetic routes to nefopam (1)

Over the years, multiple synthetic strategies have been developed to construct nefopam (**1**) framework, often varying based on the choice of key starting materials to achieve the desired functional group compatibility, process efficiency and scalability. In this study, we present a brief overview of the major synthetic approaches toward nefopam (**1**) reported in the scientific literature as well as patent documentations.

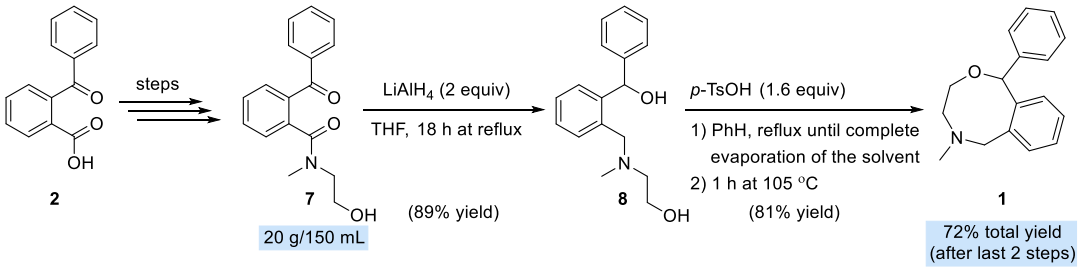
The synthetic routes presented below (paragraphs 2.2.1.–2.2.5.) are categorized according to the principal starting materials employed in each case, namely: *o*-benzoylbenzoic acid (**2**), *o*-carboxybenzhydrol-*γ*-lactone (**3**), *N*-(2-hydroxyethyl)-3-phenyl-1-phthalanamine (**4**), *tert*-butyl-*N*-benzyl-*N*-methylcarbamate (**5**), and phthalic anhydride (**6**) (Scheme 2). Each method reflects different strategic considerations, from step economy and regioselectivity to industrial applicability.



Scheme 2. Structural formulas of starting materials used in synthetic routes toward nefopam (**1**).

2.2.1. Synthetic approaches to nefopam (1) from *o*-benzoylbenzoic acid (2). Among the various starting materials employed in the synthesis of nefopam (**1**), *o*-benzoylbenzoic acid (**2**) has been the most frequently utilized. Its structural features and commercial availability make it an attractive precursor for constructing the tricyclic core of nefopam (**1**) through diverse synthetic strategies.

One of the earliest synthesis of nefopam (**1**) using *o*-benzoylbenzoic acid (**2**) as a main raw material was reported by *Rexall Drug and Chemical Company* in patent specification published in 1969 (Scheme 3).[20]

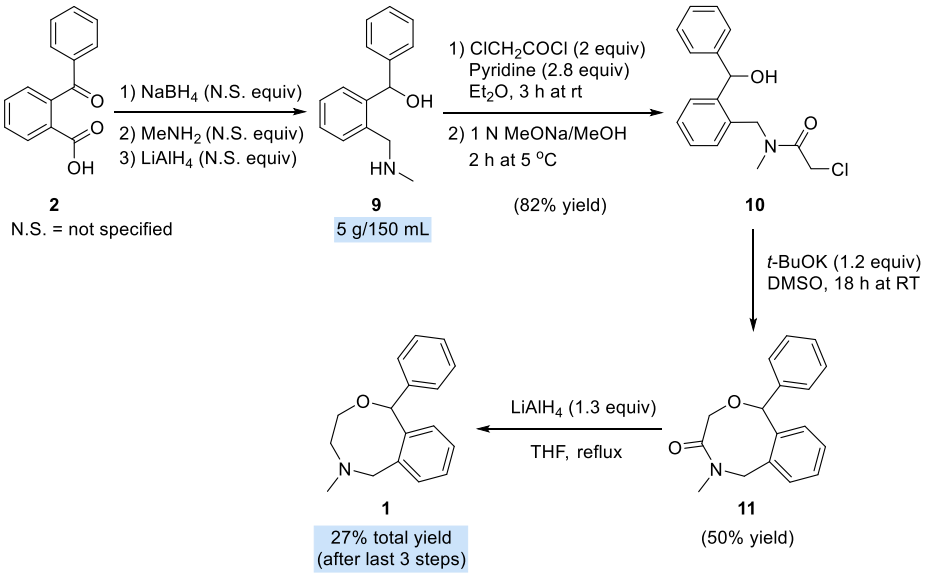


Scheme 3. Synthesis of nefopam (**1**) as reported in the original patent specification by *Rexall Drug and Chemical Company*. Method leading *via* 2-((2-(hydroxy(phenyl)methyl)benzyl)(methyl)amino)ethan-1-ol (**8**).

In the initial two steps, *o*-benzoylbenzoic acid (**2**) was transformed into 2-benzoyl-*N*-(2-hydroxyethyl)-*N*-methylbenzamide (**7**) *via* sequential treatment with sodium borohydride ($NaBH_4$) and 2-methylaminomethanol under conventional synthetic conditions (not reported therein). Subsequent reduction of intermediate **7** with lithium aluminium hydride ($LiAlH_4$) in dry tetrahydrofuran (THF) furnished 2-((2-(hydroxy(phenyl)methyl)benzyl)(methyl)amino)ethan-1-ol (**8**) in 89% yield. Cyclization of **8** in the presence of *p*-toluenesulfonic acid (*p*-TsOH) in benzene (PhH) afforded the target nefopam (**1**) in 81% yield. The overall yield for the final two steps of the patented process was reported to be 72%.

The principal advantages of this approach lie in its consistently high yield of all steps of the synthetic pathway and reliance on readily accessible commercial reagents. Nevertheless, the method presents notable limitations with regard to large-scale implementation, primarily due to the use of flammable and/or cancerogenous solvents such as benzene, the handling of highly reactive and hazardous reducing agent ($LiAlH_4$), and the requirement for subsequent removal of aluminium-based byproducts.

An alternative synthetic route (Scheme 4), also disclosed in the aforementioned patent specification,[20] involves the conversion of *o*-benzoylbenzoic acid (**2**) to the corresponding lactam intermediate, namely 5-methyl-1-phenyl-5,6-dihydro-1*H*-benzo[*f*][1,4]oxazocin-4(3*H*)-one (**11**) as a key intermediate.



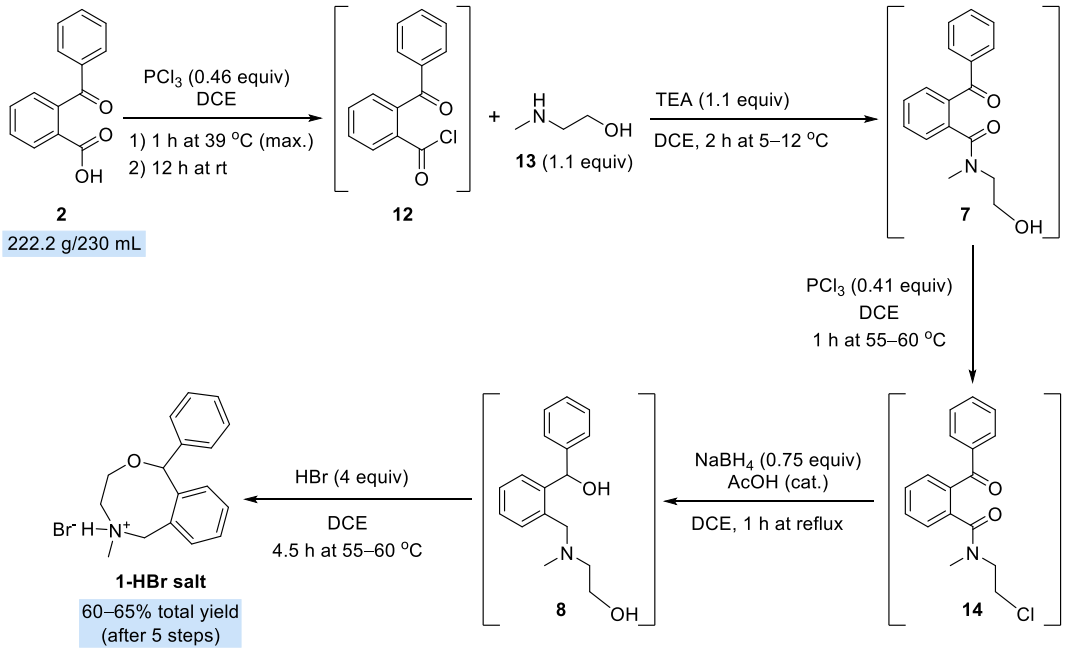
Scheme 4. Synthesis of nefopam (**1**) as reported in the original patent specification developed and published by *Rexall Drug and Chemical Company*. Method leading *via* 5-methyl-1-phenyl-5,6-dihydro-1*H*-benzo[*f*][1,4]oxazocin-4(3*H*)-one (**11**).

This multistep synthesis commences with the chemoselective transformation of *o*-benzoylbenzoic acid (**2**). Initial treatment with $NaBH_4$, followed by the subsequent treatment of the lactone (not shown) with methylamine ($MeNH_2$), followed by reduction with $LiAlH_4$ under standard reaction conditions, furnished 2-(*N*-methylaminomethyl)benzhydrol (**9**). This intermediate is then acylated with 2 equiv of chloroacetyl chloride in the presence of pyridine in diethyl ether (Et_2O) at room temperature. The resulting chloroacetamide undergoes base-mediated methanolysis using sodium methoxide (MeONa) at 5 °C, yielding benzhydrol chloroacetate (**10**) in 82% overall yield for the two-step sequence. Intramolecular cyclization of **10** promoted by potassium *tert*-butoxide (*t*-BuOK) in dry dimethyl sulfoxide (DMSO) *via* a multistage heating protocol, afforded the eight-membered lactam intermediate **11** in 50% yield. Final reductive conversion of the amide

moiety using $LiAlH_4$ in refluxing THF delivered nefopam (**1**), thereby completing the synthetic sequence with an overall yield of 27% for the final three steps.

The advantages of this synthetic strategy include the use of simple and readily available commercial reagents. However, the overall efficiency is significantly limited by modest yields, reliance on flammable reducing agents, and the necessity for chromatographic purification steps — factors that render the process suboptimal for large-scale production.

In another invention patented in 1980 by P. G. Watson from *Riker Laboratories, Inc.*,[25] *o*-benzoylbenzoic acid (**2**) was converted *in situ* to the corresponding acid chloride intermediate (**12**) using phosphorus trichloride (PCl_3) in 1,2-dichloroethane (DCE) under mild heating (**Scheme 5**).

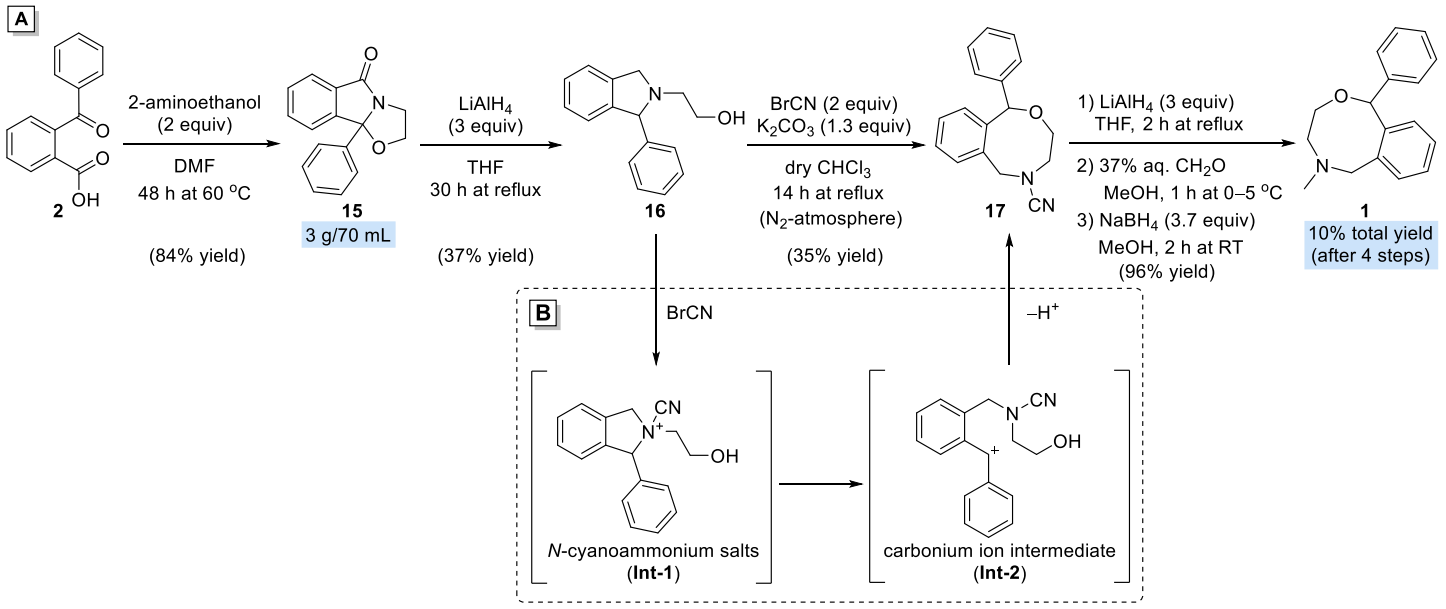


Scheme 5. Synthesis of nefopam hydrobromide (**1-HBr salt**) developed by *Riker Laboratories, Inc.*

Without isolation, the reactive intermediate was subsequently treated with 2-(methylamino)ethanol (**13**) in the presence of triethylamine (TEA), furnishing the amide alcohol derivative (**7**). Transformation of the 2-hydroxyethyl moiety into a 2-chloroethyl group was then achieved *via* a second PCl_3-mediated chlorination step, yielding the respective intermediate, namely 2-benzoyl-*N*-(2-chloroethyl)-*N*-methylbenzamide (**14**). Subsequent reduction of **14** with $NaBH_4$ in the presence of catalytic amount of acetic acid (AcOH) under reflux conditions provided benzhydrol derivative (**8**), which underwent acid-catalyzed intramolecular cyclization upon treatment with aqueous hydrobromic acid. This final step afforded nefopam hydrobromide (**1-HBr salt**) in an overall yield of 60–65% across the five-step reaction sequence.

Noteworthy, the principal advantage of this synthetic route lies in its cost-efficiency and overall high yield, despite encompassing five individual steps—an outcome largely attributed to the telescoped nature of the sequence, wherein intermediates are not isolated. Although coupling five steps into single sequential cascade allowed to omit laborious, time- and material-consuming isolation and purification steps, it unfortunately limits the ability to control the impurity profile, a critical requirement in pharmaceutical manufacturing. Furthermore, the use of DCE, a genotoxic Class 1 solvent (according to the EMA)[26] and a Group 2B carcinogen (according to the WHO and the International Agency for Research on Cancer, IARC),[27] with significant environmental concerns, poses a major limitation to its implementation on an industrial scale.

Another method, reported by Bremner and Thirasasana,[28] illustrates a four-step synthetic sequence toward nefopam base (**1**) (Scheme 6).

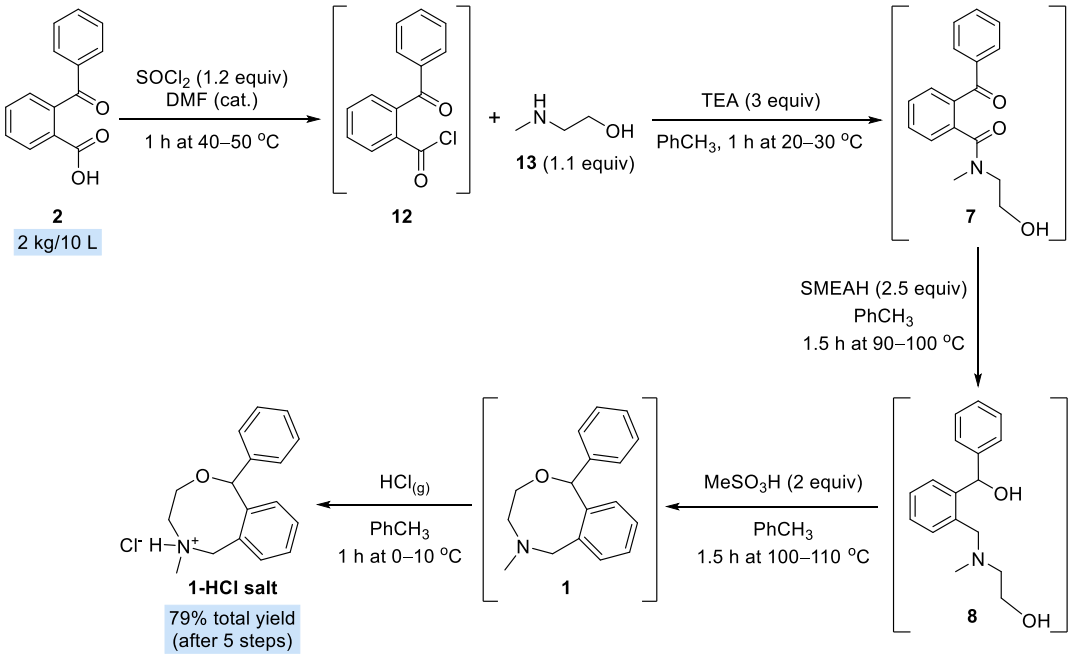


Scheme 6. Synthesis of nefopam (**1**) leading *via 9b*-phenyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9bH*)-one (**15**).

The synthetic pathway begins with the condensation of *o*-benzoylbenzoic acid (**2**) with 2-aminoethanol in DMF at 60 °C for 48 h, affording lactam intermediate **15** in 84% yield. This transformation likely proceeds *via* nucleophilic attack of the aminoalcohol on the carboxylic acid followed by cyclodehydration, yielding a dihydroisoindolone scaffold according to procedure reported by Aeberli and Houlihan.[29] Afterward, reduction of lactam **15** using 3 equiv of $LiAlH_4$ in refluxing THF for 30 h furnished the corresponding secondary amine **16** in 37% yield. The relatively low yield, in this case, may be attributed to competing side reactions or partial over-reduction of the lactam functionality. Nevertheless, compound **16** serves as a valuable intermediate for subsequent heterocycle formation. Treatment of dihydroisoindolylethanol **16** with cyanogen bromide (BrCN) in dry (ethanol-free) chloroform ($CHCl_3$) in the presence of an excess of potassium carbonate (K_2CO_3) under a nitrogen atmosphere protective conditions promotes the formation of the *N*-cyano derivative **17** (also called *N*-cyano-nor-nefopam). This transformation likely proceeds *via* an initial nucleophilic attack of BrCN on tertiary amine moiety in **16** to generate a quaternary *N*-cyanoammonium salt intermediate (**Int-1**), which spontaneously forms carbonium ion intermediate (**Int-2**) that subsequently cyclizes under basic conditions to form the benzoxazocine core structure (Scheme 6B). The moderate 35% yield of the cyanogen-bromide-induced ring enlargement reflects the complexity of this transformation and the formation of numerous unidentified side-products. In the final step, compound **17** undergoes reductive methylation *via* nitrile cleavage under modified Eschweiler-Clarke conditions. This transformation was accomplished *via* a $LiAlH_4$-mediated reduction of **17**, yielding the corresponding amine, which is subsequently methylated *in situ* using 37% aqueous formaldehyde (formalin) in methanol (MeOH) at 0–5 °C followed by *in situ* $NaBH_4$-mediated reduction carried out for 2 h at room temperature. A one-pot, three-step decyanative *N*-methylation delivered nefopam base (**1**) in an excellent 96% yield. However, due to moderate yields in preceding steps, the overall yield of the four-step sequence was only 10%, which is considered to be rather unpractical from the industrial point of view.

Although the sequence efficiently constructs the tricyclic core and introduces the requisite *N*-methyl group via interesting decyanation-methylation procedure, the overall step economy and low throughput in terms of the total yield render this approach more suitable for exploratory synthetic studies than for a large-scale pharmaceutical production. Furthermore, the use of BrCN and $LiAlH_4$ raises concerns regarding toxicity, handling safety, and scalability. In particular, the potential risk of cyanide contamination should be carefully considered and avoided during synthesis planning for pharmaceutical manufacturing.

Bodireddy and co-workers[30] developed a multikilogram-scale, one-pot synthesis of nefopam hydrochloride (**1·HCl**) utilizing toluene ($PhCH_3$) as the sole reaction medium, achieving an impressive overall yield of 79% over five steps (Scheme 7). The process begins with the conversion of *o*-benzoylbenzoic acid (**2**) to the corresponding acid chloride **12** *via* reaction with thionyl chloride ($SOCl_2$) in the presence of catalytic amount of dimethylformamide (DMF) under classical Vilsmeier–Haack chlorination conditions. Furthermore, the crude intermediate **12** was directly coupled with 2-(methylamino)ethanol (**13**) in $PhCH_3$ in the presence of TEA as a base, affording amide alcohol intermediate **7**. Subsequent reduction of this derivative using sodium bis(2-methoxyethoxy)aluminium hydride (SMEAH, also known under trade names: Red-Al, Synhydrid, or Vitride) furnishes the corresponding benzhydrol derivative **8**, which undergoes subsequent cyclodehydration promoted by methanesulfonic acid ($MeSO_3H$, MsOH) to generate nefopam base (**1**). The final transformation of nefopam (**1**) into the hydrochloride salt (**1-HCl salt**) was accomplished by purging of a solution of crude **1** in $PhCH_3$ with dry hydrogen chloride gas ($HCl_{(g)}$) at low temperature. Notably, the final product **1-HCl salt** was isolated with excellent purity (≥99.9%).

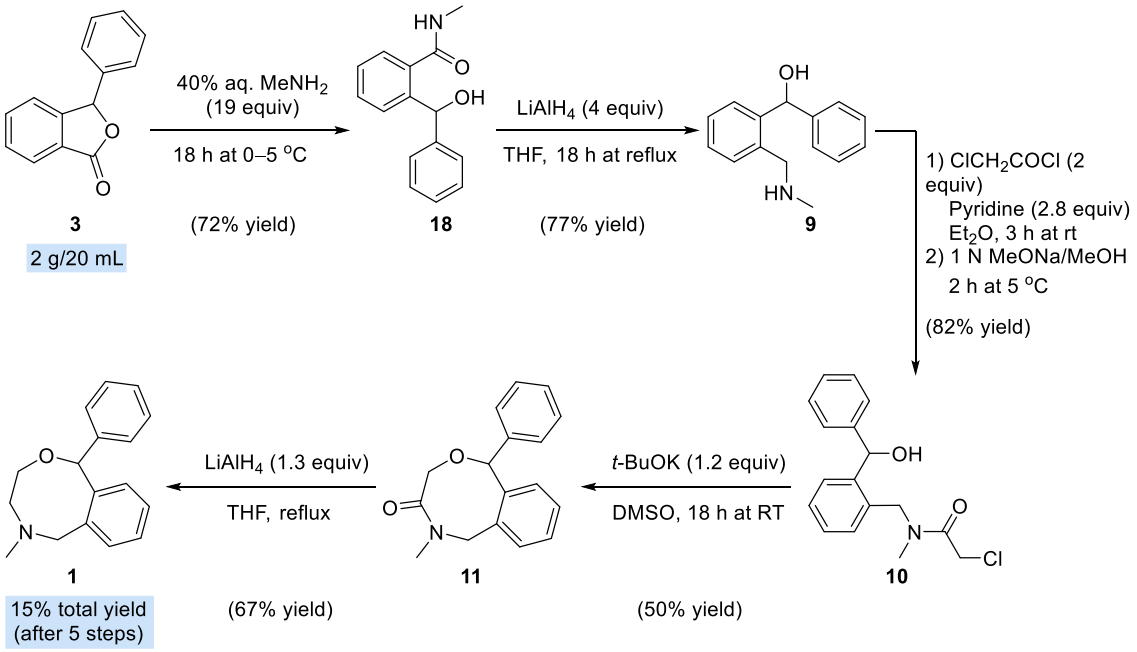


Scheme 7. Synthesis of nefopam hydrochloride (**1-HCl salt**) developed by *Micro Labs Ltd.*

In general, the telescoped, solvent-unified strategy offers several key advantages: (i) a streamlined process configuration that minimize isolation and purification operations; (ii) high conversion and yields (>90%) at each step; (iii) enhanced impurity control through stepwise monitoring; (iv) cost-effective and operationally friendly process, (v) improved safety and environmental compatibility, notably by avoiding alkyl chlorides and alkyl methanesulfonates that could lead to genotoxic impurities, and (vi) very good overall yield

(≥79%) provided by the one-pot operation. Moreover, the present study addresses several critical challenges to render the synthetic sequence amenable to multikilogram-scale production. A key advancement lies in the optimization of reaction conditions for the selective reduction of both amide and ketone functionalities using a minimal quantity (2.5 equiv) of SMEAH, thereby enhancing efficiency and sustainability. It is worth to note that this process ensures effective control and removal of key impurities, specifically process impurity such as 2-{[(2-benzoylphenyl)methyl](methyl)amino}ethan-1-ol (not shown) and carryover impurities such as **2**, **7**, and **8**. Moreover, SMEAH reagent, used at the critical step of the reduction of carbonyl group in benzophenone moiety, represents a safer and more user-friendly alternative to $LiAlH_4$. Moreover, while exhibiting comparable reducing power, SMEAH circumvents several key limitations associated with $LiAlH_4$, including its pyrophoric nature, poor solubility in common organic solvents, and limited shelf life. Although SMEAH reacts exothermically upon exposure to air or moisture, it does not spontaneously ignite and remains thermally stable at temperatures up to 200 °C, thereby offering enhanced safety and operational convenience in both laboratory and industrial settings. From both an economic and operational standpoint, this protocol exemplifies a scalable, industry-relevant synthesis of nefopam hydrochloride (**1-HCl salt**) and should be recommended as one of the method of choice when considering synthesis of this API in a multikilogram-scale.

2.2.2. Synthetic approaches to nefopam (1) from *o*-carboxybenzhydrol-*γ*-lactone (3). *o*-Carboxybenzhydrol-*γ*-lactone (**3**), also known as 3-phenyl-1,3-dihydro-2-benzofuran-1-one or 3-phenylisobenzofuran-1(3*H*)-one, serves as an alternative starting material to *o*-benzoylbenzoic acid (**2**), holding a great potential for use in synthetic routes toward nefopam (**1**). A notable example of its application was reported by *Riker Laboratories, Inc.* in a patent specification published in 1974 (Scheme 8).[31]



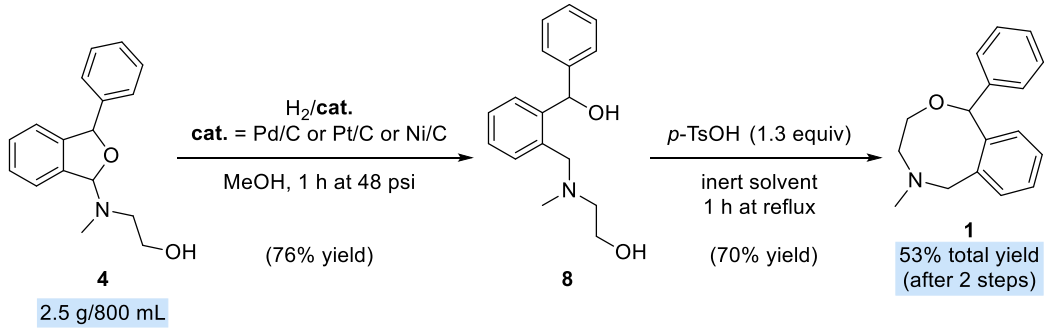
Scheme 8. Synthesis of nefopam (**1**) developed by *Riker Laboratories, Inc.*

The synthetic sequence reported in this patent document consists of a five-step approach to nefopam (**1**) as a free-base, commencing from above-mentioned lactone **3**. Initial treatment of **3** with 40% aqueous methylamine ($MeNH_2$) solution at low temperature furnished the corresponding carbamoylbenzhydrol intermediate **18** in 72% yield. Subsequent reduction of the amide moiety with $LiAlH_4$ in anhydrous THF under

reflux conditions afforded secondary amine **9** in 77% yield. The key step of the whole synthetic route was a transformation of the afore-obtained intermediate **9** into the tricyclic core of nefopam (**1**). This procedure was initiated with acylation of amine moiety using chloroacetyl chloride ($ClCH_2COCl$) in Et_2O in the presence of pyridine, followed by basification with sodium methoxide (MeONa). The corresponding benzhydrol chloroacetamide **10** was isolated in 82% yield. The subsequent treatment of **10** with potassium *tert*-butoxide (*t*-BuOK) in dry DMSO induced efficient intramolecular cyclization to afford the eight-membered heterocyclic lactam **11** in 50% yield. Final reduction of the cyclic amide using $LiAlH_4$ in THF under reflux conditions gave nefopam (**1**) in 67% yield for the final step, completing the synthesis in an overall 15% yield over five steps.

This route offers a mechanistically distinct approach to the construction of the 2,5-benzoxazocine core, utilizing a strategically timed intramolecular cyclization *via* a chloroacetamide intermediate. Despite its moderate overall yield, the sequence demonstrates efficient functional group interconversions and provides valuable insight into the reactivity and synthetic potential of benzhydrol-based scaffolds in the context of tricyclic amines syntheses. Nevertheless, this method has several drawbacks, including a lengthy and labor-intensive process, low overall yield, and the use of flammable reducing agents. Moreover, the developed synthesis was conducted only on the gram scale, employing chromatography on acid-washed alumina with chloroform ($CHCl_3$) as the eluent for the purification of most intermediates and the final product. Particularly the reliance on chromatographic purification using highly hepatotoxic and nephrotoxic (kidney-damaging) volatile chlorinated organic solvent, such as $CHCl_3$, necessitates further modifications and then scale-up optimization to render the procedure suitable for adaptation in an industrial setting.

2.2.3. Synthetic approaches to nefopam (1) from *N*-(2-hydroxyethyl)-3-phenyl-1-phtalanamine (4). Another synthetic approach utilized *N*-(2-hydroxyethyl)-3-phenyl-1-phthalanamine (**4**) as the starting material is presented in Scheme 9.[20] In general, the key intermediate **4** can be prepared by conventional methods from phthalaldehyde by its treatment with a Grignard-type reagent phenylmagnesium bromide (PhMgBr), followed by reflux with *N*-methylethanolamine (not shown). In the presented method, the thus prepared derivative **4** underwent low-pressure hydrogenation in methanol (MeOH) using a metallic catalyst (specifically Pd/C, Pt/C, or Ni/C) to furnish the benzhydrol derivative **8** in 76% yield after 1 h at 48 psi (3.31 bar). Subsequently, compound **8** was subjected to cyclization in anhydrous (inert) solvent (e.g., benzene, toluene, or xylene) in the presence of 1.3 equiv of *p*-TsOH, affording the target API **1** in 70% yield. The overall two-step sequence provided nefopam (**1**) in moderate 53% total yield.

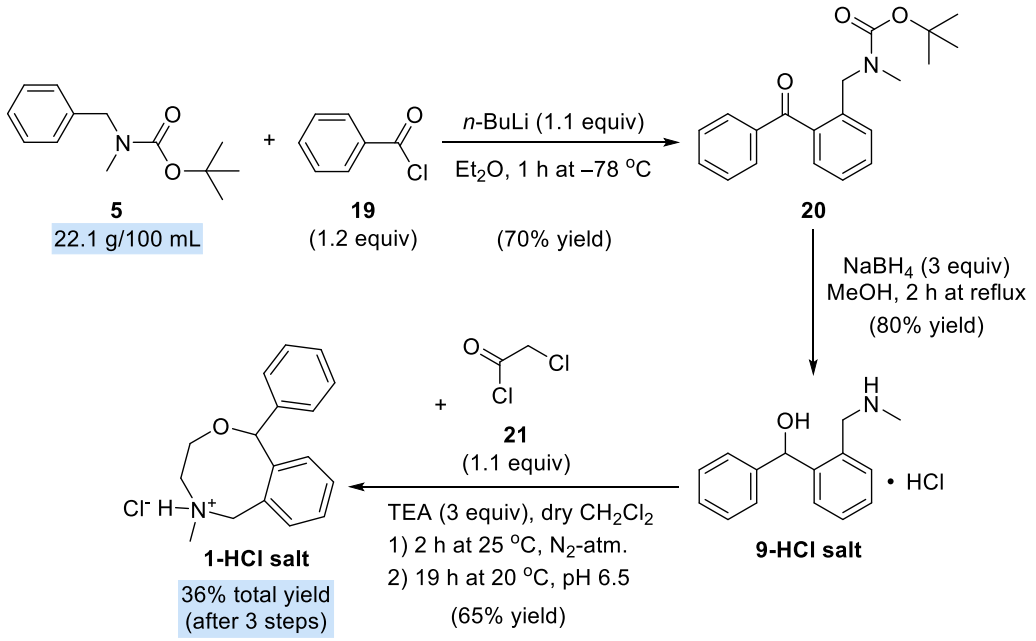


Scheme 9. Synthesis of nefopam (**1**) developed by *Rexall Drug and Chemical Company*.

The main advantages of this method are its brevity, simplicity, and low-pressure hydrogenation conditions (p = 2.44 atm), which do not necessitate specialized equipment. However, the use of flammable and

hazardous hydrogen gas demands particular caution and adherence to strict safety protocols. Moreover, the productivity of this method is very low due to the high dilution of the starting material **4** in MeOH, resulting in a final concentration of 12 mM.

2.2.4. Synthetic approaches to nefopam (1) from *tert*-butyl-*N*-benzyl-*N*-methyl carbamate (5). An intriguing synthetic approach for the preparation of nefopam hydrochloride (**1-HCl salt**) developed by *Kangmei Pharmaceutical Co., Ltd.* is illustrated in Scheme 10.[32] This method utilizes *tert*-butyl-*N*-benzyl-*N*-methylcarbamate (**5**) and benzoyl chloride (**19**) as the starting materials, which, under the action of *n*-butyllithium (*n*-BuLi) at –78 °C in Et_2O, afforded the ketone intermediate **20** in 70% yield. Subsequent reduction with $NaBH_4$ in MeOH under reflux conditions furnished the corresponding secondary alcohol moiety. Notably, the subsequent acidolysis step liberates the amine moiety, generating 1-((2-(methylamino)methyl)phenyl)-1-phenylmethanol hydrochloride (**9-HCl salt**) in 80% yield.

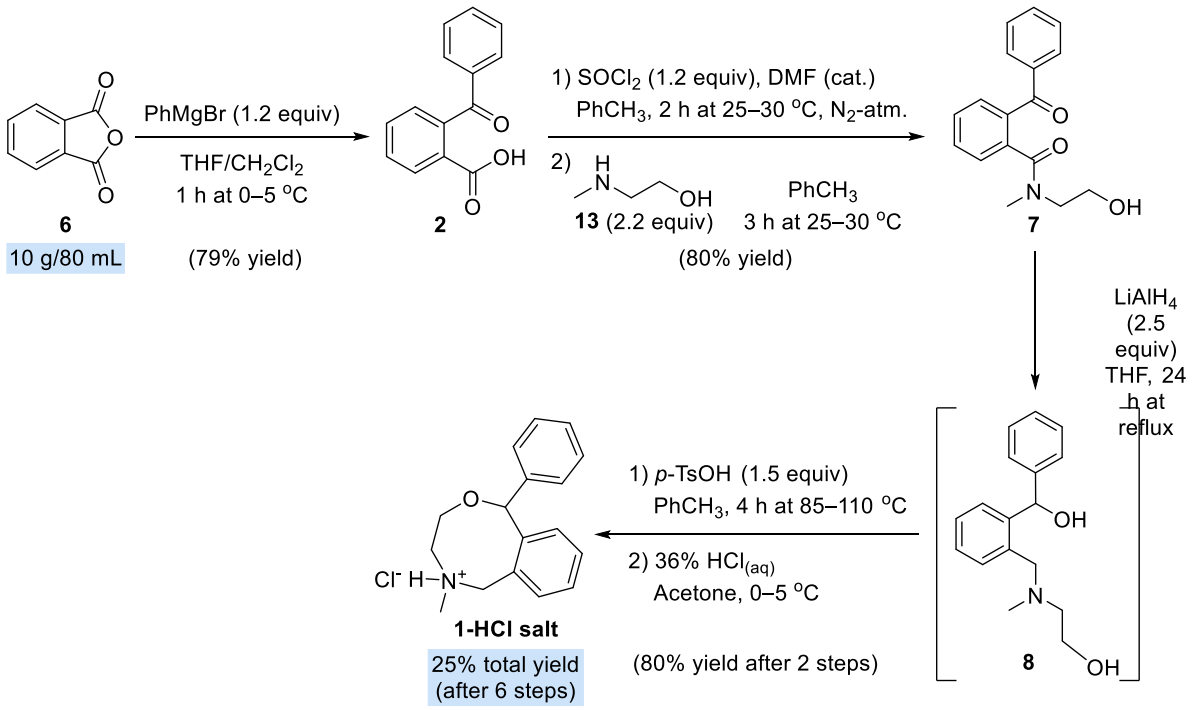


Scheme 10. Synthesis of nefopam hydrochloride (**1-HCl salt**) developed by *Kangmei Pharmaceutical Co., Ltd*.

The synthesis proceeds through a one-pot, three-steps reaction sequence involving amide formation, cyclization, and reduction, ultimately yielding nefopam hydrochloride (**1-HCl salt**) *via* additional reaction of **9-HCl salt** with chloroacetyl chloride (**21**) in the presence of triethylamine under anhydrous conditions. The overall process achieves a total yield of 36% over three steps, which is notable for its conceptual divergence from previously reported synthetic routes. Moreover, unique selection of intermediates and starting materials distinguishes this method from the above-mentioned routes, charting a synthetic pathway that avoids the more classical phthalide derivatives typically used in nefopam (**1**) synthesis. However, the use of *n*-BuLi, a highly reactive and pyrophoric organolithium reagent, introduces substantial safety concerns, particularly for scale-up. Moreover, the overall yield remains relatively modest compared to alternative routes reported elsewhere, thus limiting its attractiveness for industrial application.

In summary, while this synthetic strategy offers an elegant and mechanistically distinct route to nefopam hydrochloride (**1-HCl salt**), its reliance on hazardous reagents and the relatively low overall efficiency suggest that it is better suited for small-scale laboratory synthesis rather than large-scale production.

2.2.5. Synthetic approaches to nefopam (1) from phthalic anhydride (6). Another gram-scale synthetic procedure for the preparation of nefopam hydrochloride (**1-HCl salt**), outlined in Scheme 11, was developed by *Aurobindo Pharma Ltd*.[33] The synthetic sequence commenced from commercially available phthalic anhydride (**6**), which was transformed into the corresponding 2-benzoylbenzoic acid (**2**) *via* treatment with 1.2 equiv. of PhMgBr. This intermediate **2** was subsequently converted to the corresponding amide (**7**) through $SOCl_2$-mediated activation followed by condensation with *N*-methylaminoethanol (**13**). The next step was the $LiAlH_4$-mediated reduction of the resulting amide **7**, which proceeds efficiently under reflux in dry THF, followed by intramolecular cyclization catalyzed by *p*-TsOH in $PhCH_3$. The sequence culminates with the formation of nefopam hydrochloride (**1-HCl salt**), isolated in 25% overall yield after six-steps synthesis.



Scheme 11. Synthesis of nefopam hydrochloride (**1-HCl salt**) developed by *Aurobindo Pharma Ltd*.

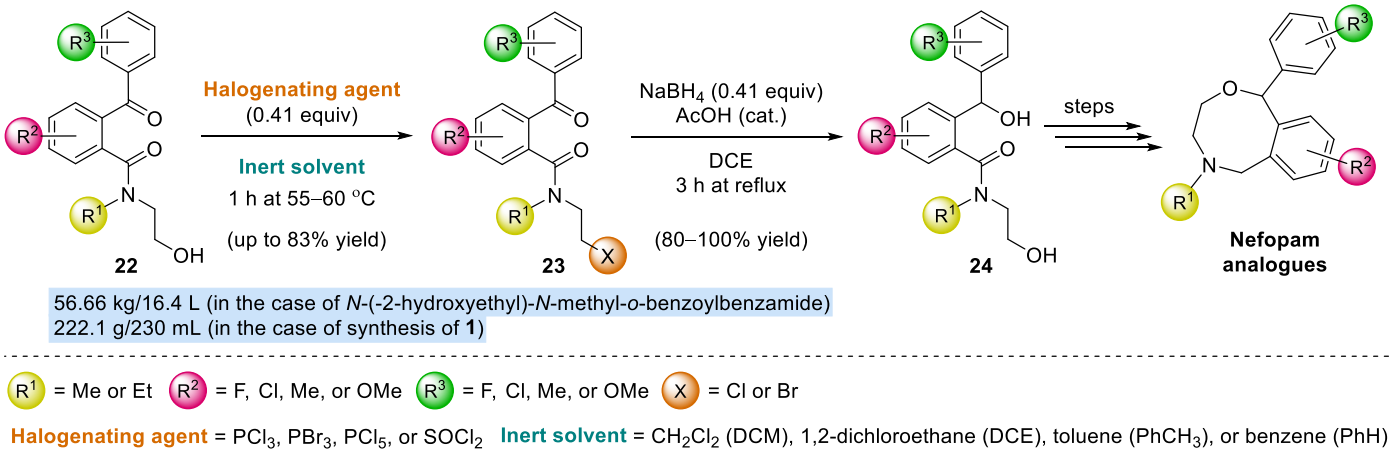
The principal advantages of this route include the use of simple, readily available reagents and solvents, which enhances its accessibility at the laboratory scale. However, the method also shares several drawbacks such as the reliance on $LiAlH_4$ as a reducing agent, which is associated with significant handling hazards and scale-up limitations. Moreover, a relatively low overall yield of this synthesis also restricts its attractiveness for industrial application. Therefore, future optimization efforts focusing on improving the efficiency and safety profile of this approach, particularly by replacing hazardous reagents and minimizing step count, are required to adapt this method. Despite these limitations, this work provides valuable insight into the modular synthesis of nefopam derivatives (not shown), demonstrating how variation in *N*-alkylated amine reagents can be integrated into the synthetic route to expand chemical diversity within the benzoxazocine core structure.

2.4. Synthetic routes to nefopam analogues

The synthesis of nefopam analogues, particularly functionalized benzoxazocines, has garnered significant attention due to their potential pharmacological applications, including analgesic, antidepressant, anti-inflammatory, and neurokinin 1 (NK-1) receptor-modulating activities.[34–37] In this context, many functionalized

benzoxazocines, besides serving as active agents for pain management, are also considered promising drug candidates, potentially useful for the treatment of emesis, depression, posttraumatic stress disorder (PTSD), attention deficit disorder (ADD), obsessive-compulsive disorder (OCD), sexual dysfunction, urinary incontinence, and as centrally acting skeletal muscle relaxants.[38–42]

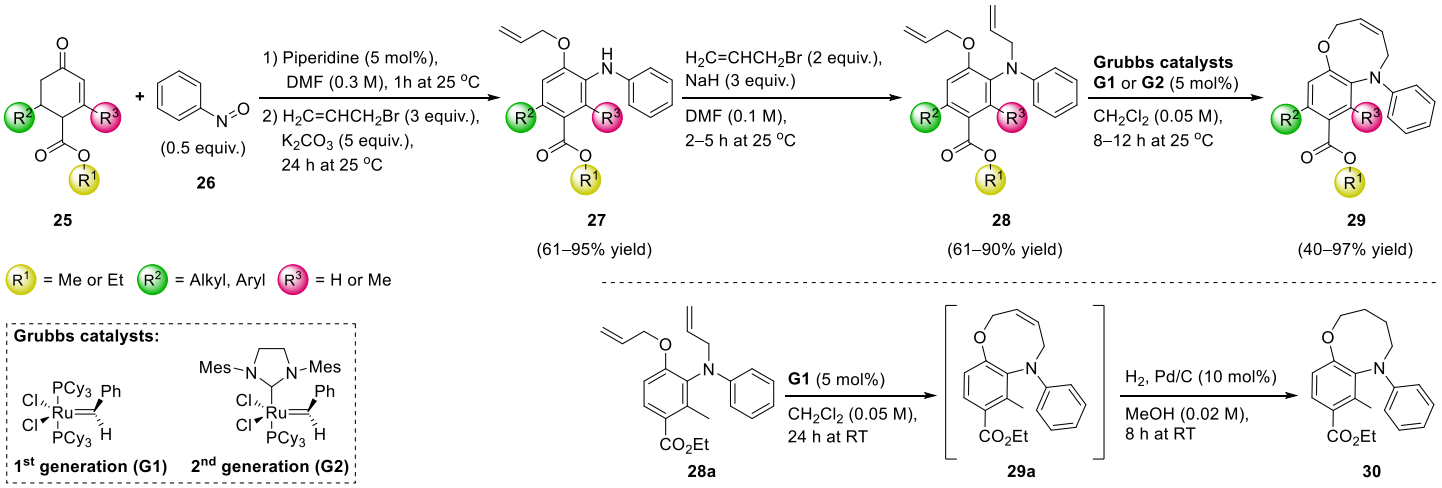
One of the earliest attempts toward structural analogues of nefopam was reported by *Riker Laboratories, Inc.*[43] (Scheme 12).



Scheme 12. Synthesis of potential precursors **24** for nefopam analogues developed by *Riker Laboratories, Inc.*

The patented invention included the halogenation of a series of derivatives **22**, accomplished using PCl_3, PBr_3, PCl_5, or $SOCl_2$. In the case the halogenation of one of the derivatives from the series **22**, the reaction yield reached 83%, while for the others, it was not determined due to the intermediates **23** not being isolated. Subsequently, the reduction of the obtained derivatives **23** with $NaBH_4$ in the presence of AcOH as an acid catalyst allowed for a decrease in the amount of reducing agent to 0.41 equivalents. Notably, both the halogenated derivative and AcOH were added gradually, which effectively minimized hydrogen evolution. The reaction was conducted under reflux, achieving very high yields (80–100%), while eliminating the need for strong reducing agents, which are unfavorable on a production scale. Unfortunately, this methodology required the use of aliphatic chlorinated hydrocarbon solvents, which pose an environmental accumulation risk. In addition, this patent did not cover biological activity assays.

Ramachary and co-workers[44] have developed an elegant and high-yielding multi-catalytic approach that efficiently constructs a series of nefopam analogues **29** and **30** through sequential one-pot cascade operations (Scheme 13). At the heart of this methodology is the combination of organocatalytic enamine amination/iso-aromatization, *O*- and *N*-allylation (EA/IA/A) reactions, and the subsequent ruthenium-catalyzed ring-closing metathesis (RCM). This strategy, starting from the reaction between Hagemann's esters (**25**) and nitrosobenzene (Ph–N=O, **26**), bypasses the traditional need for intermediate purification steps, thereby improving overall yield at relatively high level. Notably, the use of the Grubbs 1st (**G1**) or 2nd generation (**G2**) catalysts enabled successful RCM transformations even on free amines, a significant advancement considering the usual incompatibility of free amines with olefin metathesis catalysts.

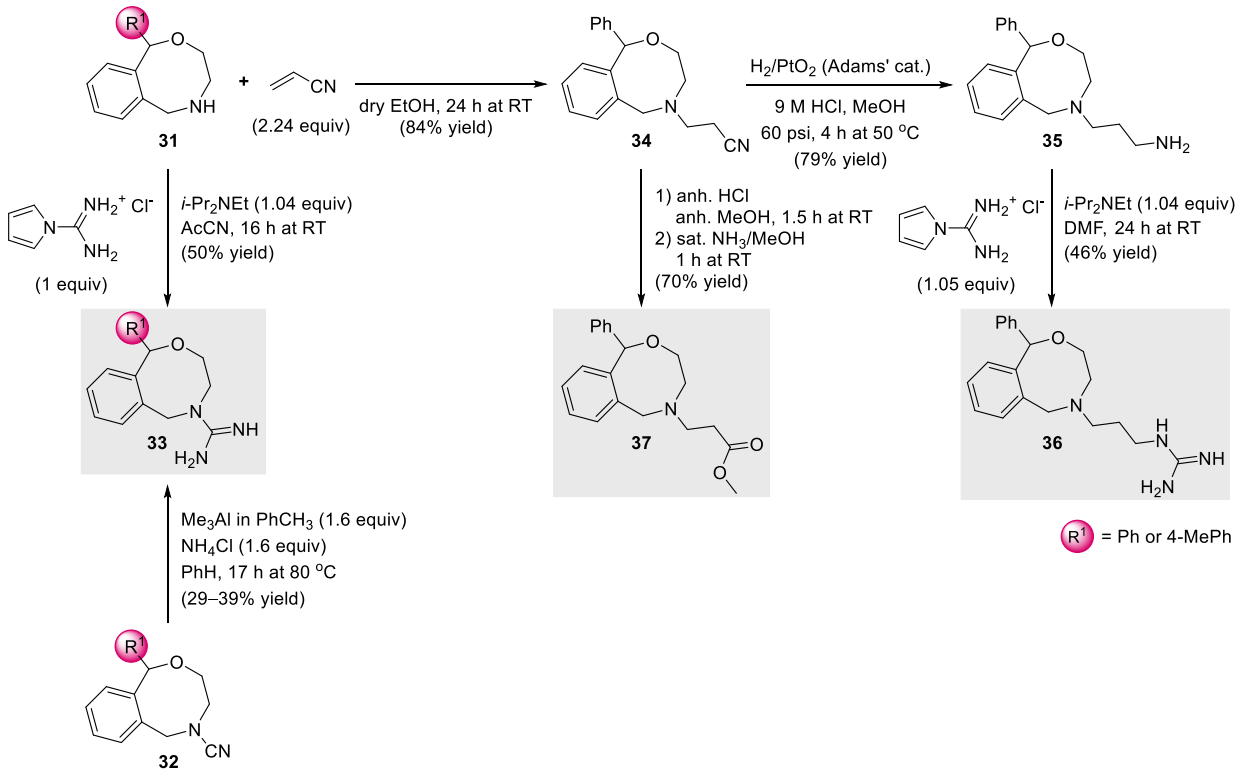


Scheme 13. Synthesis of nefopam analogues **29** using sequential cascade EA/IA/A/RCM reactions.

The developed approach was further expanded to include sequential combination of Ru- and Pd-catalysis in one-pot for the synthesis of exemplary 3,4,5,6-tetrahydro-2*H*-benzo[*b*][1,4]oxazocine (**30**). In general, such multi-step, one-pot strategy aligns with green chemistry principles, minimizing waste and resource consumption while delivering structurally complex molecules with impressive yields for **27**–**29**, often reaching 70–90%. Despite these advances, certain limitations remain, such as the use of highly toxic nitrosobenzene (**26**), the non-recyclability of ruthenium catalysts in homogeneous solutions, and the requirement for relatively high catalyst loading (10 mol%) in the case of costly palladium on activated carbon (Pd/C). Addressing these limitations could further enhance scalability and sustainability, opening avenues for broader application in medicinal chemistry and drug discovery.

The last example, reported by Rosamilia et al.,[45] encompasses the synthesis and pharmacological evaluation of novel nefopam analogues possessing *N*-alkyl-guanidine **33** and **36** or *N*-alkyl-ester **37** moieties. The desired products were synthesized from derivatives of nor-nefopam (**31**) or *N*-cyano-nor-nefopam (**32**) as staring materials according to multi-step synthetic procedure depicted in Scheme 14.

This work provides valuable insights into how structural modifications can modulate analgesic activity of parent API **1**, while influencing pharmacokinetic properties such as central nervous system (CNS) penetration. The study demonstrated that the introduction of guanidine substituents, which are protonated at physiological pH, successfully increased hydrophilicity and prevented blood–brain barrier permeation, potentially shifting analgesic effects toward peripheral sites. However, the synthesized guanidine derivatives **33** and **36** exhibited reduced potency in noradrenaline uptake inhibition compared to the parent nefopam (**1**), likely due to decreased affinity at the transporter site. Interestingly, the ester derivative **37** emerged as the most promising candidate for further investigation, as it retained potent noradrenaline uptake inhibition without displaying α_1-adrenoceptor antagonist activity, a side effect noted in the case of nefopam (**1**) and its *N*-alkyl-guanidine analogues **33** and **36**. The pharmacological results suggest that selective structural tuning can balance peripheral versus central activity and improve therapeutic profiles, although the authors caution that these preliminary assays warrant further validation through specific binding studies and expanded *in vivo* testing.



Scheme 14. Synthesis of nefopam analogues exhibiting promising noradrenaline reuptake inhibitory activity.

From a synthetic perspective, the work highlights both the utility and the challenges of modifying the nefopam (**1**) scaffold on its nitrogen atom. While the guanidine and amidine routes offer conceptually appealing strategies, they face practical limitations in yields and synthetic complexity, especially under large-scale or industrial conditions. Moreover, the use of certain reagents, such as trimethylaluminium (Me_3Al), poses safety and environmental concerns that must be addressed if these methodologies are to advance toward practical pharmaceutical applications.

Overall, these studies underscore the importance of combining synthetic ingenuity with rigorous pharmacological assessment to optimize nefopam analogues as potential non-opioid analgesics. Future work should focus on expanding the chemical space explored, integrating green chemistry principles, and validating the most promising candidates in clinically relevant models.

3. Conclusions

In conclusion, the synthetic methodologies developed to access nefopam and its structurally related analogues reflect a remarkable evolution in modern organic synthesis, showcasing advances in strategic synthesis planning, catalytic innovation, and process intensification. While early synthetic routes laid the groundwork for the preparation of this pharmaceutically valuable scaffold, they are frequently encumbered by significant drawbacks, including the use of hazardous or environmentally burdensome reagents (such as lithium aluminum hydride, cyanogen bromide, or volatile and genotoxic chlorinated hydrocarbons), labor-intensive multistep sequences, and modest overall yields.

More recently, innovative approaches incorporating telescoped operations, one-pot cascade reactions, and multi-catalytic systems have provided powerful tools for constructing the complex benzoxazocine core of

nefopam and its structural analogues. These developments align with the principles of green chemistry, offering enhanced atom economy, reduced waste generation, and improved operational efficiency. Particularly noteworthy is the recent multikilogram-scale protocol elaborated by *Micro Labs Ltd.* that have succeeded in minimizing the need for isolation and purification steps as well as hazardous reagents by employing more benign reducing agents such as sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH), and achieving excellent overall yields under scalable, industry-relevant conditions.

Nonetheless, several critical challenges persist in many of the other recent approaches. The reliance on costly, non-recyclable homogeneous catalysts, the necessity for relatively high catalyst loadings, and the dependence on toxic and hazardous reagents as well as volatile and genotoxic organic solvents continue to pose barriers to widespread industrial implementation. Moreover, the impurity profiles associated with certain telescoped processes demand careful control to meet the stringent requirements of pharmaceutical manufacturing. Addressing these issues will be essential to further optimize the synthesis of nefopam and its analogues, ensuring not only economic viability but also environmental sustainability.

We anticipate that future research efforts will increasingly focus on the development of catalytic systems that combine high selectivity with recyclability, as well as on the implementation of greener, solvent-and steps-minimized protocols. Advances in biocatalysis, flow chemistry, and photo- or electrochemical transformations may also play pivotal roles in shaping the next generation of synthetic routes toward nefopam. Ultimately, the continued refinement of synthetic methodologies for nefopam promises to advance both the industrial manufacture and medicinal exploration of this versatile class of non-opioid (non-narcotic) analgesics, supporting their broader integration into modern pain management strategies.

4. Acknowledgements

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5. References

1. Bader, N. A.; Al-Ahmad, M. M.; Naeem, W. A.; Amer, M. G. *J. Appl. Pharm. Sci.* **2025**, *15*, 024–039. https://doi.org/10.7324/japs.2025.203223
2. Heel, R. C.; Brogden, R. N.; Pakes, G. E.; Speight, T. M.; Avery, G. S. *Drugs* **1980**, *19*, 249–267. https://doi.org/10.2165/00003495-198019040-00001
3. Girard, P.; Le Guern, M.-E.; Gillardin, J.-M.; Hublot, B. (Biocodex SAS), Synergestic combination of analgesic compounds, US Pat. 8,598,221 B2, **2013**.
4. Schulz, T.; Lalande, L.; Aubrun, F.; Dziadzko, M. *Pan African Med. J.* **2022**, *41*, 213. https://doi.org/10.11604/pamj.2022.41.213.33365
5. Kim, K. H.; Abdi, S. *Korean J. Pain* **2014,** *27*, 103–111. https://doi.org/10.3344/kjp.2014.27.2.103
6. Sharma, N.; Arora, S.; Madan, J. *Artif. Cells, Nanomed. Biotechnol.* **2018**, *46*, 138–146. https://doi.org/10.1080/21691401.2017.1301459

7. Moon, J. Y.; Choi, S. S.; Lee, S. Y.; Lee, M. K.; Kim, J. E.; Lee, J. E.; Lee, S. H. *Korean J. Pain* **2016**, *29*, 110–118. https://doi.org/10.3344/kjp.2016.29.2.110
8. Tigerstedt, I.; Tammisto, T.; Leander, P. *Acta Anaesth. Scand.* **1979**, *23*, 555–560. https://doi.org/10.1111/j.1399-6576.1979.tb01486.x
9. Girard, P.; Chauvin, M.; Verleye, M. *Clin. Exp. Pharmacol. Physiol.* **2016**, *43*, 3–12. https://doi.org/10.1111/1440-1681.12506
10. Klotz, A. L. *Curr. Ther. Res. Clin. Exp.* **1974**, *16*, 602–608.
11. Mather, G. G.; Labroo, R.; Le Guern, M.-E.; Lepage, F.; Gillardin, J.-M.; Levy, R. H. *Chirality* **2000**, *12*, 153–159. https://doi.org/10.1002/(sici)1520-636x(2000)12:3<153::aid-chir9>3.0.co;2-v
12. Isaksson, R.; Sandstrom, J.; Eliaz, M.; Israely, Z.; Agranat, I. *J. Pharm. Pharmacol.* **1988**, *40*, 48–50. https://doi.org/10.1111/j.2042-7158.1988.tb05148.x
13. Buritova, J.; Besson, J. M. *Eur. J. Pharmacol.* **2002**, *441*, 67–74. https://doi.org/10.1016/s0014-2999(02)01418-8
14. Yang, F.; Du, Y.; Chen, B.; Fan, Q.; Xu, G. *Chromatographia* **2010**, *72*, 489–493. https://doi.org/10.1365/s10337-010-1670-2
15. Hunskaar, S.; Fasmer, O. B.; Broch, O. J.; Hole, K. *Eur. J. Pharmacol.* **1987**, *138*, 77–82. https://doi.org/10.1016/0014-2999(87)90339-6
16. Esposito, E.; Romandini, S.; Merlo-Pich, E.; Mennini, T.; Samanin, R. *Eur. J. Pharmacol.* **1986**, *128*, 157–164. https://doi.org/10.1016/0014-2999(86)90762-4
17. Fasmer, O. B.; Berge, O. G.; Jorgensen, H. A.; Hole, K. *J. Pharm. Pharmacol.* **1987**, *39*, 508–511. https://doi.org/10.1111/j.2042-7158.1987.tb03167.x
18. Rosland, J. H.; Hole, K. *J. Pharm. Pharmacol.* **1990,** *42*, 437–438. https://doi.org/10.1111/j.2042-7158.1990.tb06587.x
19. Biella, G. E.; Groppetti, A.; Novelli, A.; Fernandez-Sanchez, M. T.; Manfredi, B.; Sotgiu, M. L. *J. Neurotrauma* **2003**, *20*, 593–601. https://doi.org/10.1089/089771503767168519
20. Rexall Drug and Chemical Company, Phenylbenz (*f*)-2,5-oxazocine derivatives and homologues and pharmaceutical compositions, GB Pat. 1,148,717, **1969**.
21. Bassett, J. R.; Cairncross, K. D.; Hacket, N. B.; Story, M. *Br. J. Pharmacol.* **1969**, *37*, 69–78. https://doi.org/10.1111/j.1476-5381.1969.tb09523.x
22. Tobin, W. E.; Gold, R. H. *J. Clin. Pharmacol. New Drugs* **1972**, *12*, 230–238. https://doi.org/10.1002/j.1552-4604.1972.tb00167.x
23. Koe, B. K. *J. Pharmacol. Exp. Ther.* **1976**, *199*, 649–661. https://doi.org/10.1016/S0022-3565(25)30726-3
24. https://www.iqvia.com/solutions/real-world-evidence/real-world-data-and-insights?utm_source=google&utm_medium=cpc&utm_campaign=2025_GAdsAIMLCxUS_COMSOL_ST&adgroup=&utm_content=&utm_term={matchtype}_iqvia%20real%20world%20data&network=g&device=c&placement=&gad_source=1&gad_campaignid=22196945927&gbraid=0AAAACju_6tLCQcSn--gPfduN_o23gmAz&gclid=EAIaIQobChMI-PDL6snJjQMVw6WDBx3I9yZSEAAYASAAEgItaPD_BwE
25. Watson, P. G. Riker Laboratories Inc., Process for the preparation of 2-[*N*-(2-hydroxyethyl)-*N*-lower alkylaminomethyl]benzhydrols, US Pat. 4,208,349, **1980**.

26. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ich-guideline-q3c-r8-impurities-guideline-residual-solvents-step-5_en.pdf?utm_source=chatgpt.com
27. https://www.who.int/docs/default-source/wash-documents/wash-chemicals/1-1-dichloroethane-chemical-fact-sheet.pdf?utm_source=chatgpt.com
28. Bremner, J. B.; Thirasasana, N. *Aust. J. Chem.* **1982**, *35*, 2307–2314. https://doi.org/10.1071/ch9822307
29. Aeberli, P.; Houlihan, W. J. *J. Org. Chem.* **1969**, *34*, 165–170. https://doi.org/10.1021/Jo00838a036
30. Bodireddy, M. R.; Krishnaiah, K.; Babu, P. K.; Bitra, C.; Gajula, M. R.; Kumar, P. *Org. Proc. Res. Dev.* **2017**, *21*, 1745–1751. https://doi.org/10.1021/acs.oprd.7b00228
31. Klohs, M. W.; Draper, M. D.; Petracek, F. J. Riker Laboratories Inc., 5-loweralkyl-1-phenyl-1,3,4,6-tetrahydro-5H-benz[f]-2,5-oxazocines and 4-ones, US Pat. 3,830,803, **1974**.
32. Zhang, C.; Liu, D.; Wu, J.; Zhang, J. Kangmei Pharmaceuticals Co Ltd., A kind of preparation method of nefopam hydrochloride, Chinese Pat. CN 107556263A, **2018**.
33. Srinivasachary, K.; Tiwari, S.; Somannavar, Y. S.; Ramadevi, B. *Int. J. Pharm. Sci. Res.* **2019,** *10*, 4613–4635. https://doi.org/10.13040/IJPSR.0975-8232.10(10).4613-35
34. Baxter, A. D. (Sosei R & D Ltd.), Benzoxazocines and their therapeutic use, PCT Int. Appl. WO 2006/095187 A1, **2006**.
35. Baxter, A. D.; Walmsley, A.; Lasterra, E. (Sosei R&D Ltd.), Benzoxazocine derivatives and their use as analgesics, U.S. Pat. Appl. Publ. US 2006/019940 A1, **2006**.
36. Bernstein, P. (AstraZeneca AB), Cyclized benzamide neurokinin antagonists for use in therapy, PCT Int. Appl. WO 2002/026724, **2002**.
37. Tanaka, S.; Hashimoto, K. (Eisai K K, Tokio), 6-substituierte 6,7-dihydro-5*H*-dibenzo[*b*,*g*][1,5]oxazocine und thiazocine und verfahren zu deren herstellung, *Ger. Offen.* DE 2044508 A1, **1971**.
38. Seto, S.; Tanioka, A.; Ikeda, M.; Izawa, S. *Bioorg. Med. Chem.* **2005**, *13*, 5717–5732. https://doi.org/10.1016/j.bmc.2005.06.015
39. Seto, S.; Tanioka, A.; Ikeda, M.; Izawa, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1479–1484. https://doi.org/10.1016/j.bmcl.2004.12.091
40. Seto, S.; Tanioka, A.; Ikeda, M.; Izawa, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1485–1488. https://doi.org/10.1016/j.bmcl.2004.12.089
41. Ohnmacht, C. J.; Albert, J. S.; Bernstein, P. R.; Rumsey, W. L.; Masek, B. B.; Dembofsky, B. T.; Koether, G. M.; Andisik, D. W.; Aharony, D. *Bioorg. Med. Chem.* **2004**, *12*, 2653–2669. https://doi.org/10.1016/j.bmc.2004.03.015
42. Stillings, M. R.; Freeman, S.; Myers, P. L.; Readhead, M. J.; Welbourn, A. P.; Rance, M. J.; Atkinson, D. C. *J. Med. Chem.* **1985**, 28, 225–233. https://doi.org/10.1021/jm00380a013
43. P. G. Watson (Riker Laboratories Inc.), Process for the preparation of 2-(n-(2-hydroxyyethyl)-n-lower alkylaminomethyl) benzhydrols, British Pat. 1,586,578, **1981**.
44. Ramachary, D. B.; Narayana, V. V.; Prasad, M. S.; Ramakumar, K. *Org. Biomol. Chem.* **2009**, *7*, 3372–3378. https://doi.org/10.1039/b910397j

45. Rosamilia, A. E.; Mayes, P. A.; Papadopoulos, R.; Campi, E. M.; Jackson, W. R.; Rash, L.; Jarrott, B. *Aust. J. Chem.* **2002**, *55*, 577–585. https://doi.org/10.1071/ch02097

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