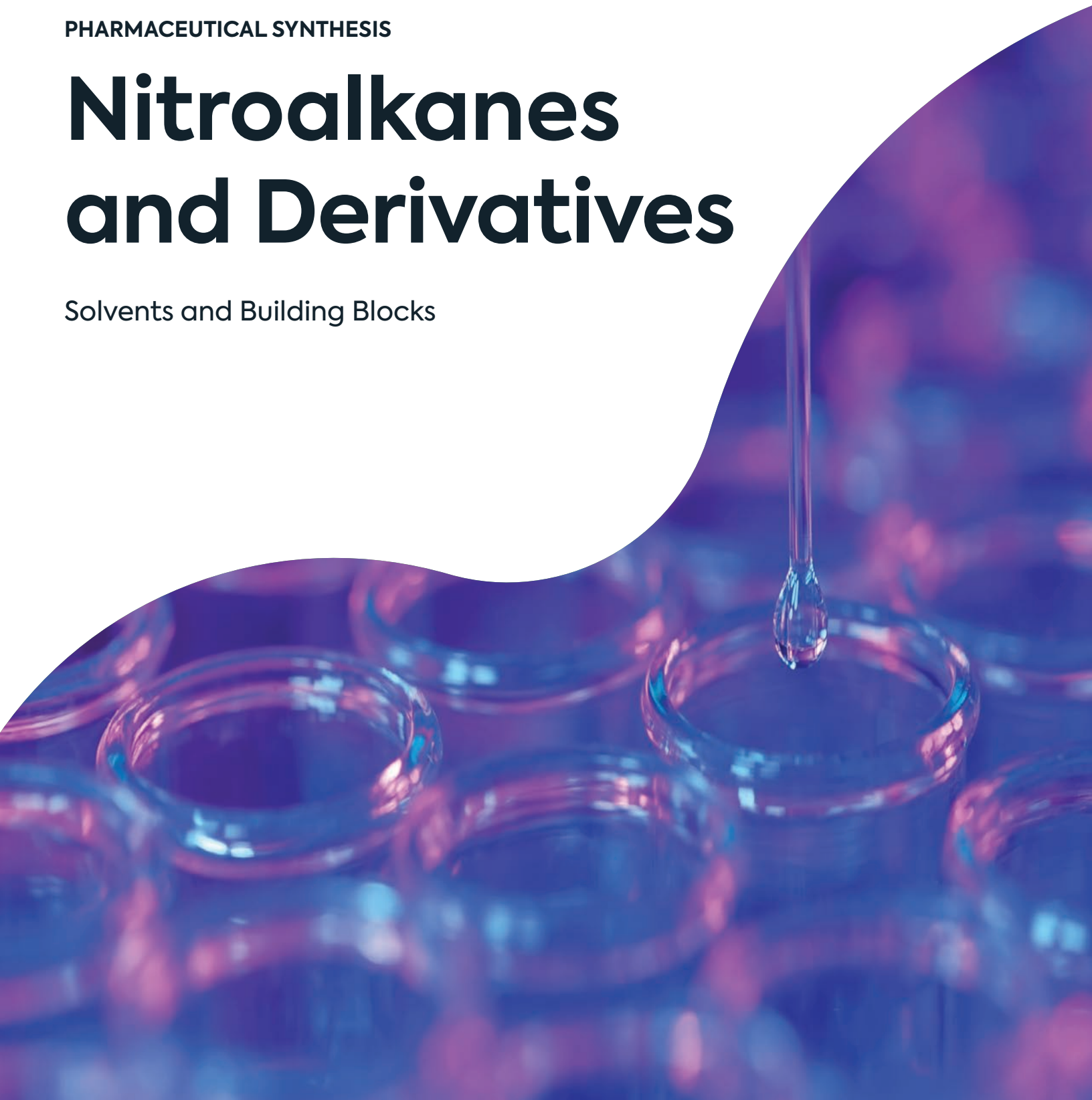


PHARMACEUTICAL SYNTHESIS

Nitroalkanes and Derivatives

Solvents and Building Blocks



Efficiently Create Complex Molecules. Reduce Reaction Steps. Optimize Synthesis Costs.

Unique and Versatile Chemistries

Advancion is a leading global manufacturer of novel nitroalkane chemistries that have been utilized for more than 50 years in the synthesis and formulation of small molecule pharmaceuticals.

Today, Advancion is the world's only fully integrated manufacturer of basic nitroalkanes – nitromethane, nitroethane, 1-nitropropane and 2-nitropropane – as well as numerous nitroalkane derivatives. These chemistries offer unique utility and value for small molecule synthesis by providing reactivity to efficiently create complex molecules, reduce reaction steps and optimize synthesis costs.

Nitroalkanes and nitroalkane derivatives manufactured by Advancion have been used safely and effectively in many commercial applications, including:

AS SYNTHESIS BUILDING BLOCKS

IN API SALT FORMATION

AS REACTION SOLVENTS



KEY BENEFITS AS BUILDING BLOCKS

- Highly versatile reagents
- Efficient carbon skeleton synthesis
- High reactivity / mild reaction conditions
- Cost-effective synthetic feedstocks
- Provide unique capabilities

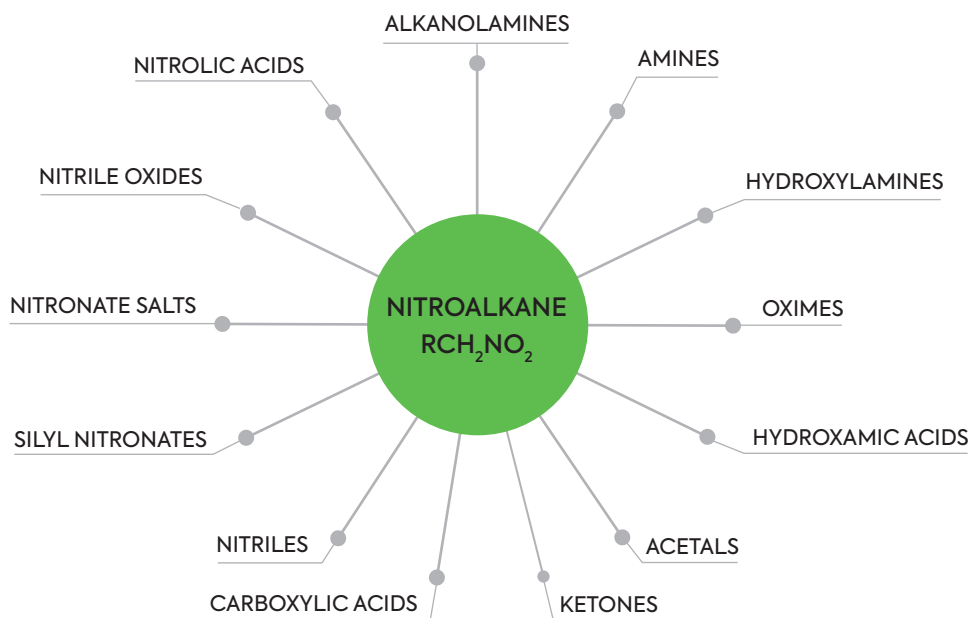
Discover the Potential

Over decades, numerous, highly successful pharmaceuticals have been based on nitroalkane chemistry, such as ranitidine, methyl DOPA, ethambutol, and pamabrom. However, the full potential of this novel class of compounds is often overlooked by synthetic chemists during drug discovery and development.

Basic Nitroalkane Building Blocks

The effectiveness of nitroalkanes lies in their ability to provide alternative synthetic routes to existing compounds, as well as highly efficient routes to new compounds. The exceptional versatility and high reactivity of nitroalkanes provide a means to conduct synthetic transformations under mild conditions. Nitroalkanes can be used as effective precursors to the creation of highly substituted alkanes and alkenes, amines, carboxylic acids, aldehydes, ketones, complex heterocyclic structures and more.

Nitroalkane chemistry provides the reactivity to efficiently create complex molecules often by the most direct route. Nitroalkanes produced by Advancion undergo efficient C-C bond forming chemistry using the Henry, Michael and Mannich reactions. All others represented in the diagram are nitroalkane functional group transformations.





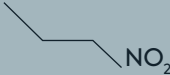

Amino Alcohol Building Blocks

Advancion also derivatizes basic nitroalkanes into highly versatile primary aminohydroxy compounds (amino alcohols), such as AMP™, AMPD™ and TRIS AMINO™. These compounds are used in the synthesis of active pharmaceutical ingredients and salts, such as Fosfomicin, Ketorolac, Lodoxamide, and Pamabrom. Advancion amino alcohols have both amine and alcohol functionality and provide the physical features and chemical reactivity of both classes of compounds. Together with an extensive research library of experimental nitroalkane derivatives, Advancion has the synthesis and applications expertise to help customers explore the potential of nitroalkane chemistry to solve their problems.

Nitroalkane Chemistries

In addition to their functionality as synthesis building blocks, Advancion's nitroalkane chemistries are commonly used as solvents for Friedel-Crafts reactions. The Lewis acids form 1:1 complexes with the nitroalkanes providing excellent solvency, and moderating their reactivity and minimizing side reactions or rearrangements. As crystallization solvents, nitroalkanes have shown the ability to drive polymorph selectivity. The combination of high polarity and low water solubility can also provide a number of advantages in solvent-extraction systems.

Basic Nitroalkanes as Building Blocks and Solvents

PROPERTIES				
CHEMICAL NAME	CHEMICAL STRUCTURE	cGMP	COO	CAS#
Nitromethane		No	USA	75-52-5
Nitroethane		No	USA	79-24-3
1-Nitropropane		No	USA	108-03-2
2-Nitropropane		No	USA	79-46-9

*The building block and solvent chemistries represented in the table have the potential to be used as intermediates in the synthesis of pharmacologically active materials.

CUSTOMER CASE STUDY



Advancion developed a nitroalkane-based synthesis route that **cut raw material costs by 50%**, enabling our customer to **expand their commercial business by 300%**. Additionally, Advancion worked closely with this customer to further optimize their synthesis process by improving production and reducing waste.



KEY BENEFITS AS SOLVENTS

- High solubility of Lewis acids
- Stable 1:1 complex with AlCl_3
- PELs favorable compared to many alternatives
- Unique combination of high polarity / low water solubility

CHEMICAL FORMULA	MW	EXAMPLES OF DOCUMENTED USE*	APPLICATIONS	
			SOLVENT	BUILDING BLOCK
CH_3NO_2	61	Ranitidine ¹ , Ropinirole ²	Yes	Yes
$\text{C}_2\text{H}_5\text{NO}_2$	75.1	Methyldopa ³ , Norephedrine ⁴	Yes	Yes
$\text{C}_3\text{H}_7\text{NO}_2$	89.1	Ethambutol ⁵	Yes	Yes
$\text{C}_3\text{H}_7\text{NO}_2$	89.1	Phentermine ⁶ , Bucindolol ⁷	No	Yes

¹Patent DE 3521456 A1

²Patent US 7230118B2, WO 2011072704 A1

³Patent US 2,868,818, 3,158,648

⁴Patent US 5962737 A

⁵Patent US 3847991 A

⁶Patent US 9125948 B2

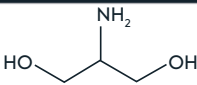
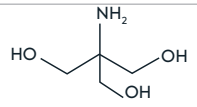
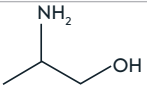
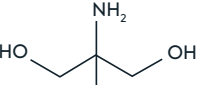
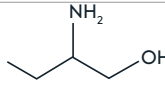
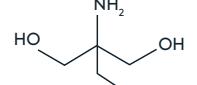
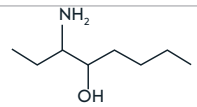
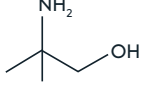
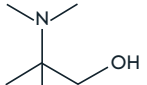
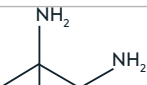
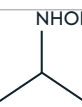
⁷Patent US 4,234,595, DE 3,421,252



Beyond Basic Nitroalkanes

Advancion also manufactures nitroalkane derivatives and amino alcohols that can be used as intermediates in the synthesis of pharmacologically active materials to impart critical performance attributes, such as activity and solubility.

Amino Alcohols As Building Blocks

CHEMICAL NAME	CHEMICAL STRUCTURE	PROPERTIES	
		cGMP	COO
2-amino-1,3-propanediol		Yes	Germany
2-amino-2-hydroxymethyl-1,3-propanediol		Yes	USA / Germany
dl-2-amino-1-propanol		No	Germany
2-amino-2-methyl-1,3-propanediol		No	USA / Germany
d,l-2-amino-1-butanol		No	Germany
2-amino-2-ethyl-1,3-propanediol		No	USA / Germany
3-amino-4-octanol		No	Germany
2-amino-2-methyl-1-propanol		No	USA / Germany
2-(dimethylamino)-2-methyl-1-propanol		No	Germany
2-amino-2-methyl-propylamine		No	France
N-isopropylhydroxylamine		No	USA

*The chemistries represented in the table have the potential to be used as intermediates in the synthesis of pharmacologically active materials.



KEY BENEFITS AS BUILDING BLOCKS

- Enables ability to systematically adjust drug hydrophilicity
- Proven, safe use in commercial drug products
- High-purity reagents with fully traceable supply chain

APPLICATIONS

CAS#	CHEMICAL FORMULA	MW	EXAMPLES OF DOCUMENTED USE*
534-03-2	C ₃ H ₉ NO ₂	91.1	Iopamidol ¹ , Voglibose ²
77-86-1	C ₄ H ₁₁ NO ₃	121.1	Ketorolac ³ , Fosfomycin ⁴ , Lodoxamide ⁵ , Dinoprost ⁶ , Fingolimod ⁷
6168-72-5	C ₃ H ₉ NO	75.1	Ofloxacin ⁸
115-69-5	C ₄ H ₁₁ NO ₂	105.1	Crisnatol ⁹
96-20-8	C ₄ H ₁₁ NO	89.1	Ethambutol ¹⁰ , Methylethergonovine ¹¹
115-70-8	C ₅ H ₁₃ NO ₂	119.2	Fingolimod ¹²
1001354-72-8	C ₈ H ₁₉ NO	145.2	
124-68-5	C ₄ H ₁₁ NO	89.1	Pamabrom ¹³ , Ambuphylline ¹⁴
7005-47-2	C ₆ H ₁₅ NO	117.2	
811-93-8	C ₄ H ₁₂ N ₂	88.1	Anagliptin ¹⁵ , Arterolane ¹⁶
5080-22-8	C ₃ H ₉ NO	75.1	

¹Patent WO 2018/104228

²Patent WO 2003080561 A1; KR 714197 B1

³Patent US 6191285 B1

⁴Patent CN 101928300 A, CN 1060470 A

⁵Patent WO 2008011836 A2

⁶Patent US 2005/0239742, Anim Reprod Sci. 2009 Jul; 113(1-4):71-81

⁷Synthesis (2006), (5), 753-755, Tetrahedron Letters (2011), 52(43), 5672-5675

⁸Patent US 4,777,253

⁹Patent US 4,719,046

¹⁰Huagong (2004), 21(12), 943-945, 949, Youji Huaxue, 11(3), 310-13; 1991, Ger. Offen., 3517108, 13 Nov 1986, Faming Zhuanli Shenqing, 107235847, 10 Oct 2017

¹¹Chemicke Listy pro Vedu a Prumysl (1957), 51, 123-6

¹²Patent CN 106397224

¹³Patent US 2711411

¹⁴Patent US 2,404,319; Journal of Thermal Analysis and Calorimetry (2016), 123(2), 1031-1036

¹⁵Patent WO 2015/150887

¹⁶Patent US 8,754,243



From Discovery to Launch

Uncovering innovative solutions is only the beginning. Our commitment to customers is supported by state-of-the-art analytical laboratories, world-class manufacturing facilities, and deep synthesis and applications expertise that help our customers explore the potential of nitroalkane chemistry.

Tightly Controlled Manufacturing Ensures Quality and 100% Traceability

The proprietary manufacturing processes used by Advancion to produce nitroalkanes and their derivatives not only reduces the use of highly toxic compounds, but it also avoids the potential incorporation of toxic impurities associated with raw materials produced by other manufacturers. This unique process allows Advancion to control the manufacture of all key intermediates by producing them in-house at our facilities in the U.S. and Europe, providing clear line of sight back to base materials.

Product Stewardship

Through our investments in application and new product development, we have a deep understanding of where our chemistries are (and can potentially be) used to actively address global trends in Life Sciences, Beauty and Personal Care, and other essential industries to help make our lives healthier, and more sustainable and comfortable. To help ensure that Advancion products are not used in ways for which they are not intended, Advancion personnel will assist customers in dealing with environmental and product safety considerations. Before handling any of the products, obtain available product safety information including the Safety Data Sheet(s) and take the necessary steps to ensure safety of use. For assistance, product Safety Data Sheets, or other information, please visit advancionsciences.com or contact us at info@advancionsciences.com.

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