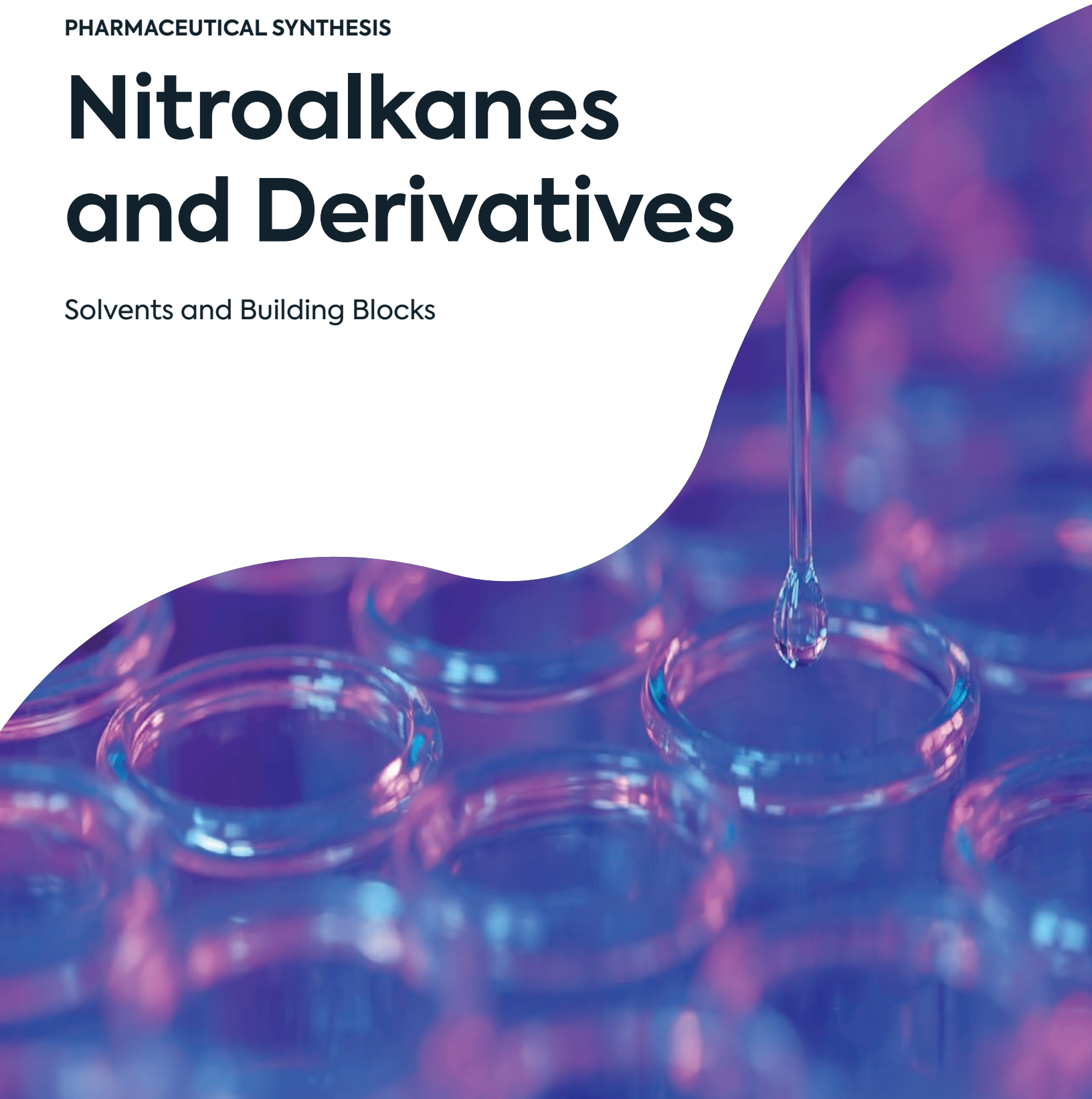
Advancion

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

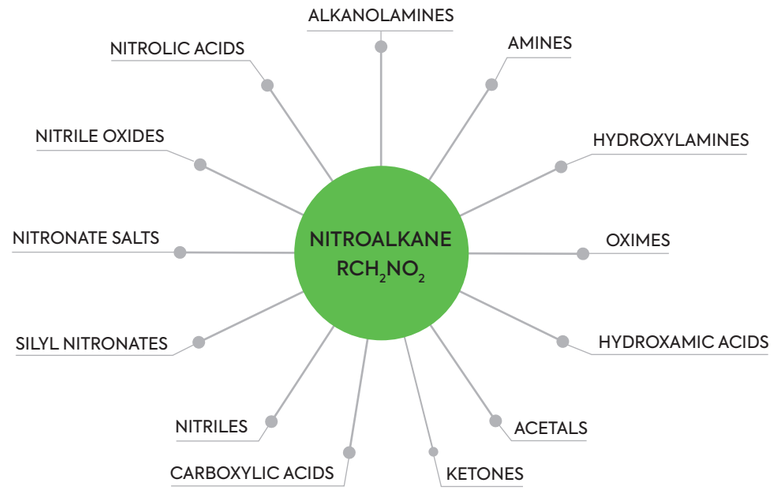
Discover the Potential

Over decades, numerous, highly successful pharmaceuticals have been based on nitroalkane chemistry, such as ofloxacin, 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 Fosfomycin, 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.

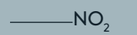
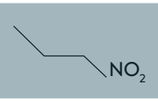
Nitroalkane Chemistries

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.

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

Basic Nitroalkanes as Building Blocks and Solvents

		PROPERTIES						APPLICATIONS	
CHEMICAL NAME	CHEMICAL STRUCTURE	cGMP	COO	CAS#	CHEMICAL FORMULA	MW	EXAMPLES OF DOCUMENTED USE*	SOLVENT	BUILDING BLOCK
Nitromethane		No	USA	75-52-5	CH3NO2	61	Ropinirole[1]	Yes	Yes
Nitroethane		No	USA	79-24-3	C2H5NO2	75.1	Methyldopa[2], Norephedrine[3]	Yes	Yes
1-Nitropropane		No	USA	108-03-2	C3H7NO2	89.1	Ethambutol[4]	Yes	Yes
2-Nitropropane		No	USA	79-46-9	C3H7NO2	89.1	Phentermine[5], Bucindolol[6]	No	Yes

*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.

[1]Patent US 7230118B2, WO 2011072704 A1
[2]Patent US 2,868,818, 3,158,648
[3]Patent US 5962737 A
[4]Patent US 3847991 A
[5]Patent US 9125948 B2
[6]Patent US 4,234,595, DE 3,421,252

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.

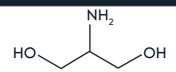
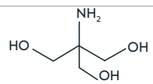
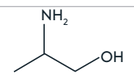
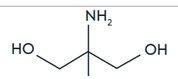
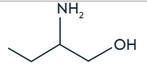
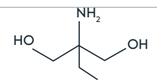
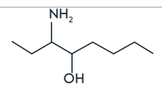
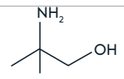
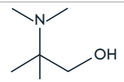
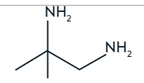
Beyond Basic Nitroalkanes

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.

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

Amino Alcohols As Building Blocks

		PROPERTIES					APPLICATIONS
CHEMICAL NAME	CHEMICAL STRUCTURE	cGMP	COO	CAS#	CHEMICAL FORMULA	MW	EXAMPLES OF DOCUMENTED USE*
2-amino-1,3-propanediol		Yes	Germany	534-03-2	C3H9NO2	91.1	Iopamidol[1], Voglibose[2]
2-amino-2-hydroxymethyl-1,3-propanediol		Yes	USA / Germany	77-86-1	C4H11NO3	121.1	Ketorolac[3], Fosfomycin[4], Lodoxamide[5], Dinoprost[6], Fingolimod[7]
dl-2-amino-1-propanol		No	Germany	6168-72-5	C3H9NO	75.1	Ofloxacin[8]
2-amino-2-methyl-1,3-propanediol		No	USA / Germany	115-69-5	C4H11NO2	105.1	Crisnatol[9]
d,l-2-amino-1-butanol		No	Germany	96-20-8	C4H11NO	89.1	Ethambutol[10], Methylergonovine[11]
2-amino-2-ethyl-1,3-propanediol		No	USA / Germany	115-70-8	C5H13NO2	119.2	Fingolimod[12]
3-amino-4-octanol		No	Germany	1001354-72-8	C8H19NO	145.2	
2-amino-2-methyl-1-propanol		No	USA / Germany	124-68-5	C4H11NO	89.1	Pamabrom[13], Ambuphylline[14]
2-(dimethylamino)-2-methyl-1-propanol		No	Germany	7005-47-2	C6H15NO	117.2	
2-amino-2-methyl-propylamine		No	France	811-93-8	C4H12N2	88.1	Anagliptin[15], Arterolane[16]
N-isopropylhydroxylamine		No	USA	5080-22-8	C3H9NO	75.1	

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

[1]Patent WO 2018/104228
[2]Patent WO 2003080561 A1; KR 714197 B1
[3]Patent US 6191285 B1
[4]Patent CN 101928300 A, CN 1060470 A
[5]Patent WO 2008011836 A2
[6]Patent US 2005/0239742, Anim Reprod Sci. 2009 Jul; 113(1-4):71-81
[7]Synthesis (2006), (5), 753-755, Tetrahedron Letters (2011), 52(43), 5672-5675
[8]Patent US 4,777,253
[9]Patent US 4,719,046
[10]Huagong (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
[11]Chemicke Listy pro Vedu a Prumysl (1957), 51, 123-6
[12]Patent CN 106397224
[13]Patent US 2711411
[14]Patent US 2,404,319; Journal of Thermal Analysis and Calorimetry (2016), 123(2), 1031-1036
[15]Patent WO 2015/150887
[16]Patent 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.