NITROALKANES AND DERIVATIVES
As solvents and building blocks for pharmaceutical synthesis
UNIQUE AND VERSATILE CHEMISTRIES

ANGUS 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, ANGUS 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 ANGUS 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 ANGUS 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

ANGUS 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. ANGUS 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, ANGUS 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, ANGUS’ 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 crystalization 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.

CUSTOMER CASE STUDY

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

### BASIC NITROALKANES AS BUILDING BLOCKS AND SOLVENTS

<table>
<thead>
<tr>
<th>CHEMICAL NAME</th>
<th>CHEMICAL STRUCTURE</th>
<th>cGMP</th>
<th>COO</th>
<th>CAS#</th>
<th>CHEMICAL FORMULA</th>
<th>MW</th>
<th>EXAMPLES OF DOCUMENTED USE*</th>
<th>SOLVENT</th>
<th>BUILDING BLOCK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitromethane</td>
<td>NO₂</td>
<td>No</td>
<td>USA</td>
<td>75-52-5</td>
<td>CH₃NO₂</td>
<td>61</td>
<td>Ranitidine¹, Ropinirole²</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Nitroethane</td>
<td>NO₂</td>
<td>No</td>
<td>USA</td>
<td>79-24-3</td>
<td>C₂H₅NO₂</td>
<td>75.1</td>
<td>Methyl dopa³, Norephedrine⁴</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>1-Nitropropane</td>
<td>NO₂</td>
<td>No</td>
<td>USA</td>
<td>108-03-2</td>
<td>C₃H₇NO₂</td>
<td>89.1</td>
<td>Ethambutol⁵</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>2-Nitropropane</td>
<td>NO₂</td>
<td>No</td>
<td>USA</td>
<td>79-46-9</td>
<td>C₃H₇NO₂</td>
<td>89.1</td>
<td>Phentermine³, Bucindolol⁷</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*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.

- Patent DE 1024143 A1
- Patent US 2,868,818, 3,158,648
- Patent US 5962737 A
- Patent US 8,233,994 B2
- Patent US 8,233,994 B2
- Patent US 6,102,192
- Patent US 5,479,743 A
- Patent US 5,479,743 A

KEY BENEFITS AS SOLVENTS

- High solubility of Lewis acids
- Stable 1:1 complex with AlCl₃
- PEL’s favorable compared to many alternatives
- Unique combination of high polarity / low water solubility
**BEYOND BASIC NITROALKANES**

ANGUS 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**

<table>
<thead>
<tr>
<th>CHEMICAL NAME</th>
<th>CHEMICAL STRUCTURE</th>
<th>cGMP</th>
<th>COO</th>
<th>CAS#</th>
<th>CHEMICAL FORMULA</th>
<th>MW</th>
<th>EXAMPLES OF DOCUMENTED USE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-amino-1,3-propanediol</td>
<td><img src="https://example.com/structure1.png" alt="Chemical Structure" /></td>
<td>Yes</td>
<td>Germany</td>
<td>534-03-2</td>
<td>C3H9NO2</td>
<td>91.1</td>
<td>Iopamidol&lt;sup&gt;1&lt;/sup&gt;, Voglibose&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>2-amino-2-hydroxymethyl-1,3-propanediol</td>
<td><img src="https://example.com/structure2.png" alt="Chemical Structure" /></td>
<td>Yes</td>
<td>USA / Germany</td>
<td>77-86-1</td>
<td>C4H11NO3</td>
<td>121.1</td>
<td>Ketorolac&lt;sup&gt;3&lt;/sup&gt;, Fosfomycin&lt;sup&gt;4&lt;/sup&gt;, Lododoxamide&lt;sup&gt;5&lt;/sup&gt;, Dinoprost&lt;sup&gt;6&lt;/sup&gt;, Fingolimod&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
<tr>
<td>dl-2-amino-1-propanol</td>
<td><img src="https://example.com/structure3.png" alt="Chemical Structure" /></td>
<td>No</td>
<td>Germany</td>
<td>6168-72-5</td>
<td>C3H8NO</td>
<td>75.1</td>
<td>Oftoacin&lt;sup&gt;8&lt;/sup&gt;</td>
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<tr>
<td>2-amino-2-methyl-1,3-propanediol</td>
<td><img src="https://example.com/structure4.png" alt="Chemical Structure" /></td>
<td>No</td>
<td>USA / Germany</td>
<td>115-69-5</td>
<td>C4H11NO2</td>
<td>105.1</td>
<td>Crisnatol&lt;sup&gt;9&lt;/sup&gt;</td>
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<tr>
<td>dl-2-amino-1-butanol</td>
<td><img src="https://example.com/structure5.png" alt="Chemical Structure" /></td>
<td>No</td>
<td>Germany</td>
<td>96-20-8</td>
<td>C4H9NO2</td>
<td>89.1</td>
<td>Ethambutol&lt;sup&gt;10&lt;/sup&gt;, Methylergonovine&lt;sup&gt;11&lt;/sup&gt;</td>
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<tr>
<td>2-amino-2-ethyl-1,3-propanediol</td>
<td><img src="https://example.com/structure6.png" alt="Chemical Structure" /></td>
<td>No</td>
<td>USA / Germany</td>
<td>115-70-8</td>
<td>C5H13NO2</td>
<td>119.2</td>
<td>Fingolimod&lt;sup&gt;12&lt;/sup&gt;</td>
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<tr>
<td>3-amino-4-octanol</td>
<td><img src="https://example.com/structure7.png" alt="Chemical Structure" /></td>
<td>No</td>
<td>Germany</td>
<td>1001354-72-8</td>
<td>C8H19NO2</td>
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<tr>
<td>2-amino-2-methyl-1-propanol</td>
<td><img src="https://example.com/structure8.png" alt="Chemical Structure" /></td>
<td>No</td>
<td>USA / Germany</td>
<td>124-68-5</td>
<td>C5H11NO2</td>
<td>89.1</td>
<td>Pamabrom&lt;sup&gt;13&lt;/sup&gt;, Ambuphylline&lt;sup&gt;14&lt;/sup&gt;</td>
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<td>2-(dimethylamino)-2-methyl-1-propanol</td>
<td><img src="https://example.com/structure9.png" alt="Chemical Structure" /></td>
<td>No</td>
<td>Germany</td>
<td>7005-47-2</td>
<td>C8H15NO</td>
<td>117.2</td>
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<tr>
<td>2-amino-2-methyl-propylamine</td>
<td><img src="https://example.com/structure10.png" alt="Chemical Structure" /></td>
<td>No</td>
<td>France</td>
<td>811-93-8</td>
<td>C4H12N2</td>
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<td>Anagliptin&lt;sup&gt;15&lt;/sup&gt;, Arterolane&lt;sup&gt;16&lt;/sup&gt;</td>
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<tr>
<td>N-isopropylhydroxylamine</td>
<td><img src="https://example.com/structure11.png" alt="Chemical Structure" /></td>
<td>No</td>
<td>USA</td>
<td>5080-22-8</td>
<td>C3H8NO</td>
<td>75.1</td>
<td></td>
</tr>
</tbody>
</table>

*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
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 ANGUS 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 ANGUS 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

ANGUS encourages its customers to review their applications of ANGUS products from the standpoint of human health and environmental quality. To help ensure that ANGUS products are not used in ways for which they are not intended, ANGUS personnel will assist customers in dealing with environmental and product safety considerations. For assistance, product Safety Data Sheets, or other information, please visit angus.com or contact us at info@angus.com.