# Fluoro-Intermediates: An Overview

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Organo-fluorine chemistry is gaining a lot of importance in the Indian chemical industry and a lot of research work is going on in this area as the intermediates of fluorine find major applications in the pharmaceutical and the agrochemical industry, both of which have shown tremendous growth potential in the recent times. A wide range of pharmaceutical molecules require organic fluoro intermediates - either aliphatic or aromatic - in their synthesis.

**Manufacture**

Fluoro-intermediates are manufactured by one of the following three processes:

***HF diazotisation***

In this method, aromatic compounds containing one or two fluorine substituents are produced commercially by the diazotisation of the aromatic amines, using dry sodium nitrite in anhydrous HF at 0-20°C.

***Balz-Schiemann Reaction***

In this method, water insoluble diazonium fluoroborates are prepared by the diazotisation of aromatic amines with sodium nitrite in the presence of 40% fluoroboric acid or sodium/ammonium tetrafluoroborate in HCl.

***Chlorine-Fluorine exchange (Halex process)***

This involves replacement of activated chlorine atoms with the aid of alkali-metal fluorides. Theoretically, the Halex process is shown to be preferred over the HF diazotisation process because of it is a single-step procedure and due to structural specifications. HF is a key raw material in the manufacture of fluoro-intermediates. Most global players are vertically integrated, with the capability to manufacture right from HF to complex advanced intermediates.

**Applications**

Fluoro-intermediates are used in the manufacture of a number of APIs and in the agrochemical industry, for intermediates. In the pharmaceutical industry, the fluoroquinolone segment constitutes a major market for these intermediates. Fluoroquinolones, such as ciprofloxacin, gatifloxacin, norfloxacin, moxifloxacin, levofloxacin and ofloxacin are manufactured with these fluoro-intermediates.

Currently, China is actively into the manufacturing of aromatic fluoro-chemicals such as benzo trifluorides, fluorobenzenes, fluoroanilines and fluorotoluenes. In addition to its large domestic API market, China exports large volume of aromatic fluoro-chemicals all over the world. As per industry estimates, China's dominance in these intermediates will continue for the coming years, due to its manufacturing

**ABOUT THE AUTHOR**

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**Table 1**
**Fluoro-intermediates in the API industry**

| Intermediate | End use | Application |
|---|---|---|
| Fluorobenzene | Ciprofoxacin, Fluvastatin, Bicaltuamide | Anticancer, Antibacterial, Anticholestrol |
| 2,4-Dichlorofluorobenzene | Ciprofloxacin, Norfloxacin | Antibacterial |
| 2,4-Dichloro-5-fluoroacetophenone | Ciprofloxacin | Antibacterial |
| 1,3-Difluorobenzene | Fluconazole | Antifungal |
| o-Fluoronitrobenzene | Olanzapine | Anti-psychotic |
| 3-Chloro-4-fluoroaniline | Norfloxacin | Antibacterial |
| 4-Fluoroaniline | Ezetimibe | Anticholestrol |
| p-Fluoronitrobenzene | Pioglitazone | Antifungal |

**Table 2**
**Fluoro-intermediates in the Agrochemical industry**

| Intermediate | End use | Application |
|---|---|---|
| 4-Fluorobenzaldehyde | Bifenthrin | Herbicide |
| 4-Fluorobenzaldehyde | Cyfluthrin | Insecticide |
| 4-Fluoroaniline | Fluquiconozole | Fungicide |
| 4-Fluoroaniline | Fluromide | Fungicide |
| 4-Fluorophenol | Pentaxazone | Herbicide |
| Trifluoroacetic acid | Thifluzamide | Fungicide |
| Trifluoroethanol | Triflusulfuron | Herbicide |
| 4-Trifluoromethoxyaniline | Indoxicarb | Insecticide |
| 3,4 Difluorobenzotrifluoride | Flufenoxuron | Insecticide |

**Table 3**
**Global Aliphatic Fluoro-chemical Manufacturers**

| | Product |
|---|---|
| Rhodia, France | CF2 and CF3 products like trifluoroacetic acid and trifluoroacetyl chloride |
| Solvay Fluor | Similar range as Rhodia |
| Tosoh Corporation, Japan | Trifluoroethanol |
| Halocarbon Corporation, US | Trifluoroethanol |
| Miteni, Italy | Aliphatic and aromatic fluoro-intermediates |

competency and large scale manufacturing capacity for these intermediates. In the aliphatic fluoro-chemicals market, Rhodia and Solvay Fluor are two dominant players with their CF2 and the CF3 product range. The future for fluorointermediates is bright as it is linked to the pharmaceutical industry, which is on a growth path. In fact, the industry experts are of the opinion that in future, one in every three new APIs will be based on fluorine chemistry.

Although, at present, China and the European countries are actively into manufacturing of these intermediates, India will not be far behind in the race and fluoro-intermediates, which are restricted to a few manufacturers, will also attract other large Indian organic intermediate manufacturers.

With the gaining popularity of these intermediates, they can aptly be termed as organic intermediates of the future.