Part - A

Introduction

Studies on Flufenamic acid Derivatives
Flufenamic acid (FFA), 2-[[3-(trifluoromethyl)phenyl]amino]benzoic acid: \( \text{C}_{14}\text{H}_{10}\text{F}_3\text{N}_2\text{O}_2 \) is an aromatic consisting compound. It is a member of a group of compounds known as fenamates. It has a carboxylic acid consisting of two benzene ring fused to a \(-\text{NH}\) group. It is also known as Flufty or Fluf.

Flufenamic acid is a solid at room temperature. It is a White to light green crystalline powder. M. P. 132-135 \(^\circ\)C. It is a water insoluble compound. Stable under ordinary conditions.

Flufenamic acid (FFA), \( N-(\alpha,\alpha,\alpha\text{-trifluoro-}m\text{-tolyl})\text{anthranilic acid} \) is non-steroidal anti-inflammatory drugs (NSAIDs) used as potent analgesic and anti-inflammatory agents in the treatment of osteoarthritis, rheumatoid arthritis and other painful musculoskeletal illnesses.\(^1\) Its pharmacologic actions similar to those of aspirin. It is potent inhibitors of cyclooxygenase, there by inhibiting the release of prostaglandins.\(^2\)

Flufenamic acid hydrazides are important key intermediates in the synthesis of many series of biologically active heterocycles, and their synthesis has attracted significant attention due to their utility as building blocks and aroused our interest in exploring the utility of hydrazides as versatile precursors for the synthesis of a variety of substituted heterocycles.\(^3\)

Flufenamic acid is one of most attractive frameworks with a wide range of biological and pharmacological activities. Many researchers have described synthesis of flufenamic acid and its derivatives along with its applications in literature.
SYNTHETIC ASPECT

1. V. Dokorou et al.\textsuperscript{4} have reported one step synthesis of flufenamic acid by Ullman-Goldberg condensation.

\[
\begin{align*}
\text{F}_3\text{C} & \text{C} \text{N} \text{H}_2 + \text{Br} \text{C} \text{O} \text{H} & \xrightarrow{4\text{-ethyl morpholine}} & \text{F}_3\text{C} \text{C} \text{N} \text{H} \\
\text{Cu(OAc)}_2 & \text{DMF} & 3 \text{ hrs.} 146 ^\circ \text{C} & \text{COOH}
\end{align*}
\]

2. Y. Safari et al.\textsuperscript{5} have reported microwave-assisted chemoselective copper-catalyzed amination of o-bromo benzoic acid using aromatic amines under solvent free conditions.

\[
\begin{align*}
\text{F}_3\text{C} & \text{C} \text{N} \text{H}_2 + \text{R} \text{C} \text{O} \text{H} & \xrightarrow{\text{K}_2\text{CO}_3 \text{Cu(OAc)}_2} & \text{F}_3\text{C} \text{C} \text{N} \text{H} \\
\text{R} & \text{Cl, Br} & \text{Cu(OAc)}_2 & \text{Na(OAc)}_2 & 13 \text{ min.} \text{MW} & \text{COOH}
\end{align*}
\]

3. C. Zheng et al.\textsuperscript{6} have synthesized flufenamic acid using disodium carbonate.

\[
\begin{align*}
\text{F}_3\text{C} & \text{C} \text{N} \text{H}_2 + \text{C} \text{C} \text{O} \text{H} & \xrightarrow{(\text{Cu}) \text{CaCO}_3} & \text{F}_3\text{C} \text{C} \text{N} \text{H} \\
\text{Cu(OAc)}_2 & \text{DMF} & \text{COOH}
\end{align*}
\]

4. R. Carrasco et al.\textsuperscript{7} have reported one step synthesis of Flufenamic acid by use of ultrasound technique.

\[
\begin{align*}
\text{F}_3\text{C} & \text{C} \text{N} \text{H}_2 + \text{Cl} \text{C} \text{O} \text{H} & \xrightarrow{\text{K}_2\text{CO}_3 \text{Cu(II)Cu}} & \text{F}_3\text{C} \text{C} \text{N} \text{H} \\
\text{CaCO}_3 & \text{DMF} & \text{COOH}
\end{align*}
\]

5. D. K. Chalmers et al.\textsuperscript{8} have reported one step process for synthesis of flufenamic acid.

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\begin{align*}
\text{F}_3\text{C} & \text{C} \text{N} \text{H}_2 + \text{Br} \text{C} \text{O} \text{H} & \xrightarrow{\text{Cu}_2\text{O}} & \text{F}_3\text{C} \text{C} \text{N} \text{H} \\
\text{Cu(OAc)}_2 & \text{Dioxane} & \text{COOH}
\end{align*}
\]

6. F. J. Wilkinson et al.\textsuperscript{9} have reported synthesis of flufenamic acid from m-amino benzo trifluoride and o-iodobenzoic acid.

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\begin{align*}
\text{F}_3\text{C} & \text{C} \text{N} \text{H}_2 + \text{I} \text{C} \text{O} \text{H} & \xrightarrow{\text{Cu} \text{K}_2\text{CO}_3} & \text{F}_3\text{C} \text{C} \text{N} \text{H} \\
\text{H}_2\text{O} & \text{K}_2\text{CO}_3 & \text{COOH}
\end{align*}
\]
The reaction of 3-(trifluoromethyl)aniline with 2-chlorobenzoic acid in presence of base K$_2$CO$_3$ and copper iodide by ullmann condensation reaction.

Flufenamic acid...
Flufenamic acid represents a privileged structure in drug discovery. The number of bioactive compounds containing this moiety is so vast that complete range of their biological activities.

1. Epileptic\textsuperscript{10} 
2. Analgesic\textsuperscript{11} 
3. Anti-Inflammatory\textsuperscript{12} 
4. Antibacterial\textsuperscript{13} 
5. Anticonvulsant\textsuperscript{14} 
6. Antihistamines\textsuperscript{15} 
7. Antitumer\textsuperscript{16} 
8. Antiviral\textsuperscript{17} 
9. Antituberculosis\textsuperscript{18} 
10. Cardiovascular\textsuperscript{19} 
11. Arthritis\textsuperscript{20}

W. Zhu et al.\textsuperscript{21} have reported flufenamic acid inhibits the expression of the androgen receptor in LNCaP cells. NSAIDs play potential roles in chemoprevention of colon cancer and others by inhibiting prostaglandin synthesis. C. H. Lopez et al.\textsuperscript{22} have reported flufenamic acid action on sulfate transport in the Isolated perfuse rat liver. M. C. Jordani et al.\textsuperscript{23} have reported flufenamic acid as an inducer of mitochondrial permeability transition. H. Wagner et al.\textsuperscript{24} reported flufenamic acid used as a human skin penetration.

D. H. Boschelli et al.\textsuperscript{25} have reported 1,3,4-Oxadiazole, 1,3,4-Thiadiazole, 1,2,4-Triazole analoges of fenamates gives in vitro inhibition of cycloxygenase and 5-lipoxygenase activities.

M. Sakarellos-Daitsiotis et al.\textsuperscript{26} have reported thrombolytic properties of some flufenamate derivatives.
L. B. Seop et al.\textsuperscript{27} reported anticancer activity of flufenamic acid Nanoprodugs. J. P. Burnier et al.\textsuperscript{28} reported fibrinolytic activity of flufenamic acid. D. G. Wang et al.\textsuperscript{29} have reported flufenamic acid on fictive locomotion, plateau potentials, calcium channels and NMDA receptor in the lamprey spinal cord as an anticancer agent.

C. Sinning et al.\textsuperscript{30} have reported flufenamic acid most potent TRPV1 agonist.

Marketed drug with flufenamic acid substructures

\textit{Flufenamic acid}....
Thus the important role displayed by flufenamic acid and its for various and biological activities prompted us to synthesize some Imidazolone, pyrazolone, Oxadiazole, Thiazolidinone, Thiadiazine, Thiadiazole and Mannich Base derivatives bearing flufenamic acid moiety in order to achieve compounds having better therapeutic activities described as in the following parts.

STUDIES ON FLUFENAMIC ACID DERIVATIVES

PART-I: STUDIES ON IMIDAZOLONE DERIVATIVES
PART-II: STUDIES ON PYRAZOLONE DERIVATIVES
PART-III: STUDIES ON OXADIAZOLE DERIVATIVES
PART-IV: STUDIES ON THIAZOLIDINONE DERIVATIVES
PART-V: STUDIES ON THIADIAZINE DERIVATIVES
PART-VI: STUDIES ON 1,3,4-THIADIAZOLE DERIVATIVES
PART-VII: STUDIES ON MANNICH BASE DERIVATIVES
REFERENCES


*Flufenamic acid*...
Studies on heterocyclic...