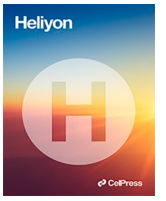
Heliyon 10 (2024) e32434

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Diverse role, structural trends, and applications of fluorinated sulphonamide compounds in agrochemical and pharmaceutical fields

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ARTICLE INFO

Keywords:
Fluorinated sulphonamide
Crop protection
Pharmaceuticals
Agrochemicals
Diseases
And disorders

ABSTRACT

Our knowledge of fluorine's unique and complex properties has significantly increased over the past 20 years. Consequently, more sophisticated and innovative techniques have emerged to incorporate this feature into the design of potential drug candidates. In recent years, researchers have become interested in synthesizing fluoro-sulphonamide compounds to discover new chemical entities with distinct and unexpected physical, chemical, and biological characteristics. The fluorinated sulphonamide molecules have shown significant biomedical importance. Their potential is not limited to biomedical applications but also includes crop protection. The discovery of novel fluorine and Sulfur compounds has highlighted their importance in the chemical sector, particularly in the agrochemical and medicinal fields. Recently, several fluorinated sulphonamide derivatives have been developed and frequently used by agriculturalists to produce food for the growing global population. These molecules have also exhibited their potential in health by inhibiting various human diseases. In today's world, it is crucial to have a steady supply of innovative pharmaceutical and agrochemical molecules that are highly effective, less harmful to the environment, and affordable. This review summarizes the available information on the activity of Fluorine and Sulphonamide compounds, which have proven active in pharmaceuticals and agrochemicals with excellent environmental and human health approaches. Moreover, it focuses on the current literature on the chemical structures, the application of fluorinated

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https://doi.org/10.1016/j.heliyon.2024.e32434
Received 17 November 2023; Received in revised form 2 June 2024; Accepted 4 June 2024
Available online 8 June 2024

sulphonamide compounds against various pathological conditions, and their effectiveness in crop protection.

1. Introduction

Fluorinated sulphonamide organic compounds have recently gained prominence in agrochemicals and medicine. Introducing a fluorine atom to different sulphonamide compounds can improve their biological properties while reducing environmental and health risks. The fluorine atom is unique because it is smaller than hydrogen as per the atomic radii (with a van der Waals radius of 1.47 Å compared to hydrogen's 1.20 Å). Additionally, the C–F bond is more stable than the C–H bond, which increases the half-life period. Furthermore, fluorine is the most electronegative atom in the periodic table, making it an excellent electron-withdrawing agent [1,2].

Fluorine has higher lipophilicity than hydrogen, making it more hydrophilic with intrinsic potency. It also improves metabolic stability [1,2] and membrane permeability and affects metabolic pathways due to steric hindrance. Fluorinated molecules have better electronic and inductive properties than non-fluorinated ones, with higher thermal and oxidative stability, smaller surface tension than hydrocarbons, and weak intermolecular interaction [2]. Additionally, ^{18}F is a practical positron-emitting isotope for in vivo imaging technology, which is useful in drug development and discovery [3].

Fluorine is a versatile element that plays a crucial role in various industries, including pharmaceuticals [4–7], agrochemicals [8–11], refrigerant gases, spectroscopy, polymers, electronic devices [12], flavors, and fragrance [13] development. It produces polymers such as Teflon [14,15] and inhalation anesthetics [16]. The fluorine scan is now a routine approach for developing drug and agrochemical molecules. Currently, over half of all agrochemicals contain at least one fluorine atom. Adding one or more fluorine atoms to a biologically active compound can significantly improve its properties. In the past, incorporating fluorine atoms into molecules using molecular fluorine or anhydrous fluorine was challenging and costly. However, with the advancement of technology, these processes have become more accessible, cost-effective, and efficient [17,18].

Sulphonamide drugs, commonly known as sulfa drugs [19], are a significant class of amide isosteres [20] chemical molecules with pharmacological and agrochemical properties [21–23]. They are widely used in the medical field [24] for the treatment of various diseases such as antifungal, antiviral, antioxidant [25], antimicrobial [26–28], anti-inflammatory [29], and anticancer [30–33]. They can also be used as carbonic anhydrase inhibitor [34,35], anti-HIV drugs [36,37], anti-malarial agents, and typhoid fever relievers. Sulphonamide drugs are effective against gram-positive and gram-negative bacteria [38] and can stimulate insulin secretion, act as diuretics, and treat high blood pressure and diabetes. In the agrochemical field, sulphonamide drugs are used as fungicides, insecticides, herbicides, and pesticides, including azo dyes with antimicrobial activity [39].

Many agrochemical compounds developed recently show improved biological activity [40] when they bind with one or more fluorine atoms and sulphonamide derivatives. Coupling these fluorinated molecules with sulphonamide offers several benefits, including lower cost, lesser toxicity, and environmental friendliness. The sulphonamide derivative and fluorine atom combination can further enhance and modulate the target biological properties [41]. The fluorinated sulphonamide is particularly useful for power storage chemical preparation [42]. Additionally, the Isatin sulphonamide fluorinated derivative is an efficient PET and SPECT radiotracer for apoptosis imaging technique [43].

2. Agrochemical active fluorinated sulphonamide derivatives

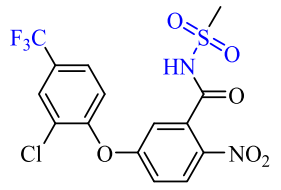
2.1. Active fluorinated sulphonamides derivatives as herbicides

Many countries are facing a shortage of workers to handle weed fields due to industrialization, which has caused people to migrate from rural to urban areas. While hand weeding has always been an effective method of weed control, it is more time-consuming and expensive than other methods. Tilling can cause harm to the environment, so herbicide use is becoming more widely accepted. Herbicides are superior to tilling because they reduce fuel use, greenhouse gas emissions, soil erosion, and nutrient runoff while preserving water and saving time [44]. Recently developed fluorinated herbicides are very effective, with fewer side effects on the environment and living matter. Over 25 % of the most up-to-date developed herbicides contain at least one fluorine atom [9]. Combining Fluorine and Sulphonamide groups also plays an essential role in preparing effective herbicides.

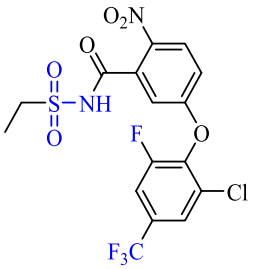
Many old herbicide agrochemicals are being reapplied in higher doses, which can cause more harm to living organisms and generate a high residual effect on soil and water. However, modern agrochemical chemistry has led to the discovery of novel herbicides that are highly efficient in weed control, requiring a lower dose. Sulfur-containing agrochemicals are part of this modern approach and can help improve crop yields. Over 30 % of discovered agrochemicals contain at least one sulfur atom, mainly in pesticides. The advantages and disadvantages of some important herbicides are highlited in Table 1.

Table 1
The advantages and disadvantages of some important herbicides [53,68–78].

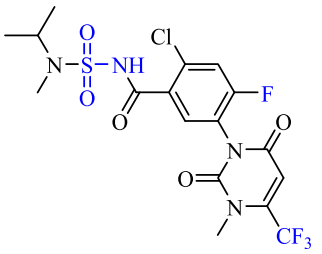
Fomesafen	Advantages	Fomesafen is an herbicide that targets protoporphyrinogen IX oxidase. It has low toxicity and selectivity, making it environmentally safe. Fomesafen can control certain germinating broadleaf weeds, grasses, and sedges by soil residual activity. It is most effective when used postemergence through contact action.
	Disadvantages	When using Fomesafen Herbicide, avoid applying it to stressed weeds or crops. A 1-h rain-free period is recommended after postemergence application. The chemical can persist in soil and affect subsequent crops, particularly in regions with permeable soils and shallow water tables. It has the potential to seep through soil and pollute groundwater and also it reduces the bacterial diversiy.
Saflufenacil	Advantages	Saflufenacil is a herbicide that controls broadleaf weeds in crops such as soybeans and corn. It inhibits the enzyme protoporphyrinogen oxidase and is effective in controlling glyphosate-tolerant weeds. Roots and foliage rapidly absorb Saflufenacil, and its effects are seen within two days or less. Its use reduces the overall level of herbicide use and environmental risk.
	Disadvantages	Saflufenacil can impact surface water through rainwater runoff for several weeks after application, especially in poorly draining soils and soils with shallow groundwater. To reduce potential runoff, maintain a buffer strip between areas of application and surface water features, and avoid application when rainfall is forecast within 48 h. This product should not contact workers or other persons directly or through drift. Note that Saflufenacil CS does not control grass weeds and must be used with a grass herbicide for complete weed control.
Flumetsulam	Advantages	Flumetsulam is a herbicide that controls broadleaf weeds in corn and soybeans by interfering with the production of amino acids, resulting in the death of the weed. It offers advantages like labor and time-saving, low cost, and ensures normal crop growth. It is widely used and has a good weeding effect when used properly [74].
	Disadvantages	Improper application of flumetsulam herbicide can cause phytotoxicity to crops. Herbicides damage foliage and stems, causing plant death. They can also remain in soil and harm root development, leading to delayed growth and reduced yield. Adopting proper application methods is crucial to minimize these negative effects.
Pyroxsulam	Advantages	Pyroxsulam is a herbicide that inhibits plant enzymes and causes death in susceptible plants. It is systemic and absorbed via leaves, shoots, and roots. The proposed use of CRUSADER will not likely present risks to birds or aquatic plants, provided appropriate amendments are made. Similarly, risk to native and non-target plants is expected to be acceptable with adherence to the Protection of Crops statement [75].
	Disadvantages	Toxicological data for pyroxsulam, primarily based on animal testing, is extensive. However, high doses in these tests don't necessarily indicate adverse effects in humans. It is harmful by inhalation, irritating the skin, may cause sensitivity by skin contact, and poses a risk of serious eye damage.
Diclosulam	Advantages	Diclosulam is a highly effective herbicide that can be applied to Soybean and Groundnut crops within three days of sowing. Its systemic action ensures excellent control of essential broadleaf weeds in soybeans and suppresses critical grasses and sedges. This versatile herbicide is perfect for controlling annual and some perennial broadleaf weeds in crops such as sugar cane, peanuts, and soybeans, as well as forestry applications. Whether applied as soil, foliar, or burndown treatments, Diclosulam delivers superior results every time [76].
	Disadvantages	Diclosulam technical is very highly toxic to aquatic organisms on an acute basis. It is practically nontoxic to birds, mammals, insects, earthworms, fish, and aquatic invertebrates. It is very toxic to aquatic life and has long-lasting effects [77].
Cloransulam-methyl	Advantages	Cloransulam-methyl is an herbicide used to control the post-emergence of broad-leaved weeds in soybeans. It inhibits the synthesis of amino acids in plants. It is not approved for use in Europe and can degrade quickly in shallow sunlit water.
	Disadvantages	Studies on cloransulam-methyl metabolism in rats showed that at 5 mg/kg, over 90 % of a single or repeated dose was absorbed. At 1000 mg/kg, only 28–30 % of a single dose was absorbed. Due to rapid elimination, cloransulam-methyl has little potential to accumulate upon repeated administration. Its use as a herbicide will result in its direct release to the environment. Cloransulam-methyl is expected to have very high to low mobility in soil.
Triafamone	Advantages	This herbicide is highly efficient, low-toxic, and highly selective in controlling weeds in paddy fields before and after emergence. Triafamone works by inhibiting the acetolactate synthase (ALS) enzyme, which is responsible for the biosynthesis of branched-chain amino acids. Due to its high selectivity to rice, this herbicide effectively controls valerian, alfalfa, Isachne globosa, and sedge, including ALS-resistant strains [53].
	Disadvantages	Improper application of flumetsulam herbicide can cause phytotoxicity to crops. It is harmful by inhalation, irritating the skin, may cause sensitivity by skin contact, and poses a risk of serious eye damage. To reduce potential runoff, maintain a buffer strip between areas of application and surface water features, and avoid application when rainfall is forecast.
Tolylfluanid	Advantages	Tolylfluanid belongs to the group of sulfamides, with dichlofluanid as its precursor, wherein a methyl group replaces the hydrogen atom located at the para position of the phenyl group. This fungicide was introduced in 1971 and is commonly used in the cultivation of fruits and vegetables as a wood preservative.
	Disadvantages	Tolylfluanid is not approved in the European Union due to its genotoxic and antifungal properties. It has low toxicity, except for metalaxyl, which is slightly hazardous. The compound can cause skin sensitization and lead to sedation, decreased motility, disturbed behavior, and dyspnea. Liver toxicity has been reported in mice, rats, and dogs after intraperitoneal injection [78].



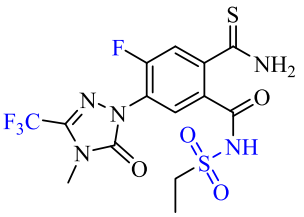
1 Fomesafen



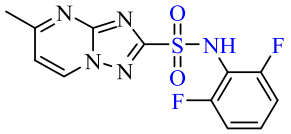
2 (Halosafen)



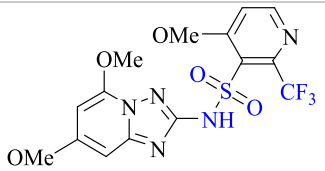
3 (Saflufenacil)



4 (Bencarbazone)



5 (Flumetsulam)



6 (Pyroxsulam)

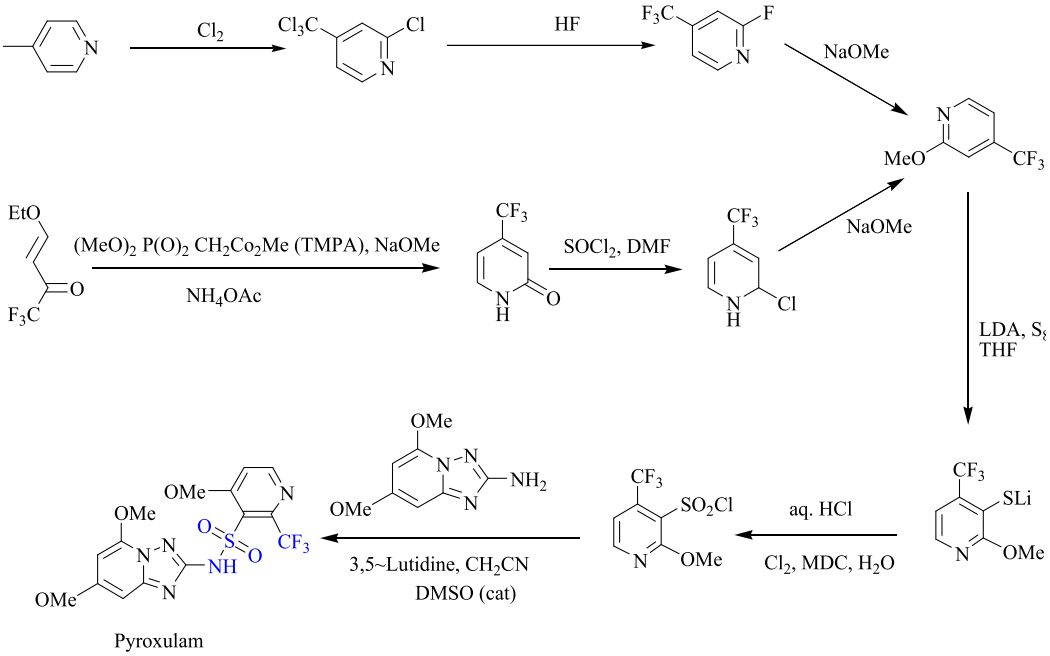


Fig. 1. Commercial synthesis process of Pyroxsulam [46].

Some of these herbicides contain active sulphonamide and fluorine groups, which are useful for pre- and post-emergence weed control, such as broadleaf weeds, sedges in soybeans, and grasses [45]. Two second-generation diphenyl ether herbicides, 1 (Fomesafen) and 2 (Halosafen), contain sulphonamide and fluorine as active sites. A few types of second-generation herbicides, such as 3 (Saflufenacil) and 4 (Bencarbazone), have a combined herbicidal effect with sulphonamide and fluorine. These herbicides belong to the proton inhibitor class. Triazolopyrimidine sulphonamide is another interesting class of herbicides. As a Sulphonylurea, Triazolopyrimidine targets Acetolactate synthase, an enzyme generally found in branched-chain amino acid biosynthesis. Most agrochemical companies produce bulk herbicides for post-emergence control of broad-leaf weeds. Some commercially available Triazolopyrimidine herbicides include 5-(Flumetsulam) and 6 (Pyroxsulam). Mode of action of 1 (Fomesafen): When fomesafen and related nitrophenyl ether herbicides were first developed, their precise mode of action was unknown. Chlorosis and desiccation have visible effects on entire plants; various theories have been proposed regarding the molecular-level interactions that could account for these symptoms. According to the currently accepted theory, these substances cause an accumulation of protoporphyrin IX in the plant cells by inhibiting the enzyme protoporphyrinogen oxidase. This is a strong photosensitizer that causes lipid peroxidation by activating oxygen. Both light and oxygen are required for this process to kill the plant. Mechanism of action of 3 (Saflufenacil): Saflufenacil functions by blocking the production of chlorophyll by inhibiting the enzyme protoporphyrinogen IX oxidase (PPO), which leads to the accumulation of protoporphyrin IX, a strong photosensitizer. This turns on oxygen, which leads to lipid peroxidation and a quick loss of membrane function and integrity. The effects of necrosis and chlorosis on entire plants are necrosis and chlorosis. The effects are not strong enough to seriously harm corn and some types of soybeans, providing beneficial selectivity.

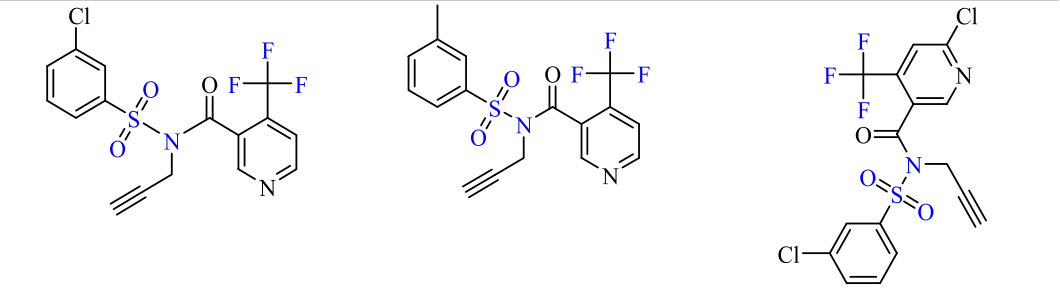
The 5 (Flumetsulam) herbicide controls broadleaf weeds in maize, soybeans, and metosulam crops. The 6 (Pyroxsulam) herbicide was discovered by Dow Agro science in 2008 [46]. It is a selective post-emergence herbicide that controls broadleaf weeds in durum, spring wheat, winter wheat, and wild oats. Generally, 6 (Pyroxsulam) is mixed with water and applied as a uniform broadcast spray. This herbicide can inhibit the production of the ALS enzyme in plants, which is necessary for making certain essential amino acids. Fig. 1 shows the reaction process using commercially available raw materials, and this synthesis method can be scaled up to the plant level [46].

Florasulam herbicide is used exclusively to control broadleaf weeds in cereals and wheat crops. Penoxsulam, on the other hand, is used to control sedges, broadleaf weeds, and grasses in rice culture. Developed by Dow Agro science in 2004, Penoxsulam is a broad-spectrum herbicide that can be applied in a low dose, making it eco-friendly. The 8 (Penoxsulam) is a novel post-emergence herbicide [47–49], and it is an Acetolactate synthase inhibitor herbicide that is effective against broadleaf weeds of drained and semi-flooded paddies, rice fields, and cereal crops. Some of the broadleaf weeds that can be controlled with Penoxsulam include barnyard grass (*Echinochloa crusgalli*), wild buckwheat (*Paspalum dilatatum*), and young water grass (*Paspalum dilatatum*). Penoxsulam is absorbed through leaves, roots, and shoots and is generally phloem and xylem mobile.

7 (Florasulam) **8 (Penoxsulam)**

Some of the synthesized N-(Heterocyclylcarbonyl) sulphonamide compounds are frequently useful as herbicides, and such a kind of herbicide applies to pre-emergence and post-emergence control of monocot and dicot weeds [50].

The herbicidal compounds 9, 10, and 11 (Fig. 2), which contain fluorinated sulphonamide, are very useful in controlling weeds in crops such as cotton, rice, corn, and soybean. These compounds can be applied in different ways, such as through soil or plants. Active



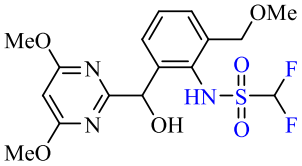
9 **10** **11**

Fig. 2. N- (Heterocyclylcarbonyl) fluorinated sulphonamide as an herbicides.

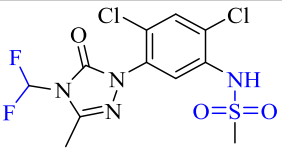
sulphonamide, heterocyclic components, and fluorine achieve the best herbicidal activity. Among the compounds, those containing sulphonamide with fluorine, N- (heterocyclic aminocarbonyl) aryl group, and thienyl group baring heterocyclic radicals are the most important for use as plant growth regulators and pre-emergence and post-emergence herbicides [51].

Compounds 12, 13, 14, 15, and 16 (Fig. 3) are effective agrochemicals for crop protection. Weeds can cause serious damage to desirable crops such as corn, rice, wheat, and cotton, so preventing these unwanted weeds is extremely important to improve crop yield. Developed fluorinated sulphonamide compounds play a vital role as plant growth regulators.

Herbicides are useful for controlling weeds and are typically available in granules, pellets, emulsions, and dust. However, spray formulations generally provide more advantages. Compound 17 (Pyrimisulfan) is a novel systematic herbicide that can be used for pre- and post-emergence [52,53] weed control in turf. This herbicide is an Acetolactate synthase inhibitor, which blocks the enzyme responsible for the biosynthesis of three essential plant growth amino acids.



17 (Pyrimisulfan)



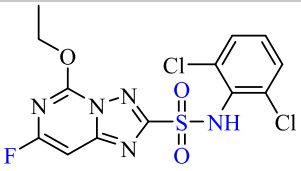
18 (Sulfentrazone)

Pyrimisulfan herbicide is effective for controlling both warm and cold season turf. It can target broadleaf and kyllinga weed species and annual weeds like Echinochloa oryzicola, Schoenoplectus juncoides, and subsp. *Ohwianus,* some broadleaf weed with perennials like *cyperus serotinus*, *Eleocharis kuroguwai, sagittaria pygmaea*, *Seaside bulrush*, spike rush, and three-leaf arrowhead. This herbicide was discovered by Kumiai in 20 and has relatively low soil adsorption and water solubility characteristics compared to other rice herbicides [54]. The granular formulation of Pyrimisulfan is most effective for pre-emergence up to the three-leaf stage of rice. It has also been proven to be reliable under simulated excess conditions. The fluorine bonds in Pyrimisulfan provide stability and effectiveness, ranging from about half to slightly more than half of a normal hydrogen bond. This leads to the self-assembly of organic crystals. Due to the halogen atom in the compound, it proves to have metabolic, thermal, and oxidative properties.

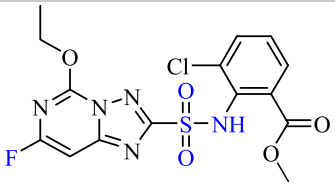
The active ingredient 18 (Sulfentrazone) is commonly used as an herbicide to control weeds. It works by disrupting the membranes that inhibit photosynthesis in weeds, a process known as PPO inhibition. The weed absorbs sulfentrazone through its roots; when exposed to light, it dies. This herbicide effectively controls pre- and post-emergence weeds in cool and warm seasons and is particularly useful in soybean crops [55,56].

The Triazolopyridine herbicide 19 (Diclosulam), developed by Dow Agro Science, has a very good crop-specific pathway on cotton, soybean, maize, and wheat [57].

The 20 (Cloransulam-methyl) is a methyl ester of Cloransulam and is used as an inhibitor of acetohydroxy acid synthase (AHAS) [58]. This herbicide can prevent the synthesis of amino acids in plants and is effective for post-emergence control of broadleaf weeds in soybeans [59]. Cloransulam-methyl, or de-565, is solid and typically insoluble in water.

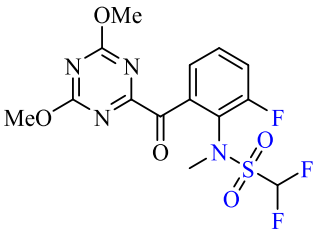


19 (Diclosulam)

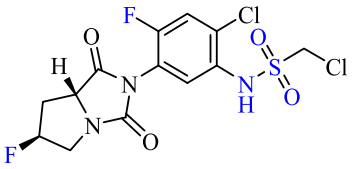


20 (Cloransulam-methyl)

21 (Triafamone) is a new-generation herbicide approved by the International Organization for Standardization (ISO) and developed by Bayer Crop Science. It works by inhibiting the Acetolactate synthase (ALS) enzyme in plants, making it effective for weeding paddy fields such as *Echinochloa colonum, Echinochloa crus-galli, Isachne global*, and *Paspalum distichum* [60]. Triafamone can be used in direct-seeded and transplanted rice from seeding through granular formulation or spray. This herbicide is also known for its minimal hazard profile to the environment and consumers alike.

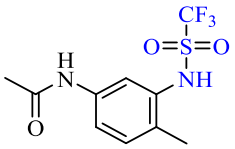


21 (Triafamone)

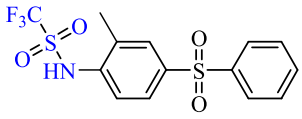


22 (Profluazol)

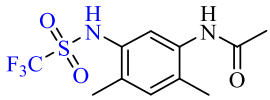
The herbicides 22 (Profluazol) and 24 (Perfluidone) are obsolete but still useful for controlling broad-leaved and nutsedge species of broadleaf weeds in flue-cured tobacco and certain grasses. The herbicide Profluazol can be used for pre-emergence or post-emergence weed control and is a protoporphyrinogen oxidase (PPO) inhibitor. DuPont developed it, and can be combined with other herbicides for increased efficacy [61]. The herbicide Perfluidone interferes with protein biosynthesis with cellular respiration and its activity via root absorption and contact. As for the herbicide, 23 (Fluoridamide) is an obsolete plant growth regulator that is also useful as an herbicide. It controls plant height and can be combined with other chemicals like fosamine, chlorpropham, carbaryl, chlorophonium chloride, jasmonic acid, and maleic acid. to exhibit insecticide, fungicide, and plant growth regulator properties [62]. Perfluidone interferes with protein biosynthesis, cellular respiration, and its activity via root absorption and contact [63].



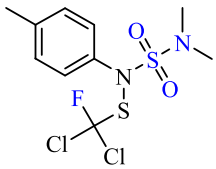
23 (Fluoridamide)



24 (Perfluidone)



25 (Mefluidide)



26 (Tolylfluanid)

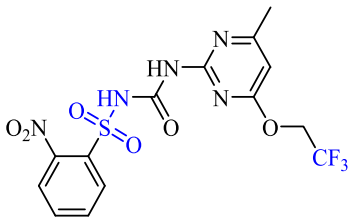
The herbicide and plant growth regulator 25 (Mefluidide) is useful for regulating plant growth [64] by preventing seed head formation and controlling vegetative growth in various types of woody plants and turfgrass. It can be absorbed through the root, stem, and leaves of plants. It is effective as a post-emergence herbicide in soybean crops to control seeding and shattering, rhizomatous Johnson grass, volunteer wheat, volunteer corn, and sorghum. The effectiveness of Mefluidide depends on the rate and timing of application [65]. 26 (Tolylfluanid) is an active ingredient fungicide that can also be used as a wood preservative [21]. It is effective against grey mold [66], powdery mildew on cucumber, and late blight on tomatoes, apples, soybeans, and strawberry plants [67]. Tolylfluanid works by acutely suppressing pyruvate metabolism in an isolated mitochondrion.

Mechanism of action of 8 Pyroxulam herbicide: Pyroxsulam inhibits the enzyme acetolactate synthase (ALS) and is a member of the triazolopyrimidine sulfonamide family. This enzyme is necessary for plants to produce the branched-chain amino acids valine, leucine, and isoleucine. In 19 Diclosulam mode of action, the most prevalent method of diclosulam tolerance is methyl hydroxylation, followed by glucose conjugation in the metabolism of herbicide molecules.

Mode of action of 20 Cloransulam-metyl: The acetolactate synthase enzyme, essential for synthesizing three amino acids needed for cell division and growth, is the target of the herbicide. When the concentration of cloransulam-methyl reaches a toxic level, cell division in roots and shoots slows or stops. Mode of action of 21 Triafamone: By preventing the acetolactate synthase (ALS) enzyme from functioning, triafamone weeds prevent the synthesis of branched-chain amino acids.

2.2. *Active fluorinated sulphonamides derivatives as pesticides*

Pesticides control pests and disease carriers like insects, fungi, ticks, rats, mosquitoes, mice, and weeds. There are different types of pesticides, such as herbicides, insecticides, molluscicides, nematicides, bactericides, rodenticides, antimicrobials, fungicides, and insect repellents. These pesticides protect crops or plants from insects, fungi, and weeds. Fluorine and sulphonamide groups in



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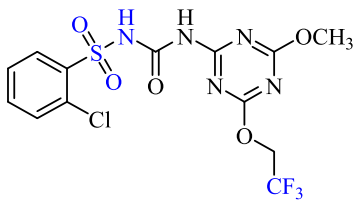

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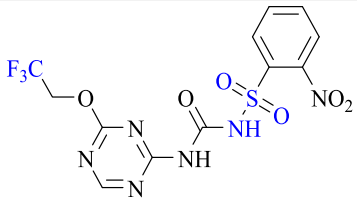

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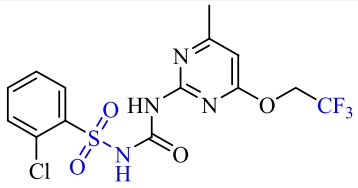

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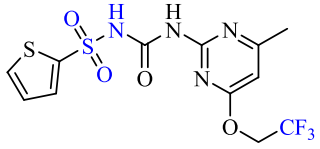

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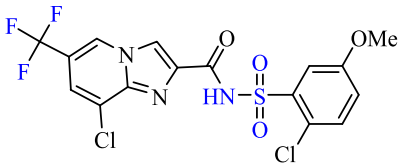
Fig. 3. Herbicidal plant growth regulators with fluorinated sulphonamide group.

pesticides have proved effective in protecting plants against harmful organisms such as fungicides, insecticides, and nematicides. Pesticides also help in regulating plant growth and preserving plant products. Fluorine-containing pesticides [79,80] have efficiently controlled crop diseases with considerably lower side effects. Farmers use pesticides to produce safe and worthy foods at an affordable price. More than half of essential crops would be lost to disease and pests without pesticides. Novel 27 is a pesticide useful for controlling pests like nematodes and insects that harm essential crops [81,82]. It can be used in combination with other compounds like Thiamethoxam, Fipronil, Clothianidin, and Imidacloprid by maintaining a ratio of 20:1 to 1:200.



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The mixture of granules can be incorporated into the soil at a depth of 20–60 cm. This granulating compound is useful for controlling pests by treating the soil to improve the growth of crops such as rice, cotton, soybean, sugar beet, sunflower, sugarcane, and corn. The Fluopyram pesticide can also be used alongside other nematodes, fungicides, plant growth regulators, and herbicides to provide positive results on essential crops. This invention works against various insects and nematodes such as hemipteran pest, lepidopteran pest, Thysanoptera pest, dipteral pest, elytron pest, aphids, noctuids, thrips, click beetles as insects and southern root-knot nematodes, northern root-knot nematodes, potato cyst nematodes, north meadow nematodes. Fig. 4 illustrates the commercially feasible and easy route for the synthesis of various analogs of Fluopyram herbicide.

Fluorinated sulphonamide compounds are very useful in controlling harmful nematodes [83] that attack the roots of plants. This is important as it helps increase crop yield by preventing major damage to tissue or diseases in plants and animals.

Novel fluorinated compounds have been tested at 250 ppm and effectively destroyed unessential nematodes without any negative effects on the crops. These compounds include compound-28; 5-Chloro-N-(4-cyano-2,5-dimethylcyclohexa-1,5-diene-1-sulfonyl)-7 (Trifluoromethyl) imidazo [63,84] pyridine-2-carboxamide and compound-29; 5-chloro-N-(5-chloro-3,4-dimethylthiophene-2-sulfonyl)-7-(trifluoromethyl) imidazo pyridine-2-carboxamide [29] (Fig. 5).

Developed compounds are often used to control parasitic nematodes in agriculture and nano-agriculture. A fluorinated sulphonamide has been innovatively used to protect seeds from these parasitic nematodes. Soil nematodes can cause significant crop yield

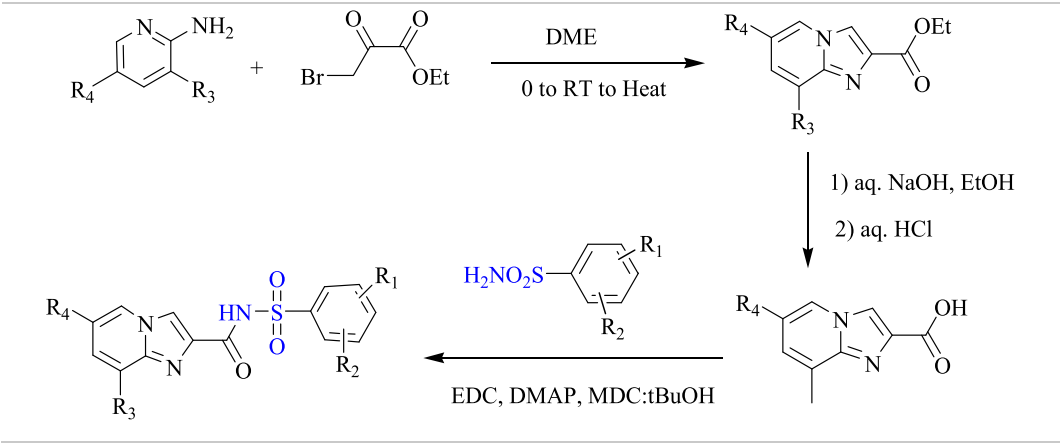


Fig. 4. Reaction scheme for preparation of nematocidal fluorinated sulphonamide derivatives [82].

loss in agricultural fields. The government has banned using most chemicals previously used to control soil nematodes, such as Carbamates aldicarb, Carbofuran, and Organophosphates fenamiphos, due to their acute toxicity to the environment and living organisms. Nowadays, many organic molecules have been developed to control soil nematodes with a novel mechanism of action that causes lesser harm to living organisms. Bayer Agro Company claims 30 to have reduced the use of chemical nematicides by implementing these organic molecules.

The 30-Fluopyram is a novel agrochemical that acts as both nematicide and fungicide for controlling soil nematodes and fungi Table 2. Many sulfur-containing fluorochemicals are effective against nematodes and fungi with lower mortality rates [84]. The combination of amide, fluoro group, and sulfur atoms has resulted in excellent fungicidal and nematicidal properties. Scientists have synthesized many compounds in the backbone of Fluopyram. Compound 31 has shown excellent fungicidal activity, possibly due to six-member heterocyclic rings with Fluoro, Nitro, and Sulphoxide groups. On the other hand, compounds 32 and 33 exhibit nematicidal properties, as they contain common Sulfur, Fluorine, Nitrogen, and Heterocyclic rings Fig. 6.

Mode of action of 30- Fluopyram: Mycelium growth, sporulation, germination of spores, and germ tube elongation are all inhibited by Fluopyram.

2.3. Active fluorinated sulphonamides derivatives as fungicides

Fungicides are biological organisms or chemical compounds that destroy parasitic fungi and their spores. Fungi can cause significant damage to agriculture, resulting in crop losses in terms of quality and quantity. Fungicides are used to treat both plants and animals. Most fungicides are liquid, and sulfur is the most active and common element. Fungicides are crucial in conserving healthy crops and ensuring trustworthy yields of high-quality products [86]. Fluorine-containing building blocks, particularly fungicides, have become increasingly important in crop protection [87]. Many fungicides have been developed with at least one fluorine atom [88], and fluorinated organic compounds represent a growing and important family of commercial agrochemicals with novel action modes [89].

Fungicides are biological organisms or chemical compounds that destroy parasitic fungi and their spores. Fungi can cause significant damage to crops by reducing both their quality and quantity. Therefore, fungicides are essential for the treatment of plants and animals. The majority of fungicides come in liquid form, with sulfur being the most common and active element. Fluorine-containing building blocks are crucial for crop protection, particularly in the form of fungicides [86,87]. Many fungicides contain at least one fluorine atom [88], and fluorinated organic compounds are a growing and important family of commercial agrochemicals with unique action modes [89]. Ultimately, fungicides are crucial for maintaining healthy crops and ensuring high-quality yields. Advantages and disadvantages of some important herbicides are highlited in Table 3.

Most older herbicide agrochemicals are reapplied in higher doses, causing more harm to living matter and producing a high

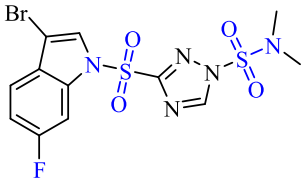
28 **29**

Fig. 5. Pesticides containing trifluoromethyl imidazo pyridine carboxamide group [84].

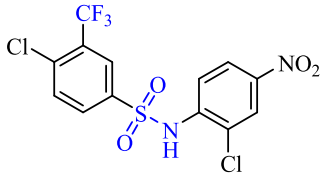
Table 2
The advantages and disadvantages of Fluopyram [74,85].

Fluopyram	Advantages	Fluopyram is an SDHI fungicide that was introduced last decade. They protect soybean seedlings from soil-borne diseases. Fluopyram is a broad-spectrum fungicide with low toxicity and can be applied to plant foliage. Field tests show that fluopyram SC has a significant suppressive effect against PWD, with an average control efficiency of 90.48 %. It is useful for the enhancing of the plant growth.
	Disadvantages	Limited information is available in China regarding the efficacy of fluopyram via chemigation against root-knot nematode and its effects on soil properties. Fluopyram significantly impacts the functional diversity of the soil microbial community. Toxic to aquatic life with long-lasting effects. Fluopyram was highly toxic to *M. incognita*'s J2 and eggs, with LC50 values of 2.78 and 1.70 mg L−1, respectively.

residual effect on soil and water. However, scientists have discovered novel herbicides that are highly efficient in weed control, requiring a lower dosage. One such herbicide is 34 (Amisulbrom), a sulfamoyl-triazole group chemical developed by Nissan Chemical Industries Ltd. This agrochemical is very effective in controlling late blight (*Phytophthora infestans*) and downy mildew (*Plasmopara viticola*) on the stems and leaves of potatoes [45]. However, it is moderately toxic to honey bees and birds and more hazardous to earthworms and aquatic species.

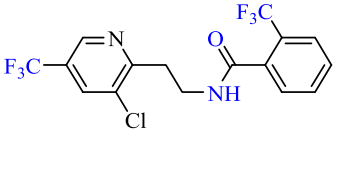


34 (Amisulbrom)

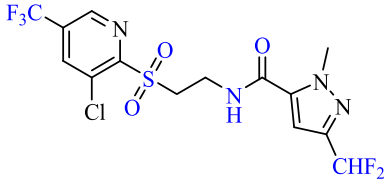


35 (Flusulfamide)

The 35 (Flusulfamide) is a fungicide primarily used when applied to soil. It is effective against various fungi, including Spongospora



30 (Fluopyram)



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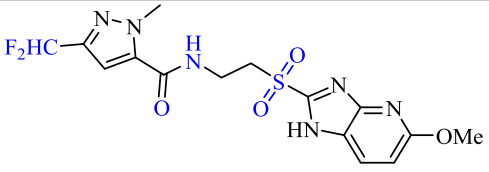

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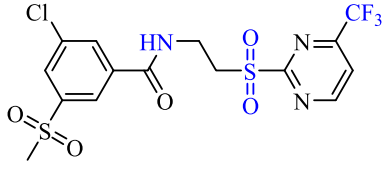

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Fig. 6. Active pesticide containing six six-membered heterocyclic rings [84].

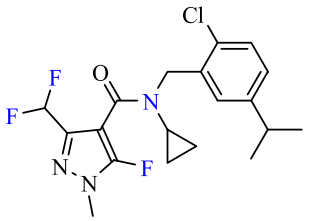
Table 3
The advantages and disadvantages of some important fungicides [92–94].

Amisulbrom	Advantages	This is a fungicide used on potatoes to control late blight and downy mildew. It is an antifungal agrochemical and a mitochondrial cytochrome-bc1 complex inhibitor. The substance has low aqueous solubility, slight volatility, and moderate mobility, which means that there is low risk of leaching to groundwater.
	Disadvantages	This substance is a reproduction toxicant and can be harmful if inhaled. It is moderately toxic to birds and honeybees but poses a greater risk to aquatic species and earthworms. It may persist in soil systems but not in water systems.
Isoflucypram	Advantages	Isoflucypram (ISY) is a new and highly effective fungicide that belongs to the SDHI family It offers long-lasting control against major foliar diseases in cereals and is likely to set new standards in the cereal fungicide market.
	Disadvantages	Very toxic to aquatic life with long lasting effect. May causes damage to organs through prolonged or repeated exposure
Chesulfamide	Advantages and disadvantages	Chesulfamide is a new fungicide that controls Botrytis cinerea effectively. It does not interact with other commercial fungicides such as carbendazim, diethofencarb, iprodione, and procymidone, indicating that it has a unique mechanism of action. This fungicide is toxic to aquatic life with long lasting effect

subterranean, myxomycete fungi, Plasmodiopora brassicas, and Streptomyces Scabies, a common cause of potato scab.

The succinate dehydrogenase inhibitor is an important tool when controlling diseases in cereals. The first complex-II inhibitor, 37 (Isoflucypram), was invented and has proven to be unparalleled in its long-term effectiveness against most foliar diseases in cereals. This makes it a significant discovery in succinate dehydrogenase inhibitors [90]. Compound 36 has fungicidal properties in a greenhouse, but it shows weak efficiency against cereals. However, by making structural modifications, we have discovered very active compounds that show acute activity against cereals. Replacing the SO_2 group with a CH_2 group has led to changes in several useful biological activities. Compound 36a can act as a succinate dehydrogenase inhibitor for *Zymoseptoria, Agaricus,* and *Botrytis* species, but it shows only moderate in-vitro activity on *Ustilago* SDH. Structural modifications of these fungicides have resulted in next-level solutions with improved biological activities compared to previous formulations Fig. 7.

A newly synthesized compound called 37 (Isoflucypram) has been designed and evaluated, which provides an excellent balance of efficiency and safety compared to succinate dehydrogenase inhibition. This new compound, along with other Isoflucypram-based compounds, has shown a high level of efficacy. This is a good example of how structural modifications based on binding sites can improve the efficacy of drugs.



37 (Isoflucypram)

One of these novel compounds, a fluorinated sulphonamide [91], is effective against the *Botrytis Cinerea* pathogen. *Botrytis Cinerea* is a fungus that affects more than 200 essential dicotyledonous plant species. This fungus is considered a distinctive necrotroph that uses a programmed cell death pathway in the host to complete infection. Field trials were carried out using a mycelium inhibition test, tomato pot test, and spore germination inhibition test against the *Botrytis Cinerea* strain. The results showed superior fungicidal activity against *B. Cinerea*.

Compound 39 has been found to exhibit exceptional fungicidal activity against boscalid, procymidone, and pyrisoxazole in both in vivo and in vitro tests Fig. 9. Interestingly, no positive cross-resistance was observed in other fungicides such as boscalid, azoxystrobin, fludioxonil, pyrisoxazole, and diethofencarb. Fig. 8 guides the preparation of various fluorinated sulphonamide derivatives [91]

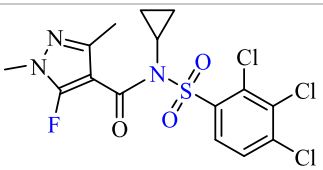
The widely known 38 (Chesulfamide) fungicide can control the *Botrytis Cinerea* species with strong preventive, beneficial, and osmotic activity. Using sulfamide as a basic structure, novel sulphonamide compounds have been developed that are capable of inhibiting fungal activity. Some of these compounds exhibit greater activity than the standard chesulfamide (Fig. 9).

Compounds 41, 42, and 43 have shown superior fungicidal action against DL-11, resulting in inhibition of mycelium growth against three strains of *Botrytis Cinerea* (DL-11, 5055, K2-9). Most end molecules exhibit a moderate inhibition effect on spore germination using a 10–50 μg mL-1 concentration. However, increasing the concentration of a specific molecule up to 100 μg mL-1 can inhibit spore activity.

Compounds 39, 41, 42, and 43 (Fig. 10) were successfully applied to tomato seedlings, achieving over 80 % control efficiency. However, compound 39 showed a control efficiency of up to 90.27 %, making it superior to the other compounds for positive fungicidal control. A combination of compound 39 and boscalid (in a 1:1 ratio) showed an average control efficiency of around 86 %.

Introducing the trifluoromethyl group in sulphonamide compounds improves the physicochemical properties of a molecule, such as metabolic stability and lipophilicity. The activity of the electron-withdrawing group with the benzene ring is superior to the electron-donating group. The developed fungicidal molecule contains different mechanisms of action, such as single sterol biosynthesis inhibitors, respiration inhibitors, signal transduction inhibitors, and biosynthesis inhibitors.

Mechanism of action of 34-Amisulbrom: The Amisulbrom is a sulfonamide fungicide that attaches to the Qi center and obstructs respiration to inhibit mitochondrial complex III activity.



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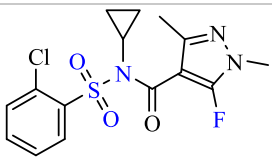

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Fig. 7. Modified derivatives of Isoflucypram baring fungicidal properties [90].

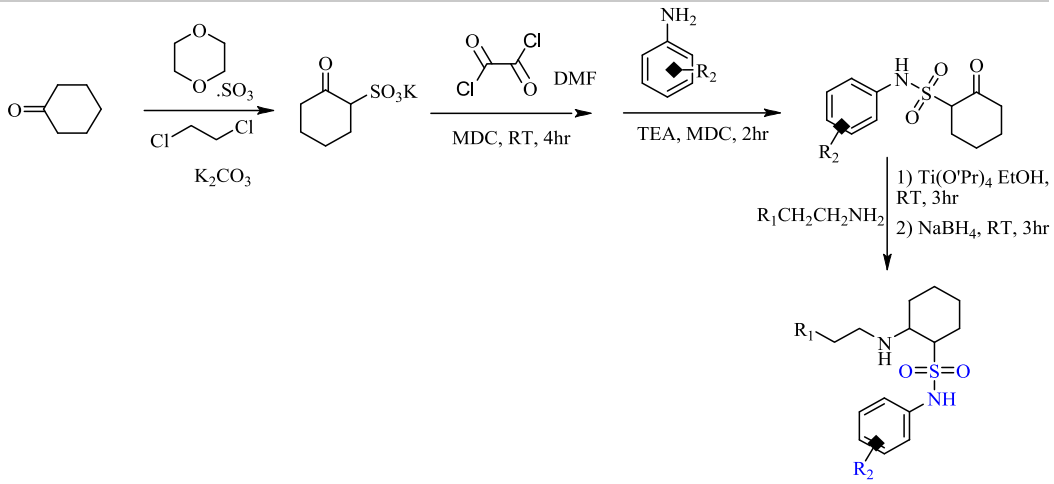
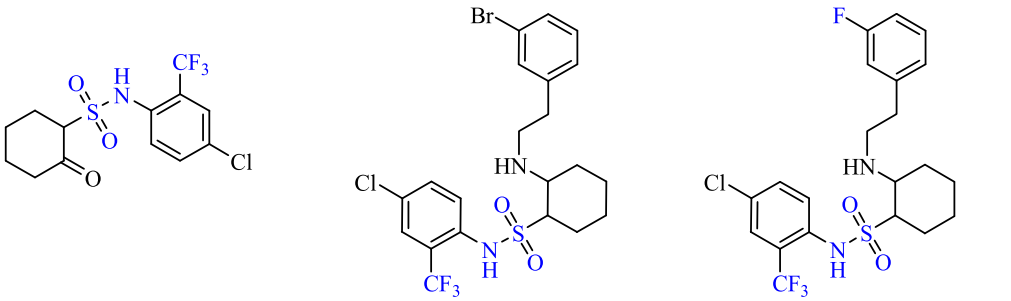


Fig. 8. General reaction scheme for preparation of Fluorinated sulphonamide derivatives [91].



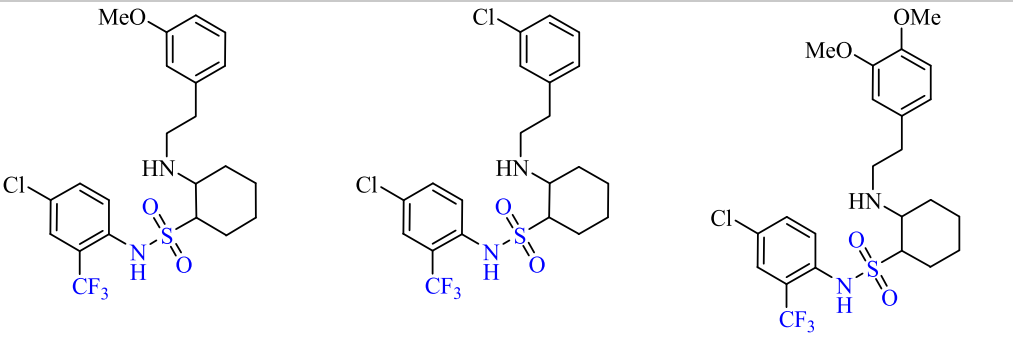
38 (Chesulfamide)	39	40

Fig. 9. Chesulfamide and its structurally modified derivatives with fungicidal efficiency [91].

3. Pharmaceutically active fluorinated sulphonamide derivatives

3.1. Carbonic anhydrase inhibition by fluorinated sulphonamide compounds

Carbonic anhydrase inhibitors are commonly used to treat several conditions, including glaucoma, seizure disorder, edema caused by congestive heart failure, acute mountain sickness, and gout. These inhibitors help to solubilize and secrete uric acid. Carbonic anhydrase is an enzyme in various body tissues, such as the gastric mucosa, renal cortex, lung, red blood cells, and central nervous



41	42	43

Fig. 10. Chesulfamide and its structurally modified derivatives with fungicidal efficiency [91].

system. Carbonic anhydrase inhibitors, such as CA-I and CA-II, are found in the corneal endothelium and lens. These inhibitors also decrease the formation of aqueous humor in the eyes. They are used to lower intraocular pressure in open-angle glaucoma and before surgery in the case of angle-closure glaucoma [95,96]. Many fluorine-containing sulfonamides have been identified as effective carbonic anhydrase inhibitors, including those that inhibit the tumor-associated isozyme IX. Polyfluorinated organic sulfonamide molecules have shown excellent activity inhibiting carbonic anhydrase isoenzymes [97]. In one study, researchers developed 2,3,5,6-tetrafluophenylsulfonyl compounds with heterocyclic or aromatic sulfonamide groups.

Combining perfluorobutylsulphonamide and Perfluorophenylsulphonyl with heterocyclic or aromatic sulphonamide has proven to be highly effective carbonic anhydrase inhibitors (CAIs). These inhibitors exhibit good water solubility and effectively treat glaucoma in animal models. The evidence suggests that CAIs with polyfluorophenyl tails are useful for developing active and bioavailable inhibitors.

It is important to note that the fluorine group was not directly attached to the sulphonamide due to its high reactivity. Instead, the perfluorinated molecules are covalently bound to thiol reagents such as cysteine and glutathione through a nucleophilic aromatic substitution reaction. However, this binding may result in the replacement of thiol protein.

Compounds 44 and 46 are more effective than the parental sulphonamide from which they were derived Fig. 11. Similarly, compounds 47 and 49 have shown to be more potent inhibitors of the enzyme CA-IX, as compared to CA-I inhibitors (Fig. 12) [97]. A new compound has been synthesized, which is known as 2,3,5,6-tetrafluorophenyl sulphonamide carboxamide heterocyclic/aromatic sulphonamide, and has demonstrated the ability to impede transmembrane, tumor-released isozyme CA-IX. These newly prepared compounds have been tested against standard drugs such as Acetazolamide, Methazolamide, Dorzolamide, and Brinzolamide.

The combination of fluorine and sulphonamide groups is effective for most pharmaceutical molecules [4]. This combination is useful for developing the cyclooxygenase-2 (COX-2) inhibitor, Celecoxib (Compound 51). Compound 50 can inhibit cyclooxygenase-2 (COX-2), but it has a long half-life which is undesirable. To solve this problem, a fluorine atom is removed, and a methyl group is introduced, resulting in a half-life of 3.5 h. The CF_3 group from the 3-position of pyrazole is the most favorable for potency and selectivity (Fig. 13). Advantages and disadvantages of some important COX inhibitor are highlited in Table 4.

Carbonic anhydrase-II (CAII) is a zinc metalloenzyme that catalyzes the hydration of CO_2, forming bicarbonate and proton. Simple aliphatic sulfonamide compounds ($CH_3SO_2NH_2$) are typically weak acids with a pKa value of 10.5, making them weak inhibitors of carbonic anhydrase. On the other hand, fluorinated sulfonamide ($CF_3SO_2NH_2$) is an excellent inhibitor of carbonic anhydrase, exhibiting a pKa value of 5.8, which means it is a stronger acid. The CF_3 group's presence, with its stronger electron-withdrawing tendency, exhibits such activity.

Compound 52 is a chemical moiety of CAII inhibitor, N-(4-sulfonamido-benzoyl) benzyl amide. Fluorinated sulfonamide dissociates at neutral pH and binds with the enzyme more strongly than simple aliphatic sulfonamide (Fig. 14).

The derivatives of 1,3,5 triazine-fluorinated sulphonamide have the ability to inhibit β-class carbonic anhydrase derivatives found in *Mycobacterium tuberculosis*. These molecules may also be useful for developing anti-infective drugs, as they are potent inhibitors of the leading human carbonic anhydrase isoforms (hCA-I and hCA-II) [98].

Fig. 15 shows novel fluorinated sulphonamide compounds (53,54,55,56, and 57) that can be used to inhibit β-carbonic anhydrase (CAs, EC 4.2.1.1) found in the *Mycobacterium tuberculosis* bacterial pathogen, specifically mtCA-1, mtCA-2, and mtCA-3. Some of these compounds may be relevant to developing antimycobacterial agents. The human pathogen *Mycobacterium tuberculosis* genome contains at least three carbonic anhydrases belonging to the β-class.

Fluorinated sulphonamide derivatives potently inhibit bacterial CAs from pathogens such as B. suis, *H. pylori*, and S. pneumonia. The primary sulphonamide is widely used as a systematic antiglaucoma or diuretic drug. This molecule has shown equivalent

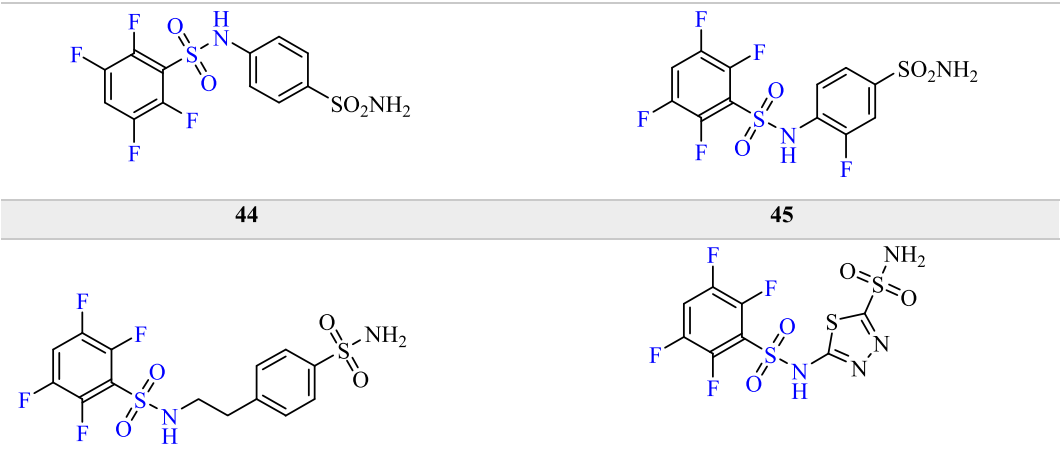
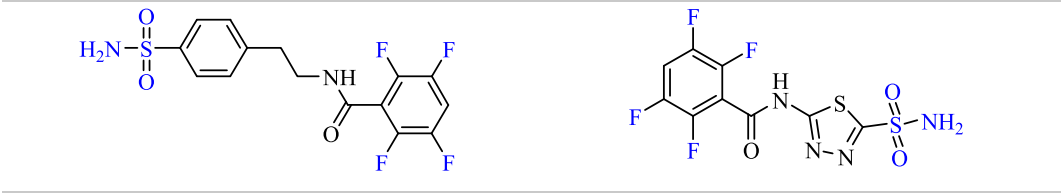
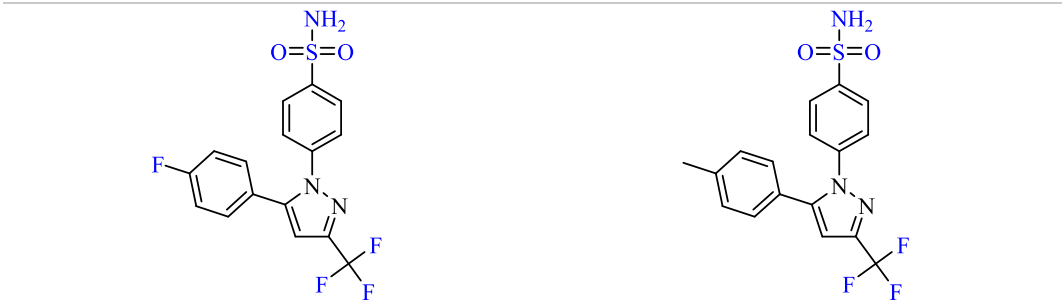


Fig. 11. Perfluorophenylsulphonyl heterocyclic molecules with CAI activity [97].



48 **49**

Fig. 12. Perfluorophenylsulphonyl heterocyclic molecules with CAI activity [97].



50 **51** (Celecoxib)

Fig. 13. Active CAIs Celecoxib (44) and its structural modified derivative [4].

Table 4
The advantages and disadvantages of some important COX inhibitors [106–108].

Celecoxib	Advantages	Celecoxib is a nonsteroidal anti-inflammatory drug used to treat pain and inflammation caused by various conditions. It belongs to a specific class of NSAIDs called COX-2 selective inhibitors, which work by preventing the body from producing a substance that causes pain and inflammation. It's commonly used for arthritis, ankylosing spondylitis, migraines, menstrual pain, and short-term pain due to injuries or medical procedures. It's also used in kids with juvenile rheumatoid arthritis who are 2 years old or older.
	Disadvantages	Celecoxib can cause serious stomach ulcers and bleeding, and increase the risk of fatal heart attack or stroke, especially if you have smoking, alcohol, or poor health habits. Avoid using this medication before or after heart bypass surgery. It may also cause intestinal bleeding, especially in older adults, and should be avoided if you already have bleeding in your stomach or intestines. Watch out for symptoms such as stomach pain, heartburn, gas, diarrhea, constipation, nausea, vomiting, swelling in your hands or feet, dizziness, or cold symptoms like a stuffy nose, sneezing, or sore throat.
JTE-522	Advantages and Disadvantages	JTE-522 (Tilmacoxib) is a COX-2 inhibitor with effective chemopreventive properties against liver fibrosis and colon cancer in rats. It inhibits the development of preneoplastic lesions and tubular adenocarcinomas in rats' colon. Also, it has a significant inhibitory effect on ACF. The drug possesses low toxicity and is a potent chemopreventive agent for rat liver fibrosis. No significant side aeefects or disadvantages were reported.

β-inhibition activity against mycobacterium inhibition as compared to known compounds like AAZ (Acetazolamide), DCP (Dichlorophenamide), and BZA (Benzolamide). The position and number of fluorine atoms alter the rate of bio potency. The triazine-substituted fluorinated sulphonamide showed good inhibition potency against mtCA-3, followed by mtCA-2 and mtCA-1 at least.

Fluorinated sulphonamide is a superior group of carbonic anhydrase inhibitors. Recent studies have been conducted on β-carbonic inhibition from the pathogenic bacterium *Vibrio cholerae* using different sulphonamide derivatives. Identification of potency towards selective inhibitors of VchCAβ may be a familiar pharmacological tool [99].

The genome of the pathogenic bacterium *Vibrio cholerae* encodes for three types of carbonic anhydrases (CAs), classified as α, β, and γ. CAs are enzymes in most pathogenic species essential to the microbe's virulence. CAs are universally metalloenzymes that catalyze

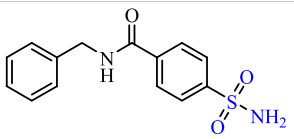


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Fig. 14. CA-II inhibitor with sulphonamide benzoyl benzyl group [4].

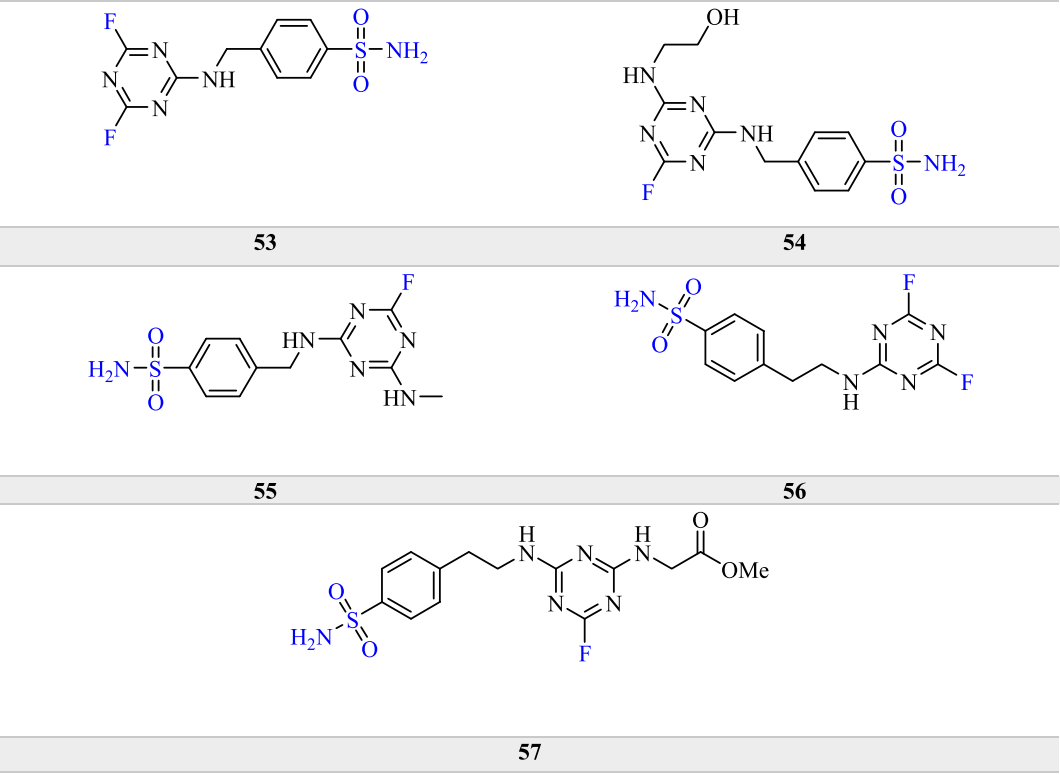


Fig. 15. 1,3,5 Triazine -Fluorinated sulphonamide as CAIs [98].

the reversible hydration process of carbon dioxide, producing proton and bicarbonate. The best inhibition of VchCAβ was reported with the help of methazolamide, deacetylated acetazolamide, and hydrochlorothiazide. The inhibition constant was found to be between 68.2 and 87.0 μM.

The *Vibrio cholerae* bacterium's genome is responsible for causing cholera in humans. However, this disease does not have any sequence homologous to the bicarbonate transporter system. An inhibition study of VchCA, with the help of sulphonamide, has led to the discovery of some low nanomolar inhibitions like brinzolamide, methazolamide, ethoxzolamide, and insular (K1 value between 0.69 and 8.1 μM). Some derivatives, Fig. 16 (Compound-58, 59, and 51), have been studied against the inhibition of the enzyme cloned so far in *Vibrio cholerae*, VchCAβ, and have shown effective pharmacological activity.

Compounds 58 and 59 are simple analogs of fluorinated aromatic sulphonamide derivatives. Compound Celecoxib 51 (CLX) is a COX2 selective inhibitor. This sulphonamide shows inhibition data of VchCAβ, which is achieved by a stopped-flow CO_2 hydrase assay monitoring most of the physiological reaction catalyzed with the help of carbonic anhydrase.

A compound CLX sulphonamide was studied per micromolar VchCAβ inhibitor with a K1S range between 2.21 and 9.12 μM. These derivatives contain the presence of primary sulphonamide moiety. Generally, VchCAβ inhibition profiles are different from the human isoforms hCA-I and hCA-II. Some sulphonamide derivatives are useful for inhibiting pathogens over the hCA-I enzyme. Compound 59 is the best VchCAβ inhibitor and has a selectivity ratio for inhibiting the bacterial over human enzyme 126.2. However, these compounds have no inhibiting activity against bacterial enzymes over hCA-II.

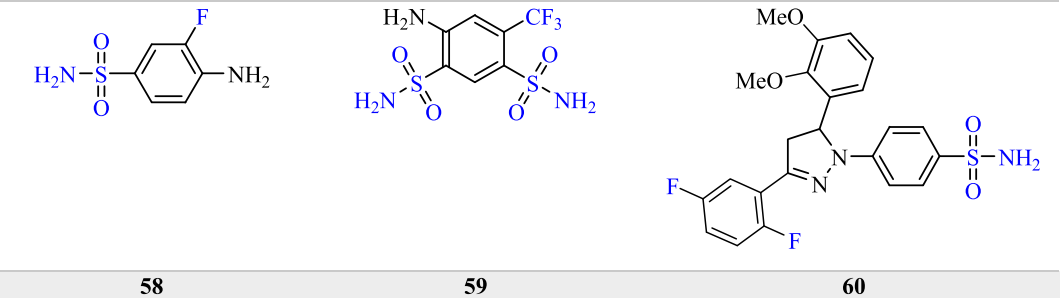


Fig. 16. Active CAIs CLX and its basic backbone.

The study delves into newly developed sulfonamides 60 and their effects as enzyme inhibitors. Enzyme inhibition assays revealed that these sulfonamides demonstrated significant inhibitory effects against hCA I, hCA II, and AChE enzymes at the nanomolar level. The compound 60 displayed Ki values ranging from 3.30 ± 1.09–5.95 ± 2.26 nM for hCA I and 4.29 ± 0.91–7.14 ± 3.15 nM for hCA II. Additionally, the Ki values for AChE were calculated within a range of 3.28 ± 1.47–9.77 ± 1.86 nM. This compound shows potential as inhibitors for both AChE and CA and could lead to the development of new bioactive molecules [100].

The protein-ligand affinity of fluoroaromatic sulphonamide inhibitors to carbonic anhydrase-II has [101] been observed to some extent. CA-II is a zinc metalloenzyme that normally catalyzes the process of CO_2 hydration, creating bicarbonate and a proton. N-(4-sulfamylbenzoyl) benzylamine (SBB) has been found to have the tightest binding in human CA-II. Fluorinated SBB displays effective electrostatic interaction due to introducing an electronegative fluorine atom. At the same time, attaching the fluorine group to the carbonyl ketone group enhances the electrophilicity of the ketone group, allowing the fluorinated molecule to bind with a hydrolytic enzyme in the form of a covalent adduct. This condition provides active site nucleophiles and effective binding as a transition state.

Replacing the electropositive hydrogen atom with an electronegative fluorine atom significantly alters the modulators of electronic properties of the attached aromatic ring. According to the study, the complex between the fluorinated SBB derivative and zinc metalloenzyme CA-II was more interesting and applicable in the binding process. At the same time, the complete structure of carbonic anhydrase-II remains unaffected upon the binding of each inhibitor.

The affinity difference observed in Fig. 17 (Compounds 61 to 65) is due to the substitution of fluorine in the benzyl ring. The presence of fluorine atoms affects the binding affinity due to their inductive and electronegative effects. These CA-II inhibitors show significant potential for ophthalmology and are applicable in lowering intraocular pressure in glaucoma patients. The fluorinated CA-II is particularly useful in glaucoma therapy. By replacing hydrogen with fluorine, there is a significant increase in tight binding affinity with adjacent enzyme residue and a boost in weakly polar interaction. Perfluoroalkanesulphonamides and their long-chain derivatives effectively inhibit carbonic anhydrase and bind with metal ions, particularly divalent cations [102]. The $CF_3SO_2NH_2$ molecule is particularly effective in inhibiting carbonic anhydrase. To further investigate, perfluoroalkanesulphonamides derivatives were synthesized and analyzed in Fig. 18 (Compounds-66 to 70). These compounds showed good activity in inhibiting bovine carbonic anhydrase (bCA). Replacing the hydrogen substituent with fluorine increases the inhibition activity of carbonic anhydrase 66 and 67. The sodium salt of perfluoro alkane sulphonamides is more soluble in water, so adding extra solvent is unnecessary to determine its activity. These perfluoroalkane sulphonamides are also impactful on human carbonic anhydrase isoenzyme-II, which is mainly considered the therapeutic target of sulphonamide carbonic anhydrase inhibitor 67.

These compounds have a hydrophobic character due to the fluorine atoms' presence, making them attractive. The F-alkylated chain becomes a favorable position for the enzymatic site, allowing for interaction between the hydrophobic pockets of the enzyme and the F-alkylated chain. Perfluoroalkanesulphonamides sodium salt compounds do not have cellular cytotoxicity. However, trifluoromethane sulphonamide and perfluorohexanesulphonamide have cellular cytotoxicity at 1000 μm concentration.

Some fluorinated tertiary benzene sulphonamide derivatives are highly selective towards hCAIX inhibition [103]. These derivatives demonstrate a novel mode of carbonic anhydrase inhibition activity. The fluorinated compounds 71, 72, 73, 74, and 75 are useful for inhibiting human carbonic anhydrase (h CAs, EC 4.2.1.1) and show good selectivity towards tumors that are linked to hCA-IX without inhibiting the off-target hCA-II (Fig. 19).

Compound-71 can inhibit hCA-IX at the nanomolar level, in addition to the target of hCA-II. Meanwhile, Compound-75 has a better affinity towards tumor-associated isoenzyme than the cytosolic isoenzyme CA-I and excellent selectivity in hCA-IX inhibition.

The discovery of isoforms of cyclooxygenases (COX-1 and COX-2) led to a new generation of NSAIDs, including fluorinated sulphonamide derivatives [104]. These newly discovered drugs can reduce side effects, including some of the old-fashioned developed simple non-fluorinated NSAIDs drugs that inhibit COX-1 as well as COX-2 (such as Aspirin and Indomethacin).

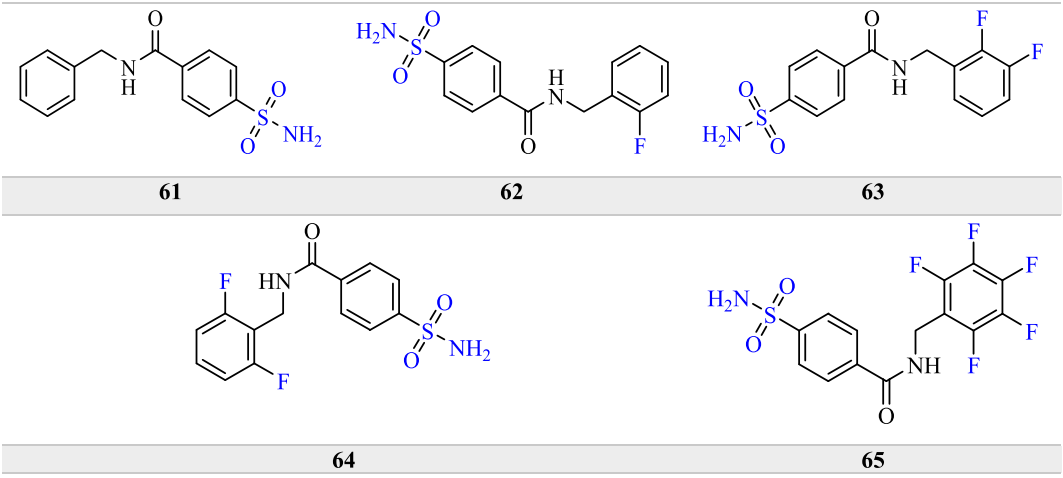


Fig. 17. Active CAIs containing fluorinated sulphonamide derivative.

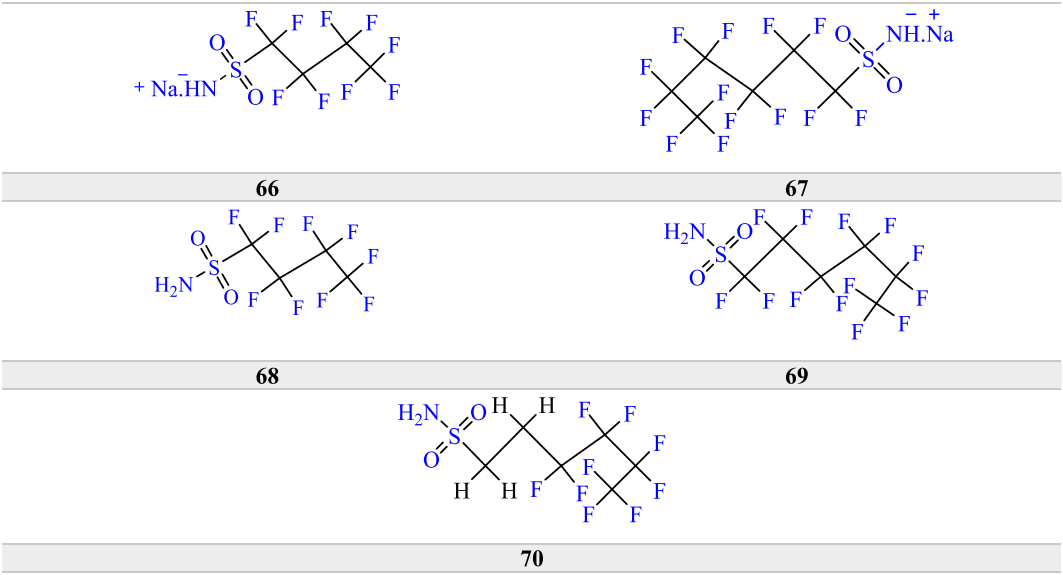


Fig. 18. Perfluoroalkanesulphonamides derivatives as CAIs.

To address the earlier problems, some fluorinated sulphonamide compounds can selectively inhibit COX-1 (such as 51 -Celecoxib). The study revealed that Vioxx and Bextra have side effects such as increased heart disease and stroke. Therefore, discovering novel derivatives like Compound-77 (SC-558) and Compound-78 (JTE-522) can resolve such a problem. These compounds mentioned in (Fig. 20) are fluorinated analogs of Valdecoxib and Rofecoxib.

The interaction of perfluorinated aliphatic tails with the hydrophobic pocket can potentially enhance inhibitor potency during the prebinding stage (Compound-76). However, substituents other than fluorine (such as alkyl groups) can also lead to increased affinity due to their large hydrophobic surface areas upon ligand binding. The potency and selectivity of studied inhibitors are also strongly impacted by the fluorination of the aromatic tail, which is mainly due to a combination of the pKa-lowering effect and finely tuned-dispersive interactions. Additionally, the insertion of perfluoroaromatic tails can improve the hydro/lipophilic profile of CAIs, ultimately enhancing their pharmacokinetic properties. Overall, the insertion of fluorine on CAIs of the sulfonamide type contributes to a variety of effects, including increased molecular complexity of the scaffolds and the strength of the sulfonamide-zinc coordination, which is the primary contributor to binding and may overshadow other interactions mediated by the fluorine atom [105].

Mechanism of action of 51 -Celecoxib: The mechanism of action of celecoxib involves the selective inhibition of cyclooxygenase-2 (COX-2), an enzyme required for prostaglandin synthesis, which is implicated in the development of pain and inflammation. Its pharmacologic activity results from Celecoxib's analgesic, anti-inflammatory, and antipyretic effects.

The mode of action of 78-JTE-522 (4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamid e), a novel selective cyclooxygenase (COX)-2 inhibitor, was tested and its inhibitory activity against human COX-1 and COX-2 was compared to that of reference compounds.

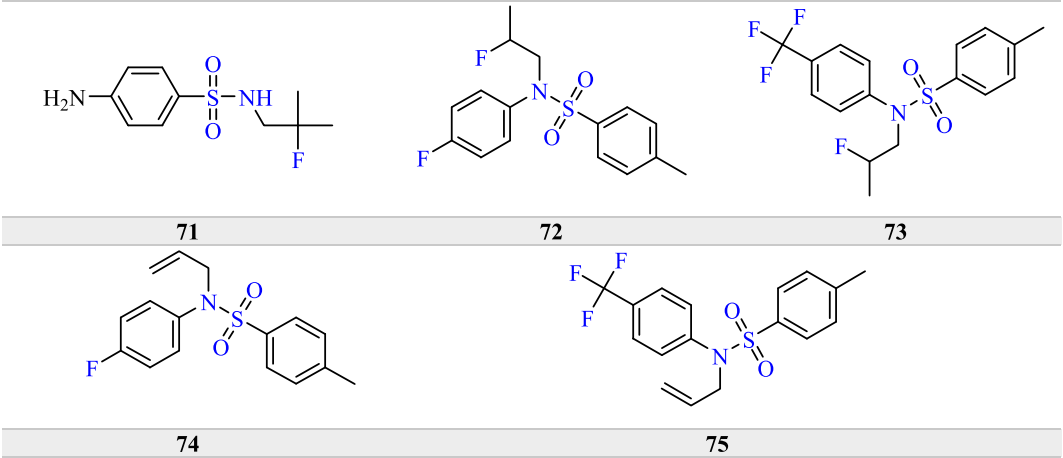
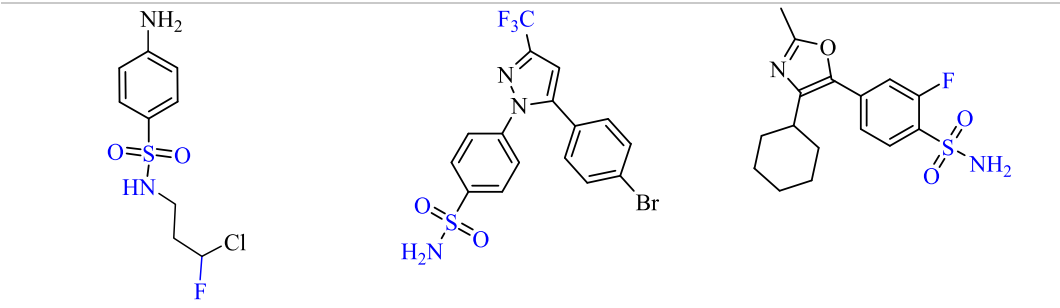


Fig. 19. Novel hCAIX inhibitors baring fluorine and sulphonamide groups [103].



76 **77 (SC-558)** **78 (JTE-522)**

Fig. 20. Celecoxib and its structural modification for COX inhibitors.

3.2. Fluorinated sulphonamide applications as an anti-cancer drug

Cancer is a disease in which abnormal cells divide uncontrollably and destroy body tissue. Cancer can start almost anywhere in the human body. Nowadays, more than 100 types of cancer affect human. The most common cancers are prostate cancer, breast cancer, basal cell cancer, skin cancer, colon cancer, lung cancer, leukemia, and lymphoma. The possible symptoms of cancer are abnormal bleeding, lumps, prolonged cough, change in bowel movement, and weight loss. Cancer is a difficult disease, including numerous tempo spatial changes in cell physiology, which eventually leads to malignant tumors [109]. Sometimes, the same genes also produce cancer cells in the body as they come across harmless in situ tumors. Some of the happenings also propose that either an increase or decrease in the angiogenic resistance can alter the rate of cancer development [110]. Sulphonamide drugs are very useful as anti-cancer drugs [24]. Some fluorinated sulphonamide drugs were recently developed to treat cancer, summarized below. Advantages and disadvantages of some impotant anti cancer drugs are highlited in Table 5.

The drugs 79 (Debrafenib) and 80 (Vemurafenib) have shown efficacy in treating cancer associated with mutated versions of the BRAF gene. These drugs work by inhibiting the enzyme B-Raf, which is responsible for regulating cell growth [104,111]. A team led by Kataja developed an efficient process for preparing Vemurafenib with high yield and purity of the final product. Fig. 21 illustrates this synthesis method, which is suitable for commercial production.

Vemurafenib, drug number 80, is commonly used to treat skin cancer, specifically metastatic melanoma. This form of skin cancer is highly fatal. Vemurafenib belongs to a class of drugs called mutant BARF kinase inhibitors and was developed using a scaffold-based drug design approach. BRAF is the most frequently mutated protein kinase in human cancer, with the oncogenic mutation being most common in melanoma. This type of tumour is responsible for the RAF/MEK/ERK pathway, which can be targeted by inhibiting BARF activity. Vemurafenib selectively blocks the RAF/MEK/ERK pathway in cells with mutant BRAF. As a result, it is an effective inhibitor

Table 5
The advantages and disadvantages of some important anticancer drugs [112,126–128].

Debrafenib	Advantages	Dabrafenib is used to treat melanoma that has spread or cannot be removed by surgery. It is also used to prevent melanoma from coming back after surgery. It is used only if the melanoma cells have the BRAF mutation. Dabrafenib is also used to treat non-small cell lung cancer and anaplastic thyroid cancer that has spread and has no satisfactory treatment options. It is used only if the cancer cells have the BRAF mutation. Additionally, it is used to treat solid tumors that have spread, cannot be removed by surgery, or have worsened and have no satisfactory treatment options, in combination with trametinib [127]
	Disadvantages	Dabrafenib may cause heart problems and other side effects such as bleeding gums, dry mouth, headache, nausea, skin rash, tingling in hands and feet, vomiting, and more. Contact your doctor immediately if you experience any of these side effects. Blurred vision, eye pain, and sensitivity to sunlight are less common side effects.
Vemurafenib	Advantages	Vemurafenib treats melanoma and Erdheim-Chester Disease. It's used if the melanoma cells have the BRAF mutation. The drug shrinks tumors and helps patients live longer. In a clinical trial, the overall response rate was 53 %. The probability of surviving 12 months with vemurafenib was 40.5 % [112].
	Disadvantages	Vemurafenib can cause side effects such as skin reactions, photosensitivity, headache, and arthralgia. More serious side effects include bloody urine, blurred vision, fainting, and paralysis of nerves. Some side effects are common and can go away during treatment, while others may require immediate medical attention. Researchers are working to expand the use of vemurafenib and prevent drug resistance.
Navitoclax	Advantages	Navitoclax is an experimental anti-cancer drug that inhibits Bcl-2 family proteins. It has been used in trials for solid tumors, lymphoma, and leukemia. Its dose-limiting side effect is thrombocytopenia [129].
	Disadvantages	Thrombocytopenia was the most common adverse event seen in about 80 % of patients during the study of navitoclax. It was a predictable and manageable side effect since the target of navitoclax is highly expressed on thrombocytes. There were no clinically meaningful bleeds observed in the study. There is an algorithm for managing thrombocytopenia since it is a side effect of both navitoclax and ruxolitinib.
Linperlisib	Advantages	Linperlisib inhibits PI3K-delta, which reduces the growth and induces cell death in tumor cells that over-express PI3K-delta. It has shown promising results and manageable tolerability for patients with FL who had received two prior systemic therapies.
	Disadvantages	The incidence of Grade ≥3 treatment-related adverse events was highest for infectious pneumonia (19.0 %), neutropenia (15.5 %), decreased lymphocyte count (4.8 %), decreased leukocyte count (4.8 %), increased lipase (3.6 %), decreased platelet count (3.6 %), hypertriglyceridemia (3.6 %), and interstitial lung disease (3.6 %) [126]

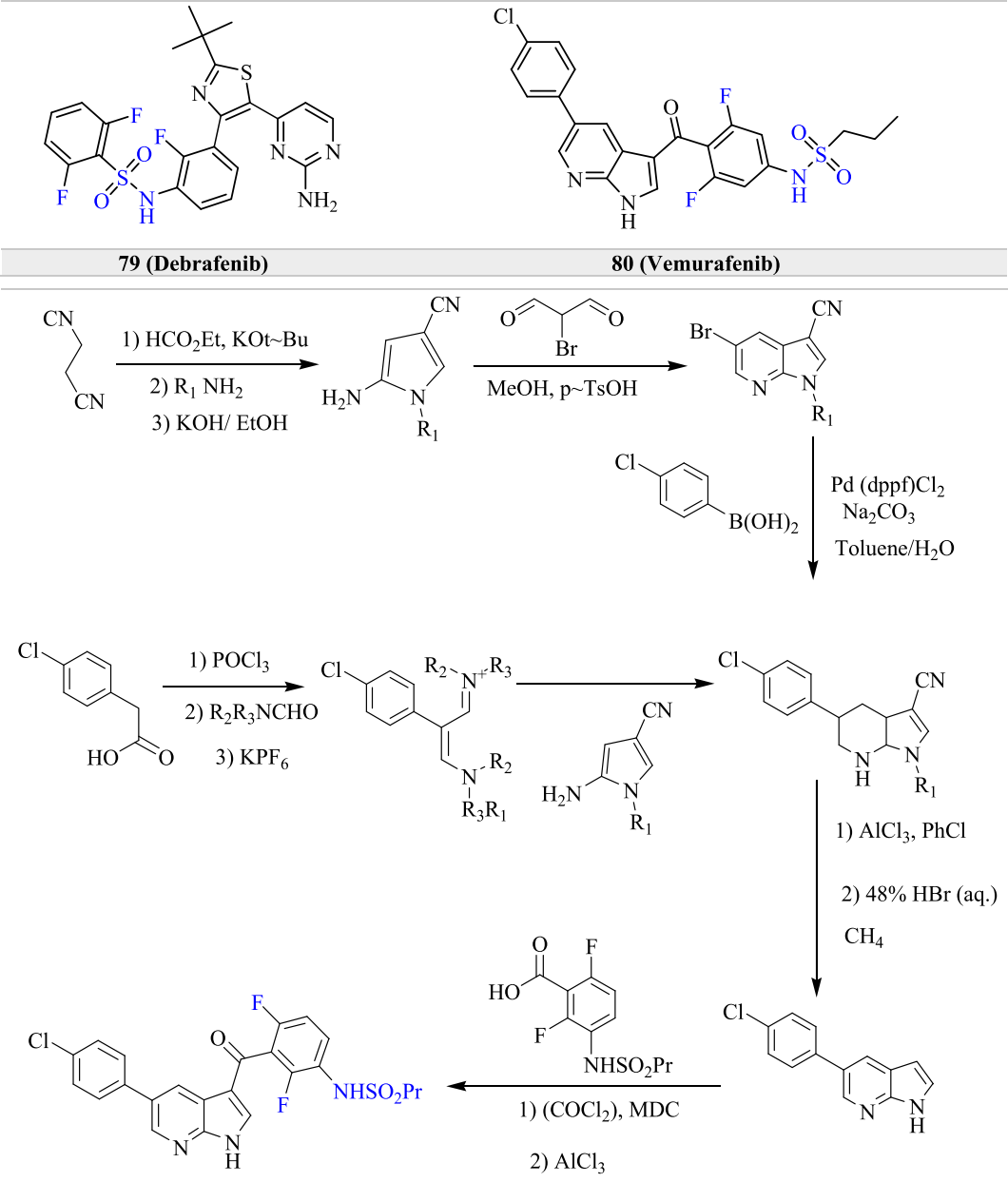


Fig. 21. Reaction scheme of preparation of Vemurafenib.

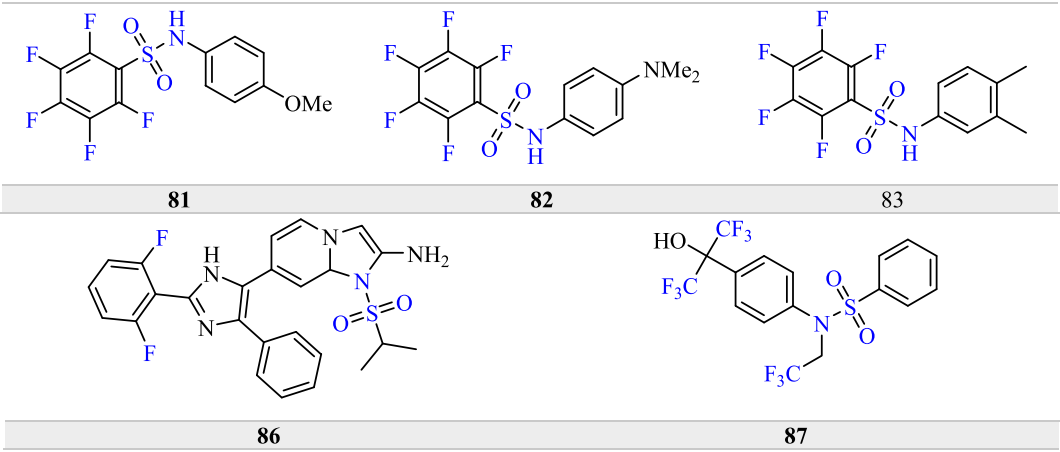


Fig. 22. Anticancerous agents having penta fluoro sulphonamide group.

of oncogenic BRAF. This drug has been approved for use in the US and Europe for treating metastatic melanoma [112] caused by mutated BRAF. It is most effective in cells containing BRAF mutations at codon-600.

Vemurafenib is known for its inhibition activity against the propagation of melanoma, papillary thyroid cancer, and colorectal cancer. A toxicology study has confirmed that Vemurafenib has extensive safety boundaries with a high level of selectivity. In melanoma patients, the inhibition pathway was examined in two weeks, and it showed excellent inhibition progress of ERK phosphorylation. After two weeks of dosing with twice daily doses, Vemurafenib shows good results in most biopsies. In patients with tumor regression pathways, results usually demonstrate more than 80 % of cytoplasm ERK phosphorylation inhibition.

Medina and associates have developed novel antineoplastic agents that apply to tumor cell resistance. The fluorinated sulphonamide derivatives, mostly pentafluorobenzene sulphonamide, are extremely potent in inhibiting the growth of various human tumor cells. These pentafluorobenzene sulphonamide were analyzed on the multidrug resistance (MDR) cell line and MCF-7/ADR.

Multidrug-resistant (MDR) tumors are a major problem in cancer chemotherapy treatment. Such tumors are resistant to a variety of cytotoxic agents such as colchicine, vinblastine, paclitaxel, doxorubicin and antinomycin-D, and exhibit the MDR phenotype. However, the MDR pump in P388/ADR and MCF-7/ADR cells does not seem to influence the cytotoxicity of discovered fluorinated sulphonamide derivatives.

In a study, fluorinated sulphonamide compounds (81, 82, 83, 84, and 85) (Fig. 22) were able to inhibit the in vitro development of cancer cells from human lung leukemia, CNS, colon, ovarian, breast, and renal tumors. The compounds were analyzed against standard Suforhodamine-B assay and showed positive inhibition activity against the cancerous cell. The cellular growth rate was measured 72 h after treatment, using the Alamar blue metabolic dye assay, to have around 50 % growth inhibition (GI_{50}). Among the compounds mentioned above, 81 was found to be the most active cytotoxic agent. The study concluded that the pentafluorobenzene ring plays a very important role in biological activity. Fluorinated compounds are important in the medical and agrochemical fields because of their high target selectivity and less side effect nature on living matter

A new class of drugs has been developed to treat acute and chronic inflammatory diseases. These drugs are fluorinated analogs of

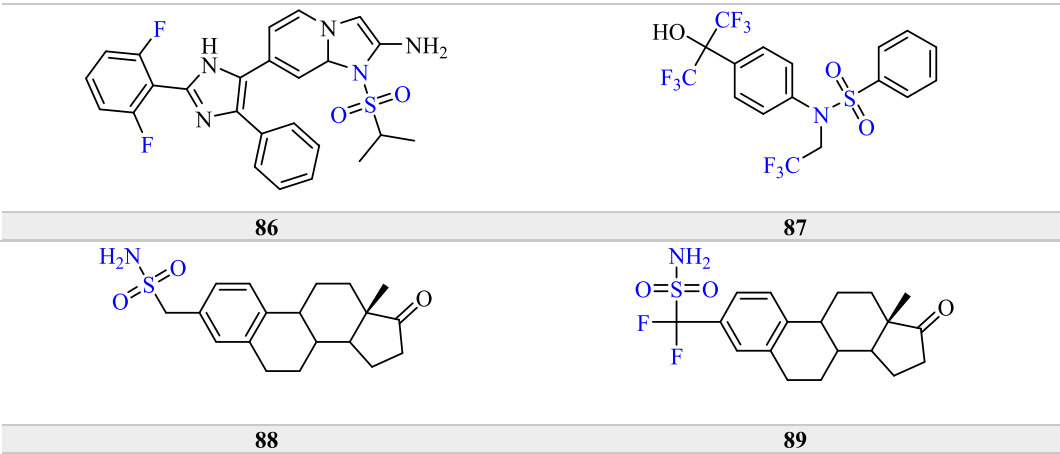
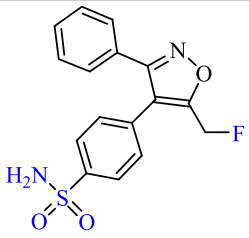


Fig. 23. Fluorinated sulphonamide having an anti-cancerous application [104].



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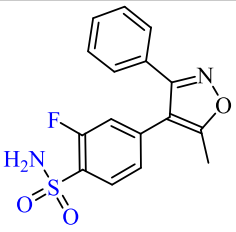

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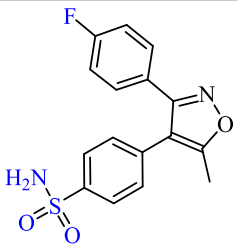

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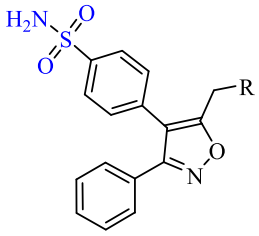


Comp. No.	R
93 (Valdecoxib)	H
94	18F
95	^{19}F

Fig. 24. Valdecoxib-modified derivatives contain fluorine and sulphonamide groups with anti-cancerous application [104].

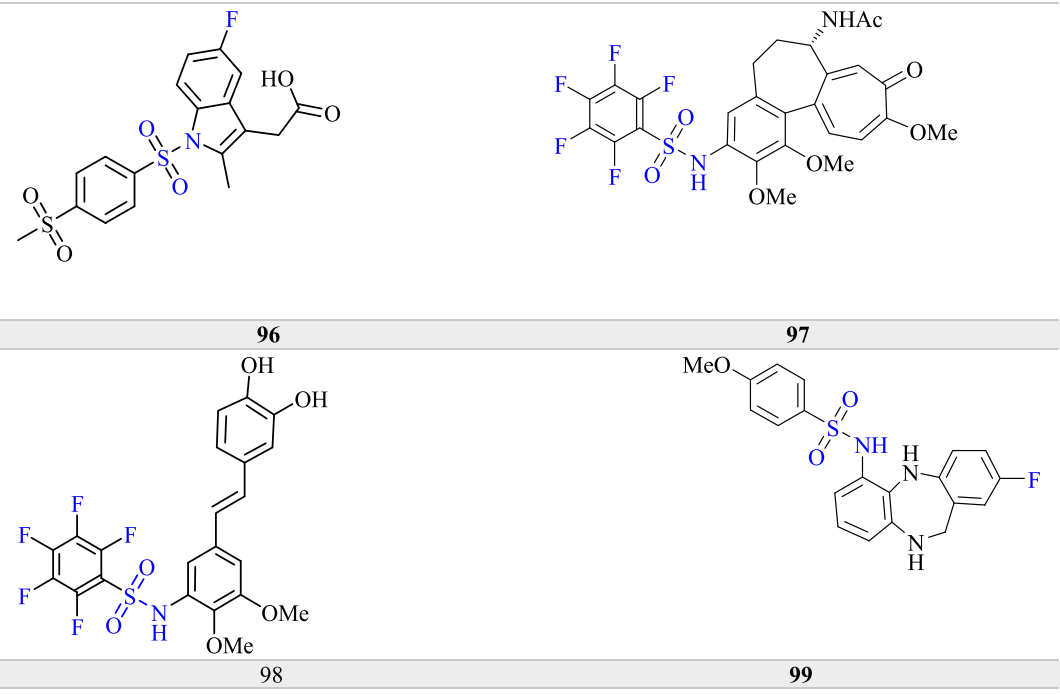


Fig. 25. Valdecoxib modified derivative and other fluorinated Sulphonamide derivatives with anti-cancerous application [116].

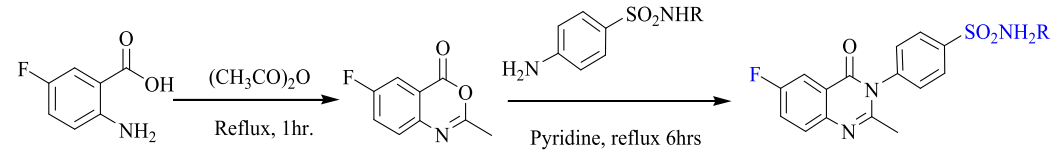


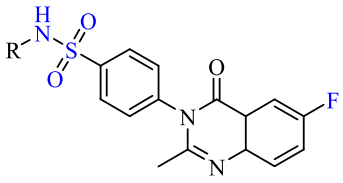
Fig. 26. Reaction scheme of preparation of anticancerous fluorinated sulphonamide [117].

pyridinyl imidazole prototypical inhibitors, such as compound 86. Fluorinated drugs have been shown to have multiple bioactivities, including anti-cancer, anti-diabetic, immunosuppressive, and chronic obstructive pulmonary disease treatment. Compound 87 is an impressive modulator of farnesoid X receptor (FXR), effective against inflammation and cancer. Compound 89 is a more potent fluorinated steroid sulphatase inhibitor analog than its non-fluorinated analog, compound 88. The compound 88 is suitable for inhibiting steroid-dependent cancer (Fig. 23).

Compounds 90, 91, 92, and 93 are new positron emission tomography (PET) developments for ^{19}F imaging in cancer disease. PET is a useful tool for diagnosing the majority of cancer diseases. Fluorinated molecules are particularly effective due to their relatively long half-life of positron emission isotope Fluorine-18 (with a half-life period of 110 min). Compound-90 Fluoroalkyl and compound-94 Fluoroaryl are labeled with radiolabel ^{18}F, while compounds 91 and 92 are analogs of Valdecoxib. These are useful in radiotracer for imaging COX-2 drugs with EGFR and PET biosensors. Many fluorinated sulphonamide non-steroidal anti-inflammatory drugs have been reported and distributed depending on their inhibition properties (Fig. 24). The novel sequence of –N-fluorinated sulfonyl acid-96 has been described and can work against anti-inflamation [113].

Recently, positron emission tomography has been useful as a diagnostic apparatus for numerous cancers [114,115]. Penta-fluorophenyl sulphonamide compound-98 has good antimitotic properties. This tubulin-binding compound achieves facile arylation of the Cys-239 residue of β-tubulin. The compound-97 is also useful as a tubulin-binding compound. The compound-99 shows marginal antitumor activity. The two sulphonamide moieties linking with an aromatic ring and fluorine atoms help improve the overall pharmacological properties of the compounds. The NH group, an ortho position of the sulphonamide moiety, plays a critical role in antitumor activity by cell-based assays. It is a generation antimitotic sulphonamide, also known as ER-34410, and is applicable as an antibacterial derivative. It exhibits excellent activity against panels of various human tumor cell lines in vitro and can be administered intravenously. The para methoxybenzene sulphonamide moiety is essential in overall antitumor activity [116] (see Fig. 25).

The derivatives of fluorinated quinazoline-sulphonamide are effective against cancer diseases [117]. These derivatives are considered highly effective as anticancer agents because they show low toxicity as compared to standard drugs like methotrexate and



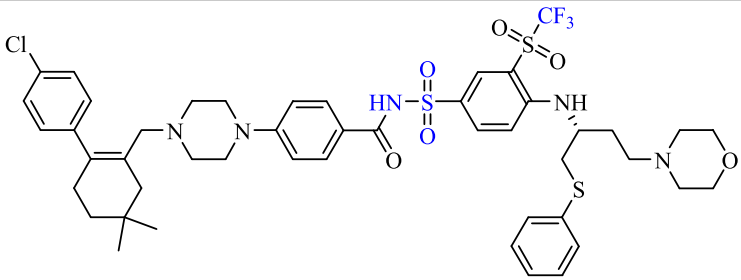
Compound No.	R
100	Pyridin-2-yl
101	3,4-dimethyl isoxazole-5-yl
102	Thiazole-2-yl
103	H
104	5- methylisoxazol-3-yl
105	4-mehtyl pyrimidin-2-yl
106	Diminomethylene
107	4,6-dimethyl pyrimidine-2-yl

Fig. 27. Anticancerous agents having fluorine and sulphonamide group [117].

exhibit lower toxicity on normal cells (see Figs. 26 and 27).

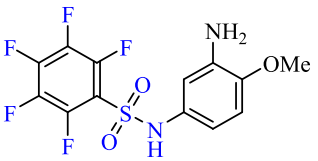
AbbVie has developed a promising anti-cancer drug, compound 108 (Navitoclax) [118]. This drug is used as an experimental oral cancer disease treatment for small-cell lung cancer (SCLC), lymphoid malignancies, solid tumors, and hematological malignancies. Navitoclax is capable of inhibiting Bcl-2 along with Bcl-XL and Bcl-w proteins. However, the Navitoclax can inhibit Bcl-XL and reduce the platelet lifetime, leading to thrombocytopenia and making it dose-limiting. Despite this, it produces complete tumor regression in SCLC and ALL xenograft models. The drug also has excellent pharmacological and physicochemical properties. The anticancer activity of fluorinated quinazoline derivatives is due to their potent inhibition of various enzymes like dihydrofolate reductase, epidermal growth factor receptor tyrosine kinase, tyrosine kinase, and aldose reductase.

Compound 109 (Batabulin) is an orally active antitumor derivative [119]. It binds covalently and selectively to a subgroup of β-tubulin isotopes, disrupting microtubule polymerization. The Batabulin sodium affects cell morphology, leading to cell cycle arrest and eventually causing apoptotic cell death.

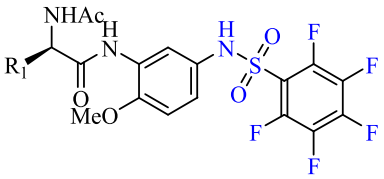


108 (Navitoclax) or (ABT-263)

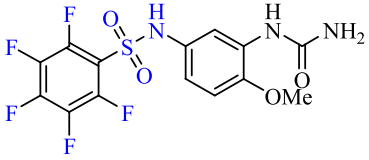
Batabulin (TI38067) is a useful drug for treating advanced non-small cell lung cancer and hepatocellular carcinoma [120–123]. However, it is important to note that TI 38067, present in Batabulin, can penetrate the blood-brain barrier. While this can be advantageous in some cases, it can also create difficulties in certain hydrophilic activities and lead to neurotoxicity. Compounds 111 and 112 cannot cross the blood-brain barrier, while Compound 114 has shown to be equally efficient in vivo and is better tolerated than Batabulin. Compound 115, also known as Linperlisib, has poor penetration in mice's blood-brain barrier, resulting in brain tubulin modification and reduced neurotoxicity (Fig. 28).



110

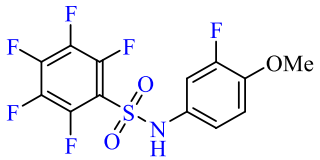


Comp. No.	R^1
111	H
112	Me
113	CH_2OH
114	CHMeOH



115

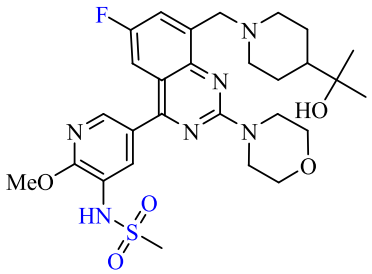
Fig. 28. P13Kδ inhibitor with fluorinated sulphonamide group [120].



109 (Batabulin) or (TI38067)

Linperlisib, which is being developed by Shanghai Yingli Pharmaceutical, is a drug that exhibits high selectivity towards P13Kδ inhibition. It has shown specific selectivity against P13Kδ expressing human tumor cell growth both in-vivo and in vitro. However, this drug is currently under clinical trials.

Linperlisib is capable of inhibiting primary tumor growth in immune-competency mice. This efficiency is largely mediated by T-cell [124,125].



116 (Linperlisib)

The 79-Dabrafenib is a medication that works by binding to BRAF and MEK inhibitors in the body. Doing so creates a blockade point

Table 6
The advantages and disadvantages of Bendroflumethiazide drugs [134,135].

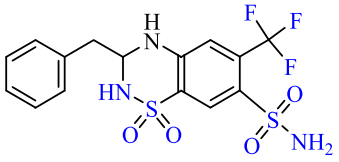
Bendroflumethiazide	Advantages	Bendroflumethiazide is a medication that aids in the suppression of lactation and is also utilized in the management of hypertension, edema, and urinary tract disorders. It has also shown promise in treating familial hyperkalemia. As a diuretic, it works by increasing the volume of urine expelled by the kidneys.
	Disadvantages	Possible side effects of diuretic therapy include nausea, upset stomach, dizziness upon standing, cardiovascular complications, dermatologic reactions, and phototoxic dermatitis. Hypersensitivity reactions may affect various systems, such as the skin, gastrointestinal, genitourinary, and respiratory systems.

in the MAPK pathway at two different levels. This, in turn, inhibits the oncogenic downstream signaling and causes cell cycle arrest. This mechanism of action makes dabrafenib an effective treatment option for certain types of cancer that are driven by the mutation in the BRAF gene.

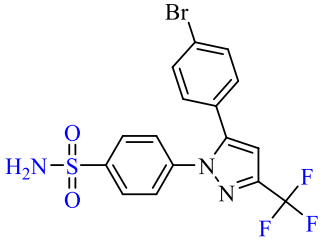
The mode of action of 116-Linperlisib is an oral medication that selectively targets PI3K-delta, inhibiting the activation of the PI3K/AKT signaling pathway. This leads to decreased proliferation and cell death in PI3K-delta over-expressing tumor cells. Whereas in 108-Navitoclax selectively binds to apoptosis suppressor proteins Bcl-2, Bcl-XL, and Bcl-w, which are often overexpressed in various cancers, including lymphoma, breast, lung, prostate, and colon. These proteins have been linked to cancer drug resistance.

3.3. Inhibition of COX enzyme by fluorinated sulphonamide compounds

The cyclooxygenase (COX) enzyme, also known as prostaglandin-endoperoxide synthase (PTGS), produces prostanoids like thromboxane and prostaglandins such as prostacyclin from arachidonic acid. COX-1 is present in interstitial cells, blood vessels, smooth muscle cells, mesothelial cells, and platelets, whereas COX-2 is found in parenchymal cells of many tissues, chondrocytes, and endothelial cells. Inhibiting COX can relieve inflammation and pain symptoms. Most NSAID drugs work by inhibiting COX. Inhibiting COX-2 can provide therapeutic benefits typically associated with NSAIDs without the traditional side effects. COX isoforms differ mainly in their blood expression level and messenger RNA regulation [130,131]. Recent US-FDA medicines contain sulfur atoms; among all sulfur-containing drugs, sulphonamide is the most important class. It is effective against fungal and bacterial infections, high blood pressure, diabetes, HIV, malaria, typhoid, and fever and stimulates insulin secretion. Sulphonamide, fluorine, and heterocyclic compounds are highly active against their targets.



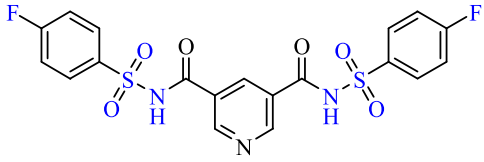
117 (Bendroflumethiazide)



118 (SC-558)

The drug 117 Bendroflumethiazide, is highly effective in treating two conditions: high blood pressure and Edema [111].

119



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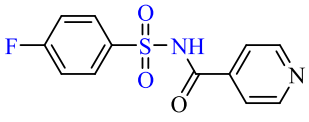

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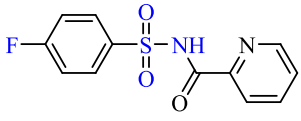

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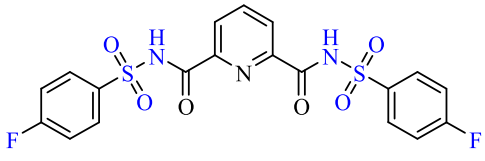
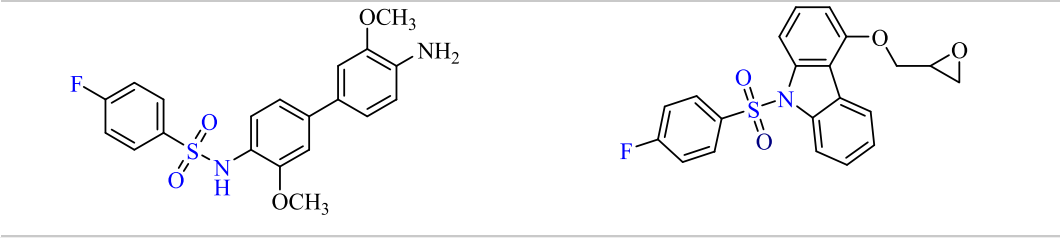


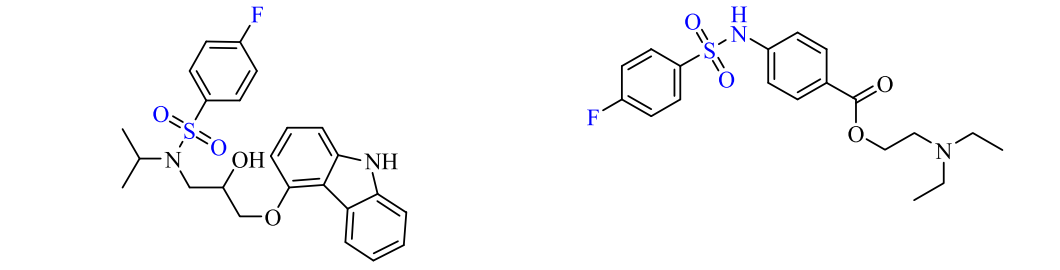
123

Fig. 29. Pyridine-based fluorinated sulphonamide as an anticancer agent [133].



124	125

Fig. 30. Antifungal fluorinated sulphonamide [136].



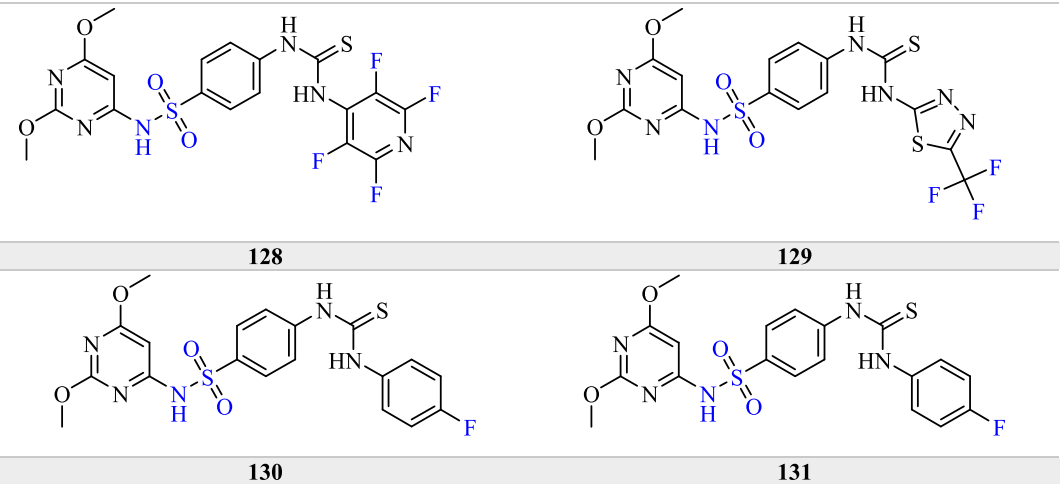
126	127

Fig. 31. Fluorinated sulphonamide derivatives contain antifungal and antioxidant activity [136].

Meanwhile, the drug Celecoxib is a non-steroidal anti-inflammatory drug that is mainly a COX2 inhibitor. It helps alleviate pain and swelling and treats acute pain, menstrual pain, and discomfort. Celecoxib is also beneficial in reducing the occurrence of stomach ulcers and the effects of platelet aggregation Table 6.

The chemical compound 118 SC-558 shares a similar structure to celecoxib, which includes a pyrazole base. However, it features a bromine substitution on the phenyl ring instead of a methyl group. This category of COX inhibitors incorporates substituted diaryls onto a central core of heterocycle scaffolds composed of five- and six-membered rings, including pyrazole (as seen in celecoxib). Vital sulfonamide and methanesulfonyl groups are present to achieve selective COX-2 inhibition. In the case of celecoxib, a diaryl pyrazole-based COX-2 inhibitor, the –SO2NH2 group binds to amino acids His90 and Arg513 through sulfonyl oxygen atoms. Additionally, it interacts with amino acid Phe518 via carbonyl oxygen atoms and can further substitute with Val434 and Arg513 residues [132].

Some novel COX-2 inhibitor pyridine acyl sulphonamide compounds [133] show highly accurate activity on the target. The cyclooxygenases (COXs) are mainly responsible for the production of prostaglandins H2, which are the precursors of prostacyclins, prostaglandins, and thromboxanes. COX comes in two types, namely COX-1 (a constitutive form of cyclooxygenase-1) and COX-2 (inducible form of cyclooxygenase-2). COX-1 is a housekeeping enzyme commonly found in inactive cells of most tissues involved



128	129
130	131

Fig. 32. Fluorinated sulphonamide baring antifungal and antibacterial activity [137].

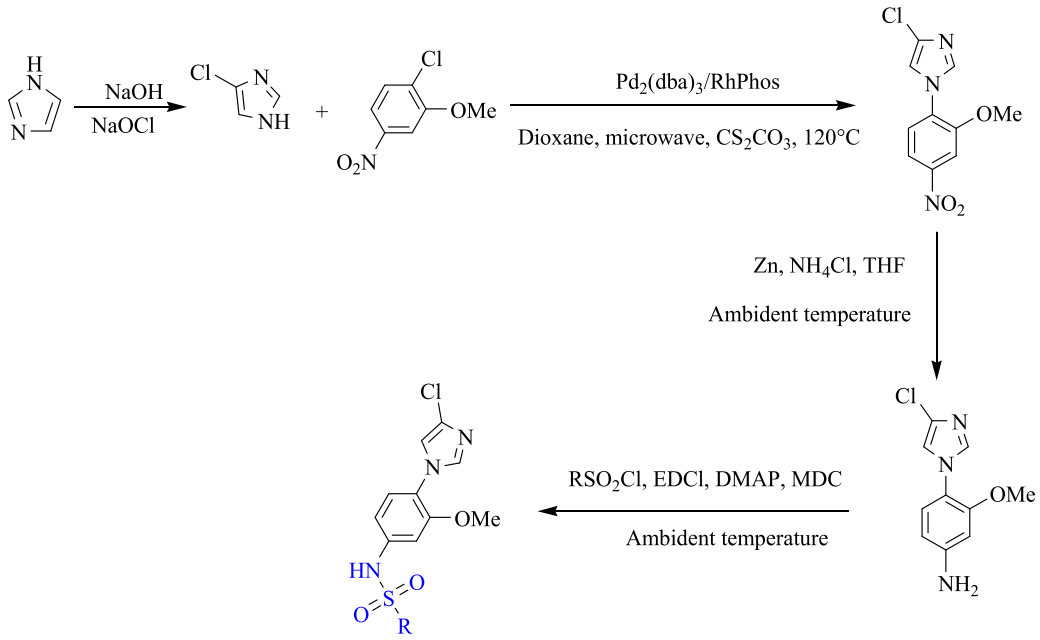


Fig. 33. General reaction scheme for the preparation of fluorinated sulphonamide derivatives [25].

in protecting gastric mucosa, renal blood flow, and platelet aggregation. On the other hand, COX-2 is useful in reacting quickly to a variety of pro-inflammatory stimuli such as interleukins, tumor necrosis factor (TNFα), and growth factors.

COX-2 enzyme plays a significant role in chronic pain and cancer development. However, standard non-steroidal anti-

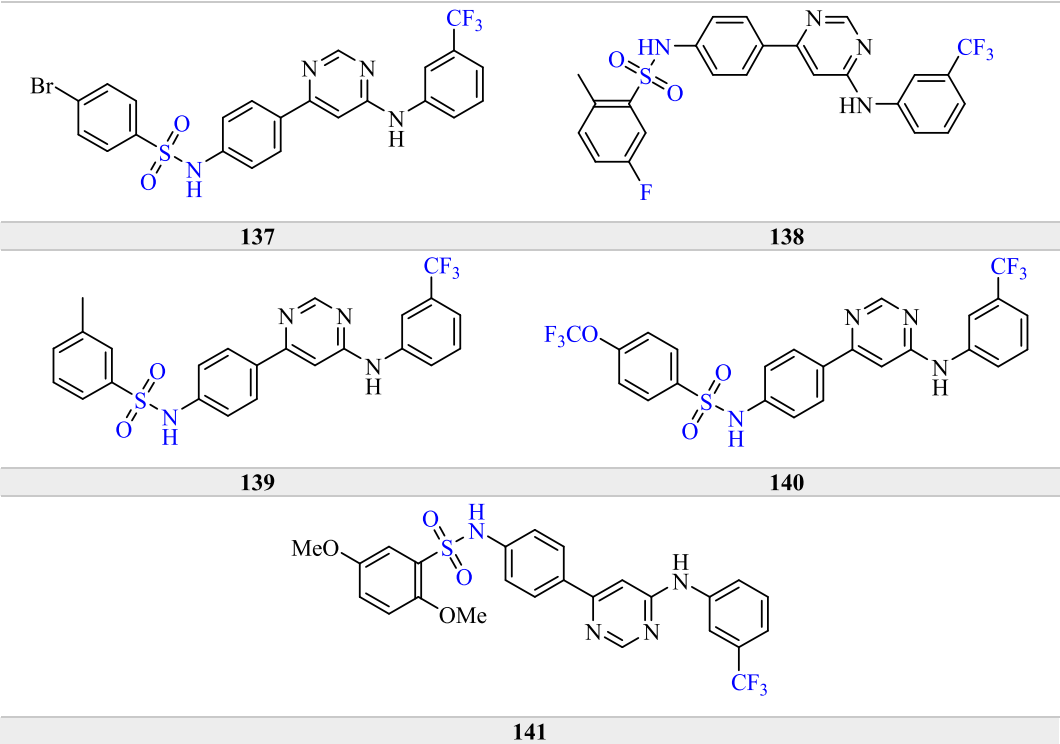


Fig. 34. Antibacterial and antifungal fluorinated sulphonamide derivatives [139].

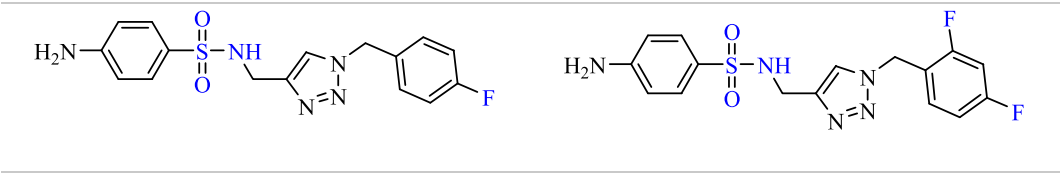


Fig. 35. Antibacterial compounds contain fluorine and sulphonamide groups [139].

inflammatory drugs used for treating inflammation can cause side effects like gastrointestinal irritation, leading to bleeding and ulcers due to their inhibition of COX-1 enzyme. Researchers have synthesized sulphonamide derivatives such as Valdecoxib, Celecoxib, and Nimesulide to selectively inhibit COX-2 enzymatic activity to overcome this challenge. The pyridine ring and sulphonamide derivatives exhibit a synergistic effect in anti-inflammatory and anti-tumor activity, making them effective in the medical field. The study showed that the developed compounds (119, 120, 121, 122, and 123) (Fig. 29) exhibited extraordinary and selective inhibition activity towards COX-2 while showing poor activity in terms of COX-1 inhibition. Synthesized compounds showed very good inhibitory activity against human breast cancer, melanoma, and liver cancer cell lines. The study indicated that para substitution on the phenyl ring exhibits good COX-2 inhibition activity (IC50 value in-between 1.2 to 22.2 μM), and the electron-withdrawing halogen group might be responsible for improving COX-2 inhibition activity. The molecular asymmetry of these molecules might be suitable for obtaining potent new COX-2 inhibition agents.

3.4. Antifungal, antibacterial, anti-inflammatory and antimicrobial compounds based on fluorinated sulphonamide

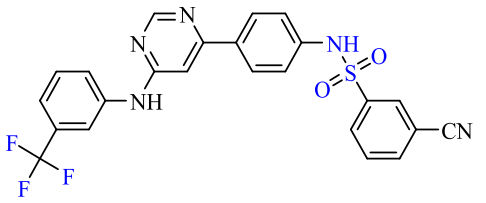
The activity of antiviral and antibacterial molecules is closely related to their ability to destroy viruses and bacteria aggressively or to slow down their growth rate without causing widespread toxicity to surrounding tissues. Anti-inflammatory drugs are generally used to reduce inflammation and swelling. These drugs usually contain analgesic ingredients that help to reduce pain and inflammation, as opposed to opioids, which affect the central nervous system and block pain signals to the brain. Antimicrobial compounds are used to destroy microorganisms or inhibit their growth, such as antibiotics, typically used to kill bacteria, and antifungal drugs, which are used to treat fungi.

Biologically active sulphonamide fluoro derivatives have been synthesized and tested for their antibacterial, antifungal, and antioxidant activities in vitro. The results showed significant impact on these activities [136]. Compounds such as N, N'-(3,3-dimethoxybiphenyl-4,4-diyl) bis (4-fluorobenzenesulfonamide) 124 and (S)-9-methyl-4-(oxiran-2-ylmethoxy)-9H-carbazole 125 demonstrated very good antifungal activity as compared to the Chloramphenicol molecule (Fig. 30). These compounds were tested against the fungi Curvularia lunata and Aspergillus Niger. Another fluorinated sulphonamide, N-(3-(9H-carbazol-4-yloxy)-hydroxypropyl)-4--fluoro-N-isopropylbenzenesulfonamide 126, showed more activity towards fungi than the standard compound Ketoconazole. Additionally, 2-(diethyl amino) ethyl 4-(4- fluorophenylsulfo-namido) benzoate 127 exhibited antioxidant activity, which was analyzed by the radical scavenging and DPPH methods. The developed novel fluorinated molecules showed higher activity towards their target, possibly due to the introduction of active fluorine molecules with sulphonamide (see Fig. 31).

Fluorinated sulphonamide and thiourea functional groups are used to create various molecules with antimicrobial, anticancerous, and antifungal properties [137]. Fluorinated pyridine derivatives enhance the pharmacological activity of sulphonamide compounds. Among these derivatives, Compound-128 displays the highest activity against gram-positive and gram-negative bacteria while Compound-131 shows moderate antibacterial activity. The antibacterial activity increases as the number of fluorine atoms in the molecule increases. The combination of tetrafluoro-pyridine and sulphonamide gives even more benefits for the increase of antibacterial activity. This molecule was also tested against the standard anticancerous drugs 5-Flourouracil and *cis*-platin and showed excellent activity against tumor cells, thus exhibiting anticancerous activity. Additionally, Compound-128 and Compound-130 display antifungal activity.

Compounds 128, 129, and 130, which are fluorinated sulphonamides, were docked and fit onto the active site of the MK-2 enzyme. These compounds exhibit higher activity against liver carcinoma cell lines than 5-Fluorouracil and *Cis*-platin (Fig. 32).

Compounds 132, 133, and 135 show excellent antibacterial and antifungal activity compared to the standard compounds Miconazole and Ciprofloxacin. However, these molecules exhibit low or no anti-inflammatory activity. Compound-135 displays high potency towards anti-inflammatory activity, possibly due to a thiourea group combined with pyrimidine and fluorinated atoms. On the other hand, compound-132 is not highly efficient for antifungal and antibacterial agents. The coupled benzene ring to the backbone of these compounds is mainly responsible for most of their biological activity. The substituent on the benzene ring to sulphonamide, thiourea terminus, and its position strongly relates to their biological activity, and the presence of F, CF_3 group gives them significant-high potency.



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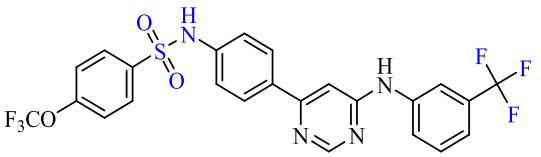
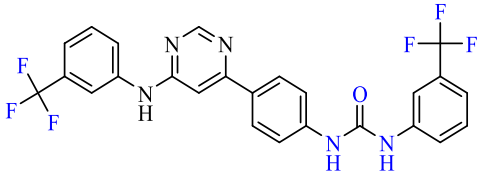


133



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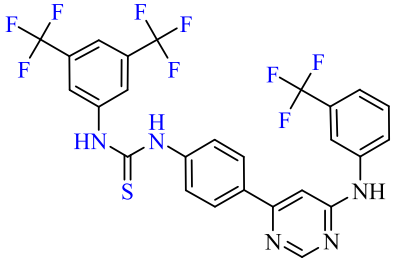
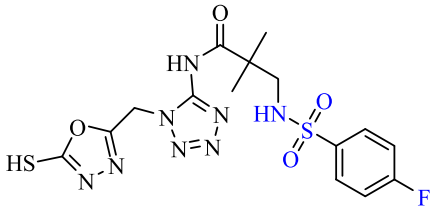


135

Certain sulphonamide derivatives that possess antimicrobial and antioxidant properties have been developed (Fig. 33). These derivatives contain a tetrazole, oxadiazole ring, and fluorine atom [25], known for their potency. The sulphonamide derivatives have been prepared with a halogen atom that is highly effective against bacteria and fungi. The biological activity of these derivatives has been tested against gram-positive bacteria like *Bacillus subtilis* and *Staphylococcus aureus*, and gram-negative bacteria like *Escherichia coli* and *Klebsiella pneumonia*. Analysis of these compounds has shown that they exhibit better activity than standard chemical compounds.



136

Compound-136 has been found to have good antibacterial activity against the targeted organism. Additionally, it shows excellent antioxidant activity and remarkable antifungal activity[25]. The sequence of the new 4-(3-(Trifluoromethyl) phenylamino-6-(4-(3-aryl sulfonamide)-pyrimidine derivative has potent antimicrobial and anti-inflammatory activity [138].

In general, pyrimidine-containing compounds have shown potency in many biological activities, such as being an analgesic agent, anti-HIV, anti-tumor, anti-microbial, and so on. The above compounds (137–141) exhibit moderate or negligible anti-inflammatory activity. This fluorinated sulphonamide was analyzed for in vivo antibacterial and antifungal activity against gram-positive and gram-negative bacteria. Antifungal activity was evaluated using the agar well diffusion method (Fig. 34).

Compounds 138, 140, and 141 exhibit antibacterial activity that is equal to or even better than standard Ciprofloxacin. They also demonstrate good antifungal activity when compared to standard Miconazole compounds. Specifically, compounds 140 and 141 are particularly effective against bacteria such as *Staphylococcus aureus*, *Salmonella typhimurium*, and *Bacillus subtillis.*

The fluorinated sulphonamide group is significant in medical chemistry, as it has various biological activities and potency in supramolecular medicinal chemistry [139]. Most Ag-sulfadiazine compounds have proven their effectiveness against microbial burning diseases and even show better activity than $AgNO_3$ or free ligand compounds.

Sulphonamide has good combinational pharmacological activity with trimethoprim. Compound 143, which bears the sulphonamide group, is more potent as an antibacterial activity than standard fluconazole and chloramphenicol molecules. These compounds also show activity against *S. aureus*, methicillin-resistant *S. aureus* (MRSA), and *B. subtilis*. The alkyl substituents on the benzyl moiety and chain length play a vital role in the antimicrobial activity of fluorinated sulphonamide in vitro (Fig. 35).

Novel 1-acetyl-3,5-diaryl-4,5-dihydro (1H) pyrazole derivatives combined with different sulphonamides exhibit good antifungal and antibacterial activity [138]. Pyrazole compounds have proven to have key pharmacological activities, making them the most promising scaffold in pharmaceutical research. The compounds mentioned below (Fig-36) show promising antimicrobial activity, with MIC values ranging from 70 to 10 μg/mL against pathogenic fungi and bacteria.

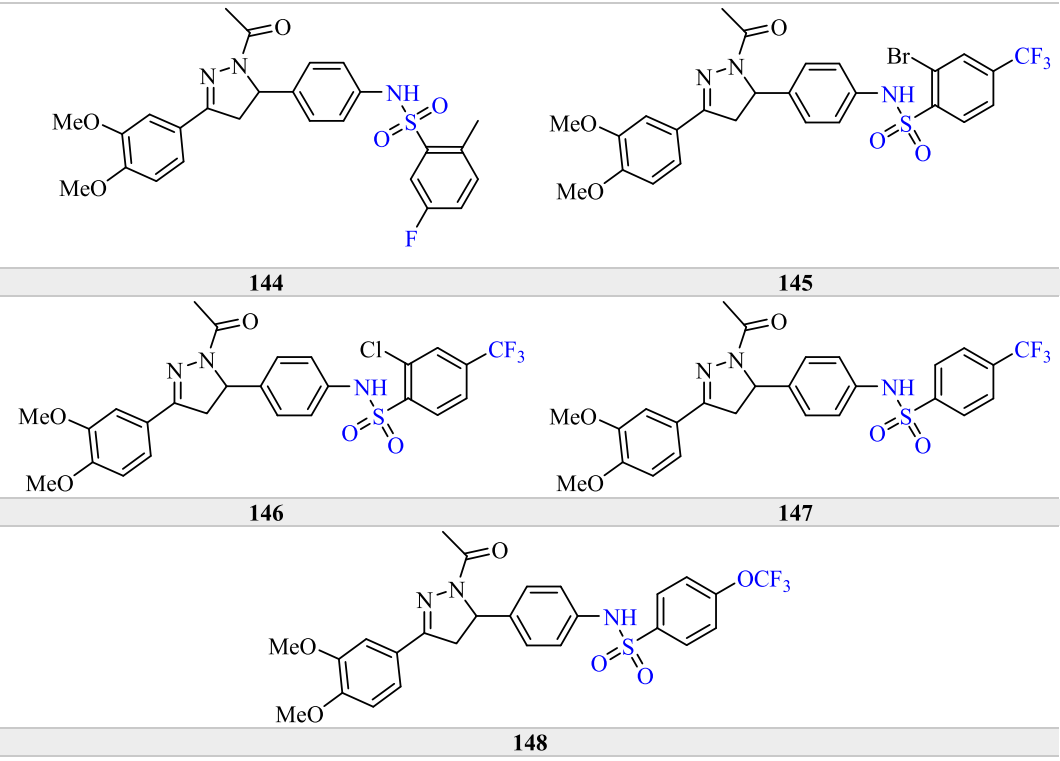


Fig. 36. Anti-inflammatory fluorinated sulphonamide [138].

Various biological activities such as antifungal, antipyretic, antiviral, anti-inflammatory, antimicrobial, and anticancer activity can be demonstrated by pyrazole coupled with sulphonamide compounds. Synthesized novel pyrazole-based sulphonamide molecules can exhibit multifunctional activity for treating various diseases. These molecules can target anti-inflammatory and antimicrobial activity, making them beneficial for treating multiple diseases. The compounds 144, 145, 146, 147, and 148 (Fig. 36) were analyzed for in-vitro anti-inflammatory activity by using the pro-inflammatory cytokines TNF-α and IL-6 inhibition assay. Fungal activity was determined using the Agar well diffusion method, and antimicrobial activity was performed against gram-positive and gram-negative bacteria.

Compound 146 showed moderate activity in the anti-inflammatory study, whereas the rest of the compounds did not contain anti-inflammatory activity. However, all the mentioned compounds exhibited higher antibacterial activity than the standard Ciprofloxacin

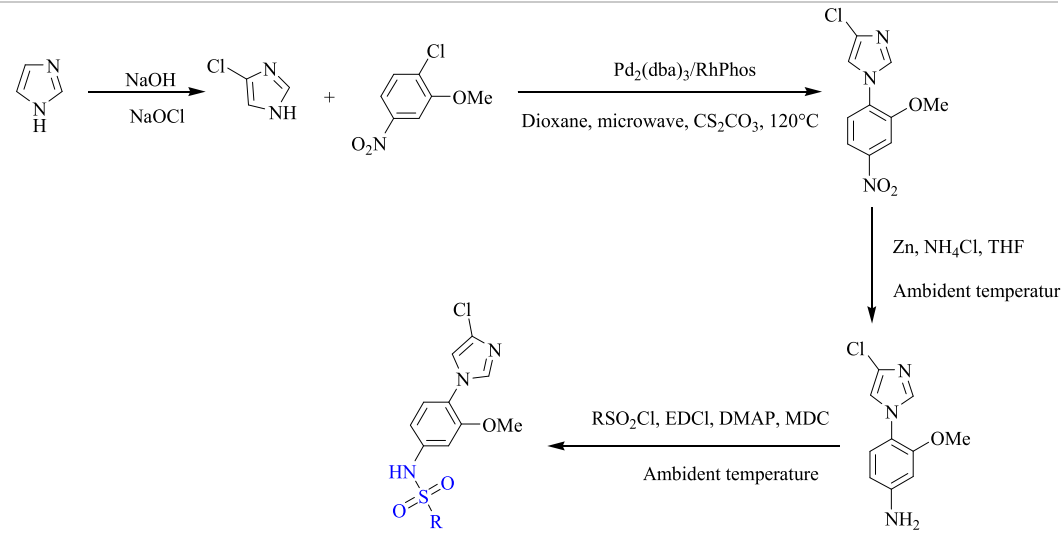
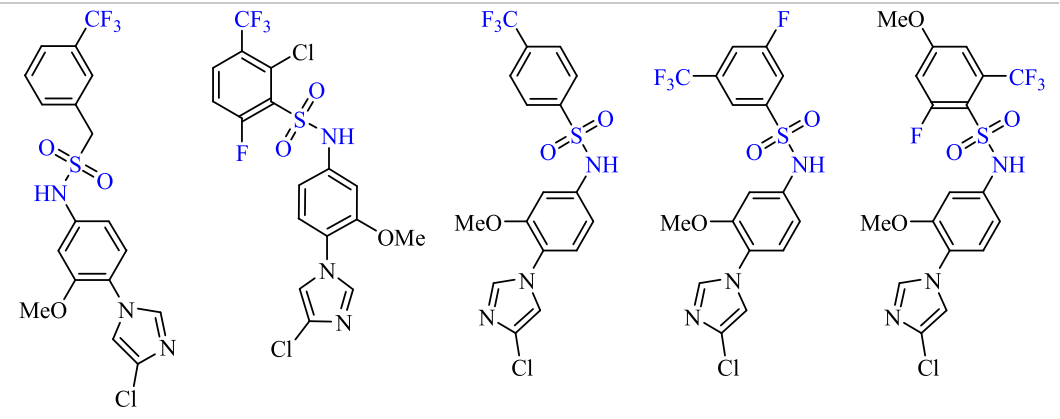
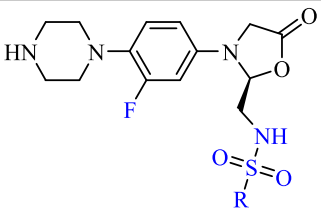


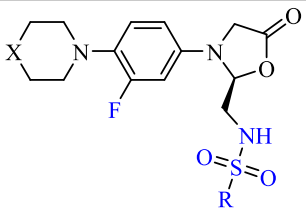
Fig. 37. Reaction scheme of preparation of fluorinated sulphonamide antimicrobial and antitubercular derivatives [140].



149	150	151	152	153

Fig. 38. N-(4-(4-chloro-1H-imidazole-1-yl)3-methoxyphenyl) sulphonamide baring antitubercular and antimicrobial activity [140].



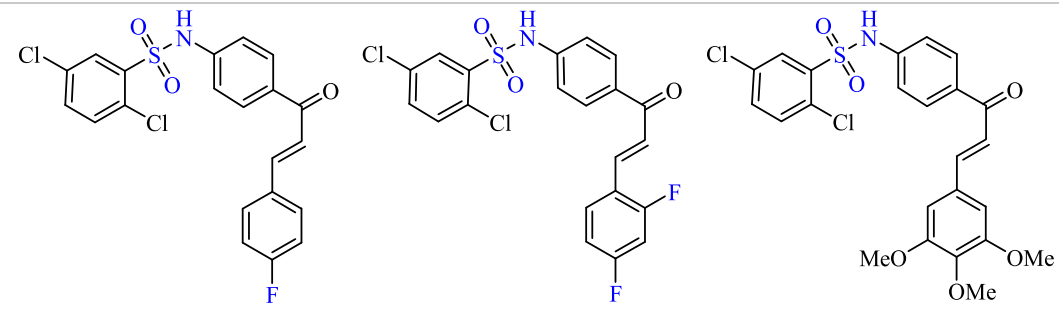


Comp. No.	R
154	4-CF_3-C_6H_4
155	4-F-C_6H_4

Comp. No.	X	R
156	O	4-CF_3-C_6H_4
157	O	4-F-C_6H_4
158	S	4-CF_3-C_6H_4
159	S	4-F-C_6H_4

Fig. 39. Fluorinated sulphonamide compounds having antimicrobial activity [141].

strain. Compound 145 showed higher antibacterial activity because of the presence of CF_3 and bromo group on the benzene ring. This compound showed double potency against *Salmonella typhimurium* and *Staphylococcus aureus*. Compound 146 showed 1.5 times more activity against *Escherichia coli* due to the chlorine and trifluoromethyl group on the sulphonamide terminus benzene ring. The compound 147 contained a trifluoromethyl group at the para position of the sulphonamide terminus benzene ring, making it doubly



160	161	162

Fig. 40. β-hematin inhibitor contains fluorine and sulphonamide group.

Table 7
The advantages and disadvantages of some anti-HIV drugs [157–159].

Tipranavir	Advantages	Tipranavir is a protease inhibitor medication used with ritonavir and other drugs to treat HIV. It lowers the amount of HIV in the body, improving the immune system and reducing the risk of complications from the virus. However, it is not a cure for HIV infection. To decrease the risk of spreading the virus, it is important to take all HIV medications exactly as prescribe.
	Disadvantages	Unusual side effects, including bleeding gums, coughing up blood, difficulty breathing or swallowing, prolonged bleeding, or yellow eyes and skin. Other side effects, such as diarrhea, rash, or trouble sleeping, may occur but usually do not require medical attention. Contact your healthcare professional if they continue or are bothersome.
Lenacapavir	Advantages	Lenacapavir is a first-in-class HIV-1 capsid function inhibitor. It is approved by the FDA for the treatment of MDR HIV-1 infection in adults with multiple drug resistance where current antiretroviral therapy is ineffective. It can be taken orally or through subcutaneous injection.
	Disadvantages	Common side effects of this medicine include reactions at the injection site and nausea, bleeding, blistering, burning, coldness, discoloration of skin, hives, infection, inflammation, itching, numbness, pain, rash, redness, scarring, soreness, stinging, swelling, tenderness, tingling, ulceration, or warmth at the injection site. Other side effects such as dark urine, fever, joint pain, muscle tenderness or weakness, skin rash, sudden numbness in the limbs, unusual tiredness, upper right abdominal or stomach pain, weight loss, and yellowing of the eyes and skin may also occur.

potential in opposition to *Aspergillus flavus*.

The presence of Cl, Br, F, OCF_3, and CF_3 groups at the para and ortho position of the sulphonamide terminus benzene ring makes the molecule highly effective against antimicrobial activity. Furthermore, different groups and their position on the substrate alter the biological activity and lipophilic character. Novel N-(4-(4-chloro-1H-imidazole-1-yl)3-methoxyphenyl) amide/sulphonamide derivatives exhibit antitubercular and antimicrobial activity [140].

Compounds 150, 151, and 152 have shown significant effectiveness against the *Mycobacterium tuberculosis* H37Rv strain. Tuberculosis is a highly contagious disease caused by *Mycobacterium tuberculosis*, which affects both pulmonary and non-pulmonary tissues. It is a chronic disease that takes a long time to develop. Imidazole derivative is known to exhibit antimicrobial activity, and in the case of Fig. 38 compounds, the lipophilicity plays a vital role, particularly the halogenated or CF_3 substituents that increase the lipophilic nature of the derivatives. Meanwhile, the methoxy and methyl groups act as electron donors, and the sulphonamide group is essential in enhancing the biological activity of the mentioned compounds. The N-(4-(4-chloro-1H-imidazole-1-yl) 3-methoxyphenyl) sulphonamide derivatives were synthesized successfully using Fig. 37 route.

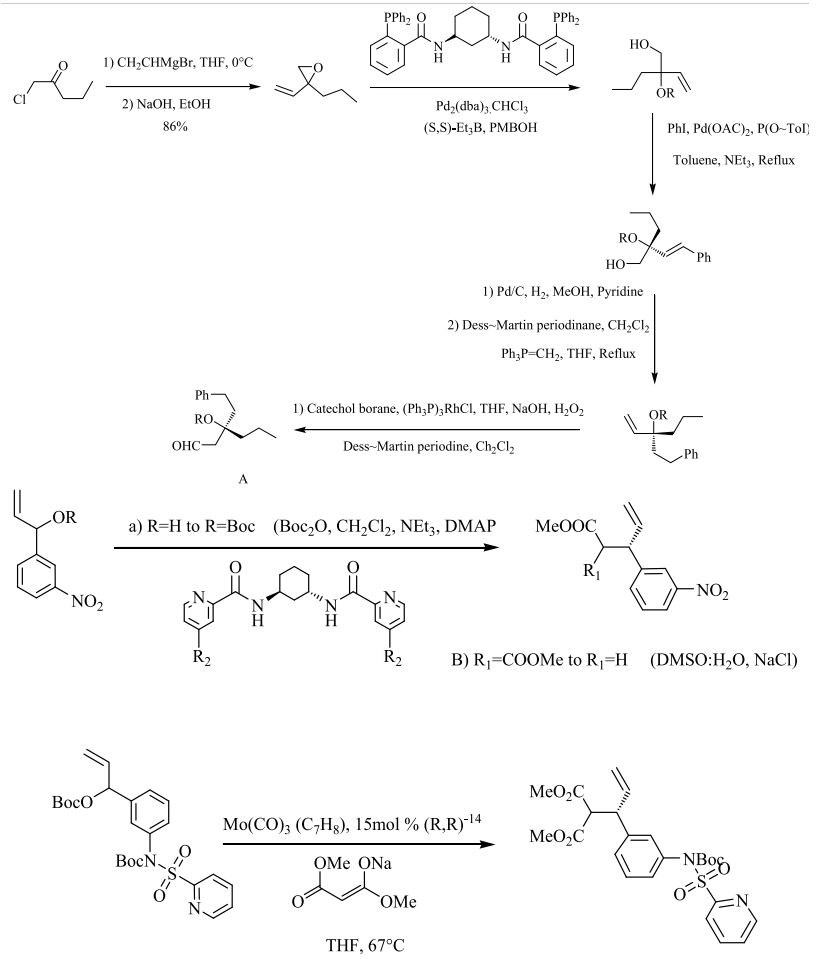
Novel oxazolidinone-sulphonamide derivatives (Fig. 39) were evaluated for their antimicrobial activity against standard gram-positive bacteria such as Bacillus subtilis (MTCC 121), Micrococcus luteus (MTCC 2470), *Escherichia coli* (MTCC 739), and found to have good antimicrobial properties [141]. Compounds 154, 155, 156, 157, and 158 showed good antimicrobial activity against the evaluated strain, ranging from 2.0 to 8.0 μg/mL. The electron-withdrawing groups like F and CF_3 on the aryl ring of sulphonamide are responsible for significant antimicrobial activity.

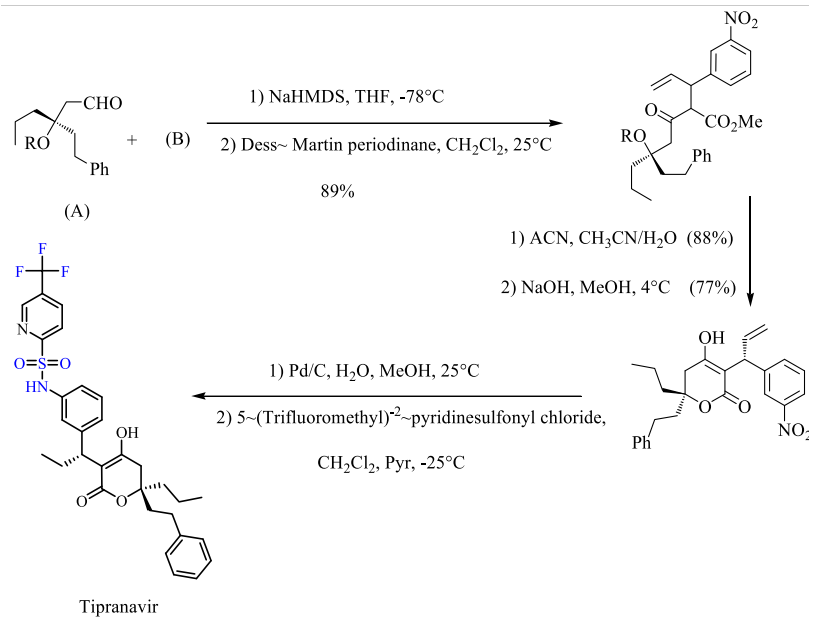
3.5. Applications of fluorinated sulphonamide as anti-malarial compounds

Malaria remains one of the leading causes of mortality and morbidity worldwide. The Laveran described *Plasmodium* species, and Ross confirmed that the disease gets transmitted by female anopheline mosquitoes. After developing some antimalarial drugs, the transmission rate has slowed down. *Plasmodium falciparum* is the most virulent species responsible for most of the deaths, followed by *Plasmodium Vivax* [142]. Pregnant women and newborn children are the most vulnerable to this disease [143,144]. Malaria spreads mainly when resources are limited and cannot provide proper diagnosis and treatment [145]. Over the last fifteen to twenty years, with renewed efforts in the medical field, malaria has been reduced by more than half by developing novel antimalarial drugs [146,147]. Some of the fluorinated sulphonamide derivatives have shown great effectiveness against malarial diseases. The sulphonamide chalcone derivatives have shown good anti-malarial activity [148]. They can inhibit in vitro β-hematin formation and show good action against cultured *Plasmodium falciparum* parasite.

Malaria is a serious infectious disease that affects humans worldwide. Every year, around 275 million cases of malaria are reported, and out of them, 2 million result in death. *P. Plasmodium falciparum* is a virulent species responsible for causing human infection in most cases of malaria. Recently, Chloroquine has been used to treat malaria by inhibiting hemozoin formation, which is a process that is exclusive to the malaria parasite and can be targeted to develop new anti-malarial drugs.

A newly synthesized fluorinated sulphonamide (Fig-40) was evaluated for its ability to inhibit β-hematin formation using *P. falciparum* parasite culture. The study found that compounds 161 and 162 effectively inhibited β-hematin formation and had better IC_{50} than Chloroquine. The anti-malarial activity of these compounds was attributed to the presence of fluorine, an alkoxy group with an aromatic ring, and mono, di, and trimethoxy substituted groups with an aromatic ring. Compounds with more methoxy substitutions were found to be more potent, demonstrating higher activity against β-hematin formation. Compound 162, which contains a methoxy group, was found to have superior activity toward anti-malarial drugs compared to chloroquine. The difluoro group in the compound is responsible for its electronegative effect, leading to a stronger chemical interface on the biological substrate site.





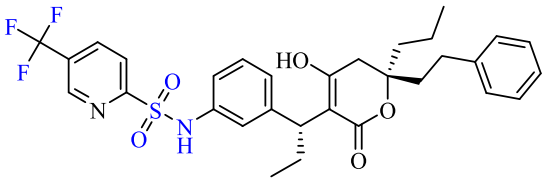
(caption on next page)

Fig. 41. Reaction scheme for the preparation of Tipranavir [151].

3.6. Anti-HIV compounds based on fluorinated sulphonamide

Human Immunodeficiency Virus (HIV) is a virus that mainly attacks the immune system of humans. If the virus is not treated effectively, it can lead to AIDS (Acquired Immunodeficiency Syndrome) [149,150]. Unfortunately, there is currently no cure for HIV, but with proper medical care, people can still live long and healthy lives and protect their partners. HIV is commonly transmitted through semen, vaginal fluid, and infected blood. Fortunately, many drugs are available to control HIV, and certain fluorinated sulphonamide derivatives have been shown to be effective in treating the virus. Some important anti-HIV drugs advantages and limitations are highited in Table 7.

Tipranavir [151,152], also known as Tipranavir disodium, is a non-peptide protease inhibitor drug that is used to treat HIV infection when combined with Ritonavir [111]. This drug is particularly effective against viruses that resist other protease inhibitors. Sulfur is a versatile atom found in most essential drugs, including Tipranavir. Aptivus is the trade name for Tipranavir (163), which was manufactured by Boehringer Ingelheim. The FDA approved this drug in 2005. The advantage of Tipranavir over other protease inhibitors is that it is a managed protease inhibitor of a reduced peptide nature, which shows advanced pharmacokinetic properties. With the increasing number of protease inhibitors, Tipranavir becomes increasingly useful for treating AIDS. Additionally, it shows lower toxicity and tolerable drug delivery along with distribution features. Fig. 41 shows the stepwise chemical synthesis of Tipranavir .

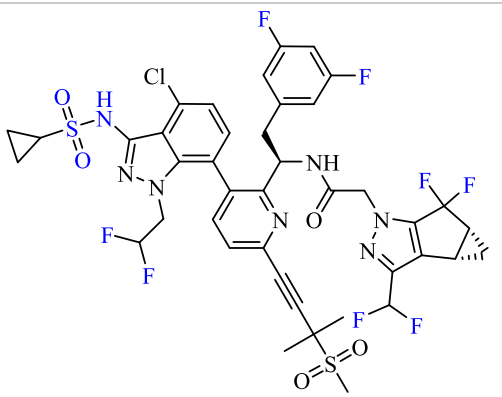


163 (Tipranavir)

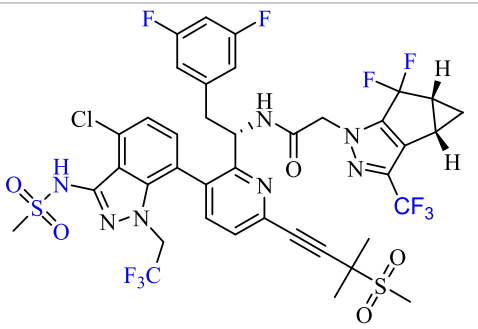
Certain derivatives of fluorinated sulphonamide with pyrimidine bases exhibit potent HIV-1 protease inhibition activity and have shown some promising preliminary SAR [37]. Inserting pyrimidine bases, which are the basic components of nucleic acid, to the P2 ligand can enhance the potency of HIV-1 protease inhibitors. This happens because the aminocarbonyl group facilitates the formation of hydrogen bonding interactions. Out of the six compounds mentioned (164, 165, 166, 167, 168, and 169), compound 167 has exhibited a promising inhibition ratio against wild-type HIV-1 at a concentration of 100 nM in vivo (Fig. 42).

GS-CA1 is a novel, smaller molecule that can be used as an HIV capsid inhibitor and is more effective against all major HIV-A1 types [153]. *It* is also resistant to antiretroviral drugs and is currently undergoing clinical trials. Compound 170 (GS-CA1) binds directly to the HIV-1 capsid, affecting the capsid-mediated nuclear import of viral DNA, as well as HIV particle production and ordered capsid assembly. GS-CA1 has also demonstrated significant antiviral potency as a long-acting injectable monotherapy in a humanized mice model of HIV-1 infection.

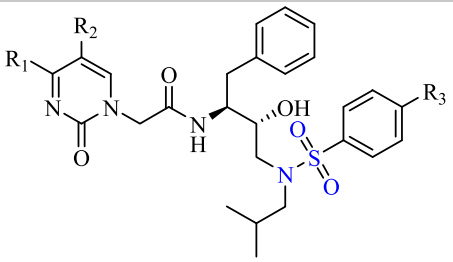
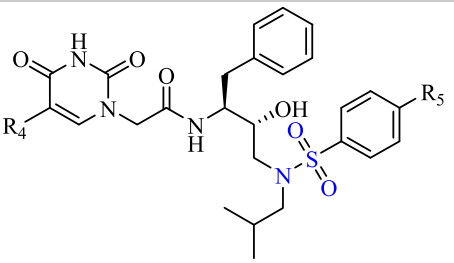
There is a new drug Lenacapavir (171) (also known as GS-6207), which is a potent inhibitor of HIV-1 capsid [154]. It belongs to the class of small molecules that bind to the viral capsid protein, preventing HIV infection. Lenacapavir has high anti-HIV activity and is currently undergoing clinical trials. Capsid-targeting molecules are expected to have high barriers to viral resistance, and ongoing research in this area is contributing to a better understanding of the molecular biology of HIV uncoating and maturation [155].



170 (GS-CA1)



171 (Lenacapavir)

Comp. No.	R_1	R_2	R_3	Comp. No.	R_4	R_5
164	**NH_2**	**F**	**OMe**	**167**	**F**	**OMe**
165	**NH_2**	**F**	**NO_2**	**168**	**F**	**NO_2**
166	**NH_2**	**F**	**NH_2**	**169**	**F**	**NH_2**

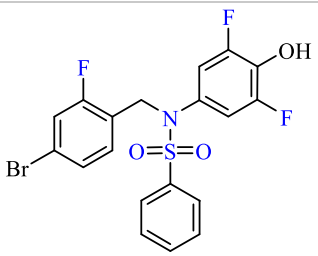
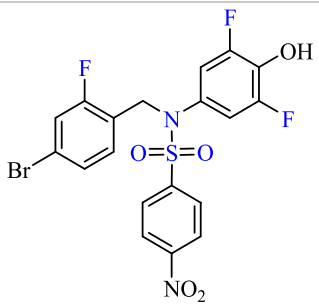
Fig. 42. Fluorinated sulphonamide compounds having anti-HIV activity [37].

Mechanism of action of Tipranavir: Tipranavir, a protease inhibitor for HIV-1, works by preventing the formation of mature virions through inhibiting virus-specific processing of viral Gag and Gag-Pol polyproteins in infected cells. It effectively inhibits laboratory strains of HIV-1 and clinical isolates in acute models of T-cell infection, with an EC50 ranging from 0.03 to 0.07 μM (18–42 ng/mL). Moreover, it has been found to display antiviral activity in cell culture against a wide range of HIV-1 group M non-clade B isolates, including A, C, D, F, G, H, CRF01 AE, CRF02 AG, and CRF12 BF.

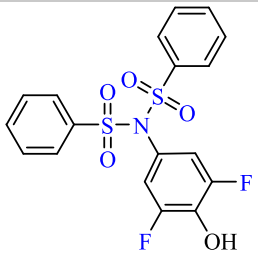
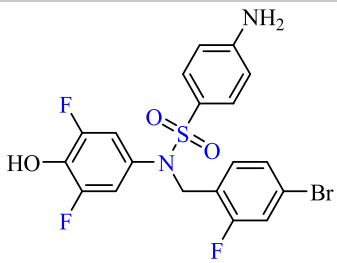
Mechanism of action of Lenacapavir: Lenacapavir functions through its direct binding to the interface between HIV-1 viral capsid protein (p24) subunits in capsid hexamers. This interference disrupts critical stages of viral replication, such as capsid-mediated nuclear uptake of HIV-1 proviral DNA, virus assembly and release, production of capsid protein subunits, and capsid core formation. It is noteworthy that the US Food and Drug Administration recognizes it as a pioneering medication [156].

3.7. Applications of fluorinated sulphonamide as aldose reductase inhibition

Aldose reductase inhibitors are a class of drugs used to inhibit eye and nerve harm in people with diabetes by reducing or inhibiting secondary complications induced by diabetes. They are particularly effective in tissues where glucose uptake is not insulin-dependent,

172 **173**

174 **175**

Fig. 43. Aldose reductase inhibitors contain fluorinated sulphonamide.

such as neutral tissue, glomerulus and the lens. In many body parts, the aldose reductase enzyme catalyzes one of the steps in the sorbitol pathway responsible for fructose development from glucose. In tissues that are not insulin delicate, such as the lenses, glomerulus, and peripheral nerves, these aldose reductase activities rise as the glucose concentration rises in diabetes. Fluorinated benzene sulphonamide derivatives are important in aldose reductase inhibition and show good antioxidant activity [160]. The aldose reductase enzyme (ALR2) of the polyol metabolic corridor and its inhibition with the help of aldose reductase inhibitors (ARIs) has played an important role in pharmaceuticals and the medical field. It is observed at a time of implication in the etiology of the long-term complications of diabetics like neuropathy, retinopathy and nephropathy.

Four compounds (172, 173, 174, 175) based on bioisosteric theory were tested in vitro in the code of behaviour of main adherence to the long-term complications of diabetics. Compound 172 shows a submicromolar inhibitory profile and ARIs (Aldose reductase inhibition) activity at $IC_{50} < 100$ μM. Additionally, the biological potential for antioxidant activity is like that of a heterogeneous and homogeneous system.

The ALR2 enzyme can become overactive at normal glucose concentrations due to factors other than high blood sugar levels. This can lead to various health complications, including cardiac hypertrophy, myocardial ischemia and ischemia-reperfusion injury, cardiomyopathy, congestive heart failure, renal insufficiency, mood disorders, ovarian abnormalities, cancer (such as ovarian, breast, and cervical cancer), and inflammation. To address these issues, researchers have developed compounds (shown in Fig. 44) that use a bioisosteric concept to inhibit the ALR2 enzyme.

One of these compounds, 2-(Phenyl sulphanamido) acetic acid, has demonstrated high in vitro ALR2 inhibitory activity. Recently, organic chemists have become interested in developing new pharmaceutical molecules using fluorinated sulphonamide compounds. 4-Bromo-2-fluoromethyl benzyl moieties are an effective scaffold that can have a combinational effect with sulphonamide derivatives.

The compound that contains tetrazole is highly stable and has a lipophilic character. To balance acidity with lipophilicity, the acetic acid moiety in the lead compound was replaced by derivatives like difluorophenol. Among the sulphonamide derivatives, compounds 172 to 184 (as shown in Figs. 43–45) containing the difluorophenol group play an important role in biological effectiveness. The ALR2 inhibition activity is boosted by the methoxy group in compound 182 and the amino group in compound 180. However, electron-withdrawn substituents such as compounds 178 and 179 don't show improvement in inhibitory activity. The insertion of the pyrrole ring in the sulphonamide derivative (compound 184) doesn't show high activity towards ALR2 inhibition.

On the other hand, introducing the benzene ring (compounds 181 and 182) significantly improves inhibition activity. ALR1 is essential in detoxifying tissue from the more reactive α-oxaldehyde glycating side, such as 3-deoxyglucosone and methylglyoxal agents, in diabetic diseases. Compounds 172 to 184 exhibit strong antioxidant properties compared to the standard Trolox compound. Therefore, it can be concluded that fluorinated sulphonamide compounds are applicable in bioisosteric drug design and are effective in ARIs.

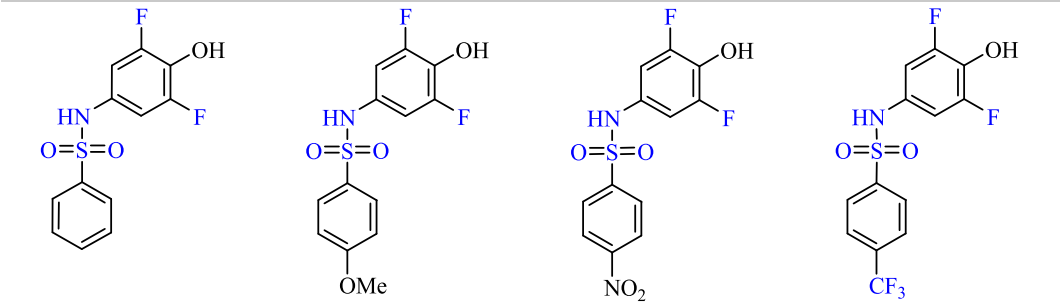
3.8. Application of fluorinated sulphonamide in fatty acid binding protein 4 (FABP4) inhibitions

In this research, different derivatives of fluorinated naphthalene-1-sulphonamide were developed by using structure-constructed technology [161]. These derivatives can potentially inhibit FABP4, a protein responsible for the metabolism and inflammatory process. FABP4 is a potential therapeutic target for immune-metabolic diseases such as atherosclerosis and diabetes.

Figs. 46 and 47 discuss some newly developed compounds and their synthetic route. As per the research, naphthalene-1-sulphonamide derivatives (185, 186, 187, 188) have shown potential to inhibit FABP4 fatty acid binding to protein by applying a structural-based design strategy. Moreover, these compounds have demonstrated good metabolic stability in liver microsomes and improved mouse lipid and glucose metabolism

3.9. Application of fluorinated sulphonamide as peroxisome proliferators activated receptor (PPARs) agonists

A new set of derivatives of trifluoromethane sulphonamide has been synthesized, which could potentially be used as peroxisome proliferator-activated receptor (PPARs) agonists [162]. PPARs are a group of nuclear transcription factors that regulate lipid



176 **177** **178** **179**

Fig. 44. ALR2 inhibitors baring fluorine and sulphonamide group.

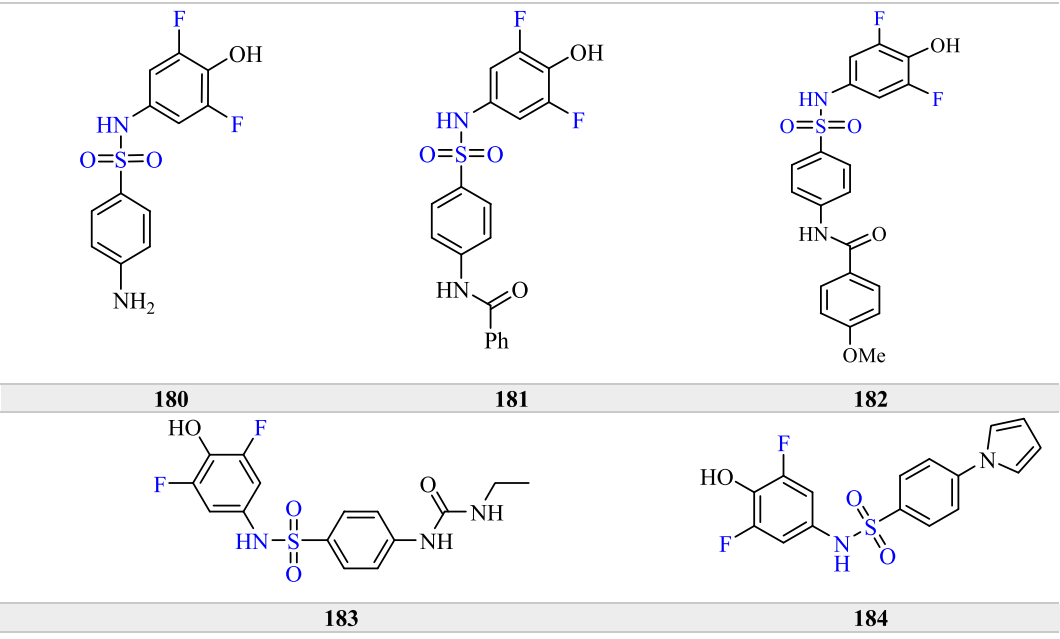


Fig. 45. ALR2 inhibitors baring fluorine and sulphonamide group.

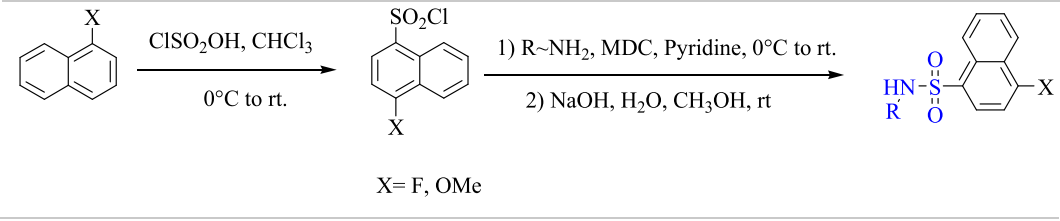


Fig. 46. Reaction scheme of preparation of FABP4 inhibitors derivatives of fluorinated sulphonamide [161].

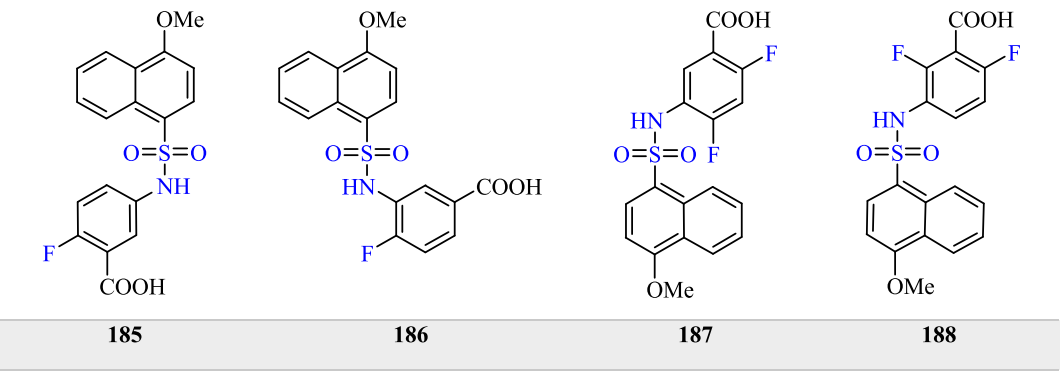


Fig. 47. FABP4 inhibitors of naphthalene-1-sulphonamide derivatives [161].

metabolism. There are three types of PPARs: PPARα, PPARδ, and PPARγ. Each type has distinct tissue-selective expression patterns, biological action, and ligand selectivity. PPARα is usually found in organs with a high rate of fatty acid catabolism, such as the liver. It regulates the expression of genes that code for proteins involved in lipid and lipoprotein metabolism.

The newly developed trifluoromethane sulphonamide derivatives are powerful human PPARα selective activators. Compound 189 is a very effective carboxylic acid bioisosteres acyl sulphonamide. It shows no in-vitro activity when analyzed for agonist activity on PPAR-GAL4 chimerical receptors in quickly transfected CV-1 cells. Compound-190 shows a good response with an EC_{50} of 60 nM on human PPARα. The sulfonyl group may overlap the carboxylate group of the fibrate end and give four hydrogen bonds with Tyr-314,

Ser-280, His-440 and Tyr-464. Also, gem-dimethyl substituents from the fibrate head group are directed into a lipophilic pocket with other amino acids. Compound-191, a fluorinated sulphonamide derivative, is ten times more active in vitro than the original fibrate (0.30 nM). Generally, sulphonamide derivatives are more active on the murine than their fibrate analog (Fig. 48).

Compound-193 is a highly potent fluorinated sulphonamide compound tested in vivo to determine its efficiency in raising HDL-cholesterol levels. In addition, the pharmacokinetic factor of Compound-193 was investigated in mice, which is appropriate for chronic administration.

Compound-193 was administered orally at a dosage of 20 mg/kg twice for 5 days, and it significantly increased HDL cholesterol while lowering serum TG and VLDL cholesterol. Therefore, according to the Apo-A-I-transgenic mouse model, it is a significant therapeutic advantage in the treatment of dyslipidemia as well as hypertriglyceridemia. This compound has excellent pharmacological effects on PPARα and weak to partial activity on PPARγ, with the absence of PPARδ activity as seen in in-vitro analysis (Fig. 49).

3.10. Application of fluorinated sulphonamide in CNS-related diseases inhibition

The Central Nervous System (CNS) encompasses a broad range of disorders that impact the brain and give rise to various conditions such as stroke, brain tumors, inherited metabolic disorders, infections, degenerative diseases, Parkinson's disease, dystonia, sleep disorders, depression, anxiety, bulimia, and migraines. Notably, some fluorinated derivatives (196–203) have been discovered to be efficacious in managing these ailments (Fig. 50).

The 5-Hydroxytrptamine (5HT) receptor, also known as the neurotransmitter serotonin, plays an important role in many biological processes [163–166]. The 5HT6 receptor is frequently utilized to treat CNS disorders and diseases. This subtype of the 5HT receptor binds the endogenous neurotransmitter serotonin.

Quinoline and Isoquinoline-sulphonamide analogs (Fig.-51) of aripiprazole novel derivatives (204, 205, 206) are effective anti-psychotic agents [167]. Schizophrenia is a debilitating psychiatric disorder that affects approximately 1 % of the global population [168]. This disorder is heterogeneous and complex, with multiple symptom domains such as negative symptoms, including emotional withdrawal, affective blunting, anhedonia, poverty of speech, and apathy.

Schizophrenia is a mental disorder that manifests itself in various ways, such as delusions, hallucinations, cognitive deficits, memory impairments, attention deficits, psychomotor abnormalities, behavior abnormalities, and disorganization of thoughts. This disorder is linked to an overactive CNS dopamine system. Although the neurotransmitter 5HT is primarily associated with mood disorders, it also plays an unexpected role in schizophrenia. Many antipsychotic drugs are now available that are effective in treating positive symptoms. However, negative symptoms and cognitive impairment are still a major cause of long-term disability [169].

Compound-207 (Fig. 52) is a potent dual dopamine D_2 and D_3 receptor ligand with a pyridine sulfonamide derivative. Currently, drugs that act as 5HT6 receptor antagonists have been proposed for the treatment of cognitive impairment in schizophrenia. The latest antipsychotic medications can cause partial agonism of dopamine D_2R/D_3R, with a preference for binding to D_3R, antagonism of 5-HT_{2B} receptor, as well as partial agonism of 5-HT_{1A} receptor.

3.11. Applications of fluorinated sulphonamide in antagonist of CCR2 receptor

CCR2 and its ligand are commonly associated with diseases in the central nervous system (CNS), such as Alzheimer's disease, multiple sclerosis, and ischemic stroke. CC chemokine receptor (CCR2) plays a vital role in the transmigration and extravasation of monocytes under inflammatory conditions. CCR2 helps regulate the mobilization of monocytes from the bone marrow to the inflammatory site and CNS inflammation [172].

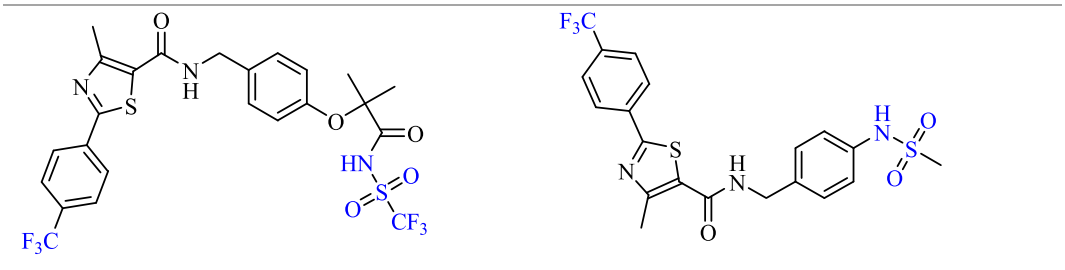
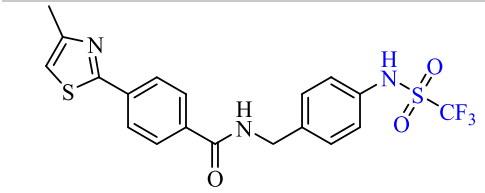


Fig. 48. Trifluoromethane sulphonamide derivatives with PPARα activity [162].



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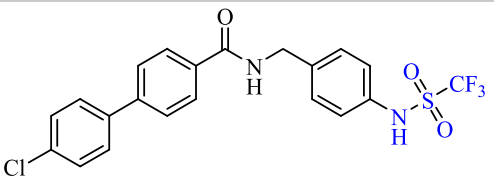

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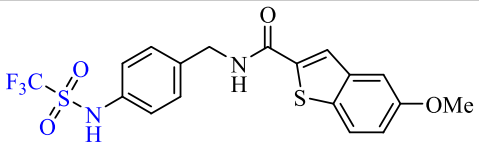

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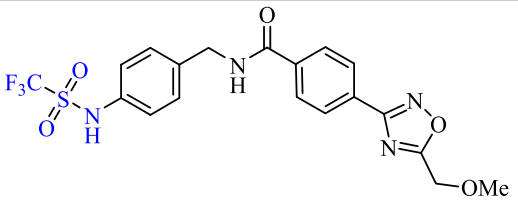

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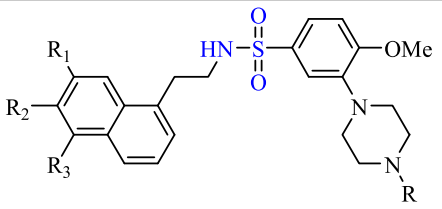
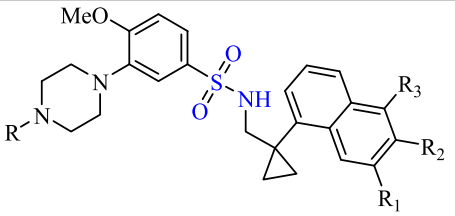
Fig. 49. Fluorinated sulphonamide derivatives with PPARα activity [162].

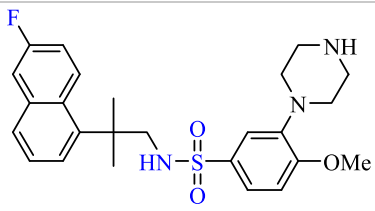




Comp. No.	R	R^1	R^2	R^3
196	H	H	F	H
197	Me	H	**F**	H
198	H	H	H	F
199	Me	H	H	F

Comp. No.	R	R^1	R^2	R^3
200	H	H	F	H
201	Me	H	**F**	H
202	H	H	H	F
203	Me	H	H	F

Fig. 50. Fluorinated sulphonamide derivatives to control CNS-related diseases [163].



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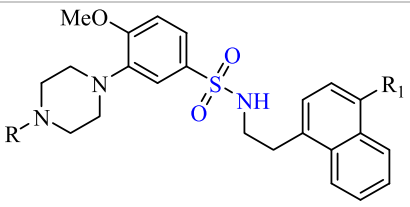
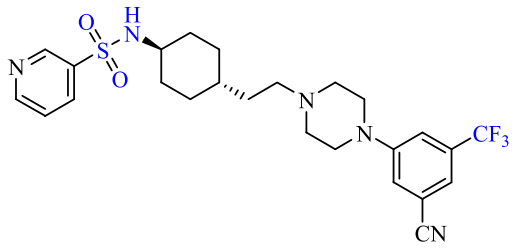


Comp.No.	R	R^1
205	H	F
206	Me	F

Fig. 51. Antipsychotic derivatives of Quinoline and Isoquinoline-sulphonamide analog of aripiprazole [163].



207

Fig. 52. Fluorinated pyridine sulfonamide derivative as potent dual dopamine D2 and D3 receptor ligands [170].

Some deuterated heteroaryl sulphonamide compounds (208, 209) have shown potency toward antagonists of the CCR2 receptor [171]. Such deuterated modifications are helpful in the pharmaceutical treatment of CCR2-mediated diseases and controls in an assay in the identification of CCR2 antagonists. These compounds and their composition effectively inhibit the binding and the function of various chemokines to chemokine receptors.

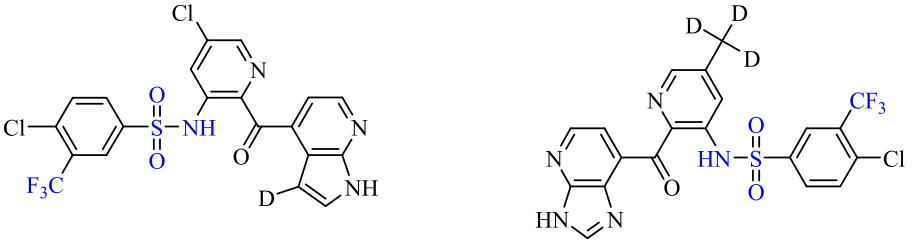
Fluorinated sulphonamide with modified deuterium derivatives (Compound-208, 209) improves the metabolic properties of many drugs (Fig. 53). These compounds are useful for treating various immune-associated disorders, conditions, and diseases. Heterocyclic sulphonamide compounds are useful against CCR2/CCR9, and these compounds show potency against antagonists of the CCR2 receptor. Animal testing shows that these derivatives are excellent for anti-inflammation and CCR2-associated diseases. Heterocyclic fluorinated sulphonamide compounds are useful in inhibiting the binding and functions of various chemokines to chemokine receptors. Along with these as antagonists or modulators of the chemokine receptor, the different fluorinated sulphonamide derivatives have utility in treating various immune disorders, diseases, and conditions [173]. Some of the derivatives are compounds 210, 211, 212, 213.

The derivatives mentioned in Fig. 54 are known to stimulate chemotaxis and chemokines. They can change responsive cells such as granule exocytosis, cell shape alterations, integrin upregulation, formation of bioactive lipids, and cell proliferation.

3.12. Application of fluorinated sulphonamide in cardiovascular diseases treatment

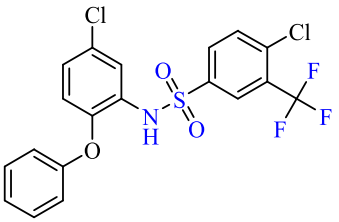
Cardiovascular disease (CVD) generally affects the blood vessels or heart. It encompasses coronary artery diseases (CAD) such as angina and myocardial infarction (heart attack), heart failure, heart valve diseases, heart muscle diseases, peripheral diseases, stroke, peripheral vascular diseases, vascular diseases, rheumatic heart diseases, and major risk factors for hypertension (HTN). CVD is the leading cause of illness and death worldwide [174,175], with systolic blood pressure (SBP), cholesterol, smoking, alcoholism, and poverty [176] being the main reasons for CVD-related mortality. Some fluorinated sulphonamide drugs help treat such diseases. Compound-214 Rosuvastatin is a medication used to prevent cardiovascular diseases in high-risk patients and treat abnormal lipids. It is sold under the trade name Crestor. When combined with a healthy diet, Rosuvastatin helps lower bad cholesterol and fats like triglycerides and LDL while increasing the levels of good cholesterol (HDL) in the blood [177,178]. The drug works as a 3-hydroxy-3--methylglutanyl coenzyme-A reductase inhibitor, reducing the conversion of acetyl COA to mevalonic acid (MVA). This step is a rate-limiting factor in the biosynthesis of cholesterol in the liver. Importance and limitations are highlited in Table 8.

Mechanism of action of Rosuvastatin: Rosuvastatin is an effective inhibitor of HMG-CoA reductase, a crucial enzyme that converts -3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, an essential component of cholesterol. Despite its potential benefits in treating chronic heart failure, using rosuvastatin may result in elevated collagen turnover markers and decreased plasma coenzyme Q10 levels, which could offset its positive effects.



208 **209**

Fig. 53. Fluorine with Deuterium sulphonamide compounds exhibiting antagonist of CCR2 receptor properties [171].



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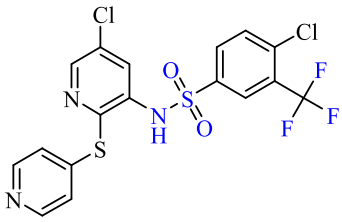

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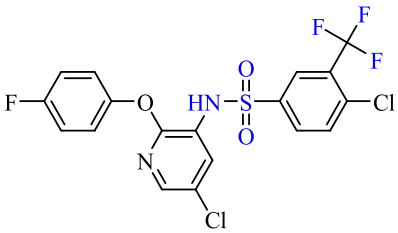

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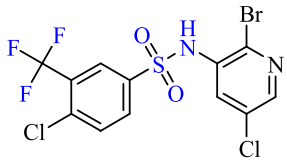
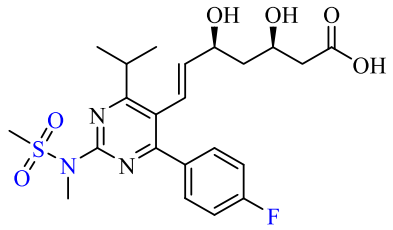


213

Fig. 54. Chemotaxis, chemokines derivative bearing fluorine and sulphonamide group [173].

Table 8
The advantages and disadvantages of Rosuvastatin drugs [179,180].

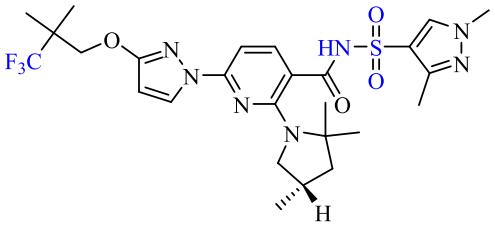
Rosuvastatin	Advantages	Rosuvastatin is a medication used to lower lipid levels and prevent cardiovascular diseases such as myocardial infarction and stroke. It competitively inhibits the enzyme HMG-CoA Reductase, which is involved in the production of cholesterol, LDL and VLDL. Statins are prescribed to people with a moderate to high risk of developing CVD, including those with Type 2 Diabetes.
	Disadvantages	Some common symptoms to watch out for while taking this medication include abdominal pain, nausea, headaches, and muscle pains. However, it is crucial to note that more severe side effects, such as rhabdomyolysis, liver problems, and diabetes, can also occur. Additionally, if you are pregnant, using rosuvastatin may cause harm to your baby. As with all statins, rosuvastatin works by inhibiting HMG-CoA reductase, which is an enzyme found in the liver that helps produce cholesterol. To ensure your safety and well-being, it is essential to discuss any concerns or questions with your healthcare provider.



214 (Rosuvastatin)

3.13. Some of the recently developed fluorinated sulphonamide drugs (under clinical trials)

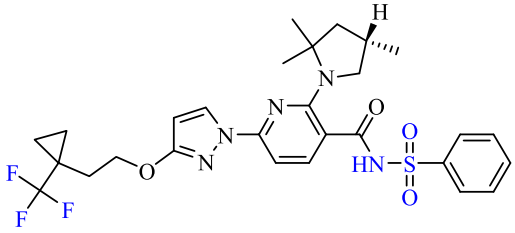
Compound-215 Elexacaftor, or VX-445, was developed by Vertex Pharma as part of a triple combination therapy called Trikafta to treat cystic fibrosis (CF) [181,182]. The USFDA has approved Trikafta to treat CF patients [183]. Elexacaftor, when used in combination with Tezacaftor (VX-661) and Iacaftor (Kalydeco), is effective in treating the most common form of CF caused by the F508 del mutation. CF is an occasional hereditary disease caused by alterations in the CFTR gene, leading to the CFTR protein being modified wrongly. CF is one of the most common fatal diseases in the white population [184,185]. Trikafta helps reduce the risk of lung infections and improves weight gain and breathing.



215 (Elexacaftor)

Mechanism of action of Elexacaftor: Elexacaftor is a CFTR corrector that operates on a distinct binding site compared to tezacaftor on the CFTR protein, resulting in enhanced functionality of the CFTR protein at the cell surface. When combined with tezacaftor and ivacaftor, it forms a tri-drug treatment that collaboratively boosts the transportation of chloride and sodium ions, thereby correcting the fluid shifts that are dysregulated in cystic fibrosis. Advantages and limitations are highlited in Table 9.

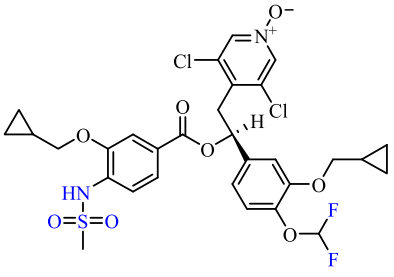
Compound-216- Bamocaftor, or VX-659, is a second-generation corrector candidate developed by Vertex Pharmaceuticals for treating cystic fibrosis [124]. It is currently undergoing clinical trials and is found to be useful in combination with Ivacaftor and Tezacaftor. The combination of VX-659-tezacaftor-Ivacaftor has shown an acceptable safety profile with mild to moderate side effects. These three drug combinations have been found to increase the percentage of predicted FEV and improve the processing of trafficking of phe508del CFTR protein and chloride transport in vivo [186].



216 (Bamocaftor)

Compound-217: Tanimilast or CHF6000, is a novel PDE4 inhibitor developed by Chinese researchers for treating pulmonary inflammation diseases. It is administered [125] via inhalation and is a very effective PDE4 inhibitor (IC50 = 0.026 nm) that displays preclinical efficiency in various classes and is well-accepted in humans. PDE4 inhibitors can destroy several inflammatory cell functions, contributing to their anti-inflammatory action in breathing diseases such as asthma and chronic obstructive pulmonary disease (COPD) [187,188].

Mechanism of action of Tanimilast: The impact of Tanimilast on the immune response of SCV2-moDCs (monocyte-derived dendritic cells stimulated with SCV2-RNA) was evaluated regarding their cytokine and chemokine secretion. Tanimilast selectively reduced the release of pro-inflammatory cytokines and chemokines, suggesting its potential anti-inflammatory effects on the immune response.



215 (Tanimilast)

4. Conclusion

This review provides an overview of the latest developments in agrochemical and pharmaceutical compounds that contain fluorine and sulphonamide moieties. Compiling these molecules highlights the significant role fluorine and sulphonamide compounds play in

Table 9
The advantages and disadvantages of some new drugs [156,189,190].

Elexacaftor	Advantages	Elexacaftor, a next-generation corrector of the CFTR protein, was approved by the FDA in October 2019 in combination with tezacaftor and ivacaftor as TrikaftaTM. It is intended for patients two years and older with cystic fibrosis with an F508del mutation or other mutations in the CFTR gene. Elexacaftor is designed to treat patients who are heterozygous for F508del-CFTR and a gene that does not produce protein or produces proteins unresponsive to ivacaftor or Tezacaftor.
	Disadvantages	The following are the most common side effects that affect more than 5 % of patients: headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, increase in alanine aminotransferase, nasal congestion, increase in blood creatine phosphokinase, increase in aspartate aminotransferase, rhinorrhea, rhinitis, influenza, sinusitis, and increase in blood bilirubin.

modern active ingredients. Fluorine and sulfur are versatile elements with unique properties and play important roles in various fields, including crop protection and medicine. The information in the manuscript provides an exclusive opportunity to visually analyse the diverse application of fluorinated sulphonamide compounds in different fields. The current review paper contains commercially available reaction schemes that guide further preparation of these valuable fluorinated sulphonamides.

The review shows that fluorinated sulphonamide derivatives are used in various drug discovery and agriculture areas. The development of multitarget agents of fluorinated sulphonamide compounds has recently gained more attraction from synthetic organic chemists. Overall, the review demonstrates that fluorinated sulphonamide chemistry has the potential to become one of the largest biologically relevant organic compound libraries.

Future research on single or multi-target applications of novel fluorinated sulphonamide compounds is probably on a rising path.

5. Future scope

Incorporating fluorine into a molecule can significantly impact the properties of the resulting compound, which is particularly relevant in medication creation. Understanding how to utilize this element in complex organic compounds, where the effects may not be straightforward and additive, can lead to improved therapeutic possibilities. This, in turn, increases the likelihood of success in developing compounds, which is crucial in an environment where failures are common.

Fluorine is a commonly used element in pharmaceuticals due to its ability to enhance drug selectivity, dissolve in fats, and slow down the drug's metabolism, allowing it more time to act. While traditional non-fluorinated sulphonamide drugs and agrochemical molecules are becoming obsolete, this trend does not apply to fluorinated sulphonamide pharmaceuticals and agrochemicals. These compounds have unique and advanced bioactivity on the target molecule, making them highly attractive. The potential for fluoro-sulphonamide pharmaceuticals is expected to grow, along with advancements in fluoro-sulphonamide synthesis methodology. Furthermore, developing various techniques for synthesizing fluorinated heterocyclic compounds, particularly asymmetrical processes, could facilitate the expansion of fluorine-based drugs in the future.

Fluorinated sulphonamide molecules have traditionally been widely used in drug and agrochemical discovery due to their high potency and low side effects. In fact, more than 25 % of the drugs and agrochemicals currently available are fluoro pharmaceuticals or agrochemicals. Consequently, many fluorinated sulphonamide drugs have emerged as rising stars of the pharmaceutical and agrochemical industry, positively impacting living things. The number of fluorinated sulphonamide drug candidates showing promising chemo activity is increasing rapidly, and their development relies heavily on the availability of synthesis methodology to target specific molecules. Advanced research is required better to understand the effects of fluorine and sulphonamide molecules.

We have discussed the fluorinated sulphonamide compounds and their applications in medicine and agrochemicals. Most of these compounds have become feasible due to a better understanding of their basic properties. Although fluorine plays a significant role in commercially available drugs, agrochemicals, and advancement candidates, its use is likely limited due to difficulties in correctly implementing this atom and synthesizing fluorinated key components. In addition to its importance in pharmaceutical research, the 18F isotope has become an attractive positron emitter with significant utility in both clinical and preclinical settings. Labeled ligands provide useful tools for studying drug judgment and analyzing drug target involvement. These advances generate a tremendous incentive for developing novel synthetic techniques allowing fluorine to be used more widely in drug and agrochemical creation. As a result, there will be more opportunities to define the subtle role of this element in more complex circumstances. We expect that our knowledge of fluorine's organic and medicinal chemistry will progress, allowing us to contribute to designing and developing crucial future medications and agrochemicals to meet the significant unmet clinical needs and improve the farming field.

Informed consent statement

Not applicable.

CRediT authorship contribution statement

Shankar B. Chaudhari: Writing – original draft, Conceptualization. **Anupam Kumar:** Writing – original draft, Data curation. **Viraj H. Mankar:** Writing – original draft, Investigation. **Shaibal Banerjee:** Writing – original draft, Funding acquisition. **Deepak Kumar:** Writing – original draft, Funding acquisition. **Nabisab Mujawar Mubarak:** Resources, Formal analysis. **Mohammad Hadi Dehghani:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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