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Review Article

Serendipity of fluorine in discovery and development of antidiabetic agents: A bottleneck Systemic Review

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ABSTRACT

Type 2 diabetes is metabolic disorder characterized by insulin resistance at peripheral target tissues and pancreatic β-cell dysfunction. Fluorine is an element of a wide range of modern drugs with anti-cancer and anti-viral agents, anti-inflammatory drugs, antibiotics, central nervous system agents, diuretics and antihypertensive agents and antiarrhythmic heart drugs. There will be focus on topics that include fluorinated drugs for treatment of diabetes. The resultant hyperglycemia if left untreated can eventually lead to the debilitating vascular complications of type 2 diabetes, including retinopathy, end stage renal disease, neuropathy and cardiovascular disease. Current therapies may also be associated with an increased risk of hypoglycemia, weight gain and gastrointestinal intolerance, which represents major barriers to optimal glycemic control. These huge successes of fluorine-containing drugs continue to stimulate research on fluorine in medicinal chemistry for drug discovery. It would not be an exaggeration to say that currently every new drug discovery and development program without exception explores fluorine-containing drug candidates. Accordingly a wide variety of fluorine-containing compounds based either on known natural products or on new skeletons have been synthesized or subjected to biological evaluation. Lipophilicity of Fluorine and Fluorine containing groups play important role in drug receptor interaction and selectivity of drugs. The absorption and distribution of a drug molecule *in-vivo* are controlled by its balance of lipophilicity and hydrophilicity as well as ionization. Enhanced lipophilicity together with change in amine often leads to increase in blood-brain barrier (BBB) permeability or binding free energy through favorable partition between the polar aqueous solution and the less-polar binding site. Inhibition of dipeptidyl peptidase 4 is a promising new approach for the treatment of type 2 diabetes. Fluorine play important role in development of DPP-4 inhibitors like Denagliptin, Gemigliptin and Sitagliptine. Hence, DPP-4 inhibition has the potential to be a novel, efficient and tolerable approach to treat type 2 diabetes to its solution form.

Key Words: Type 2 diabetes, DPP-4 inhibitor, Sitagliptin, Fluorine

INTRODUCTION

The fluorine atom being very electronegative changes quite drastically the charge distribution in compounds into which it is placed, thereby altering their biological effects. Fluorine is a element of a wide range of modern drugs including anti-cancer and anti-viral agents, anti-inflammatory drugs, antibiotics, central nervous system agents, diuretics and antihypertensive agents and antiarrhythmic heart drugs. The importance of fluorine in medicinal chemistry is well recognized. There is an increasing number of drugs on the market contain fluorine, the presence of which often is of major importance to activity. There are of course an enormous number of topics that remain to be considered, encompassing the entire range of disease targets contained in the domain of medicinal chemistry. There will be focus on topics that include fluorinated drugs for treatment of diabetes. These topics were chosen because fluorine substitution has played and continues to play an important role in the development of more active and more selective agents. Certain of these are well known such as the fluoroquinolone

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antibacterial agents and azole antifungal agents. Inhibit the fungal cytochrome P450 enzyme, (α-demethylase) which is responsible for converting lanosterol to ergosterol.

Inhibition of mitochondrial cytochrome oxidase leading to accumulation of peroxides that causes auto digestion of the fungus. Imidazoles may alter RNA& DNA metabolism. Discussions of the processes of discovery and lead development where appropriate will include the rationale for fluorine substitution.

It is one of the fastest growing health diseases in the world. Pancreatic islet cells are initially able to respond to increased insulin resistance by increasing insulin secretion to maintain normoglycemia. As the disease develops, however, there is a progressive loss of, β-cell function.

The resultant hyperglycemia, if left untreated, can eventually lead to the debilitating vascular complications of type 2 diabetes, including retinopathy, end stage renal disease, neuropathy and cardiovascular disease. Furthermore, current therapies may also be associated with an increased risk of hypoglycemia (sulphonylureas and insulin), weight gain (sulphonylureas, thiazolidinediones and insulin) and gastrointestinal intolerance (metformin), which represents major barriers to optimal glycemic control. Research into the pathophysiology of diabetes has revealed that a complex interplay of hormonal and neural stimuli, not just insulin and glucagon, are involved in the regulation of plasma glucose levels. But the development of incretin hormone analogues and compounds that delay their degradation and therefore raise their concentration and/or compounds that bind to their receptors, may facilitate achievement of optimal glycemic control. Furthermore, such therapies may target physiological defects not addressed by current medications, or may exhibit a mode of action that is additive or synergistic with current therapies. Current treatments are often inefficient at sustaining glycemic control and may cause undesirable side effects, such as weight gain and episodes of hypoglycemia. Dipeptidyl peptidase-4 enzyme plays major role in glucose metabolism.

It is responsible for the degradation of incretins such as GLP-1.[1] Therefore, new and more effective drugs have been developed with DPP-4 inhibitors playing a significant role. The development of the DPP-4 inhibitors, which potentiate the incretin hormones by inhibiting the enzyme responsible for their degradation, has recently emerged as one such approach that appears promising for the treatment of type 2 diabetes. New class of oral hypoglycemics dipeptidylpeptidase-4 inhibitors work by inhibiting the action of this enzyme, thereby prolonging incretin effect *in-vivo*.[2] Inhibition of the DPP-4 enzyme prolongs and enhances the activity of incretins that play an important role in insulin secretion and blood glucose control regulation.[5]

History Since its discovery in 1967, serine protease DPP-4 has been a popular subject of research. Inhibitors of DPP-4 have long been sought as tools to elucidate the functional significance of the enzyme. The first inhibitors were characterized in the late 1980s and 1990s. Each inhibitor was important to establish an early structure activity relationship for subsequent investigation. It should be noted that the inhibitors fall into two main classes, those that interact covalent with DPP-4 and those that do not.[3] DPP-4 is a dipeptidase that selectively binds substrates that contain proline at the P1-position, thus many DPP-4 inhibitors have 5-membered heterocyclic rings that mimic proline, e.g. pyrrolidine, cyanopyrrolidine, thiazolidine and cyanothiazolidine.[4] These compounds commonly form covalent bonds to the catalytic residue Ser630.[5]

In 1994, researchers from Zeria Pharmaceuticals unveiled cyanopyrrolidines with a nitrile functional group that was assumed to form an imidate with the catalytic serine. Concurrently other DPP-4 inhibitors without a nitrile group were published but they contained other serine-interacting motifs, e.g. boronic acids, phosphonates or diacyl hydroxylamines. These compounds were not as potent because of the similarity of DPP-4 and prolyl oligopeptidase and also suffered from chemical instability. Ferring Pharmaceuticals filed for patent on two cyanopyrrolidine DPP-4 inhibitors which they published in 1995.

These compounds had excellent potency and improved chemical stability. In 1995, Edwin B. Villhauer at Novartis started to explore *N*-substituted glycinyl-cyanopyrrolidines based on the fact that DPP-4 identifies *N*-methylglycine as an *N*-terminal amino acid. This group of new cyanopyrrolidines became extremely popular field of research. In the following years. Some trials with dual inhibitors of DPP-4 and vasopeptidase have been represented, since vasopeptidase inhibition is believed to enhance the antidiabetic effect of DPP-4 inhibition by stimulating insulin secretion. Vasopeptidase-inhibiting motif is connected to the DPP-4 inhibitor at the *N*-substituent.[6]

History, Role and properties of fluorine:

Hydrogen fluoride (HF) was first reported by Scheele in 1771. In 1836 Dumas and Pelig reported the synthesis of organo fluorine compound fluoro methane. In 1886 Henri Moissan isolated molecular elemental fluorine gas (F_2). Belgian chemist Swarts' work between 1890 and 1938 on simple aliphatic fluorocarbons is widely considered as establishing the foundations of organofluorine chemistry. The chemistry of perfluorinated (fully fluorinated) organic compounds began in 1926 when Lebeau and Damiens. In the 1930's, Midgley and Henne extended Swarts'exchange reaction methods for chlorofluorocarbon (CFC). In WWII, Uranium hexafluoride (UF_6) used in the U-235 enrichment process for making atomic bombs. DuPont and GM were the pioneers of the application of CFCs as refrigerants. Later CFC's found diverse applications as fire extinguishers, blowing/cleaning agents. Most recent applications are related to organofluorine products (containing F-C bonds In spite of such scarcity, enormous numbers of synthetic fluorine-containing compounds have been widely used in a variety of fields because the incorporation of fluorine atom(s) or fluorinated group(s) often furnishes molecules with quite unique properties that cannot be attained using any other element. Two of the most notable examples in the field of medicinal chemistry are 9-fluorohydrocortisone (an anti-inflammatory drug) and 5-fluorouracil (an anticancer drug), discovered and developed in 1950s, in which the introduction of just a single fluorine atom to the corresponding natural products brought about remarkable pharmacological properties.

Since then, more than half a century has passed, and the incorporation of fluorine into pharmaceutical and veterinary drugs to enhance their pharmacological properties has become almost standard practice. In 2006, the best- and the second-best-selling drugs in the world were atorvastatin by Pfizer. These fluorine-containing drugs are followed by Risperidone for schizophrenia by Janssen, and Lansoprazole, a proton pump inhibitor, by Takeda/Abbott.

These huge successes of fluorine-containing drugs continue to stimulate research on fluorine in medicinal chemistry for drug discovery. It would not be an exaggeration to say that currently every new drug discovery and development program without exception explores fluorine-containing drug candidates. Accordingly a wide variety of fluorine-containing compounds based either on known natural products or on new skeletons have been synthesized or subjected to biological evaluation. In most cases, 1-3 fluorines are incorporated in place of hydroxyl groups or hydrogen atoms. Representative examples include efavirenz HIV antiviral.

Torcetrapib is a potent inhibitor of cholesterol ester transfer protein which possesses three C groups (Pfizer), and sitagliptin has three fluorine atoms and one C group.[7]

In order to synthesize a variety of fluorine-containing biologically active compounds, development of efficient synthetic methods applicable to fluorine-containing organic compounds is necessary. There is a strong demand for expansion of the availability of versatile fluorine-containing synthetic building blocks and intermediates to promote target-oriented synthesis as well as diversity-oriented synthesis.

The limited availability of fluorochemicals for bioorganic and medicinal chemistry as well as pharmaceutical and agrochemical applications is mainly due to the exceptional properties and hazardous nature of fluorine and fluorochemical sources. Also in many cases, synthetic methods developed for ordinary organic molecules do not work well for fluorochemicals because of their unique reactivity.

Assistances of Fluorine in Pharmaceutical chemistry: An essential strategy for medicinal chemists when inventing new drugs is to take a molecule, frequently from nature and make variations to its structure to alter its activity. Replacing hydrogen and other functional groups with fluorine can have a intense effect on biological activity. It is more electronegative than hydrogen and so swapping a fluorine atom for a hydrogen atom can be expected to exert a large electronic effect on adjacent carbon centers, changing both the dipole moment and the pK_a of the molecule. It can also have a knock-on effect on the stability and reactivity of other functional groups in the compound.

Fluorine's van der Waals radius of 1.35Å may appear larger than that of hydrogen, 1.10Å, but studies have shown that, size-wise, fluorine is actually a good hydrogen mimic, adding only limited extra steric demand at receptor sites.[8]

In addition, its bond length to carbon of 1.26–1.41Å is reasonably similar to that of a carbon–hydrogen bond, which is in the region of 1.08–1.10Å. Therefore, replacing hydrogen with fluorine gives little change in the overall steric bulk of the molecule. Though, the selective fluorination reactions to make these drugs are rarely

straightforward. They often use dangerous or expensive reagents. Therefore, the best route is often to let someone like Halocarbon Products worry about introducing the fluorine and form the drug molecule around one of their commercially available fluorinated intermediates.

Lipophilicity of Fluorine and Fluorine-containing Groups: The absorption and distribution of a drug molecule *in-vivo* are controlled by its balance of lipophilicity and hydrophilicity as well as ionization. Enhanced lipophilicity together with change in amine often leads to increase in blood-brain barrier (BBB) permeability or binding free energy through favorable partition between the polar aqueous solution and the less-polar binding site. It is generally conceived that incorporation of fluorine or fluorinated groups increases the lipophilicity of organic compounds, especially aromatic compounds. Fluorine substitutions may greatly increase a molecule's lipophilicity, an important consideration when making molecules that are designed to be active *in-vivo*. Including fluorine increases fat solubility, improving its partitioning into membranes and hence increasing bioavailability. Fluorination can also aid hydrophobic interactions between the drug and binding sites on receptors or enzymes. Carbon forms some of its strongest bonds with fluorine, with a higher oxidative and thermal stability than a carbon–hydrogen bond. The fluorine can also make reversible electrostatic bonds with some other functional groups.

Fluorination can increase a molecules binding affinity to a target protein and by a combination of factors interfere with specific enzyme action. As a result, fluorine plays a huge role in the current areas of pharmaceutical chemistry and agrochemistry, with many of the most important new drugs and agents containing propitiously placed fluorine, trifluoromethyl, difluoromethyl or other fluorinated groups.

Despite the strength of the carbon–fluorine bond, however, as the conjugate base of a strong acid, fluoride is a good leaving group and this can be factored into the design of drugs which are intended to form stable covalent bonds with their targets.

Inductive Effect of Fluorine and Fluorine-containing Groups: Since fluorine is the most electronegative element, it is natural that groups containing fluorine have unique inductive effects on the physicochemical properties of the molecules bearing them. For example, substantial changes in values of carboxylic acids, alcohols or protonated amines are observed upon incorporation of fluorine into these molecules. Thus, when fluorine(s) and/or fluorine-containing group(s) are incorporated into bioactive compounds, these substituents will exert strong effects on the binding affinity for the receptors or target enzymes, biological activities and pharmacokinetics.

Role of fluorine in development of DPP-4 inhibitors: Dipeptidyl-peptidase IV (DPP-4) inhibitors inhibit the degradation of the incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). The first available DPP-4 inhibitors are sitagliptin and vildagliptin. These compounds are orally active and have been shown to be efficacious and well tolerated. Two additional DPP-4 inhibitors are under review and there are several others in clinical development. This article gives an overview on the mechanism of action of DPP-4 inhibitors and focuses on their development and their important physiological actions with regard to the treatment of type 2 diabetes. Drugs like Sitagliptin, Gemigliptin belonging to DPP-4 inhibitors contain fluorine atom.

Denagliptin is an advanced compound with a branched side chain at the P2 position, but also has (4S)-fluoro substitution on the cyanopyrrolidine ring.[9] It is a well-known DPP-4 inhibitor developed by GlaxoSmithKline. Biological evaluations have shown that the *S*-configuration of the amino acid portion is essential for the inhibitory activity since the R-configuration showed reluctantly inhibition. These findings are useful in future for designing and synthesis of DPP-4 inhibitors.[10]

The main physiologic role of glucagon, a linear 29 amino acid peptide, is to stimulate increased sugar concentration in the blood, essentially having the opposite effect of insulin. Glucagon-like peptide 1 (GLP-1) is released from the gut in response to food uptake. GLP-1 plays an important role in glucose homeostasis by stimulating the biosynthesis and release of insulin and by inhibiting glucagon release.

Reflecting its regulatory role, the biological half-life of GLP-1 is short, being rapidly inactivated by the action of the serine protease Dipeptidyl peptidase IV (DPP-IV) that cleaves a dipeptide from the N-terminus of GLP-1. Recognition that an inhibitor of DPP-IV would prolong the beneficial effects of GLP-1 has stimulated research into the preparation of such inhibitors as an approach to the treatment of type 2 diabetes. The triazolopiperazine-based DPP-IV inhibitor 10 was

developed by Merck from β-amino acid-based piperazine inhibitors 11 that had poor pharmacodynamic properties. Replacement of the piperazine moiety with the more robust triazolopyrazine having various substitutents to give 12 improved metabolic and other pharmacodynamic properties. Structure–activity relationship (SAR) studies, including optimization of fluorine substitution on the aromatic ring, produced compound 10 having a 3,4,5-trifluoro substituted phenyl ring and a 3-trifluoromethyl substituent that had optimum DPP-IV inhibitory activity (IC_{50}=18 nM), excellent selectivity for this enzyme and promising pharmacodynamic properties. The importance of the CF_3 group is clear, since its deletion drastically reduced bioavailability in the rat and led to a fourfold decrease in enzyme affinity.[11]

Following compounds 1, 2 and 3 all showed improved oral bioavailability. The DPP-4 inhibitory potencies of 19 and 20 were superior to that of 1. Both 2 and 3 are selective inhibitors and are effective *in-vivo*. A significant advantage of 3 over 2 is improved cardiovascular safety in the dog.

CONCLUSION

Drug discovery and development is important in current scenario in pharmaceutical industry. Fluorine is seen in various potent drugs with wide spectrum of activity for treatment of certain diseases. Type 2 diabetes is associated with various micro and macro vascular complications which diminish quality of human life. The fluorine is most electronegative element in periodic table which gives lipophilicity of molecule that provides better pharmacological action. Fluorination can increase a molecules binding affinity to a target protein and by a combination of factors interfere with specific enzyme action. In this era DPP-4 inhibitors are being developed for the treatment of type 2 diabetes. Drugs like Sitagliptin, Gemigliptin and Denagliptin belonging to DPP-4 inhibitors explain the importance of fluorine atom.

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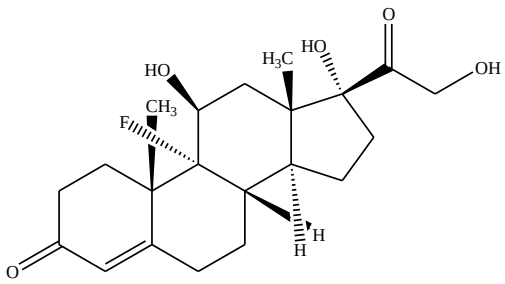
Figure 1: Neuropathy

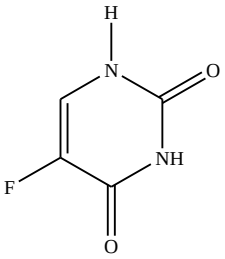
Figure 2: Cardiovascular disease

Figure 3: Diabetic retinopathy



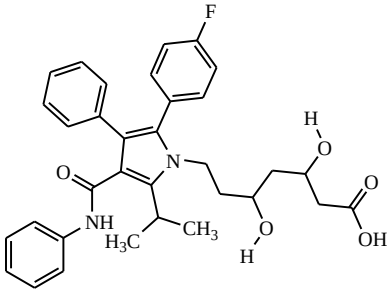
9-Fluorohydrocortisone

(8*S*,9*R*,10*S*,11*S*,13*S*,14*S*,17*R*)-9-Fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13-dimethyl-1,7,8,10,11,12,13,15,16,17-decahydro-2*H*-cyclopenta[*a*]phenanthren-3(6*H*,9*H*,14*H*)-one



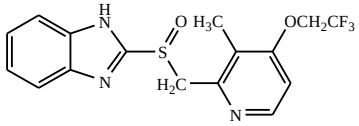
5-Fluorouracil

5-Fluoropyrimidine-2,4(1*H*,3*H*)-dione



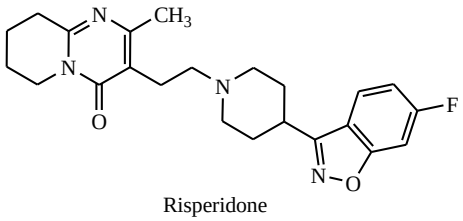
Atrovastatin

7-(2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl) -1*H*-pyrrol-1-yl)-3,5-dihydroxyheptanoic acid



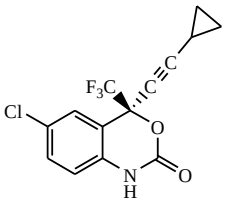
Lansoprazole

2-((3-methyl-4-(2,2,2-trifluoroethoxy)pyridin-2-yl) methylsulfinyl)-1*H*-benzo[*d*]imidazole



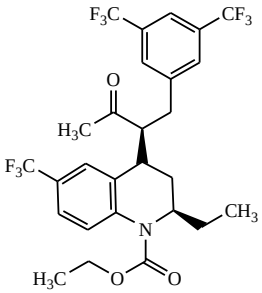
Risperidone

3-(2-(4-(6-Fluorobenzo[*d*]isoxazol-3-yl)piperidin-1-yl)ethyl)-2-methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidin-4-one



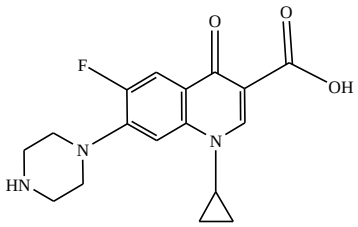
Efavirenz

(*R*)-6-Chloro-4-(2-cyclopropylethynyl)-4-(trifluoromethyl)-1*H*-benzo[*d*][1,3]oxazin-2(4*H*)-one



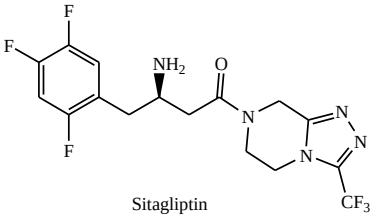
Torcetrapib

(2*R*,4*S*)-ethyl 4-((*S*)-1-(3,5-bis(trifluoromethyl)phenyl)-3-oxobutan-2-yl)-2-ethyl-6-(trifluoromethyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate



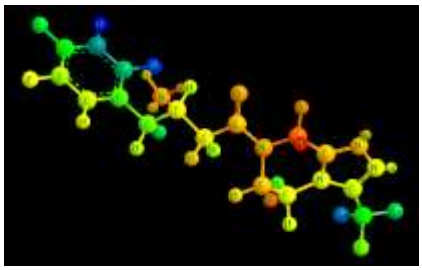
Ciprofloxacin

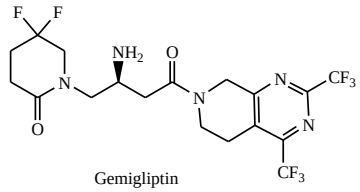
1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid



Sitagliptin

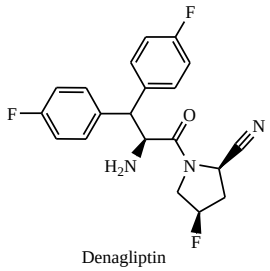
(*R*)-3-Amino-1-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl)-4-(2,4,5-trifluorophenyl)butan-1-one





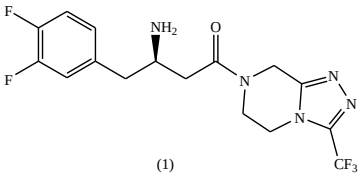
Gemigliptin

(*S*)-1-(4-(2,4-Bis(trifluoromethyl)-5,6-dihydropyrido[3,4-*d*]pyrimidin-7(8*H*)-yl) -2-amino-4-oxobutyl)-5,5-difluoropiperidin-2-one



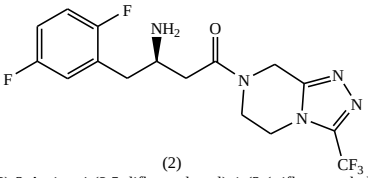
Denagliptin

(2*R*,4*R*)-1-((*S*)-2-amino-3,3-bis(4-fluorophenyl) propanoyl)-4-fluoropyrrolidine-2-carbonitrile



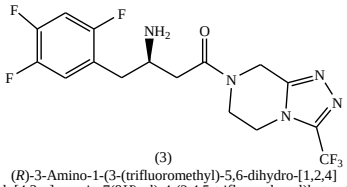
(1)

(*R*)-3-amino-4-(3,4-difluorophenyl)-1-(3-(trifluoromethyl)-5,6-dihydro- [1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl)butan-1-one



(2)

(*R*)-3-Amino-4-(2,5-difluorophenyl)-1-(3-(trifluoromethyl) -5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl)butan-1-one



(3)

(*R*)-3-Amino-1-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4] triazolo[4,3-*a*]pyrazin-7(8*H*)-yl)-4-(2,4,5-trifluorophenyl)butan-1-one