ADRENERGIC AND ANTI-ADRENERGIC AGENTS AND THEIR RECENT ADVANCES

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AIM AND OBJECTIVE

Aim: Systematic study of adrenergic and anti-adrenergic agents and the recent advances.

Objective:

1. The study of adrenergic and anti-adrenergic agents including their classification, mechanism of action, structure – activity relationship, synthesis of drugs, therapeutic uses and adverse effects.
2. Recent advances of adrenergic agonists and antagonists.
3. Marketed adrenergic agonists and antagonists.

INTRODUCTION

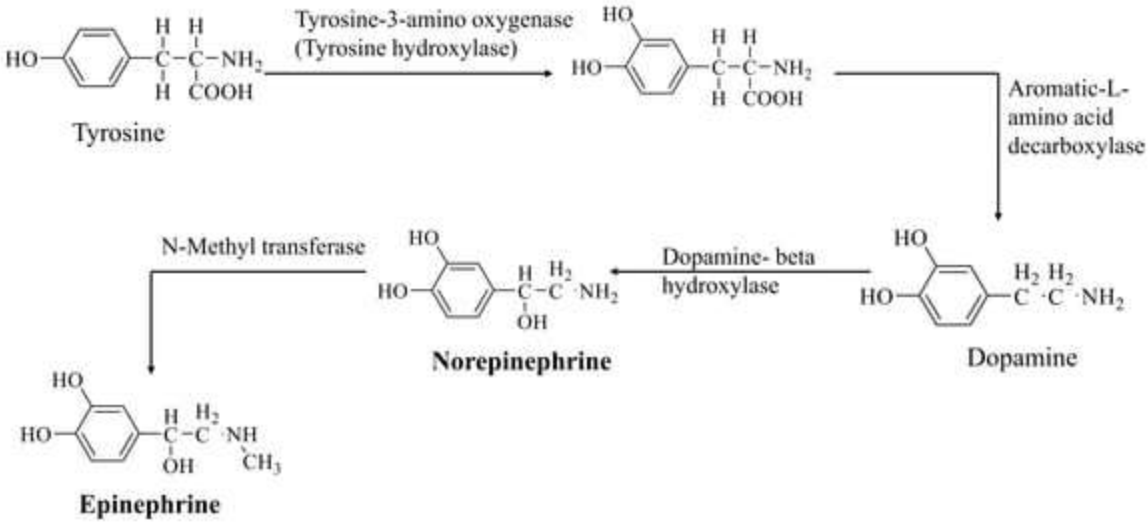
- **Adrenergic agents / Adrenergic agonists:** Adrenergic agents are defined as, "the drugs that produce similar effects to those produced by sympathetic nervous system", also known as sympathomimetic agents.

- Adrenergic drugs act on effector cells through adrenoceptors that normally are activated by the neurotransmitter norepinephrine (noradrenaline), thus producing "fight or flight" response.

- **Anti- Adrenergic agents / Adrenergic antagonists:** These are defined as, "the drugs which antagonize the receptor action of adrenaline and related drugs".

- **Adrenergic receptors:** They are membrane bound G-protein coupled receptors and classified as α (alpha) and β (beta) adrenoceptors. The α (alpha) receptor are further classified into α_1 and α_2. The β receptors are further subdivided into three subtypes and distributed in the body, that is, β_1 (heart), β_2 (bronchi, smooth muscles), and β_3 (adipose tissue).

Biosynthesis of norepinephrine and epinephrine

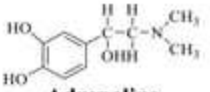


ADRENERGIC AGENTS

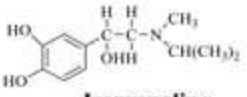
Based on the Chemical Structure the adrenergic agents are classified as follows:

1) Catecholamines:

Compounds with hydroxyl (–OH) substitution in the third and fourth position of the benzene ring are termed as catecholamines.



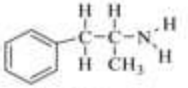
Adrenaline



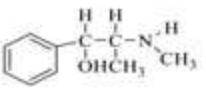
Isoprenaline

2) Non-catecholamines:

Those compounds that lack the hydroxyl at third and fourth position of the benzene ring are non-catecholamines.

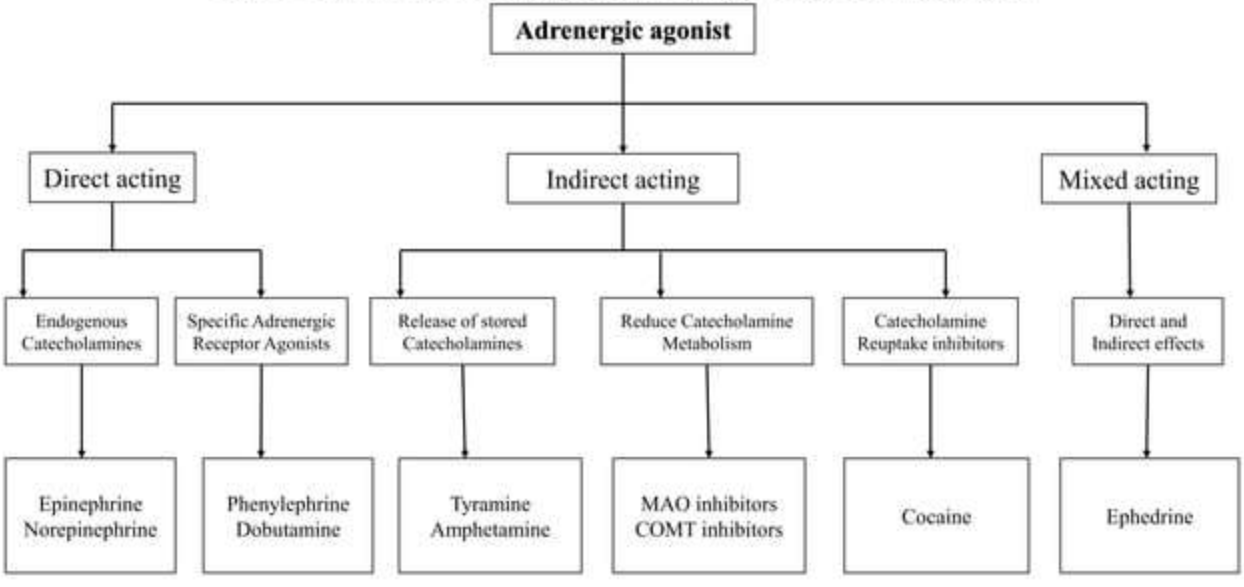


Amphetamine



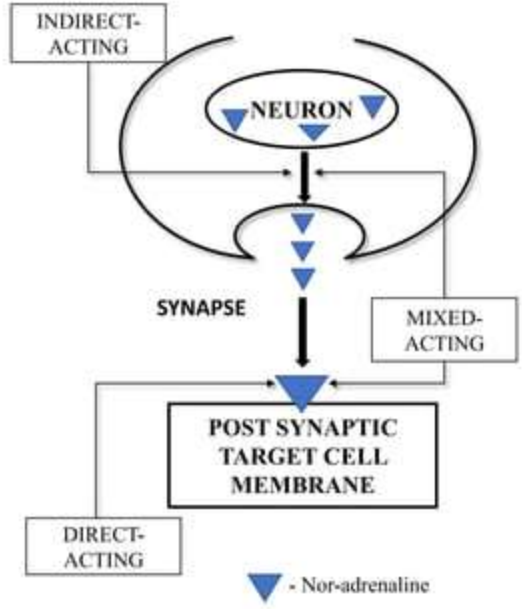
Ephedrine

Based on their mechanism, they are also classified as follows:



Mechanism of action

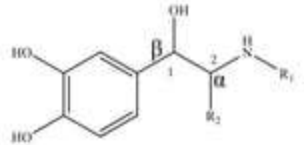
- **Direct acting agents**: Drugs such as phenylephrine, isoprenaline act directly as agonists on both α (alpha) and β (beta) adrenoceptors.
- **Indirect acting agents:** Drugs such as tyramine, amphetamine act on adrenergic neuron to release non-adrenaline, which then acts on adrenoceptors.
- **Mixed acting agents:** Drugs like ephedrine, dopamine, act both directly as well as indirectly.



Structure- activity relationship

Structure required for activity:

- β- phenylethylamine
- 1R- (OH)



R_1 Substitution on N
- ↑ size of R_1
- • ↑ β- activity
- • ↓ α- activity

t- butyl: ↑ β_2- activity
↓ in degradation by MAO

Aromatic substitutions

$3^1,4^1$-diOH for both α and β agonist activity
- metabolized by COMT ⟶ short oral activity and short DOA
- hydrophilic ⟶ poor CNS activity

$3^1,5^1$-diOH (e.g., metaproterenol)

3^1–CH_2OH, 4^1- OH (e.g., albuterol)
- ↑ β_2 activity
- ↓ degradation by COMT ⟶ ↑ absorption, oral activity, and DOA

4^1- OH is more important for β activity
3^1- OH is more important for α activity
(e.g., phenylephrine: α-agonist)

No phenolic substitution
↓ in both α and β activity
Direct or indirect activity

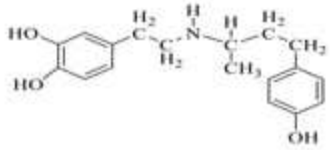
R_2 substitution on C_2
Small alkyl groups (Me, Et) tolerated

Et group:
- • ↓ α >> β (more β- selective, e.g., ethyl norepinephrine)
- • ↑ CNS activity
- • ↑ Oral activity and DOA

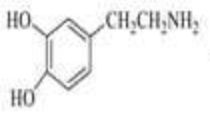
(2S)methyl group: ↑ α_2 activity

Synthesis

1. Catecholamine: e.g., Dobutamine

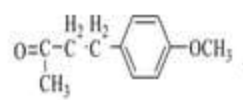


N-[1-methyl-3-(4-hydroxy phenyl)propyl]3,4-dihydroxy phenyl ethylamine



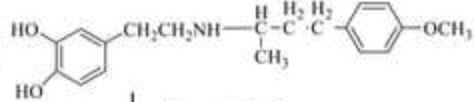
Dopamine

+

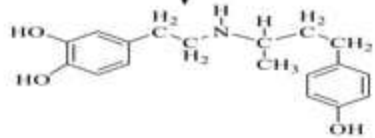


4-(4-methoxyphenyl)-2-butanone

PdC_2H_5
Reductive amination

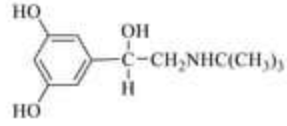


Demethylation
Alc. KOH

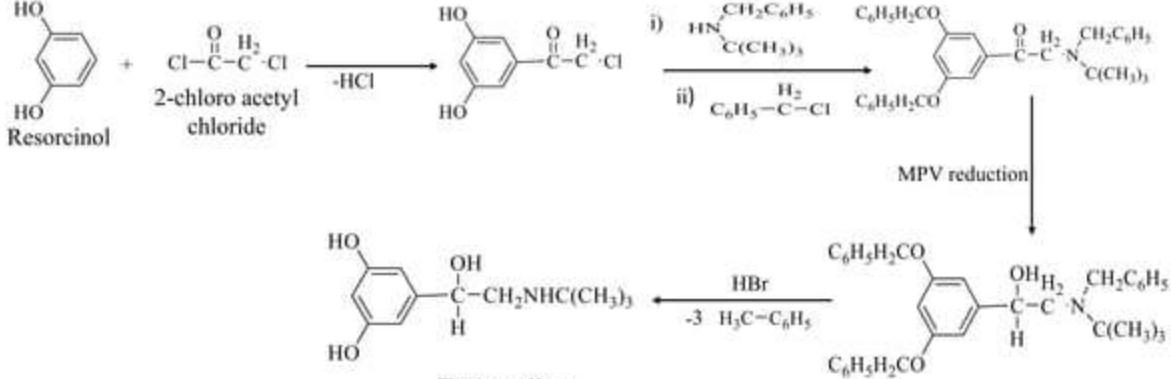


Dobutamine

2. Non-catecholamine: e.g., Terbutaline



5-(2-(tert-butyl amino)-1-hydroxyethyl)benzene-1,3-diol



Therapeutic uses

1. **Vascular uses:** Hypotensive state, with local anaesthetics, control of local bleeding, nasal decongestant, peripheral vascular diseases like Raynaud's phenomena, gangrene.
2. **Cardiac uses:** Cardiac arrest, Partial or complete A-V block, Congestive heart failure.
3. **Bronchial asthma**
4. **Allergic disorders**
5. **Obesity**
6. **Nocturnal enuresis in children and urinary incontinence**
7. **Uterine relaxant**
8. **Insulin hypoglycaemia**

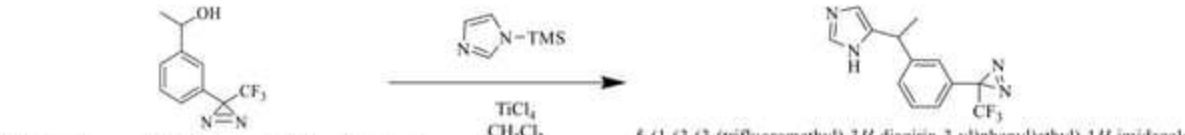
Adverse effects

- Anxiety, fear, tension, headache, and tremor
- Haemorrhage
- Cardiac Arrythmia
- Pulmonary oedema
- Hyperthyroidism

Recent advances

Azi -medetomidine: Synthesis Novel α_2 Adrenergic Photoaffinity Ligand

- Photoaffinity ligands have been used with great success to reveal binding locations, configurations, and even identify previously unknown molecular binding targets by making permanent the natively ephemeral ligand-receptor interaction.
- Azi-medetomidine competes with the α_2 agonist clonidine at α_{2A} adrenergic receptors, which is potentiated by photolabeling, and azi-medetomidine labels moieties on the α_{2A} adrenergic receptor which is determined by mass spectrometry.
- The synthesis is accomplished by a recent modification in the synthesis of medetomidine as follows:



1-(3-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)ethan-1-ol

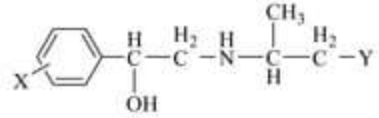
5-(1-(3-(3-(trifluoromethyl)-3*H*-diazirin-3-yl)phenyl)ethyl)-1*H*-imidazole

Azi-medetomidine

Reference: Azi-medetomidine: Synthesis and Characterization of a Novel #2 Adrenergic Photoaffinity Ligand- ACS Chemical Neuroscience, 2019, DOI: 10.1021/acschemneuro.9b00484

New potential β_3 adrenergic agonists with β-phenylethylamine structure, synthesized for the treatment of Dyslipidemia and Obesity

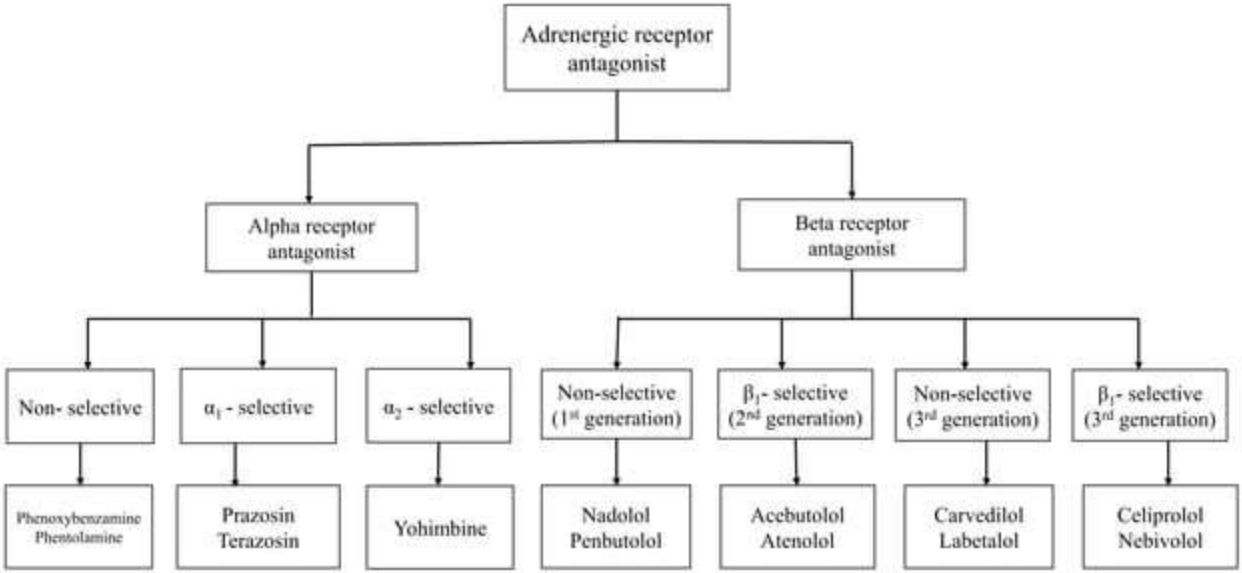
- β_3 adrenergic receptors have important physiological implications, being expressed in many places in the body, including brown adipose tissue. In this study, 13 newly synthesized compounds of β-phenylethylamine structure and reference BRL 37344 were investigated in order to identify a potential affinity for β_3 adrenergic receptors. The antidiabetic and hypolipemiant effects were investigated on a rat model of alloxan-induced diabetes.
- The results demonstrated that new β-phenylethylamine derivatives produced marked biological activity over lipid profile. All compounds have markedly decreased the values of total cholesterol, LDL cholesterol, and triglycerides and also have increased the values of antiatherogenic HDL cholesterol. The effects were significantly more intense than the reference substance BRL 37344.



X = H, alkoxy, halogen, dihalogen
Y = 4-carbopropoxy-phenoxy,
4-carbomethoxymethylene-phenoxy,
4-carbomethoxyethylene-phenoxy.

Reference: New Potential Beta-3 Adrenergic Agonists with Beta-Phenylethylamine Structure, Synthesized for the Treatment of Dyslipidemia and Obesity- Adiposity - Epidemiology and Treatment Modalities, 2017, Chapter-13, Page no. 220-236, DOI: 10.5772/65328

ANTI-ADRENERGIC AGENTS



Mechanism of action

The adrenergic blockers or antagonist binds to the adrenoreceptor thus blocking or inhibiting the stimulation of sympathetic nervous system. They antagonize the receptor action of adrenaline and related drugs.

α adrenergic blocking agents: These drugs inhibit adrenergic responses mediated through the α adrenergic receptors. They can act non-selectively on α_1 or α_2 receptors or selectively on either of the receptor. These agents may be competitive which is reversible or they may cause inhibition by forming covalent bond, that is, irreversible inhibition.

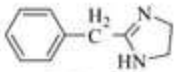
β adrenergic blocking agents: These drugs inhibit adrenergic responses mediated through the β receptors. They are competitive antagonists. Similar to α blocking agents, they are also non-selective to β_1, β_2 and β_3 or selective to β_1.

* The third generation beta-blockers such as Labetalol, Carvedilol, Celiprolol, Nebivolol possess additional α blocking and/or vasodilator property.

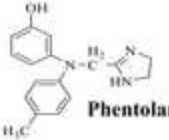
Structure- activity relationship

1. α adrenergic blocking agents: These blockers consist of several compounds of diverse chemical structure that bear little obvious resemblance to the agonist.

Non-selective α blockers: They are imidazoline consisting competitive blockers having a similar structure as that of imidazoline α agonists except for that of the lipophilic substituents which makes them antagonist.



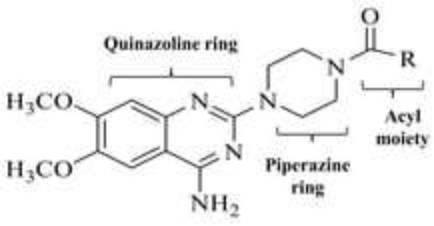
Tolazoline

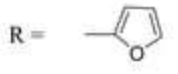


Phentolamine

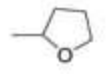
Selective α_1 blockers: They are a class of quinazoline compounds.

- The amino group on 4th position of quinazoline ring is essential for antagonist activity.
- The piperazine ring can be replaced by other heterocycles (e.g., piperidine) without any change in affinity.
- The nature of the acyl group has a significant effect on the pharmacokinetic properties.

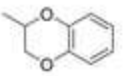




R = **Prazosin**

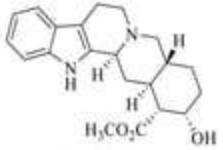


R = **Terazosin**

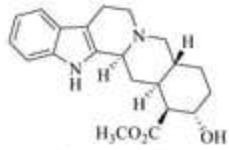


R = **Doxazosin**

Selective α_2 blockers: e.g., Yohimbine and Corynanthine are indolealkylamine. The only difference between these two is relative stereochemistry of carbon containing carbomethoxy substituent.



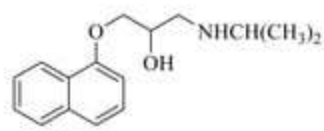
Yohimbine



Corynanthine

2. β adrenergic blocking agents: Most of these agents are aryloxypropanolamines. Propranolol considered prototype of β blockers.

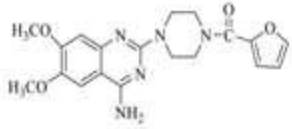
- The important features for the activity are aryl ring, and a side chain containing propanolamine.
- The amine group must be secondary for efficient activity.
- The nature of aromatic ring and its substitutions affect the antagonistic activity and also the ADME properties of the compound.
- The carbon containing OH in the side chain must be of S configuration.



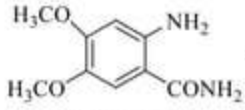
Propranolol

Synthesis

1. α adrenergic blocking agents: e.g., Prazosin

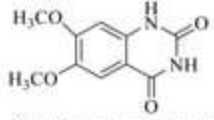


1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanyl carbonyl)-piperazine



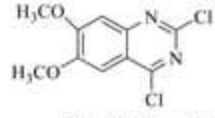
4,5-dimethoxy anthranilamide

NaOCN



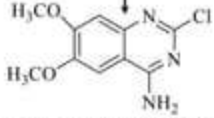
6,7-dimethoxy tetrahydro quinazolin-2,4-dione

$POCl_3$/ PCl_5

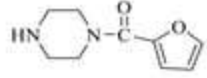


2,4-dichloro 6,7-dimethoxy quinazoline

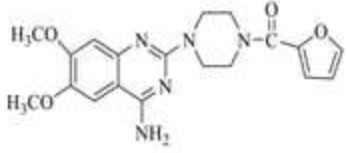
NH_3
-HCl



4-amino 2-chloro 6,7-dimethoxy quinazoline

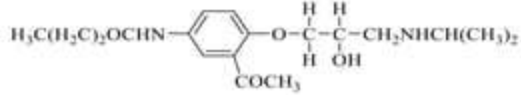


1-(2-furfuroyl)-piperazine
-HCl



Prazosin

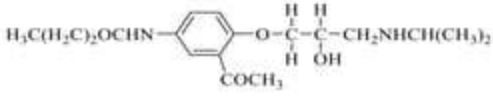
2. β adrenergic blocking agent: e.g., Acebutalol



N-[3-acetyl-4-(2-hydroxy-3-(isopropyl)amino propoxy)phenyl] butyramide

N-(4-hydroxyphenyl)butyramide

Isopropylamine + Epichlorohydrin



Acebutalol

Therapeutic uses

1. Hypertension
2. Angina pectoris
3. Cardiac arrhythmias
4. Myocardial Infarction
5. Congestive heart failure
6. Dissecting aortic aneurysm
7. Pheochromocytoma
8. Thyrotoxicosis
9. Migraine
10. Anxiety
11. Glaucoma
12. Hypertrophic obstructive cardiomyopathy

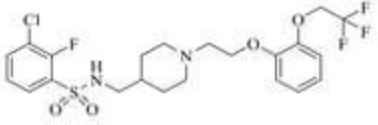
Adverse affects

1. Hypotension
2. Bradycardia
3. Heart block
4. CHF
5. Increased airway resistance
6. Vertigo
7. Lethargy
8. Fatigue
9. Depression
10. Insomnia
11. Hallucinations
12. Agranulocytosis

Recent Advances

Synthesis and Pharmacological Evaluation of Novel Silodosin-Based Arylsulfonamide Derivatives as α_{1A}/α_{1D}-Adrenergic Receptor Antagonist with Potential Uroselective Profile

- A series of arylsulfonamide derivatives of (aryloxy)ethyl alicyclic amines was designed, synthesized, and biologically evaluated as potent α_1-adrenoceptor antagonists with uroselective profile. One of the optimized compound from series, that is, (3-chloro-2-fluoro-N-([1-(2-(2-(2,2,2-trifluoroethoxy)phenoxy]ethyl)piperidin-4-yl) methyl) benzenesulfonamide) showed adequate metabolic stability in rat-liver microsome assay similar to the reference drug tamsulosin.
- The data from this study supported development of uroselective agents in the group of arylsulfonamides of alicyclic amines with potential efficacy in the treatment of lower urinary tract symptoms associated to benign prostatic hyperplasia.
- The structure is synthesized from silodosin and arylsulfonamide derivatives.

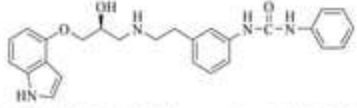


(3-chloro-2-fluoro-N-([1-(2-(2-(2,2,2-trifluoroethoxy)phenoxy]ethyl)piperidin-4-yl) methyl) benzenesulfonamide)

Reference: Design and Synthesis of aryloxypropanolamine as β3-adrenergic receptor antagonist in cancer and lipolysis, European Journal of Medicinal Chemistry, 2018, DOI: 10.1016/j.ejmech.2018.03.032

Design and Synthesis of aryloxypropanolamine as β_3-adrenergic receptor antagonist in cancer and lipolysis

- A few antagonists of β_3-AR have been identified. At present, there are two typical β_3-AR inhibitors: aryloxy propanolamine tetrahydrate β_3-AR inhibitor (SR59230A) and aryloxypropanolamine β_3-AR inhibitor (L-748,337).
- SR59230A displays high affinity at human cloned β_1-AR and β_2-AR. Therefore, SR59230A is a potent and nonselective β-AR antagonist. In contrast, L-748,337 displays more than 90-fold selectivity for human β_3-AR over β_1-AR, 45-fold selectivity for human β_3-AR over β_2-AR, respectively.
- A series of novel L-748,337 compounds were synthesized and evaluated on animal models for their activity against tumour and also the capability of lipolysis.
- One compound among the series showed excellent activity which displayed 23-fold more potent β_3-AR antagonist activity and it alleviated weight loss and inhibit tumor growth in C26 tumor cachexia animal model.



(*S*)-1-(3-(2-((3-(1*H*-indol-4-yl)oxy)-2-hydroxypropyl)amino)ethyl)phenyl)-3-phenylurea

Reference: Synthesis and Pharmacological Evaluation of Novel Silodosin-Based Arylsulfonamide Derivatives as α_{1A}/α_{1D} -Adrenergic Receptor Antagonist with Potential Uroselective Profile, Molecules 2018, DOI :10.3390/molecules23092175

MARKETED PRODUCTS

Adrenergic agonists

Epinephrine

Norepinephrine

Phenylephrine

Dobutamine

Amphetamine

Clonidine

Adrenergic antagonists

Prazosin

Yohimbine

Nadolol

Acebutolol

Carvedilol

Nebivolol

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THANK YOU