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A Comprehensive Review of Structure–Activity Relationships of Drugs Used in Asthma and Allergic Airway Diseases

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Abstract

Asthma is a chronic inflammatory airway disorder characterized by bronchoconstriction, airway hyperresponsiveness, mucus hypersecretion, and reversible airflow obstruction. The pharmacological management of asthma involves several classes of drugs, including corticosteroids, β_2-adrenergic bronchodilators, anticholinergic agents, antihistamines, and nasal decongestants. The therapeutic efficacy and safety of these agents are strongly influenced by their chemical structures. Structure–Activity Relationship (SAR) studies help in understanding how structural modifications affect receptor selectivity, potency, lipophilicity, onset and duration of action, metabolic stability, and adverse effects. Corticosteroids require a steroid nucleus with appropriate substitutions to enhance glucocorticoid activity and pulmonary selectivity. β_2-Agonists depend on aromatic substitutions, ethanolamine side chains, and lipophilic groups for bronchodilator activity and receptor selectivity. Anticholinergic bronchodilators contain quaternary ammonium groups and lipophilic aromatic rings that improve antimuscarinic action and reduce systemic absorption. Antihistamines require aromatic rings, spacer chains, and tertiary amines for H_1 receptor antagonism, while nasal decongestants depend on imidazoline or phenyl ethanolamine structures for α-adrenergic activity. Advances in SAR have enabled the development of safer and more effective anti-asthmatic agents with improved therapeutic outcomes and reduced systemic toxicity.

Keywords: *Asthma, Structure–Activity Relationship (SAR), Corticosteroids, β_2-Adrenergic Agonists, Bronchodilators, Anticholinergics, Antihistamines.*

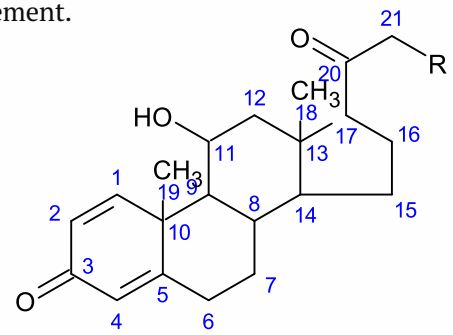
Introduction

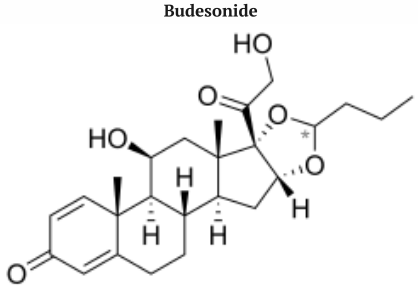
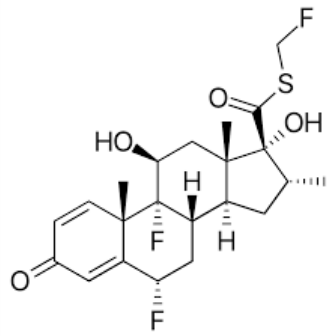
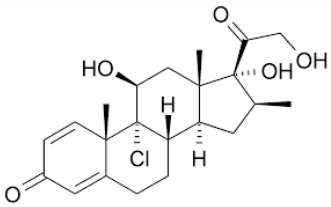
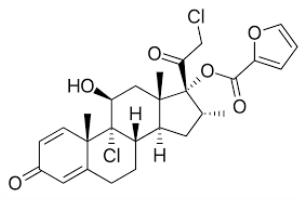
Asthma is a chronic inflammatory disease of the airways associated with bronchoconstriction, airway edema, mucus hypersecretion, and reversible airflow obstruction. It affects individuals of all age groups and is commonly triggered by allergens, respiratory infections, pollutants, exercise, and environmental irritants. The pharmacological treatment of asthma aims to relieve bronchospasm, suppress airway inflammation, reduce allergic responses, and improve respiratory function [1-2]. Various classes of anti-asthmatic drugs, including corticosteroids, β_2-adrenergic bronchodilators, anticholinergic bronchodilators, antihistamines, and nasal decongestants, are widely used in clinical practice. Structure–Activity Relationship (SAR) studies play an important role in medicinal chemistry by correlating chemical structure with biological activity.

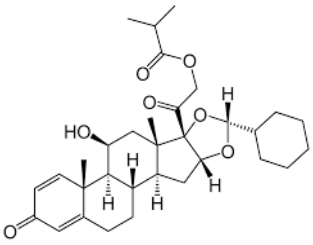
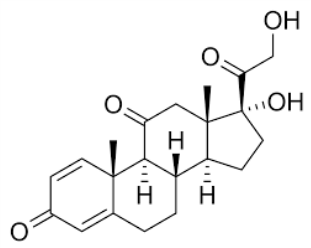
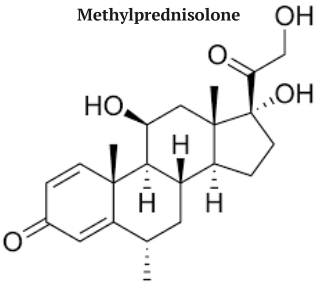
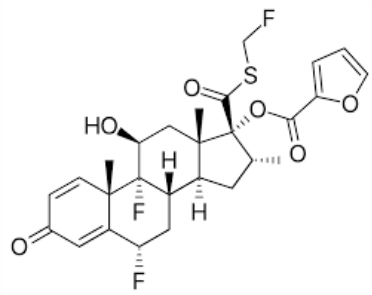
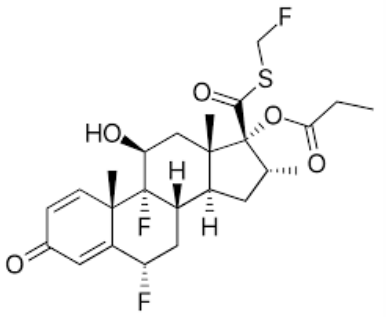
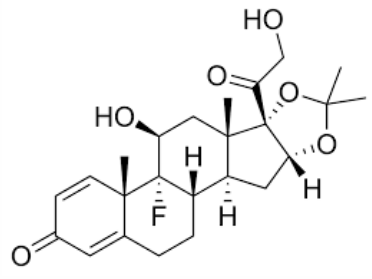
SAR analysis helps in understanding how structural modifications influence receptor binding, selectivity, potency, onset of action, duration of effect, metabolic stability, lipophilicity, and adverse effects [3-5]. Modifications such as halogen substitution, esterification, aromatic ring substitution, quaternary ammonium formation, and lipophilic side-chain addition have significantly improved the efficacy and safety of modern anti-asthmatic drugs. Understanding the SAR of anti-asthmatic agents has contributed to the development of highly selective inhaled corticosteroids, long-acting β_2-agonists, selective anticholinergic bronchodilators, non-sedating antihistamines, and effective nasal decongestants with reduced systemic toxicity. These advancements have greatly improved asthma control, patient compliance, and therapeutic outcomes.

Structure–Activity Relationship (SAR) of Anti-Asthmatic Corticosteroids

Anti-asthmatic corticosteroids are synthetic glucocorticoids mainly used as inhaled or systemic anti-inflammatory agents in asthma management. These drugs possess a common cyclopentanoperhydrophenanthrene steroid nucleus (17-carbon tetracyclic ring system), which is essential for glucocorticoid activity. Corticosteroids act by binding to glucocorticoid receptors and suppressing the production of inflammatory mediators involved in asthma [6]. Structure–Activity Relationship (SAR) studies explain how structural modifications at specific carbon positions influence glucocorticoid potency, receptor affinity, lipophilicity, duration of action, topical selectivity, and systemic adverse effects. Changes such as halogen substitution, hydroxyl groups, double bonds, and esterification enhance anti-inflammatory activity and improve therapeutic efficacy while reducing toxicity. Understanding the SAR of corticosteroids has led to the development of effective inhaled corticosteroids with improved safety profiles for asthma management.



Drug/structure	Drug Class	Important SAR Features	Therapeutic Benefit
Budesonide 	Inhaled Corticosteroid (ICS)	Contains an acetal group that increases topical anti-inflammatory activity; moderate lipophilicity provides good lung selectivity	Potent local anti-inflammatory effect with fewer systemic adverse effects
Fluticasone 	Inhaled Corticosteroid (ICS)	Fluorinated corticosteroid with high lipophilicity; strong glucocorticoid receptor affinity	Prolonged lung retention and minimal oral bioavailability
Beclomethasone 	Inhaled Corticosteroid (ICS)	Chlorine substitution increases anti-inflammatory activity; lipophilic ester groups improve lung deposition	Effective inhaled anti-inflammatory activity with reduced systemic exposure
Mometasone 	Inhaled Corticosteroid (ICS)	Chlorinated and highly lipophilic structure enhances receptor binding and local activity	Potent topical action with low systemic absorption

Ciclesonide 	ICS Prodrug	Esterified prodrug activated in lungs; increased pulmonary selectivity	Reduced oral and systemic side effects
Prednisone 	Oral Corticosteroid	Prodrug converted to prednisolone in the liver; carbonyl at C11 reduces mineralocorticoid activity	Effective systemic anti-inflammatory action with lower sodium retention
Methylprednisolone 	Systemic Corticosteroid	The methyl group at C6 increases glucocorticoid potency and decreases the sodium-retaining effect	Enhanced anti-inflammatory activity with reduced mineralocorticoid effects
Fluticasone Furoate 	Inhaled Corticosteroid (ICS)	Furoate ester markedly increases lipophilicity and receptor binding affinity	Long duration of action and improved once-daily dosing
Fluticasone Propionate 	Inhaled Corticosteroid (ICS)	Propionate ester and fluorination increase potency and lipophilicity	Strong local activity with minimal systemic effects
Triamcinolone Acetonide 	Corticosteroid	The acetonide group enhances anti-inflammatory activity and topical potency	Improved local anti-inflammatory action

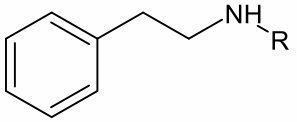
General SAR of Corticosteroids

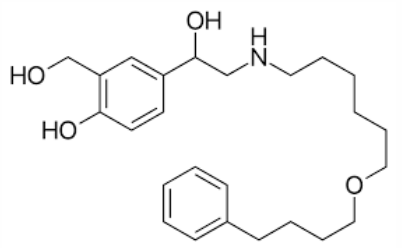
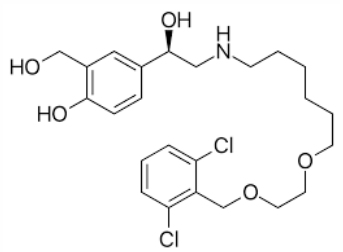
1. The steroidal nucleus is essential for glucocorticoid activity.
2. A double bond between C1–C2 increases anti-inflammatory potency.
3. Hydroxyl groups at C11 and C17 are important for glucocorticoid receptor binding.
4. Substitutions at C6 and C16 modify glucocorticoid and mineralocorticoid activity.
5. C6 methyl substitution reduces mineralocorticoid activity while increasing potency.
6. Lipophilic ester groups prolong lung retention and reduce systemic bioavailability.
7. Increased lipophilicity enhances membrane penetration, topical activity, lung retention, and duration of action while reducing systemic absorption.
8. Halogen substitution, especially fluorine or chlorine, increases glucocorticoid potency and receptor affinity.
9. Halogen substitution improves anti-inflammatory action and receptor binding.
10. Acetonide and acetal groups enhance topical anti-inflammatory activity.
11. Some corticosteroids act as prodrugs and are converted into active metabolites in the lungs or liver.
12. Prodrug formation improves pulmonary selectivity and minimizes systemic adverse effects.

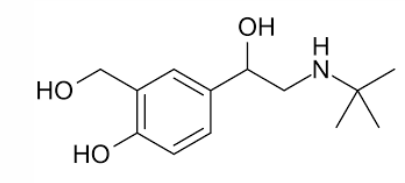
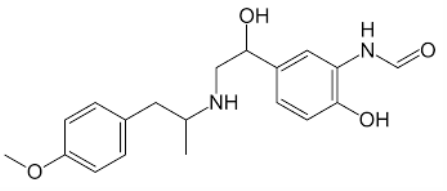
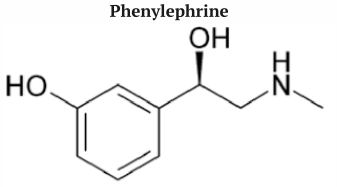
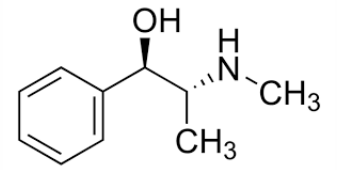
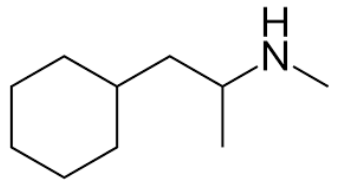
The therapeutic efficacy of anti-asthmatic corticosteroids is highly dependent on structural modifications of the steroid nucleus. Alterations such as fluorination, esterification, halogen substitution, and acetonide formation improve glucocorticoid potency, receptor affinity, pulmonary selectivity, and duration of action while minimizing systemic adverse effects. These SAR modifications have enabled the development of highly.

2. Structure–Activity Relationship (SAR) of β_2-Adrenergic Bronchodilators

β_2-Adrenergic bronchodilators are sympathomimetic agents used in the treatment of asthma and other obstructive airway diseases. These drugs act by stimulating β_2-adrenergic receptors in bronchial smooth muscle, producing bronchodilation and relief of bronchospasm. Structurally, most β_2-agonists possess a phenyl ethanolamine nucleus containing an aromatic ring, ethanolamine side chain, and substituted amino group, which are essential for adrenergic activity [7]. Structure–Activity Relationship (SAR) studies explain how modifications in the aromatic ring, amino substituents, hydroxyl groups, and lipophilic side chains influence β_2 selectivity, potency, onset, duration of action, metabolic stability, and adverse effects. These structural modifications have led to the development of short-acting and long-acting β_2-adrenergic bronchodilators with improved therapeutic efficacy and safety in the management of asthma and chronic obstructive pulmonary disease (COPD).



Drug/structure	Drug Class	Important SAR Features	Therapeutic Benefit
Salmeterol 	Long-Acting β_2-Agonist (LABA)	Long lipophilic side chain anchors the drug to the receptor membrane; bulky N-substitution increases β_2 selectivity	Produces prolonged bronchodilation for about 12 hours
Vilanterol 	Ultra-Long-Acting β_2-Agonist (Ultra-LABA)	Highly lipophilic aromatic groups increase receptor affinity and duration of action	Provides prolonged bronchodilation with once-daily activity

Albuterol (Salbutamol) 	Short-Acting β_2-Agonist (SABA	Contains tert-butyl group on nitrogen, producing selective β_2 activity; hydroxyl substitutions improve bronchodilator activity; resistant to COMT metabolism	Rapid bronchodilation with fewer cardiac side effects
Formoterol 	Long-Acting β_2-Agonist (LABA)	Moderate water solubility provides a rapid onset; lipophilic aromatic groups prolong the duration	Fast onset with prolonged bronchodilator action
Phenylephrine 	Sympathomimetic Decongestant	The phenyl ring with hydroxyl substitution is essential for adrenergic activity; the ethanolamine side chain is required for receptor stimulation	Nasal decongestion and mild bronchodilator effect
Pseudoephedrine 	Sympathomimetic Decongestant	Increased polarity reduces CNS penetration; the ethanolamine side chain is essential for sympathomimetic action	Reduced CNS effects with effective nasal decongestion
Propylhexedrine 	Sympathomimetic Bronchodilator/Decongestant	The cyclohexyl structure produces sympathomimetic action; it lacks catechol hydroxyl groups	Bronchodilator and nasal decongestant activity

General SAR of β_2-Adrenergic Bronchodilators

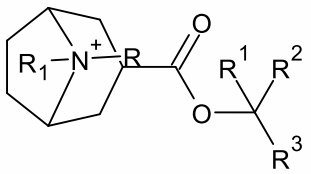
1. A two-carbon side chain between the aromatic ring and the amino group is essential for adrenergic activity.
2. Secondary amine structure is important for receptor interaction.
3. Aromatic rings such as phenyl, substituted phenyl, benzyl alcohol, phenoxy, phenol, or cyclohexyl groups influence activity and duration.
4. An aromatic ring with hydroxyl substitutions is necessary for β_2-adrenergic receptor activity.
5. Ethanolamine side chain is required for sympathomimetic and bronchodilator action.
6. Bulky substitution on the amino nitrogen increases β_2 selectivity and reduces β_1-mediated cardiac effects.
7. Increased lipophilicity prolongs the duration of bronchodilator action.
8. Long lipophilic side chains anchor the drug to the receptor membrane, producing prolonged activity.
9. Short lipophilic chains provide a rapid onset but shorter duration of action.
10. Hydroxyl substitutions improve bronchodilator activity and receptor affinity.
11. Resistance to catechol-O-methyltransferase (COMT) metabolism prolongs the duration of action.
12. Increased polarity decreases CNS penetration and reduces systemic adverse effects.

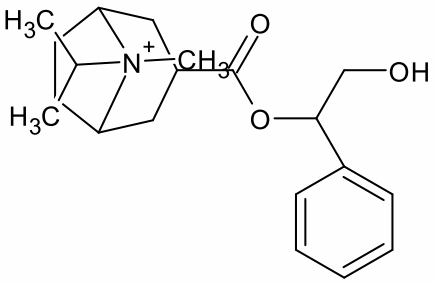
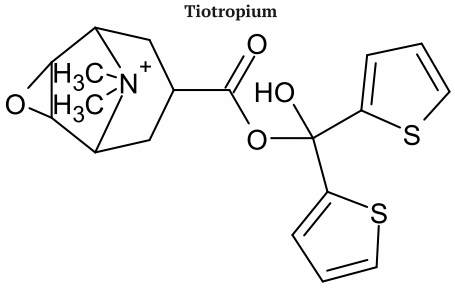
The SAR of β_2-adrenergic bronchodilators demonstrates that modifications in the aromatic ring, amino substituents, and lipophilic side chains strongly influence receptor selectivity, onset, and duration of action. Bulky N-substitutions enhance β_2 selectivity, while increased lipophilicity prolongs bronchodilator activity. These structural modifications have resulted in effective short-acting and long-acting bronchodilators with improved therapeutic efficacy and reduced adverse effects in asthma management.

3. Structure–Activity Relationship (SAR) of Anticholinergic Bronchodilators

Anticholinergic bronchodilators are muscarinic receptor antagonists used in the treatment of asthma and chronic obstructive pulmonary disease (COPD) [8]. These drugs act by blocking muscarinic (M_3) receptors in bronchial smooth muscle, thereby inhibiting acetylcholine-mediated bronchoconstriction and producing bronchodilation.

Structurally, most anticholinergic agents possess a quaternary ammonium group, an ester linkage, and bulky hydrophobic aromatic rings that are important for antimuscarinic activity. Structure–Activity Relationship (SAR) studies show that modifications in these structural features influence receptor selectivity, duration of action, lipophilicity, and systemic adverse effects. Such structural modifications have led to the development of short-acting and long-acting anticholinergic bronchodilators with improved therapeutic efficacy and safety.



Drug/structure	Drug Class	Important SAR Features	Therapeutic Benefit
Ipratropium 	Short-Acting Muscarinic Antagonist (SAMA)	Quaternary ammonium group limits CNS penetration and reduces systemic effects; ester linkage and bulky aromatic groups enhance antimuscarinic activity	Produces bronchodilation with minimal central nervous system adverse effects
Tiotropium 	Long-Acting Muscarinic Antagonist (LAMA)	Quaternary ammonium structure reduces systemic absorption; thiophene rings and high receptor affinity prolong binding to muscarinic receptors	Provides prolonged bronchodilation with once-daily activity

General SAR of Anticholinergic Bronchodilators

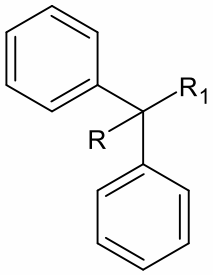
1. Structurally derived from atropine.
2. A quaternary ammonium group limits absorption across biological membranes and prevents CNS penetration.
3. Ester linkage contributes to antimuscarinic activity.
4. Bulky hydrophobic substituents increase selectivity for bronchial muscarinic receptors.
5. Blockade of M_3 receptors inhibits vagal-mediated bronchoconstriction and produces bronchodilation.
6. Quaternary ammonium compounds reduce systemic adverse effects because of poor lipid solubility.
7. Thiophene or other lipophilic aromatic rings increase muscarinic receptor affinity and potency.
8. Slow receptor dissociation prolongs the duration of bronchodilator action.
9. Increased receptor selectivity for M_3 receptors improves airway selectivity and reduces cardiac adverse effects.
10. Increased lipophilicity contributes to prolonged retention in bronchial tissues and longer duration of action.

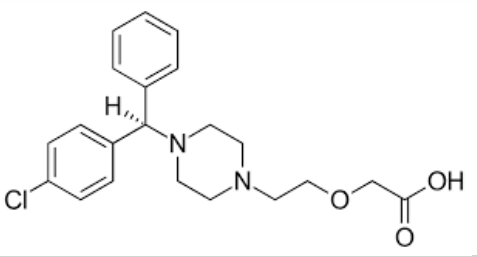
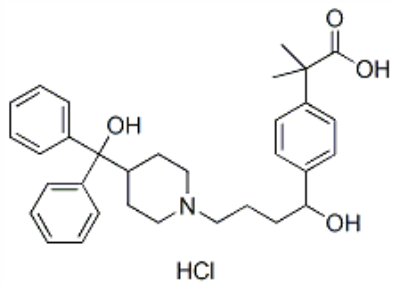
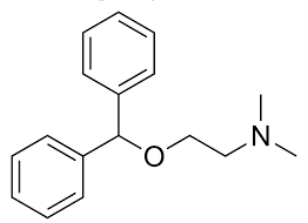
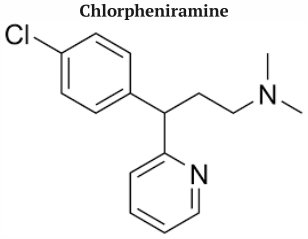
The SAR of anticholinergic bronchodilators demonstrates that structural features such as quaternary ammonium groups, ester linkages, and lipophilic aromatic rings are essential for antimuscarinic activity and bronchodilation. Modifications that enhance receptor selectivity and prolong receptor binding have resulted in effective short-acting and long-acting bronchodilators with improved therapeutic efficacy and reduced systemic adverse effects in asthma and COPD management.

4. Structure–Activity Relationship (SAR) of First- and Second-Generation Antihistamines

Antihistamines are drugs that block the action of histamine at H_1 receptors and are widely used in the treatment of allergic disorders such as allergic rhinitis, urticaria, and asthma-associated allergies. These agents mainly act by competitively inhibiting histamine-mediated responses, including vasodilation, bronchoconstriction, and increased vascular permeability. Structurally, most H_1-antihistamines contain two aromatic rings, a spacer chain, and a terminal tertiary amine that are essential for antihistaminic activity. Structure–Activity Relationship (SAR) studies show that modifications in aromatic substitution, lipophilicity, polarity, and stereochemistry influence receptor selectivity, potency, duration of action, and central nervous system (CNS) effects

such as sedation [9]. These structural modifications have led to the development of first-generation sedating antihistamines and second-generation non-sedating antihistamines with improved safety and therapeutic efficacy.



Drug/structure	Drug Class	Important SAR Features	Therapeutic Benefit
Cetirizine 	Second-Generation H_1 Antihistamine	Contains a polar carboxylic acid group; reduced CNS penetration decreases sedation; active metabolite of hydroxyzine	Effective antiallergic action with minimal drowsiness
Fexofenadine 	Second-Generation H_1 Antihistamine	Polar carboxyl group increases polarity and reduces blood–brain barrier penetration; active metabolite of terfenadine	Non-sedating antihistamine with selective peripheral H_1 action
Diphenhydramine 	First-Generation H_1 Antihistamine	Ether linkage and lipophilic aromatic rings enhance CNS penetration	Produces strong antihistaminic action with marked sedation
Chlorpheniramine 	First-Generation H_1 Antihistamine	Alkylamine derivative with potent antihistaminic activity; moderate CNS penetration produces drowsiness	Effective relief of allergic symptoms

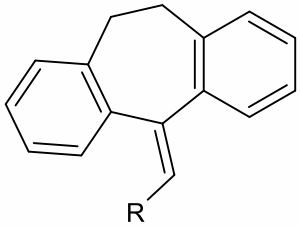
General SAR of Antihistamines

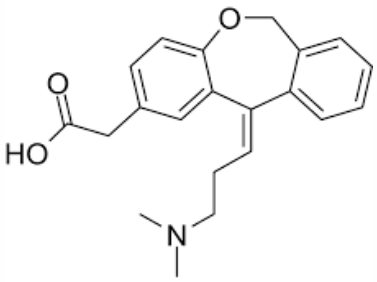
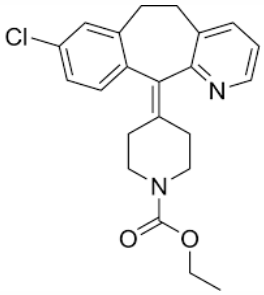
1. Two aromatic rings are essential for H_1 receptor binding.
2. A spacer chain of 2–3 carbon atoms connects the aromatic rings to the terminal amine.
3. A tertiary amine is important for antihistaminic activity.
4. Increased lipophilicity enhances CNS penetration and sedation.
5. Polar groups reduce blood–brain barrier penetration and decrease drowsiness.
6. Carboxyl groups increase polarity and reduce CNS adverse effects.
7. Second-generation antihistamines possess greater peripheral selectivity and minimal sedation.
8. First-generation antihistamines are more lipophilic and readily cross the blood–brain barrier, producing sedation.
9. Ether linkages and hydrophobic aromatic rings contribute to antihistaminic potency.
10. Stereochemical modifications, such as active enantiomers, improve receptor selectivity and potency.

The SAR of antihistamines demonstrates that structural features such as aromatic rings, spacer chains, and tertiary amines are essential for H_1-receptor antagonistic activity. Modifications that increase lipophilicity enhance CNS penetration and sedation, whereas the introduction of polar groups reduces blood–brain barrier penetration and minimizes drowsiness. Structural optimization has led to the development of first-generation and second-generation antihistamines with improved receptor selectivity, therapeutic efficacy, longer duration of action, and reduced adverse effects in the management of allergic disorders.

5. Structure–Activity Relationship (SAR) of Second-Generation Antihistamines for Allergic Rhinitis

Second-generation antihistamines used in allergic rhinitis act by selectively blocking peripheral H_1 receptors and reducing histamine-mediated allergic symptoms such as sneezing, rhinorrhea, and nasal itching. These agents are structurally modified to minimize penetration across the blood–brain barrier, thereby reducing sedation and other CNS adverse effects [10]. SAR studies indicate that increased polarity, reduced lipophilicity, and specific aromatic substitutions improve receptor selectivity, duration of action, and safety profiles. Such structural optimization has resulted in highly selective, long-acting, and non-sedating antihistamines with improved therapeutic efficacy in allergic rhinitis and related allergic disorders.



Drug/structure	Drug Class	Important SAR Features	Therapeutic Benefit
Olopatadine 	Second-Generation H_1 Antihistamine	Dual antihistaminic and mast-cell stabilizing activity; polar groups reduce CNS penetration	Effective control of allergic rhinitis with minimal sedation
Loratadine 	Second-Generation H_1 Antihistamine	Tricyclic structure increases H_1 selectivity; reduced lipophilicity lowers sedative effects	Long-acting non-sedating antihistamine for allergic rhinitis

General SAR of Antihistamines

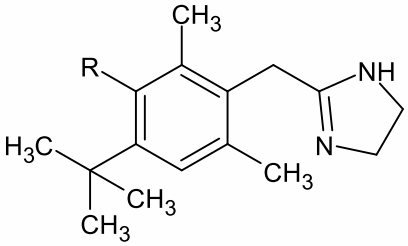
1. Two aromatic rings are essential for H_1 receptor binding.
2. A spacer chain links the aromatic rings to the terminal amine.
3. Tertiary amines are important for antihistaminic activity.
4. Increased lipophilicity enhances CNS penetration and sedation.
5. Polar functional groups reduce blood–brain barrier penetration and decrease drowsiness.
6. Tricyclic structures improve receptor selectivity and duration of action.
7. Second-generation antihistamines possess greater peripheral selectivity with minimal CNS effects.
8. Structural modifications improve potency, safety, and therapeutic efficacy in allergic rhinitis.

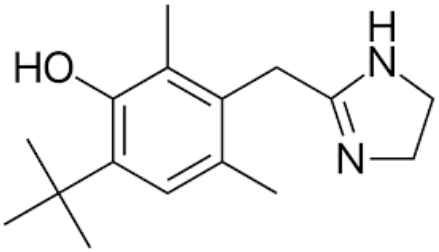
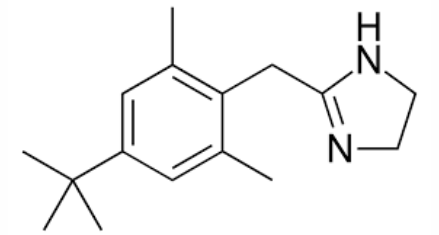
The SAR of antihistamines shows that aromatic rings, tertiary amines, and structural modifications strongly influence H_1-receptor selectivity, potency, and CNS effects. The introduction of polar groups and reduced lipophilicity has resulted in second-generation antihistamines with minimal sedation and improved safety profiles.

These structural advances have enhanced the therapeutic management of allergic rhinitis and related.

6. Structure–Activity Relationship (SAR) of Nasal Decongestants

Nasal decongestants are sympathomimetic agents used to relieve nasal congestion associated with allergic rhinitis, sinusitis, and upper respiratory tract infections. These drugs mainly act by stimulating α-adrenergic receptors in nasal blood vessels, causing vasoconstriction and reduction of mucosal edema. Structurally, most nasal decongestants contain aromatic or imidazoline rings with side-chain substitutions that influence receptor selectivity, potency, and duration of action. Structure–Activity Relationship (SAR) studies show that modifications in lipophilicity, ring structure, and substituents significantly affect α-adrenergic activity and systemic adverse effects. These structural modifications have led to the development of effective topical decongestants with prolonged duration and reduced systemic toxicity.



Drug/structure	Drug Class	Important SAR Features	Therapeutic Benefit
Oxymetazoline 	Topical Nasal Decongestant	The imidazoline structure provides prolonged α-adrenergic action; hydroxyl substitutions enhance receptor affinity	Produces prolonged nasal decongestion
Xylometazoline 	Topical Nasal Decongestant	The imidazoline ring increases α-adrenergic selectivity and duration of action	Rapid and prolonged nasal decongestion

General SAR of Nasal Decongestants

1. Imidazoline or phenyl ethanolamine structures are important for α-adrenergic activity.
2. Aromatic ring substitutions influence receptor selectivity and potency.
3. Imidazoline rings provide prolonged α-adrenergic action and longer duration of effect.
4. Hydroxyl substitutions improve receptor binding and vasoconstrictor activity.
5. Increased lipophilicity prolongs local action in nasal tissues.
6. Tertiary butyl substitution enhances receptor selectivity and prolongs duration of action.
7. Xylene (dimethyl-substituted aromatic) groups increase lipophilicity and improve local decongestant activity.
8. α-Adrenergic receptor stimulation causes vasoconstriction and reduces nasal mucosal edema.
9. Topical formulations reduce systemic adverse effects compared with oral decongestants.

The SAR of nasal decongestants demonstrates that imidazoline rings, aromatic substitutions, tertiary butyl groups, and lipophilic xylene moieties are important for α-adrenergic activity and prolonged vasoconstriction. Structural modifications improve receptor selectivity, duration of action, and local therapeutic efficacy while minimizing systemic adverse effects. These developments have resulted in effective topical decongestants for the management of nasal congestion.

Conclusion

Structure–Activity Relationship (SAR) studies have significantly contributed to the development and optimization of anti-asthmatic drugs.

Structural modifications in corticosteroids, β_2-adrenergic agonists, anticholinergic bronchodilators, antihistamines, and nasal decongestants strongly influence receptor selectivity, potency, lipophilicity, duration of action, pulmonary selectivity, and safety profiles. Features such as halogen substitution, esterification, aromatic ring modifications, quaternary ammonium groups, tertiary amines, and lipophilic side chains enhance therapeutic efficacy while minimizing systemic adverse effects. The development of inhaled corticosteroids with improved pulmonary selectivity, long-acting bronchodilators with prolonged receptor binding, and second-generation antihistamines with minimal CNS penetration demonstrates the importance of SAR in modern medicinal chemistry. Understanding these relationships has enabled the design of safer, more effective, and patient-friendly anti-asthmatic therapies for asthma, COPD, allergic rhinitis, and related respiratory disorders.

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