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Review Article

REVIEW OF IMIDAZOLE HETEROCYCLIC RING CONTAINING COMPOUNDS WITH THEIR BIOLOGICAL ACTIVITY

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ABSTRACT

Imidazole is a five membered**,** heterocyclic ring, which contains two hetero (nitrogen) atoms and two double bonds. There are so many compounds which contain Imidazole ring and exhibit different types of pharmacological and biological activities like metronidazole and nitrosoimidazole as bactericidal, 1-vinyl imidazole as fungicidal, megazol as trypanocidal, imidazole-2-one as antileishmanial and other antimicrobial activities.

Keywords: Imidazole, Heterocyclic Ring, Biological activity.

INTRODUCTION

During the past decade, the concept of Imidazoline (I) receptors has been developed and gained consensus. Different rank order of affinity of ligands indicates the existence of at least two major classes of Imidazoline receptors I_1 and I_2.[1] Findings from different laboratories have been shown that they are widely distributed in different tissues and species and may participate in the regulation of various physiological functions. Therefore a more definite knowledge of the structure and function of this receptor system could help to the search for therapeutic agents useful for treating efficaciously a variety of disorders such as hypertension, diabetes mellitus, gastric ulcer, endogenous depression and stroke. Some Imidazole containing compounds like clonidine, guanfacine and newly synthesize lofexidine hydrochloride also act as α_2-agonists and clinically useful for the treatment of hypertension. α_2 –adrenergic agonist also exhibit activity in human platelets and peripherally act in ocular hypertension (glaucoma).[2] A novel series of (phenoxyalkyl) imidazoles and phenylimidazolidine -2-one derivatives are potent $5HT_3$ receptor antagonist.[3] 1-(3-cyano-benzyl piperdin-4-yl)-5-methyl-4-phenyl-1,3-dihydroimid-azole-2-one is a selective high affinity dopamine D_4 receptor antagonist. 5-Nitro and Nitroso Imidazole compounds exhibit antibacterial and antimicrobial activities.Some newely synthesized 1-[[[5-(Substitutediphenyl)-2-oxazolyl]methylene] amino]-2,4 imidazolidinediones are muscle relaxants and 5-amino-4(diazoacetyl)-1-β-ribofuranosylimdazole is new antileukemic agent.

The [(Biphenylyloxy) alkyl] imidazoles were found to be potent anticonvulsants. (Imidazolyl) aroylimidazolones and Imidazole-substituted 6-phenyldihydropyridazinone synthesized as potent and selective positive ionotropic agents (Cardiotonic agents).[4] Substituted imidazo-[1, 2-a] pyridine and Imidazo[1,2-a] pyrazines are used as antiulcer agents.

Quarternary salts of 2-[(hydroxyimino) methyl] imidazole were prepared and evaluated for reactivation of organophosphorus-inhibited acetylcholinestrases.[5] Some drugs of imidazole containing ring are synthesized and evaluated as radiosensitizer and bioreductively activated cytotoxins.[6] 1, 3-Dihydro-2H-Imidazo[4, 5-b] quinolin -2-one derivatives inhibit blood platelets cAMP-phosphodiesterase. 1, 5-substituted 1H-imidazo [4, 5-C] quinolin-4-(5H)-ones act as bronchodilators.[7,8,9] 2-Imidazolidinylidine-propane dinitrile stimulates gastrointestinal motility and imidazolines stimulate insulin secretion.

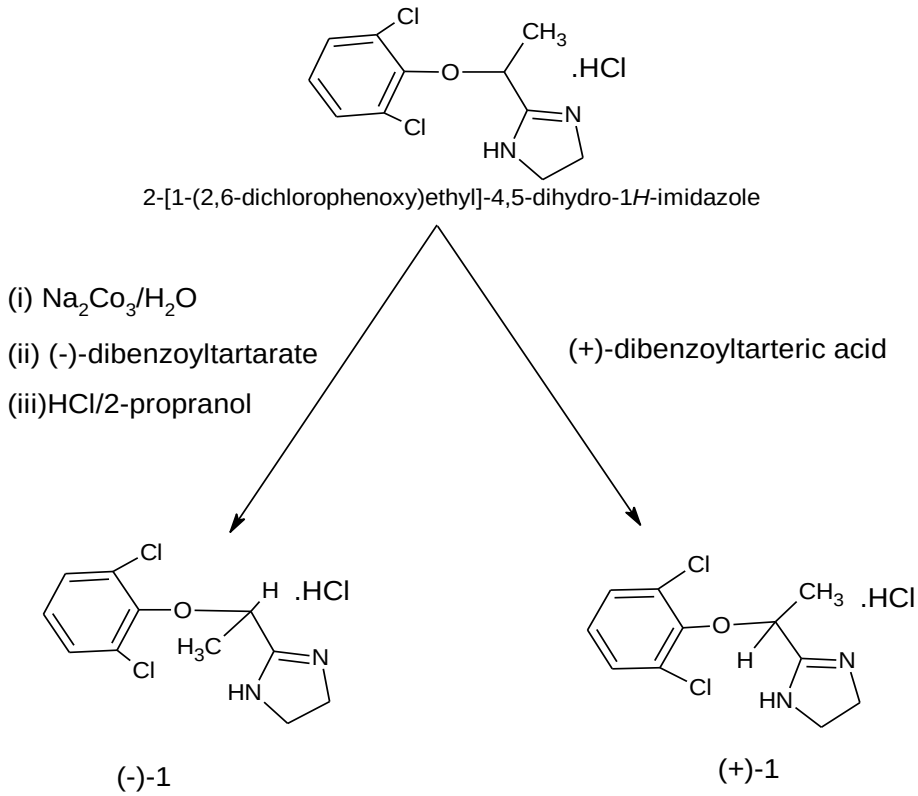
DRUGS ACT ON RECEPTORS

Imidazole containing drugs act on different type of receptor e.g. adrenoceptor, histaminic receptor, dopamine receptor etc.

Adrenoceptor

These are further divided in α (subtype α_1 & α_2) and β (subtype β_1 & β_2) receptors. Clonidine, guanfancine and (-)Lofexidine are centrally acting α_2-agonist and clinically useful for the treatment of hypertension[10,11]

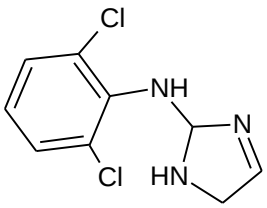
Jurgen Biedermann *et al.*[12] synthesized (-)-2-[1-(2, 6-dichlorophenoxy) ethyl-2-imidazoline hydrochloride (levofexidine). (-)Lofexidine exhibit antihypertensive activity at low doses.



Some α_2-adrenoceptor agonists like clonidine, napamazole, idazoxan act peripherally to reduce intra- ocular pressure in glaucoma.

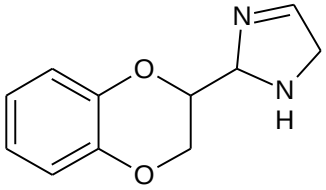
The identification of α_2-adrenergic receptors at presynaptic nerve terminal sites in the central and peripheral nervous systems has intensified the search for the agents that selectively activate or block these receptor sites. Clonidine stimulates both central and peripheral α_2-adrenergic receptors and decrease sympathetic outflow and tone. This is manifested as hypotension and bradycardia. The α_2-adrenergic antagonists like idazoxan and napamezole are undergoing clinical evaluation as antidepressants.[13,14] α_2-Adrenergic antagonists should prove useful as antidepressants since they increase norepinepherine release centrally.

Clonidine



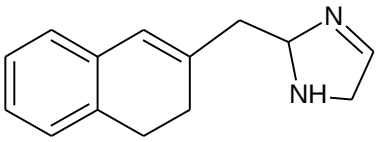
N-(2,6-dichlorophenyl)-2,5-dihydro-1*H*-imidazol-2-amine

Idazoxan



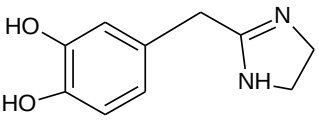
2-(2,3-dihydro-1,4-benzodioxin-2-yl)-2,5-dihydro-1*H*-imidazole

Napamazole

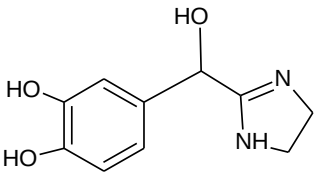


2-(3,4-dihydronaphthalen-2-ylmethyl)-2,5-dihydro-1*H*-imidazole

Miller et al[14] synthesized catecholimidazole and catecholimidazolines analogues that act as as α_2 antagonist and induce aggregation of platelets.



4-(4,5-dihydro-1*H*-imidazol-2-ylmethyl)benzene-1,2-diol

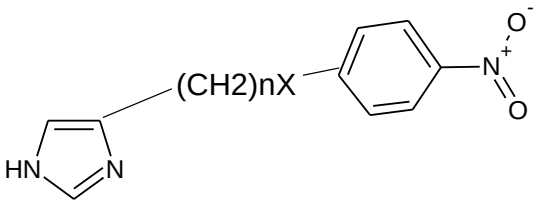


4-[4,5-dihydro-1*H*-imidazol-2-yl(hydroxy)methyl]benzene-1,2-diol

Histamine receptor

Histamine H_3-receptors are presynaptic autoreceptors, which modulate the synthesis and release of histamine in histaminergic neurons in the central nervous system.[15] The H_3-receptors also appears to occur as hetero-receptors on non-histaminergic axon terminals, modulating the

release of other neurotransmitters both in CNS and the periphery.C. Robin Ganellin et al[16] synthesized [[4-nitrophenyl) X] alkyl]imidazole iso-steres.



n=2,X=NH

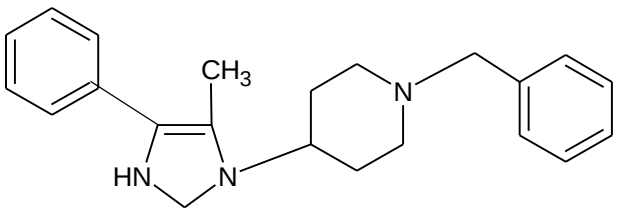
n=2,X=S

n=1,X=SCH2

A possible bioisoterism between benzimido and the phenylimidazolidin-2-one moieties has suggested on the basis of the similarity between the molecular electrostatics potential of metoclopramide, a D_2 receptor antagonist with weak $5HT_3$ receptor antagonist properties and zetidoline at D_2 receptor antagonist. A series of phenylimidazoline-2-one derivatives bearing a basic azabicycloalkyl moiety were synthesized and evaluated for $5HT_3$ receptor radio-ligand binding. $5HT_3$ antagonists are potential candidate as antiemetic.

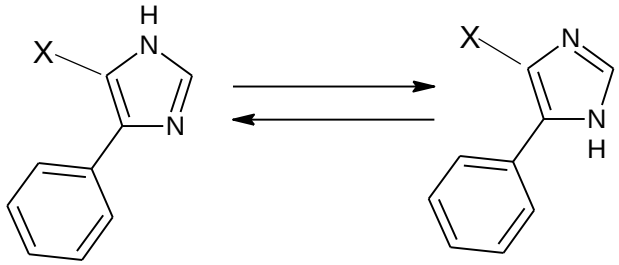
Dopaminergic receptor

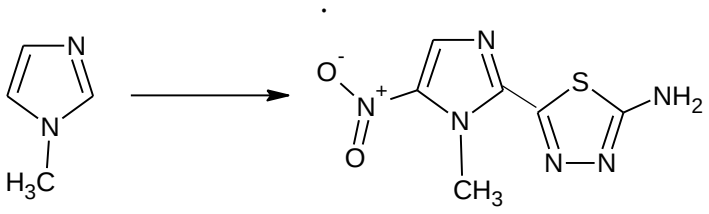
For the debilitating mental illness schizophrenia, it is widely accepted that brain dopamine receptors (D_2 & D_4) are primary targets for medical treatment. D_4 receptor antagonist prepared as 4-(2-oxo, 1, 3 dihydroimidazole-2-yl]piperidine.[17]



Antimicrobial agents

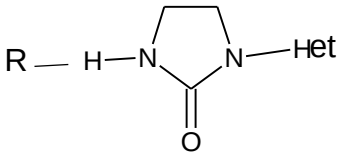
Substances containing the imidazole nucleus have been synthesized because they exhibit antifungal activity. In recent years Masura Ogata et al found a new imidazole transfer reaction using N,N`-sulfinyldiimidazoleII and the monoimidazole III from carbonyl compounds. Thus they synthesized 1-vinyl imidazole which exhibit antifungal avtivity.[18] Metronidazole and related –5-nitro-imidazoles are valuable drugs for the treatment of several protozoal diseases as well as for treating infections due to anaerobic bacteria. Several types of evidence strongly suggest that reduction of the nitro group is obligatory for the biological effects that are responsible for the therapeutic activity of these drugs. Nitro imidazoles also exhibit this type of activity.[19] New synthesis of megazol derivatives also act as trypnocidal lead. [20]





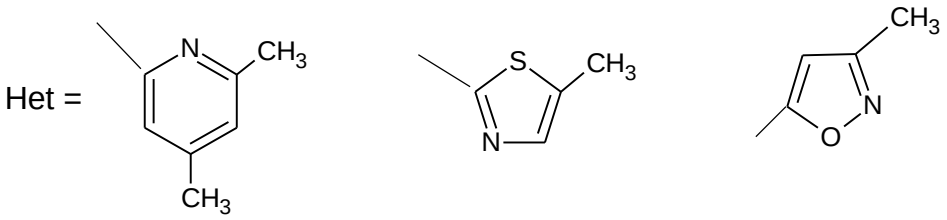
Megazol

Jean Michal H. Robert et al[21] synthesized new imidazolidin-2-one which is used in the treatment of leishmaniasis disease. The pentavalent antimonials, sodium stibogluconate and meglumine are presently recommended first line drugs. However they are not orally active and they require long courses of the treatment. The second line drugs pentamine, azole derivatives (Ketoconazole, itroconazole) and amphotericin B are even less acceptable because of long term parentral administration and toxicity. These drawbacks explain that several investigations are oriented to searching new compounds for better treatment.



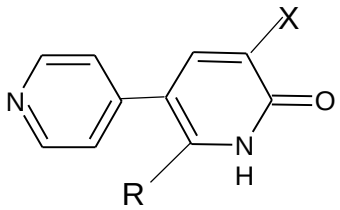
R = alkyl, aryl,benzyl

H = CH2,CO,SO2



Cardiotonic agents

For some 200 years, digitalis and its constituent cardiac glycosides such as digitoxin and digoxin have been used as positive ionotropic agents for the treatment of congestive heart failure.[22] Although these drugs are selective in their ionotropic effects and exhibit no significant direct effects on the vasculature but their potential for producing cadiac arrythmia leads to undesirably low therapeutic ratios.[23] This problem and increasingly high death rate from congestive heart failure have spurred attempts to find an orally available digitalis replacement. The discovery of amrinone has led to the synthesis of a number of agents that show varying promise for congestive heart failure treatment.[24] A few compounds have shown.



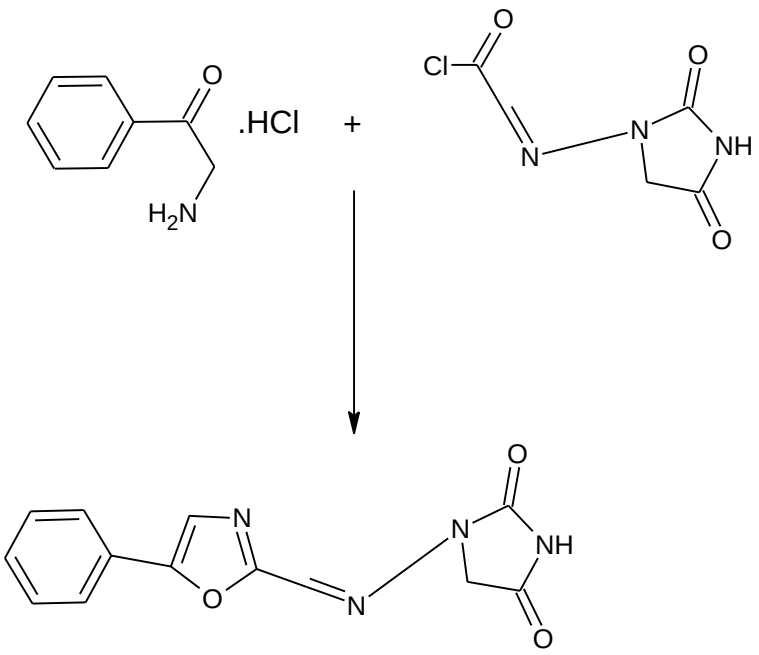
R=H, X=NH_2(Amrinone)

R=Me, X=CN (Milrinone)

Muscle relaxant

In the research for compounds for the treatment of skeletomuscular disorders, a series designed to be direct skeletal muscle relaxants was synthesized and pharmacologically evaluated. Dantrolene sodium and other similar 1-[[[5-(substituted phenyl)2-furanyl] methylene] amino] 2,4-

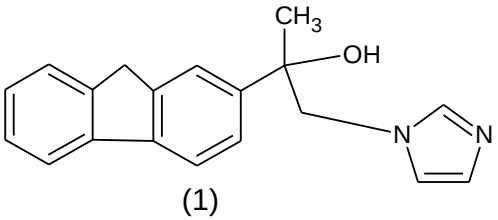
imidazolidinediones have been found to exhibit direct skeletal muscle relaxant activity.[25]



1-{[(5-phenyl-1,3-oxazol-2-yl)methylene]amino}imidazolidine-2,4-dione

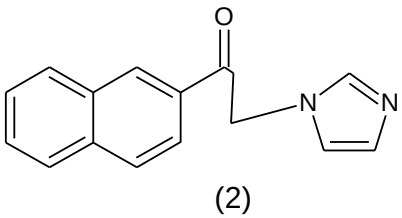
Anticonvulsant

David W. Robertson et al[26] reported the potent and highly selective anticonvulsant activity of α-9H-fluoren-2-yl-α-methyl-1H-imidazole-1-ethanol (1) and its congeners. This agent, along with denzimol (2) and nafimidone (3) is member of a structurally novel class of anticonvulsant, the (arylalkyl) imidazoles. Previous structure activity relationship studies suggested that the pharmacophore of this class of anticonvusants is the alkylimidazole portion of the molecule with the lipophilic aryl portion enabling penetration of blood brain barrier. An impressive feature of the pharmacology of these drugs is their higher degree of selectivity. They antagonize maximal electroshocks (MES) induced seizures at doses far below required to produce sedation or neurological impairment.



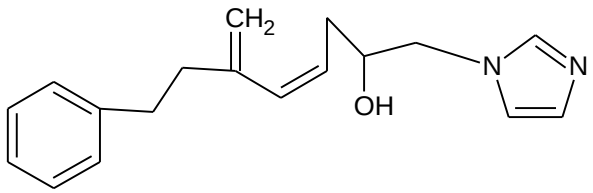
(1)

2-(9*H*-fluoren-2-yl)-1-(1*H*-imidazol-1-yl)propan-2-ol



(2)

3-(1*H*-imidazol-1-yl)-1-(2-naphthyl)propan-1-one



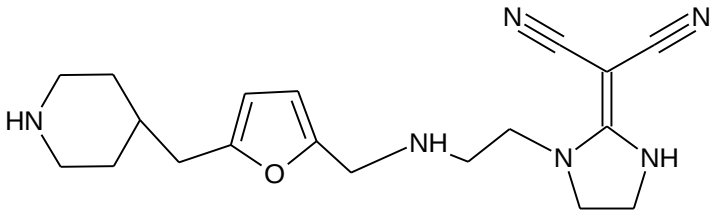
(3)

2-(1*H*-imidazol-1-yl)-1-[4-(2-phenylethyl)phenyl]ethanol

Gastrointestinal motility promoter

Alterations in the motility of the alimentary canal are associated with many symptoms of gastrointestinal disease. Examples of the digestive systems diseases that are manifested by a disturbance in motor activity are *dysphagia*, *gastric stasis, vomiting, abdominal pain, paralytic ileus and constipation*.

Ranitidine the histamine H_2 receptor antagonists, has been previously reported to increase gastric emptying and gastric motility by inhibition of acetylcholinestrase (AchE) and enhancement of Acetylcholine (Ach) release. In order to obtain potent gastro-prokinetic agents, a new series of ranitidine derivatives possessing a nitrogen atom instead of a sulfur atom was synthesized and their AchE inhibitory activity and potentiating action on electrically evoked contractions of guinea pig ileum were evaluated.[27]

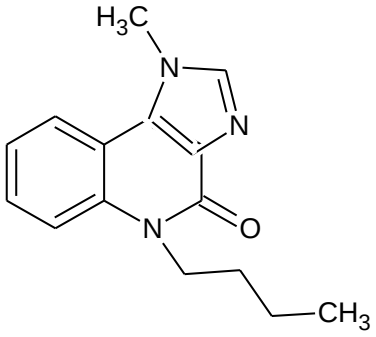


1-{2-[(5-piperidinomethyl)-2--furanyl]methyl]amino]-ethyl]-2-imidazoli dinylidene]propane dinitrile

New bronchodilator

Bronchial asthma is chronic debilitating disease, which in its severe forms can threaten life. Efforts but without its CNS and cardiovascular side effects. A series of novel xanthine-based tricyclic hetero-cycles in 1H-imdazo[4,5-c]quinolin-4(5H)-ones was designed, synthesized and tested as potential active bronchodilators.[28]

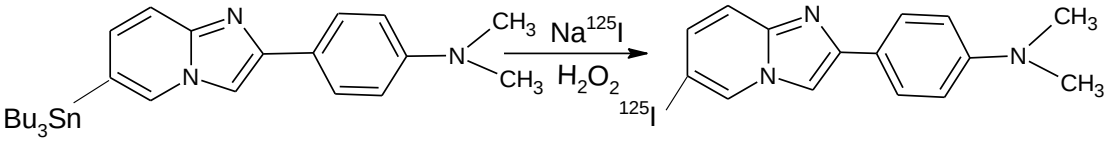
have been done to develop new xanthine derivatives, which relax the bronchial smooth muscle in a fashion similar to that of theophylline



[5-butyl 1-methyl-1H-imidazo [4, 5-c] quinolin-4-(5H)-one]

Agents used in diagnosis of alzheimer`s disease

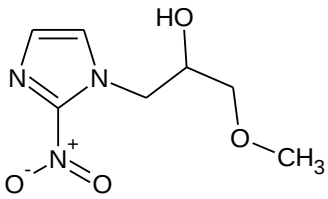
Formation of β(Aβ) plaques in the brain is pivotal event in the pathology of Alzheimer's disease. Zhi Ping Zhuang et al[29] synthesized a series of novel β-amyloid (Aβ) aggregate specific ligands 2-(4`-dimethylaminophenyl)6-iodoimidazo[1,2-a]pyridine and its related derivatives were labeled with suitable isotopes for PET (position emission tomography) and SPET (single photon emission computed tomography) so they are useful for detecting β-amyloid in brain in Alzheimer's disease.



[^{125}I](IMPY)

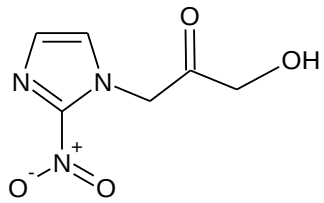
Radiosensitizer and bireductly activated cytotoxins

It is generally known that many solid tumors contained areas of diminished oxygen supply while the underlying reasons for this hypoxia can vary depending upon the type and environment of the tumors. α- [1-Aziridinyl] methyl-2-nitro 1H-imidazole-1-ethanols of general formula. $ImCH_2CH(OH)CH_2NCR^1R^2CR^3R^4$ where Im= 2-nitroimidazole and R^1, R^2, R^3, R^4=H, Me are selective bioreductively activated Cytotoxins toward hypoxy tumor cell *in vivo* and *in vitro* and radiosensitizers[30].



1-methoxy-3-(2-nitro-1*H*-imidazol-1-yl)propan-2-ol

(Misonidazole)



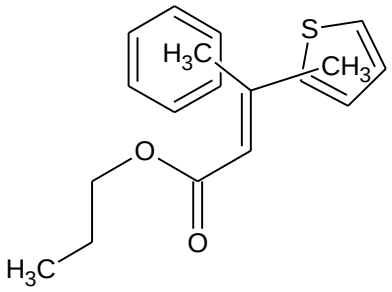
1-hydroxy-3-(2-nitro-1*H*-imidazol-1-yl)acetone

(Etanidazole)

Stimulators of insulin secretion

Jakoben et al31 synthesized a series of imidazolines with glucose dependent effects on insulin exocytosis from pancreatic β-cells. Regioisomers and enantiomers were found to

exhibit marked differences in exocytotic effects as well as different activities on the K_{ATP}-Channel.



Anti-arrhythmic agents

Antiarrhythmic agents that selectively prolong the action potential duration (ADP) and concomitantly increase the refractory period (FRP) of heart cells without significant effects on cardiac conduction are termed class III anti-arrhthymic agents in Vaughan Williams classification. Randall et al[32] reported the synthesis and class III anti-arrhythymic activity of a new series of 3-alkyl-1-[ω-(4-(alkylsulfonyl) amino] phenyl] - ω- hydroxy alkyl) imidazolium salts and additional derivatives.

CONCLUSION

Vast number of imidazole containing compounds have been synthesized and evaluated for their biological activity. A large number of imidazole containing agents work through receptors such as adrenoceptors (α,β), histaminic receptor ($5HT_3$), dapaminergic receptors (D_2 and D_4). α_2- agonists act centrally to decrease hypertension and some act peripherally resulting in the inhibition of sympathetic tone and decrease intraocular pressure in glaucoma. β_1-receptor is cardioselective. Some agents act on $5HT_3$ receptor to inhibit vomiting. Dopaminegic drugs act in schizophrenia. Agents like 1-vinylimidazole, 5-nitroimidazole, megazole etc. act as antiprotozoal and antimicrobial. Other types of activities has been shown by these agents are anti-convulsant, muscle relaxant, antileukemic, cardiotonic, antiarrhythmic, antiulcer, gastric motility stimulators etc.

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