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A Review on Hypertensive Analytics

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ABSTRACT

Due to changed life style, sustained arterial hypertension triggers the possible damage of blood vessels in kidney, heart, and brain, and leads to an increased incidence of renal failure, coronary disease, cardiac failure, and stroke. Hypertension is a cause of morbidity and mortality, worldwide. This review presents a comprehensive overview on three dimensional study of hypertension within the analytics of mechanism, management and the potent heterocyclic moieties for the antihypertensive activity. The antihypertensive derivatives of moieties azitidinone, imidazole, indole, oxadiazole pyridine, quinazoline and thiadiazoles have been covered.

Keywords: Azitidinone, Imidazole, Indole, Oxadiazole pyridine, Quinazoline, Thiadiazoles

INTRODUCTION

World Health Statistics 2012 report, India has low rates of hypertension compared to world figures. Here, 23.10% men and 22.60% women above 25 years suffer from hypertension. India also fares better than the global average of 29.20 in men and 24.80 in women respectively. As the population ages, the prevalence of hypertension will increase even further unless broad and effective preventive measures are implemented. Recent data from the Framingham Heart Study suggest that individuals who are normotensive at age 55 have a 90 percent lifetime risk for developing hypertension [1].

The relationship between Blood Pressure (BP) and risk of Cardiovascular Disease (CVD) events is continuous, consistent and independent of other risk factors. The higher the BP, the greater is the chance of heart attack, heart failure, stroke and kidney disease. For individuals 400-70 years of age, each increment of 20 mmHg in Systolic BP (SBP) or 10 mmHg in Diastolic BP (DBP) doubles the risk of CVD across the entire BP range from 115/75-185/115 mmHg [2].

Taking all these facts into account, an effort of comprehensive audit for hypertension has been done in the present work. An emphasis has been given to understand the pathophysiology of hypertension followed by management with available medication and their mode of action. Sincere efforts have been made for the screening of heterocyclic moieties with potent antihypertensive activity.

MECHANISM OF HYPERTENSION

Blood pressure, pressure is generated when the heart contracts against the resistance of the blood vessels. It can be measured by following Equation [3].

$$MAP = CO \times SVR$$
$$CO = SV \times HR$$

Where, MAP: Mean Arterial Blood Pressure, estimated by DBP+(SBP-DBP)/3, CO: Cardiac Output, SVR: Systemic Vascular Resistance, DBP: Diastolic Blood Pressure, SBP: Systolic Blood Pressure, SV: Stroke Volume (dependent on pre-load, contractility, after-load), HR: Heart Rate.

Arterial pressure is regulated by changes in cardiac output and systemic vascular resistance. Cardiac output is determined by the product of stroke volume and heart rate, essentially equivalent to the effective circulating volume. Total blood volume is regulated by renal function, particularly renal handling of sodium and water. Systemic vascular resistance is the net result balance of vasoconstrictor and vasodilator effectors. Vasoconstrictor effectors include angiotensin II, norepinephrine, vasopressin and endothelin, while vasodilator effectors include prostaglandins, nitric oxide and bradykinin. The autonomic nervous system also affects BP regulation, with the sympathetic system acting to stimulate the heart and constrict blood vessels, and the parasympathetic system acting to depress cardiac function and dilating selected vascular beds. Hypertension typically occurs because of an increase in systemic vascular resistance with normal CO [4].

MANAGEMENT OF HYPERTENSION

Hypertension is the result of activation of many systems in the body. The CNS, automatic pathways, spinal loci, the peripheral vasculature and the osmotic pressure of the blood flowing therein are all factors that influence the degree of blood pressure. Drugs affecting any of these diverse factors are therefore bound to affect the blood pressure. There are dozens of different medications to treat high blood pressure. They are known as antihypertensive agents. They are divided into 12 categories based on how they work. Each has its own benefit and side effect profile. With so many options available, finding the best one sometimes takes a little time and patience. It is well worth the effort since the stakes for the health are so high. The antihypertensive agents with their mode of action are listed in Table 1 [5].

Table 1: Anti-hypertensive agents with category, available drugs and mode of action

Antihypertensive agents	Category	Available drugs	Mode of action
Diuretics	Thiazide diuretics	Hydrochlorothiazide, Chlorthalidone	Acts on kidneys to increase excretion of Na^+ and H_2O–decrease in blood volume–decreased BP
	Loop diuretics	Furosemide and Bumetanide	
	K^+ sparing diuretics	Spironolactone, Triamterene, Amiloride	
Sympathoplegic agents	Centrally-acting adrenergic drugs (A2-agonists)	Clonidine and α-Methyldopa	Act on central α2A receptors to decrease sympathetic outflow-fall in BP
	Drugs that act on peripheral nervous system (B-blockers)	Propranolol, Metoprolol, Nadolol, Carteolol, Atenolol, Betaxolol, Bisoprolol, Pindolol, Acebutolol, Penbutolol, Labetolol, Carvedilol, Timolol	Bind to beta adrenergic receptors and blocks the activity
	A1-blockers/α-adrenergic blockers	Prazosin, Tetrazosin, Doxazosin, Phentolamine, Phenoxybenzamine	Blocking of alpha adrenergic receptors in smooth muscles–vasodilatation
	Ganglion-blocking agents	Trimethaphan	-
	Agents that block adrenergic neurotransmitter synthesis and/or release	Reserpine, Guanethidine, Pargyline	-
Direct vasodilators	K^+ Channel activators	Hydralazine, Minoxidil, Sodium nitroprusside, Diazoxide, Pinacidil and Nicorandil	Leaking of K^+ due to opening-hyper polarization of SMCs–relaxation of SMCs
	Calcium channel blockers	Verapamil, Diltiazem, Dihydropyridine, Nifedipine, Felodipine, Amlodipine, Nimodipine etc.	Blocks influx of Ca^{++} in smooth muscle cells–relaxation of SMCs–decrease BP
ACE inhibitors and Angiotensin receptor antagonists	Angiotensin-converting Enzyme (ACE) inhibitors	Captopril, Enalapril, Benazepril, Fosinopril, Moexipril, Quinapril, Ramipril, Lisinopril etc.	Inhibit synthesis of angiotensin II–decrease in peripheral resistance and blood volume
	Angiotensin-II antagonists/Angiotensin (AT1) blockers	Losartan, Valsartan, Candesartan, Irbesartan, Telmisartan, Eprosartan and Zolasartan	Blocks binding of angiotensin II to its receptors

Heterocyclic moieties as potent antihypertensive agents

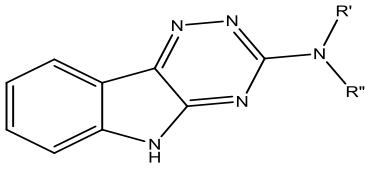
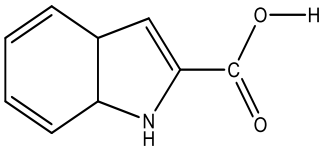
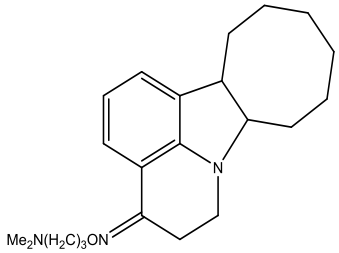
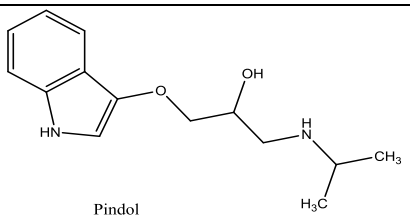
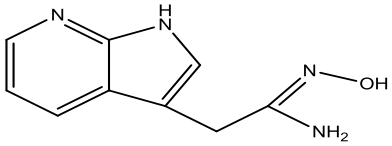
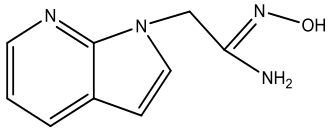
Heterocyclic chemistry has been the area of interest for majority of researchers since ages, mainly because it is a habitat of potent moieties for biological activity. In present time, the chemists are playing the role just like engineers because of designing unlimited combinations of fused heterocyclic structures. In short they are synthesizing library of compounds with the most diverse physical, chemical and biological properties. Therefore, efficient methodologies resulting in polycyclic structures from biologically active heterocyclic templates are always of interest to both organic and medicinal chemists. Indoles, azitidinones, oxadiazoles, pyridines, imidazoles etc., are few heterocyclic moieties which have reflected diverse activities such as cardiovascular, antihypertensive, analgesic, anticancer, antidepressant, antipsychotic, antiasthmatic, antiviral, antibacterial, antipsychotic etc. The literature survey reveals that heterocyclic moieties as stated in Figure 1 have been found remarkable role in antihypertensive activity as diuretics, sympathoplegic agents, direct vasodilators and ACE inhibitors and angiotensin receptor antagonists.

Figure 1: Heterocyclic moieties for antihypertensive activity

Indole derivatives

Indoles are an important class of heterocycles not only because they are among the most ubiquitous compounds in nature, but also because they have a wide range of biological activities. Indole derivatives constitute an important class of therapeutic agents in medicinal chemistry including antihypertensive, antiproliferative, antiviral, antitumor, analgesic, anti-inflammatory, antimicrobial, antifungal activities etc. The literature search reveals that indole derivatives have shown remarkable antihypertensive activity as listed in the Table 2.

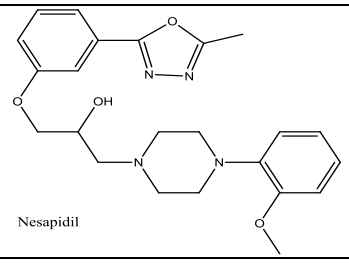
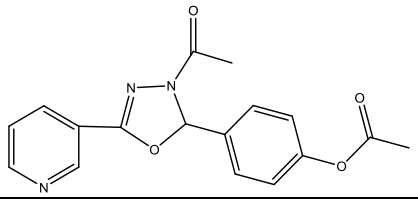
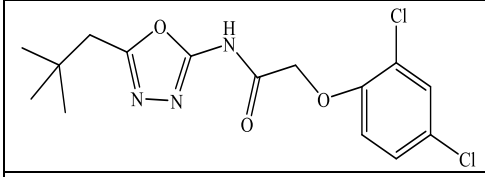
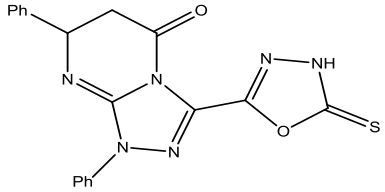
Table 2: Indoles derivatives for antihypertensive activity

Indole derivatives	Name	Reference
 1,2,4- triazino[5,6-b]indoles	N,N-substitutedalkyl/phenyl-5H-[1,2,4]triazino[5,6-b]indol-3-amine	[6]
	3a,7a-dihydro-1H-indole-2-carboxylic acid	[7]
	(Z)-5,6,7a,8,9,10,11,12,13,13a-decahydro-4H-cycloocta[4,5]pyrrolo[3,2,1-ij]quinolin-4-one O-(3-(dimethylamino)propyl)oxime	[8]
 Pindol	1-((1H-indol-3-yl)oxy)-3-(isopropylamino)propan-2-ol	[9]
 7-azaindole-3-acetamidoxime	(Z)-N'-hydroxy-2-(1H-pyrrolo[2,3-b]pyridin-3-yl)acetimidamide	[10]
 7-azaindole-1-acetamidoxime	(Z)-N'-hydroxy-2-(1H-pyrrolo[2,3-b]pyridine-1-yl)acetimidamide	

Oxadiazole derivatives

Compounds containing 1,3,4-oxadiazole moiety have been found to exhibit wide range of biological activities including anticancer, antibacterial, antifungal, analgesic, anti-inflammatory, anticonvulsant, antihypertensive, antiviral, anti HIV and antidiabetic properties. Variety of therapeutically active compounds currently being used in clinical medicine are: HIV-integrase inhibitor Raltegravir®, an antiretroviral drug Zibotentan®, an anticancer agent, a nitrofuran, antibacterial: Furamizole, antihypertensive agent-s tiodazosin and nesapidil etc., are based on 1,3,4-oxadiazole moiety. Since many of 1,3,4-oxadiazoles display a remarkable antihypertensive activity, their synthesis and transformations have been receiving particular interest for a long time. Few of the oxadiazoles as antihypertensive agents have been demonstrated in Table 3.

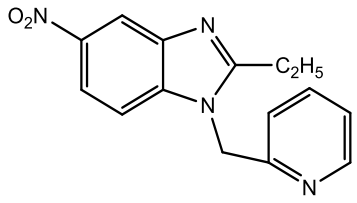
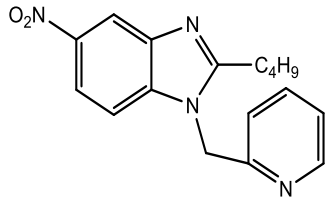
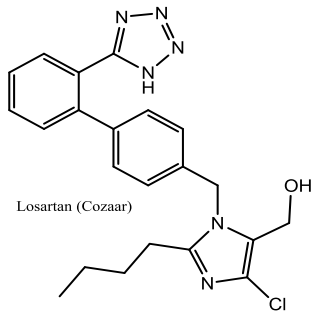
Table 3: Oxadiazole derivatives for antihypertensive activity

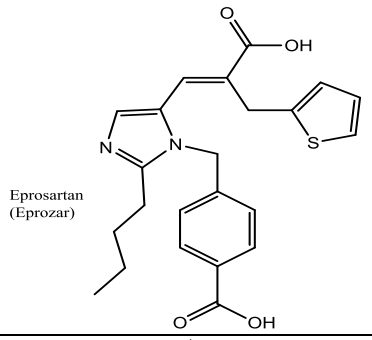
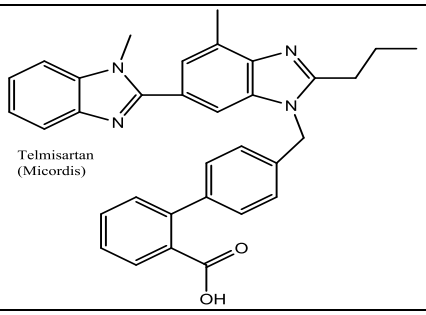
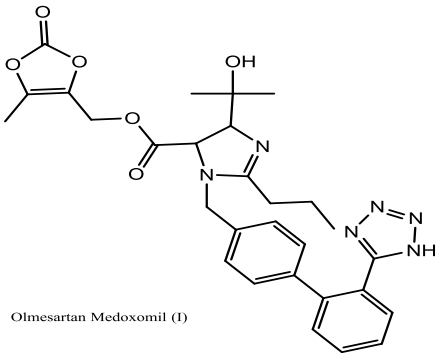
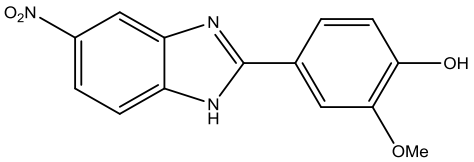
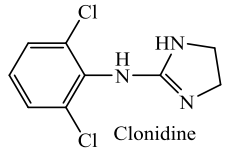
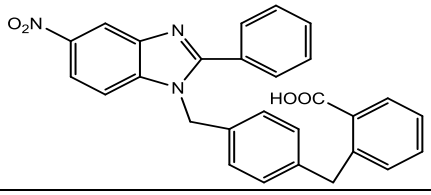
Oxadiazole derivatives	Name	Reference
 Nesapidil	1-(4-(2-methoxyphenyl)piperazin-1-yl)-3-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenoxy)propan-2-ol	[11]
	4-(3-acetyl-5-(pyridine-3-yl)-2,3-dihydro-1,3,4-oxadiazol-2-yl) phenyl acetate	[12]
	2-(2,4-dichlorophenoxy)-N-(5-neopentyl-1,3,4-oxadiazol-2-yl)acetamide	[13]
	1,7-diphenyl-3-(5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-6,7-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one	[14]

Imidazole derivatives

The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine and nucleic acid. Benzimidazole derivatives play very efficient role in the medical field with plenty of useful therapeutic activities like antiviral, antihistaminic, anticancer, antiulcer, antihypertensive, antidiabetic, antifungal and antimicrobial activity. The Table 4 has been summarized to know about the different antihypertensive derivatives of imidazole.

Table 4: Imidazole derivatives for the antihypertensive activity

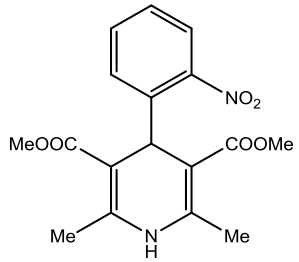
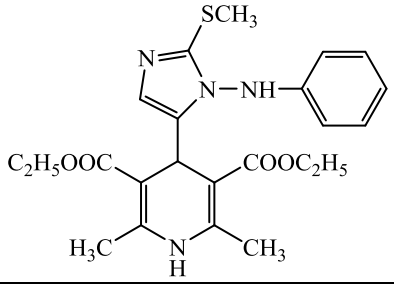
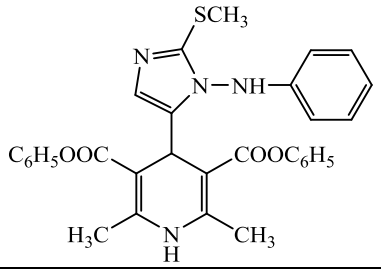
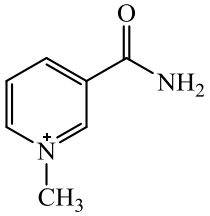
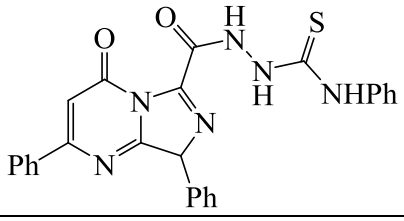
Imidazole derivatives	Name	Reference
	2-ethyl-5-nitro-1-(pyridin-2-ylmethyl)-1H-benzo[d]imidazole	[15]
	2-butyl-5-nitro-1-(pyridin-2-ylmethyl)-1H-benzo[d]imidazole	
 Losartan (Cozaar)	(1-((2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl]-4-yl)methyl)-2-butyl-4-chloro-1H-imidazol-5-yl)methanol	[16]

 Eprosartan (Eprozar)	(E)-4-((2-butyl-5-(2-carboxy-3-(thiophen-2-yl)prop-1-en-1-yl)-1H-imidazol-1-yl)methyl)benzoic acid	
 Telmisartan (Micordis)	4'-((1,7'-dimethyl-2'-propyl-1 H,3'H-[2,5'-bibenzo[d]imidazol]-3'-yl)methyl-[1,1'-biphenyl]-2-carboxylic acid	
 Olmesartan Medoxomil (I)	(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl-1-((2'-(1H-tetrazol-5-yl)-[1,1'-biphenyl-4-yl)methyl)-4-(2-hydroxypropane-2-yl)-2-propyl-4,5-dihydro-1H-imidazole-5-carboxylate	[17]
	2-methoxy-4-(5-nitro-1H-benzo[d]imidazol-2-yl)phenol	[18]
 Clonidine	N-(2,6-dichlorophenyl)-4,5-dihydro-1 H-imidazol-2-amine	[19]
	5-nitro-2-phenyl-[(2'carbonylphenyl-4-yl)methyl]benzimidazole	[20]

Pyridine derivatives

1,4-dihydropyridine is a six membered aromatic ring containing N at 1st position, which is saturated at 1 and 4th position. The most feasible position for substitution is 4th which exhibits various activities i.e., as the calcium channel antagonists and the heterocyclic ring is the common feature for various pharmacological activities such as antihypertensive, antianginal, antitumor, anti-inflammatory activity, antitubercular activity, analgesic activity, antithrombotic. Antihypertensive activity of various 1,4-dihydropyridines derivatives have been published in various papers and their brief review is given in Table 5.

Table 5: Pyridine derivatives for antihypertensive activity

Pyridine derivatives	Name	Reference
 Nifedipine	Dimethyl-2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate	[21]
	Diethyl 2,6-dimethyl-4-(2-(methylthio)-1-(phenylamino)-1 H-imidazol-5-yl)-1,4-dihydropyridine-3,5-dicarboxylate	[22]
	Diphenyl 2,6-dimethyl-4-(2-(methylthio)-1-(phenylamino)-1 H-imidazol-5-yl)-1,4-dihydropyridine-3,5-dicarboxylate	
	3-carbamoyl-1-methylpyridin-1-ium	[23]
	2-(4-oxo-2,8-diphenyl-4,8-dihydroimidazo[1,5-a]pyrimidine-6-carbonyl-N-phenylhydrazine-1-carbothioamide	[24]

Quinazoline derivatives

Quinazoline derivatives have been very well known for antihypertensive activity. Different quinazoline analogous having antihypertensive activity (example: Prazosin, terazosin, doxazosin, bunazosin, tiodazosin, trimazosin and alfuzosin) are available in the market. They have many advantages like dictating both resistance and capacitance of blood vessels, favorable hemodynamic effects and maintenance of renal blood flow and glomerular filtration rate with intact auto regulation of noradrenaline due to non-blockade of presynaptic α2-adrenergic. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anticancer, anti-inflammation, anti-bacterial, analgesia, antivirus, anticytotoxin, antispasm, antituberculosis, antioxidation, antimalarial, antihypertension, antiobesity, antipsychotic, antidiabetes etc. The aim of this review is to provide an overview of antihypertensive activity of Quinazoline moiety as cited in Table 6.

Thiadiazoles derivatives

A number of thiadiazoles have been successfully used as antibacterial, anticancer, antipyretic, schistosomicidal, hypoglycemic, antihypertensive, antitubercular, anti-inflammatory and anti-HIV agents. Literature search reveals that 1,3,4-thiadiazole derivatives possess remarkable diuretic, vasodilators and β-blockers properties and is used as antihypertensive agents. Few of the Thiadiazole derivatives for antihypertensive activity, have been quoted in Table 7.

Azitidinone derivatives

A large number of azetidinones containing β-lactam rings are known to exhibit various biological activities like antibacterial, antifungal cardiovascular activities, antihypertensive activity and antibiotic activities. More particularly and recently these types of compounds have been found in the treatment of TB and other chemotherapeutic diseases. Few of the azitidinone derivatives having potent antihypertensive activity have been listed in Table 8.

Table 6: Quinazoline derivatives for antihypertensive activity

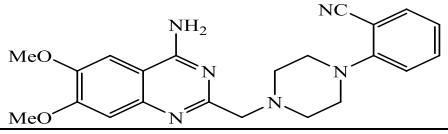
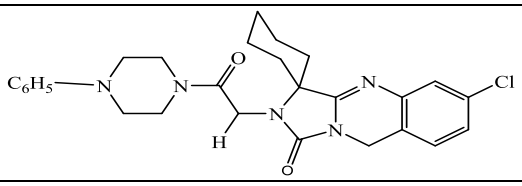
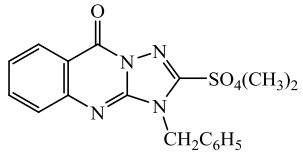
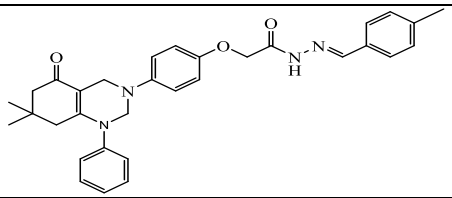
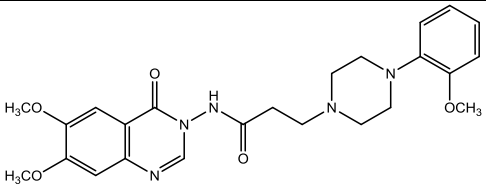
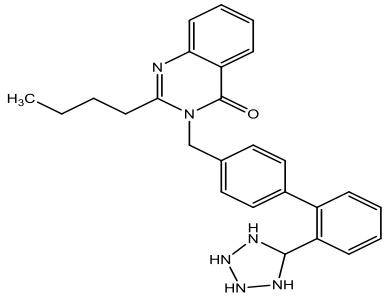
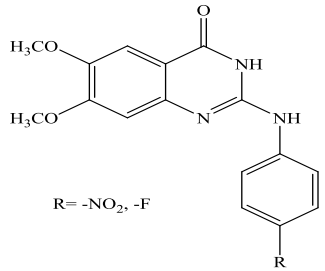
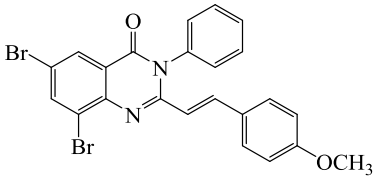
Quinazoline derivatives	Name	Reference
	2-(4-((4-amino-6,7-dimethoxyquinazolin-2-yl)methyl)piperazin-1-yl)benzonitrile	[25]
	6'-chloro-2'-(2-oxo-2-(4-phenylpiperazin-1-yl)ethyl)-9'H-spiro[cyclohexane-1,3'-imidazo[5,1-b]quinazolin]-1'(2'H)-one	[26]
	$1\lambda^5$-ethyl 3-benzyl-9-oxo-3,9-dihydro-[1,2,4]triazolo[5,1-b]quinazoline-2-sulfonoperoxcate	[27]
	(E)-2-(4-(7,7-dimethyl-5-oxo-1-phenyl-1,4,5,6,7,8-hexahydroquinazolin-3(2H)-yl)phenoxy)-N-(4-methylbenzyliden)acetohydrazide	[28]
	N-(6,7-dimethoxy-4-oxoquinazolin-3(4H)-yl)-3-(4-(2-methoxyphenyl)piperazin-1-yl)propanamide	[29]
	2-butyl-3-((2'-(tetrazolidin-5-yl)-[1,1'-biphenyl]-4-yl)quinazolin-4(3H)-one	[30]
	6,7-dimethoxy-2-(4-substitutedphenyl)quinazolin-4(3H)-one	[31]
	(E)-6,8-dibromo-2-(4-methoxystyryl)-3-phenylquinazolin-4(3H)-one	[32]

Table 7: Thiadiazoles derivatives for antihypertensive activity

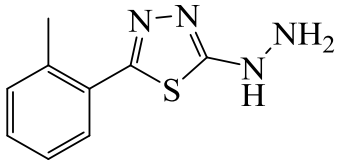
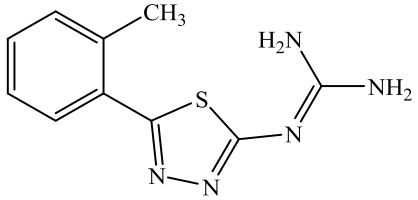
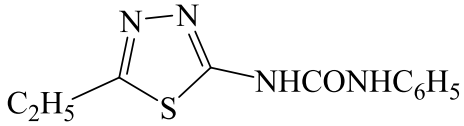
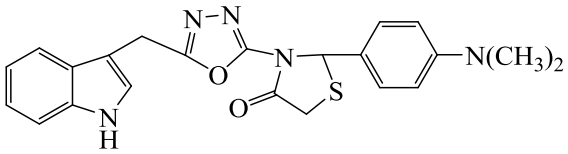
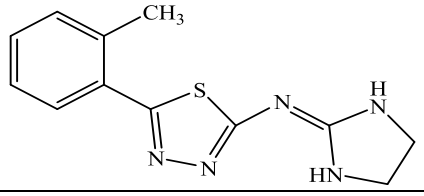
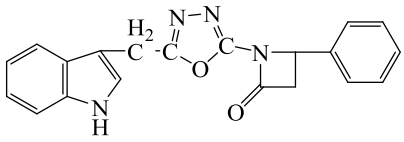
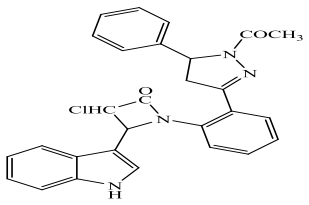
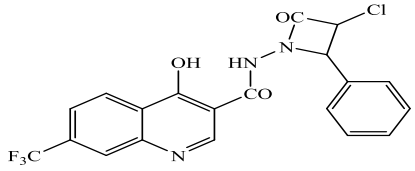
Thiadiazoles derivatives	Name	Reference
	2-hydrazinyl-5-(o-tolyl)-1,3,4-thiadiazole	[33]
	2-(5-(o-tolyl)-1,3,4-thiadiazol-2-yl)guanidine	
	1-(5-ethyl-1,3,4-thiadiazol-2-yl)-3-phenylurea	[34]
	3-[5'-(3"-indolomethylene) -1', 3', 4'– oxadiazol-2'-yl]-2–(p-N, N-dimethylphenyl)- 4–thiazolidinone	[35]
	N-(5-(o-tolyl)-1,3,4-thiadiazol-2-yl)imidazolidin-2-imine	-

Table 8: Azitidinone derivatives for antihypertensive activity

Azitidinone derivatives	Name	Reference
	1-(5-((1H-indol-3-yl)-1,3,4-oxadiazol-2-yl)-4-phenylazetidin-2-one	[36]
	1-(2-(1-acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-3-chloro-4-(1H-indol-3-yl)azetidin-2-one	[37]
	N-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-4-hydroxy-7-(trifluoromethyl)quinoline-3-carboxamide	[38]

CONCLUSION

Hypertension silently causes many problems, including chest pain (angina), heart attack, heart failure, kidney failure, stroke, blocked arteries in legs or arms (peripheral artery disease), eye damage and aneurysms. Few of the popular drugs such as doxazosin (Generic)/Carduran (Brand) for alpha blockers, lofexidine (Generic)/Britlofex (Brand) for alpha-2 agonists, losartan (Generic)/Cozaar (Brand) for angiotensin II receptor blockers, captopril (Generic)/Capoten (Brand) for ACE inhibitors, pindolol (Generic)/Visken (Brand) for beta-blockers, nimodipine (Generic)/Nimotop (Brand) for calcium channel blockers, bumetanide (Generic)/Bumex (Brand) for loop diuretics, diazoxide (Generic)/Proglycem (Brand) for vasodilators etc., are popularly sharing the majority of onus in the present time.

Despite having better understanding of mechanism and management of hypertension, the known derivatives of heterocyclic moieties such as indole, oxadiazole, imidazole, pyridine, quinazoline, thiadiazoles and azitidinone moieties are providing insufficient solution to the global population due to the side effects associated with the medication. The need of hour is to invent few more active heterocyclic moieties and their derivatives which can have better antihypertensive activity and fewer side effects because mortality and morbidity are two factors which on proper address can ensure better life style.

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