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Review Paper

4-Aryl-1,4-dihydropyrimidines as Potential agents against Congestive Heart Failure: A Review

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Abstract

Owing to great possibilities of biological activities exhibited by pyrimidines and dihydropyrimidines, these are subject of great interest which helps in developing new synthetic routes, with innovative methods and using new technology. A series of tetrahydropyrimidines were prepared under microwave irradiations which was an efficient, time saving method also resulting in good yield. Tetrahydropyrimidines were converted to S-alky/benzyl-1,4-dihydropyrimidines. The purpose for synthesizing these dihydroprimidines was to design aza-analog of nifedipine. Pharmacological activities were determined for these synthesized compounds where standard drug taken for comparison purpose was nifedipine. The best part came out after screening these compounds for biological activity as these were smooth muscle relaxant, anti hypertensive and can be used in Congestive Heart Failure. These compounds edge over nifedipine in their biological activity as nifedipine cannot be used and if administered for Congestive Heart Failure, it can worsen the condition.

Keywords: 1,4-dihydropyrimidines, anti-hypertensive, congestive heart failure, smooth muscle relaxant.

Introduction

Pyrimidines derivatives[1-3] show vivid biological activities such as anti-microbial[4], anti-inflamatory[5] and analgesic[6] activities. Due to their biological importance these are subject of considerable synthetic activity. Interestingly, dihydropyrimidines which are aza-analogs of dihydropyridines, nifedipine shows very similar pharmacological activities. Infact these dihydropyrimidines mimc these dihydropyridines and act as calcium channel modulators like nifedipine. With their introduction into clinically proven medicines from way back to 1975, these have become so essential that their pharmacological efficiency have given them an important place.

Biginelli pyrimidine synthesis[7] has attracted the interest of researchers. The procedure for preparing derivatives was first described by Biginelli in 1893. Aromatic aldehydes combine with β-keto ester and urea in alcoholic solution form tetrahydropyrimidines[8,9]. Nifedipine block the movement of Ca^{+2}. These calcium channel blockers[10] are useful as anti-hypertensive agents and helps in relieving heart pain.

These act as coronary vasodilators so are quite useful for cardiovascular medicine. These are available for treatment of various cardiovascular diseases[11-13] and helps in lowering of blood pressure, for relieving heart pain and irregular heartbeats. The main objective was synthesis of dihydropyrimidines which show advanced pharmacological profile than its aza-analog, nifedipine.

Congestive Heart Failure

It is the inability of heat to pump the required amount of blood that is needed for normal functioning of body. There occurs weakness of heart muscle which leads to collection of fluids in body tissues. This results in congession and swelling in body. In Congestive Heart Failure (CHF) heart do not stops working but its ability to pump enough blood to body gets affected. Heart cannot pump all the blood it receives so blood and fluids back up into lungs abdomen, and other parts of body. When body is not able to get the required amount of blood it needed and due to accumulation of fluids in lungs symptoms like that of heart failure[14] occurs. There are many factors leading to CHF. Heart valve disease where blood may leak through defective valves due to which blood and fluids get collected in lungs, high blood pressure, coronary artery disease in which fats get deposited in coronary arteries due to which blood vessels are narrowed and clogged are some of the factors causing CHF. The heart loses its ability and efficiency to pump blood. This results in poor blood supply due to which all organs of body fail working effectively. In Congestive heart failure, blood[15,16] gets collected leading to congession. There is inefficient blood circulation[17] to other organs of body due to which various vital organs of body stop working normally. Kidneys cannot excrete sodium and water which results in kidney failure. It is more common in old age. This can lead to degeneration of health and body condition. Though heart keeps working but its efficiency is reduced. Arterial plaque, stress, smoking, old age, can worsen heart condition leading to CHF.

Diuretic, vasodilators and β-blockers are some of the agents that are used in treatment of CHF. Diuretics help to remove excess fluids that get collected in lungs, stomach and other parts of body. Removal of these excess fluids from body helps in decreasing workload of heart. β-blockers decrease blood pressure, lowers the heart rate and improves functioning and pumping of heart. These decreases hearts oxygen demand which makes them useful for angina pectoris. ACE inhibitors block angiotensin II, a hormone[18] that constricts blood vessels. ACE inhibitors[19] relaxes the blood vessels, thus helps in reducing blood pressure by decreasing arterial pressure in hypertensive individuals. Digoxin helps muscles of heart to pump blood more effectively. The main pharmacological effect of digoxin is on the heart. It also helps in regulating irregular heartbeats. It makes heart beat stronger and improves the pumping action of heart. Adequate supply of blood is necessary for heart to function normally. Due to blocking of arteries normal blood supply is restricted which causes various diseases. Cardiovascular agents act on the heart or some parts of vascular system and helps in distribution of blood. Cardiotonic agents strengthens heart which results in increase in cardiac output. These increases myocardial contraction without any corresponding increase in oxygen consumption due to which heart pumps effectively and is able to meet the demands of the circulatory system.

Antihypertensive agents

Hypertension occurs when blood pressure[20] exceeds the normal limit value as defined[21] when systolic blood pressure is higher than or equal to 140 mm Hg or a diastolic blood pressure is higher than or equal to 90 mm Hg. Hypertension damages blood vessels, increases chances of stroke, heart and kidney failure. Anti-hypertensive agents[22,23] helps in reducing blood pressure and symptoms which accompany increase in blood pressure by increasing urinary volume and excretion of sodium. With increase in blood pressure chances of cardiovascular diseases, stroke and heart failure increases.

Diuretics[24] causes reduction in water and sodium level so preventing blood vessels from holding excessive fluids thus resulting in antihypertensive activity. This reduces the risk of stroke. β-blockers are effective in reducing high blood pressure and force and frequency with which heart beats so blood passes with less force through blood vessels. Calcium channel blockers along with working as anti-hypertensive agents are also helpful in conditions like asthma, diabetes and renal dysfunction[25,26]. Calcium channel blockers are more effective than diuretics and β-blockers to patients with hypertension and diabetes and these slow the progressive loss of renal function. Verapamil is useful in lowering blood pressure, abnormal heart rate and angina. Diltiazem is helpful in decreasing blood pressure and is quite effective in decreasing heart[27] rate. Due to hypertension risk of diabetes increases. Angiotensin converting enzyme inhibitors prevents making of angiotensin II hormone which causes narrowing of blood vessels. Antihypertensive treatment based on dihydropyridine is beneficial for patients with long history of diabetes[28].

Vasodilators or Coronary dilators

These medications work by relaxing the smooth muscles[29]of blood vessels which dilates the blood vessels which results in flow of blood more easily. These are used in hypertension as these relax smooth muscles of arterioles and decreases peripheral vascular resistance, resulting in decrease[30] in blood pressure. These helps in relaxation of blood vessels by which blood vessels get widen thus helps in maintaining proper blood pressure thereby decreasing the chances of heart failure in anti-hypertensive individuals. These work best in combination with other antihypertensive drugs (β-blockers and diuretics). Vasodilators act either directly on the smooth muscle or indirectly through the innervations of blood vessels. The coronary vessels are dilated resulting in increase in the blood supply to the heart muscle. The rapid relaxation and dilation produced by the coronary dilators serves to relieve the pain[31-33] in acute angina pectoris. In the treatment of unstable angina, calcium channel blockers are found to be particularly useful as vasospasm occurs in some patients.

Antiarrhythmic agents

Antiarrhythmic agents are helpful in treating abnormal heart rhythms. Due to excessive heart rate there is inefficient blood supply to all parts of body so chances of atrial fibrillation[34,35] increases. Atrial Fibrillation increases the risk of stroke, chest pain and heart failure. These antiarrhythmic agents are quite useful in preventing atrial fibrillation. In normal heart, an increase in cardiac rate within moderate limits does not affect the cardiac output. When heart rate is slowed or accelerated its efficiency decreases and it is unable to pump an adequate amount of blood. The arrhythmias[36-39] of heart consists of electrocardiographic tracing which shows rapid regular or irregular impulse propogation.

Beta blockers are helpful in controlling abnormal heart rhythms, control high blood pressure and angina. These infact improve the pumping action of heart. Verapamil reduces the heart rate and appears to be effective in treatment of several forms of cardiac arrhythmias including paraoxysmal supraventricular tachycardia and atrial fibrillation. Verapamil is used as an anti-arrhythmic agent due to its ability to prolong atrio-ventricular node[40] refractoriness by direct action on the node. Diltiazem slows the process of arrhythmias.

Calcium Channel Blockers

Calcium channel blockers prevent entry of calcium in conducting cells in heart thereby slowing down the heart rate. Calcium Channel Blockers abrupt the movement of Ca^{+2} ions into heart and blood vessels. These lower blood pressure by relaxing the blood vessels and increasing the supply of blood and oxygen towards heart. Thus making the flow of blood

easier. These helps in vascular and smooth muscles[41] relaxation. Dihydropyridine Calcium Channel Blockers nifedipine blocks L-type Ca^{+2} channels and is quite effective as anti-hypertensive agent and for angina pectoris. Nifendipine, nitrendipine are effective in lowering blood pressure at smaller doses. CCBs are quite effective in treatment of diastolic heart failure. Nimodipine inhibits the entry of Ca^{+2} and prevents contraction of vascular smooth muscle. It increases vasodilation, thus lowers the blood pressure. CCB helps in slowing the heart rate which helps heart to fill with blood more easily which leads to relaxation of heart muscles[42-44] thus lowering of blood pressure. These are thus quite effective in treating diastolic heart failure. Nifendipine, nitrendipine are effective in lowering blood pressure at smaller doses[45].

Verapamil, a non-dihydropyridine Calcium Channel Blockers helps in dilation of coronary arteries and decreases myocardial contractility. Verapamil impairs atrioventricular conduction resulting in slowing of heart rate and decreasing blood pressure which makes it very useful in hypertension and angina pectoris. It dilates coronary arteries and decreases myocardial oxygen demand. Diltiazem is a member of group of drugs benzothiazepines, is a coronary dialator, control high blood pressure and chest pain. Diltiazem interferes in the release of Calcium ions and also prevents their accumulation across myocardial and vascular smooth muscle cell membrane. Mibefradil inhibits and selectively binds T-type calcium channels.

CCBs restrict narrowing of blood vessels by blocking the entry of Ca^{+2} ions into cells. Cardiac muscle is highly dependent upon calcium influx for normal function. CCB were initially used in treatment of patients with angina pectoris[46,47]. CCBs have been found to be effective in stopping contractions and resulting in fewer maternal side effects and lower incidence of neonatal morality. These are avoided in diabetes mellitus as they increase the chances of proteinuria

Structure Activity Relationship

Dihydropyridines (DHP) are most studied class of organic CCBs. They possess high affinity for the receptor bonding site on the calcium channels[48]. When substitution on DHP is carried out appropriately, it can alter the biological activity to great extent. The structure activity relationship[49] study has shown that at position 3 and 5, ester group is most effective and these are non-identical, the C_4 carbon is chiral and for optimal activity aryl group should be at position 4 of 1,4-DHP ring, the position and type of electron withdrawing group on phenyl group at position 4 affects receptor binding activity, for optimal activity there should be no substitution at DHP nitrogen. In DHP with phenyl ring at position 4 having substitution[50] with hydrophobic groups increases potency. The substituted aryl ring is placed axially and is perpendicular and bisects the boat like DHP ring which has 4-aryl substituent in synperiplanar arrangement[51] (relative to C_4-H) orientation. It was presented that changes on right hand side donot affect the activity[52] so substitution on right side was labeled as non-essential but the results of PKI to PKV shows that right side is equally essential. Individual isomers of dihydropyridines show blocking activity or stimulant activity on the calcium channels. Bay K8644 and CGP 28392, which increase cardiac contractibity[53] and divalent cation influx despite being DHPs. Tissue selectivity and duration of action of DHPs can be varied by modification of both the esters and alkyl constituents. Nifedipine is a dihydropyridine Calcium Channel Blocker that lowers blood pressure rapidly. Nifedipine inhibits the influx[54] of Ca^{+2} ions and binds to sites near calcium channels. Nimodipine is effective in preventing cerebral hemorrhage termed vasospasm. Dihydropyrimidines behave like dihydropyridine calcium channel blockers as these are potent mimics of them. Their conformation is similar to dihydropyridine Calcium Channel Blockers The modification in structure may produce compounds that are more potent and longer acting than nifedipine[55]. Nifedipine causes concentration dependent depression of maximum response[56]. It is also noted that Ca^{+2} sensitizer's favours myocardial energy consumption[57] but these impair cardiac relaxation.

Material and Methods

Tetrahydropyrimidines (1, 3) were prepared under acidic conditions using benzoyl acetone/ethyl benzoyl acetate, differently substituted aromatic aldehydes and thiourea. A mixture of benzoyl acetone (scheme-1) /ethyl benzoyl acetate (Scheme-2) (0.015 mole), thiourea (0.01 mole), substituted aromatic aldehyde (0.01 mole), ethanol (5 ml) and HCl as a catalyst were subjected to microwave irradiations for the time duration of 4 to 5 minutes. This reaction mixture was kept for 25-36 hours after which the solid separated was filtered under reduced pressure followed by recrystallisation with methanol. These tetrahydropyrimidines were converted into S-alkyl/benzyl derivatives (2, 4). so as to make aza-analogs of nifedipine.

Results and Discussion

For determining biological activities of synthesized compounds, rats and rabbit were medium of study. The drug taken as standard for comparison was nifedipine. IC_{50} values of these compounds on rat uterus were measured to report activity. This IC_{50} (inhibitory concentration) is the molar dose which produced 50% relaxation. To study K^+ induced contractions experiments were carried on rat uterus and female albino rats were used for the purpose. Priming was carried out 24 hours prior every experiment. Diethylstibestrol was administered 0.1 mg/kg body weight which was done subcutaneously. Dissection was done and preparation was mounted in De Jalon solution as per the method described by Ghosh[58]. This suspension was added to bath in geometric doses (0.1, 0.2, 0.4, 0.8, 1.6). The active compounds produced a dose dependent relaxant effect. Mean relaxing effect of increasing doses of compounds PKI to PKV were observed on rat uterus (table-1).

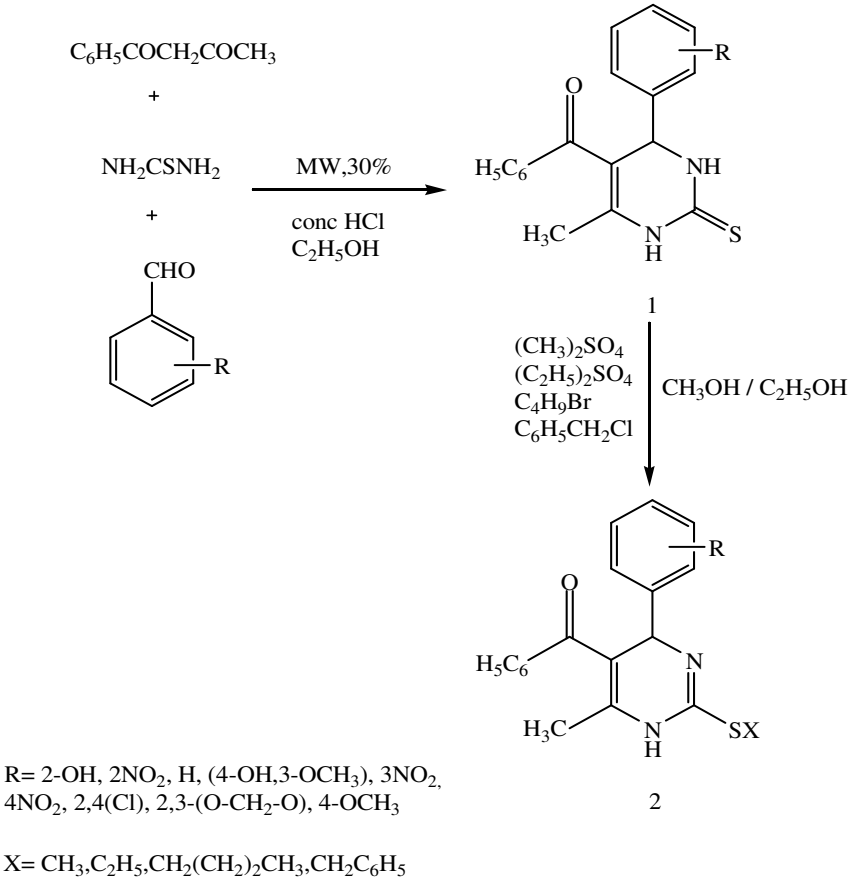
At bath conc of 128 µg/ml PKI, PKII and PKIII showed mean percentage inhibition 100%, PKIV showed mean percentage inhibition at 256 µg/ml and PKV showed mean percentage inhibition at 64 µg/ml, other dose was not required for PKV. IC_{50} for PKI was 0.74 x 10^{-5} M , PKII was 0.52 x10^{-4} M, PKIII was 1.38 x 0^{-4} M, PKIV was 1.17 x10^{-4} M and PKV was 0.53 x 10^{-4} M. It was found that all these compounds have dose dependent relaxant effect on K+ induced contractions on rat uterus.

Table-1
Mean Relaxing Effect of Increasing Doses of Compound PK I to PKV on K^+ Induced contraction of isolated rat Uterus

S.No	Bath Conc (µg/ml)	Mean percentage inhibition				
		PKI	PKII	PKIII	PKIV	PKV
1	16	7.69%	23.9%	3.52%	2.04%	44.3%
2	32	60.84%	82.6%	21.1%	18.36%	93.9%
3	64	92.30%	94.6%	71.83%	59.18%	100%
4	128	100%	100%	100%	91.84%	--

Table-2
Mean Percentage Change in Amplitude and Coronary Flow (ml/min) of Isolated Perfused Rabbit Heart for PKI to PKV

S.No	Effect on Amplitude					Effect on Coronary Flow				
Dose (µg/ml)	PKI	PKII	PKIII	PKIV	PKV	PKI	PKII	PKIII	PKIV	PKV
10	↑7.5%	↑15.69%	↑23.53%	↑55.17%	↑32.6%	↑13.33%	↑21.05%	↑13.51%	↑8.57%	↑5.26%
20	↑19.3%	↑22.64%	↑82.35%	↑48.57%	↑37.04%	↑10.64%	↑11.90	↑16.22%	↑5.56%	↑10.53%
40	↑22.1%	↑21.11%	↑42.31%	↑47.73%	↑26.67%	↑8.69%	↑11.90	↑20.59%	↑15.0%	↑11.11%
80	↑77.34%	↑50.0%	↑18.75%	↓20.0%	↑80.0%	↑18.60%	↑17.95%	↑12.5%	↑11.11%	↑11.11%

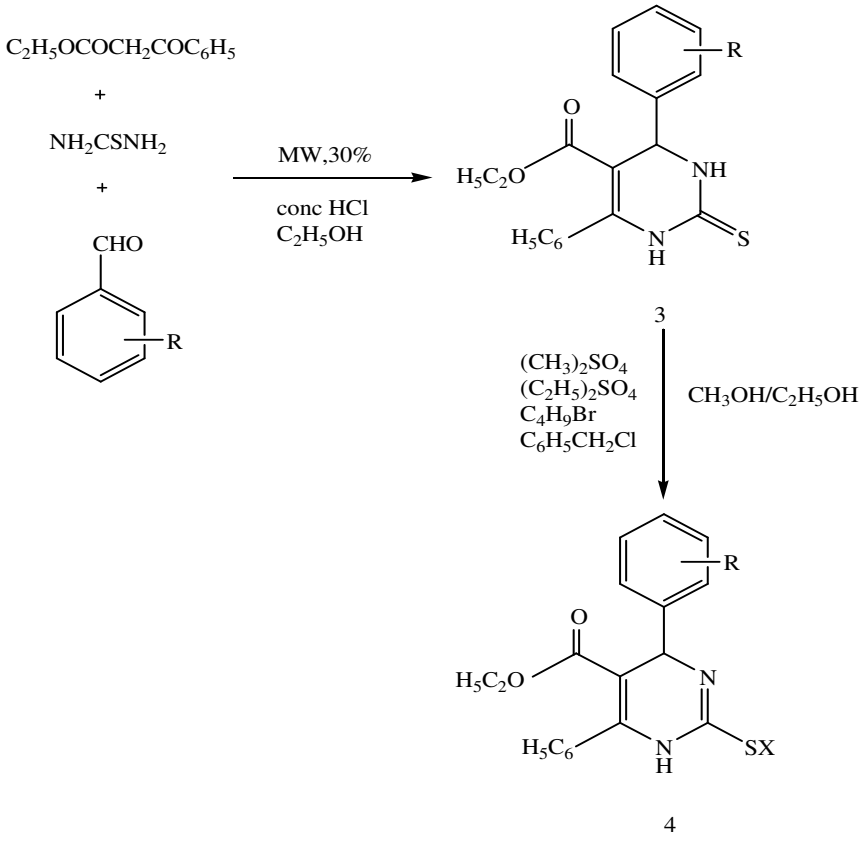


R= 2-OH, $2NO_2$, H, (4-OH,3-OCH_3), $3NO_2$, $4NO_2$, 2,4(Cl), 2,3-(O-CH_2-O), 4-OCH_3

X= CH_3,C_2H_5,$CH_2(CH_2)_2CH_3$,$CH_2C_6H_5$

2

Scheme-1
Synthesis of 5-benzoyl-6-methyl-4-substituted phenyl-2-S-alkyl/benzyl-1,4-dihydropyrimidine



Scheme-2

Synthesis of 6-phenyl-4-substituted phenyl-2S-alkyl/benzyl-1, 4-dihydropyrimidin-5-carboxylic acid ethyl ester

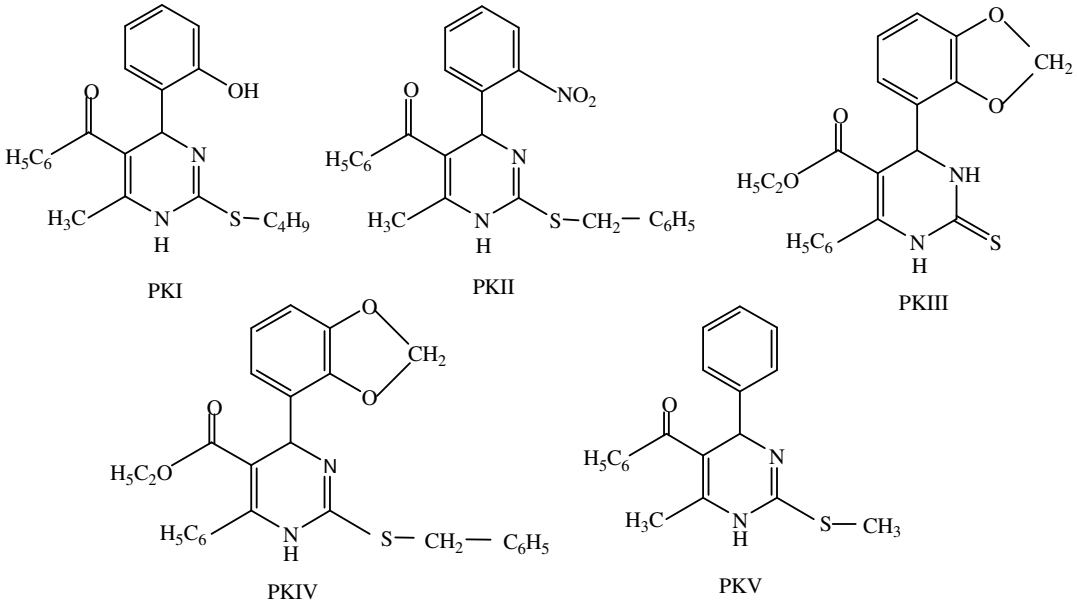


Figure-1

Compound PKI, PKII, PKIII, PKIV, PKV

For studying the effect of amplitude and coronary flow rabbit heart was mounted as per methods by Burn[59] and Perry[60] in the Langedorff's assembly and perfused with oxygenated Ringer Locke solution at 37ºC. There was significant increase in amplitude and coronary flow of compound PKI, PKII,PKIII,PKIV,PKV (Table-2) at all doses (except for small decrease at 80 µg/ml in PKIV). Amplitude and Coronary flow increases in these compounds which make them quite suitable for use in Congestive Heart Failure. The research carried out on PKI, PKII, PKIII, PKIV and PKV shows that right side is equally essential as variation on this side changes the anti-hypertensive activity to considerable extent. On comparison of these compounds with nifedipine these were found more potent, particularly PKV shows that it is most potent as S-methyl moiety in it is on right side of boat shaped conformation. The substitution of aryl ring at position 4 with substitutents like 2-NO_2, 2-OH changes biological activity. It was also noted that when benzoyl group was substituted at position 5, it increased the force of contraction of heart resulting in making these compounds more potent and useful in Congestive Heart Failure. Some agents described above are either used alone or in combination for CHF with few worsening the condition where CCB are avoided in it so these 4-aryl-1,4-dihydropyrimidines reported makes a valuable contribution for it.

Conclusion

These compounds are smooth muscle relaxant like Calcium Channel Blockers as they show relaxing effect on rat uterus. Increase in amplitude and coronary flow in rabbit heart makes them useful to the patients of Congestive Heart Failure. These compounds PKI, PKII, PKIII, PKIV, PKV show similarity in pharmacological activity like well known medicine digoxin which is mostly prescribed for Congestive Heart Failure whereas nifedipine cannot be used for CHF as it decrease force of contraction of heart so these compounds are pharmacologically more active than nifedipine.

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