

**CARDIOPROTECTIVE ACTIVITY OF 2-SUBSTITUTED -1, 3-OXAZOLIDINES
ON CaCl₂-INDUCED ARRHYTHMIAS IN ISOLATED FROG HEART**

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Summary

Sudden cardiac death is a primary cause of mortality in patients with cardiovascular diseases, is caused by the loss of regular cardiac rhythm. In the present study 1, 3-oxazolidines were synthesized and their physiochemical parameters like melting point, retardation factor were analyzed. All the compounds were screened for their antiarrhythmic activity by calcium chloride- induced arrhythmias in isolated frog heart at graded dose level. Compounds 4-[3-(2-furylmethyl)-4-phenyl-1,3-oxazolidin-2-yl]-2-methoxy phenol (8), 4-[3-(2-furylmethyl)-4-phenyl-1,3-oxazolidin-2-yl]phenol (9) and 2-(4-chlorophenyl)-3-(2-furylmethyl)-4-phenyl-1, 3-oxazolidine (10) showed very good negative chronotropic and inotropic effect by blocking the calcium entry. All other compounds showed moderate activity. Compounds containing 4-hydroxy and 3-methoxy, 4-hydroxy and 4-chloro substitutions were found to increase the antiarrhythmic activity.

Key words: 1, 3-oxazolidine, antiarrhythmic activity, calcium chloride, chronotropic and inotropic effect.

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Introduction

Since the 1st observation of arrhythmic activity of cinchona alkaloid preparation in a malaria patient in 1914, they are identified as an important antiarrhythmic agent. But are ineffective for the prevention of sudden cardiac death by ventricular fibrillation (1). Alteration in cellular Ca⁺⁺ or addition of myocardial ischemia produces abnormalities in these cardiac electrical properties and there by trigger malignant arrhythmias. This ischemically induced ectopic and rhythm is critically dependant on Ca⁺⁺ or addition of Ca⁺⁺ channel antagonist can abolish this spontaneous rhythm. Therefore, the initiation of ventricular fibrillation dependant upon a slow Ca⁺⁺ inward current (2). This made us to work on new agents which have negative inotropic and chronotropic effect. The derivation of 1, 3-oxazolidines have gained importance in recent years, because of their various biological activities like anti-arrhythmic (3), antimicrobial (4), antidiabetic (5) and antidepressant (6) activity. The literatures revealed that 1, 3-oxazolidines have potent arrhythmic activity and also they are having calcium channel blocking property (7, 8). 2-amino alcohols were reported for their antiarrhythmic activity (7). The titled compounds were synthesized from phenylglycinol which is a 2-amino alcohol; hence they were expected to give the similar activity. More over propranolol, which is used to treat arrhythmias, is metabolized to 1, 3-oxazolidines (9). So based on all these observations, it was thought worthwhile to synthesize 1, 3-oxazolidines and screen for their arrhythmic activity.

Materials and methods

Synthesis of the 2-substituted-1, 3-oxazolidines

The Schiff base was prepared by refluxing R(+) Phenylglycinol (0.0729 mol) and furfuraldehyde (0.087 mol) in toluene (25 ml) at 110-120^o using Dean stark condenser for 2 h. After completion of the reaction toluene was distilled off under reduced pressure (10). The equimolar quantities (0.01 mol) of Schiff base and sodiumborohydride was added in tetrahydrofuran and refluxed at 45-50^o for 2 h. The reaction mixture was monitored by TLC. Then pH of the solution was adjusted to 6.8-7.2 by the addition of conc.HCl with stirring. The reaction mixture was filtered and the excess of solvent was removed under reduced pressure to get reduced Schiff base (11). It was dissolved in toluene with various aromatic or hetero aromatic aldehyde (0.018 mol) and refluxed for about 17 h at 110^o C using Dean Stark apparatus. The excess solvent was removed under reduced pressure. The solid obtained was vacuum dried and recrystallized from toluene.

Antiarrhythmic activity

Frog was pithed to expose the heart. The inferior vena cava was cannulated for perfusing the heart with the frogs Ringer solution (12). The basal cardiac contraction was recorded on a smoked kymographic drum after the administration of frog Ringer solution and gum

acacia (5%). The administration of gum acacia was done to see that it did not contribute to the effect of 1, 3-oxazolidines. The synthesized compounds were administered through the cannula. The heart rate was noticed. Graded dose response of the drug at 100, 200 and 300 μ g (13) and the effect of drug followed by different dose of CaCl₂ were recorded. The frog heart was washed with the ringer solution after every administration of compound, till it was brought back to the normal state.

Results

The compounds were synthesized and their yield and physicochemical parameters were given in Table-1.

General structure of the synthesized compounds

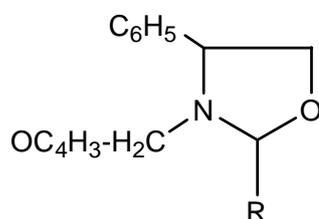
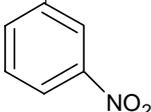
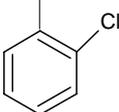
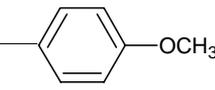
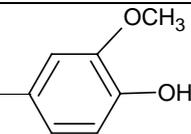
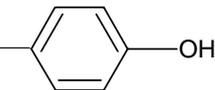


Table-1: Physicochemical parameters of the synthesized compounds.

Cpd	R	Yield (%)	Melting point (^o C)	Retardation factor
1		70	190-192	0.11
2		63	158-159	0.86
3		70	157-156	0.28
4		73	112-110	0.34

5		61	126-125	0.16
6		83	149-151	0.42
7		76	134-137	0.11
8		86	150-152	0.64
9		94	108-107	0.42
10		86	141-142	0.56

Calcium chloride showed a dose dependant increase in the rate and force of contraction in the frog heart (Fig.1).

Fig.1- Dose dependant effect of CaCl₂ on normal frog heart.



The effect of compounds on the normal and arrhythmia induced heart were recorded and shown (Fig.2-11).

Fig.2 - Effects of the compound 1 and compound 1 with CaCl₂ in the isolated frog heart.

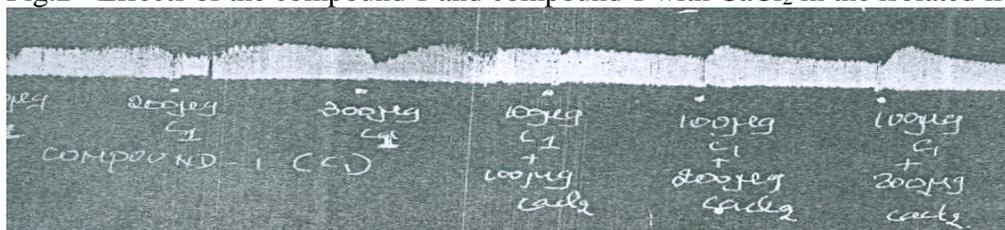


Fig.3 - Effects of the compound 2 and compound 2 with CaCl₂ in the isolated frog heart.

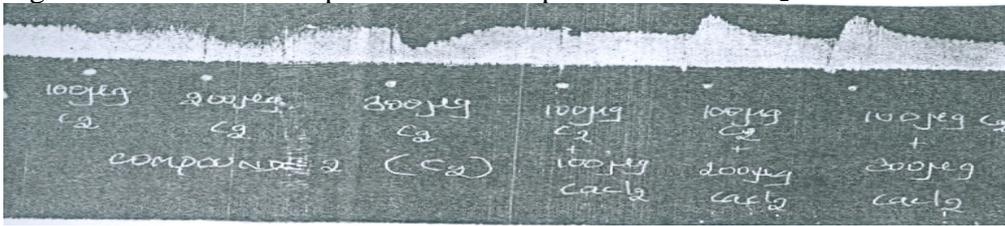


Fig.4 - Effects of the compound 3 and compound 3 with CaCl₂ in the isolated frog heart.

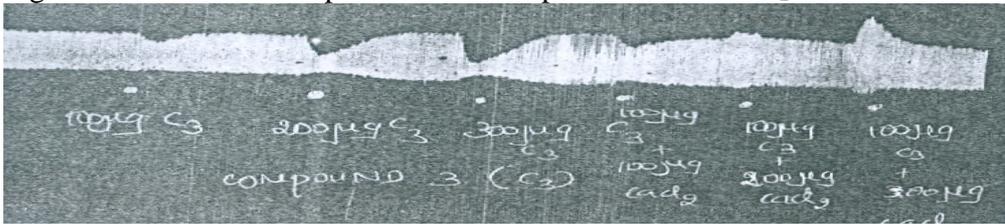


Fig.5 - Effects of the compound 4 and compound 4 with CaCl₂ in the isolated frog heart.

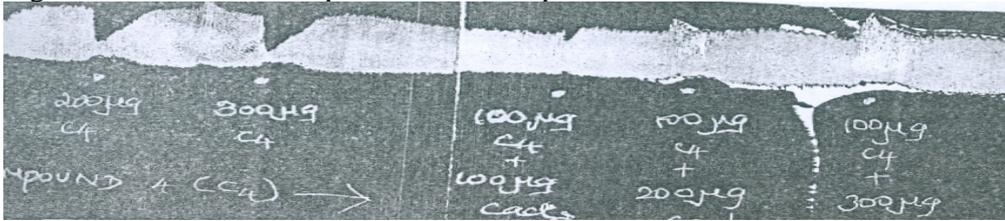


Fig.6 - Effects of the compound 5 and compound 5 with CaCl₂ in the isolated frog heart.

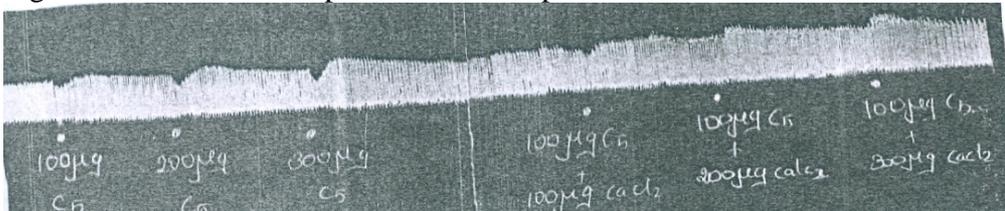


Fig.7 - Effects of the compound 6 and compound 6 with CaCl₂ in the isolated frog heart.

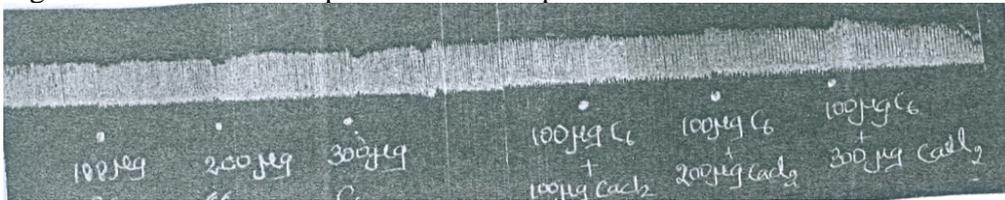


Fig.8 - Effects of the compound 7 and compound 7 with CaCl₂ in the isolated frog heart.

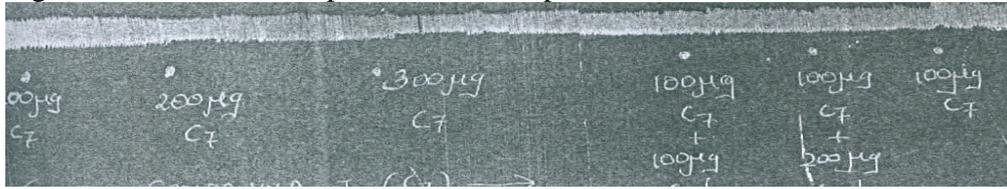


Fig.9 - Effects of the compound 8 and compound 8 with CaCl₂ in the isolated frog heart.

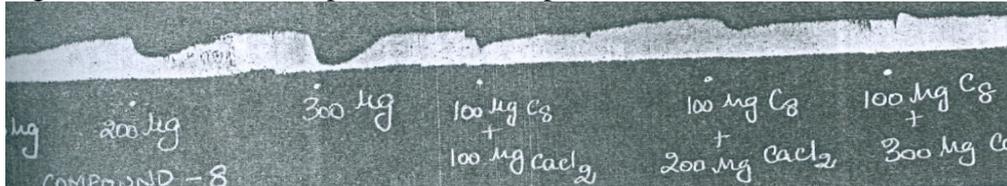
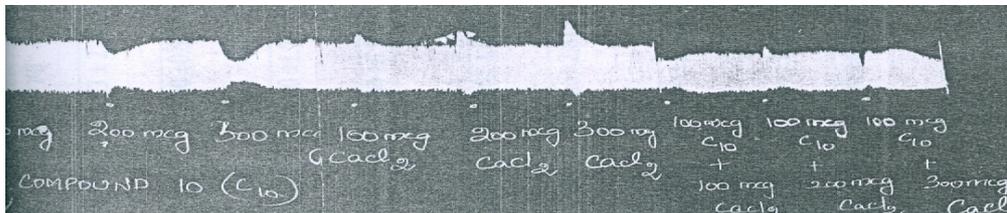


Fig.10 - Effects of the compound 9 and compound 9 with CaCl₂ in the isolated frog heart.



Fig.11 - Effects of the compound 10 and compound 10 with CaCl₂ in the isolated frog heart.



The synthesized compounds showed a decrease in the force of contraction as reflected by decrease in the amplitude and heart rate (Fig.12 & 13).

Fig.12 – Effect of synthesized compounds (cpd1-10) in the isolated normal heart.

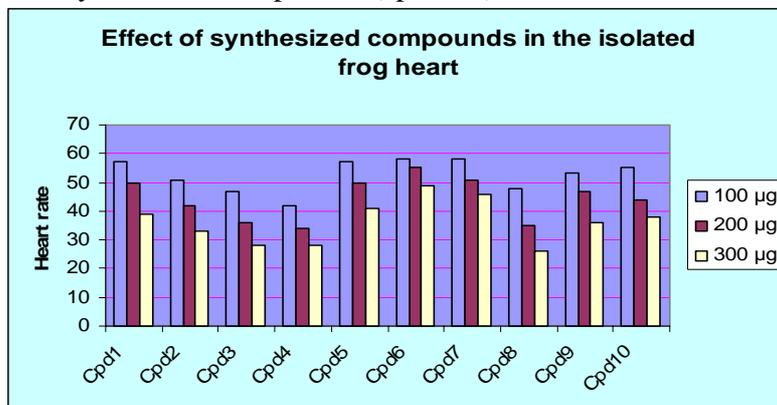
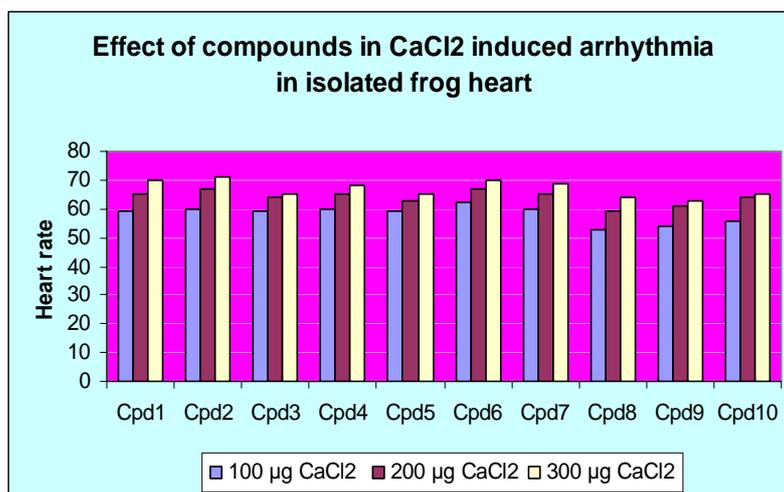


Fig.13 – Effect of compounds in CaCl₂ – induced arrhythmia in isolated frog heart.

Discussion

Alteration in cellular Ca⁺⁺ induced by myocardial ischemia produces abnormalities in these cardiac electrical properties and there by trigger malignant arrhythmias. This ischemically induced ectopic and rhythm is critically dependant on Ca⁺⁺ entry, as lowering extra cellular Ca⁺⁺ or addition of Ca⁺⁺ channel antagonist can abolish this spontaneous rhythm. Therefore, the initiation of ventricular fibrillation depends upon a slow Ca⁺⁺ inward current (2). In present study the 1, 3-oxazolidines showed dose dependant decrease in the rate of contraction and force of contraction of heart (Fig.2-11). When myocardium is excited, action potential is generated followed by contraction of myocardium. In this process one electrical and other mechanical event are coupled together and the coupling agent is calcium (14). The dose dependant effect of CaCl₂ on the isolated frog heart was given in Fig-1. The movement of Ca⁺⁺ into the blood vessels causes them to narrow or contract. Calcium channel blockers (CCBs) block some of this Ca⁺⁺ so that the blood vessels relax and open wider. This action lowers the blood pressure also when the blood vessels in body become more relaxed blood flow will be easy. This lessens the workload of heart. So this indicates that 1, 3-oxazolidines also may reduce the heart rate by blocking Ca⁺⁺ entry when they were introduced along with CaCl₂ (Fig.2-11). 3-(2-furylmethyl)-2-(3,4,5-trimethoxyphenyl)-4-phenyl-1,3-oxazolidine (cpd3), 2-[3-(2-furylmethyl)-4-phenyl-1,3-oxazolidin-2-yl]phenol (cpd4) and Compound 4-[3-(2-furylmethyl)-4-phenyl-1,3-oxazolidin-2-yl]-2-methoxyphenol (Cpd8) showed significant reduction in the normal heart rate. They showed significant improvement in cardiac symptom by reducing the heart rate from 63 to 26, 36 and 38 respectively at 300µg level. Compound 4-[3-(2-furylmethyl)-4-phenyl-1,3-oxazolidin-2-yl]-2-methoxyphenol (Cpd8), 4-[3-(2-furylmethyl)-4-phenyl-1,3-oxazolidin-2-yl]phenol (Cpd9) and 2-(4-chlorophenyl)-3-(2-furylmethyl)-4-phenyl-1,3-oxazolidine (Cpd10) showed very good antiarrhythmic activity in CaCl₂ induced model.

All other compounds showed moderate activity. These results revealed that the substitutions at C-2 position may be responsible for the antiarrhythmic activity, which also showed that compounds containing 4-hydroxy and 3-methoxy, 4-hydroxy and 4-chloro substitutions were found to increase the antiarrhythmic activity. Therefore this study is worthwhile to make further studies of these molecules on antiarrhythmic activity.

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