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CARDIOPROTECTIVE EFFECT OF 3-(BENZOXAZOL-2-YLIMINO)-5-FLUOROINDOLIN-2-ONE IN RATS

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ABSTRACT

The present study was aimed to evaluate the cardio protective activity of 3-(benzoxazol-2-ylimino)-5-fluoroindolin-2-one against the Doxorubicin (15mg/kg, i.p, single dose) induced cardiotoxicity in rats. Four groups of female wistar albino rats were used. Group 1 was used as control (0.5% CMC, oral); the other groups were treated with Doxorubicin (single i.p. dosage of 15mg/kg) or Doxorubicin plus test compound (50mg/kg/day & 100mg/kg/day, p.o) respectively. Animals were treated with test Compound or CMC for 7 days. On 6th day, a single dose of DOX was administered to rats. Blood was collected on 7th day. Evaluation of cardioprotective activity was done by estimating biochemical parameters like plasma Aspartate aminotransferase (AST), Creatinine kinase (CK-MB), Lactic acid dehydrogenase (LDH) and Triglyceride (TG) levels. Pre-treatment with test compound significantly reduced the elevated levels of cardiotoxic biomarkers in plasma.

Keywords: Cardiotoxicity; Cardioprotective; 3-(Benzoxazol-2-ylimino)-5-fluoroindolin-2-one; Doxorubicin; LDH; CK-MB; AST; TG.

INTRODUCTION

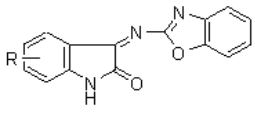
Myocardial Infarction accounts for majority of deaths and disabilities [1]. Myocardial infarction is defined as cardiac myocyte death due to prolonged ischemia to heart tissue [2-5]. This is most commonly due to occlusion of a coronary artery. Then it is followed by the rupture of a vulnerable atherosclerotic plaque which is an unstable collection of lipids (fatty acids) and white blood cells (especially macrophages) in the wall of an artery. So ischemia, if left untreated for a sufficient period of time, can cause damage or death (infarction) of heart muscle tissue. Currently numbers of drugs are available to limit the extent of myocardial damage or to prevent myocardium from necrosis.

But still there is need of synthetic compounds for management of Myocardial infarction. So the present is aimed to establish cardio protective activity of a newly synthesized isatin derivative i.e 3-(benzoxazol-2-ylimino)-5-fluoroindolin-2-one in rats.

MATERIALS & METHODS

Drug and chemicals: Doxorubicin (Cadila pharamceuticals, Hyd, India), Creatine kinase kit, Lactate dehydrogenase kit, Triglyceride kit (Erba Mannheim, Daman, India), Glutamic Oxaloacetic Transaminase Kit (Coral clinical systems, Verna, Goa, India),.

Test compound: We have selected the following newly synthesized Isatin derivative, which was previously synthesized and reported by us[3] to evaluate cardio protective activity. The anticancer, antioxidant and antimicrobial activities of the selected compound was reported[3]. The structure of the compound is as follows.



Structure of test compound [3-(benzoxazol-2-ylimino)-5-fluoroindolin-2-one

S. No	Compound Code	Mol. Formula	R_1	R_2	Mol. wt	% yield	m. p (^{o}C)
1	Test compound	$C_{15}H_8O_2N_3F$	F	H	281	35	134

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Experimental animals

24 female Wistar Albino rats (180-200g) were obtained from Mahaveera Enterprises (Hyderabad, India). The animals were housed in cages under hygienic conditions and placed in a controlled environment (12 h light–dark cycle, 25±2 °C and 45±10% humidity) with free access to water and fed with standard diet *ad libitum*. Care was taken to avoid stressful conditions.

Study design: Rats were randomly divided into 4 groups ($n = 6$).

Group 1: received 0.5%CMC (orally) daily for 7days and served as control.

Group 2: received 0.5% CMC (orally) daily for 7 days and on 6th day single dose of doxorubicin (15mg/kg., i.p) [4] and served as cardiotoxic control.

Group 3: received test compound (50mg/kg/day, orally) daily for 7 days and on 6th day single dose of doxorubicin (15mg/kg., i.p).

Group 4: received test compound (100mg/kg/day, orally) daily for 7 days and on 6th day single dose of doxorubicin (15mg/kg., i.p).

On the 7th day of the study, blood samples were collected through retro orbital puncture method. After centrifugation, plasma was separated and stored at -20°C for biochemical analysis.

Analysis of blood samples

Plasma samples were analyzed for cardiotoxic biomarkers like Aspartate amino transferase (AST), lactic acid dehydrogenase (LDH) and Creatine kinase (CK-MB) and also for plasma Triglyceride levels using commercially available diagnostic kits.

Statistical analysis

All the values were expressed as Mean ±Standard deviation (S.D) (n=6). Statistical comparisons between different groups were done by using one way analysis of variance followed by Tuckey post test. $P < 0.05$ was considered as statistically significant.

Table 1. Effect of test compound on AST, CK-MB, and LDH and TG levels in rats treated with doxorubicin

Parameter/ Group	Normal control	Test compound (10mg/kg)	DOX	Test 5mg/kg+ DOX	Test 10mg/kg+ DOX
AST(IU/L)	58.71±6.45	56.28±4.91	88.52±10.5$^{\#}$	65.15±6.07*	50.63±7.17**
CK-MB (IU/L)	48.62±6.18	56.66±7.54	150.35±25.6$^{\#}$	84.24±9.68**	64.36±7.85**
LDH (IU/L)	77.28±6.98	90.61±8.40	159.5±19.4$^{\#}$	114.4±8.86*	94.6±8.25**
TG (mg/dL)	87.68±5.74	83.14±6.58	178.49±12.2$^{\#}$	124.56±11.9**	96.84±8.55**

Data values are expressed as Mean ±S.D, (n=6); $^{\#}$ $P < 0.001$ vs. Normal control, * $P < 0.01$, ** $P < 0.001$ vs DOX.

RESULTS & DISCUSSION

In the present study, we have evaluated the cardio protective activity of indoline derivative i.e.3-(benzoxazol-2-ylimino)-5-fluoroindolin-2-one against doxorubicin induced cardio toxicity in rats. In the present study, Doxorubicin (15mg/kg., i.p) successfully induced the cardiotoxicity in rats by elevating the plasma AST, LDH, and CK enzyme activities, which are important measures of both early and late phases of cardiac injury[5]. No mortality was observed in all groups. Rats in the DOX alone treated group showed scruffy fur and developed a light yellow tinge. These animals appeared to sicker, weaker and lethargic as compared to test compound +DOX treated group.

The Cardio protective effects of test compound in rats was evaluated by measuring plasma Aspartate aminotransferase (AST), Lactate dehydrogenase (LDH), Creatine kinase (CK-MB), Triglyceride (TG), Glutathione (GSH) levels in citrated blood. The results were shown in table 1.In this study, plasma markers indicating myocardial injury like plasma AST, LDH, CK-MB and TG were significant elevated (P<0.001) in Doxorubicin treatment group when compared with normal control group (Table 1). Pre-treatment with test compound in test compound +DOX groups at different doses (50mg/kg/day and 10mg/kg/day, respectively) almost restored the raised AST, CK-MB,LDH and TG levels when compared with DOX only treated group (P<0.001). This concludes that test compound treatment significantly inhibited the DOX elevated plasma AST, LDH, TG and CK enzyme levels (Table 1). So the maintenance of the cardiomyocyte integrity in test compound treated groups would lead to decreased leakage of cardiac markers.

CONCLUSION

Based on our experimentation, it may be worthy to suggest that the test compound have the cardio protective effect as evidenced by decreased cardiac injury markers.

REFERENCES

1. Aronow WS. Epidemiology, pathophysiology, prognosis, and treatment of systolic and diastolic heart failure. *Cardiol Rev*, 14, 2006, 108–124.

2. Roger VL, Killian JM, Weston SA, Jaffe AS, Kors J, Santrach PJ, Pedoe HT and Jacobsen SJ. Redefinition of Myocardial Infarction, Prospective Evaluation in the Community. *Circulation*, 114, 2006, 790-797.
3. Rajyalakshmi G, Rama NRA, Kiran G, Reddy YN and Sarangapani M. Synthesis, antimicrobial, antioxidant and anticancer activities of some novel 3-(benzoxazol-2-ylimino) indolin-2-one derivatives. *Journal of Chilean Chemical Society*, 57, Nº 4, 2012, 1199-1202.
4. Nagi MN, Mansour MA. Protective effect of thymoquinone against Doxorubicin–induced cardiotoxicity in rats, a possible Mechanism of protection. *Pharmacological Research*, 41, 2000, 3.
5. Saad SY, Najjar TA, Al-Rikabi AC. The preventive role of deferoxamine against acute doxorubicin-induced cardiac. *Pharmacol Res*, 43, 2001, 211–8.