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BIO-ASSAY OF CARDIOVASCULAR [CVS] ACTIVITY OF SOME HETEROCYCALLY SUBSTITUTED CHROMONES

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Cardiovascular drugs have major action on heart or blood vessels. They are used in CVS-disorders like output of heart as well as distribution of blood, hence, blood pressure as well. In this paper bio-assay of some heterocycally substituted chromones synthesized earlier by author as cardiovascular agents is being reported. Though compounds showed no significant activity but few tested compounds showed a decrease in blood pressure [B.P.] which was transient. For instance, a transient decrease of 40 mm Hg was shown by 3-[2-(4-morpholinyl) thiazol-4-yl]-6-chloro-2-methylchromone. Almost all tested 3-heterocycally substituted chromones showed decrease in B.P. except imidazo [2,1-b] thiazol-3-yl system at C3-position of chromones which exhibited increase in B.P. for around 4 minutes at dose level of 1mg/kg. Compound 3-(7-methyl-5H-thiazolo [3, 2-a] pyrimidin-5-one-3-yl)-2-methylchromone is important to mention which caused 16mm Hg decrease in B.P. for 20 minutes at dose level of 5.0 mg/kg. Further research is needed on heterocycally substituted chromones as CVS-agents.

KEYWORDS : Chromones, heterocyclic, cardiovascular activity, blood pressure, ALD_{50}.

INTRODUCTION

Hypertension is a common cardiovascular disease. Increased arterial pressure brings about pathological changes in vasculature and hypertrophy of left ventricle, hence, is a major cause of stroke leading to sudden death. It is a contributor to cardiac failure. Hypertension is defined as a blood pressure ≥ 140/90 systolic and/or diastolic B.P.; such persons have risk of hypertension related CVS diseases. Adults with systolic B.P. lesser than 120 mm Hg and diastolic B.P. less than 80 mm Hg have lowest risk of CVS diseases. Risks are higher with higher B.P. [1].

Severe level of hypertension [systolic ≥ 210 and / or diastolic ≥ 120] is cause of endothelial injury and proliferation of cells in intima resulting in intimal thickening and ultimately to arteriolar occlusion which is cause of syndrome of malignant hypertension that may lead to renal problems like kidney failure and disease of other organs such as retina, brain etc. Reduction of diastolic B.P. to 85 mm Hg is therapeutic benefit than reduction to 90 mm Hg particularly in diabetic patients [2].

As arterial pressure is product of total cardiac output and peripheral vascular resistance, it can be lowered by the action of drugs on cardiac output or peripheral resistance or both. Diuretics control Na^+ balance [3], hence, they may be useful as anti- hypertensive agents [4]. As a number of substituted chromones have been found to be diuretic [5], therefore, they may be effective as antihypertensive agents. With this concept in mind a number of chromones synthesized by author [5-9] were screened for CVS activity results of which are being discussed in this publication.

Table-1. Effect of different chromones on cardiovascular system at 1 mg/Kg

Entry	Name of compound	B.P. mm Hg (min)	Anti-acetylcholine B.P.	Anti-adrenaline B.P.	Anti-histamine B.P.	Anti-isoprenaline B.P.	ALD50
1.	3-[2-(4-morpholinyl) thiazol-4-yl]-6-chloro-2-methyl chromone	↓40 (Tr)	23[a]	20[c]	16[a]	nil	825
2.	3-[2-(4-morpholinyl) thiazol-4-yl]-6-chloro-2,7-dimethyl chromone	↓20 (Tr)	14	12 pt [a]	20 [a]	20 [a]	>1000
3.	6-(2-aminothiazol-4-yl)-2,3- dimethyl chromone	↓28 (4)	30	33 pt[a]	30	50	>1000
4.	6-(2-methylamino thiazol-4-yl)-2,3-dimethyl chromone	↓32 (3)	20pt[a]	20 pt[c]	25 pt	20 pt	>1000
5.	6-(2-ethylamino thiazol-4-yl)-2,3-dimethyl chromone	nil	25 pt[b]	20	nil	33 pt [b]	>1000
6.	3-(6-(p)-chlorophenyl imidazo[2,1-b]thiazol-3-yl)-2-methyl chromone	↑16 (4)	35 pt	100 pt[a]	45[b]	45	681
7.	3-(6-(p)-bromophenyl imidazo[2,1-b]thiazol-3-yl)-2-methyl chromone	↑26 (4)	40	20 pt	23	23, 30pt[b]	>1000
8.	Ethyl(E)-3-[[4-(6-chloro-2,7-dimethyl-4-oxo-4H-1-benzopyran-3-yl)-2-thiazolyl] amino]crotonate	↓32 (Tr)[c]	25 pt	16[b]	32 pt[a]	50 pt[a]	1000
9.	3-(7-methyl-5H-thiazolo[3,2-a]pyrimidin-5-one-3-yl)-2-methyl chromone	↓16 (20)[b]	11[b]	44	12[c]	35[c]	825

10.	3-[2-(3-methyl-5-(2-furyl)-1H-pyrazol-1-yl)-4-thiazolyl]-6-chloro-2,7-dimethyl chromone	↓12 (2)	71 pt[a]	46 pt[b]	52 pt[b]	35[c]	>1000
11.	3-[2-(3,5-dimethyl-1H-pyrazol-1-yl)-4-thiazolyl]-2,6-dimethyl chromone	nil	20	25 pt[b]	17[c]	33 pt	681

↓ = decrease

↑ = increase

a = at 2.5 mg / kg

b = at 5.0 mg /kg

c = at 10.0 mg / kg

Experimental

Synthesis of compounds has been already published [5-9]. Compounds were screen for CVS activity in CDRI- Lucknow according to following procedure:

The CVS activity was tested in cats. Sodium pentabarbital (40 mg/kg) was administered intraparitoneally for anaesthetizing the cats. Right common carotid artery was cannulated and blood pressure was recorded on smoke paper or kymnograph. All the tested drugs and reference materials viz. acetylcholine, adrenaline, isoprenaline and histamine were administered through an indwelling polythene cannula in right femoral vein. In experiments where carotoid response was recorded, the blood pressure was recorded from femoral artery using the procedure used for recording from common carotid artery and the test drugs and reference agents were injected through the jugular vein. Procedure for injecting was same as through femoral vein. The results of screening are presented in Table-1.

Results and discussion

Though heterocycally substituted chromones have not been found to be good cardiovascular agents; but few results need to be discussed. The values are expressed in mm Hg at 1.0 mg/kg except mentioned otherwise.

3-[2-(4-Morpholinyl)thiazol-4-yl]-6-chloro-2-methylchromone (1) has shown important decrease in B.P. *i.e*. a decrease of 40 mm Hg; but it is transient. 3-[2-(4-Morpholinyl)thiazol-4-yl]-6-chloro-2, 7-dimethylchromone (2) has shown transient decrease of 20 mm Hg in B.P. which indicates that one additional methyl group decreases activity but it shows increase in ALD50 from 825 to > 1000 which is in agreement with the literature report [10-12]. 6-(2-Aminothiazol-4-yl)-2, 3-dimethylchromone (3) has shown decrease in B.P. by 28 mm Hg for 4 minutes. decrease in B.P. as compared to (2) might have been on account of removal of chloro substituent [10 and 13]. This compound has shown good interactive B.P. with

acetylcholine, adrenaline, histamine and isoprenaline with the values 30, 33(pt), 30 and 50, respectively.

Compound (4) *i.e*. 6-(2-methylaminothiazol-4-yl)-2, 3-dimethylchromone showed decrease of 32 mm Hg for three minutes. This compound is not much toxic (ALD_{50} > 1000). Additional decrease in B.P. of this compound as compared to (3) may be attributed to additional methyl group in it. 6-(2-ethylaminothiazol-4-yl)-2,3-dimethylchromone (5) does not affect B.P.; but compound (6) *i.e*. 3-(6-(p)-chlorophenyl imidazo [2, 1-b]thiazol-3-yl)-2-methylchromone as well as 3-(6-(p)-bromophenyl imidazo [2, 1-b]thiazol-3-yl)-2-methylchromone (7) show an increase of 16 mm Hg and 26 mm Hg for 4 minutes which indicates that though thiazole system at C-3 position decreases B.P., but imidazothiazole system at the same position results in increase in B.P.

Ethyl(E)-3-[4-(6-chloro-2, 7-dimethyl-4-oxo-4H-1-benzopyran-3-yl)-2-thiazolyl amino] crotonate (8) like other 2-aminothiazoles attached to C-3 position of chromone showed decrease in B.P. by 32 mm Hg which was transient. Compound (9) which is 3-(7-methyl-5H-thiazolo [3, 2-a]pyrimidin-5-one-3-yl)-2-methyl chromone that was obtained by the cyclization of compound of type (8) with no substitution on benzene ring showed decrease in B.P. by 16 mm Hg for 20 minutes at the dose level 5.0 mg/Kg indicating that 5H-thiazolo [3, 2-a] pyrimidin-5-one system at C-3 position of chromone may result in decrease of B.P. for a longer time period. Compounds (11) and (10) *i.e*. 3-[2-(3, 5-dimethyl-1H-pyrazol-1-yl)-4-thiazolyl]-2, 6-dimethylchromone and 3-[2-(3-methyl-5-(2-furyl)-1H-pyrazol-1-yl)-4-thiazolyl]-6-chloro 2, 7-dimethylchromone do not effect B.P. much. Compound (10) has one furyl ring in place of methyl group, therefore, has decrease in B.P. as compared to (11) which is in agreement with literature report that furyl ring generally result in increase in activity [11]. In this compound Cl substituent might also has decreased B.P.

Conclusion

Additional methyl group on chromone as well as other heterocyclic systems attached to it decrease activity as well as toxicity. Halogen substitution on chromones though decrease the CVS activity (B.P.), but increase the toxicity. Imidazo [2, 1-b]thiazol-3-yl system at C-3 position of chromone, however, cause increase in B.P.

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