SHORT COMMUNICATION

STUDY ON STRUCTURE ACTIVITY RELATIONSHIP OF SOME 3- OR 6-(2-AMINO OR N- SUBSTITUTED AMINOTHIAZOL-4-YL)-2-METHYLCHROMONES

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Abstract: Medicinal plants are important source of diuretics. But, significance of synthetic drugs in emergency cannot be denied as they have quick and remedial action in hypertension, heart failure, renal failure, nephrosis etc. Thus synthetic diuretics are important. Therefore, present study is carried out on structure activity relationship of 3- or 6-(2-Amino or N-substituted aminothiazol-4-yl)-2-methylchromones to find new and useful diuretic drugs. Compounds VPS-1 to VPS-6 were tested and found to posses diuretic activity.

Keywords: Diuretic activity; 3- or 6 -(2-Amino or N- substituted aminothiazol-4-yl)-2-methylchromones; 3-[2-(3,5-disubstituted -1H-pyrazol-1-yl)-4-thiazolyl]-2-methylchromones

INTRODUCTION

One of the important use of plant products is as diuretic agent [Dutta et al, ; 2014]. Diuretics are effective to cure oedema, heart failure, renal failure , nephrosis and hypertension etc. They increase urine volume & increase excretion of sodium and either chloride or bicarbonate [Barrar; 2003]. There are more than 650 mono & poly herbal preparations used in the form of decoctions , tablets , tinctures and capsules etc .from more than 75 plants [Chopra et al. ; 1986]. Aqueous extract of bark of *Mangifera indica* is good diuretic [Shree Devi; 2011]. Diuretic activity is also reported in *Achyranthes aspera* Linn. [Srivastav *et al.,* 2011]. Ethanolic extract of *Euphorbia thymifolia* potentiate the diuretic activity as compared to standard drug [Kane *et al*., 2009]. *Allium sativum* (garlic) due to dose dependent effect on sodium, potassium and ATPase causes dieresis [Pantoja *et al.,* 2000]. Though, herbal treatment is safer way to dieresis; even than synthetic diuretic drugs are better options in emergency due to their fast actions. Therefore, present study is carried out on structure activity relationship of 3- or 6-(2-Amino or substituted aminothiazol-4-yl)-2-methylchromones to find new and useful diuretic drugs. Compounds VPS-1 to VPS-6 were tested and found to posses diuretic activity.

MATERIAL AND METHOD

Compounds VPS-1 to VPS-6 were synthesized by author in Department of Chemistry, Kurukshetra University , Kurukshetra [Garg et al., 1985; Kapoor et al., 1988 and Sharma et al.,2004] and were screened for ALD_{50} [Approximate lethal dose around 50 % mortality] and diuretic activity at Pharmacology Division of CDRI , Lucknow. Activities were compared with chlorothiazide standard, value for which was taken as 100. Results are reported in Table-1.

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RESULT AND DISCUSSION

3-(2-Aminothiazol-4-yl)-2-methylchromone [VPS-1] has shown diuretic activity equal to 89. Introduction of methyl group at C_6- position of chromone ring of VPS-1 resulting in the formation of VPS-2 caused decrease in activity by 15 units. This indicates methyl group at C_6- position of chromone ring decreases diuretic activity, but it increases ALD_{50} value from 316 to > 1000 indicating that this change makes compound safer to biological systems as toxicity decreases which is in conformity with the trend reported in literature [Gupta, 2013 and Silverman, 2004]. Thus, electron releasing methyl group at C_6- position of chromone ring results in decrease in diuretic activity, Compound 6-(2-Aminothiazol-4-yl)-2,3-dimethylchromone [VPS-3] shows highly decreased diuretic activity [equal to 13] ; however , this compound is safer [ALD_{50} > 1000]. Number of methyl groups is same in VPS-2 and VPS-3 , therefore , it is inferred that heterocyclic 2-aminothiazol-4-yl system is effective at pyran-4-one ring only and electron release by this system at position-6 of chromone ring decreases the activity. Compounds VPS-4, VPS-5 and VPS-6 also have 2-substituted aminothiazol-4-yl system at position-3 of chromone nucleus and in them at 2-position of thiazole is a tertiary amino substituent i.e. 1-pyrazolyl system is present. 6-Chloro-3-[2-(3-methyl-5-(2-furyl)-1H-pyrazol-1-yl)-4-thiazolyl]-2-methylchromone (VPS-4) showed diuretic activity equal to 51 and ALD_{50} value of 681 indicating that this compound is not only mildly diuretic but is also toxic. Introduction of one methyl group at position-7 of chromone ring in VPS-4 resulted in the formation of 6-Chloro-3-[2-(3-methyl-5-(2-furyl)-1H-pyrazol-1-yl)-4-thiazolyl]-2,7-dimethylchromone (VPS-5) which showed an activity increase of 27 units [from

51 to 78] ; it also made compound safer [ALD_{50} value increased from 681 to > 1000]. Compound VPS-6 is 3-[2-(3, 5-dimethyl-1H-pyrazol-1-yl)-4-thiazolyl]-2, 6-dimethylchromone that contains four methyl groups. Here high electron release by methyl groups decreased activity substantially to the value 28 [a decrease of 50 units from VPS-5]. However, this compound is safe due to the presence of four methyl groups. As diuretic activity of VPS-4 and VPS-5 are greater than VPS-6, hence, 2-furyl substituent at position-5 of pyrazole ring is responsible for greater activity.

CONCLUSION

Electron releasing methyl groups though decrease the activity but makes compounds safer for use. On the other hand electron withdrawing – Cl substituent at the same position favours higher activity and at the same time increases toxicity also. As all the tested compounds exhibited diuretic activity, hence, 2-amino or N-substituted aminothiazol-4-yl system at C_3 – position of chromone moiety is a **lead** for diuretic activity [same system at position-6 of chromone ring showed highly decreased activity]. Moreover, 2-furyl substituent favours high activity as compared to methyl substituent.

Table 1: ALD_{50} and diuretic activities of 3- or 6- [2-amino or N- substituted aminothiazol-4-yl]-2-methylchromones.

S. No.	Compound code	Name of the compound	ALD_{50}	Diuretic activity
1.	VPS-1	3-[2-Aminothiazol-4-yl]-2-methylchromone	316	89
2.	VPS-2	3-[2-Aminothiazol-4-yl]-2,6-dimethylchromone	> 1000	74
3.	VPS-3	6-[2-Aminothiazol-4-yl]-2,3-dimethylchromone	> 1000	13
4.	VPS-4	6-Chloro-3-[2-(3-methyl-5-(2-furyl)-1H-pyrazol-1-yl)-4-thiazolyl]-2-methylchromone	681	51
5.	VPS-5	6-Chloro-3-[2-(3-methyl-5-(2-furyl)-1H-pyrazol-1-yl)-4-thiazolyl]-2,7-dimethylchromone	> 1000	78
6.	VPS-6	3-[2-(3,5-dimethyl-1H-pyrazol-1-yl)-4-thiazolyl]-2,6-dimethylchromone	1000	28
7.	Standard	Chlorothiazide	Drug	100

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