ISSN: 0974 - 7516 Volume 8 Issue 8

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 8(8), 2012 [299-302]

Synthesis and biological evaluation of novel pyridone derivatives as cardio tonic agents

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Received: 6th January, 2012 ; Accepted: 31st January, 2012

ABSTRACT

Two derivatives of 3-acetyl-4-amino-3,4-dihydropyridin-2(1H)-one and 3-acetyl-3,4-dihydro-4-(phenylamino)pyridin-2(1H)-one were prepared by reaction of enamine and diethyl malonate and tested for cardio tonic activity by isolated frog heart perfusion technique will be used as a model to evaluate the activity of various synthesized 2-pyridone derivatives in different concentration and anti-hypertensive activity was done by the tail cuff method in albino rats. The basal cardiac contraction will be recorded on a kymograph after the administration of calcium free Ringer solution. The cardiac activity in terms of heart rate (HR) and height of force of contraction (HFR) will be recorded. These two compounds showed good activity as compared to the standard drugs.

KEYWORDS

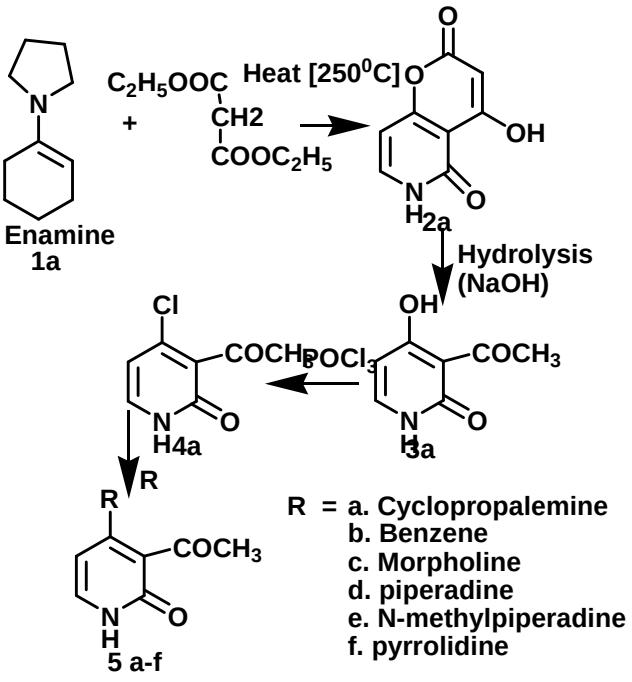
Cardio tonic activity;
Milrinone;
Amrinone;
2-pyridone.

INTRODUCTION

Congestive heart failure is a life threatening condition in which myocardial contractility is depressed so that the heart is unable to adequately pump the blood returning to it. Normal pathogenic sequence include decreased cardiac output, venous pooling, increased venous pressure, edema, increase heart size, increased myocardial wall tension and eventually cessation of contractility.

For many years, digitalis glycosides have been used for the treatment of CHF. This use, however, is limited because of their narrow therapeutic index and their tendency to cause life-threatening arrhythmias (arrhythmogenic lability).

The search for orally active 'non-glycoside' cardiotonic drugs displaying a greater safety profile and improved efficacy on patient survival resulted in new



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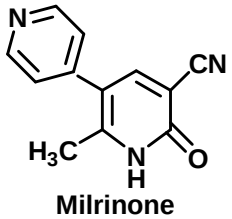
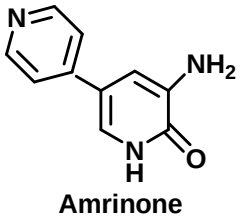
class of cardio tonics with a different mechanism of action. Amrinone and Milrinone are the prototypes of this series of analogues, proposed as a replacement for digitalis, referred to as inhibitors of cGMP-inhibited cAMP phospodiesterase (PDE), also called Type 3 PDE or PDE3.

Amrinone is new bipyridine derivative, which increases cardiac output and reduces filling pressure in patients with cardiac failure.



Milrinone



Amrinone

CHEMISTRY:

The general synthesis of 3-acetyl-4-amino-3,4-dihydropyridin-2(1H)-one and 3-acetyl-3,4-dihydro-4-(phenylamino)-

pyridin-2(1H)-one is illustrated in sheme. Enamine(1a) and diethyl malonate heated to 200-250^{0}C for 4 hours to form hydroxy-

pyropyridone (2a) and again treated with sodium hydroxide to form 3-acetyl-4-hydroxy-2-pyridone(3a) and react with $POCl_3$ to form form 3-acetyl-4-Chloro-2-pyridone(4a) again react with different type of compounds to form pyridine derivatives 5a-f and tested for cardio tonic activity by isolated frog heart perfusion technique will be used as a model to evaluate the activity of various synthesized (5a-f) derivatives in different concentration and after testing 5c and 5g showing good activity.

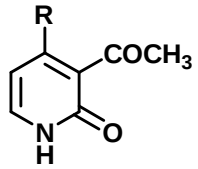
And 5c and 5g also showing good antihypertensive activity by testing tail cuff method.

RESULT AND DISCUSSION

In vitro studies

Cardiotonic effect on isolated atria

Biological evaluation of the test compounds as cardio-tonic agents was determined using spontaneously beating atria model from reserpine-treated



Compound No.	R_1	Yield (%)	M. point(^{0}C)
a.	Cyclopropalamine	79	295
b.	Benzene	72	290
c.	Morpholine	68	285
d.	Piperdine	65	275
e.	N-methyl piperadine	58	278
f.	Pyrrolidine	60	265

guinea pigs to eliminate the influence of noradrenaline upon contractility. Inotropic and chronotropic activities were expressed as percentage change in the force of contraction and frequency rate over control (TABLE 1).

In general, at concentration of 10^{-5} and 5×10^{-5} M most test compounds showed a minimal response, whereas, most test compounds in a final concentration of 5×10^{-4} M, caused an increase in the force of contraction of spontaneously beating guinea pig atria. Some 4-amino derivatives 4a-f possessed good contractile activity. compounds 5c 5d and 5e (% change of developed tention over control =94.4±5.2, 89.2±4.7, 87.5±5.1, respectively) showed contractile activity higher or comparable to milrinone (% change of developed tention over control = 84±1.6).

Isolated heart perfusion technique

The newly synthesized analogues 5a,5b,5c,5d,5e,5f

TABLE 1

Compound numbers	Developed tension (% change over control)[a]	Frequency rate (% change from control)[b]
Milrinone	84.0±4.6	38±3.2
5a	5a 54.4±5.2	b
5b	5b 39.2±4.7	b
5c	5c 94.4±5.2	-4.66±2.1
5d	5d 89.2±4.7	-3.33±3.6
5e	5e 87.5±5.1	-8.33±3.8
5f	5f 34.4±5.2	b

[b]No inotropic or chronotropic effect; [a] Mean ± S.E.M. from four atria.

were tested for their effects on the force of contraction. and basal cardiac contraction will be recorded on a kymograph after the administration of calcium free Ringer solution. The cardiac activity in terms of heart rate (HR) and height of force of contraction (HFR) will be recorded.

EXPERIMENTAL PROTOCOLS

Melting points were determined in open glass capillaries using a Thomas capillary melting point apparatus and are-uncorrected. Infrared (IR) spectra were recorded on 470- Shimadzu IR- spectrophotometer using the KBr disc technique.

4-hydroxy-9H-pyrano[2-pyridone-2,5-dione(2a)

IR (cm^{-1}):

1613.97 (-C=O amide);1730.12 (-C=O lactone); (3260-NH); 3453 (-OH).

^{1}H -NMR of compound 5a: *d* 7.11 (s, 1H, sec. amide 7.58–7.59 (d, 2H, lactone), 2.09 (d, 3H, methyl),

3-acetyl-4-hydroxy-3,4-dihydropyridin-2(1H)-one(3a)

IR (cm^{-1}):

1613.97 (-C=O amide); (3260-NH); 3453 (-OH).

^{1}H -NMR of compound 5a: *d* 7.11 (s, 1H, sec. amide 2.09 (d, 3H, methyl),

3-acetyl-4-chloro-3,4-dihydropyridin-2(1H)-one(4a)

IR (cm^{-1}):

1613.97 (-C=O amide); (3260-NH).

^{1}H -NMR of compound 5a: *d* 7.11 (s, 1H, sec. amide 7.58–7.59 2.09 (d, 3H, methyl).

3-acetyl-4-amino-3,4-dihydropyridin-2(1H)-one (5a).

IR (cm^{-1}):

3285–3260 (NH), 1654 (C = O)

^{1}H -NMR of compound 5a: *d* 7.11 (s, 1H, sec. amide 7.58–7.59 (d, 2H, amino), 2.09 (d, 3H, methyl), 12.92 (br s, 1H, NH).

3-acetyl-3,4-dihydro-4-phenylpyridin-2(1H)-one (5b).

IR (cm^{-1}):

3285–3260 (NH), 1654 (C = O)

^{1}H -NMR of compound 5a: *d* 8.11 (s, 1H, sec. amide, 7.58 (m,3H,phenyl-H), 7.44(m,2H,phenyl-H) 2.09 (s, 3H, methyl), 12.92 (br s, 1H, NH).

3-acetyl-3,4-dihydro-4-(phenylamino)pyridin-2(1H)-one(5c).

IR (cm^{-1}):

3285–3260 (NH), 1654 (C = O)

^{1}H-NMR of compound 5c: *d* 8.11 (s, 1H, sec. amide, 7.58 (m,3H,phenyl-H), 7.44(m,2H,phenyl-H),4.2(s, 1H, aromatic C-NH) 2.09 (s, 3H, methyl), 12.92 (br s, 1H, NH).

3-acetyl-3,4-dihydro-4-(piperidin-1-yl)pyridin-2(1H)-one(5d).

IR (cm^{-1}):

3285–3260 (NH), 1654 (C = O)

^{1}H -NMR of compound 5c: *d* 8.11 (s, 1H, sec. amide, 1.50 (m,3H,piperadine), 2.50 (m,2H, piperadine), 2.09 (s, 3H, methyl),

3-acetyl-4-methyl-3,4-dihydro-pyridin-2(1H)-one(5e).

IR (cm^{-1}):

3285–3260 (NH), 1654 (C = O)

^{1}H -NMR of compound 5c: *d* 8.11 (s, 1H, sec. amide, 1.16(s,3H,methyl-H),2.09 (s, 3H, methyl),

3-acetyl-4-ethyl-3,4-dihydro-pyridin-2(1H)-one (5f).

IR (cm^{-1}):

3285–3260 (NH), 1654 (C = O)

^{1}H -NMR of compound 5c: *d* 8.11 (s, 1H, sec. amide, 1.16(m,2H,methylene-H),0.96 (s,3H,methyl-H)2.09 (s, 3H, methyl)

CONCLUSION

The cardiotonic effect on isolated guinea pigs atia clearly showed that compounds 5c, 5d and 5e exhibited better cardiotonic activity.

As a result, the studied milrinone analogs 5c, 5d and 5e proved to exert cardio tonic activity. The presence of oxo group at 2-position and secondary amine and piperdine at 4-position of pyridine ring system are essential for the cardio tonic activity.

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