Med Chem Res (2011) 20:287–292
DOI 10.1007/s00044-010-9319-0

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and anti-congestive heart failure activity of novel levosimendan analogues

Lisheng Wang · Hongxiang Zhou · Bin Yang · Zhigang Chen · Hua Yang

Received: 7 May 2009 / Accepted: 12 February 2010 / Published online: 27 February 2010

Abstract A series of levosimendan analogues were designed and synthesized, employing the Friedel–Crafts reaction, hydrolysis, and cyclization from the key intermediate compound *R*(−)-6-(4-aminophenyl)-5-methyl-4, 5-dihydro-3(2H)-pyridazinone, which was obtained from the starting material, acetanilide. These compounds, except **1b**, exhibited potent anti-congestive heart failure activities, especially the compounds **1e** and **1k**, which showed more effective action than levosimendan.

Keywords Pyridazinone · Anti-congestive heart failure · Levosimendan analogues · Synthesis

Introduction

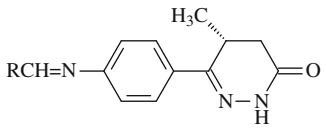
Heart failure has been one of the most important causes of morbidity and mortality in developed countries (Nieminen *et al.*, 2005), with an increase in the numbers of patients hospitalized for ischemic heart disease and chronic heart failure related to aging populations (Cherng *et al.*, 2006; Gottdiener *et al.*, 2000; Krum and Liew, 2003; McCullough *et al.*, 2002). Therefore, more research attention has been paid to it. In recent years, a large number of compounds with diverse structures have been synthesized and evaluated for potent, but less toxic, anti-congestive heart failure (CHF) drugs. Among anti-CHF drug candidates, *R*(−)-6-(4-substitutedphenyl)-5-methyl-4, 5-dihydro-3(2H)-pyridazinone compounds showed good inhibition of platelet aggregation and cardiac failure (Bristol *et al.*, 1984; Hayes *et al.*, 1987). They selectively inhibited phosphodiesterase III and increased cAMP levels (Nobuo *et al.*, 1993). The pharmacological activity of 4,5-dihydro-6-phenyl-3(2H)-pyridazinones has been extensively studied and is known for its cardiovascular effects (Abouzid *et al.*, 2009; Bansal *et al.*, 2009; Thota and Bansal, 2009). Among these pyridazinone compounds, levosimendan, *R*(−){[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrozono} propanedinitrile, has been the most effective drug in the treatment of CHF (Hosenpud, 1999). Therefore, in this study, levosimendan was chosen as the leading compound for screening potential anti-CHF analogues. In addition, 11 previously unreported analogues of levosimendan were synthesized and tested for their anti-CHF activity in blood pressure experiments (Fig. 1).

L. Wang (✉) · H. Zhou · B. Yang · Z. Chen · H. Yang
College of Chemistry and Chemical Engineering, Guangxi University, Nanning 530004, China
e-mail: lswang@gxu.edu.cn; w_lsheng@163.com

Results and discussion

Chemistry

The syntheses of compounds **1a–1k** are shown in Scheme 1. Acetanilide was chosen as the starting material and the intermediate (R)(-)-6-(4-aminophenyl)-5-methyl-4,5-dihydro-3(2H)-pyridazinone was synthesized via seven steps of the Friedel–Crafts reaction, hydrolysis, cyclization, etc. (Ali and Yar, 2007; Austel *et al.*, 1982). The above intermediate reacted with appropriate aldehydes and yielded 11 target compounds (Scheme 1). In the first step, the maximum yield was up to 60.1% when the molar ratio of acetanilide and anhydrous aluminum trichloride was 1:2.8. The yield did not increase when additional anhydrous aluminum trichloride was used. The reaction was simpler and easier when sodium hydride and the solvent THF were replaced with sodium ethoxide and ethanol, respectively, in



1a-1k

Fig. 1 Levosimendan analogues. **1a**: R = 4-nitrophenyl; **1b**: R = 3-nitrophenyl; **1c**: R = 3,4-dihydroxyphenyl; **1d**: R = 4-hydroxyphenyl; **1e**: R = 2-hydroxyphenyl; **1f**: R = 2-chlorophenyl; **1g**: R = 3,4,5-trimethoxyphenyl; **1h**: R = 3,4-dichlorophenyl; **1i**: R = 2-pyridyl; **1j**: R = phenylvinyl; **1k**: R = 2-furanyl

the third step. The economical sulfuric acid was used as a decarboxylation reagent instead of biphenyl ether in the fifth step. In the last step of the synthesis, 95% ethanol was used instead of anhydrous ethanol for comparison.

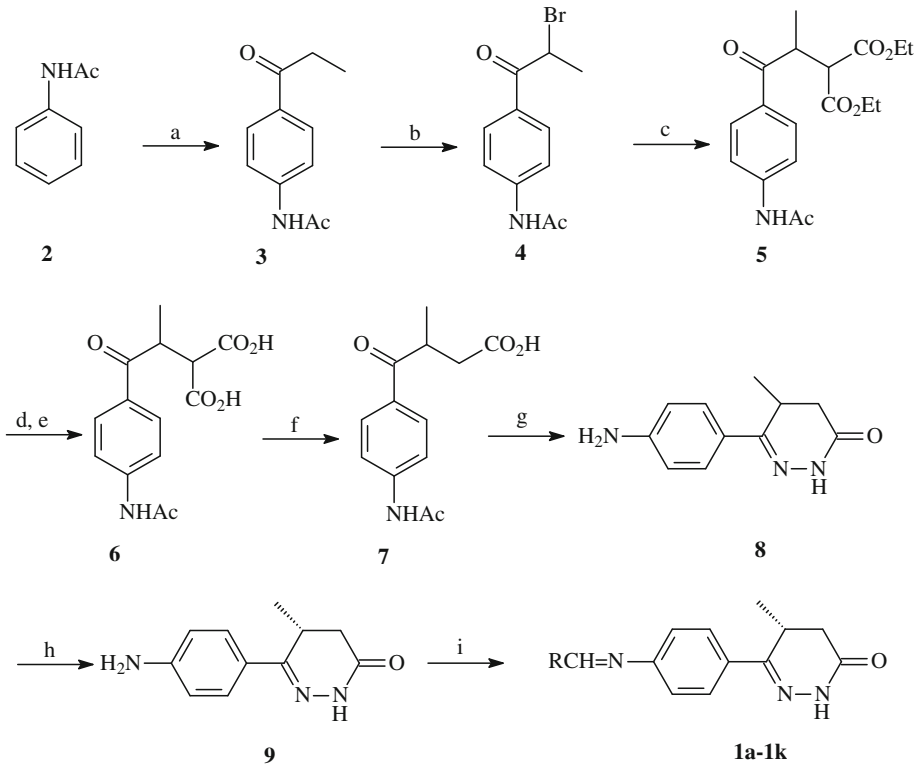
Biological activity

The in vivo anti-CHF activities of these compounds were tested in blood pressure experiments with levosimendan as the positive control group. The tracheal intubation method was utilized to measure blood pressures. The preliminary results revealed that these levosimendan analogues, except **1b**, were effective against CHF by dilating blood vessels. The anti-CHF activities of **1a**, **1c**, **1d**, and **1f–1j** at different time intervals were similar to those of levosimendan ($P < 0.01$). The anti-CHF activities of compound **1e** at intervals of 10 and 20 min, however, were significantly stronger than that of levosimendan ($P < 0.05$). The anti-CHF activities of **1k** at intervals of 15, 20, and 25 min were also significantly better than that of levosimendan ($P < 0.05$; Table 1).

In comparison with the *p*-substituted phenyl compound **1d**, the *o*-hydroxyl-substituted compound **1e** showed higher anti-CHF activity, whereas the *m*-hydroxyl-substituted compound **1c** showed lower activity. The results indicated that the position of the hydroxyl group on the phenyl ring greatly influenced anti-CHF activity, at an activity order of $o > p > m$. When the R group was a furan ring, the anti-CHF activity of compound **1k** was obviously better than that of levosimendan. For example, after treating with **1k** for 15, 20, and 25 min, the blood pressures were 25, 25, and 24 mmHg, respectively. However, with levosimendan at the same treatment times, the blood pressures were 34, 36, and 34 mmHg, respectively. The results indicated that the furan ring of compound **1k** played an important role in anti-CHF activity. As a kinetophore, the furan ring may have changed the electron density of the pyridazinone ring, which increased the level of cAMP in cells and inhibited ADP III as well, and finally resulted in better anti-CHF activity.

Conclusions

A series of levosimendan analogues were successfully synthesized and characterized by IR, ^{1}H NMR, MS, and elemental analyses. The results of the tracheal intubation



Scheme 1 Synthesis route for levosimendan analogues. Reagents and conditions: **a** CH_3CH_2COCl, $AlCl_3$, CS_2, reflux for 3 h; **b** Br_2, HOAc, stirred at room temperature; **c** $CH_2(CO_2Et)_2$, EtOH, C_2H_5ONa, room temperature, 8 h; **d** NaOH aq; **e** 3 mol/l HCl, 25–70°C; **f** H_2SO_4 (v:v = 1:1), reflux; **g** $NH_2NH_2{\cdot}H_2O$, HOAc, 8 h; **h** L (+) tartaric acid, isopropanol; **i** RCHO, EtOH, or $CHCl_3$, heated and stirred for 5 h

Table 1 The blood pressures of rats at different times after administration (50 mg/kg) of compounds **1a**–**1k** in comparison with those in the negative control and levosimendan control

Compound	Dosage (mmol/kg)	Average blood pressure (mmHg) at different time intervals (min)					
		5	10	15	20	25	30
Control group	–	97 ± 3	95 ± 3	86 ± 3	81 ± 4	79 ± 4	88 ± 3
Levosimendan	0.179	51 ± 2a	39 ± 3a	34 ± 3a	36 ± 3a	34 ± 3a	31 ± 3a
1a	0.149	56 ± 3a	35 ± 3a	31 ± 3a	29 ± 4a	28 ± 3a	29 ± 2a
1b	0.149	77 ± 4b	71 ± 4a	69 ± 3a	68 ± 3	67 ± 3	67 ± 2b
1c	0.224	77 ± 3b	63 ± 3a	53 ± 3a	53 ± 2a	53 ± 3a	53 ± 3a
1d	0.163	80 ± 2	44 ± 3a	32 ± 3a	30 ± 2a	29 ± 3a	30 ± 4a
1e	0.163	55 ± 2a	28 ± 3aB	28 ± 4a	26 ± 3aB	26 ± 3a	26 ± 2a
1f	0.145	81 ± 4	68 ± 2a	55 ± 2a	34 ± 3a	34 ± 3a	32 ± 3a
1g	0.131	77 ± 3b	46 ± 3a	37 ± 3a	28 ± 3a	27 ± 3a	27 ± 3a
1h	0.139	52 ± 3a	33 ± 3a	25 ± 2a	24 ± 4a	25 ± 3a	25 ± 4a
1i	0.171	52 ± 2a	39 ± 3a	30 ± 3a	30 ± 2a	29 ± 2a	29 ± 3a
1j	0.158	59 ± 3a	36 ± 2a	33 ± 2a	36 ± 3a	36 ± 2a	31 ± 3a
1k	0.178	45 ± 3a	30 ± 3a	25 ± 2aB	25 ± 3aB	23 ± 2aB	24 ± 3a

Comparison with control group: a: $P < 0.01$; b: $P < 0.05$

Comparison with levosimendan group: A: $P < 0.01$; B: $P < 0.05$

tests showed that all target compounds, except **1b**, significantly reduced the blood pressures of tested rats, suggesting that these compounds have good anti-CHF activities. The research results obtained in this study provided useful information for further structural modification of these compounds and the synthesis of potent new anti-CHF agents.

Experimental

Instrumentation

All compounds were characterized with MS, IR, ^{1}H NMR, and elemental analysis data. ^{1}H NMR data were recorded on a Bruker Avance 500 (500 MHz) spectrometer with DMSO as the solvent and tetramethylsilane as the internal standard. MS and IR spectra were taken on a Shimadzu GS-MS/QP5050A mass spectrometer and a Shimadzu FTIR-8700, respectively. Elemental analysis data were obtained with a Perkin–Elmer 2400. Melting points were determined in open capillary tubes on a Buchi 530 melting point apparatus without correction. Optical rotation values were measured on a WZZ-1S automatic spectropolarimeter. All chemical reagents used in the experiments were of analytical grade and were obtained from Sinopharm Chemical Reagent Co., Ltd., China.

General procedures

*Synthesis of 4-propionacetylanilide (**3**)*

A flame-dried round-bottomed flask (100 ml) connected to a reflux condenser was charged with carbon disulfide (60 ml), **2** (0.148 mol, 20 g), and anhydrous aluminum chloride (0.412 mol, 55 g). The mixture was gently heated and stirred until a colorless solution formed. After the mixture was stirred for another 10 min, propionyl chloride (0.160 mol, 14 ml) was added dropwise with a dropping funnel for more than 30 min. Then, the mixture was stirred at 50°C for 3 h. Removal of the solvent under normal pressure yielded a pale red oil. The oil was then transferred to a 250-ml beaker. A 55-ml mixture of ice, water, and hydrochloric acid (5 ml) was added to yield **3** in the form of a yellow solid. Recrystallization with 95% ethanol produced a pale yellow solid (17 g, 60%).

*4-(2-Bromopropionyl) acetylanilide (**4**)*

A 250-ml round-bottomed flask was charged with **3** (0.05 mol, 10 g) and chloroform (100 ml). Bromine (0.05 mol, 2.7 ml) was added dropwise to the mixture while stirring. Next, the solvent was evaporated with a rotary evaporator. The residue was adjusted to a pH of 8.0 using a saturated solution of sodium carbonate. After the mixture was stirred for over 24 h at room temperature, the solvent was evaporated with a rotary evaporator to form a yellowish solid **4**. Recrystallization with 95% ethanol produced a white solid (10.2 g, 72%).

*2-Ethoxycarbonyl-3-(4-acetylaminobenzoyl)-ethyl butyrate (**5**)*

Diethyl malonate (0.016 mol, 2.4 ml) was added portionwise in an ice-water bath to an ethanol solution of sodium ethoxide prepared from absolute ethyl alcohol (60 ml) and sodium (0.013 mol, 3 g). The resulting solution was gradually warmed to 35°C and then an ethanol solution of **4** (0.0078 mol, 2.1 g) was added dropwise for 10 min. The mixture was stirred at 75°C for 8 h and then evaporated

under reduced pressure (65°C, 40 mmHg) to yield **5** in the form of a brown solid, which was used directly with no further purification.

*2-Carboxyl-3-(4-aminobenzoyl) butyric acid (**6**)*

A sodium hydroxide solution (200 ml, 15%) was added to **5**. The mixture was stirred for 4 h, and then adjusted to a pH of 1.0 using concentrated hydrochloric acid (34 ml). Next, the mixture was stirred for 3 h at 100°C and concentrated with a rotary evaporator (40 mmHg, 70°C). Then, 20 ml of methanol was added to the residue while stirring and a white solid precipitated. The mixture was filtered to remove the white solid by washing it with methanol (10 ml). The combined organic phases were concentrated with a rotary evaporator (50°C, 40 mmHg) to form the crude product **6**, which was used directly with no further purification.

*3-(4-Aminobenzoyl) butyric acid (**7**)*

An aqueous solution of sulfuric acid (40 ml, 1:1, v/v) was added to **6**. The mixture was refluxed for 3.5 h and then adjusted to a pH of 4.0 using a sodium carbonate aqueous solution (20%) to yield the product **7** in the form of a yellow solid (2.1 g, 55%).

*6-(4-Aminophenyl)-5-methyl-4, 5-dihydro-3(2H)-pyridazinone (**8**)*

Hydrazine hydrate (85%, 0.0034 mol, 2 ml) was added to a 25-ml ethanol solution (95%) of **7** (0.0097 mol, 2 g). The solution was stirred at 80°C for 3 h and then cooled to room temperature to yield **8** in the form of a yellow solid. Recrystallization with 90% aqueous ethanol produced a white solid (1.8 g, 92%).

*R(−)-6-(4-Aminophenyl)-5-methyl-4, 5-dihydro-3(2H)-pyridazinone (**9**)*

A 500-ml round-bottomed flask connected to a reflux condenser was charged with **8** (0.049 mol, 10 g), isopropanol (250 ml), and L-tartaric acid (0.1 mol, 15 g). The mixture was heated and stirred for 30 min. The mixture was then cooled to room temperature and kept for 8 h to yield a white solid. The solid was collected using filtration followed by recrystallization in isopropanol (125 ml). Then, it was transferred to a 200-ml beaker containing 50 ml of distilled water, and this mixture was adjusted to a pH of 7–8 using potassium carbonate and filtered to yield the solid. The solid was then washed with water (50 ml) and dried to yield 7.3 g of a white solid. The white solid was added to 1,4-dioxane (60 ml) and heated under reflux for over 30 min. The solution was cooled to room temperature and a white crystalline substance formed. The white solid was collected by filtration and dried to produce **9** (0.8 g, 8%), $[\alpha]_D^{20} = -380°$ ($c = 1$, $V_{C_2H_5OH} : V_{H_2O} : V_{conc.HCl} = 17 : 2 : 1$), m.p. 205–207°C. [Literature (Bäckström *et al.*, 1992) data: $[\alpha]_D^{25} = -383°$ (ethanol–water-concentrated HCl 17:2:1), m.p. 207–210°C, optical purity 99.5%].

*General synthesis procedures for compounds **1a–1e** and **1g–1j***

A 100-ml round-bottomed flask connected to a reflux condenser was charged with **9** (0.0296 mol, 6 g), absolute methanol (20 ml) (instead of the absolute ethanol used for **1g–1j**), and aldehyde (0.0298 mol). The mixture was stirred and refluxed for 5 h and then cooled to ambient temperature. The solid was collected by filtration followed by recrystallization with acetone (instead of the absolute ethanol used for **1g–1j**) to yield products **1a–1e** and **1g–1j**.

*General synthesis procedures for compounds **1f** and **1k***

A 250-ml round-bottomed flask connected to a reflux condenser was charged with **9** (0.0246 mol, 5 g), chloroform (200 ml), and the appropriate aldehyde (0.248 mol). The mixture was refluxed for 4 h. After removal of the solvent, the residue was recrystallized using ethanol to yield products **1f** and **1k**.

*R(−)-6-[4-(4-nitrobenzal)amino]phenyl-5-methyl-4,5-dihydro-3(2H)-pyridazinoe (compound **1a**)*

Yield: 86%; m.p.: 110–112°C; $[\alpha]_D^{20}$: −421° ($c = 1$, MeOH); IR (KBr, cm^{-1}): 3210, 3110, 3020, 2940, 1690, 1600, 1510, 1350, 1560, and 1220; ^{1}H NMR (DMSO-d_6, δ ppm): 1.12 (3H, d, $J = 7$), 2.29 (1H, d, $J = 1$), 2.71 (1H, dd, $J = 7$), 3.44 (1H, m, $J = 7.5$), 7.40 (2H, d, $J = 7$), 7.87 (2H, d, $J = 7$), 8.20 (2H, d, $J = 7$), 8.35 (2H, d, $J = 7$), 8.84 (1H, s), and 10.95 (1H, s); MS: *m/z* 336 (M^+), 44, 321, 279, 251, 204, 151, 129, 115, 96, 77, 69, and 57; elemental analysis (%): calculated: C, 64.28; H, 4.79; N, 16.66; found: C, 64.34; H, 4.88; N, 16.65.

*R(−)-6-[4-(3-nitrobenzal)amino]phenyl-5-methyl-4,5-dihydro-3(2H)-pyridazinone (compound **1b**)*

Yield: 92%; m.p.: 215–217°C; $[\alpha]_D^{20}$: −382° ($c = 1$, MeOH); IR (KBr, cm^{-1}): 3210, 3080, 2960, 1690, 1350, 1540, 1600, and 1200; ^{1}H NMR (DMSO-d_6, ppm): 1.12 (3H, d, $J = 7$), 2.28 (1H, d, $J = 1$), 2.71 (1H, dd, $J = 7$), 3.44 (1H, m, $J = 7.5$), 7.40 (2H, d, $J = 7$), 7.84 (2H, m, $J = 7$), 7.88 (2H, d, $J = 7$), 8.35 (1H, d, $J = 7$), 8.74 (1H, s), 8.86 (1H, s), and 10.96 (1H, s); MS: *m/z* 336 (M^+), 321,

279, 251, 217, 204, 129, 115, 102, 77, 63, and 44; elemental analysis (%): calculated: C, 64.28; H, 4.79; N, 16.66; found: C, 64.41; H, 4.84; N, 16.62.

*R(−)-6-[4-(3,4-dihydroxybenzal)amino]phenyl-5-methyl-4,5-dihydro-3(2H)-pyridazinone (compound **1c**)*

Yield: 94%; m.p.: 222–224°C; $[\alpha]_D^{20}$: −412° ($c = 1$, MeOH); IR (KBr, cm^{-1}): 3350, 2980, 1650, 1600, 1580, and 1280 ^{1}H NMR (DMSO-d_6, δ ppm): 1.08 (3H, d, $J = 7$), 2.27 (1H, d, $J = 1$), 2.68 (1H, dd, $J = 7$), 3.41 (1H, m, $J = 7.5$), 7.22 (2H, m, $J = 8$), 7.25 (2H, d, $J = 2.5, 7$), 7.42 (1H, s), 7.80 (2H, d, $J = 2, 7$), 8.42 (1H, s), 9.23 (1H, s), 9.70 (1H, s), and 10.88 (1H, s); MS: *m/z* 323(M^+), 203, 118, 188, 130, 146, 160, 308, 91, 77, and 65; elemental analysis (%): calculated: C, 66.86; H, 5.30; N, 13.00; found: C, 66.66; H, 5.44; N, 12.78.

*R(−)-6-[4-(4-hydroxybenzal)amino]phenyl-5-methyl-4,5-dihydro-3(2H)-pyridazinone (compound **1d**)*

Yield: 92%, m.p.: 253–254°C; $[\alpha]_D^{20}$: −339° ($c = 1$, MeOH); IR (KBr, cm^{-1}): 3180, 1650, 2960, 1600, 1580, 1510, and 1280; ^{1}H NMR (DMSO-d_6, δ ppm): 1.10 (3H, d, $J = 7$), 2.26 (1H, d, $J = 1$), 2.68 (1H, dd, $J = 7$), 3.41 (1H, m, $J = 7.5$), 6.90 (2H, d, $J = 2, 7.8$), 7.26 (2H, d, $J = 2, 7$), 7.78 (4H, m, $J = 1.5, 7$), 8.49 (1H, s), 10.07 (1H, s), and 10.878 (1H, s); MS: *m/z* 307 (M^+), 221, 203, 115, 132, 57, 292, 236, 250, 41, 264, 102, 77, and 65; elemental analysis (%): calculated: C, 70.34; H, 5.58; N, 13.67; found: C, 70.50; H, 5.56; N, 13.67.

*R(−)-6-[4-(2-hydroxybenzal)amino]phenyl-5-methyl-4,5-dihydro-3(2H)-pyridazinone (compound **1e**)*

Yield: 93%; m.p.: 187–189°C; $[\alpha]_D^{20}$: −442° ($c = 1$, MeOH); IR (KBr, cm^{-1}): 3230, 2920, 1680, 1600, 1580, and 1260; ^{1}H NMR (DMSO-d_6, δ ppm): 1.10 (3H, d, $J = 7$), 2.28 (1H, d, $J = 1$), 2.71 (1H, dd, $J = 7$), 3.44 (1H, m, $J = 7.5$), 6.98 (2H, m, $J = 7$), 7.43 (1H, m, $J = 7$), 7.47 (2H, d, $J = 7.5$), 7.67 (1H, d, $J = 7$), 7.87 (2H, d, $J = 7.7$), 9.00 (1H, s), 10.94 (1H, s), and 12.94 (1H, s); MS: *m/z* 307 (M^+), 221, 203, 115, 132, 292, 236, 250, 264, 102, 77, 65, 57, and 41; elemental analysis (%): calculated: C, 70.34; H, 5.58; N, 13.67; found: C, 70.38; H, 5.62; N, 13.66.

*R(−)-6-[4-(2-chlorobenzal)amino]phenyl-5-methyl-4,5-dihydro-3(2H)-pyridazinone (compound **1f**)*

Yield: 78%; m.p.: 163–164°C; $[\alpha]_D^{20}$: −415° ($c = 1$, MeOH); IR (KBr, cm^{-1}): 3200, 3080, 2960, 1680, 1600, 1580, 1500, 1330, and 750; ^{1}H NMR (DMSO-d_6, δ ppm): 1.08 (3H, d, $J = 7$), 2.28 (1H, d, $J = 1$), 2.70 (1H, dd, $J = 7$), 3.43 (1H, m, $J = 7.5$), 7.34 (2H, d, $J = 1.5, 7.7$), 7.48 (1H, m, $J = 2, 7.8$), 7.57 (2H, m, $J = 2, 7.5$), 7.85 (2H, d, $J = 7$), 8.17 (1H, d, $J = 2, 7.7$), 8.89 (1H, s), and 10.93 (1H, s); MS: *m/z* 325 (M^+), 115, 310, 268, 254, 129, 239, 102, 141, 89, and 75; elemental analysis (%): calculated: C, 66.36; H, 4.95; N, 12.90; found: C, 66.17; H, 5.00; N, 12.88.

*R(−)-6-[4-(3,4,5-trimethoxybenzal)amino]phenyl-5-methyl-4,5-dihydro-3(2H)-pyridazinone (compound **1g**)*

Yield: 83%; m.p.: 165–167°C; $[\alpha]_D^{20}$: −318° ($c = 1$, MeOH); IR (KBr, cm^{-1}): 3330, 2960, 1690, 1600, 1580, 1500, 1320, and 1120; ^{1}H NMR (DMSO-d_6, δ ppm): 1.11 (3H, d, $J = 7$), 2.26 (1H, d, $J = 16.5$), 2.70 (1H, dd, $J = 7$), 3.42 (1H, m, $J = 6.5$), 3.76 (6H, s), 3.87 (3H, s), 7.30 (2H, s), 7.48 (2H, d, $J = 2, 7$), 7.83 (2H, d, $J = 2, 7$), 8.57 (1H, s), and 10.92 (1H, s); MS: *m/z* 381 (M^+), 115, 366, 324, 309, 102, 271, 91, and 77; elemental analysis (%): calculated: C, 66.13; H, 6.08; N, 11.01; found: C, 66.02; H, 6.01; N, 11.04.

*R(−)-6-[4-(3,4-dichlorobenzal)amino]phenyl-5-methyl-4,5-dihydro-3(2H)-pyridazinone (compound **1h**)*

Yield: 86%; m.p.: 158–160°C; $[\alpha]_D^{20}$: −348° ($c = 1$, MeOH); IR (KBr, cm^{-1}): 3210, 3100, 2960, 1680, 1600, 1580, 1500, and 1320; ^{1}H NMR (DMSO-d_6, δ ppm); 1.12 (3H, d, $J = 7.5$), 2.29 (1H, d, $J = 1$), 2.70 (1H, dd, $J = 7$), 3.42 (1H, m, 6.5), 7.34 (2H, d, $J = 4.5$), 7.76 (1H, d, $J = 8.5$), 7.85 (2H, d, $J = 7$), 7.92 (1H, dd, $J = 2, 8.5$), 8.14 (1H, s), 8.67 (1H, s), and 10.93 (1H, s); MS: *m/z* 360(M^+), 115, 245, 303, 288, 102, 248, 77, and 51; elemental analysis (%): calculated: C, 60.01; H, 4.20; N, 11.66; found: C, 60.08; H, 4.39; N, 11.70.

*R(−)-6-[4-(2-pyridinylmethylene)amino]phenyl-5-methyl-4,5-dihydro-3(2H)-pyridazinone (compound **1i**)*

Yield: 83%; m.p.: 210–211°C; $[\alpha]_D^{20}$: −422° ($c = 1$, MeOH); IR (KBr, cm^{-1}): 3200, 3100, 3060, 1680, 1300, 1600, 1580, and 1500; ^{1}H NMR (DMSO-d_6, δ ppm): 1.11 (3H, d, $J = 7$), 2.26 (1H, d, $J = 17$), 2.70 (1H, dd, $J = 7$), 3.44 (1H, m, $J = 7$), 7.39 (2H, d, $J = 8.5$), 7.54 (1H, m, $J = 7$), 7.87 (2H, d, 8.5), 7.95 (2H, m, $J = 7.5$), 8.18 (1H, d, $J = 8$), 8.63 (1H, s), 8.82 (1H, d, $J = 6.5$), and 10.93 (1H, s); MS: *m/z* 292 (M^+), 79, 180, 206, 45, 105, 115, 221, 248, 235, 276, 264, 167, and 128; elemental analysis (%): calculated: C, 69.85; H, 5.52; N, 19.16; found: C, 69.83; H, 5.78; N, 19.22.

*R(−)-6-[4-(phenylvinylmethylene)amino]phenyl-5-methyl-4,5-dihydro-3(2H)-pyridazinone (compound **1j**)*

Yield: 81%; m.p.: 217–219°C; $[\alpha]_D^{20}$: −422° ($c = 1$, MeOH); IR (KBr, cm^{-1}): 3200, 3100, 2960, 1680, 1600, 1580, and 1500; ^1H NMR (DMSO-d_6, δ ppm): 1.10 (3H, d, $J = 7$), 2.27 (1H, d, $J = 16$), 2.68 (1H, dd, $J = 7$), 3.41 (1H, m, $J = 7$), 6.85 (1H, m, $J = 8$), 7.13 (1H, m, $J = 9$), 7.24 (2H, d, $J = 2$, 9), 7.42 (2H, m, 7.5), 7.70 (2H, m, $J = 7$), 7.82 (2H, d, $J = 6.5$), 8.43 (1H, d, $J = 8.5$), 9.67 (1H, d, $J = 8$), and 10.90 (1H, s); MS: *m/z* 316 (M^+), 300, 231, 115, 44, 102, 77, 91, 128, 137, 205, and 57; elemental analysis (%): calculated: C, 75.69; H, 6.03; N, 13.24; found: C, 75.76; H, 5.78; N, 13.21.

*R(−)-6-[4-(2-furanylmethylene)amino]phenyl-5-methyl-4,5-dihydro-3(2H)-pyridazinone (compound **1k**)*

Yield: 73%; m.p.: 175–177°C; $[\alpha]_D^{20}$: −465° ($c = 1$, MeOH); IR (KBr, cm^{-1}): 3200, 3100, 1680, 1600, 1580, and 1500; ^1H NMR (DMSO-d_6, δ ppm): 1.10 (3H, d, $J = 7$), 2.27 (1H, d, $J = 16$), 2.69 (1H, dd, $J = 7$), 3.41 (1H, m, $J = 7.5$), 6.77 (1H, m, $J = 3.5$), 7.18 (1H, d, $J = 3.5$), 7.30 (2H, d, 6.5), 7.82 (2H, d, $J = 7$), 7.95 (1H, d, $J = 1$), 8.48 (1H, s), and 10.91 (1H, s); MS: *m/z* 281 (M^+), 68, 94, 224, 209, and 266; elemental analysis (%): calculated: C, 68.31; H, 5.37; N, 14.94; found: C, 68.29; H, 5.51; N, 15.11.

Biological activity

The tracheal intubation method of measuring blood pressure was used to evaluate preliminary anti-CHF activity. The trachea were separated from anesthetized rats with urethane (5 ml/kg) and intubated. The carotid of the rats was separated and then connected to a biological function examination system, BL-420E. 2% solutions of levosimendan and the target compounds with 1% CMC were then inserted in the rats' duodenums (50 mg/kg). Blood pressure values were recorded and analyzed statistically (Table 1).

Acknowledgment This study was supported by the Scientific Research Startup Foundation of the Chinese Ministry of Education for Returnees (*jiaowaisiliu*[2007]1108).

References

Abouzid KAM, Khalil NA, Ahmed EM et al (2009) Structure-based molecular design, synthesis, and in vivo anti-inflammatory activity of pyridazinone derivatives as nonclassic COX-2 inhibitors. Med Chem Res. doi:10.1007/s00044-009-9218-4

Ali MA, Yar MS (2007) Synthesis and antimycobacterial activity of novel 4-[5-(substituted phenyl)-1-phenyl-4,5-dihydro-1H-3-pyrazolyl]-2-methyl phenol derivatives. Med Chem Res 15:463–470. doi:10.1007/s00044-007-9000-4

Austel V, Herder J, Eberlein W et al (1982) Pyridazinone-substituted benzimidazoles and salts. US Patent 4361563

Bäckström RJ, Haarala JV, Honkanen EJ et al (1992) (−)-[[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]-hydrazono]propanedinitrile. UK Patent 2251615A

Bansal R, Kumar D, Carron R et al (2009) Synthesis and vasodilatory activity of some amide derivatives of 6-(4-carboxymethyloxyphenyl)-4,5-dihydro-3(2H)-pyridazinone. Eur J Med Chem. doi:10.1016/j.ejmech.2009.06.006

Bristol JA, Sircar L, Moos WH et al (1984) 4,5-Dihydro-6-[4-(1H-imidazol-1-yl)phenyl]-3(2H)-pyridazinones: novel positive inotropic agents for the treatment of congestive heart failure. J Med Chem 27(9):1099–1103

Cherng SC, Huang WH, Shiau CY et al (2006) Mechanisms of antiplatelet activity of PC-90, a newly synthesized pyridazinone derivative. Eur J Pharmacol 532:32–37

Gottdiener JS, Arnold AM, Aurigemma GP et al (2000) Predictors of congestive heart failure in the elderly: the cardiovascular health study. JACC 35(6):1628–1637

Hayes JS, Pollock GD, Wilson H et al (1987) Pharmacology of LY195115, a potent, orally active cardiotonic with a long drug of action. J Cardiovasc Pharmacol 9:425–434

Hosenpud JD (1999) Levosimendan, a novel myofilament calcium sensitizer, allows weaning of parenteral inotropic therapy in patients with severe congestive heart failure. Am J Cardiol 83:9(I)–11(I)

Krum H, Liew D (2003) New and emerging drug therapies for the management of acute heart failure. Intern Med J 33(11):515–520

McCullough PA, Philbin EF, Spertus JA et al (2002) Confirmation of a heart failure epidemic: findings from the Resource Utilization among Congestive Heart Failure (REACH) study. J Am Coll Cardiol 39(1):60–69

Nieminen MS, Bohm M, Cowie MR et al (2005) Executive summary of the guidelines on the diagnosis and treatment of acute heart failure: the task force on acute heart failure of the European Society of Cardiology. Eur Heart J 26(4):384–416

Nobuo M, Seiichi U, Hiroo M (1993) Cardiovascular effects of NSP-804 and NSP-805, novel cardiotonic agents with vasodilator properties. J Cardiovasc Pharmacol 21(6):983–995

Thota S, Bansal R (2009) Synthesis of new pyridazinone derivatives as platelet aggregation inhibitors. Med Chem Res. doi:10.1007/s00044-009-9232-6