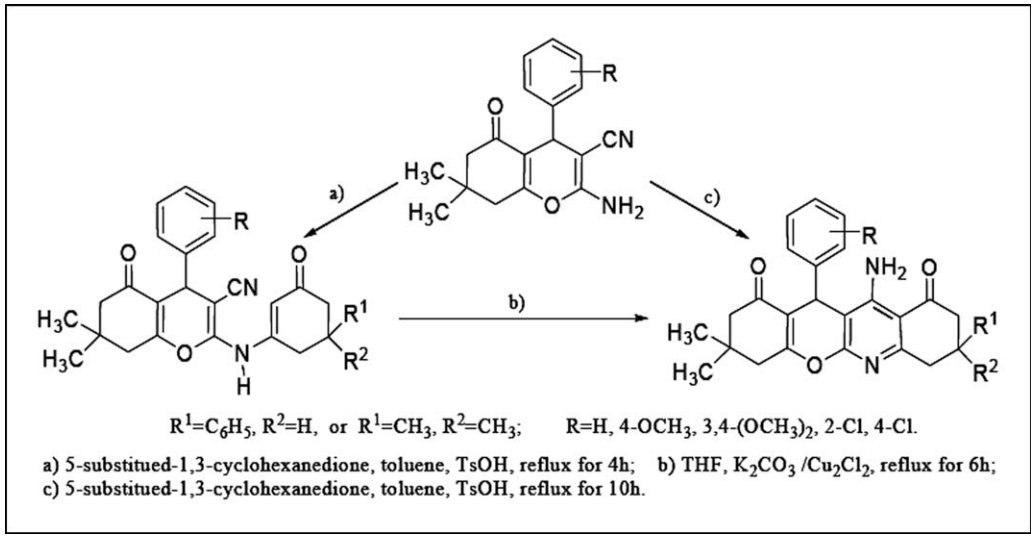
Guangfan Han,* Bin Cui, Lizhuang Chen, and Yan Jin

School of Material Science and Engineering, Jiangsu University of Science and Technology, Zhenjiang, Jiangsu 212003, China
*E-mail: gf552002@yahoo.com.cn

Received December 29, 2009
DOI 10.1002/jhet.470
Published online 23 August 2010 in Wiley Online Library (wileyonlinelibrary.com).



A series of novel 11-amino-3,3-dimethyl-8-substituted-12-aryl-3,4,7,8,9,12-hexahydro-2*H*-benzopyran[2,3-*b*]quinoline-1,10-dione derivatives **4** were synthesized by 2-amino-3-cyano-4-aryl-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyran **2** with 5-substituted-1,3-cyclohexanedione using *p*-toluenesulfonic acid, K_2CO_3, and Cu_2Cl_2 as catalysts. The compounds **2** as easily accessible precursors were obtained from 5,5-dimethyl-1,3-cyclohexanedione by Michael addition with β-dicyanostyrenes **1**, prepared by Knoevenagel condensation of different aromatic aldehydes and malononitrile. The synthesis of the title compounds **4** completed by one-pot reaction of 4-aryl-4*H*-benzopyran derivatives with 5-substituted-1,3-cyclohexanediones by refluxing in toluene using TsOH as catalyst. The structures of all compounds were characterized by elemental analysis, IR, MS, and ^{1}H NMR spectra.

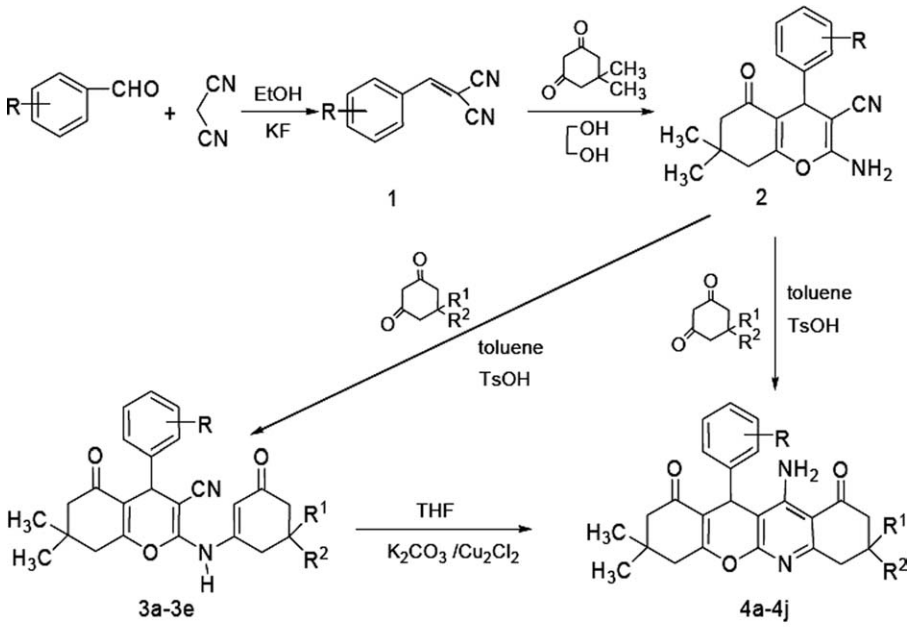
J. Heterocyclic Chem., **47**, 1335 (2010).

INTRODUCTION

Many of the multirings occurring products containing simultaneously oxygen and nitrogen atoms on their carbon frameworks display various pharmacological activities [1]. Tacrine, a potent and reversible AChE inhibitor, was the first drug approved in the United States for the palliative treatment of Alzheimer's disease [2]. Jose [2] reported some new multipotent tetracyclic tacrine analogs, which had the similar structure with the title compounds and these tacrine analogs are modest AChE inhibitors but proved to be very selective. And some of them show a significant neuroprotective effect on neuroblastoma cells subjected to Ca^{2+} overload or free radical induced toxicity. In addition, these compounds bind AChE to the peripheral anionic site of AChE. And, consequently, are potential agents that can prevent the aggregation of *b*-amyloid.

Among which benzopyran[2,3-*b*]quinolinone not only possesses the structure of benzopyran but also contains a quinoline ring. Benzopyran, as the parent ring of many natural products, are widely found in the nature. Their derivatives have been approved to possess good biological activity, and also exhibit antitumor activity. In addition, benzopyran derivatives could serve as the moderator for the potassium ion channel [3–5]. Quinoline belongs to the class benzopyridines (a class with six-membered nitrogened heterocyclic-fused polycyclic rings). The compounds of quinoline with aromatic or heterocyclic compounds have rigid planar with a conjugated structure. These compounds exhibit strong fluorescence properties as well as a variety of biological activities. They can be used by DNA and other biological macromolecules to embed into the body, and also can be served as the fluorescent probes and synthetic drugs. They have been widely used in the medical and molecular biology [6]. Nitrogen-containing

Scheme 1



3a: R^1=C_6H_5, R^2=H, R=H; 3b: R^1=C_6H_5, R^2=H, R=4-OCH_3;
3c: R^1=C_6H_5, R^2=H, R=3,4-$(OCH_3)_2$; 3d: R^1=CH_3, R^2=CH_3, R=4-OCH_3;
3e: R^1=CH_3, R^2=CH_3, R=4-Cl;
4a: R^1=C_6H_5, R^2=H, R=H; 4b: R^1=C_6H_5, R^2=H, R=4-OCH_3;
4c: R^1=C_6H_5, R^2=H, R=3,4-$(OCH_3)_2$; 4d: R^1=CH_3, R^2=CH_3, R=4-OCH_3;
4e: R^1=CH_3, R^2=CH_3, R=4-Cl; 4f: R^1=C_6H_5, R^2=H, R=4-Cl;
4g: R^1=C_6H_5, R^2=H, R=2-Cl; 4h: R^1=CH_3, R^2=CH_3, R=H;
4i: R^1=CH_3, R^2=CH_3, R=3,4-$(OCH_3)_2$; 4j: R^1=CH_3, R^2=CH_3, R=2-Cl.

heterocyclic compounds have shown a strong trend of development and broad application prospects in the fields of sterilization, anti-malaria, and anti-malignant tumor [7].

To search for medicinal compounds, and enrich the tetracyclic compounds, we first synthesized a series of new six-membered tetracyclic compounds, benzopyran [2,3-*b*]quinolinone derivatives with oxygen and nitrogen atoms inlaying in the ring.

RESULTS AND DISCUSSION

11-Amino-12-aryl-2,3,4,7,8,9,10,12-octahydro-3,3-dimethyl-1*H*-chromeno[2,3-*b*]quinoline-1-one derivatives have been synthesized by 4-aryl-4*H*-chromenes and cyclohexanone using $AlCl_3$ as catalyst in 1,2-dicholonethane [2]. Pyrano[2,3-*b*]pyridines were achieved by the Friedlander reaction of 2-amino-3-cyano-4*H*-pyrans with cyclopentanone/cyclohexanone using $SnCl_2{\cdot}2H_2O$ under solvent-free condition [8]. Both methods have been tried in our investigation, but they are found to suffer from several drawbacks, such as low yield, no reaction, more byproducts, and long reaction time. Compared with these methods, our method has many advantages, such as higher yield, shorter reaction time, less side reaction and so on. In this study, β-dicyanostyrene **1** were prepared as building block from aromatic aldehyde, malononitrile in dry ethanol with $KF{\cdot}2H_2O$ as catalyst. And 4-aryl-4*H*-benzopyran derivatives **2** were synthesized by β-dicyanostyrene and 5,5-dimethyl-1,3-cyclohexanedione in ethylene glycol. The intermediate enamines **3** were obtained by condensation reaction of compounds **2** with 5-substituted-1,3-cyclohexanedione using *p*-toluenesulfonic acid as catalyst in toluene. 11-Amino-3,3-dimethyl-8-substituted-12-aryl-3,4,7,8,9,12-tetrahydro-2*H*-benzopyran[2,3-*b*]quinoline-1,10-dione derivatives **4** were synthesized by cyclization of the intermediate enamines **3** in the presence of K_2CO_3 and Cu_2Cl_2 [9,10]. Meanwhile, these series of novel compounds **4** could also be obtained via a one-step reaction by 4-aryl-4*H*-benzopyran **2** with 5-substituted-1,3-cyclohexanedione, using *p*-toluenesulfonic acid as catalyst in toluene. The synthetic pathway was shown in Scheme 1.

Each of compounds **4a–c**, **4f–g** should be as a diastereomeric mixture. It was speculated from the ^{1}H NMR spectrum that the yields of the major product was above 90%. The diastereomeric were difficult to be isolated by silica gel flash chromatography, and therefore, the major product was purified by multiple-step crystallizing. As

Table 1

Synthesis of 2-*N*-(5-Substituted-3-oxo-1-cyclohexanyl)-amino-3-cyano-4-aryl-5,6,7,8-tetrahydro-5-oxo-benzopyran (compounds **3**).

Entry	R^1	R^2	R	Yield (%)
3a	C_6H_5	H	H	60.2
3b	C_6H_5	H	4-OCH_3	45.3
3c	C_6H_5	H	3,4-$(OCH_3)_2$	64.8
3d	CH_3	CH_3	4-OCH_3	48.5
3e	CH_3	CH_3	4-Cl	50.6

shown in the ^{1}H NMR spectrum, it was a single peak for the C12—H. The specific stereostructure of the main product need to be further studied.

The data of ^{1}H NMR, MS, and IR shown in the experimental section are in accordant with the chemical structures of the target compounds. In the ^{1}H NMR spectrum of compound **3a**, the broad single proton peaks at δ 6.38 was the characteristic absorption proton peak of the amino group. The single peak at δ 5.84 was the typical proton peak of the vinyl group. In the ^{1}H NMR spectrum of compound **4a**, two broad single peaks at δ 5.07 and δ 9.14 were observed. They disappeared after D_2O exchange, and therefore, were attributed to the two N—H of the amino group. Because of the existing of intramolecular hydrogen bond between one proton of the amino group and the oxygen atom of the carbonyl group nearby, its proton peak was drifted to δ 9.14. The structures of these compounds were further supported by their IR spectra. Server typical absorption bands at 2204 cm^{-1} for **3a** (C≡N), 1655 cm^{-1} for **4a** (C—O), and 3410 cm^{-1} for (N—H) were observed, respectively.

CONCLUSIONS

During our investigate, it is found that the toluene, TSOH, and raw materials are drier, the corresponding yields are more excellent and the side reactions are less; and when the ratio of 4-aryl-4*H*-benzopyran derivatives and 5-substituted-1,3-cyclohexanedione is 1:1.2, it can give the corresponding products in best yields. It is also found that the intermediate enamines **3** can be obtained using 4-aryl-4*H*-benzopyran derivatives and 5-substituted-1,3-cyclohexanedione in water with catalytic amount of HCl, and the corresponding yields are also relatively high, however, the side reactions are more. Therefore, using this method to synthesize our target compounds need to be further investigated.

In summary, during the synthesis of benzopyran[2,3-*b*]quinolinone derivatives, we used two methods and both could obtain the target compounds. Compared with the two methods, the method B extended the first step reaction time based on the method A. But we achieved one-step ring closure, reduced the kinds of catalysts and organic solvents, and shortened the total reaction time. Both the method and the benzopyran[2,3-*b*]quinolinone derivatives have not been reported. The purpose to enrich the tetracyclic heterocyclic compounds was achieved. These compounds contain atoms and groups that they can be modified according to the need, which can conduct further reaction.

EXPERIMENTAL

Melting points were determined on an electrothermal apparatus and the temperature was not calibrated. Microanalysis was performed by the Perkin-Elmer 2400 Microanalytical Service. Infrared spectra were recorded as thin films on KBr using a Perking-Elmer 1700 spectrophotometer. The NMR spectra were recorded by a Bruker ARX-300 spectrometer. Sample solutions were prepared in $CDCl_3$ or DMSO containing TMS as an internal reference. Mass spectra were recorded by JMS-DX300 at 70 eV. All chemical reagents were commercially available and purified with standard methods before use. Solvents were dried in routine ways and redistilled. 5-Substituted-1,3-cyclohexanedione were obtained from aromatic aldehyde, acetone and diethyl malonate according to the literature [1] method with slightly modification.

General method for the synthesis of β-dicyanostyrene(1). To a solution of the corresponding aldehyde (1 equiv) in dry ethanol (1 mL/mmol), malonodinitrile (1 equiv), and a catalytic amount of $KF{\cdot}2H_2O$ [11] were added. The mixture was stirred at 60°C for 2–4 h. Then, the reaction mixture was cooled to rt. To this mixture was added 100 mL water and the precipitated solid was isolated by filtration, washed with cold ethanol, recrystallized from 95% ethanol.

General method for the synthesis of 2-Amino-3-cyano-4-aryl-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyran(2). To a solution of the corresponding β-dicyanostyrene (1 equiv) in ethylene glycol (1 mL/mmol), 5,5-dimethyl-1,3-cyclohexanedione (1 equiv) were added. The mixture was stirred at 80°C for 2–4 h. Then, the resultant mixture was cooled to rt. To this mixture was added 100 mL water and the precipitated solid was isolated by filtration, washed with water, recrystallized from methanol.

General method for the synthesis of 2-*N*-(5-substituted-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-aryl-7,7-dimethyl-5,6,7,8-tetrahydro-5-oxo-4*H*-benzopyran (3a–3e). 2-Amino-3-cyano-4-aryl-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4*H*-benzopyran (1 equiv) and 5-substituted-1,3-cyclohexanedione (1.2 equiv) were suspended in toluene (1 mL/mmol) containing *p*-

Table 2

Synthesis of 11-amino-3,3-dimethyl-8-substituted-12-aryl-3,4,7,8,9,12-hexahydro-2*H*-benzopyran[2,3-*b*]quinoline-1,10-dione (compounds **4**).

Entry	R^1	R^2	R	Yield (%)
4a	C_6H_5	H	H	59.6
4b	C_6H_5	H	4-OCH_3	57.6
4c	C_6H_5	H	3,4-$(OCH_3)_2$	40.8
4d	CH_3	CH_3	4-OCH_3	54.5
4e	CH_3	CH_3	4-Cl	73.5
4f	C_6H_5	H	4-Cl	65.5
4g	C_6H_5	H	2-Cl	62.3
4h	CH_3	CH_3	H	59.6
4i	CH_3	CH_3	3,4-$(OCH_3)_2$	56.8
4j	CH_3	CH_3	2-Cl	55.4

toluenesulfonic acid monohydrate (0.2 equiv). The mixture was refluxed for 4 h and the water was collected in a Dean-Stark water separator. At the end of the reaction, the reaction mixture was chilled to rt and the compound was filtered off. The yellow powder was recrystallized from ethyl acetate.

General method for the synthesis of 11-amino-3,3-dimethyl-8-substituted-12-aryl-3,4,7,8,9,12-tetrahydro-2*H*-benzopyran [2,3-*b*]quinoline-1,10-dione(4a–4j). ***Method A.*** 2-*N*-(5-Substituted-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-aryl-5,6,7,8-tetrahydro-5-oxo-4*H*-benzopyran (1 equiv) was added to tetrahydrofuran (1 mL/mmol) containing potassium carbonate (0.5 equiv) and cuprous chloride (0.25 equiv). The reaction mixture was refluxed for 6 h and the hot mixture was filtered into hexane (2 mL/mmol). The precipitated was filtered off and washed with ethanol. The yellow powder was purified by silica gel flash chromatography using ethyl acetate/hexane mixture(1:2) as eluent to give purecompounds. The compounds **4a–4e** were synthesized by this method.

Method B. In this study, we discovered that these series of novel compounds **4** could also be obtained via a one-step reaction by 4-aryl-4*H*-benzopyran **2** with 5-substituted-1,3-cyclohexanedione, using *p*-toluenesulfonic acid as catalyst in toluene refluxed for 10 h. Then, the hot mixture was filtered into hexane (2 mL/mmol). The precipitated was filtered off and washed with ethanol. The yellow powder was purified by silica gel flash chromatography using ethyl acetate/hexane mixture (1:2) as eluent to give pure compounds. The compounds **4f–j** were synthesized by this method. Data of compounds are shown below.

*2-N-(5-phenyl-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-pheny-7, 7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-benzopyran (**3a**).* Yield: 60.2%, m.p. 214–216°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.03(s, 3H, CH_3), 1.15(s, 3H, CH_3), 2.51–2.82(m, 6H, 8-, 4′-, and 6′-H), 3.38–3.41(m, 1H, 5′-H), 4.50(s, 1H, 4-H), 5.84(s, 1H, 2′-H), 6.38(br s, 1H, NH), 7.21–7.40(m, 10H, Ph-H); IR (KBr) υ: 3464(NH), 1687(C=O), 2204(C≡N); MS (70 eV) *m*/*z* (%): 465.0 (M+1, 100); *Anal*. calcd. for $C_{30}H_{28}N_2O_3$: C 77.56, H 6.08, N 6.03; found C 77.50, H 5.98, N 6.15.

*2-N-(5-phenyl-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-(4-methoxy-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8- tetrahydro-4H-benzopyran (**3b**).* Yield: 55.3%, m.p. 224–226°C; ^{1}H NMR (DMSO, 300 MHz) δ: 1.03(s, 3H, CH_3), 1.13(s, 3H, CH_3), 2.07–2.22(m, 4H, 6-, and 8-H), 2.27–2.49(m, 4H, 4′-, and 6′-H), 3.34–3.45(m, 1H, 5′-H), 3.71(s, 3H, OCH_3), 4.41(s, 1H, 4-H), 4.85(s, 1H, 2′-H), 5.84(br s, 1H, NH), 6.83–7.11(m, 8H, Ph-H); IR (KBr) υ: 3399(NH), 1719(C=O), 2254(C≡N); MS (70 eV) *m*/*z* (%): 495.2 (M + 1, 100).

*2-N-(5-phenyl-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-(3,4-dimethoxy-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-benzopyran (**3c**).* Yield**:** 64.8%, m.p. 188–190°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.07(s, 3H, CH_3), 1.15(s, 3H, CH_3), 2.27–2.58(m, 2H, 8-H), 2.61–2.76(m, 6H, 6-, 4′-, and 6′-H), 3.42–3.45(m, 1H, 5′-H), 3.84(s, 3H, OCH_3), 3.86(s, 3H, OCH_3), 4.44(s, 1H, 4-H), 5.83(s, 1H, 2′-H), 5.87(br s, 1H, NH), 6.71–7.40(m, 8H, Ph-H); IR (KBr) υ: 3442(NH), 1682(C=O), 2205(C≡N); MS (70eV) *m*/*z* (%): 525.3 (M + 1, 100); *Anal*. calcd. for $C_{32}H_{32}N_2O_5$: C 73.26, H 6.15, N 5.34; found C 73.39, H 6.22, N 5.20.

*2-N-(5,5-dimethyl-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-(4-methoxy-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-benzopyran (**3d**).* Yield: 48.5%, m.p. 192–194°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.04(s, 3H, CH_3), 1.10(s, 6H, 2 × CH_3), 1.26(s, 3H, CH_3), 2.18–2.31(m, 6H, 8-, 4′-, and 6′-H), 2.54(s, 2H, 6-H), 3.78(s, 3H, OCH_3), 4.45(s, 1H, 4-H), 5.79(s, 1H, 2′-H), 6.45(br s, 1H, NH), 6.82–7.18(m, 5H, Ph-H); IR (KBr) υ: 3460(NH), 1672(C=O), 2210(C≡N); MS (70 eV) *m*/*z* (%): 447.2 (M + 1, 100); *Anal*. calcd. for $C_{27}H_{30}N_2O_4$: C 72.62, H 6.77, N 6.27; found C 72.50, H 6.69, N 6.35.

*2-N-(5,5-dimethyl-3-oxo-1-cyclohexenyl)-amino-3-cyano-4-(4-chlorine-phenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-benzopyran (**3e**).* Yield: 50.6%, m.p. 194–196°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.04(s, 3H, CH_3), 1.12(s, 6H, 2 × CH_3), 1.14(s, 3H, CH_3), 2.19–2.32(m, 6H, 8-, 4′-, and 6′-H), 2.56(s, 2H, 6-H), 4.48(s, 1H, 4-H), 5.82(s, 1H, 2′-H), 6.21(br s, 1H, NH), 7.17–7.32(m, 5H, Ph-H); IR (KBr) υ: 3385(NH), 1719(C=O), 2238(C≡N); MS (70 eV) *m*/*z* (%): 449.9 (M^+, 100).

*11-amino-3,3-dimethyl-8,12-diphenyl-3,4,7,8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4a**).* Yield: 59.6% .m.p. 244–246°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.96(s, 3H, CH_3), 1.10(s, 3H, CH_3), 2.17–2.30(m, 2H, 4-H), 2.57(s, 2H, 2-H), 2.75–2.92(m, 2H, 9-H), 3.09–3.29(s, 2H, 7-H), 3.39–3.50(m, 1H, 8-H), 4.85 (s, 1H, 12-H), 5.07(br s, 1H, NH),7.17–7.38(m, 10H, Ph-H), 9.14(br,s, 1H, N-H); IR (KBr) υ: 3410, 1655, 1167, 1125 cm^{-1}; MS (70 eV) *m*/*z* (%): 465.2 (M + 1, 100); *Anal*. calcd. for $C_{30}H_{28}N_2O_3$: C 77.56, H 6.08, N 6.03; found C 77.44, H 6.15, N 5.96.

*11-amino-3,3-dimethyl-8-phenyl-12-(4-methoxy-phenyl)-3,4,7,8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4b**).* Yield: 57.6 % , m.p. 210–212°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.98(s, 3H, CH_3), 1.10(s, 3H, CH_3), 2.17–2.30(m, 2H, 4-H), 2.56(s, 2H, 2-H), 2.75–2.93(m, 2H, 9-H), 3.09–3.31(m, 2H, 7-H), 3.39–3.51(m, 1H, 8-H), 3.75(s, 3H, OCH_3), 4.81(s, 1H, 12-H), 5.10(br s, 1H, NH),6.79–7.39(m, 9H, Ph-H), 9.16(br s, 1H, NH); IR (KBr) υ: 3450, 1654, 1182, 1029 cm^{-1}; MS (70 eV) *m*/*z* (%): 495.2 (M + 1, 100); *Anal*. calcd. for $C_{31}H_{30}N_2O_4$: C 75.28, H 6.11, N 5.66; found C 75.21, H 6.21, N 5.58.

*11-amino-3,3-dimethyl-8-phenyl-12-(3,4-dimethoxy-phenyl)-3,4,7,8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4c**).* Yield: 40.8%, m.p. 216–218°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.03(s, 3H, CH_3), 1.11(s, 3H, CH_3), 2.16–2.30(m, 2H, 4-H), 2.56(s, 2H, 2-H), 2.76–2.95(m, 2H, 9-H), 3.09–3.30(m, 2H, 7-H), 3.37–3.51(m, 1H, 8-H), 3.75(s, 3H, OCH_3), 3.80(s, 3H, OCH_3),4.81(s, 1H, 12-H), 5.16(br s, 1H, NH), 6.89–7.38(m, 8H, Ph-H), 9.26(br s, 1H, NH); IR (KBr) υ: 3430, 1640, 1180, 1025cm^{-1};MS (70 eV) *m*/*z* (%): 525.3 (M + 1, 100).

*11-amino-3,3,8,8-tetramethyl-12-(4-methoxy-phenyl)-3,4,7,8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4d**).* Yield: 54.5%, m.p. 230–232°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.00(s, 6H, 2 × CH_3), 1.10(s, 6H, 2 × CH_3), 2.14–2.27(m, 4H, 4-H, 7-H), 2.46(s, 4H, 2-H, 9-H), 3.74(s, 3H, OCH_3), 4.70(s, 2H, 12-H), 5.15(br s, 1H, NH), 6.74–7.22(m, 4H, Ph-H), 9.13(br s, 1H, NH); IR (KBr) υ: 3448, 1668, 1195, 1137 cm^{-1}; MS (70 eV) *m*/*z* (%): 447.2 (M + 1, 100).

*11-amino-3,3,8,8-tetramethyl-12-(4-chlorine-phenyl)-3,4,7,8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4e**).* Yield: 73.5%, m.p. 236–238°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.96(s, 3H, CH_3), 1.08(s, 3H, CH_3), 1.09(s, 3H, CH_3), 1.10(s, 3H, CH_3), 2.16–2.29(m, 2H, 4-H), 2.45(s, 2H, 2-H), 2.56(s, 2H, 9-H), 2.83(s, 2H, 7-H), 4.82(s, 1H, 12-H), 5.09(br s, 1H, NH), 7.22–7.30(m, 4H, Ph-H), 9.10(br s, 1H, NH); IR (KBr) υ: 3484, 1654, 1184, 1126 cm^{-1}; MS (70 eV) *m*/*z* (%): 449.9 (M^+, 100).

*11-amino-3,3-dimethyl-8-phenyl-12-(4-chlorine-phenyl)-3,4,7, 8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4f**)*. Yield: 65.5%, m.p. 230–232°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.97(s, 3H, CH_3), 1.11(s, 3H, CH_3), 2.17–2.30(m, 2H, 4-H), 2.57(s, 2H, 2-H), 2.82–2.88(m, 2H, 9-H), 3.14–3.24(m, 2H, 7-H), 3.44–3.47(m, 1H, 8-H), 4.84(s, 1H, 12-H), 5.10(br s, 1H, NH), 7.23–7.39(m, 9H, Ph-H), 9.17(br s, 1H, NH); IR (KBr) υ: 3484, 1656, 1216, 1168 cm^{-1}; MS (70 eV) *m*/*z* (%): 499.2(M + 1, 100); *Anal*. calcd. for $C_{30}H_{27}N_2O_3Cl$: C 72.21, H 5.45, N 5.61; found C 72.13, H 5.36, N 5.70.

*11-amino-3,3-dimethyl-8-phenyl-12-(2-chlorine-phenyl)-3,4,7, 8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4g**)*. Yield: 62.3%, m.p. 184–186°C; ^{1}H NMR ($CDCl_3$, 300MHz) δ: 1.01(s, 3H, CH_3), 1.13(s, 3H, CH_3), 2.17–2.32(m, 2H, 4-H), 2.63(s, 2H, 2-H), 2.82–2.88(m, 2H, 9-H), 3.08–3.25(m, 1H, 8-H), 3.37–3.50(m, 2H, 7-H), 5.26(s, 1H, 12-H), 5.73(br s, 1H, NH), 7.15–7.36(m, 9H, Ph-H), 9.39(br s, 1H, NH); IR (KBr) υ:3476, 1655, 1169,1138 cm^{-1}; MS (70eV) *m*/*z* (%): 499.2(M + 1, 100).

*11-amino-3,3,8,8-tetramethyl-12-phenyl-3,4,7,8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4h**)*. Yield: 59.6%, m.p. 246–248°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.98(s, 6H, 2 × CH_3), 1.10(s, 6H, 2 × CH_3), 2.22–2.24(m, 2H, 4-H), 2.44(s, 2H, 2-H), 2.59(s, 2H, 9-H), 2.86(s, 2H, 7-H), 4.83(s, 1H, 12-H), 5.09(br s, 1H, NH),7.17–7.36(m, 5H, Ph-H), 9.10(br s, 1H, NH); IR (KBr) υ: 3422, 1660, 1195,1152 cm^{-1}; MS (70 eV) *m*/*z* (%): 417.1 (M + 1, 100); *Anal*. calcd. for $C_{26}H_{28}N_2O_3$: C 74.97, H 6.78, N 6.73; found C 74.93, H 6.72, N 6.82.

*11-amino-3,3,8,8-tetramethyl-12-(3,4-dimethoxy-phenyl)-3,4,7, 8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4i**)*. Yield: 56.8%, m.p. 266-268°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.01(s, 6H, 2 × CH_3), 1.11(s, 6H, 2 × CH_3), 2.15–2.28(m, 4H, 4-H, 7-H), 2.46(s, 4H, 2-H, 9-H), 3.80(s, 3H, OCH_3), 3.86(s, 3H, OCH_3) 4.71(s, 2H, 12-H), 5.18(br s, 1H, NH), 6.74–6.91(m, 3H, Ph-H), 9.12(br s, 1H, NH); IR (KBr) υ: 3415, 1649, 1186,1125 cm^{-1}; MS (70 eV) *m*/*z* (%):477.2 (M + 1, 100).

*11-amino-3,3,8,8-tetramethyl-12-(2-chlorine-phenyl)-3,4,7, 8,9,12-tetrahydro-2H-benzopyran[2,3-b]quinoline-1,10-dione (**4j**)*. Yield: 55.4%, m.p.174–176°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 1.12(s, 6H, 2 × CH_3), 1.15(s, 6H, 2×CH_3), 2.35(s, 2H, 2-H), 2.54–2.61(m, 2H, 4-H), 2.87(s, 2H, 9-H), 2.93–2.99(m, 2H, 7-H), 4.75(s, 1H, 12-H), 5.18(br s, 1H, NH), 6.89–7.19(m, 4H, Ph-H), 9.10(br s, 1H, NH); IR (KBr) υ: 3484, 1654, 1184, 1126cm^{-1}; MS (70 eV) *m*/*z* (%): 449.9 (M^+, 100).

REFERENCES AND NOTES

[1] Han, G. F.; Wang, J. J.; Jiang, G. J. Chin J Org Chem 2003, 23, 1004 (in Chinese).

[2] Jose, M. C.; Rafael, L.; Cristobal, R.; Antonio, G. G.; Manuela, G. L.; Mercedes, V. Bioorg Med Chem 2006, 14, 8176.

[3] Isabelle, K.; Marc, H.; Stephane, C. Eur J Med Chem 2008, 43, 2735.

[4] Siegfriend, E.; Drewes, F.; Fatima, K.; Alvaro, K. Eur J Med Chem 2005, 66, 1812.

[5] Franco, C.; Bruna, B.; Adriana, B. Photosynth Res 2006, 41, 208.

[6] Noble, S.; Fauldsd, A. Drugs 1998, 31, 115.

[7] Hoock, C.; Reichert, J.; Schmidtke, M. Molecule 1999, 4, 264.

[8] Selvam, N. P.; Babu, T. H.; Perumal, P. T. Tetrahedron 2009, 65, 8524.

[9] Han, G. F.; Wang, R. H.; Zhang, W. T. Synth Commun 2009, 39, 2492.

[10] Shutske, G. M.; Pierrat, F. A.; Kapples, K. J.; Cornfeldt, M. L.; Szewczak, M. R.; Huger, F. P.; Bores, G. M.; Haroutunian, V.; Davis, K. L. J Med Chem 1989, 32, 1805.

[11] Dai, G. Y.; Shi, D. Q.; Zhou, L. H. Chinareagent 1996, 18, 39.