

Cite this: *RSC Adv.*, 2017, 7, 44680Received 14th August 2017
Accepted 13th September 2017

DOI: 10.1039/c7ra08990b

rsc.li/rsc-advances

A short synthesis of 7-amino alkoxy homoisoflavonoid†

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The synthesis of novel derivatives of homoisoflavonoids as potentially interesting medicinally important heterocycles in an efficient catalytic two step route is introduced. In the first step, 7-aminoalkoxychromane-4-ones are synthesized *via* reaction between 7-hydroxychroman-4-one and aminoethylchlorides in the presence of potassium carbonate as a Brønsted base catalyst. In the next step, obtained 7-aminoalkoxychromane-4-ones are reacted with a wide range of arylaldehydes in the presence of hydrochloric acid as Brønsted acid catalyst to obtain homoisoflavonoids. Target products are medicinally very important heterocycles, because their analogs show cytotoxic activities towards human cancer cell lines.

Introduction

Homoisoflavonoids are a class of flavonoid-type natural products which have been isolated from numerous plants,¹ notably in the Hyacinthaceae family.² Their chemical structures consist of two aromatic carbocycles (phenyl) and one non-aromatic heterocycle (dihydropyran-4-one). The homoisoflavonoids can be divided into five categories: the 3-benzyl-4-chromanones (A), the 3-hydroxy-3-benzyl-4-chromanones (B), the 3-benzyl-chrom-2-en-4-ones (C), the scillascillins (D), and the 3-benzylidene-4-chromanones (E or Z) (E) (Fig. 1).³

To date, a wide range of biological behaviors of homoisoflavonoids, their synthesis and biosynthesis have been studied and reported in the literature.^{1,4} These types of compounds have shown many biological activities such as antiangiogenic,⁵ anti-fungal,⁶ hypocholesterolemic,⁷ antimutagenic,⁸ anti-inflammatory,⁹ and antiviral activities.^{10,11}

Among natural products containing homoisoflavonoid scaffold, Bonducellin (isolated from *Caesalpinia bonducella* and *Caesalpinia pulcherrima*)¹² acts as inhibitor of multidrug resistance efflux pump.¹³ Also, isobonducellin, (the *Z*-isomer of Bonducellin), and 8-methoxybonducellin (isolated from *C. pulcherrima*)^{14,15} have been shown anti-oxidant activity.¹⁶ In addition, Sappanone A (isolated from the heartwood of *Caesalpinia*)

is another homoisoflavonoid type compounds which exhibits antioxidant activity (Fig. 2).¹⁷

Considering above and existence the great interest in synthesis of important pharmacological active heterocycles,¹⁸ the synthesis of homoisoflavonoids has also attracted the interest of chemists and pharmaceutics.

Nowadays, there are numerous successful attempts to the laboratory synthesis of these kinds of compounds. In general, there are two protocols for the synthesis of these compounds. In the first approach, homoisoflavonoids are obtained from condensation reaction between 4-chromanones and arylaldehydes in methanol as solvent and by passing HCl gas as Brønsted acid catalyst or by using piperidine as a Brønsted base

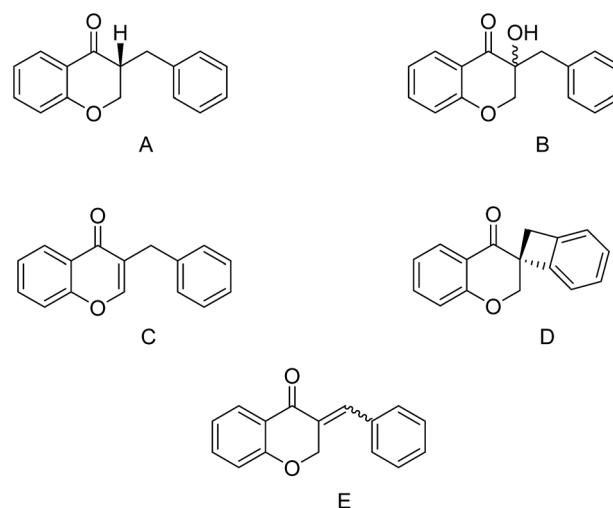


Fig. 1 Chemical structure classification of homoisoflavonoids.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c7ra08990b



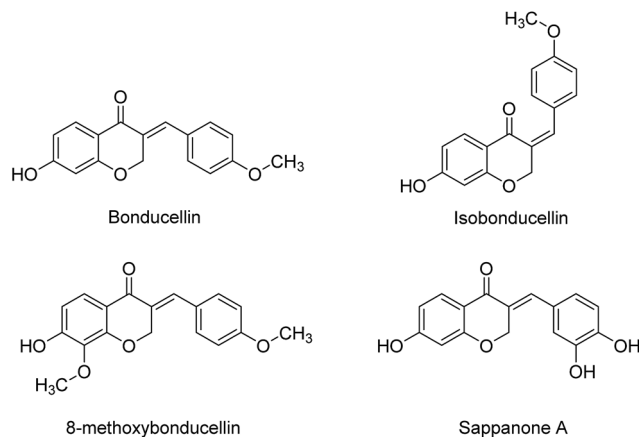
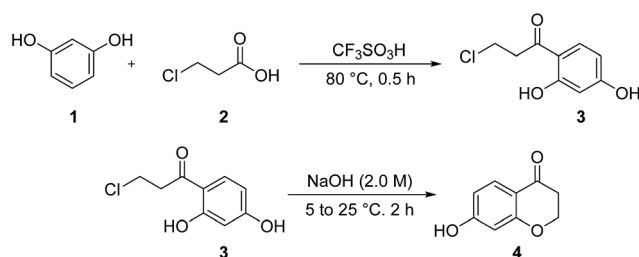


Fig. 2 Some selected homoisoflavonoids having pharmacological activity.



Scheme 1 Alternative two steps route to the synthesis of 7-hydroxychroman-4-one.

catalyst^{19,20} followed by isomerisation of the double bond in the presence of Pd/C at 250°C . In second ones homoisoflavonoids are obtained by hydrogenation of chalcones followed by one carbon extension by the use of ethyl formate/sodium²¹ or methanesulfonyl chloride/DMF.²² Based on all the above, herein, we wish to report an efficient route to the synthesis of a wide range of novel homoisoflavonoids by rely on first mentioned protocol. By this achievement the scope of homoisoflavonoids as medicinally important molecules was developed.

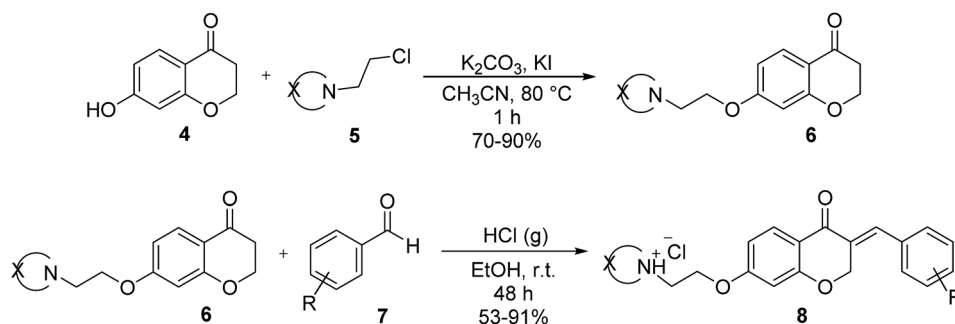
Results and discussion

Following to our continuous attempts to develop the new and green strategies for the synthesis of newly prepared organic compounds²³ especially new chemical intermediates and heterocycles,^{24,25} and also alternative multi-steps routes to the synthesis of medicinally important and biological active heterocycles,²⁶ in this study, our attention, is turned towards the synthesis of new homoisoflavonoid derivatives. For this purpose, we first had to prepare 7-hydroxychroman-4-one 4 *via* a two-step reported method¹⁷ including the Friedel-Crafts acylation and then intramolecular cyclization (Scheme 1). As can be seen from Scheme 1, at first, 2,4'-dihydroxy-3-chloro propiophenone 3 is synthesized from acylation reaction between resorcinol (1) and 3-chloropropionic acid (2), in the presence of $\text{CF}_3\text{SO}_3\text{H}$ as catalyst. Then, 2,4'-dihydroxy-3-chloro propiophenone 3 in the presence of NaOH, undergoes intramolecular cyclization to obtain 7-hydroxychroman-4-one 4.

In the next step, 7-hydroxychroman-4-one 4 *via* a reaction which is well-known as Williamson ether synthesis is reacted with appropriate aminoethylchlorides 5 to obtain 7-aminoalkoxychroman-4-ones 6. The role of KI in this reaction is activation of aminoethylchloride to nucleophilic attack. Also K_2CO_3 has been used as Brønsted catalyst to activation of phenolic OH. After preparation, purification, and characterization of 7-aminoalkoxychroman-4-ones 6, they are employed in the reaction with a wide range of arylaldehydes 7 containing both electron donor and electron withdrawing groups *via* Knoevenagel condensation reaction to give novel homoisoflavonoid derivatives 8 (Scheme 2). The role of HCl in this reaction is inevitable and acts as Brønsted acid catalyst to activation of both 7-aminoalkoxychroman-4-ones and aryl aldehydes to condense together.

By this achievement, a broad range of novel homoisoflavonoids as important potentially interesting biological active products were synthesized and the scope of these compounds were developed (Table 1).

It was clearly observed that the process can tolerate both electron-withdrawing and electron-donating groups on the phenyl ring. All target products were fully characterized by spectral data (H NMR, C NMR, and IR), along with elemental



X: $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2-$
R: 4- NO_2 , 3,4,5-(OCH_3)₃, 4-F, 4-Cl, 4- OCH_3 , 3,4-(OCH_3)₂, 4- CH_3 , 3- NO_2 , 4-OH

Scheme 2 Cascade two step routes to the synthesis of homoisoflavonoid derivatives.



Table 1 Alternative synthesis of 7-amino alkoxy homoiso-flavonoides

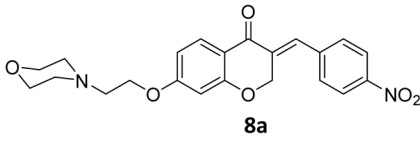
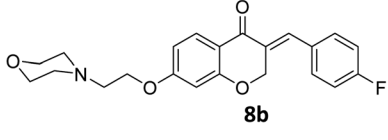
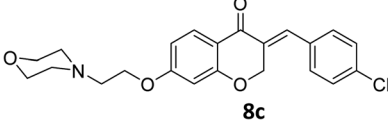
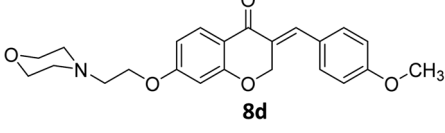
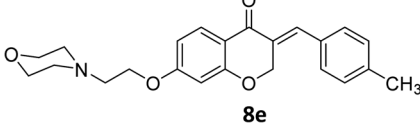
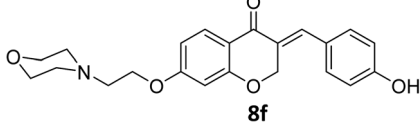
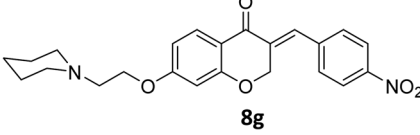
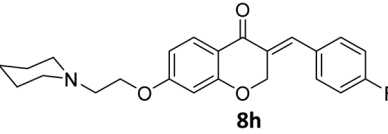
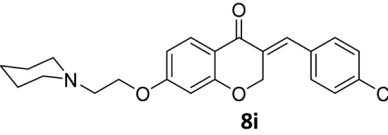
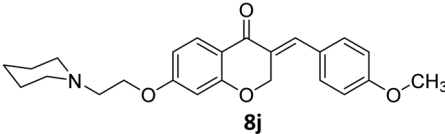
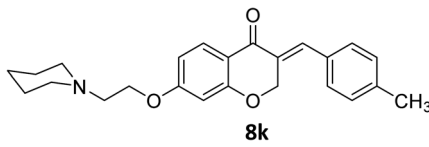
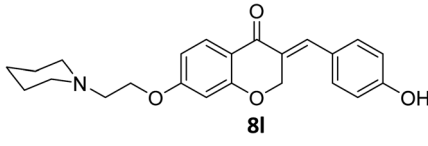
Entry	Product	Yield ^a (%)	M.p. (°C)
1	 8a	90	194–196
2	 8b	57	222–223
3	 8c	69	228–230
4	 8d	77	174–176
5	 8e	66	170–172
6	 8f	57	235–237
7	 8g	90	189–192
8	 8h	66	205–207
9	 8i	63	189–191
10	 8j	83	174–176



Table 1 (Contd.)

Entry	Product	Yield ^a (%)	M.p. (°C)
11	 8k	72	218–220
12	 8l	53	249–252

^a Isolated yield.

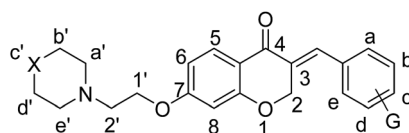


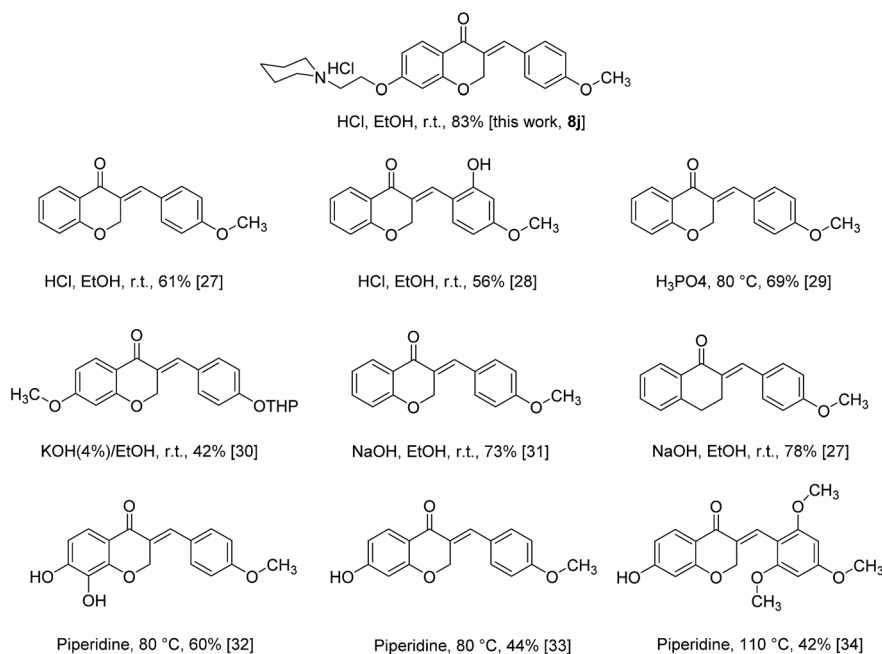
Fig. 3 Atom numbering refers to the order of real atoms in interpretation of NMR data.

analysis. The data of all products were in good agreement with the expected structures (see ESI[†]). Also, the numbering of atoms in the target compounds for interpretation of NMR data is indicated in Fig. 3.

In another investigation, we examined other conditions such as using various solvents including H₂O, CHCl₄, CH₃CN, dioxane, toluene, DMF, DMSO in different temperatures at r.t.,

40 °C, 60 °C, 80 °C, 100 °C, and 120 °C, and also the effect of other homogeneous and heterogeneous basic and acidic catalysts such as SSC, K₂CO₃, NaOH, KOH, piperidine, and triethylamine, ZnO, MgCl₂, FeCl₃, CF₃COOH, CH₃COOH, H₃PO₄ on model reaction (**8j**) was evaluated. The results obtained from this experiment show that only using HCl_(g) at room temperature in ethanol provides best conditions to obtain our products with highest yields. Because of our target products have containing amine side chain, the use of HCl_(g) in our procedure cause to obtain amine containing HCl as salt products which leads to precipitate target products and subsequently results to improve the yield of reaction.

As all of our synthesized products are novel compounds, for comparison of our current approach to others available, we selected compound **8j** as model and compared its obtaining



Scheme 3 Comparison of homoisoflavonoids synthesis under different conditions with our current protocol.



method with other homoisoflavonoids containing 4-OR substituted on benzylidene moiety under different conditions (Scheme 3). The results show that best and more efficient condition to the synthesis of homoisoflavonoids is provided by using HCl in ethanol at room temperature which leads to achieve the product with highest yield than others.^{27–34}

Based on the above, by this achievement, the scope of homoisoflavonoids as very medicinally important compounds was developed. Rapid formation and easily purification of target products, needing a little of HCl_(g) to accelerate reaction can be countered as other advantages of this protocol. However, this protocol tolerate some disadvantages such as using HCl_(g) as hazardous material, the excessing use of HCl_(g) lead to obtain unfavorable products, and working with HCl_(g) needs to observe more safety principles in the laboratory.

Experimental

All reagents, starting materials, and solvents applied in this work were purchased from commercial Merck AG, Aldrich, and Acros Organics chemical companies. Melting points of compounds were determined on Kolfer hot stag apparatus and are uncorrected. IR spectra were taken using Nicolet FT-IR Magna 550 spectrographs on KBr plates. The NMR spectra were recorded on Bruker Avance 400 or 500 MHz, FT-NMR spectrometers, Germany. ¹H NMR data are reported in the following order: chemical shifts (δ) in part per million (ppm) down field from TMS as internal standard; approximate coupling constant values (J) in Hertz (HZ); spin multiplicities (s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet; br, broad; quin, quintet). Thin-layer chromatography (TLC) was performed on pre-coated Silica Gel F254 plates for controlling the reaction progress.

Typical procedure to the synthesis of 2',4'-dihydroxy-3-chloro propiophenone 3³⁵

Trifluoromethanesulfonic acid (100 g, 0.67 mol) was added to a stirred mixture of resorcinol (**1**) (20.0 g, 0.182 mol) and 3-chloropropionic acid (**2**) (20.0 g, 0.184 mol) at room temperature. It was allow to solution reaching 80 °C for 30 min, and then cooled to room temperature over 15 min. In the following step, the solution was poured into chloroform (400 mL), and then slowly poured into water (400 mL). Afterwards, the layers were separated from each other. The aqueous phase was extracted with 2 × 200 mL of CHCl₃. The combined organic phases were washed with brine, dried over Na₂SO₄, and finally filtered. The highly viscous product was obtained by concentration in vacuum as an orange semisolid (24.1 g, 66%). ¹H-NMR δ 12.56 (1H, s), 7.63 (1H, d, J = 7.6 Hz), 6.37–6.46 (2H, m), 3.92 (2H, t, J = 6.3 Hz), 3.41 (2H, t, J = 6.3 Hz).

Typical procedure to the synthesis of 7-hydroxychroman-4-one 4³⁵

2',4'-Dihydroxy-3-chloro propiophenone **3** (24.1 g, 0.12 mol) was added to a stirred solution of NaOH (2 M, 1.0 L) at 5 °C. Then the solution was allowed to warm around room temperature over

2 h. Afterwards, the reaction mixture was re-cooled to 5 °C, and by the use of H₂SO₄ (6 M, 100 mL), the pH was adjusted to 2. At the end, the mixture was extracted three times with EtOAc (3 × 200 mL), washed with brine, dried over Na₂SO₄, and then filtered. The crude product was obtained by concentration in vacuum as a tan solid. The crude product was softened by hexanes, filtrated, and then recrystallized by water to give colorless crystals (18.4 g, 61%): mp: 143 °C; ¹H-NMR δ 7.84 (1H, d, J = 9.4 Hz), 6.73 (1H, brd s), 6.55 (1H, dd, J = 9.4, 1.8 Hz), 6.43 (1H, d, J = 1.8 Hz), 4.54 (2H, t, J = 6.5 Hz), 2.78 (2H, t, J = 6.5 Hz); IR (cm⁻¹): 3160, 1660, 1596, 1451, 1370, 1254.

General procedure for the synthesis of 7-(2-aminoethoxy) chroman-4-ones 6^{23b}

To a mixture of 7-hydroxychroman-4-one **1** (1 mmol) and appropriate aminoethyl chloride hydrochloride (1.1 mmol) in acetonitrile (10 mL) in a single-neck round bottom flask, potassium carbonate (3 mmol) and a catalytic amount of potassium iodide (5% mol) were added. The mixture was stirred under reflux for 10–14 h and regularly monitored for reaction progress by TLC using 10% methanol/dichloromethane as the solvent system. After cooling down to room temperature, the entire content was filtered under suction and the solid inorganic salts were washed with acetonitrile (3 × 10 mL). The resulting filtrate was evaporated to dryness under reduced pressure and residue was purified by silica column chromatography (1–9% methanol in dichloromethane, v/v as eluent) to afford compounds **6** in 70–90% yields.

General procedure for the synthesis of E-7-(2-aminoethoxy)-3-aryliden-2,3-dihydrochromen-4-one hydrochloride derivatives 8

A solution of 7-aminoalkoxychroman-4-ones **6** (1 mmol), and appropriate arylaldehyde (1 mmol) in EtOH (5 mL) was stirred at room temperature for 1 min, under passing a steam of HCl gas. After the time, the insertation of HCl was blockade, and the mixture was stirred overnight at room temperature to precipitate product. Subsequently, filter-off the precipitated product and crystallized from EtOH to give compounds **8**. In some cases which the crystals need to further purification, silica gel column chromatography with ethyl acetate/*n*-hexane (1 : 2) as eluent was applied to obtain crystalline pure products.

Typical procedure for the synthesis of E-7-(2-morpholinoethoxy)-3-(4-nitrobenzyliden)-2,3-dihydrochromen-4-one hydrochloride 8a

To a stirred mixture of 7-morpholinoethoxychroman-4-one **6** (0.277 g, 1 mmol) in EtOH (5 mL) at room temperature equipped with bypassing HCl_(g) valve, 4-nitrobenzaldehyde **7a** (0.151 g, 1 mmol) was added. Afterwards, it was permitted to HCl_(g) to insert in reaction mixture for 1 min. When inserting of HCl to the mixture was completed, it was allowed to the mixture to remain overnight at room temperature to precipitate product. Then, the mixture was filtered, and obtained crude product was recrystallized in boiling EtOH to afford crystalline pure **8a**. The obtained product was characterized by IR, ¹H NMR, ¹³C NMR and elemental analysis (C, H and N).



Spectral data of product 8

(E)-3-(4-Nitrobenzyliden)-7-(2-morpholinoethoxy)-2,3-dihydro chromen-4-one hydrochloride (8a). FT-IR (KBr, cm^{-1}) ν_{max} : 3374 (N-H), 1654 (C=O), 1613 (C=C alkene); ^1H NMR (CDCl_3 , 500 MHz) δ : 8.31 (d, 2H, H-a, $J = 8$ Hz), 7.97 (d, 1H, H-6, $J = 8$ Hz), 7.83 (s, 1H, H-8), 7.46 (d, 2H, H-b, $J = 8$ Hz), 6.68 (d, 1H, H-5, $J = 8$ Hz), 6.24 (s, 1H, vinylic-H), 5.28 (s, 2H, H-2), 4.16 (br s, 2H, H-1'), 3.74 (br, 4H, H-b'), 2.82 (br s, 2H, H-2'), 2.58 (br s, 4H, H-a'); ^{13}C NMR (125 MHz, CDCl_3) δ : 180.1, 165.5, 163.1, 147.7, 140.9, 133.9, 133.7, 130.4, 129.8, 123.9, 115.7, 115.5, 111.2, 101.5, 67.4, 66.8, 66.4, 57.2, 54.0. Anal. calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_6 \cdot \text{HCl}$ (446.88): C, 59.13; H, 5.19; N, 6.27. Found: C, 59.18; H, 5.21; N, 6.29.

(E)-3-(4-Fluorobenzyliden)-7-(2-morpholinoethoxy)-2,3-dihydro chromen-4-one hydrochloride (8b). IR (KBr, cm^{-1}) ν_{max} : 3348 (N-H), 1662 (C=O), 1614 (C=C alkene); ^1H NMR (DMSO-d_6 , 400 MHz), δ : 11.56 (s, 1H, NH), 7.87 (d, 1H, H-5, $J = 8.8$ Hz), 7.72 (s, 1H, H-8), 7.53 (dd, 1H, H-Ar, $J = 5.6$ and 3.2 Hz), 7.34 (m, 2H, H-Ar), 6.79 (dd, 1H, H-6, $J = 8.8$ and 2.4 Hz), 6.67 (d, 1H, vinylic-H, $J = 2.2$ Hz), 5.41 (d, 2H, H-2, $J = 2.2$ Hz), 4.55 (t, 2H, H-1', $J = 5$ Hz), 3.96–3.82 (br m, 4H, H-b'), 3.56 (br s, 2H, H-2'), 3.47 (br s, 2H, H-a'), 3.20 (br s, 2H, H-a'). ^{13}C NMR (100 MHz, DMSO-d_6) δ : 180.2, 164.3, 163.0, 161.8, 135.4, 133.2, 133.1, 130.9, 129.6, 116.4, 116.2, 116.0, 111.4, 102.4, 68.1, 63.6, 63.2, 55.0, 52.0. Anal. calcd for $\text{C}_{22}\text{H}_{22}\text{FNO}_4 \cdot \text{HCl}$ (419.87): C, 62.93; H, 5.52; N, 3.34. Found: C, 62.91; H, 5.50; N, 3.34.

(E)-3-(4-Chlorobenzyliden)-7-(2-morpholinoethoxy)-2,3-dihydro chromen-4-one hydrochloride (8c). IR (KBr, cm^{-1}) ν_{max} : 3435 (N-H), 1666 (C=O), 1613 (C=C alkene); ^1H NMR (DMSO-d_6 , 400 MHz), δ : 11.47 (br s, 1H, NH), 7.87 (d, 1H, H-5, $J = 8.8$ Hz), 7.71 (s, 1H, H-8), 7.55 (d, 2H, H-a, $J = 8.4$ Hz), 7.50 (d, 2H, H-b, $J = 8.4$ Hz), 6.79 (dd, 1H, H-6, $J = 8.8$ and 2.4 Hz), 6.67 (d, 1H, vinylic-H, $J = 2.2$ Hz), 5.41 (d, 2H, H-2, $J = 2.2$ Hz), 4.55 (t, 2H, H-1', $J = 4.8$ Hz), 3.93–3.86 (br d, 4H, H-b'), 3.55 (br s, 2H, H-2'), 3.47 (br s, 2H, H-a'), 3.19 (br s, 2H, H-a'). ^{13}C NMR (100 MHz, DMSO-d_6) δ : 180.1, 164.3, 163.0, 135.1, 134.7, 133.2, 132.5, 131.7, 129.7, 129.3, 116.0, 111.4, 102.4, 68.1, 63.6, 63.3, 55.0, 52.1. Anal. calcd for $\text{C}_{22}\text{H}_{22}\text{ClNO}_4 \cdot \text{HCl}$ (436.33): C, 60.56; H, 5.31; N, 3.21. Found: C, 60.57; H, 6.19; N, 3.34.

(E)-3-(4-Methoxybenzyliden)-7-(2-morpholinoethoxy)-2,3-dihydro chromen-4-one hydrochloride (8d). FT-IR (KBr, cm^{-1}) ν_{max} : 3417 (N-H), 1728 (C=O), 1663 (C=C alkene); ^1H NMR (DMSO-d_6 , 400 MHz) δ : 11.51 (s, 1H, NH), 7.85 (d, 1H, H-5, $J = 8.8$ Hz), 7.68 (s, 1H, H-8), 7.44 (d, 2H, H-a, $J = 8.4$ Hz), 7.07 (d, 2H, H-b, $J = 8.4$ Hz), 6.77 (dd, 1H, H-6, $J = 8.8$ and 2 Hz), 6.65 (d, 1H, vinylic-H, $J = 2$ Hz), 5.43 (d, 2H, H-2, $J = 2$ Hz), 4.54 (br s, 2H, H-1'), 3.92 (br s, 4H, H-b'), 3.82 (s, 3H, -OMe), 3.55 (br s, 2H, H-2'), 3.47 (br s, 2H, H-a'), 3.19 (br s, 2H, H-a'). ^{13}C NMR (100 MHz, DMSO-d_6) δ : 180.2, 164.1, 162.8, 136.4, 132.2, 132.1, 129.6, 129.1, 128.9, 126.8, 116.2, 114.8, 111.2, 102.3, 68.3, 67.9, 63.6, 63.2, 55.9, 55.0, 52.1. Anal. calcd for $\text{C}_{23}\text{H}_{25}\text{ClNO}_5 \cdot \text{HCl}$ (431.91): C, 63.96; H, 6.07; N, 3.24. Found: C, 63.97; H, 6.12; N, 3.31.

(E)-3-(4-Methylbenzyliden)-7-(2-morpholinoethoxy)-2,3-dihydro chromen-4-one hydrochloride (8e). IR (KBr, cm^{-1}) ν_{max} : 3390 (N-H), 1659 (C=O), 1603 (C=C alkene); ^1H NMR (DMSO-d_6 , 400 MHz), 11.38 (s, 1H, NH), 7.86 (d, 1H, H-5, $J = 8.8$ Hz), 7.69 (s, 1H, H-8), 7.35 (d, 2H, H-a, $J = 8.4$ Hz), 7.32 (d, 2H, H-b, $J = 8.4$ Hz), 6.77

(dd, 1H, H-6, $J = 8.8$ and 2.4 Hz), 6.66 (d, 1H, vinylic-H, $J = 2$ Hz), 5.42 (d, 2H, H-2, $J = 2$ Hz), 4.53 (t, 2H, H-1', $J = 5$ Hz), 3.92 (br s, 4H, H-b'), 3.55 (t, 2H, H-2', $J = 5$ Hz), 3.45 (br s, 2H, H-a'), 3.20 (br s, 2H, H-a'), 2.37 (s, 3H, -CH₃). ^{13}C NMR (100 MHz, DMSO-d_6) δ : 180.3, 164.2, 162.9, 140.1, 136.5, 131.5, 130.8, 130.3, 129.9, 129.6, 116.1, 111.3, 102.4, 68.2, 63.6, 63.2, 55.0, 52.1, 21.5. Anal. calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_4 \cdot \text{HCl}$ (415.91): C, 66.42; H, 6.30; N, 3.37. Found: C, 66.66; H, 6.39; N, 3.39.

(E)-3-(4-Hydroxybenzyliden)-7-(2-morpholinoethoxy)-2,3-dihydro chromen-4-one hydrochloride (8f). IR (KBr, cm^{-1}) ν_{max} : 3077 (N-H), 1670 (C=O), 1582 (C=C alkene); ^1H NMR (DMSO-d_6 , 500 MHz), 11.54 (s, 1H, NH), 10.22 (s, 1H, OH), 7.83 (d, 1H, H-5, $J = 8.8$ Hz), 7.63 (s, 1H, H-8), 7.32 (d, 2H, H-a, $J = 8.6$ Hz), 6.90 (d, 2H, H-b, $J = 8.6$ Hz), 6.76 (dd, 1H, H-6, $J = 8.8$ and 2.35 Hz), 6.64 (d, 1H, vinylic-H, $J = 2$ Hz), 5.41 (d, 2H, H-2, $J = 2$ Hz), 4.54 (br s, 2H, H-1'), 3.96–3.81 (br m, 4H, H-b'), 3.56–3.44 (br s, 4H, H-a'), 3.22 (t, 2H, H-2', $J = 9.2$ Hz). ^{13}C NMR (125 MHz, DMSO-d_6) δ : 179.8, 163.5, 162.3, 159.3, 159.1, 136.4, 132.7, 129.0, 127.4, 124.8, 115.8, 110.6, 101.8, 67.9, 63.1, 62.7, 54.5, 51.6. Anal. calcd for $\text{C}_{22}\text{H}_{23}\text{NO}_5 \cdot \text{HCl}$ (417.88): C, 63.23; H, 5.79; N, 3.35. Found: C, 63.61; H, 5.88; N, 3.37.

(E)-3-(4-Nitrobenzyliden)-7-((2-piperidine-1-yl)ethoxy)-2,3-dihydro chromen-4-one hydrochloride (8g). IR (KBr, cm^{-1}) ν_{max} : 3355 (N-H), 1657 (C=O), 1609 (C=C alkene); ^1H NMR (DMSO-d_6 , 500 MHz) δ : 10.55 (br s, 1H, NH), 8.31 (d, 2H, H-a, $J = 6.75$ Hz), 7.87 (d, 1H, H-5, $J = 8.8$ Hz), 7.79 (s, 1H, H-8), 7.72 (d, 2H, H-b, $J = 6.75$ Hz), 6.79 (d, 1H, H-6, $J = 8.8$ Hz), 6.67 (s, 1H, vinylic-H), 5.42 (s, 2H, H-2), 4.51 (br s, 2H, H-1'), 3.48 (br s, 4H, H-a'), 2.99 (br s, 2H, H-2'), 1.78–1.37 (br m, 6H, H-c' and H-b'). ^{13}C NMR (125 MHz, DMSO-d_6) δ : 180.1, 164.8, 163.1, 133.9, 133.7, 130.4, 130.0, 129.6, 123.9, 123.5, 115.9, 111.0, 101.5, 67.5, 65.7, 55.3, 53.8, 22.6, 22.2. Anal. calcd for $\text{C}_{23}\text{H}_{24}\text{N}_2\text{O}_5 \cdot \text{HCl}$ (444.91): C, 62.09; H, 5.66; N, 6.30. Found: C, 62.26; H, 5.79; N, 6.34.

(E)-3-(4-Fluorobenzyliden)-7-((2-piperidine-1-yl)ethoxy)-2,3-dihydro chromen-4-one hydrochloride (8h). IR (KBr, cm^{-1}) ν_{max} : 3387 (N-H), 1667 (C=O), 1616 (C=C alkene); ^1H NMR (CDCl_3 , 300 MHz) δ : 12.53 (s, 1H, NH), 7.97 (br s, 1H, H-5), 7.80 (s, 1H, H-8), 7.30–7.14 (m, 4H, H-a and H-b), 6.63 (br s, 1H, H-6), 6.45 (br s, 1H, vinylic-H), 5.31 (s, 2H, H-2), 4.68 (br s, 2H, H-1'), 3.66–3.50 (br s, 4H, H-a'), 2.84 (br s, 2H, H-2'), 1.92–1.47 (br m, 6H, H-b' and H-c'). ^{13}C NMR (75 MHz, CDCl_3) δ : 180.8, 164.8, 163.3, 163.0 (d, $J = 112.4$), 136.1, 135.9, 132.0, 131.9, 130.4, 130.1, 116.1, 115.8, 110.7, 102.2, 67.9, 63.6, 55.0, 52.0, 23.0, 22.0. Anal. calcd for $\text{C}_{23}\text{H}_{24}\text{FNO}_3 \cdot \text{HCl}$ (417.9): C, 66.10; H, 6.03; N, 3.35. Found: C, 66.26; H, 6.14; N, 3.37.

(E)-3-(4-Chlorobenzyliden)-7-((2-piperidine-1-yl)ethoxy)-2,3-dihydro chromen-4-one hydrochloride (8i). IR (KBr, cm^{-1}) ν_{max} : 3420 (N-H), 1664 (C=O), 1583 (C=C alkene); ^1H NMR (DMSO-d_6 , 500 MHz) δ : 10.84 (br s, 1H, NH), 7.84 (d, 1H, H-5, $J = 8.8$ Hz), 7.69 (s, 1H, H-8), 7.55 (d, 2H, H-a, $J = 7.5$ Hz), 7.48 (d, 2H, H-b, $J = 7.5$ Hz), 6.77 (d, 1H, H-6, $J = 8.8$ Hz), 6.65 (s, 1H, vinylic-H), 5.39 (s, 2H, H-2), 4.51 (br s, 2H, H-1'), 3.47 (br s, 4H, H-a'), 2.98 (br s, 2H, H-2'), 1.78–1.37 (br m, 6H, H-c' and H-b'). ^{13}C NMR (125 MHz, DMSO-d_6) δ : 179.6, 163.9, 162.6, 134.7, 134.3, 132.8, 132.1, 131.2, 129.2, 128.8, 115.5, 111.0, 101.8, 67.6, 62.9,



54.3, 52.5, 23.3, 21.2. Anal. calcd for $C_{23}H_{24}ClNO_3 \cdot HCl$ (434.36): C, 63.60; H, 5.80; N, 3.22. Found: C, 63.66; H, 6.09; N, 3.34.

(*E*)-3-(4-Methoxybenzyliden)-7-((2-piperidine-1-yl)ethoxy)-2,3-dihydro chromen-4-one hydrochloride (**8j**). IR (KBr, cm^{-1}) ν_{max} : 3417 (N-H), 1728 (C=O), 1663 (C=C alkene); 1H NMR (DMSO- d_6 , 400 MHz) δ : 11.51 (s, 1H, NH), 7.85 (d, 1H, H-5, $J = 8.8$ Hz), 7.68 (s, 1H, H-8), 7.44 (d, 2H, H-a, $J = 8.4$ Hz), 7.07 (d, 2H, H-b, $J = 8.4$ Hz), 6.77 (dd, 1H, H-6, $J = 8.8$ and 2 Hz), 6.65 (d, 1H, vinylic-H, $J = 2$ Hz), 5.43 (d, 2H, H-2, $J = 2$ Hz), 4.54 (br s, 2H, H-1'), 3.92 (br s, 4H, H-b'), 3.82 (s, 3H, OMe), 3.55 (br s, 2H, H-2'), 3.47 (br s, 2H, H-a'), 3.19 (br s, 2H, H-a'). ^{13}C NMR (100 MHz, DMSO- d_6) δ : 180.2, 164.1, 162.8, 136.4, 132.2, 132.1, 129.6, 129.1, 128.9, 126.8, 116.2, 114.8, 111.2, 102.3, 68.3, 67.9, 63.6, 63.2, 55.9, 55.0, 52.1. Anal. calcd for $C_{24}H_{27}ClNO_4 \cdot HCl$ (431.91): C, 63.96; H, 6.07; N, 3.24. Found: C, 63.97; H, 6.12; N, 3.31.

(*E*)-3-(4-Methylbenzyliden)-7-((2-piperidine-1-yl)ethoxy)-2,3-dihydro chromen-4-one hydrochloride (**8k**). IR (KBr, cm^{-1}) ν_{max} : 3384 (N-H), 1664 (C=O), 1611 (C=C alkene); 1H NMR (DMSO- d_6 , 500 MHz) δ : 11.06 (br s, 1H, NH), 7.84 (d, 1H, H-5, $J = 8.6$ Hz), 7.68 (s, 1H, H-8), 7.34 (d, 2H, H-a, $J = 7.6$ Hz), 7.30 (d, 2H, H-b, $J = 7.6$ Hz), 6.76 (d, 1H, H-6, $J = 8.6$ Hz), 6.64 (s, 1H, vinylic-H), 5.41 (s, 2H, H-2), 4.53 (br s, 2H, H-1'), 3.47 (br s, 2H, H-a'), 3.39 (br s, 2H, H-a'), 2.98 (t, 2H, H-2', $J = 10.40$ Hz), 2.35 (s, 3H, CH₃), 1.84–1.34 (br m, 6H, H-b' and H-c'). ^{13}C NMR (125 MHz, DMSO- d_6) δ : 180.3, 164.2, 162.9, 140.1, 136.5, 131.5, 130.8, 130.3, 129.9, 129.6, 116.1, 111.3, 102.4, 68.2, 63.6, 63.2, 55.0, 52.1, 21.5. Anal. calcd for $C_{24}H_{27}NO_3 \cdot HCl$ (413.94): C, 69.64; H, 6.82; N, 3.38. Found: C, 66.63; H, 6.69; N, 3.34.

(*E*)-3-(4-Hydroxybenzyliden)-7-((2-piperidine-1-yl)ethoxy)-2,3-dihydro chromen-4-one hydrochloride (**8l**). IR (KBr, cm^{-1}) ν_{max} : 3134 (N-H), 1666 (C=O), 1605 (C=C alkene); 1H NMR (300 MHz, DMSO- d_6) δ : 10.80 (s, 1H, NH), 10.24 (s, 1H, -OH), 7.83 (d, 1H, H-5, $J = 8.7$ Hz), 7.62 (s, 1H, H-8), 7.32 (d, 2H, H-a, $J = 7.5$ Hz), 6.90 (d, 2H, H-b, $J = 7.5$ Hz), 6.75 (d, 1H, H-6, $J = 8.7$ Hz), 6.62 (s, 1H, vinylic-H), 5.41 (s, 2H, H-2), 4.50 (br s, 2H, H-1'), 3.44 (br s, 4H, H-a'), 2.97 (br s, 2H, H-2'), 1.78–1.36 (br m, 6H, H-b', H-c'). ^{13}C NMR (75 MHz, DMSO- d_6) δ : 180.2, 164.0, 162.8, 159.7, 136.9, 136.8, 133.1, 129.6, 127.8, 125.2, 116.2, 116.2, 111.1, 102.2, 68.4, 63.2, 54.8, 53.0, 22.7, 21.6. Anal. calcd for $C_{23}H_{25}NO_4 \cdot HCl$ (415.91): C, 66.42; H, 6.30; N, 3.37. Found: C, 66.56; H, 6.34; N, 3.39.

Conclusions

In summary, for the first time, we presented an efficient route to the synthesis of novel homoisoflavonoids as potentially interesting pharmacological active compounds *via* a cascade four steps reaction from 7-aminoalkoxychroman-4-ones and arylaldehydes. Medicinally and pharmacologically point of view, with respect to the importance of homoisoflavonoids, by this achievement, the scope of this class of compounds was developed. Also this protocol may be attracted the interest for further investigations and synthetic manipulations to the synthesis and development of medicinally important heterocycles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors gratefully acknowledge from Pharmaceutics Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences for partial support of this work.

Notes and references

- 1 K. Du-Toit, S. E. Drewes and J. Bodenstern, *Nat. Prod. Res.*, 2010, **24**, 457.
- 2 K. Du-Toit, E. E. Elgorashi, S. F. Malan, D. A. Mulholland, S. E. Drewes and J. Van-Staden, *S. Afr. J. Bot.*, 2007, **73**, 236.
- 3 D. A. Mulholland, S. L. Schwikkard and N. R. Crouch, *Nat. Prod. Rep.*, 2013, **30**, 1165.
- 4 B. M. Abegaz, J. Mutanyatta and M. Nindi, *Nat. Prod. Commun.*, 2007, **2**, 475.
- 5 B. Lee, W. Sun, H. Lee, H. Basavarajappa, R. S. Sulaiman, K. Sishtla, X. Fei, T. W. Corson and S. Y. Seo, *Bioorg. Med. Chem. Lett.*, 2016, **26**, 4277.
- 6 T. Nakib, V. Bezjak, M. J. Meegan and R. Chandy, *Eur. J. Med. Chem.*, 1990, **25**, 455.
- 7 B. S. Kirkiacharian, M. Gomis and P. Koutsourakis, *Eur. J. Med. Chem.*, 1989, **24**, 309.
- 8 M. E. Wall, M. C. Wani, G. Manikumar, H. Taylor and R. McGivney, *J. Nat. Prod.*, 1989, **52**, 774.
- 9 A. Gupta and S. R. Chaphalkar, *J. HerbMed Pharmacol.*, 2016, **5**, 120.
- 10 N. Askarian-Dehkordi, H. Shirzad, L. Salimzadeh, B. Zamanzad, R. Meshkate and M. Kiyani, *J. HerbMed Pharmacol.*, 2014, **3**, 125.
- 11 N. Desideri, S. Olivieri, M. L. Stein, R. Sgro, N. Orsi and C. Conti, *Antiviral Chem. Chemother.*, 1997, **8**, 545.
- 12 K. K. Purushothaman, K. Kalyani, K. Subramaniam and S. P. Shanmughanathan, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1982, **21**, 383.
- 13 D. D. McPherson, G. A. Cordell, D. D. Soejarto, J. M. Pezzuto and H. H. S. Fong, *Phytochemistry*, 1983, **22**, 2835.
- 14 K. V. N. S. Srinivas, Y. K. Rao, I. Mahender and B. Das, *Phytochemistry*, 2003, **63**, 789.
- 15 P. Zhao, Y. Iwamoto, I. Kouno, Y. Egami and H. Yamamoto, *Phytochemistry*, 2004, **65**, 2455.
- 16 S. K. Roy, U. C. Agrahari, R. Gautam, A. Srivastava and S. M. Jachak, *Nat. Prod. Res.*, 2012, **26**, 690.
- 17 A. Foroumadi, A. Samzadeh-Kermani, S. Emami, G. Dehghan, M. Sorkhi, F. Arabsorkhi, M. R. Heidari, M. Abdollahi and A. Shafiee, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6764.
- 18 (a) K. Eskandari and M. Rafeiean-Kopaei, *Chem. Heterocycl. Compd.*, 2016, **52**, 158; (b) C. Li and F. Zhang, *Tetrahedron Lett.*, 2017, **58**, 1572; (c) H. Nagarajaiah, A. Mukhopadhyay and J. Narasimha-Moorthy, *Tetrahedron Lett.*, 2016, **57**, 5135.
- 19 S. Malhotra, V. K. Sharma and V. S. Parmar, *J. Chem. Res.*, 1988, 179.
- 20 L. Farkas, A. Gottsegen and M. Nogradi, *Tetrahedron*, 1970, **26**, 2787.
- 21 F. A. Davis and B. C. Chen, *J. Org. Chem.*, 1993, **58**, 1751.



- 22 A. C. Jain and P. Paliwal, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1989, **28**, 416.
- 23 (a) K. Eskandari, B. Karami, M. Farahi and V. Mouzari, *Tetrahedron Lett.*, 2016, **57**, 487; (b) Y. Pourshojaei, A. Gouranourimi, S. Hekmat, A. Asadipour, S. Rahmani-Nezhad, A. Moradi, H. Nadri, F. Homayouni-Moghadam, S. Emami and A. Foroumadi, *Eur. J. Med. Chem.*, 2015, **97**, 181; (c) S. Rahmani-Nezhad, L. Khosravani, M. Saeedi, K. Divsalar, L. Firoozpour, Y. Pourshojaei, Y. Sarrafi, H. Nadri, A. Moradi, M. Mahdavi, A. Shafiee and A. Foroumadi, *Synth. Commun.*, 2015, **45**, 751; (d) S. Khodabakhshi, B. Karami, K. Eskandari and M. Farahi, *Tetrahedron Lett.*, 2014, **55**, 3753; (e) L. Poorali, B. Karami, K. Eskandari and M. Azizi, *J. Chem. Sci.*, 2013, **125**, 591.
- 24 (a) K. Eskandari, B. Karami and S. Khodabakhshi, *J. Chem. Res.*, 2014, **38**, 600; (b) K. Eskandari, B. Karami, S. Khodabakhshi and M. Farahi, *Lett. Org. Chem.*, 2015, **12**, 38; (c) B. Karami, R. Ferdosian and K. Eskandari, *J. Chem. Res.*, 2014, **38**, 41.
- 25 (a) K. Eskandari and B. Karami, *Monatsh. Chem.*, 2016, **147**, 2119; (b) B. Karami, K. Eskandari, Z. Zare and S. Gholipour, *Chem. Heterocycl. Compd.*, 2014, **49**, 1715; (c) K. Eskandari and B. Karami, *Comb. Chem. High Throughput Screening*, 2016, **19**, 728.
- 26 (a) F. Mehrabi, Y. Pourshojaei, A. Moradi, M. Sharifzadeh, L. Khosravani, R. Sabourian, S. Rahmani-Nezhad, M. Mohammadi-Khanaposhtani, M. Mahdavi, A. Asadipour, H. R. Rahimi, S. Moghimi and A. Foroumadi, *Future Med. Chem.*, 2017, **9**, 659; (b) S. Rahmani-Nezhad, M. Safavi, M. Pordeli, S. Kabudanian, L. Khosravani, Y. Pourshojaei, M. Mahdavi, S. Emami, A. Foroumadi and A. Shafiee, *Eur. J. Med. Chem.*, 2014, **86**, 562; (c) N. Azizi, F. Aryanasab and M. R. Saidi, *Tetrahedron Lett.*, 2009, **50**, 32; (d) M. R. Saidi, Y. Pourshojaei and F. Aryanasab, *Synth. Commun.*, 2009, **39**, 1109.
- 27 T. A. Nakibl, V. Bezjakl, M. J. Meeganz and R. Chandyl, *Eur. J. Med. Chem.*, 1990, **25**, 455.
- 28 N. Desideri, A. Bolasco, R. Fioravanti, L. P. Monaco, F. Orallo, M. Yanez, F. Ortuso and S. Alcaro, *J. Med. Chem.*, 2011, **54**, 2155.
- 29 N. Desideri, S. Olivieri, M. L. Stein, R. Sgro, N. Orsin and C. Conri, *Antiviral Chem. Chemother.*, 1997, **8**, 545.
- 30 S. W. Yee, L. Jarno, M. S. Goma, C. Elford, L. L. Ooi, M. P. Coogan, R. McClelland, R. I. Nicholson, B. A. J. Evans, A. Brancale and C. Simons, *J. Med. Chem.*, 2005, **48**, 7123.
- 31 X. Zong, J. Cai, J. Chen, C. Sun, L. Lib and M. Ji, *RSC Adv.*, 2015, **5**, 24814.
- 32 V. Siddaiah, M. Maheswara, C. V. Rao, S. Venkateswarlub and G. V. Subbaraju, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 1288.
- 33 Y. Sun, J. Chen, X. Chen, L. Huang and X. Li, *Bioorg. Med. Chem.*, 2013, **21**, 7406.
- 34 Y. Jacquot, C. Byrne, A. Xicluna and G. Leclercq, *Med. Chem. Res.*, 2013, **22**, 681.
- 35 K. Koch and M. S. Biggers, *J. Org. Chem.*, 1994, **59**, 1216.

