Med Chem Res (2014) 23:1031–1036
DOI 10.1007/s00044-013-0706-1

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Catalyst-free efficient synthesis of polyhydroquinolines using polyethylene glycol as a solvent and evaluation of their cytotoxicity

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Received: 8 February 2013 / Accepted: 9 August 2013 / Published online: 22 August 2013

Abstract An eco-friendly one-pot synthesis of polyhydroquinolines by four-component coupling of aldehydes, dimedone, ethylacetoacetate, and ammonium acetate using polyethylene glycol as a solvent at room temperature has been accomplished. The conversion was complete within 2–4 h, and the products were formed in high yields (83–95 %). No any additional catalyst was required. Several known and unknown polyhydroquinolines have been prepared. Some of the compounds exhibited impressive cytotoxic activity.

Keywords Polyhydroquinoline · Four-component coupling · Polyethylene glycol · Catalyst-free conversion · Cytotoxicity

Introduction

Polyhydroquinolines containing 1,4-dihydropyridine moiety possess various important biological activities. They can cure the disordered heart ratio as a chain-cutting agent of factor IV channel and also exhibit the calcium channel agonist–antagonist modulation properties (Kawase *et al.*, 2002; Shan *et al.*, 2004; Sawada *et al.*, 2004). Moreover, these compounds act as cerebral anti-ischaemic agents, neuroprotectants, and chemosensitizers (Klusa, 1995; Boer and Gekeler, 1995). In view of the biological importance of polyhydroquinoline derivatives, several synthesis of these compounds have recently been accomplished (Tu *et al.*, 2001; Ji *et al.*, 2004; Wang *et al.*, 2005; Ko *et al.*, 2005; Donelson *et al.*, 2006; Das *et al.*, 2006; Mekheimer *et al.*, 2008; Sapkal *et al.*, 2009; Undale *et al.*, 2011; Ranjbar-Karimi *et al.*, 2011). Various catalysts, such as triflates of Yb and Sc, I_2, HY-zeolite, and nickel nanoparticle, have been utilized. (Wang *et al.*, 2005; Donelson *et al.*, 2006; Ko *et al.*, 2005; Das *et al.*, 2006; Sapkal *et al.*, 2009). Microwave irradiation and solar heat have also been employed (Mekheimer *et al.*, 2008). In adddition, ionic liquids have been used for the preparation of several polyhydroquinolines (Ji *et al.*, 2004). However, many of these methodologies are associated with different drawbacks, such as application of costly and toxic catalysts, longer reaction times, high temperatures, unsatisfactory yields, and complex work-up procedures. Moreover, the multistep procedures are the disadvantages in many of these methods. Here, we report an efficient catalyst-free synthesis of polyhydroquinolines using polyethylene glycol (PEG-400) as a solvent. The cytotoxic activity of these compounds has also been reported.

Chemistry

In continuation of our work (Ravindranath *et al.*, 2001; Das *et al.*, 2005, 2007a, 2009, 2011) on the development of useful synthetic methodologies, we have observed that the four-component coupling of aldehydes (1) dimedone (**2**),

Part 232 in the series "Studies on novel synthetic methodlogies".

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ethyl acetoacetate (**3**) and NH_4OAc (**4**) using PEG-400 as a solvent at room temperature afforded the polyhydroquinolines (**5**) within 2–4 h (Scheme 1).

Various aromatic and heteroaromatic aldehydes have been used to prepare the polyhydroquinoline derivatives (Table 1) following the above method. The aromatic aldehydes contained electron-donating and electron-withdrawing groups. 2-Naphtaldehyde **(5h)** and 3-indolyl aldehyde **(5g)** also underwent the conversion smoothly. The products were formed in high yields (83–95 %). Several known compounds along with four new compounds (**5f, 5j–l**) have been synthesized and well characterised. The structures of the products were established from their spectral (IR, ^1H and ^{13}C, and Mass) and analytical data.

In the present conversion, PEG works as a solvent and also as a catalyst. The plausible mechanism of the reaction is shown below (Scheme 2).

Polyethylene glycol is environmentally benign, less expensive, and easily available. (Dickerson *et al.*, 2002; Chandrasekhar *et al.*, 2004; Das *et al.*, 2007b). Due to its eco-friendly nature, it is considered as a green solvent. It is water soluble and can easily be separated from the reaction mixture. It has efficiently been utilized here for the synthesis of polyhydroquinolines.

Table 1 Synthesis of polyhydroquinoline derivatives (5)

Entry	Ar (1)	Time (min)	Product[a]	Yield[b] (%)	M.P (°C)
1	4-OH–C_6H_4	120	**5a**	83	231–233
2	2-OH–C_6H_4	120	**5b**	87	110–111
3	4-Me–C_6H_4	120	**5c**	91	260–261
4	4-i-Pr–C_6H_4	180	**5d**	93	165–167
5	4-Cl–C_6H_4	120	**5e**	85	245–246
6	2-Cl–3-Pyridinyl	240	**5f**	92	121–122
7	3-Indolyl	120	**5g**	87	168–170
8	2-Naphthyl	120	**5h**	85	239–241
9	4-NO_2–C_6H_4	180	**5i**	91	242–244
10	2-Cl–5-CF_3–C_6H_3	120	**5j**	89	181–183
11	4-F–3-OMe–C_6H_3	120	**5k**	88	214–215
12	4-Br–2-F–C_6H_3	120	**5l**	95	261–263
13	2,4,6-$(OMe)_3$–C_6H_2	120	**5m**	93	157–159

Reaction conditions: Aldehyde (1.0 mmol), dimedone (1.0 mmol), ethylacetoacetate (1.0 mmol), ammonium acetate (1.0 mmol) and PEG-400 (1.0 g), room temperature, 2–4 h

[a] The structures of the products were established from their spectral (IR,^1H and ^{13}C NMR, ESI–MS) and analytical data

[b] Isolated yields after purification

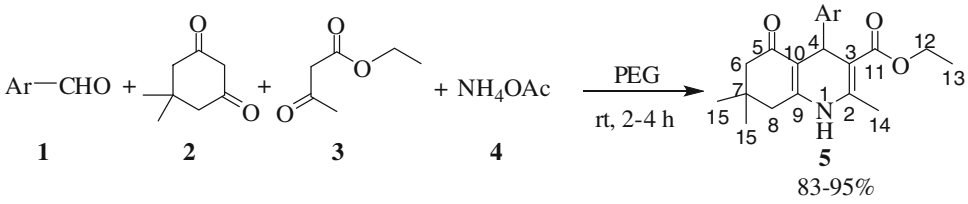
Bioactivity

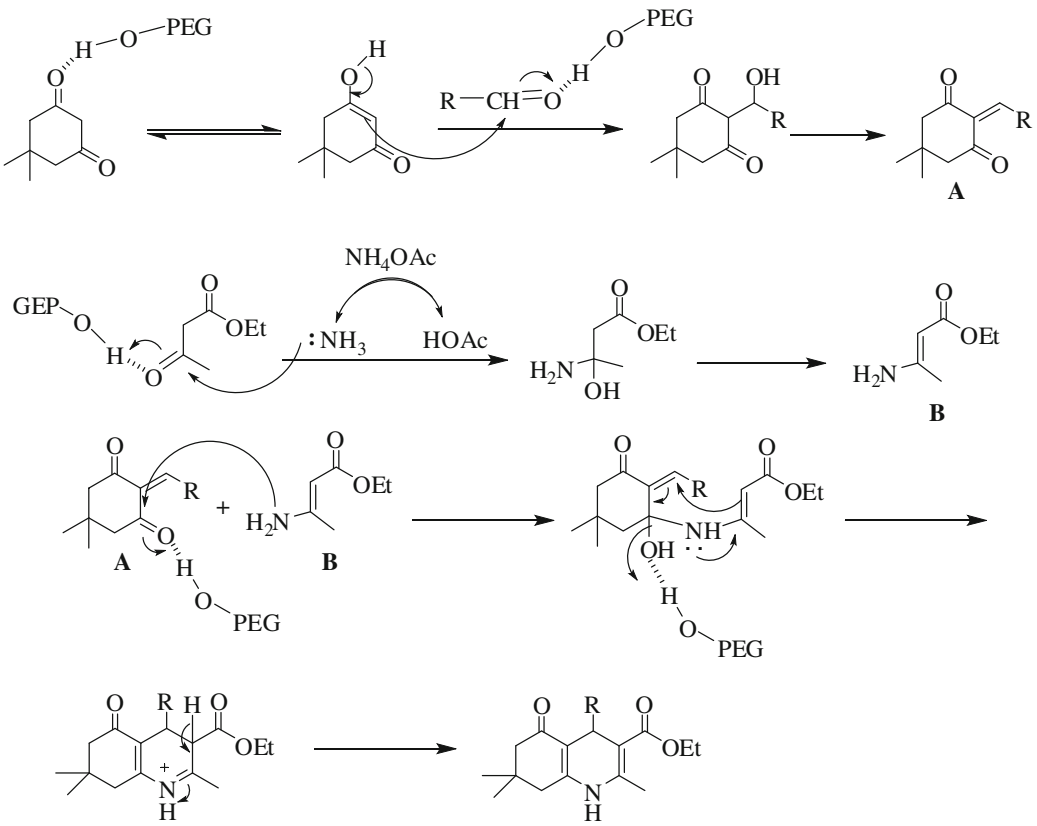
The prepared polyhydroquinolines were examined for in vitro cytotoxicity against three cancerous cell lines: MCF-7 (human breast adenocarcinoma), HeLa (human cervical cancer), and SK-N-SH (human neuroblastoma). Doxorubicin was used as the positive control. The MTT assay was utilised to evaluate the cytotoxicity. (Myadarabiona *et al.*, 2010). The IC_{50} value for each cell line was determined after three individual observations (Table 2). The result indicated that **5j** possessed significant activity against all the three cell lines. The compounds **5e**, **5f**, and **5g** exhibited promising activities against HeLa and SK-N-SH cell lines, while compounds **5d**, **5h, 5l**, and **5m** against only the SK-N-SH cell line. During this bioevaluation, **5g**, **5j**, and **5l** have been identified as the most active compounds against HeLa, MCF-7, and SK-N-SH cell lines, respectively.

It has been observed that all the polyhydroquinolines containing chlorine (**5e, 5f**, and **5j**) exhibited impressive cytotoxic activity. Organochlorine compounds (such as vancomycine, loratadine, sertraline, etc.) as well as organofluorine compounds (such as 5-fluorouracil, fluoxetine, paroxetine, etc.) are known to be used as important medicines to combat different diseases. However, in our case, only the chlorine-containing compounds were found to possess cytotoxic properties but the fluorine-containing compound (**5k**) was inactive. The presence of a heterocyclic moiety (as for example, in **5f** and **5g**) enhanced the cytotoxic activity against HeLa and SK-N-SH cell lines. However, a polyhydroquinoline having an aromatic ring with an electron-withdrawing group (such as **5i**) was found to be totally inactive. The products with a free phenolic moiety (**5a** and **5b**) were also inactive.

The cytotoxic activity of all the polyhydroquinolines has been graphically presented in Fig. 1.

Scheme 1 Preparation of polyhydroquinolines using PEG





Scheme 2 Plausible mechanism of the preparation of polyhydroquinolines

Table 2 IC_{50} values (μM) of test compounds against different cancer cell lines

Entry	Sample code	IC_{50} values (in μM)		
		MCF-7	HeLa	SK-N-SH
1	**5a**	>100	>100	>100
2	**5b**	>100	>100	>100
3	**5c**	>100	>100	>100
4	**5d**	>100	>100	9.25 ± 0.50
5	**5e**	>100	14.14 ± 0.72	12.54 ± 0.24
6	**5f**	>100	12.14 ± 0.21	7.78 ± 0.21
7	**5g**	>100	8.46 ± 0.08	9.12 ± 0.28
8	**5h**	>100	>100	7.33 ± 0.08
9	**5i**	>100	>100	>100
10	**5j**	6.87 ± 0.14	9.23 ± 0.02	6.69 ± 0.32
11	**5k**	>100	>100	>100
12	**5l**	>100	>100	6.84 ± 0.70
13	**5m**	>100	>100	12.44 ± 0.22
STD	Doxorubicin	2.4 ± 0.12	1.12 ± 0.21	0.97 ± 0.03

Conclusion

We have developed a simple and efficient method for the synthesis of polyhydroquinolines using polyethylene glycol as a solvent. The method has several advantages, such as mild reaction conditions, catalyst-free conversion, short reaction times, high yields, and convenient experimental procedure. The evaluation of cytotoxic property of these polyhydroquinoline derivatives has been accomplished. Some of the compounds containing chlorine group have shown significant activity. The polyhydroquinolines having heterocyclic moiety also exhibited impressive cytotoxicity against HeLa and SK-N-SH cell lines.

Experimental

General

All commercially available reagents were used directly without further purification unless otherwise stated. The solvents used were all of AR grade and were distilled under a positive pressure of dry nitrogen atmosphere wherever necessary. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) performed on Merck Silica Gel 60 F_{254} plates. Column chromatography was carried out using silica gel 60–120 mesh (Qingdao Marine Chemical, China). IR spectra were recorded on a

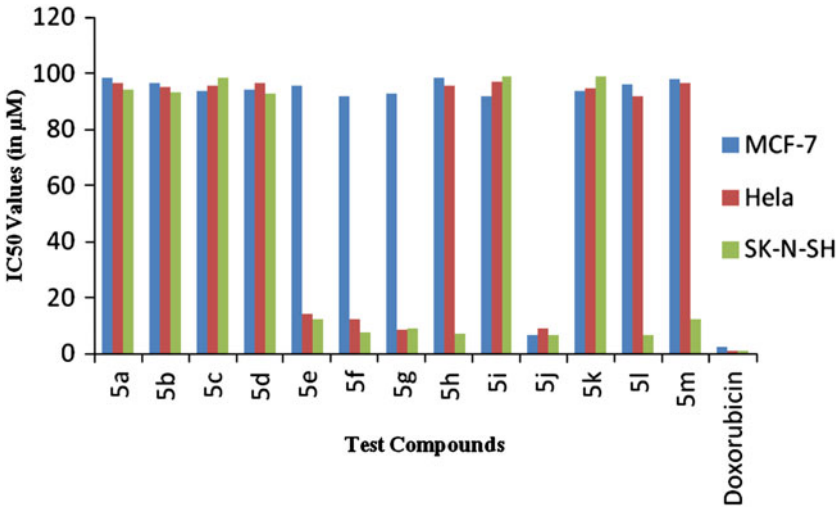


Fig. 1 Graphical presentation of the cytotoxic activity of the polyhydroquinolines

Perkin-Elmer RX1 FT-IR spectrophotometer and mass spectra on VG-Autospec micromass. NMR spectra were recorded on Gemini 200 MHz spectrometer with tetramethylsilane as internal standard using $CDCl_3$. The chemical shifts are expressed as δ values in parts per million (ppm), and the coupling constants (J) are given in Hertz (Hz). Yields were of purified compounds and were not optimized.

General experimental procedure

Corresponding aldehyde (1.0 mmol), dimedone (1.0 mmol), ethylacetoacetate (1.0 mmol), and ammonium acetate (1.0 mmol) were taken in PEG-400 (1.0 g). The mixture was stirred at room temperature, and the reaction was monitored by TLC. After completion, water was added and the reaction mixture was extracted with EtOAc (3 × 10 mL). The organic layer was separated and concentrated. The residue was subjected to column chromatography (silica gel, hexane/EtOAc = 70:30) to obtain a pure product (**5**).

The spectral and analytical data of the unknown products are given here

*Ethyl 4-(2-chloropyridin-3-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5f**)*

IR: 3282, 1719, 1376, 1224 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) : δ 8.75 (1H, brs, Ar–H), 8.09 (1H, m, Ar–H), 7.70 (1H, d, J = 8.0 Hz, Ar–H), 7.12 (1H, m, Ar–H), 5.14 (1H, s, H-4), 3.98 (2H, q, J = 7.0 Hz, H_2-12), 2.22–1.91 (7H, m, H_3-14, H_2-6, H_2-8), 1.53 (3H, s, H_3-15), 1.31 (3H, s, H_3-15), 1.28 (3H, t, J = 7.0 Hz, H_3-13); ^{13}C NMR (50 MHz, DMSO-d_6): 194.9 (C-5), 167.5 (C-11), 150.4 (C-2), 149.2 (C-9), 147.0 (Ar–C–Cl), 146.0 (Ar–C), 124.0 (Ar–C), 116.2 (Ar–C), 114.4 (Ar–C), 109.6 (C-10), 101.3 (C-3), 60.2 (C-12), 50.9 (C-6), 31.2 (C-4), 29.1 (C-8), 26.4 (C-7), 24.9 (C-15), 21.1 (C-14), 14.8 (C-13); ESI–MS: *m/z* 375, 377 $[M+H]^{+;}$ Anal. Calcd. for $C_{20}H_{23}ClN_2O_3$: C, 63.82; H, 6.11; N, 7.44 % Found: C, 63.76; H, 6.07; N, 7.39 %.

*Ethyl 4-(2-chloro-5-(trifluoromethyl)phenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5j**)*

IR: 3299, 1702, 1612, 1492, 1328, 1217 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ 8.78 (1H, brs, H-1), 7.59 (1H, d, J = 2.0 Hz, Ar–H), 7.40–7.29 (2H, m, Ar–H), 5.22 (1H, s, H-4), 3.95 (2H, q, J = 7.0 Hz, H_2-12), 2.38 (1H, d, J = 14.0 Hz, H_2-6), 2.30 (3H, s, H_3-14), 2.23 (1H, d, J = 14.0 Hz, H_2-6), 2.12 (1H, d, J = 14.0 Hz, H_2-8), 1.95 (1H, d, J = 14.0 Hz, H_2-8), 1.11 (3H, t, J = 7.0 Hz, H_3-15), 1.04 (3H, s, H_3-15), 0.89 (3H, s, H_3-13); ^{13}C NMR (50 MHz, DMSO-d_6): 194.8 (C-5), 165.2 (C-11), 150.2 (C-2), 146.1 (C-9), 145.2 (Ar–C), 136.3 (Ar–C–Cl), 130.4 (Ar–C), 129.0 (Ar–C–CF_3), 126.8 (q, J = 30.0 Hz, (Ar–C)), 124.5 (Ar–CF_3), 109.2 (C-10), 101.5 (C-3), 59.4 (C-12), 50.0 (C-6), 35.8 (C-4), 31.7 (C-8), 29.5 (C-7), 25.2 (C-15), 18.6 (C-14), 14.4 (C-13); (ESI–MS): *m/z* 442, 444 $[M+H]^{+;}$ Anal. Calcd. for $C_{22}H_{23}ClF_3NO_3$: C, 59.59; H, 5.19; N, 3.16 % Found: C, 59.52; H, 5.12; N, 3.11 %.

*Ethyl 4-(4-fluoro-3-methoxyphenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylate (**5k**)*

IR: 3296, 1699, 1610, 1481, 1380, 1238; ^1H NMR (200 MHz, DMSO-d_6) : δ 8.70 (1H, brs, H-1), 6.98–6.79 (2H, m, Ar–H), 6.66 (1H, m, Ar–H), 4.83 (1H, s, H-4), 4.01 (2H, q, J = 7.0 Hz, H_2-12), 3.80 (3H, s, OCH_3-Ar), 2.34 (1H, d, J = 14.0 Hz, H_2-6), 2.32 (3H, s, H_3-14), 2.31 (1H,

d, $J = 14.0$ Hz, H_2-6), 2.12 (1H, d, $J = 14.0$ Hz, H_2-8), 2.01 (1H, d, $J = 14.0$ Hz, H_2-8), 1.21 (3H, t, $J = 7.0$ Hz, H_3-15), 1.05 (3H, s, H_3-15), 0.91 (3H, s, H_3-13); ^{13}C NMR (50 MHz, DMSO-d_6): 194.9 (C-5), 166.0 (C-11), 149.9 (C-2), 148.3 (d, $J = 280.0$ Hz, (Ar–C–F), 144.9 (Ar–C–OMe), 144.1 (Ar–C), 119.9 (Ar–C), 114.9 (Ar–C), 114.8 (Ar–C), 113.2 (Ar–C), 110.0 (C-10), 104.2 (C-3), 59.6 (C-12), 55.2 (Ar–OCH_3), 50.1 (C-6), 35.1 (C-4), 31.5 (C-8), 28.7 (C-7), 26.1 (C-15), 18.4 (C-14), 14.5 (C-13); (ESI–MS): *m/z* 388, $[M+H]^{+;}$ Anal. Calcd. for $C_{22}H_{26}FNO_4$: C, 68.21; H, 6.71; N, 3.61 % Found: C, 68.18; H, 6.68; N, 3.57 %.

*Ethyl 4-(4-bromo-2-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5l**)*

IR: 3279, 1702, 1609, 1482, 1381, 1218; ^{1}H NMR (200 MHz, DMSO-d_6) : δ 8.51 (1H, brs, H-1), 7.22–6.99 (3H, m, Ar–H), 5.04 (1H, s, H-4), 3.99 (2H, q, $J = 7.0$ Hz, H_2-12), 2.32 (1H, q, $J = 14.0$ Hz, H_2-6), 2.29 (3H, s, H_3-14), 2.21 (1H, d, $J = 14.0$ Hz, H_2-6), 2.12 (1H, d, $J = 14.0$ Hz, H_2-8), 2.00 (1H, d, $J = 14.0$ Hz, H_2-8), 1.16 (3H, t, $J = 14.0$ Hz, H_3-15), 1.07 (3H, s, H_3-15), 0.91 (3H, s, H_3-13); ^{13}C NMR (50 MHz, DMSO-d_6) : 194.8 (C-5), 166.0 (C-11), 159.8 (d, $J = 280.0$ Hz, Ar–C–F), 150.0 (Ar–C), 145.4 (Ar–C), 132.5 (Ar–C), 126.4 (Ar–C), 119.6 (Ar–C–Br), 119.0 (Ar–C), 118.6 (Ar–C), 109.1 (C-10), 101.5 (C-3), 59.8 (C-12), 50.0 (C-6), 32.1 (C-4), 30.8 (C-8), 29.6 (C-7), 25.8 (C-15), 19.5 (C-14), 14.2 (C-13); (ESIMS): *m/z* 436, 438 $[M+H]^+$; Anal. Calcd. for $C_{21}H_{23}BrFNO_3$: C, 57.66; H, 5.26; N, 3.20 % Found: C, 57.69; H, 5.21; N, 3.17 %.

Evalution of cytotoxic activity

Cell lines used for testing in vitro cytotoxicity included MCF-7 derived from human breast adenocarcinoma cells, HeLa derived from human cervical cancer cells and SK-N-SH derived from human neuroblastoma cells. These cell lines were obtained from American Type Culture Collection, Manassas, VA, USA.

All tumor cell lines were maintained in a modified Eagle's medium (Sigma-Aldrich, USA) supplemented with 10 % fetal bovine serum (Sigma), along with 1 % nonessential amino acids without L-glutamine (Sigma), 0.2 % sodium bicarbonate, 1 % sodium pyruvate (Sigma), and 1 % of antibiotic mixture (10,000 U penicillin and 10 mg streptomycin per mL, Sigma). Cellular viability in the presence of test compounds was determined by MTT-microcultured tetrazoli assay. The cells seeded to flat bottomed 96 (10,000 cells/100 UL) well plates and cultured in the media containing 10 % ser and allowed to attach and recover for 24 h in a hid chamber containing 5 % CO_2 MTT (3-(4,5-dimethylthiazol-2yl)-2,5diphenyl tetrazoli bromide; sigma catalog no M2128) was dissolved in PBS at 5 mg/mL and filtered to sterilize and remove a small amount of insoluble residue present MTT. Different concentrations of compounds were added to the cells. After 48 h, stock MTT solution (10 UL) was added to the culture plate. Cells were again kept in CO_2 incubator for 2 h. After incubation, 100 UL of DMSO was added and mixed. The absorbance was read at 562 nm in a plate reader. Trypsin–EDTA solution (0.25 %, 2.5 g porcine trypsin, and 0.2 g EDTA) used for detaching cells during subculturing process. The results were represented as percentage of cytotoxicity/viability. All the experiments were carried out in duplicates. From the percentage of cytotoxicity, the IC_{50} value is calculated. IC_{50} values (in μM) are expressed as the average of two independent experiments.

Acknowledgments The authors thank CSIR and UGC, New Delhi for financial assistance.

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