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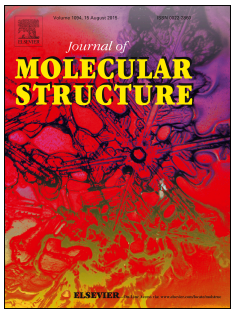

Efficient and easy synthesis of new Benzo[h]chromene and Benzo[h]quinoline derivatives as a new class of cytotoxic agents

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Efficient and Easy Synthesis of New Benzo[h]chromene and Benzo[h]quinoline Derivatives as a New Class of Cytotoxic Agents

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Abstract:

The present study presents easy and rapid methods to synthesize new benzo[*h*]chromene and benzo[*h*] quinoline derivatives. Cytotoxic evaluations of most of the examined compounds indicated that they had significant cytotoxic activities against HepG-2 (human cancer cells) and MCF-7 (breast cancer cells). Compounds 4 and 11 had stronger cytotoxic activity against HepG-2 human cancer cells than the reference drug Doxorubicin. All the examined compounds were significantly active against MCF-7 human cancer cells and were more potent than Doxorubicin. The structures of the new compounds were established from their spectral and elemental data. In addition the structures of benzo[h] chromene 3 and benzo[h]quinoline 7 were recognized by x-ray crystallography. Herein detailed syntheses, spectroscopic information and biological actions of the tested compounds are reported.

Key words: Benzo[h]chromene, Benzo[h]quinoline, Cytotoxicity, X-ray crystallography.

INTRODUCTION

Cancer is considered to be one of the most common causes of death worldwide. One of the most primary bases for cancer treatment is chemotherapy. The undesirable side effects of chemotherapy treatment, promote researchers for developing new chemotherapeutic agents with more potent anticancer activity. Our recent literature report [(1)] revealed significant cytotoxic activity of benzo[h] chromene 2a and benzo[h]quinoline 6a against human glioblastoma cells. These results endorsed us to design a new series of benzo[h]chromene and benzo [h] quinoline

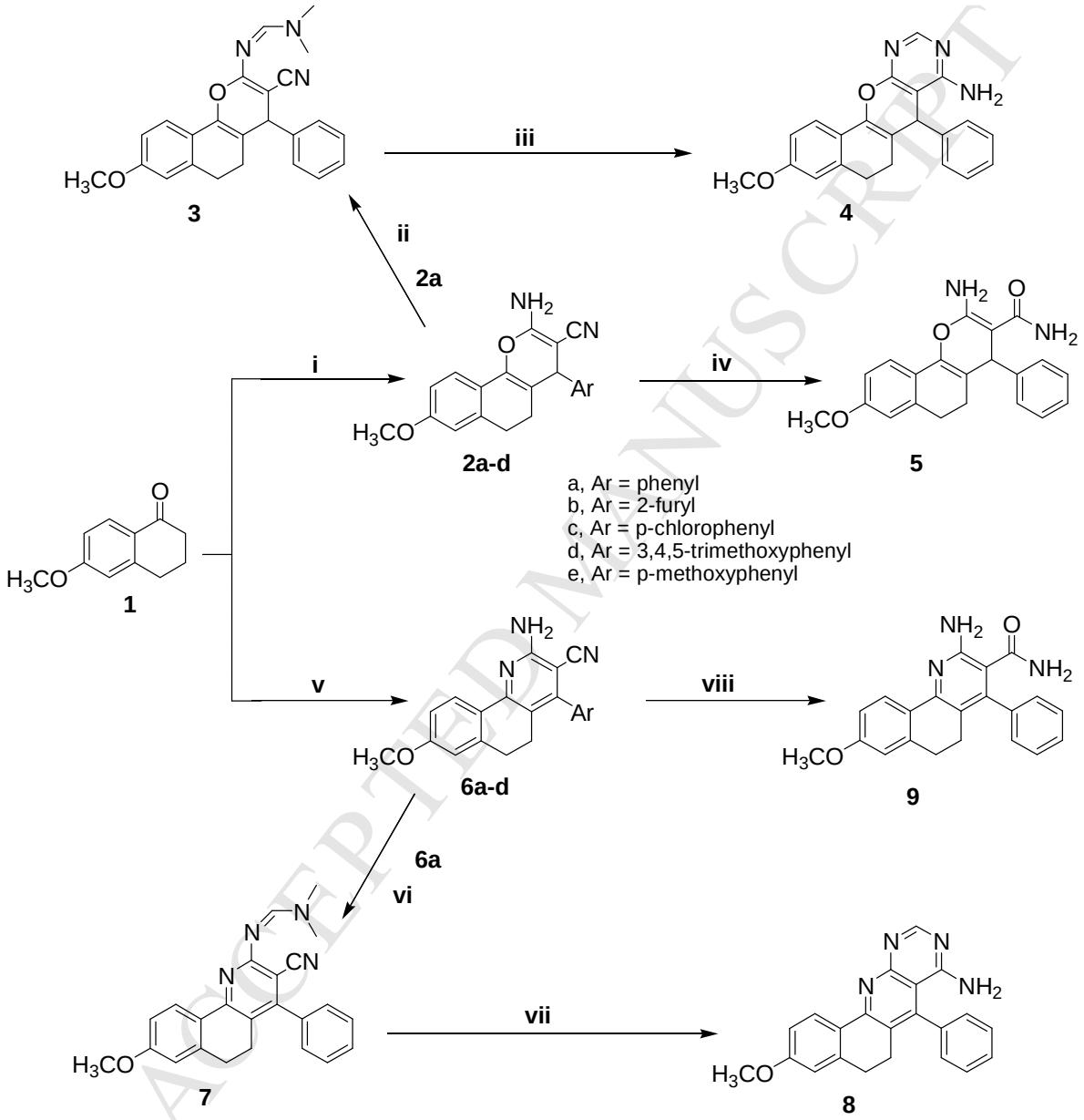
derivatives, which were easily, synthesized describing efficient, clean reaction profiles and short reaction times. Most reactions were carried out under microwave irradiation or through solvent-free conditions. Literature reports demonstrated the importance of chromene derivatives as anticancer [1-4], antimicrobial [5,6], antioxidant [7,8], anti-inflammatory [9,10] and in treatment of Alzheimer's disease[11]. On the other hand, literature survey reported that numerous quinoline derivatives were recognized as potent antimicrobial [12-14], antimalarial [15], anticancer [16,17], HIV-integrase inhibitory [18], antifungal [19], antitubercular [20] and anti-inflammatory [21]. The main objective of our research was to synthesize new benzo[h] chromene and benzo[h]quinoline derivatives, to examine their biological activity, hoping to develop therapeutic drugs for treatment of different types of cancer, using 6-methoxytetralone as the starting material.

RESULTS AND DISCUSSION

The synthesized compounds were constructed via the routes illustrated in schemes 1-3.

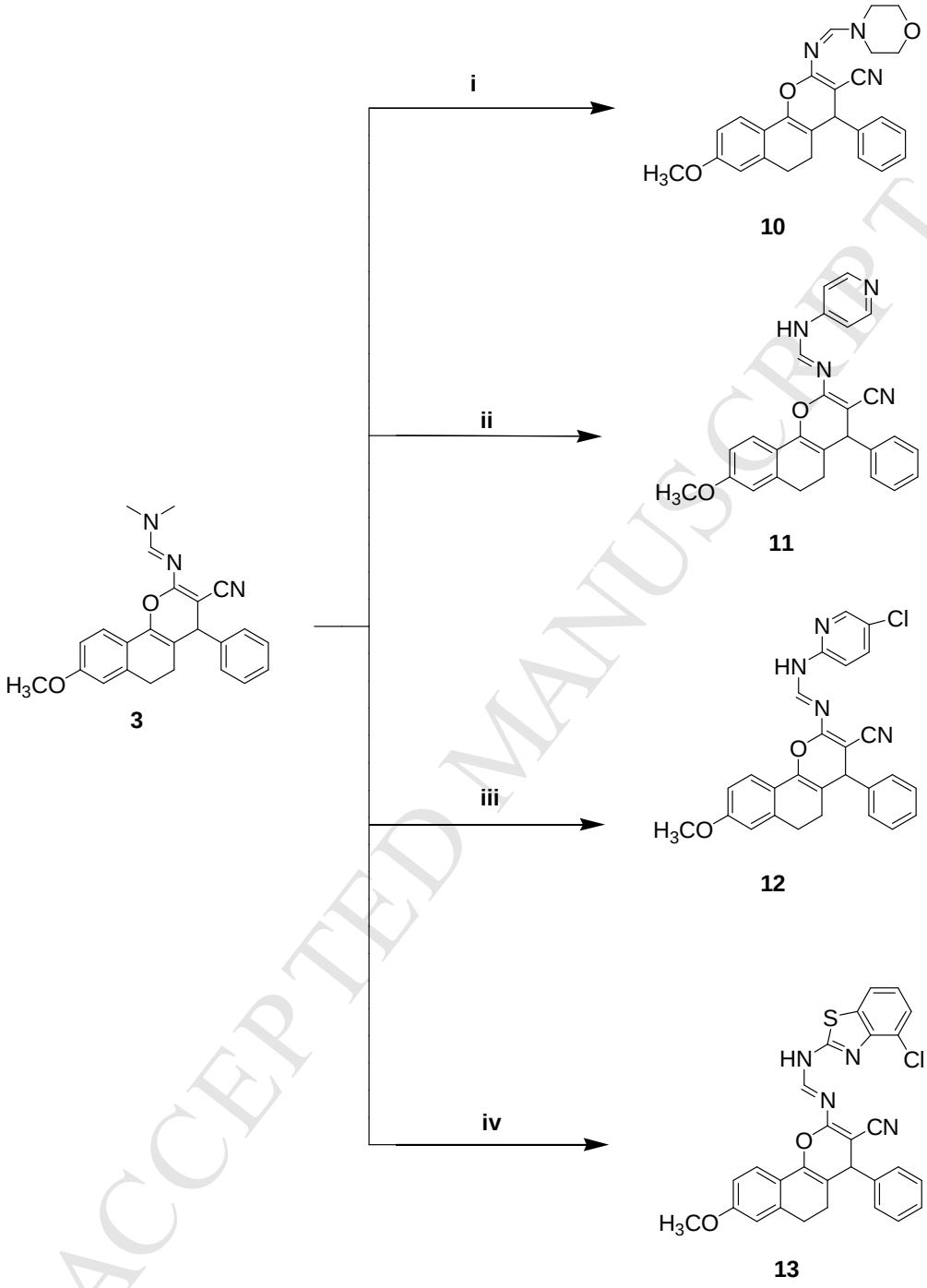
Condensation of 6-methoxy-1-tetralone 1 with different substituted arylidenemalononitriles, namely, 2-(benzylidenemalononitrile), 2-((furan-2-yl) methylene) malononitrile, 2-(4-chlorobenzylidene) malononitrile, 2-(3,4,5-trimethoxybenzylidene) malononitrile and 2-(*p*-methoxybenzylidene) malononitrile, in the presence of catalytic quantities of piperidine under microwave irradiation, gave the corresponding chromene carbonitriles (2a-d), within 15 minutes in 90-65% yields. Condensation of the chromene carbonitrile 2a with dimethylformamide-dimethylacetal (DMF-DMA), under solvent-free conditions produced chromene derivative 3 within 1h**.,** in 90% yield, which was reacted with formamide to give the pyrimidine derivative 4 within 1 h., in 90% yield. Reaction of 6-methoxy-1-tetralone 1 with the same substituted arylidenemalononitriles, under similar conditions as formerly described, but in the presence of ammonium acetate, gave the corresponding quinoline carbonitriles (6a-d), within 15 minutes in 90-65% yields. Reaction of the derivative 6a with DMF-DMA under solvent-free conditions produced the enamine derivative 7 within 1 h., in 85% yield**,** which was reacted with formamide to form the pyrimido quinoline derivative 8 in 85% yield. Stirring compounds 2a or 6a with concentrated sulfuric acid at 20-22 ^{o}C yielded the targeting carboxamide derivatives 5 and 9 within 30 minutes in 85-90% yields respectively (Scheme 1). Reaction of formamidine derivative 3 with heterocyclic amines namely; morpholine, 4-aminopyridine, 2-amino-5-chloropyridine or 2-amino-4-chlorobenzothiazole, in the presence of glacial acetic acid generated

products 10-13 (Scheme 2). Moreover, quinoline derivative **7** was reacted with 4-aminopyridine or morpholine to produce formamidine derivatives 14 and 15 within 1h., in 85-80% yields respectively (Scheme 3).



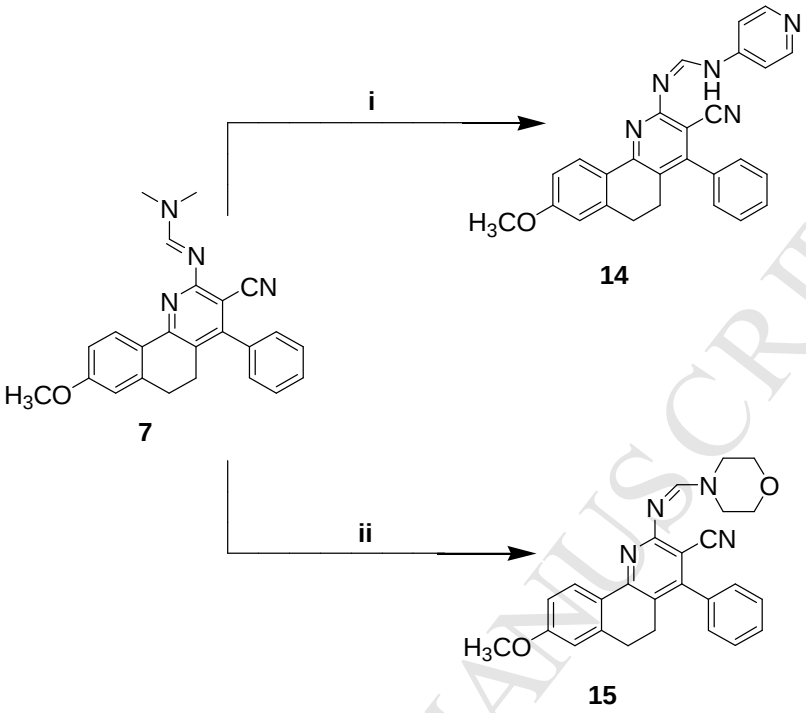
Scheme **1**: Synthetic routes of compounds $\mathbf{2_{a\text{-}e}}$-**9**

Reagents and conditions: (i) microwave, arylidenemalononitriles, ethanol, 15 min; (ii) and (vi) DMF-DMA, reflux, 1h; (iii) and (vii) formamide, reflux, 1h; (iv) and (viii) H_2SO_4, r.t., 1h; (v) microwave, arylidene malononitriles, ethanol, ammoniumacetate, 15 min.



Scheme **2**: Synthetic routes of compounds **10-13**

Reagents and conditions: (i), (ii), (iii), (iv) CH_3COOH, reflux, 2-3 h; morpholine, 4-aminopyridine, 2-amino-5-chloropyridine, 2-amino-5-chlorobenzoyhiazole respectively



Scheme **3**: Synthetic routes of compounds **14** and **15**

Reagents and conditions: (i), (ii) reflux, 15-20 min; morpholine and 4-aminopyridine respectively

X-ray crystallographic analysis

Products 3 and 7 were obtained as single crystals by slow evaporation of ethanol from the pure compounds at room temperature. Data were collected on a Bruker APEX-II D8 Venture area diffractometer fitted with graphite monochromatic Mo Kα radiation at 293 (2) and 100 (2) K, respectively Cell improvement and data reduction were carried out with Bruker SAINT. SHELXS-97 [22, 23] was used to resolve the structures. Refinements were made by the full-matrix least-squares techniques using anisotropic thermal data for non-hydrogen atoms on *F*. CCDC 1404393 and CCDC 1543562 contain the supplementary crystallographic data for these compounds and are available free of charge from the Cambridge Crystallographic Data Centre at http://www.ccdc.cam.ac.uk/data_request/cif.

The crystallographic records and refinement information for $C_{24}H_{23}N_3O_2$ compound 3 and $C_{24}H_{22}N_4O$ compound 7 are summarized in (Table 1). The asymmetric units of compounds 3 and 7 consist of one independent molecule as shown in Figure 1. All bond lengths and angles are within normal ranges [24]. Selected bond lengths and angles are listed in (Table 2). Figure 2a shows that the molecules of compound 3 are packed together with no hydrogen interactions. In Figure 2b, the molecules of compound 7 are linked by single intermolecular non-classical hydrogen interactions (Table 3).

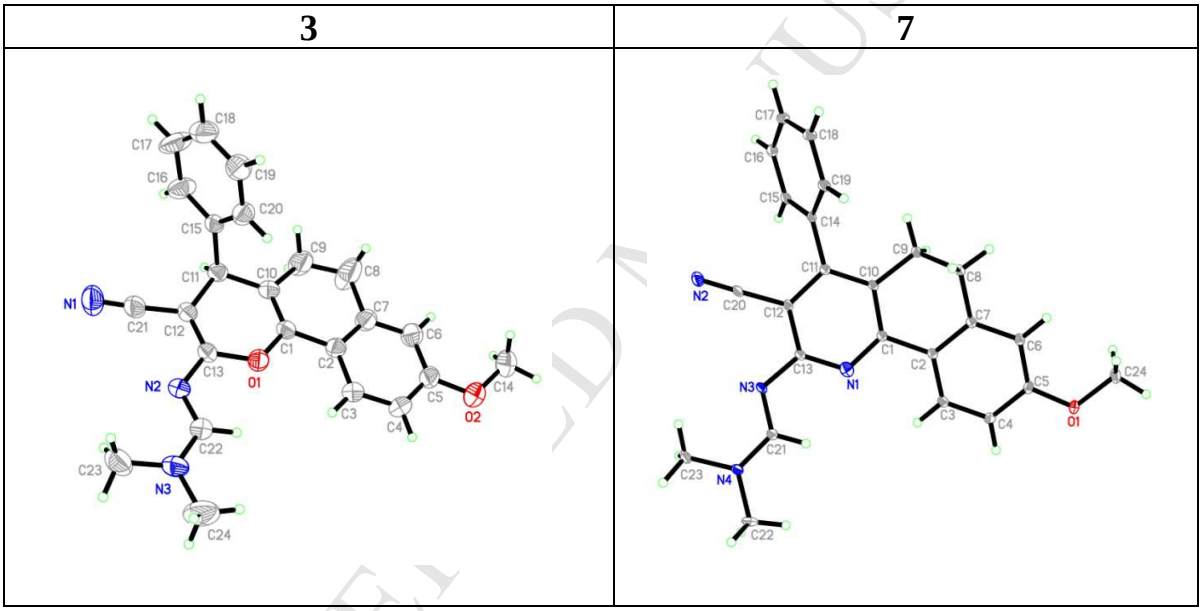


Fig. 1 ORTEP diagrams of the products 3 and 7. Displacement ellipsoids are plotted at the 40% probability level for non-H atoms.

Table 1: X-Ray crystallography specifics for products 3 and 7

Crystal data	**3**	**7**
Chemical formula	$C_{24}H_{23}N_3O_2$	$C_{24}H_{22}N_4O$
*M*r	385.45	382.46
Crystal system, space group	Triclinic, *P*-1	Monoclinic, $P2_1/n$
Temperature (K)	293	100
a, *b*, *c* (Å)	8.3125 (5), 10.0564 (6), 13.5434 (9)	10.8672 (5), 14.3735 (6), 12.9222 (5)
α, β, γ (°)	69.197 (2), 78.218 (3), 76.214 (2)	90, 99.561 (2), 90
V (Å^3)	1018.90 (11)	1990.41 (15)
Z	2	4
Radiation type	Mo *K*α	Mo *K*α
μ (mm^{-1})	0.08	0.08
Crystal size (mm)	0.32 × 0.25 × 0.21	0.51 × 0.40 × 0.15
Data collection		
Diffractometer	Bruker APEX-II D8 venture diffractometer	Bruker APEX-II D8 venture diffractometer
Absorption correction	Multi-scan SADABS Bruker 2014	Multi-scan SADABS Bruker 2014
T_{min}, T_{max}	0.975, 0.983	0.960, 0.988
No. of measured, independent and observed [I > 2σ(I)] reflections	41937, 4227, 2182	24576, 4558, 3773
R_{int}	0.187	0.081
Refinement		
R[F^2 > 2σ(F^2)], wR(F^2), S	0.074, 0.228, 1.04	0.058, 0.171, 1.03
No. of reflections	4227	4558
No. of parameters	266	265
No. of restraints	0	0
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.28, −0.32	0.40, −0.33
CCDC No.	1543562	1404393

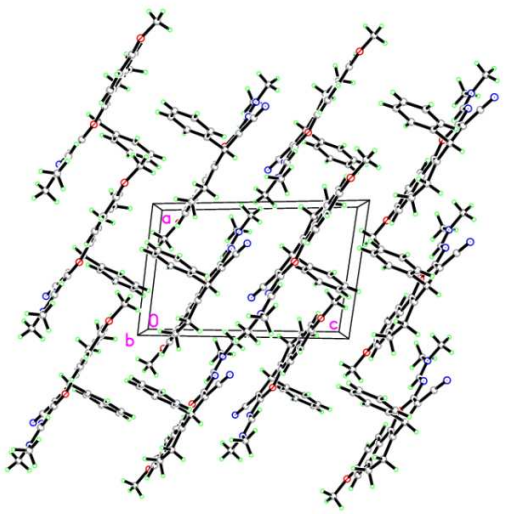
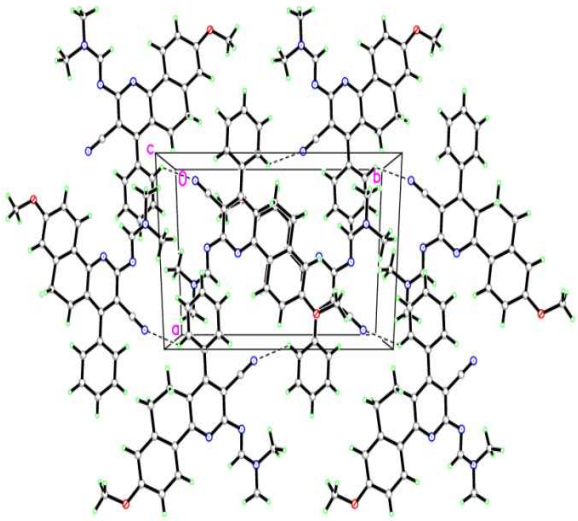
Fig. 2a (3)	Fig. 2b (7)
	

Fig. 2 Molecular packing of titled compounds. Hydrogen interactions are drawn as dashed lines.

Table 2: Selected geometric parameters (Å, °)

Compound 7			
Bond Lengths			
O1—C5	1.3676 (18)	N3—C13	1.3913 (18)
O1—C24	1.4307 (18)	N3—C21	1.3017 (19)
N1—C1	1.3408 (18)	N4—C21	1.3362 (19)
N1—C13	1.3383 (18)	N4—C22	1.450 (2)
N2—C20	1.149 (2)	N4—C23	1.457 (2)
Bond angles			
C5—O1—C24	117.13 (12)	O1—C5—C4	115.79 (13)
C1—N1—C13	119.00 (12)	O1—C5—C6	124.25 (13)
C13—N3—C21	116.97 (12)	N1—C13—N3	121.93 (13)
C21—N4—C22	121.53 (12)	N1—C13—C12	121.17 (12)
C21—N4—C23	120.85 (13)	N3—C13—C12	116.86 (12)
C22—N4—C23	116.95 (12)	N2—C20—C12	178.59 (17)
N1—C1—C2	116.89 (12)	N3—C21—N4	122.02 (13)
N1—C1—C10	123.62 (12)		
Compound 3			
Bond Lengths			
O1—C1	1.389 (4)	N2—C13	1.359 (4)
O1—C13	1.375 (4)	N2—C22	1.292 (4)
O2—C5	1.375 (5)	N3—C22	1.319 (4)
O2—C14	1.415 (6)	N3—C23	1.434 (5)

N1—C21	1.142 (5)	N3—C24	1.445 (5)
Bond angles			
C1—O1—C13	118.8 (2)	O2—C5—C4	115.7 (4)
C5—O2—C14	117.2 (3)	O2—C5—C6	124.3 (4)
C13—N2—C22	119.8 (3)	O1—C13—N2	116.2 (3)
C22—N3—C23	120.3 (3)	O1—C13—C12	120.9 (3)
C22—N3—C24	121.9 (3)	N2—C13—C12	122.9 (3)
C23—N3—C24	117.8 (3)	N1—C21—C12	176.3 (4)
O1—C1—C2	112.6 (3)	N2—C22—N3	122.4 (3)
O1—C1—C10	123.2 (3)		

Table 3: Hydrogen interactions geometry (Å, °) for compound **7**

Compound 7				
D—H···A	**D—H**	**H···A**	**D···A**	**D—H···A**
C19—H19A···N2^{i}	0.9500	2.6100	3.304 (2)	130.00
Symmetry codes: (i) −x+1/2, y+1/2, −z+5/2.				

Cytotoxicity screening

Anti-tumor activity

Thirteen compounds were scanned in vitro for their activities against HepG-2 and MCF-7 using MTT assay. The percentages of intact cells were calculated and compared to those of the control (Fig. 3). Activities of these products against the two carcinoma cell lines were compared to the activity of doxorubicin. All compounds suppressed both tumor cells in a dose-dependent manner. Figure 3 shows that, compounds 4 and 11 had significant cytotoxic activity against HepG-2 at 100 µM and were more potent than doxorubicin. Compounds 2d, 10, 12 and 15 also presented with significant cytotoxic activity. All other compounds were moderately active against HepG-2. All thirteen investigated compounds were significantly active against MCF-7 and were more potent than doxorubicin. The IC_{50} of all investigated compounds are shown in Table 4.

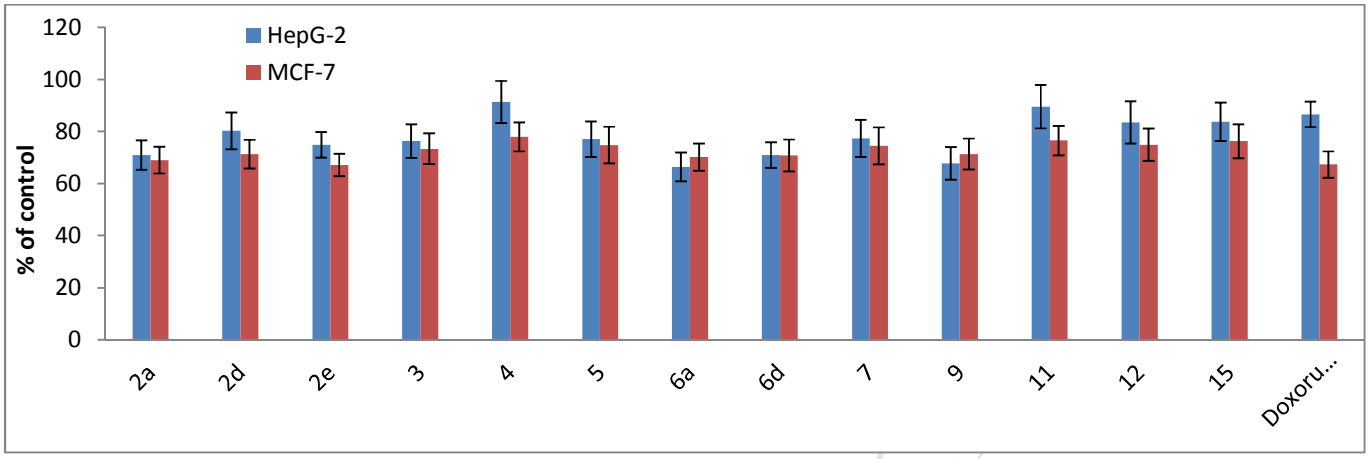


Figure 3: Cytotoxic actions of the thirteen products against two cancer cell lines according to the MTT assay at 100 µM.

Table 4: IC_{50} of the thirteen products against the two cancer cell lines according to the MTT assay

Compound	HepG-2	MCF-7
	IC_{50} (µM) ± SD	
2a	70.5 ± 3.1	72.4 ± 5.3
2d	62.3 ± 5.2	70.1 ± 2.9
2e	66.7 ± 7.4	74.5 ± 5.1
3	65.5 ± 3.8	68.1 ± 4.7
4	54.7 ± 4.1	64.1 ± 2.7
5	64.8 ± 2.5	66.8 ± 4.1
6a	75.3 ± 2.9	71.2 ± 3.2
6d	70.4 ± 1.8	70.6 ± 3.5
7	64.6 ± 3.2	67.1 ± 5.1
9	73.8 ± 2.7	70.1 ± 3.9
11	55.8 ± 4.5	65.3 ± 2.5
12	59.8 ± 3.6	66.7 ± 5.5
15	59.6 ± 3.5	65.5 ± 4.7
Doxorubicin	57.7 ± 2.1	74.3 ± 4.2

Experimental

Chemistry

Melting points were uncorrected and recorded on a Barnstead 9001 Electrothermal melting point apparatus (Cole-Parmer, Vernon Hills, IL, USA). IR spectra were recorded with KBr discs on a PerkinElmer FT-IR Spectrum BX Spectrometer (PerkinElmer, Inc., Waltham, MA, USA) at a cm^{-1} scale. The ^{1}H-NMR or ^{13}C-NMR spectra were plotted on a JEOL 500 MHz spectrometer (JEOL, Ltd., Akishima, Tokyo Japan). Chemical shifts were expressed in δ (ppm) relative to a tetramethylsilane internal standard. Coupling constants are given in Hz. The mass spectra were recorded on a GCMC-QP 1000 EX Shimadzu gas chromatograph-mass spectrometer (GC-MS; Shimadzu Corp. Kyoto, Japan) at electron ionization (EI) of 70 eV. Elemental analyses (C, H, and N) were conducted at the Microanalytical Center of the Faculty of Science of Cairo University, Cairo, Egypt. They aligned with the proposed structures within ±0.1-0.2% of the theoretical values. All reagents were commercial grade and used without further purification. Reaction progress was monitored by thin layer chromatography (TLC) on precoated (0.75 mm) silica gel GF254 plates (Merck Group, Darmstadt, Germany). Products were visualized under ultraviolet (UV) light. Reactions that carried out by microwave irradiation were done using Biotage microwave reactor (Biotage® Initiator+, EXP EU, 400 W).

General procedure for the synthesis of 2-amino-5,6-dihydro-8-methoxy-4-phenyl (or substituted phenyl)-4H-benzo [h] chromene-3-carbonitrile 2a-e

A mixture of 2-substituted arylidenemalononitriles (0.001mol), namely; 2-Benzylidene malononitrile, 2-((furan-2-yl) methylene) malononitrile, 2-(4-chlorobenzylidene) malononitrile, 2-(3,4,5-trimethoxybenzylidene) malononitrile, or 2-(4-methoxybenzylidene) malononitrile, in ethanol (3 mL), were added to a mixture of 6-methoxy-1-tetralone (**1**) (0.001 mol), and few drops of piperidine. The reaction mixture was subjected to microwave irradiation at 130 ^{o}C, (400 W) for ~ 15 minutes. Completion of the reaction (was monitored by TLC). After cooling the product was filtered, and recrystallized from dilute ethanol to give compounds **2a-e.**

2-amino-5,6-dihydro-8-methoxy-4-phenyl-4H-benzo[h]chromene-3-carbonitrile 2a [(1)]

Compound 2a was prepared and characterized as described in our literature report [(1)]

2-amino-5,6-dihydro-8-methoxy-4-furyl-4H-benzo [h] chromene-3-carbonitrile 2b

Yield: 90%; m.p.: >300 ^{o}C; IR (υ_{max} / cm^{-1}): 3440, 3332 (NH_2), 2192 (CN); ^{1}H-NMR (DMSO-d_6): δ, 2.05 (m, 2H, CH_2-5), 2.4 (m, 2H, CH_2-6), 3.8 (s, 3H, OCH_3), 3.9 (s, 1H, CH, CH-4), 5.1 (s, 2H, NH_2), 6.6 (s, 1H, CH-7), 6.7-6.8 (m, 4H, Ar-H), 7.9 (d, *J*=7.5 Hz, 1H, CH-10); ^{13}C-NMR (DMSO-d_6): δ, 24.1 (CH_2, C-5), 27.08 (CH_2, C-6), 39.8 (CH, C-4) 55.1 (OCH_3), 56.4 (C-3) 108.8, 111.2, 113.4, 120.5, 121.1, 121.9, 126.9, 127.7, 128.5, 137.1, 139.7, 144.00, 159.1, 159.8 (Ar-C); MS: m/z (%): 320 (M^{+1}, 1.09) consistent with the molecular formula $C_{19}H_{16}N_2O_3$.

2-amino-5,6-dihydro-8-methoxy-4-*p*-chlorophenyl-4H-benzo[h]chromene-3-carbonitrile 2c

Yield: 65%; m.p.: >300 ^{o}C; IR (υ_{max} / cm^{-1}): 3354, 3310 (NH_2), 2194 (CN); ^{1}H-NMR ($CDCl_3$): δ, 2.55 (t, *J* =7.2 Hz, 2H, CH_2-5), 2.75 (t, *J* =7.2 Hz, 2H, CH_2-6), 3.7 (s, 1H, CH-4), 3.8 (s, 3H, OCH_3), 6.7 (s, 1H, CH-7), 6.8 (d, *J* =7 Hz, 1H, CH-9), 7.3 (d,d, *J* =7.5 Hz, 2H, CH-2`, 6`) 7.4 (d,d, *J* =7.5 Hz, 2H, CH-3`, 5`), 8.01 (d, *J* =7 Hz,1H, CH-10); ^{13}C-NMR ($CDCl_3$): δ, 25.9 (CH_2-5), 28.3 (CH_2-6), 37.9 (CH-4), 50.1 (C-3), 55.3 (OCH_3), 93.3, 112.6, 112.8, 119.4, 127.01, 127.9, 128.6, 128.9, 130.06, 131.05, 134.8, 141.03, 153.4, 161.3 (Ar-C and CN); MS: m/z (%): 364, 366 (M^{+}, 2.5) consistent with the molecular formula $C_{21}H_{17}ClN_2O_2$.

2-amino-5,6-dihydro-8-methoxy-4-(trimethoxyphenyl)-4H-benzo[h]chromene-3-arbonitrile 2d

Yield: 90%; m.p.: 185-187 ^{o}C; IR (υ_{max} / cm^{-1}): 3454, 3331 (NH_2), 2196 (CN); ^{1}H-NMR (DMSO-d_6): δ, 2.1 (m, 2H, CH_2-5), 2.5 (m, 2H, CH_2-6), 3.80 (s, 3H, OCH_3), 3.86 (s, 1H, CH-4), 3.90 (s, 3H, OCH_3), 3.97 (s, 6H, 2OCH_3), 6.5 (s, 1H, CH-7), 6.6 (d, *J*=7.5 Hz, 1H, CH-9), 7.1 (s, 2H, CH-2`, 6`), 7.6 (s, 2H, NH_2), 8.2 (d, *J*=7.5 Hz, 1H, CH-10); ^{13}C-NMR (DMSO-d_6): δ, 24.3 (CH_2-5), 28.5 (CH_2-6), 42.0 (CH, C-4), 50.9 (C-3), 55.1 (OCH_3), 56.2 (3OCH_3), 102.1, 102.5, 106.2, 108.2, 112.7, 113.1, 113.9, 125.9, 127.9, 132.8, 143.9, 153.2, 153.5, 159.3, (Ar-C and CN); MS: m/z (%): 420 (M^{+}, 1.8) consistent with the molecular formula $C_{24}H_{22}N_4O_3$.

2-amino-5,6-dihydro-8-methoxy-4-(*p*-methoxyphenyl)-4H-benzo[h]chromene-3-carbonitrile 2e

Yield: 88%; m.p.: >300 ^{o}C; IR (υ_{max} / cm^{-1}): 3448, 3354 (NH_2), 2189 (CN); ^{1}H-NMR ($CDCl_3$): δ, 2.2 (m, 2H, CH_2-5), 2.6 (m, 2H, CH_2-6), 3.7 (s, 1H, CH, C-4), 3.8 (s, 3H, OCH_3), 3.89 (s, 3H,

OCH_3), 6.7 (d, *J*=7 Hz, 1H, CH-9), 6.85 (m, 3H, Ar-H), 6.9 (d, *J*=7 Hz, 2H, CH-3`,5`), 7.7 (d, *J*=7 Hz, 1H, CH-10), 8.1 (s, 2H, NH_2); ^{13}C-NMR ($CDCl_3$): δ, 25.1 (CH_2-5), 27.8 (CH_2-6), 41.3 (CH, C-4), 50.4 (C-3) 55.2 (OCH_3), 55.3 (OCH_3), 93.3, 112.6, 112.8, 119.4, 127.01, 127.9, 128.6, 128.9, 130.06, 131.05, 134.8, 141.03, 153.4, 161.3MS: m/z (%): 361 (M^{+1}, 1.09) consistent with the molecular formula $C_{22}H_{20}N_2O_3$.

General procedure for the synthesis of (1E)-N`-(3-cyano-5,6-dihydro-8-methoxy-4-phenyl benzo[h]chromene or quinoline-2-yl) *N,N*-dimethylformamidine 3, 7

A mixture of 2a or 6a (0.001 mol) and DMF-DMA (2 mL) was refluxed for ~ 1 h., after cooling the solid product was filtered, washed with petroleum ether, dried, and recrystallized from ethanol to give compounds 3 and 7**,** respectively.

N`-(3-cyano-5,6-dihydro-8-methoxy-4-phenylbenzo[h]chromene-2-yl) *N,N*-dimethyl form-amidine 3

Yield: 90%; m.p.: 202-204 ^{o}C; IR (υ_{max} / cm^{-1}): 2191 (CN); ^{1}H-NMR (DMSO-d_6): δ, 1.7-2.1 (m, 2H, CH_2-5), 2.5-2.7 (m, 2H, CH_2-6), 2.9, 3.1 (2s, 6H, -$N(CH_3)_2$), 3.7 (s, 3H, OCH_3), 4.1 (s, 1H, CH-4), 6.7 (s, 1H, CH-7), 6.7 (d, *J*=8.4 Hz, 1H, CH-9), 7.2-7.3 (m, 5H, Ar-H), 7.5 (d, *J*=8.4 Hz, 1H, CH-10), 8.3 (s, 1H, N=CH); ^{13}C-NMR (DMSO-d_6): δ, 24.8 (CH_2-5), 27.6 (CH_2-6), 34.6 ($N(CH_3)_2$), 44.1 (CH, C-4), 55.5 (OCH_3), 73.0 (C-3), 108.8, 111.8, 113.7, 120.7, 121.9, 123.0, 127.6, 128.3, 129.0, 137.7, 140.7, 143.8, 154.7, 159.5, 159.7(Ar-C and CN); MS: m/z (%): 385 (M^{+}, 100) consistent with the molecular formula $C_{24}H_{23}N_3O_2$.

General procedure for the synthesis of 6,7-dihydro-4-amino-9-methoxy-5-phenyl-5H-benzo [h]chromeno[2,3-d]pyrimidine 4

A mixture of compound 3 (0.001 mol) and formamide (3 mL) was refluxed for 1 h., after cooling, the solid product was filtered, washed with dilute ethanol, dried, and recrystallized from ethanol to give compound 4.

Yield: 90%; m.p.: 260-262 ^{o}C; IR (υ_{max} / cm^{-1}): 3400, 3298 (NH_2); ^{1}H-NMR (DMSO-d_6): δ, 2.4 (m, 2H, CH_2-5), 2.7 (m, 2H, CH_2-6), 3.8 (s, 3H, OCH_3), 4.5 (s, 1H, CH-5), 6.85 (s, 1H, CH-8), 6.9 (d, *J*=7.5 Hz, 1H, CH-10), 7.4-7.7 (m, 5H, Ar-H), 8.3 (d, *J*=7.5 Hz, 1H, CH-11), 8.4 (s, 1H, pyrimidine), ^{13}C-NMR (DMSO-d_6): δ, 25.5 (CH_2-6), 27.6 (CH_2-7), 40.4 (CH-5), 55.7 (OCH_3),

106.1, 113.03, 113.8, 126.7, 128.4, 128.6, 129.6, 130.1, 137.7, 142.1, 145.9, 157.3, 157.9, 158.4, 161.8, 162.5 (Ar-C and CN); MS: m/z (%): 357(M^+, 2.9) consistent with the molecular formula $C_{22}H_{19}N_3O_2$.

General procedure for the synthesis of 2-amino-5,6-dihydro-8-methoxy-4-phenyl benzo[h] chromene-3-carboxamide 5

Compound **2a** (0.001mol) in concentrated sulfuric acid (5 mL) was stirred for ~ 30 min., at room temperature ~ 22 ^oC. After completion of the reaction, the mixture was poured onto cold water. The solid product was filtered and recrystallized from ethanol to give compound 5**.**
Yield: 85%; m.p.: 195-197 ^oC; IR (υ_{max} / cm^{-1}): 3311 (br, NH_2), 1670 (C=O); ^{1}H-NMR (DMSO-d_6): δ, 2.4 (m, 2H, CH-5), 2.7 (m, 2H, CH-6), 3.8 (s, 3H, OCH_3), 3.9 (br. s, 1H, CH-4), 6.8 (s, 1H, CH-7), 6.9 (d, *J*=7 Hz, 1H, CH-9), 7.3-7.5 (m, 6H, Ar-H), 8.3, 8.5 (2s, 4H, 2 NH_2), 8.5 (s, 2H, NH_2); ^{13}C-NMR (DMSO-d_6): δ, 24.3 (CH_2-5), 28.01 (CH_2-6), 55.9 (OCH_3), 56.2 (CH-4), 88.4 (C-3), 111.3, 117.2, 117.7, 124.2, 127.1, 128.5, 128.8, 129.2, 135.06, 136.5, 142.7, 153.6, 158.5, 163.7 (Ar-C, CO and CN); MS: m/z (%): 348(M^+, 2.9) consistent with the molecular formula $C_{21}H_{20}N_2O_3$.

General procedure for the synthesis of 2-amino-5,6-dihydro-8-methoxy-4-phenyl (or substituted phenyl) benzo [h] quinoline-3-carbonitrile 6a-e

A mixture of suitable 2-substituted arylidenemalononitriles (0.001mol), namely; 2-Benzylidene malononitrile, 2-((furan-2-yl) methylene) malononitrile, 2-(4-chlorobenzylidene) malononitrile, 2-(3,4,5-trimethoxybenzylidene) malononitrile, and/or 2-(4-methoxybenzylidene) malononitrile, in ethanol (3 mL), were added to a mixture of 6-methoxy-1-tetralone (**1**) (0.001 mol), ammonium acetate (0.002 mol), and few drops of piperidine. The reaction mixture was subjected to microwave irradiation at 130 ^oC, (400 W) for ~ 15 minutes. Completion of the reaction (was monitored by TLC), after cooling the product was filtered, and recrystallized from dilute ethanol to give compounds **6a-e.**

2-amino-5,6-dihydro-8-methoxy-4-phenyl benzo[h]quinoline-3-carbonitrile 6a [(1)]

Compound 6a was prepared and characterized as described in our literature report [(1)]

2-amino-5,6-dihydro-8-methoxy-4-*p*-furyl benzo [h] quinoline-3-carbo nitrile 6b

Yield: 65%; m.p.: >300 ^{o}C; IR (υ_{max} / cm^{-1}): 3425, 395 (NH_2), 2212 (CN); ^{1}H-NMR (DMSO-d_6): δ, 2.6 (m, 2H, CH_2-5), 2.77 (m, 2H, CH_2-6), 3.8 (s, 3H, OCH_3), 6.5 (m, 4H, Ar-H), 7.5-7.7 (m, 4H, 2Ar-H and NH_2); ^{13}C-NMR (DMSO-d_6): δ, 24.1 (CH_2-5), 28.2 (CH_2-6), 55.5 (OCH_3), 86.1, 106.8, 107.9, 111.2, 112.4, 1140.6, 119.5. 120.5, 123.1, 126.9, 144.00, 150.6, 155.8, 159.1, 159.8, 160.2 (Ar-C); MS: m/z (%): 317 (M^{+1}, 3) consistent with the molecular formula $C_{19}H_{15}N_3O_2$.

2-amino-5,6-dihydro-8-methoxy-4-*p*-chlorophenyl benzo [h] quinoline-3-carbonitrile 6c

Yield: 65%; m.p.: >300 ^{o}C; IR (υ_{max} / cm^{-1}): 3410, 3320 (NH_2), 2218 (CN) ; ^{1}H-NMR ($CDCl_3$): δ, 2.5 (t, *J*=7.2 Hz, 2H, CH_2-5), 2.6 (t, *J*=7.2 Hz, 2H, CH_2-6), 3.8 (s, 3H, OCH_3), 6.7 (s, 1H, CH-7), 6.8 (d, *J*=7.5 Hz, 1H, CH-9), 7.3 (m, 4H, Ar-H) 7.8 (d, *J*=7.5 Hz, 1H, CH-10), 8.7 (s, 2H, NH_2); ^{13}C-NMR ($CDCl_3$): δ, 26.2 (CH_2-5), 28 (CH_2-6), 55.2 (OCH_3), 83.3, 111.4, 113.7, 116.9, 127.01, 122.5, 124.1, 127.9, 129.0, 133.2, 134.5, 136.7, 149.2, 156.8, 158.1, 160.3 (Ar-C and CN); MS: m/z (%): 360, 361(M^{+}, 100, 23) consistent with the molecular formula $C_{21}H_{16}ClN_3O$.

2-amino-5,6-dihydro-8-methoxy-4-3,4,5-trimethoxyphenylbenzo[h]quinoline-3-carbonitrile 6d

Yield: 90%; m.p.: 175-177 ^{o}C; IR (υ_{max} / cm^{-1}): 3481, 3361 (NH_2), 2202 (CN) ; ^{1}H-NMR ($CDCl_3$): δ, 2.6 (m, 2H, CH_2-5), 2.75 (m, 2H,CH_2-6), 3.84 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3) 5.5 (s, 2H, NH_2), 6.5 (s, 1H, CH-7), 7.1 (s, 2H, CH-2`, 6`), 7.2 (d, *J*=7.5 Hz, 1H, CH-9), 7.6 (d, *J*=7.5 Hz, 1H, CH-10); ^{13}C-NMR ($CDCl_3$): δ, 24.3 (CH_2-5), 28.5 (CH_2-6), 55.3 (OCH_3), 56.2, 56.3 (3O-CH_3), 80.5, 102.1, 102.5, 105.7, 108.2, 112.7, 113.1, 113.9, 125.9, 126.3, 127.9, 143.9, 153.2, 153.3, 154.1, 159.3 (Ar-C and CN); MS: m/z (%): 417 (M^{+}, 2) consistent with the molecular formula $C_{24}H_{23}N_3O_4$.

2-amino-5,6-dihydro-8-methoxy-4-*p*-methoxyphenyl benzo [h] quinoline-3-carbonitrile 6e

Yield: 75%; m.p.: >300^{o}C; IR (υ_{max} / cm^{-1}): 3456, 3373 (NH_2), 2223 (CN) ; ^{1}H-NMR ($CDCl_3$): δ, 2.6 (t, *J*=6.6 Hz, 2H, CH_2-5), 2.7 (t, *J*=6.6 Hz, 2H, CH_2-6), 3.8, 3.9 (2s, 6H, 2-OCH_3), 5.07 (s, 2H, NH_2), 6.7 (s, 1H, CH-7), 6.8 (d, *J*=7 Hz, 1H, CH-9), 7.0 (d, d, *J*=7.5 Hz, 2H, CH3`, 5`), 7.6 (s, 2H, NH_2), 7.9 (d, *J*=9 Hz, 2H, CH-2`,6`), 8.1 (d, *J*=7 Hz, 1H, CH-10); ^{13}C-NMR ($CDCl_3$): δ,

24.5 (CH_2-5), 28.5 (CH_2-6), 53.8, 55.7 (2-OCH_3), 99, 112.7, 114.02, 114.4, 115.1, 124.01, 126.3, 127.9, 129.8, 129.9, 133.4, 130.7, 133.4, 158.8, 160.8, 161.1 (Ar-C and CN); MS: m/z (%): 357 (M^+, 4.1) consistent with the molecular formula $C_{22}H_{19}N_3O_2$.

N`-(3-cyano-5,6-dihydro-8-methoxy-4-phenylbenzo[h]quinoline-2-yl) *N,N*-dimethyl form-amidine 7

Yield: 85%; m.p.: 173-175 ^oC; IR (υ_{max} / cm^{-1}): 2212 (CN); ^{1}H-NMR (DMSO-d_6): δ, 2.6 (t, *J*=6.5 Hz, 2H, CH_2-5), 2.7 (t, *J*=6.5 Hz,, 2H, CH_2-6), 3.09, 3.20 (2s, 6H, $N(CH_3)_2$), 3.8 (s, 3H, OCH_3), 6.83 (s, 1H, CH-7), 6.93 (d,d, *J*=6.5 Hz, 1H, CH-4`), 7.3 (d, *J*=7.5 Hz, 2H, CH3`, 5`), 7.4-7.5 (m, 3H, Ar-H), 8.2 (d, 1H, *J*=8 Hz, CH-9), 8.8 (s, 1H, N=CH); ^{13}C-NMR (DMSO-d_6): δ, 24.7 (CH_2-5), 27.9 (CH_2-6), 34.8 ($N(CH_3)_2$), 55.7 (OCH_3), 99.2 (C-3) 112.9, 113.4, 117.9, 122.0, 127.0, 128.3, 128.9, 129.02, 129.09, 136.5, 141.4, 153.3, 153.7, 156.5, 161.3, 161.8 (Ar-C and CN); MS: m/z (%): 382 (M^+, 5.77) consistent with the molecular formula $C_{24}H_{22}N_4O$.

Synthesis of 6,7-dihydro-4-amino-9-methoxy-5-phenylpyrimido [4,5-b]benzo[h]quinoline 8

A mixture of compound 7 (0.001 mol) and formamide (2 mL) was refluxed for ~ 1 h., after cooling, the solid product was filtered, washed with dilute ethanol, dried, and recrystallized from ethanol to give compound 8.

Yield: 85%; m.p.: >300 ^oC; IR (υ_{max} / cm^{-1}): 3400, 3298 (NH_2); ^{1}H-NMR (DMSO-d_6): δ, 2.6 (m, 2H, CH_2-5), 2.7 (m, 2H, CH_2-6), 3.8 (s, 3H, OCH_3), 6.8 (s, 1H, CH-8), 6.9 (d, *J*=7 Hz, CH-10), 7.4-7.7 (m, 6H, Ar-H), 8.2 (d, *J*=7 Hz, 1H, CH-11), 8.5 (s, 1H, pyrimidine), ^{13}C-NMR (DMSO-d_6): δ, 26.2 (CH_2-5), 28.1 (CH_2-6), 55.7 (OCH_3), 116.1, 117.03, 117.8, 126.5, 128.3, 128.6, 129.6, 136.1, 137.8, 142.4, 145.5, 158.3, 158.9, 159.4, 161.8, 162.5 (Ar-C and CN); MS: m/z (%): 357 (M^+, 2.9) consistent with the molecular formula $C_{22}H_{19}N_3O_2$.

Synthesis of amino-5,6-dihydro-8-methoxy-4-phenyl benzo [h] quinoline-3-carboxamide 9

A mixture of 6a (0.001mol) and concentrated sulfuric acid (5 mL) was stirred for ~ 30 min., at room temperature at ~ 22 ^oC . After completion of the reaction, the mixture was poured onto cold water the solid product was filtered and recrystallized from ethanol to give compound 9.

Yield: 90%; m.p.: 290-292 ^{o}C; IR (υ_{max} / cm^{-1}): 3350 (br, NH_2), 1685 (C=O); ^{1}H-NMR (DMSO-d_6): δ, 2.6 (t, *J*=6 Hz, 2H, CH_2-5), 2.8 (t, *J*=6 Hz, CH_2-6), 3.8 (s, 3H, OCH_3), 6.7 (s, 1H, CH-7), 6.8 (d, *J*=7 Hz, 1H, CH-9), 7.1 (br. s, 2H, NH_2), 7.2-7.6 (m, 5H, Ar-H), 7.9 (d, *J*=7.5 Hz,, 1H, CH-10), 8.3 (s, 2H, NH_2); ^{13}C-NMR (DMSO-d_6): δ, 24.7 (CH_2-5), 27.9 (CH_2-6), 55.4 (OCH_3), 106.5, 112.9, 113.1, 115.0, 124.7, 125.8, 128.3, 129.5, 131.7, 134.9, 141.2, 145.6, 150.6, 153.3, 155.1, 162.1 (Ar-C and CN); MS: m/z (%): 345 (M^+, 1.9) consistent with the molecular formula $C_{21}H_{19}N_3O_2$.

General procedure for the synthesis of N'-(3-cyano-5,6-dihydro-8-methoxy-4-phenyl-4H-benzo[h]chromen-2-yl)-N-(substituted) formamidine 10-13

To a solution of compound 3 (0.001 mol) in glacial acetic acid (7 mL), morpholine, 4-aminopyridine, 2-amino-5-chloro pyridine, or 2-amino-4-chlorobenzothiazole (0.002 mol), were added and the mixture was refluxed for 2-3 h., excess solvent was evaporated under reduced pressure. The solid product was filtered, washed with water, dried, and recrystallized from ethanol to give compounds 10-13.

5,6-dihydro-8-methoxy-2-(morpholinomethyleneamino)-4-phenyl-4H-benzo[h] chromene-3-carbonitrile 10

Yield: 80%; m.p.: 86-88 ^{o}C; IR (υ_{max} / cm^{-1}): 2222(CN); ^{1}H-NMR (DMSO-d_6): δ, 2.1 (m, 2H, CH_2-5), 2.4 (m, 2H, CH_2-6), 2.5 (m, 4H, $2CH_2$-N), 3.1 (m, 4H, $2CH_2$-O), 3.7 (s, 3H, OCH_3), 4.1 (s, 1H, CH-4), 6.7-6.9 (m, 4H, Ar-H), 7.2-7.4 (m, 3H, Ar-H), 7.5 (d, *J*=7 Hz, 1H, CH-10), 8.3 (s, 1H, N=CH), ^{13}C-NMR (DMSO-d_6): δ, 24.8 (CH_2-5), 27.6 (CH_2-6), 44.09 (CH-4), 55.5 (OCH3), 64.6 ($2CH_2$-N), 72.9 ($2CH_2$-O), 78.6 (C-3), 105.06, 111.8, 113.7, 122.2, 123.02, 125.8, 127.6, 128.3, 128.6, 129.07, 140.8, 147.4, 154.7, 159.5, 159.7 (Ar-C and CN); MS: m/z (%): 427 (M^{+1}, 2) consistent with the molecular formula $C_{26}H_{25}N_3O_3$.

N'-(3-cyano-5,6-dihydro-8-methoxy-4-phenyl-4H-benzo[h]chromen-2-yl)-N-(pyridin-4-yl) formamidine 11

Yield: 90%; m.p.: 78-80 ^{o}C; IR (υ_{max} / cm^{-1}): 3443 (NH), 2219 (CN), ^{1}H-NMR ($CDCl_3$): δ, 2.07 (t, *J*=6.5 Hz, 2H, CH_2-5), 2.8 (t, *J*=6.5 Hz, 2H, CH_2-6), 3.8 (s, 3H, OCH_3), 4.5 (s, 1H, CH-4), 6.6 (s, 1H, CH-7), 7.1-7.38 (m, 10H, Ar-H), 7.9 (s, 1H, N=CH-), 7.99 (d, *J*=7.5 Hz, 1H, CH-10), 8.9

(s, 1H, NH); ^{13}C-NMR ($CDCl_3$): δ, 27.5 (CH_2-5), 28.7 (CH_2-6), 40.6 (CH-4), 55.4 (OCH_3), 62.3 (C-3), 112.3, 113.4, 113.7, 122.8, 127.4, 127.8, 128.14, 128.19, 128.3, 128.4, 128.70, 128.78, 128.81, 128.88, 128.90, 128.97, 129.1, 129.4, 130.1, 163.8 (Ar-C and CN); MS: m/z (%): 434 (M^+, 16) consistent with the molecular formula $C_{27}H_{22}N_4O_2$.

N-(5-chloropyridin-2-yl)-N'-(3-cyano-5,6-dihydro-8-methoxy-4-phenyl-4H-benzo[h] chromen -2-yl)formamidine 12

Yield: 85%; m.p.: 100-102 ^oC; IR (υ_{max} / cm^{-1}): 3471 (NH), 2220 (CN); ^{1}H-NMR (DMSO-d_6): δ, 2.2 (m, 2H, CH_2-5), 2.7 (m, 2H, CH_2-6), 3.8 (s, 3H, OCH_3), 4.4 (s, 1H, CH-4), 6.2 (d, *J*=7 Hz, 1H, CH-7), 7.30-7.37 (m, 9H, Ar-H), 7.6 (d, *J*=7 Hz, 1H, CH-10), 7.8 (s, 1H, N=CH), 10.9 (s, 1H, NH), ^{13}C-NMR (DMSO-d_6): δ, 25.02 (CH_2-5), 27.9 (CH_2-6), 40.8 (CH-4), 55.7 (OCH_3), 89.5 (C-3) 107.4, 110.9, 111.3, 113.09, 113.3, 113.7, 122.8, 127.06, 127.4, 127.9, 128.3, 128.5, 128.6, 128.9, 137.6, 140.7, 141.7, 142.8, 146.9, 165.1 (Ar-C and C=N); MS: m/z (%): 467, 468, 469 (M^+, 30, 8, 4) consistent with the molecular formula $C_{27}H_{21}ClN_4O_2$.

N-(4-chlorobenzothiazol-2-yl)-N'-(3-cyano-5,6-dihydro-8-methoxy-4-phenyl-4H-benzo [h] chromen-2-yl)formamidine 13

Yield: 86%; m.p.: 120-122 ^oC; IR (υ_{max} / cm^{-1}): 3348 (NH), 2210 (CN); ^{1}H-NMR ($CDCl_3$): δ, 2.4 (t, *J*=6 Hz, 2H, CH_2-5), 2.8 (t, *J*=6 Hz, 2H, CH_2-6), 3.8 (s, 3H, OCH_3), 4.2 (s, 1H, CH-4), 6.7 (d, *J*=14 Hz, 1H, CH-9), 6.8 (s, 1H, CH-7), 7.2-7.6 (m, 9H, Ar-H), 7.8 (s, 1H, N=CH), 12.4 (s, 1H, NH), ^{13}C-NMR ($CDCl_3$): δ, 24.1 (CH_2-5), 29.8 (CH_2-6), 55.6 (OCH_3), 41.9 (CH-4), 81.6 (C-3) 108.1, 111.02, 111.3, 113.1, 113.5, 113.7, 120.2, 122.01, 122.5, 127.1, 127.8, 129.1, 137.5, 141.5, 142.2, 145.3, 145.6, 148.1, 165.1, 166.8, 165.1 (Ar-C and CN); MS: m/z (%): 524, 525, 526 (M^+, 5, 4, 2) consistent with the molecular formula $C_{29}H_{21}ClN_4O_2S$.

General procedure for the synthesis of N'-(3-cyano-5,6-dihydro-8-methoxy-4-phenyl benzo [h]quinolin-2-yl)-N-(substituted) formamidine 14 and 15

A mixture of compound **7** (0.001 mol) and 4-aminopyridine or morpholine (2 mL) was refluxed for ~15-20 minutes, after cooling excess amine was evaporated and the reaction mixture was triturated with ethanol and poured onto cold water. The solid product was dried and recrystallized from ethanol to give compounds 14 and 15 respectively.

N'-(3-cyano-5,6-dihydro-8-methoxy-4-phenylbenzo[h]quinolin-2-yl)-N-(pyridin-4-yl) form amidine 14

Yield: 85%; m.p.: 119-121 ^{o}C; IR (υ_{max} / cm^{-1}): 3761 (NH), 2210 (CN); ^{1}H-NMR ($CDCl_3$): δ, 2.7 (t, *J*=6.5 Hz, 2H, CH_2-5), 2.8 (t, *J*= 6.5 Hz, 2H, CH_2-6), 3.8 (s, 3H, OCH_3), 6.7 (s, 1H, CH-7), 6.9 (dd, *J*=7.5 Hz, 2H, CH-2, 6, pyridine), 7.3 (d, *J*=7 Hz, 1H, CH-9), 7.5-7.3 (m, 8H, Ar-H), 8.2 (d, *J*=7 Hz, 1H, CH-10), 9.7 (s, 1H, NH), ^{13}C-NMR ($CDCl_3$): δ, 24.7 (CH_2-5), 27.9 (CH_2-6), 55.4 (OCH3), 98.6 (C-3), 106.5, 112.9, 113.1, 115.0, 124.7, 125.8, 128.3, 128.4, 128.9, 129.5, 131.7, 134.9, 141.2, 145.6, 150.6, 153.3, 155.1, 161.6, 162.1 (Ar-C and CN); MS: m/z (%): 431(M^+, 3) consistent with the molecular formula C_{27} H_{21} N_5 O.

5,6-dihydro-8-methoxy-2-(morpholinomethyleneamino)-4-phenylbenzo[h]quinoline-3-carbonitrile 15

Yield: 80%; m.p.: 94-96 ^{o}C; IR (υ_{max} / cm^{-1}): 2214 (CN); ^{1}H-NMR (DMSO-*d*$_6$): δ, 2.5 (m, 2H, CH_2-5), 2.7 (m, 2H, CH_2-6), 3.05 (m, 4H, 2CH_2-N), 3.1 (m, 4H, 2CH_2-O), 3.7 (s, 3H, OCH_3), 6.8 (s, 1H, CH-7), 6.9 (d, *J*=7.5 Hz, 1H, CH-9), 7.3 (d,d, *J*=6, Hz 2H, CH-2`, 6`), 7.4-7.5 (m, 3H, Ar-H), 8.2 (d, *J*=7.5 Hz, 1H, CH-10), 8.6 (s, 1H, N=CH), ^{13}C-NMR (DMSO-*d*$_6$): δ, 24.7 (CH_2-5), 27.9 (CH_2-6), 34.8 (2CH_2-N), 55.6 (OCH3), 66.4 (2CH_2-O), 99.2 (C-3), 112.8, 113.4, 117.8, 122.0, 126.9, 128.3, 128.6, 128.9, 129.1, 136.4, 141.4, 153.3, 153.7, 156.5, 161.3, 161.8 (Ar-C and CN); MS: m/z (%): 427 (M^+, 1.9) consistent with the molecular formula $C_{26}H_{24}N_4O_2$.

Cell lines and cell culture

HepG-2 (human liver carcinoma) and MCF-7 (human breast adenocarcinoma) cell lines, were purchased from the American Type Culture Collection (Rockville, MD, USA) and maintained in Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum (FBS), 100 U/ml penicillin, and 100 U/ml streptomycin, the cells were grown at 37 °C in a humidified atmosphere of 5% CO_2.

MTT cytotoxicity assay

Cytotoxicity evaluation against HepG-2 and MCF-7 was assessed by the 3-[4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay. This test is based on MTT reduction by mitochondrial dehydrogenases in viable cells [25-27]. Cells were placed in a 96 well

sterile microplate (5 x 10^4 cells/well) and incubated at 37 ^oC in serum-free media containing dimethyl sulfoxide (DMSO) and either a series of various concentrations (12.5, 25, 50 and 100 µM.) of each compound or doxorubicin (positive control) for 48 h. before the MTT assay. After incubation, the media were removed and 40 µL MTT (2.5 mg/ml) was added to each well. Incubation was resumed for an additional 4 h. The purple formazan dye crystals were solubilized with 200 µL DMSO. Absorbance was measured at 570 nm in a Spectra Max Paradigm Multi-Mode microplate reader (Molecular Devices, LLC, San Jose, CA, USA) [25-27]. Relative cell viability was expressed as the mean percentage of viable cells compared to the untreated control cells.

Statistical analysis

All experiments were conducted in triplicate and repeated on three different days. All values were reported as mean ± SD. IC_{50} were determined by SPSS Inc probit analysis (IBM Corp., Armonk, NY, USA).

Conclusion

The present study deals with easy and rapid methods of the synthesis of new series of benzo[h]chromene and benzo[h] quinoline derivatives. Cytotoxic evaluation of thirteen compounds, against HepG-2 (human liver carcinoma) and MCF-7 (human breast adenocarcinoma) cell lines was estimated. All the tested compounds, showed significant cytotoxic activity against HepG-2 carcinoma cells, two of them were more potent than the reference drug doxorubicin. In addition, it is obvious that all examined compounds had significant cytotoxic activity against MCF-7, and were more potent than the effect of doxorubicine. Benzo[h]chromene 3 and benzo[h] quinoline 7 were established by x-ray crystallography.

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