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$Sc(OTf)_3$ Catalyzed Synthesis of Novel 6-Phenyl-6*H*-chromeno[4,3-*b*]quinolines and Evaluation of Their Cytotoxicity[1]

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Abstract—Novel 6-phenyl-6*H*-chromeno[4,3-*b*]quinoline derivatives have been prepared by reaction of 4-chloro-2-phenyl-2*H*-chromene-3-carbaldehyde with various aromatic amines using 5 mol % of $Sc(OTf)_3$ in acetonitile. This is the first example of one-pot synthesis of 6-phenyl-6*H*-chromeno[4,3-*b*]quinoline from 4-chloro-2-phenyl-2*H*-chromene-3-carbaldehyde at ambient temperature. Preliminary evaluation of cytotoxic activity of these chromeno[4,3-*b*]quinoline derivatives has been carried out. Some products exhibited anti cancer activity against two carcinoma cell lines A549 and B-16.

Keywords: 6-phenyl-6*H*-chromeno[4,3-*b*]quinoline, $Sc(OTf)_3$, anti cancer

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INTRODUCTION

Most of Lewis acids decompose in presence of water [1], whereas $Sc(OTf)_3$ is stable and acts as a Lewis acid catalyst in water solutions. Its catalytic activity could be higher than that of $[Ln(OTf)_3]$ [2].

Chromenes are oxygen containing heterocycles that exhibit distinctive pharmaceutical activities such as antimicrobial [3], anticancer [4], antioxidant, and anti-inflammatory [5]. Quinoline derivatives also found vast applications as pharmaceuticals [6]. A combination of chromene with quinoline in one molecule, for example 6, 6-dimethyl-6*H*-chromeno[4, 3-*b*]quinoline [7], has been studied and it demonstrated promising bioactivity. Herein, we report the synthesis of 6-phenyl-6*H*-chromeno[4, 3-*b*]quinolines from 4-chloro-2-phenyl-2*H*-chromene-3-carbaldehyde and aniline and its derivatives by using $Sc(OTf)_3$ as a catalyst and evaluation of their anticancer activity.

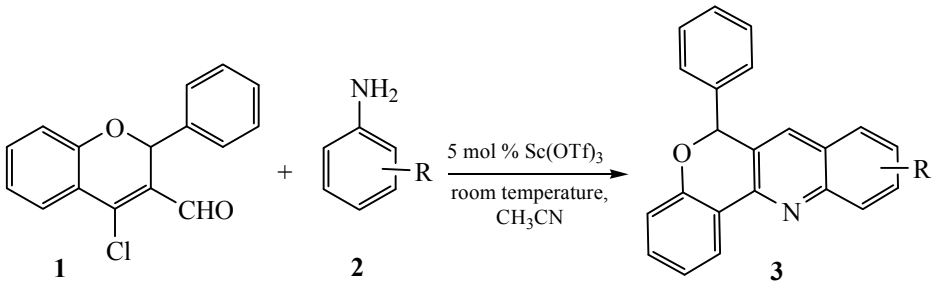
[1] The text was submitted by the authors in English.

RESULTS AND DISCUSSION

6-Phenyl-6*H*-chromeno[4, 3-*b*]quinoline (**3a**) was synthesized previously from (*E*)-3-(2-nitrobenzylidene)-2-phenylchroman-4-one using $TiCl_2$ as a catalyst [8]. We developed the synthetic approach to 6-phenyl-6*H*-chromeno[4, 3-*b*]quinoline (**3**) from 4-chloro-2-phenyl-2*H*-chromene-3-carbaldehyde (**1**) and anilines (**2**) under $Sc(OTf)_3$ catalysis (Scheme 1). The starting material **1** was prepared from 2-phenylchroman-4-one under Vilsmeier–Haack reaction conditions [9]. It reacted with aromatic amines [10] in CH_3CN under $Sc(OTf)_3$ catalysis at room temperature to give **3** with high yields (Table 1). The products were characterized by FT-IR, ^1H and ^{13}C NMR and mass spectroscopy.

In all cases chromeno[4,3-*b*]quinoline was found to be the major product. Among several solvents, ethanol, tetrahydrofuran, toluene, benzene, dichloromethane, and CH_3CN, the latter one was found to be the most efficient. Reaction of compound **1** with **2** in the presence of 5 mol % of $BF_3.OEt_2$, $Ln(OTf)_3$ or $Sc(OTf)_3$ gave **3a** in 52%, 76%, and 95% yields respectively (Table 2).

Scheme 1. Synthesis of 6-phenyl-6*H*-chromeno [4,3-*b*]quinoline from 4-chloro-2-phenyl-2*H*-chromene-3-carbaldehyde.



Cytotoxicity. Some chromeno[4, 3-*b*]quinoline homologous were subjected to *insemination* cytotoxicity to human alveolar epithelial cell line (A549) and mouse macrophage cell (B-16). Cytotoxicity of test compounds in cells was determined by MTT [3-(4,5-dimethylthaizol-2-yl)-2, 5-diphenyl tetrazolium bromide] assay.

In general, majority of the tested compounds demonstrated moderate to strong cytotoxicity to the above two cell lines. The product **3c** demonstrated most potent cytotoxicity to A549 (IC50 0.19 μg/mL) (Table 3) and **3f** exhibited the strongest cytotoxicity to B-16 cell and significant cytotoxicity to A549cell lin. Both compounds **3c** and **3f** (Table 3) contain the methoxy substituent on the quinoline ring, which indicated its influence on cytotoxicity.

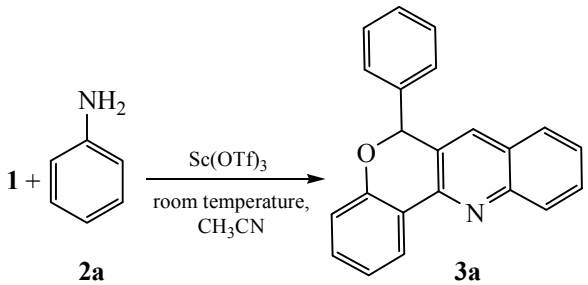
EXPERIMENTAL

All chemicals were purchased from Aldrich and Merk. Melting points were measured in open capillary tubes. IR spectra were recorded as KBr pellets with a Shimadzu FT-IR-8400s spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured with a Bruker Avance II 400 spectrometer using TMS as the internal standard in $CDCl_3$ solutions. Mass spectra were measured with a Hewlett-Packard 1100 LC/MSD spectrometer.

Synthesis of 6-phenyl-6*H*-chromeno[4,3-*b*]quinolines (3a–3i). To a solution of 4-chloro-2-phenyl-2*H*-chromene-3-carbaldehyde (**1**) (1 equiv.) and $Sc(OTf)_3$ (5 mol %) in dry CH_3CN under argon at room temperature was added slowly a solution of aromatic amine **2** (1.5 equiv.) through a syringe pump over 30 min. The mixture was stirred for 30 min. Progress of the reaction was monitored by TLC. Upon completion of the process the solvent was removed under reduced pressure and the residue subjected to column chromatography on silica gel (EtOAc–hexane) to give the pure product.

6-Phenyl-6*H*-chromeno[4,3-*b*]quinoline (3a). Yield 98%, white solid, mp 184–186°C. IR spectrum, ν, cm^{-1}: 3035 (Ar, C–H), 2923 (=C–H), 1723 (C=C), 1028 (C–O). ^{1}H NMR spectrum, δ, ppm: 8.52 d.d (1H, Ar-H, J = 7.8, 1.6 Hz), 8.14 d (1H, Ar-H, J = 8.5 Hz), 7.50–7.72 m (1H, Ar-H), 7.62 d (1H, Ar-H, J = 8.1 Hz), 7.49–7.40 m (7H, Ar-H), 7.45–7.26 m (1H, Ar-H), 7.19–7.14 m (1H, Ar-H), 7.04 d.d (1H, Ar-H, J = 8.1, 0.9 Hz), 6.34 s (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 156.5, 148.9, 148.1, 138.7, 132.9, 132.0, 129.8, 129.3, 128.9, 128.8, 128.5, 128.2, 127.8, 127.5, 126.2,

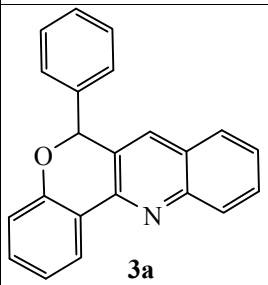
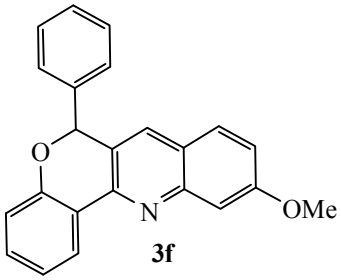
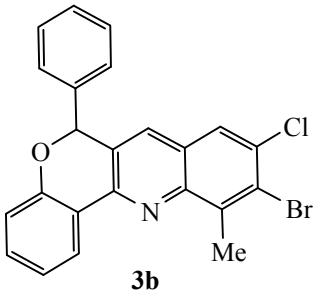
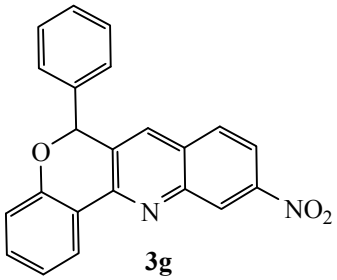
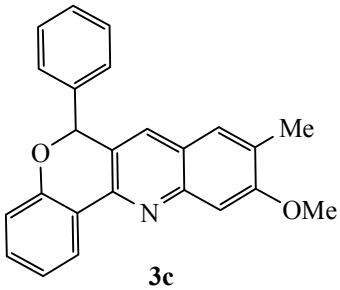
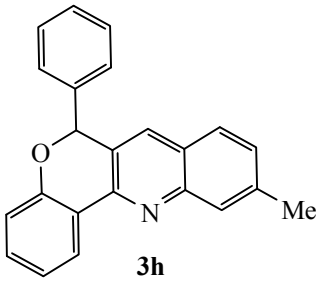
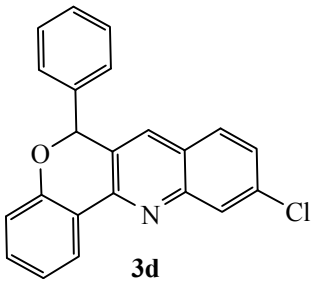
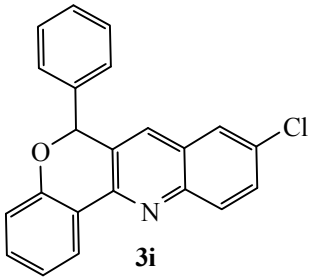
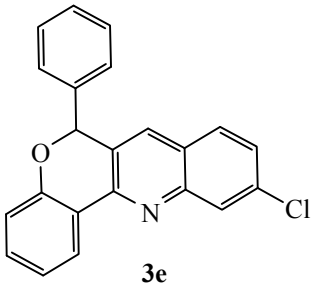
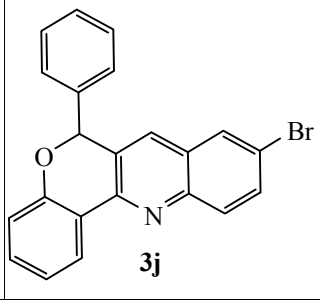
Table 1. Effect of catalyst on the reaction of chloroaldehyde (**1**) and aniline (**2a**)



Entry	Acid	Molecular mass, mol %	Solvent[a]	Time, h	Yield[b] of **3**, %
1	$BF_3 \cdot OEt_2$	5	CH_3CN	6	52
2	$BF_3 \cdot OEt_2$	5	Toluene	6	Traces
3	$Ln(OTf)_3$	5	CH_3CN	3	76
4	$Sc(OTf)_3$	5	CH_3CN	1	95
5	$Sc(OTf)_3$	5	Water	4	10
6	$AlCl_3$	5	CH_3CN	6	10

[a] All the reactions were carried out using **1** (1.0 mmol) and **2a** (1.5 mmol). [b] Isolated yield.

Table 2. Synthesis of 6-phenyl-6*H*-chromeno[4,3-*b*]quinoline (**3**) from **1** (see Scheme 1)

Entry	Compound **2**	Product **3**	Yield[a], %	Entry	Compound **2**	Product **3**	Yield[a], %
1	**2a**; R = H	 **3a**	81	6	**2f**; R = 3-OMe	 **3f**	81
2	**2b**; R = 2-Me, 3Br, 5-Cl	 **3b**	80	7	**2g**; R = 3NO_2	 **3g**	81
3	**2c**; R = 3-OMe, 4-Me	 **3c**	78	8	**2h**; R = 3-Me	 **3h**	80
4	**2d**; R = 3-Cl	 **3d**	83	9	**2i**; R = 4-Cl	 **3i**	78
5	**2e**; R = 3-Br	 **3e**	79	10	**2j**; R = 4-Br	 **3j**	81

[a] Yield refers to pure product after column chromatography.

125.6, 123.2, 122.6, 117.7, 80.3. $C_{22}H_{15}NO$. MS (ESI): *m*/*z* 310 $[M + H]^+$.

10-Bromo-8-chloro-11-methyl-6-phenyl-6*H*-chromeno[4,3-*b*]quinoline (3b). Yield 81%, white solid, mp 195–196°C. IR spectrum, ν, cm^{-1}: 3025 (Ar, C–H), 2974 (=C–H), 1704 (C=C), 1019 (C–O). ^1H NMR spectrum, δ, ppm: 8.60 d (1H, Ar-H, *J* = 2.5 Hz), 8.07 d (1H, Ar-H, *J* = 8.9 Hz), 7.67–7.62 m (2H, Ar-H), 7.45 d.d (1H, Ar-H, *J* = 8.6, 2.5 Hz), 7.41 s (1H, Ar-H), 7.31 d (2H, Ar-H, *J* = 8.1 Hz), 7.25 d (2H, Ar-H, *J* = 7.9 Hz), 6.92 d (1H, *J* = 8.6 Hz), 6.32 s (1H, =CH, 2.40 s (3H, CH_3). ^{13}C NMR spectrum, δ, ppm: 156.6, 149.1, 138.2, 132.4, 132.2, 132.0, 130.8, 130.6, 129.5, 129.1, 128.9, 128.1, 128.0, 126.4, 125.6, 122.7, 117.7, 80.2, 10.0. $C_{23}H_{15}BrClNO$. MS (ESI): *m*/*z* 438 $[M + H]^+$.

10-Methoxy-9-methyl-6-phenyl-6*H*-chromeno-[4,3-*b*]quinoline (3c). Yield 82%, white solid, mp 203–205°C. IR spectrum, ν, cm^{-1}: 3025 (Ar, C–H), 2929 (=C–H), 1724 (C=C), 1035 (C–O). ^1H NMR spectrum, δ, ppm: 8.58 d (1H, Ar-H, *J* = 2.5 Hz), 8.04 d (1H, Ar-H, *J* = 9.2 Hz), 7.42–7.39 m (2H, Ar-H), 7.38–7.31 m (3H, Ar-H), 7.24 d (2H, Ar-H, *J* = 7.9 Hz), 6.94 d (1H, *J* = 2.7 Hz), 6.90 d (1H, *J* = 8.6 Hz), 6.31 s (1H, =CH), 3.88 s(3H, OCH_3), 2.40 s (3H, CH_3). ^{13}C NMR spectrum, δ, ppm: 159.6, 148.1, 137.2, 132.1, 132.1, 132.8, 130.0, 129.6, 129.4, 129.0, 128.6, 128.3, 128.1, 126.2, 125.4, 122.4, 117.7, 80.8, 56.8 15.2. $C_{24}H_{19}NO_2$. MS (ESI): *m*/*z* 354 $[M + H]^+$

10-Chloro-6-phenyl-6*H*-chromeno[4,3-*b*]quinoline (3d). Yield 81%, white solid, mp 172–174°C. IR spectrum, ν, cm^{-1}: 3063 (Ar, C–H), 2945 (=C–H), 1743 (C=C), 1023 (C–O).^1H NMR spectrum, δ, ppm: 8.54 d (1H, Ar-H, *J* = 6.9 Hz), 8.15 s (1H, Ar-H), 7.63 d.d (2H, Ar-H, *J* = 12.0, 3.0 Hz), 7.51–7.35 m (7H, Ar-H, 7.19 d (1H, Ar-H, *J* = 7.5 Hz), 7.07 t (1H, Ar-H, *J* = 12.2 Hz), 6.34 s (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 158.6, 149.6, 149.1, 139.7, 134.9, 134.0, 131.8, 131.2, 129.0, 128.7, 128.4, 128.1, 127.9, 127.6, 126.3, 125.8, 123.4, 122.9, 118.7, 81.3. $C_{22}H_{14}ClNO$. MS (ESI): *m*/*z* 344 $[M + H]^+$.

10-Bromo-6-phenyl-6*H*-chromeno[4,3-*b*]quinoline (3e). Yield 85%, white solid, mp 204–206°C. IR spectrum, ν, cm^{-1}: 3085 (Ar, C–H), 2966 (=C–H), 1752 (C=C), 1074 (C–O).^1H NMR spectrum, δ, ppm: 8.62 d (1H, Ar-H, *J* =7.2 Hz), 8.23 s (1H, Ar-H), 7.80 d (2H, Ar-H, *J* = 12.0 Hz), 7.72–7.52 m (7H, Ar-H), 7.23 d (1H, Ar-H, *J* = 7.6 Hz), 7.10 t (1H, Ar-H, *J* = 12.5 Hz), 6.89 s (1H, =CH). ^{13}C NMR spectrum, δ, ppm: δ 156.6, 149.1, 138.2, 132.4, 132.2, 132.0, 130.8, 130.6, 129.5, 129.1, 128.9, 128.1, 128.0, 126.4, 125.6, 122.78, 117.7, 80.2. $C_{22}H_{14}BrNO$. MS (ESI): *m*/*z 389* $[M + H]^+$.

Table 3. Cytotoxicity of novel polycyclic quinoline analogs **3**

Entry	Compound **3**	Cytotoxicity to carcinoma cells $1C_{50}$[a], μM	
		A549	B-16
1	**3a**	18.76	11.45
2	**3b**	22.42	12.43
3	**3c**	**0.19**	8.47
4	**3d**	9.58	35.70
5	**3e**	14.02	12.00
6	**3f**	**3.20**	**1.90**
7	**3g**	No activity	7.69
8	**3h**	11.36	11.30
9	**3i**	20.36	12.42
10	**3j**	11.26	7.32
Doxorubicin (control)		<0.1	<0.1

[a] The IC_{50} value corresponded to the compound concentration causing 50%mortality in carcinoma after 72 h incubation. The data is a mean value of three repeated experiments.

10-Methoxy-6-phenyl-6*H*-chromeno[4,3-*b*]quinoline (3f). Yield 81%, white solid, mp 184–186°C. IR spectrum, ν, cm^{-1}: 3037 (Ar, C–H), 2977 (=C–H), 1778 (C=C), 1029 (C–O). ^1H NMR spectrum, δ, ppm: 8.86 d (1H, Ar-H, *J* = 7.9, Hz), 8.12 d (1H, Ar-H, *J* = 7.5 Hz), 7.80-7.72 m (1H, Ar-H), 7.52 d (1H, Ar-H, *J* = 8.3 Hz), 7.49–7.30 m (6H, Ar-H), 7.25-7.16 m (1H, Ar-H), 7.06–6.94 m (1H, Ar-H), 6.64 d.d (1H, Ar-H, *J* = 8.9, 1.1 Hz), 6.44 s (1H, =CH), 3.83 s (3H, OCH_3). ^{13}C NMR spectrum, δ, ppm: 57.6, 156.1, 146.6, 144.2, 138.8, 131.6, 131.4, 130.7, 128.8, 128.8, 128.5, 128.3, 125.1, 123.4, 122.6, 122.5, 117.6, 105.39, 80.3, 55.5. $C_{22}H_{17}NO_2$. MS (ESI): *m*/*z* 340 $[M + H]$.

10-Nitro-6-phenyl-6*H*-chromeno[4,3-*b*]quinoline (3g). Yield 76%, white solid, mp 224–226°C. IR spectrum, ν, cm^{-1}: 3047 (Ar, C–H), 2943 (=C–H), 1706 (C=C), 1082 (C–O). ^1H NMR spectrum, δ, ppm: 8.94 d (1H, Ar-H, *J* = 7.9 Hz), 8.35 s (1H, Ar-H), 7.93 d (2H, Ar-H, *J* = 9.0 Hz), 7.56–7.45 m (6H, Ar-H), 7.19–7.10 m (2H, Ar-H), 7.06 t (1H, Ar-H, *J* = 11.2 Hz), 6.54 s (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 161.6, 155.6, 150.1, 140.7, 137.0, 135.1, 133.2, 133.0, 130.0, 129.7,

128.9, 128.5, 127.6, 127.3, 126.2, 125.4, 123.2, 122.4, 119.8, 82.5. $C_{22}H_{14}N_2O_3$. MS (ESI): *m*/*z* 355 $[M + H]^+$.

10-Methyl-6-phenyl-6*H*-chromeno[4,3-*b*]quinoline (3h). Yield 83%, white solid, mp 164–166°C. IR spectrum, ν, cm^{-1}: 3087 (Ar, C–H), 2912 (=C–H), 1743 (C=C), 1020 (C–O). ^{1}H NMR spectrum, δ, ppm: 8.46 d (1H, Ar-H, *J* = 7.2, Hz), 8.09 d (1H, Ar-H, *J* = 8.2 Hz), 7.50-7.42 m (1H, Ar-H), 7.35 s (1H, Ar-H), 7.29–7.18 m (6H, Ar-H), 7.15–7.09 m (1H, Ar-H), 7.04–6.84 m (1H, Ar-H), 6.34 d (1H, Ar-H, *J* = 7.8 Hz), 6.24 s (1H, =CH), 2.79 s (3H, CH_3). ^{13}C NMR spectrum, δ, ppm: 157.5, 156.8, 145.5, 143.3, 139.6, 132.0, 131.6, 130.8, 129.9, 129.7, 128.5, 128.2, 125.3, 123.2, 122.3, 122.2, 117.8, 105.49, 80.6, 25.6. $C_{22}H_{17}NO$. MS (ESI): *m*/*z* 324 $[M + H]$.

9-Chloro-6-phenyl-6*H*-chromeno[4,3-*b*]quinoline (3i). Yield 86%, white solid, mp 202–204°C. IR spectrum, ν, cm^{-1}: 3045 (Ar, C–H), 2941 (=C–H), 1713 (C=C), 1098 (C–O). ^{1}H NMR spectrum, δ, ppm: 8.45 d (1H, Ar-H, *J* = 6.8 Hz), 8.23 s (1H, Ar-H), 7.63 d.d (2H, Ar-H, *J* = 11.1, 4.2 Hz), 7.51–7.35 m (7H, Ar-H, 7.19 s (1H, Ar-H), 7.08 d (1H, Ar-H, *J* = 11.2 Hz), 6.54 s (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 157.9, 149.8, 149.2, 139.4, 134.2, 133.2, 131.9, 131.0, 129.2, 128.9, 128.5, 128.2, 127.4, 127.3, 126.2, 124.8, 123.6, 121.8, 117.6, 80.2. $C_{22}H_{14}ClNO$. MS (ESI): *m*/*z* 344 $[M + H]^+$.

9-Bromo-6-phenyl-6*H*-chromeno[4,3-*b*]quinoline (3j). Yield 82%, white solid, mp 210–212°C. IR spectrum, ν, cm^{-1}: 3041 (Ar, C–H), 2941 (=C–H), 1713 (C=C), 1041 (C–O).^{1}H NMR spectrum, δ, ppm: 8.36 d (1H, Ar-H, *J* = 7.2 Hz), 8.19 s (1H, Ar-H), 7.59 d.d (2H, Ar-H, *J* = 10.2, 3.2 Hz), 7.68–7.69 m (7H, Ar-H, 7.26 s (1H, Ar-H), 7.06 d (1H, Ar-H, *J* = 10.4 Hz), 6.53 s (1H, =CH). ^{13}C NMR spectrum, δ, ppm: 156.2, 148.6, 146.3, 138.2, 134.9, 133.5, 131.6, 131.3, 129.1, 128.1, 128.2, 128.3, 127.2, 126.9, 126.2, 124.6, 123.4, 121.6, 117.2, 80.8. $C_{22}H_{14}BrNO$. MS (ESI): *m*/*z* 389 $[M + H]^+$.

CONCLUSIONS

We have worked out the synthetic approach to novel 6-phenyl-6*H*-chromeno[4,3-*b*]quinoline derivatives by the reaction of 4-chloro-2-phenyl-2*H*-chromene-3-carbaldehyde with aromatic amines. Some of the products (**3c** and **3f**) demonstrated cytotoxicity against two carcinoma cell lines.

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