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Synthesis of halogen derivatives of benzo[*h*]chromene and benzo[*a*]anthracene with promising antimicrobial activities

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Abstract

The synthesis of novel 7-(4-halophenyl)-8,9-dihydro-7*H*-12-oxa-9,11-diaza-benzo[*a*]anthracene derivatives has been reported. The key intermediate 3-amino-9-chloro-1-(4-halophenyl)-1*H*-benzo[*h*]chromene-2-carbonitrile (**3**) was obtained by treating 4-halobenzylidenmalononitriles (**1a**–**c**) and ethyl 4-halobenzylidenmalonates (**1d**–**f**) with 4-chloro-1-naphthol (**2**) in ethanolic piperidine solution. Antimicrobial activity was shown for most of the synthesized compounds. © 2002 Éditions scientifiques et médicales Elsevier SAS. All rights reserved.

Keywords: 4-Halobenzylidenmalononitriles; Ethyl 4-halobenzylidenmalonates; 4-Chloro-1-naphthol; Benzo[*h*]chromenes; Benzo[*a*]anthracenes; Antimicrobial activity

1. Introduction

Chromenes and fused chromenes are biologically interesting compounds with antimicrobial activities [1–3], inhibitors of influenza virus sialidases [4,5], DNA stand-breaking activity and mutagenicity [6], antiviral agent [7], antiproliferation agent [8], sex pheromone [9], antitumor [10] and central nervous system (CNS) activity [11].

Benzylidenmalononitriles and ethyl benzylidenmalonates are versatile reagents for construction of heterocyclic system [12–14]. They are prone to react with a variety of compounds containing acidic hydrogen atoms to provide Michael adducts as intermediate, which undergo spontaneous cyclization to β-enaminonitriles and β-enaminocarboxylic esters, respectively [15–19]. The present study is part of our program aimed at developing new approaches for the synthesis of fused heterocyclic systems. We report here the synthesis of benzo[*h*]chromene derivatives and their utility as building blocks in the synthesis of novel fused chromenes aiming at the evaluation of their antimicrobial activity.

2. Chemistry

In continuation of our previous work [1–3,15–17] on the synthesis of fused chromenes using enaminonitriles, we report here the synthesis of a variety of new heterocyclic compounds. Thus condensation of various substituted benzylidenmalononitriles (**1a**–**c**) and ethyl benzylidenmalonates (**1d**–**f**) with 4-chloro-1-naphthol (2) in ethanolic piperidine afforded 1:1 adducts (Scheme 1).

On the basis of ^{1}H NMR and UV data, structure **4** was excluded [15–19]. Structure **3** was established on the basis of ^{1}H NMR spectra, which showed 1-*H* at δ 4.97–5.00 ppm **3a**–**f**. The UV spectrum of **3a**–**f** revealed a weak shoulder [16–20] characteristic for 1*H*-chromene at λ_{max} ($CHCl_3$) 275 nm (log ε 2.70–2.86), respectively.

Interaction of 3-amino-9-chloro-1-(4-halophenyl)-1*H*-benzo[*h*]chromene-2-carbonitrile (**3a**–**c**) with acetic anhydride for 30 min. afforded the *N*-acetyl derivative (**5a**–**c**), while heating of **3a**–**c** with acetic anhydride for 6 h afforded 5-chloro-10-methyl-7-(4-halophenyl)-8,9-dihydro-7*H*-12-oxa-9,11-diaza-benzo[*a*]anthracene-8-one (**6a**–**c**) (Scheme 1). Structure **5a**–**c** was established on the basis of IR which showed the presence of CN (2214, 2219, 2222 cm^{-1}) and CO of acetyl (1705, 1712, 1728

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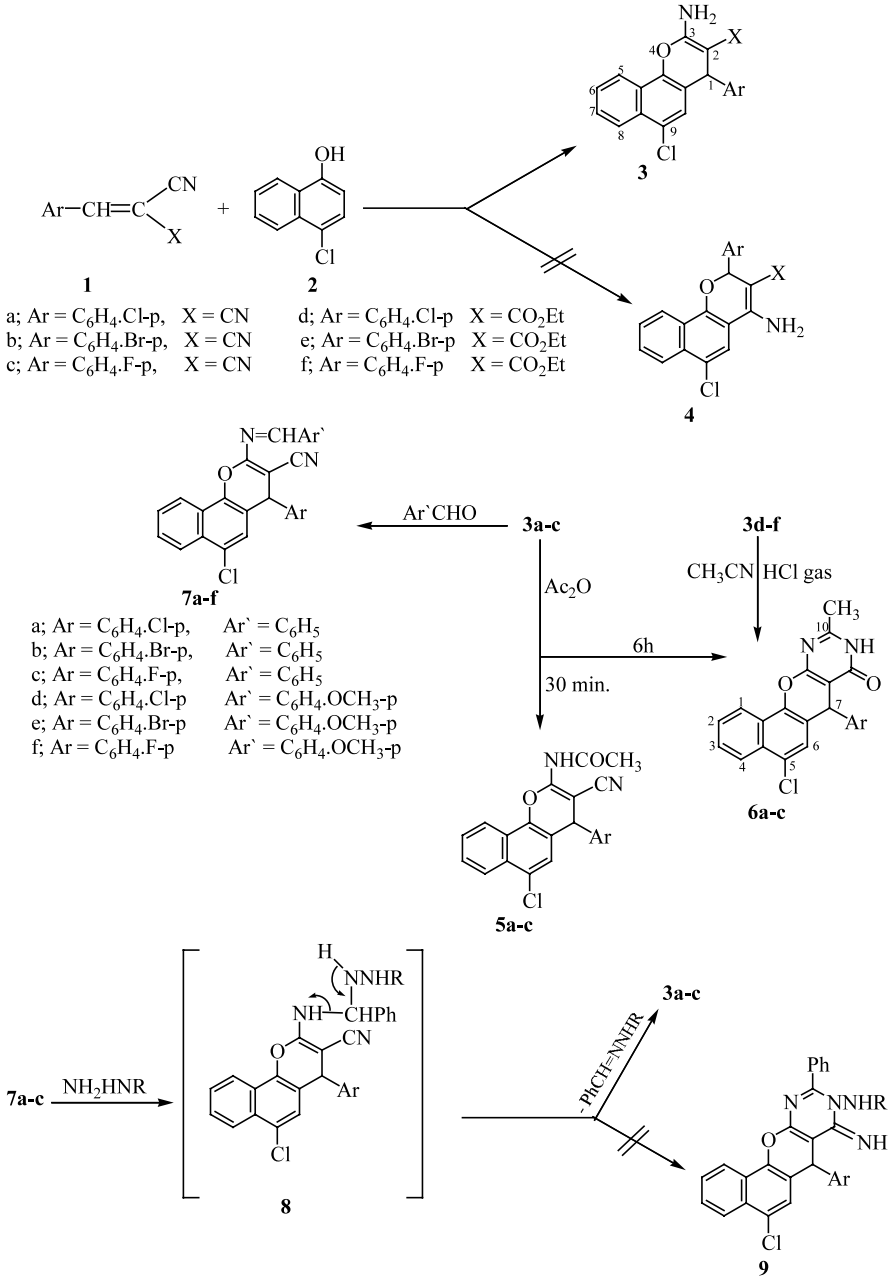
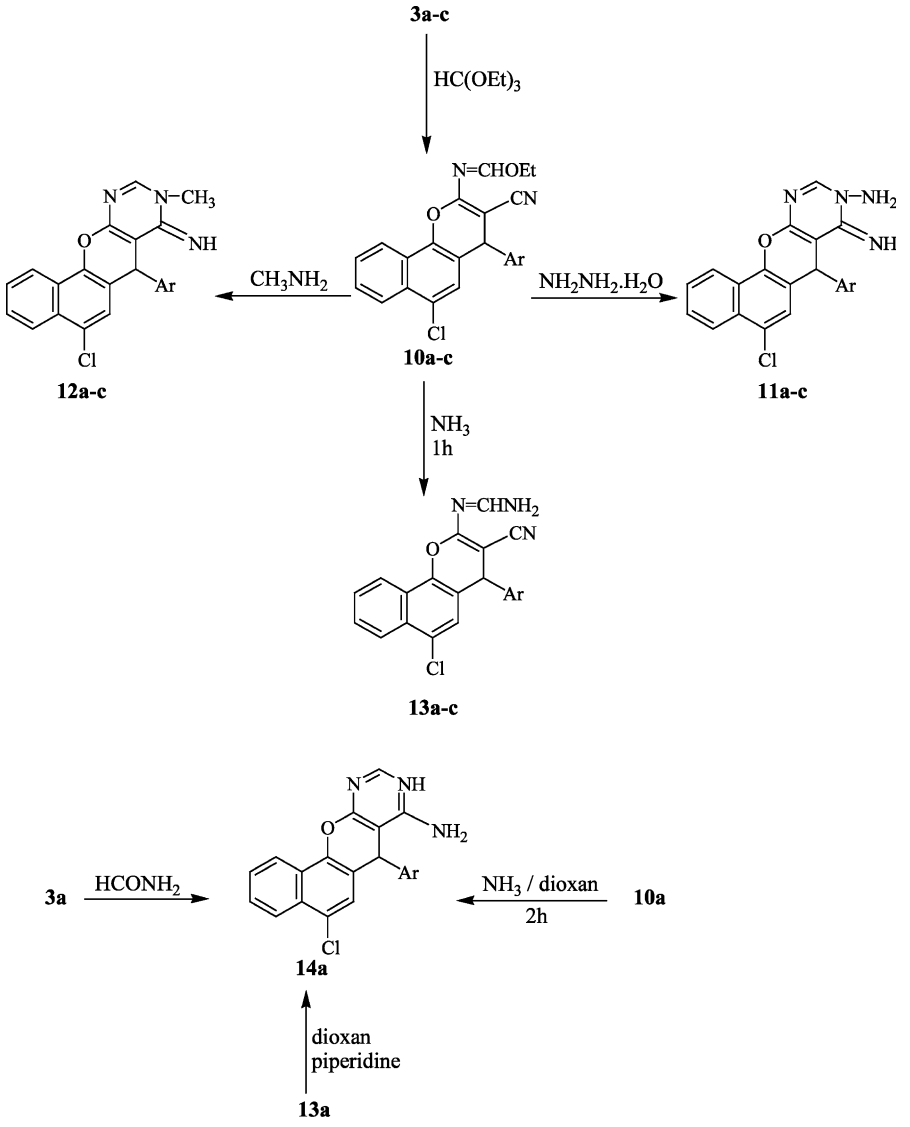
cm^{-1}), respectively, while for **6a**–**c** the absence of CN and the presence of CO of amide (1659, 1658, 1659 cm^{-1}), respectively. ^1H NMR spectra for **5a**–**c** revealed the presence of signal at δ 2.55, 2.66, 2.71 ppm (3H, s, $COCH_3$) and 10.14, 10.35, 10.40 ppm (1H, br, NH), while for **6a**, **c** showed δ 2.51, 2.52 (3H, s, 10-CH_3) and 12.60, 12.63 ppm (1H, br, NH; exchangable). Structures **6a**–**c** were also supported by an independent synthesis of the same products from **3d**–**f** and acetonitrile in the presence of HCl gas [21] (m.p. and mixed m.p.) (Scheme 1).

Condensation of **3a**–**c** with benzaldehyde or 4-methoxybenzaldehyde in dioxan-piperidine solution under reflux afforded the corresponding 3-arylmethyleneamino derivatives (**7a**–**f**) (Scheme 1). When 3-arylmethyleneamino-9-chloro-1-(4-halophenyl)-1*H*-benzo[*h*]chromene-2-carbonitriles (**7a**–**c**) were treated with hydrazine or phenylhydrazine in absolute ethanol under stirring at room temperature or under reflux, an addition product **8** formed, from which elimination of benzaldehyde hydrazon/4-methoxybenzaldehyde hydrazone and benzaldehyde phenylhydrazone/4-methoxybenzaldehyde phenylhydrazone, respectively, gave the



Scheme 1.



Scheme 2.

β-enaminonitriles **3a**–**c** [16,22] instead of the anthracene derivatives (**9**) (Scheme 1). Structures **5**–**7** were established by spectral data and analogy with our previous work [1–3,15–17].

Treatment of **3a**–**c** with triethyl orthoformate in acetic anhydride at reflux gave the corresponding 3-ethoxymethyleneamino derivatives (**10a**–**c**) (Scheme 2). Hydrazinolysis of **10a**–**c** in ethanol at room temperature under stirring afforded the anthracene derivatives (**11a**–**c**) (Scheme 2). Reaction of **10a**–**c** with methylamine in methanol at room temperature yielded the anthracene derivatives (**12a**–**c**) (Scheme 2). Ammonolysis of (**10a**–**c**) in methanol at room temperature for 1 h gave the open-chain products (**13a**–**c**), while ammonolysis of (**10a**) in dioxan solution for 2 h afforded 8-amino-5-chloro-7-(4-chlorophenyl)-7*H*-12-oxa-9,11-diaza-benzo[*a*]anthracene (**14a**) (Scheme 2). Structure **14a** was established by an independent synthesis of the same product from **3a** and formamide under reflux (m.p. and mixed m.p.). Also cyclization of **13a** in dioxan–piperidine under reflux afforded **14a** (m.p. and mixed m.p.) (Scheme 2). Structures **13a**–**c** were established on the basis of IR which showed the presence of CN (2206, 2206, 2199 cm^{-1}) and NH_2 at (3464, 3155; 3464, 3348, 3155; 3395, 3163 cm^{-1}) respectively, while for **14a** the absence of CN and the presence of NH_2 at (3294, 3148 cm^{-1}). ^1H NMR spectrum for **13c** revealed the presence of signal at δ 8.30 (1H, s, N=CH) and δ 7.21 ppm (2H, br, NH_2), while for **14a** showed δ 8.33 (1H, s, 10-H) and δ 6.78 ppm (2H, br, NH_2). The mass spectrum of **13c** exhibited a molecular ion peak *m*/*z* 377 (M^+, 43%) and 379 ($M^+ + 2$, 14.5%) together with a base peak at *m*/*z* 282 (100%).

3. Experimental

M.p.s are uncorrected and were determined on a Stuart Scientific Co. Ltd. m.p.s apparatus. IR spectra ν_{max} KBr, cm^{-1} were recorded on a FT IR/5300 spectrometer. UV spectra were measured on a Perkin–Elmer Lambda-3B UV–Visible spectrophotometer; ^1H NMR spectra δ (ppm) on Varian Gemini (200 MHz) spectrometer and mass spectra on a Shimadzu GC-MS-QP 1000 EX spectrometer. Elemental analyses were determined on a Perkin–Elmer 240 C microanalyser and the results for C, H, N were within $\pm 0.2\%$ of the calculated values. Characteristics of the prepared compounds are given in (Table 1) and spectral data are shown in (Table 2).

3.1. Reaction of *1a–f* with 4-chloro-1-naphthol (*2*)

3.1.1. General procedure

A solution of **1a–f** (0.01 mol) in EtOH (30 ml) was treated with 4-chloro-1-naphthol (**2**) (0.01 mol) and piperidine (0.5 ml). The reaction mixture was heated until complete precipitation (reaction times: 15 min for **1a–c**; 120 min for **1d–f**). The solid product which formed was collected by filtration and recrystallized from a suitable solvent to give 3-amino-9-chloro-1-(4-halophenyl)-1*H*-benzo[*h*]chromene-2-carbonitriles (**3a–c**) and ethyl 3-amino-9-chloro-1-(4-halophenyl)-1*H*-benzo-[*h*]chromene-2-carboxylates (**3d–f**) (Table 1).

3.2. 3-Acetylamino-9-chloro-1-(4-halophenyl)-1H-benzo[h]chromene-2-carbonitrile (*5a–c*)

A solution of **3a–c** (0.01 mol) in Ac_2O (20 ml) was heated under reflux for 30 min. The solid product formed was filtered, washed with cooled EtOH, dried and recrystallized from suitable solvent to give **5a–c** (Table 1).

3.3. 5-Chloro-10-methyl-7-(4-halophenyl)-8,9-dihydro-7H-12-oxa-9,11-diaza-benzo[a]anthracene-8-one (*6a–c*)

3.3.1. Method (a)

A solution of **3a–c** (0.01 mol) in Ac_2O (20 ml) was heated under reflux for 6 h. The solid product formed was filtered, washed with cooled EtOH, dried and recrystallized from suitable solvent to give **6a–c** (Table 1).

Table 1
Analytical data for the synthesized compounds

Comp.	Solvent	Colour	Yield (%)	M.p. (°C)	Molecular formula
3a	Benzene	Colourless	89	224	$C_{20}H_{12}Cl_2N_2O$
3b	Benzene	Colourless	90	226	$C_{20}H_{12}BrClN_2O$
3c	Benzene	Yellow	88	246	$C_{20}H_{12}ClFN_2O$
3d	Ethanol	Colourless	73	170	$C_{22}H_{17}Cl_2NO$
3e	Ethanol	Colourless	76	162	$C_{22}H_{17}BrClNO_3$
3f	Ethanol	Yellow	78	184	$C_{22}H_{17}ClFNO_3$
5a	Ethanol	Pale yellow	80	220	$C_{22}H_{14}Cl_2N_2O_2$
5b	Ethanol	Pale yellow	81	224	$C_{22}H_{14}BrClN_2O_2$
5c	Ethanol	Pale yellow	82	232	$C_{22}H_{14}ClFN_2O_2$
6a	Dioxan	Colourless	78	315	$C_{22}H_{14}Cl_2N_2O_2$
6b	Dioxan	Colourless	80	325	$C_{22}H_{14}BrClN_2O_2$
6c	Dioxan	Colourless	79	> 325	$C_{22}H_{14}ClFN_2O_2$
7a	Benzene	Yellow	86	270	$C_{27}H_{16}Cl_2N_2O$
7b	Benzene	Yellow	82	262	$C_{27}H_{16}BrClN_2O$
7c	Benzene	Yellow	81	280	$C_{27}H_{16}ClFN_2O$
7d	Benzene	Yellow	79	260	$C_{28}H_{18}Cl_2N_2O_2$
7e	Benzene	Yellow	83	265	$C_{28}H_{18}BrClN_2O_2$
7f	Benzene	Yellow	86	272	$C_{28}H_{18}ClFN_2O_2$
10a	Benzene	Colourless	72	185	$C_{23}H_{16}Cl_2N_2O_2$
10b	Benzene	Colourless	76	176	$C_{23}H_{16}BrClN_2O_2$
10c	Benzene	Colourless	79	168	$C_{23}H_{16}ClFN_2O_2$
11a	Benzene	Colourless	82	218	$C_{21}H_{14}Cl_2N_4O$
11b	Benzene	Colourless	85	216	$C_{21}H_{14}BrClN_4O$
11c	Benzene	Colourless	84	204	$C_{21}H_{14}ClFN_4O$
12a	Benzene	Colourless	83	245	$C_{22}H_{15}Cl_2N_3O$
12b	Benzene	Colourless	80	249	$C_{22}H_{15}BrClN_3O$
12c	Benzene	Colourless	81	260	$C_{22}H_{15}ClFN_3O$
13a	Dioxan	Colourless	79	275	$C_{21}H_{13}Cl_2N_3O$
13b	Dioxan	Colourless	78	266	$C_{21}H_{13}BrClN_3O$
13c	Dioxan	Colourless	80	272	$C_{21}H_{13}ClFN_3O$
14a	Dioxan	Colourless	78	214	$C_{21}H_{13}Cl_2N_3O$

Table 2
Spectral data for the synthesized compounds

Comp.	IR (KBr) cm^{-1}	^1H NMR (δ ppm) (in DMSO-d_6)
3a	3472, 3333, 3194 (NH_2); 3040, 2940, 2900 (CH stretching); 2191 (CN)	4.98 (1H, s, 1-H); 7.30–8.36 (11H, m, Ar–H + NH_2)
3b	3464, 3325, 3194 (NH_2); 3050, 2945, 2950 (CH stretching); 2191 (CN)	4.90 (1H, s, 1-H); 7.28–8.37 (11H, m, Ar–H + NH_2)
3c	3464, 3325, 3194 (NH_2); 3060, 2930 (CH stretching); 2191 (CN)	4.97 (1H, s, 1-H); 7.13–8.32 (11H, m, Ar–H + NH_2)
3d [a]	3387, 3287 (NH_2); 3078, 2978, 2901 (CH stretching); 1674 (CO)	1.18 (3H, t, CH_3, $J = 7.2$ Hz); 4.12 (2H, q, CH_2, $J = 7.2$ Hz); 4.99 (1H, s, 1-H); 6.49 (2H, br, NH_2); 7.20–8.26 (9H, m, Ar–H)
3e [a]	3485, 3325 (NH_2); 3026, 2980, 2936, 2891 (CH stretching); 1684 (CO)	1.19 (3H, t, CH_3, $J = 7.2$ Hz); 4.12 (2H, q, CH_2, $J = 7.2$ Hz); 4.98 (1H, s, 1-H); 6.49 (2H, br, NH_2); 7.20–8.26 (9H, m, Ar–H)
3f [a]	3387, 3287 (NH_2); 3078, 2978, 2908 (CH stretching); 1674 (CO)	1.18 (3H, t, CH_3, $J = 7.2$ Hz); 4.11 (2H, q, CH_2, $J = 7.2$ Hz); 5.00 (1H, s, 1-H); 6.48 (2H, br, NH_2); 6.88–8.26 (9H, m, Ar–H)
5a [a]	3256 (NH); 3000, 2940 (CH stretching); 2214 (CN); 1705 (CO)	2.55 (3H, s, $COCH_3$); 4.76 (1H, s, 1-H); 6.91–8.11 (9H, m, Ar–H); 10.14 (1H, br, NH, exchangeable)
5b [a]	3280 (NH); 3010, 2960 (CH stretching); 2219 (CN); 1712 (CO)	2.66 (3H, s, $COCH_3$); 5.30 (1H, s, 1-H); 7.12–8.56 (9H, m, Ar–H); 10.35 (1H, br, NH, exchangeable)
5c [a]	3340 (NH); 3040, 2930 (CH stretching); 2222 (CN); 1728 (CO)	2.71 (3H, s, $COCH_3$); 5.37 (1H, s, 1-H); 7.10–8.57 (9H, m, Ar–H); 10.40 (1H, br, NH, exchangeable)
6a	3260 (NH); 3009, 2855, 2786, 2708 (CH stretching); 1659 (CO)	2.51(3H, s, CH_3); 5.32 (1H, s, 7-H); 7.33–8.37 (9H, m, Ar–H); 12.60 (1H, br, NH, exchangeable)
6b	3240 (NH); 3010, 2862, 2790, 2720 (CH stretching); 1658 (CO)	
6c	3200 (NH); 3010, 2862, 2793, 2708 (CH stretching); 1659 (CO)	2.52 (3H, s, CH_3); 5.31 (1H, s, 7-H); 7.04–8.37 (9H, m, Ar–H); 12.63 (1H, br, NH, exchangeable)
7a	3020, 2960, 2920 (CH stretching); 2214 (CN), 1605 (C=N)	
7c [a]	3060, 2950, 2900 (CH stretching); 2214 (CN); 1597 (C=N)	5.05 (1H, s, 1-H); 7.12–8.35 (14H, m, Ar–H); 9.16 (1H, s, N=CH)
7e	3050, 3000, 2900, 2805 (CH stretching); 2212 (CN); 1641 (C=N)	3.91 (3H, s, OCH_3); 5.00 (1H, s, 1-H); 6.99–8.34 (13H, m, Ar–H); 9.06 (1H, s, N=CH)
10a [a]	3060, 3015, 2986, 2957, 2900 (CH stretching); 2206 (CN); 1620 (C=N)	1.43 (3H, t, CH_3, $J = 7.2$ Hz); 4.50 (2H, q, CH_2, $J = 7.2$ Hz); 4.91 (1H, s, 1-H); 7.07–8.24 (9H, m, Ar–H); 8.59 (1H, s, N=CH)
10b [a]	3065, 2971, 2955, 2915 (CH stretching); 2206 (CN); 1620 (C=N)	1.43 (3H, t, CH_3, $J = 7.2$ Hz); 4.50 (2H, q, CH_2, $J = 7.2$ Hz); 4.92 (1H, s, 1-H); 7.08–8.25 (9H, m, Ar–H) 8.59 (1H, s, N=CH)
10c [a]	3050, 2992, 2973, 2870 (CH stretching); 2206 (CN); 1620 (C=N)	1.43 (3H, t, CH_3, $J = 7.2$ Hz); 4.50 (2H, q, CH_2, $J = 7.2$ Hz); 4.91 (1H, s, 1-H); 6.99–8.23 (9H, m, Ar–H); 8.59 (1H, s, N=CH)
11a	3340, 3294 (NH_2); 3148 (NH); 1659 (C=N)	5.39 (1H, s, 7-H); 5.72 (2H, br, NH_2, exchangeable); 6.78 (1H, br, NH, exchangeable); 7.30–836 (10H, m, Ar–H + 10-H)
11b	3350, 2394 (NH_2); 3194 (NH); 1660 (C=N)	5.37 (1H, s, 7-H); 5.71 (2H, br, NH_2, exchangeable); 6.79 (1H, br, NH, exchangeable); 7.36–8.36 (10H, m, Ar–H + 10-H)
11c	3335, 3249 (NH_2); 3140 (NH); 1659 (C=N)	5.38 (1H, s, 7-H); 5.72 (2H, br, NH_2, exchangeable); 6.72 (1H, s, br, NH, exchangeable); 7.06–8.36 (10H, m, Ar–H + 10-H)
12a [a]	3333 (NH); 2950, 2855 (CH stretching); 1650 (C=N)	3.41 (3H, s, N–CH_3); 4.94 (1H, s, 7-H); 7.16–9.46 (10H, m, Ar–H + 10-H); 7.83 (1H, br, NH)
12b [a]	3348 (NH); 3000, 2955 (CH stretching); 1655 (C=N)	
12c [a]	3341 (NH); 2993, 2940, 2870 (CH stretching); 1660 (C=N)	3.43 (3H, s, N–CH_3); 4.98 (1H, s, 7-H); 6.96–8.48 (10H, m, Ar–H + 10-H); 7.48 (1H, br, NH)
13a	3464, 3155 (NH_2); 2206 (CN); 1674 (C=N)	
13b	3464, 3348, 3155 (NH_2); 2206 (CN); 1674 (C=N)	
13c [a]	3395, 3163 (NH_2); 2199 (CN); 1674 (C=N)	4.56 (1H, s, 1-H); 6.67–8.30 (10H, m, Ar–H + N=CH); 7.21 (2H, br, NH_2)
14a	3294, 3148 (NH_2); 1659 (C=N)	5.36 (1H, s,7-H); 6.78 (2H, br, NH_2, exchangeable); 7.32–8.32 (9H, m, Ar–H); 8.33 (1H, s, 10-H)

[a] ^1H NMR in $CDCl_3$.

3.3.2. Method (b)

A stream of dry HCl gas was passed through a mixture of **3d**–**f** (0.01 mol) and MeCN (30 ml) for 4–6 h. The reaction mixture was poured into ice-water and basified with 10% ammonium hydroxide solution to give **6a**–**c** (m.p. and mixed m.p.) yield (60–68%).

3.4. 3-Arylmethyleneamino-9-chloro-1-(4-halophenyl)-1H-benzo[h]chromene-2-carbonitrile (7a–f)

3.4.1. General procedure

A mixture of **3a**–**c** (0.01 mol), benzaldehyde or 4-methoxybenzaldehyde (0.01 mol), dioxan (20 ml) and

piperidine (0.5 ml) was refluxed for 4 h. The solid product, which formed, was collected by filtration and recrystallized from suitable solvent to give **7a**–**f** (Table 1).

3.5. Reaction of 7a–c with hydrazine derivatives

A mixture of **7a**–**c** (0.01 mol), hydrazine hydrate or phenyl hydrazine (0.01 mol) in EtOH was stirring at room temperature or reflux for 2 h to give **3a**–**c** (m.p. and mixed m.p.) yield (75–80%).

3.6. 9-Chloro-3-ethoxymethyleneamino-1-(4-halophenyl)-1H-benzo[h]chromene-2-carbonitrile (10a–c)

A mixture of β-enaminonitrile **3a**–**c** (0.01 mol), triethyl orthoformate (0.01 mol) and Ac_2O (30 ml) was refluxed for 4 h. The solvent was removed under reduced pressure and the separated solid was recrystallized from proper solvent to give the ethoxymethyleneamino derivatives **10a**–**c** (Table 1).

3.7. 9-Amino-5-chloro-8-imino-7-(4-halophenyl)-8,9-dihydro-7H-12-oxa-9,11-diaza-benzo[a]anthracene (11a–c)

A solution of **10a**–c (0.01 mol) and hydrazine hydrate (99%, 5 ml) in EtOH (50 ml) was stirred at room temperature for 45 min. The solid product, which formed, was collected by filtration and recrystallized from suitable solvent to give **11a**–**c** (Table 1).

3.8. 5-Chloro-8-imino-9-methyl-7-(4-halophenyl)-8,9-dihydro-7H-12-oxa-9,11-diaza-benzo[a]anthracene (12a–c)

Compound **12a**–**c** was prepared from **10a**–**c** (0.01 mol) and $MeNH_2$ (0.01 mol) according to the procedure described for **11** (Table 1).

3.9. 3-Aminomethyleneamino-9-chloro-1-(4-halophenyl)-1H-benzo[h]chromene-2 carbonitrile (13a–c)

A stream of NH_3 gas was passed through **10a**–**c** (0.01 mol) in MeOH at room temperature for 1 h. The solid

Table 3
Antibacterial activity of the synthesized compounds

Comp.	*S. aureus* (NCTC-7447)	*Bacillus cereus* (ATCC-14579)	*S. marcescens* (IMRU-70)	*P. mirabilis* (NTCC-289)
3a	19	15	19	15
3b	18	12	18	18
3c	19	17	16	19
3d	20	19	18	20
3e	19	20	19	21
3f	19	21	20	22
5a	20	21	26	25
5b	28	20	27	26
5c	26	25	25	26
6a	22	19	27	26
6b	21	22	24	23
6c	20	20	24	25
7a	21	22	20	22
7b	23	26	26	25
7c	22	21	22	21
7d	20	18	20	18
10a	19	20	19	20
10b	20	21	20	21
10c	22	22	22	22
11a	18	14	18	15
11b	21	20	22	20
11c	21	23	21	22
12a	23	22	23	23
12b	22	21	22	22
12c	25	22	28	27
13a	24	23	25	24
13b	25	22	25	23
13c	24	22	23	23
14a	22	20	22	22
Ampicillin [a] (25 μg)	26	25	26	25

[a] Paper discs manufactured by Bristol-Myers Squibb, Giza, Egypt.

product formed upon cooling was collected to give the open-chain product **13a–c** (Table 1).

3.10. 8-Amino-5-chloro-7-(4-chlorophenyl)-7H-12-oxa-9,11-diaza-benzo[a]anthracene (**14a**)

3.10.1. Method (a)

A mixture of **3a** (0.01 mol) and formamide (0.01 mol) was reflux for 3 h. The solvent was removed under vacuum. The solid obtained was recrystallized from proper solvent to give **14a** (Table 1).

3.10.2. Method (b)

Compound **14a** was prepared from **10a** (0.01 mol) and NH_3 gas in dioxan solution (2 h, the mixture left in refrigerator overnight) according to the procedure described for **13** to give **14a** (m.p. and mixed m.p.) yield (61%).

Table 4
Antifungal activity of the synthesized compounds

Comp.	*Aspergillus ochraceus Wilhelm* (AUCC-230)	*Penicillium chrysogenum Thom* (AUCC-530)
3a	12	13
3b	5	8
3c	15	16
3d	18	20
3e	19	21
3f	19	22
5a	18	21
5b	21	22
5c	20	21
6a	19	20
6b	20	21
6c	18	19
7a	17	17
7b	17	20
7c	19	20
7d	19	13
10a	18	18
10b	19	20
10c	22	20
11a	14	12
11b	17	15
11c	18	20
12a	19	20
12b	20	19
12c	20	21
13a	20	22
13b	18	21
13c	20	20
14a	19	19
Mycostatine (30 μg)	22	24

[a]Paper discs manufactured by Bristol-Myers Squibb, Giza, Egypt.

Table 5
Analytical data for the synthesized compounds

Comp.	Molecular formula	Found (required) %		
		C	H	N
3a	$C_{20}H_{12}Cl_2N_2O$	65.22 (65.41)	3.19 (3.29)	7.42 (7.62)
3b	$C_{20}H_{12}BrClN_2O$	58.15 (58.35)	3.63 (3.93)	6.50 (6.80)
3c	$C_{20}H_{12}ClFN_2O$	71.45 (71.75)	3.41 (3.61)	8.26 (8.36)
3d	$C_{22}H_{17}Cl_2NO$	63.62 (63.72)	4.03 (4.13)	3.22 (3.52)
3e	$C_{22}H_{17}BrClNO_3$	57.30 (57.60)	3.53 (3.73)	3.00 (3.05)
3f	$C_{22}H_{17}ClFNO_3$	66.32 (66.42)	4.10 (4.30)	3.22 (3.52)
5a	$C_{22}H_{14}Cl_2N_2O_2$	64.10 (64.40)	3.38 (3.68)	6.52 (6.82)
5b	$C_{22}H_{14}BrClN_2O_2$	57.80 (58.10)	3.12 (3.32)	6.06 (6.16)
5c	$C_{22}H_{14}ClFN_2O_2$	66.88 (67.09)	3.53 (3.83)	7.00 (7.11)
6a	$C_{22}H_{14}Cl_2N_2O_2$	64.26 (64.56)	3.34 (3.44)	6.54 (6.84)
6b	$C_{22}H_{14}BrClN_2O_2$	58.00 (58.23)	3.00 (3.11)	6.07 (6.17)
6c	$C_{22}H_{14}ClFN_2O_2$	67.00 (67.26)	3.29 (3.59)	7.00 (7.13)
7a	$C_{27}H_{16}Cl_2N_2O$	70.90 (71.22)	3.34 (3.54)	6.05 (6.15)
7b	$C_{27}H_{16}BrClN_2O$	64.80 (64.90)	3.02 (3.22)	5.40 (5.60)
7c	$C_{27}H_{16}ClFN_2O$	73.69 (73.89)	3.37 (3.67)	6.18 (6.38)
7d	$C_{28}H_{18}Cl_2N_2O_2$	69.00 (69.28)	3.53 (3.73)	5.47 (5.77)
7e	$C_{28}H_{18}BrClN_2O_2$	63.18 (63.48)	3.12 (3.42)	5.18 (5.28)
7f	$C_{28}H_{18}ClFN_2O_2$	71.21 (71.41)	3.55 (3.85)	5.64 (5.94)
10a	$C_{23}H_{16}Cl_2N_2O_2$	65.00 (65.26)	3.50 (3.80)	6.41 (6.61)
10b	$C_{23}H_{16}BrClN_2O_2$	59.00 (59.06)	3.34 (3.44)	5.88 (5.98)
10c	$C_{23}H_{16}ClFN_2O_2$	67.70 (67.900	3.66 (3.96)	6.78 (6.88)
11a	$C_{21}H_{14}Cl_2N_4O$	61.42 (61.62)	3.34 (3.44)	13.38 (13.68)
11b	$C_{21}H_{14}BrClN_4O$	55.39 (55.59)	3.00 (3.11)	12.14 (12.34)
11c	$C_{21}H_{14}ClFN_4O$	64.00 (64.21)	3.29 (3.59)	14.07 (14.27)
12a	$C_{22}H_{15}Cl_2N_3O$	64.62 (64.72)	3.40 (3.70)	10.09 (10.29)
12b	$C_{22}H_{15}BrClN_3O$	58.16 (58.36)	3.13 (3.33)	8.92 (9.28)
12c	$C_{22}H_{15}ClFN_3O$	57.13 (67.43)	3.52 (3.82)	10.42 (10.72)
13a	$C_{21}H_{13}Cl_2N_3O$	63.90 (64.01)	3.12 (3.32)	10.45 (10.65)
13b	$C_{21}H_{13}BrClN_3O$	57.21 (57.51)	2.88 (2.98)	9.27 (9.57)
13c	$C_{21}H_{13}ClFN_3O$	66.57 (66.77)	3.36 (3.46)	11.00 (11.11)
14a	$C_{21}H_{13}Cl_2N_3O$	63.90 (64.01)	3.22 (3.32)	10.35 (10.65)

3.10.3. Method (c)

Compound **13a** (0.01 mol) was heated under reflux in dioxan (20 ml) and piperidine (0.5 ml) for 3 h to give **14a** (m.p. and mixed m.p.) yield (58%).

4. Biological screening

4.1. Antibacterial activity

The newly synthesized compounds were screened for their antibacterial activity against four species of bacteria, gram-positive bacteria namely *Staphylococcus aureus* (NCTC- 7447), *Bacillus cereus* (ATCC-14579) and gram-negative bacteria *Serratia marcescens* (IMRU-70) and *Proteus mirabilis* (NCTC-289) using Ampicillin (25 μg) as reference compound [23]. The tested compounds were dissolved in (DMF) to get a solution of 1% concentration. Filter paper discs (whatman No. 3 filter paper, 5 mm diameter) were saturated with former solution. The saturated filter paper discs were placed on the nutrient agar (Difco) dishes seeded

by test bacterial. The inhibition zone was measured in mm at the end of an incubation period of 48 h at 28 °C. DMF showed no inhibition zone. The results are illustrated in (Table 3).

4.2. Antifungal activity

The newly synthesized compounds were screened for their antifungal activity against two species of fungi, namely *Aspergillus ochraceus Wilhelm* (AUCC-230) and *Penicillium chrysogenum Thom* (AUCC-530) using the Mycostatine (30 μg) as reference compound [24]. The tested compounds were dissolved in DMF to get a solution of 1% concentration. Filter paper discs (Whatman No. 3 filter paper, 5 mm diameter) were saturated with the former solution. The saturated filter paper discs were placed on the Glucose–Czapek's agar medium (Difco) dishes seeded by test fungi. The inhibition zone was measured in mm at the end of an incubation period of 48 h at 28 °C. DMF showed no inhibition zone. The results are illustrated in (Tables 4 and 5).

5. Conclusion

From the biological assay it was found that compound **5b** possess high activity against *S. aureus*, *S. marcescens* and *P. mirabilis*, while compounds **6a** and **12c** showed high activity against *S. marcescens* and *P. mirabilis*. For antifungal activity, compounds **3f**, **5b** and **13a** showed the same activity of the reference drug (Mycostatine).

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