European Journal of Chemistry

Journal webpage: www.eurjchem.com

Heteroaromatization with 4-phenyldiazenyl-1-naphthol. Part II: Synthesis of some new benzochromens, benzochromenopyrimidines, benzochromenotriazolopyrimidines, benzochromenopyrimidotriazepine and antimicrobial activities

Ibrahim Ali Radini [1], Hany Mostafa Hamed [1,2], Mohammed Abdo Yahya Kharir [1] and Ashraf Hassan Fekry Abd Elwahab [1,2,*]

[1] *Department of Chemistry, Faculty of Science, Jazan University, 2097, Jazan, Kingdom of Saudi Arabia*
[2] *Chemistry Department, Faculty of Science, Al-Azhar University, 11884, Nasr City, Cairo, Egypt*

** Corresponding author at: Department of Chemistry, Faculty of Science, Jazan University, 2097, Jazan, Kingdom of Saudi Arabia. Tel.: +966.054.0963753. Fax: +966.017.3230028. E-mail address: ash_abdelwahab@yahoo.com (A.H.F.A. Elwahab).*

ARTICLE INFORMATION

DOI: 10.5155/eurjchem.8.3.240-247.1599

Received: 12 June 2017
Received in revised form: 12 July 2017
Accepted: 12 July 2017
Published online: 30 September 2017
Printed: 30 September 2017

KEYWORDS

Benzochromene
Antimicrobial activities
Benzochromenopyrimidine
4-Phenenyldiazenyl-1-naphthol
Benzochromenotriazolopyrimidine
Benzochromenopyrimidotriaziepine

ABSTRACT

Synthesis of several new of benzochromenes (4-7), benzochromenopyrimidines (8 and 9), 14-(4-chlorophenyl)-12-(phenyldiazenyl)-14*H*-benzo[7,8]chromeno[3,2-e][1, 2, 4]triazolo[1, 5-c]pyrimidines, 4-amino-16-(4-chlorophenyl)-14-(phenyldiazenyl)-16*H*-benzo[7', 8']chromeno[2',3':4,5]pyrimido[1,6-b][1,2,4]triazepine-3-carbonitrile (10a-e, 13) and 9-(benzylideneamino)-7-(4-chlorophenyl)-5-(phenyldiazenyl)-7, 9-dihydro-8*H*-benzo[7,8]chromeno [2,3-d]pyrimidin-8-imine (12), form starting from 2-amino-4-(*p*-chlorophenyl)-6-phenyldiazenyl-4*H*-benzochromene-3-carbonitrile (3). The structure of these new compounds was confirmed using IR, ^{1}H NMR and ^{13}C NMR as well as MS spectroscopy. The structure activity relationship studies of the target compounds in agreement with the *in vitro* essays and confirmed higher potent antimicrobial activity against some of the tested microorganisms. The structure-activity relationship study revealed that the antimicrobial activity of benzochromenopyrimido triazepine nucleus was more beneficial than benzochromenotriazolopyrimidine nucleus for antimicrobial activity.

Cite this: *Eur. J. Chem.* **2017**, *8(3)*, 240-247

1. Introduction

Nowadays, synthetic azo compounds are widely used in different application fields, such as medicines, cosmetics, food, paints, plastics, shipbuilding, automobile industry, cable manufacture [1-12]. Moreover azo compounds are known for their antineoplastics [13], antidiabetics [14], antiseptics [15], antibacterial [16] and antitumor [17]. Benzochromene represent a class of heterocyclic compounds endowed with potent antimicrobial agents [18-23], antileishmanial [24,25], anticancer [26,27], antiproliferative [28], antioxidant [29,30], hypertensive [31], antitumor [32-35] effects and activities, as well as for the treatment of Alzheimer's disease [36], schizophrenia disorders [37], and fused chromene ring systems also displayed blood platelet antiaggregating [38], antihistaminic [39], analgesic [40-42], hypolipidemic [43], DNA breaking and mutagenicity activities [44].

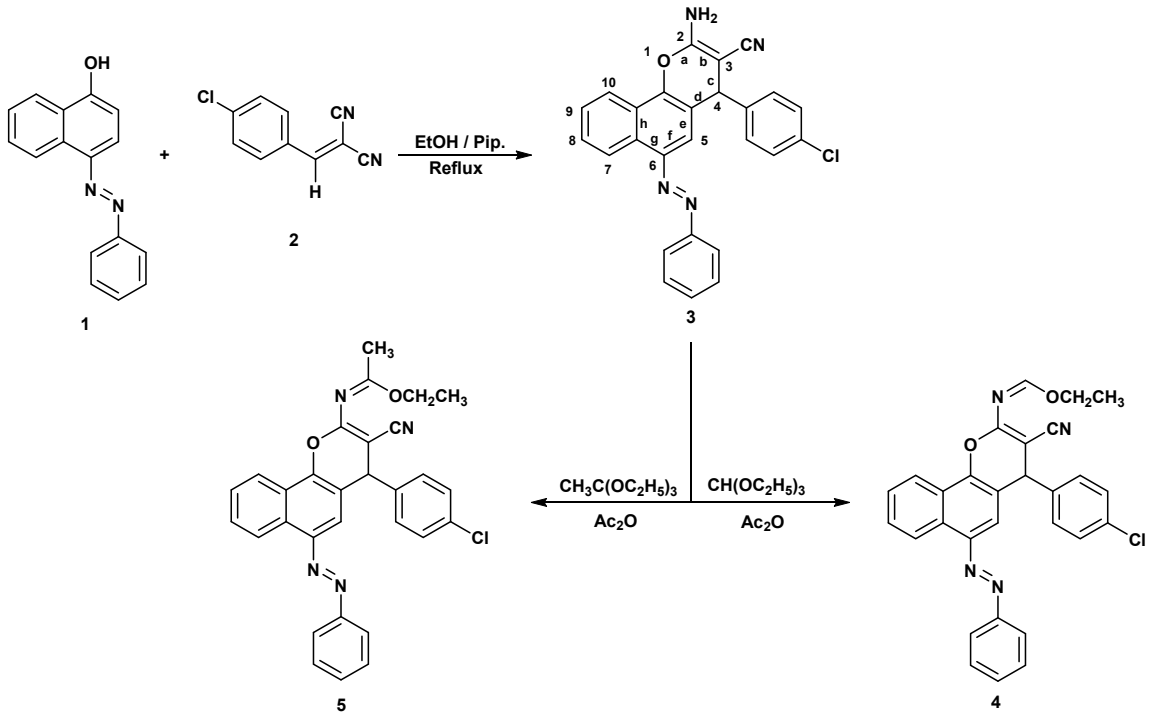
The promising results of previous studies [18,23,45] prompted us to further extend our research towards the synthesis of annulation of heterocyclic systems of potential biological application. In continuation of our previous work we are reporting here the synthesis of some more analogues of benzochromene moiety as a base unit and antimicrobial activities. The structure activity relationships (SAR) are discussed in this work to correlate between the substituent effects and the activities that aid in drug design.

2. Experimental

2.1. Instrumentation

Melting points were determined with a Stuart Scientific Co., Ltd. apparatus. IR spectra were determined as KBr pellets on a Jasco FT/IR 460 plus spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker AV 400 MHz spectrometer. Mass spectra were measured on a Shimadzu GC/MS-QP5050A spectrometer.

ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online)
http://dx.doi.org/10.5155/eurjchem.8.3.240-247.1599



1 2 3 5 4

Scheme 1

All the reagents and solvents were purchased from Sigma-Aldrich or S.D. fine chemicals limited and used without further purification. Thin-layer chromatography (TLC) was performed using Merck silica gel $60F_{254}$ pre-coated plates (0.25 mm) and silica gel (particle size 60-120 mesh) used for column chromatography. Elemental analyses were carried out at the Regional Centre for Mycology and Biotechnology (RCMP, Al-Azhar University, Cairo, Egypt) and the results were within ±0.3% of calculated values.

2.2. Synthesis

2.2.1. Synthesis of 2-amino-4-(4-chlorophenyl)-6-(phenyl diazenyl)-4H-benzo[h]chromene-3-carbonitrile (3)

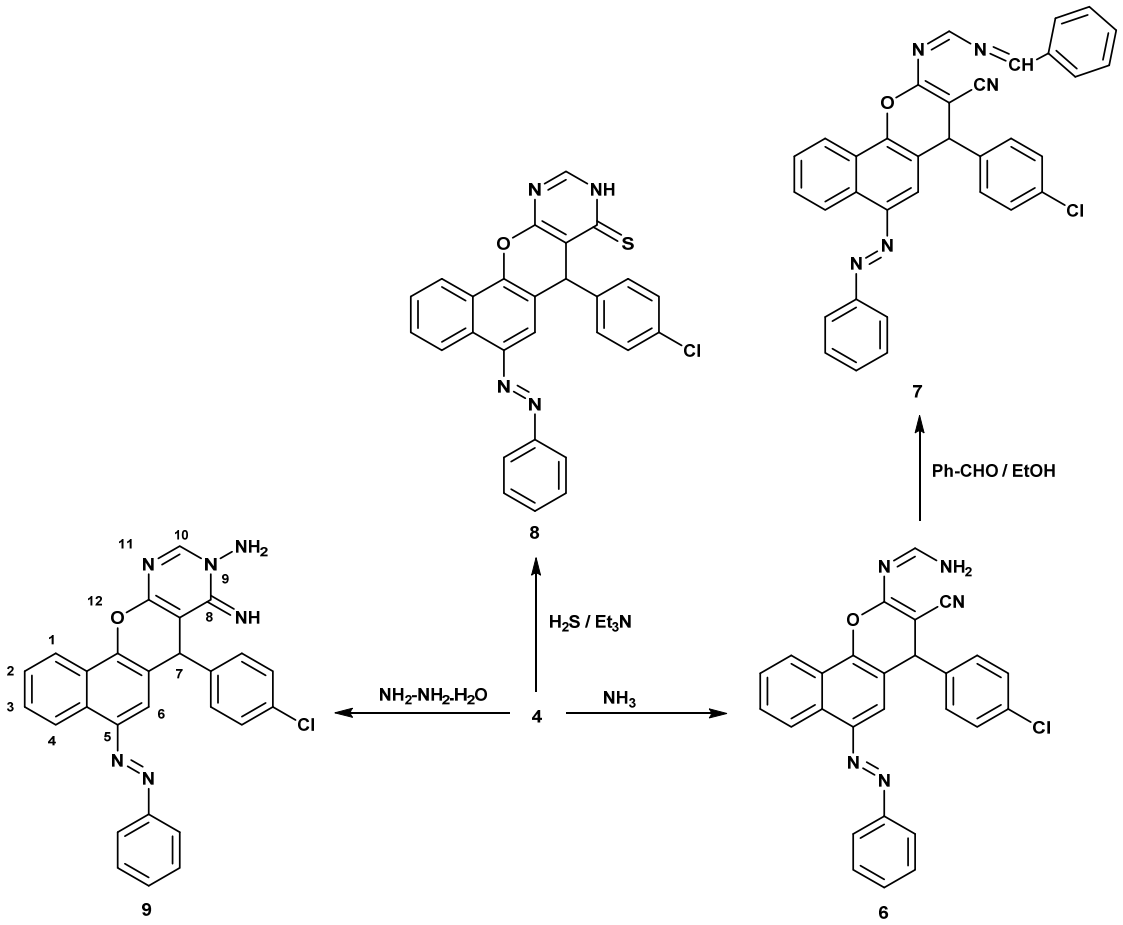
A solution of 4-phenyldiazenyl-1-naphthol (**1**) (2.48 g, 10 mmol) in EtOH (20 mL) was treated with 2-(4-chloro benzylidene)malononitrile (**2**) (1.88 g, 10 mmol) and piperidine (0.5 mL) under reflux 2 hr. The reaction mixture was heated until complete precipitation. The solid product which formed was collected by filtration and recrystallized from dioxane. This compound was prepared according to the literature [45] (Scheme 1). Color: Orange solid. Yield: 90 %. M.p.: 245-246 °C. FT-IR (KBr, ν, cm^{-1}): 3417, 3327, 3207 (NH_2), 3001, 2960, 2812 (CH-str.), 2196 (CN), 1666 (C=C), 1510 (N=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.93-7.24 (m, 14H, Ar-H), 4.95 (s, 1H, H-4), 4.84 (brs, 2H, NH_2, exchangeable by D_2O). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 158.59 (C-2), 152.94 (C-6), 144.70, 142.63, 133.44, 131.41, 133.29, 129.45, 129.20, 129.14, 127.82, 127.43, 123.75, 123.71, 123.28, 123.17, 120.90, 112.25 (Ar-C), 116.98 (CN), 61.33 (C-3), 40.74 (C-4). MS (EI, *m/z* (%)): 438 (M^++2, 1.0), 436 (M^+, 20.4), 77 (100). Anal. calcd. for $C_{26}H_{17}ClN_4O$: C, 71.48; H, 3.92; N, 12.82. Found: C, 71.01; H, 3.40; N, 12.39%.

2.2.2 Synthesis of 4H-benzo[h]chromene derivatives 4 and 5

General procedure: A mixture of compound **3** (4.36 g, 10 mmol), triethyl orthoformate or triethyl orthoacetate (10 mmol) and Ac_2O (30 mL) was refluxed for 3 hr. The solvent was removed under reduced pressure and the resulting solid was crystallized from benzene to give compound **4** and **5**, respectively (Scheme 1).

Ethyl (Z)-N-(4-(4-chlorophenyl)-3-cyano-6-((E)-phenyl diazenyl)-4H-benzo[h]chromen-2-yl)formimidate (**4**): Color: Yellow solid. Yield: 83%. M.p.: 238-240 °C. FT-IR (KBr, ν, cm^{-1}): 2977, 2936, 2874 (CH-str.), 2201 (CN), 1668 (C=C), 1491 (N=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.94 (s, 1H, N=CH), 8.92-7.20 (m, 14H, Ar-H), 5.01 (s, 1H, H-4), 4.54 (q, *J* = 7.2 Hz, 2H, CH_2), 1.44 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 159.44 (C-2), 158.63 (N=C), 145.73 (C-6), 144.60, 142.66, 137.54, 133.80, 133.64, 132.73, 132.60, 131.55, 131.33, 129.52, 129.30, 127.80, 127.48, 123.69, 120.28, 120.90, 120.85 (Ar-C), 116.97 (CN), 81.30 (C-3), 64.51 (CH_2), 40.95 (C-4), 18.45 (CH_3). MS (EI, *m/z* (%)): 494 (M^++2, 9.12.), 492 (M^+, 23.70), 77 (100). Anal. calcd. for $C_{29}H_{21}ClN_4O_2$: C, 70.66; H, 4.29; N, 11.37. Found: C, 70.34; H, 4.02; N, 11.08%.

Ethyl (Z)-N-(4-(4-chlorophenyl)-3-cyano-6-((E)-phenyl diazenyl)-4H-benzo[h]chromen-2-yl)acetimidate (**5**): Color: Yellow solid. Yield: 80%. M.p.: 241-243 °C. FT-IR (KBr, ν, cm^{-1}): 2979, 2940, 2887 (CH-str.), 2199 (CN), 1667 (C=C), 1495 (N=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.93-7.25 (m, 14H, Ar-H), 5.05 (s, 1H, H-4), 4.37 (q, *J* = 7.2 Hz, 2H, CH_2), 2.19 (s, 3H, CH_3), 1.43 (t, *J* = 7.2 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 168.46 (N=C), 159.99 (C-2), 152.97, 146.39, 144.77, 142.25, 133.63, 131.51, 131.27, 129.60, 129.30, 127.87, 127.41, 124.08, 123.68, 121.30 (Ar-C), 118.09 (C-3), 116.07 (CN), 64.05 (CH_2), 42.64 (C-4), 18.40 (CH_3), 13.94 (CH_3). MS (EI, *m/z* (%)): 506 (M^+, 7.65), 44 (100). Anal. calcd. for $C_{30}H_{23}ClN_4O_2$: C, 71.07; H, 4.57; N, 11.0. Found: C, 70.90; H, 4.36; N, 10.67 %.



Scheme 2

2.2.3. Synthesis of N'-(4-(4-chlorophenyl)-3-cyano-6-((E)-phenyldiazenyl)-4H-benzo[h] chromen-2-yl)formimidamide (6)

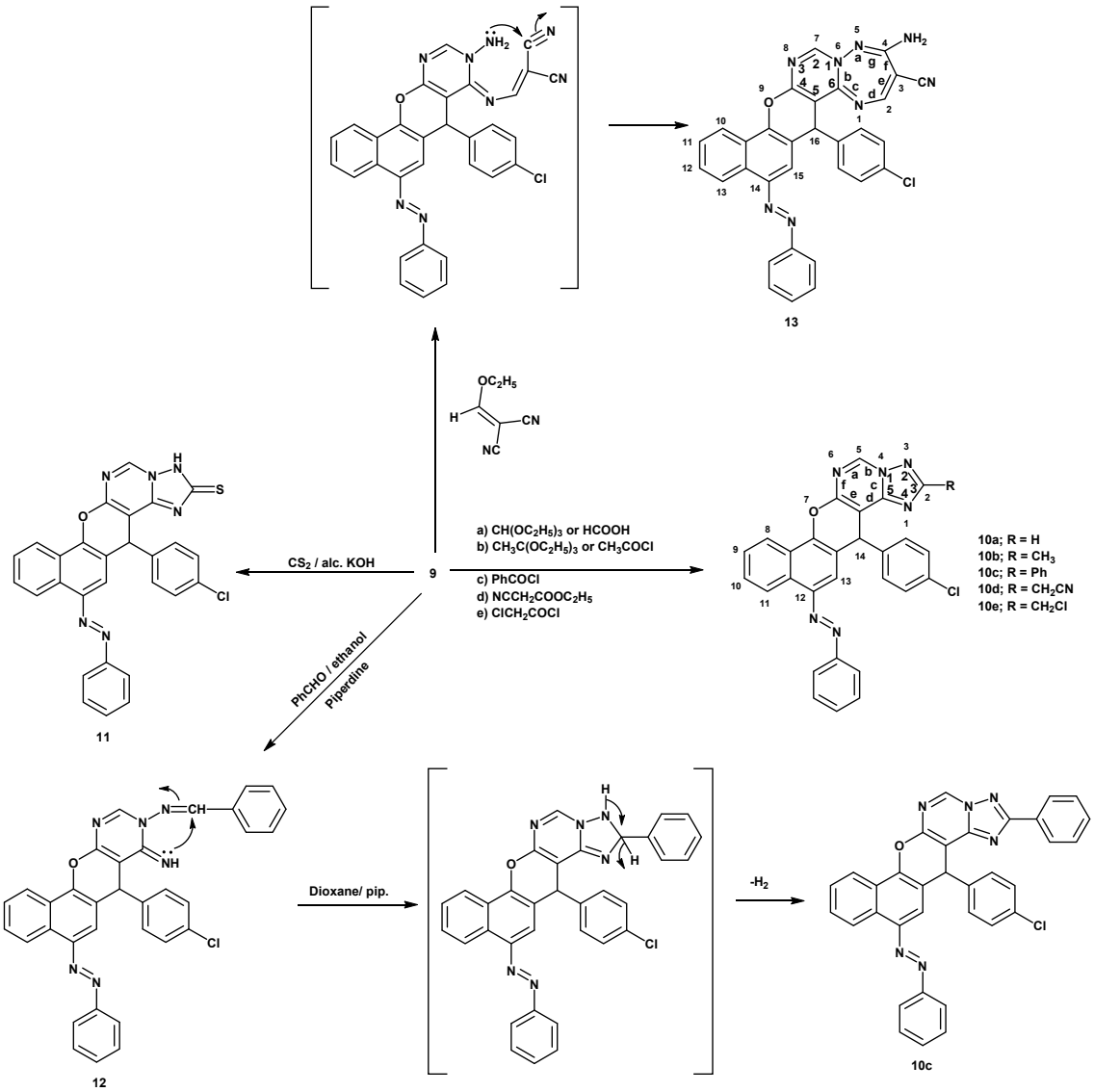
A stream of NH_3 gas was passed through compound **4** (4.92 g, 10 mmol) in methanol (20 mL) at room temperature for 1 h. Then the mixture was left overnight. The solid product was collected and crystalized from benzene (Scheme 2). Colour: Pale yellow solid. Yield: 77%. M.p.: 266-268 °C. FT-IR (KBr, ν, cm^{-1}): 3342, 3328, (NH_2) 2980, 2962, 2894 (CH-str.), 2203 (CN), 1664 (C=C), 1501 (N=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.88 (s, 1H, N=CH), 8.87-7.35 (m, 16H, Ar-H + NH_2), 5.22 (s, 1H, H-4). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 160.21 (C-2), 155.47 (N=CH), 146.43 (C-6), 152.87, 144.43 143.48, 132.42, 132.06, 131.20, 130.40, 129.97, 129.38, 128.89, 128.09, 124.16, 123.53, 123.29, 121.85, 120.19 (Ar-C), 117.66 (CN), 112.65 (C-4a), 72.81 (C-3), 41.85 (C-4). MS (EI, *m/z* (%)): 465 (M^++ 2, 1.09), 463 (M^+, 3.84), 77 (100). Anal. calcd. for $C_{27}H_{18}ClN_5O$: C, 69.90; H, 3.91; N, 15.10. Found: C, 69.64; H, 3.72; N, 14.86%.

2.2.4. Synthesis of N-benzylidene-N'-(4-(4-chlorophenyl)-3-cyano-6-((E)-phenyldiazenyl)-4H-benzo[h]chromen-2-yl) formimidamide (7)

A mixture of compound **6** (4.63 g, 10 mmol), benzaldehyde (0.01 mol), dioxane (20 mL) and piperidine (0.5 mL) was refluxed for 2 h. The solid product was collected by filtration and crystallized from dioxane (Scheme 2). Colour: Yellow solid. Yield: 70%. M.p.: 300-302 °C. FT-IR (KBr, ν, cm^{-1}): 2989, 2970, 2885 (CH-str.), 2220 (CN), 1667 (C=C), 1546 (N=N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.01 (s, 1H, N=CH), 8.77 (s, 1H, N=CH), 8.70-7.63 (m, 19H, Ar-H + NH_2), 5.81 (s, 1H, H-4). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 166.54 (C-2), 159.20 (N=CH), 148.01 (C-6), 153.32, 145.21 144.02, 133.10, 132.92, 132.53, 131.65, 130.72, 130.51, 129.80, 129.52, 128.75, 128.34, 127.66, 127.43, 124.20, 123.84, 123.50, 121.92, 120.38 (Ar-C), 117.01 (CN), 112.89 (C-4a), 72.45 (C-3), 41.53 (C-4). MS (EI, *m/z* (%)): 552 (M^++2, 1.45), 551 (M^+, 3.76), 77 (100). Anal. calcd. for $C_{34}H_{22}ClN_5O$: C, 73.98; H, 4.02; N, 12.69. Found: C, 73.70; H, 3.84; N, 12.53 %.

2.2.5. Synthesis of 7-(4-chlorophenyl)-5-(phenyldiazenyl)-7,9-dihydro-8H-benzo[7,8]chromeno [2,3-d]pyrimidine-8-thione (8)

Gaseous hydrogen sulfide was bubbled through compound **4** (4.92 g, 10 mmol) in presence of triethylamine (0.5 mL) in methanol for 2 hours. The solid formed was collected to give compound **8** and recrystallized from benzene (Scheme 2). Color: Pale brown solid. Yield: 76%. M.p.: 280-282 °C. FT-IR (KBr, ν, cm^{-1}): 3220 (NH), 3010, 3000, 2987 (CH-str.), 1668 (C=C), 1560 (N=N), 1310 (C=S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 8.95 (s, 1H, N=CH), 8.74-7.62 (m, 15H, Ar-H + NH), 5.73 (s, 1H, H-4). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 183.62 (C-8), 161.04 (C-11a), 156.63 (C-10), 153.63, 144.41, 143.50, 132.61, 132.33, 131.28, 130.49, 129.90, 129.40, 128.91, 128.23, 124.38, 123.75, 123.38, 122.15, 121.23 (Ar-C), 111.90 (C-7a), 42.05 (C-7).



Scheme 3

MS (EI, *m/z* (%)): 481 (M^+ + 1, 1.41), 480 (M^+, 9.33), 69 (100). Anal. calcd. for $C_{27}H_{17}ClN_4OS$: C, 67.43; H, 3.56; N, 11.65. Found: C, 67.11; H, 3.25; N, 11.37 %.

2.2.6. Synthesis of 7-(4-chlorophenyl)-8-imino-5-(phenyl diazenyl)-7H-benzo[7,8]chromeno[2,3-d]pyrimidin-9(8H)-amine (9)

A solution of compound **4** (4.92 g, 10 mmol), hydrazine hydrate (5 mL, 99%), in ethanol (50 mL) was stirred at room temperature for h. The yellow solid product formed was washed with cold ethanol, dried and recrystallized from dioxane (Scheme 2). Color: Yellow solid. Yield: 85%. M.p.: 225-227 °C. FT-IR (KBr, ν, cm^{-1}): 3320, 3280 (NH_2), 3210 (NH), 2954, 2921, 2881 (CH-str.), 1647 (C=N), 1544 (N=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.83 (s, 1H, H-10), 8.82-7.31 (m, 14H, Ar-H), 6.81 (br, 1H, NH), 5.74 (s, 2H, NH_2, exchangeable by D_2O), 5.45 (s, 1H, H-7). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 155.87 (C-11a), 152.89 (C-8), 151.43 (C-10), 146.78, 144.06, 143.62, 131.96, 131.03, 130.44, 129.93, 129.08, 128.77, 128.54, 128.06, 124.11, 123.49, 123.28, 121.66 (Ar-C), 40.63 (C-7), 112.84 (C-7a). MS (EI, *m/z* (%)): 480 (M^++ 2, 12.28), 478 (M^+, 26.86), 77 (100). Anal. calcd. for $C_{27}H_{19}ClN_6O$: C, 67.71; H, 4.00; N, 17.55. Found: C, 67.45; H, 3.84; N, 17.24 %.

2.2.7. Synthesis of triazolo derivatives 10a-e

General procedure: A mixture of compound **9** (4.78 g, 10 mmol), triethyl orthoformate or formic acid, (0.01 mol), acetyl chloride or triethyl orthoacetate (0.01 mol), benzoyl chloride (10 mmol) and chloro acettylchloirde (10 mmol) in dry benzene (20 mL) was refluxed for 3 h to give compound **10a-c** and **10e**, while a mixture of compound **9** (0.01 mol), ethyl cyanoacetate (10 mmol) in absolute ethanol (20 mL) was refluxed for 5 h to give compound **10d**, respectively, the solvent was extracted and the resulting product was recrystallized from 1,4-dioxane (Scheme 3).

14-(4-Chlorophenyl)-12-(phenyldiazenyl)-14H-benzo[7, 8] chromeno[3,2-e][1,2,4]triazolo [1,5-c]pyrimidine (**10a**): Color: Pale yellow solid. Yield: 83%. M.p.: 320-322 °C. FT-IR (KBr, ν, cm^{-1}): 3001, 2961, 2888 (CH-str.), 1650 (C=N), 1547 (N=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 9.06 (s, 1H, H-2), 8.92-6.88

(m, 15H, Ar-H + H-5), 5.80 (s, 1H, H-14). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 160.11 (C-6a) 152.74 (C-12), 151.34 (C-2), 150.62 (C-14b), 144.91 (C-8b), 142.76, 142.27, 141.10, 132.51, 132.10, 131.01, 130.33, 129.70, 129.10, 128.32, 128.02, 123.96, 123.40, 122.66, 121.43 (Ar-C), 117.73 (C-14a), 40.51 (C-14). MS (EI, *m/z* (%)): 490 (M$^+$+2, 1.90), 488 (M$^+$, 3.64), 127 (100). Anal. calcd. for $C_{28}H_{17}ClN_6O$: C, 68.78; H, 3.50; N, 17.19. Found: C, 68.60; H, 3.32; N, 17.01%.

14-(4-Chlorophenyl)-2-methyl-12-(phenyldiazenyl)-14H-benzo[7, 8]chromeno[3, 2-e][1, 2, 4]triazolo[1, 5-c]pyrimidine (**10b**): Color: Pale yellow solid. Yield: 80%. M.p.: > 360 °C. FT-IR (KBr, ν, cm^{-1}): 3010, 2975, 2897 (CH-str.), 1643 (C=N), 1549 (N=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 9.62 (s, 1H, H-5) 8.90-7.34 (m, 14H, Ar-H), 6.09 (s, 1H, H-14), 2.46 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 161.44 (C-6a), 153.93 (C-12), 153.32 (C-2), 152.82 (C-14b), 146.70 (C-8b), 121.55, 123.29, 123.52, 124.07, 128.29, 129.18, 129.94, 130.77, 131.11, 132.09, 143.29, 141.16, 132.41, 128.74 (Ar-C), 118.70 (C-14a), 112.91 (C-13a), 104.09 (C-13), 40.30 (C-14), 14.50 (CH_3). MS (EI, *m/z* (%)): 504 (M$^+$ + 2, 24.46), 502 (M$^+$, 65.05), 77 (100). Anal. calcd. for $C_{29}H_{19}ClN_6O$: C, 69.25; H, 3.81; N, 16.71. Found: C, 69.04; H, 3.63; N, 16.54%.

14-(4-Chlorophenyl)-2-phenyl-12-(phenyldiazenyl)-14H-benzo[7, 8]chromeno[3, 2-e][1, 2, 4]triazolo[1, 5-c]pyrimidine (**10c**): Color: Yellow solid. Yield: 76%. M.p.: 275-277 °C. FT-IR (KBr, ν, cm^{-1}): 3012, 2976, 2899 (CH-str.), 1641 (C=N), 1548 (N=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 8.87 (s, 1H, H-5), 8.78-6.82 (m, 19H, Ar-H), 6.01 (s, 1H, H-14). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 161.44 (C-6a), 153.93 (C-12), 153.32 (C-2), 152.82 (C-14b), 146.70 (C-8b), 143.90, 143.29, 141.16, 132.41, 132.09, 131.11, 130.77, 129.93, 129.45, 128.97, 128.77, 123.93, 123.65, 123.45, 121.33 (Ar-C), 118.70 (C-14a), 112.91 (C-13a), 104.09 (C-13), 37.95 (C-14). MS (EI, *m/z* (%)): 565 (M$^+$+1, 2.49), 564 (M+, 6.50), 77 (100). Anal. calcd. for $C_{34}H_{21}ClN_6O$: C, 72.27; H, 3.75; N, 14.87. Found: C, 72.05; H, 3.52; N, 14.62 %.

2-(14-(4-Chlorophenyl)-12-(phenyldiazenyl)-14H-benzo [7,8]chromeno[3, 2-e][1, 2, 4]triazolo[1,5-c]pyrimidin-2-yl)aceto nitrile (**10d**): Color: Yellow solid. Yield: 74%. M.p.: 268-270 °C. FT-IR (KBr, ν, cm^{-1}): 2973, 2962, 2901 (CH-str.), 2240 (CN), 1636 (C=N), 1545 (N=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 9.76 (s, 1H, H-5), 8.90-7.30 (m, 14H, Ar-H), 6.09 (s, 1H, H-14), 4.46 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 161.44 (C-6a), 153.93 (C-12), 153.32 (C-2), 152.82 (C-14b), 146.70 (C-8b), 143.90, 143.29, 141.16, 132.41, 132.09, 131.11, 130.77, 129.94, 129.18, 128.74, 128.29, 124.07, 123.52, 123.29, 121.55 (Ar-C), 117.73 (C-14a), 116.92 (CN), 112.81 (C-13a), 101.69 (C-13), 40.61 (C-14), 18.43 (CH_2). MS (EI, *m/z* (%)): 529 (M$^+$ + 2, 34.39), 527 (M$^+$, 81.52), 77 (100). Anal. calcd. for $C_{30}H_{18}ClN_7O$: C, 68.25; H, 3.44; N, 18.57. Found: C, 68.05; H, 3.16; N, 18.31 %.

2-(Chloromethyl)-14-(4-chlorophenyl)-12-(phenyldiazenyl)-14H-benzo[7,8]chromeno[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine (**10e**): Color: Yellow solid. Yield: 70%. M.p.: > 360 °C. FT-IR (KBr, ν, cm^{-1}): 2961, 2934, 2890 (CH-str.), 1654 (C=N), 1542 (N=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 9.84 (s, 1H, H-5), 8.94-7.32 (m, 14H, Ar-H), 6.10 (s, 1H, H-14), 4.51 (s, 2H, CH_2). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 161.48 (C-6a), 153.96 (C-12), 153.36 (C-2), 153.04 (C-14b), 147.71 (C-8b), 144.74, 143.45, 141.43, 132.40, 132.11, 131.15, 130.58, 129.63, 129.33, 128.66, 128.40, 124.35, 123.81, 123.63, 121.73 (Ar-C), 117.70 (C-14a), 112.85 (C-13a), 101.72 (C-13), 40.73 (C-14), 18.60 (CH_2). MS (EI, *m/z* (%)): 537 (M$^+$ + 1, 0.83), 536 (M$^+$, 1.44), 77 (100). Anal. calcd. for $C_{29}H_{18}Cl_2N_6O$: C, 64.82; H, 3.38; N, 15.64. Found: C, 64.65; H, 3.08; N, 15.32 %.

2.2.8. Synthesis of 14-(4-chlorophenyl)-12-(phenyl diazenyl)-14H-benzo[7,8]chromeno[3,2-e][1,2,4]triazolo [1,5-c]pyrimidine-2(3H)-thione (11)

A mixture of compound **9** (4.78 g, 10 mmol) with carbon disulfide (0.01 mol) and potassium hydroxide (10 mmol) in ethanol (15 mL) was heated under reflux for 5 h. After removal of ethanol, water was added and the resulting alkaline solution was acidified with acetic acid and the precipitate formed collected by filtration, washed with water and dried and crystallized from 1,4-dioxane (Scheme 3). Color: Yellow solid. Yield: 69%. M.p.: 290-292 °C. FT-IR (KBr, ν, cm^{-1}): 3300 (NH), 3020, 2951, 2850 (CH-str.), 1646 (C=N), 1533 (N=N), 1043 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 10.21 (s, 1H, NH), 8.73-6.69 (m, 14H, Ar-H), 8.95 (s, 1H, H-5), 5.74 (s, 1H, H-14). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 170.03 (C=S), 162.32 (C-6a), 157.21 (C-14b), 156.92 (C-2), 155.83 (C-12), 148.64 (C-8b), 145.30, 144.65, 142.86, 133.60, 132.76, 131.95, 130.86, 129.72, 129.52, 128.53, 128.27, 124.31, 123.96, 123.54, 121.95 (Ar-C), 118.54 (C-14a), 113.05 (C-13a), 108.11 (C-13), 40.10 (C-14). MS (EI, *m/z* (%)): 522 (M$^+$ + 2, 3.34), 520 (M$^+$, 6.05), 63 (100). Anal. calcd. for $C_{28}H_{17}ClN_6OS$: C, 64.55; H, 3.29; N, 16.13. Found: C, 64.31; H, 3.12; N, 15.89 %.

2.2.9. Synthesis of 9-(benzylideneamino)-7-(4-chloro phenyl)-5-((E)-phenyldiazenyl)-7,9-dihydro-8H-benzo[7,8] chromeno[2,3-d]pyrimidin-8-imine (12)

A mixture of compound **9** (4.78 g, 10 mmol), benzaldehyde (10 mmol), piperidine (0.05 mL) and dioxane (30 mL) was refluxed for 6 h. The solvent was extracted and the resulting product was recrystallized from 1,4-dioxane (Scheme 3). Color: Yellow solid. Yield: 72%. M.p.: 242-244 °C. FT-IR (KBr, ν, cm^{-1}): 3211 (NH), 3068, 3010, 2964 (CH-str.), 1637(C=N), 1528 (N=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 11.07 (br, 1H, NH), 8.89 (s, 1H, N=CH), 8.50 (s, 1H, H-10), 8.35-6.91 (m, 19H, Ar-H), 6.05 (s, 1H, H-7). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 163.83 (C-8), 160.98 (C-11a), 158.42 (C-10), 156.56 (N=CH), 151.65 (C-11a), 144.88, 144.51, 137.55, 134.64, 132.64, 130.23, 129.62, 128.91, 127.54, 126.74, 126.33, 124.54, 124.01, 121.74, 119.82, 117.57, 102.79 (Ar-C), 97.60 (C-7a), 39.36 (C-7). MS (EI, *m/z* (%)): 568 (M$^+$ + 2, 005), 566 (M$^+$, 1.34), 356 (100). Anal. calcd. for $C_{34}H_{23}ClN_6O$: C, 72.02; H, 4.09; N, 14.82. Found: C, 71.88; H, 3.92; N, 14.67 %.

2.2.10. Synthesis of 4-amino-16-(4-chlorophenyl)-14-(phenyldiazenyl)-16H-benzo[7',8'] chromeno[2',3':4,5] pyrimido[1,6-b][1,2,4]triazepine-3-carbonitrile (13)

A mixture of compound **9** (4.78 g, 10 mmol), 2-(ethoxymethylene)malononitrile (0.01 mol), piperidine (0.05 mL) and ethanol (30 mL) was refluxed for 5 h. The solvent was extracted and the resulting product was recrystallized from *N,N*-dimethylformamide (DMF) (Scheme 3). Color: Pale yellow solid. Yield: 68%. M.p.: 290-292 °C. FT-IR (KBr, ν, cm^{-1}): 3340, 3332 (NH_2), 3001, 2986, 2923 (CH-str.), 2217 (CN), 1670 (C=N), 1507 (N=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 5.72 (s, 1H, H-16), 8.89 (s, 1H, N=CH), 8.50 (s, 1H, H-7), 8.76-6.83 (m, 16H, Ar-H + NH_2). ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 162.21 (C-8a), 160.11 (C-6a), 154.72 (C-2), 151.20 (C-4), 149.70 (C-7), 147.71, 145.53, 144.34, 133.21, 133.01, 132.81, 132.62, 130.70, 130.18, 129.62, 129.15, 124.16, 123.90, 123.48, 123.26, 121.59, 121.43 (Ar-C), 116.83 (CN), 105.62 (C-3), 92.31 (C-16a), 39.81 (C-16). MS (EI, *m/z* (%)): 555 (M$^+$ + 1, 0.92), 554 (M$^+$, 1.25), 77 (100). Anal. calcd. for $C_{31}H_{19}ClN_8O$: C, 67.09; H, 3.45; N, 20.19. Found: C, 68.85; H, 3.17; N, 19.89 %.

2.3. Antimicrobial Assay

All the newly synthesized compounds **3-13** were screened for their in vitro antimicrobial activity at 25 μg/mL to determine the zone of inhibition against four Gram-positive bacteria: *Staphylococcus aureus* (RCMB 000106) and *Bacillis subtilis* (RCMB 000108) and two Gram-negative pathogenic bacteria: *Pseudomonas aeruginosa* (RCMB 000102) and

Table 1. Antimicrobial activity of the new compounds.

Compound [a]	Minimum inhibitory concentration (MIC) (µg/mL) [b]					
	Bacterial strains				Fungal strains	
	Gram-positive bacteria		Gram-negative bacteria			
	S. aureus	*B. subtilis*	*P. aeruginosa*	*E. coli*	*A. fumigatus*	*C. albicans*
3	13.2±0.3	15.1±0.2	16.6±01	NA	NA	NA
4	16.1±0.1	18.2±0.1	NA	NA	NA	NA
5	13.2±0.3	15.1±0.2	NA	NA	NA	NA
6	12.9±0.1	18.1±0.1	NA	NA	NA	NA
7	15.1±0.1	12.1±0.3	NA	NA	NA	NA
8	17.1±0.1	14.9±0.1	18.2±0.1	NA	NA	NA
9	18.1±0.1	15.5±0.2	17.6±02	18.8±0.1	16.7±0.1	13.7±0.2
10a	23.2±0.1	20.5±0.2	19.6±01	24.2±0.1	23.7±0.2	21.7±0.2
10b	20.4±0.2	21.3±0.1	22.1±0.2	24.1±0.1	20.9±0.2	23.1±0.1
10c	22.6±0.1	20.9±0.2	20.3±01	24.2±0.3	23.9±0.1	24.6±0.2
10d	28.1±0.3	27.2±0.1	25.3±02	26.1±0.4	25.2±0.1	23.2±0.2
10e	26.1±0.1	23.8±0.2	25.6±01	23.6±0.3	29.1±0.6	20.3±0.1
11	16.9±0.3	18.5±0.1	14.9±01	16.1±0.2	19.2±0.4	14.8±01
12	20.5±0.3	19.8±0.1	21.7±0.2	28.7±0.1	27.6±0.2	23.1±0.3
13	25.7±0.1	28.5±0.3	27.3±01	27.2±0.3	23.6±0.3	22.8±0.2
Ampicillin	27.4±0.1	29.4±0.7	26.3±0.3	28.5±0.1	-	-
Mycostatine	-	-	-	-	29.5±0.1	27.1±0.1

[a] c = 1 mg/mL of new compounds in DMF

[b] NA = Not active, Diameter of the hole = 6 mm, Data are expressed in the form of mean±SD.

Escherichia coli (RCMB 000103) using standard antibiotics (Ampicillin) as reference drugs, and two fungi: *Aspergillus fumigatus* (RCMB 002003) and *Candida albicans* (RCMB 005002) using standard antibiotics (Mycostatine) as reference drugs. The activities of these compounds were tested by agar diffusion method using Mueller-Hinton agar medium for bacteria and Sabouraud's agar medium for fungi [46,47]. The tested compounds were dissolved in *N,N*-dimethylformamide to give a solution of 1 mg/mL. The inhibition zones (diameter of the hole) were measured in millimeters (6 mm) at the end of an incubation period of 48 h at 28 °C; *N,N*-dimethylformamide showed no inhibition zone. The inhibitory effects of the synthetic compounds against these organisms are given in Figure 1 and Table 1.

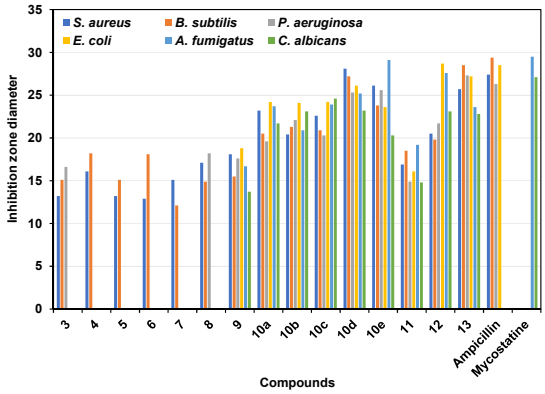


Figure 1. Antimicrobial activity of the tested compounds compared to ampicillin and mycostatine.

3. Results and discussion

Condensation of 4-phenyldiazenyl-1-naphthol (**1**) with 2-(*p*-chlorobenzylidene)malonoitrile (**2**) in ethanolic piperidine afforded the corresponding 2-amino-4-(*p*-chlorophenyl))-6-phenyldiazenyl-4*H*-naphtho[1,2-*b*]pyran-3-carbonitrile (**3**) [45], while treatment of compound **3** with triethyl orthoformate or triethyl orthoacetate in acetic anhydride for 5 h afforded ethyl *N*-(4-(4-chlorophenyl)-3-cyano-6-(phenyl diazenyl)-4*H*-benzo[h]chromen-2-yl)formimidate (**4**) and ethyl *N*-(4-(4-chlorophenyl)-3-cyano-6-(phenyldiazenyl)-4*H*-benzo[h]chromen-2-yl)acetimidate (**5**), respectively (Scheme 1). The structure of compound **4** and **5** were in accord with its spectroscopic data. The IR spectrum of compounds showed the principal absorption band at 2201 and 2199 cm^{-1}, indicating the presence of a cyano group (CN) and disappear of amino group (NH_2) in the molecule. Thus, the ^1H NMR spectrum of compound **4** and **5** showed a singlet at δ 5.01 and δ 5.05 ppm for the 4*H*-pyran, a triplet at δ 1.44-1.43 ppm and a quartet at δ 4.37-4.54 ppm indicating ethoxy group, a singlet at δ 8.94 ppm to the N=CH group and a singlet at δ 2.19 ppm to the CH_3 group.

Reaction of compound **4** with ammonia (NH_3) gas in methanol at room temperature for 1 h yielded the open chain product *N*'-(4-(4-chlorophenyl)-3-cyano-6-(phenyldiazenyl)-4*H*-benzo[*h*]chromen-2-yl)formimidamide (**6**), follow by benzaldehyde under reflux afforded Schiff base product **7**, while treatment of compound **4** with hydrogen sulfide in ethanol/triethyl amine at room temperature for 2 h afforded 7-(4-chlorophenyl)-5-(phenyldiazenyl)-7,9-dihydro-8*H*-benzo[7,8] chromeno[2,3-d]pyrimidine-8-thione 8. Reaction of compound **4** with hydrazine hydrate in ethanol at room temperature for 2 h afforded 7-(4-chlorophenyl)-8-imino-5-(phenyldiazenyl)-7*H*-benzo[7,8]chromeno[2,3-d]pyrimidin-9(8*H*)-amine (**9**) (Scheme 2).

The structure of compounds **6**-**9** were established by spectral data. The IR spectrum of compound **6** showed absorptions at ν 3342, 3328 (NH_2), 2203 cm^{-1} (CN), while compound **7** showed absorption at 3220 (NH), 1310 cm^{-1} (C=S) and compound **9** showed absorptions at 3320, 3280 (NH_2), 3210 cm^{-1} (NH). The ^1H NMR of compound **6** showed chemical shifts at δ 8.88 (s, 1H, N=CH), 5.22 (s, 1H, H-4), while compound **9** showed chemical shifts at δ 8.83 (s, 1H, H-10), 6.81 (br, 1H, NH), 5.74 (s, 2H, NH_2) and 5.45 (s, 1H, H-7). While the ^{13}C NMR of compound **6** showed δ 41.85 (C-4), 72.81 (C-3), 117.66 (CN), 155.47 (N=CH) and 160.21 (C-2). ^{13}C NMR of compound **8** showed δ 42.05 (C-7), 111.90 (C-7a), 156.63 (C-10), 161.04 (C-11a) and 183.62 (C-8). ^{13}C NMR of compound **9** showed δ 40.63 (C-7), 151.43 (C-10) and 152.89 (C-8). The mass spectra of compounds **6**-**9** displayed [M^+] ion peaks *m/z* 463 (M^+, 3.84), 551 (M^+, 3.76), 480 (M^+, 9.33) and 478 (M^+, 26.86), respectively.

Condensation of compound **9** with carboxylic acid derivatives such as formic acid or triethyl orthoformate, acetyl chloride or triethyl orthoacetate, benzoyl chloride, ethyl cyanoacetate, and chloroacetyl chloride, afforded benzochromenotriazolo pyrimidines **10a**-**e**, respectively. Reaction of compound **9** with benzaldehyde in ethanol/piperdine gave the open chain product 9-(benzylideneamino)-7-(4-chlorophenyl) -5-((*E*)-phenyldiazenyl)-7,9-dihydro-8*H*-benzo[7,8]chromeno [2,3-d]pyrimidin-8-imine, **12**. Compound **10c** was also

prepared by cyclization of compounds **12** in dioxane/ piperidine solution under reflux as confirmed by the M.p., mixed M.p., and their identical IR, NMR and MS spectra. Treatment of compound **9** with carbon disulfide in alcoholic potassium hydroxide solution gave the 14-(4-chlorophenyl)-12-(phenyldiazenyl)-14*H*-benzo[7, 8]chromeno[3, 2-e][1, 2, 4] triazolo[1,5-c]pyrimidine-2(3*H*)-thione, while reaction of compound **9** with 2-(ethoxymethylene)malononitrile in dioxane under reflux afforded 4-amino-16-(4-chlorophenyl)-14-(phenyldiazenyl)-16*H*-benzo[7', 8']chromeno[2', 3':4, 5] pyrimido [1,6-b][1,2,4]triazepine-3-carbonitrile (Scheme 3).

The structure of compounds **10**-**13** were established by spectral data. The IR spectrum of compound **11** showed absorptions at 3300 (NH), 1043 cm^{-1} (C=S), compound **12** showed absorptions at 3211 cm^{-1} (NH) and compound **13** showed absorptions at 3340, 3332 (NH_2), 2217 cm^{-1} (CN). The ^1H NMR of compound **10b** showed chemical shifts at δ 9.62 (s, 1H, H-5), 6.09 (s, 1H, H-14), 2.46 ppm (s, 3H, CH_3), compound **10d** showed chemical shifts δ 9.76 (s, 1H, H-5), 6.09 (s, 1H, H-14), 4.46 ppm (s, 2H, CH_2), compound **11** showed chemical shifts δ 10.21 (s, 1H, NH), 8.95 (s, 1H, H-5), 5.74 ppm (s, 1H, H-14) and compound **13** showed chemical shifts δ 5.72 (s, 1H, H-16), 8.89 (N=CH), 8.50 (s, 1H, H-7), 8.76-6.83 ppm (m, 16H, Ar-H + NH_2), while the ^{13}C NMR of compound **10a** showed δ 40.51 (C-14), 151.34 ppm (C-2), compound **10b** showed δ 14.50 (CH_3), 40.30 (C-14), 153.32 ppm (C-2), compound **10d** showed δ 18.43 (CH_2), 40.61 (C-14), 116.92 (CN), 153.32 ppm (C-2) and compound **13** showed δ at 39.81 (C-16), 116.83 (CN), 149.70 (C-7), 151.20 (C-4), 154.72 ppm (C-2). The mass spectra of compounds **10**-**13** displayed [M^+] ion peaks *m/z* 488 (M^+, 3.64), 502 (M^+, 65.05), 564 (M^+, 6.50), 527 (M^+, 81.52), 536 (M^+, 1.44), 520 (M^+, 6.05), 566 (M^+, 1.34) and 554 (M^+, 1.25), respectively.

The structure activity relationship studies of compounds **3**-**13** revealed that compounds **10d**, **e**, **12** and **13** with inhibitory effects of 28.1±0.3, 29.1±0.6, 28.7±0.1 and 28.5±0.3 µg/mL good activities than the against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Aspergillus fumigatus*, respectively, compared to the standard antibiotics, ampicillin and mycostatine as reference drugs. Other compounds showed almost equipotent activities or were inactive, implying that the benzochromenotriazolopyrimidine and benzochromenepyrimidine nucleus was more active than the benzochromene and 2-methyleneaminobenzochromene.

Compounds **10a-e**, **12**, and **13** were found to be the with inhibitory effects ranging 27.4±0.1 to 29.4±0.7 µg/mL more activities as compared to the standard antibiotics ampicillin and mycostatine, while compounds **9** and **11** with inhibitory effect of 13.7±0.2 to 19.2±0.4 µg/mL were exhibited moderate activities as compared to the standard antibiotics ampicillin and mycostatine and compounds **3** and **8** showed moderate activity against *Pseudomonas aeruginosa* with inhibitory effect ranging 16.6±0.1 and 18.2±0.1 µg/mL as compared to the standard antibiotics ampicillin, while compounds **3**, **4**, **5**, **6** , **7** and **8** moderate to weak activity against *Staphylococcus aureus*, *Bacillis subtilis* and *Pseudomonas aeruginosa* with inhibitory effect ranging 13.2±0.3 and 18.1±0.1 µg/mL as compared to the standard antibiotics ampicillin. Compounds **4**, **5**, **6** and **7** inactive against *Pseudomonas aeruginosa*, while compounds **3**, **4**, **5**, **6**, **7** and **8** inactive against *Escherichia coli*, and *Aspergillus fumigatus*, respectively, compared to the standard antibiotics, ampicillin and mycostatine as reference drugs.

4. Conclusions

In conclusion, a series of novel methyleneaminobenzochemene, benzochromenotriazolopyrimidine were synthesized successfully in good yield, starting from 4*H*-benzochromene derivative. All the new compounds were fully spectroscopically characterized. The title compounds were synthesized as new compounds with antimicrobial activity in vitro. Compounds **4**, **5**, **6** and **7** inactive against *Pseudomonas aeruginosa*, while compounds **3**, **4**, **5**, **6**, **7** and **8** inactive against *Escherichia coli*, and *Aspergillus fumigatus*, respectively, compared to the standard antibiotics, ampicillin and mycostatine as reference drugs, while compounds **10a-e**, **12**, **13** showed high to good activities compared to the standard antibiotics, The structure-activity relationship study revealed that the antimicrobial activity of benzochromenopyrimidotriazepine nucleus was more beneficial than benzochromenotriazolopyrimidine nucleus for antimicrobial activity.

Acknowledgements

The authors profoundly thank the Regional Center for Mycology & Biotechnology (RCMP), Al-Azhar University, Cairo, Egypt, for providing the facilities to determine the antibacterial and antifungal activities. The authors thank the Deanship of Scientific Research of Jazan University to support the research.

References

[1]. Wojciechowski, K.; Wyrebak, A.; Gumulak, J.; *Dyes Pigments* **2003**, *56*, 99-106.
[2]. Rudyk, H.; Knaggs, M. H.; Vasiljevic, S.; Hope, J.; Birkett, C.; Gilbert, I. H. *Eur. J. Med. Chem*. **2003**, *38* , 567-579.
[3]. Mittal, A.; Kurup, L.; Mittal, J. *Materials* **2007**, *146*, 243-248.
[4]. Wainwright, M. *Dyes Pigments* **2008**, *76*, 582-589.
[5]. Ahmed, A. E. I.; Hay, J. N.; Bushell, M. E.; Wardell, J. N.; Cavalli, G.; *Reac. Funct. Polym.* **2008**, *68*, 248-260.
[6]. Simu, G.; Chicu, S. A.; Morin, N.; Schmid, W.; Sisu, E. *Turk. J. Chem.* **2004**, *28*, 579-585.
[7]. Simu, G. M.; Hora, S. G.; Sisu, E.; Sisu, I. *Rev. Roum. Chim.* **2011**, *56*, 527-536.
[8]. Bae, S. J.; Freeman, H. S.; El-Shafei, A. *Dyes Pigments* **2003**, *57*, 121-129.
[9]. Hildenbrand, S.; Schmahl, F. W.; Wodarz, R.; Kimmel, R.; Dartsch, P. C. *Int. Arch. Occup. Environ. Hlth.* **1999**, *72*, 52-57.
[10]. Pinson, J.; Podyorica, F. *Chem. Soc. Rev*. **2005**, *34*, 429-444.
[11]. Dabbagh, H. A.; Teimouri, A.; Chermahini, A. N. *Azo Comp. Pigments* **2007**, *73*, 239-244.
[12]. Murray, P. S.; Ralph, S. F. *Electrochimica Acta* **2006**, *51*, 2471-2476.
[13]. Garg, H. G.; Praksh, C. J. *J. Med. Chem.* **1972**, *15,* 435-436.
[14]. Browing, C. H.; Cohen, J. B.; Ellingworth, S.; Gulbransen, R. *J. Storage* **1926**, *100*, 293-325.
[15]. Khalid, A; , Arshad, M.; Crowley, D. E. *Appl. Microbiol. Biotech.* **2008**, *78*, 361-369.
[16]. Pagga, U.; Brown, D. *Chemosphere* **1986**, *15*, 479-491.
[17]. Farghaly, T. A.; Abdallah, Z. A. *Arkivoc* **2008**, *17*, 295-305.
[18]. El-Agrody, A. M.; Abd El-Latif, M. S.; El-Hady, N. A.; Fakery, A. H.; Bedair, A. H. *Molecules* **2001**, *6*, 519-527.
[19]. Bedair, A. H.; El-Hadd, N. A.; Abd El-Latif, M. S.; Fakery, A. H.; El-agrody, A. M. *Il Farmaco* **2000**, *55*, 708-714.
[20]. El-Agrody, A. M.; El-Hakim, M. H.; Abd El-Latif, M. S.; Fakery, A. H.; El-Sayed, E. S. M.; El-Ghareab, K. A. *Acta Pharm.* **2000**, *50*, 111-120.
[21]. Abd El-Wahab, A. H. F. *Pharmaceuticals* **2012**, *5,* 745-757.
[22]. Bedair, A. H.; Emam, H. A.; El-Hady, N. A.; Ahmed, K. A. R.; El-Agrody, A. M. *Il Farmaco* **2001**, *56*, 965-973.
[23]. Khafagy, M. M.; Abd El-Wahab, A. H. F.; Eid, F. A.; El-Agrody, A. M. *Il Farmaco* **2002**, *57,* 715-722.
[24]. Foroumadi, A.; Emami, S.; Sorkhi, M.; Nakhjiri, M.; Nazarian, Z.; , Heydar, S.; Ardestani, S.; Poorrajab, F.; Shafiee, A.; *Chem. Biol. Drug Des.* **2010**, *75*, 590-596.
[25]. Narender, T.; Shweta, S. A.; Gupta, O. *Org. Med. Chem. Lett.* **2009**, *14,* 3913-3916.
[26]. Sabry, N. M.; Mohamed, H. M.; Khattab, E. S. A. E. H.; Motlaq, S. S.; El-Agrody, A. M. *Eur. J. Med. Chem.* **2011**, *46,* 765-777.
[27]. Rampa, A.; Bisi, A.; Belluti, F.; Gobbi, S.; Piazzi, L.; Valenti, P.; Zampiron, A.; Caputo, A.; Varani, K.; Borea, P. A.; Carrara M. *Il Farmaco* **2005**, *60*, 135-148.
[28]. Magedov, I. V.; Manpadi, M.; Evdokimov, N. M.; Elias, E. M.; Rozhkova, E.; Ogasawara, M. A.; Bettale, J. D.; Przheval'skii, N. M.; Rogelj, S.; Kornienko, A. *Bioorg. Med. Chem. Lett.* **2007**, 17, 3872-3876.
[29]. Singh, O. M.; Devi, N. S.; Thokchom, D. S.; Sharma, G. J. *Eur. J. Med. Chem.* **2010**, *45*, 2250-2257
[30]. Vukovic, N.; Sukdolak, S.; Solujic, S.; Niciforovic, N. *Food Chem.* **2010**, *120*, 1011-1018.
[31]. Tandon, V. K.; Vaish, M.; Jain, S.; Bhakuni, D. S.; Srimal, R. C. *Indian J. Pharm. Sci.* **1991**, *53*, 22-23.

[32]. Mahmoodi, M.; Aliabadi, A.; Emami, S.; Safavi, M.; Rajabalian, S.; Mohagheghi, M. A.; Khoshzaban, A.; Samzadeh, A. K.; Lamei, N.; Shafiee, A. *Arch. Pharm. Chem.* **2010**, *343*, 411-416.
[33]. Endo, S.; Matsunaga, T.; Kuwata, K.; Zhao, H. T.; El-Kabbani, O.; Kitade, Y.; Hara, A. *Bioorg. Med. Chem.* **2010**, *18*, 2485-2490.
[34]. Tseng, T. H.; Chuang, S. H.; Hu, C. C.; Chang, C. F.; Huang, Y. C.; Lin, C. W.; Lee, Y. J. *Tetrahedron* **2010**, *66*, 1335-1340.
[35]. El-Agrody, A. M.; Fouda, A. M.; Khattab, E. S. A. E. H. *Med. Chem. Res.* **2013**, *22*, 6105-6120.
[36]. Bruhlmann, C.; Ooms, F.; Carrupt, P.; Testa, B.; Catto, M.; Leonetti, F.; Altomare, C.; Cartti, A. *J. Med. Chem.* **2001**, *44*, 3195-3198.
[37]. Kesten, S. R.; Heffner, T. G.; Johnson, S. J.; Pugsley, T. A.; Wright, J. L.; Wise, D. L. *J. Med. Chem.* **1999**, *42*, 3718-3725.
[38]. Lee, K. S.; Khil, L. Y.; Chae, S. H.; Kim, D.; Lee, B. H.; Hwang, G. S.; Moon, C. H.; Chang, T. S.; Moon, C. K. *Life Sci.* **2006**, *78*, 1091-1097.
[39]. Coudert, P.; Coyquelet, J. M.; Bastide, J.; Marion, Y.; Fialip, J. *Ann. Pharm. Fr.* **1988**, *46*, 91-96.
[40]. El-Sayed, A. T.; Ibrahim, M. A. *J. Braz. Chem*. **2010**, *21*, 1006-1007.
[41]. Narasimhan, B.; Kumar, P.; Sharma, D. *Acta Pharm. Sci.* **2010**, *52*, 169-180.
[42]. Keri, R. S.; Hosamani, K. M.; Shingalapur, R. V.; Hugar, M. H. *Eur. J. Med. Chem.* **2010**, *45*, 2597-2605.
[43]. Sashidhara, K. V.; Kumar, M.; Modukuri, R. K.; Srivastava, A.; Puri, A. *Bioorg. Med Chem. Lett.* **2011**, *21*, 6709-6713.
[44]. Hiramoto, K.; Nasuhara, A.; Michiloshi, K.; Kato, T.; Kikugawa, K. *Mutat. Res.* **1997**, *395*, 47-56.
[45]. Ibrahim, A. A.; Ashraf, H. F. A. *Eur. J. Chem.* **2016**, *7(2)*, 230-237.
[46]. European Committee for Antimicrobial Susceptibility Testing (EUCAST) of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Determination of minimum inhibitory concentrations (MICs) of antibacterial agents by agar dilution. *Clin. Microbiol. Infect.* **2000**, *6*, 509-515.
[47]. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*, 5th ed.; National Committee for Clinical Laboratory Standards (NCCLS): Wayne, PA, USA, **2000** Approved Standard M7-A5.