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Il Farmaco 55 (2000) 227–232

IL FARMACO

A novel synthesis of dibenzo[*c*,*f*]chromenes, dibenzo[*c*,*h*]chromenes and benzo[7,8]chromeno[3,4-*f*]isoindoles as antimicrobial agents

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Received 30 July 1999; accepted 3 February 2000

Abstract

Naphtho[2,1-*b*]pyranone (**3**) was allowed to react with arylmethylenemalononitriles to yield 4-amino-5-oxo-2-aryl-5*H*-dibenzo[*c*,*f*]chromene-3-carbonitriles (**4a**,**b**); with ethyl 3,4-dichlorobenzylidene cyanoacetate to furnish dibenzo[*c*,*f*]chromene (**5**) and with elemental sulfur in dioxane containing piperidine to give thieno[3,4-*d*]naphtho[2,1-*b*]pyranone (**6**). Similarly, naphtho[1,2-*b*]pyranone (**7**) was reacted with arylmethylenemalononitriles and elemental sulfur to furnish dibenzo[*c*,*h*]chromenes (**8**) and thieno[3,4-*d*]naphtho[1,2-*b*]pyranone (**10**), respectively. Compound **10** underwent cycloaddition with *N*-arylmaleimides to yield benzo[7,8]chromeno[3,4-*f*]isoindoles (**11a**–**c**). Some of these compounds were screened in vitro for their antimicrobial activities.

Keywords: Chromenes; Isoindoles; Antimicrobial

1. Introduction

Naphthopyranones are biologically interesting compounds with antimicrobial [1] and antihypertensive [2] activities. Arylmethylenemalononitriles and ethyl α-cyanocinnamates are versatile reagents for the construction of carbo- and heterocyclic systems [3–6]. They are prone to react with a variety of compounds containing acidic hydrogen atoms to provide Michael adducts as intermediates, which undergo spontaneous cyclization to *o*-aminonitriles or *o*-aminocarboxylic esters, respectively [7,8]. 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 naphtho[2,1-*b*]pyran derivatives and their utility as building block in the synthesis of novel heterocycles to evaluate the antimicrobial activity.

2. Chemistry

It has been found that 1-acetyl-2-naphthol (**1**) reacted with ethyl cyanoacetate in the presence of catalytic amount of ammonium acetate for which two products **2** and **3** seemed possible. Structure **2** was readily ruled out on the basis of analytical and spectral data. Thus, the IR spectrum of **3** exhibited absorption bands for C≡N (2196 cm^{-1}) and C=O (1717 cm^{-1}), while ^1H NMR revealed the presence of a signal at δ 3.3 (3H, s, CH_3) and the absence of an OCH_2CH_3 fragment. The mass spectrum of **3** also exhibited a molecular ion peak m/z 235, which is the base peak in the spectrum whose fragmentation pattern is illustrated in Scheme 2. Further confirmation of the structure **3** was obtained by studying the reactivity of the reaction product towards various chemical reagents. Thus, compound **3** reacted with arylmethylenemalononitriles in ethanol containing a few drops of piperidine to afford 4-amino-2-aryl-5-oxo-5*H*-dibenzo[*c*,*f*]chromene-3-carbonitriles (**4a**,**b**). The IR spectra of **4a**,**b** revealed the presence of amino, cyano and carbonyl functions and the absence of a methyl function in ^1H NMR spectra. The formation of

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0014-827X/00/$ - see front matter
PII: S0014-827X(00)00008-2

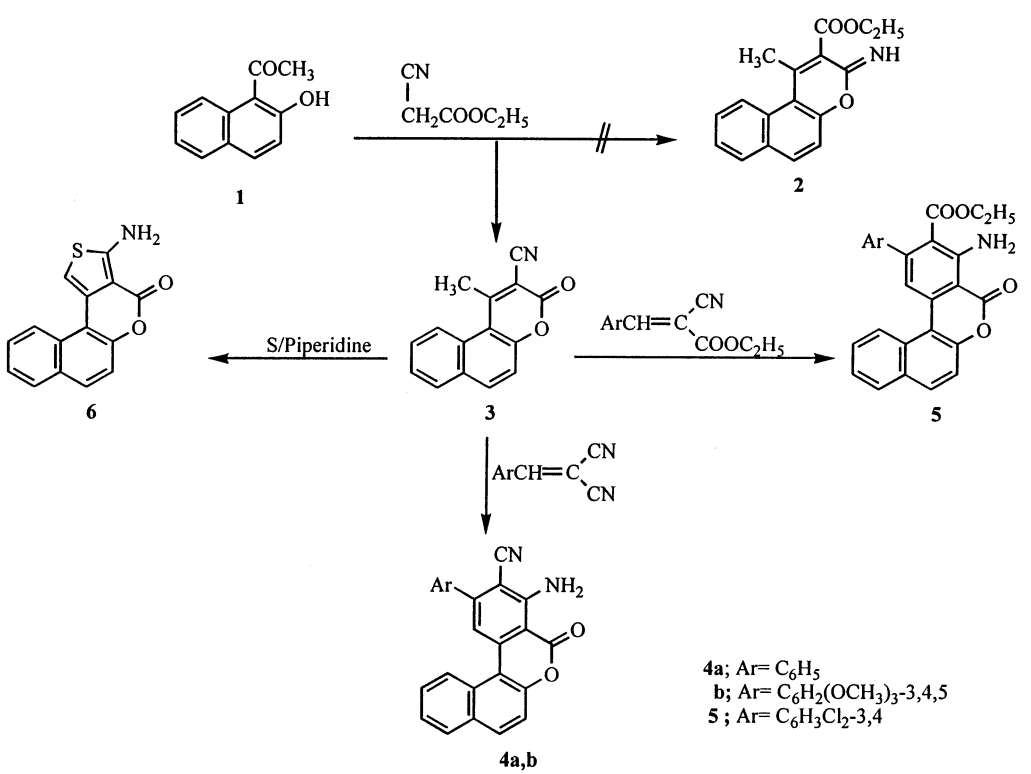
4 from the reaction of **3** with arylmethylenemalononitriles was assumed to proceed via Michael type addition [8] of the methyl function of **3** to the activated double bond to afford the acyclic Michael adduct that readily cyclizes and loses hydrogen cyanide to yield **4**, which was observed with 3-cyano-4-methylcoumarin [9].

In addition, treatment of compound **3** with ethyl 3,4-dichlorobenzylidene cyanoacetate gave a product, which was confirmed to be the ethyl 4-amino-5-oxo-2-(3,4-dichlorophenyl)-5*H*-dibenzo[*c*,*h*]chromene-3-carboxylate (**5**) on the basis of its elemental analysis and spectral data. Compound **3** also reacts with elemental sulfur in dioxane–piperidine solution to yield 3-amino-4*H*-thieno[3,4-*d*]naphtho[2,1-*b*]pyran-4-one (**6**). The IR spectrum of **6** revealed the presence of amino and carbonyl functions and the absence of a cyano group. The formation of **6** is related to the Gewald synthesis of alkylheterocyclic carbonitriles [10] (Scheme 1).

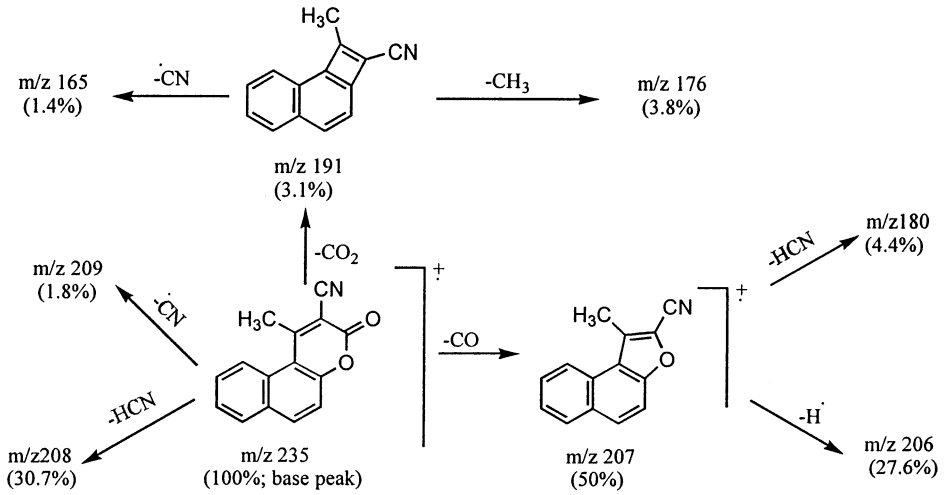
4-Methyl-2-oxo-3*H*-naphtho[1,2-*b*]pyran-3-carbonitrile (**7**) was obtained by fusion of 2-acetyl-1-naphthol with ethyl cyanoacetate in the presence of ammonium acetate [11]. Reaction of **7** with arylmethylenemalononitriles in ethanol in the presence of piperidine gave 7-amino-6-oxo-9-aryl-6*H*-dibenzo[*c*,*h*]chromene-8-carbonitriles (**8**) as established from their elemental analyses and spectral data. Compound **7** also reacted with ethyl 4-chlorobenzylidenecyanoacetate to afford dibenzo[*c*,*h*]chromenes (**9**). In addition, compound **7** reacted with sulfur in dioxane in the presence of few drops of piperidine to yield 3-aminothieno[3,4-*d*]naphtho[1,2-*b*]pyran-2-one (**10**) [11]. Treatment of compound **10** with *N*-arylmaleimides as electron-poor [11] olefins in dioxane containing a few drops of glacial acetic acid to yield 7-amino-9-(4-substitutedphenyl)-6,8,9,10-tetrahydrobenzo[7,8]chromeno[3,4-*f*]isoindole-6,8,10-trione derivatives (**11a–c**). Analytical and spectral data were consistent with the assigned structure. The formation of these products is assumed to proceed via a [4 + 2] cycloadduct, which is aromatized by hydrogen sulfide liberation [11,12] to yield **11**. Refluxing **10** with acetic anhydride afforded 3-acetylamino-2*H*-thieno[3,4-*d*]-naphtho[1,2-*b*]pyran-2-one (**12**) in high yield (Scheme 3).

3. Experimental

Melting points were measured by Griffen melting point apparatus (England) and are uncorrected. IR spectra $\nu_{max.}$ (cm^{-1}) were recorded on a Shimadzu 440 infrared spectrophotometer (Shimadzu, Japan) using the KBr technique. ^1H NMR spectra δ (ppm) were measured on a Varian Em 360 (90 MHz) spectrophotometer (Varian, UK) using TMS as internal standard. The mass spectra were performed by a Shimadzu GC–MS-GP 100 EX using the direct inlet system. Analytical data were obtained from the Microanalytical Data Center at Cairo University.



Scheme 1.



Scheme 2. Fragmentation pattern of compound **3**.

3.1. Synthesis of 1-methyl-3-oxo-3H-naphtho-[2,1-b]pyran-2-carbonitrile (3)

A mixture of equimolar amounts of **1** (1.86 g, 0.01 mol), ethyl cyanoacetate (1.13 g, 0.01 mol) and anhydrous ammonium acetate (1 g) was fused at 120°C for 15 min. The resulting product was then triturated with ethanol and the solid product formed was collected by filtration and recrystallized from dioxane to form green crystals. Yield 1.65 g (70%); m.p. 260°C. Found: C, 76.50; H, 3.80; N, 5.90. $C_{15}H_9NO_2$ requires: C, 76.59; H, 3.86; N, 5.96%. IR: 2196 (CN), 1717(CO). ^{1}H NMR (DMSO-d_6): 3.35 (3H, s, CH_3), 7.54–8.63 (m, 6H, Ar-H); MS: m/z 235 [M^+].

3.2. General procedure for the preparation of 4a,b

To a solution of **3** (2.35 g, 0.01 mol) in 20 ml of absolute ethanol, arylmethylenemalononitriles (0.01 mol) and a catalytic amount of piperidine were added. The reaction mixture was heated under reflux for 3 h, then poured into ice–HCl to give **4a**,**b**.

3.2.1. 4-Amino-5-oxo-2-phenyl-5H-dibenzo[c,f]chromene-3-carbonitrile (4a)

Compound **4a** was obtained as yellow crystals from ethanol. Yield 2.17 g (60%); m.p. 110°C. Found: C, 79.40; H, 3.70; N, 7.70. $C_{24}H_{14}N_2O_2$ requires: C, 79.54; H, 3.84; N, 7.73%. IR: 3335, 3184 (NH_2), 2058 (Ar–H), 2205 (CN), 1706 (CO). ^{1}H NMR (DMSO-d_6): 3.4 (2H, s, NH_2; exchangeable), 7.1–7.9 (12H, m, Ar–H); MS: m/z 362 [M^+].

3.2.2. 4-Amino-5-oxo-2-(3,4,5-trimethoxyphenyl)-5H-dibenzo[c,f]chromene-3-carbonitrile (4b)

Compound **4b** was obtained as yellow crystals from ethanol. Yield: 2.94 g (65%); m.p. 125°C. Found: C, 71.70; H, 4.50; N, 6.20. $C_{27}H_{20}N_2O_5$ requires: C, 71.68; H, 4.42; N, 6.19%. IR: 3420, 3380 (NH_2), 2935 (CH–aliph), 2207 (CN), 1724 (CO). ^{1}H NMR (DMSO-d_6): 4.0 (3H, s, OCH_3), 4.1 (6H, s, $2OCH_3$), 4.8 (2H, broad, NH_2; exchangeable), 7.2–8.4 (9H, m, Ar–H).

3.3. Ethyl 4-amino-5-oxo-2-(3,4-dichlorophenyl)-5H-dibenzo[c,f]chromene-3-carboxylate (5)

To a solution of **3** (2.35 g, 0.01 mol) in 20 ml of dioxane, ethyl 3,4-dichlorobenzylidene cyanoacetate (2.71 g, 0.01 mol) and a catalytic amount of piperidine were added. The reaction mixture was refluxed for 4 h, then poured into ice–HCl. The solid product was collected by filtration to give **5** as yellow crystals from benzene–petroleum ether. Yield: 2.87 g (60%); m.p. 70°C. Found: C, 65.30; H, 3.40; N, 2.70%. $C_{26}H_{17}Cl_2NO_4$ requires: C, 65.28; H, 3.58; N, 2.93%. IR: 3350, 3210 (NH_2), 1720, 1690 (CO). ^{1}H NMR (DMSO-d_6): 0.8(3H, t, CH_3), 3.2 (2H, s, NH_2; exchangeable), 4.1 (2H, q, OCH_2), 7.25–7.89 (10H, m, Ar–H). MS: m/z 478 [M^+].

3.4. Synthesis of 3-amino-4H-thieno[3,4-d]naphtho-[2,1-b]pyran-4-one (6)

To a solution of **3** (2.35 g, 0.01 mol) in 30 ml dioxane, elemental sulfur (0.32 g, 0.01 mol) and a catalytic amount of piperidine were added. The reaction mixture was heated under reflux for 3 h. The solid product formed on dilution with water was collected by filtration and crystallized from ethanol. Yield: 2.14 g, (80%); m.p. 240°C. Found: C, 67.30; H, 3.40; N, 5.30. $C_{15}H_9NO_2S$ requires: C, 67.40; H, 3.39; N, 5.24%. IR: 3410, 3330 (NH_2), 1677 (CO); MS: m/z 267 [M^+].

3.5. General procedure for the preparation of (**8a–c**)

To a solution of **7** [11] (2.35 g, 0.01 mol) in 20 ml ethanol, arylmethylenemalononitriles (0.01 mol) and a catalytic amount of piperidine were added. The reaction mixture was heated for 4 h, then poured into ice–HCl. The solid product was collected by filtration and crystallized from dioxane to give **8a–c**.

3.5.1. 7-Amino-6-oxo-9-phenyl-6H-dibenzo[c,h]chromene-8-carbonitrile (**8a**)

Compound **8a** was obtained as green crystals from dioxane. Yield: 2.17 g, (60%); m.p. 270°C. Found: C, 79.50; H, 3.70; N, 7.60. $C_{24}H_{14}N_2O_2$ requires: C, 79.54; H, 3.89; N, 7.73%. IR: 3405, 3330 (NH_2), 3035 (CH–Ar); 2185 (CN), 1687 (CO). ^{1}H NMR (DMSO-d_6): 3.57 (2H, s, NH_2; exchangeable), 7.43–8.11 (12H, m, Ar–H); MS: m/z 362 [M^+].

3.5.2. 7-Amino-6-oxo-9-(3,4,5-trimethoxyphenyl)-6H-dibenzo[c,h]chromene-8-carbonitrile (**8b**)

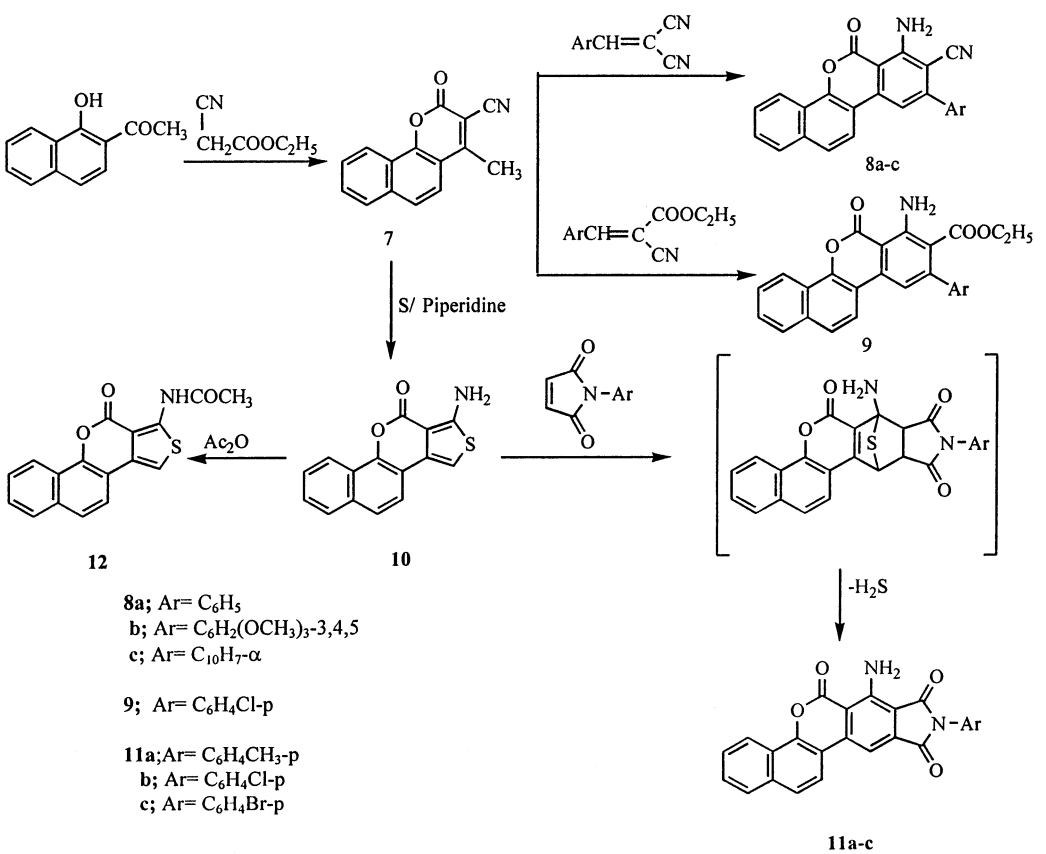
Compound **8b** was obtained as yellow crystals from ethanol. Yield: 2.26 g (50%); m.p. 120°C. Found: C, 71.60; H, 4.50; N, 6.20. $C_{27}H_{20}N_2O_5$ requires: C, 71.68; H, 4.42; N, 6.19%. IR: 3334, 3310 (NH_2), 2204(CN); 1705(CO). ^{1}H NMR (DMSO-d_6): 4.1 (3H, s, OCH_3), 4.2(6H, s, $2OCH_3$); 5.0 (2H, broad, NH_2; exchangeable), 7.1–8.4 (9H, m, Ar–H).

3.5.3. 7-Amino-6-oxo-9-(1-naphthyl)-6H-dibenzo[c,h]chromene-8-carbonitrile (**8c**)

Compound **8c** was obtained as yellow crystals from ethanol. Yield: 2.07 g (55%); m.p. 130°C. Found: C, 81.60; H, 3.60; N, 6.90. $C_{28}H_{16}N_2O_2$ requires: C, 81.54; H, 3.88; N, 6.80%. IR: 3328, 3300 (NH_2), 2199 (CN); 1702 (CO). ^{1}H NMR: 4.0 (2H, broad, NH_2; exchangeable), 7.2–8.3 (14H, m, Ar–H).

3.6. Synthesis of ethyl 7-amino-6-oxo-9-(4-chlorophenyl)-6H-dibenzo[c,h]chromene-8-carboxylate (**9**)

To a solution of **7** (2.35 g, 0.01 mol) in 20 ml of dioxane, ethyl 4-chlorobenzylidene cyanoacetate (2.35 g, 0.01 mol) and a catalytic amount of piperidine were added. The reaction mixture was refluxed for 4 h, then poured into ice–HCl. The solid product was collected by filtration and crystallized from benzene–petroleum ether to give **9** as yellow crystals. Yield: 2 g, (45%); m.p. 275°C. Found: C, 70.40; H, 4.10; N, 3.00. $C_{26}H_{18}ClNO_4$ requires: C, 70.35; H, 4.20; N, 3.16%. IR: 3438, 3317 (NH_2), 3057 (CH–Ar), 2931 (CH–aliph), 1709, 1680



Scheme 3.

Table 1
Diameter of inhibition zones (mm) as a criterion of antibacterial and antifungal activity of the tested compounds

Comp.	*Staphylococcus aureus*	*Escherichia coli*	*Candida albicans*
3	16		17
4b	18	19	15
5		12	
6	15		21
7	17	11	17
8a	18		16
9	18	14	14
10	15	18	19
11b	16	10	11
Reference [a]	24	22	24

[a] For bacteria: streptomycin (25 μg) For fungi: mycostatin (30 μg).

(2C=O). ^{1}H NMR (DMSO-d_6): 0.8(3H, t, CH_3), 1.5 (2H, broad, NH_2; exchangeable); 4.0 (2H, q, OCH_2), 7.38–8.00 (11H, m, Ar–H); MS: m/z 444 [M^+].

3.7. General procedure for the preparation of **11a–c**

To a solution of **10** [11] (2.67 g, 0.01 mol) in 20 ml dioxane, *N*-arylmaleimides (0.01 mol) and 2 ml glacial acetic acid were added. The reaction mixture was heated under reflux for 3 h. The solid obtained was filtered to give **11a–c**.

3.7.1. 7-Amino-9-(4-methylphenyl)-6,8,9,10-tetrahydrobenzo[7,8]chromeno[3,4-f]isoindole-6,8,10-trione (**11a**)

Compound **11a** was obtained as brown crystals from ethanol. Yield: 2.1 g (50%); m.p. 130°C. Found: C, 74.30; H, 3.8; N, 6.70. $C_{26}H_{16}N_2O_4$ requires: C, 74.28; H, 3.8; N, 6.67%. IR: 3403, 3302 (NH_2), 1710, 1660, 1650 (CO). ^{1}H NMR (DMSO-d_6): 2.2 (3H, s, CH_3), 4.2 (2H, broad, NH_2; exchangeable); 7.4–8.6 (11H, m, Ar–H); MS: m/z 420 [M^+].

3.7.2. 7-Amino-9-(4-chlorophenyl)-6,8,9,10-tetrahydrobenzo[7,8]chromeno[3,4-f]isoindole-6,8,10-trione (**11b**)

Compound **11b** was obtained as brown crystals from ethanol. Yield: 2.42 g (55%); m.p. 120°C. Found: C, 68.00; H, 2.80; N, 6.20. $C_{25}H_{13}ClN_2O_4$ requires: C, 68.11; H, 2.97; N, 6.36%. IR: 3410, 3279 (NH_2), 1730, 1665, 1650 (CO). ^{1}H NMR (DMSO-d_6): 4.0 (2H, broad, NH_2; exchangeable), 7.2–8.3 (11H, m, Ar–H).

3.7.3. 7-Amino-9-(4-bromophenyl)-6,8,9,10-tetrahydrobenzo[7,8]chromeno[3,4-f] isoindole-6,8,10-trione (**11c**)

Compound **11c** was obtained as brown crystals from ethanol. Yield: 2.76 g (57%); m.p. 128°C. Found: C, 61.70; H, 2.70; N, 5.60. $C_{25}H_{13}BrN_2O_4$ requires: C, 61.87; H, 2.70; N, 5.77%). IR: 3406, 3277 (NH_2), 1708, 1695, 1650 (CO). ^{1}H NMR (DMSO-d_6): 4.4 (2H, broad, NH_2; exchangeable), 7.3–8.5 (11H, m, Ar–H).

3.8. Formation of 1-acetylamino-11H-thieno[3,4-d]naphtho[1,2-b]pyran-11-one (**12**)

A solution of **10** (2.67 g, 0.01 mol) in 8 ml acetic anhydride was heated under reflux for 0.5 h. The solid product was collected by filtration and crystallized from ethanol to give **12** as brown crystals. Yield: 1.85 g (90%); m.p. 260°C. IR: 3273 (NH), 2935 (CH–aliph), 1697, 1670 (CO). ^{1}H NMR: (DMSO-d_6), 3.25 (3H, s, $COCH_3$), 7.39–7.9 (6H, m, Ar–H), 8.6 (1H, d, thiophene proton), 10.9 (1H, s, NH; exchangeable).

4. Antimicrobial activity

The antimicrobial activity of the nine naphthopyranone derivatives **3**, **4b**, **5**, **6**, **7**, **8a**, **9**, **10** and **11b** was determined by the agar diffusion technique [13,14]. The organisms tested were *Staphylococcus aureus* (gram positive), *Escherichia coli* (gram negative) and *Candida albicans* (pathogenic fungus). The agar media were inoculated with the test organisms and a solution of the tested compound in DMSO (3 mg/ml) was placed separately in cups (8 mm diameter) in the agar medium. Streptomycin (25 μg) and mycostatin (30 μg) were used as a reference for antibacterial and antifungal activities, respectively. The inhibition zones were measured after 24 h incubation. The results are represented in Table 1.

The antimicrobial activity of the naphthopyranone derivative **3** was assumed as the base level of activity. Enhanced activity was obtained with dibenzochromene **4b**. The thienonaphthopyranone **6** offered an improvement over the parent **3** against *C. albicans*. While, on the contrary, the ester derivative **5** showed a marked decrease in activity. It is interesting to note that the naphtho[1,2-*b*]pyran derivative (**7**) showed higher activity than the parent naphtho[2,1-*b*]pyran (**3**). However, none of the tested compounds showed superior activity than the reference.

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