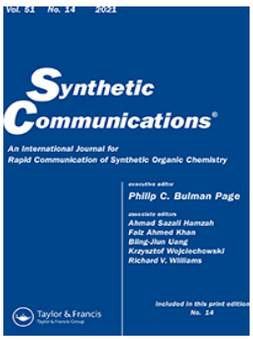

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An efficient approach for the synthesis and antimicrobial evaluation of some new benzocoumarins and related compounds

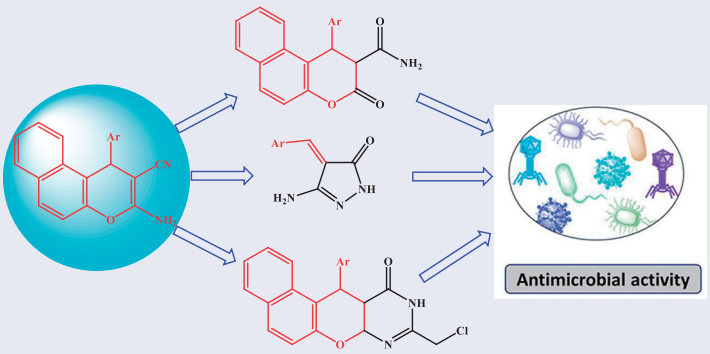
Mohamed H. Hekal, Fatma S. M. Abu El-Azm, and Sandy S. Samir

Chemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt

ABSTRACT

A convenient synthetic approach for pharmaceutically important benzocoumarin-based heterocyclic compounds has been studied. β-enaminonitrile has been used for the synthesis of a broad diversity of new benzocoumarins and related compounds over different reaction steps. Various synthetic approaches were used in this research for synthesis of heterocyclic systems such as acid-catalyzed hydrolysis, decarboxylation, deamination, ring opening and ring closure. The molecular structures of the newly synthesized derivatives were established by elemental analyses and spectral data (IR, ^{1}H-NMR, and ^{13}C-NMR). Some of the newly synthesized compounds were explored for their antimicrobial activities.

GRAPHICAL ABSTRACT



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Benzo[f]coumarin; β-enaminonitrile; deamination; keto-enol tautomerism; nitrogen nucleophiles; ring opening of benzo[f]coumarin

Introduction

On account of the rise in the number of immune-compromised hosts, further cases of microbial infections have been announced significantly. Many of the microorganisms acquire resistance through a period of time against available medications. Subsequently, there is an imperative necessity to develop alternate antimicrobial agents. Coumarin compounds are considered as a remarkable category in the field of organic synthesis and natural products. So, researchers are interested from many years to examine the

CONTACT Mohamed H. Hekal mohahekal2007@yahoo.com Chemistry Department, Faculty of Science, Ain Shams University, Cairo, Egypt.

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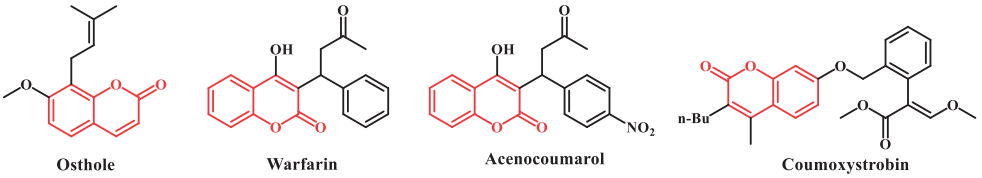


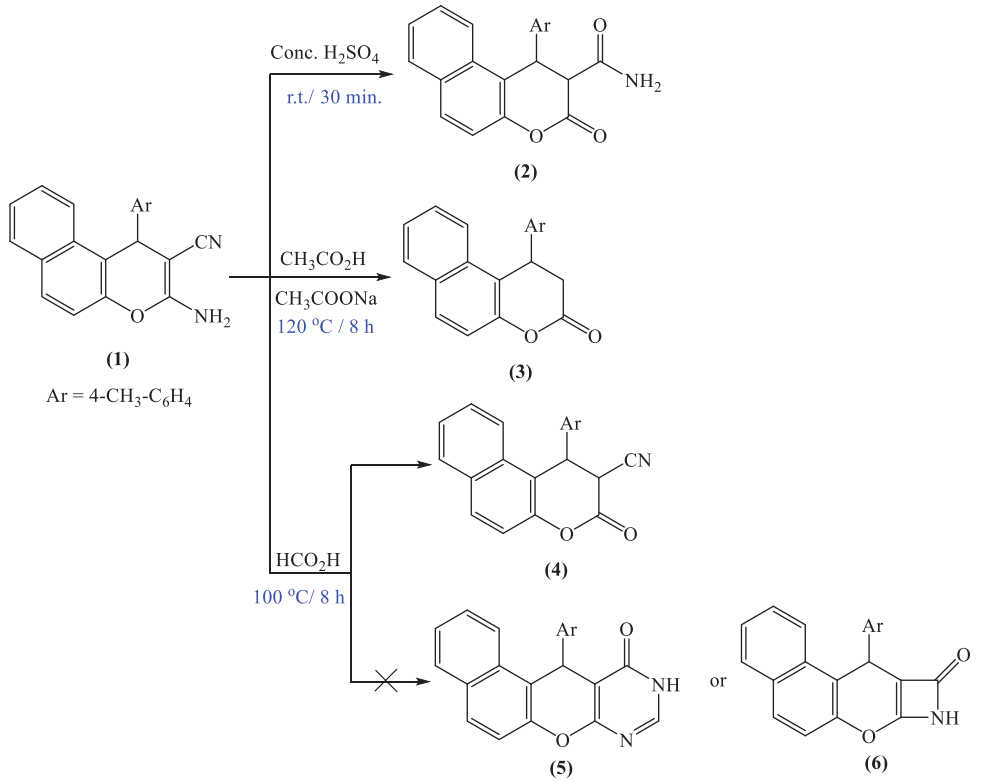
Figure 1. Several drugs and agrochemicals bearing coumarin as a core moiety.

important biological properties of these natural coumarins or to prepare their analogs for curative purposes.[1] Coumarin skeleton was used as an intermediate for the synthesis of bioactive heterocyclic compounds which exhibit several pharmacological effects including anti-inflammatory,[2,3] antimicrobial,[4] anti-cancer,[3,5] antifungal,[6] anti-coagulant [7–9] antioxidant,[10] and anti-tubercular [11] properties. Coumarins exist greatly in drugs, agrochemicals and natural products (Figure 1). The natural Osthole is *O*-methylated coumarin present in *Cnidium MONNIERI*, a classic Chinese herbal drug that has been applied as a fungicidein China for a long time, and displays antifungal activity against *Rhizoctonia solani* and a broad series of other phytopathogenic fungi;[12–14] Acenocoumarol and Warfarin are anticoagulants work as the vitamin K antagonists and usually used in the prevention of thrombosis and thromboembolism;[15–17] and Coumoxystrobin (SYP-3375) is a strobilurin fungicide that displays a wide spectrum of antifungal activity.[18–20]

Results and discussion

As a part of our interest in the synthesis of a broad scope of heterocyclic systems with biological evaluations[21–29] and in continuation of our investigation on the reactivity of 3-amino-1-aryl-1H-benzo[f]chromene-2-carbonitriles **(1)**,[30–34] we are interested in our running study on the utility of 3-amino-1-(*p*-tolyl)-1H-benzo[f]chromene-2-carbonitrile **1**[30] in the synthesis of new benzo[f]coumarins and related compounds. Thus, in this research, the behavior of *β*-enaminonitrile **1** toward different organic and inorganic acids has been examined. Subsequently, stirring the *β*-enaminonitrile **1** with concentrated H_2SO_4 at room temperature yielded benzo[f]coumarin-2-carboxamide derivative **2** in which the cyano group in the *β*-enaminonitrile **1** undergoes partial hydrolysis to the carboxamide group alongside the deamination of the amino group (Scheme 1). The supportive evidence for structure **2** derived from the IR spectrum which displayed absorption bands at 3311, 3230, 1758 and 1686 cm^{-1} corresponding to (NH_2), (C=O of lactone) and (C=O of amide group), respectively with the absence of absorption band for C≡N group. Also, the ^{1}H-NMR (DMSO-d_6) spectrum exhibited the following signals at *δ* (ppm): 2.21 (s, 3H, CH_3), 4.04 (d, 1H, $J = 1.5$ Hz), 5.37 (d, 1H, $J = 1.5$ Hz), 6.99–8.00 (m, 12H, Ar-H + NH_2).

On the other hand, heating the *β*-enaminonitrile **1** with glacial acetic acid in presence of fused sodium acetate produced 1-(p-tolyl)-1,2-dihydro-3H-benzo[f]coumarin **(3)** (Scheme 1). In this reaction, full hydrolysis followed by decarboxylation of the cyano group occurred with the deamination. However, compound **3** was previously synthesized by different methodology through one-pot condensation of Meldrum's acid with



Scheme 1. Behavior of *β*-enaminonitrile **1** toward different organic and inorganic acids.

β-naphthol and 4-methylbenzaldehyde.[35] The structure of benzo[f]coumarin derivative **3** was characterized by IR, ^{1}H-NMR, ^{13}C-NMR and microanalysis.

Likewise, refluxing *β*-enaminonitrile **1** with formic acid involved only the deamination of the amino group to give the unexpected product 1-(*p*-tolyl)-2,3-dihydro-1H-benzo[f]coumarin-2-carbonitrile **(4)** rather than the corresponding fused pyrimidinone derivative **5**[36,37] or our recently obtained novel chromeno[2,3-b]azet-9-one derivative **6** (Scheme 1).[32]

Inspection of the present literature, revealed that the 2-cyano-benzo[f]coumarin derivative **4** has been formerly prepared under similar reaction conditions,[38] displaying in the ^{1}H-NMR spectrum δ values [4.39 (d, 1H, $J = 6.1$ Hz), 5.14 (d, 1H, $J = 6.1$ Hz)] different to ours [5.58 (s, 2H, H_a and H_b (exchangeable with D_2O))]. This is owing to in the solution compound **4** exists in the enol tautomer **[B]** as a result of keto-enol tautomerism (cf. Figure 2). So we conclude that the ^{1}H-NMR spectrum of benzo[f]coumarin derivative **2** showed the predominance of the tautomeric form **[B]** in solution.

Surprisingly, the 2-cyano-benzo[f]coumarin derivative **4** was also obtained from endeavor to chloroacetylate the *β*-enaminonitrile **1** with chloroacetyl chloride in glacial acetic acid rather than the corresponding chloroacetamido derivative **8** (Scheme 2). 9-(Chloromethyl)-12-(*p*-tolyl)-10,12-dihydro-11H-benzo[5, 6]chromeno[2,3-d]pyrimidin-11-one **(7)** was likewise formed from another attempt to chloroacetylate the *β*-enaminonitrile **1** with chloroacetyl chloride in dioxane containing a catalytic amount

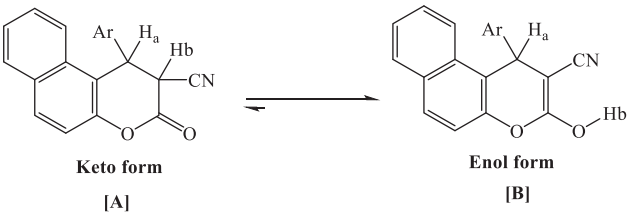
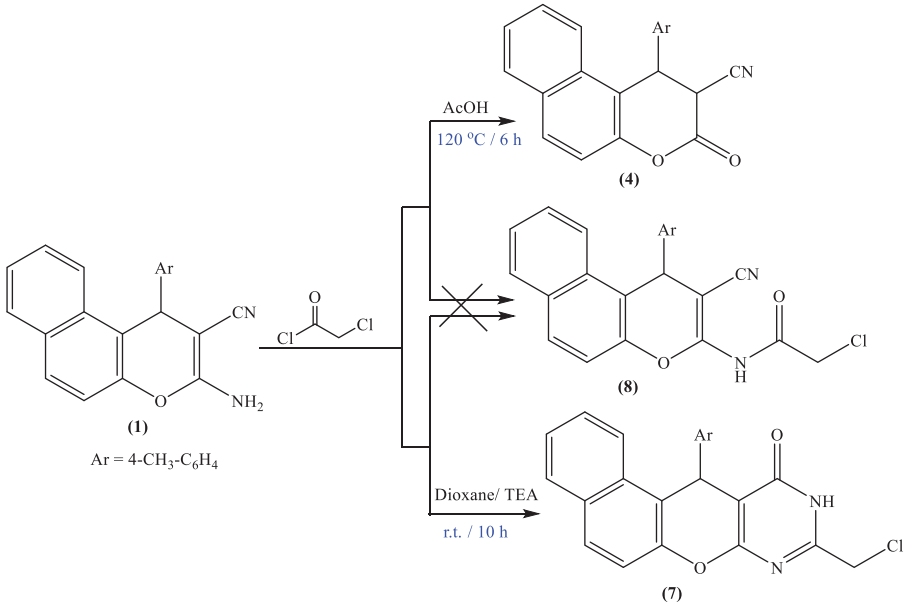


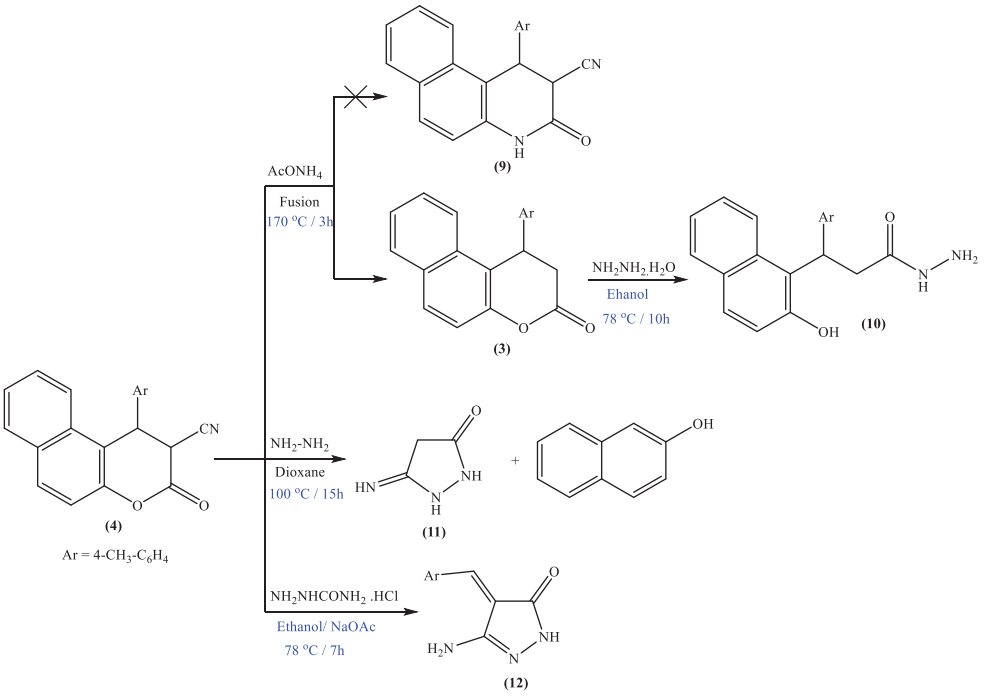
Figure 2. The predominance of the tautomeric form **[B]** in solution of compound **4**.



Scheme 2. Reaction of β-enaminonitrile **1** with chloroacetyl chloride.

of triethylamine (0.2 mL) (Scheme 2). Compound **7** was previously synthesized via Radziszewski's reaction of the chloroacetamido derivative **8** using urea hydrogen peroxide (UHP).[39] The demise of νC≡N in the IR spectrum of compound **7** and the existence of νNH at 3166 cm^{-1} and νC=O at 1654 cm^{-1} corroborative the suggested structure. The ^{1}H-NMR and ^{13}C-NMR spectra were completely in accord with the assigned structure **7**. (c.f. Experimental section)

Moreover, the chemical behavior of 2-cyano-benzo[f]coumarin **4** toward selected nitrogen nucleophiles was also studied. Thus, when compound **4** was subjected to react with ammonium acetate in an oil bath gave unexpected product that was identified as the benzo[f]coumarin derivative **3** instead of the benzo[f]quinolin-3(2H)-one derivative **9** (Scheme 3). Chemical evidence for benzo[f]coumarin derivative **3** was gained from its reaction with hydrazine hydrate in boiling ethanol which yielded the hydrazide derivative **10** as a sole product in fairly good yield (Scheme 3). The appearance of ν_{OH} at 3313 cm^{-1}, ν_{NH2} at 3268, 3217 cm^{-1} alongside $\nu_{C=O}$ at 1650 cm^{-1} in the IR spectrum of compound **10** as well as the appearance of acidic protons in the ^{1}H-NMR spectrum at 4.12 (br.s, 2H, NH_2, exchangeable by D_2O), 9.05 (br.s, 1H, NH, exchangeable by D_2O) and 9.60 (br.s, 1H, OH, exchangeable by D_2O) was in favor with the designated



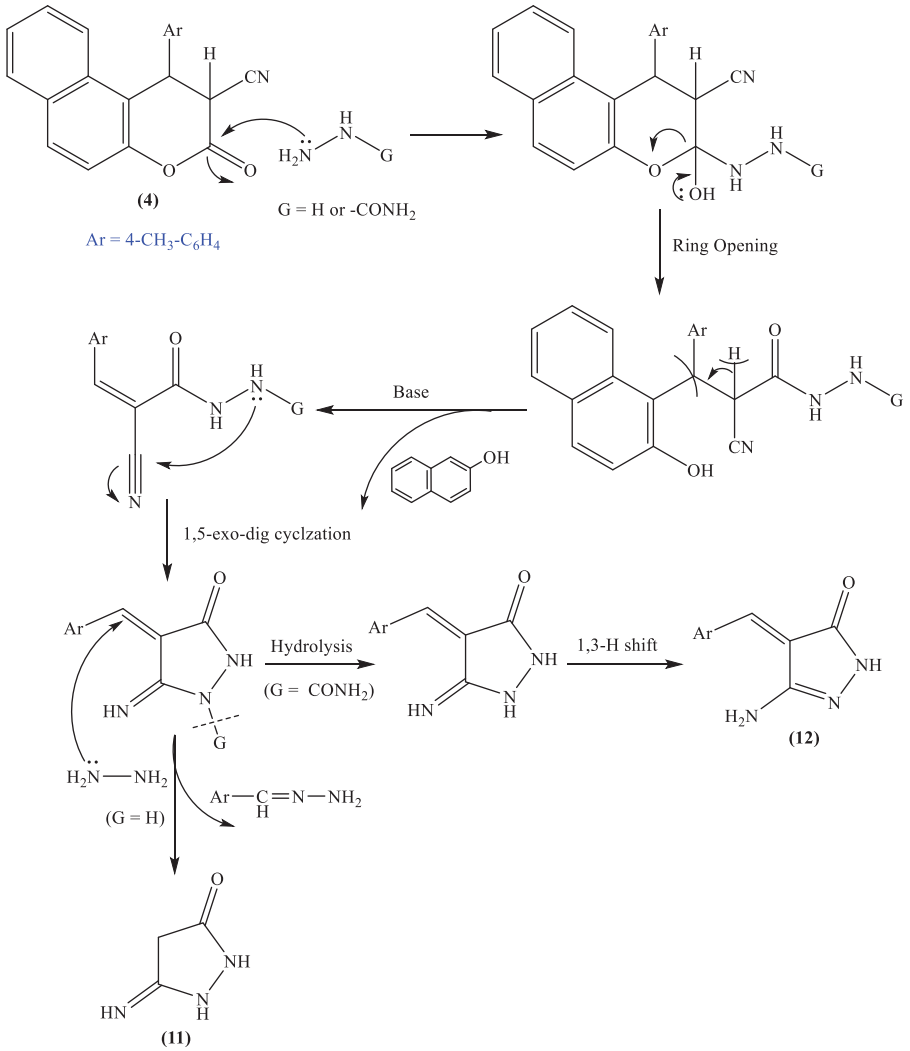
Scheme 3. Reaction of compound **4** with some nitrogen nucleophiles.

structure. Compound **10** was supposed to be formed *via* nucleophilic attack of hydrazine hydrate to carbonyl group of benzo[f]coumarin **3** followed by ring opening.

It is noteworthy that hydrazinolysis of 2-cyano-benzo[f]coumarin **4** using excess hydrazine hydrate in refluxing dioxane undergoes degradation process in which 5-iminopyrazolidin-3-one **(11)** was deposited on hot in addition to β-naphthol which was obtained after acidification of the mother liquor (Scheme 3). The structures of β-naphthol and 5-iminopyrazolidin-3-one **(11)** were confirmed by IR, ^{1}H-NMR and ^{13}C-NMR (c.f. Experimental section).

In like manner, 2-cyano-benzo[f]coumarin **4** was subjected to degradation when treated with semicarbazide hydrochloride in presence of fused sodium acetate under reflux to furnish the unexpected product that was identified as 5-amino-4-(4-methylbenzylidene)-2,4-dihydro-3H-pyrazol-3-one **(12)** (Scheme 3). Structure **12** was fully supported by spectral data beside the elemental analyses. IR spectrum of compound **12** lacked the absorption band of cyano group and showed presence of absorption band at 3279, 3192 cm^{-1} corresponding to NH_2 group in addition to absorption band at 1712 cm^{-1} for CO group. Whereas, its ^{1}H-NMR spectrum displayed a singlet signal at δ 2.29 ppm attributed to methyl group beside two singlet signals at δ 6.46 and 10.20 ppm assigned acidic protons of NH_2 and NH groups, respectively. Also, aromatic protons appeared at δ 7.16–7.60 ppm and the olefinic proton at δ 7.81 ppm which completely agree with the proposed structure **12**.

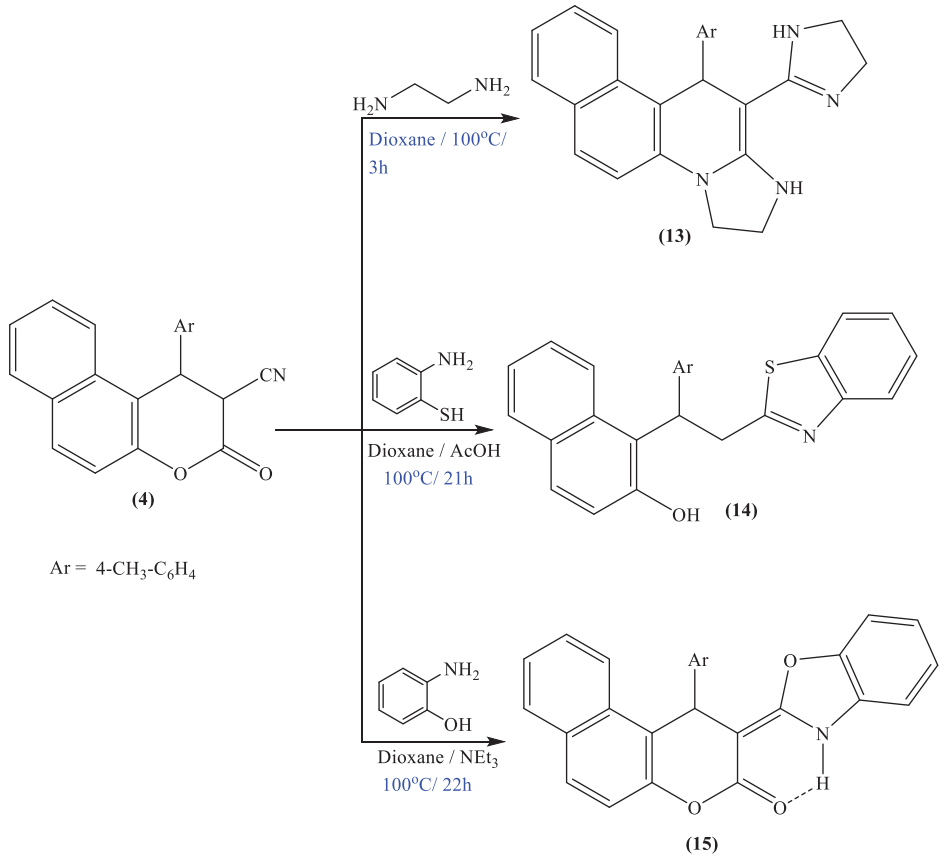
A conceivable mechanism for the formation of compounds **(11)** and **(12)** from 2-cyano-benzo[f]coumarin **4** is outlined in Scheme 4.



Scheme 4. Degradation of 2-cyano-benzo[f]coumarin **4**.

Moreover, our current study was prolonged to explore the chemical behavior of 2-cyano-benzo[f]coumarin **4** toward some bidentate nucleophiles. Therefore, refluxing of compound **4** with 1,2-diamino ethane in dioxane afforded benzo[f]imidazo[1,2-a]quinoline **13** which deposited on hot as a white crystalline solid in a good yield (Scheme 5). IR spectrum of compound **13** showed two broad bands at 3353, 3247 cm^{-1} corresponds to 2NH groups and absence of the absorption bands of both carbonyl and cyano functional groups. In addition, ^{1}H-NMR and ^{13}C-NMR spectra of compound **13** strongly confirmed the assigned structure (c.f. Experimental section).

On the other hand, ring opening of 2-cyano-benzo[f]coumarin **4** was achieved *via* its reaction with *o*-aminothiophenol in refluxing dioxane in presence of few drops of glacial acetic acid to yield benzo[d]thiazole derivative **14** as a sole product (Scheme 5). Whereas, Refluxing of compound **4** with *o*-aminophenol in presence of a catalytic



Scheme 5. Reaction of 2-cyano-benzo[f]coumarin **4** toward some bidentate nucleophiles.

amount of triethylamine gave 2-(benzo[d]oxazol-2(3H)-ylidene)-1-(p-tolyl)-1,2-dihydro-3H-benzo[f]chromen-3-one **(15)** (Scheme 5). Structures of compounds **14** and **15** were well supported by elemental analyses as well as spectral data. IR spectrum of compound **15** devoid the absorption band of nitrile group and showed presence of a broad absorption band at 3232 cm^{-1} related to NH group alongside with α,β-unsaturated carbonyl group at 1682 cm^{-1}. While, its ^{1}H-NMR spectrum revealed that in solution, compound **15** presents in two forms **[C]** and **[D]** (cf. Figure 3) in ratio 56.7:43.3 due to 1,3-proton shift. Thus, the ^{1}H-NMR spectrum of **15** displayed two singlet signals at δ 2.12, 2.24 ppm attributed to protons of methyl group in the two forms **[C]** and **[D]**, two singlet signals at δ 5.16, 12.23 ppm for NH_b & NH_d, respectively which were exchangeable by D_2O, and two singlet signals at δ 5.74, 5.79 ppm assigned to H_a & H_c, respectively in addition to a multiplet signal in the region of δ 6.99–7.92 ppm attributed to 14 aromatic protons.

Antimicrobial evaluation

The antimicrobial activity of some of the newly synthesized compounds **(2–4, 7, 10, 12–15)** was determined using agar well diffusion method. These compounds were tested

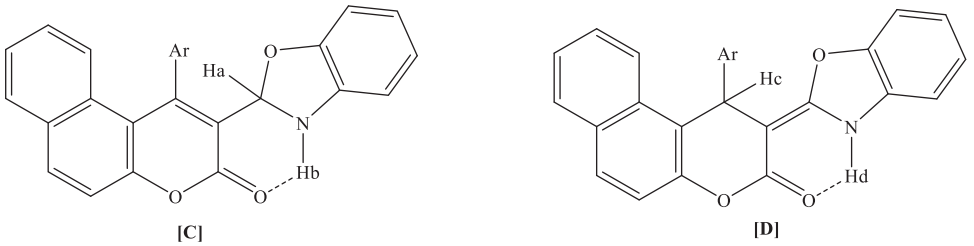


Figure 3. 1,3-proton shift of compound **15**.

Table 1. Antimicrobial screening results of the tested compounds.

Compd. no.	*E. coli*	*K. pneumonia*	*S. aureus*	*C. albicans*
2	NA	NA	16.3 ± 0.5	NA
3	NA	NA	NA	NA
4	NA	NA	17.3 ± 0.5	NA
7	NA	NA	20.3 ± 0.6	NA
10	NA	14.6 ± 0.5	NA	NA
12	NA	NA	11.6 ± 0.5	NA
13	NA	NA	10.6 ± 0.5	NA
14	NA	NA	NA	NA
15	NA	NA	12.3 ± 0.5	NA
Gentamicin	27 ± 0.5	25 ± 0.5	NA	NA
Ampicillin	NA	NA	22 ± 0.1	NA
Nystatin	NA	NA	NA	21 ± 0.5

00, no activity (inhibition zone < 7 mm); weak activity (7–10 mm); moderate activity (11–15 mm); strong activity (>15 mm). Solvent: DMSO.

in vitro for their antibacterial activity against two Gram negative bacteria, namely, *Escherichia coli* (ATCC:10536) and *Klebsiella pneumonia* (ATCC:10031), one Gram positive bacteria, namely, *Staphylococcus aureus* (ATCC:13565) in addition to the pathogenic fungi *Candida albicans* (ATCC:10231) using nutrient agar medium. A strong activity was observed with compounds **2**, **4**, and **7** against *Staphylococcus aureus* while moderate activity was observed with compounds **12**, **13**, and **15** against *Staphylococcus aureus*. The inhibitory concentration was determined for each of the active compounds along with Gentamicin, Ampicillin and Nystatin as positive controlled. Only compound **10** exhibit moderate activity against *Klebsiella pneumonia* while other compounds have no activity against *Klebsiella pneumonia*. No activity was detected for all the synthesized compounds toward *Escherichia coli* and *Candida albicans*. Results are shown in Table 1.

The presence of amino and carbonyl groups in ampicillin help this antibiotic to pass through the pores of the outer membrane of Gram-positive bacteria, such as *Staphylococcus aureus* and thus inhibits the third and final stage of bacterial cell wall synthesis in binary fission, which ultimately leads to cell lysis. Likewise, compounds **2**, **4**, and **7** exhibited strong activity; this is may be due to the presence of NH_2, NH and CO groups (cf. Figure 4).

Experimental

All melting points were measured on a Griffin and George melting-point apparatus (Griffin & Georgy Ltd., Wembley, Middlesex, UK) and are uncorrected. IR spectra were

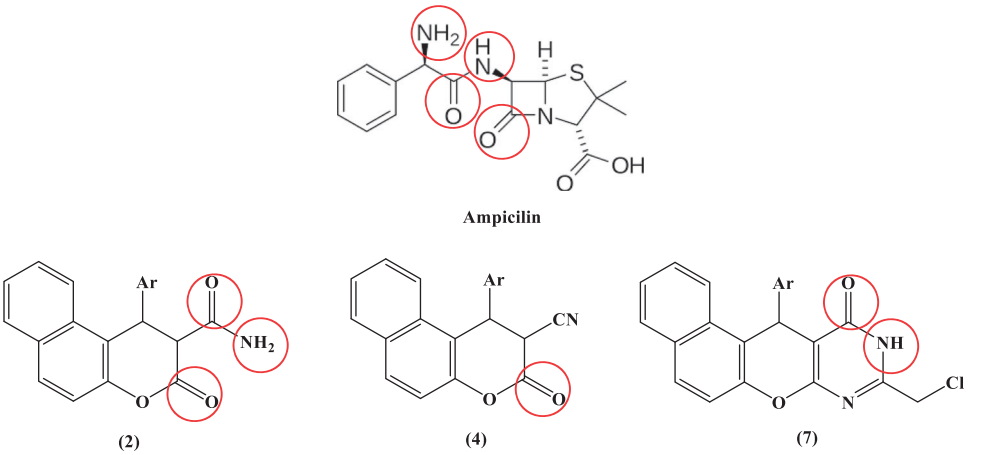


Figure 4. Structure of ampicillin and some of the designed target compounds.

recorded on Pye Unicam SP1200 spectrophotometer (Pye Unicam Ltd., Cambridge, UK) by using the KBr wafer technique. ^{1}H-NMR spectra were determined on a Varian Gemini 300 MHz on Bruker Avance III using tetramethylsilane as an internal standard (chemical shifts in δ scale), while ^{13}C NMR spectra were run at 75 MHz. Elemental analyses were carried out at the Microanalytical Unit, Faculty of Science, Ain Shams University, using a Perkin-Elmer 2400 CHN elemental analyzer (Waltham, MA), and satisfactory analytical data (±0.4) were obtained for all compounds. The homogeneity of the synthesized compounds was controlled by thin layer chromatography (TLC), using aluminum sheet silica gel F_{254} (Merck). Antimicrobial activity was carried out at biochemistry central lab, Faculty of Science, Cairo University.

3-Oxo-1-(p-tolyl)-2,3-dihydro-1H-benzo[f]chromene-2-carboxamide (2)

A mixture of enaminonitrile **1** (1.56 g, 5 mmol) and concentrated sulfuric acid (10 mL) was stirred at room temperature for 30 min, then poured on cold water (50 mL). The precipitated solid was filtered off, dried and recrystallized from benzene (15 mL) to give compound **2** as beige crystals, mp 266–268 °C, and yield: 56%. IR (KBr, ν, cm^{-1}): 3311, 3230 (NH_2), 3030 (CH aromatic), 1758 ($C{=}O_{lactone}$), 1686 ($C{=}O_{amide}$). ^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 2.21 (s, 3H, CH_3), 4.04 (d, 1H, $J = 1.5$ Hz), 5.37 (d, 1H, $J = 1.5$ Hz), 6.99–8.00 (m, 10H, Ar-H), 7.28 (br s, 2H, NH_2, exchangeable with D_2O). ^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm): 20.52, 55.31, 116.14, 117.15, 120.32, 120.33, 122.85, 125.21, 126.68, 126.88, 127.50, 128.32, 128.69, 129.58, 129.81, 130.26, 130.71, 136.74, 136.98, 149.25, 164.76, 168.06, and 178.92. MS *m/z* (%): 331 (M+, 16.2), 318 (70.4), 237 (51.8), 185 (48.6), 125 (100), 87 (57.5). Anal. Calcd. for $C_{21}H_{17}NO_3$ (331.37): C, 76.12; H, 5.17; N, 4.23. Found: C, 76.33; H, 5.25; N, 4.09.

Antimicrobial assay

The sterilized media was poured onto the sterilized Petri dishes (20–25 mL, each petri dish) and allowed to solidify at room temperature. Microbial suspension was prepared

in sterilized saline equivalent to McFarland 0.5 standard solution (1.5×10^5 CFU mL^{-1}) and its turbidity was adjusted to OD = 0.13 using spectrophotometer at 625 nm. Optimally, within 15 min after adjusting the turbidity of the inoculum suspension, a sterile cotton swab was dipped into the adjusted suspension and was flooded on the dried agar surface then allowed to dry for 15 min with lid in place. Wells of 6 mm diameter was made in the solidified media with the help of sterile borer. 100 μL of the solution of the tested compound was added to each well with the help of micropipette. The plates were incubated at 37 °C for 24 h in case of antibacterial activity. This experiment was carried out in triplicate and zones of inhibition were measured in mm. scale.

Full experimental details and spectroscopic data (IR, ^{1}H-NMR and ^{13}C-NMR spectra) for compounds 3, 4, 7, 10–15 can be found via the Supplementary Content section of this article's Web page.

ORCID

Mohamed H. Hekal http://orcid.org/0000-0001-6059-9666

References

[1] Musa, M. A.; Cooperwood, J. S.; Omar, M.; Khan, F. A Review of Coumarin Derivatives in Pharmacotherapy of Breast Cancer. *Curr. Med. Chem.* **2008**, *15*, 2664–2679. DOI: 10.2174/092986708786242877.

[2] Arora, R. K.; Kaur, N.; Bansal, Y.; Bansal, G. Novel Coumarin-Benzimidazole Derivatives as Antioxidants and Safer Anti-inflammatory Agents. *Acta Pharm. Sin. B.* **2014**, *4*, 368–375. DOI: 10.1016/j.apsb.2014.07.001.

[3] Bansal, Y.; Sethi, P.; Bansal, G. Coumarin: A Potential Nucleus for anti-Inflammatory Molecules. *Med. Chem. Res.* **2013**, *22*, 3049–3060. DOI: 10.1007/s00044-012-0321-6.

[4] Nagamallu, R.; Kariyappa, A. K. Synthesis and Biological Evaluation of Novel Formylpyrazoles Bearing Coumarin Moiety as Potent Antimicrobial and Antioxidant Agents. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6406–6409.

[5] Bigi, F.; Chesini, L.; Maggi, R.; Sartori, G. Montmorillonite KSF as an Inorganic, Waterstable, and Reusable Catalyst for Knoevenagel Synthesis of Coumarin-3-Carboxylic Acids. *J. Org. Chem.* **1999**, *64*, 1033–1035. DOI: 10.1021/jo981794r.

[6] Al-Amiery, A. A.; Kadhum, A. A. H.; Mohamad, A. B. Antifungal Activities of New Coumarins. *Molecules* **2012**, *17*, 5713–5723. DOI: 10.3390/molecules17055713.

[7] Weigt, S.; Huebler, N.; Strecker, R.; Braunbeck, T.; Broschard, T. H. Developmental Effects of Coumarin and the Anticoagulant Coumarin Derivative Warfarin on Zebrafish (*Danio rerio*) Embryos. *Reprod. Toxicol.* **2012**, *33*, 133–141. DOI: 10.1016/j.reprotox.2011.07.001.

[8] Dey, S.; Lo, H. J.; Wong, C. H. An Efficient Modular One-Pot Synthesis of Heparin-Based Anticoagulant Idraparinux. *J. Am. Chem. Soc.* **2019**, *141*, 10309–10314. DOI: 10.1021/jacs.9b03266.

[9] Dey, S.; Lo, H. J.; Wong, C. H. Programmable One-Pot Synthesis of Heparin Pentasaccharide Fondaparinux. *Org. Lett.* **2020**, *22*, 4638–4642. DOI: 10.1021/acs.orglett.0c01386.

[10] Gacche, R. N.; Jadhav, S. G. Antioxidant Activities and Cytotoxicity of Selected Coumarin Derivatives: Preliminary Results of Astructure-Activity Relationship Study Using Computational Tools. *J. Exp. Clin. Med.* **2012**, *4*, 165–169. DOI: 10.1016/j.jecm.2012.04.007.

[11] Kawate, T.; Iwase, N.; Shimizu, M.; Stanley, S. A.; Wellington, S.; Kazyanskaya, E.; Hung, D. T. Synthesis and Structure-Activity Relationships of Phenyl-substituted Coumarins with Anti-tubercular Activity that Target FadD32. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6052–6059. DOI: 10.1016/j.bmcl.2013.09.035.

[12] Vogl, S.; Zehl, M.; Picker, P.; Urban, E.; Wawrosch, C.; Reznicek, G.; Saukel, J.; Kopp, B. Identification and Quantification of Coumarins in *Peucedanum ostruthium* (L.) Koch by HPLC-DAD and HPLC-DAD-MS. *J. Agric. Food Chem.* **2011**, *59*, 4371–4377. DOI: 10.1021/jf104772x.

[13] Wei, Y.; Zhang, T.; Ito, Y. Preparative Isolation of Osthol and Xanthotoxol from Common Cnidium Fruit (Chinese Traditional Herb) Using Stepwise Elution by High-Speed Counter-Current Chromatography. *J. Chromatogr. A*. **2004**, *1033*, 373–377. DOI: 10.1016/j.chroma.2004.01.058.

[14] Shi, Z.; Wang, F.; Zhou, W.; Zhang, P.; Fan, Y. J. Application of Osthol Induces a Resistance Response against Powdery Mildew in Pumpkin Leaves. *IJMS*. **2007**, *8*, 1001–1012. DOI: 10.3390/i8091001.

[15] Holbrook, A. M.; Pereira, J. A.; Labiris, R.; McDonald, H.; Douketis, J. D.; Crowther, M.; Wells, P. S. Systematic Overview of Warfarin and Its Drug and Food Interactions. *Arch. Intern. Med.* **2005**, *165*, 1095–1106. DOI: 10.1001/archinte.165.10.1095.

[16] Cesar, J. M.; Avello, A. G.; Navarro, J. L.; Herraez, M. V. Aging and Oral Anticoagulant Therapy Using Acenocoumarol. *Blood Coagul. Fibrinolysis*. **2004**, *15*, 673–676. DOI: 10.1097/00001721-200412000-00007.

[17] Ufer, M. Comparative Pharmacokinetics of Vitamin K Antagonists: Warfarin, Phenprocoumon and Acenocoumarol. *Clin. Pharmacokinet*. **2005**, *44*, 1227–1246. DOI: 10.2165/00003088-200544120-00003.

[18] Guan, A. Y.; Liu, C. L.; Li, M.; Zhang, H.; Li, Z. N.; Li, Z. M. Design, Synthesis and Structure-Activity Relationship of Novel Coumarin Derivatives. *Pest Manag. Sci.* **2011**, *67*, 647–655. DOI: 10.1002/ps.2103.

[19] Liu, C.; Guan, A.; Yang, J.; Chai, B.; Li, M.; Li, H.; Yang, J.; Xie, Y. Efficient Approach to Discover Novel Agrochemical Candidates: Intermediate Derivatization Method. *J. Agric. Food Chem*. **2016**, *64*, 45–51. DOI: 10.1021/jf5054707.

[20] Guan, A.; Liu, C.; Yang, X.; Dekeyser, M. Application of the Intermediate Derivatization Approach in Agrochemical Discovery. *Chem. Rev*. **2014**, *114*, 7079–7107. DOI: 10.1021/cr4005605.

[21] Hekal, M. H.; Abu El-Azm, F. S. M. New Potential Antitumor Quinazolinones Derived from Dynamic 2-Undecyl Benzoxazinone: Synthesis and Cytotoxic Evaluation. *Synth. Commun*. **2018**, *48*, 2391–2402. DOI: 10.1080/00397911.2018.1490433.

[22] Hekal, M. H.; Abu El-Azm, F. S. M. Efficient MW-Assisted Synthesis of Some New Isoquinolinone Derivatives with In Vitro Antitumor Activity. *J. Het. Chem.* **2017**, *54*, 3056–3064. DOI: 10.1002/jhet.2916.

[23] Mahmoud, M. R.; Abou-Elmagd, W. S. I.; Derbala, H. A.; Hekal, M. H. Synthesis and Spectral Characterisation of Some Phthalazinone Derivatives. *J. Chem. Res. (S)* **2012**, *36*, 75–82. DOI: 10.3184/174751912X13274297624330.

[24] Mahmoud, M. R.; Abu El-Azm, F. S. M.; Ismail, M. F.; Hekal, M. H.; Ali, Y. M. Synthesis and Antitumor Evaluation of Novel Tetrahydrobenzo[4′,5′]Thieno[3′,2′:5,6]Pyrimido[1,2-b]Isoquinoline Derivatives. *Synth. Commun.* **2018**, *48*, 428–438. DOI: 10.1080/00397911.2017.1406520.

[25] Mahmoud, M. R.; El-Shahawi, M. M.; Abou-Elmagd, W. S. I.; Hekal, M. H. Novel Synthesis of Isoquinoline Derivatives Derived from (Z)-4-(1,3-Diphenylpyrazol-4-yl)Isochromene-1,3-Dione. *Synth. Commun.* **2015**, *45*, 1632–1641. DOI: 10.1080/00397911.2015.1030760.

[26] Hekal, M. H.; El-Naggar, A. M.; Abu El-Azm, F. S. M.; El-Sayed, W. M. Synthesis of New Oxadiazol-Phthalazinone Derivatives with anti-Proliferative Activity; Molecular Docking, Pro-Apoptotic, and Enzyme Inhibition Profile. *RSC Adv.* **2020**, *10*, 3675–3688. DOI: 10.1039/C9RA09016A.

[27] Hekal, M. H.; Abu El-Azm, F. S. M.; Atta-Allah, S. R. Ecofriendly and Highly Efficient Microwave-Induced Synthesis of Novel Quinazolinone-Undecyl Hybrids with In Vitro Antitumor Activity. *Synth. Commun.* **2019**, *49*, 2630–2641. DOI: 10.1080/00397911.2019.1637001.

[28] Mahmoud, M. R.; Abou-Elmagd, W. S. I.; Derbala, H. A.; Hekal, M. H. Novel Synthesis of Some Phthalazinone Derivatives. *Chin. J. Chem.* **2011**, *29*, 1446–1450. DOI: 10.1002/cjoc.201180264.

[29] Abdelgawad, N.; Ismail, M. F.; Hekal, M. H.; Marzouk, M. I. Design, Synthesis, and Evaluation of Some Novel Heterocycles Bearing Pyrazole Moiety as Potential Anticancer Agents. *J. Heterocyclic Chem.* **2019**, *56*, 1771–1779. DOI: 10.1002/jhet.3544.

[30] Ali, A. M.; Hekal, M. H. Convenient Synthesis and anti-Proliferative Activity of Some Benzochromenes and Chromenotriazolopyrimidines under Classical Methods and Phase Transfer Catalysis. *Synth. Commun.* **2019**, *49*, 3498–3509. DOI: 10.1080/00397911.2019.1675173.

[31] Abu El-Azm, F. S. M.; El-Shahawi, M. M.; Elgubbi, A. S.; Madkour, H. M. F. Design, Synthesis, anti-Proliferative Activity, and Molecular Docking Studies of Novel Benzo[*f*]Chromene, Chromeno [2,3-d]Pyrimidines and Chromenotriazolo[1,5-c]Pyrimidines. *Synth. Commun.* **2020**, *50*, 669–683. DOI: 10.1080/00397911.2019.1710850.

[32] Abu El-Azm, F. S. M.; El-Shahawi, M. M.; Elgubbi, A. S.; Madkour, H. M. F. Synthesis of New Benzo[f]Chromene-Based Heterocycles Targeting anti-Proliferative Activity. *J. Iran. Chem. Soc.* **2021**, *18*, 1081–1092. DOI: 10.1007/s13738-020-02092-w.

[33] Dey, S.; Wong, C.-H. Programmable One-Pot Synthesis of Heparin Pentasaccharides Enabling Access to Regiodefined Sulfate Derivatives. *Chem. Sci.* **2018**, *9*, 6685–6691. DOI: 10.1039/C8SC01743C.

[34] Cheng, C. W.; Zhou, Y.; Pan, W. H.; Dey, S.; Wu, C. Y.; Hsu, W. L.; Wong, C. H. Hierarchical and Programmable One-Pot Synthesis of Oligosaccharides. *Nat. Commun.* **2018**, *9*, 5202–5210. DOI: 10.1038/s41467-018-07618-8.

[35] Mehrabi, H.; Ashraf, F. N.; Karimi, R. R. One-Pot Three-Component Condensation of *β*-Naphthol with Arylaldehydes and Meldrum's Acid: Synthesis of 1-Aryl-1,2-Dihydro-Benzo[f]Chromen-3-Ones. *J. Chem. Res.* **2017**, *41*, 250–252. DOI: 10.3184/174751917X14902201357374.

[36] Okasha, R.; Alblewi, F.; Afifi, T.; Naqvi, A.; Fouda, A.; Al-Dies, A.-A.; El-Agrody, A. Design of New Benzo[h]Chromene Derivatives: Antitumor Activities and Structure-Activity Relationships of the 2,3-Positions and Fused Rings at the 2,3-Positions. *Molecules* **2017**, *22*, 479–496. DOI: 10.3390/molecules22030479.

[37] Salem, M. S.; Farhat, M.; Errayes, A. O.; Madkour, H. M. F. Antioxidant Activity of Novel Fused Heterocyclic Compounds Derived from Tetrahydropyrimidine Derivative. *Chem. Pharm. Bull.* **2015**, *63*, 866–872. DOI: 10.1248/cpb.c15-00452.

[38] Mkaouar, K.; Iriepa, I.; Iriepa, D. D.; Contelles, J. M.; Ismaili, L.; Chabchoub, F. Synthesis of (±)-*Cis*-1-Aryl-3-Oxo-2,3-Dihydro-1*H*-Benzo[*f*]Chromene-2-Carbonitriles and (±)-*Tra ns*-4-Aryl-2-Oxo-3,4-Dihydro-2*H*-Benzo[*h*]Chromene-3-Carbonitriles. *Chem. Select* **2019**, *4*, 12902–12905.

[39] Chaker, A.; Zribi, F.; Nepveu, F.; Chabchoub, F. Microwave Irradiation: Novel and Facile Methods for the Synthesis of New Pyrimidinones. *Chin. Chem. Lett.* **2014**, *25*, 1207–1210. DOI: 10.1016/j.cclet.2014.03.048.