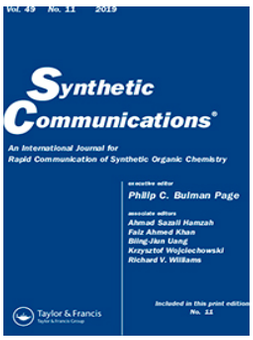

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Synthesis of novel bis(chromenes) and bis(chromeno[3,4-*C*]pyridine) incorporating piperazine moiety

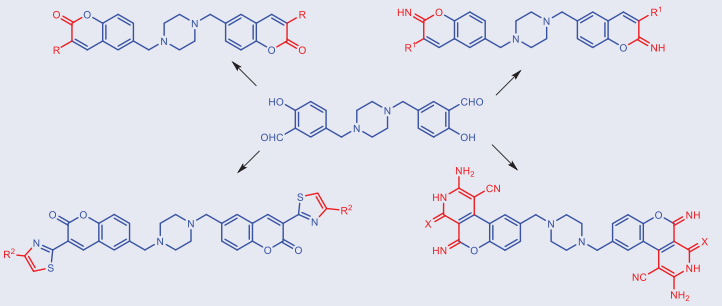
Ahmed E. M. Mekky and Sherif M. H. Sanad

Chemistry Department, Faculty of Science, Cairo University, Giza, Egypt

ABSTRACT

Novel bis(2-oxo-2*H*-chromene) as well as bis(2-imino-2*H*-chromene) derivatives incorporating piperazine moiety were prepared by the cyclocondensation reaction of bis(2-hydroxybenzaldehyde) with two equivalents of each of the appropriate *β*-ketoesters or acetonitrile derivatives. The bis(2-imino-2*H*-chromene-3-carbothioamide) derivative was used as a key synthon for construction of novel bis(3-(4-substituted thiazol-2-yl)-2*H*-chromen-2-one) derivatives *via* its cyclocondensation with a series of the appropriate *α*-halocarbonyl derivatives. Moreover, the bis(2-hydroxybenzaldehyde) reacted with four equivalents of the appropriate acetonitrile derivatives to afford the corresponding bis(3*H*-chromeno[3,4-*c*]pyridine) derivatives. Elucidation of the structure of the novel bis(chromenes) bearing piperazine nucleus was established by the spectral data and elemental analyses.

GRAPHICAL ABSTRACT



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Introduction

Chromenes represent a noteworthy class of both naturally occurring and synthetic heterocyclic derivatives incorporating oxygen with typical benzopyrone skeleton. In recent years, using of chromenes in medicinal chemistry attracts more interest.[1] Chromenes

CONTACT Sherif M. H. Sanad sherif_hamed1980@yahoo.com Chemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt.
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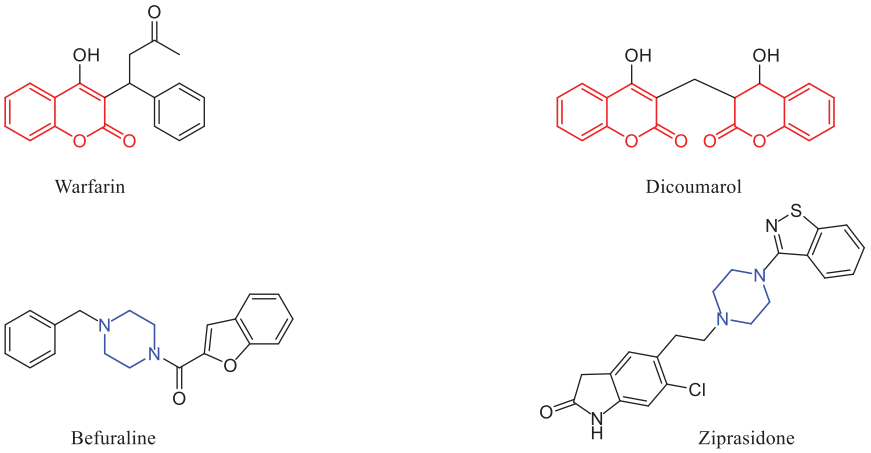


Figure 1. Some bioactive drugs bearing chromene or piperazine core.

exhibit excellent contributions in both the inhibition and healing of various diseases.[2–4] Thus, chromenes show a wide spectrum of bioactivities such as antioxidant,[5–7] antimicrobial[8–10] and anti-inflammatory, analgesic,[11–13] and anticancer agents.[14–16] Moreover, chromenes such as warfarin and dicoumarol have been used as essential oral anticoagulant drugs (Figure 1).[17,18] Also, chromenes exhibit a wide range of anti neurodegenerative activities such as anti-Alzheimer's disease[19–22] and anti-Parkinson's disease.[23–25]

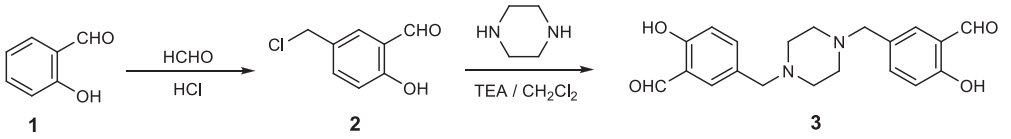
On the other hand, piperazine core is included in various synthetic drugs as antianginals, antidepressants, antihistamines, antiserotonergics, and antipsychotics. Befuraline and ziprasidone are examples of therapeutic drugs, incorporating piperazine moiety, approved by the FDA (Figure 1).[26–30] Molecules bearing both bis- and hybrid-heterocycles were found to show wide bioactivities, especially as fungicidal, antimicrobial, and anthelmintic.[31–34] Various publications reported the synthesis of chromene and piperazine derivatives in addition to bis-heterocyclic compounds due to their important biological activity.[35–45]

Inspired by the above-mentioned findings, and in continuation of our attention in the preparation of bis(heterocycles),[46–55] our research group report herein, the synthetic potential of the bis(2-hydroxybenzaldehyde) as key intermediate for the synthesis of novel hybrid bis(chromenes) bearing piperazine moiety.

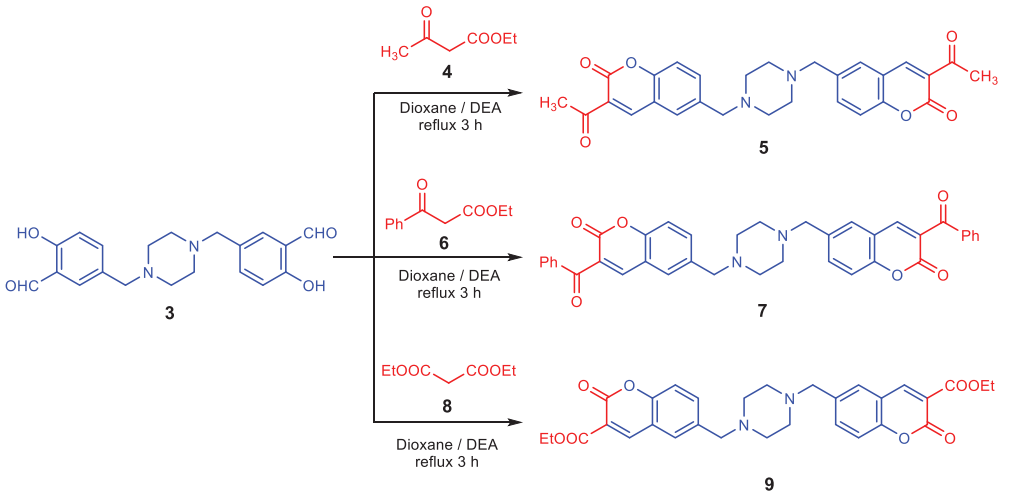
Results and discussion

Initially, our goal was to design facile synthetic route for the preparation of piperazine-chromene hybrids. 1,4-Bis[(3-formyl-4-hydroxyphenyl)methyl]piperazine **3**[56] was chosen as the key synthon for this purpose. Compound **3** was simply prepared from the reaction of 5-(chloromethyl)-2-hydroxybenzaldehyde **2** with piperazine in dichloromethane in the presence of triethylamine (TEA). Compound **2** was prepared by the reaction of salicylaldehyde with formaldehyde in hydrochloric acid (Scheme 1).[57]

The bis(2-hydroxybenzaldehyde) **3** has encouraged us to study its reactivity as a synthon for construction of a novel bis(2-oxo-2*H*-chromene) derivatives by its treatment



Scheme 1. Synthesis of bis(2-hydroxybenzaldehyde) **3**.

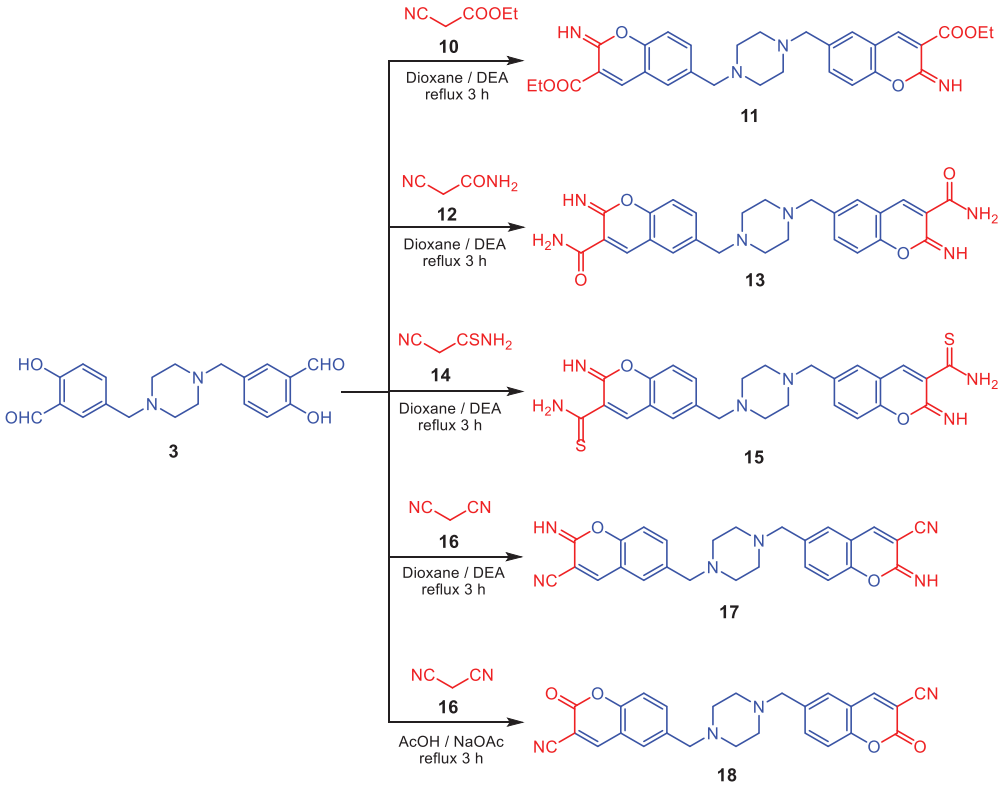


Scheme 2. Synthesis of bis(2-oxo-2*H*-chromenes) **5**, **7**, and **9**.

with β-ketoesters and diethyl malonate, respectively. Generally, such synthetic approach involves a Knoevenagel condensation followed by an intramolecular cyclization. Thus, the treatment of bis(2-hydroxybenzaldehyde) **3** with two equivalents of ethyl acetoacetate **4** in refluxing dioxane in the presence of a catalytic amount of diethyl amine (DEA) within three hours produces one product that has been identified as bis(2-oxo-2*H*-chromene) derivative **5** (Scheme 2). The mass spectrum of the formed product gave a molecular ion peak at $m/z = 486$. Its ^{1}H NMR spectrum revealed three singlet signals at δ 2.40, 2.57 and 3.53 due to piperazine, acetyl and methylene protons, two doublets, and one singlet signals in the region δ 7.40–7.83 due to aromatic protons, accompanied by chromene H-4 as singlet signal at δ 8.62 (see Experimental section).

Similarly, ethyl benzoylacetate **6** and diethyl malonate **8** were reacted with bis(2-hydroxybenzaldehyde) **3**, under the same reaction condition, affording bis(2-oxo-2*H*-chromene) **7** and **9**, respectively (Scheme 2).

Also, bis(2-hydroxybenzaldehyde) **3** was reacted with active methylene compounds containing nitrile function to obtain a series of bis(2-imino-2*H*-chromenes). For example, the cyclocondensation of two equivalents of ethyl cyanoacetate **10** with bis(2-hydroxybenzaldehyde) **3** in refluxing dioxane in the presence of catalytic amount of DEA afforded bis(2-imino-2*H*-chromene-3-carboxylate) derivative **11** (Scheme 3). The elemental analysis and spectral data were fully well-matched with the given structure **11**. For example, its IR spectrum showed the absence of nitrile group absorption band and presence of NH absorption band at 3315 cm^{-1}. Its mass spectrum gave a molecular ion peak at $m/z = 544$. The ^{1}H NMR spectrum of **11** offered triplet and quartet signals at δ 1.05 and δ 4.31 due to ethyl group protons, two singlet signals at δ 2.41 and 3.52

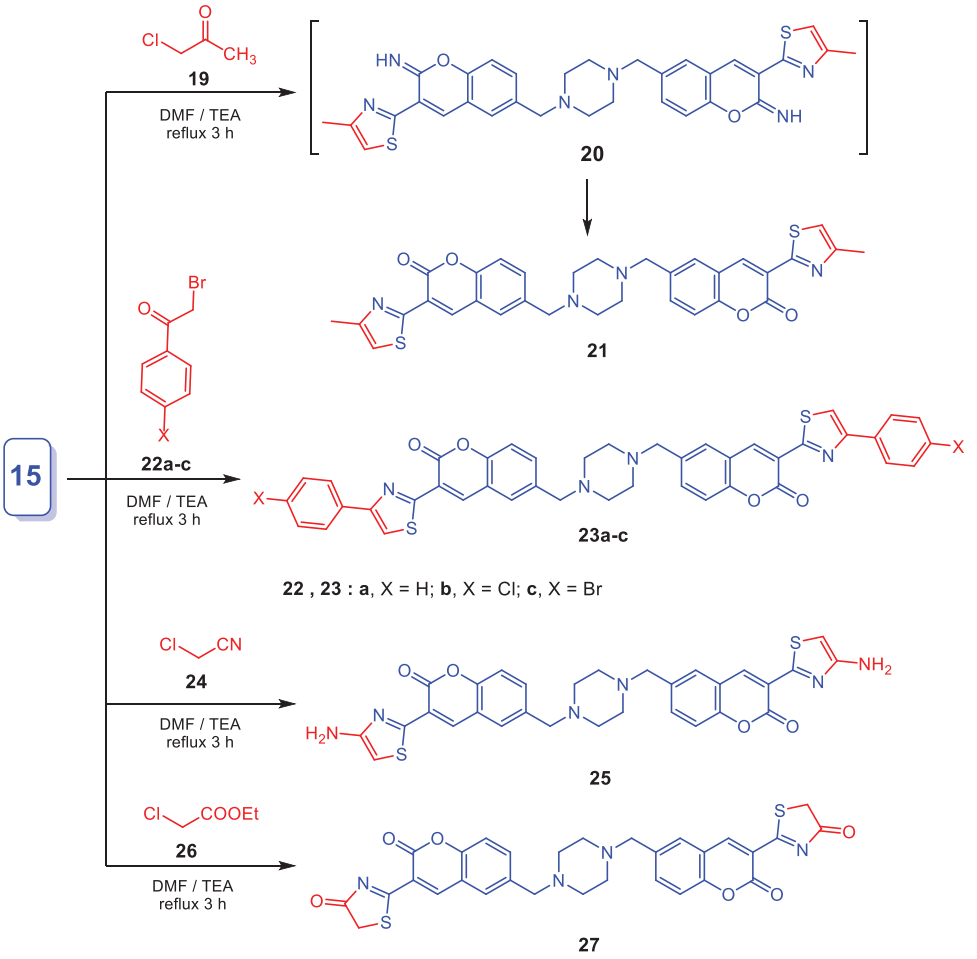


Scheme 3. Synthesis of bis(2-imino-2*H*-chromenes) **11**, **13**, **15**, **17**, and bis(2-oxo-2*H*-chromene) **18**.

due to piperazine and methylene protons, doublet and multiplet signals in the region δ 7.44–7.72 for aromatic protons, a singlet signal at δ 8.90 attributable to chromene H-4, in addition D_2O-exchangeable singlet signal at δ 9.31 due to NH protons (see Experimental section).

Analogously, bis(2-hydroxybenzaldehyde) **3** was cyclocondensed with two equivalents of 2-cyanoacetamide **12** and two equivalents 2-cyanoethanethioamide **14** under the same previous reaction conditions obtaining bis(2-imino-2*H*-chromene-3-carboxamide) **13** and bis(2-imino-2*H*-chromene-3-carbothioamide) **15**, respectively (Scheme 3). The structures of the formed bis(2-imino-2*H*-chromene) derivatives **13** and **15** were elucidated by elemental analyses, spectral data (see Experimental section).

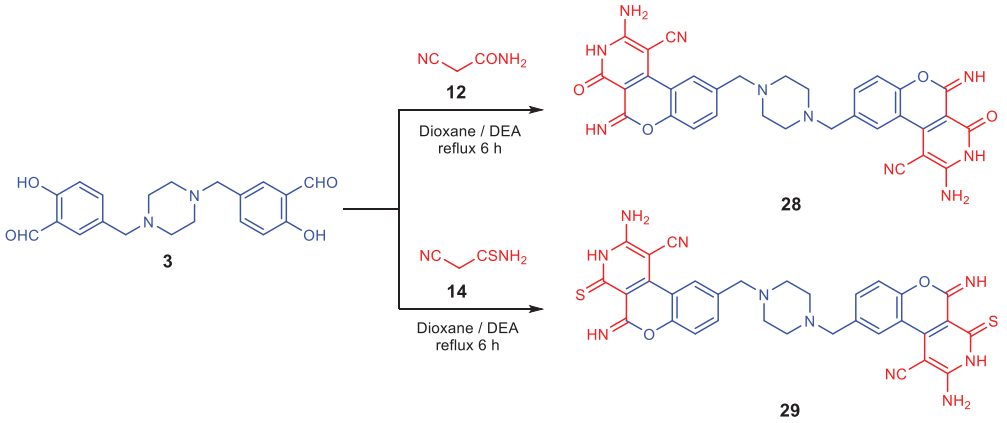
The treatment of bis(2-hydroxybenzaldehyde) **3** with two equivalents of malononitrile **16** in refluxing dioxane in the presence of DEA afforded the corresponding bis(2-imino-2*H*-chromene-3-carbonitrile) derivative **17** (Scheme 3). The IR spectrum of **17** revealed absorption bands at 3301 and 2187 cm^{-1} due to (NH) and (CN), respectively. Its ^1H NMR showed the presence of a singlet signal at δ 8.35 due to chromene H-4 and a typical D_2O-exchangeable singlet signal at δ 8.78 attributed to imino proton (NH). All other protons were seen at the expected chemical shifts and integral values (see Experimental section). On the other hand, two equivalents of malononitrile **16** were reacted with bis(2-hydroxybenzaldehyde) **3** in acetic acid and sodium acetate mixture yielding bis(2-oxo-2*H*-chromene-3-carbonitrile) derivative **18** (Scheme 3). The structure



Scheme 4. Synthesis of bis(3-(thiazol-2-yl)-2*H*-chromen-2-ones) **21**, **23a-c**, **25,** and **27**.

of the latter compound **18** was confirmed by elemental analysis, spectral data (see Experimental section).

Bis(2-imino-2*H*-chromene-3-carbothioamide) derivative **15** has encouraged us to hybrid the chromene ring with thiazole moiety *via* its cyclocondensation with α-halocarbonyl compounds and chloroacetonitrile, respectively. Thus, the reaction of bis(2-imino-2*H*-chromene-3-carbothioamide) derivative **15** with chloroacetone **19** in refluxing dimethylformamide (DMF) in the presence of TEA as a catalyst yielded bis(3-(4-methylthiazol-2-yl)-2*H*-chromen-2-one) derivative **21** (Scheme 4). The IR spectrum of **21** revealed the absence of (NH) and (NH_2) absorption bands and presence of (C = O) absorption band at 1719 cm^{-1}. Its mass spectrum gave a molecular ion peak at *m/z* = 596. Its ^{1}H NMR showed the presence of a characteristic two singlet signals at *δ* 2.60 and 8.38 due to thiazole CH_3 group and chromene H-4, respectively (see Experimental section). It is worth mentioning that bis(2-imino-2*H*-chromene-3-carbothioamide) derivative **15** easily cyclocondensed with chloroacetone **19** to form the corresponding bis(3-(4-methylthiazol-2-yl)-2*H*-chromen-2-imine) **(20)**. We failed to obtain



Scheme 5. Synthesis of bis(4-oxo-3*H*-chromeno[3,4-*c*]pyridine) **28** and bis(4-thioxo-3*H*-chromeno[3,4-*c*]pyridine) **29**.

the latter due to its rapid hydrolysis under the reaction conditions to give bis(3-(4-methylthiazol-2-yl)-2*H*-chromen-2-one) derivative **21** (Scheme 4).

In the same manner, 2-bromo-1-phenylethanone **22a**, 2-bromo-1-(4-chlorophenyl)ethan-1-one **22b**, **2**-bromo-1-(4-bromophenyl)ethan-1-one **22c**, 2-chloroacetonitrile **24**, and ethyl chloroacetate **26** were reacted with bis(2-imino-2*H*-chromene-3-carbothioamide) derivative **15** in DMF, in the presence of a catalytic amount of TEA to afford the corresponding bis(3-(4-arylthiazol-2-yl)-2*H*-chromen-2-one) **23a–c**, bis(3-(4-aminothiazol-2-yl)-2*H*-chromen-2-one) **25**, and bis(3-(4-oxothiazol-2-yl)-2*H*-chromen-2-one) **27**, respectively (Scheme 4).

In continuation of our work, we take a peek into the reaction of bis(2-hydroxybenzaldehyde) **3** with four equivalents of active methylene compounds containing nitrile function. For example, four equivalents of 2-cyanoacetamide **12** was reacted with compound **3** in refluxing dioxane and few drops of DEA as a basic catalyst, affording bis(4-oxo-3*H*-chromeno[3,4-*c*]pyridine) derivative **28** (Scheme 5). The ^{1}H NMR of **28** showed three D_2O-exchangeable singlet signals δ at 7.59, 8.91, and 11.60 due to NH_2, imino proton, and pyridine NH, respectively. All other protons revealed at the expected chemical shifts and integral values (see Experimental section). Similarly, bis(2-hydroxybenzaldehyde) **3** was reacted with four equivalents of 2-cyanoethanethioamide **14** under the same conditions to afford bis(4-thioxo-3*H*-chromeno[3,4-*c*]pyridine) **29** (Scheme 5).

Conclusion

We describe a facile synthetic route for a series of novel bis(2-oxo-2*H*-chromenes), bis(2-imino-2*H*-chromenes) and bis(3*H*-chromeno[3,4-*c*]pyridines) incorporating piperazine moiety *via* the cyclocondensation of bis(2-hydroxybenzaldehyde) with the appropriate *β*-ketoesters or acetonitriles. Also, bis(3-(4-substituted thiazol-2-yl)-2*H*-chromen-2-ones) are prepared by the cyclocondensation of bis(2-imino-2*H*-chromene-3-carbothioamide) with a series of the appropriate α-halocarbonyl derivatives. The structure of the target chromene-piperazine hybrids was elucidated by both spectral data and elemental analyses.

Experimental

All organic solvents used in this study were commercial. All other chemicals were acquired from Merck (Merck KGaA, Darmstadt, Germany) or Aldrich (Sigma-Aldrich Corporation as a subsidiary of Merck KGaA, St. Louis, Missouri, USA) and not subjected for further purification. The melting points are uncorrected and measured on a Stuart melting point device. IR spectra were recorded on a Smart iTR, which is an ultra-high-performance, versatile Attenuated Total Reflectance (ATR) sampling accessory on the Nicolet iS10 FT-IR spectrometer. NMR spectra were recorded on Varian Mercury spectrophotometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) using TMS as an internal standard and DMSO-d_6 as solvent and chemical shifts were expressed as δ ppm units. units. Mass spectra were recorded on a GC-MS-QP1000EX spectrometer using inlet type at 70 eV. Elemental analyses were performed using a EuroVector instrument C, H, N, S analyzer EA3000 Series. Compounds **2**[57] and **3**[56] were prepared according to the literature procedure.

Synthesis of bis(2-oxo-2H-chromene) derivatives 5, 7, and 9

A mixture of bis(2-hydroxybenzaldehyde) **3** (5 mmol) and each of ethyl acetoacetate **4**, ethyl benzoylacetate **6** or diethyl malonate **8** (10 mmol) in dioxane (20 mL) in the presence of five drops of DEA was heated at reflux for 3 h. The reaction was cooled, filtrated, washed with cold ethanol and the reaction products were recrystallized from the proper solvent.

1,4-Bis[(3-acetyl-2-oxo-2H-chromen-6-yl)methyl]piperazine (5)

Yellow crystals (glacial acetic acid, 91%); m.p. 239–241 °C; IR (υ cm^{-1}): 1725, 1678 (CO); ^{1}H NMR (DMSO-d_6): δ 2.40 (s, 8H, 4 piprazine CH_2), 2.57 (s, 6H, 2 CH_3), 3.53 (s, 4H, 2 CH_2), 7.40 (d, $J = 8.5$ Hz, 2H, ArH), 7.65 (d, $J = 8.5$ Hz, 2H, ArH), 7.83 (s, 2H, ArH), 8.62 (s, 2H, 2 chromene H-4); ^{13}C NMR (DMSO-d_6): δ 30.5, 52.3, 60.6, 117.2, 122.0, 124.5, 129.1, 131.3, 137.0, 147.4, 153.8, 159.2, 195.4; MS *m/z* (%): 486 (M^+, 65.2); Anal. for $C_{28}H_{26}N_2O_6$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.38; H, 5.60; N, 5.59%.

ORCID

Ahmed E. M. Mekky http://orcid.org/0000-0002-8226-010X
Sherif M. H. Sanad http://orcid.org/0000-0002-0186-6418

References

[1] Peng, X.-M.; Damu, G. L. V.; Zhou, C.-H. Current Developments of Coumarin Compounds in Medicinal Chemistry. *Curr. Pharm. Des.* **2013**, *19*, 3884–3930. DOI: 10.2174/1381612811319210013.
[2] Bairagi, S. H.; Salaskar, P. P.; Loke, S. D.; Surve, N. N.; Tandel, D. V.; Dusara, M. D. Medicinal Significance of Coumarins: A Review. *Int. J. Pharm. Res.* **2012**, *4*, 16–19.

[3] Kontogiorgis, C.; Detsi, A.; Hadjipavlou-Litina, D. Coumarin-Based Drugs: A Patent Review (2008 – Present)). *Expert Opin. Ther. Pat.* **2012**, *22*, 437–457. DOI: 10.1517/13543776.2012.678835.

[4] Mirunalini, S.; Krishnaveni, M. Coumarin: A Plant Derived Polyphenol with Wide Biomedical Applications. *Int. J. Pharm. Tech. Res.* **2011**, *3*, 1693–1696. ISSN: 0974-4304

[5] Kostova, I.; Bhatia, S.; Grigorov, P.; Balkansky, S.; S Parmar, V.; K Prasad, A.; Saso, L. Coumarins as Antioxidants. *Curr. Med. Chem.* **2011**, *18*, 3929–3951. DOI: 10.2174/092986711803414395.

[6] Borges, M. F. M.; Roleira, F. M. F.; Milhazes, N. J. S. P.; Villare, E. U.; Penin, L. S. Simple Coumarins: Privileged Scaffolds in Medicinal Chemistry. *Front. Med. Chem* **2010**, *4*, 23–85. DOI: 10.2174/97816080520731090401.

[7] Vukovic, N.; Sukdolak, S.; Solujic, S.; Niciforovic, N. Substituted Imino and Amino Derivatives of 4-Hydroxycoumarins as Novel Antioxidant, Antibacterial and Antifungal Agents: Synthesis and in Vitro Assessments. *Food Chem.* **2010**, *120*, 1011–1018. DOI: 10.1016/j.foodchem.2009.11.040.

[8] Patel, D.; Kumari, P.; Patel, N. B. In Vitro Antimicrobial and Antimycobacterial Activity of Some Chalcones and Their Derivatives. *Med. Chem. Res.* **2013**, *22*, 726–744. DOI: 10.1007/s00044-012-0073-3.

[9] Patel, R. V.; Kumari, P.; Rajani, D. P.; Chikhalia, K. H. Synthesis of Coumarin-Based 1,3,4-Oxadiazol-2ylthio-N-Phenyl/Benzothiazolyl Acetamides as Antimicrobial and Antituberculosis Agents. *Med. Chem. Res.* **2013**, *22*, 195. DOI: 10.1007/s00044-012-0026-x.

[10] Dekić, V.; Radulović, N.; Vukićević, R.; Dekić, B.; Stojanović-Radić, Z.; Palić, R. Influence of the Aryl Substituent Identity in 4-Arylamino-3-Nitrocoumarins on Their Antimicrobial Activity. *Afr. J. Pharm. Pharmacol.* **2011**, *5*, 371–375. DOI: 10.5897/AJPP10.408.

[11] Cho, J. Y.; Hwang, T. L.; Chang, T. H.; Lim, Y. P.; Sung, P. J.; Lee, T. H.; Chen, J. J. New Coumarins and anti-Inflammatory Constituents from Zanthoxylum Avicennae. *Food Chem.* **2012**, *135*, 17–23. DOI: 10.1016/j.foodchem.2012.04.025.

[12] Timonen, J. M.; Nieminen, R. M.; Sareila, O.; Goulas, A.; Moilanen, L. J.; Haukka, M.; Vainiotalo, P.; Moilanen, E.; Aulaskari, P. H. Synthesis and anti-Inflammatory Effects of a Series of Novel 7-Hydroxycoumarin Derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 3845–3850. DOI: 10.1016/j.ejmech.2011.05.052.

[13] Behrenswerth, A.; Volz, N.; Toräng, J.; Hinz, S.; Bräse, S.; Müller, C. E. Synthesis and Pharmacological Evaluation of Coumarin Derivatives as Cannabinoid Receptor Antagonists and Inverse Agonists. *Bioorg. Med. Chem.* **2009**, *17*, 2842–2851. DOI: 10.1016/j.bmc.2009.02.027.

[14] Riveiro, M. E.; De Kimpe, N.; Moglioni, A.; Vazquez, R.; Monczor, F.; Shayo, C.; Davio, C. Coumarins: Old Compounds with Novel Promising Therapeutic Perspectives. *Cmc.* **2010**, *17*, 1325–1338. DOI: 10.2174/092986710790936284.

[15] Iranshahi, M.; Masullo, M.; Asili, A.; Hamedzadeh, A.; Jahanbin, B.; Festa, M.; Capasso, A.; Piacente, S. Sesquiterpene Coumarins from Ferula Gumosa. *J. Nat. Prod.* **2010**, *73*, 1958–1962. DOI: 10.1021/np100487j.

[16] Kim, N. H.; Kim, S. N.; Oh, J. S.; Lee, S.; Kim, Y. K. Anti-Mitotic Potential of 7-Diethylamino-3 (2′-Benzoxazolyl)-Coumarin in 5-Fluorouracil-Resistant Human Gastric Cancer Cell Line SNU620/5-FU. *Biochem. Biophys. Res. Commun.* **2012**, *418*, 616–621. DOI: 10.1016/j.bbrc.2012.01.049.

[17] Gomez-Outes, A.; Luisa Suarez-Gea, M.; Calvo-Rojas, G.; Lecumberri, R.; Rocha, E.; Pozo-Hernández, C.; Isabel Terleira-Fernandez, A.; Vargas-Castrillón, E. Discovery of Anticoagulant Drugs: A Historical Perspective. *Cddt.* **2012**, *9*, 83–104. DOI: 10.2174/157016381120902083.

[18] Bhatia, M. S.; Ingale, K. B.; Choudhari, P. B.; Bhatia, N. M.; Sawant, R. L. Application Quantum and Physico Chemical Molecular Descriptors Utilizing Principal Components to Study Mode of Anticoagulant Activity of Pyridyl Chromen-2-One Derivatives. *Bioorg. Med. Chem.* **2009**, *17*, 1654–1662. DOI: 10.1016/j.bmc.2008.12.055.

[19] Anand, P.; Singh, B.; Singh, N. A Review on Coumarins as Acetylcholinesterase Inhibitors for Alzheimer's Disease. *Bioorg. Med. Chem.* **2012**, *20*, 1175–1180. DOI: 10.1016/j.bmc.2011.12.042.

[20] Ma, K.; Thomason, L. A.; McLaurin, J. Scyllo-Inositol, Preclinical, and Clinical Data for Alzheimer's Disease. *Adv. Pharmacol.* **2012**, *64*, 177–212. DOI: 10.1016/B978-0-12-394816-8.00006-4.

[21] Wong, K. Y.; Duchowicz, P. R.; Mercader, A. G.; Castro, E. A. QSAR Applications during Last Decade on Inhibitors of Acetylcholinesterase in Alzheimer's Disease. *Mini Rev Med Chem.* **2012**, *12*, 936–946. DOI: 10.2174/138955712802762365.

[22] Viña, D.; Matos, M. J.; Yáñez, M.; Santana, L.; Uriarte, E. 3-Substituted Coumarins as Dual Inhibitors of AChE and MAO for the Treatment of Alzheimer's Disease. *Med. Chem. Comm.* **2012**, *3*, 213–218. DOI: 10.1039/C1MD00221J.

[23] Matos, M. J.; Viña, D.; Quezada, E.; Picciau, C.; Delogu, G.; Orallo, F.; Santana, L.; Uriarte, E. A New Series of 3-Phenylcoumarins as Potent and Selective MAO-B Inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3268–3270. DOI: 10.1016/j.bmcl.2009.04.085.

[24] Matos, M. J.; Viña, D.; Janeiro, P.; Borges, F.; Santana, L.; Uriarte, E. New Halogenated 3-Phenylcoumarins as Potent and Selective MAO-B Inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5157–5160. DOI: 10.1016/j.bmcl.2010.07.013.

[25] Pisani, L.; Muncipinto, G.; Miscioscia, T. F.; Nicolotti, O.; Leonetti, F.; Catto, M.; Caccia, C.; Salvati, P.; Soto-Otero, R.; Mendez-Alvarez, E. Discovery of a Novel Class of Potent Coumarin Monoamine Oxidase B Inhibitors: development and Biopharmacological Profiling of 7-[(3-Chlorobenzyl)Oxy]-4-[(Methylamino) Methyl]-2*H*-Chromen-2-One Methanesulfonate (NW-1772) as a Highly Potent, Selective, Reversible, and Orally Active Monoamine Oxidase B Inhibitor. *J. Med. Chem.* **2009**, *52*, 6685–6706. DOI: 10.1021/jm9010127.

[26] Lassen, J. F.; Holm, N. R.; Stankovic, G.; Lefèvre, T.; Chieffo, A.; Hildick-Smith, D.; Pan, M.; Darremont, O.; Albiero, R.; Ferenc, M.; et. al. Percutaneous Coronary Intervention for Coronary Bifurcation Disease: consensus from the First 10 Years of the European Bifurcation Club Meetings. *EuroIntervention* **2014**, *10*, 545–560.DOI: 10.4244/EIJV10I5A97.

[27] Boksay, I. J.; Popendiker, K.; Weber, R. O.; Soeder, A. Synthesis and Pharmacological Activity of Befuraline (*N*-Benzo[*b*]Furan-2-ylcarbonyl-*N*'-Benzylpiperazine), a New Antidepressant Compound. *Arzneimittelforschung* **1979**, *29*, 193–204. DOI: 10.1002/chin.197924249.

[28] Gastpar, M.; Gastpar, G.; Gilsdorf, U. Befuraline, Its Safety and Efficacy in Depressed Inpatients. *Pharmacopsychiatry* **1985**, *18*, 351–355. DOI: 10.1055/s-2007-1017396.

[29] Howland, R. H. Odds and Ends in Psychopharmacology from the past 10 Years. J Psychosoc Nurs Ment Health Serv **2015**, *53*, 9–12. DOI: 10.3928/02793695-20141222-01.

[30] Mattei, C.; Rapagnani, M. P.; Stahl, S. M. Ziprasidone Hydrocloride: What Role in the Management of Schizophrenia? *J. Cent. Nerv. Syst. Dis.* **2011**, *3*, 1 DOI: 10.4137/JCNSD.S4138.

[31] Hassaneen, H. M.; Shawali, A. S.; Saleh, F. M. A Convenient Synthesis of Novel 1,3-Phenylene Bridged Bis-Heterocyclic Compounds. *J. Sulfur Chem.* **2016**, *37*, 241–250. DOI: 10.1080/17415993.2015.1126592.

[32] Shaker, R. M. Synthesis of 1,4-Phenylene Bridged Bis-Heterocyclic Compounds. *Arkivoc* **2012**, *i*, 1–44.

[33] Shawali, A. S.; Sherif, S. M.; El-Merzabani, M. M.; Darwish, M. A. Synthesis and Antitumor Activity of Novel Pyrazolylenaminone and Bis(Pyrazolyl) Ketones via Hydrazonoyl Halides. *J. Heterocyclic Chem.* **2009**, *46*, 548–551. DOI: 10.1002/jhet.113.

[34] Csuk, R.; Barthel, A.; Raschke, C.; Kluge, R.; Ströhl, D.; Trieschmann, L.; Böhm, G. Synthesis of Monomeric and Dimeric Acridine Compounds as Potential Therapeutics in Alzheimer and Prion Diseases. *Arch. Pharm. Chem. Life. Sci.* **2009**, *342*, 699–709. DOI: 10.1002/ardp.200900065.

[35] Fouad, S. A.; Hessein, S. A.; Abbas, S. Y.; Farrag, A. M.; Ammar, Y. A. Synthesis of Chromen-2-One, Pyrano[3,4-*c*]Chromene and Pyridino[3,4-*c*]Chromene Derivatives as Potent Antimicrobial Agents. *Croat. Chem. Acta* **2018**, *91*, 99–107.

[36] Sayed, O. M.; Moustafa, H.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. Synthesis, Reactions and DFT Calculations of Novel Bis (Chalcones) Linked to a Thienothiophene Core through an Oxyphenyl Bridge. *RSC Adv.* **2016**, *6*, 10949–10961. DOI: 10.1039/C5RA27322F.

[37] Sayed, O. M.; Mekky, A. E. M.; Farag, A. M.; Elwahy, A. H. M. 3. 4-Dimethyl-2,5-Functionalized Thieno [2,3-*b*] Thiophenes: Versatile Precursors for Novel Bis-Thiazoles. *J. Sulfur Chem.* **2015**, *36*, 124–134. DOI: 10.1080/17415993.2014.975131.

[38] Mekky, A. E. M.; Elwahy, A. H. M. Synthesis of Novel Benzo-Substituted Macrocyclic Ligands Containing Thienothiophene Subunits. *J. Heterocyclic Chem.* **2014**, *51*, E34–E41. DOI: 10.1002/jhet.2012.

[39] Yang, G.; Luo, C.; Mu, X.; Wang, T.; Liu, X. Y. Highly Efficient Enantioselective Three-Component Synthesis of 2-Amino-4*H*-Chromenes Catalysed by Chiral Tertiary Amine-Thioureas. *Chem. Commun.* **2012**, *48*, 5880–5882. DOI: 10.1039/c2cc30731f.

[40] Dyachenko, V. D.; Pugach, Y. Y. Synthesis of 2-(4′-Morpholin-4″-yl-5H-Chromeno[2,3-*d*]Pyrimidin-2′-yl) Phenol from Salicylaldehyde and Substituted Acrylonitriles. *Russ. J. Gen. Chem.* **2012**, *82*, 921–926. DOI: 10.1134/S1070363212050209.

[41] Salem, M. A.; Thabet, H. K.; Ismail, M. A.; Ammar, Y. A. *N*-Aryl 2-Cyanothioacetamide Intermediates in Heterocyclic Synthesis: synthesis and Antimicrobialevaluation of 3-Cyano-2(1*H*)-Pyridinethione, Chromene-3-Carbothioamide and Chromeno [3,4-*c*] Pyridinethione Derivatives. *Chem. Sci.* **2011**, *2011*, 1–11.

[42] Costa, M.; Areias, F.; Abrunhosa, L.; Venâncio, A.; Proença, F. The Condensation of Salicylaldehydes and Malononitrile Revisited: Synthesis of New Dimeric Chromene Derivatives. *J. Org. Chem.* **2008**, *73*, 1954–1962. DOI: 10.1021/jo702552f.

[43] Chaudhary, P.; Kumar, R.; Verma, A. K.; Singh, D.; Yadav, V.; Chhillar, A. K.; Sharma, G. L.; Chandra, R. Synthesis and Antimicrobial Activity of *N*-Alkyl and *N*-Aryl Piperazine Derivatives. *Bioorg. Med. Chem.* **2006**, *14*, 1819–1826. DOI: 10.1016/j.bmc.2005.10.032.

[44] Sadashiva, C. T.; Chandra, J. N. S.; Ponnappa, K. C.; Gowda, T. V.; Rangappa, K. S. Synthesis and Efficacy of 1-[Bis (4-Fluorophenyl)-Methyl] Piperazine Derivatives for Acetylcholinesterase Inhibition, as a Stimulant of Central Cholinergic Neurotransmission in Alzheimer's Disease. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3932–3936. DOI: 10.1016/j.bmcl.2006.05.030.

[45] Ryckebusch, A.; Deprez-Poulain, R.; Maes, L.; Debreu-Fontaine, M. A.; Mouray, E.; Grellier, P.; Sergheraert, C. Synthesis and in Vitro and in Vivo Antimalarial Activity of *N*-(7-Chloro-4-Quinolyl)-1,4-Bis(3-Aminopropyl)Piperazine Derivatives. *J. Med. Chem.* **2003**, *46*, 542–557. DOI: 10.1021/jm020960r.

[46] Hawass, M. A. E.; Sanad, S. M. H.; Ahmed, A. A. M.; Elneairy, M. A. A. Facile Synthesis and Characterization of Novel Bis(2-*S*-Alkyl-Pyridines) and Bis(3-Aminothieno[2,3-*b*]Pyridines) Incorporating 1,3-Diarylpyrazole Moiety. *J. Sulfur Chem.* **2018**, *39*, 388–401. DOI: 10.1080/17415993.2018.1435657.

[47] Sanad, S. M. H.; Abdel Fattah, A. M.; Attaby, F. A.; Elneairy, M. A. A. Synthesis and Characterization of Novel Bis(Pyridine-2(1*H*)-Thiones) and Their Bis(2-Methylsulfanylpyridines) Incorporating 2,6-Dibromophenoxy Moiety. *Can. J. Chem.* **2019**, *97*, 53–60. DOI: 10.1139/cjc-2017-0721.

[48] Sanad, S. M. H.; Hawass, M. A. E.; Ahmed, A. A. M.; Elneairy, M. A. A. Efficient Synthesis and Characterization of Novel Pyrido[3',2':4,5]Thieno[3,2-*d*]Pyrimidines and Their Fused [1,2,4]Triazole Derivatives. *J. Heterocyclic Chem.* **2018**, *55*, 2823–2833. DOI: 10.1002/jhet.3352.

[49] Sanad, S. M. H.; Hefny, M. I. M.; Ahmed, A. A. M.; Elneairy, M. A. A. J Synthesis of Novel Bis[(5-Cyanopyridin-6-yl)Sulfanyl]Butanes, Bis(2-*S*-Alkylpyridines) and Bis(3-Aminothieno[2,3-*b*]Pyridines) Incorporating 2,6-Dibromophenoxy Moiety. *J. Heterocyclic Chem.* **2018**, *55*, 2046–2054. DOI: 10.1002/jhet.3239.

[50] Sanad, S. M. H.; Elwahy, A. H. M.; Abdelhamid, I. A. Bis(2-Cyanoacetamides): Versatile Precursors for Bis(Dihydropyridine-3,5- Dicarbonitriles). *Arkivoc* **2018**, *vii*, 39–49. DOI: 10.24820/ark.5550190.p010.683.

[51] Sanad, S. M. H.; Hawass, M. A. E.; Ahmed, A. A. M.; Elneairy, M. A. A. Facile Synthesis and Characterization of Novel Pyrido[3',2':4,5]Thieno[3,2-*d*]Pyrimidin-4(3*H*)-One and Pyrido[2',3':3,4]Pyrazolo-[1,5-*a*]Pyrimidine Incorporating 1,3-Diarylpyrazole Moiety. *Synth. Commun.* **2018**, *48*, 1847–1856. DOI: 10.1080/00397911.2018.1468911.

[52] Sanad, S. M. H.; Abdel Fattah, A. M.; Attaby, F. A.; Elneairy, M. A. A. Pyridine-2(*1H*)-Thiones: Versatile Precursors for Novel Pyrazolo[3,4-*b*]Pyridine, Thieno[2,3-*b*]Pyridines and Their Fused Azines. *J. Heterocyclic Chem.* **2018**, *56*, 651–662. DOI: 10.1002/jhet.3444.

[53] Al-Bogami, A. S.; Mekky, A. E. M. Microwave-Assisted Regioselective Synthesis of Novel Bis(Azoles) and Bis(Azoloazines). *J. Heterocyclic Chem.* **2016**, *53*, 1554–1562. DOI: 10.1002/jhet.2462.

[54] Mekky, A. E. M.; Al-Bogami, A. S. Ultrasound Assisted Synthesis of Some Novel Bis-Pyridazine Derivatives. *J. Heterocyclic Chem.* **2016**, *53*, 595–605. DOI: 10.1002/jhet.2328.

[55] Sanad, S. M. H.; Kassab, R. M.; Abdelhamid, I. A.; Elwahy, A. H. M. Microwave Assisted Multi-Component Synthesis of Novel Bis (1,4-Dihydropyridines) Based Arenes or Heteroarenes. *Heterocycles* **2016**, *92*, 910–924.

[56] Guieu, S.; Rocha, J.; Silva, A. M. Synthesis of Unsymmetrical Methylenebisphenol Derivatives. *Synlett* **2013**, *24*, 762–764. DOI: 10.1055/s-0032-1318394.

[57] Farag, A. M.; Algharib, M. S. Synthesis and Reactions of *C*-(2-Thenoyl)-*N*-Arylformhydrazidoyl Bromides. *Org. Prep. Proced. Int.* **1988**, *20*, 521–526. DOI: 10.1080/00304948809356298.