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Synthesis of New Pyrazolo[5,1-*c*]triazine, Triazolo[5,1-*c*]triazine, Triazino[4,3-*b*]indazole and Benzimidazo[2,1-*c*]triazine Derivatives Incorporating Chromen-2-one Moiety

Mohamed A. Khalil, Samia M. Sayed, and Mohamed A. Raslan*
Chemistry Department, Faculty of Science, Aswan University, 81528 Aswan, Egypt.
**E-mail: raslanma47@yahoo.com*
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ABSTRACT. The versatile, hitherto unreported 3-(4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-yl)-3-oxopropanenitrile **3** was prepared by two convenient routes: either by the reaction of ethyl 4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-carboxylate **2** with acetonitrile in the presence of sodium hydride or by treatment of 4-(2-phenyldiazenyl)-3-(2-bromoacetyl)-2*H*-chromen-2-one **5** with potassium cyanide. Reaction of **3** with heterocyclic diazonium salts **6**, **7**, **14** and **17** furnished the corresponding hydrazones **8**, **9**, **15** and **18**. The latter hydrazones underwent intramolecular cyclization into the corresponding pyrazolo[5,1-*c*]-1,2,4-triazine **10**, 1,2,4-triazolo[5,1-*c*]-1,2,4-triazine **11**, 1,2,4-triazino[4,3-*b*]indazole **16** and imidazo[2,1-*c*]-1,2,4-triazine **19** derivatives, respectively upon refluxing in pyridine.

Key words: 3-Oxopropanenitrile, Pyrazolo[5,1-*c*]triazine, Triazolo[5,1-*c*]triazine, Triazino[4,3-*b*]indazole, Benzimidazo[2,1-*c*]triazine

INTRODUCTION

Coumarins are a structural scaffold in the numerous natural products[1] and one of the well-known oxygen containing heterocycles showing a variety of biological activities.[2] In addition, they have technological applications[3] and used as intermediates for the synthesis of important molecules.[4]

The pharmacodynamic versatility of chromene moiety has been documented not only in many of its synthetic derivatives but also in several naturally occurring flavones and khellins.[5–7] These synthesized and naturally-isolated derivatives were found to have a wide range of biological properties including anti-inflammatory[8] analgesic,[9] antimicrobial,[10–12] antitumor[13] and anticancer.[14] The synthesis of coumarins and their derivatives has attracted considerable attention from organic and medicinal chemists for many years as a large number of natural products contain this heterocyclic nucleus.[15] They are widely used as additives in food, perfumes, cosmetics, pharmaceuticals[16] and optical brighteners[17] and dispersed fluorescent and laser dyes.[18] Thus the synthesis of this heterocyclic nucleus is of much interest.

Moreover, coumarin-based dyes and pigments are organic fluorescent materials exhibiting unique photochemical and photophysical properties, which render them useful in a variety of applications such as dye lasers, anion sensors, organic light emitting diodes, and solar cells.[19,20]

Coumarins also exhibit anticoagulant activity and some coumarin drugs are widely used as anticoagulants, warfarin and acenocoumarol.[21–25] Also, the considerable biological and medicinal activities of pyrazolotriazines and triazolotriazines, as adenine analogues, antagonists, antischistosomal and antitumor agents[26–28] have stimulated interest in the synthesis of these ring systems. In addition, benzimidazole has been an important pharmacophore and privileged structure in medicinal chemistry[29] encompassing a diverse rang of biological activities including antiarrhythmic, antiulcer, antihistamine, antifungal, antiviral and cytotoxicity.[30]

As part of our program aimed at developing new approaches for the synthesis of fused ring systems with bridgehead nitrogen atoms,[31–35] we report here the synthesis of the versatile, hitherto unreported 3-(4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-yl)-3-oxopropanenitrile 3 and its utility as building block in the synthesis of different biodynamic nitrogen heterocycles such as 1,2,4-triazolo[5,1-*c*]-1,2,4-triazine, 1,2,4-triazino[4,3-*b*]indazole and imidazo [2,1-*c*]-1,2,4-triazine derivatives in which the chromone moiety is incorporated.

Chemistry

It has been found that buffered solution of benzendiazonium chloride couples smoothly with ethyl 2-oxo-2*H*-chromen-3-carboxylate **1** to afford the corresponding ethyl 4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-carboxylate **2**. The structure of the latter product was established on the basis

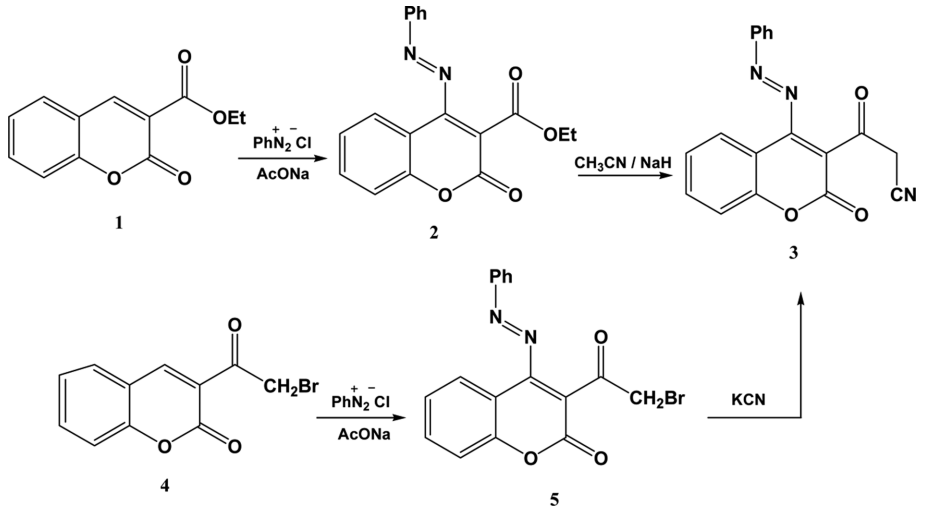
of its elemental analysis and spectral data. Its IR showed absorption bands in the region at 1732 cm^{-1} and 1709 cm^{-1} assignable to carbonyl ester and lactone, respectively. Its ^1H NMR spectrum revealed a triplet signal in the region δ 1.22–1.26 ppm and quartet signal at δ 4.19–4.21 ppm and multiplet at δ 6.81–7.97 ppm characteristic for methyl, methylene and aromatic protons, respectively, in addition to the disappearance of pyrane H-4 proton. Its mass spectrum showed a molecular ion peak at m/z = 322 corresponding to a molecular formula $C_{18}H_{14}N_2O_4$.

Then, when **2** was treated with acetonitrile in the presence of sodium hydride in refluxing benzene, it afforded 3-(4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-yl)-3-oxopropanenitrile **3**. The structure of **3** was established on the basis of its elemental analysis and spectral data. Its IR showed absorption bands at 2238 cm^{-1}, 1717 cm^{-1} and 1705 cm^{-1} assignable to cyano and two carbonyl functions, respectively. Its ^1H NMR ($CDCl_3$) spectrum a revealed a singlet signal at δ 4.65 ppm assignable to methylene protons, in addition to multiplet signals at 7.12–7.85 ppm due to aromatic protons. Its mass spectrum showed a molecular ion peak at m/z = 317 corresponding to a molecular formula $C_{18}H_{11}N_3O_3$.

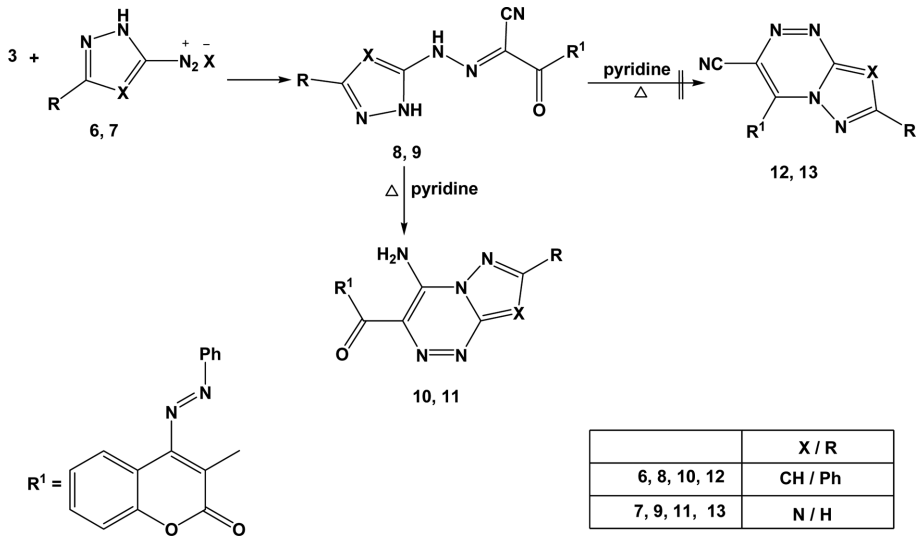
Coupling buffered solution of benzendiazonium chloride with 3-(2-bromoacetyl)-2*H*-chromen-2-one **4** to afforded the corresponding 4-(2-phenyldiazenyl)-3-(2-bromoacetyl)-2*H*-chromen-2-one **5**. The structure of the latter product was established on the basis of their elemental analysis and spectral data. Its IR showed absorption bands in the region at 1709 cm^{-1} and 1690 cm^{-1} assignable to two carbonyl functions. Its ^1H NMR ($CDCl_3$) spectrum a revealed a singlet signal at δ 4.43 ppm assignable to methylene protons, in addition to a multiplet at 7.21–7.54 ppm due to aromatic protons, with disappearance of pyrane H-4 proton. Reaction of **5** with ethanolic potassium cyanide gave a compound identical in all respects (TLC, mp and spectra) with **3** (*Scheme* 1).

Treatment of 3-(4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-yl)-3-oxopropane-nitrile **3** with 3-phenylpyrazole-5-diazonium chloride **6** in cold ethanol buffered with sodium acetate furnished a brown product identified as 2-(2-(3-phenyl-1-*H*-pyrazol-5-yl)hydrazono)-3-(4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-yl)-3-oxopropanenitrile **8** on the basis of its elemental analyses and spectral data. The IR spectrum of **8** showed five absorption bands at 3335, 3182, 2212, 1693 and 1663 cm^{-1} assignable to 2NH, CN and 2CO groups, respectively. The latter hydrazone underwent intramolecular cyclization when refluxed in pyridine to afford a pale brown product. The structure of the obtained product was established on the basis of their elemental analysis and spectral data as 4-amino-3-(4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-yl)carbonyl-7-phenyl-pyrazolo[5,1-*c*]-1,2,4-triazine **10**. Thus, the appearance of absorption bands due to amino group at 3348, 3199 cm^{-1}, at 1678 and 1641 cm^{-1} due to two carbonyl groups and the lack of cyano absorption band in the IR spectrum of the reaction product corroborated the assigned structure **10** and ruled out the other possible structure **12** as depicted in *Scheme* 2.

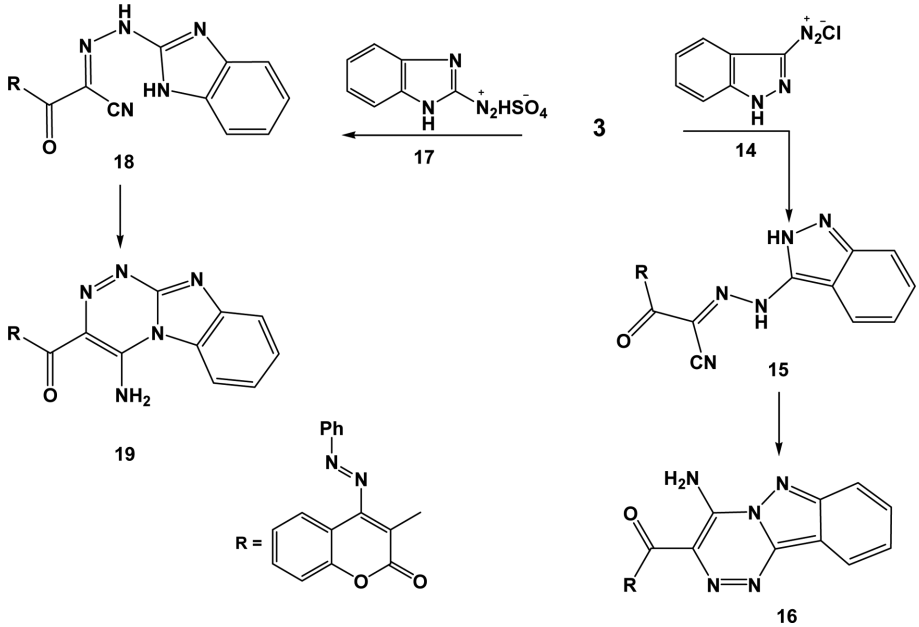
In the a similar manner, when 3-oxopropanenitrile **3** was treated with 1,2,4-triazole-5-diazonium nitrate **7**, the corresponding hydrazone 2-(2-(2*H*-1,2,4-triazol-3-yl)hydrazono)-3-(4-(2-phenyldiazenyl)-2*H*-chromen-3-yl)-3-oxopropanenitrile **9** was obtained. The latter product underwent intramolecular cyclization when boiled with pyridine to



***Scheme* 1.** Synthesis of 3-(4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-yl)-3-oxopropanenitrile **3**.



***Scheme* 2.** Synthesis of pyrazolo[5,1-*c*]-1,2,4-triazine **10** and triazolo[5,1-*c*]-1,2,4-triazine **11** derivatives.



***Scheme* 3.** Synthesis of [1,2,4]triazino[4,3-*b*]indazole **16** and benzimidazo[2,1-*c*][1,2,4]triazine **19**.

afford the corresponding 4-amino-3-(4-(2-phenyldiazenyl)-2*H*-chromen-2-one)carbonyl-1,2,4-triazolo[5,1-*c*]1,2,4-triazine **11** and not the other possible structure **13**. Both of structures **9** and **11** were assigned on the basis of their elemental analyses and spectral data (*see experimental section*).

Similarly, indazole-3-diazonium chloride **14** also coupled readily with 3-oxopropanenitrile **3** to afford product which gave analytical and spectral data in accordance with its formulation as the expected hydrazone **15**. The IR spectrum of the latter product showed absorption bands at 2223 cm^{-1} and 3340, 3160 cm^{-1} due to CN and NH, respectively, and at 1683 and 1652 cm^{-1} due to 2CO groups. Heating the hydrazone 14 under reflux, in pyridine, gave the corresponding (4-amino-1,2,4-triazino[4,3-*b*]indazol-3-yl)(2-oxo-4-phenylazo-2*H*-chromene-3-yl)methanone **16**. The structure of the latter product was substantiated from its elemental analyses and spectral data. Its IR showed an absence of nitrile absorption band but revealed amino absorption band at 3400, 3295 cm^{-1}.

Analogous reaction of **3** with the benzimidazole-2-diazonium sulphate **17** afforded the corresponding hydrazone **18**. The latter product was readily converted almost quan-

titatively into the corresponding (4-aminobenzimidazo[2,1-c]-1,2,4-triazine-3-yl)(2-oxo-4-phenylazo-2*H*-chromene-3-yl)methanone **19** upon heating in pyridine (*Scheme* 3). Both elemental analyses and spectral data of the products **18** and **19** are compatible with their assigned structures (*see experimental section*).

In conclusion, the present study illustrates that reaction of the readily accessible heterocyclic diazonium salts with 3-(4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-yl)-3-oxopropanenitrile **3** and subsequent cyclization of the resulting hydrazones provides an easy and general route for the synthesis of several heterocyclic fused-ring system containing pyrazole, 1,2,4-triazole, 1,2,4-triazine, indazole and benzimidazole moieties incorporating chromene moiety which could possess interesting and useful biological and pharmacological properties.

EXPERIMENTAL

Melting points were measured on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on Shimadzu FTIR 8101 PC infrared spectrophotometer. The ^{1}H NMR spectra were determined in DMSO-d_6 at 300 MHz on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70Ev. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

Ethyl 4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-carboxylate (2) and 4-(2-Phen-yldiazenyl)-3-(2-bromoacetyl)-2*H*-chromen-2-one (5).

General procedure

To a cold solution of ethyl 2-oxo-2*H*-chromen-3-carboxylate **1** (10 mmol) or 3-(2-bromoacetyl)-2*H*-chromen-2-one **4** (10 mmol) in ethanol (50 ml) containing sodium acetate (sodium hydroxide in case of **1**) was added benzenediazonium chloride (10 mmol) portionwise with stirring at 0–5 °C over period of 30 minute. After complete addition, the reaction mixture was left to stir overnight, then kept in ice-chest over night and finally diluted with water. The precipitate solid was collected, washed with water, dried and finally recrystallized from ethanol to afford the corresponding hydrazones **2** and **5**, respectively.

Compound **2** was obtained as yellow powder (EtOH), (65%), mp 110–112 °C; IR υ_{max}/cm^{-1} (KBr) 1732 (CO), 1709 (CO); ^{1}H NMR (DMSO-d$_6$) δ 1.22–1.26 (t, 3H), 4.19–4.21 (q, 2H), 6.81–7.97 (m, 9H); m/z 322 (M$^+$, 19.27). Anal. Calcd. For $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69%. Found: C, 67.01; H, 4.32; N, 8.6%.

Compound **5** was obtained as pale brown (EtOH), (52%), mp 132–133 °C; IR υ_{max}/cm^{-1} (KBr) 1709 (CO), 1690 (CO); ^{1}H NMR (CDCl$_3$) δ 4.43 (s, 2H), 7.21–7.54 (m, 9H). Anal. Calcd. For $C_{17}H_{11}N_2O_3Br$: C, 55.01; H, 2.99; N, 7.55; Br, 21.53%. Found:. C, 54.94; H, 2.94; N, 7.49; Br, 21.46%.

3-(4-(2-Phenyldiazenyl)-2-oxo-2*H*-chromen-3-yl)-3-oxopropanenitrile (3).

Route A

To a mixture of **2** (50 mmol) and acetonitrile (50 mmol) in dry benzene (150 ml) and DMF (10 ml) was added sodium hydride (1.2 g, 80%). The reaction mixture was refluxed for 4 h., then allowed to cool. The solid product that precipitated was collected, washed with ether and dried. The product was dissolved in water and the resulting solution was treated with concentrated hydrochloric acid until it becomes neutral. The precipitate product was collected, washed with water, dried and finally recrystallized from toluene/petroleum ether (60/80) to afford (46%) of **3**.

Route B

To a solution of **5** (50 mmol) in absolute ethanol (50 ml) was added a solution of potassium cyanide (50 mmol in 15 ml water) with stirring. The reaction mixture was stirred at room temperature for further 6 h., then dilute with water. The solid that precipitated was filtered off, washed with water, dried and finally recrystallized from toluene/ petroleum ether (60/80) to afford (54% yield) of compound **3** identical in all respects (mp., mixed mp. and spectral data) with that obtained by route A above.

Compound **3** was obtained as brown powder (toluene/ petroleum ether (60/80)), (46%), mp 161–162 °C; IR υ_{max} /cm^{-1} (KBr) 2238 (CN), 1717 (CO), 1705 (CO); ^{1}H NMR (DMSO-d$_6$) δ 4.65 (s, 2H), 7.12–7.85 (m, 9H); m/z 317 (M$^+$, 35.42). Anal. Calcd. For $C_{18}H_{11}N_3O_3$: C, 68.14; H, 3.49; N, 13.24%. Found:. C, 68.08; H, 3.45; N, 13.21%

Synthesis of 2-(2-(3-Phenyl-1-*H*-pyrazol-5-yl)hydrazono)-3-(4-(2-phenyldiazen-yl)-2-oxo-2*H*-chromen-3-yl)-3-oxopropanenitrile (8), 2-(2-(2*H*-1,2,4-Triazol-3-yl)-hydrazono)-3-(4-(2-phenyldiazenyl)-2*H*-chromen-3-yl)-3-oxopropanenitrile (9), 2-(2-(2*H*-Indazol-3-yl)hydrazono)-3-(4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-yl)-3-oxopropanenitrile (15), 2-(2-(1*H*-Benzo[d]imidazol-2-yl)hydrazono)-3-(4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-yl)-3-oxopropanenitrile (18).

General Procedure

To a cold solution of 3-(4-(2-phenyldiazenyl)-2-oxo-

2H-chromen-3-yl)-3-oxopropanenitrile **3** (4 mmol) in ethanol (50 ml) containing sodium acetate was added the appropriate heterocyclic diazonium salt 6, 7, 14 and 17 (4 mmol) portionwise with stirring at 0–5 °C over period of 30 minute. After complete addition, the reaction mixture was stirred for 6 h., then kept in ice-chest over night and finally diluted with water. The precipitate solid was collected, washed with water, dried and finally recrystallized from dioxane to afford the corresponding hydrazones **8**, **9**, **15** and **18**, respectively.

8: Yield (61%), mp 245–247 °C; IR υ_{max}/cm^{-1} (KBr) 3335, 3182 (2NH), 2212 (CN), 1693 (CO), 1663 (CO); ^{1}H NMR (DMSO-d$_6$) δ 6.54 (s, 1H), 7.36–7.91 (m, 14H), 9.84 (br, 1H), 11.12 (br, 1H). Anal. Calcd. For $C_{27}H_{17}N_7O_3$: C, 66.53; H, 3.52; N, 20.11%. Found: C, 66.49; H, 3.45; N, 20.01%.

9: Yield (64%), mp 263–264 °C; IR υ_{max}/cm^{-1} (KBr) 3433, 3241 (2NH), 2215 (CN), 1698 (CO), 1660 (CO); ^{1}H NMR (DMSO-d$_6$) δ 6.24 (s, 1H), 7.22–7.91 (m, 9H), 10.1 (br, 1H), 10.73 (br, 1H). Anal. Calcd. For $C_{20}H_{12}N_8O_3$: C, 58.25; H, 2.93; N, 27.17%. Found: C, 58.19; H, 2.87; N, 27.05%.

15: Yield (74%), mp 286–288 °C; IR υ_{max}/cm^{-1} (KBr) 3340, 3160 (2NH), 2223 (CN), 1683 (CO), 1652 (CO); ^{1}H NMR (DMSO-d$_6$) δ 7.3–8.11 (m, 13H), 9.95 (br, 1H), 11.09 (br, 1H). Anal. Calcd. For $C_{25}H_{15}N_7O_3$: C, 65.07; H, 3.28; N, 21.25%. Found: C, 65.0; H, 3.22; N, 21.21%.

18: Yield (67%), mp 272–274 °C; IR υ_{max}/cm^{-1} (KBr) 3275, 3171 (2NH), 2209 (CN), 1686 (CO), 1648 (CO); ^{1}H NMR (DMSO-d$_6$) δ 7.12-8.21 (m, 13H), 9.81 (br, 1H), 11.37 (br, 1H). Anal. Calcd. For $C_{25}H_{15}N_7O_3$: C, 65.07; H, 3.28; N, 21.25%. Found: C, 65.02; H, 3.2; N, 21.19%.

Synthesis of 4-Amino-3-(4-(2-phenyldiazenyl)-2-oxo-2*H*-chromen-3-yl)carbonyl-7-phenylpyrazolo[5,1-*c*]-1,2,4-triazine (10), 4-Amino-3-(4-(2-phenyldiazenyl)-2*H*-chromen-2-one)carbonyl-1,2,4-triazolo[5,1-*c*]1,2,4-triazine (11), (4-Amino-1,2,4-triazino[4,3-*b*]indazol-3-yl)(2-oxo-4-phenylazo-2*H*-chromene-3-yl)methanone (16) and (4-Aminobenzimidazo[2,1-*c*]-1,2,4-triazine-3-yl)(2-oxo-4-phenylazo-2*H*-chro-mene-3-yl)methanone (19)

General Procedure

A solution of the appropriate hydrazone **8**, **9**, **15** and **18** (2 mmol) in pyridine (20 ml) was refluxed for 4 h., then left to cool, triturated with ice water containing hydrochloric acid. The solid that formed on standing was filtered off, washed with water and dried. Recrystallization from DMF afforded the corresponding fused-ring system **10**, **11**, **16** and **19**, respectively.

10: Yield (79%), mp 313–315 °C; IR υ_{max}/cm^{-1} (KBr) 3348, 3199 (NH$_2$), 1678 (CO), 1641 (CO); ^{1}H NMR (DMSO-d$_6$) δ 6.58 (s, 1H), 7.21–8.18 (m, 16H). Anal. Calcd. For $C_{27}H_{17}N_7O_3$: C, 66.53; H, 3.52; N, 20.11%. Found: C, 66.49; H, 3.45; N, 20.01%.

11: Yield (67%), mp 308–310 °C; IR υ_{max}/cm^{-1} (KBr) 3300, 3132 (NH$_2$), 1675 (CO), 1655 (CO); ^{1}H NMR (DMSO-d$_6$) δ 6.23 (s, 1H), 7.21–8.18 (m, 11H). Anal. Calcd. For $C_{20}H_{12}N_8O_3$: C, 58.25; H, 2.93; N, 27.17%. Found: C, 58.19; H, 2.87; N, 27.05%.

16: Yield (71%), mp 318–320 °C; IR υ_{max}/cm^{-1} (KBr) 3400, 3295 (NH$_2$), 1673 (CO), 1643 (CO); ^{1}H NMR (DMSO-d$_6$) δ 7.19–8.21 (m, 15H); m/z 461 (M$^+$, 64.11). Anal. Calcd. For $C_{25}H_{15}N_7O_3$: C, 65.07; H, 3.28; N, 21.25%. Found: C, 65.01; H, 3.22; N, 21.20%.

19: Yield (65%), mp 300–302 °C; IR υ_{max}/cm^{-1} (KBr) 3300, 3142 (NH$_2$), 1673 (CO), 1642 (CO); ^{1}H NMR (DMSO-d$_6$) δ 7.11–8.23 (m, 15H). Anal. Calcd. For $C_{25}H_{15}N_7O_3$: C, 65.07; H, 3.28; N, 21.25%. Found: C, 65.03; H, 3.21; N, 21.21%.

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