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Developments of coumarinanalogues from 2-acetyl-benzo[*f*]chromen-3-one.

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ABSTRACT

The starting compound 2-(3-(dimethylamino)acryloyl)-3*H*-benzo[*f*]chromen-3-one (**4**) was prepared from the reaction of 2-acetylbenzo[*f*]coumarin-3-one (**3**) with DMFDMA in refluxing xylene. Reaction of enaminone**4** with 6-aminothiouracil in acetic acid afforded 2-thioxo-2,3-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-4-one **6**.The latter compound was used as the key molecule for synthesis of pyridotriazolopyrimidinones**9a-d** via its reactionwith various hydrazonoyl halides in dioxane and triethylamine.

Introduction

Coumarins are naturally occurring compounds that found in plant kingdom.(Molnar*et al*.,2020)Literature survey showed that coumarin dervatives exhibited such as antimicrobial(Abdel-Aziem *et al*.,2020, 2021, Abdel-Aziem2015)antiviral(Mishra *et al*.,2020) antitumor(Yerer *et a*.,2020)anti-HIV(Chen*et al*.,2021)analgesic(Sudha&Sastry.2016),anti-SARS-CoV-2agents(Abdelmohsen *et al*,.2021)as well as antioxidant (Basappa *et al*.,2021) a ctivities.The activity of coumarins received a considerable interest owing to their cytotoxic activity against various types of cancer cells, including gastric cancer, liver cancer, colon cancer, breast cancer, prostate cancer(Sairam,*et al*.,2016, AbdulRahman *et al*.,2016). In addition, some reported anticoagulant drugs such as warfarin, acenocoumarol and phenprocoumon are derivatives of coumarin(Schliengerat *al*.,2000, Lengyel *et al*.,2004, Williamson *et al*.,1980)

Experimental

Melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a Shimadzu FT-IR 8201 PC spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz and JNM-LA 400 FT-NMR system spectrometer and chemical shifts are expressed in ppm units using TMS as an internal reference. Massspectra were recorded on a GC-MS QP1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

Synthesis of enaminone (4)

2-acetylbenzo[*f*]coumarin-3-one 0.02 mol and 0.02mole of DMFDMA in xylene was refluxed for 2 h. cooled, leave until the xylene evaporated and washed with petroleum ether 40-60. m.p.: 200°C as reported earlier in the literature.

Synthesis of 2,3-dihydro-5-(3-oxo-3H-benzo[f]chromen-2-yl)-2-thioxo pyrido[2,3-d]pyrimidin-4(1H)-one (6)

A mixture of **4** (2.93g, 10 mmol) and 6-amino-2-thiouracile (**5**) (1.43g, 10 mmol) in glacial acetic acid (15 mL) was heated under reflux for 4hrs. The solid that separated after cooling was filtered and recrystallized from DMF to give **6**. Orange solid in 80% yield; m.p.: >360°C; IR (KBr, cm^{-1}): 3314, 3191 (2NH), 3094, 2965 (CH), 1720, 1639 (C=O), 1600 (C=N), 1547 (C=C), 1287 (C=S); ^{1}H NMR (DMSO-d_6, δ, ppm): 7.41-7.82 (m, 5H), 8.05 (d, 1H, *J* = 8Hz), 8.30 (d, 1H, *J* = 8Hz), 8.41 (d, 1H, *J* = 8Hz), 9.22 (s,1H), 12.58 (s, 1H, NH-D_2O exchangeable), 13.11 (s, 1H, NH-D_2O exchangeable); MS (m/z): 373.Anal. calcd. for $C_{20}H_{11}N_3O_3S$ (373.38): C, 64.33; H, 2.97; N, 11.25; S, 8.59; found: C, 64.45; H, 2.86; N, 11.12; S, 8.49.

General method for synthesis of pyrido triazolo[4,3-*a*]pyrimidinones 9a-d

To a mixture of **6** (0.373g, 1mmol) and the appropriate hydrazonoyl halides **7a-d** (1mmol each) in dioxane (10 mL) was added triethylamine (0.14 mL, 1 mmol). The reaction mixture was refluxed until all hydrogen sulfide gas ceased to evolve (10 hrs). The solvent was evaporated and the solid that formed was filtered and recrystallized from ethanol to give compounds **9a-d**, respectively.

(3-(Benzofuran-2-oyl)-1-phenyl-1,5-dihydropyrido[2,3-d][1,2,4]triazolo[4,3-a] pyrimidin-5-one-6-yl)-3H-benzo[f]chromen-3-one (9a)Yellow solid in 70% yield; m.p.: 237-239 °C; IR (KBr, cm^{-1})3064, 2919 (CH), 1715 (C=O), 1609 (C=N), 1556 (C=C);^{1}H NMR ($CDCl_3$), δ, ppm): 7.50-7.69 (m, 15H), 7.88 (d, 1H, *J* = 8Hz), 8.13 (d, 1H, *J* = 8Hz), 8.60 (d, 1H, *J* = 8Hz), 9.23 (s,1H);MS (m/z):

601. Anal. calcd. for $C_{36}H_{19}N_5O_5$ (601.57): C, 71.88; H, 3.18; N, 11.64; found: C, 71.99; H, 3.27; N, 11.53.

Ethyl-5-oxo-6-[3H-benzo[f]chromen-3-one-2-yl]-1-phenyl-1,5-dihydropyrido [2,3-d][1,2,4]triazolo[4,3-a]pyrimidine-3-carboxylate (9b)

Off-white solid in 70% yield; m.p.: 200-201°C; IR (KBr, cm^{-1}): 3070, 2980, 2927 (CH), 1740, 1645 (C=O), 1602 (C=N), 1554 (C=C);^{1}H NMR ($CDCl_3$, δ, ppm): 1.27 (t, 3H, *J* = 7*Hz*, $CH_2\mathbf{CH_3}$), 4.29 (q, 2H, *J* = 7*Hz*, $\mathbf{CH_2}CH_3$), 7.27 (s, 2H), 7.41-7.82 (m, 7H), 7.96 (d, 1H, *J* = 8Hz), 8.10 (d, 1H, *J* = 8Hz), 8.39 (d, 1H, *J* = 8Hz), 8.42 (d, 1H, *J* = 8Hz), 9.22 (s,1H);MS (m/z): 529.Anal. calcd. for $C_{30}H_{19}N_5O_5$ (529.5): C, 68.05; H, 3.62; N, 13.23; found: C, 68.16; H, 3.51; N, 13.34.

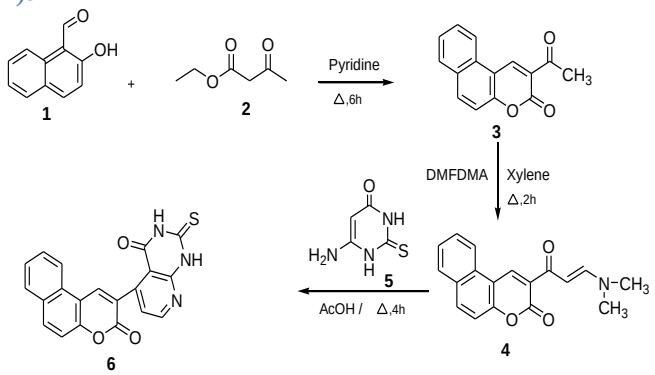
(3-Acetyl-1-phenyl-1,5-dihydropyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one-6-yl)-3H-benzo[f]chromen-3-one (9c)

Yellow solid in 71% yield; m.p.: 234-235°C; IR (KBr, cm^{-1}):3072, 2920 (CH), 1720, 1685 (C=O), 1602 (C=N), 1547 (C=C);^{1}H NMR (DMSO-d_6, δ, ppm): 2.43 (s, 3H, $COCH_3$), 7.43 (t, 1H, *J* = 7.5Hz), 7.56-7.67 (m, 7H), 7.74 (t, 1H, *J* = 7.5Hz), 8.00 (d, 1H, *J* = 8Hz), 8.08 (d, 1H, *J* = 8Hz), 8.31 (d, 1H, *J* = 8Hz), 8.66 (d, 1H, *J* = 8Hz), 9.25 (s,1H);MS (m/z): 499.Anal. calcd. for $C_{29}H_{17}N_5O_4$ (499.48): C, 69.74; H, 3.43; N, 14.02; found: C, 69.61; H, 3.32; N, 14.13.

(3-Benzoyl-1-phenyl-1,5-dihydropyrido[2,3-d][1,2,4]triazolo[4,3-a]pyrimidin-5-one-6-yl)-3H-benzo[f]chromen-3-one (9d)Brown solid in 70% yield; m.p.: 270-271°C; IR (KBr, cm^{-1}): 3059, 2920 (CH), 1719, 1668 (C=O), 1556 (C=N);^{1}H NMR (DMSO-d_6, δ, ppm): 7.50-7.71 (m, 15H), 8.00 (d, 1H, *J* = 8Hz), 8.31 (d, 1H, *J* = 8Hz), 8.66 (d, 1H, *J* = 8Hz), 9.25 (s,1H); MS (m/z): 561. Anal. calcd. for $C_{34}H_{19}N_5O_4$ (561.55): C, 72.72; H, 3.41; N, 12.47; found: C, 72.60; H, 3.29; N, 12.60.

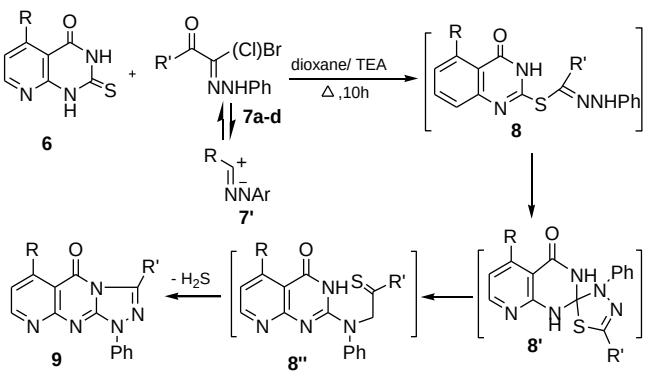
Results and discussion

Condensation of 2-hydroxynaphthaldehyde (**1**) and ethylacetoacetate (**2**) in pyridine under reflux afforded 3-acetyl benzocoumarin (**3**) (Abdel-Aziem *et al.*, 2021) . Reaction of the latter with dimethylformamide dimethylacetal (DMFDMA) afforded 2-(3-(dimethylamino)acryloyl)-3H-benzo[f]chromen-3-one (**4**)(Moustaha *et al.*,2005)2-Thioxo-2,3-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-4-one **6** was accomplished via reaction of enaminone **4** with 6-amino-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (**5**) in refluxing glacial acetic acid. Spectral data and microelemental analysis are in consistent with the collected product **6** (Scheme 1). Its IR spectrum exhibited absorption bands at 3314 and 3191cm^{-1}, attributable to 2NH groups, in addition to the presence of strong stretching frequencies at 1720, 1639 cm^{-1}due to 2C=O functions and 1287 cm^{-1} was assignable for C=S group. The ^{1}H NMR spectrum of **6** displayed two new singlet signals at 12.58 ppm. and 13.11 ppm. exchangeable with D_2O due to 2NH protons.



Scheme 1: Synthesis of 2-thioxopyridopyrimidinone 6

Treatment of **6** with different hydrazonoyl halide derivatives **7a-d** in refluxing dioxane in the presence of trimethylamine afforded the corresponding pyrido[2,3-*d*][1,2,4]triazolo[4,3-*a*]pyrimidinones **9a-d** as the end products based on spectral data (Scheme 2). IR spectral analyses for compounds **9a-d** revealed the disappearance of bands corresponding to NH and C=S functions. The ^{1}H NMR spectra of **9b** for example, recorded the appearance of new triplet and quartet signals at δ 1.27 and 4.29 ppm, attributed to the signals of the ester group. The mechanism explained in Scheme 2 seems to be the most acceptable pathway for the formation of **9** from the reaction of thione **6** with **7** *via* two pathways, the first pathway is 1,3-addition of the thiol tautomer to the nitrilimines **7'** to give the thiohydrazonate ester **8** which underwent nucleophilic cyclization reaction to give the spiro compounds **8'**. The latter undergo ring opening to give **8'',** then cyclized to afford **9** through the loss of hydrogen sulfide. The second pathway is 1,3-cycloaddition reaction of nitrilimines**7'** to the (C=S) double bond of **6** to afford **8'** directly.



Scheme 2 Synthesis of pyridotriazolopyrimidinones 9a-d

Conclusions

In this research, 2-(3-(dimethylamino)acryloyl)-3*H*-benzo[*f*]chromen-3-one (**4**) was utilized as a key for synthesis of new heterocycles. Thus reaction of enaminone **4** with 6-aminothiouracil in acetic acid afforded 2-thioxo-2,3-dihydro-1*H*-pyrido[2,3-*d*]pyrimidin-4-one **6** which reacted with various hydrazonoyl halides in dioxane and triethylamine..**to give** pyridotriazolopyrimidinones **9a-d**.

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