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Synthesis Of Some New Interesting Chromeno[2,3-d]Pyrimidine Derivatives

A. A. Fadda[1], K. S. Mohamed[2], D. I. Ghafur[1]

[1] Chemistry Department, Faculty of Science, Mansoura University, Mansoura 35516, Egypt
[2] Engineering Chemistry Departments, Higher Institute for Engineering and Technology New Damietta, Egypt.

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Abstract
Synthesis of 2-amino-7-hydroxy-4-(4-hydroxyphenyl)-4H-chromene-3-carbonitrile (1) was achieved by reaction of resorcinol and p-hydroxybenzylidine malononitrile to be used in the synthesis of several heterocyclic compounds containing pyrimidine. Compound 1 reacted with bifunctional reagent (malononitrile, formic acid, formamide, phenyl isothiocyanate, carbon disulphide, urea , thiourea)which lead to formation of pyrimidine ring. Structures of the new products were elucidated based on their microanalyses and spectroscopic data.

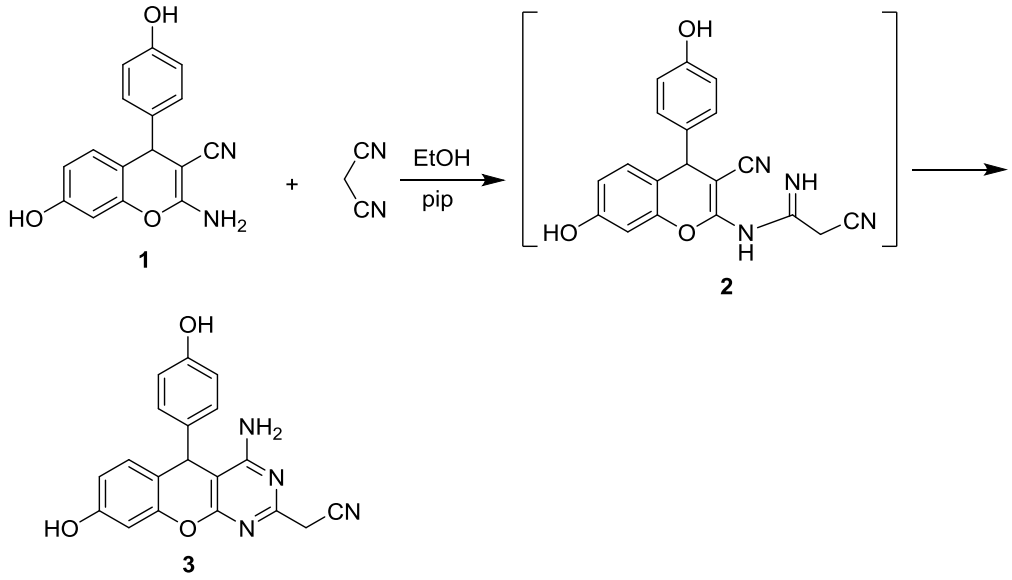
Introduction

4H-Chromene and its derivatives are biologically interesting compounds known for their antimicrobial and antifungal (Zamocka and Misikova, et al., 1992), antioxidant (Alvey and Prado, et al., 1993), antileishmanial (Narender and Shweta, et al., 2004), antitumor (Mohr and Chirigos, et al., 1975), hypotensive (Tandon and Vaish, et al., 1991), antiproliferation (Brunavs and Dell, et al., 1993), local anesthetic (Longobardi and Bargagna, et al., 1990), antiallergenic (Narender and Shweta, et al., 1993, Coudert and Coyquelet, et al., 1988), central nervous system (CNS) activities and effects (Eiden and Denk, et al., 1991), as well as treatment of Alzheimer's disease (Bruhlmann and Ooms, et al., 2001) and Schizophrenia disorder (Kesten and Heffner, et al., 1999). Fused chromene ring systems have platelet antiaggregating, local anesthetic (Bargagna and Longobardi, et al., 1990, Bargagna and Longobardi, et al., 1991, Bargagna and Longobardi, et al., 1992) and antihistaminic activities (Gorlitzer and Dehre, et al., 1984). They also exhibit antidepressant effects (Ermili and Roma, et al., 1979), inhibitory effect on influenza virus sialidases (Taylor and Anne, et al., 1998, Taylor and Cleasby, et al., 1998), DNA breaking activities and mutagenicity (Hiramoto and Nasuhara, et al., 1997), antiviral activities (Martinez and Marco, et al., 1997) and act as sex pheromone homologes (Bianchi and Tava, et al., 1987).

Results and Discussion

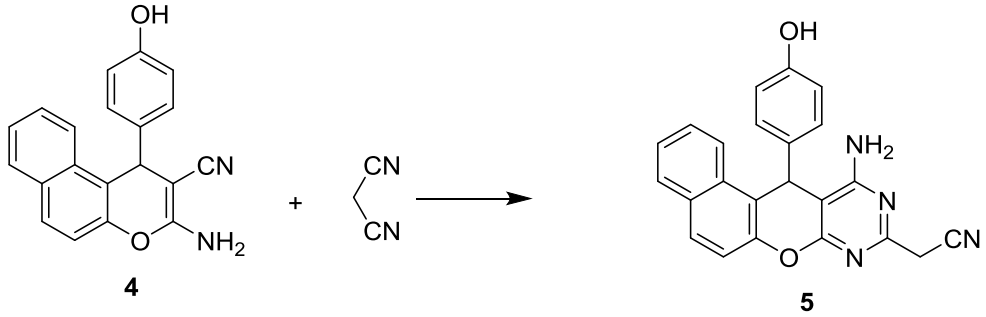
The research done in this article could be regarded as an extension to our previous work (Fadda and Adel, et al.,2012) for constructing fused chromenopyrimidines heterocycles through reactions of the key compound 1 with a variety of reagents.
The title compound 1 was prepared according to the reported procedure in literature (Sandip and Sandeep, et al.,2013), and it was proved to

be highly reactive towards various reagents, resulting in the formation of a wide range of annulated chromenopyrimidine systems. With compound **1** in hand, a number of valuable heterocycles could be prepared. Firstly, the interaction between **1** and malononitrile in refluxing ethanol delivered the 2-(4-amino-8-hydroxy-5-(4-hydroxyphenyl)-5H-chromeno [2,3-d]pyrimidin-2-yl)acetonitrile (**3**) (Scheme 1). The structure assessment was based on their spectroscopic data. The IR spectra showed absorption bands at 3475, 3426 (two OH), 3405, 3389 (NH_2) and 2206 (CN), while the mass spectra revealed molecular ion peaks consistent with the proposed structure. The ^{1}H-NMR spectrum of compound **3** showed enrichment of the aromatic signals due to two aromatic rings , in addition to two singlet signals at δ 3.92 and δ 4.68 ppm due to CH_2 and C_4-H pyran respectively, while three signals at δ 6.48 , 9.20 and 9.90 ppm for three D_2O exchangeable protons (NH_2, two OH).



Scheme 1

In the same manner, 2-(11-amino-12-(4-hydroxyphenyl)-12H-benzo [5,6] chromeno[2,3-d]pyrimidin-9-yl)acetonitrile (5), was synesized via reaction of compound 4 (Maalej & Chabchoub et al.,2011) with malononitrile (Scheme 2)



Scheme 2

Structure 5 was elucidated from its spectroscopic data. The mass spectrum showed a peak at m/z = 380 corresponding to the molecular formulae $C_{23}H_{16}N_4O_2$, while the ^{1}H-NMR displayed a signal at δ 4.29 ppm attributable to a CH_2 group, singlet signal at δ 5.11 due to C_4-H pyran, three signals at δ 6.50 and 9.10 ppm for two D_2O exchangeable protons (NH_2, OH), respectively in addition to multiplet signal at δ 7.0-8.20 ppm due to aromatic protons.

The cyano and amino substituents, in combination with chromene double bond, provide a rich opportunity for heterocyclic construction. Reaction of chromene **1** and formamide furnished the aminopyrimidine **6** in 70% yield (Scheme 3). The IR spectrum of compound **6** is devoid of an absorption band for the cyano group but does show two bands for an

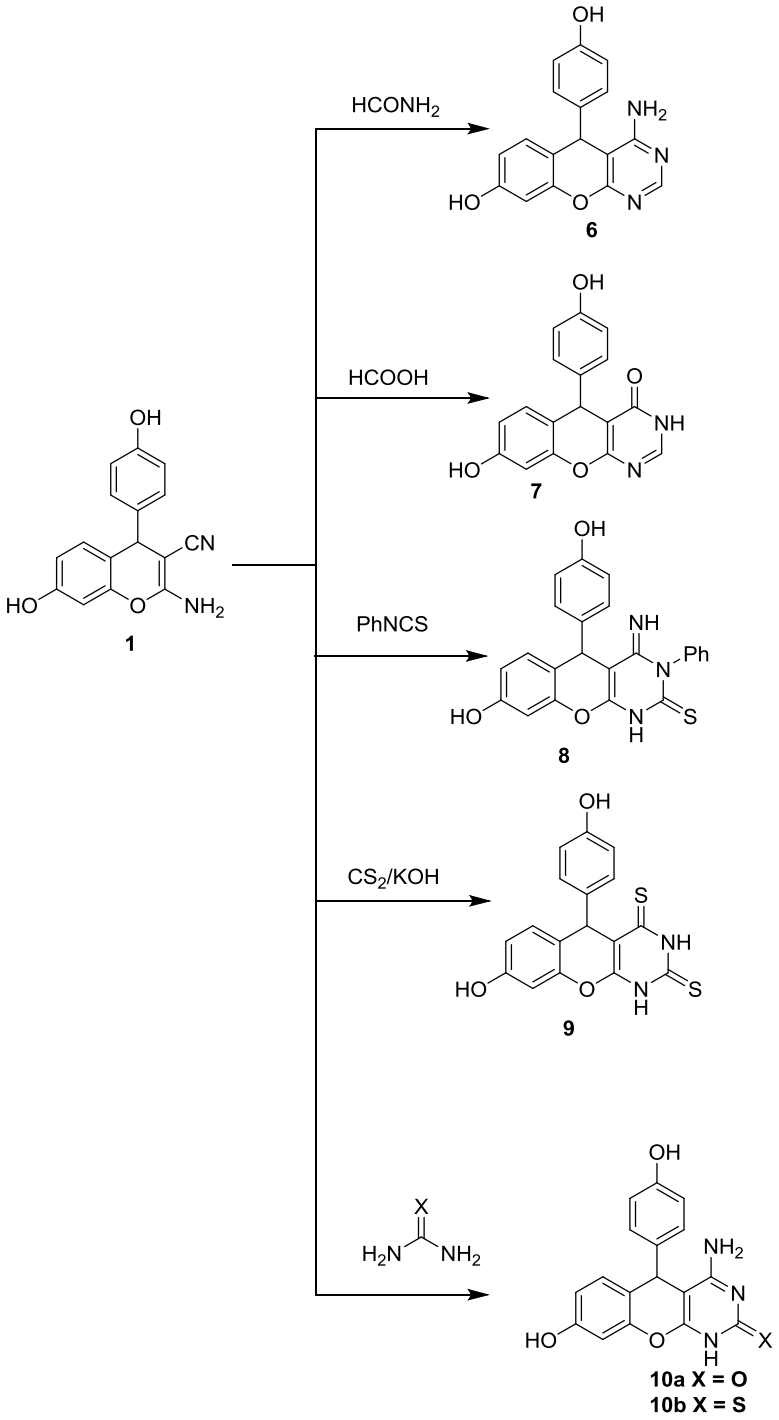
amino group at 3372 and 3396 cm^{-1}. The mass spectrum of structure **6** showed a molecular ion peak at m/z 307. The ^1H NMR data supported the proposed structure **6.**

In contrast, cyclocondensation of compound **1** with hot formic acid resulted in the formation of the pyrimidinone **7** in 20% yields (Scheme 3). The expected pyrimidinone **7**, presumably formed by partial nitrile hydrolysis, amine formylation and cyclodehydration, which showed a characteristic C=O stretching at 1654 cm^{-1} and the absence of any peak in the region 2000-2250 due to cyano group which indicate that cyano group was involved in the reaction. The ^1H NMR displayed singlet signal at δ 8.80 ppm for C_2-H pyrimidine in addition to three D_2O exchangeable signals at 9.20, 9.90 and 11.38 ppm (two OH and NH respectively). Also, the mass spectrum gave supporting evidence for the suggested structure by giving molecular ion peak at m/z 310 corresponding to the proposed structure.

The interaction between the chromene **1** and phenyl isothiocyanate in refluxing absolute ethanol led to the formation of 8-hydroxy-5-(4-hydroxyphenyl)-4-imino-3-phenyl-1,3,4,5-tetrahydro-2H-chromeno[2,3-d]pyrimidine-2-thione (**8**). The chemichal and spectral data, where element test showed the presence of sulfur in 8, also the IR spectrum showed the absence of peaks in the region of 2000- 2250 cm^{-1}, due to the CN stretching frequency which confirm that the cyano group was involved in the reaction. ^1H NMR spectrum showed singlet signal at δ 4.69 ppm integrating for one proton (C_4-H pyran) and three downfield characteristic signal (D_2O exchangeable) corresponding to two OH protons and NH at δ 9.00, 9.79 and 11.18 ppm respectively. Mechanistically, it is presumed that the amino group of chromene **1** reacts with the isothiocyanate to give the corresponding thiourea moiety, which can then undergo cycloaddition reaction onto the cyano group yielding the corresponding compound **8**.

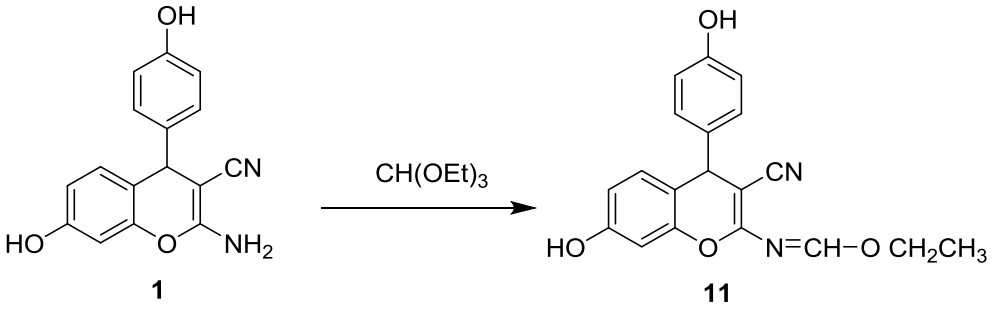
Moreover , reaction of **1** with carbon disulphide in presence of KOH afforded the corresponding 8-hydroxy-5-(4-hydroxyphenyl)-1,5-dihydro-2H-chromeno[2,3-d]pyrimidine-2,4(3H)-dithione (**9)** (Scheme 3) The identity of the product was established on the basis of elemental analyses and spectral data. The IR spectrum of the reaction product **9** revealed bands at 3475, 3224 attributable to two OH, two bands at 3222, 3188 due to two NH groups, also showed the absence of any band due to cyano group. The mass spectrum gave molecular ion peak at m/z 356 corresponding to the molecular formulae $C_{17}H_{12}N_2O_3S_2$,^1H NMR spectrum displayed four downfield signals (D_2O exchangeable) at 9.15, 9.80 , 10.60, 11.20 owing to two OH and two NH respectively (Sabry & Mohamed et al.,2011).

Quite similar chemistry was involved in the formation of the aminopyrimidines **10a,b** by reaction of **1** with urea and/or thiourea (Scheme 3). The structure of compounds **10a,b** were established on the basis of elemental analysis and spectral data of the isolated reaction products. (cf. experimental part)



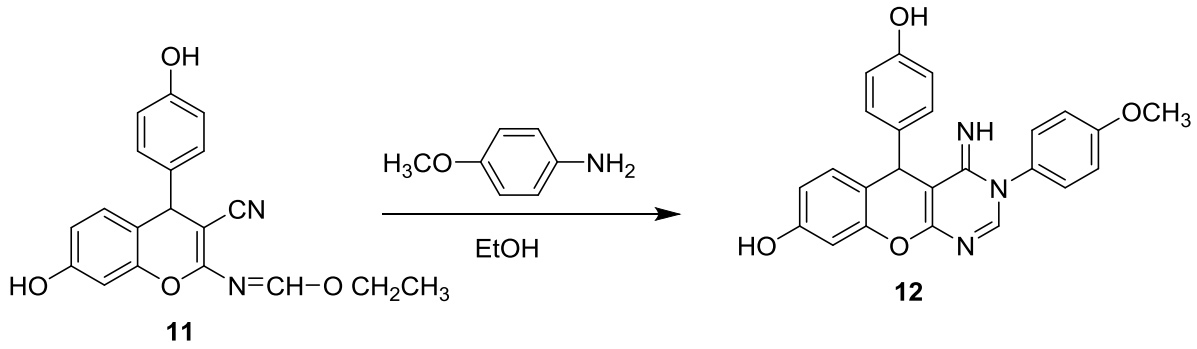
Scheme 3

Treatment of **1** with triethylorthoformate at reflux gave the corresponding ethyl N-(3-cyano-7-hydroxy-4-(4-hydroxyphenyl)-4H-chromen-2-yl)formimidate **11** (scheme 4)



Scheme 4

The structural assignment of **11** was based on spectral evidence and microanalyses. The mass spectrum of **11** showed the molecular ion peaks at the expected *m/z* values. In its IR spectrum, the appearance of two absorption bands in the range 3400-3373 cm^{-1} confirmed the presence of two OH, and showed no any band for NH_2, also the appearance of absorption band at 1646 cm^{-1} attributable to C=N. The ^{1}H-NMR spectrum of **11** revealed triplet-quartet pattern characteristic for the ethoxy protons, a new characteristic signal at 8.96 ppm assignable for CH=N protons. Compound **11** was used as precursor for the synthesis of substituted pyrimidine ring by refluxing **11** with p-ansidine in absolute ethanol to give the corresponding pyrimidine derivative **12** (Scheme 5)



Scheme 5

Structure **12** was proved based on its elemental and spectral data. The mass spectrum of **12** revealed peak at characteristic *m/z* values corresponding to its molecular weight. In the ^{1}H-NMR spectrum, a singlet signal at δ 3.97 ppm due to methyl group, singlet signal at δ 4.70 ppm due to C_4-H pyran, single signal at δ 8.88 ppm due to C_2-H pyrimidine, in addition to three signals at δ 9.10 , 9.20 (two OH) and 9.47 ppm (NH) for three D_2O exchangeable protons

Experimental

Melting points were recorded on Gallenkamp electric melting point apparatus (Electronic Melting Point Apparatus, Great Britain, London) and are uncorrected. Infrared spectra were recorded on Pye Unicam SP 1000 IR spectrophotometer (Thermoelectron Co. Egelsbach, Germany) using a KBr wafer technique. The ^{1}H NMR spectra were determined on Varian Gemini 200 MHz (Varian Co., Fort Collins, USA). DMSO-d_6 was used as solvent, TMS was used as internal standard and chemical shifts were measured in δ ppm. Mass spectra were determined on a GC-MS.QP-100 EX Shimadzu (Japan). Elemental analyses were recorded on Perkin-Elmer 2400 Elemental analyzer at the Microanalytical Center at Cairo University, Cairo, Egypt.

Synthesis of 2-(4-amino-8-hydroxy-5-(4-hydroxyphenyl)-5H-chromeno[2,3-d]pyrimidin-2-yl)acetonitrile (3)

A mixture of **1** (2.8g, 10 mmol) and malononitrile (0.66g, 10 mmol) was heated under reflux for 6 hours in absolute ethanol (20ml) in presence of pipredine (5 drops). The reaction mixture was left to stand overnight, the solid product was filtrated off, washed with

absolute ethanol, dried and recrystallized from absolute ethanol.

Brawn crystals yield 80%. m.p. 273°C. IR υ(KBr) cm^{-1} broad bands at 3475, 3426 (two OH), 3405, 3389 (NH_2) and 2206 (CN); ^{1}H NMR (DMSO-d_6): δ ppm= 3.92 (s, 2H, CH_2), 4.68 (s, 1H, CH), 6.48 (s, 2H, NH_2), 7.20-8.40 (m, 7H, Ar-H), 9.20 (s, 1H, OH), 9.90 (s, 1H, OH). MS(*m/z, %*):347, 24,92%. Anal. Calcd. for $C_{19}H_{14}N_4O_3$: C, 65.89; H, 4.07; N, 16.18%; found: C, 65.87;H, 3.45; N, 21.41%.

Synthesis of 2-(11-amino-12-(4-hydroxyphenyl)-12H-benzo[5,6]chromeno[2,3-d]pyrimidin-9-yl)acetonitrile (5)

A solution of **4** (3.14 g , 10 mmol) with malononitrile (0,66 g ,10 mmol) and Piperidine (5 drops) in absolute ethanol (20ml) ,was refluxed for 6 hours , the solution was cooled and the precipitate formed was collected , dried to give compound **5**

Green solid; yield= 65 % , mp= 245-250°C. IR υ (KBr) cm^{-1} 3452 (OH), 3309 3283 (NH_2), 2216 (CN); ^{1}H NMR (DMSO-d_6): 4.29 (s, 2H, CH_2), 5.11 (s, 1H, CH), 6.50 (s, 2H, NH_2), 7.00-8.20 (m, 10H, Ar-H), 9.10 (s,1H, OH). MS(*m/z,%*): 382, 98.9% .Anal. Calcd. for $C_{23}H_{16}N_4O_2$: C, 72.62; H, 4.24; N, 14.73%;found: C, 72.54; H, 4.15; N, 14.65%

Synthesis of 4-amino-5-(4-hydroxyphenyl)-5H-chromeno[2,3-d]pyrimidin-8-ol (6)

The chromene **1** (2.8 g, 10 mmol) in excess formamide (20ml) , the mixture was refluxed at 110 ºC for 24 hours , after cooling, the mixture diluted with water (50ml) and neutralized with diluted hydrochloric acid , the precipitated product was collected by the filtration and washed with water. The crude product was purified by crystallization from absolute ethanol to give **6.**

Red solid; yield= 70 % , mp >300°C. IR υ (KBr) cm^{-1} 3434, 3402 (two OH), 3372, 3396 (NH_2),1610 (C=N). ^{1}H NMR (DMSO-d_6): δ ppm= 4.98 (s, 1H, C_4-H pyran), 7.20-8.20 (m, 11H, Ar-H + NH_2), 9.10 (s, 1H, OH), 9.92 (s, 1H, OH). MS(*m/z, %*): 307, 71.7% , Anal. Calcd. for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67%; found: C, 66.35;H, 4.18; N, 13.75%.

Synthesis of 8-hydroxy-5-(4-hydroxyphenyl)-3,5-dihydro-4H-chromeno[2,3-d]pyrimidin-4-one (7)

A mixture of Compound **1** (2.8g, 10mol) and excess of formic acid (20ml) was refluxed on sand bath for 10 hours (monitored by TLC, the solvent was distilled off under reduced pressure, and the obtained solid was purified by recrystallization from absolute ethanol to give compound 7

Red solid; yield= 20 % , mp =210°C. IR υ (KBr) cm^{-1} 3402, 3372 (two OH), 3200 (NH stretching), 1654(C=O),1607 (C=N at pyrimidine ring); ^{1}H NMR (DMSO-d_6): δ ppm= . 4.71 (s, 1H, CH), 7.20-8.40 (m, 7H, Ar-H), 8.80 (s, 1H, CH), 9.20 (s, 1H, OH D_2O exchangeable), 9.90 (s, 1H, OH D_2O exchangeable), 11.38 (s, 1H, NH D_2O exchangeable). MS(*m/z, %*): 310, 80.95%. Anal. Calcd. for $C_{17}H_{12}N_2O_4$: C, 66.23; H, 3.92; N, 9.09%; found: C, 66.11;H, 4.00; N, 8.99%.

Synthesis of 8-hydroxy-5-(4-hydroxyphenyl)-4-imino-3-phenyl-1,3,4,5-tetrahydro-2H-chromeno[2,3-d]pyrimidine-2-thione (8).

A mixture of the chromene **1** (2.8 g, 5 mmol), and phenyl isothiocyanate (0.6 ml , 5 mmol) in absolute ethanol (15 ml) containing catalytic amount of triethylamine was refluxed for 11 hours , the solvent was evaporated and the formed solid was collected and crystallized from absolute ethanol as yellowish crystals was obtained

Yellow solid; yield= 75 % , mp =225-230°C. IR υ (KBr) cm^{-1} broad 3480 , 3415 (two OH), 3353, 3216 (two NH); ^{1}H NMR (DMSO-d_6): δ ppm= 4.69 (s, 1H, CH), 7.20-8.40 (m, 7H, Ar-H), 9.00 (s, 1H, OH D_2O exchangeable), 9.40 (s, 1H, imino NH D_2O exchangeable), 9.79 (s, 1H, OH D_2O exchangeable), 11.18 (s, 1H, NH D_2O exchangeable). MS(*m/z, %*): 415, 50.34%, Anal. Calcd. for $C_{23}H_{17}N_3O_3S$: C, 66.49; H, 4.12; N,10.11%; found: C, 66.38;H, 4.00; N, 10.00%.

Synthesis of 8-hydroxy-5-(4-hydroxyphenyl)-1,5-dihydro-2H-chromeno[2,3-d]pyrimidine-2,4(3H)-dithione (9)

A mixture of **1** (2.8g , 10mmol), carbon disulphide (10 ml) and KOH (1g) in EtOH (10 ml) was refluxed for 2 hours on water bath , after removal of absolute ethanol, water was added and the alkaline solution was acidified with HCl and the formed precipitate was collected by filtration, washed with water, dried and crystallized from EtOH.

Dark brown solid; yield= 35 % , mp >300˚C. IR υ (KBr) cm^{-1} two broad bands at 3475, 3224 (two OH), 3222, 3188 (two NH); ^{1}H NMR (DMSO-d_6): δ ppm= 5.12 (s, 1H, CH), 7.20-8.40 (m, 7H, Ar-H), 9.15 (s, 1H, OH), 9.80 (s, 1H, OH) 10.60 (s, 1H, NH), 11.20 (s, 1H, NH). MS(*m/z, %*): 356, 368.89%. Anal. Calcd. for $C_{17}H_{12}N_2O_3S_2$: C, 57.29; H, 3.39; N, 7.86%; found: C, 57.00;H, 3.45; N, 7.41%.

4-amino-8-hydroxy-5-(4-hydroxyphenyl)-1,5-dihydro-2H-chromeno[2,3-d]pyrimidin-2-one (2-thione)

A mixture of compound **1** (2.8g , 10mol) and urea (0.6 g ,10mol) or thiourea (0.76 g ,10mol) with catalytic amount of sodium ethoxide in absolute ethanol was refluxed for 6–8 hours (TLC controlled) , after completion of the reaction, the reaction mixture was poured in crushed ice and neutralized with diluted hydrochloric acid, the precipitated product was collected by the filtration and washed with water , the crude product was purified by crystallization from absolute ethanol

4-amino-8-hydroxy-5-(4-hydroxyphenyl)-1,5-dihydro-2H-chromeno[2,3-d]pyrimidin-2-one (10a)

Brown solid; yield= 60 % , mp =227-232˚C. IR υ (KBr) cm^{-1} 3487, 3402 (two OH), 3363,3354 (NH_2), 3254 (NH); ^{1}H NMR (DMSO-d_6): δ ppm= . 4.71 (s, 1H, CH), 7.20-8.40 (m, 9H, Ar-H + NH_2), 9.09 (s, 1H, OH D_2O exchangeable), 9.80 (s, 1H, OH D_2O exchangeable), 11.00 (s, 1H, NH D_2O exchangeable). MS(*m/z, %*): 324, 100% . Anal. Calcd. for $C_{17}H_{13}N_3O_4$: C, 63.16; H, 4.05; N, 13.00%; found: C, 63.03;H, 4.00; N, 12.95%.

4-amino-8-hydroxy-5-(4-hydroxyphenyl)-1,5-dihydro-2H-chromeno[2,3-d]pyrimidine-2-thione (10b)

Green solid; yield= 60 % , mp >300˚C. IR υ (KBr) cm^{-1} 3487, 3404 (two OH), 3366,3352 (NH_2), 3262 (NH); ^{1}H NMR (DMSO-d_6): δ ppm= 4.69 (s, 1H, CH), 7.20-8.40 (m, 9H, aromatic protons + NH_2), 9.11 (s, 1H, OH D_2O exchangeable), 9.82 (s, 1H, OH D_2O exchangeable), 10.78 (s, 1H, NH D_2O exchangeable). MS(*m/z, %*): 340, 80.77% . Anal. Calcd. for $C_{17}H1_3N_3O_3S$: C, 60.17; H, 3.86; N, 12.38%; found: C, 60.03;H, 3.75; N, 12.27%.

Synthesis of ethyl N-(3-cyano-7-hydroxy-4-(4-hydroxyphenyl)-4H-chromen-2-yl)formimidate (11)

A mixture of compound **3** (2.8 g, 10 mmol) and triethyl orthoformate (10 ml) was heated under reflux for 12 hours , the excess of triethyl orthoformate was removed under reduced pressure , and then the residue was washed with absolute ethanol and crystallized from the EtOH-DMF to give **11**

Yellow solid; yield= 90 % , mp =99-101˚C. IR υ (KBr) cm^{-1} two broad bands from 3400-3373 (two OH), 2210 (CN), 1646 (C=N); ^{1}H NMR (DMSO-d_6): δ ppm= 1.07 (t, 3H, CH_3), 3.86 (q, 2H, CH_2), 4.73 (s, 1H, C_4-H pyran), 7.20-8.20 (m, 7H, Ar-H), 8.96 (s, 1H, CH), 9.10 (s, 1H, OH), 9.90 (s, 1H, OH). MS(*m/z, %*): 337, 93.83% . Anal. Calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.80; N, 8.33%; found: C, 67.78; H, 4.71; N, 8.25%.

5-(4-hydroxyphenyl)-4-imino-3-(4-methoxyphenyl)-3,5-dihydro-4H-chromeno[2,3-d]pyrimidin-8-ol (12)

Equimolar amounts of **11** (3.36 g, 10 mmol) and p-ansidine (1.23 g, 10 mmol) in absolute ethanol (15ml) in presence of 3 drops TEA, was refluxed for 12hours. On cooling the precipitate was filtered off and recrystallized from EtOH to give **12**

Brownish red solid; yield= 85 % , mp =150-160˚C. IR υ (KBr) cm^{-1} broad band at 3725-3355 (two OH), 3286 (NH). ^{1}H NMR (DMSO-d_6): δ ppm= 3.97 (s, 3H, CH_3), 4.70 (s, 1H, C_4-

H pyran), 7.20-8.20 (m, 11H, Ar-H), 8.88 (s, 1H, CH), 9.10 (s, 1H, OH), 9.47 (s, 1H, NH), 9.90 (s, 1H, OH). MS(*m/z, %*): 414, 32.66 . Anal. Calcd. for $C_{24}H_{19}N_3O_4$: C, 69.72; H, 4.63; N, 10.16%;found: C, 69.79;H, 4.71; N, 10.25%.

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الملخص العربى

يعمل هذا البحث على تخليق مركبات الكرومونو برميدين الجديدة نظرا لأهمية هذه المركبات من الناحية البيولوجية وذلك عن طريق مركب ٢-امينو-٧-هيدروكسى-٤-(٤-هيدروكسى فينيل)-H٤-كرومين-٣-كاربونايترايل (١) بتفاعلها مع كواشف التي تحتوى على اثنين من المجموعات الوظيفية مثل (مالونونايترايل ، حمض فورميك ، فورمآميد، فينيل ثيوسيانات ، ثاني كبريتيد الكربون ، يوريا ، ثايو يوريا) والتى بدوره يؤدى الى تكوين حلقة بريميدين . وقد تم اثبات التركيب البنائى للمركبات المخلقة حديثا من خلال التحاليل الدقيقة و البيانات الطيفية.