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Synthesis of some novel chromene derivatives

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ABSTRACT

2-Amino-4-aryl-7-alkoxy-4*H*-chromene-3-carbonitriles 2a&b were intended to be used for the preparation of novel substituted triycyclic chromopyrimidine derivatives for their expected antitumor activity. Reaction of aminocyanochromenes with different carboxylic acids and their derivatives deemed to be the passage to those goal compounds yet unexpectedly 4-arylchrome-2-ones 4a&b and 6a&b and N,N- diacetyl aminocyanochromene 5a&b were resulted from the reaction of the aminocyanochromene 2a&b with the acids, acid chlorides and acetic anhydride sequentially this was proved using supporting evidence provided by single X-ray crystallography.

KEYWORDS

Heterocycles;
Synthesis;
7-alkoxy-2-amino-3-cyanochromenes;
Chromo[2,3-*d*]pyrimidines;
X-ray crystallography.

INTRODUCTION

Condensed heterocyclic systems are of considerable interest not only because of their potential biological activity, but also because of their versatility as synthones in organic transformations[1]. Chromene derivatives are important class of compounds, as they constitute the basic structural back bone of many types of tannin and polyphenols widely present in plants e.g. green tea, fruits and vegetables[2]. These compounds have become more important as a result of their health-promoting effects.

On the other hand, numerous bioactive natural products have been identified, and the presence of the chromene-containing structure has been associated with the capability to prevent several diseases[3]. Synthetic analogues have attracted considerable attention from organic and medicinal chemists due to their useful biological and pharmacological properties including antimicrobial[4-14], anticancer[15-18] and central nervous system activities[13,19]. Furthermore, 4*H*-pyran derivatives are potential calcium channel antagonists[20] which are structurally similar to biologically active 1,4-dihydropyridines.

Keeping this in mind, it was aimed in this work to synthesize a new series of heterocyclic compounds containing 4-aryl-4*H*-chromene moiety.

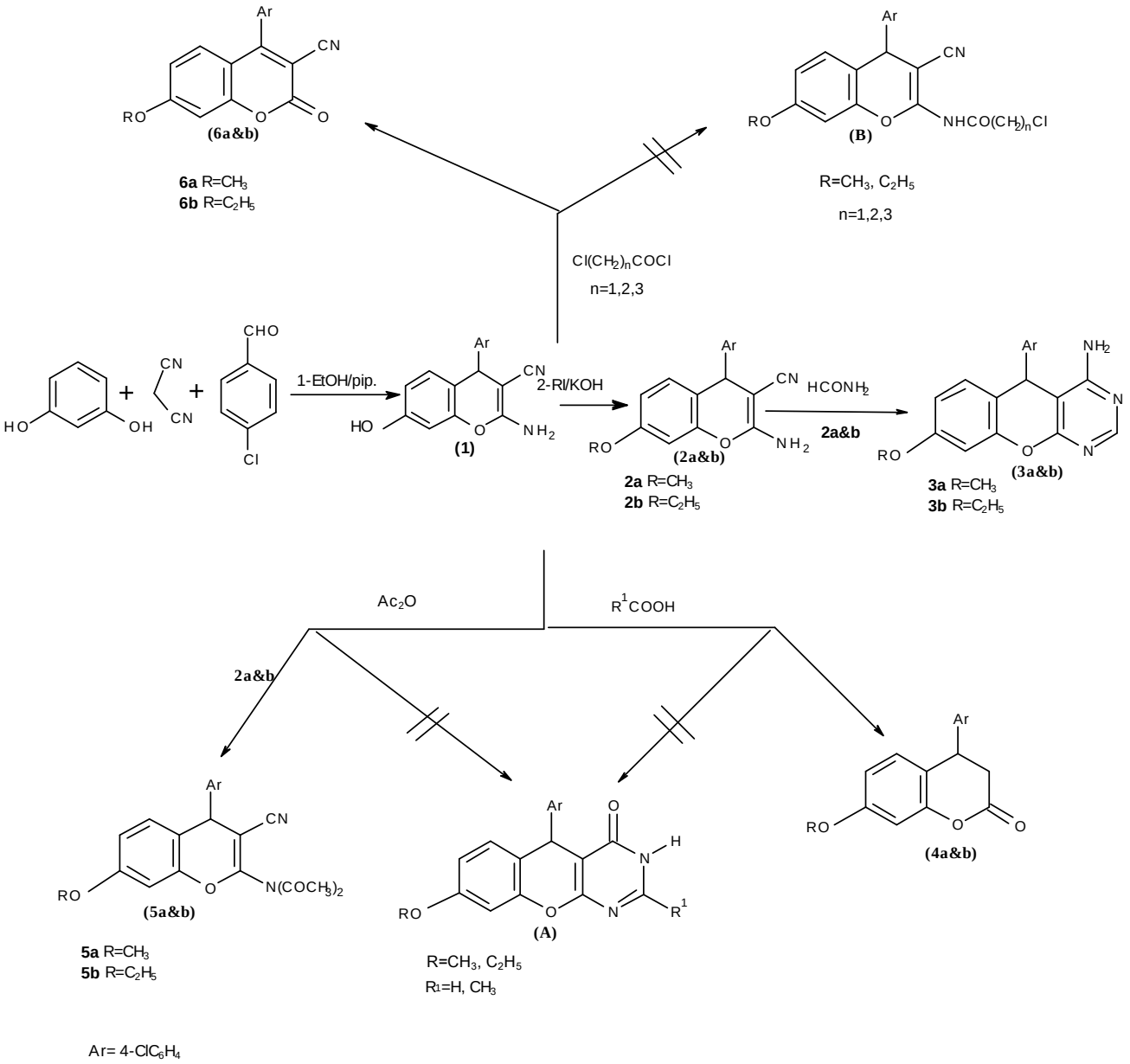
For this purpose the 2-amino-4-(4-chlorophenyl)-7-hydroxy-4*H*-chromene-3-carbonitrile (1)[21], alongside with its alkylated derivatives 2a&b were synthesized (Scheme 1).

RESULTS AND DISCUSSION

One pot three-component reaction of resorcinol, malononitrile and 4-chlorobenzaldehyde with few drops

of piperidine base afforded aminocyanochromene 1 which upon alkylation using different alkyl halides in basic medium gave the corresponding 7-alkoxyaminocyanochromenes 2a&b. Reacting 2a&b with formamide smoothly yielded 4-aminochromeno-[2,3-*d*]pyrimidines 3a&b that were confirmed using microanalyses and spectral data. The IR spectra showed the disappearance of the cyano group band while the ^{1}H NMR revealed the appearance of a proton (C2H) at δ 8.18 and 8.09 ppm for compounds 3a&b sequentially. 7-Alkoxychromeno-[2,3-*d*]pyrimidin-4-ones A were intended to be synthesized via reacting 1,2a&b with either formic acid or a mixture of conc. hydrochloric acid / acetic acid (1:3) but unexpectedly both reactions gave one and the same compound assigned structure 4a&b that were confirmed using microanalysis, spectral data and X-ray crystallography (Figure 1). The IR spectrum of compound 4a&b showed an absorption band at 1761 cm^{-1} attributed to (C=O), the disappearance of the absorption band of C=N group, NH_2 group and NH group as well.

Further evidence was obtained from ^{1}H NMR spectrum which showed a multiplet signal at δ 2.96-3.04 ppm corresponding to (CH_2) and a triplet signal



Scheme 1

at δ 4.27 ppm corresponding to (C4H) and no NH signal. Additionally, the mass spectrum of compound 4a revealed that the molecular ion peak was the base peak at *m/z* 288

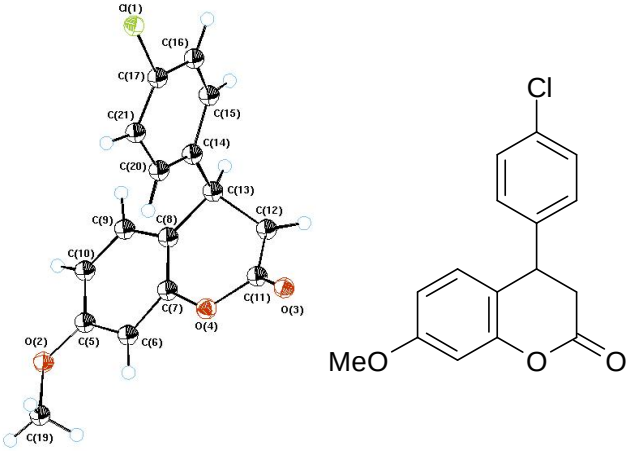


Figure 1 : The structure refinement of compound 4a

The outlined mechanism may be suggested for the formation of compound 4a&b where the insitu acid hydrolysis of the cyano group at high temperature with concometent decarboxylation followed by hydrolysis of the iminochromene (the stable conformer of tautomeric form of aminochromene since the pyran ring is allowed to be at the full chair conformer which make this tautmer a stable one besides the aromaticity did not affected[20]) afforded compound 4a&b as described in (Figure 2).

Since the chromeno[2,3-*d*]pyrimidin-4-one is a new ring system, Surveying the literature disclosed that, some comparative studies stated that the pyrimidinone ring could be obtained via refluxing compounds 2a&b with acetic anhydride for several hours[13,14]. These studies suggested a probable route to the formation of these compounds *via* formation of the oxazine intermediate,

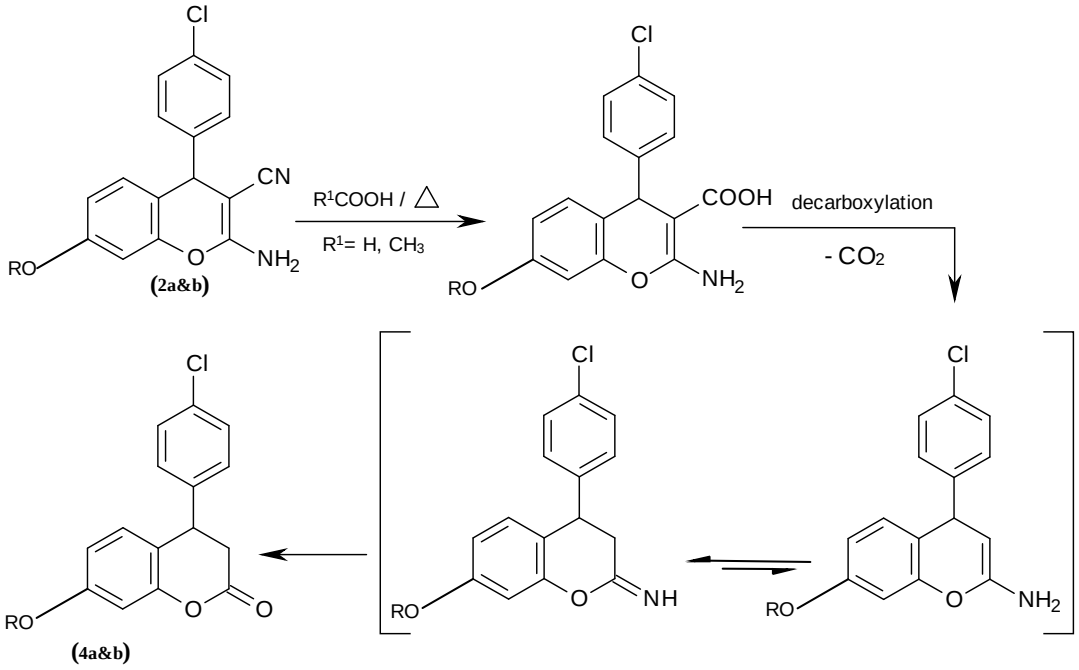


Figure 2

which was not isolated and suffered Dimroth rearrangement to pyrimidinone derivatives A under the same reaction conditions[24].

On contrary, several attempts were carried out to prepare these target compounds A adopting the reported method[21] but these attempts were unsuccessful since it was found out during monitoring the reaction using (TLC) that both the mono and diacetyl derivatives were formed at the exact same time. However, in the reaction of compounds 2a&b with acetic anhydride either in a boiling water bath or under reflux temperature for five hours, the formation of diacetyl derivatives 5a&b was considered[22]. The absence of NH and NH_2 absorption bands and the presence of absorption band corresponding to C=N group at 2220, 2219 cm^{-1} in IR spectra confirming the formed product was neither compounds A nor the starting material, also the appearance of broad absorption band

1744 cm^{-1} corresponding to (2 C=O).

^{1}H NMR spectra of compounds 5a&b indicated a singlet signal at δ 2.46 and δ 2.46 ppm for compounds 5a&b sequentially each characteristic for six protons of diacetyl moiety (2 $COCH_3$) and the disappearance of D_2O exchangeable signal of either NH_2 or NH group. In addition, the mass spectrum of compound 5b revealed ion peaks at *m/z* 410 and at *m/z* 412 corresponding to $(M)^{+}$ and $(M+2)^{+}$ respectively.

For the preparation of chloroacylaminochromene B; reacting the aminocyanochromenes 2a&b with the appropriate chloro acid chloride was carried out but unexpectedly this reaction did not afford the expected acyl derivatives B but gave compounds that identified as 2-oxo-2*H*-chromene derivatives 6a&b. The formation of the target acyl derivatives B was eliminated on the basis of element analysis and spectral data. IR spectra revealed the absence of NH group signal and the appearance of signal at 1727, 1730 cm^{-1} attributed to C=O respectively of 6a&b. ^{1}H NMR spectra showed the absence of the NH group as well as the absence of C4H and the CH acyl protons that existed in the target compounds B. Additional support for the structures of compounds 6a&b was provided by ^{13}C NMR spectrum of compound 6a, hence the disappearance of peak corresponding to C-4 in chromene ring (present in compound 2a) and the appearance of C=C instead confirming the structure of these compounds.

A suggested mechanism for the formation of compounds 6a,b is thought to be, after the formation of the chloroacylaminochromene the bond become very weak due to the inductive effect and carbon number 2 become highly partially positive center and hence the attack with the conjugated carbonate base was easier with simultaneous break of the bond of the good leaving amide group (Figure 3).

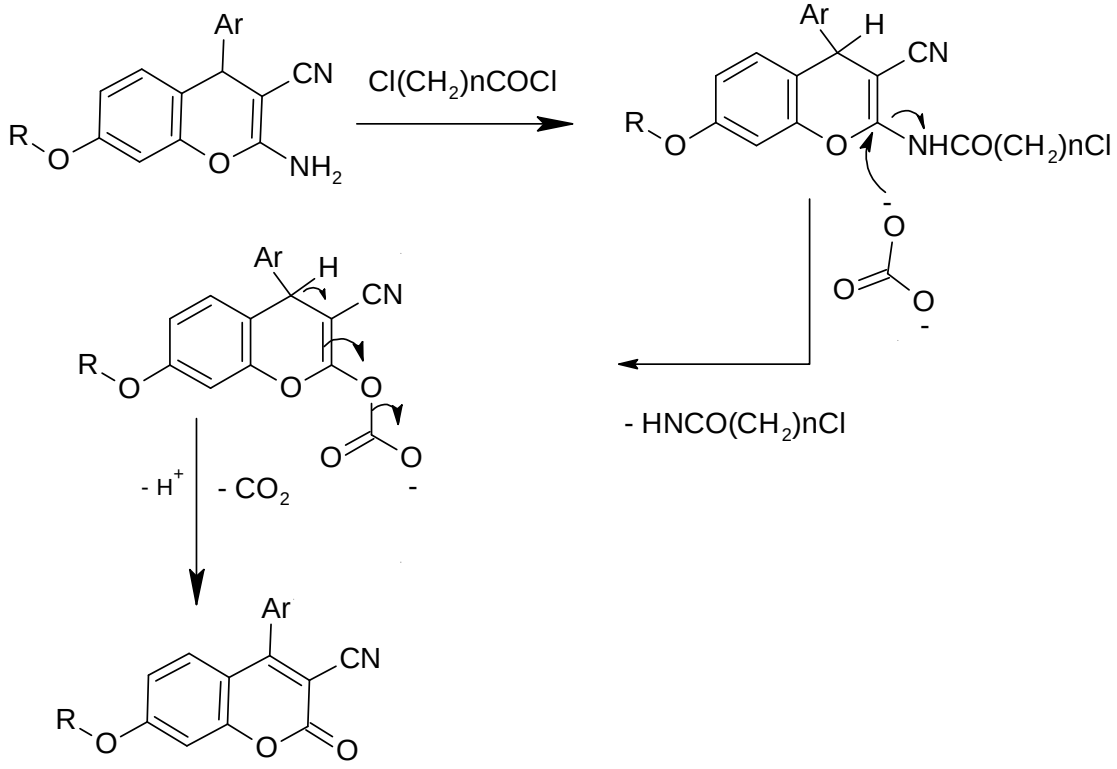


Figure 3

EXPERIMENTAL

General

Reactions were routinely monitored by thin-layer chromatography (TLC) on silica gel sheets that precoated with UV fluorescent silica (MERCK 60 F 254) and spots were developed using I_2 vapour / UV light as visualizing agents. Solvent system was chloroform: methanol (in different ratio). ^{1}H NMR spectra were determined in $CDCl_3$, or DMSO-d_6 solvent with Varian Gemini 300 MHZ Spectrometer. Peak positions

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TABLE 1 : Physical and microanalytical data of the compounds 2a&b, 3a-c, 4, 5a&b and 6a&b.

Compounds	R	Yield %	m.p (°C)	M. Wt.	Mol. Formula	Analysis % calculated (found)		
						C	H	N
2a	CH_3	84	167-168	312.76	$C_{17}H_{13}ClN_2O_2$	65.29 (65.50)	4.19 (4.31)	8.96 (9.16)
2b	C_2H_5	85	181-182	326.79	$C_{18}H_{15}ClN_2O_2$	66.16 (66.42)	4.63 (4.42)	8.57 (8.43)
3a	CH_3	96	226-227	339.78	$C_{18}H_{14}ClN_3O_2$	63.63 (63.92)	4.15 (4.29)	12.37 (12.08)
3b	C_2H_5	92	209-210	353.81	$C_{19}H_{16}ClN_3O_2$	64.50 (64.80)	4.56 (4.69)	11.88 (11.98)
4	CH_3	60[a] 77[b]	141-142	288.73	$C_{16}H_{13}ClO_3$	66.56 (66.61)	4.54 (4.49)	- -
5a	CH_3	78	134-135	396.83	$C_{21}H_{17}ClN_2O_4$	63.56 (63.81)	4.32 (4.24)	7.06 (7.05)
5b	C_2H_5	74	164-165	410.86	$C_{22}H_{19}ClN_2O_4$	64.32 (64.20)	4.66 (4.80)	6.82 (6.80)
6a	CH_3	83	207-208	311.73	$C_{17}H_{10}ClNO_3$	65.50 (65.30)	3.23 (3.52)	4.49 (4.39)
6b	C_2H_5	78	171-172	325.75	$C_{18}H_{12}ClNO_3$	66.37 (66.14)	3.71 (3.84)	4.30 (3.99)

[a]**Method A;** [b]**Method B**

were given in parts per million (δ) downfield the tetramethylsilane as internal standard. ^{13}C NMR spectra were carried out on Gemini 300 MHZ Spectrometer. IR spectra were recorded on a Shimadzu 435 Spectrometer, using KBr discs and values were represented in cm^{-1}. GC Mass spectra were run on Shimadzu QP-2010 spectrometer and Mass spectra were run on Hewlett Packard 5988 spectrometer at the Microanalytical Center, Cairo University, Egypt. X-ray crystallography was performed by the X-ray laboratory of National Research Center, Cairo, Egypt. Melting points were determined on a Griffin instrument and are uncorrected. All reported products showed ^1H NMR spectra in agreement with the assigned structures. Elemental analyses were performed at the Micro-analytical Center, Cairo University, Egypt. Compound 1 was prepared adopting a reported procedure[21].

(A) General procedure for the preparation of compounds (*RS*) 2-Amino-7-alkoxy-4-(4-chlorophenyl)-4*H*-chromene-3-carbonitrile (2a&b)

A mixture 1 (2.98 g, 0.01 mol) and potassium hydroxide (0.56 g, 0.01 mol) in ethanol (20 mL) was stirred at ambient temperature for 1 h then the appropriate alkyl halide (0.015 mol) was added and the mixture was heated under reflux for 24h. The reaction mixture was cooled, filtered and the formed precipitate was washed with ethanol and crystallized from absolute ethanol to yield 2a&b.

(a) (RS) 2-Amino-7-methoxy-4-(4-chlorophenyl)-4*H*-chromene-3-carbonitrile (2a)

(2a): IR (KBr): 3432, 3347 (forked, NH_2), 3055 (CH arom.), 2960 (CH aliph.), 2185 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.79 (s, 3H, OCH_3), 4.68 (s, 1H, C4H), 6.55-7.30 (m,7 H, Ar-H + 2 H, NH_2 (D_2O exchangeable); ^{13}C NMR ($CDCl_3$): 39.90, 55.52, 76.57, 101.43, 111.79, 114.27, 119.55, 128.96, 129.22, 130.12, 133.03, 143.28, 149.13, 159.07, 159.56; MS: *m/z* 314 ($M^{+\cdot}$+2), $M^{+\cdot}$ 312 (8.4%), 201(100%).

(b) (*RS*) 2-Amino-7-ethoxy-4-(4-chlorophenyl)- 4*H*-chromene-3-carbonitrile (2b)

(2b): IR (KBr):3424, 3332 (forked, NH_2), 3070 (CH arom.), 2976 (CH aliph.), 2196(C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.29 (t, 3H, CH_3); 3.98 (q, 2H, CH_2); 4.72 (s, 1H, C4H); 6.53-6.92 (m, 3H, Ar-H + 2H, NH_2, D_2O exchangeable); 7.20 (d, J_{value} = 8.4 Hz, 2H, ArH); 7.37 (d, J_{value} = 8.4 Hz, 2H, ArH)

(B) General procedure for the preparation of compounds (*RS*) 8-alkoxy-5-(4-chlorophenyl)-5*H*-chromeno[2,3-*d*]pyrimidin-4-amine (3a&b)

A solution of 2a&b (0.01 mol) in formamide (20 mL) was heated under reflux for 2 h then cooled and poured into ice-cold water (20 mL). The precipitated solid was filtered, washed with water and crystallized from the appropriate solvent to afford 3a-c.

(a) (*RS*) 8-methoxy-5-(4-chlorophenyl)-5*H*-chromeno[2,3-*d*]pyrimidin-4-amine (3a)

Compound 3a was recrystallized from benzene: acetone (1: 1) mixture, the following spectral data were recorded for compound 3a: IR (KBr): 3206 (NH_2), 1626 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.80 (s, 3H, OCH_3); 5.30 (s, 1H, C5H); 6.72-7.42 (m, 7H,

Ar-H + 2H, NH_2, D_2O exchangeable); 8.18 (s, 1H, C2H) ppm.

(b) (*RS*) 8-ethoxy-5-(4-chlorophenyl)-5*H*-chromeno[2,3-*d*]pyrimidin-4-amine (3b)

Compound 3b was recrystallized from benzene, the following spectral data were recorded for compound 3b: IR (KBr): 3385, 3335 (NH_2), 3165 (CH arom.), 2979 (CH aliph.), 1653 (C=N)cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 1.38 (t, 3H, CH_3); 3.98 (q, 2H, CH_2); 4.85 (s, 2H, NH_2, D_2O exchangeable); 4.89 (s, 1H, C5H); 6.57-7.27 (m, 7H, Ar-H), 8.09 (s, 1H, C2H) ppm.

(C) Two procedures for the preparation of (*R*) 4-(4-Chlorophenyl)-7-methoxychroman-2-one (4)

Method A

A mixture of compound 2a (3.12 g, 0.01 mol) and formic acid (10 mL) was heated under reflux for 8 h. The reaction mixture was then cooled, filtered and the formed crystals were washed with ethanol then recrystallized from absolute ethanol to give compound 4.

Method B

A mixture of compound 2a (3.12 g, 0.01 mol), concentrated hydrochloric acid (3 mL) and acetic acid (9 mL) was heated under reflux for 3 h. The reaction mixture was then poured into ice-cold water (20 mL) and the formed solid was filtered and crystallized from absolute ethanol to give compound 4.

The following spectral data were recorded for compound 4: IR (KBr): 3046 (CH arom.), 2973 (CH aliph.), 1761 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.96-3.04 (m, 2H, CH_2); 3.81 (s, 3H, OCH_3); 4.27 (t, 1H, C4H); 6.64-7.33 (m, 7H, Ar-H) ppm; MS: *m/z* ($M^{+\cdot}$+2) 290 (35.48%), $M^{+\cdot}$ 288 (100%).

(D) General procedure for the preparation of compounds *(RS)* *N*-Acetyl-*N*-[7-alkoxy-4-(4-chlorophenyl)-3-cyano-4*H*-chromen-2-yl]acetamide (5a&b)

A mixture of 2a&b (0.01 mol) and acetic anhydride (20 mL) was heated under reflux for 5 h. The precipitated crystals formed after cooling were filtered and recrystallized from ethanol to give compounds 5a&b.

(a) (*RS*) *N*-Acetyl-*N*-[7-methoxy-4-(4-chlorophenyl)-3-cyano-4*H*-chromen-2-yl]acetamide (5a)

The following spectral data were recorded for compound 5a: IR (KBr): 3069 (CH arom.), 2949 (CH aliph.), 2220 (C=N), 1744 (2 acetyl C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ δ 2.46 (s, 6H, $2COCH_3$); 3.79 (s, 3H, OCH_3); 4.90 (s, 1H, C4H); 6.59-7.37 (m, 7H, Ar-H) ppm.

(b) (*RS*) *N*-Acetyl-*N*-[7-ethoxy-4-(4-chlorophenyl)-3-cyano-4*H*-chromen-2-yl]acetamide (5b)

The following spectral data were recorded for compound 5b: IR (KBr): 3106 (CH arom.), 2982 (CH aliph.), 2219 (C=N), 1744 (2 acetyl C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ δ 1.40 (t, 3H, CH_2CH_3); 2.46 (s, 6H, $2COCH_3$); 4.01 (q, 2H, CH_2); 4.90 (s, 1H, C4H); 6.58-7.37 (m, 7H, Ar-H) ppm; GCMS: *m/z* $M^{+\cdot}$ +2 (1.54), $M^{+\cdot}$ 410 (4.71%), 215 (100%).

(E) General procedure for the preparation of compounds 7-Alkoxy-4-(4-chlorophenyl)-2-oxo-2*H*-chromene-3-carbonitrile (6a&b)

A mixture of 2a&b (0.01 mol), the appropriate acid chloride (0.01 mol) and anhydrous potassium carbonate (2.07 g, 0.015 mol) in tetrahydrofuran (30 mL) was heated under reflux for 2 h. The solid that separated after cooling was collected by filtration, washed with water, dried and crystallized from ethanol to afford compounds 6a&b

(a) 7-Methoxy-4-(4-chlorophenyl)-2-oxo-2*H*-chromene-3-carbonitrile (6a)

The following spectral data were recorded for compound 6a: IR (KBr): 3096 (CH arom.), 2990 (CH aliph.), 2219 (C=N), 1727 (C=O)cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.94 (s, 3H, OCH_3); 6.85-7.61 (m, 7H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$): δ 56.24, 97.92, 101.27, 111.49, 113.79, 114.11, 129.53, 129.86, 130.44, 137.41, 156.43, 157.29, 162.58, 165.72; GCMS: *m/z* ($M^{+\cdot}$+2) (35.63%), $M^{+\cdot}$ 311 (100%).

(b) 7-Ethoxy-4-(4-chlorophenyl)-2-oxo-2*H*-chromene-3-carbonitrile (6b)

The following spectral data were recorded for compound 6b: IR (KBr): 3095 (CH arom.), 2966 (CH aliph.), 2224 (C=N), 1730 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.48 (t, 3H, CH_3); 4.15 (q, 2H, CH_2); 6.83-7.60 (m, 7H, Ar-H) ppm.

CONCLUSION

Since no precedent publication described the syn-

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thesis of this triycyclic 5(4-chlorophenyl)chromo[2,3-*d*]pyrimidine ring system A, B, during the course of this work these chromo[2,3-*d*]pyrimidine derivatives were the target. It was speculated that these novel nucleus could be obtainable via the interaction between 2-amino-4-(4-chloro-phenyl)-7-hydroxy(alkoxy)-4*H*-chromene-3-carbonitriles 1,2a&b and several commercially available reagents. Reaction of 1,2a&b with formamide gave softly one of the goal derivatives 3a&b while the interaction of the same starting materials with other reagents e.g. formic acid, mixture of acetic acid and hydrochloric acid, acetic anhydride, and chloro acid chlorides unexpectedly afforded compounds 4,5a&b and 6a&b respectively. This may be attributed to the electronic nature of this aminocyanochromene ring system where the amino group is a very weak basic center to the extent that could not react with aromatic aldehyde[25] and C2 is carrying a highly partial positive charge which encourage and facile the bond breakage.

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