Available online at www.worldscientificnews.com

World Scientific News

An International Scientific Journal

WSN 123 (2019) 258-264 EISSN 2392-2192

SHORT COMMUNICATION

Synthesis and characterization of 2-(methylthio)-6-oxo-6H-chromeno[3,4-e]pyrazolo[1,5-a]pyrimidine-3-carbonitrile derivatives

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ABSTRACT

Some new 2-(methylthio)-6-oxo-6H-chromeno[3,4-e]pyrazolo[1,5-a]pyrimidine-3-carbonitrile derivatives Having coumarine nucleus were synthesized by novel synthetic rout from 4-chloro 3-carbaldehyde coumarine derivatives and previously prepared 5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile using methanol as a solvent and catalytic amount of glacial acetic acid. All the synthesised libraries were characterized by IR, NMR and mass spectral analysis.

***Keywords*:** coumarine, Schiff base, Pyrazolo pyrimidine

1. INTRODUCTION

Biaryls and heterobiaryls have attracted significant attention from the scientific community because of their relevance in medicinal chemistry. Heterobiaryls frequently can be

(Received 26 February 2019; Accepted 08 March 2019; Date of Publication 09 March 2019)

observed in numerous bioactive small molecules, and in particular, heterobiaryls fused with various heterocycles, such as pyrazole, pyridine, and pyrimidine, have been used as key pharmacophores [1]. Pyrazolo[1,5-*a*]pyrimidines have attracted considerable interest because of their biological activity. For instance, this heterocyclic system is found as purine analogues and has useful properties as antimetabolites in purine biochemical reactions [2-4]. Several compounds of this class display interesting antitrypanosomal [5] and antischistosomal activities [6]. They are used as HMG-CoA reductaseinhibitors [7], COX-2 selective inhibitors [8], 30,50-cyclic-AMP phosphodiesteraseinhibitors [9]. CRF1 antagonists [10-13], selective peripheral benzodiazepine receptor ligands [14-16], potassium channel [17] and histamine-3 receptor ligands [18] and antianxiety agents [19]. The pyrazolopyrimidine derivatives have considerable chemical and pharmacological importance because a broad range of biological activities have been displayed by these classes of molecules. As we demonstrated, the tremendous biological potential of pyrazolopyrimidine derivatives encouraged us to synthesize some new highly functionalized pyrazolopyrimidine derivatives. Various methodologies have been described for the synthesis of pyrazolopyrimidine derivatives. However, the existing methods are suffer with some drawbacks, such as; yield, time, product isolation, isomer formation. Various methodologies have been described for the synthesis of pyrazolo[1,5-*a*]pyrimidines. Very well-known method for this is one pot synthesis of ethylacetoacetate, 3-aminopyrazole and aldehyde through Biginelli reaction. In our work we introduced novel 4-chloro-3-carbaldehyde coumarin as and 5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile as key starting material for the formation of chromeno[3,4-e]pyrazolo[1,5-a]pyrimidine ring system. The newly synthesized compounds were characterized by IR, Mass, ^{1}H NMR, ^{13}C NMR spectroscopy and elemental analysis. All the synthesized compounds were evaluated for their antimicrobial activity.

2. REACTION SCHEME

Table 1. Physical Properties of Synthesized 2-(methylthio)-6-oxo-6H-chromeno[3,4-e] pyrazolo[1,5-a]pyrimidine-3-carbonitrile derivatives

Code	Molecular Formula	R	Molecular Weight	Melting Point °C	Yield %
AYM-1a	$C_{15}H_9ClN_4O_2S$	H	344	122-124	68
AYM -1b	$C_{16}H_{11}ClN_4O_2S$	2-CH_3	358	134-136	62
AYM -1c	$C_{16}H_{11}ClN_4O_2S$	3-CH_3	358	130-132	61
AYM -1d	$C_{16}H_{11}ClN_4O_2S$	4-CH_3	358	138-140	64
AYM -1e	$C_{17}H_{13}ClN_4O_2S$	2,3-diCH_3	372	142-144	75
AYM -1f	$C_{17}H_{13}ClN_4O_2S$	3,4-diCH_3	372	162-264	76
AYM -1g	$C_{17}H_{13}ClN_4O_2S$	3,5-diCH_3	372	160-162	75

AYM -1h	$C_{17}H_{13}ClN_4O_2S$	2,5-diCH_3	372	154-156	78
AYM -1i	$C_{15}H_8BrClN_4O_2S$	4-Br	421	176-178	70
AYM -1j	$C_{15}H_8ClFN_4O_2S$	4-F	362	170-172	77

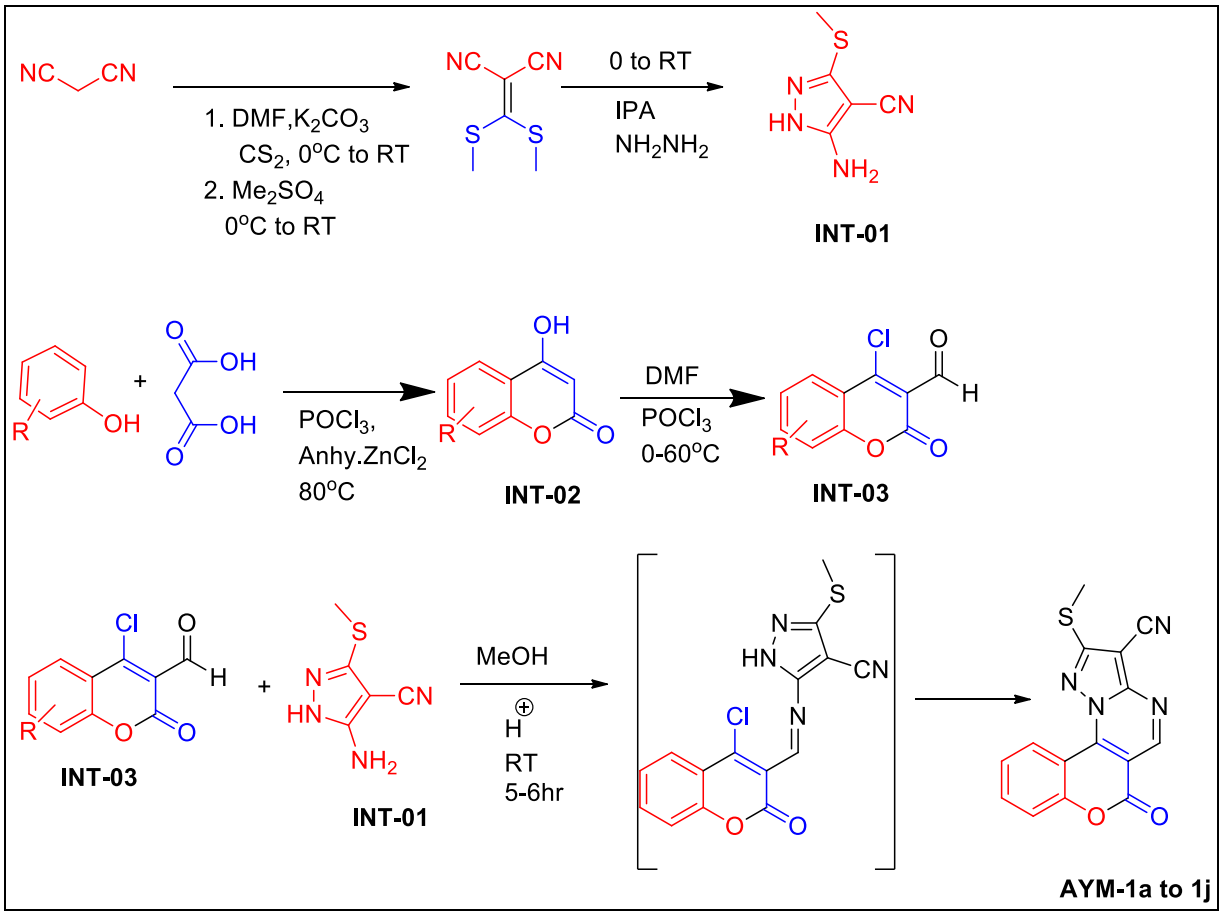

Figure 1. 2-(methylthio)-6-oxo-6H-chromeno[3,4-e]pyrazolo[1,5-a]pyrimidine-3-carbonitrile derivatives

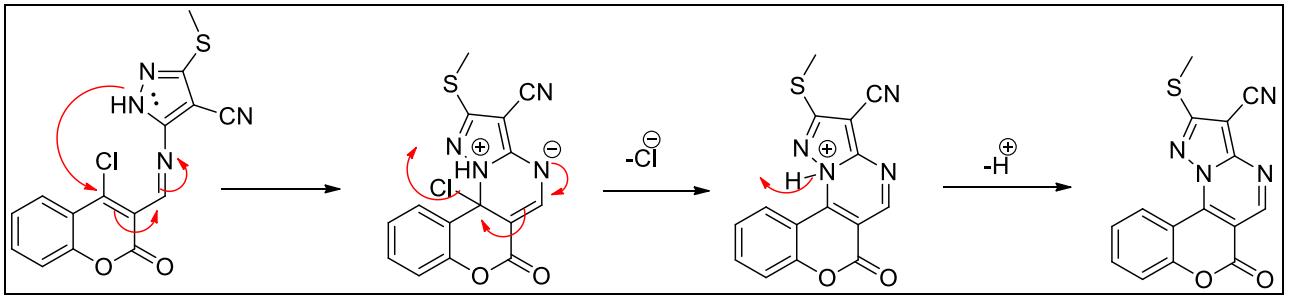

Figure 2. Proposed Mechanism for intra molecular cyclization

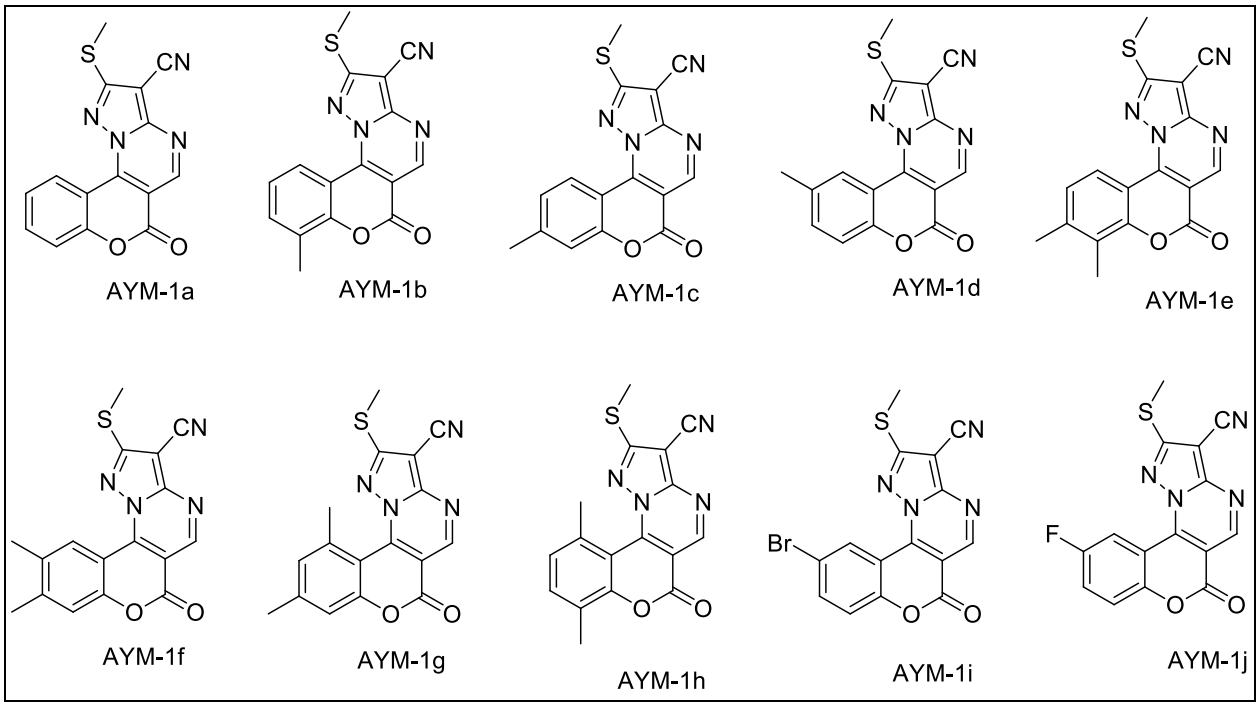

Figure 3. Structure of the synthesized library

3. EXPERIMENTAL

Thin-layer chromatography was accomplished on 0.2-mm percolated plates of silica gel G60 F_{254} (Merck). Visualization was made with UV light (254 and 365nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. ^{1}H (400 MHz), and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in $CDCl_3$ and DMSO.

Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected.Physical constants of the synthesized compounds **AYM-1a to AYM-1j** are shown in Table 1.

Synthesis of 4-hydroxy coumarin (int-2)

Various Substituted phenols (0.1 mole) and malonic acid were added to a mixture of phosphorus oxychloride (40 ml) and anhydrous zinc chloride (30 gms) which was preheated to get rid of any moisture. The reaction mixture was heated on a water bath at 700C for 8-10 hours. It was cooled and decomposed with ice and water to afford buff-yellow coloured solid. The solid was then filtered and washed thoroughly with water. It was then triturated with 10% sodium carbonate solution and filterd.

The filtrate was slowly acidified with dilute HCl till the effervescence ceased. The product was filtered, dried and recrystallized with methanol.

Synthesis of 4-chloro, 3-formayl coumarin (int-3)

To a stirred mixture of 4-hydroxycoumarin (0.06 mol) in anhydrous DMF (0.6 mol) were added dropwise $POCl_3$ (0.18 mol) at –10 °C to –5 °C. The reaction mixture was then stirred for 1 h at room temperature and heated and stirred for 2 h at 60 °C. After the reaction completed, the mixture was poured onto crushed ice under vigorous stirring. After storing the mixture overnight at 0°C the pale yellow solid was collected by filtration and washed successively with Na_2CO_3 (5%) and water, and then was air–dried. Recrystallization from acetone gave 85% of 4-chloro-3-formyl coumarin as a pale yellow powder with m.p. 115–120 °C.

Synthesis of 2-(bis(methylthio)methelene)Malanonitrile.

A 100 mL conical flask equipped with magnetic stirrer and septum was charged with a solution of malononitrile, (10 mmol) in DMF (10 mL). Dry K_2CO_3 (10 mmol) was added and the mixture was stirred at room temperature for 2 h. CS_2 (30 mmol) was added and the mixture was stirred for an additional 2 h at room temperature. Then, methyl iodide (20 mmol) was added at 0-5 ºC and the mixture was stirred for 4 h at room temperature. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, it was poured into 50ml cold water. The precipitated crude product was purified by filtration followed by crystallization from EtOH.

Synthesis of 2-amino-4-(Methylthio)-1H-pyrrole-3-Carbonitrile (INT-1).

A 100 mL conical flask equipped with magnetic stirrer and septum was charged 2-(bis(methylthio)methelene)malanonitrile (**3**) (0.1 mol) in isopropyl alcohol (100 mL). cool the reaction mixture at 0 ºC and then add hydrazine hydrate (0.1 mol). The Reaction mixture was stirred to rt for 2 h. After completion of the reaction, it was poured into 50 mL cold water. The precipitated crude product was purified by filtration followed by crystallization from EtOH.

General synthesis of 2-(methylthio)-6-oxo-6H-chromeno[3,4-e]pyrazolo[1,5-a] pyrimidine -3-carbonitrile (AYM-1a to 1j)

To a solution of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde **(INT-03)** (2gm, 0.0090 mmol) and methanol (10ml, 5v), 5-amino-3-(methylthio)-1H-pyrazole-4-carbonitrile **(INT-1)** was added at rt. Maintain the temperature further 0-5 ºC and add two drops of glacial acetic acid as a catalyst. After addition, reaction mixture was stir rat RT for 30 min. after completion of reaction mixture was cooled. The obtained solid was filtered, wash with methanol and dried it in oven.

4. SPECTRAL DATA OF THE SYNTHESIZED COMPOUNDS

2-(methylthio)-6-oxo-6H-chromeno[3,4-e]pyrazolo[1,5-a]pyrimidine-3-carbonitrile(AYM-1a) Yellow solid, Rf Value 0.21 (MDC:Methanol-9:1), MP-122-124 ºC, IR (KBR Disc) CM^{-}, 3278, 1680, 1608, 1558, 1516, 1481, 1375, 1317, 1242, 1062, 840, 752, 690, 623 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δppm; 2.75(3H, S, $-CH_3$); 7.74 to7.76 (2H, Multiplet, Ar-H);7.78 (1H, S, Ar-H); 10.11 (1H, Singlet, NH); ^{13}C NMR (100 MHz, DMSO) δppm; 12.8, 130.5, 129.1, 123.2, 126.2, 159.1, 164.0, 158.3, 158.5, 89.3, 148.3, 150.5MS (*m/z*); 344:

Elemental analysis calculated for $C_{15}H_9ClN_4O_2S$ is Elemental Analysis: C, 58.43; H, 2.62; N, 18.17; S, 10.40

8-methyl-2-(methylthio)-6-oxo-6H-chromeno[3,4-e]pyrazolo[1,5-a]pyrimidine-3-carbonitrile(AYM-1b)

Yellow solid, Rf Value 0.23 (MDC:Methanol-9:1), MP-134-136 ºC, IR(KBR Disc) CM^{-}, 3268, 1685, 1609, 1568, 1526, 1481, 1355, 1327, 1247, 1052,850, 759, 680, 613 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δppm; 2.76 (3H, S, $-CH_3$); 7.74 to 7.76 (2H, Multiplet, Ar-H); 7.78 (1H, S, Ar-H); 10.11 (1H, Singlet, NH); ^{13}C NMR (100 MHz, DMSO), δppm, 150.5, 148.3, 158.5, 152.3, 164.0, 159.1, 123.2, 126.1, 132.3, 127.5, 131.0, 125.9, 89.3, 12.8; MS (*m/z*); 358: Elemental analysis calculated for $C_{16}H_{11}ClN_4O_2S$ is Elemental Analysis: C, 59.62; H, 3.13; N, 17.38; O,S, 9.95

5. CONCLUSION

We have established facile and convenient new method for the synthesis of 2-(methylthio)-6-oxo-6H-chromeno[3,4-e]pyrazolo[1,5-a]pyrimidine-3-carbonitrile with 2-amino-4-methylthio-1H-pyrrole-3-Carbonitrile under a conventional reagent and condition. By using this novel synthetic rout we obtain high yield and purity of compounds. All synthesized compounds were obtained in good to moderate yield. All synthesized compounds were characterized by IR, NMR and Mass spectrometry.

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