Asian Journal of Chemistry; Vol. 32, No. 8 (2020), 2067-2074

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2020.22771

Tannic Acid Catalyzed Green Synthesis of Functionalized Chromeno-Pyrimidine-2,5-dione/thione Derivatives

J. PUVITHRA and D. PARTHIBAN*

P.G. & Research Department of Chemistry, Rajeshwari Vedhachalam Government Arts College, Chengalpattu-603001, India

*Corresponding author: E-mail: nidhaksha@yahoo.co.in

Received: 13 April 2020; *Accepted*: 1 June 2020; *Published online*: 27 July 2020; AJC-19992

Diversely functionalized chromeno-pyrimidine-2,5-dione/thione compounds were synthesized by cyclocondensation of 4-hydroxy coumarin, aldehydes and urea/thiourea using tannic acid as a green catalyst and 1:1 (EtOH:H_2O) as a green solvent. Different acids were screened for their catalytic activity of chromeno-pyrimidine-2,5-dione/thione derivatives. Tannic acid (10 mol%) was used as a suitable catalyst with increased catalytic activity. By utilizing this protocol, chromeno-pyrimidine scaffolds were prepared in acceptable to excellent yield without the use of conventional volatile organic solvent and toxic metal catalyst. To our best of knowledge, this is the first report, in which tannic acid is utilized successfully as an eco-safe catalyst for synthesis of fused pyrimidines.

Keywords: Chromeno-pyrimidine-2,5-dione, Tannic acid, Nitrogen heterocycles, 4-Hydroxy coumarins, Multicomponent reaction.

INTRODUCTION

Chromenes and their structural analogues are of great interest because they are frequently found in a number of natural products like flavonoids, tocopherols, anthocyanins and alkaloids as well as biologically active molecules like rhodomyrtone, myrtucommulone-E and HA14-1 [1] (Fig. 1). Chromenes are a promising class of heterocycles that have been explored as antioxidant [2,3], anticancer [4-7], antimicrobial agent [8-11]. Apart from these, this class of compounds have also been explored as cognitive enhancers [12,13], Alzheimer drug [14] and Schizophrenia drug [15]. Many plant sources having coumarin derivatives [16] have also been extensively investigated as anticoagulation, antiviral [17], anti-inflammatory [18], antibacterial [19] and anticancer agents [20].

Pyrimidine derivatives are well-known compounds for their biological activities [21,22]. Numerous pyrimidine containing compounds have found application in medicine and therapeutics especially, some are used in the chemotherapy of cancer [23]. Some drugs such as lamivudine, raltegravir, imatinib, erlotinib, lapatinib are types of drugs with pyrimidine core [24] (Fig. 2).

Coumarin derivatives have been used as drugs, *e.g.*, the warfarin [25] is an anticoagulant. Acenocoumarin [26] and phenprocoumon [27] are vitamin K antagonists. The novobiocin [28] is a potent inhibitor of bacterial DNA gyrase (Fig. 3).

Tannic acid is a lustrous yellowish to light brown amorphous naturally occurring plant polyphenol having the composition of $C_{76}H_{52}O_{46}$; it is a polymer of gallic acid molecules and glucose (Fig. 4). The ingestion of tannic acid causes constipation, which allowed it to act as traditional medicine to treat diarrhoea. Externally, tannic acid is used to treat ulcers, toothache and wounds. Tannic acid is also used in leather tanning, cytoprotection, drug delivery, protein immobilization, mesoporous silica preparation [29]. Only two articles are appearing in the literature for utilization of tannic acid as a catalyst. Singh *et al.* reported tannic acid as a catalyst for the synthesis of 1,5-benzodiazepines [30] and 1-amidoalkyl-2-naphthols [31]. Due to its weakly acidic (pK_a ~6) nature, hydrogen donor properties, tannic acid can be used as mild catalyst.

It has been discerned that commonly used acids and transition metal catalysts are not environmentally safe because of their eco-toxicity and resistance to biodegradation. Therefore, development of a new and efficient protocol for synthesis of fused pyrimidines using simple, low-cost, easily available and eco-safe catalyst with operational simplicity has become thrust area of research. Despite the extensive use of various catalytic

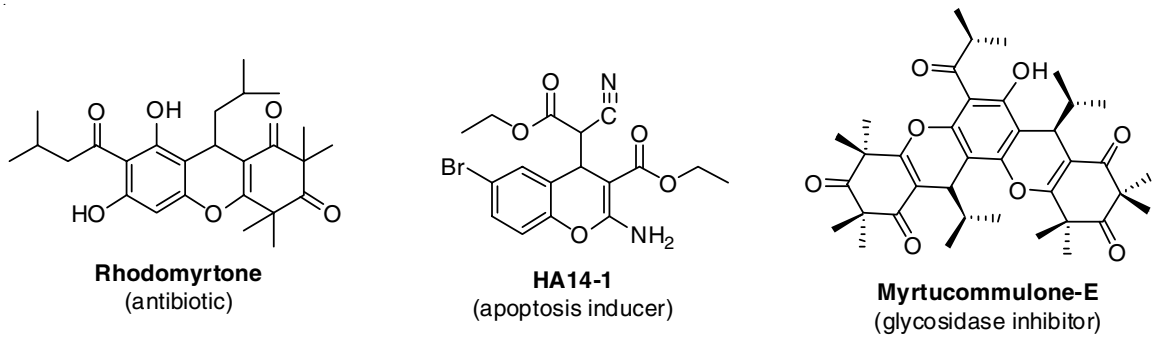


Fig. 1. Biologically active chromenes

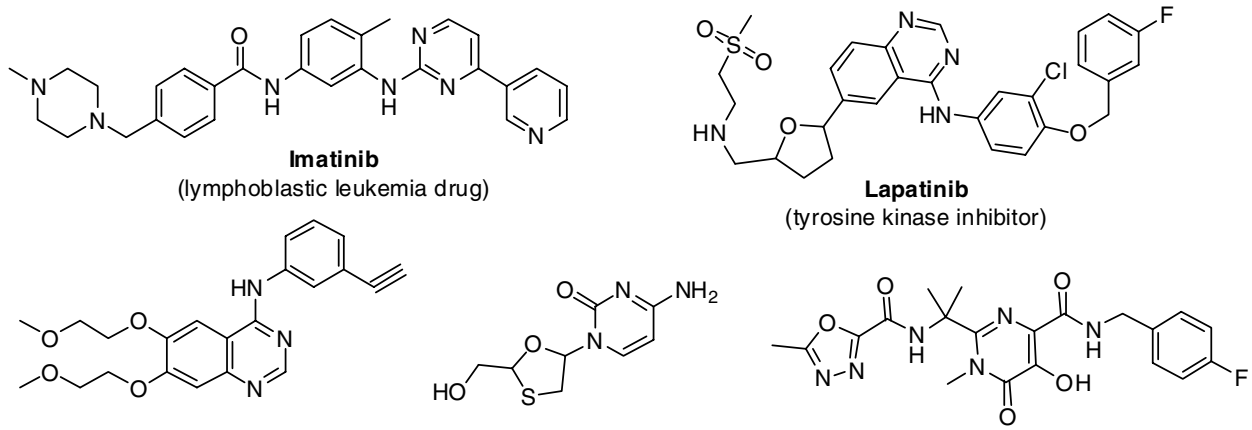


Fig. 2. Drugs with pyrimidine core

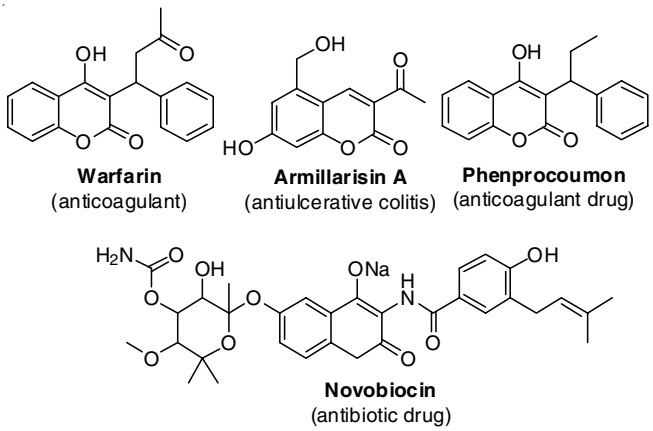


Fig. 3. Drugs with coumarin core

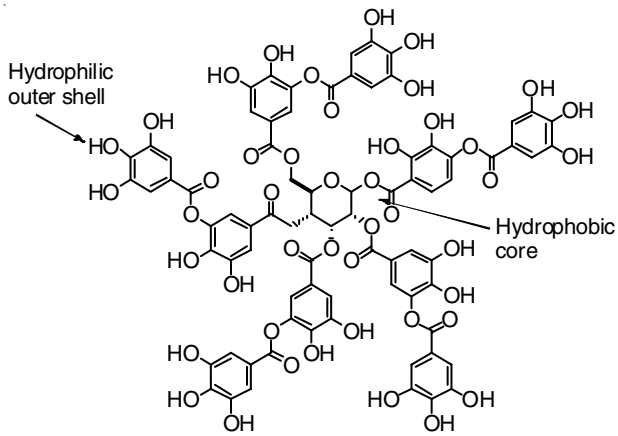


Fig. 4. Structure of tannic acid

systems for synthesis of fused chromeno[4,3-*d*]pyrimidine-2,5-dione derivatives that have been described in the literature, nobody has reported the application of tannic acid as a green catalyst for synthesis of fused pyrimidine derivatives. Tannic acid was chosen as a catalyst for one pot multicomponent reaction of 4-hydroxycoumarin, benzaldehydes and urea, because tannic acid has several acidic hydroxyl (-OH) group in its structure. This key feature makes it as an efficient acidic catalyst. From green chemistry point of view, design of synthetic organic transformations should involve high selectivity, benign conditions, ease of manipulation and substances exhibiting zero or low toxicity to the surrounding. EtOH-H_2O (1:1) has budding as a potential solvent system for many organic synthetic methods, because EtOH-H_2O (1:1) is inexpensive, non-toxic and less volatile [32]. Capello *et al*. [33] reported that EtOH-H_2O system are safer than pure alcohol for synthesis. For the first time, an efficacy of tannic acid as a novel, eco-benign acidic catalyst for ecofriendly synthesis of functionalized chromeno-pyrimidine-2,5-dione/thione derivatives in 1:1 (EtOH:H_2O) solvent through one pot multicomponent reaction of 4-hydroxy-coumarin, benzaldehydes and urea is reported.

EXPERIMENTAL

Various substituted aromatic aldehydes, urea, thiourea, 4-hydroxycoumarin and other chemicals were purchased from TCI chemicals and used without further purification. Silica gel (column grade) was purchased from S.D. fine chemicals. The solvents were purified as per procedure mentioned in the literature. Melting points were measured in open capillary tubes on Guna melting point apparatus and are reported uncorrected. Thin layer chromatography was carried out on precoated sheets of silica gel containing 60 F_{254} indicator (Merck). Column chromatography was performed with silica gel (60-120 mesh; S.D. fine chemicals). ^{1}H-NMR spectra were recorded on 400 MHz Brucker Advance instrument in DMSO-d_6 solvent. ^{13}C-NMR spectra were recorded on 100 MHz Brucker Advance instrument in DMSO-d_6 solvent, chemical shifts (δ) are expressed in ppm value relative to the internal standard trimethyl silane (TMS). FT-IR analyses were recorded on Brucker alpha-P spectrophotometer. Mass spectra were recorded on Jeol GC Mate II mass spectrometer.

Synthesis of 4-phenyl-3,4-dihydro-1*H*-chromeno[4,3-*d*]pyrimidine-2,5-dione: A mixture of 4-hydroxycoumarin (10 mmol), aromatic aldehyde (10 mmol), urea (10 mmol), tannic acid(10 mol%) and 10 ml of 1:1 (EtOH:H_2O) solvent was taken in 100 mL round bottom flask and the mixture was stirred and refluxed on water bath for appropriate time and the progress of the reaction was monitored by TLC. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature. The solid formed upon cooling was filtered, dried and purified either by recrystallizing in hot ethanol or by column chromatography on silica gel (60-120 mesh, 20% EtOAc/petroleum ether mixture) (**Scheme-I**).

Spectral data

4-Phenyl-3,4-dihydro-1*H*-chromeno[4,3-*d*]pyrimidine-2,5-dione (4a): Off white powder, yield: 96%; m.p.: 163-165 ºC; IR (neat, ν_{max}, cm^{-1}): 3298 (N-H), 2970 (C-H, Ar), 1613 (C=O),1512 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 6.39 (s, 1H, -CH), 7.16-7.63 (m, 9H, Ar-H), 7.91 (s, 1H, NH), 7.93 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): 36, 104, 116, 118, 124, 126, 127, 128, 132, 140,157. ESI-MS: *m/z* calcd. for $C_{17}H_{12}N_2O_3$ 292.29; found [M]$^+$ 293.3; Elemental analysis found: C, 69.86; H, 4.14; N, 9.58; O, 16.42.

4-(2-Chlorophenyl)-3,4-dihydro-1*H*-chromeno[4,3-*d*]pyrimidine-2,5-dione (4b): Off white powder, yield: 82%; m.p.: 194-196 °C; IR (neat, cm^{-1}): 3298 (N-H), 2990 (C-H, Ar), 1623 (C=O), 1523 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.26 (s, 1H, -CH), 7.11 (d, 1H, Ar-H), 7.13-7.32 (m, 7H, Ar-H), 7.54 (t, 2H, Ar-H), 7.83 (d, 1H, Ar-H), 9.64 (s, 1H, -NH), 9.79 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): 37, 105, 117, 119, 125, 129, 130, 131, 138, 154, 162, 165, 166; ESI-MS: *m/z* Calculated for $C_{17}H_{11}N_2O_3Cl$: 326.05, Found [M]+ 326.1; Elemental Analysis: C, 62.47; H, 4.21; N, 9.58; O, 14.69.

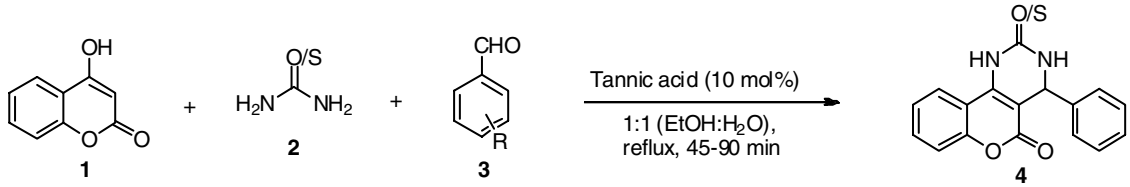
4-(4-Chlorophenyl)-3,4-dihydro-1*H*-chromeno[4,3-*d*]pyrimidine-2,5-dione (4c): Off white powder, yield: 86%; m.p.: 193-195 °C; IR (neat, cm^{-1}): 3289 (N-H), 2974 (C-H, Ar), 1617 (C=O), 1515 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.25 (s, 1H, CH), 7.11 (d, 2H, Ar-H), 7.52-7.32 (m, 6H, Ar-H), 7.54 (s, 1H, NH), 7.85 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): 37, 103, 114, 116, 121, 127, 131, 132, 133, 135, 139, 151, 163, 165; ESI-MS: *m/z* Calculated for $C_{17}H_{11}N_2O_3Cl$: 326.05, Found [M]+ 326.1; Elemental Analysis: C, 62.41; H, 3.43; N, 8.57; O, 14.59

4-(4-Bromophenyl)-3,4-dihydro-1*H*-chromeno[4,3-*d*]pyrimidine-2,5-dione (4d): Off white powder, yield: 87%; m.p.: 185-187 °C; IR (neat, cm^{-1}): 3276 (N-H), 2997 (C-H, Ar), 1625 (C=O), 1515 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.28 (s, 1H, -CH), 7.15 (d, 1H, Ar-H), 7.27-7.39 (m, 5H, Ar-H), 7.52-7.57 (m, 2H, Ar-H), 7.78 (s, 1H, -NH), 7.95 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): 37, 107, 116, 117, 123, 128, 129, 130, 131, 132, 137, 152, 164, 166; ESI-MS: *m/z* Calculated for $C_{17}H_{11}N_2O_3Br$ 370.0, Found [M]+ 371.1; Elemental Analysis: C, 55.10; H, 2.92; N, 7.09; O, 12.72.

4-(2-Hydroxyphenyl)-3,4-dihydro-1*H*-chromeno[4,3-*d*]pyrimidine-2,5-dione (4e): Off white powder, yield: 80%; m.p.: 238-239 °C; IR (neat, cm^{-1}): 3288 (N-H), 2957 (C-H, Ar), 1623 (C=O), 1517 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.17 (s, 1H, -CH), 6.41-6.51 (m, 2H, Ar-H), 6.69 (d, 2H, Ar-H), 6.90 (t, 1H, Ar-H), 7.21-7.37 (m, 2H, Ar-H), 7.41 (t, 1H, Ar-H), 7.57 (1, 1H, -NH), 7.77 (s, 1H, -NH), 9.54 (s, 1H, OH); ^{13}C NMR (100 MHz, DMSO-d_6): 37, 101, 109, 112, 116, 118, 122, 128, 130, 139, 149, 156, 164, 65; ESI-MS: *m/z* Calculated for $C_{17}H_{12}N_2O_4$ 308.08, Found [M]+ 309; Elemental Analysis: C, 66.23; H, 3.92; N, 9.09; O, 20.72.

4-(4-Hydroxyphenyl)-3,4-dihydro-1*H*-chromeno[4,3-*d*]-pyrimidine-2,5-dione (4f): Off white powder, m.p.: 225-227 ºC; IR (neat, ν_{max}, cm^{-1}): 3308 (N-H), 2955 (C-H, Ar), 1613 (C=O), 1512 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 5.57 (s, 1H, CH), 7.22-7.63 (m, 8H, Ar-H), 7.73 (s, 1H, NH), 8.12 (s, 1H, -NH), 12.23 (s, 1H, -OH); ^{13}C NMR (100 MHz, DMSO-d_6): 35, 114, 116, 122, 123, 124, 125.04, 125.85, 128, 132, 149, 152, 156; ESI-MS: *m/z* calculated for $C_{17}H_{12}N_2O_4$: 308.08; found [M]$^+$ 309; Elemental analysis: C, 66.23; H, 3.92; N, 9.09; O, 20.76.

4-(2-Nitrophenyl)-3,4-dihydro-1*H*-chromeno[4,3-*d*]pyrimidine-2,5-dione (4g): Off white powder, yield: 79%; m.p.: 160-162 °C; IR (neat, cm^{-1}): 3276 (N-H), 2982 (C-H,



Scheme-I

Ar), 1622 (C=O), 1518 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.37 (s, 1H, -CH), 7.27-7.36 (m, 4H, Ar-H), 7.37 (d, 2H, Ar-H), 7.53 (t, 2H, Ar-H), 7.87 (s, 1H, -NH), 8.15 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): 37, 103, 115, 118, 123, 123, 125, 127, 130, 131, 145, 150, 152, 163, 166; ESI-MS: *m/z* Calculated for $C_{17}H_{11}N_3O_5$ 337.0, Found [M]+ 337.2; Elemental Analysis: C, 60.23; H, 3.92; N, 12.49; O, 20.73.

4-(3-Nitrophenyl)-3,4-dihydro-1*H*-chromeno[4,3-*d*]pyrimidine-2,5-dione (4h): Off white powder, yield: 85%; m.p.: 170-172 °C; IR (neat, cm^{-1}): 3277 (N-H), 2987 (C-H, Ar), 1624 (C=O), 1518 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.35 (s, 1H, -CH), 7.26-7.34 (m, 4H, Ar-H), 7.35 (d, 2H, Ar-H), 7.49 (t, 2H, Ar-H), 7.81 (s, 1H, -NH), 8.11 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): 35, 103, 115, 118, 123, 123, 125, 127, 130, 131, 145, 150, 152, 164, 166; ESI-MS: *m/z* Calculated for $C_{17}H_{11}N_3O_5$ 337.0, Found [M]+ 337.2; Elemental Analysis: C, 60.23; H, 3.92; N, 12.49; O, 20.73.

4-(*p*-Tolyl)-3,4-dihydro-1*H*-chromeno[4,3-*d*]pyrimidine-2,5-dione (4i): Off white powder, yield: 85%; m.p.: 162-164 °C; IR (neat, cm^{-1}): 3430 (-NH), 2987 (C-H, Ar), 1725 (C=O), 1612 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 2.34 (s, 3H, CH3) 6.24 (s, 1H, -CH), 6.53 (d, 1H, Ar-H), 6.66 (d, Ar-H), 7.36 (m, 4H, Ar-H), 7.89 (s, 1H, NH), 8.20 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): 36, 55, 104, 114, 116, 119, 124, 128, 132, 134, 145, 152, 164, 164 ESI-MS: *m/z* Calculated for $C_{18}H_{14}N_2O_3$ 308.3, Found [M]+ 308.2; Elemental Analysis: C, 70.23; H, 4.62; N, 9.19; O, 15.73.

4-(4-Methoxyphenyl)-3,4-dihydro-1*H*-chromeno[4,3-*d*]-pyrimidine-2,5-dione (4j): Off white powder, m.p.: 185-186 ºC; IR (neat, ν_{max}, cm^{-1}): 3273 (N-H), 2948 (C-H, Ar), 1608 (C=O), 1514 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 3.87 (s, 1H,-OCH_3), 6.23 (s, 1H, -CH), 7.16-7.63 (m, 8H, Ar-H), 7.93 (1, 1H, -NH), 8.91 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): 35, 104, 111, 112, 113, 117, 123, 129, 131, 141, 152, 154, 157; ESI-MS: *m/z* calculated for $C_{18}H_{14}N_2O_4$ 332.29, found $[M]^+$ 332.08; Elemental analysis: C, 67.07; H, 4.38; N, 8.69; O, 19.86.

4-(Furan-2-yl)-3,4-dihydro-1*H*-chromeno[4,3-*d*]pyrimidine-2,5-dione (4k): Mud colour powder, yield: 89%; m.p.: 174-176 °C; IR (neat, cm^{-1}): 3297 (N-H), 2993 (C-H, Ar), 1619 (C=O), 1521 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.24 (s, 1H, -CH), 7.12 (d, 1H, Ar-H), 7.11-7.37 (m, 4H, Ar-H), 7.521 (t, 2H, Ar-H), 9.64 (s, 1H, -NH), 9.71 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): 105, 117, 119, 125, 129, 130, 131, 138, 154, 162, 165; ESI-MS: *m/z* Calculated for $C_{15}H_{10}N_2O_4$: 282.05, Found [M]+ 283.07; Elemental Analysis: C, 63.27; H, 3.51; N, 9.58; O, 22.69.

4-(Thiophen-2-yl)-3,4-dihydro-1*H*-chromeno[4,3-*d*]-pyrimidine-2,5-dione (4l): Off white powder, yield: 87%; m.p.: 154-156 °C; IR (neat, cm^{-1}): 3291 (N-H), 2999 (C-H, Ar), 1618 (C=O), 1524 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.29 (s, 1H, -CH), 7.11 (d, 1H, Ar-H), 7.23-7.42 (m, 4H, Ar-H), 7.54 (t, 2H, Ar-H), 9.64 (s, 1H, -NH), 9.79 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): 105, 117, 119, 125, 129, 130, 131, 138, 154, 162, 165; ESI-MS: *m/z* Calculated for $C_{15}H_{10}N_2O_3S$: 298.04, Found [M]+ 299.07; Elemental Analysis: C, 60.27; H, 3.31; N, 9.38; O, 16.09.

4-Phenyl-2-thioxo-3,4-dihydro-1*H*-chromeno[4,3-*d*]-pyrimidin-5-one (4m): White powder, mp 185-187 ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm 6.24 (s, 1H, -CH), 7.14-7.29 (m, 9H, Ar-H), 7.79 (s, 1H, -NH), 8.11 (s, 1H, -NH); ^{13}C NMR (100 MHz, DMSO-d_6): 36, 103, 115, 119, 123, 123, 127, 131, 132, 145, 150, 152, 164, 166; ESI-MS: *m/z* calculated for $C_{17}H_{12}N_2O_2S$: 308.35, found $[M]^+$ 308.4; Elemental analysis: C, 66.22, H, 3.92, N, 9.08.

RESULTS AND DISCUSSION

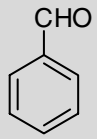
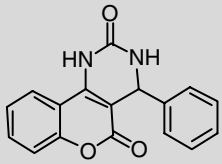
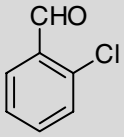
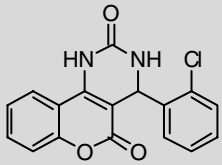
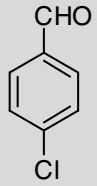
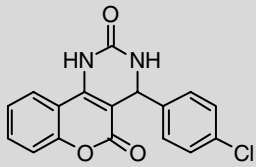
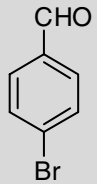
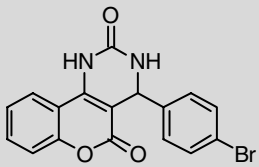
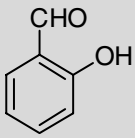
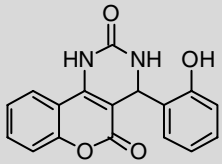
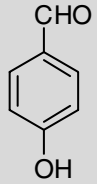
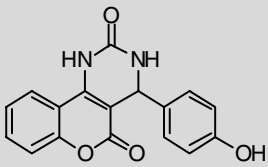
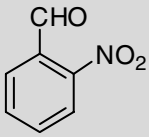
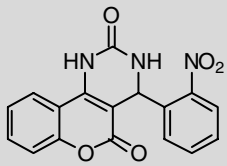
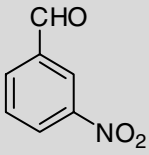
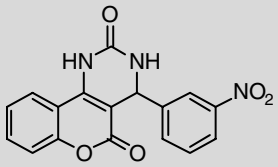
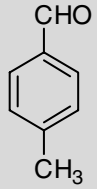
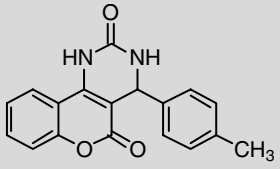
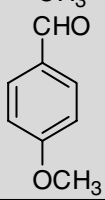
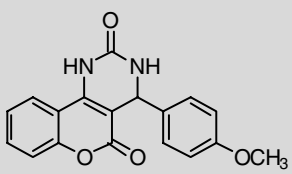
Initially, synthesis of chromeno-pyrimidine-2,5-dione derivatives *via* one pot three-component approach is evaluated. The reaction was performed by the consecutive addition of reagents: 4-hydroxy coumarin (10 mmol), aromatic aldehyde (10 mmol), (thio)urea (10 mmol) in round bottom flask with 10 mL of 1:1 (EtOH:H_2O) solvent at reflux temperature. The mixture was stirred to complete the reaction as monitored using TLC. Finally, the precipitated solid was filtered off under reduced pressure, washed with EtOH and recrystallized from EtOH to give the target product **4a** in high yield.

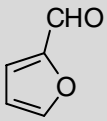
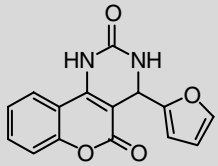
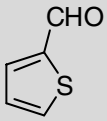
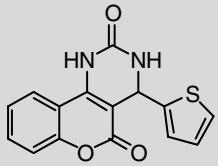
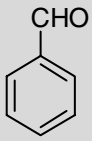
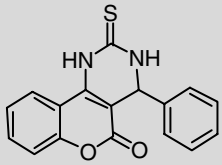
Characterization: All the synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. IR spectra of the compounds show characteristic absorption band at 3331-3279 cm^{-1} for N-H *str*., 3100-3000 cm^{-1} for aromatic C-H, 1619-1606 cm^{-1} for C=O group and around 1512-1478 cm^{-1} for C=C group. The ^{1}H NMR spectrum of all 4-phenyl-3,4-dihydro-1*H*-chromeno[4,3-*d*]pyrimidine-2,5-dione derivatives shows characteristic multiplet peaks at 7.65- 7.07 ppm (aromatic protons), two sharp singlet at 7.93-8.91 ppm (proton of 2º amine group) a sharp singlet 5.57-6.41 ppm (3º methine proton). The other signals and peaks of the ^{1}H NMR, ^{13}C NMR and IR are in agreement with the assigned structures. The mass spectra of the compounds displayed a molecular ion peak at *m/z* values, which corresponds well with the theoretical value.

Substrate scope: By having standardized procedure in hand, it is decided to pay our attention to check the versatility of this cyclocondensation, different aromatic aldehyde tethered with halogen group (-Cl, -Br, -I) and electron donating groups (-CH_3,-OCH_3) were employed and found that corresponding product (**4a-l**) obtained in good yields. The complicated amine such as 4-butylaniline also underwent this cyclocondensation reaction smoothly to provide the corresponding spiro[cyclohexane-1,2′-quinazolin]-4′(3′H)-one in good yield. The results are summarized in Table-1.

Choice of catalyst: From literature survey, it is realized that acids were used as a catalyst for synthesis of simple chromeno-pyrimidine-2,5-dione derivatives from 4-hydroxy coumarin, aromatic aldehyde, (thio)urea. Hence, it was decided to check the suitability of different acid as a catalyst for the synthesis of chromeno-pyrimidine-2,5-dione derivatives. Therefore, at first we started to study the formic acid (10 mol%) catalyzed one pot cyclocondensation of 4-hydroxy coumarin, aromatic aldehyde, (thio)urea of 10 mmol each as model reaction at reflux temperature using ethanol as solvent, it was found that the desired product 4-phenyl-3,4-dihydro-1*H*-chromeno[4,3-d]pyrimidine-2,5-dione (**4a**) was obtained with 23% of product

TABLE-1
SUBSTRATE SCOPE

Entry	Aldehyde (**3**)	Product (**4**)	Time (min)	Yield (%)
a			60	96
b			60	82
c			45	86
d			45	87
e			60	80
f			75	81
g			90	79
h			90	85
i			60	93
j			45	95

k			60	89
l			60	87
m			60	93

yield after 360 min. In order to achieving higher product yield, we performed the same reaction in oxalic acid by keeping in the mind that oxalic acid is stronger than formic acid, and then employed chloroacetic acid as catalyst and obtained unsatisfactory yield of 35% and 49%, respectively. Then we employed tannic acid as a catalyst, a satisfactory yield of 74% yield in 1 h was obtained. This observation made us to examine the reaction further by optimizing reaction conditions such as choice of solvent, temperature and catalyst load. It is also ascertained that the product yield was very low, when the same reaction was performed in the absence of catalyst for about 12 h (Table-2).

TABLE-2
SCREENING OF CATALYST*

Entry	Catalysts	Time (h)	Yield (%)
1	Formic acid	8	23
2	Oxalic acid	8	35
3	Chloroacetic acid	8	49
4	Tannic acid	2	74
5	No catalyst	12	Trace

*Reaction conditions: 4-hydroxy coumarin (10 mmol), benzaldehyde (10 mmol) and urea (10 mmol) using ethanol solvent.

Effect of solvent: In order to enhance the reaction viability and to check the effect of solvent, the cyclocondensation of 4-hydroxy coumarin (10 mmol), aromatic aldehyde (10 mmol), urea (10 mmol) using tannic acid as a catalyst in different solvent such as ethanol, methanol, acetone, dichloromethane, *etc*. was performed and realized that aqueous ethanol (EtOH: H_2O, 1:1, v/v) performed well and gave highest yield of 96% within 30 min. The results are summarized in Table-3.

Effect of mol% of catalyst: The investigation on effect of mol% of catalyst on cyclocondensation reaction was studied by employing 5, 10, 15 mol% of tannic acid, obtained results revealed that 10 mol% of the catalyst was more than enough to produce the highest yield of 95%. The increase in the catalyst load up to 15% of tannic acid by keeping other reaction parameter same did not alter the product yield significantly (Table-4).

Plausible mechanism: The carbonyl group (C=O) of aromatic aldehyde is polarized extensively by interaction with the catalyst (tannic acid). Polarized aromatic aldehyde reacts with urea by undergoing dehydrtion to form benzylideneurea (**4**), which is on interaction with 4-hydroxycoumarin forms an intermediate (**6**), this intermediate undergoes cyclization followed by dehydration to form the desired product (**8**) (**Scheme-II**).

TABLE-3
OPTIMIZATION OF SOLVENTS*

Entry	Solvents	Time (h)	Yield (%)
1	Ethanol	1	74
2	Methanol	2	55
3	Acetone	2.5	65
4	Dichloromethane	3	35
5	EtOH:H_2O (1:2)	1	81
6	EtOH:H_2O (1:1)	1	96
7	EtOH:H_2O (2:1)	1	76

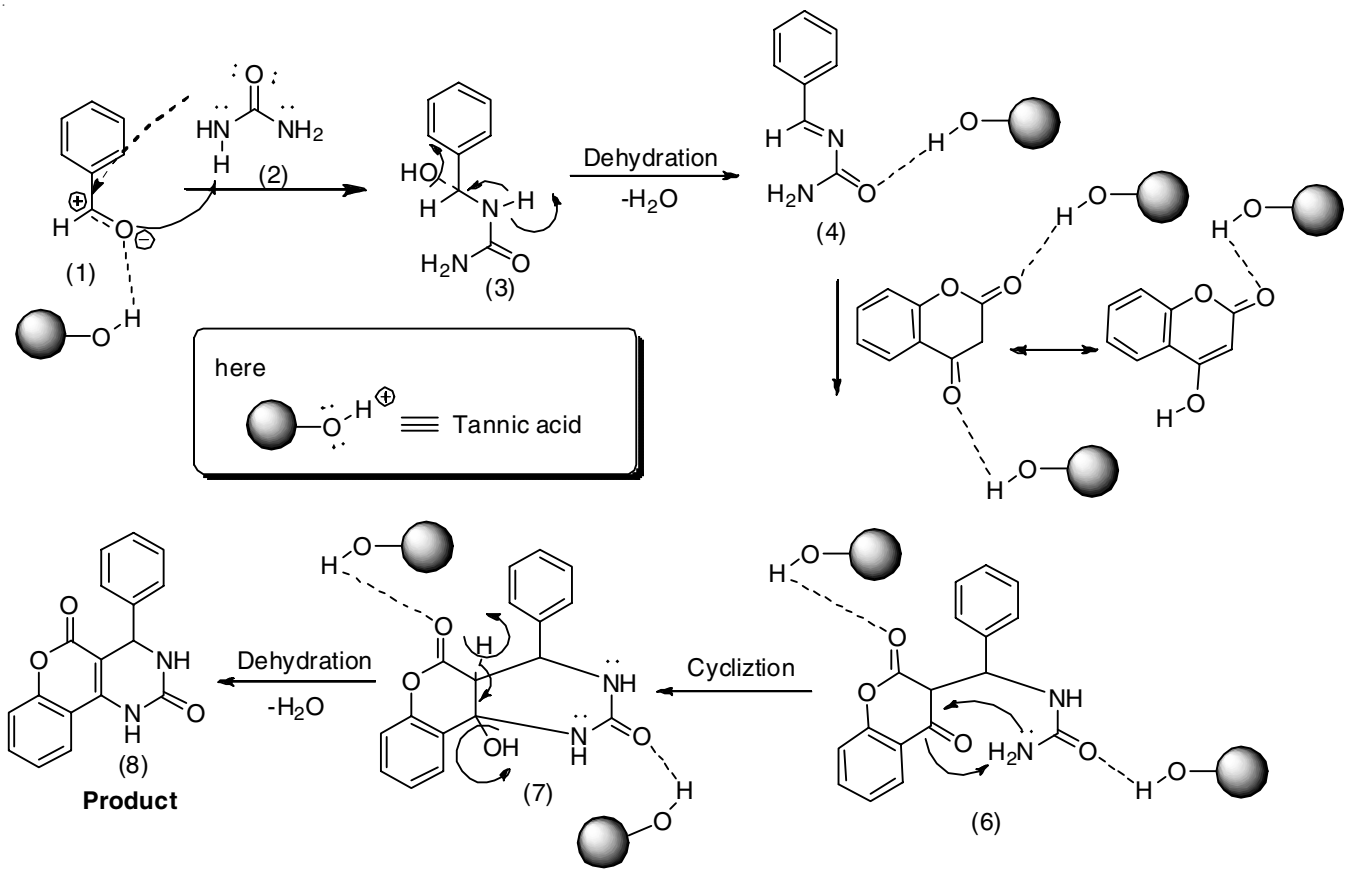
*Reaction conditions: 4-hydroxy coumarin (10 mmol), benzaldehyde (10 mmol) and urea (10 mmol) using tannic acid (10 mol%).

TABLE-4
OPTIMIZATION OF CATALYST LOAD*

Entry	Catalyst load (mol%)	Yield (%)
1	5	75
2	10	95
3	15	96

*Reaction conditions: 4-hydroxy coumarin (10 mmol), benzaldehyde (10 mmol) and urea (10 mmol) using 10 mL of 1:1 (EtOH:H_2O)

The presence of many hydroxyl group (-OH) in tannic acid makes it unique that the higher efficiency of tannic acid to accelerate this condensation attributes to its ability to act as dominant hydrogen-bond donor through hydroxyl group. Moreover, it was reported that central core of tannic acid has hydrophobic functional group and outer shell has hydrophilic hydroxyl group [34]. The enhanced reaction rate is due to the fact that non-polar organic reactants *viz*. hydroxycoumarin, benzaldehyde and urea are trapped easily inside the hydrophobic core of the catalyst, which ensures the close proximity and increased local concentrations of reactants inside the core, leads to better interaction between reactants and thereby the reaction rates improves significantly; hydrophilic outer shell containing hydroxyl groups helps in making hydrogen bonding. This



Scheme-II: Mechanism of the reaction

feature of the catalyst plays a key role in the synthesis of fused chromeno-pyrimidine-2,5-dione.

Conclusion

In this work, diversely functionalized chromeno-pyrimidine-2,5-dione/thione compounds were synthesized by cyclocondensation of 4-hydroxycoumarin, aldehydes and urea/thiourea using tannic acid as a green catalyst and 1:1 (EtOH:H_2O) as a green solvent. By utilizing this protocol, different fused chromeno-pyrimidine scaffolds were prepared in acceptable to excellent yield without the use of conventional volatile organic solvent and toxic metal catalyst.

ACKNOWLEDGEMENTS

This study was financially supported by student mini project grants (D.O.Rc.No.835/2019) from Tamil Nadu State Council for Higher Education (TNSCHE), Chennai, India.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

REFERENCES

1. G.P. Ellis and I.M. Lockhart, ed.: G.P. Ellis, The Chemistry of Heterocyclic Compounds: Chromenes, Chromanones and Chromones, Wiley-VCH: Weinheim, Germany, vol. 31 (2007).
2. L. Alvey, S. Prado, V. Huteau, B. Saint-Joanis, S. Michel, M. Koch, S.T. Cole, F. Tillequin and Y.L. Janin, *Bioorg. Med. Chem.*, **16**, 8264 (2008); https://doi.org/10.1016/j.bmc.2008.06.057
3. T. Symeonidis, M. Chamilos, J. Hadjipavlou-Litina, M. Kallitsakis and E. Litinas, *Bioorg. Med. Chem. Lett.*, **19**, 1139 (2009); https://doi.org/10.1016/j.bmcl.2008.12.098
4. J.L. Wang, D. Liu, Z.J. Zhang, S. Shan, X. Han, S.M. Srinivasula, C.M. Croce, E.S. Alnemri and Z. Huang, *Proc. Natl. Acad. Sci. USA*, **97**, 7124 (2000); https://doi.org/10.1073/pnas.97.13.7124
5. J.F. Cheng, A. Ishikawa, Y. Ono, T. Arrhenius and A. Nadzan, *Bioorg. Med. Chem. Lett.*, **13**, 3647 (2003); https://doi.org/10.1016/j.bmcl.2003.08.025
6. D. Gree, S. Vorin, L. Manthati, F. Caijo, G. Viault, F. Manero, P. Juin and R. Grée, *Tetrahedron Lett.*, **49**, 3276 (2008); https://doi.org/10.1016/j.tetlet.2008.03.070
7. W. Kemnitzer, S. Jiang, H. Zhang, S. Kasibhatla, C. Crogan-Grundy, C. Blais, G. Attardo, R. Denis, S. Lamothe, H. Gourdeau, B. Tseng, J. Drewe and S.X. Cai, *Bioorg. Med. Chem. Lett.*, **18**, 5571 (2008); https://doi.org/10.1016/j.bmcl.2008.09.011
8. M.M. Khafagy, A.H.F. Abd El-Wahab, F.A. Eid and A.M. El-Agrody, *Farmaco*, **57**, 715 (2002); https://doi.org/10.1016/S0014-827X(02)01263-6
9. M. Kidwai, S. Saxena, M.K.R. Khan and S.S. Thukral, *Eur. J. Med. Chem.*, **40**, 816 (2005); https://doi.org/10.1016/j.ejmech.2005.02.009
10. B. Sunil Kumar, N. Srinivasulu, R.H. Udupi, B. Rajitha, Y.T. Reddy, P. Narsimha Reddy and P.S. Kumar, *Russ. J. Org. Chem.*, **42**, 1813 (2006); https://doi.org/10.1134/S1070428006120098
11. R.R. Kumar, S. Perumal, P. Senthilkumar, P. Yogeeswari and D. Sriram, *Bioorg. Med. Chem. Lett.*, **17**, 6459 (2007); https://doi.org/10.1016/j.bmcl.2007.09.095

12. A.H. Bedair, N.A. El-Hady, M.S.A. El-Latif, A.H. Fakery and A.M. El-Agrody, *Farmaco*, **55**, 708 (2000); https://doi.org/10.1016/S0014-827X(00)00097-5
13. M.M. Heravi, K. Bakhtiari, V. Zadsirjan, F. Bamoharram and O.M. Heravi, *Bioorg. Med. Chem. Lett.*, **17**, 4262 (2007); https://doi.org/10.1016/j.bmcl.2007.05.023
14. C. Bruhlmann, F. Ooms, P. Carrupt, B. Testa, M. Catto, F. Leonetti, C. Altomare and A. Carotti, *J. Med. Chem.*, **44**, 3195 (2001); https://doi.org/10.1021/jm010894d
15. S.R. Kesten, T.G. Heffner, S.J. Johnson, T.A. Pugsley, J.L. Wright and L.D. Wise, *J. Med. Chem.*, **42**, 3718 (1999); https://doi.org/10.1021/jm990266k
16. O. Prakash, K. Hussain, R. Kumar, D. Wadhwa, C. Sharma and K.R. Aneja, *Org. Med. Chem. Lett.*, **1**, 5 (2011); https://doi.org/10.1186/2191-2858-1-5
17. J. Kempson, W.J. Pitts, J. Barbosa, J. Guo, O. Omotoso, A. Watson, K. Stebbins, G.C. Starling, J.H. Dodd, J.C. Barrish, R. Felix and K. Fischer, *Bioorg. Med. Chem. Lett.*, **15**, 1829 (2005); https://doi.org/10.1016/j.bmcl.2005.02.025
18. O. Bruno, C. Brullo, S. Schenone, F. Bondavalli, A. Ranise, M. Tognolini, M. Impicciatore, V. Ballabeni and E. Barocelli, *Bioorg. Med. Chem.*, **14**, 121 (2006); https://doi.org/10.1016/j.bmc.2005.07.066
19. A.V. Ivachtchenko, E.S. Golovina, M.G. Kadieva, A.G. Koryakova, S.M. Kovalenko, O.D. Mitkin, I.M. Ravnyeyko, S.E. Tkachenko, I.M. Okun and O.V. Zaremba, *Bioorg. Med. Chem.*, **18**, 5282 (2010); https://doi.org/10.1016/j.bmc.2010.05.051
20. S.A. Said, A.E.-G. Amr, N.M. Sabry and M.M. Abdalla, *Eur. J. Med. Chem.*, **44**, 4787 (2009); https://doi.org/10.1016/j.ejmech.2009.07.013
21. J.D. Brown, eds.: A.R. Katrizky and C.W. Rees, Comprehensive Heterocyclic Chemistry, Pergamon: Oxford, vol. 3, p. 57 (1984).
22. K.N. Mohana, B.N. Prasanna Kumar and L. Mallesha, *Drug Invention Today*, **5**, 216 (2013); https://doi.org/10.1016/j.dit.2013.08.004
23. C. Heidelberger, eds.: J.F. Holland and E. Frei, Pyrimidine and Pyrimidine Antimetabolites in Cancer Medicine, Lea and Febiger: Philadelphia, p. 801 (1984).
24. 24 M.S. Kaurav, P.K. Sahu, P.K. Sahu, M. Messali, S.M. Almutairi, P.L. Sahu and D.D. Agarwal, *RSC Adv.*, **9**, 3755 (2019); https://doi.org/10.1039/C8RA07517D
25. Y. Liu, S. Liu, Y. Shi, M. Qin, Z. Sun and G. Liu, *Xenobiotica*, **48**, 818 (2018); https://doi.org/10.1080/00498254.2017.1361051
26. S.S. Rathore, S.K. Agarwal, S. Pande, S.K. Singh, T. Mittal and B. Mittal, *PLoS One*, **7**, e37844 (2012); https://doi.org/10.1371/journal.pone.0037844
27. J.H. Prochaska, S. Göbel, K. Keller, M. Coldewey, A. Ullmann, H. Lamparter, C. Jünger, Z. Al-Bayati, C. Baer, U. Walter, C. Bickel, H. ten Cate, T. Münzel and P.S. Wild, *BMC Med.*, **13**, 14 (2015); https://doi.org/10.1186/s12916-015-0268-9
28. V. Rodriguez-Cerrato, G. Del Prado, L. Huelves, P. Naves, V. Ruiz, E. Garcia, C. Ponte and F. Soriano, *Int. J. Antimicrob. Agents*, **35**, 544 (2010); https://doi.org/10.1016/j.ijantimicag.2010.02.007
29. C. Hou, Y. Wang, H. Zhu and H. Wei, *J. Taiwan Inst. Chem. Eng.*, **60**, 438 (2016); https://doi.org/10.1016/j.jtice.2015.11.005
30. A. Sandhar, D.N. Prasad and R.K. Singh, *Asian J. Chem.*, **24**, 5643 (2012).
31. R.K. Singh and R. Duvedi, *Arab. J. Chem.*, **11**, 91 (2018); https://doi.org/10.1016/j.arabjc.2014.08.022
32. J. Zhang, D. Ren, Y. Ma, W. Wang and H. Wu, *Tetrahedron*, **70**, 5274 (2014); https://doi.org/10.1016/j.tet.2014.05.059
33. C. Capello, U. Fischer and K. Hungerbuhler, *Green Chem.*, **9**, 927 (2007); https://doi.org/10.1039/b617536h
34. J.C. Isenburg, N.V. Karamchandani, D.T. Simionescu and N.R. Vyavahare, *Biomaterials*, **27**, 3645 (2006); https://doi.org/10.1016/j.biomaterials.2006.02.016