



***p*-Toluene-sulfonic Acid-catalyzed One-pot, Three-component Synthesis of 4-(4-(Piperidin-1-yl)phenyl)-2-Thioxo-1,2,3,4-Tetrahydro-5H-Chromeno[4,3-d]Pyrimidin-5-One**

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ABSTRACT

Here we communicate a method for the synthesis of 4-(4-(piperidin-1-yl)phenyl)-2-thioxo-1,2,3,4-tetrahydro-5H-chromeno[4,3-d]pyrimidin-5-one in one step. The compound was prepared by reacting 4-hydroxy-coumarin, 4-piperidinobenzaldehyde, and thiourea in a catalytic quantity of *p*-toluenesulfonic acid. The novelty of the compound was checked by Sci-finder. The compound was analyzed by NMR spectroscopy (¹H, ¹³C), and mass spectrometry. The computational studies indicate that the synthesized compound possesses suitable physicochemical properties, drug-likeness features, and good oral bioavailability.

Keywords: Chromeno[4,3-d]pyrimidine, Piperidine, *p*-Toluenesulfonic acid.

INTRODUCTION

Pyrimidines have a special place in chemistry because of their antibacterial, antiviral, antifungal, anticancer, analgesic, properties CNS depressants¹⁻⁷. The multicomponent reactions (MCR) have emerged as a safe, efficient, inexpensive, ecofriendly, tool for the synthesis of drugs⁸⁻¹⁰. The piperidine ring is also considered an important moiety among medicinal chemists due to its diverse therapeutic effects ((analgesic, antihypertensive, CNS depressant antiviral, and

bactericidal activity)¹¹⁻¹⁶. *p*-Toluene sulfonic acid (*p*-TSA) is a well-known catalyst in organic synthesis because of its non-toxic/eco-friendly nature, selectivity, easy handling, commercial availability, less cost, and stability¹⁷⁻³⁰. Accordingly, the authors decided to perform the titled study.

MATERIAL AND METHODS

General

The Stuart melting point apparatus was used to determine the melting points of the



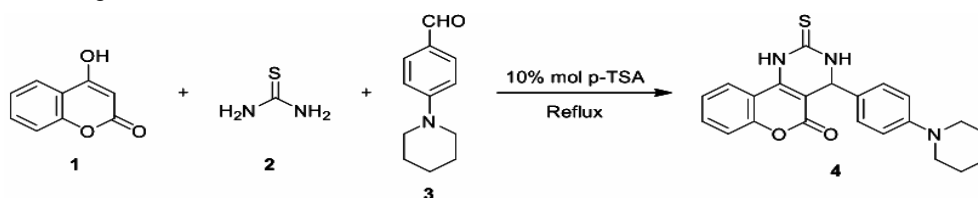
compounds ($^{\circ}\text{C}$). The Shimadzu 440 spectrometer (IR in KBr, ν in cm^{-1}), JEOL ECA-500 spectrometer (NMR spectrum, δ in ppm), and the microanalytical device (elemental analysis) were used for obtaining the spectral data of the compound.

Preparation of 4-(4-(piperidin-1-yl)phenyl)-2-thioxo-1,2,3,4-tetrahydro-5H-chromeno[4,3-d]pyrimidin-5-one (4)

A mixture of 4-hydroxycoumarin 1 (0.01 mol, 1.62 g) and thiourea (0.01 mol, 0.76 g), 4-piperidinobenzaldehyde 3 (0.01 mol, 1.89 g), and *p*-TSA (10 mol%) in ethanol (20 mL) was refluxed for 3 hours. After completion of the reaction, the obtained product was collected, washed with ethanol, then recrystallized from dioxane to afford the product 4 in 93% yield (Scheme 1). Yield 3.63 g (93%); m.p. 173-175 $^{\circ}\text{C}$ (dioxane); IR (KBr, cm^{-1}): 3153 (NH), 3069 (arom.-CH), 1693 (C=O); ^1H NMR (500 MHz, DMSO-d_6 , δ /ppm): 1.57 (brs, 2H, piperidine-H), 1.75 (brs, 4H, piperidine-H), 3.12 (brs, 4H, piperidine-H), 6.13 (s, 1H, pyrimidine-H), 6.98-7.44 (m, 8H, Ar-H), 7.68 (s, 2H, 2NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 23.18, 28.88, 56.46, 58.57, 103.87, 116.04, 118.76, 122.02, 124.19, 128.38, 132.94, 136.64, 153.78, 164.95, 168.18. MS m/z (relative intensity%): 392 ($\text{M}^+ + 2$, 35), 391 (M^+ , 81), 343 (86), 307 (66), 283 (60), 333 (100), 255 (92). Elemental Analysis: C, 67.50; H, 5.41; N, 10.73. Found: C, 67.32; H, 5.26; N, 10.58.

Computational studies

The physicochemical and bioavailability radar of compound 4 was determined by employing Swiss-ADME software³¹. The chemical structure of compound 4 was inserted in the software and the software was run to obtain the data. The physicochemical property (Table 1) and the bioavailability radar of the compound are provided in Figure 1.



Scheme 1. Synthesis of compound 4

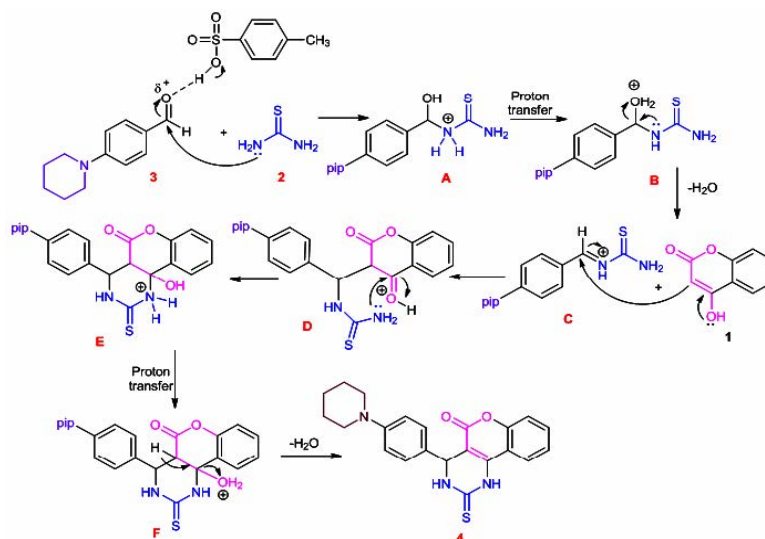
RESULTS AND DISCUSSION

Chemistry

Refluxing of 4-hydroxycoumarin 1 with 4-piperidinobenzaldehyde 3 and thiourea in absolute ethanol in the presence of *p*-toluenesulfonic acid gave the 4-(4-(piperidin-1-yl)phenyl)-2-thioxo-1,2,3,4-tetrahydro-5H-chromeno[4,3-d]pyrimidin-5-one 4 (Scheme 1). The reaction product was isolated in a 93% yield. The molecular structure of the reaction product was established by spectral data.

The IR spectrum of compound 4 displayed the presence of an amino group at 3215 cm^{-1} , a carbonyl group at 1693 cm^{-1} . The ^1H -NMR of 4 displayed the presence of three broad singlets at δH 1.57, 1.75, 3.12 for piperidine protons, δH 6.13 for pyrimidine-H, 7.68 for two-imino groups, and the aromatic protons (Ar-H) were found in the spectrum at δH 6.98-7.44. ^{13}C -NMR (DMSO-d_6) showed signals at δC 168.18 assigned to the thiocarbamoyl group, δC 164.95 assigned to the carbonyl group, 153.78 ppm assigned to C-O, in addition to aromatic carbons at δC 103.87-136.64 ppm, δC at 58.57 ppm assigned to the pyrimidine-C, and δC at 23.18, 28.88, 56.46 ppm assigned to the piperidine-C. The mass spectrum of compound 4 showed a molecular ion peak at $m/z=391$ (81%) and the base peak in the spectrum was found at $m/z=333$.

The mechanistic route to the formation of reaction product 4 was depicted in Scheme 2. Firstly, thiourea 2 reacts with 4-piperidinobenzaldehyde 3 in the presence of *p*-TSA to give the intermediate A which undergoes loss of water molecule in two steps to give the non-isolable N-acyl-thioiminium ion C. Secondly, Michael's addition of 4-hydroxycoumarin 1 to the intermediate C gave the Michael adduct D which undergoes intramolecular cyclization and aromatization via elimination of water molecule to yield the final product 4 (Scheme 2).



Scheme 2. Mechanism of reaction

Computational studies

The computational Physico-chemical data of compound 4 exhibits that it has moderate water solubility, and moderate lipophilicity. This compound also follows Lipinski's rule indicating its potential to convert into a drug provided it shows potential biological activity. If used as a drug,

compound 4 will be orally bioavailable, and will not cross the blood-brain barrier (Fig. 1). The red line in Fig. 1 indicates that compound 4 has all the required physicochemical characteristics for good bioavailability. Accordingly, the biological activity evaluation of compound 4 is under investigation in our laboratory.

Table 1: Swiss ADME data of compound 2

Consensus Log Po/w	Solubility in water	Drug-likeness	Synthetic accessibility	GI absorption	BBB permeant
3.39	Moderate	Follows Lipinski rule	Good	High	No

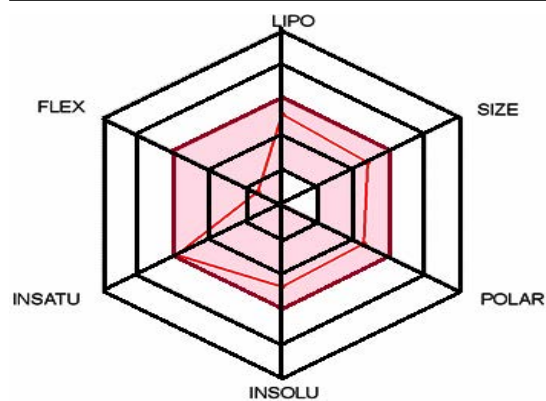


Fig. 1. Oral bioavailability radar of compound 4

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Conflicts of interest

The author declares no conflict of interest.

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