SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF 3-(2-(5-AMINO-1H-PYRAZOL-4-YL) THIAZOL-4-YL)-2H-CHROMEN-2-ONE AND ITS DERIVATIVES

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ABSTRACT

A simple and convenient method for the preparation of 3-(2-(5-amino-1H-pyrazole-4-yl)thiazol-4-yl)-2H-chromene-2-one and 3-(2-(5-amino-3-methyl-1H-pyrazole-4-yl)thiazol-4-yl)-2H-chromene-2-ones (**3a-f** and **5a-f**) have been prepared in good yields. The compounds have been synthesized from 2-(4-(2-oxo-2H-chromene-3-yl)thiazol-2-yl)acetonitrile (**1a-f**), with DMF-DMA, DMA-DMA and hydrazine hydrochloride in ethanol resulted in the formation of title compounds. In this regard the whole compounds were tested for promising antibacterial activity, characterized by analytical and spectral data.

Keywords: Coumarin, Thiazole, Pyrazole, Thiazolyl-pyrazoles, Cyclisation reaction.

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INTRODUCTION

Thiazolyl-pyrazole¹ derivatives have been shown remarkable therapeutic applications in medicinal chemistry and pharmaceutical chemistry. Previously, thiazoles were synthesized in the year 1887 by Hantzsch and Weber. These are a significant set of heterocyclics, to establish in a lot of active drugs such as Sulfathiazole (antimicrobial), Abafungin (antifungal), Tiazofurin (antineoplastic) and Ritonavir (antiretroviral). Hence, it is present in many compounds, it shows important biological activities such as antihypertensive¹, antimicrobial, antifungal², anticancer³, anti-inflammatory⁴, anti-HIV⁵, antidiabetic⁶, and anticonvulsant⁷ activities. Pyrazoles are an essential class of heterocyclics in medicinal chemistry, which represent the basic frame-work of drugs such as Celecoxib and as well studied heterocyclic compounds with huge therapeutic value⁸. Consequently, many pyrazoles have been displayed a variety of biological activities⁹⁻¹³ such as antitubercular, antiviral, antitumor and anticancer properties. All these derivatives have been considered as adaptable building blocks and intermediates. The earlier study reports as well derived from coumarin.¹⁴⁻¹⁵ During this protocol we have developed the latest heterocyclic systems on 3rd position of coumarin.

Coumarin derivatives are widely distributed in several drugs, and the literature study reports of entire coumarin derivatives shown important biological activities among them are anti-microbial,¹⁶⁻¹⁷ antifungal,¹⁸ anti-inflammatory,¹⁹ anticancer,²⁰⁻²¹ anti-tubercular,²² and antitumor activity.²³ The earlier literature work reveals that the synthesis of different kind of heterocyclic systems derived from coumarin.¹⁴⁻¹⁵ It appears to be valuable to synthesize a few coumarin containing derivatives of 3-(2-(5-amino-1H-pyrazole-4-yl)thiazol-4-yl)-2H-chromene-2-one and 3-(2-(5-amino-3-methyl-1H-pyrazole-4-yl)thiazol-4-yl)-2H-chromene-2-one. In view that herein we report the synthesis and antibacterial activity of title compounds and its derivatives.

EXPERIMENTAL

Materials and Methods

All the chemicals were purchased from viable sources, used without purification. The prepared materials were checked by TLC on silica plates (E-Merk, Mumbai, India). Melting points were checked with an open capillary tube with a “Centex” melting point apparatus, Mumbai, India and were uncorrected. IR spectra were recorded in KBr pellets on a Bruker WM-200 MHz spectrometer. ^1H - and ^{13}C -NMR spectra were documented on a Bruker WM-400 spectrometer (in δ ppm) using TMS as an internal standard. The mass spectra (EI-MS) were determined by Jeol-D-300 spectrometer at 70 eV. CHN analyses were recorded on Carlo Erba 1108 Heraeus analyzer. The 3-(2-bromoacetyl)chromen-2-ones were prepared by reported procedures¹⁵ which on further reaction with thioacetamide in ethanol to gave 2-(4-(2-oxo-2H-chromene-3-yl)thiazol-2-yl)acetonitrile (**1a-f**).

Synthesis of (E)-3-(dimethylamino)-2-(4-(2-oxo-2H-chromene-3-yl)thiazol-2-yl)acrylonitrile(**2a-f**)

A mixture of 2-(4-(2-oxo-2H-chromene-3-yl)thiazol-2-yl)acetonitrile **1a-f** (1 mmol), N,N-Dimethyl formamide dimethyl acetal (DMF-DMA) (1.5 mmol) in toluene was refluxed for 2 hours. Then the reaction mixture was checked by TLC, after completion of reaction the solvent was distilled out and added hexane to get the crude solid, was filtered, dried and recrystallized from Hexane/EtOAc.

(E)-3-(dimethylamino)-2-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)acrylonitrile **2a**

Brown solid. Yield 90%. m.p. 253 – 255⁰C. IR (KBr): 1607 (C=N), 1720 (lactone, C=O) cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6): δ 2.84 (s, 6H, 2-CH₃), 6.86 (s, 1H, C=CH), 7.32-7.48 (m, 2H, Ar-H of C₆& C₈-H), 7.64 (m, 1H, Ar-H of C₇-H), 7.78 (d, 1H, C₅-H of Ar-H, J = 9 Hz), 8.16 (s, 1H, C₅'-H of thiazole), 8.68 (s, 1H, C₄-H of coumarin); ^{13}C NMR (400 MHz, DMSO- d_6): δ 45.4, 86.8, 116.5, 118.6, 121.4, 124.2, 125.8, 127.8, 128.5, 129.5, 149.2, 156.7, 158.9, 164.6, 166.5, MS: m/z 323. Anal. Calcd for C₁₇H₁₃N₃O₂S: C, 63.14; H, 4.05; N, 12.99. Found: C, 63.10; H, 4.02; N, 12.96%.

Synthesis of 3-(2-(5-amino-1H-pyrazole-4-yl)thiazol-4-yl)-2H-chromene-2-one(**3a-f**)

To a solution of (E)-3-(dimethylamino)-2-(4-(2-oxo-2H-chromene-3-yl)thiazol-2-yl)acrylonitrile **2a-f** (1 mmol), in ethanol was added hydrazine hydrochloride (1 mmol) was refluxed for 8 hours. After that checked the reaction mixture by TLC, then solvent was distilled out under reduced pressure to get the residue to this added methyl tertiary butyl ether and filtered insoluble material. This organic layer was washed with 10% NaOH solution, followed by dil.HCl and water. This was dried in sodium sulfate and concentrated on getting the crude compound was recrystallized from toluene/EtOAc.

Spectral Characterization

3-(2-(5-Amino-1H-pyrazol-4-yl)thiazol-4-yl)-2H-chromen-2-one **3a**

White solid. Yield 86%. m.p. 260 – 262⁰C. IR (KBr): 1607 (C=N), 1719 (lactone, C=O) and 3418 (pyrazole, -NH) cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6): δ 5.41 (br, 2H, -NH₂), 7.34-7.46 (m, 2H, Ar-H of C₇& C₈-H), 7.61 (m, 1H, Ar-H of C₆-H), 7.74 (d, 1H, C₅-H of Ar-H, J = 9 Hz), 7.79 (s, 1H, NH Pyrazole), 8.11 (s, 1H, C₅'-H of thiazole), 8.68 (s, 1H, C₄-H of coumarin); ^{13}C NMR (400 MHz, DMSO- d_6): δ 91.3, 116.9, 121.4, 124.1, 125.8, 127.8, 128.5, 129.5, 132.9, 134.8, 146.0, 149.6, 153.9, 156.7, 166.5, MS: m/z 310. Anal. Calcd for C₁₅H₁₀N₄O₂S: C, 58.05; H, 3.25; N, 18.05. Found: C, 58.01; H, 3.21; N, 18.01%.

3-(2-(5-amino-1H-pyrazol-4-yl)thiazol-4-yl)-8-methoxy-2H-chromen-2-one **3b**

White solid. Yield 84%. m.p. 255 – 257⁰C. IR (KBr): 1608 (C=N), 1721 (lactone, C=O) and 3416 (pyrazole, -NH) cm^{-1} ; ^1H NMR (400 MHz, DMSO- d_6): δ 3.89 (s, 3H, OCH₃), 5.46 (br, 2H, -NH₂), 7.21-7.36 (m, 2H, Ar-H of C₇& C₆-H), 7.63 (d, 1H, C₅-H of Ar-H), 7.79 (s, 1H, NH Pyrazole), 8.12 (s, 1H, C₅'-H of thiazole), 8.64 (s, 1H, C₄-H of coumarin); ^{13}C NMR (400 MHz, DMSO- d_6): δ 91.3, 116.9, 121.4, 124.1, 125.8, 127.8, 128.5, 129.5, 132.9, 134.8, 146.0, 149.6, 153.9, 156.7, 166.5, MS: m/z 340. Anal. Calcd for C₁₆H₁₂N₄O₃S: C, 56.46; H, 3.55; N, 16.46. Found: C, 56.41; H, 3.51; N, 16.42%.

3-(2-(5-amino-1H-pyrazol-4-yl)thiazol-4-yl)-6-chloro-2H-chromen-2-one 3c

White solid. Yield 80%. m.p. 267 – 269⁰C. IR (KBr): 1606 (-C=N), 1720 (lactone, -C=O) and 3421 (pyrazole, -NH) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 5.51 (br, 2H, -NH₂), 7.36-7.56 (m, 2H, Ar-H of C₇& C₈-H), 7.79 (d, 1H, C₅-H of Ar-H, *J* = 9 Hz), 7.81 (s, 1H, NH Pyrazole), 8.21 (s, 1H, C₅'-H of thiazole), 8.61 (s, 1H, C₄-H of coumarin).

3-(2-(5-amino-1H-pyrazol-4-yl)thiazol-4-yl)-6,8-dichloro-2H-chromen-2-one 3d

White solid. Yield 81%. m.p. 260 – 262⁰C. IR (KBr): 1605 (-C=N), 1723 (lactone, -C=O) and 3410 (pyrazole, -NH) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 5.41 (br, 2H, -NH₂), 7.61 (d, 1H, *J* = 1Hz, C₇-H of Coumarin), 7.88 (d, 1H, C₅-H of Ar-H, *J* = 9 Hz), 8.10 (s, 1H, NH Pyrazole), 8.34 (s, 1H, C₅'-H of thiazole), 8.66 (s, 1H, C₄-H of coumarin).

3-(2-(5-amino-1H-pyrazol-4-yl)thiazol-4-yl)-6-bromo-2H-chromen-2-one 3e

White solid. Yield 84%. m.p. 268 – 270⁰C. IR (KBr): 1608 (-C=N), 1720 (lactone, -C=O) and 3414 (pyrazole, -NH) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 5.45 (br, 2H, -NH₂), 7.31-7.45 (m, 2H, Ar-H of C₇& C₈-H), 7.76 (d, 1H, C₅-H of Ar-H, *J* = 9 Hz), 7.78 (s, 1H, NH Pyrazole), 8.46 (s, 1H, C₅'-H of thiazole), 8.71 (s, 1H, C₄-H of coumarin).

3-(2-(5-amino-1H-pyrazol-4-yl)thiazol-4-yl)-6,8-dibromo-2H-chromen-2-one 3f

White solid. Yield 80%. m.p. 263 – 265⁰C. IR (KBr): 1610 (-C=N), 1723 (lactone, -C=O) and 3421 (pyrazole, -NH) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 5.43 (br, 2H, -NH₂), 7.65 (d, 1H, *J* = 1Hz, C₇-H of Coumarin), 7.80 (d, 1H, C₅-H of Ar-H, *J* = 9 Hz), 7.91 (s, 1H, NH Pyrazole), 8.31 (s, 1H, C₅'-H of thiazole), 8.71 (s, 1H, C₄-H of coumarin).

Synthesis of (E)-3-(dimethylamino)-2-(4-(2-oxo-2H-chromene-3-yl)thiazol-2-yl)but-2-enenitrile(4a-f)

A mixture of 2-(4-(2-oxo-2H-chromene-3-yl)thiazol-2-yl)acetonitrile **1a-f** (1 mmol), N,N-Dimethyl acetamide dimethyl acetal (DMA-DMA) (1.5 mmol) in toluene was refluxed for 2 hours. Then the reaction mixture was checked by TLC, after completion of reaction the solvent was distilled out and added hexane to get the crude solid, which was filtered, dried and recrystallized from hexane/EtOAc.

(E)-3-(dimethylamino)-2-(4-(2-oxo-2H-chromen-3-yl)thiazol-2-yl)but-2-enenitrile 4a

Brown solid. Yield 88%. m.p. 258 – 260⁰C. IR (KBr): 1608 (-C=N), 1721 (lactone, -C=O) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.23 (s, 3H, -CH₃), 3.45 (s, 6H, N(CH₃)₂), 7.44-7.60 (m, 2H, Ar-H of C₆& C₈-H), 7.66 (m, 1H, Ar-H of C₇-H), 7.8 (d, 1H, C₅-H of Ar-H, *J* = 9 Hz), 8.46 (s, 1H, C₅'-H of thiazole), 8.66 (s, 1H, C₄-H of coumarin); ¹³C NMR (400 MHz, DMSO-*d*₆): δ 20.141.4, 78.6, 116.4, 120.6, 124.4, 125.7, 127.5, 128.5, 129.5, 149.2, 164.2, 166.1, 168.0, MS: *m/z* 337. Anal. Calcd for C₁₈H₁₅N₃O₂S: C, 64.08; H, 4.48; N, 12.45. Found: C, 64.04; H, 4.45; N, 12.41%.

Synthesis of 3-(2-(5-amino-3-methyl-1H-pyrazole-4-yl)thiazol-4-yl)-2H-chromene-2-one(5a-f)

To a solution of (E)-3-(dimethylamino)-2-(4-(2-oxo-2H-chromene-3-yl)thiazol-2-yl)but-2-enenitrile **4a-f** (1 mmol), in ethanol was added hydrazine hydrochloride (1 mmol) was refluxed for 8 hours. After that reaction mixture was checked by TLC, then solvent was distilled out under reduced pressure to get the residue to this added methyl tertiarybutylether and filtered insoluble material. This organic layer was washed with 10% NaOH solution, followed by dil.HCl and water. This was dried in sodium sulphate and concentrated to get the crude compound was recrystallized from toluene/EtOAc.

3-(2-(5-amino-3-methyl-1H-pyrazol-4-yl)thiazol-4-yl)-2H-chromen-2-one 5a

Brown solid. Yield 86%. m.p. 271 – 273⁰C. IR (KBr): 1610 (-C=N), 1722 (lactone, -C=O) and 3420 (pyrazole, -NH) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.34 (s, 3H, -CH₃), 5.46 (br, 2H, -NH₂), 7.34-7.46 (m, 2H, Ar-H of C₇& C₈-H), 7.60 (m, 1H, Ar-H of C₆-H), 7.76 (d, 1H, C₅-H of Ar-H, *J* = 9 Hz), 7.8

(s, 1H, NH Pyrazole), 8.36 (s, 1H, C₅'-H of thiazole), 8.71 (s, 1H, C₄-H of coumarin); ¹³C NMR (400 MHz, DMSO-*d*₆): δ 13.26, 94.3, 116.4, 121.4, 124.3, 125.8, 127.8, 128.5, 129.3, 139.8, 146.0, 149.5, 153.9, 156.7, 166.8, MS: *m/z* 324. Anal. Calcd for C₁₆H₁₂N₄O₂S: C, 59.25; H, 3.73; N, 17.27. Found: C, 59.21; H, 3.70; N, 17.24%.

3-(2-(5-amino-3-methyl-1H-pyrazol-4-yl)thiazol-4-yl)-8-methoxy-2H-chromen-2-one5b

White solid. Yield 80%. m.p. 273 – 275°C. IR (KBr): 1609 (-C=N), 1720 (lactone, -C=O) and 3410 (pyrazole, -NH) cm⁻¹; ¹H NMR (400 MHz, DMSO-*d*₆): δ 2.36 (s, 3H, CH₃), 3.86 (s, 3H, OCH₃), 5.46 (br, 2H, -NH₂), 7.31-7.47 (m, 2H, Ar-H of C₇ & C₆-H), 7.64 (d, 1H, C₅-H of Ar-H), 7.74 (s, 1H, NH Pyrazole), 8.10 (s, 1H, C₅'-H of thiazole), 8.67 (s, 1H, C₄-H of coumarin); ¹³C NMR (400 MHz, DMSO-*d*₆): δ 13.28, 56.2, 91.3, 113.9, 121.4, 123.3, 124.4, 126.9, 129.6, 139.2, 146.2, 149.7, 153.6, 156.7, 166.8, MS: *m/z* 354. Anal. Calcd for C₁₇H₁₄N₄O₃S: C, 57.62; H, 3.98; N, 15.81. Found: C, 57.58; H, 3.94; N, 15.78%.

RESULTS AND DISCUSSION

In the present protocol, the title compounds have been prepared unlike the literature methods; we synthesized the title compounds **3** & **5** in two steps without using cyclization reagent. This reaction takes place here to expand the scope of synthetic transformation and offer a convenient method for 3-(2-(5-amino-1H-pyrazol-4-yl)thiazol-4-yl)-2H-chromene-2-one and its derivatives. The title compounds (**3,5**) have been synthesized from (Step-1) readily available starting materials like 2-(4-(2-oxo-2H-chromene-3-yl)thiazol-2-yl)acetonitrile (**1a-f**), with DMF-DMA/DMA-DMA in toluene resulted as uncyclized compounds **2, 4** which on further reaction with hydrazine hydrochloride in ethanol given the title compounds of Scheme-1 and 2.

The yields of products (Scheme-1 and 2) are 80-90%. The entire synthesized materials were characterized by analytical and spectral data for various representative compounds **2a, 4a**, and **3a-f, 5a-b** have given. The IR spectra of compound **2a** confirmed prominent peaks at 1608 (-C=N), 1720 (lactone, -C=O), cm⁻¹, in the ¹H NMR spectra six protons appears as a singlet around δ 2.84 for two methyl groups, -C=CH proton is appeared as a singlet at δ 6.86. The mass spectrum of **2a** confirmed the molecular ion at *m/z* 323. The IR spectra of compound **3a** confirmed prominent peaks 1607 (-C=N), 1719 (lactone, -C=O), 3418 (pyrazole, -NH) cm⁻¹, consistent with the assigned structures. The ¹H NMR (DMSO-*d*₆) spectrum of

3a confirmed signals around δ 5.41 (b, 2H, NH₂), 7.34-7.46 (m, 2H, Ar-H), 7.61(m, 1H, of C₆-H coumarin), 7.74 (d, 1H, Ar-H of C₅-H), 7.79 (s, 1H, NH of pyrazole), 8.1 (s, 1H, C₅'-H of thiazole) and 8.68 (s, 1H, C₄-H coumarin), in the mass spectrum **3a** confirmed the molecular ion peak at m/z 310 (100%).

The IR spectra of compounds **4a** confirmed prominent peaks at 1606 (-C=N), 1721 (lactone, -C=O), cm⁻¹, in the ¹H NMR spectra =CCH₃ protons appear as a singlet at δ 2.86, the remaining six protons appeared at δ 3.46 as a singlet. The mass spectrum of **4a** confirmed the molecular ion at m/z 337. The IR spectra of compounds **5a** showed prominent peaks 1610 (-C=N), 1722 (lactone, -C=O), 3420 (pyrazole, -NH) cm⁻¹, consistent with the assigned structures. The ¹H NMR (DMSO-*d*₆) spectrum of **5a** confirmed signals around δ 2.34 (s, 3H, -CH₃), 5.46 (b, 2H, NH₂), 7.34-7.46(m, 2H, Ar-H), 7.60 (m, 1H, of C₆-H coumarin), 7.76 (d, 1H, Ar-H of C₅-H), 7.8 (s, 1H, NH of pyrazole), 8.36 (s, 1H, C₅'-H of thiazole) and 8.68 (s, 1H, C₄-H coumarin), in the mass spectrum **5a** confirmed the molecular ion peak at m/z 324 (100%).

Biological Activity

Antibacterial Activity

The entire prepared compounds (Table-1) **3a-f** and **5a-f** were screened for antibacterial activity by using agar well diffusion method²⁴ against bacterial species (Gram-positive and Gram-negative) were cultured on nutrient agar plates at 37⁰C. A plate containing 20 ml of nutrient agar was spread with 100 μ l of culture. Ciprofloxacin has been used as a standard drug for the evaluation of antibacterial activity. Compounds in table-1, **3a, b, c** and **5a, b, c** were found to be active for all bacterial strains. While the substitution of chloro groups at the 6th position of coumarin gives satisfactory results. In the case of Gram-positive bacteria methoxy group at 8th position, coumarin increases the bacterial activity of the compounds. In the case of Gram-negative bacteria substitution of a methoxy grouping at the 8th position of coumarin decreases the antibacterial activity of compounds.

Table-1: Antibacterial Activity Data of Compounds **3a-f** and **5a-f**

Compound	Conc. (μ g/ml)	Antibacterial Activity Diameter of Zone of Inhibition (in mm)			
		S.aureus	B.subtilis	E. coli	S.paratyphib
3a	100	17	18	16	15
b	100	19	20	17	16
c	100	18	19	20	19
d	100	15	18	14	16
e	100	11	10	12	13
f	100	16	14	15	16
5a	100	17	18	17	18
b	100	20	20	16	15
c	100	17	19	18	19
d	100	10	14	13	16
e	100	13	16	12	11
f	100	12	15	17	14
Ciprofloxacin (Stand.)	100	20	20	25	25

CONCLUSION

This protocol mostly describes the antibacterial activity for title compounds (3a-f and 5a-f) and its derivatives. Some of these synthesized compounds (3a, b, c and 5a, b, c) have been confirmed a wide range of potentially promising antibacterial activity. The remarkable lead of this procedure are good yields (80-90%), little reaction times, fair reaction conditions, easy workup procedure, and finally simple preparation and using without a catalyst for the cyclization.

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