# SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL EVALUTION OF TRAIZOLE-PYRIMIDINE AND TETRAZOLE-PYRIMIDINE DERIVATIVES

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**Abstract**

The 3-(5-(5-substituted furan-2-yl)-3-thioxo-2,3,7,8-tetrahydro-[1,2,4] triazolo [4,3-a]pyrimidin-7-yl)-2H-chromen-2-one (2a-c), 5-(5- substituted furan-2-yl)-7-(2-oxo-2H-chromen-3-yl)-7,8-dihydro-[1,2,4] triazolo [4,3-a] pyrimidin-3(2H)-one (3a-c) and 3-(7-(5- substituted furan-2-yl)-4,5-dihydro tetrazole [1,5-a] pyrimidin-5-yl)-2H-chromen-2-one (4a-c) were synthesised by reaction of 3-(6-(5-substitutd furan-2-yl)-2-hydrazinyl-1,4-dihydropyrimidin-4-yl)-2H-chromen-2-one (1a-c) with $CS_2$/Pyridine, ClCOOEt / Pyrimidine and $NaNO_2$/HCl respectiverly. All these synthesised derivatives were characterized by elemental and spectral analysis. All the derivatives were also monitored for antimicrobial activity.

**Key words:** Coumarin, Triazolo-pyrimidine, tetrazole-pyrimidine, Spectral analysis, and Antimicrobial evalution.

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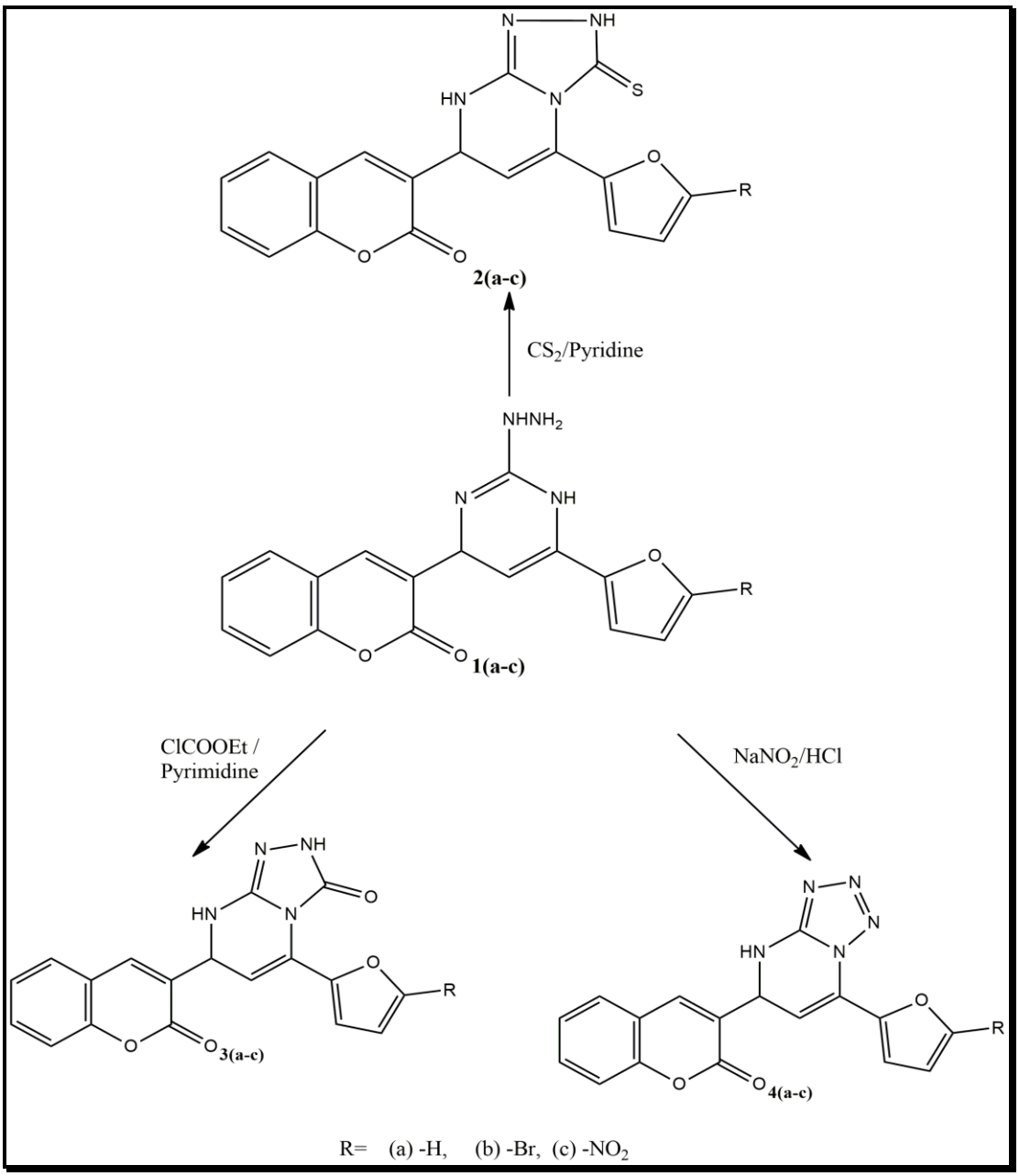
## Introduction

Coumarins fused with other heterocyclic derivatives are reported for their antioxidant, anti-HIV, anti-tumor, anticancer, anti-microbial, anti-asthmatic, anti-viral and many other activities [1-13]. The present work was carried out the various reactions on 3-(6-(5-substitutd furan-2-yl)-2-hydrazinyl-1,4-dihydropyrimidin-4-yl)-2H-chromen-2-one. The reagent such as $CS_2$/pyridine, ClCOOEt/ pyridine and $NaNO_2$/HCl were used. The synthetic route is shown below. All the derivatives characterized duly and studied their antimicrobial activity.

## Experimental

3-(6-(5-substitutd furan-2-yl)-2-hydrazinyl-1,4-dihydropyrimidin-4-yl)-2H-chromen-2-one (1a-c) were prepared by reported in our earlier communication [8,9]. Melting points were determined in open capillary tubes and were uncorrected. The IR spectra were recorded in KBr pellets on a Nicolet 400D spectrometer and $^1$H NMR spectra were acquired at 400 MHz on a Bruker NMR spectrometer using DMSO–d6 as a solvent as well as TMS an internal reference standard. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046.




**Scheme-1 Reaction steps**

***Synthesis of 3-(5-(5-substituted furan-2-yl)-3-thioxo-2,3,7,8-tetrahydro-[1,2,4] triazolo [4,3-a]pyrimidin-7-yl)-2H-chromen-2-one (2a-c)***

A mixture of 3-(6-(5-substitutd furan-2-yl)-2-hydrazinyl-1,4-dihydropyrimidin-4-yl)-2H-chromen-2-one (1a-c) (0.05 mol) and $CS_2$ (0.1mol) in pyridine (25 mL) was refluxed for 4hrs. Cool the reaction mixture, and then added to ice water mixture. The precipitate formed was filtered, dried and recrystallized from ethanol to afford (2a-c). The yields, melting points and other characterization data of these compounds are given in Table-1.

**Table: - 1 Elemental analysis of (2a-c), (3a-c) and (4a-c) derivatives**

| Compd. | Molecular formula Mol.wt. | LC-MS Data (m/z) | Yield % | M.P.* $^0$C | Elemental Analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | %C | % H | %N | %S | %Br |
| | | | | | Calcd. Found | Calcd. Found | Calcd. Found | Calcd. Found | Calcd. Found |
| **2a** | $C_{18}H_{12}N_4O_3S$ 364 | 364.8 | 67 | 183 | 59.33 59.3 | 3.32 3.3 | 15.38 15.3 | 8.80 8.7 | - |
| **2b** | $C_{18}H_{11}N_4O_3SBr$ 442 | 443.0 | 64 | 177 | 48.77 48.7 | 2.50 2.4 | 12.64 12.6 | 7.23 7.2 | 18.03 18.0 |
| **2c** | $C_{18}H_{11}N_5O_5S$ 409 | 410.2 | 60 | 195 | 52.81 52.7 | 2.71 2.7 | 17.11 17.1 | 7.83 7.8 | - |
| **3a** | $C_{18}H_{12}N_4O_4$ 348 | 348.7 | 71 | 206 | 62.07 62.0 | 3.47 3.4 | 16.09 16.0 | - | - |
| **3b** | $C_{18}H_{11}N_4O_4Br$ 426 | 427.1 | 65 | 200 | 50.61 50.6 | 2.60 2.5 | 13.11 13.1 | - | 18.70 18.6 |
| **3c** | $C_{18}H_{11}N_5O_6$ 393 | 393.9 | 68 | 211 | 54.97 54.9 | 2.82 2.8 | 17.81 17.8 | - | - |
| **4a** | $C_{17}H_{11}N_5O_3$ 333 | 333.8 | 69 | 220 | 61.26 61.2 | 3.33 3.3 | 21.01 21.0 | - | - |
| **4b** | $C_{17}H_{10}N_5O_3Br$ 411 | 412.2 | 63 | 203 | 49.54 49.5 | 2.45 2.4 | 16.99 16.9 | - | 19.38 19.3 |
| **4c** | $C_{17}H_{10}N_6O_5$ 378 | 379.0 | 59 | 227 | 53.97 53.9 | 2.66 2.6 | 22.22 22.2 | - | - |

***** Uncorrected

***Synthesis of 5-(5- substituted furan-2-yl)-7-(2-oxo-2H-chromen-3-yl)-7,8-dihydro-[1,2,4] triazolo [4,3-a] pyrimidin-3(2H)-one (3a-c)***

To 3-(6-(5-substitutd furan-2-yl)-2-hydrazinyl-1,4-dihydropyrimidin-4-yl)-2H-chromen-2-one (1a-c) (0.05 mol) in pyridine (25 mL) was added ClCOOEt (0.05 mol). The reaction mixture was refluxed for 3.5 hrs. After cooling, the solid formed was filtered, dried and recrystalized from toluene to obtained 5-(5- substituted furan-2-yl)-7-(2-oxo-2H-chromen-3-yl)-7,8-dihydro-[1,2,4] triazolo [4,3-a] pyrimidin-3(2H)-one (3a-c). The yields, melting points and other characterization data of these compounds are given in Table -1.

**Synthesis of 3-(7-(5- substituted furan-2-yl)-4,5-dihydro tetrazole [1,5-a] pyrimidin-5-yl)-2H-chromen-2-one (4a-c)**

A solution of sodium nitrite in water (0.05 mol) was added to a solution of 3-(6-(5-substitutd furan-2-yl)-2-hydrazinyl-1,4-dihydropyrimidin-4-yl)-2H-chromen-2-one (1a-c) (0.05 mol) in concentrated HCl (12 mL) at 0 °C over a period of 15 mins with constant stirring. The solid formed was filtered, dried and recrystallized from toluene to afford 3-(7-(5- substituted furan-2-yl)-4,5-dihydro tetrazole [1,5-a] pyrimidin-5-yl)-2H-chromen-2-one (4a-c). The yields, melting points and other characterization data of these compounds are given in Table -1.

**Biological Screening**

The antibacterial activities of all the compounds of three series were studied against gram-positive bacteria (*Staphylococcus aureus and Bacillus subtilis*) and gram-negative bacteria (*E.coli, and klebsiella promioe*) at a concentration of 50µg/ML by agar cup plate method [16-18]. A methanol system was used as control in this method. Similar conditions using tetracycline as a control was used as standard for comparison. The area of inhibition of zone was measured in mm. Compounds 4c, 3c and 2c were found more toxic for microbes. Other compounds found to be less or moderate active shown in Tables -2.

**Table: - 2 Antibacterial Activity of Compounds (2a-c), (3a-c) and (4a-c)**

| Compounds | Gram +Ve | | Gram –Ve | |
|---|---|---|---|---|
| | ***Bacillus subtilis*** | ***Staphylococcus aureus*** | ***Klebsiella promioe*** | ***E. coli*** |
| **2a** | 9 | 11 | 9 | 9 |
| **2b** | 11 | 12 | 11 | 10 |
| **2c** | 13 | 14 | 13 | 13 |
| **3a** | 8 | 10 | 8 | 7 |
| **3b** | 10 | 11 | 10 | 9 |
| **3c** | 11 | 13 | 12 | 11 |
| **4a** | 8 | 11 | 10 | 10 |
| **4b** | 12 | 12 | 10 | 11 |
| **4c** | 13 | 13 | 12 | 11 |
| **Tetracycline** | 13 | 15 | 15 | 14 |

The fungicidal activity of all the compounds of three series was studied at 1000 ppm concentration in vitro. Plant pathogenic organisms used were *Aspergillus niger, Botrydepladia thiobromine, Nigrospora Sp, and Fusarium oxyporium*. The antifungal activities of all the compounds were measured on each of these plant pathogenic strains on a potato dextrose agar (PDA) medium. Such a PDA medium contained potato 200g, dextrose 20g, agar 20g and water 1c. Five days old cultures were employed. The compounds to be tested were suspended (1000ppm) in a PDA medium and autoclaved at 120$^{o}$ C for 15 min. at 15atm. pressure. These media were poured into sterile Petri plates and the organisms were inoculated after cooling the Petri plates. Fluconazole was used as standard. The percentage inhibition for fungi was calculated after five days using the formula given below:

**Percentage of inhibition = 100(X-Y) / X**

Where, X = Area of colony in control plate

Y = Area of colony in test plate

Compounds 4c, 3c and 2c were found more toxic for microbes. Other compounds found to be less or moderate active shown in Tables -4.

**Table: - 3 Antifungal Activity of Compounds (2a-c), (3a-c) and (4a-c)**

| **Zone of Inhibition at 1000 ppm (%)** | | | | |
|---|---|---|---|---|
| **Compounds** | ***Aspergillus Niger*** | ***Botrydepladia Thiobromine*** | ***Nigrospora Sp.*** | ***Fusarium oxyporium*** |
| **2a** | 50 | 54 | 58 | 60 |
| **2b** | 70 | 64 | 69 | 65 |
| **2c** | 74 | 65 | 70 | 66 |
| **3a** | 49 | 52 | 56 | 59 |
| **3b** | 68 | 62 | 67 | 63 |
| **3c** | 70 | 60 | 68 | 62 |
| **4a** | 50 | 53 | 57 | 60 |
| **4b** | 72 | 63 | 68 | 64 |
| **4c** | 71 | 64 | 69 | 66 |
| **Fluconazole** | 95 | 93 | 94 | 92 |

## Results and Discussion

The 3-(5-(5-substituted furan-2-yl)-3-thioxo-2,3,7,8-tetrahydro-[1,2,4] triazolo [4,3-a]pyrimidin-7-yl)-2H-chromen-2-one (2a-c) have been synthesized by the reaction of 3-(6-(5-substitutd furan-2-yl)-2-hydrazinyl-1,4-dihydropyrimidin-4-yl)-2H-chromen-2-one (1a-c) with $CS_2$. The structures of (2a-c) were confirmed by elemental analysis and IR(KBr,$cm^{-1}$) spectra showing an absorption band at 3070-3020 (–C–H aromatic st.), 2930,2860(C-H str.), 1670 (–C=N st.), 1600-1500 (conjugated C=C),1540 (–C=C–st.),1240(–N–N=C–st.),1675-1640 (C=O), 1120 (C-O-C), 3465-3450(-NH), 1070(C-Br),1530, 1375 (-$NO_2$). $^1$H NMR (DMSO–$d_6$,δ ppm): 7.45–8.00 (m, 5H, Ar–H), 4.02(d, 1H, –CH), 6.25(d,1H,=CH), 4.22,7.84 (s,2H,-NH) and (a) 7.90-6.95 (m, 3H, furan),(b) 6.60-6.50 (m, 2H, furan) and (c) 7.60-7.15 (m, 2H, furan). The C, H, N analysis data of all compounds are presented in Table -1.

The Synthesis of 5-(5- substituted furan-2-yl)-7-(2-oxo-2H-chromen-3-yl)-7,8-dihydro-[1,2,4] triazolo [4,3-a] pyrimidin-3(2H)-one (3a-c) have

been synthesized by the reaction 3-(6-(5-substitutd furan-2-yl)-2-hydrazinyl-1,4-dihydropyrimidin-4-yl)-2H-chromen-2-one (1a-c) with ClCOOEt. The structures of (3a-c) were confirmed by elemental analysis and IR(KBr,$cm^{-1}$) spectra showing an absorption band at 3065-3030(–C–H aromatic st.), 2930,2860(C-H str.), 1650 (–C=N st.), 1590-1500 (conjugated C=C),1540(–C=C– st.),1230(–N–N=C–st.),1660-1640 (C=O),1250(C=S), 1120 (C-O-C), 3465-3450(-NH), 1060(C-Br),1530, 1375 (-$NO_2$). $^1$H NMR (DMSO–$d_6$,δ ppm):7.45–8.00(m,5H,Ar–H),4.02(d, 1H, –CH), 6.25 (d,1H, =CH), 4.22,8.00 (s,2H,-NH) and (a) 7.90-6.95 (m, 3H, furan),(b) 6.60-6.50 (m, 2H, furan) and (c) 7.60-7.15 (m, 2H, furan). The C, H, N analysis data of all compounds are presented in Table -1.

The Synthesis of Synthesis of 3-(7-(5- substituted furan-2-yl)-4,5-dihydro tetrazole [1,5-a] pyrimidin-5-yl)-2H-chromen-2-one (4a-c) have been synthesized by the reaction 3-(6-(5-substitutd furan-2-yl)-2-hydrazinyl-1,4-dihydropyrimidin-4-yl)-2H-chromen-2-one (1a-c) with sodium nitrite/HCl. The structures of (4a-c) were confirmed by elemental analysis and IR(KBr,$cm^{-1}$) spectra showing an absorption band at 3060-3020 (–C–H aromatic st.), 2930,2865(C-H str.), 1660(–C=N st.),1590-1500(conjugated C=C),1545(–C=C–st.),1230(–N–N=C–st.), 1670-1640 (C=O),1120 (C-O-C), 3455(-NH), 1060(C-Br),1530, 1375 (-$NO_2$). $^1$H NMR (DMSO–$d_6$,δ ppm): 7.45–8.00 (m, 5H, Ar–H), 4.02(d, 1H, –CH), 6.28 (d,1H,=CH), 5.30(s,1H,-NH) and (a) 7.80-6.55 (m, 3H, furan),(b) 6.60-6.45 (m, 2H, furan) and (c) 7.60-7.10 (m, 2H, furan). The C, H, N analysis data of all compounds are presented in Table -1.

The examination of elemental analytical data reveals that the elemental contents are consistent with the predicted structure shown in Scheme-1. The IR and NMR spectral data also direct for assignment of the predicted structure. The final structure of all compounds is confirmed by LC-MS. LC-MS data of all compounds are presented in Tables.

## References

[1] M. Zhu, L. Ma, J. Wen, B. Dong, Y. Wang, Z. Wang, J. Zhou,G. Zhang, J. Wang, Y. Guo, C. Liang, S. Cen, Y. Wang, Eur. J.Med. Chem. **186**, 111900 (2020)

[2] Y.-P. Liu, G. Yan, Y.-T. Xie, T.-C. Lin, W. Zhang, J. Li, Y.-J.Wu, J.-Y. Zhou, Y.-H. Fu, Bioorg. Chem. **97**, 103699 (2020)

[3] J.-W. Zhao, Z.-H. Wu, J.-W. Guo, M.-J. Huang, Y.-Z. You,H.-M. Liu, L.-H. Huang, Eur. J. Med. Chem. **181**, 111520(2019)

[4] M.-H. Lin, J.-S. Wang, Y.-C. Hsieh, J.-H. Zheng, E.-C. Cho, Chem.-Biol. Interact. **309**, 108708 (2019)

[5] M. Sanduja, J. Gupta, H. Singh, P.P. Pagare, A. Rana, J. Saudi Chem. Soc. **24**, 251 (2020)

[6] L.K.A.M. Leal, A.H. Silva, G.S. de Barros Viana, Rev. Bras.Farmacogn. **27**, 794 (2017)

[7] M.Z. Hassan, H. Osman, M. Ashraf Ali, M. Jawed Ahsan, Eur.J. Med. Chem. **123**, 236 (2016)

[8] S. Massari, G. Nannetti, J. Desantis, G. Muratore, S. Sabatini, G. Manfroni, B. Mercorelli, V. Cecchetti, G. Palu, G. Cruciani, A. Loregian, L. Goracci, O. Tabarrini, *J. Med. Chem*.,**58**, 3830–3842(2015).

[9] F. S. Sabra, M. S. Mahmoud, *Asian J. Agric Food Sci.,* **3**, 103–108(2015).

[10] D. A. Pyatakov, A. N. Sokolov, A. V. Astakhov, A. Chernenko, A. Yu, A. N. Fakhrutdinov, V. B. Rybakov, V. V. Chernyshev, V. M. Chernyshev, *J. Org. Chem.*, **80**, 10694–10709(2015).

[11] A. M. Gamal-Eldeen, N. A. Hamdy, H. A. Abdel-Aziz, E. A. El-Hussieny, I. M. I. Fakher, *Eur. J. Med. Chem*.,**77**, 323–333(2014).

[12] P J Shah; H S Patel and B P Patel, *Journal of Saudi Chemical Society*,**17**,307 (2013).

[13] Standard Test method for Determinating the Antimicrobial activity of Anti-microbial agents under Dynamic contact conditions,ASTM-E2149-20,USA(2020).