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PTSA CATALYZED AN EFFICIENT SYNTHESIS OF NOVEL THIAZOLO [3,2-A]PYRIMIDINONE DERIVATIVES AND THEIR BIOLOGICAL EVALUATION

Banoth Sonyanaik,[1] Boda Sakram*[1] and Kudle karunakar Rao[2]

[1]*Department of Chemistry, Osmania University, Hyderabad-500007, Telangana, India*
[2]*Department of Biochemistry, Osmania University, Hyderabad-500007, Telangana, India*
**Email: bschemou@gmail.com*

ABSTRACT: A highly proficient protocol has been enlarged for the construction of thiazolo[3,2-a]pyrimidinone scaffolds in the presence of *p*-toluenesulfonic acid involving 7-phenyl-10-thioxo-7,9,10,11-tetrahydro-8H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-ones with chloroacetic under reflux conditions analytically pure products are furnished with good yields. All these newly synthesized compounds were confirmed by their spectral data IR, ^{1}H-NMR, Mass spectral data and elemental analyses. All these compounds **(8a-i)** were screened for their systemic biological evaluation of antibacterial and fungal activities among them compounds **8g** and **8b** showed highest antibacterial and antifungal activity.

KEYWORDS: Thiazolo[3,2-a]pyrimidinone, PTSA, 2-chloroacetic acid, Antimicrobial activity.

INTRODUCTION

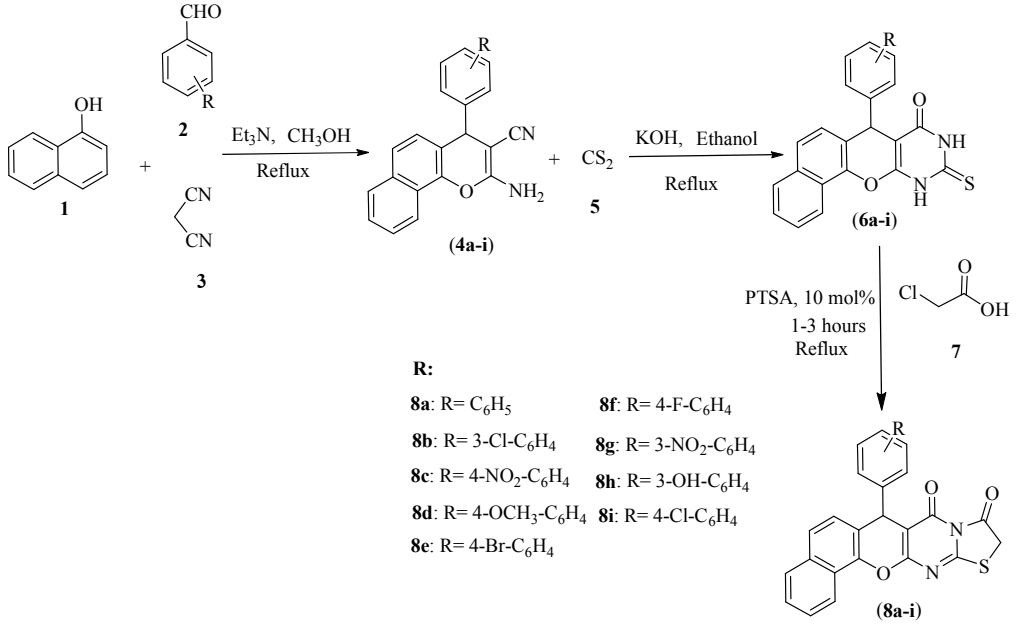
The thiazolo[3,2-a]pyrimidinone interior is a fashionable motif in medicinal chemistry and has been implicated in biological activity in a variety of therapeutic components and thiazolo[3,2-a]pyrimidinone scaffolds continue to attract a synthetic organic researchers and industrialists owing to their great practical efficacy and wide spectrum of their beneficial biological activities such as antimicrobial[i, ii] anti-inflammatory[iii] antioxidant[iv] antiviral[v] anticonvulsant[vi] antitumour[vii] anti-nociceptive[viii] anti-parkinsonian[ix] and anti-biofilm properties [x].

Due to these remarkably extensive pharmacological properties a variety of synthetic procedure have been reported in the literature for the construction of thiazolo[3,2-a]pyrimidinone derivatives concerning the cyclization of dihydropyrimidin-thiones with electrophilic building blocks for example 2-chloroacetic acid [iii, iv, x, xi] bromoacetic acid[vii, ix] chloroacetyl chloride [xii] methyl 2-chloroacetate[xiii] 2-haloacetamides [xiv]. Most of these methods utilize bases such as sodium acetate, triethylamine, and potassium hydroxide and Abbas *et al*.[xv] have reported a regioselective isocyanide-based three-component reaction for the synthesis of thiazolo[3,2-a]pyrimidinone derivatives at ambient temperature and Recently Janardhan *et al* [xvi] reported synthesis of fused thiazolo[3,2-a]pyrimidinones in acetic acid solvent. In continuation, of our previous studies on the development eco-freiendly

methodologies and biologically active compounds [xvii-xiv] Here in, we report the utilization of 2-chloroacetic acid as the source of building blocks for the ring annulation of 7-phenyl-10-thioxo-7,9,10,11-tetrahydro-8H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-one to furnished thiazolo[3,2-a] pyrimidinone scaffolds in the presence of a PTSA formed desired products with excellent yields 84-89%. To the best of our knowledge no report has been made about the use of *p*-toluenesulfonic acid as catalyst for the preparation of these compounds **(8a-i)**.

RESULTS AND DISCUSSIONS

The representation for the construction of chromeno [2,3-d]thiazolo[3,2-a]pyrimidinone derivatives **(8a-i)** has shown in **Scheme 1**. The intermediate 2-amino-4-phenyl-4H-benzo[h]chromene-3-carbonitrile **(4a–i)** were synthesized via three-component condensation of a-napthol (**1**), various aromatic aldehyde (**2**) and malanonitrile (**3**) utilizing triethylamine as catalyst under conventional method obtained desired products (**4a-i**) with good yields then carbon disulfide (**5**) reacted with 2-amino-4-phenyl-4H-benzo[h]chromene-3-carbonitrile derivatives in the presence of 10% KOH formed products (**6a-i)** with excellent yields.



Scheme-1: Synthesis of fused chromeno[2,3-d]thiazolo[3,2-a]pyrimidinone derivatives catalyzed by PTSA.

To get the desired products (8a–i) we carried out a model reaction to take equimolar quantities of 7-phenyl-10-thioxo-7,9,10,11-tetrahydro-8H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-one (**6**) and 2-chloroacetic acid (**7**) in 5 mL of acetic acid. As per the literature, we expected the product to be the thiazolo[3,2-a]pyrimidine (8a); on the other hand, the product obtained was identified as the thiazolo[3,2-a]pyrimidinone (8a) based on analytical and spectral data. The product 8a was obtained in only low yield (68%) in acetic acid even after12 hour reflux. In try to improve the yield of product 8a, the above reactions were carried out in the presence of PTSA 5 mole % obtained 72 % yield. Later, the same reaction was carried out in presence of 10 mol% *p*-toluenesulfonic acid observing maximum yield (88 %) of the product (8a) in acetic acid within 3 hours. By adopting the above optimized (10 % PTSA, 120 ^{O}C, acetic acid) reaction conditions, we have synthesized a new series of thiazolo[3,2-a]pyrimidinone derivatives is shown in Table 1.

Table 1 Synthesis of thiazolo[3,2-a]pyrimidinone derivatives catalyzed by PTSA

Analog	Aryl	Time (h)	Yield (%)[a]	Melting points (^{o}C)
8a	Benzaldehyde	1.5	74	182
8b	3-Chlorobenzaldehyde	1.0	78	215
8c	4-Nitrobenzaldehyde	1.5	70	227
8d	4-Methoxybenzaldehyde	2.5	82	185
8e	4-Bromobenzaldehyde	3.0	86	302
8f	4-Fluorobenzaldehyde	2.5	81	233
8g	3-Nitrobenzaldehyde	1.5	72	204
8h	3-Hydroxybenzaldehyde	3.0	82	297
8i	4-Chlorobenzaldehyde	2.5	82	201

[a]Isolated yields of the pure compounds

EXPERIMENTAL

All the solvents and chemicals were purchased from Aldrich/Fisher and used without further purification. The melting points were determined on a Buchi melting point apparatus and are uncorrected. The progresses of the reaction as well as the purity of the compounds were checked by using F254 silica-gel pre-coated TLC plates. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on a Bruker 400 MHz using DMSO-d_6 as solvent and TMS as internal standard and mass spectra were obtained using a Jeol JMSD-400 spectrometer. Elemental analyses were performed on a Carlo-Erba model EA1108 analytical unit and the values are ± 0.4% of theoretical values.

Antibacterial activity: The synthesized compounds were evaluated for their in vitro antibacterial activity using agar well diffusion technique according to the literature procedure[xx] Streptomycin was used as standard drugs for comparison. We tested against representative Gram-positive organisms such as *Staphylococcus epidermidis, Bacillus subtilis* and Gram-negative organisms such as *Escherichia coli* and *Klebsiella pneumonia.* All the synthesized compounds exhibit moderate antibacterial activity among them compounds **8g** and **8b** showed highest antibacterial activity against all the tested organisms.

Table-2: Antibacterial activity data at concentration used 250 µg/mL of DMSO.

Compounds	*S. epidermidis*	*B. Subtilis*	*E. coli*	*K. pneumoniae*
8a	14	12	11	13
8b	**18**	**17**	**18**	**16**
8c	19	18	20	18
8d	14	16	14	13
8e	13	15	11	12
8f	15	13	16	12
8g	**17**	**21**	**19**	**20**
8h	16	22	13	12
8i	14	12	15	13
Streptomycin	21	23	21	25

Anti fungal activity: All these synthesized compounds were tested for their *in-vitro* antifungal activity against the fungal strains *Candida Metapsilosis*, *Saccharomyces cerevisiae*, *Aspergillus niger* and *Aspergillus flavus* by agar well diffusion method[xxi] at the concentration 250 µg/mL compared with standard reference drug Mycostatin. All products

exhibited moderate to high inhibition activity against the tested fungal strains among them compounds **8g** and **8b** showed excellent antifungal activity shown in **Table 3**.

Table -3: Antifungal activity of compounds (**8a–i)** at concentration used 250 µg/mL of DMSO.

Compounds	*C. Metapsilosis*	*S. cerevisiae*	*Aspergillus niger*	*Aspergillus flavus*
8a	12	9	13	14
8b	**18**	**16**	**20**	**17**
8c	14	12	11	13
8d	15	17	12	14
8e	13	12	14	11
8f	15	14	16	13
8g	**19**	**17**	**20**	**19**
8h	14	12	15	14
8i	15	17	14	16
Mycostatin	**24**	**22**	**25**	**22**

General procedure for the synthesis of 2-amino-4-phenyl-4H-benzo[h]chromene-3-carbonitrile (4a-i)

A mixture of α-naphthol **1** (1 mmol, 0.144mg), aromatic aldehydes **2** (1 mmol), malononitrile **3** (3 mmol) and added catalytic amount of triethylamineas then reflux 4-6 hours. After completion of the reaction (monitored by TLC) the mixture was poured into ice cold water and The solid separated out was filtered, washed with water, and recrystallized from methanol obtained pure yields

General procedure for the synthesis of 7-phenyl-10-thioxo-7,9,10,11-tetrahydro-8H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-one (6a-i)

A mixture of 2-amino-4-phenyl-4H-benzo[h]chromene-3-carbonitrile **4** (1 mmol) added to CS_2 (1 mmol) in the presence of 10% KOH reflux 3-5 hours monitored by TLC after completion of the reaction poured into cold water and separated solid layer and recrystalised from methanol obtained pure products **(6a-k).** Yields of the products varied between 80-89%.

General procedure for synthesis of chromeno[2,3-d]thiazolo[3,2-a]pyrimidinone derivatives (8a-i)

A mixture of an appropriately substituted 7-phenyl-10-thioxo-7,9,10,11-tetrahydro-8H-benzo[7,8]chromeno[2,3-d]pyrimidin-8-one **6** (1 mmol) and 2-chloroacetic acid **7** (1 mmol) and 10% PTSA was mixed with 10 mL of glacial acetic acid and the mixture stirred at reflux temperature for 1-2 hours. After completion of the reaction (monitored by TLC), the reaction mixture was kept aside overnight. During this time, the crude thiazolo[3,2-a]pyrimidinone product separated out as a solid, and was filtered and quenched three times with 10 mL of cold acetic acid. All the compounds were purified by recrystallization from acetic acid then obtained pure products (**8a-i).**

7-phenyl-11-hydro-7H,8H-benzo[7,8]chromeno[2,3-d]thiazolo[3,2-a]pyrimidine-8,10-dione (8a)

IR (KBr): 1716 cm^{-1} (C=O), 1634 cm^{-1} (C=N), 1598 cm^{-1} (C=C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21- 8.10 (d, J = 7.4 Hz, 2H), 7.98 (d, J = 7.6 Hz, 2H), 7.82 (s, 1H), 7.75-7.38 (m, 5H), 7.31 (m, 1H), 4.91 (s, 1H), 4.24 (s, 2H). MS (m/z): 398.07 (M+H). (Found: C, 70.13; H, 3.14; N, 7.24. $C_{23}H_{14}N_2O_3S$ requires C, 69.33; H, 3.54; N, 7.03)

7-(3-chlorophenyl)-11-hydro-7H,8H-benzo[7,8]chromeno[2,3-d]thiazolo[3,2-a]pyrimidine-8,10-dione (8b)

IR (KBr): 1721 cm^{-1} (C=O), 1637 cm^{-1} (C=N), 1584 cm^{-1} (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.17- 8.09 (d, J = 7.2 Hz, 2H), 7.81 (s, 1H), 7.73 (m, J = 7.6 Hz, 4H), 7.61-7.51

(m, 3H), 7.46 (m, 1H), 4.95 (s, 1H), 4.13 (s, 2H). MS (m/z): 432.03 (M+H). (Found: C, 63.56; H, 3.14; N, 6.63. $C_{23}H_{13}ClN_2O_3S$ requires C, 63.82; H, 3.03; N, 6.47)

7-(4-nitrophenyl)-11-hydro-7H,8H-benzo[7,8]chromeno[2,3-d]thiazolo[3,2 a]pyrimidine-8,10-dione (8c)

IR (KBr): 1720 cm^{-1} (C=O), 1635 cm^{-1} (C=N), 1598 cm^{-1} (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 8.21- 8.16 (d, J = 7.4 Hz, 2H), 8.09 (m, 3H), 7.72 (s, 1H), 7.59-7.42 (m, 4H), 4.96 (s, 1H), 4.13 (s, 2H). MS (m/z): 443.06 (M+H). (Found: C, 62.48; H, 3.12; N, 9.74. $C_{23}H_{13}N_3O_5S$ requires C, 62.30; H, 2.96; N, 9.48)

7-(4-methoxyphenyl)-11-hydro-7H,8H-benzo[7,8]chromeno[2,3-d]thiazolo[3,2-a]pyrimidine-8,10-dione (8d)

IR (KBr): 1718 cm^{-1} (C=O), 1631 cm^{-1} (C=N), 1592 cm^{-1} (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 8.14 (d, J = 7.2 Hz, 2H), 7.98 (s, 1H), 7.72 (m, 2H), 7.48 (m, 2H), 4.95 (s, 1H), 4.07 (s, 2H), 3.87 (s, 3H). MS (m/z): 428.08 (M+H). (Found: C, 67.82; H, 3.49; N, 6.85. $C_{24}H_{16}N_2O_4S$ requires C, 67.28; H, 3.76; N, 6.54)

7-(4-bromophenyl)-11-hydro-7H,8H-benzo[7,8]chromeno[2,3-d]thiazolo[3,2-a]pyrimidine-8,10-dione (8e)

IR (KBr): 1722 cm^{-1} (C=O), 1630 cm^{-1} (C=N), 1594 cm^{-1} (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 8.21- 8.16 (d, J= 6.8 Hz 2H), 8.01 (m, 3H), 7.97 (s, 1H), 7.46 (d, 2H), 7.38 (d, J = 7.2 Hz, 2H), 4.95 (s, 1H), 4.03 (s, 2H). MS (m/z): 475.98 (M+H). (Found: C, 57.42; H, 2.58; N, 5.96. $C_{23}H_{13}BrN_2O_3S$ requires C, 57.87; H, 2.75; N, 5.87)

7-(4-fluorophenyl)-11-hydro-7H,8H-benzo[7,8]chromeno[2,3-d]thiazolo[3,2-a]pyrimidine-8,10-dione (8f)

IR (KBr): 1718 cm^{-1} (C=O), 1629 cm^{-1} (C=N), 1589 cm^{-1} (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 8.21- 8.19 (d, J= 7.4 Hz, 2H), 8.04 (d, J = 7.6 Hz, 2H), 7.82 (m, 3H), 7.61 (m, 1H), 7.49 (d, J = 7.2 Hz, 2H), 4.84 (s, 1H), 4.03 (s, 2H). MS (m/z): 416.06 (M+H). (Found: C, 66.65; H, 3.38; N, 6.86. $C_{23}H_{13}FN_2O_3S$ requires C, 66.34; H, 3.15; N, 6.73)

7-(3-nitrophenyl)-11-hydro-7H,8H-benzo[7,8]chromeno[2,3-d]thiazolo[3,2-a]pyrimidine-8,10-dione (8g)

IR (KBr): 1724 cm^{-1} (C=O), 1635 cm^{-1} (C=N), 1598 cm^{-1} (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 8.22- 8.18 (d, J = 7.6 Hz, 2H), 8.14 (d, J = 7.2 Hz, 2H), 7.97 (m, 5H), 7.86 (m, 1H), 4.96 (s, 1H), 4.02 (s, 2H). MS (m/z): 443.06 (M+H). (Found: C, 62.47; H, 2.75; N, 9.29. $C_{23}H_{13}N_3O_5S$ requires C, 62.30; H, 2.96; N, 9.48)

7-(3-hydroxyphenyl)-11-hydro-7H,8H-benzo[7,8]chromeno[2,3-d]thiazolo[3,2-a]pyrimidine-8,10-dione (8h)

IR (KBr): 1724 cm^{-1} (C=O), 1635 cm^{-1} (C=N), 1598 cm^{-1} (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 9.19 (s, 1H), 7.81 (d, J = 7.4 Hz, 2H), 7.78 (m, 3H), 7.13 (d, 2H), 6.87 (s, 1H), 6.54 (d, J = 6.8 Hz, 2H), 4.82 (s, 1H), 4.02 (s, 2H). MS (m/z): 414.07 (M+H). (Found: C, 66.92; H, 3.65; N, 6.81. $C_{23}H_{14}N_2O_4S$ requires C, 66.66; H, 3.41; N, 6.76)

7-(3-hydroxyphenyl)-11-hydro-7H,8H-benzo[7,8]chromeno[2,3-d]thiazolo[3,2-a]pyrimidine-8,10-dione (8i)

IR (KBr): 1718 cm^{-1} (C=O), 1637 cm^{-1} (C=N), 1587 cm^{-1} (C=C); ^1H NMR (400 MHz, DMSO-d_6): δ 8.21- 8.18 (d, J = 7.2 Hz, 2H), 8.15 (d, J = 7.6 Hz, 2H), 7.92 (d, 2H), 7.63 (m, 2H), 7.51 (d, J = 7.2 Hz, 2H), 4.85 (s, 1H), 4.06 (s, 2H). MS (m/z): 432.03 (M+H). (Found: C, 63.57; H, 3.29; N, 6.69. $C_{23}H_{13}ClN_2O_3S$ requires C, 63.82; H, 3.03; N, 6.47)

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