Organic Preparations and Procedures International
The New Journal for Organic Synthesis

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/uopp20

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To cite this article: Samaneh Ghaffari, Abbas Ali Esmaeili & Amir Khojastehnezhad (2021) One-pot Three-component Synthesis of Novel 1,3,4-Thiadiazole-thiazolo[3,2-*a*]pyrimidine Derivatives Catalyzed by Molecular Iodine, Organic Preparations and Procedures International, 53:6, 537-545, DOI: 10.1080/00304948.2021.1971914

To link to this article: https://doi.org/10.1080/00304948.2021.1971914

ORGANIC PREPARATIONS AND PROCEDURES INTERNATIONAL
2021, VOL. 53, NO. 6, 537–545
https://doi.org/10.1080/00304948.2021.1971914

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EXPERIMENTAL PAPER

One-pot Three-component Synthesis of Novel 1,3,4-Thiadiazole-thiazolo[3,2-*a*]pyrimidine Derivatives Catalyzed by Molecular Iodine

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ARTICLE HISTORY Received 20 October 2020; Accepted 3 June 2021

In addition to their applications in organic synthesis,[1–4] thiadiazoles have broad pharmaceutical and biological activities, including anti-inflammatory,[5,6] anticancer,[7,8] antimicrobial,[9,10] antifungal,[11] and antidiabetic[12] properties. As examples, we may note the important biological activities of the 1,3,4-thiadiazoles **A** and **B** (Fig. 1).[7,12]

Another important heterocyclic family is comprised of thiazolo[3,2-a]pyrimidines.[13–15] These compounds are pharmacophores for antibacterial,[16] general antimicrobial,[17] anticancer,[18] anti-inflammatory,[19] antinociceptive,[20] antihypertensive[21] and psychopharmacological[22] activities. Out of many examples, we may cite thiazolo[3,2-a]pyrimidine **C**,[23] which has been used for treatment of cancer, and compound **D**,[24] which acts as an inhibitor for kinases (Fig. 1). In our previous studies, we demonstrated the regioselective synthesis of some highly functionalized pyrimidines through the three-component reaction of acetylenedicarboxylates, isocyanides, and 2-imino-1,3-thiazolidin-4-ones.[25] In a related project, novel spiropyrimidines were prepared *via* the three-component reaction of malononitrile, 2,3-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidine-5,7(6H)-dione, and isatin units, with diisopropylethylamine as catalyst.[26] We now disclose for the first time a one-pot three-component synthesis of novel [1,3,4]thiadiazol-thiazolo[3,2-*a*]pyrimidines. This was accomplished using 2-amino-5-phenyl[1,3,4]-thiadiazoles, 2,3-dihydrodiazolo[3,2-*a*]pyrimidine and a number of aromatic aldehydes in the presence of I_2 as a cheap and readily available catalyst (Scheme 1).

The 2,3-dihydrothiazolo[3,2-*a*]pyrimidine was prepared by our previous method.[26] The reaction of 2-amino-5-phenyl[1,3,4]thiadiazole, 2,3-dihydrothiazolo[3,2-a]pyrimidine and 4-nitrobenzaldehyde was selected as a model (Table 1). As shown in Table 1, the yield was low when the reaction was carried out without any catalyst even after six hours (Table 1, entry 1). Acidic catalysts (Table 2, entries 3-5) gave better yields for the synthesis of **4a** (Scheme 1, R_1 = H, R_2 = NO_2) compared to triethylamine as a basic catalyst (Table 1, entry 2), but the best result was observed with the use of molecular iodine.

Different amounts of molecular iodine were then investigated in the model reaction (Table 2). Nearly no reaction took place in the absence of catalyst, even after 6 hours (Table 2, entry 1). The best amount of molecular iodine was 30 mol %. Using lower or

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Supplemental data for this article is available online at https://doi.org/10.1080/00304948.2021.1971914.

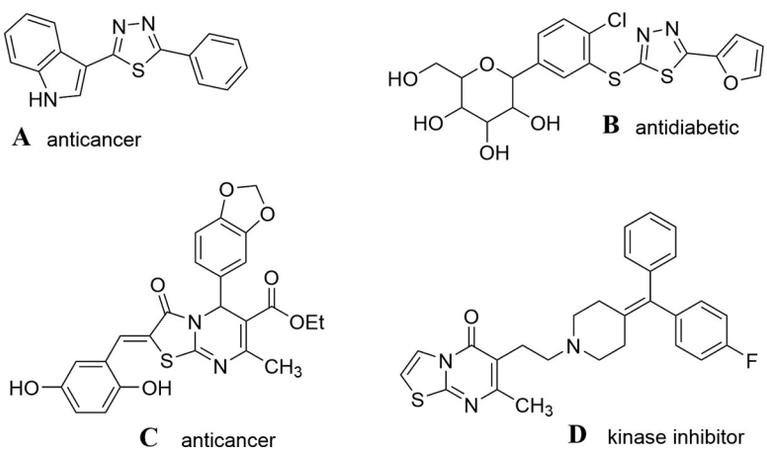
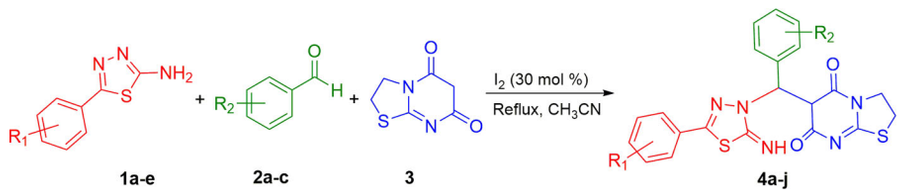


Figure 1. Biologically active [1,3,4]thiadiazoles and thiazolo[3,2-*a*]pyrimidines.



Scheme 1. Synthesis of [1,3,4]thiadiazol-thiazolo[3,2,*a*]pyrimidine derivatives in the presence of molecular iodine as a catalyst.

Table 1. Optimization of catalysts for synthesis of compound **4a**.[a]

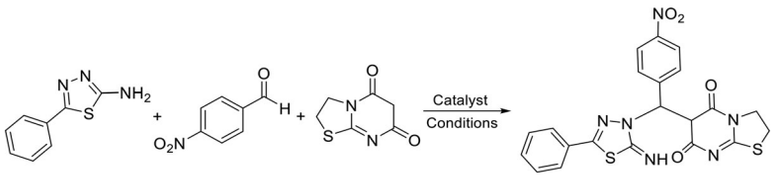
Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (min)	Yield
1	None	CH_3CN	reflux	360	10
2	Triethylamine (30)	CH_3CN	reflux	240	—
3	*p*-Toluenesulfonic acid (30)	CH_3CN	reflux	240	15
4	Trifluoroacetic acid (30)	CH_3CN	reflux	240	27
5	Sulfamic acid (30)	CH_3CN	reflux	240	32
6	I_2 (30)	CH_3CN	reflux	240	82

[a]Mixture of 2-amino-5-phenyl [1,3,4]thiadiazole (1.2 mmol), 4-nitrobenzaldehyde (1.2 mmol) and 2,3-dihydrothiazolo[3,2-*a*]pyrimidine (1.2 mmol) in the presence of specified catalysts.

higher amounts did not improve the yield (Table 2, entries 2-5). Different solvents (CH_2Cl_2, $C_2H_4Cl_2$, CH_3CN, 1,4-dioxane, THF, DMF, MeOH, EtOH, H_2O/EtOH and H_2O) were used for the synthesis of **4a** (Table 1, entries 6-15). To obtain the highest yield, refluxing acetonitrile was the best solvent (Table 2, entry 4). If the temperature was decreased to 70 °C, the yield of the product was reduced (Table 2, entry 16).

The scope and generality of the method were checked under optimized reaction conditions (Table 3). In examining different substituted aldehydes, we observed that aromatic aldehydes carrying strong electron-withdrawing groups gave the desired products in good to excellent yields; however, no product was formed when the reaction was done with benzaldehyde or with aromatic aldehydes bearing electron-donating groups. Moreover, 2-amino-5-phenyl-[1,3,4]thiadiazoles with electron-withdrawing groups such as chlorine and bromine increased the yield of the reaction moderately. The mean yield for the reactions in Table 3 was very good (80%).

Table 2. Optimization of the reaction conditions for synthesis of compound **4a**.[a]



Entry	Catalyst (mol%)	Solvent	Temperature (°C)	Time (min)	Yield (%)
1	None	CH_3CN	reflux	360	trace
2	I_2 (20)	CH_3CN	reflux	240	59
3	I_2 (25)	CH_3CN	reflux	240	71
4	I_2 (30)	CH_3CN	reflux	240	82
5	I_2 (35)	CH_3CN	reflux	240	82
6	I_2 (30)	EtOH	reflux	240	47
7	I_2 (30)	1,4-Dioxane	reflux	240	61
8	I_2 (30)	$C_2H_4Cl_2$	reflux	240	56
9	I_2 (30)	THF	reflux	240	15
10	I_2 (30)	DMF	reflux	240	55
11	I_2 (30)	H_2O	reflux	240	38
12	I_2 (30)	MeOH	reflux	240	42
13	I_2 (30)	H_2O/EtOH (1:1)	reflux	240	60
14	I_2 (30)	H_2O/EtOH (2:1)	reflux	240	53
15	I_2 (30)	H_2O/EtOH (1:2)	reflux	240	45
16	I_2 (30)	CH_3CN	70	360	35

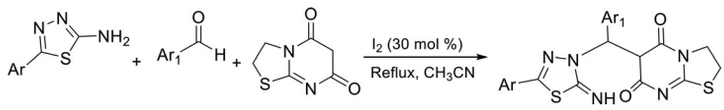
[a]Mixture of 2-amino-5-phenyl[1,3,4]thiadiazole (1.2 mmol), 4-nitrobenzaldehyde (1.2 mmol) and 2,3-dihydrothiazolo[3,2-a]pyrimidine (1.2 mmol) in the presence of catalyst.

The structures of all the novel products were confirmed by rigorous characterization (see Experimental section and Supplementary Material). For example, in regard to compound **4a**, the characteristic absorptions at 3270, 1637, 1598, 1535 and 1345 cm^{-1} in the IR spectrum are consistent with the stretching vibrations of NH, C = O, C = N and NO_2 groups, respectively. The proton NMR spectrum demonstrates two triplets at δ 3.56 (t, $J = 7.5$ Hz, 2H, CH_2S) and 4.34 (t, $J = 7.8$ Hz, 2H, CH_2N). The required four doublets appear at δ 6.50 (d, $J = 8.1$ Hz, 1H, CO-CH-CO), 7.74 (d, $J = 6.6$ Hz, 2H, Ar-H) 8.20 (d, $J = 8.4$ Hz, 2H, Ar-H), 8.64 (d, $J = 8.1$ Hz, 1H, CH benzyl). There is a singlet at 12.30 (s, 1H, NH). The carbon NMR spectrum shows 17 distinct resonances, consistent with the proposed structure. A satisfactory elemental analysis was obtained.

A proposed mechanism for product formation is shown in Scheme 2, indicating the key role of the catalyst. We found that compounds **4** were very stable and resisted all attempts at intramolecular annulation. This was true in the presence of a variety of dehydrating agents, including P_2O_5, $POCl_3$/Py, $SOCl_2$/Py, and *p*-TSA in CH_3CN under refluxing conditions.

In summary, a new and efficient approach has been reported for the synthesis of novel [1,3,4]thiadiazol-thiazolo[3,2-*a*]pyrimidines, using the one-pot three-component reaction of 2-amino-5-phenyl[1,3,4]thiadiazoles with 2,3-dihydrothiazolo[3,2-*a*]pyrimidine and aromatic aldehydes. This was done in the presence of molecular iodine in refluxing acetonitrile. The scope of the reaction has been probed. Now that the compounds are readily available, we hope that our method will accelerate the investigation and application of these novel heterocyclic systems.

Table 3. Synthesis of 1,3,4-thiadiazole-thiazolo[3,2-*a*]pyrimidines with molecular iodine.[a]



Entry	Ar	Ar_1	Product	Yield
1	C_6H_5	4-$NO_2C_6H_4$	**4a**	82
2	4-BrC_6H_4	4-$NO_2C_6H_4$	**4b**	78
3	4-ClC_6H_4	4-$NO_2C_6H_4$	**4c**	89
4	C_6H_5	4-CNC_6H_4	**4d**	68
5	4-BrC_6H_4	4-CNC_6H_4	**4e**	73
6	C_6H_5	2,4-$(Cl)_2C_6H_3$	**4f**	71
7	4-BrC_6H_4	2,4-$(Cl)_2C_6H_3$	**4g**	94
8	3-ClC_6H_4	2,4-$(Cl)_2C_6H_3$	**4h**	74
9	4-ClC_6H_4	2,4-$(Cl)_2C_6H_3$	**4i**	86
10	$C_6H_5CH_2$	4-$NO_2C_6H_4$	**4j**	91

[a]All reactions were carried out with 2-amino-5-phenyl[1,3,4]-thiadiazole (1.2 mmol), aromatic aldehydes (1.2 mmol), 2,3-dihydrothiazolo[3,2-*a*]pyrimidine (1.2 mmol) in the presence of I_2 (30 mol%) in CH_3CN (3.0 mL).
[b]Isolated yield.

Experimental section

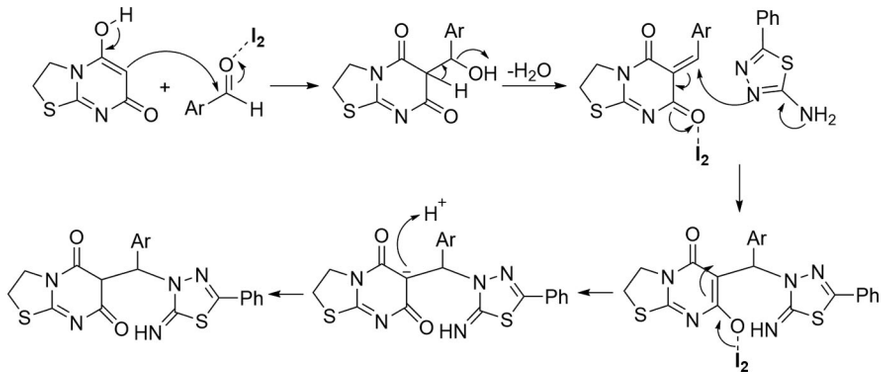
Melting points were taken on an Electrothermal type 9100 melting point apparatus and are uncorrected. The FT-IR spectra were performed on an Avatar 370 FT-IR Thermo-Nicolet spectrometer. Proton and carbon NMR spectra were obtained with a Bruker DRX-300 Avance spectrometer. TLC was done using silica gel and *n*-hexane/ethyl acetate. All materials were purchased from Sigma-Aldrich and Merck companies, and 2,3-dihydrothiazolo[3,2-a]pyrimidine was synthesized according to our previous study.[26]

General procedure for synthesis of 2-amino-5-phenyl[1,3,4]-thiadiazoles

These compounds (**1a**-**1e**) are all well-known materials and are available as articles of commerce. However, their preparation from thiosemicarbazides and benzonitriles continues to be of interest to current workers.[27] We found the following method to be useful in generating sufficient amounts of material for direct application to the synthesis of the title compounds. To a mixture of the appropriate thiosemicarbazide (33 mmol) and benzonitrile (29.75 mmol), 9.0 mL trifluoroacetic acid was added and refluxed for 6 h. After the reaction was complete, the mixture was permitted to cool to rt. Ammonia was then added to the solution dropwise until a yellow residue was formed. Then, the mixture was filtered off and washed with cold ethanol. For further purification, the yellow residue was recrystallized from ethanol to give the final product.

General procedure for synthesis of 1,3,4-thiadiazole-thiazolo[3,2-a]pyrimidines

To a mixture of 2-amino-5-(substituted)phenyl-[1,3,4]thiadiazole (1.2 mmol), 2,3-dihydrothiazolo [3,2-a]pyrimidine-5,7-dione (1.2 mmol) and an aromatic aldehyde (1.2 mmol), 30 mol % of molecular iodine and 3.0 mL acetonitrile was added and refluxed for 4 hours. The progress of the reaction was monitored by TLC. When the



Scheme 2. Proposed mechanism for synthesis of [1,3,4]thiadiazol-thiazolo[3,2-a]pyrimidines in the presence of molecular iodine.

solid product was formed and TLC indicated completion of the reaction, the mixture was filtered off and washed with cold acetonitrile. Then, for further purification, the residue was boiled in ethanol; and, after hot filtration, it was dried in a vacuum oven at 80 °C for 6 h to give the pure thiadiazolethiazolopyrimidine derivatives **4a**-**j**.

6-[(2-Imino-5-phenyl-[1,3,4]thiadiazol-3-yl)-(4-nitro-phenyl)-methyl]-2,3-dihydro-thiazolo[3,2-a]pyrimidine-5,7-dione (4a)

Yellow powder; (0.23 g, 82% yield); m.p. 255-258 °C; IR (KBr) ν_{max} (cm^{-1}): 3270, 1637, 1598, 1535, 1345 (NH, C = O, C = N, NO_2); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.57 (t, J = 7.6 Hz, 2H, CH_2S), 4.34 (t, J = 7.6 Hz, 2H, CH_2N), 6.50 (d, J = 8.1 Hz, 1H, CO-CH-CO), 7.46-7.51 (m, 3H, Ar-H), 7.64 (d, J = 8.7 Hz, 2H, Ar-H), 7.74 (d, J = 6.6 Hz, 2H, Ar-H) 8.20 (d, J = 8.4 Hz, 2H, Ar-H), 8.64 (d, J = 8.1 Hz, 1H, CH benzyl), 12.30 (s, 1H, NH); 13C NMR (75.46 MHz, DMSO-d_6): δ 27.2, 49.3, 52.6, 97.4, 123.7, 126.8, 127.6, 129.6, 130.2, 131.3, 146.7, 150.5, 157.5, 161.1, 164.9, 166.1, 167.8; MS (m/z, %): 307 $[M\text{-}173]^+$ (9), 283 (14), 254 (12), 176 (8), 121 (100), 101 (23), 77 (56).

Anal. Calcd for $C_{21}H_{16}N_6O_4S_2$: C, 52.49; H, 3.36; N, 17.49. Found: C, 52.28; H, 3.44; N, 17.65.

6-[[5-(4-Bromophenyl)-2-imino-[1,3,4]thiadiazol-3-yl]-(4-nitro-phenyl)-methyl]-2,3-dihydro-thiazolo[3,2-a]pyrimidine-5,7-dione (4b)

Yellow powder; (0.25 g, 78% yield); m.p. 246-249 °C; IR (KBr) ν_{max} (cm^{-1}): 3281, 1639, 1603, 1536, 1345 (NH, C = O, C = N, NO_2); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.56 (t, J = 7.6 Hz, 2H, CH_2S), 4.34 (t, J = 7.6 Hz, 2H, CH_2N), 6.51 (d, J = 8.1 Hz, 1H, CO-CH-CO), 7.62-7.69 (m, 6H, Ar-H), 8.19 (d, J = 8.1 Hz, 2H, Ar-H), 8.71 (d, J = 8.1 Hz, 1H, CH benzyl), 12.30 (s, 1H, NH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ 27.2, 49.3, 52.5, 97.3, 123.3, 123.7, 127.8, 128.6, 130.5, 132.6, 146.7, 150.4, 156.4, 161.1, 164.9, 166.1, 168.0 ppm; MS (m/z, %): 392 $[M + 2\text{-}168]^+$ (7), 390 $[M\text{-}168]^+$ (7) 387 (21), 369 (5), 339 (14), 300 (30), 283 (67), 254 (98), 200 (98), 119 (99), 89 (81), 74 (100), 60 (98).

Anal. Calcd for $C_{21}H_{15}BrN_6O_4S_2$: C, 45.09; H, 2.70; N, 15.02. Found: C, 45.23; H, 2.62; N, 15.31.

6-[[5-(4-Chlorophenyl)-2-imino-[1,3,4]thiadiazol-3-yl]-(4-nitro-phenyl)-methyl]-2,3-dihydro-thiazolo[3,2-a]pyrimidine-5,7-dione (4c)

Yellow powder; (0.28 g, 89% yield); m.p. 255-257 °C; IR (KBr) ν_{max} (cm^{-1}): 3278, 1638, 1601, 1533, 1344 (NH, C = O, C = N, NO_2); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.57 (t, J = 7.6 Hz, 2H, CH_2S), 4.34 (t, J = 7.6 Hz, 2H, CH_2N), 6.51 (d, J = 8.1 Hz, 1H, CO-CH-CO), 7.52-7.55 (m, 2H, Ar-H), 7.64 (d, J = 8.4 Hz, 2H, Ar-H), 7.76-7.80 (m, 2H, Ar-H), 8.19 (d, J = 8.4 Hz, 2H, Ar-H), 8.71 (d, J = 8.1 Hz, 1H, CH benzyl), 12.31 (s, 1H, NH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ 27.2, 49.3, 52.5, 97.3, 123.7, 127.8, 128.4, 129.7, 130.1, 134.6, 146.7, 150.4, 156.3, 161.1, 164.9, 166.1, 168.0; MS (m/z, %): 348 $[M + 2\text{-}168]^+$ (5), 346 $[M\text{-}168]^+$ (5), 324 (3), 300 (8), 283 (23), 254 (21), 210 (43), 154 (100), 111 (68).

Anal. Calcd for $C_{21}H_{15}ClN_6O_4S_2$: C, 48.98; H, 2.94; N, 16.32. Found: C, 49.16; H, 2.74; N, 16.55.

4-[(5,7-Dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-a]pyrimidin-6-yl)-(2-imino-5-phenyl-[1,3,4]thiadiazol-3-yl)-methyl]-benzonitrile (4d)

White powder; (0.20 g, 73% yield); m.p. 250-252 °C; IR (KBr) ν_{max} (cm^{-1}): 3272, 2224, 1639, 1606 (NH, CN, C = O, C = N); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.56 (t, J = 7.8 Hz, 2H, CH_2S), 4.34 (t, J = 7.8 Hz, 2H, CH_2N), 6.48 (d, J = 8.2 Hz, 1H, COCHCO), 7.45-7.50 (m, 3H, Ar-H), 7.58 (d, 2H, J = 8.1 Hz, Ar-H), 7.74-7.80 (m, 4H, Ar-H), 8.61 (d, J = 8.2 Hz, 1H, CH benzyl), 12.29 (s, 1H, NH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ 27.2, 49.3, 52.7, 97.4, 109.7, 119.4, 126.8, 127.7, 129.6, 130.2, 131.3, 132.4, 148.3, 157.5, 161.1, 164.8, 166.0, 167.8; MS (m/z, %): 286 $[M\text{-}175]^+$ (15), 279 (47), 251 (8), 175 (82), 126 (70), 120 (100), 103 (60), 76 (98).

Anal. Calcd for $C_{22}H_{16}N_6O_2S_2$: C, 57.38; H, 3.50; N, 18.25. Found: C, 57.58; H, 3.46; N, 18.32.

4-[[5-(4-Bromophenyl)-2-imino-[1,3,4]thiadiazol-3-yl]-(5,7-dioxo-2,3,6,7-tetrahydro-5H-thiazolo[3,2-a]pyrimidin-6-yl)-methyl]-benzonitrile (4e)

White powder; (0.21g, 68% yield); m.p. 250-253 °C; IR (KBr) ν_{max} (cm^{-1}): 3266, 2225, 1640, 1607 (NH, CN, C = O, C = N); ^{1}HNMR (300.13 MHz, DMSO-d_6): δ 3.56 (t, J = 8.2 Hz, 2H, CH_2S), 4.33 (t, J = 8.2 Hz, 2H, CH_2N), 6.46 (d, J = 8.1 Hz, 1H, CO-CH-CO), 7.54 (t, J = 8.1 Hz, 2H, Ar-H), 7.65-7.74 (m, 4H, Ar-H), 7.78 (d, J = 7.8 Hz, 2H, Ar-H), 8.67 (d, J = 8.1 Hz, 1H, CH benzyl), 12.28 (s, 1H, NH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ 27.2, 49.3, 52.7, 97.4, 109.7, 119.4, 123.2, 127.6, 128.6, 130.5, 132.4, 132.6, 148.2, 156.4, 161.1, 164.8, 166.0, 168.1; MS (m/z, %): 282 $[M\text{-}256]^+$ (7), 279 (34), 252 (23), 197 (30), 126 (58), 119 (72), 101 (27), 73 (89), 60 (91), 42 (25).

Anal. Calcd for $C_{22}H_{15}N_6O_2S_2$: C, 48.98; H, 2.80; N, 15.58. Found: C, 48.79; H, 2.93; N, 15.33.

6-[(3,4-Dichlorophenyl)-(2-imino-5-phenyl-[1,3,4]thiadiazol-3-yl)-methyl]-2,3-dihydro-thiazolo[3,2-a]pyrimidine-5,7-dione (4f)

White powder; (0.28 g, 94% yield); m.p. 214-217 °C; IR (KBr) ν_{max} (cm^{-1}): 3280, 1634, 1592 (NH, C = O, C = N); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.55 (t, J = 7.5 Hz, 2H,

CH_2S), 4.25-4.40 (m, 2H, CH_2N), 6.40 (d, $J = 7.1$ Hz, 1H, COCHCO), 7.36-7.52 (m, 5H, Ar-H), 7.68-7.76 (m, 3H, Ar-H), 8.58 (d, $J = 7.1$ Hz, 1H, CH benzyl), 12.08 (s, 1H, NH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ 27.1, 49.3, 51.1, 95.6, 126.7, 126.8, 128.8, 129.6, 130.1, 131.3, 131.6, 132.2, 133.4, 138.2, 157.2, 161.0, 164.7, 166.5, 167.2; MS (m/z, %): 335 $[M\text{-}168]^+$ (3), 328 (39), 294 (42), 287 (98), 260 (14), 204 (27), 175 (98), 134 (90), 120 (95), 85 (82).

Anal. Calcd for $C_{21}H_{15}C_{l2}N_5O_2S_2$: C, 50.00; H, 3.00; N, 13.88. Found: C, 50.28; H, 3.17; N, 13.73.

6-[[5-(4-Bromophenyl)-2-imino-[1,3,4]thiadiazol-3-yl]-(3,4-dichloro-phenyl)-methyl]-2,3-dihydro-thiazolo[3,2-a]pyrimidine-5,7-dione (4g)

White powder; (0.25 g, 71% yield); m.p. 226-228 °C; IR (KBr) ν_{max} (cm^{-1}): 3272, 1636, 1590 (NH, C = O, C = N); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.56 (t, $J = 7.5$ Hz, 2H, CH_2S), 4.24-4.39 (m, 2H, CH_2N), 6.37 (d, $J = 7.1$ Hz, 1H, COCHCO), 7.37 (d, $J = 8.4$ Hz, 1H, Ar-H), 7.52 (s, 1H, Ar-H),7.68 (t, $J = 10.2$ Hz, 5H, Ar-H), 8.62 (d, $J = 7.1$ Hz, 1H, CH benzyl), 12.06 (s, 1H, NH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ 27.1, 49.3, 51.1, 95.5, 123.2, 126.7, 128.6, 128.8, 130.5, 131.6, 132.2, 132.6, 133.4, 138.1, 156.1, 161.0, 164.8, 166.4, 167.4; MS (m/z, %): 415 $[M + 2\text{-}163]^+$ (5), 413 $[M\text{-}163]^+$ (5), 375 (7), 288 (100), 254 (46), 197 (33), 169 (23), 119 (52).

Anal. Calcd for $C_{21}H_{14}BrCl_2N_5O_2S_2$: C, 43.24; H, 2.42; N, 12.01. Found: C, 43.36; H, 2.60; N, 11.91.

6-[[5-(3-Chlorophenyl)-2-imino-[1,3,4]thiadiazol-3-yl]-(3,4-dichloro-phenyl)-methyl]-2,3-dihydro-thiazolo[3,2-a]pyrimidine-5,7-dione (4h)

White powder; (0.23 g, 74% yield); m.p. 204-207 °C; IR (KBr) ν_{max} (cm^{-1}): 3280, 1633, 1592 (NH, C = O, C = N); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.56 (t, $J = 7.5$ Hz, 2H, CH_2S), 4.28-4.35 (m, 2H, CH_2N), 6.37 (d, $J = 7.2$ Hz, 1H, COCHCO), 7.36-7.40 (m, 1H, Ar-H), 7.50-7.53 (m, 3H, Ar-H), 7.64-7.70 (m, 2H, Ar-H), 7.77 (d, $J = 7.2$ Hz, 1H, Ar-H), 8.65 (d, $J = 7.2$ Hz, 1H, CH benzyl), 12.06 (s, 1H, NH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ 27.1, 49.26, 51.2, 95.5, 125.6, 125.9, 126.7, 128.8, 129.8, 131.6, 131.6, 132.2, 133.2, 133.4, 134.3, 138.1, 155.6, 161.0, 164.7, 166.4, 167.6; MS (m/z, %): 373 $[M + 4\text{-}168]^+$ (4), 371 $[M + 2\text{-}168]^+$ (8), 369 $[M\text{-}168]^+$ (8), 368 (4), 364 (21), 329 (25), 288 (96), 209 (84), 154 (100), 110 (39), 74 (100).

Anal. Calcd for $C_{21}H_{14}Cl_3N_5O_2S_2$: C, 46.81; H, 2.62; N, 13.00. Found: C, 46.95; H, 2.52; N, 13.11.

6-[[5-(4-Chlorophenyl)-2-imino-[1,3,4]thiadiazol-3-yl]-(3,4-dichloro-phenyl)-methyl]-2,3-dihydro-thiazolo[3,2-a]pyrimidine-5,7-dione (4i)

White powder; (0.27 g, 86% yield); m.p. 237-240 °C; IR (KBr) ν_{max} (cm^{-1}): 3265, 1636, 1596 (NH, C = O, C = N); ^{1}H NMR (300.13 MHz, DMSO-d_6): δ 3.56 (t, $J = 7.8$ Hz, 2H, CH_2S), 4.27-4.37 (m, 2H, CH_2N), 6.37 (d, $J = 7.1$ Hz, 1H, COCHCO), 7.35-7.39 (m, 1H, Ar-H), 7.52-7.54 (m, 3H, Ar-H), 7.66 (d, $J = 8.4$ Hz, 1H, Ar-H), 7.76 (d, $J = 8.4$ Hz, 2H, Ar-H), 8.62 (d, $J = 7.1$ Hz, 1H, CH benzyl), 12.06 (s, 1H, NH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ 27.1, 31.2, 49.3, 51.1, 126.7, 128.4, 128.8, 129.7, 130.1, 131.6, 132.2, 133.4,

134.6, 138.1, 156.0, 161.0, 164.8, 166.4, 167.4; MS (m/z, %): 373 $[M+4\text{-}168]^+$ (3), 371 $[M+2\text{-}168]^+$ (6), 369 $[M\text{-}168]^+$ (6), 331 (3), 289 (40), 210 (18), 169 (25), 154 (68), 111 (17), 74 (42), 60 (63), 42 (33), 29 (100).

Anal. Calcd for $C_{21}H_{14}Cl_3N_5O_2S_2$: C, 46.81; H, 2.62; N, 13.00. Found: C, 46.67; H, 2.71; N, 13.14.

6-[(5-Benzyl-2-imino-[1,3,4]thiadiazol-3-yl)-(4-nitro-phenyl)-methyl]-2,3-dihydro-thiazolo[3,2-a]pyrimidine-5,7-dione (4j)

White powder; (0.26 g, 91% yield); m.p. 231-234 °C; IR (KBr) ν_{max} (cm^{-1}): 3291, 1634, 1601, 1542, 1346 (NH, C = O, C = N, NO_2); ^1H NMR (300.13 MHz, DMSO-d_6): δ 3.54 (t, J = 8.1 Hz, 2H, CH_2S), 4.16 (s, 2H, CH_2), 4.31 (t, J = 8.1 Hz, 2H, CH_2N), 6.40 (d, J = 7.9 Hz, 1H, CO-CH-CO), 7.26-7.36 (m, 5H, Ar-H), 7.59 (d, J = 8.4 Hz, 2H, Ar-H), 8.17 (d, J = 8.4 Hz, 2H, Ar-H), 8.30 (d, J = 7.9Hz, 1H, CH benzyl), 12.25 (s, 1H, NH); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ 27.2, 31.2, 35.9, 49.2, 52.40, 97.5, 123.6, 127.3, 127.8, 129.1, 138.4, 146.6, 150.7, 158.8, 161.0, 164.8, 166.0, 168.2; MS (m/z, %): 324 $[M\text{-}168]^+$ (3), 283 (57), 254 (44), 190 (73), 148 (100), 134 (32), 122 (58), 91 (96).

Anal. Calcd for $C_{22}H_{18}N_6O_4S_2$: C, 53.43; H, 3.67; N, 16.99. Found: C, 53.61; H, 3.58; N, 16.77.

Acknowledgements

The Research Council of Ferdowsi University of Mashhad is acknowledged for financial support (Grant No. 3/45204).

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