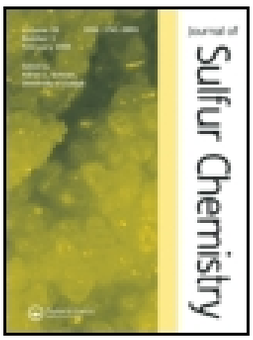

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Rapid synthesis of (*E*)-5-amino-*N*′-benzylidene-8-nitro-7-aryl-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carbohydrazide derivatives

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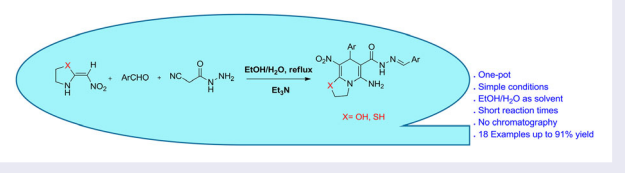
ABSTRACT

A variety of novel thiazolo/oxazolo pyridine derivatives were synthesized *via* an efficient, one-pot, multi-component reaction of enamines derived from the addition of cysteamine hydrochloride/ethanolamine to 1,1-bis(methylthio)-2-nitroethene with aromatic aldehydes and cyanoacetohydrazide in the presence of catalytic amount of Et_3N. This reaction includes some important aspects like simple operation under mild conditions, high atom economy, easy accessibility of reactants, simple workup procedure, and the use of EtOH/H_2O as a green reaction medium.



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Thiazolo/oxazolo pyridine; multi-component reaction; enamines; cysteamine hydrochloride/ethanolamine; aromatic aldehydes; cyanoacetohydrazide

1. Introduction

Heterocyclic compounds are of very much interest in our daily life [1]. They are frequently found in pharmacophores and play important roles in drug discovery and in other fields relating to bioactive compounds [2]. Among them, compounds containing thiazole and oxazole skeletons have been reported to furnish various biological activities [3–10]. For examples thiazolo pyridine derivatives exhibit significant pharmacological properties including anticancer [11], antimicrobial [12], antihypertensive, muscle relaxing [13,14], anti-inflammatory, antifungal [15], and oxazolo pyridine derivatives display antimicrobial, anticancer, anti-inflammatory, analgesic, and anticoagulant activities [16].

During the recent years the use of enamines and dienamines derived from 1,1-bis(methylthio)-2-nitroethene for the synthesis of various fused heterocycles and

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pharmacologically interesting heterocyclic compounds has attracted the attention of many chemists [17–23]. To continue our studies on the synthesis of drug-like compounds and development of 1,1-bis(methylthio)-2-nitroethene in organic synthesis, herein we report an efficient synthesis of novel thiazolo and oxazolo pyridine derivatives *via* an one-pot, multi-component reaction of enamines derived from the addition of cysteamine hydrochloride or ethanolamine to 1,1-bis(methylthio)-2-nitroethene, with cyanoacetohydrazide and aromatic aldehydes.

2. Results and discussion

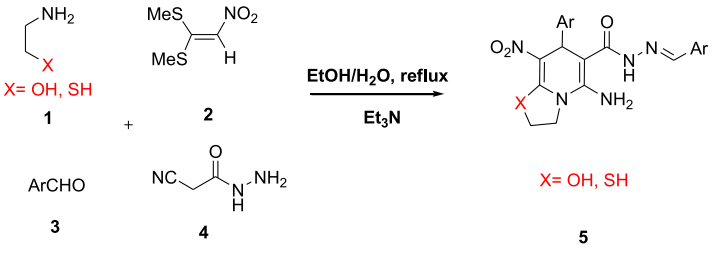
The reactions of cysteamine hydrochloride/ethanolamine **1**, 1,1-bis(methylthio)-2-nitroethene **2**, aromatic aldehydes **3** and cyanoacetohydrazide **4** in the presence of catalytic amount of Et_3N in $EtOH/H_2O$ as a green medium at reflux led to the corresponding thiazolo/oxazolo pyridine derivatives **5a–r**, in good to high yields (Scheme 1).

We explored the scope of this reaction by varying the structure of the aromatic aldehyde component. The reaction proceeds very cleanly under the same reaction conditions to afford a series of thiazolo/oxazolo pyridine derivatives **5** in 73–91% yields. The results are shown in Table 1.

The structures of compounds **5a–r** (Table 1) were characterized on the basis of their IR, ^{1}H NMR, ^{13}C NMR and mass spectra. The ^{1}H NMR spectrum of **5a** showed two singlets for the NH_2 (amine) and NH (amide) groups (δ 8.01, 10.76, respectively), two singlets for the methine and imine protons (δ 5.65, 8.28, respectively), and characteristic multiplets for the two CH_2 groups (.3.36–3.41, 4.20–4.38) and multipets for the aromatic groups (.7.09–7.60). The ^{1}H-decoupled ^{13}C NMR spectrum of **5a** showed 17 distinct resonances which was consistent with the proposed structure.

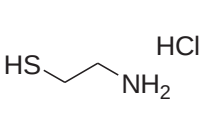
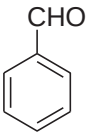
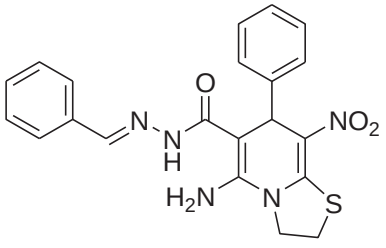
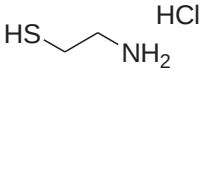
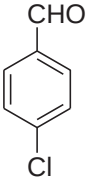
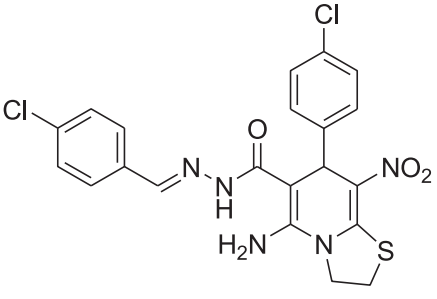
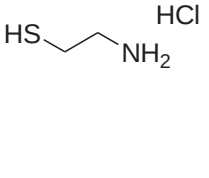
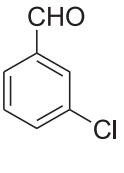
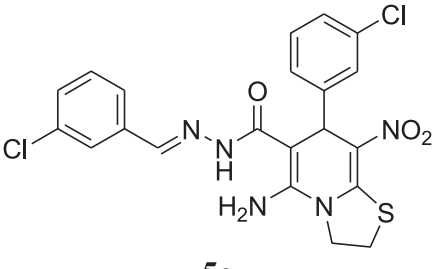
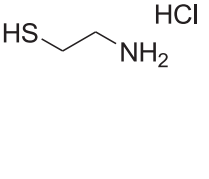
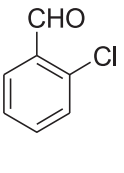
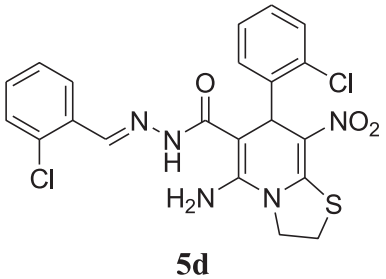
The mass spectrum of **5a** displayed the molecular ion peak at *m/z* 421, which was in agreement with the proposed structure. The IR spectrum of **5a** displayed characteristic absorption bands (3433, 3277, 3143, 1634, 1568, 1528, 1386 and 1244 cm^{-1}) due to the NH_2, NH, C9O, Ar, NO_2 and C–N groups.

A plausible mechanism for the formation of **5** based on the chemistry of 1,1-bis(methylthio)-2-nitroethene [19] is shown in Scheme 2. Initially, the reaction between cysteamine hydrochloride/ethanolamine **1** and 1,1-bis(methylthio)-2-nitroethene **2** affords 2-(nitromethylene)thiazolidine/oxazolidine **6** [21–23], while the condensation of cyanoacetohydrazide **4** with aldehyde **3** furnishes adduct **7**. Then, the 2-(nitromethylene)thiazolidine/oxazolidine **6** and adduct **7** undergo a Michael addition



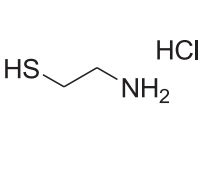
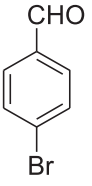
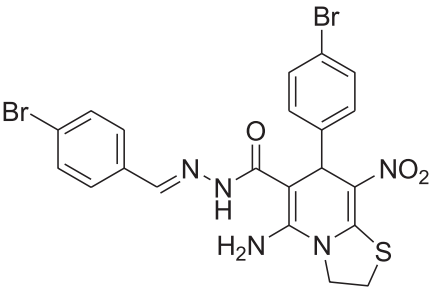
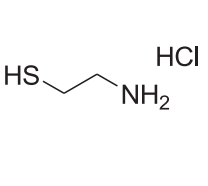
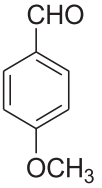
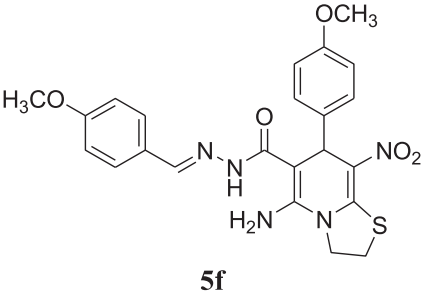
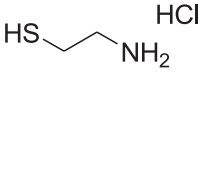
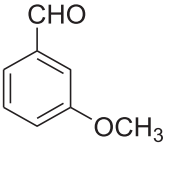
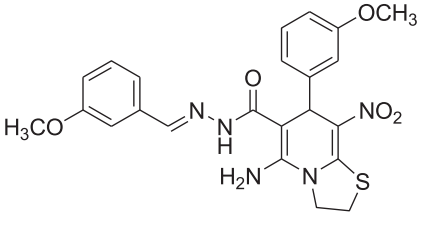
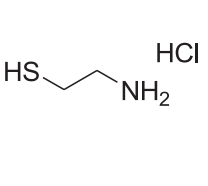
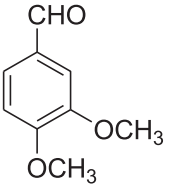
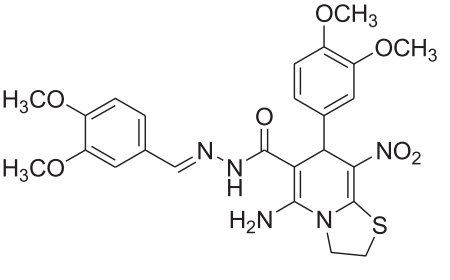
Scheme 1. Synthetic scheme for the products **5a–r.**

Table 1. Products **5a–s**.

Entry	Amine[a]	ArCHO[a]	Product **5**	Time (min)	Yield (%)
1			 **5a**	10	78
2			 **5b**	10	89
3			 **5c**	10	90
4			 **5d**	60	73

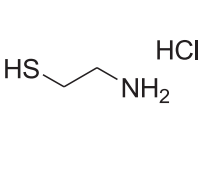
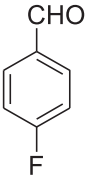
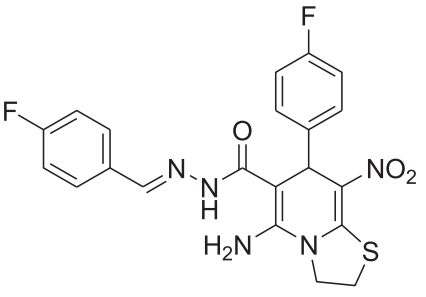
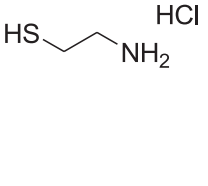
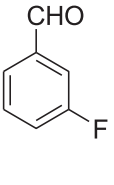
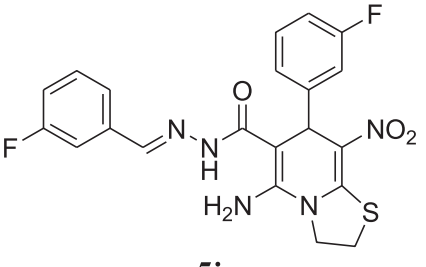
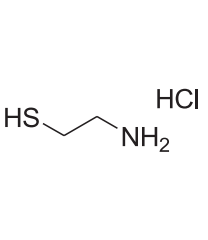
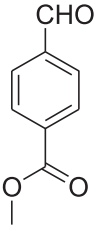
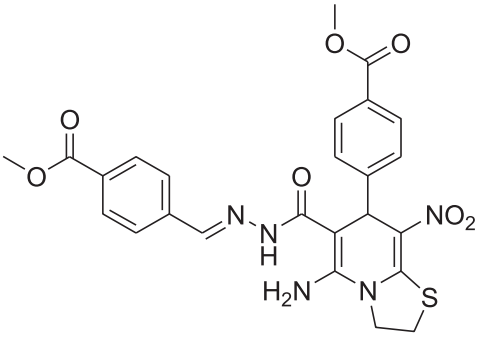
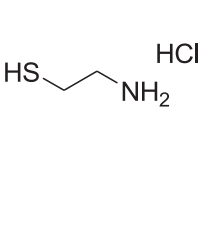
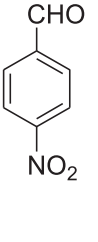
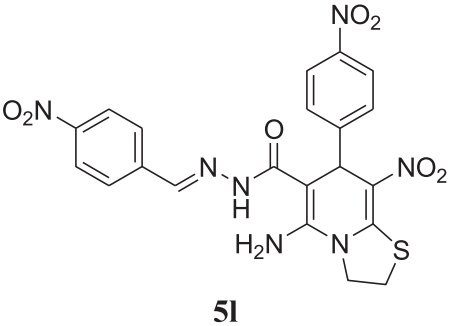
(*continued*).

Table 1. Continued.

Entry	Amine[a]	ArCHO[a]	Product **5**	Time (min)	Yield (%)
5			 **5e**	10	91
6			 **5f**	45	82
7			 **5g**	15	85
8			 **5h**	30	81

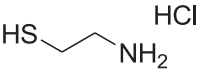
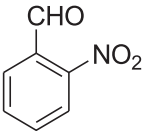
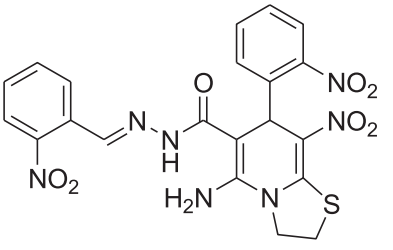
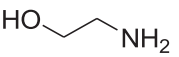
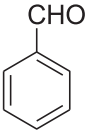
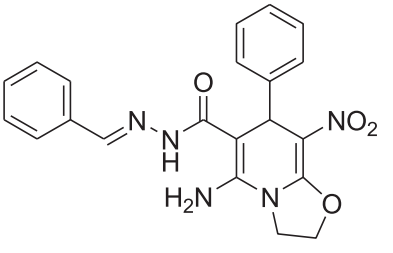
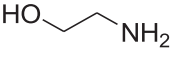
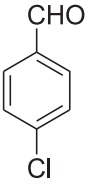
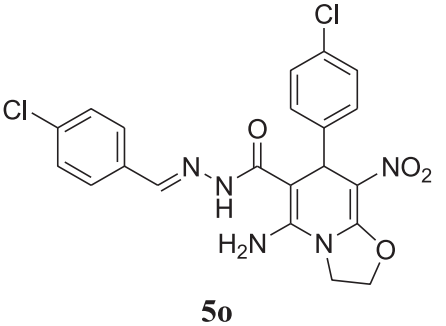
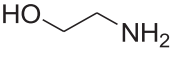
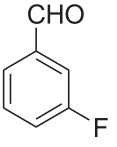
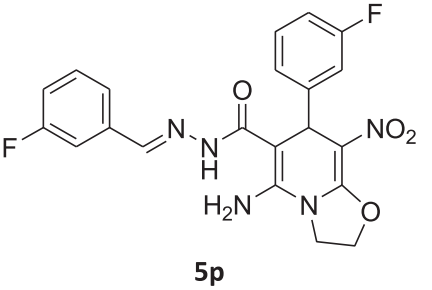
(*continued*).

Table 1. Continued.

Entry	Amine[a]	ArCHO[a]	Product **5**	Time (min)	Yield (%)
9			 **5i**	40	79
10			 **5j**	10	83
11			 **5k**	10	88
12			 **5l**	10	82

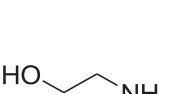
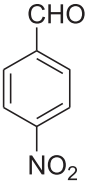
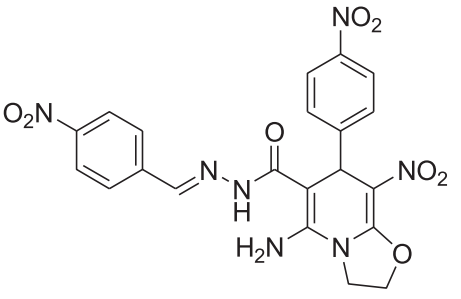
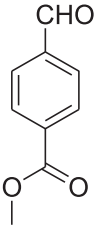
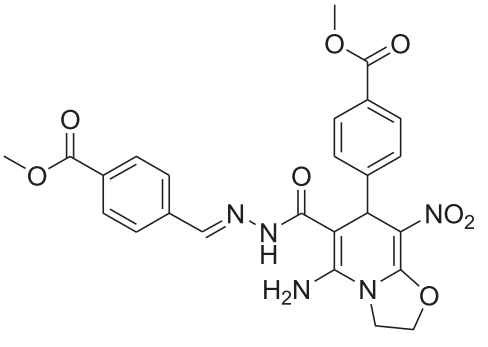
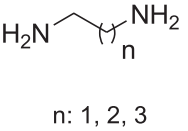
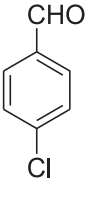
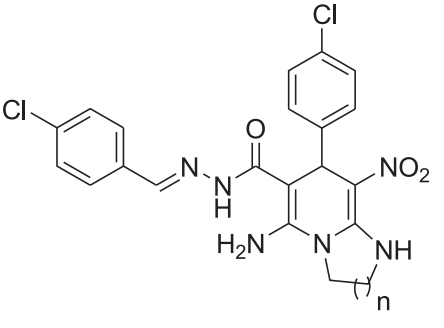
(*continued*).

Table 1. Continued.

Entry	Amine[a]	ArCHO[a]	Product **5**	Time (min)	Yield (%)
13			 **5m**	15	75
14			 **5n**	50	80
15			 **5o**	15	88
16			 **5p**	30	82

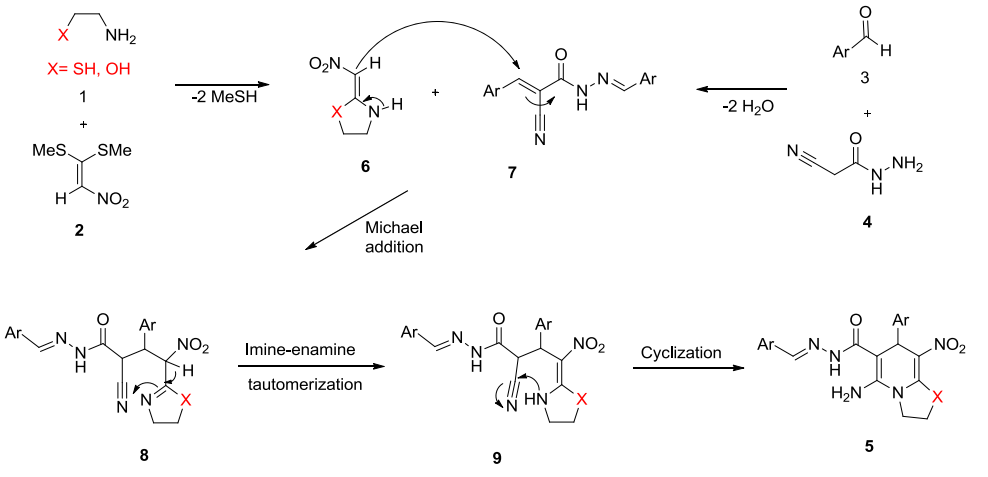
(*continued*).

Table 1. Continued.

Entry	Amine[a]	ArCHO[a]	Product **5**	Time (min)	Yield (%)
17			 **5q**	20	81
18			 **5r**	10	89
19[b]	 n: 1, 2, 3		 n: 1, 2, 3 **5s**	10–15	78–90

[a]Cysteamine hydrochloride/ethanolamine (1 mmol), 1,1-bis(methylthio)-2-nitroethene (1 mmol), aromatic aldehyde (2 mmol) and cyanoacetohydrazide (1 mmol) were used.

[b][17].



Scheme 2. Plausible mechanism for the formation of product **5**.

to give intermediate **8**, which undergoes successive imine–enamine tautomerization, followed by nucleophilic addition of the secondary amino group to the cyano group, leading to the formation of **5**.

3. Conclusion

We have developed a facile, and efficient methodology for the Et_3N-catalyzed rapid preparation of new class of thiazolo/oxazolo pyridine derivatives *via* one-pot, multi-component reaction of 2-(nitromethylene)thiazolidine/oxazolidine, aromatic aldehydes and cyanoacetohydrazide in ethanol/water as a green medium. The mild reaction conditions, experimental simplicity, short reaction times, easy workup procedure, good to high yields and compatibility with various functional groups make this approach attractive for synthesizing a variety of such derivatives.

4. Experimental

4.1. General

The cysteamine hydrochloride, ethanolamine, 1,1-bis(methylthio)-2-nitroethene, cyanoacetohydrazide, aromatic aldehydes and trimethylamine (Et_3N) were obtained from Merck and Aldrich and were used without further purification. NMR spectra were recorded with a Bruker DRX-300 Avance instrument (300 MHz for ^1H and 75.4 MHz for ^{13}C) with DMSO as solvent. Chemical shifts are given in ppm (δ) relative to internal TMS and coupling constant (J) are reported in hertz (Hz). Melting points were measured with an electrotherma1 9100 apparatus. Mass spectra were recorded with an Agilent 5975C VL MSD with Triple-Axis Detector operating at an ionization potential of 70 eV. IR spectra were measured with a Bruker Tensor 27 spectrometer. Elemental analyses for C, H and N were performed using a PerkinElmer 2004 series [II] CHN elemental analyzer.

4.2. General procedure for the synthesis of product 5

Synthesis of product **5a–m:** A mixture of cysteamine hydrochloride (0.113 g, 1 mmol), 1,1-bis(methylthio)-2-nitro ethylene (0.165 g, 1 mmol), 10 mL H_2O/EtOH (1:1) and Et_3N (140 µL, 1 mmol) in a 50 mL flask was refluxed for 5 h. After completion of the reaction (monitored by TLC, ethyl acetate/n-hexane, 1:1), aromatic aldehyde (2 mmol), cyanoacetohydrazide (0.099 g, 1 mmol) and one drop Et_3N as a catalyst were added to the reaction mixture, and it was stirred under reflux for the time given in Table 1. Then, the reaction mixture was cooled to room temperature and filtered to give the crude product. The solid was washed with H_2O/EtOH to give product **5a–m** in excellent yield.

Synthesis of product **5n–r:** A mixture of ethanolamine (60 µL, 1 mmol), 1,1-bis(methylthio)-2-nitro ethylene (0.165 g, 1 mmol) and 10 mL H_2O/EtOH (1:1) in a 50 mL flask was refluxed for 6 h. After completion of the reaction (monitored by TLC, ethyl acetate/n-hexane, 1:1), aromatic aldehyde (2 mmol), cyanoacetohydrazide (0.099 g, 1 mmol) and one drop Et_3N as a catalyst were added to the reaction mixture, and it was stirred under reflux for the time given in Table 1. Then, the reaction mixture was cooled to room temperature and filtered to give the crude product. The solid was washed with H_2O/EtOH to give product **5n–r** in excellent yield.

4.2.1. (E)-5-Amino-N′-benzylidene-8-nitro-7-phenyl-3,7-dihydro-2H-thiazolo[3,2-a] pyridine-6-carbohydrazide (5a)

Orange solid; yield: 0.328 g (78%); m.p. 246–248°C. ^{1}H NMR (300 MHz, DMSO): δ 3.36–3.41 (*m*, 2H, CH_2S), 4.20–4.38 (*m*, 2H, CH_2N), 5.65 (*s*, 1H, CH), 7.09–7.60 (*m*, 10H, Ar), 8.01 (*s*, 2H, NH_2), 8.28 (*s*, 1H, CH), 10.76 (*s*, 1H, NH). ^{13}C NMR (75.4 MHz, DMSO): δ 28.1 (CH), 37.8 (CH_2S), 51.2 (CH_2N), 82.6, 124.2, 127.0, 127.8, 128.6, 129.1, 129.8, 135.3, 144.6, 145.5, 150.2, 157.2, 165.9 (C9O). IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3433 and 3277 and 3143 (NH_2 and NH), 1634 (C9O), 1568 (Ar), 1528 and 1386 (NO_2), 1244 (C–N). MS (EI, 70 eV): *m/z* (%) = 421 (M^+, 2.5), 404 (42), 274 (80), 258 (100), 227 (74), 198 (54), 171 (27), 128 (36), 90 (78), 51 (36). Anal. Calc. for $C_{21}H_{19}N_5O_3S$ (421.47): C, 59.84; H, 4.54; N, 16.61. Found: C, 60.2; H, 4.1, N, 16.4.

4.2.2. (E)-5-Amino-N′-(4-chlorobenzylidene)-7-(4-chlorophenyl)-8-nitro-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbohydrazide (5b)

Orange solid; yield: 0.436 g (89%); m.p. 258–260°C. ^{1}H NMR (300 MHz, DMSO): δ 3.36–3.41 (*m*, 2H, CH_2S), 4.20–4.38 (*m*, 2H, CH_2N), 5.65 (*s*, 1H, CH), 7.27 (*d*, $^3J_{HH}$ = 8.1 Hz, 2H, Ar), 7.34 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.44 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.61 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 8.09 (*s*, 2H, NH_2), 8.26 (*s*, 1H, CH), 10.85 (*s*, 1H, NH). ^{13}C NMR (75.4 MHz, DMSO): δ 28.1 (CH), 37.2 (CH_2S), 51.2 (CH_2N), 81.8, 123.7, 128.5, 128.6, 129.3, 129.7, 131.6, 134.2, 143.4, 144.3, 150.3, 157.6, 165.9 (C = O). IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}): 3471 and 3222 (NH_2 and NH), 1633 (C = O), 1550 (Ar), 1488 and 1380 (NO_2), 1214 (C–N). MS (EI, 70 eV): *m/z* (%) = 490 (M^+, 0.31), 430 (11), 385 (14), 292 (100), 261 (74), 222 (21), 165 (34), 124 (50), 89 (86), 63 (25). Anal. Calc. for $C_{21}H_{17}Cl_2N_5O_3S$ (490.36): C, 51.43; H, 3.49; N, 14.28. Found: C, 51.0; H, 3.1; N, 14.6.

4.2.3. (E)-5-Amino-N′-(3-chlorobenzylidene)-7-(3-chlorophenyl)-8-nitro–3,7-dihydro- 2H-thiazolo[3,2-a]pyridine-6-carbohydrazide (5c)

Orange solid; yield: 0.441 g (90%); m.p. 255–257°C. ^{1}H NMR (300 MHz, DMSO): δ 3.37–3.42 (*m*, 2H, CH_2S), 4.22–4.40 (*m*, 2H, CH_2N), 5.69 (*s*, 1H, CH), 7.19–7.65 (*m*, 8H, Ar), 8.12 (*s*, 2H, NH_2), 8.25 (*s*, 1H, CH), 10.92 (*s*, 1H, NH). ^{13}C NMR (75.4 MHz, DMSO): δ 28.1 (CH), 37.5 (CH_2S), 51.3 (CH_2N), 81.5, 123.5, 125.9, 126.1, 126.6, 127.1, 127.6, 129.4, 130.6, 131.1, 133.1, 134.0, 137.5, 142.9, 147.7, 150.6, 157.7, 165.8 (C = O). IR (KBr) ($\bar{\upsilon}_{max}$ /cm^{-1}): 3293 and 3156 (NH and NH), 1632 (C = O), 1523 (Ar), 1473 and 1379 (NO_2), 1234 (C–N). Anal. Calc. for $C_{21}H_{17}Cl_2N_5O_3S$ (490.36): C, 51.43; H, 3.49, N, 14.28. Found: C, 51.9; H, 3.8; N, 14.6.

4.2.4. (E)-5-Amino-N′-(2-chlorobenzylidene)-7-(2-chlorophenyl)-8-nitro–3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbohydrazide (5d)

Orange solid; yield: 0.357 g (73%); m.p. 243–245°C. ^{1}H NMR (300 MHz, DMSO): δ 3.36–3.40 (*m*, 2H, CH_2S), 4.30–4.40 (*m*, 2H, CH_2N), 5.88 (*s*, 1H, CH), 7.11–7.49 (*m*, 8H, Ar), 7.84 (*s*, 2H, NH_2), 8.55 (*s*, 1H, CH), 10.94 (*s*, 1H, NH). ^{13}C NMR (75.4 MHz, DMSO): δ 28.0 (CH), 37.8 (CH_2S), 51.0 (CH_2N), 81.7, 122.9, 126.9, 127.6, 127.9, 128.8, 130.2, 130.3, 131.2, 131.9, 132.2, 132.4, 133.0, 140.1, 142.1, 149.9, 166.0 (C = O). Anal. Calc. for $C_{21}H_{17}Cl_2N_5O_3S$ (490.36): C, 51.43; H, 3.49; N, 14.28. Found: C, 50.9; H, 3.1; N, 14.5.

4.2.5. (E)-5-Amino-N′-(4-bromorobenzylidene)-7-(4-bromorophenyl)-8-nitro–3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbohydrazide (5e)

Orange solid; yield: 0.526 g (91%); m.p. 271–273°C. ^{1}H NMR (300 MHz, DMSO): δ 3.35–3.41 (*m*, 2H, CH_2S), 4.22–4.40 (*m*, 2H, CH_2N), 5.64 (*s*, 1H, CH), 7.28 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.41 (*d*, $^3J_{HH}$ = 8.1 Hz, 2H, Ar), 7.53 (*d*, $^3J_{HH}$ = 8.7 Hz, 2H, Ar), 7.58 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 8.08 (*s*, 2H, NH_2), 8.24 (*s*, 1H, CH), 10.83 (*s*, 1H, NH). ^{13}C NMR (75.4 MHz, DMSO): δ 28.1 (CH), 37.3 (CH_2S), 51.2 (CH_2N), 81.8, 120.1, 122.9, 123.7, 128.9, 130.1, 131.4, 132.1, 134.5, 143.5, 144.7, 150.3, 157.5, 165.7 (C = O). IR (KBr) ($\bar{\upsilon}_{max}$ /cm^{-1}): 3472 and 3228 (NH_2 and NH), 1632 (C = O), 1552 (Ar), 1484 and 1382 (NO_2), 1216 (C–N). MS (EI, 70 eV): *m/z* (%) = 579 (M^+, 0.40), 520 (8), 475 (10), 366 (56), 336 (100), 307 (65), 249 (33), 209 (68), 182 (34), 155 (41), 127 (22), 89 (81), 50 (35). Anal. Calc. for $C_{21}H_{17}Br_2N_5O_3S$ (579.26): C, 43.54; H, 2.95; N, 12.09. Found: C, 43.9; H, 2.5; N, 12.4.

4.2.6. (E)-5-Amino-N′-(4-methoxybenzylidene)-7-(4-methoxyphenyl)-8-nitro–3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbohydrazide (5f)

Orange solid; yield: 0.394 g (82%); m.p. 244–246°C. ^{1}H NMR (300 MHz, DMSO): δ 3.34–3.39 (*m*, 2H, CH_2S), 3.64 (*s*, 3H, OCH_3), 3.76 (*s*, 3H, OCH_3), 4.15–4.32 (*m*, 2H, CH_2N), 5.56 (*s*, 1H, CH), 6.77 (*d*, $^3J_{HH}$ = 8.1 Hz, 2H, Ar), 6.95 (*d*, $^3J_{HH}$ = 8.1 Hz, 2H, Ar), 7.23 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.53 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.94 (*s*, 2H, NH_2), 8.21 (*s*, 1H, CH), 10.56 (*s*, 1H, NH). ^{13}C NMR (75.4 MHz, DMSO): δ 28.1 (CH), 36.9 (CH_2S), 51.2 (CH_2N), 55.4 (OCH_3), 55.6 (OCH_3), 82.8, 113.9, 114.7, 124.4, 127.9, 128.5, 128.9, 137.5, 144.6, 149.8, 156.9, 158.3, 160.7, 165.7 (C = O). IR (KBr) ($\bar{\upsilon}_{max}$ /cm^{-1}): 3472 and 3240 (NH_2 and NH), 1632 (C = O), 1552 (Ar), 1506 and 1383 (NO_2), 1215 (C–N). MS (EI, 70 eV): *m/z* (%) = 481 (M^+, 0.15), 422 (7), 377 (9), 335 (12), 288 (100), 257 (81), 217

(27), 186 (13), 161 (32), 120 (19), 77 (22), 51 (10). Anal. Calc. for $C_{23}H_{23}N_5O_5S$ (481.52): C, 57.37; H, 4.81; N, 14.54. Found: C, 57.8; H, 4.3; N, 14.2.

4.2.7. (E)-5-Amino-N′-(3-methoxybenzylidene)-7-(3-methoxyphenyl)-8-nitro–3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbohydrazide (5g)

Orange solid; yield: 0.408 g (85%); m.p. 234–236°C. ^{1}H NMR (300 MHz, DMSO): δ 3.35–3.41 (*m*, 2H, CH_2S), 3.65 (*s*, 3H, OCH_3), 3.75 (*s*, 3H, OCH_3), 4.19–4.39 (*m*, 2H, CH_2N), 5.65 (*s*, 1H, CH), 6.69–7.33 (*m*, 8H, Ar), 8.02 (*s*, 2H, NH_2), 8.25 (*s*, 1H, CH), 10.76 (*s*, 1H, NH). ^{13}C NMR (75.4 MHz, DMSO): δ 28.1 (CH), 37.6 (CH_2S), 51.2 (CH_2N), 55.3 (OCH_3), 55.5 (OCH_3), 82.3, 110.9, 111.5, 114.4, 116.1, 119.9, 120.1, 124.0, 129.7, 130.3, 136.7, 144.4, 146.9, 150.3, 157.3, 159.3, 159.9, 165.9 (C = O). MS (EI, 70 eV): *m/z* (%) = 481 (M^+, 0.50), 422 (10), 377 (4), 335 (7), 288 (100), 257 (73), 217 (23), 186 (10), 161 (28), 134 (19), 77 (31), 51 (15). Anal. Calc. for $C_{23}H_{23}N_5O_5S$ (481.52): C, 57.37; H, 4.81; N, 14.54. Found: C, 57.1; H, 5.1; N, 14.8.

4.2.8. (E)-5-Amino-N′-(3,4-dimethoxybenzylidene)-7-(3,4-dimethoxyphenyl)-8-nitro–3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbohydrazide (5h)

Orange solid; yield: 0.430 g (81%); m.p. 240–242°C. ^{1}H NMR (300 MHz, DMSO): δ 3.34–3.39 (*m*, 2H, CH_2S), 3.65 (*s*, 6H, OCH_3), 3.75 (*s*, 6H, OCH_3), 4.20–4.35 (*m*, 2H, CH_2N), 5.60 (*s*, 1H, CH), 6.63–7.20 (*m*, 6H, Ar), 7.97 (*s*, 2H, NH_2), 8.20 (*s*, 1H, CH), 10.55 (*s*, 1H, NH). ^{13}C NMR (75.4 MHz, DMSO): δ 28.1 (CH), 37.2 (CH_2S), 51.2 (CH_2N), 55.7 (OCH_3), 55.9 (OCH_3), 82.7, 108.1, 111.9, 112.3, 119.8, 121.7, 124.3, 128.0, 138.1, 144.8, 147.9, 148.5, 149.4, 150.0, 150.6, 156.9, 165.9 (C = O). Anal. Calc. for $C_{23}H_{27}N_5O_7S$ (541.58): C, 55.44; H, 5.03; N, 12.93. Found: C, 55.7; H, 5.5; N, 12.6.

4.2.9. (E)-5-Amino-N′-(4-fluorobenzylidene)-7-(4-fluorophenyl)-8-nitro–3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbohydrazide (5i)

Orange solid; yield: 0.361 g (79%); m.p. 246–248°C. ^{1}H NMR (300 MHz, DMSO): δ 3.36–3.41 (*m*, 2H, CH_2S), 4.22–4.39 (*m*, 2H, CH_2N), 5.65 (*s*, 1H, CH), 7.01–7.66 (*m*, 8H, Ar), 8.04 (*s*, 2H, NH_2), 8.27 (*s*, 1H, CH), 10.77 (*s*, 1H, NH). ^{13}C NMR (75.4 MHz, DMSO): δ 28.1 (CH), 37.0 (CH_2S), 51.2 (CH_2N), 82.2, 115.2 (*d*, $^2J_{CF}$ = 21 Hz), 116.2 (*d*, $^2J_{CF}$ = 21 Hz), 124.0, 129.0, 129.8, 131.9, 141.6, 143.6, 150.2, 157.4, 162.4 (*d*, $^1J_{CF}$ = 243 Hz), 162.8 (*d*, $^1J_{CF}$ = 243 Hz), 165.7 (C = O). IR (KBr) ($\bar{\nu}_{max}$ /cm^{-1}): 3470 and 3215 (NH_2 and NH), 1634 (C = O), 1550 (Ar), 1501 and 1383 (NO_2), 1218 (C–N). Anal. Calc. for $C_{21}H_{17}F_2N_5O_3S$ (457.45): C, 55.14; H, 3.75; N, 15.31. Found: C, 55.5; H, 3.9; N, 15.1.

4.2.10. (E)-5-Amino-N′-(3-fluorobenzylidene)-7-(3-fluorophenyl)-8-nitro–3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbohydrazide (5j)

Orange solid; yield: 0.379 g (83%); m.p. 280–282°C. ^{1}H NMR (300 MHz, DMSO): δ 3.37–3.42 (*m*, 2H, CH_2S), 4.19–4.42 (*m*, 2H, CH_2N), 5.71 (*s*, 1H, CH), 6.93–7.43 (*m*, 8H, Ar), 8.11 (*s*, 2H, NH_2), 8.28 (*s*, 1H, CH), 10.90 (*s*, 1H, NH). ^{13}C NMR (75.4 MHz, DMSO): δ 28.1 (CH), 37.5 (CH_2S), 51.3 (CH_2N), 81.6, 112.8 (*d*, $^2J_{CF}$ = 22 Hz), 113.9 (*d*, $^2J_{CF}$ = 21 Hz), 114.6 (*d*, $^2J_{CF}$ = 21 Hz), 116.5 (*d*, $^2J_{CF}$ = 21 Hz), 123.4, 123.6, 123.9, 130.6, 131.2, 137.8, 143.2, 148.1, 150.5, 157.7, 162.4 (*d*, $^1J_{CF}$ = 243 Hz), 162.8 (*d*, $^1J_{CF}$ = 243 Hz),

165.8 (C = O). Anal. Calc. for $C_{21}H_{17}F_2N_5O_3S$ (457.45): C, 55.14; H, 3.75; N, 15.31. Found: C, 55.6; H, 3.3; N, 15.6.

4.2.11. (E)-Methyl-4-(5-amino-6-(2-(4-(methoxycarbonyl)benzylidene) hydrazincarbonyl)-8-nitro–3,7-dihydro-2H-thiazolo[3,2-a]pyridin-7-yl)benzoate (5k)

Orange solid; yield: 0.472 g (88%); m.p. 240–242°C. ^{1}H NMR (300 MHz, DMSO): δ 3.36–3.43 (*m*, 2H, CH_2S), 3.76 (*s*, 3H, OCH_3), 3.83 (*s*, 3H, OCH_3), 4.24–4.36 (*m*, 2H, CH_2N), 5.76 (*s*, 1H, CH), 7.47 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.72 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.82 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.95 (*d*, $^3J_{HH}$ = 8.1 Hz, 2H, Ar), 8.13 (*s*, 2H, NH_2), 8.33 (*s*, 1H, CH), 10.98 (*s*, 1H, NH). ^{13}C NMR (75.4 MHz, DMSO): δ 28.2 (CH), 37.9 (CH_2S), 51.3 (CH_2N), 52.4 (OCH_3), 52.6 (OCH_3), 81.6, 123.5, 127.1, 127.7, 128.2, 128.4, 129.6, 130.0, 130.1, 139.8, 143.2, 150.6, 157.8, 165.8 (C = O), 166.3 (C = O), 166.4 (C = O). Anal. Calc. for $C_{25}H_{23}N_5O_7S$ (537.54): C, 55.86; H, 4.31; N, 13.03. Found: C, 55.3; H, 4.0; N, 13.4.

4.2.12. (E)-5-Amino-8-nitro-N′-(4-nitrobenzylidene)-7-(4-nitrophenyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbohydrazide (5l)

Orange solid; yield: 0.419 g (82%); m.p. 235–237°C. ^{1}H NMR (300 MHz, DMSO): δ 3.39–3.45 (*m*, 2H, CH_2S), 4.22–4.43 (*m*, 2H, CH_2N), 5.83 (*s*, 1H, CH), 7.61 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.83 (*d*, $^3J_{HH}$ = 8.7 Hz, 2H, Ar), 8.09 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 8.36 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 8.38 (*s*, 2H, NH_2), 9.44 (*s*, 1H, CH), 11.17 (*s*, 1H, NH). ^{13}C NMR (75.4 MHz, DMSO): δ 28.2 (CH), 37.7 (CH_2S), 51.3 (CH_2N), 81.0, 123.2, 123.9, 124.4, 127.8, 129.1, 141.6, 142.3, 146.6, 147.7, 150.9, 152.6, 158.1, 165.7 (C = O). Anal. Calc. for $C_{21}H_{17}N_7O_7S$ (511.47): C, 49.31; H, 3.35; N, 19.17. Found: C, 49.6; H, 3.7; N, 19.5.

4.2.13. (E)-5-Amino-8-nitro-N′-(2-nitrobenzylidene)-7-(2-nitrophenyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbohydrazide (5m)

Orange solid; yield: 0.383 g (75%); m.p. 265–267°C. ^{1}H NMR (300 MHz, DMSO): δ 3.38–3.47 (*m*, 2H, CH_2S), 4.29–4.40 (*m*, 2H, CH_2N), 5.95 (*s*, 1H, CH), 7.40–8.02 (*m*, 8H, Ar), 8.28 (*s*, 2H, NH_2), 8.39 (*s*, 1H, CH), 10.76 (*s*, 1H, NH). Anal. Calc. for $C_{21}H_{17}N_7O_7S$ (511.47): C, 49.31; H, 3.35; N, 19.17. Found: C, 49.8; H, 3.5; N, 19.6.

4.2.14. (E)-5-Amino-N′-benzylidene-8-nitro-7-phenyl-3,7-dihydro-2H-oxazolo[3,2-a]pyridine-6-carbohydrazide (5n)

Yellow solid; yield: 0.324 g (80%); m.p. 234–236°C. ^{1}H NMR (300 MHz, DMSO): δ 4.10–4.15 (*m*, 2H, CH_2N), 4.82–4.88 (*m*, 2H, CH_2O), 5.60 (*s*, 1H, CH), 7.07–7.60 (*m*, 10H, Ar), 7.96 (*s*, 2H, NH_2), 8.27 (*s*, 1H, CH), 10.69 (*s*, 1H, NH).^{13}C NMR (75.4 MHz, DMSO): δ 38.3 (CH), 44.1 (CH_2N), 71.2 (CH_2O), 81.7, 109.6, 126.7, 127.0, 127.9, 128.4, 129.1, 129.7, 135.3, 144.3, 146.2, 148.9, 157.0, 165.6 (C = O). MS (EI, 70 eV): *m/z* (%) = 405 (M^+, 2), 388 (37), 359 (12), 259 (44), 242 (75), 207 (81), 171 (99), 131 (92), 104 (52), 77 (100), 51 (73). Anal. Calc. for $C_{21}H_{19}N_5O_4$ (405.41): C, 62.22; H, 4.72; N, 17.27. Found: C, 62.6; H, 4.3.5; N, 17.0.

4.2.15. (E)-5-Amino-N′-(4-chlorobenzylidene)-7-(4-chlorophenyl)-8-nitro–3,7-dihydro-2H-oxazolo[3,2-a]pyridine-6-carbohydrazide (5o)

Yellow solid; yield: 0.417 g (88%); m.p. 263–265°C. ^{1}H NMR (300 MHz, DMSO): δ 4.09–4.14 (*m*, 2H, CH_2N), 4.82–4.88 (*m*, 2H, CH_2O), 5.61 (*s*, 1H, CH), 7.25 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.39 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.60 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.74 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 8.01 (*s*, 2H, NH_2), 8.25 (*s*, 1H, CH), 10.77 (*s*, 1H, NH).^{13}C NMR (75.4 MHz, DMSO): δ 37.8 (CH), 44.2 (CH_2N), 71.3 (CH_2O), 81.1, 109.2, 128.3, 128.6, 129.2, 129.8, 131.3, 134.1, 134.3, 143.1, 145.1, 149.1, 157.0, 165.5 (C = O). MS (EI, 70 eV): *m/z* (%) = 474 (M^+, 0.08), 276 (81), 247 (55), 205 (100), 165 (34), 124 (60), 89 (96), 63 (26). Anal. Calc. for $C_{21}H_{17}Cl_2N_5O_4$ (474.30): C, 53.18; H, 3.61; N, 14.77. Found: C, 53.7; H, 3.3; N, 14.5.

4.2.16. (E)-5-Amino-N′-(3-fluorobenzylidene)-7-(3-fluorophenyl)-8-nitro-3,7-dihydro-2H-oxazolo[3,2-a]pyridine-6-carbohydrazide (5p)

Yellow solid; yield: 0.361 g (82%); m.p. 241–243°C. ^{1}H NMR (300 MHz, DMSO): δ 4.10–4.15 (*m*, 2H, CH_2N), 4.83–4.88 (*m*, 2H, CH_2O), 5.66 (*s*, 1H, CH), 7.15–7.42 (*m*, 8H, Ar), 8.04 (*s*, 2H, NH_2), 8.27 (*s*, 1H, CH), 10.83 (*s*, 1H, NH).^{13}C NMR (75.4 MHz, DMSO): δ 38.1 (CH), 44.2 (CH_2N), 71.4 (CH_2O), 81.0, 109.1, 112.8 (*d*, $^2J_{CF}$ = 22 Hz), 113.6 (*d*, $^2J_{CF}$ = 21 Hz), 114.6 (*d*, $^2J_{CF}$ = 21 Hz), 116.5 (*d*, $^2J_{CF}$ = 21 Hz), 123.4, 124.0, 130.2, 131.3, 137.9, 142.9, 149.0, 149.3, 157.1, 162.8 (*d*, $^1J_{CF}$ = 243 Hz), 163.2 (*d*, $^1J_{CF}$ = 243 Hz), 165.5 (C = O). MS (EI, 70 eV): *m/z* (%) = 260 (17), 231 (16), 189 (25), 133 (40), 107 (100), 76 (10), 57 (21). Anal. Calc. for $C_{21}H_{17}F_2N_5O_4$ (441.39): C, 57.14; H, 3.88; N, 15.87. Found: C, 57.6; H, 3.4; N, 15.5.

4.2.17. (E)-5-Amino-8-nitro-N′-(4-nitrobenzylidene)-7-(4-nitrophenyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbohydrazide (5q)

Orange solid; yield: 0.401 g (81%); m.p. 201–203°C. ^{1}H NMR (300 MHz, DMSO): δ 4.10–4.16 (*m*, 2H, CH_2N), 4.84–4.90 (*m*, 2H, CH_2O), 5.79 (*s*, 1H, CH), 7.66 (*d*, $^3J_{HH}$ = 8.1 Hz, 2H, Ar), 7.83 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 8.07 (*d*, $^3J_{HH}$ = 8.1 Hz, 2H, Ar), 8.23 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 8.18 (*s*, 2H, NH_2), 8.37 (*s*, 1H, CH), 11.10 (*s*, 1H, NH).^{13}C NMR (75.4 MHz, DMSO): δ 38.3 (CH), 44.2 (CH_2N), 71.6 (CH_2O), 80.4, 108.7, 123.7, 124.5, 127.8, 129.1, 141.7, 142.0, 146.5, 147.7, 149.7, 153.6, 157.3, 165.4 (C = O). Anal. Calc. for $C_{21}H_{17}N_7O_8$ (495.40): C, 50.91; H, 3.47; N, 19.79. Found: C, 51.3; H, 3.0; N, 19.4.

4.2.18. (E)-Methyl-4-(5-amino-6-(2-(4-(methoxycarbonyl)benzylidene) hydrazincarbonyl)-8-nitro–3,7-dihydro-2H-oxazolo[3,2-a]pyridin-7-yl) benzoate (5r)

Yellow solid; yield: 0.463 g (89%); m.p. 260–262°C. ^{1}H NMR (300 MHz, DMSO): δ 3.76 (*s*, 3H, OCH_3), 3.82 (*s*, 3H, OCH_3), 4.11–4.16 (*m*, 2H, CH_2N), 4.85–4.90 (*m*, 2H, CH_2O), 5.71 (*s*, 1H, CH), 7.52 (*d*, $^3J_{HH}$ = 8.1 Hz, 2H, Ar), 7.71 (*d*, $^3J_{HH}$ = 8.4 Hz, 2H, Ar), 7.80 (*d*, $^3J_{HH}$ = 8.1 Hz, 2H, Ar), 7.94 (*d*, $^3J_{HH}$ = 8.1 Hz, 2H, Ar), 8.08 (*s*, 2H, NH_2), 8.32 (*s*, 1H, CH), 10.92 (*s*, 1H, NH).^{13}C NMR (75.4 MHz, DMSO): δ 38.4 (CH), 44.2 (CH_2N), 52.4 (OCH_3), 52.6 (OCH_3), 71.4 (CH_2O), 80.9, 109.0, 127.1, 128.2, 128.3, 129.4, 130.0, 130.1, 139.8, 143.0, 149.4, 151.5, 157.2, 165.5 (C = O), 166.3 (C = O), 166.5

(C = O). Anal. Calc. for $C_{25}H_{23}N_5O_8$ (521.48): C, 57.58; H, 4.45; N, 13.43. Found: C, 57.9; H, 4.8, N, 13.1.

Disclosure statement

No potential conflict of interest was reported by the authors.

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