Tetrahedron 67 (2011) 9522–9528

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

An efficient one-pot multicomponent approach to 5-amino-7-aryl-8-nitrothiazolo[3,2-*a*]pyridines

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ARTICLE INFO

Article history:
Received 15 August 2011
Received in revised form 20 September 2011
Accepted 3 October 2011
Available online 8 October 2011

Keywords:
Multicomponent reactions
Heterocycles
Pyridine
Thiazoline
Knoevenagel reaction
Nitrile

ABSTRACT

A series of thiazolo[3,2-*a*]pyridines have been prepared using a multicomponent reaction between aromatic aldehydes, 2-nitromethylenethiazolidine and nitriles containing an active methylene group (malononitrile, ethyl 2-cyanoacetate and 2-phenylsulfonylacetonitrile) in the presence of Et_3N under mild conditions with high yields. One of the compounds shows promising anticancer activity across a range of cancer cell lines.

1. Introduction

Multicomponent reactions (MCRs) have found increasing application for the synthesis of libraries of complex pharmacologically important structures with multiple points of diversity in a small number of steps.[1] Among these structures, thiazolopyridine compounds have been studied[2] due to their importance in a number of biologically relevant areas, including cytotoxicity,[3] antimicrobial activity,[4] α-glucosidase inhibition[5] and hypolipemic activity.[6]

Heterocyclic enamines, including 2-methylenethiazolines, have a great deal of synthetic utility, particularly as bis-nucleophiles for the construction of more complex heterocyclic arrays.[7] However, while such compounds containing electron-withdrawing groups such as esters are common, the reactions of 2-nitromethylenethiazolidine have rarely been investigated.[8–10]

We now report that the reaction of 2-nitromethylenethiazolidine[11] with a range of aldehydes and active methylene compounds provides access to a library of thiazolo[3,2-*a*]pyridines. The reactions of malononitrile, as a representative active methylene compound, were investigated first. The reaction of 2-nitromethylenethiazoline with malononitrile and a broad range of aldehydes was carried out in dry acetonitrile with triethylamine at room temperature. Typically 0.5 equiv of triethylamine was used, although smaller quantities can be used with little reduction in yield. After 3 h, reactions were complete (TLC analysis) in all cases, with excellent yields being obtained with aldehydes possessing electron-withdrawing and electron-donating substituents, as well as those with *ortho* substituents (Table 1).

The identity of these compounds is fully supported by the spectroscopic data obtained. Compound **4g**, with two *ortho* substituents, showed hindered rotation of the aryl ring, with all 14 carbon atoms giving distinct resonances in the ^{13}C NMR spectrum, as well as distinct ^{1}H peaks for the 3 hydrogen atoms on the aromatic ring. As an additional complication, these compounds are only fully soluble in DMSO. Running the ^{1}H NMR spectra in DMSO-d_6 gave good results, although the peak due to adventitious water in the DMSO invariably obscured the CH_2S resonance. In the ^{13}C NMR spectrum, the methine resonance (C-7) in some instances overlapped with the deuterated solvent peak, although careful examination of the DEPT spectra allowed unambiguous assignment. The same products were formed, albeit in much lower yield and purity, with aliphatic aldehydes.

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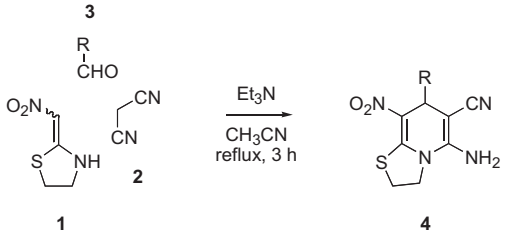
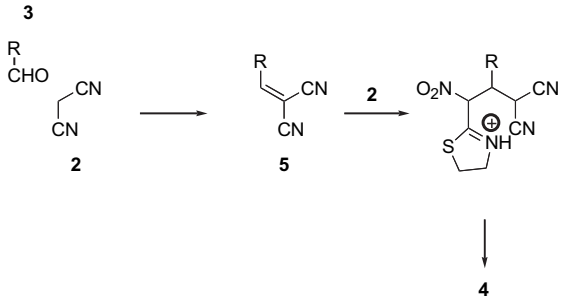
doi:10.1016/j.tet.2011.10.005

Table 1
Reactions of 2-nitromethylenethiazoline with malononitrile and aldehydes



Compound	R	Yield/%
4a	C_6H_5	95
4b	4-FC_6H_4	90
4c	4-ClC_6H_4	94
4d	4-BrC_6H_4	79
4e	2-FC_6H_4	93
4f	2,4-$Cl_2C_6H_3$	99
4g	2,6-$Cl_2C_6H_3$	97
4h	2-BrC_6H_4	97
4i	2-HO−5-BrC_6H_3	82
4j	4-$O_2NC_6H_4$	99
4k	4-$Me_2NC_6H_4$	90

This reaction presumably proceeds by an initial Knoevenagel condensation of the aldehyde and active methylene compound followed by conjugate addition of the enamine and cyclisation (Scheme 1).



Scheme 1. Likely sequence of steps for the formation of compounds **4**.

The reaction also works with ethyl 2-cyanoacetate, with three representative examples being shown in Table 2. In this case, the intermediate could cyclise onto either the nitrile or the ester; only the products (**7**) of cyclisation onto the nitrile were observed. Although these reactions were carried out for a shorter time compared to the experiments in Table 1, the reactions with malononitrile were not closely monitored, and it is likely that they were also complete within 1 h. The reactions can also be carried out under solvent-free conditions by simply grinding the reagents together for 10 min in a mortar, making this a particularly attractive protocol.

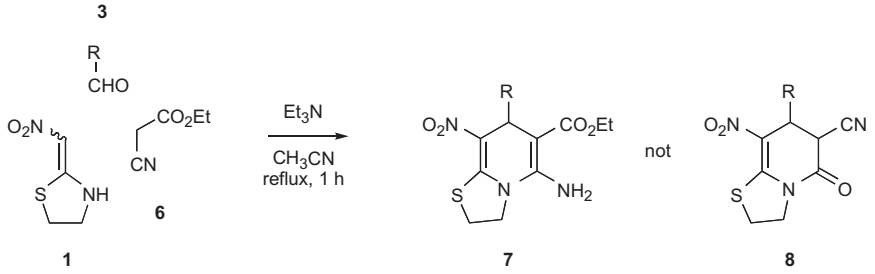
Reactions with 2-phenylsulfonylacetonitrile also gave a similar outcome, although in this case the spectra were complicated by the presence of enamine and imine tautomers **10** and **11**. As shown in Table 3, the relative proportions of the tautomers are close to 1:1 with the exception of **10e**/**11e**. The ratios observed vary only slightly when the spectra are re-run on a different sample from the same batch of compound, so we are confident that compound **10e**/**11e** is a genuine anomaly.

It is tempting to attribute the dramatically different ratio of compounds **10e**/**11e** to steric hindrance, although one might have then expected that the imine tautomer would permit the phenylsulfonyl group to position itself further from the 2,6-dichlorophenyl ring. It would appear that the imine tautomer is present in each case as a single diastereoisomer. In order to understand this process, calculations were carried out on compounds **10a**, **11a**, **10e** and **11e**. The minimum energy conformations of these four compounds were located using Spartan 10[12] at the AM1 semi-empirical level. These conformations were then minimised at the Hartree−Fock level using the 3-21G basis set. The first observation is that the H−C−C−H dihedral angle defining the imine stereochemistry is 74.3° and 85.6° in compounds **11a** and **11e**, respectively. This is suggestive of trans stereochemistry based on the apparent lack of coupling between these hydrogen atoms.

In both cases the enamine tautomer **10** is calculated to be more stable. In the case of **10a**/**11a** the difference is 22.5 kJ mol^{-1}, while in the case of **10e**/**11e** the difference is 30.6 kJ mol^{-1}. Therefore, while the calculations are unable to reproduce the similar levels of stability for the tautomers **10a** and **11a**, they do show that the preference for the enamine tautomer in **10e**/**11e** should be more pronounced compared to **10a**/**11a**, as observed. It is clear from the structures (Fig. 1) that the 2,6-dichlorophenyl ring in compounds **10e** and **11e** must be perpendicular to the dihydropyridine ring as a result of the bulk of the chlorine atoms. This results in destabilisation of the imine tautomer, since the methine hydrogen at position 7 is pushed closer to the sulfone (H7···O=2.360 Å in compound **11a**; 2.254 Å in compound **11e**).

As with the previous case, compound **10e** showed hindered rotation of the 2,6-dichlorophenyl ring, with the ^{13}C resonances for the methine carbon atoms in this ring being broadened and the quaternary carbons not readily distinguished.

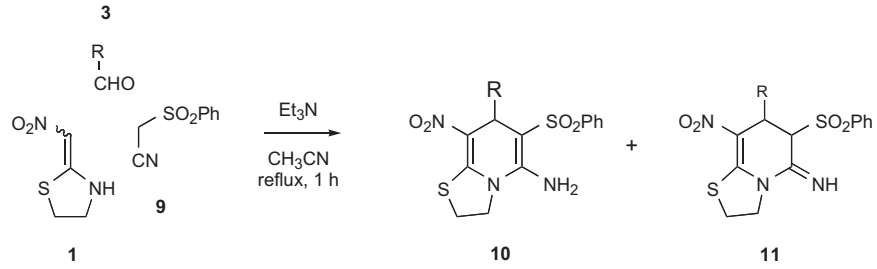
Table 2
Reactions of 2-nitromethylenethiazoline with ethyl 2-cyanoacetate and aldehydes



Compound	R	Yield/%[a]
7a	4-ClC_6H_4	78 (88)
7b	4-BrC_6H_4	73
7c	4-$NO_2C_6H_4$	70 (79)

[a] Yields in parentheses refer to reactions carried out under solvent-free conditions grinding with a pestle in a mortar.

Table 3
Reaction of 2-nitromethylenethiazoline with 2-phenylsulfonylacetonitrile and aldehydes



Compound	R	Ratio **10**/**11**	Yield/%
10a/**11a**	C_6H_5	1:1.35	77
10b/**11b**	4-FC_6H_4	1.25:1	80
10c/**11c**	4-ClC_6H_4	1:1.5	80
10d/**11d**	4-BrC_6H_4	1.4:1	63
10e/**11e**	2,6-$Cl_2C_6H_3$	5:1	83
10f/**11f**	4-$NO_2C_6H_4$	1.4:1	76

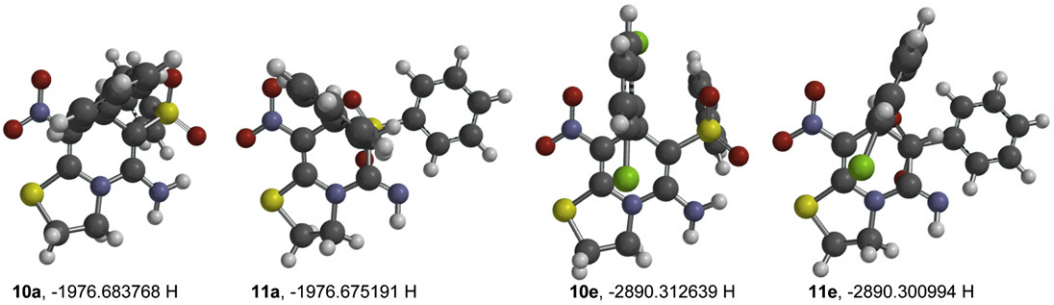


Fig. 1. Lowest energy conformations and calculated gas phase heats of formation (Hartrees) of **10a**, **11a**, **10e**, **11e** (HF 3-21G).

2. Biological evaluation

New compounds were subjected to in vitro anticancer evaluation using the MTT assay in four human cancer cell lines representative of major cancer sub-types—PC3 (prostate), LoVo (colorectal), MCF-7 (breast) and A549 (non-small cell lung). GI_{50} values (50% growth inhibitory concentrations) are presented in Table 4. In general the compounds were found to be fairly inactive, however the low micromolar GI_{50} values for compound **4h** in three cell lines (PC3, LoVo and MCF-7) are encouraging and provide a starting point for optimisation of anticancer activity.

3. Conclusion

In conclusion, we have accomplished a very efficient synthesis of the new nitrothiazolo[3,2-*a*]pyridines using an efficient multi-component coupling reaction. One of the compounds prepared shows promising anticancer activity in a range of cell lines.

4. Experimental section

4.1. General

2-Nitromethylenethiazolidine was prepared according to a literature procedure.[9] Infrared spectra were recorded on a SHIMADZU FTIR-8400S instrument (KBr disc). Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^1H and at 100 MHz for ^{13}C at 25 °C. All chemical shifts are reported in parts per million downfield from TMS. Coupling constants (*J*) are reported in hertz. Melting points were determined on a MELTEMP apparatus and uncorrected. TLC was done using precoated plates with fluorescent indicator (Merck 5735). Solutions of permanganate and PMBA were used for visualisation of the TLC spots.

Table 4
Activity of 5-amino-7-aryl-8-nitrothiazolo[3,2-*a*]pyridines against human breast cancer cell lines[a]

	GI_{50} values (μM)[b] in cell lines[c]			
Compound	PC3	LoVo	MCF-7	A549
4a	>100	>100	>100	>100
4b	>100	>100	>100	>100
4c	>100	>100	>100	>100
4d	>100	>100	>100	>100
4e	>100	>100	>100	>100
4f	>100	>100	>100	>100
4g	95	50	>100	>100
4h	25	15	24	>100
4i	21	>100	>100	>100
4j	>100	>100	>100	>100
4k	>100	>100	>100	>100
7a	>100	>100	>100	>100
7b	61	12	>100	>100
7c	>100	>100	>100	>100
10a/**11a**	>100	>100	>100	>100
10b/**11b**	>100	>100	>100	>100
10c/**11c**	>100	>100	>100	>100
10d/**11d**	>100	>100	>100	>100
10e/**11e**	17	>100	>100	>100
10f/**11f**	33	>100	>100	>100

[a] Determined by MTT assay (96 h drug exposure), see Biological, Experimental for details.
[b] Compounds tested in triplicate, data expressed as mean values.
[c] Cancer cell line origin: PC-3 (prostate), LoVo (colorectal), MCF-7 (breast), A549 (non-small cell lung).

4.2. General reaction procedure for preparation of thiazolo [3,2-*a*]pyridines

Aromatic aldehyde (1 mmol, 1.0 equiv), 2-nitromethylenethiazolidine (1 mmol, 1 equiv, 146 mg) and appropriate nitrile (1 mmol, 1.0 equiv) were mixed in MeCN (10 mL) in a round-bottomed flask and the reaction mixture was stirred and heated until all reactants dissolved. Triethylamine (50 mg, 0.5 mmol) was added and the reaction mixture heated under reflux for 1–3 h (see Tables 1–3). After cooling, the solvent was removed under reduced pressure and the residue recrystallised from hexane/ethyl acetate mixtures to give the pure products with data given below.

4.3. 5-Amino-8-nitro-7-phenyl-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile (4a)

Obtained as an orange solid (285 mg, 95%), mp 198–199 °C. Found: M^+, 300.0685. $C_{14}H_{12}N_4O_2S$ requires M, 300.0681; ν_{max} (KBr) 3345 (NH_2), 2184 (CN) and 1658 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 7.31 (2H, app. t, *J* 7.3, aromatic CH), 7.22 (1H, t, *J* 7.3, aromatic CH), 7.19 (2H, d, *J* 7.0, aromatic CH), 6.57 (2H, br s, NH_2), 4.77 (1H, s, C*H*Ph), 4.34–4.18 (2H, m, CH_2N) and 3.41–3.30 (2H, m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; DMSO-d_6) 157.9 (C), 149.6 (C), 144.5 (C), 128.9 (CH), 127.5 (CH), 127.4 (CH), 127.3 (C), 120.8 (C), 62.5 (C), 51.6 (CH_2), 41.4 (CH) and 28.3 (CH_2); *m*/*z* (TOF EI$^+$) 300 (M^+, 20%), 267 (60), 233 (100) and 223 (90).

4.4. 5-Amino-7-(4-fluorophenyl)-8-nitro-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile (4b)

Obtained as a yellow solid (287 mg, 90%), mp 232–233 °C. Found: $(M-H)^-$, 317.0511. $C_{14}H_{10}N_4O_2SF$ requires M, 317.0509; ν_{max} (KBr) 3433 (NH_2), 2195 (CN) and 1659 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 7.28–7.22 (2H, m, aromatic CH), 7.16–7.10 (2H, m, aromatic CH), 6.60 (2H, br s, NH_2), 4.80 (1H, s, C*H*Ar), 4.34–4.42 (2H, m, CH_2N) and 3.44–3.32 (2H, m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; DMSO-d_6) 161.2 (d, $^1J_{C-F}$ 241.3, C–F), 157.6 (C), 149.2 (C), 140.3 (d, $^4J_{C-F}$ 3.0, C *para* to F), 129.0 (d, $^3J_{C-F}$ 8.2, CH *meta* to F), 121.8 (C), 120.3 (C), 115.2 (d, $^2J_{C-F}$ 21.2, CH *ortho* to F), 61.9 (C), 51.2 (CH_2), 40.4 (CH) and 27.9 (CH_2); *m*/*z* (TOF ES$^-$) 317 (M–H, 100%).

4.5. 5-Amino-7-(4-chlorophenyl)-8-nitro-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile (4c)

Obtained as an orange solid (315 mg, 94%), mp 213–215 °C. Found: $(M-2H)^+$, 332.0137. $C_{14}H_9N_4O_2S^{35}Cl$ requires M, 332.0135; ν_{max} (KBr) 3439 (NH_2), 2189 (CN) and 1649 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 7.37 (2H, d, *J* 8.4, aromatic CH), 7.23 (2H, d, *J* 8.4, aromatic CH), 6.62 (2H, br s, NH_2),4.80 (1H, s, C*H*Ar), 4.33–4.19 (2H, m, CH_2N) and 3.40–3.10 (2H, m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; DMSO-d_6) 158.2 (C), 149.6 (C), 143.5 (C), 132.0 (C), 129.4 (CH), 128.9 (CH), 122.0 (C), 120.7 (C), 62.1 (C), 51.6 (CH_2), 41.0 (CH) and 28.3 (CH_2); *m*/*z* (TOF EI$^+$) 334 (M^+, 28%), 332 (M^+, 86), 267 (60) and 84 (100).

4.6. 5-Amino-7-(4-bromophenyl)-8-nitro-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile (4d)

Obtained as a yellow solid (299 mg, 79%), mp 240 °C (dec). Found: $(M-H)^+$, 376.9694. $C_{14}H_{10}N_4O_2S^{79}Br$ requires M, 376.9708; ν_{max} (KBr) 3416 (NH_2), 2193 (CN) and 1640 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 7.50 (2H, d, *J* 8.4, aromatic CH), 7.16 (2H, d, *J* 8.4, aromatic CH), 6.62 (2H, br s, NH_2), 4.78 (1H, s C*H*Ar), 4.33–4.17 (2H, m, CH_2N), 3.40–3.30 (2H, m, CH_2S); δ_C (100 MHz; DMSO-d_6) 157.8 (C), 149.2 (C), 143.5 (C), 131.4 (CH), 129.3 (CH), 121.5 (C), 120.3 (C), 120.1 (C), 61.6 (C), 51.2 (CH_2), 40.7 (CH) and 27.9 (CH_2); *m*/*z* (TOF ES$^-$) 379 ($M-H^+$, 100%) and 377 (95).

4.7. 5-Amino-7-(2-fluorophenyl)-8-nitro-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile (4e)

Obtained as a yellow solid (297 mg, 93%), mp 230 °C (dec). Found: $(M-H)^-$, 317.0495. $C_{14}H_{10}N_4O_2SF$ requires M, 317.0509; ν_{max} (KBr) 3431 (NH_2), 2187 (CN) and 1659 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 7.30–7.20 (2H, m, aromatic CH), 7.17–7.11 (2H, m, aromatic CH), 6.62 (2H, br s, NH_2), 5.10 (1H, s, C*H*Ar), 4.27 (2H, app. t, *J* 7.7, CH_2N) and 3.45–3.30 (2H, m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; DMSO-d_6) 159.7 (d, $^1J_{C,F}$ 245.7, C–F), 158.1 (C), 149.4 (C), 130.7 (d, $^2J_{C-F}$ 13.1, C), 129.5 (d, $^3J_{C-F}$ 4.1, CH *meta* to F), 129.1 (d, $^3J_{C-F}$ 8.3, CH *meta* to F), 124.8 (d, $^4J_{C-F}$ 3.3, CH *para* to F), 120.8 (C), 120.2 (C), 115.5 (d, $^2J_{C-F}$ 21.2, CH *ortho* to F), 60.7 (C), 51.2 (CH_2), 35.2 (CH) and 27.9 (CH_2); *m*/*z* (TOF ES$^-$) 353 ($M+^{35}Cl$, 45%) and 317 (M–H, 100).

4.8. 5-Amino-7-(2,4-dichlorophenyl)-8-nitro-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile (4f)

Obtained as a yellow solid (363 mg, 99%), mp 263–264 °C. Found: $(M-H)^-$, 366.9829. $C_{14}H_9N_4O_2^{35}Cl_2S$ requires M, 366.9823; ν_{max} (KBr) 3396 (NH_2), 2191 (CN) and 1658 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 7.55 (1H, d, *J* 1.6, aromatic CH), 7.37 (1H, dd, *J* 8.3, 1.6, aromatic CH), 7.33 (1H, d, *J* 8.3, aromatic CH), 6.65 (2H, br s, NH_2), 5.30 (1H, s, C*H*Ar), 4.28 (2H, app. t, *J* 7.6, CH_2N) and 3.4–3.3 (2H, m, CH_2S); δ_C (100 MHz; DMSO-d_6) 158.6 (C), 149.5 (C), 140.3 (C), 132.8 (C), 132.2 (C), 131.3 (CH), 128.8 (CH), 127.9 (CH), 120.9 (C), 119.8 (C), 60.2 (C), 51.2 (CH_2), 38.1 (CH) and 27.9 (CH_2); *m*/*z* (TOF ES$^-$) 371 (M, 14), 369 (M, 70) and 367 (M, 100).

4.9. 5-Amino-7-(2,6-dichlorophenyl)-8-nitro-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile (4g)

Obtained as an orange solid (356 mg, 97%), mp 279–281 °C. Found: $(M-H)^-$, 366.9810. $C_{14}H_9N_4O_2^{35}Cl_2S$ requires M, 366.9823; ν_{max} (KBr) 3466 (NH_2), 2180 (CN) and 1643 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 7.46 (1H, d, *J* 7.0, aromatic CH), 7.39 (1H, d, *J* 7.4, aromatic CH), 7.27 (1H, app. t, *J* 7.7, aromatic CH), 6.69 (2H, br s, NH_2), 5.87 (1H, s, C*H*Ar), 4.42–4.37 (1H, m, one of CH_2N) and 4.25–4.17 (1H, m, one of CH_2N) (CH_2S peak obscured by broad water peak from DMSO); δ_C (100 MHz; DMSO-d_6) 160.2 (C), 150.8 (C), 136.2 (C), 136.0 (C), 134.8 (C), 130.9 (CH), 129.7 (CH), 129.0 (CH), 120.0 (C), 119.9 (C), 58.2 (C), 51.4 (CH_2), 38.1 (CH) and 28.1 (CH_2); *m*/*z* (TOF ES$^-$) 371 (M, 10%), 369 (M, 47), 367 (M, 63) and 221 (100).

4.10. 5-Amino-7-(2-bromophenyl)-8-nitro-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile (4h)

Obtained as a yellow solid (368 mg, 97%), mp 242–244 °C. Found: $(M-H)^+$, 376.9713. $C_{14}H_{10}N_4O_2S^{79}Br$ requires M, 376.9708; ν_{max} (KBr) 3446 (NH_2), 2185 (CN) and 1649 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 7.55 (1H, d, *J* 7.9, aromatic CH), 7.30 (1H, app. t, *J* 7.4, aromatic CH), 7.27 (1H, dd, *J* 7.7, 1.5, aromatic CH), 7.16 (1H, app. td, *J* 7.6, 1.5, aromatic CH), 6.60 (2H, br s, NH_2), 5.31 (1H, s, C*H*Ar), 4.28 (2H, app. t, *J* 7.7, CH_2N) and 3.45–3.20 (2H, m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; DMSO-d_6) 158.3 (C), 149.4 (C), 142.8 (C), 132.7 (CH), 130.0 (CH), 128.9 (CH), 128.3 (CH), 122.3 (C), 121.5 (C), 119.8 (C), 60.9 (C), 51.1 (CH_2), 40.6 (CH) and 27.8 (CH_2); *m*/*z* (TOF ES$^-$) 379 ($M-H^+$, 100) and 377 (97).

4.11. 5-Amino-7-(5-bromo-2-hydroxyphenyl)-8-nitro-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile (4i)

Obtained as a yellow solid (325 mg, 82%), mp 210 °C (dec). Found: $(M-H)^-$, 392.9674. $C_{14}H_{10}N_4O_3S^{79}Br$ requires M, 392.9657; ν_{max} (KBr) 3471 (NH_2), 2191 (CN) and 1649 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 9.86 (1H, s, OH), 7.19 (1H, dd, *J* 8.6, 2.5, aromatic CH), 7.11 (1H, d, *J* 2.5, aromatic CH), 6.71 (1H, d, *J* 8.6, aromatic CH), 6.48 (2H, br s, NH_2), 5.00 (1H, s, C*H*Ar), 4.39–4.31 (1H, app. td, *J* 10.7, 7.8, one of CH_2N), 4.18–4.11 (1H, app. td, *J* 10.7, 7.7, one of CH_2N) and 3.40–3.30 (2H, m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; DMSO-d_6) 158.2 (C), 154.6 (C), 149.7 (C), 132.0 (C), 131.2 (CH), 130.5 (CH), 120.9 (C), 120.4 (C), 117.8 (CH), 109.9 (C), 60.7 (C), 51.1 (CH_2), 36.6 (CH) and 27.8 (CH_2); *m*/*z* (TOF ES^-) 395 (M, 100), 393 (M, 100), 249 (81) and 247 (84).

4.12. 5-Amino-8-nitro-7-(4-nitrophenyl)-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile (4j)

Obtained as a yellow solid (342 mg, 99%), mp 214 °C (dec). Found: $(M-H)^-$, 344.0455. $C_{14}H_{10}N_5O_4S$ requires M, 344.0454; ν_{max} (KBr) 3331 (NH_2), 2187 (CN) and 1661 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 8.19 (2H, d, *J* 8.5, aromatic CH), 7.51 (2H, d, *J* 8.5, aromatic CH), 6.72 (2H, br s, NH_2), 4.98 (1H, s, C*H*Ar), 4.35–4.20 (2H, m, CH_2N) and 3.50–3.33 (2H, m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; DMSO-d_6) 158.4 (C), 151.4 (C), 149.4 (C), 146.6 (C), 128.4 (CH), 123.9 (CH), 121.0 (C), 120.1 (C), 60.8 (C), 51.3 (CH_2), 40.0 (CH), 28.0 (CH_2); *m*/*z* (TOF ES^-) 407 (M+CH_3CN+Na−H, 60%) and 344 (M−H, 100%).

4.13. 5-Amino-7-(4-(dimethylamino)phenyl)-8-nitro-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carbonitrile (4k)

Obtained as a brick-red solid (308 mg, 90%), mp 226 °C (dec). Found: $(M-H)^-$, 342.1018. $C_{16}H_{16}N_5O_2S$ requires M, 342.1025; ν_{max} (KBr) 3343 (NH_2), 2184 (CN) and 1649 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 6.98 (2H, d, *J* 8.7, aromatic CH), 6.64 (2H, d, *J* 8.7, aromatic CH), 6.48 (2H, br s, NH_2), 4.64 (1H, s, C*H*Ar), 4.30–4.19 (2H, m, CH_2N), 3.40–3.30 (2H, m, obscured by water in DMSO, CH_2S) and 2.85 (6H, s, NMe_2); δ_C (100 MHz; DMSO-d_6) 157.0 (C), 149.8 (C), 149.1 (C), 131.9 (C), 127.9 (CH), 122.8 (C), 120.8 (C), 112.6 (CH), 63.1 (C), 51.3 (CH), 40.4 (2×CH_3), 40.2 (CH) and 28.1 (CH_2); *m*/*z* (TOF ES^-) 342 (M−H, 100%).

4.14. Ethyl 5-amino-7-(4-chlorophenyl)-8-nitro-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate (7a)

Obtained as an orange solid (295 mg, 78%), mp 214–216 °C. Found: $(M-H)^-$, 380.0486. $C_{16}H_{15}O_4N_3S^{35}Cl$ requires M, 380.0472; ν_{max} (KBr) 3420 (NH_2), 1667 (CO) and 1632 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 7.27 (4H, app. s, aromatic CH), 6.57 (2H, br s, NH_2), 5.36 (1H, s, C*H*Ar), 4.41–4.32 (1H, m, one of CH_2N), 4.17–4.08 (3H, m, one of CH_2N and OCH_2), 3.43–3.35 (2H, m, CH_2S) and 1.25 (3H, t, *J* 8.5, CH_3); δ_C (100 MHz; $CDCl_3$) 169.0 (C), 154.9 (C), 149.9 (C), 143.1 (C), 132.4 (C), 129.7 (CH), 128.2 (CH), 125.7 (C), 84.0 (C), 60.1 (CH_2), 49.9 (CH_2), 39.1 (CH), 28.3 (CH_2) and 14.4 (CH_3); *m*/*z* (TOF ES^-) 382 (M−H, 40%) and 380 (M−H, 100).

4.15. Ethyl 5-amino-7-(4-bromophenyl)-8-nitro-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate (7b)

Obtained as an orange solid (310 mg, 73%), mp 213–214 °C. Found: $(M-H)^-$, 423.9980. $C_{16}H_{15}N_3O_4S^{79}Br$ requires M, 423.9967; ν_{max} (KBr) 3416 (NH_2), 1667 (CO) and 1632 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 7.34 (2H, d, *J* 8.5, aromatic CH), 7.15 (2H, d, *J* 8.5, aromatic CH), 6.50 (2H, br s, NH_2), 5.31 (1H, s, C*H*Ar), 4.35–4.24 (1H, m, one of CH_2N), 4.20–4.03 (3H, m, one of CH_2N and OCH_2), 3.48–3.20 (2H, m, CH_2S) and 1.19 (3H, t, *J* 7.1, CH_3); δ_C (100 MHz; $CDCl_3$) 169.0 (C), 154.6 (C), 150.0 (C), 143.7 (C), 131.2 (CH), 130.0 (CH), 125.8 (C), 120.6 (C), 84.1 (C), 60.1 (CH_2), 49.9 (CH_2), 39.2 (CH), 28.3 (CH_2) and 14.4 (CH_3); *m*/*z* (TOF ES^-) 426 (M−H, 100%) and 424 (M−H, 97).

4.16. Ethyl 5-amino-8-nitro-7-(4-nitrophenyl)-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridine-6-carboxylate (7c)

Obtained as a yellow solid (275 mg, 70%), mp 145 °C (dec). Found: $(M-H)^-$, 391.0699. $C_{16}H_{15}O_6N_4S$ requires M, 391.0712; ν_{max} (KBr) 3425 (NH_2), 1665 (CO) and 1630 (C=C) cm^{-1}; δ_H (400 MHz; DMSO-d_6) 8.10 (2H, d, *J* 8.3, aromatic CH), 7.40 (2H, d, *J* 8.5, aromatic CH), 6.60 (2H, br s, NH_2), 5.40 (1H, s, C*H*Ar), 4.41–4.29 (1H, m, one of CH_2N), 4.16–4.02 (3H, m, one of CH_2N and OCH_2), 3.55–3.29 (2H, m, CH_2S) and 1.18 (3H, t, *J* 7.1, CH_3); δ_C (100 MHz; $CDCl_3$) 168.7 (C), 155.3 (C), 151.9 (C), 150.2 (C), 146.9 (C), 129.3 (CH), 125.1 (C), 123.5 (CH), 83.3 (C), 60.2 (CH_2), 50.1 (CH_2), 39.9 (CH), 28.4 (CH_2) and 14.4 (CH_3); *m*/*z* (TOF ES^-) 393 (M−H, 100%).

4.17. 8-Nitro-7-phenyl-6-(phenylsulfonyl)-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5-amine (10a) and 8-nitro-7-phenyl-6-(phenylsulfonyl)-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5(3*H*)-imine (11a)

Obtained as a pale yellow solid (320 mg, 77%, 1:1.35 mixture of **10a**/**11a** according to ^1H NMR spectroscopic data), mp 227–230 °C. Found: $(M-H)^-$, 414.0569. $C_{19}H_{16}O_4N_3S_2$ requires M, 414.0582; ν_{max} (KBr) 3298 (NH_2), 1636 (C=C), 1555, 1445, 1381, 1211 and 1138 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 9.70 (1H of **11a**, s, NH), 7.87–7.77 (3H of **11a**, m, aromatic CH of SO_2Ph), 7.68 (2H of **11a**, app. dd, *J* 8.3, 7.3, aromatic CH of SO_2*Ph*), 7.64 (2H of **10a**, d, *J* 7.2, aromatic CH of SO_2*Ph*), 7.52 (1H of **10a**, app. t, *J* 7.4, aromatic CH of SO_2*Ph*), 7.40 (2H of **10a**, app. t, *J* 7.7, aromatic CH of SO_2*Ph*), 7.35–7.23 (3H of **11a**, m, aromatic CH), 7.18–7.08 (5H of **10a**, m, aromatic CH), 6.96 (2H of **11a**, app. d, *J* 7.0, aromatic CH), 6.92 (2H of **10a**, br s, NH_2), 5.10 (1H of **10a**, s, C*H*Ph), 4.92 (1H of **11a**, s, C*H*Ph), 4.91 (1H of **11a**, s, C*H*SO_2Ph), 4.41 (1H of **11a**, ddd, *J* 11.8, 8.7, 3.3, one of CH_2N), 4.35–4.23 (2H of **10a**, m, CH_2N), 4.13 (1H of **11a**, app. td, *J* 11.4, 8.5, one of CH_2N), 3.37 (2H of **10a**, app. t, *J* 7.6, CH_2S), 3.33–3.27 (1H of **11a**, m, one of CH_2S) and 3.09 (1H of **11a**, app. td, *J* 11.1, 8.8, one of CH_2S); δ_C (100 MHz; DMSO-d_6) 159.7 (C, **11a**), 157.1 (C, **10a**), 149.6 (C, **11a**), 147.7 (C, **10a**), 143.6 (C, **11a**), 143.5 (C, **10a**), 138.6 (C, **11a**), 135.7 (C, **11a**), 135.3 (CH, **11a**), 132.4 (CH, **10a**), 129.7 (CH, **10a**), 129.4 (CH, **11a**), 129.0 (CH, **10a**), 128.6 (CH, **11a**), 128.1 (CH, **10a**), 128.1 (CH, **11a**), 127.7 (CH, **11a**), 126.8 (CH, **10a**), 126.6 (CH, **11a**), 125.7 (CH, **10a**), 123.7 (C, **10a**), 119.6 (C, **11a**), 86.3 (C, **10a**), 69.9 (CH, **11a**), 51.5 (CH_2, **11a**), 51.0 (CH_2, **10a**), 40.2 (CH, **11a**), 39.9 (CH, **10a**), 28.2 (CH_2, **10a**) and 27.8 (CH_2, **11a**); *m*/*z* (TOF ES^-) 414 (M−H, 100%) and 340 (21).

4.18. 7-(4-Fluorophenyl)-8-nitro-6-(phenylsulfonyl)-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5-amine (10b) and 7-(4-fluorophenyl)-8-nitro-6-(phenylsulfonyl)-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5(3*H*)-imine (11b)

Obtained as a pale yellow solid (345 mg, 80%, 1.25:1 mixture of **10b**/**11b** according to ^1H NMR spectroscopic data), mp 243–244 °C. Found: $(M-H)^-$, 432.0497. $C_{19}H_{16}O_4N_3S_2F$ requires M, 432.0488; ν_{max} (KBr) 3293 (NH_2), 1638 (C=C), 1562, 1449, 1379, 1215 and 1138 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 9.69 (1H of **11b**, s, NH), 7.85–7.77 (3H of **11b**, m, aromatic CH of SO_2*Ph*), 7.71–7.62 (2H of **10b** and 2H of **11b**, m, aromatic CH of SO_2*Ph*), 7.53 (1H of **10b**, app. t, *J* 7.4, aromatic CH of SO_2*Ph*), 7.41 (2H of **10b**, app. t, *J* 7.7, aromatic CH of SO_2*Ph*), 7.19–7.12 (4H of **10b**, m, aromatic CH of *Ar*–F), 7.05–7.00

(2H of **11b**, m, aromatic CH of *Ar*–F), 6.98–6.91 (2H of **11b**, m, aromatic CH of *Ar*–F), 6.95 (2H of **10b**, br s, NH_2), 5.08 (1H of **10b**, s, C*H*Ar), 4.92 (2H of **11b**, app. s, C*H*Ar, C*H*SO_2Ph), 4.40 (1H of **11b**, ddd, *J* 11.9, 7.0, 2.7, one of CH_2N), 4.34–4.24 (2H of **10b**, m, CH_2N), 4.14 (1H of **11b**, app. td, *J* 11.3, 8.5, one of CH_2N), 3.37 (2H of **10b**, app. t, *J* 7.6, CH_2S), 3.35–3.27 (1H of **11b**, m, one of CH_2S) and 3.08 (1H of **11b**, app. td, *J* 11.1, 8.8, one of CH_2S); δ_C (100 MHz; DMSO-d_6) 161.6 (d, $^1J_{C-F}$ 244.3, C–F, **11b**), 161.0 (d, $^1J_{C-F}$ 242.8, C–F, **10b**), 157.1 (C, **10b**), 149.6 (C, **11b**), 147.7 (C, **10b**), 143.5 (C, **10b**), 139.8 (d, $^4J_{C-F}$ 3.2, C *para* to F, **11b**), 135.6 (C, **10b**), 135.3 (CH, **11b**), 134.7 (d, $^4J_{C-F}$ 3.0, C *para* to F, **11b**), 132.4 (CH, **11b**), 129. 7 (CH, **10b**), 129.7 (d, $^3J_{C-F}$ 7.6, CH *meta* to F, **11b**), 128.9 (CH, **10b**), 128.8 (d, $^3J_{C-F}$ 8.6, CH *meta* to F), 128.6 (C, **11b**), 125.7 (CH, **10b**), 123.4 (C, **10b**), 119.5 (C, **11b**), 116.1 (d, $^2J_{C-F}$ 21.7, CH *ortho* to F, **11b**), 114.7 (d, $^2J_{C-F}$ 21.3, CH *ortho* to F, **10b**), 86.1 (C, **10b**), 69.8 (CH, **11b**), 51.5 (CH_2, **11b**), 51.0 (CH_2, **10b**), 40.0 (CH, **10b**), 39.87 (CH, **11b**), 28.2 (CH_2, **10b**) and 27.8 (CH_2, **11b**); *m*/*z* (TOF ES$^-$) 432 (M–H, 100%) and 180 (56).

4.19. 7-(4-Chlorophenyl)-8-nitro-6-(phenylsulfonyl)-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5-amine (10c) and 7-(4-chlorophenyl)-8-nitro-6-(phenylsulfonyl)-6,7-dihydro-2H-thiazolo[3,2-*a*]pyridin-5(3*H*)-imine (11c)

Obtained as a pale yellow solid (360 mg, 80%, 1:1.5 mixture of **10c**/**11c** according to ^{1}H NMR spectroscopic data), mp 246–247 °C. Found: (M–H)$^-$, 448.0183. $C_{19}H_{16}O_4N_3S_2^{35}Cl$ requires M, 448.0193; ν_{max} (KBr) 3293 (NH_2), 1638 (C=C), 1557, 1447, 1383, 1219 and 1138 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 9.68 (1H of **11c**, s, NH), 7.85–7.77 (3H of **11c**, m, aromatic CH of SO_2Ph), 7.71–7.64 (2H of **10c** and 2H of **11c**, m, aromatic CH of SO_2Ph), 7.54 (1H of **10c**, app. t, *J* 7.4, aromatic CH of SO_2Ph), 7.42 (2H of **10c**, app. t, *J* 7.8, aromatic CH of SO_2Ph), 7.38 (2H of **11c**, d, *J* 8.5, aromatic CH of Ar–Cl), 7.20 (2H of **10c**, d, *J* 8.6, aromatic CH of Ar–Cl), 7.15 (2H of **10c**, d, *J* 8.6, aromatic CH of Ar–Cl), 6.99–7.03 (2H of **11c**, d, *J* 8.5, aromatic CH of Ar–Cl), 6.97 (2H of **10c**, br s, NH_2), 5.06 (1H of **10c**, s, C*H*Ar), 4.93 (1H of **11c**, s, C*H*Ar), 4.92 (1H of **11c**, s, C*H*SO_2Ph), 4.39 (1H of **11c**, ddd, *J* 11.9, 8.7, 3.3, one of CH_2N), 4.33–4.25 (2H of **10c**, m, CH_2N), 4.13 (1H of **11c**, app. td, *J* 11.4, 8.6, one of CH_2N), 3.37 (2H of **10c**, app. t, *J* 7.6, CH_2S), 3.34–3.26 (1H of **11c**, m, one of CH_2S) and 3.09 (1H of **11c**, app. td, *J* 11.1, 8.8, CH_2S); δ_C (100 MHz; DMSO-d_6) 159.9 (C, **10c**), 157.3 (C, **11c**), 149.5 (C, **10c**), 147.7 (C, **11c**), 143.4 (C, **11c**), 142.6 (C, **11c**), 137.5 (C, **10c**), 135.6 (C, **10c**), 135.4 (CH, **10c**), 132.7 (C, **10c**), 132.4 (CH, **11c**), 131.4 (C, **11c**), 129.7 (CH, **10c**), 129.7 (CH, **11c**), 129.3 (CH, **10c**), 129.0 (CH, **11c**), 128.6 (CH, **10c**), 128.6 (CH, **10c**), 127.9 (CH, **11c**), 125.7 (CH, **11c**), 123.1 (C, **11c**), 119.2 (C, **10c**), 85.5 (C, **10c**), 69.6 (CH, **11c**), 51.5 (CH_2, **11c**), 51.0 (CH_2, **10c**), 39.2 (CH, **10c**), 39.0 (CH, **11c**), 28.2 (CH_2, **10c**) and 27.8 (CH_2, **11c**); *m*/*z* (TOF ES$^-$) 450 (M–H, 42%), 448 (M–H, 100), 341 (48), 339 (95) and 163 (55).

4.20. 7-(4-Bromophenyl)-8-nitro-6-(phenylsulfonyl)-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5-amine (10d) and 7-(4-bromophenyl)-8-nitro-6-(phenylsulfonyl)-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5(3*H*)-imine (11d)

Obtained as a pale yellow solid (310 mg, 63%, 1.4:1 mixture of **10d**/**11d** according to ^{1}H NMR spectroscopic data), mp 243–245 °C. Found: (M–H)$^-$, 491.9710. $C_{19}H_{16}O_4N_3S_2^{79}Br$ requires M, 491.9687; ν_{max} (KBr) 3293 (NH_2), 1638 (C=C), 1555, 1447, 1383, 1219 and 1138 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 9.69 (1H of **11d**, s, NH), 7.87–7.70 (2H of **10d**, m, aromatic CH of SO_2*Ph*), 7.72–7.65 (5H of **11d**, m, aromatic CH of SO_2*Ph*), 7.58–7.50 (2H of **11d** and 1H of **10d**, m, aromatic CH), 7.43 (2H of **10d**, app. t, *J* 7.7, aromatic CH of SO_2*Ph*), 7.34 (2H of **10d**, app. d, *J* 8.4, aromatic CH of *Ar*–Br), 7.11 (2H of **10d**, app. d, *J* 8.4, aromatic CH of *Ar*–Br), 6.99 (2H of **10d**, br s, NH_2), 6.96 (2H of **11d**, app. d, *J* 8.5, aromatic CH from *Ar*–Br), 5.05 (1H of **10d**, s, C*H*Ar), 4.94 (1H of **11d**, s, C*H*Ar), 4.91 (1H of **11d**, s, C*H*SO_2Ph), 4.39 (1H of **11d**, ddd, *J* 11.2, 7.2, 2.9, one of CH_2N), 4.34–4.25 (2H of **10d**, m, CH_2N), 4.13 (1H of **11d**, app. td, *J* 11.5, 8.5, one of CH_2N), 3.38 (2H of **10d**, app. t, *J* 7.7, CH_2S), 3.35–3.28 (1H of **11d**, m, one of CH_2S) and 3.09 (1H of **11d**, app. td, *J* 11.1, 8.8, one of CH_2S); δ_C (100 MHz; DMSO-d_6) 160.0 (C, **11d**), 157.3 (C, **10d**), 149.5 (C, **11d**), 147.7 (C, **10d**), 143.4 (C, **10d**), 143.0 (C, **11d**), 137.9 (C, **11d**), 135.6 (CH, **11d**), 135.4 (C, **10d**), 132.4 (CH, **11d**), 132.2 (CH, **10d**), 130.9 (CH, **10d**), 130.1 (CH, **10d**), 129.7 (CH, **11d**), 129.0 (CH, **10d**), 128.9 (CH, **11d**), 128.6 (CH, **11d**), 125.7 (CH, **10d**), 123.1 (C, **10d**), 121.2 (C, **11d**), 119.9 (C, **10d**), 119.1 (C, **11d**), 85.7 (C, **10d**), 69.6 (CH, **11d**), 51.5 (CH_2, **11d**), 51.0 (CH_2, **10d**), 48.6 (CH, **10d**), 39.6 (CH, **11d**), 28.2 (CH_2, **10d**) and 27.8 (CH_2, **11d**); *m*/*z* (TOF ES$^-$) 494 (M–H$^+$, 48%), 492 (50), 339 (100), 325 (70), 311 (60) and 265 (75).

4.21. 8-Nitro-7-(2,6-dichlorophenyl)-6-(phenylsulfonyl)-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5-amine (10e) and 7-(2,6-dichlorophenyl)-8-nitro-6-(phenylsulfonyl)-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5(3*H*)-imine (11e)

Obtained as an orange solid (0.5 mmol scale, 200 mg, 83%, 5:1 mixture of **10e**/**11e** according to ^{1}H NMR spectroscopic data), mp 271–273 °C. Found: (M–H)$^+$, 481.9816; $C_{19}H_{14}O_4N_3S_2^{35}Cl_2$ requires M, 481.9803; ν_{max} (KBr) 3443, 3339, 1639, 1444, 1296, 1246, 1230 and 1138 cm^{-1}; δ_H (400 MHz; DMSO-d_6) (data for **10e** only) 7.66 (2H, app. d, *J* 7.5, aromatic CH of SO_2*Ph*), 7.52 (1H, app. t, *J* 7.4, aromatic CH of SO_2*Ph*), 7.42 (2H, app. t, *J* 7.7, aromatic CH of SO_2*Ph*), 7.36–7.27 (1H, m, aromatic CH of *Ar*–Cl_2), 7.20 (2H, br s, NH_2), 7.12–7.05 (2H, m, aromatic CH of *Ar*–Cl_2), 5.91 (1H, s, C*H*Ar), 4.54 (1H, app. td, *J* 11.6, 7.3, one of CH_2N), 4.23 (1H, app. td, *J* 10.5, 8.2, one of CH_2N) and 3.37–3.27 (2H, m, CH_2S); δ_C (100 MHz; DMSO-d_6) (data for **10e** only, quaternary carbon atoms of 2,6-dichlorophenyl not observed due to hindered rotation) 159.1 (C), 148.8 (C), 143.2 (C), 132.4 (CH), 129.8 (CH), 128.9 (CH), 128.8 (CH), 125.20 (CH), 120.0 (C), 82.2 (C), 50.9 (CH_2), 37.2 (CH), 27.5 (CH_2); *m*/*z* (TOF ES$^-$) 486 (M–H, 23%), 484 (M–H, 64) and 482 (M–H$^+$, 100).

4.22. 8-Nitro-7-(4-nitrophenyl)-6-(phenylsulfonyl)-3,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5-amine (10f) and 8-nitro-7-(4-nitrophenyl)-6-(phenylsulfonyl)-6,7-dihydro-2*H*-thiazolo[3,2-*a*]pyridin-5(3*H*)-imine (11f)

Obtained as light brown crystals (350 mg, 76%, 1.4:1 mixture of **10f**/**11f** according to ^{1}H NMR spectroscopic data), mp 184–186 °C. Found: (M–H)$^-$, 459.0414. $C_{19}H_{16}N_4O_6S_2$ requires M, 459.0433; ν_{max} (KBr) 3289 (NH_2), 1637 (C=C), 1559, 1443, 1383, 1219 and 1138 cm^{-1}; δ_H (400 MHz; DMSO-d_6) 9.69 (1H of **11f**, s, NH), 8.18 (2H of **11f**, d, *J* 8.7, aromatic CH of *Ar*–NO_2), 8.01 (2H of **10f**, d, *J* 8.8, aromatic CH of *Ar*–NO_2), 7.86–7.80 (3H of **11f**, m, aromatic CH of SO_2*Ph*), 7.73–7.67 (2H of **10f** and 2H of **11f**, m, aromatic CH of SO_2*Ph*), 7.54 (1H of **10f**, app. t, *J* 7.4, aromatic CH of SO_2*Ph*), 7.47–7.40 (4H of **10f**, m, aromatic CH of *Ar*–NO_2 and SO_2*Ph*), 7.33 (2H of **11f**, app. d, *J* 8.7, aromatic CH of Ar–NO_2), 7.09 (2H of **10f**, br s, NH_2), 5.19 (1H of **10f**, s, C*H*Ar), 5.09 (1H of **11f**, s, C*H*Ar), 5.03 (1H of **11f**, s, C*H*SO_2Ph), 4.41 (1H of **11f**, ddd, *J* 12.0, 8.7, 3.4, one of CH_2N), 4.37–4.30 (2H of **10f**, m, CH_2N), 4.17 (1H of **11f**, app. td, *J* 11.4, 8.6, one of CH_2N), 3.40 (2H of **10f**, app. t, *J* 7.7, CH_2S), 3.38–3.31 (1H of **11f**, m, one of CH_2S) and 3.12 (1H of **11f**, app. td, *J* 11.1, 8.9, one of CH_2S); δ_C (100 MHz; DMSO-d_6) 160.4 (C, **11f**), 157.9 (C, **10f**), 150.9 (C, **10f**), 149.4 (C, **11f**), 147.9 (C, **10f**), 147.2 (C, **11f**), 146.2 (C, **10f**), 145.7 (C, **11f**), 143.3 (C, **10f**), 135.5 (CH, **11f**), 132.5 (CH, **10f**), 129.8 (CH, **11f**), 129.2 (CH, **10f**), 129.0 (CH, **10f**), 128.6 (CH, **11f**), 128.3 (CH, **11f**), 125.7 (CH, **10f**), 124.4 (CH, **11f**), 123.2 (CH, **10f**), 122.4 (C, **10f**), 118.5 (C, **11f**), 85.1 (C, **10f**), 69.1 (CH, **11f**), 51.6 (CH_2, **11f**), 51.1 (CH_2, **10f**), 40.1 (CH,

10f), 39.6 (CH, **11f**), 28.2 (CH_2, **10f**) and 27.9 (CH_2, **11f**); *m*/*z* (TOF ES^-) 459 (M−H, 100%) and 339 (60).

4.23. General procedure for the preparation of thiazolopyridines under solvent-free conditions

2-Nitromethylenethiazolidine (0.5 mmol, 1 equiv), aromatic aldehyde (0.5 mmol, 1 equiv), ethyl cyanoacetate (0.5 mmol, 1 equiv) and triethylamine (0.25 mmol, 0.5 equiv) were ground together for 10 min using a pestle and mortar at ambient temperature. The mixture was then dissolved in ethyl acetate (25 mL) and the solution washed with water (3×15 mL). The organic solution was then dried over magnesium sulfate and the solvent removed under reduced pressure. The crude product was recrystallised from hexane/ethyl acetate mixtures to give the pure products with data as already reported.

4.24. Biology. Cell viability assay

The four human cancer cell lines used—A549 (lung), PC3 (prostate), LoVo (colorectal) and MCF-7 (breast)—are cell lines representative of major cancer types and available from American Type Culture Collection (http://www.atcc.org). All cancer cell lines were cultured in DMEM (Dulbecco's Modified Eagle Medium) containing 10% heat inactivated foetal calf serum (FCS) (A549 and MCF-7) or 10% FCS (LoVo and PC3). Cells were passaged routinely and kept at 37 °C and 5% CO_2. Exponentially growing cells were used in all experiments. Cell viability was measured using the established MTT assay,[13] a colorimetric assay that measures the reduction of MTT tetrazolium dye to purple formazan in living cells. Cells ($3–10\times10^3$/well) were seeded into 96-well microtiter plates and placed in an incubator (37 °C) for 24 h. Media was then removed and replaced with 150 μL of media containing test compounds at concentrations of 0.1, 1, 10 and 100 μM (diluted from 10 mM DMSO stock solution) for 96 h, in addition to media only control. Following exposure to test compounds, media was again removed and replaced with MTT solution in phenol red free RPMI (0.5 mg/mL). Absorbance was measured at 540 nm using a microplate reader spectrophotometer, and inhibition of proliferation was assessed as the percentage reduction of absorbance of treated cells versus control cultures. The concentration of compounds that decreased cell viability by 50% (IC_{50}) was calculated using Calcusyn software. DMSO concentration in the culture medium never exceeded 0.2%.

Acknowledgements

We are extremely grateful to the Abant İzzet Baysal University, Directorate of Research Projects Commission (BAP grant 2011.03.03.391).

Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.10.005.

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