Ring-ring Interconversions. Part 2.[1] Effect of the Substituent on the Rearrangement of 6-Aryl-3-methyl-5-nitrosoimidazo[2,1-*b*][1,3]thiazoles into 8-Aryl-8-hydroxy-5-methyl-8*H*-[1,4]thiazino[3,4-*c*][1,2,4]oxadiazol-3-ones. A Novel Class of Potential Antitumor Agents

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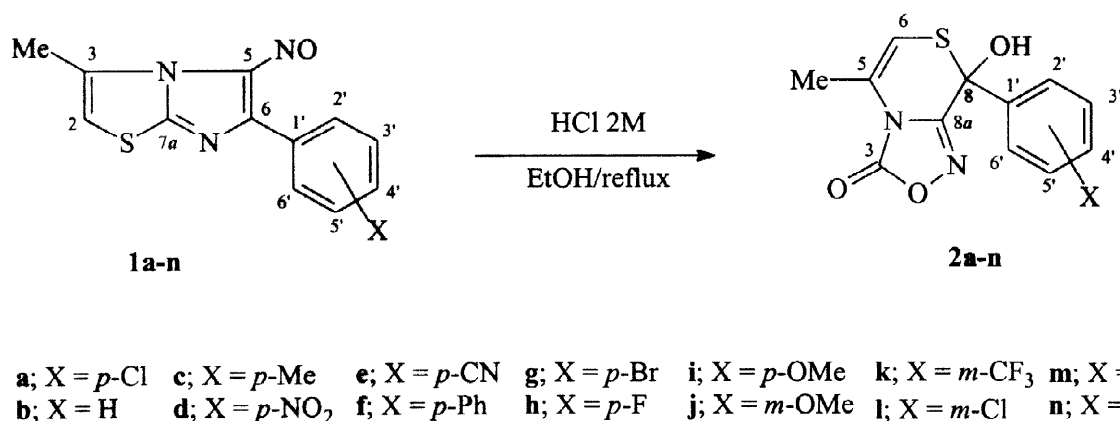Mirella Rambaldi

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Abstract: The reaction of several 6-aryl-3-methyl-5-nitrosoimidazo[2,1-*b*][1,3]thiazoles with hydrochloric acid by refluxing in ethanol gives new 8-aryl-8-hydroxy-5-methyl-8*H*-[1,4]thiazino[3,4-*c*][1,2,4]oxadiazol-3-ones for testing of their biological activity. By carrying out the reaction at room temperature it has been possible to isolate reaction intermediates to which structures have been assigned. This study has provided information on the reaction mechanism and on the effect of the substituent in the phenyl ring on the yield of the reaction. © 1999 Elsevier Science Ltd. All rights reserved.

Previous studies in our laboratories described the synthesis of 8-(4-chlorophenyl)-8-hydroxy-5-methyl-8*H*-[1,4]thiazino[3,4-*c*][1,2,4]oxadiazol-3-one (2a) in good yield (70%) from 6-(4-chlorophenyl)-3-methyl-5-nitrosoimidazo[2,1-*b*][1,3]thiazole (1a) by treatment with HCl in boiling ethanol (Scheme 1).[1] Because of the novelty of its structure, 2a was of interest to National Institutes of Health within their Drug Discovery Program, and it was tested *in vitro* for antiviral and antitumor activity. It was shown to be inactive against

| a; X = *p*-Cl | c; X = *p*-Me | e; X = *p*-CN | g; X = *p*-Br | i; X = *p*-OMe | k; X = *m*-CF$_3$ | m; X = *m*-Me |
| b; X = H | d; X = *p*-NO$_2$ | f; X = *p*-Ph | h; X = *p*-F | j; X = *m*-OMe | l; X = *m*-Cl | n; X = *m*-NO$_2$ |

Scheme 1

HIV, but it inhibited the cell growth of some tumor-derived cell lines (see Experimental) at 10^{-4} molar concentration. This low, but significant, antitumor activity induced us to extend the ring-ring interconversion 1a → 2a to thirteen 5-nitrosoimidazo[2,1-b][1,3]thiazoles (1b-n) variously substituted in the 6-aryl moiety with the aim of obtaining new compounds 2 for a study of structure/activity relationship. The effect of the substituent in the 6-aryl group on the general applicability of the ring-ring interconversion has been evaluated. In the course of this study we have also synthesized several new compounds 1 (some of them showed mutagenic activity).[2] Moreover, we have been able to observe reaction intermediates, the structures of which have been elucidated.

RESULTS

First we attempted the same reaction on the parent compound 1b (X = H),[3] obtaining the expected ring-ring interconversion into 2b with a yield (50%) significantly lower than that previously observed for 1a. We then extended the study to other examples (1c-n) with substituents ranging from the strongly electron-donating 4-methoxy group to the strongly electron-withdrawing 3- or 4-nitro groups. Among the nitroso compounds studied only 1b-d were known;[2,3] the others 1e-n were synthesised using literature methods,[2] by nitrosation of the corresponding 6-aryl-3-methylimidazo[2,1-b][1,3]thiazoles (3e-n). The products 1e-n were characterised (Table 1) and analysed by mass, ^{1}H- and ^{13}C-NMR spectra. Tables of complete mass spectra and ^{1}H- and ^{13}C-NMR spectra of 1a-n together with selected coupling constants are available on request from the authors (B. C. or D. S.).

Table 1 Characterisation Data of 6-Aryl-3-methyl-5-nitrosoimidazo[2,1-b][1,3]thiazoles (1e-n)[a]

Compd.	X	Starting Material	Mp (°C)	HRMS calc./found
1e	p-CN	ref. 4	238 (dec.)	268.04188/268.04234
1f	p-Ph	ref. 5	196 (dec.)	319.07793/319.07955
1g	p-Br	ref. 6	229 (dec.)	320.95714/320.95788[b]
1h	p-F	ref. 7	195	261.03721/261.03799
1i	p-OMe	ref. 8	199	273.05720/273.05764
1j	m-OMe	ref. 8	163	273.05720/273.05734
1k	m-CF₃	ref. 7	157	311.03402/311.03455
1l	m-Cl	3l	193	277.00766/277.00725[c]
1m	m-Me	3m	166	257.06228/257.06266
1n	m-NO₂	3n	234 (dec.)	288.03171/288.03133

[a] All the compounds are green. [b] Br-79 isotope. [c] Cl-35 isotope.

Reaction of Compounds 1 with Hydrochloric Acid

The new nitrosoimidazo[2,1-b][1,3]thiazoles 1 will be tested for their mutagenic activity; in this report we have employed them as starting materials in the ring-ring interconversion reaction to [1,4]thiazino-[3,4-c][1,2,4]oxadiazol-3-one derivatives 2. We carried out the reactions of 1 with HCl both at room temperature in dioxane and by refluxing in EtOH (Scheme 1) to gain information on the course of the reaction and on the substituent effect.

In refluxing EtOH we obtained the corresponding compounds 2 (some characterisation data and yields are collected in Table 2) as the main reaction product, except that 6-(4-nitrophenyl)- (1d) as well as 6-(3-nitrophenyl)-3-methyl-5-nitrosoimidazo[2,1-b][1,3]thiazole (1n) were practically insoluble in hot

Table 2 Characterisation Data of 8-Aryl-8-hydroxy-5-methyl-8H-[1,4]thiazino[3,4-c][1,2,4]oxadiazol-3-ones (2a-n)

Compd.	X	Mp (°C)[a]	Yield %	Methods of purification[b]	HRMS calc/found
2a	p-Cl	190	70	A: EtOH	296.00224/296.00191[c]
2b	H	129	50	A: EtOH	-
2c	p-Me	174	23	B: AcOEt/Cyclohexane 1:3, v/v	276.05686/276.05734
2d	p-NO₂	142	45	C: AcOEt and H₂O	-
2e	p-CN	147	57	A: EtOH	287.03646/287.03750
2f	p-Ph	144	36	B: AcOEt/Benzene 1:5, v/v	-
2g	p-Br	190	24	A: EtOH	339.95172/339.95201[d]
2h	p-F	161	18	B: AcOEt/Petroleum ether 1:2, v/v	280.03179/280.03256
2i	p-OMe	121	12	B: AcOEt/Petroleum ether 1:2, v/v	-
2j	m-OMe	131	34	B: Et₂O/Petroleum ether 1:1, v/v	-
2k	m-CF₃	140	30	B: AcOEt/Cyclohexane 1:3, v/v	-
2l	m-Cl	140	63	A: EtOH	296.00224/296.00191[c]
2m	m-Me	125	20	B: AcOEt/Petroleum ether 1:2, v/v	276.05686/276.05745
2n	m-NO₂	152	52	C: H₂O	-

[a] 2a-n were colourless and melted with decomposition. [b] A: crystallisation from the solvent indicated. B: flash chromatography with the eluant indicated. C: washing with the solvent indicated. [c] Cl-35 isotope. [d] Br-79 isotope.

ethanol, so that the starting materials were recovered practically unchanged even after prolonged refluxing (2.5 h). For this reason, these reactions have been repeated in tetrahydrofuran (THF) solution to obtain 2d and 2n (45 and 52%, respectively). 6-(4-Methoxyphenyl)- (1i) and 6-(3-methoxyphenyl)-3-methyl-5-nitrosoimidazo[2,1-b][1,3]thiazole (1j) in ethanol gave many decomposition products and only a very small amount of the expected thiazino[3,4-c][1,2,4]oxadiazol-3-one 2i, j: in contrast, with hydrochloric acid in THF they give the corresponding 2i, j with low or acceptable yields (12 and 34%, respectively). Lastly, in ethanol 6-(4-fluorophenyl)-3-methyl-5-nitrosoimidazo[2,1-b][1,3]thiazole (1h) gave the desired 2h (10%) together with the acetal 4 (6%) (Scheme 2). In order to avoid this side reaction, that also occurs in the other cases but to a lesser extent (≤2 %), we used THF as reaction solvent, thus obtaining the desired hemithioacetal 2h albeit with a low yield (16%).

1h → HCl 2M / EtOH/reflux

2h R = H
4 R = CH₂CH₃
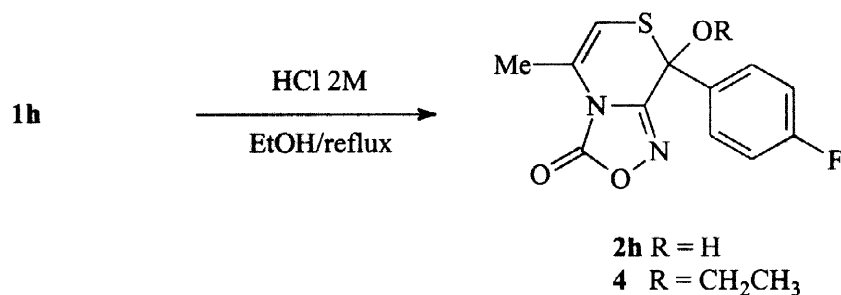
Scheme 2

All the 8-aryl-8-hydroxy-5-methyl-8H-[1,4]thiazino[3,4-c][1,2,4]oxadiazol-3-ones 2b-n obtained were characterised by means of mass, ¹H- and ¹³C-NMR spectroscopy. Complete assignments of ¹H- and ¹³C-NMR chemical shifts for 2b are indicated in formula 5. Tables of complete mass spectra and ¹H- and ¹³C-NMR spectra of 2a-n together with selected coupling constants are available on request from the authors (B. C. or D. S.).

Mass spectra showed molecular ions with very low abundance, $ArCO^+$ (from ring opening of the hemithioacetal ring) was the base peak, and other characteristic fragment ions were M^+-31 (SH loss), M^+-44 (carbon dioxide elimination from oxadiazolone ring), and $ArCOCN^+$ (from the above ring opening and a retrocycloaddition process).

The structure of compounds 2b-n were easily determined by comparison with the NMR spectra of 2a.[1] In particular, it is relevant that the substituents on the phenyl ring weakly affect the ^{1}H and ^{13}C chemical shifts of hydrogens and carbons of the 8-hydroxy-5-methyl-8H-[1,4]thiazino[3,4-c][1,2,4]oxadiazol-3-one moiety (ΔSCS 0.3–0.9 ppm). In spite of the low ΔSCS measured, the ^{13}C SCS gave significant correlations with the Hammett substituent constants and the ρ and r values calculated for SCS of some carbon atoms of the condensed rings are reported in formulas 6 and 7. Small susceptibility constants have been observed $0.2 < |\rho| < 1.3$, which was useful for signal attributions. Only the ^{1}H and ^{13}C chemical shifts of the 8-aryl ring being much affected by the nature of the substituent, excellent ($r \geq 0.994$) cross-correlations for ipso-, ortho- and para-carbon atoms versus SCS of monosubstituted benzenes[9] have been observed with slopes near to unity (s 0.98–1.09).

5

6   7
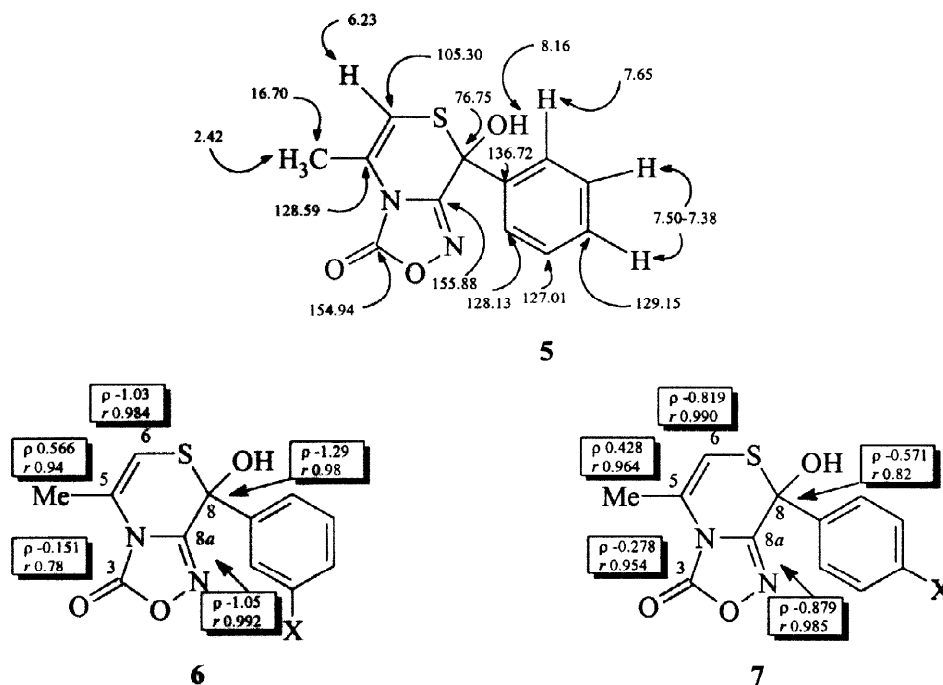
DISCUSSION

We proposed a multistep mechanism for the ring-ring interconversion 1a → 2a[1] that had, as first step, an acid-catalysed ring-opening reaction of the imidazole ring with the hydrolytic elimination of ammonia to give 8 which can evolve via several possible intermediates to 2 (Scheme 3).

Now by carrying out the reaction at room temperature in dioxane we have been able to isolate intermediates, which give an interesting insight into the reaction mechanism. Starting from 1a-n we have obtained products, the structures of which have been elucidated on the basis of their spectroscopic data: e. g. the product obtained from 1a gave HRMS for $C_{12}H_9ClN_2O_3S$ and showed an I.R. absorption (1657.6 cm^{-1})
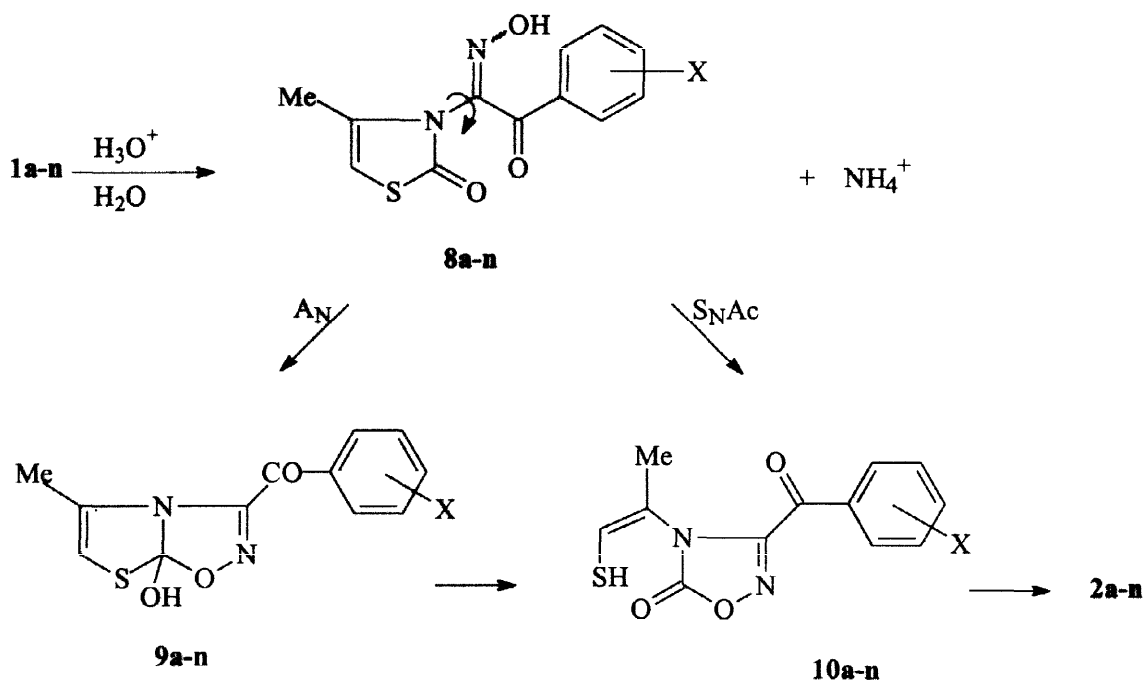
Scheme 3

typical for a ketonic carbonyl conjugated with an aryl group, as confirmed by ^{13}C-NMR (δ 182.95 ppm). For the identification of this compound and the complete assignment of ^{1}H and ^{13}C chemical shifts (see 11) a useful comparison was made with NMR spectra registered by us of 1-(4-chlorophenyl)-2-chloro-1,2-ethanedione-2-oxime 12.[10] Block A of 11 is exactly like 12 and NMR data are practically superimposable. The spectral identification of CH$_3$C=CH and of the thiocarbamic carbonyl group in Block B of 11 was straightforward. Thus, it has been possible to show that the intermediate has the structure 8a. Moreover by refluxing in EtOH 8a gave 2a. Tables of characterisation data and complete ^{1}H-NMR spectra of 8a-n are available on request from the authors (B. C. or D. S.). This result partly confirms the reaction mechanism proposed for the ring-ring interconversion 1 → 2.

The use of data concerning substituent effects on yields of reaction to gain information on reaction mechanism can be misleading (particularly in multistep reactions), but in the reactions studied the variations of the yields seem largely substituent-dependent. Nitroso derivatives 1 containing electron-repelling or -withdrawing substituents rearrange into 2 with low or high yields, respectively. This effect operates notwithstanding the distance of the substituent in the 6-aryl group from the reaction centre, at least until the stage of formation of 10.

A stage for which a relevant effect of the above substituent can be expected is the final step (the 10 → 2 ring closure), the rate of which must depend on the electron density of the carbonyl carbon atom: the lower (or higher) is its electrophilic character, then the lower (or higher) the cyclisation rate would be expected to be and therefore the decomposition of the intermediate products could be higher (or lower) Many kinetic[11] and spectroscopic[12] data have shown how the electron density on a carbonyl carbon atom directly bound to an aryl group depends on the electronic effect of the meta- and para-substituents. Accordingly, we have observed lower or higher yields when an electron-repelling or -withdrawing substituent is present in the 6-aryl group, respectively.

Block A   Block A

11   12
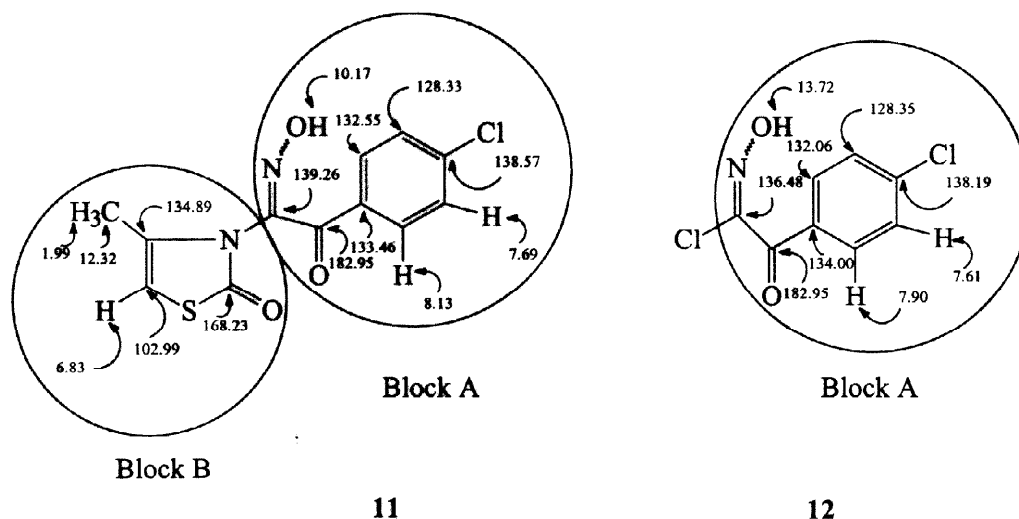
EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were recorded on a Varian Gemini 300 Instrument in the Fourier transform mode at 21 ± 0.5 °C. Chemical shifts (δ) are reported in ppm from tetramethylsilane and coupling constants in Hz. Mass spectra were recorded on a VG70 70E apparatus. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck 230-400 mesh) were used for analytical TLC and for column-chromatography, respectively. All melting points were obtained with a Perkin Elmer DSC7 apparatus. All new compounds gave satisfactory analyses (C, H, N, S and halogens; not reported) and HRMS (see Tables 1 and 2). Solvents were removed under reduced pressure.

General Procedure for the Ring-ring Interconversion of 6-Aryl-3-methyl-5-nitrosoimidazo[2,1-b][1,3]thiazoles (1b-n) *into* 8-*Aryl-8-hydroxy-5-methyl-8H-[1,4]thiazino[3,4-c]* *[1,2,4]oxadiazol-3-ones (2b-n)* – Hydrochloric acid (2 mol dm^{-3}; 3 mL) was added to a stirred suspension of the appropriate 1 (4 mmol) in 30 mL of ethanol (1a-c, e-g, k-m) or THF (1d, h-j, n). Then the reaction mixture was refluxed until complete disappearance of the green colour (*ca.* 2.5 h). Removal of the solvent left a solid which gave 2 after purification (see Table 2).

8-(4-Fluorophenyl)-8-ethoxy-8H-[1,4]thiazino[3,4-c][1,2,4]oxadiazol-3-one 4 – Operating as above (see Scheme 2, solvent: ethanol) it was possible to separate by flash chromatography (eluant AcOEt/cyclohexane 1/4, v/v) 4 (colourless) mp 88 °C; δ$_H$ (DMSO-d_6, 300 MHz) 7.63 (2H, dd, *J* 8.9, $^4J_{H,F}$ 5.3, H-2' and H-6'), 7.34 (2H, dd, *J* 8.9, $^3J_{H,F}$ 8.9, H-3' and H-5'), 6.22 (1H, q, *J* 1.2, H-5), 3.37 (2H, dq, *J* 9.2, *J* 7.0, CH_2Me), 2.41 (3H, d, *J* 1.4, 3-Me), 1.16 (3H, pt, *J* 7.0, CH$_2$*Me*); δ$_C$ (DMSO-d_6, 75 MHz) 162.63 (C-4'), 154.65 (C-3), 154.42 (C-7a), 129.77 (C-2' and C-6'), 129.58 (C-4); 129.53 (C-1'), 115.69 (C-3' and C-5'), 103.41 (C-5), 82.05 (C-7), 60.70 (CH$_2$) 16.47 (5-Me), 14.62 (CH$_2$*Me*); MS *m/z* 308 (M', 44%); 263 (32); 219 (11); 123 (100); 95 (36). HRMS 308.06358, $C_{14}H_{13}FN_2O_3S$ requires 308.06309.

General Procedure for the Synthesis of 6-Aryl-3-methyl-5-nitrosoimidazo[2,1-b][1,3]thiazoles (1e-n) – A solution of sodium nitrite (8.7 mmol) in water (10 mL) was added, under cooling and stirring, to a solution of the appropriate imidazo[2,1-b][1,3]thiazole 3 (4 mmol) in acetic acid (20 mL). After 1 h at room temperature, the mixture was neutralised with NaOH 2M and the green precipitate was collected and crystallised from ethanol (average yield 83%).

6-(3-Chlorophenyl)-3-methylimidazo[2,1-b][1,3]thiazole (3l) – 2-Bromo-3'-chloroacetophenone (5.1

g, 21.8 mmol) was added to a solution of 2-amino-4-methylthiazole (2.5 g, 21.8 mmol) in acetone (30 mL). After 1 h reflux, the crude hydrobromide of the intermediate was separated, added of EtOH (20 mL) and refluxed with HBr (2 M; 20 mL) for 30 min. The mixture was treated with NH_4OH until basic and the precipitate was collected and recrystallized from EtOH to give 3l (colourless, 3.1 g, 58%); mp 126 °C; δ_H (DMSO-d_6, 300 MHz) 8.38 (1H, s, H-5), 7.90 (1H, m, H-2'), 7.82 (1H, m, H-6'), 7.42 (1H, m, H-5'), 7.29 (1H, m, H-4'), 6.91 (1H, q, J 1.2, H-2), 2.42 (3H, d, J 1.2, 3-Me); δ_C (DMSO-d_6, 75 MHz) 148.68 (C-7a), 144.56 (C-6), 138.45 (C-1'), 133.39 (C-3'), 130.37 (C-5'), 128.03 (C-3), 126.46 (C-4'), 124.11 (C-2'), 123.00 (C-6'), 108.80 (C-5), 107.37 (C-2), 12.68 (Me); MS m/z 248 (M$^+$, 100%); 150 (ClC_6H_4CNC, 2); 137 (ClC_6H_4CN, 5); 45 (CHS, 10); 39 (CH_2CCH, 13). HRMS 248.01799, $C_{12}H_9ClN_2S$ requires 248.01750 (Cl-35 isotope).

3-Methyl-6-(3-methylphenyl)-imidazo[2,1-b][1,3]thiazole (3m) – Operating in $CHCl_3$ as above and starting from 2-bromo-3'-methylacetophenone, 3m was synthesised with analogous yield; colourless, mp 135.5 °C; δ_H (DMSO-d_6, 300 MHz) 8.22 (1H, s, H-5), 7.70 (1H, ps, H-2'), 7.64 (1H, pd, H-6'), 7.27 (1H, pt, H-5'), 7.06 (1H, pd, H-4'), 6.88 (1H, q, J 1.2, H-2), 2.42 (3H, d, J 1.2, 3-Me), 2.34 (3H, s, 3'-Me); δ_C (DMSO-d_6, 75 MHz,) 148.26 (C-7a), 144.78 (C-6), 137.40 (C-3'), 134.12 (C-1'), 128.28 (C-5'), 127.99 (C-3), 127.42 (C-4'), 125.16 (C-2'), 121.71 (C-6'), 107.62 (C-5), 106.74 (C-2), 12.65 (3-Me), 20.92 (3'-Me); MS m/z 228 (M$^+$, 100%); 227 (12); 117 (MeC_6H_4CN, 5), 63 (10); 45 (CHS, 5), 39 (CH_2CCH, 6). HRMS 228.07267, $C_{13}H_{12}N_2S$ requires 228.07212.

3-Methyl-6-(3-nitrophenyl)-imidazo[2,1-b][1,3]thiazole (3n) – Operating in EtOH as above and starting from 2-bromo-3'-nitroacetophenone, 3n was synthesised with analogous yield; colourless, mp 224 °C; δ_H (DMSO-d_6, 300 MHz) 8.65 (1H, dd, J 1.9, J' 1.9, H-2'), 8.56 (1H, s, H-5), 8.28 (1H, pd, H-6'), 8.09 (1H, dd, J 7.6, J 1.9, H-4'), 6.89 (1H, pt, H-5'), 6.95 (1H, q, J 1.4, H-2), 2.44 (3H, d, J 1.4, 3-Me); δ_C (DMSO-d_6, 75 MHz) 149.04 (C-7a), 148.31 (C-3'), 143.80 (C-6), 136.08 (C-1'), 130.15 (C-6'), 128.13 (C-3), 127.42 (C-4'), 121.29 (C-5'), 118.70 (C-2'), 109.61 (C-5), 107.83 (C-2), 12.72 (3-Me); MS m/z 259 (M$^+$, 100%); 213 (58); 102 (C_6H_4CN, 5); 45 (CHS, 6); 39 (CH_2CCH, 9). HRMS 259.04188, $C_{12}H_9N_3O_2S$ requires 259.04155.

1-(4-Chlorophenyl)-2-[4-methyl-2-oxo-1,3-thiazolo-(2H)-yl]1,2-ethandione-2-oxime   (8a) – Hydrochloric acid (2 mol dm^{-3}; 0.75 mL) was added to a stirred suspension of 6-(4-chlorophenyl)-3-methyl-5-nitrosoimidazo[2,1-b][1,3]-thiazole 1a (0.28 g, 1 mmol) in 10 mL of dioxane at room temperature. After 3 h removal of the major part of solvent gave a solid (0.22 g, mp 162-163 with decomposition). MS m/z 296 (M$^+$, 3%); 277 (M$^+$ - 19, 3), 248 (M$^+$ - 48, 19), 209 (5), 165 (ClC_6H_4COCN, 15), 157 (M$^+$ - 139, 5), 139 (ClC_6H_4CO, 100, 111 (ClC_6H_4, 32). By refluxing in EtOH (15 min) 8a gave 2a (0.20 g).

Biological Assays on 1a – 1a was submitted to primary antitumor screen. The cell panel consisted of about 60 lines against which compound was tested at 10-fold dilutions. A 48 h continuous drug exposure protocol was used and a sulforhodamine B (SRB) protein assay was used to estimate cell growth. In this first screening the compound was approximately equivalent in efficiency (10^{-4} mol dm^{-3}) against the following cell lines: colon cancer (HCC-2998 Percentage Growth = PG17) melanoma (SK-MEL-28 PG8, UACC-62257 PG-28) and breast cancer (MDA-MB-435 PG8); further screenings are in progress.

References

1. Andreani, A.; Billi, R.; Cosimelli, B.; Mugnoli, A.; Rambaldi, M.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2407; Spinelli, D.; Mugnoli, A.; Andreani, A.; Rambaldi, M.; Frascari, S. *J. Chem. Soc., Chem. Commun.*, **1992**, 1394.
2. Andreani, A.; Rambaldi, M.; Andreani, F.; Hrelia P.; Cantelli Forti, G. *Arch. Pharm. Chem. Sci. Ed.*, **1987**, *15*, 41.
3. Pyl, T.; Wünsch, K.-H.; Beyer, H. *Liebigs Ann. Chem.*, **1962**, *657*, 108.
4. Sundberg, R. J.; Dahlhausen, D. J.; Manikumar, G.; Mavunkel, B.; Biswas, A.; Srinivasan, V.; King, F. Jr.; Waid, P. *J. Heterocyclic Chem.*, **1988**, *25*, 129.
5. Buu-Hoï, N. P.; Dat Xuong, N.; Thu-Cuc, T. *Bull. Soc. Chim. Fr.*, **1966**, 1277.
6. Kano, S.; Noguchi, T. *Japan. Pat.* **32,793**, 1969; *Chem. Abstr.*, **1970**, *72*, 79041g.
7. Andreani, A.; Rambaldi, M.; Locatelli, A.; Andreani, F. *Collect. Czech. Chem. Commun.*, **1991**, *56*, 2436.
8. Andreani, A.; Rambaldi, M.; Bonazzi, D.; Lelli, G.; Bossa, R.; Galatulas, I. *Eur. J. Med. Chem. - Chim. Ther.*, **1984**, *19*, 219.
9. Bromilow, J.; Brownlee, R. T. C.; Craik, D. J.; Sadek, M.; Taft, R. W. *J. Org. Chem.*, **1980**, *45*, 2429.
10. Levin, N.; Hartung, W. H., *J. Org. Chem.*, **1942**, *7*, 408.
11. (a) Laurence, C.; Berthelot, M. *J. Chem. Soc., Perkin Trans. 2* **1979**, 98; Helbert, M.; Berthelot, M.; Laurence, C.; Spinelli, D.; Consiglio, G.; Arnone, C. *Spectrochimica Acta*, **1983**, *39A*, 703. (b) Bromilow, J.; Brownlee, R. T. C.; Craik, D. J. *Aust. J. Chem.*, **1977**, *30*, 351; Bromilow, J.; Brownlee, R. T. C.; Craik, D. J.; Fiske, P. R.; Rowe, J. E.; Sadek, M. *J. Chem. Soc., Perkin Trans. 2* **1981**, 753; Dell'Erba, C.; Sancassan, F.; Novi, M.; Petrillo, G.; Mugnoli, A.; Spinelli, D.; Consiglio, G.; Gatti, P. *J. Org. Chem.*, **1988**, *53*, 3564. (c) St. Amour, T. E.; Burgar, M. I.; Valentine, B.; Fiat, D. *J. Am. Chem. Soc.*, **1981**, *103*, 1128; Spinelli, D.; Lamartina, L.; Chimichi, S.; Noto, R.; Consiglio, G. *Acta Chem. Scand.*, **1993**, *47*, 160.
12. (a) Jones, J. R.; Marks, R. E.; Subba Rao S. C. *Trans. Faraday Soc.*, **1967**, *63*, 111; Jones, J. R.; Pearson, G. M.; Spinelli, D.; Consiglio, G.; Arnone, C. *J. Chem. Soc., Perkin Trans. 2*, **1985**, 557. (b) Cox, A. R.; Smith, C. R.; Yates, K. *Can. J. Chem.*, **1979**, *57*, 2952; Noto R.; Gruttadauria, M.; Arnone, C.; Lamartina, L.; Spinelli, D. *J. Chem. Res. (S)*, **1993**, 274. (c) March, J. Addition to Carbon-Hetero Multiple Bonds, in *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, McGraw-Hill Kogakusha, Tokyo, 1977, p. 801 and references therein.