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Synthesis and antiproliferative evaluation of 5-*oxo* and 5-thio derivatives of 1,4-diaryl tetrazoles

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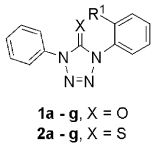
ABSTRACT

A series of 1,4-diaryl tetrazol-5-ones were synthesized by copper mediated N-arylation of 1-phenyl-1*H*-tetrazol-5(4*H*)-one with aryl boronic acids, *o*-$R_1C_6H_4B(OH)_2$ where R_1 = H, OMe, Cl, CF_3, Br, C≡CH. The 1,4-diaryl tetrazol-5-ones substituted with OMe, Cl, CF_3, Br underwent thionation with Lawesson's reagent to yield the corresponding 5-thio derivatives. The 1-(2-bromophenyl)-4-phenyl-1*H*-tetrazole-5(4*H*)-thione so obtained was subjected to lithiation/protonation and Sonogashira coupling to produce 1,4-diphenyl-1*H*-tetrazole-5(4*H*)-thione and 1-(2-ethynylphenyl)-4-phenyl tetrazole-5-thione, respectively. The title compounds were found to be stable to strong Lewis acid conditions. Three of these novel compounds were found to inhibit L1210 leukemia cell proliferation and SK-BR-3 breast cancer cell growth over several days in culture in vitro. Shorter tetrazole derivative treatments also reduced the expression of the Ki-67 marker of cell proliferation in SK-BR-3 cells and the rate of DNA synthesis in L1210 cells.

Among the various heterocycles reported to date, tetrazole and its derivatives have received much attention in recent years due to their widespread applications in biology. For instance, the 5-*oxo* and 5-thio derivatives of tetrazole form an important structural framework of many pesticides[1,2] and herbicides.[3,4] These ring systems are present in drugs patented for the treatment of central nervous system disorders,[5] HIV,[6] sexual dysfunction[7–9] asthma[10] obesity and diabetes,[11,12] as well as for injuries caused by exposure to chemical warfare agents.[13] Tetrazol-5-one and tetrazole-5-thione rings are also featured in many antiviral,[14] antibacterial,[14,15] analgesic,[16,17] anesthetic,[18,19] antihistaminic[20], antimicrobial,[21] antiinflammatory[22,23] and anticancer drugs.[24] Our interest in these heterocycles stems from their aforementioned bioactivities. In particular, we are interested in the search of new anticancer compounds based on tetrazol-5-one and tetrazole-5-thione scaffold. Herein, we report the facile synthesis of a series of 1,4-diarylated derivatives of these ring systems **1a–g** and **2a–g** (Scheme 1) and evaluation of their antiproliferative activity in rapidly-growing suspension cultures of L1210 leukemia cells and slow-growing monolayer cultures of SK-BR-3 mammary tumor cells, using tests of metabolic activity and DNA synthesis in vitro.[25,26] Since the fraction of Ki-67-positive tumor cells is often correlated with the clinical course of cancer, it was also of interest to determine whether treatments with synthesized tetrazole derivatives would inhibit the expression of human Ki-67 nuclear protein, which is an excellent marker of tumor cell proliferation.[27]

Although, there are several reports in the literature that discuss the preparation of 1,4-phenyl alkyl substituted tetrazol-5-ones,[28–31] the synthesis of the corresponding 1,4-diaryl derivatives has not been directly carried out. For instance, Quast and Nahr carried out the N-alkylation of 1-phenyl-1*H*-tetrazol-5(4*H*)-one with 3-bromocyclohexene which was followed by the dehydrogenation of the resulting compound with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone to obtain the 1,4-diaryl tetrazol-5-one.[32] The latter have also been reported as side products in the reaction of triarylbismuth diazides with aryl isocyanates to yield arylcarbamoyl azides.[33] There are no previous reports on the synthesis of 1,4-diaryl tetrazole-5-thiones. Our approach to synthesize the title compounds is described below.

In recent years, copper mediated C(aryl)–N bond formation through the cross coupling of aryl boronic acids with nitrogen nucleophiles has emerged as a powerful strategy for the synthesis



1a - g, X = O
2a - g, X = S

a, R^1 = H
b, R^1 = OMe
c, R^1 = Cl
d, R^1 = CF_3
e, R^1 = Br
f, R^1 = C≡CH
g, R^1 = OH

Scheme 1. 1,4-Diaryl tetrazol-5-ones **1a–g** and tetrazole-5-thiones **2a–g**.

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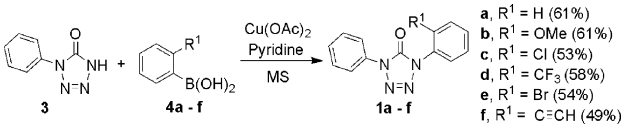
of a variety of compounds.[34] This reaction has been successfully used for the N-arylation of a wide range of functional groups such as amines, amides, imides and sulfonamides.[35] Lam et al. have also reported the C(aryl)–N bond formation during the reaction of aryl boronic acids with 5-phenyl-2*H*-tetrazole in the presence of copper acetate.[36] We successfully synthesized 1,4-diaryl tetrazol-5-one derivatives **1a–f** by the copper mediated coupling of a series of *ortho* substituted boronic acids **4a–f** (R^1 = H, OMe, Cl, CF_3, Br, C≡CH) with 1-phenyl-1*H*-tetrazol-5(4*H*)-one (**3**)[37] in the presence of pyridine and molecular sieves (Scheme 2). The boronic acids **4a–e** were commercially available while **4f** was prepared from phenyl acetylene by a reported method[38] and used without further purification due to its low yields.

Treatment of **1b–e** with Lawesson's reagent **5**[39] yielded the corresponding 1,4-diaryl tetrazole-5-thiones **2b–e** (Scheme 3). All the attempts to thionate **1a** to **2a** with **5** failed. The lack of reactivity of **1a** toward **5** may be attributed to the following reason: the mechanism of thionation with **5** is believed to involve a dissociative equilibrium involving the formation of a highly reactive dithiophosphine ylide which reacts with carbonyl compounds via the formation of a Wittig-type intermediate.[39] The lone pairs present on the *ortho* substituents in **1b–e** may provide a coordination site for electrophilic phosphorous of the ylide[40] and thus, facilitate the attack at nearby carbonyl group. Several other thionation conditions were tried to induce this transformation, such as P_4S_{10}/Al_2O_3,[41] $PSCl_3/H_2O/Et_3N$ at 63 °C[42] and $PSCl_3/H_2O/Et_3N$ under microwave conditions,[43] however, in vain.

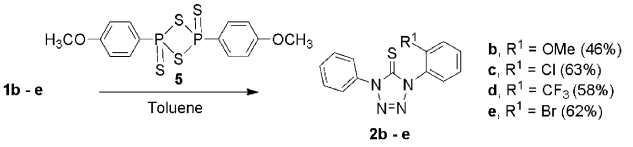
Compound **2a** was ultimately prepared by the lithiation of **2e** followed by protonation in ethanol (Scheme 4). Similarly, thionation of **1f** with **5** to yield **2f** resulted in the formation of several products that could not be identified. Since ethynyltrimethylsilane is an excellent reagent to introduce acetylene group to an aromatic ring,[44–47] we attempted to synthesize **2f** via the Sonogashira coupling of **2e** with ethynyltrimethylsilane followed by deprotection. However, our coupling reaction did not go to completion as more than 50% of **2e** remained unreacted after 60 h. Also, the reaction produced two products that eluted closely with unreacted **2e** on silica gel column and thus, were inseparable and could not be identified. We also attempted to synthesize **2f** through the Sonogashira coupling of **1e** with ethynyltrimethylsilane followed by deprotection and thionation. Again, the Sonogashira coupling reaction did not undergo completion in 48 h and resulted in an extremely low yield of the desired product. Failure of this reaction to give desired product in useful quantities for synthesis to proceed, prompted us to search for other reagents to introduce the ethynyl group into organic structures via Sonogashira coupling. Sabourin and co-workers have reported 3-methyl-2-butynol as a useful and inexpensive alternative to ethynyltrimethylsilane in palladium catalyzed cross coupling reaction with aryl halides.[48,49] Treatment of the resulting arylated methylbutynol with alkali-metal hydroxide yields the corresponding arylacetylene and acetone.[50] To our delight, the Sonogashira coupling of 1-(2-bromophenyl)-4-phenyl tetrazole-5-thione **2e** with 3-methyl-2-butynol yielded **6** which upon treatment with sodium hydroxide in toluene gave the desired 1-(2-ethynylphenyl)-4-phenyl tetrazole-5-thione **2f** (Scheme 4).

To explore a separate reaction chemistry from the synthesized tetrazol-5-ones and tetrazole-5-thiones, we subjected **1b** and **2b** to treatment with boron tribromide[51] to produce 1-(2-hydroxyphenyl)-4-phenyl tetrazol-5-one **1g** and its thio derivative **2g** (Scheme 5). This reaction demonstrated the stability of tetrazol-5-ones and tetrazole-5-thiones to withstand strong Lewis acid conditions such as boron tribromide.

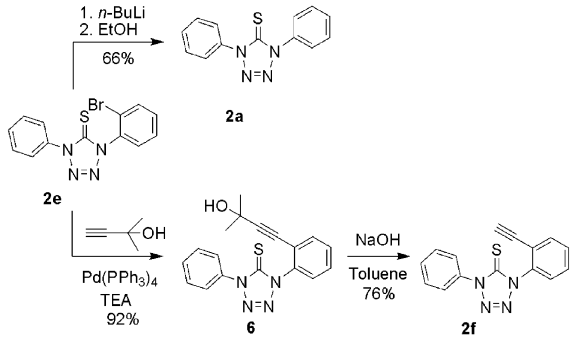
Compounds **1f**, **1g** and **2g** were most effective in inhibiting the mitochondrial ability of L1210 leukemia cells to metabolize the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2*H*-tetrazolium (MTS) reagent in the presence of phenazine methosulfate (PMS) at days 2 and 4 (Table 1, IC_{50} values in the 2.5–16.1 μM range), whereas compounds **3** and **2a** were inactive and did not significantly alter the control rate of L1210 tumor cell growth even at the highest concentrations (156.25 μM) tested. All other compounds showed moderate antiproliferative activities (IC_{50} values in the 20–50 μM range, Table 1s Supplementary data). Full concentration-response curves indicated that the



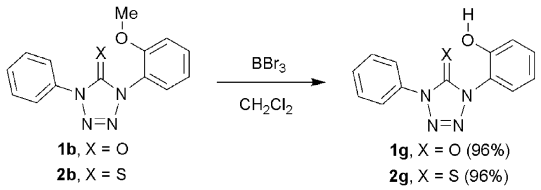
Scheme 2. Copper catalyzed N-arylation of 1-phenyl-1*H*-tetrazol-5(4*H*)-one (**3**) to **1a–f**.



Scheme 3. Thionation of tetrazol-5-ones **1b–e** to tetrazole-5-thiones **2b–e**.



Scheme 4. Synthesis of tetrazole-5-thiones **2a** and **2f** from 1-(2-bromophenyl)-4-phenyl-1*H*-tetrazole-5(4*H*)-thione **2e**.



Scheme 5. Lewis acid catalyzed conversion of **1b** and **2b** to **1g** and **2g**, respectively.

Table 1
Antiproliferative activity of the most potent tetrazole derivatives in L1210 tumor cells in vitro[a]

Compound	IC_{50} values[b] (μM)	
	Day 2	Day 4
1f	16.1 ± 0.4	12.9 ± 0.3
1g	12.0 ± 0.3	7.1 ± 0.2
2g	3.8 ± 0.1	2.5 ± 0.1

[a] Concentrations of **1f**, **1g** and **2g** required to inhibit by 50% (IC_{50} values) the metabolic activity of L1210 tumor cells, using the MTS:PMS assay after 2 or 4 days of culture in vitro. IC_{50} values were calculated from linear regression of the slopes of the log-transformed concentration-survival curves.
[b] Means ± SD (n = 3).

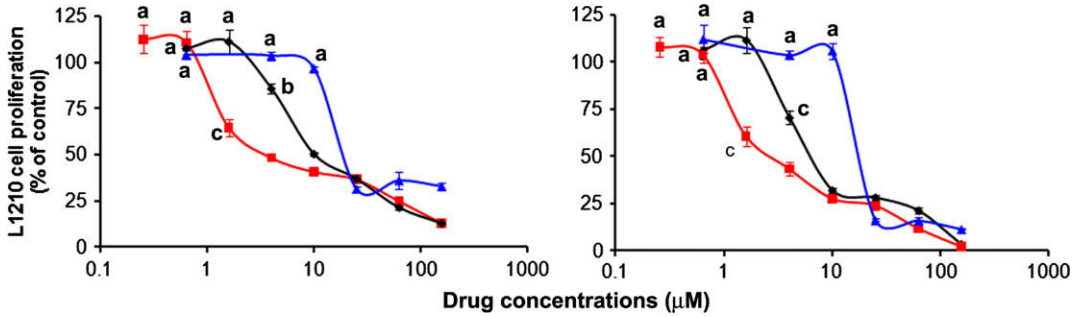


Figure 1. Comparison of the abilities of serial concentrations (plotted on a logarithmic scale) of **1f** (blue, △), **1g** (black, ◇) and **2g** (red, □) to inhibit the metabolic activity of L1210 tumor cells at days 2 (left) and 4 (right) in vitro. Cell proliferation results were expressed as % of the net absorbance of MTS/formazan after bioreduction by vehicle-treated control cells after 2 ($A_{490\ nm}$ = 1.171 ± 0.044, 100 ± 3.8%) and 4 ($A_{490\ nm}$ = 1.188 ± 0.055, 100 ± 4.6%) days in culture. The blank values ($A_{490\ nm}$ = 0.447 at day 2 and 0.471 at day 4) for cell-free culture medium supplemented with MTS:PMS reagent were subtracted from the results. Bars: means ± SD (n = 3). [a]Not different from respective controls; [b]P <0.01 and [c]P <0.005, smaller than respective controls.

inhibitions of L1210 tumor cell growth by the two most effective compounds **1g** and **2g**, began around 1.6–4 μM and became maximal or near maximal around 25–62.5 μM (Fig. 1). All other compounds **1a**–**e** and **2a**–**f** induced concentration-dependent inhibitory effects that were able to block L1210 tumor cell proliferation by 90–100% at 62.5–156.25 μM (data not shown). Moreover, the magnitudes of the antiproliferative effects of the tested compounds were generally more pronounced after 4 than 2 days in culture (Table 1 and Fig. 1), suggesting that the effectiveness of these bioactive compounds against L1210 tumor cell growth is a combination of drug concentration and duration of action.

The inactivity of **3** suggests that the presence of a second aromatic ring may be critical to reveal the antitumor effect of the tetrazole derivatives. In general, the related tetrazole-5-ones and tetrazole-5-thiones have similar antiproliferative activities but there were notable exceptions as **2a** is totally inactive while **1a** shows bioactivity, and also **2f** is much weaker than its tetrazole-5-one counterpart **1f**. The presence of a hydroxyl group in **1g** and **2g** appears to be an asset in enhancing the bioactivity of this framework. This may be attributed to the fact that an –OH group is an excellent hydrogen bond donor which may result into a stronger bonding with its biological target,[52] thereby, increasing the antiproliferative activity of **1g** and **2g**.

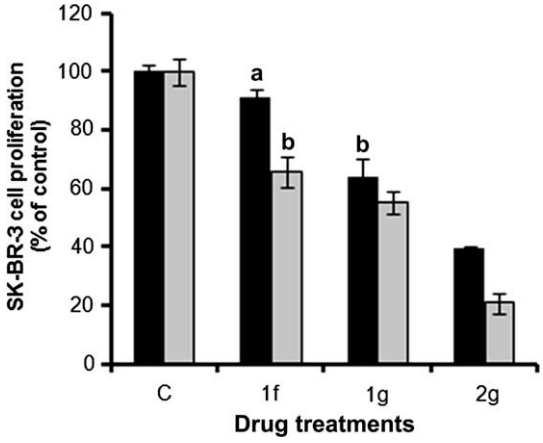


Figure 2. Comparison of the abilities of 156.25 μM concentrations of **1f**, **1g** or **2g** to inhibit the metabolic activity of SK-BR-3 tumor cells at days 2 (black columns) and 4 (grey columns) in vitro. SK-BR-3 cell proliferation results were expressed as % of the net absorbance of MTS/formazan after bioreduction by vehicle-treated control (C) cells after 2 ($A_{490\ nm}$ = 1.396 ± 0.034, 100 ± 2.4%) and 4 ($A_{490\ nm}$ = 1.291 ± 0.061, 100 ± 4.7%) days in culture. The blank values ($A_{490\ nm}$ = 0.230 at day 2 and 0.249 at day 4) for cell-free culture medium supplemented with MTS:PMS reagent were subtracted from the results. Bars: means ± SD (n = 3). [a]P <0.025 and [b]P <0.005, smaller than respective controls.

Compounds **1f**, **1g** and **2g** also inhibit the proliferation of monolayer cultures of human SK-BR-3 breast adenocarcinoma cells at days 2 and 4 (Fig. 2), however higher micromolar concentrations of these compounds must be used to achieve inhibitory effects similar to those observed in L1210 cells. For instance, 156.25 μM **2g** inhibits SK-BR-3 cell proliferation by 60.6% at day 2 and 79.3% at day 4 (Fig. 2) but these magnitudes of antiproliferation are achieved by about 25 μM **2g** in L1210 cells (Fig. 1), suggesting that this tetrazole-5-thione is at least 6.25 times more effective against leukemic than breast cancer cell lines. The fact that the concentrations of **1f**, **1g** and **2g** required to inhibit the mitochondrial ability of tumor cells to metabolize the MTS:PMS reagent at days 2 and 4 are somewhat higher in SK-BR-3 than L1210 cells suggests that the antiproliferative action of these drugs is generally greater against unsynchronized populations of rapidly-growing suspensions of leukemic cells that are frequently turning through the cell cycle than against unsynchronized populations of relatively slow-growing adherent monolayers of solid tumor cells that have smaller growth fractions.

The antitumor activity of **2g** is substantiated by the finding that this compound inhibits the expression of the human Ki-67 marker of cell proliferation in SK-BR-3 mammary tumor cells at 24 h (Fig. 3, left). The Ki-67 nuclear protein, which is absent from resting cells (G_0), is exclusively detected within the nuclei of cells progressing through all active phases of the cell cycle (G_1, S, G_2) and relocates to the surface of the chromosomes during mitosis.[27] Since Ki-67 expression may be absolutely required to maintain cell proliferation, it is an excellent marker for determining the growth fraction of tumor cell populations and the fraction of Ki-67-positive tumor cells is often correlated with the clinical course of cancer.[27] As compared to the level of Ki-67 protein detected by immunolabeling in untreated SK-BR-3 control tumor cells, the ability of 62.5–156.25 μM **2g** to inhibit Ki-67 expression by 36.5–52.4% at 24 h suggests that this novel antiproliferative compound maintains surviving tumor cells in the resting stage and prevents them from re-entering the cell cycle to divide (Fig. 3, left). After antiproliferative **2g** treatment, therefore, there are fewer tumor cells and they fail to express Ki-67, indicating that the growth fraction of tumor cells progressing through the cell cycle has been reduced.

A 90-min treatment with **2g** is sufficient to inhibit the incorporation of [^{3}H]thymidine into DNA used to assess the rate of DNA synthesis over a 30-min period of pulse-labeling in L1210 tumor cells in vitro (Fig. 3, right). Although it may be somewhat misleading to compare biological responses measured at very different times, the concentration-dependent inhibition of DNA synthesis by **2g** suggests that the ability of this compound to prevent tumor cells from synthesizing DNA at 2 h (Fig. 3, right) may play a role in

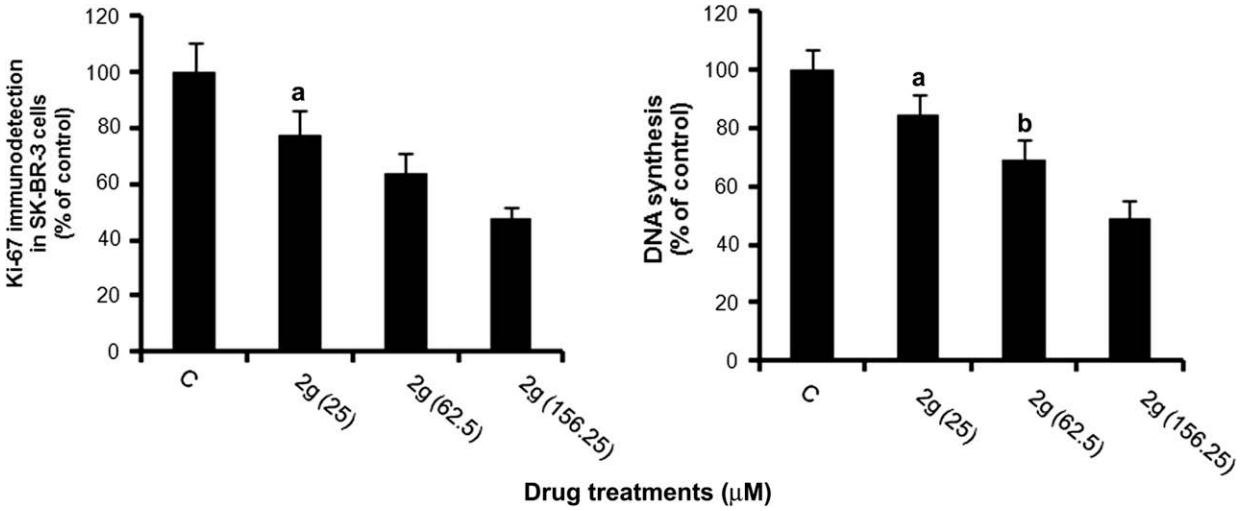


Figure 3. Left: Whole cell immunodetection of Ki-67 protein level in vitro. Comparison of the abilities of 25, 62.5 or 156.25 μM concentrations of **2g** to inhibit the Ki-67 marker of cell proliferation in SK-BR-3 cells at 24 h. The results were expressed as % of the ratio of Ki-67 protein level (relative luminescence intensity of the anti-Ki-67 primary antibody-antigen immune complex bound to horseradish peroxidase-linked secondary antibody):cell number (relative fluorescence intensity of the Hoechst reagent-DNA complex) in vehicle-treated control SK-BR-3 tumor cells at 24 h (C: 1.6248 ± 0.1771, 100 ± 10.9%). Bars: means ± SD (n = 3). [a]P <0.05, smaller than control. Right: Comparison of the abilities of 25, 62.5 or 156.25 μM concentrations of **2g** to inhibit the rate of incorporation of [^{3}H]thymidine into DNA measured in L1210 cells over 30 min following a 90-min period of incubation at 37 °C in vitro. DNA synthesis in vehicle-treated control (C) cells at 37 °C was 11,314 ± 769 cpm (100 ± 6.9%). The blank value (1282 ± 112 cpm) for control cells incubated and pulse-labeled at 2 °C with 1 μCi of [^{3}H]thymidine has been subtracted from the results. Bars: means ± SD (n = 3). [a]P <0.05 and [b]P <0.005, smaller than control.

its inhibition of Ki-67 expression at 24 h (Fig. 3, left) and antiproliferative activity at days 2 and 4 (Table 1 and Fig. 1).

Concentrations of **2g** somewhat higher than those sufficient to maximally inhibit tumor cell proliferation must be used to partially inhibit Ki-67 expression and DNA synthesis. Such apparent discrepancy may simply be due to different experimental conditions and cellular responses to various periods of drug exposure: the rate of DNA synthesis over 30 min is inhibited in cells treated for only 2 h with **2g** and the level of Ki-67 protein is reduced in cells incubated for 24 h in the presence of this antitumor compound, whereas the more spectacular inhibitions of L1210 and SK-BR-3 tumor cell proliferations are the result of 2- and 4-day long drug treatments.

In conclusion, copper mediated coupling of aryl boronic acids with 1-phenyl-1*H*-tetrazol-5(4*H*)-one is a versatile reaction to synthesize a series of 5-*oxo* derivatives of 1,4-diaryl tetrazoles. The substituents with lone pairs (such as –OMe, –Cl, –CF_3, –Br) on the aromatic ring of the 1,4-diaryl tetrazole-5-ones promote their thionation to corresponding tetrazole-5-thiones. Compound 1-(2-bromophenyl)-4-phenyl-1*H*-tetrazole-5(4*H*)-thione thus obtained is an excellent precursor to introduce other type of substituents on tetrazole-5-thione through metalation followed by electrophilic quenching, or via palladium catalyzed cross coupling reactions. The synthesized tetrazole derivatives are also stable to strong Lewis acid conditions. These compounds may have interesting bioactivity but more compounds based on 5-*oxo* and 5-thio 1,4-diaryl tetrazole scaffolds must be synthesized to elucidate structure–activity relationships, identify more potent antitumor lead compounds, and investigate their molecular targets and mechanism of action.

Acknowledgments

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Supplementary data

Supplementary data (description of compound syntheses and their spectral characterization; biological assay methods and Table 1s showing the IC_{50} values of **1a** – **e**, **2a** – **f** and **6**) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.05.012.

References and notes

1. Luo, Y.-P.; Yang, G.-F. *Bioorg. Med. Chem.* **2007**, *15*, 1716.
2. Foldenyi, R. *Monatsh. Chem.* **1995**, *126*, 1035.
3. Nishi, Y.; Miyauchi, H. *Pflanzenschutz-Nachr. Bayer (Engl. Ed.)* **2001**, *54*, 43.
4. Theodoridis, G. U.S. 1799 8501939, 1985.
5. Andres-Gil, J. I.; Alcazar-Vaca, M. J.; Pastor-Fernandez, J.; Drinkenburg, W. H. I. M.; Langlois, X. J. M.; Oyarzabal-Santamarina, J.; Vega-Ramiro, J. A. EP 56951 2006067139, 2006.
6. Show-Reid, C. A.; Miller, M. D.; Hazuda, D. J.; Ferrer, M.; Sur, S. M.; Summa, V.; Lyle, T. A.; Kinzel, O.; Pescatore, G.; Muraglia, E.; Orvieto, F.; Williams, P. D. U.S. 16671 2005115147, 2005.
7. Cirino, G.; Mirone, V.; Ignarro, L. J.; Del Soldato, P. EP 50779 2004043443, 2004.
8. Goulet, M.; Ashton, W. T.; Chu, L.; Fisher, M. H.; Lin, P.; Ponpipom, M. M.; Wyvratt, M. J.; Girotra, N. N.; Young, J. U.S. 98-115497 6200957, 2001.
9. Goulet, M.; Ashton, W. T.; Chu, L.; Fisher, M. H.; Lin, P.; Ponpipom, M. M.; Wyvratt, M. J.; Girotra, N. N.; Young, J. U.S. 15581 2000004013, 2000.
10. Janssens, F. E.; Sommen, F. M.; Surleraux, D. L. N. G.; Leenaerts, J. E.; Van Roosbroeck, Y. E. M. EP 4660 9716440, 1997.
11. Shih, T. L.; Candelore, M. R.; Cascieri, M. A.; Chiu, S.-H. L.; Colwell, L. F., Jr.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1251.
12. Chartrain, M. M.; Chung, J. Y. L.; Roberge, C. U.S. 12615 9803672, 1998.
13. Chong, J. A. U.S. 43987 2009140519, 2009.
14. Shenk, T.; Rabinowitz, J. D.; Munger, J.; Bennett, B. U.S. 6959 2009023059, 2009.
15. Kang, H. Y.; Koh, H. Y.; Koh, S. H.; Chang, M. H. *Korean J. Med. Chem.* **1991**, *1*, 18.
16. Natalini, C. C.; Robinson, E. P. *Am. J. Vet. Res.* **2000**, *61*, 1579.
17. Snijdelaar, D. G.; Katz, J.; Clairoux, M.; Sandler, A. N. *Acute Pain* **2000**, *3*, 131.
18. Abou-Arab, M. H.; Heier, T.; Caldwell, J. E. *Br. J. Anaesth.* **2007**, *98*, 604.
19. Jeleazcov, C.; Fechner, J.; Schwilden, H. *Anesth. Analg.* **2005**, *100*, 1365.

20. Janssens, F.; Torremans, J.; Janssen, M.; Stokbroekx, R. A.; Luyckx, M.; Janssen, P. A. J. *J. Med. Chem.* **1985**, *28*, 1943.
21. Sindkhedkar, M. D.; Bhavsar, S. B.; Patil, V. J.; Deshpande, P. K.; Patel, M. V. IN 208 2007023507, 2007.
22. Hepperle, M. E.; Liu, J. F.; Soucy, F.; Raman, P.; Little, J. D.; Fleming, P. E.; Reynolds, D.; Harriman, G. C. B. U.S. 2005-101998 2005239781, 2005.
23. Dunlap, R. P.; Boaz, N. W.; Mura, A. J.; Hlasta, D. J. U.S. 2434 9013549, 1990.
24. Westman, J.; Wiman, K.; Mohell, N. SE 50363 2007139497, 2007.
25. Cory, A. H.; Owen, T. C.; Barltrop, J. A.; Cory, J. G. *Cancer Commun.* **1991**, *3*, 207.
26. Perchellet, E. M.; Magill, M. J.; Huang, X.; Dalke, D. M.; Hua, D. H.; Perchellet, J.-P. *Anti-Cancer Drugs* **2000**, *11*, 339.
27. Scholzen, T.; Gerdes, J. *J. Cell. Physiol.* **2000**, *182*, 311.
28. Frija, L. M. T.; Khmelinskii, I. V.; Cristiano, M. L. S. *Tetrahedron Lett.* **2005**, *46*, 6757.
29. Petko, K. I.; Yagupol'skii, L. M. *Russ. J. Org. Chem.* **2004**, *40*, 601.
30. Luo, Y.-P.; Lin, L.; Yang, G.-F. *J. Heterocycl. Chem. F* **2007**, *44*, 937.
31. Poplavskaya, Y. V.; Alam, L. V.; Koldobskii, G. I. *Russ. J. Org. Chem.* **2000**, *36*, 1793.
32. Quast, H.; Nahr, U. *Chem. Ber.* **1985**, *118*, 526.
33. Suzuki, H.; Nakaya, C.; Matano, Y. *J. Chem. Res., Synop.* **1992**, 34.
34. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.
35. Lan, J.-B.; Zhang, G.-L.; Yu, X.-Q.; You, J.-S.; Chen, L.; Yan, M.; Xie, R.-G. *Synlett* **2004**, 1095.
36. Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941.
37. Rayat, S.; Chhabra, R.; Alawode, O.; Gundugola, A. S. *J. Mol. Struct.* **2009**, *933*, 38.
38. Laus, G.; Mueller, A. G.; Schottenberger, H.; Wurst, K.; Buchmeiser, M. R.; Ongania, K.-H. *Monatsh. Chem.* **2006**, *137*, 69.
39. Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* **2007**, *107*, 5210.
40. Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.
41. Polshettiwar, V.; Kaushik, M. P. *Tetrahedron Lett.* **2004**, *45*, 6255.
42. Bezgubenko, L. V.; Pipko, S. E.; Sinitsa, A. D. *Russ. J. Gen. Chem.* **2008**, *78*, 1341.
43. Pathak, U.; Pandey, L. K.; Tank, R. *J. Org. Chem.* **2008**, *73*, 2890.
44. Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem.* **1981**, *46*, 2280.
45. Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.
46. La Beaume, P.; Wager, K.; Falcone, D.; Li, J.; Torchilin, V.; Castro, C.; Holewa, C.; Kallmerten, A. E.; Jones, G. B. *Bioorg. Med. Chem.* **2009**, *17*, 6292.
47. Yamane, Y.; Liu, X.; Hamasaki, A.; Ishida, T.; Haruta, M.; Yokoyama, T.; Tokunaga, M. *Org. Lett.* **2009**, *11*, 5162.
48. Onopchenko, A.; Sabourin, E. T.; Selwitz, C. M. *J. Org. Chem.* **1979**, *44*, 1233.
49. Sabourin, E. T.; Selwitz, C. M. U.S. 77-840553 4128588, 1978.
50. Sabourin, E. T.; Onopchenko, A. *J. Org. Chem.* **1983**, *48*, 5135.
51. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley Interscience, 1991.
52. Hadzi, D.; Kidric, J.; Koller, J.; Mavri, J. *J. Mol. Struct.* **1990**, *237*, 139.