SELENIUM DIOXIDE–MEDIATED SYNTHESIS OF FUSED 1,2,4-TRIAZOLES AS CYTOTOXIC AGENTS

Heng Zheng, Kang Wang, Wei Zhang, and Ruihuan Liu
1Department of Gastrointestinal Surgery, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu, China
2School of Pharmaceutical Sciences, Central South University, Changsha, China

GRAPHICAL ABSTRACT

Abstract A series of fused 1,2,4-triazoles has been prepared by oxidative intramolecular cyclization of heterocyclic hydrazones with selenium dioxide. General applicability of this practical protocol was confirmed by the synthesis of moderate to good yields of 1,2,4-triazolo[4,3-a]pyridines, 1,2,4-triazolo[4,3-a]pyrimidines, 1,2,4-triazolo[4,3-a]pyramidines, and 1,2,4-triazolo[4,3-a]quinoxalines. All compounds were tested in vitro for their cytotoxic activity against HCT-116, A549, and Colo-205 cell lines. Two compounds, 3-(4-methoxyphenyl)-7-methyl-[1,2,4]triazolo[4,3-a]pyridine and 1-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]quinoxaline, showed potent antiproliferative activity against the three cell lines.

Keywords Antiproliferative activity; selenium dioxide; 1,2,4-triazole

INTRODUCTION

Triazoles are an important class of heterocyclic compounds. In particular, fused 1,2,4-triazoles express antibactericidal,[1,2] antianxiety,[3] anticancer,[4,5] and antimicrobial activities[6] and act as inhibitors of kinase[7] and fibrinogen receptors.[8] In the past few decades, the chemistry of fused 1,2,4-triazoles has received considerable attention because of their synthetic and effective biological importance. Most methods for the preparation of fused 1,2,4-triazoles are based on hydrazones or hydrazides as precursors.[2,9–15]

As part of our ongoing studies exploring novel antitumor drugs, a series of fused 1,2,4-triazole derivatives was designed. Initially, we planned to synthesize...
1,2,4-triazoles via oxidative cyclization of hydrazones with oxidizing agents such as copper(II) chloride,\textsuperscript{[9]} bis(trifluoroacetoxy)iodo]benzene (PIFA),\textsuperscript{[12]} iodobenzene diacetate (IBD),\textsuperscript{[13]} and lead(IV) acetate.\textsuperscript{[15]} Unfortunately, the results obtained with these oxidative agents were not satisfactory. Therefore, we developed a simple and practical protocol for preparing 1,2,4-triazoles by oxidative cyclization of hydrazones using SeO$_2$ (Scheme 1).

**RESULTS AND DISCUSSION**

The precursors, hydrazones, were obtained by treating the corresponding hydrazino heterocycles with aldehydes.

To achieve a generally accepted oxidizing agent for the cyclization of hydrazine, a series of additives was examined for efficiency in the heterocyclization of hydrazone ($\text{1f}$). The results listed in Table 1 indicate that the SeO$_2$ is more effective than others, although greater reaction temperature was required. Compared with

| Entry | Catalyst | Temp. (°C) | Yield (%)$^a$ |
|-------|----------|------------|--------------|
| 1     | CuCl$_2$$^b$ $^{[9]}$ | 100        | 64           |
| 2     | PIFA$^b$ $^{[12]}$   | 25         | 57           |
| 3     | IBD$^b$ $^{[13]}$    | 25         | 78           |
| 4     | Pb(OAc)$_4$$^b$ $^{[15]}$ | 25 | 45           |
| 5     | Ce(SO$_4$)$_2$$^c$   | 110        | 8            |
| 6     | Fe$_2$O$_3$$^c$      | 110        | —            |
| 7     | SeO$_2$$^c$          | 110        | 98           |

$^a$Isolated yields.
$^b$The reaction was performed according to the literature.
$^c$Reaction conditions: $\text{1f}$ (10 mmol) and catalyst (20 mmol) in DMF (10 mL) was stirred at 110 °C for 2 h.
other additives, the use of SeO₂ as a heterogeneous oxidant in this reaction has advantage of good yield, simple workup, and low cost.

In the primary experiment, the heterocyclization was performed in dimethylformamide (DMF) under air. To identify an optimal reaction condition for oxidative heterocyclization, the influence of oxidant amount was investigated (Table 2) at different temperatures with heterocyclization of hydrazine 1f as the model reaction. Encouragingly, nearly quantitative conversion of 1f to 5f was achieved when 1f was treated with 2 equiv SeO₂ at 110 °C for 2 h (Table 2, entry 5). No further improvement was obtained when the reaction was performed in different solvents (Table 2, entries 8–11).

To further probe the synthetic scope of this reagent, we investigated the oxidative cyclization of other heterocyclic hydrazones to afford the corresponding 1,2,4-triazolo derivatives. Hydrazones 1–4 of aromatic and aliphatic aldehydes with both electron-withdrawing and electron-donating substituents were oxidized to give the corresponding 1,2,4-triazolo[4,3-a]pyridines (5), 1,2,4-triazolo[4,3-a]pyrimidines (6), 1,2,4-triazolo[4,3-a]quinolone (7), and 1,2,4-triazolo[4,3-a]quinoxalines (8) in good yields (Table 3). The plausible mechanism for the oxidation of hydrazones is depicted in Scheme 2 with the oxidation of 1 to 5 as an example.

The target compounds were evaluated for cytotoxic activity against three human cancer cell lines using the sulforhodamine B (SRB) assay. 5-Fluorouracil (5-FU), which has a broad spectrum of anticancer activity, was used as reference drug. The three cell lines are human colon cancer HCT-116 and Colo-205 cell lines and non-small-cell lung carcinoma A549 cell line. The IC₅₀ values of all targeted compounds are assessed and summarized in Table 3.

As shown in Table 3, most compounds were able to inhibit the growth of the three cancer cells with IC₅₀ values between 2 and 70 µM. Among them, compounds 5a, 5b, and 8a (R = alkyl groups) were found to be inactive against all tumor cell lines (IC₅₀ > 100 µM). The cytotoxic activities of 4-methoxyphenyl analogs (5f, 6a and 8b) was superior to those of other substituted-phenyl analogs. The antiproliferative activities of 1,2,4-triazolo[4,3-a]quinoxalines seemed to be stronger than those of other triazoles. In the whole series, compound 8b showed significant growth

| Entry | Cat. (equiv) | Temp. (°C) | Solvent | Yield (%)<sup>a</sup> |
|-------|-------------|------------|---------|------------------|
| 1     | 1           | 90         | DMF     | 38               |
| 2     | 2           | 90         | DMF     | 79               |
| 3     | 3           | 90         | DMF     | 80               |
| 4     | 2           | 100        | DMF     | 86               |
| 5     | 2           | 110        | DMF     | 98               |
| 6     | 2           | 120        | DMF     | 96               |
| 7     | 2           | 140        | DMF     | 82               |
| 8     | 2           | Reflux     | DCM     | —                |
| 9     | 2           | Reflux     | Ethanol | —                |
| 10    | 2           | Reflux     | Acetonitrile | —   |
| 11    | 2           | 110        | DMSO    | 90               |

<sup>a</sup>Isolated yields. Conditions: 1f (10 mmol) in DMF (10 mL) was heated for 2 h.
Table 3. Synthesis and cytotoxic activity of the target compounds 5-8

| Compound | R               | Compound | Time (h) | Yield\(^a\) (%) | Mp (°C) | IC\(_{50}\)\(^{b,c}\) (μM) |
|----------|-----------------|----------|----------|------------------|---------|-----------------------------|
| 1a       | Ethyl           | 5a       | 2.5      | 82               | 85–87   | >100                        |
| 1b       | 3-Isobutyl      | 5b       | 2        | 84               | 102–104 | >100                        |
| 1c       | 2-(Methylthio)ethyl | 5c     | 1.5      | 92               | 106–108 | >100                        |
| 1d       | Benzyl          | 5d       | 2        | 93               | 154–156 | >100                        |
| 1e       | 4-Hydroxylphenyl | 5e       | 2        | 90               | 207–208 | >100                        |
| 1f       | 4-Methoxyneryl  | 5f       | 2        | 98               | 214–216 | >100                        |
| 1g       | 3,4,5-Trimethoxyl phenyl | 5g    | 1.5      | 92               | 244–245 | >100                        |
| 1h       | 3,4-Dichlorophenyl | 5h      | 2        | 94               | 232–234 | >100                        |
| 1i       | 3-Nitrophenyl   | 5i       | 2        | 96               | 192–194 | >100                        |
| 1j       | 4-Nitrophenyl   | 5j       | 2        | 96               | 185–186 | >100                        |
| 1k       | Thiophen-2-yl   | 5k       | 2        | 86               | 155–156 | >100                        |
| 2a       | 4-Methoxyneryl  | 6a       | 2        | 97               | 152–153 | >100                        |
| 2b       | 2-Nitrophenyl   | 6b       | 2        | 90               | 160–162 | >100                        |
| 3        | 2-Nitrophenyl   | 7        | 1.5      | 92               | 210–212 | >100                        |
| 4a       | Ethyl           | 8a       | 1.5      | 93               | 151–153 | >100                        |
| 4b       | 4-Methoxyneryl  | 8b       | 1.5      | 91               | 182–183 | >100                        |
| 4c       | 2-Nitrophenyl   | 8c       | 2        | 93               | 243–244 | >100                        |

5-Fluorouracil

\[^a\] Isolated yields.

\[^b\] The IC\(_{50}\) values represent the compound concentration required to inhibit tumor cell proliferation by 50%.

\[^c\] Assays done in replicates (n ≥ 3). Mean values are shown, and the standard deviations are <30% of the mean.
inhibition with IC_{50} values of 2.36 and 5.76 μM against HCT-116 and A549 cell lines respectively, which is almost equipotent to 5-fluorouracil.

CONCLUSIONS

In conclusion, we have developed a practical and efficient protocol for the synthesis of fused 1,2,4-triazoles by oxidation of heterocyclic substituted hydrazones using SeO_{2} as oxidizing agent. The presence of several functionalities in the substrate is tolerated and almost does not affect the yield of the desired product. Most of the target compounds displayed potent antitumor activity. Among them, compound 8b exhibited significant growth inhibition with IC_{50} values of 2.36 and 5.76 μM against HCT-116 and A549 cells respectively, which is almost equipotent to 5-fluorouracil.

EXPERIMENTAL

All the reagents and solvents for the synthesis and analysis were commercially available and used directly. Melting points were recorded on a YRT-3 melting-point apparatus and are uncorrected. 1H NMR and 13C NMR spectra were measured using a Bruker DRX 400 instrument [400 MHz for 1H NMR and 100 MHz for the 13C NMR (proton decoupled)] using dimethylsulfoxide (DMSO- d_{6}) as solvent and tetramethylsilane (TMS) as internal standard, chemical shifts (δ scale) are reported in parts per million (ppm). Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, brs = broad singlet, m = multiplet), coupling constant (Hz), integration. Mass spectra analyses of all the compounds were performed on a high-resolution q-TOF.

Typical Procedure for the Synthesis of Hydrazones (1–4)

Hydrazones 4b and 4c were prepared according to the literature procedure.[17] The new hydrazones are prepared as follows: The hydrazine (15 mmol) was dissolved in boiling ethanol (20 ml) and the aldehyde (15 mmol) dissolved in ethanol (20 ml) was added dropwise. After that, the solution was stirred and heated under reflux for 1 h. The formed hydrazone was filtered from the cooled solution and used in the next reaction without any purification.

Typical Procedure for the Synthesis of Fused 1,2,4-Triazoles (5–8)

To a solution of hydrazone (10.0 mmol) in DMF (10 ml), selenium dioxide (2.20 g, 20.0 mmol) was added while stirring. The mixture was stirred at 110 °C
and monitored by thin-layer chromatography (TLC). After the completion of
the reaction, the reaction mixture was filtered, and the filtrate was evaporated in
vacuum. The crude product was purified by recrystallization or by flash column
chromatography to give the desired product.

Spectral Data for Selected Compounds

\((E)\)-2-(2-(4-Methoxybenzylidene)hydrazinyl)-4-methylpyridine (1f).
Yellow solid, mp 234–236 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 2.31\) (s, 3 H), 3.95 (s, 3 H), 6.73 (dd, \(J = 1.3\) Hz, 7.3 Hz, 1 H), 7.10 (d, \(J = 8.5\) Hz, 2 H), 7.56 (d, \(J = 1.3\) Hz, 1 H), 7.69 (d, \(J = 8.3\) Hz, 2 H), 7.90 (s, 1 H), 8.38 (d, \(J = 7.1\) Hz, 1 H), 10.90 (s, 1 H) ppm. HRMS-ESI (\(m/z\)): [M+H]\(^+\) calcd. for C\(_{14}\)H\(_{16}\)N\(_3\)O, 242.1288; found, 242.1267.

\((E)\)-2-(2-(4-Methoxybenzylidene)hydrazinyl)pyrimidine (2a)
Yellow solid, mp 192–193 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 3.83\) (s, 3 H), 7.20 (d, \(J = 8.5\) Hz, 2 H), 7.45 (t, \(J = 8.2\) Hz, 1 H), 7.61 (d, \(J = 8.5\) Hz, 2 H), 8.12 (d, \(J = 8.2\) Hz, 2 H), 7.97 (s, 1H), 11.07 (s, 1 H) ppm. HRMS-ESI (\(m/z\)): [M+H]\(^+\) calcd. for C\(_{12}\)H\(_{13}\)N\(_4\)O, 229.1084; found, 229.1059.

\((E)\)-2-(2-(2-Nitrobenzylidene)hydrazinyl)quinoline (3)
Yellow solid, mp 227–229 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 7.13\) (d, \(J = 8.0\) Hz, 1 H), 7.40 (t, \(J = 8.1\) Hz, 1 H), 7.57 (t, \(J = 7.3\) Hz, 1 H), 7.73 (d, \(J = 8.6\) Hz, 1 H), 7.87 (d, \(J = 8.6\) Hz, 1 H), 8.01 (d, \(J = 8.0\) Hz, 1 H), 8.07–8.11 (m, 3 H), 8.23 (s, 1 H), 8.36 (d, \(J = 7.3\) Hz, 1 H), 10.56 (s, 1H) ppm. HRMS-ESI (\(m/z\)): [M+H]\(^+\) calcd. for C\(_{16}\)H\(_{13}\)N\(_4\)O\(_2\), 293.1033; found, 293.1028.

\((E)\)-2-(2-Propylidenehydrazinyl)quinoxaline (4a)
Yellow solid, mp 212–213 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 1.45\) (t, \(J = 7.2\) Hz, 3 H), 3.30 (m, 2 H), 7.68 (td, \(J = 1.0\) Hz, 8.5 Hz, 1 H), 7.77 (td, \(J = 1.2\) Hz, 8.5 Hz, 1 H), 7.95 (t, \(J = 7.2\) Hz, 1 H), 8.06 (dd, \(J = 1.2\) Hz, 8.0 Hz, 1 H), 8.06 (dd, \(J = 1.0\) Hz, 8.0 Hz, 1 H), 8.46 (s, 1 H), 11.97 (s, 1 H) ppm. HRMS-ESI (\(m/z\)): [M+H]\(^+\) calcd. for C\(_{11}\)H\(_{13}\)N\(_4\), 201.1135; found, 201.1122.

3-(4-Methoxyphenyl)-7-methyl-[1,2,4]triazolo[4,3-a]pyridine (5f)
White solid, mp 214–216 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 2.38\) (s, 3 H), 3.85 (s, 3 H), 6.83 (dd, \(J = 1.4\) Hz, 7.2 Hz, 1 H), 7.15–7.17 (m, 2 H), 7.56 (d, \(J = 0.8\) Hz, 1 H), 7.79–7.81 (m, 2 H), 8.38 (d, \(J = 7.2\) Hz, 1 H) ppm. \(^1^3\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta = 21.2, 55.8, 113.6, 115.1, 117.4, 119.4, 123.4, 129.9, 138.7, 145.9, 150.7, 160.8\) ppm. HRMS-ESI (\(m/z\)): [M+H]\(^+\) calcd. for C\(_{14}\)H\(_{14}\)N\(_3\)O, 240.1131; found, 240.1160.
3-(4-Methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyrimidine (6a)

Yellow solid, mp 152–153 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 3.91\) (s, 3 H), 7.23 (d, \(J = 8.7\) Hz, 2 H), 7.50 (dd, \(J = 1.0\) Hz, 8.3 Hz, 1 H), 7.55 (td, \(J = 1.3\) Hz, 8.4 Hz, 1 H), 7.72 (d, \(J = 10.0\) Hz, 2 H), 8.11 (dd, \(J = 1.0\) Hz, 8.0 Hz, 1 H) ppm. \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta = 55.9, 115.1, 116.2, 120.6, 126.6, 127.9, 129.8, 130.8, 132.0, 136.6, 144.5, 144.8, 149.4, 161.6\) ppm. HRMS-ESI (\(m/z\)): [M +H]+ calcd. for C\(_{12}\)H\(_{11}\)N\(_4\)O, 227.0927; found, 227.0939.

1-(2-Nitrophenyl)-[1,2,4]triazolo[4,3-a]quinoline (7)

Yellow solid, mp 210–212 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 7.18\) (d, \(J = 8.4\) Hz, 1H), 7.48 (t, \(J = 8.1\) Hz, 1 H), 7.56 (t, \(J = 7.2\) Hz, 1 H), 7.83 (d, \(J = 9.6\) Hz, 1 H), 7.91 (d, \(J = 9.6\) Hz, 1 H), 8.00 (d, \(J = 8.4\) Hz, 1 H), 8.03–8.10 (m, 3 H), 8.46 (d, \(J = 7.5\) Hz, 1 H) ppm. \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta = 114.9, 115.7, 124.5, 124.8, 126.1, 126.8, 130.2, 130.3, 130.8, 131.6, 133.2, 133.7, 135.5, 144.8, 148.6, 149.6\) ppm. HRMS-ESI (\(m/z\)): [M+H]+ calcd. for C\(_{16}\)H\(_{11}\)N\(_4\)O\(_2\), 291.0877; found, 291.0832.

1-(4-Methoxyphenyl)-[1,2,4]triazolo[4,3-a]quinoxaline (8b)

Yellow solid, mp 182.3–182.7 °C; \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 3.91\) (s, 3 H), 7.24 (d, \(J = 8.5\) Hz, 2 H), 7.49–7.51 (m, 1 H), 7.55 (td, \(J = 1.4\) Hz, 8.5 Hz, 1 H), 7.65 (td, \(J = 1.4\) Hz, 8.0 Hz, 1 H), 7.71–7.73 (m, 2 H), 8.10 (dd, \(J = 1.2\) Hz, 8.0 Hz, 1 H), 8.71 (s, 1 H) ppm. \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta = 55.9, 115.1, 116.2, 120.6, 126.6, 127.9, 129.8, 130.8, 132.0, 144.5, 144.8, 149.4, 152.5, 161.6\) ppm. HRMS-ESI (\(m/z\)): [M+H]+ calcd. for C\(_{16}\)H\(_{13}\)N\(_4\)O, 277.1084; found, 277.1108.

In Vitro Antiproliferative Activity Assays

The antiproliferative activity of the compounds was tested on HCT-116, A549, and Colo-205 cells. Cells were seeded in 96-well plates at a density of 5000 cells/well and incubated for 24 h. The cells were then incubated with serially diluted compounds for another 48 h. The final number of cells per well was assessed using the sulforhodamine B dye (SRB, Sigma–Aldrich) following the standard procedure,[16] and absorbance was measured using a microplate reader (SpectraMax M5) at a wavelength of 515 nm. The results were expressed as IC\(_{50}\) calculated using the Easy-fit software.

SUPPLEMENTAL MATERIAL

Experimental procedures, \(^1\)H NMR and \(^{13}\)C NMR spectra data, and references for all the products for this article can be accessed on the publisher’s website.

REFERENCES

1. El-Hawash, S. A. M.; Habib, N. S.; Fanaki, N. H. Pharmazie 1999, 54, 808–813.
2. Prakash, O.; Bhardwaj, V.; Kumar, R.; Tyagi, P.; Aneja, K. R. *Eur. J. Med. Chem.* **2004**, *39*, 1073–1077.

3. Amr, A. E.; Mohamed, S. F.; Abodel-Hafez, N. A.; Abdalla, M. M. *Monatsh Chem.* **2008**, *139*, 1491–1498.

4. Bhat, K. S.; Poojary, B.; Prasad, D. J.; Naik, P.; Holla, B. S. *Eur. J. Med. Chem.* **2009**, *44*, 5066–5070.

5. El-Hawash, S. A. M.; Habib, N. S.; Kassem, M. A. *Arch. Pharm.* **2006**, *339*, 564–571.

6. Prakash, O.; Hussain, K.; Aneja, D. K.; Sharma, C.; Aneja, K. *Org. Med. Chem. Lett.* **2011**, *1*, 1–9.

7. McClure, K. F.; Letavic, M. A.; Kalogutkar, A. S.; Gabel, C. A.; Audoly, L.; Barberia, J. T.; Braganza, J. F.; Carter, D.; Carty, T. J.; Cortina, S. R.; Dombroski, M. A.; Donahue, K. M.; Elliott, N. C.; Gibbons, C. P.; Jordan, C. K.; Kuperman, A. V.; Labasi, J. M.; LaLiberte, R. E.; McCoy, J. M.; Naiman, B. M.; Nelson, K. L.; Nguyen, H. T.; Peese, K. M.; Sweeney, F. J.; Taylor, T. J.; Trebino, C. E.; Abravon, Y. A.; Laird, E. R.; Volberg, W. A.; Zhou, J.; Bach, J.; Lombardo, F. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4339–4344.

8. Lawson, E. C.; Hoekstra, W. J.; Addo, M. F.; Andrade-Gordon, P.; Damiano, B. P.; Kauffman, J. A.; Mitchell, J. A.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2619–2622.

9. Ciesielski, M.; Pufky, D.; Döring, M. *Tetrahedron* **2005**, *61*, 5942–5947.

10. Moulin, A.; Martinez, J.; Fehrentz, J-A. *Tetrahedron Lett.* **2006**, *47*, 7591–7594.

11. Wang, Y.; Sarris, K.; Sauer, D. R.; Djuric, S. W. *Tetrahedron Lett.* **2007**, *48*, 2237–2240.

12. Padalkar, V. S.; Patil, V. S.; Phatangare, K. R.; Umap, P. G.; Sekar, N. *Synth. Commun.* **2011**, *41*, 925–938.

13. Sadana, A. K.; Mirza, Y.; Aneja, K. R.; Prakash, O. *Eur. J. Med. Chem.* **2003**, *38*, 533–536.

14. Reichelt, A.; Falsey, J. R.; Rzasa, R. M.; Thiel, O. R.; Achmatowicz, M. M.; Larsen, R. D.; Zhang, D. *Org. Lett.* **2010**, *12*, 792–795.

15. Butler, R. N.; Johnston, S. M. *J. Chem. Soc. Perkin Trans. 1* **1984**, 2109–2116.

16. Skenhan, P.; Storeng, R.; Scudiero, D.; Monks, A.; Memahan, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1107–1112.

17. Rodrigues, F. A. R.; Bomfim, Igor da S.; Cavalcanti, B. C.; P essoa, Claudia do Ó.; Wardell, J. L.; Wardell, S. M. S. V.; Pinheiro, A. C.; Kaiser, C. R.; Nogueira, T. C. M.; Low, J. N.; Gomes, L. R.; de Souza, M. V. N. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 934–939.